

From The Division of Global Health (IHCAR), Department of
Public Health Sciences
Karolinska Institutet, Stockholm, Sweden

MANAGING MALARIA IN UNDER-FIVES:

Prompt access, adherence to treatment and referral in rural Tanzania

Daudi Omari Simba



**Karolinska
Institutet**

Stockholm 2010

All previously published papers were reproduced with permission from the publisher.

Published by Karolinska Institutet. Printed by [Universitetservice-AB, Nanna Swartzvag
4, SE-171-77 Stockholm, Sweden]

© Daudi Omari Simba, 2010
ISBN 978-91-7457-160-8

ABSTRACT

Background: Nearly a million people die of malaria each year, the majority are children in rural African settings. These deaths could be reduced if children had prompt access to artemisinin-based combination therapy (ACTs), demonstrated adherence to treatment and to referral advice for severe malaria. However, health systems are weak to deliver the interventions. Although many African countries, including Tanzania, changed malaria treatment policy to ACTs in the last decade, few children reportedly get prompt access to ACTs.

Main aim: To determine factors influencing prompt access to effective antimalarials; adherence to treatment schedules and to referral advice among children under five, in rural settings.

Methods: Community-based studies were conducted in rural villages in Kilosa (I,II) and Mtwara rural (II,IV) districts, in Tanzania. Study I and II were prospective designed while study III and IV were nested in a community-based rectal-artesunate deployment intervention study. In study I, a total of 1,235 children from 12 randomly selected villages were followed up for six months. Caretakers of children reported to have fever were interviewed at home about the type and source of treatment using a questionnaire. In study II, all children (3918) in five selected villages were followed-up for 12 months, to determine adherence to treatment when they had malaria, diagnosed using Rapid Diagnostic Test (RDT) and treated with artemether-lumefantrine (ALu). In study III, 587 children who received pre-referral rectal artesunate during the deployment study were traced home and caretakers interviewed on a number of factors likely to influence adherence to referral advice, using a questionnaire. Study IV was qualitative, 12 focus group discussions were conducted in three purposively selected villages to explore reasons for non-adherence to referral advice.

Results: Only one-third (37.6%) of febrile children had prompt access to ALu, the recommended ACTs in Tanzania, mainland (I). Lack of prompt access was mostly (>80 percent) attributed to receiving non-recommended drugs. Less than half of the febrile children were taken to government facilities, where they were 17-times more likely to have prompt access compared to those who went elsewhere. Less than 10% (41/607) of febrile children had access to ALu (I) from faith-based organisation facilities and accredited drug dispensing outlets, despite having subsidized ALu. Reported adherence to treatment schedules was high (>80 percent) and non-adherence was attributed mainly to untimely dosing, rather than taking a fewer number of doses (II). While social economic status influenced prompt access to ALu and adherence to treatment, basic education did not (I, II). Caretakers of children with altered consciousness and convulsion were almost 4-times more likely to adhere to referral advice than those whose children had less severe symptoms (III). They seemed to weigh child condition against obstacles to accessing care at health facilities, if the condition was less severe prior to or improved after rectal artesunate dose, caretakers were likely to be deterred from adhering to referral advice (IV). Detailed understanding of provider's advice was likely to lead to adherence to the treatment schedule (II) and to referral advice (III, IV).

Conclusion: This thesis has shown that once a child had access to ALu, caretakers were likely to adhere to treatment schedule; and to referral advice, if child had severe symptoms or not improved after pre-referral treatment. More efforts should therefore be directed towards increasing access to ALu by strengthening the public health sector to reach rural remote areas. A wide coverage in prompt access to ALu will also reduce the need for the rectal artesunate strategy

Key words: Malaria, Health Systems, Access, Adherence, Referral

LIST OF PUBLICATIONS

- I. Simba, D., Warsame, M., Kakoko, D., Mrango, Z., Tomson, G., Premji, Z. & Petzold, M. (2010) Who Gets Prompt Access to Artemisinin-Based Combination Therapy? A Prospective Community-Based Study in Children from Rural Kilosa, Tanzania. *PLoS ONE*, 5, e12104.
- II. Simba, D., Kakoko, D., Tomson, G., Premji, P., Petzold, M., Mahindi, M & Gustafsson, L. High Adherence to Artemether-lumefantrine Treatment in Children Under Real-life Situation in Rural Tanzania (Submitted)
- III. Simba, D., Warsame, W., Kimbute, O., Kakoko, D., Petzold, M., Tomson, G., Premji, Z. & Gomes, M. (2009) Factors Influencing Adherence to Referral Advice Following Pre-Referral Treatment with Artesunate Suppositories in Children in Rural Tanzania. *Tropical Medicine and International Health*, 14;775-783
- IV. Simba, D., Kakoko, D., Warsame, M., Premji, Z., Gomes, M., Tomson, G. & Johansson, E. (2010) Understanding Caretakers' Dilemma in Deciding Whether or not to Adhere with Referral Advice after Pre-referral Treatment with Rectal Artesunate. *Malaria Journal*, 9,123; 775-783

The papers will be referred to by their roman numerals 1-IV

CONTENTS

1	INTRODUCTION.....	1
1.1	Global health and poverty	1
1.2	Malaria morbidity and mortality and control.....	1
1.3	Global commitment to control and eliminate malaria deaths	2
1.4	Antimalarial intervention strategies	3
1.5	The health system	4
1.5.1	Global governance of malaria control.....	5
1.5.2	Global financing of malaria control interventions	5
1.5.3	Health service delivery	6
1.5.4	Human resources for health	7
1.5.5	Drugs procurement and distribution	7
1.6	Malaria treatment	8
1.6.1	Malaria treatment policy.....	8
1.6.2	Recommended antimalarials for uncomplicated and severe malaria	9
1.6.3	Pharmacokinetics/dynamics of artemisinin-lumefantrine ..	10
1.6.4	Antimalarial drug resistance	11
1.7	Challenges in managing malaria in under fives	12
1.7.1	Prompt access to artemisinin-based combination therapy..	12
1.7.2	Community-based health care.....	12
1.7.3	Adherence to treatment schedule.....	13
1.7.4	Adherence to referral advice	14
1.8	Tanzania country profile	14
1.8.1	Economic characteristics	15
1.8.2	Demographic characteristics	16
1.8.3	Health care system	16
1.8.4	Malaria control in Tanzania - Mainland.....	22
1.9	Evidence gap and rationale for the studies	24
2	AIMS AND OBJECTIVES.....	26
3	STUDY SETTINGS	27
4	MATERIAL AND METHODS	29
4.1	Study design and sample population.....	29
4.2	Sampling and sample size	30
4.3	Data collection methods.....	31
4.4	Data analysis	33
4.5	Ethical considerations and clearance	34
4.6	Summary of methods.....	36
5	RESULTS	37
5.1	Prompt access to artemether-lumefantrine (i).....	37
5.2	Adherence to artemether-lumefantrine treatment (ii)	38
5.3	Adherence to referral advice (III)	40
5.4	Adherence to referral advice (IV).....	43
6	DISCUSSION	45
6.1	Prompt access to effective malaria treatment	45
6.1.1	Prompt access to treatment in governmental facilities	45

6.1.2	Prompt access to treatment in formal private drug outlets .	47
6.1.3	Prompt access to treatment in ordinary shops	47
6.1.4	Prompt access to treatment by community health workers	49
6.2	Caretakers' understanding of information given by providers.....	50
6.3	Poverty as a barrier to accessing care and adhering to treatment...	51
6.4	Methodological consideration	51
7	CONCLUSIONS AND RECOMMENDATIONS	54
7.1	Conclusions.....	54
7.2	Recommendations and policy implications.....	54
8	ACKNOWLEDGEMENTS.....	56
9	REFERENCES.....	58

LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
ADDO	Accredited Drug Dispensing Outlet
ALu	Artemether-Lumefantrine
AM	Artesunate intramuscular injection
AMFm	Affordable Medicine Facility for malaria
ANC	Antenatal care
AS	Artesunate intravenous injection
CBHC	Community-based Health Care
CCM	Country Coordinating Mechanisms
CE	Community Effectiveness
CDD	Community Drug Dispenser
CHF	Community Health Fund
CHMT	Council Health Management Team
CHSB	Council Health Service Board
CHW	Community Health Worker
CMR	Child Mortality Rate
CQ	Chloroquine
DDT	Dichlorodiphenyltrichloroethane
DMO	District Medical Officer
FBO	Faith-based Organisation
FGD	Focus Group Discussion
GFATM	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HBF	Health Basket Fund
HIV/AIDS	Human Immunodeficiency virus / Acquired Immunodeficiency Syndrome
HMM	Home-based Management of Malaria
HMN	Health Metrics Network
iCCM	Integrated Community Case Management
IMR	Infant Mortality Rate
IPTp	Intermittent Preventive Treatment in pregnancy
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Nets
MMAM	Primary Health Care Service Development Programme (MMAM)
MMSS	Malaria Medicines and Supplies Service
MMV	Malaria Medicine Venture
MoH&SW	Ministry of Health and Social Welfare
MSD	Medical Stores Department
MTEF	Medium Term Expenditure Framework
NHIF	National Health Insurance Fund
NMCP	National Malaria Control Programme
NGO	Non-Governmental Organisation
NSGRP	National Strategy for Growth and Reduction of Poverty (MKUKUTA)

PER	Public Expenditure Review
PHC	Primary Health Care
PMI	President Malaria Initiative
PNFP	Private Not For Profit
PPP	Public Private Partnership
PRSP	Poverty Reduction Strategy Programme
RA	Research Assistant
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
SP	Sulphadoxine-Pyrimethamine
TB	Tuberculosis
TDHS	Tanzania Demographic Health Survey
TFR	Total Fertility Rate
THMIS	Tanzania HIV Malaria Indicator Survey
THS	Tanzania Household Survey
UNICEF	United Nations Children Fund
USD	US Dollar
VHW	Village Health Worker
ACT	Artemisinin-based Combination Therapy

DEFINITIONS

Access – is the degree of fit between the needs and means of patients (users) and the existing services (providers) along the five dimensions of availability, accessibility, affordability, adequacy and acceptability, as defined below (Ricketts and Goldsmith, 2005).

- **Availability:** The extent to which the existing health services and goods meet clients' needs.
- **Accessibility:** The extent to which the location of supply is in line with the location of clients.
- **Affordability:** The extent to which the prices of services fit the clients' income and ability to pay.
- **Adequacy:** The extent to which the organisation of health care meets the clients' expectations.
- **Acceptability:** The extent to which the characteristics of providers match with those of the clients

Adherence to treatment schedule –Administration of ALu according to the recommended schedule in the national treatment guidelines (MoH&SW, 2006). In this thesis, the caretaker's report was used as the criteria for adherence to treatment as follows: administration of two doses daily for three days or, if the first dose is started in the evening or night; one dose on the first day, two doses daily for two days and one dose on the last day.

Adherence to referral advice – when a child is taken by the caretaker to a health facility after pre-referral treatment with rectal artesunate suppositories by a community drug dispenser

Artemisinin-based combination therapy (ACT) is the simultaneous use of two or more blood schizontocidal drugs with independent modes of action and thus unrelated biochemical targets in the parasite (WHO, 2010a).

Community effectiveness (CE)- the use of health care, diagnostic history-taking, diagnostic clinical examination, drug choice, drug treatment, drug-buying and drug-taking compliance (Krause and Sauerborn, 2000).

Drug resistance - is the ability of the parasite to survive or multiply despite the administration and absorption of medicine in doses equal or higher than those normally recommended within the tolerance of the subject (Bruce-Chwatt, 1986). The drug or active metabolite must be able to gain access to the parasite for the normal duration necessary for it to act.

Health systems is defined to include all actors, organisations, institutions, resources and the various activities whose primary purpose is to promote, restore, maintain and improve health (WHO, 2000). Health systems comprise of public, private formal and informal actors that include traditional medicine. The functions of health systems include: governance/stewardship, service provision, resource generation and financing

Malaria control: reducing the malaria disease burden to a level at which it is no longer a public health problem (WHO, 2009).

Malaria elimination: the interruption of local mosquito-borne malaria transmission; reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts; continued measures to prevent re-establishment of transmission are required (WHO, 2009).

Malaria eradication: permanent reduction to zero of the worldwide incidence of infection caused by a specific agent; applies to a particular malaria parasite species. Intervention measures are no longer needed once eradication has been achieved (WHO, 2009).

Off-schedule doses (or untimely doses) – doses administered outside the time range stated in the definition of adherence to treatment schedule, see above.

Private sector - includes formal private for profit and private-not for profit (PNFP) and the informal private sector which includes drug vendors and ordinary shopkeepers who sell general merchandize including as rice and sugar (World-Bank, 2010).

Prompt access to effective treatment – Ability to access appropriate antimalarial treatment within 24 hours of onset of fever (WHO, 2009). In this thesis, artemether-lumefantrine (ALu), the recommended first line drug for treatment of uncomplicated malaria in Tanzania, was regarded as the appropriate antimalarial and prompt access was defined as taking ALu on the same or next day after onset of fever (Rutebemberwa et al., 2009a).

Uncomplicated malaria – Presumptive diagnosis was used in study I based on the WHO guidelines for the treatment of malaria of 2006 (WHO, 2006), whereby, in settings where the risk of malaria is high, clinical diagnosis was recommended to be based on a history of fever in the previous 24 hours. In study II uncomplicated malaria was defined as patients with positive RDT results based on the current WHO guideline (WHO, 2009) which recommends parasitological confirmation of all malaria cases prior to treatment.

Universal coverage – 100% of patients receive locally appropriate case management interventions. Coverage is defined as follows:

- **Diagnosis:** prompt parasitological diagnosis by microscopy or rapid diagnostic tests (RDTs)
- **Treatment:** treatment with effective drugs within 24 hours after the first symptoms appear (Roll-Back-Malaria-Partnership, 2008)

PREFACE

My journey to the topic of this thesis started with inspirational words from the late, Mwalimu (teacher) Julius Kambarage Nyerere, the First President of Tanzania - I quote:

“Those who receive this privilege, therefore have a duty to repay the sacrifice that others have made. They are like the man who has been given all the food available in a starving village in order that he might have strength to bring supplies back from a distant place. If he takes this food and he does not bring help to his brothers, he is a traitor. Similarly if any of the young men and women who are given education by the people of the republic adopt an attitude of superiority, or fail to use their knowledge to help the development of this country, then they are betraying our nation”

The statement intrigued me for the first time during my secondary school days when I was forced to read it to my fellow students, in the assembly hall. It was then that I committed myself to repay my fellow citizens once I got the opportunity.

After training in medicine I had the opportunity to work as a medical officer practitioner in referral and district hospitals. The sight of so many children dying of anaemia and cerebral malaria made me realise that I could not help the children in the clinic or in the wards. It was then that I decided to enter public health with the intention of treating more of them before they became sick.

The first challenge to meet in public health was the astounding data on measles mortality which left me wondering ‘why should so many children die from measles when a potent vaccine is available?’ I took the opportunity of my Masters course to study measles vaccine effectiveness under field conditions

After graduating from the Masters course my journey took me to the Ministry of Health, where I had the opportunity to address some of the challenges and at the same time experience a number of challenges that partly explained what I found in the field. So when the next opportunity came I wanted to dwell further on the barriers to delivery of health care services so that I could gather more evidence to some of the experiences I already had and document them for sharing with others in the quest for a collective solution. This time, high measles mortality was history, thanks to high measles vaccination coverage rates, so I chose to study the health system given the fact that nearly half of patients attending outpatient services and one-third of deaths among children admitted in hospitals were due to malaria. I was perturbed by the same question ‘why should so many children die from malaria when an efficacious drug was available?’

1 INTRODUCTION

1.1 GLOBAL HEALTH AND POVERTY

About 1.4 billion of the world population lives below the poverty line of 1.25 USD a day and the income gap is widening (World-Bank, 2008). While the richest 20% were 30-times richer than the poorest in 1960, the disparity widened to 74-times in 1994 (UNDP, 2008). The rural populations account for one-quarter of the poor in the world (UNDP, 2008). As a result, one-seventh does not have access to health care services. Poverty, disease and ignorance form a vicious cycle. Although it is possible for less wealthy countries to have better health and vice versa (Lindstrand et al., 2006), countries with higher economic status are generally healthier (Debas, 2010). During the turn of this century, for the first time, the health of the poor was recognised to be of global concern (Debas, 2010). This led to the Millennium Summit developing the Millennium Development Goals (MDGs) with MDGs four, five and six being directly related to health of specific populations. This was upon the realisation that achieving the MDGs was important for world economic stability, human rights and equity.

MDG 6 aims at halting and reversing the incidence of three major diseases, HIV/AIDS, TB, Malaria and other infectious diseases by 2015. Approximately, 8.8 million children die each year before the age of 5 years, half of them during the first month of life (UNICEF, 2010). Of these, about 4 million are due to malaria, diarrhoea and pneumonia (UNICEF, 2010).

Through the implementation of a poverty reduction strategy a decline in poverty level of about 60% has been reported with China contributing to the highest decline (70%) compared to other poor countries including Africa where the decline was lowest (10%) (World-Bank, 2008).

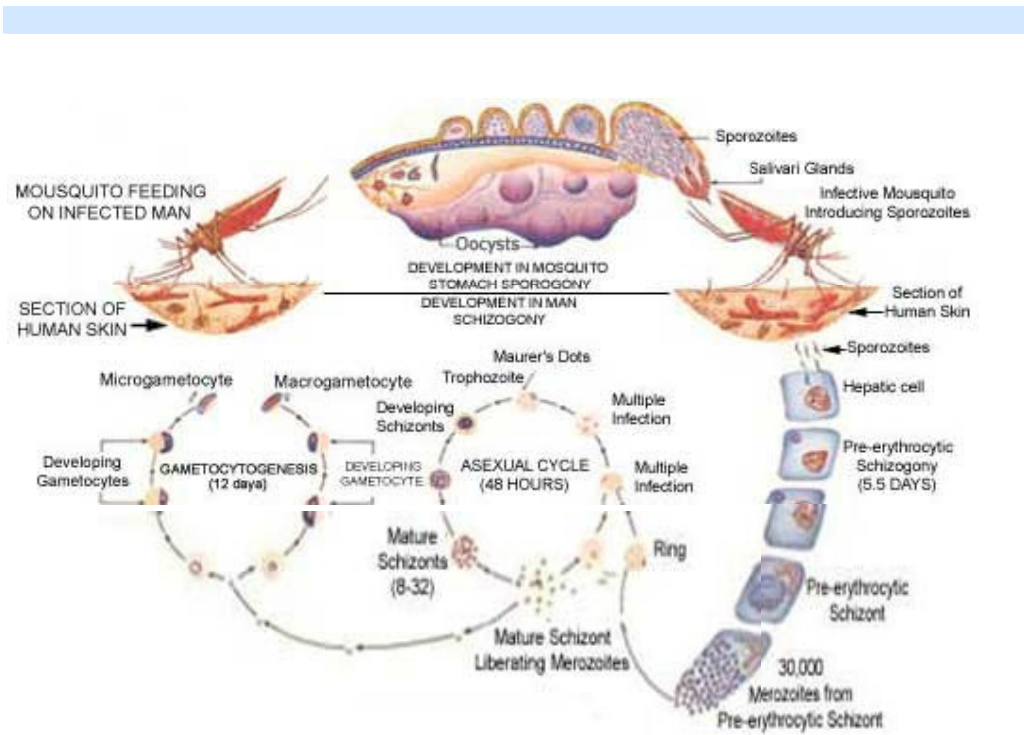
1.2 MALARIA MORBIDITY AND MORTALITY AND CONTROL

Approximately, 3.3 billion people in the world were at risk of contracting malaria in 2008 resulting in an estimated 243 million cases and 863,000 deaths (WHO, 2009). About 90% of the deaths occurred in Africa and 85% were children under five years. The majority of malaria deaths were due to cerebral malaria and anaemia (Snow and Guerra, 2005), *Plasmodium falciparum* species was the cause of deaths and *Anopheles gambiae*, the most efficient vector, commonly found in Africa.

The life cycle of *Plasmodium falciparum* starts with a bite from an infected female Anopheline mosquito on a human being releasing sporozoites from the salivary glands (Figure 1) (WHO-Website, 2010). Sporozoites enter the bloodstream and invade liver cells (liver stage) and undergo asexual multiplication to form merozoites. Hepatocytes burst to release individual merozoites that invade red blood cells (erythrocytic stage) where merozoites multiply to form a schizont. Schizonts rupture to release merozoites that invade more erythrocytes and some differentiate into male and female gametocytes which are taken from the blood stream when a female anopheles mosquito bites a human being. In the mosquito midgut, the male gametocyte undergoes nuclear division to produce flagellated microgametes which then fertilize the female macrogamete to form ookinete. Ookinete implants on the outer side of the mosquito gut wall as an

oocyst, later ruptures to release sporozoites that migrate to the mosquito salivary gland ready to be injected into a human being.

Figure 1: The life cycle of Plasmodium falciparum



Source: http://www.searo.who.int/en/Section10/Section21/Section340_4269.htm

1.3 GLOBAL COMMITMENT TO CONTROL AND ELIMINATE MALARIA DEATHS

Hippocrates was the first scientist to describe malaria associated with stagnant waters, leading to the first control intervention through the drainage of stagnant water (Malaria-Website, 2010). The first treatment of malaria started about 2,000 years ago by the Chinese using the bark of the Cinchona tree (Hsu, 2006). It was not until 1889 when the agent causing malaria was discovered by Alphonse Laveran in 1889, that the scene for malaria diagnosis was set. In 1897, Ronald Ross discovered the association of the parasite with the vector, mosquito. Paul Muller, a Nobel Laureate in Physiology or Medicine, discovered DDT in 1948 and set forth ambitions for global eradication of malaria through spraying with DDT, use of nets and treatment with chloroquine. Several European countries completely eradicated endemic malaria. But, the initial successes later failed due to social and political factors. In 1969 the global eradication policy was abandoned, leading to a resurgence of malaria in 1970s.

Renewed efforts came through the formation of the Roll Back Malaria (RBM) Global partnership in late 1998 and the declaration of the Millennium Development Goals (A/RES/55/2, 2000). The Roll Back Malaria Partnership reaffirmed its targets through the Global Strategic Plan (Roll-Back-Malaria-Partnership, 2005) that:

- By 2010, through targeting universal coverage:
 - 80% of people at risk from malaria are using Long Acting Insecticide-treated nets (LLINs), indoor residual spraying (IRS)
 - 80% of malaria patients are diagnosed and treated with artemisinin-based combination therapy (ACTs)
 - in areas of high transmission, 100% of pregnant women receive intermittent preventive treatment (IPTp); and
 - the global malaria burden is reduced by 50% from 2000 levels
- By 2015:
 - universal coverage continues with effective interventions;
 - global and national mortality is near zero for all preventable deaths;
 - global incidence reduced by 75% from 2000 levels
 - the malaria-related Millennium Development Goal is achieved: halting and beginning to reverse the incidence of malaria by 2015; and
 - at least 8-10 countries currently in the elimination stage will have achieved zero incidence of locally transmitted infection.
- Beyond 2015:
 - global and national mortality stays near zero for all preventable deaths;
 - universal coverage (which translates to ~80% utilization) is maintained
 - countries currently in the pre-elimination stage achieve elimination

The commitment was echoed by the United Nations Secretary General on the occasion of the World Malaria Day 2008, calling for efforts to ensure universal coverage with malaria prevention and treatment programmes by the end of 2010 (WHO, 2009).

1.4 ANTIMALARIAL INTERVENTION STRATEGIES

In addition to saving lives, malaria control, is highly cost effective because it is estimated that, in Africa alone, more than 12 billion USD of direct losses occur per year as a result of illness, treatment and premature deaths (WHO, 2009). Since malaria affects some of the poorest countries, reducing the malaria burden would result in economic benefits that would ultimately reduce poverty (Roll-Back-Malaria-Partnership, 2008).

The current efforts towards the control and elimination of malaria include the cost-effective interventions strategies for the prevention and control of malaria i) effective case management that includes early diagnosis and treatment of malaria using effective antimalarials –the ACTs ii) the use of effective preventive measures such as insecticide treated nets (ITN), indoor residual spraying (IRS) and intermittent preventive treatment in pregnancy (IPTp) iii) detection and intervention to control malaria epidemics and iv) enhancing local capacity for intervention (WHO, 2009).

Effective case management is the cornerstone for the control of malaria (WHO, 2009) that aims at reducing mortality through prompt diagnosis and treatment. The strategy takes advantage of tools and strategies proven to have a significant impact on decreasing malaria mortality. These include the RDTs for malaria diagnosis, which are simple to perform and easy to handle in a tropical climate (WHO, 2010a); the highly

efficacious ACTs and the life-saving rectal artesunate for children who could not take orally, living in remote rural areas, far placed from health facilities.

By mid-2008, almost all African countries had adopted ACTs as the first-line treatment for uncomplicated malaria due to *P. falciparum* (WHO, 2009). Many African countries have rolling-out RDTs as a policy. Wide coverage of malaria interventions has resulted in a decline in morbidity and mortality by over 50% in some countries (WHO, 2009). While many of these areas were islands such as Sao Tome and Principe and Zanzibar, a decline was also reported in some countries in mainland Africa, including Eritrea, Rwanda, and Zambia. In countries where a decline of over 50% in malaria cases and deaths occurred, a significant drop in under five mortality rates was also reported, thus, creating optimism that many African countries might attain the two-third decline in child mortality rate (CMR) by 2015, a target set forth in the Millennium Development Goals (MDG) (WHO, 2009).

Although the cause of the decline remains obscure, the wide coverage of ITN, IRS and ACTs are thought to be the reasons for the decline (WHO, 2009). In addition to reducing the bulk of parasite in humans, ACTs has a gametocidal effect which reduced transmission of the parasites from human to mosquitoes (Price et al., 2006). The dramatic decline in mortality which in some countries was observed within 2-3 years of widespread implementation of the three strategies inspired the RBM Partnership to aim at eliminating malaria.

Despite the reported achievements, many African countries are still far from achieving the targets. The reported decline in malaria mortality was lowest in countries with the highest incidence rates (WHO 2009). In 12 African countries where data were available, less than 15% of under fives with fever accessed ACTs, figures that are far below the RBM Partnership target of 80% (WHO, 2009). The rolling-out of RDTs for malaria in endemic countries is challenged by providers' reluctance to apply the results in making clinical decisions (Bjorkman and Martensson, 2010, d'Acremont et al., 2010).

1.5 THE HEALTH SYSTEM

Although about two thirds of the deaths in the world are amenable to prevention using existing interventions due to the existence of effective and affordable interventions, falling prices of drugs and increased funding for many priority health problems in low income countries; progress towards agreed health goals remains slow (Becerra-Posada et al., 2004). This is partly due to weak health systems in most malaria endemic countries that fail to deliver the intervention packages.

Innovative methods for controlling malaria exist, however, success interventions depends on a well functioning and efficient health system. The primary bottleneck is that the health system is facing severe shortfalls with a demoralized health workforce, constant drug shortages, poor coordination of development partners and information system (Karamagi et al., 2004, Travis et al., 2004). There is increasing consensus that stronger health systems are a key to achieving improved health outcomes. However, there is much less agreement on how to strengthen them (Travis et al., 2004).

The four functions of the health systems are: *governance/stewardship* that includes accountability, transparency and involvement of key stakeholder; *resource generation*; *financing of the health care*; and *service provision* that includes health workforce, health information system, drugs and logistic information systems (WHO, 2000). The ultimate responsibility for the overall performance of a country's health system lies with government, which should involve all sectors of society in its stewardship. Stewardship involves defining the vision and direction of the health policy, through regulations and advocacy, and collecting and using information

1.5.1 Global governance of malaria control

A number of stakeholders play an important role at the global level to fight malaria, efforts spearheaded by the RBM Partnership whose membership includes the malaria-endemic countries, development assistance partners, the private sector, research and academic institutions. The RBM Partnership aims to reduce malaria morbidity and mortality by reaching universal coverage through the strengthening of health systems as defined in the global action plan; that is, scaling up for impact (SUFI) of treatment and preventive interventions and sustaining control of malaria over time (RBM-Partnership, 2008b). RBM Partnership also aims to achieve equitable, affordable and sustained access to malaria cure and prevention through multi-sectoral approach to reach the poorest people by ensuring that cost is not a barrier. The partnership monitors equitable coverage and access; and invests in research for evidence based decision making.

Accountability and transparency are ensured through the Partnership forum that involves all stakeholders, where agendas are discussed and recommendations made. The Partnership has a Board drawn from all stakeholders and oversees activities of the secretariat. The WHO provides leadership for improving the health of all populations taking advantage of effective measures, promoting interventions based on necessary scientific evidence and articulates evidence based policy options making vulnerable groups a priority (Jong-wook, 2003b). Accountability is ensured through the World Health Assembly, the supreme decision making body and an executive board whose function is to follow up the WHO secretariat on decisions by the World Health Assembly (WHA).

1.5.2 Global financing of malaria control interventions

The main source of funding for malaria intervention is GFATM; others include development assistance partners, international NGOs; and individuals. The GFATM was created to contribute towards MDGs by ensuring rapid mobilization of funds targeted to the poor and those at risk. In 2009, 55% of the fund was allocated for HIV/AIDS and 29% for malaria control. Sub-Saharan Africa received 57% of the fund. A commitment of 11.7 USD has been made for Global Fund for 2011-2013 (GFATM, 2010) which was more than the previous commitment of 9.7 billion USD in 2000 – 2010. However, this is still less compared to 5.1 billion USD required annually for control interventions between 2011 and 2020 of which Africa alone, needs about 2.7 billion USD (Roll-Back-Malaria-Partnership, 2008). Accountability by GFATM is ensured through performance based funding where an additional fund is provided to the recipient upon demonstrating measurable and effective results. This is achieved through a rigorous system of measurement and evaluation by empowering local expertise to

monitor progress. Transparency is ensured through posting issues related to the Fund on the web-site, unedited, and in all languages.

The President's Malaria Initiative (PMI) started in June 2005 by the United States Government with a five-year, \$1.2 billion initiative; aims at rapidly scaling-up malaria prevention and treatment interventions in high-burden countries in sub-Saharan Africa (USAID, 2009). The goal was to reach 85% coverage of the most vulnerable groups with ITNs, IRS, IPTp and ACTs. PMI also supports health systems, strengthening through training of personnel, information and logistic management. Between 2007 and 2009, PMI increased ownership and use of ITN by 2-fold in six of the 15 supported countries. There was however a slow increase in the use of ACT. Through the President Obama's Global Health Initiative, expanded PMI with emphasis on strategic integration of malaria with other vertical programmes, and strengthening health systems to ensure sustainability (USAID, 2009).

1.5.3 Health service delivery

In the wake of achieving the MDGs the WHO plan is to promote the scaling-up of health-care systems based on the principles of primary health care that integrate service; building on the Alma-Ata principles of equity, universal access, community participation, and inter-sectoral approaches (WHO, 2003). Although the WHO policy statement is very clear on its intended direction, this is contradicted in practice by the vertical approach in disease control, where the control of major diseases continue to run parallel to government systems.

A functioning information system is needed at all levels to monitor health systems' performance. A Health Metric Network (HMN) was launched in 2004, using MDG as a platform for strengthening health information systems in low income countries (WHO, 2010b) to improve the availability and use of health information for policy-making, programme monitoring and assessment, monitoring of the Millennium Development Goals.

For effective service delivery, the government need to take advantage of existing strength from various actors in the country. The private sector contributes significantly to the provision of health care including management of malaria in sub-Saharan Africa (Goodman et al., 2004, Viberg, 2009). Caretakers prefer private facilities because of friendly services with flexible payment conditions (Rutebemberwa et al., 2009c) while services at government faculties are not provided all the time, have long waiting times, drug shortages and poor provider-caretaker interactions (Chuma et al., 2009, Goodman et al., 2004, Kazembe et al., 2007, Nsungwa-Sabiiti et al., 2005). However, services provided by the private sector are compromised by poor quality and weak regulatory mechanisms in many of the malaria endemic countries (Kumaranayake et al., 1997). Government policies and strategies to work in partnership with the private sector to provide better services that will reach the majority of the people remain on paper (MoH&SW, 2007a).

1.5.4 Human resources for health

Higher staff population ratios have been associated with lower child mortality after controlling for confounders (Gerein et al., 2006). Over a million trained staff are estimated to be required to meet the requirements for the implementation of interventions towards the MDGs (Gerein et al., 2006). In some countries such as Tanzania, staff numbers will need to be tripled, by 2015 (Kurowski et al., 2004). The human resources for the health crisis in African countries are likely to undermine the benefits from global commitments and the new technologies becoming available in the health sector, thus threatening efforts to attain the MDGs (Gerein et al., 2006, Jongwook, 2003b, Narasimhan et al., 2004).

Pay and income is one of the motivating factors influencing performance and staff retention. In most malaria endemic countries wages are low, ranging from 70-300 USD (Buchan and Sochalski, 2004, Friedman, 2004). This affects retention and distribution of health workers, with a wide variation between urban and rural areas and between the public and private sector (McCoy et al., 2008). The opportunities to engage in private practice, extracting informal fees from their patients, or seeking per-diem payments by attending workshops and seminars (Roenen et al., 1997) favours staff retention in urban areas making understaffing worse in rural and primary level facilities (Gerein et al., 2006).

The RBM Partnership aims to ensure investments are made to enable countries to mobilize, retain and motivate highly qualified individuals to manage malaria control. (Roll-Back-Malaria-Partnership, 2005). However, employees' pay is influenced by the ability of the government to pay. Although sub-Saharan Africa has fewer staff as a percentage of the population, staff payment consumes a higher proportion of GDP compared to other developing countries (Schiavo-Campo et al., 1997). Increasing staff payment will lead to an increase in government spending on human resources leaving a smaller proportion of the budget for drugs and other recurring expenditure (McCoy et al., 2008). This will lead to a large unsustainable fiscal deficit which was part of the reason for structural adjustment in the 1980s and 1990s that led to retrenchment and the freezing of hiring staff (Haque and Aziz, 1998) and consequently a shortage in the health workforce (Lienert and Modi, 1997). Strategy to raise health staff salaries through increasing the government budget to health is unlikely for many African countries that are still struggling to reach the Abuja target of 15% (McCoy et al., 2008). Increasing government revenue, is limited by the low tax-base, revenues in sub-Saharan Africa countries contribute an average of only 15% of the GDP, compared to high income countries (30-40%) (McCoy et al., 2008). Raising salaries through external support is not sustainable once grants are withdrawn. This leads to a stalemate where governments are unable to remunerate health staff and they in turn are not motivated to deliver, with the rural areas bearing the brunt.

1.5.5 Drugs procurement and distribution

In the effort to find alternative drugs to ACTs, the RBM Partnership fostered the creation of the Medicines for Malaria Venture (MMV) a public-private partnership that unites public and private sectors to fund and provide managerial and logistic support for research and development of new medicines to treat and prevent malaria. RBM

Partnership also works with the agricultural sector to increase the availability of *Artemisia annua* for the production of ACTs (Roll-Back-Malaria-Partnership, 2005).

Dealing with high volumes of drugs with few manufacturers for organic substances that require planting is challenging. The RBM Partnership has set up a malaria commodity procurement support system, Malaria Medicines and Supplies Service (MMSS), which seeks to remove barriers preventing required volumes of the malaria commodities needed from reaching countries (Roll-Back-Malaria-Partnership, 2005). The MMSS, assists in global forecasting, procurement and supply mechanisms, and make direct contact with manufacturers to overcome the challenges of the rapid increase in demands for anti-malarial medicines, diagnostics and bed-nets (Roll-Back-Malaria-Partnership, 2005).

Recently, the Affordable Medicine Facility for malaria (AMFm) initiative was started with the aim of availing ACTs through the private sector by applying a subsidy at the manufacturers' level. This is likely to reduce the price of ACTs to that of previous antimalarials (RBM-Partnership, 2007b).

1.6 MALARIA TREATMENT

While treatment with ACTs aims to cure patients with uncomplicated malaria which, if not well treated, might result in a severe condition and ultimately death or drug resistance, treatment of severe malaria aims at reducing mortality. In addition, to reducing the bulk of parasites circulating in the community the artemisinin component of ACTs has a gametocidal effect that reduces malaria transmission. Proper treatment of malaria requires making a correct diagnosis; in clinical practice, this is done mainly using microscopy or RDTs for malaria. Understanding the treatment of malaria requires background knowledge on treatment policy; characteristics of antimalarials used and drug pharmacokinetics and pharmacodynamics.

1.6.1 Malaria treatment policy

Diagnostics – Microscopy and RDT

Until recently, presumptive diagnosis of malaria was recommended to be treated with ACTs (MoH&SW, 2006, WHO, 2006). Currently, the WHO recommends the use of RDTs and microscopy for the diagnosis of malaria and only where these facilities are not available that the presumptive diagnosis of fever suspected to be of malaria can be used (WHO, 2010a). The use of diagnostics reduces the unnecessary prescriptions of antimalarials and is thus cost effective (Guerra et al., 2008, Ngasala et al., 2008, Shillcutt et al., 2008). In addition, the risk of misdiagnosing other severe febrile illnesses with fatal outcomes is reduced (d'Acremont et al., 2010, Drakeley and Reyburn, 2009, Hildenwall et al., 2007).

Microscopy is the gold standard, used for species diagnosis, quantification, assessment of response to treatment and diagnosis of other causes of fever (WHO, 2010a). However, major variations between readers can occur, especially, if personnel are not well trained (Ngasala et al., 2008). RDTs are comparatively easy to use, require minimal training and are cost-effective (Lubell et al., 2007, Mayxay et al., 2004,

Shillcutt et al., 2008). Thus, RDTs can be used in rural facilities and by CHWs with an acceptable quality of results (Mubi et al., 2010). However, false negative results lead to some patients with negative RDT results being treated with ACTs (Hamer et al., 2007, Reyburn et al., 2007), despite evidence that withholding treatment in these children is safe even in endemic areas (d'Acromont et al., 2010, Njama-Meya et al., 2007). However, it takes time for a new policy change to diffuse before people can implement (Eriksen et al., 2005).

Available tests include *Plasmodium falciparum* antigen based on histidine rich protein (HRP2) and an enzyme parasite lactate dehydrogenase (pLDH) which detects all four human *Plasmodium* species. The former, are generally more sensitive but with a relatively low specificity (Hopkins et al., 2007) which can persist in 35-73% cases after two weeks (Abeku et al., 2008, Swarthout et al., 2007). HRP2 is recommended in endemic areas where *P. falciparum* is dominant, due to the relatively low cost, high sensitivity and stability compared to pLDH (Abeku et al., 2008, Mayxay et al., 2004).

The WHO malaria treatment policy

The recommended treatments for uncomplicated malaria are ACTs that include artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine and dihydroartemisinin plus piperazine (WHO, 2010a). The recommended treatment for severe malaria in children, especially in the malaria endemic areas of Africa, is any of the following antimalarials administered for a minimum of 24 hours; intravenous artesunate or intramuscular quinine, intravenous infusion or divided intramuscular injection; intramuscular artemether, used if none of the alternatives are available. The WHO also recommends that patients should be given pre-referral treatment using rectal artesunate, intramuscular quinine, intramuscular artesunate or intramuscular artemether and immediate referral to an appropriate facility for further treatment if complete treatment of severe malaria is not possible.

1.6.2 Recommended antimalarials for uncomplicated and severe malaria

Artemether-Lumefantrine combination

ALu is a combination of artemether and lumefantrine, both originally developed in China. ALu has efficacy greater than 95% (Lefèvre et al., 2001, van Vugt et al., 1999). The 6-dose regimen kills a maximum of two asexual life cycles. ALu is given in six doses (Table 1) spread over three days at 8, 24, 36, 48 and 60 hours after the initial dose (WHO, 2010a). Studies have not been conducted in infants less than 5kg (White et al., 1999). ALu tablets are not light sensitive and are stable at temperatures <30°C for at least 2 years (White et al., 1999). Recently, a dispersible form for children with uncomplicated malaria has been shown to have similar high response rates compared to crushed ALu tablets (Abdulla et al., 2008).

Artesunate

Artesunate is a semi-synthetic derivative of Artemisinin, being water soluble it can be formulated as oral, rectal, intramuscular, and intravenous preparations. Unlike intravenous quinine, intravenous artesunate has less risk of low blood sugar (Jones et al., 2007) and thus causes a 35% reduction in the risk of mortality in the treatment of severe malaria (WHO, 2010a). However, there is not enough evidence of its effectiveness and potential adverse effects in children in Africa who carry the highest burden (Jones et al., 2007). As mono-therapy, its use in malaria endemic settings is challenged by the need of an extended administration period which may lead to non-compliance (Noedl et al., 2008). However, this is unlikely with rectal artesunate strategy where a single dose is given followed by immediate referral. Rectal artesunate is thermo-stable, kills parasites fast, has high bioavailability and is safe (Awad et al., 2003). A formative study done in Mtwara showed that rectal application of medicine was familiar and acceptable by community members (Warsame et al., 2007).

1.6.3 Pharmacokinetics/dynamics of artemisinin-lumefantrine

Artemether provides a rapid reduction of parasitaemia by over 90% within 24 hours, almost completely after 36 hours (White et al., 1999) and is responsible for the dramatic improvement in malaria patients. It further inhibits younger gametocytes (Table 1), thus, decreasing malaria transmission (Barnes et al., 2005). Artemether is absorbed rapidly and bio transformed to dihydroartemisinin, and both are active and eliminated fast (White et al., 1999).

Lumefantrine acts late to slowly kill the residual parasites. It is eliminated slowly and absorption depends on fat which increases bioavailability 16-fold (White et al., 1999) thus explaining the wide variation among individuals. Blood lumefantrine concentrations are measured using HPLC in serum, plasma or whole blood (van Vugt et al., 1998, Zeng et al., 1996). Plasma lumefantrine concentration on day 7 is a good determinant of therapeutic response (White et al., 1999), a concentration of 280 µg/L (524 nmol/L) on day 7 was found to predict cure (White et al., 1999), hence adherence to ALu treatment. However, background immunity of the patient facilitates parasite clearance and patients can be cured at less than 175 µg /L (331 nmol/L) in African settings (Bell et al., 2009).

Table 1: Characteristics of some of the recommended antimalarials

Drug	Indication	Formulations	Dosage	Side-effect	Action	Half-life
SP	Intermittent	Tables	500 mg of	Steven-Johnson	Schizontocidal	Sulphadoxine
	Preventive	Syrup	sulphadoxine and 25	sysndrome,		125 hrs
	Treatment in pregnancy		mg of pyrimethmine	Hepatitis, hemolysis, skin rash and megaloblastic anaemia		Pyrimethamine 80-95 hrs
ALu	Uncomplicated malaria	Tablets	Six dose of	Similar to malaria	Schizontocidal	Artemether 2-3
		Dispersible	artemether 20mg and lumefantrine 120mg.; 25-35kg each dose is 3 tablets, 15 to 25kg, 2 tablets and <15kg, one tablet	symptoms	Gametocidal	hrs Lumefantrine 3-5 days
Artesunate	Severe malaria	Rectal suppositories	2.4 mg/kg loading dose over 5 minutes	Less severe compared to quinine	Schizontocidal	1 hour
		Intravenous	1.2 mg/kg dose 12 hours later		Gametocidal	
		Intramuscular	1.2 mg/kg once daily after that			
Quinine	Severe malaria	Tablets	10 mg/kg 8 hourly for	Hypoglycaemia Blood dyscrasias Cinchonism	Schizontocidal	7-11 hrs
		Syrup	7 days			
		Intravenous				
		Intramuscular				
		Rectal				

1.6.4 Antimalarial drug resistance

Drug resistance poses a major threat to the control of malaria due to high mortality in Africa (WHO, 2009). Mortality among children treated with chloroquine was reported to increase 2 to 11-fold in areas with resistance (Trape, 2001, Zucker et al., 2003). This was observed even where efficient health services have been achieved (Trape, 2001). The high levels of resistance to switch to alternative drugs (25%) might have contributed to high mortality; this has been revised by WHO and lowered to 10% (WHO, 2010a).

Plasmodium falciparum malaria partial resistance to artemisinin has emerged on the Cambodia–Thailand border (Dondorp et al., 2010) attributed to artemisinin monotherapies and the use of sub therapeutic doses and substandard artemisinins.

The situation presents a major public health threat, especially, in high transmission areas where the impact could be high, yet difficult to quantify because of the prolonged asymptomatic infections (Bjorkman and Bhattacharai, 2005). Measures to contain the emergence of resistance includes increasing access to effective and affordable drugs in rural communities where the burden is high and ensuring adherence to the treatment schedule (Marsh, 1998). Other strategies include optimizing vector control, targeting the mobile population, strengthening management and surveillance systems, and operational research (Dondorp et al., 2010).

1.7 CHALLENGES IN MANAGING MALARIA IN UNDER FIVES

1.7.1 Prompt access to artemisinin-based combination therapy

Prior to drug policy changes, it was cautioned that when switching to ACTs, strategies must be instituted to ensure that the poorest groups are not marginalized (Hetzl et al., 2006, Njau et al., 2006). Subsidy limited to public facilities, might force caretakers to seek care from public facilities. Concerns have been raised about the quality of services provided in government facilities. These include services not being provided all the time, long waiting times and poor provider-patient interaction (Chuma et al., 2009, Kazembe et al., 2007, Nsungwa-Sabiiti et al., 2005). There has also been concern that when new interventions are introduced it is the better-off who tend to benefit (Schellenberg et al., 2003, Victora et al., 2004) and that caretakers often tend to seek cheaper alternatives for treatment and go to health facilities only when the condition is serious (Nyamongo, 1999, Rutebemberwa et al., 2009c).

Recent studies reported that prompt access to ACTs was not more than 15%, despite a policy change (Gitonga et al., 2008, Tipke et al., 2009, WHO, 2009). Studies carried out when CQ and SP were the first line drug reported several factors that influenced lack of prompt access to antimalarials, these included, drug shortages, sources of care and distance to the health facilities (Chuma et al., 2009, Rutebemberwa et al., 2009a).

A strategy to improve prompt access to antimalarial was the involvement of the private sector where drug shops in Tanzania were upgraded to Accredited Drug Dispensing Outlets (ADDOS) and allowed to dispense a selected number of essential prescription only drugs, including ALu. A study conducted in Tanzania in which private facilities were provided with subsidised ALu reported a significant rise in the purchase of ACT, from 1% to 44% compared to the control (Sabot et al., 2009). However, the study did not report the residence and social economic status of the patients.

1.7.2 Community-based health care

Task shifting by having some of the specialized tasks performed by lower cadres can be cost saving (McCoy et al., 2008). Community-Based Health Care (CBHC) is one of the practical strategies to reach the majority of the people in rural areas (Ajayi et al., 2008a, Haines et al., 2007, Onwujekwe et al., 2007). Home-based malaria treatment through CBHC has been reported to increase access to and effectiveness of antimalarials (Ajayi et al., 2008a, Nsungwa-Sabiiti et al., 2007, Smith et al., 2009).

HMM was implemented in Uganda using volunteer community drug distributors (CDDs) who provided free pre-packaged CQ-SP (Homapak), based on presumptive diagnosis, and educated mothers on correct treatment. A modest change in practice (13.5%) was observed with community effectiveness of only 25% (Nsungwa-Sabiiti et al., 2005). Reasons for the limited success were CHWs providing malaria treatment only and introducing two new policies at the same time, that is, the malaria drug combination and HMM. Other reasons were lack of appropriate sensitization and education of the communities and possible lack of personnel to provide adequate supervision and sensitization (Smith et al., 2009). A similar study conducted in Burkina Faso reported an increased prompt access to effective antimalarial treatment by more

than 2-fold, at a minimal intervention costs of 0.06 USD per child (Pagnoni et al., 1997). The WHO is currently working on integrating home-based treatment of malaria into the Community Case Management (iCCM) of childhood illnesses (WHO, 2010a). The new strategy seeks to integrate three major killer diseases that is malaria, pneumonia and diarrhoea into a community based care programme with a view to reducing child mortality, which together, claims about 4 million under five deaths each year (UNICEF, 2010).

Despite the potential contribution, effective CBHC demands a well functioning health system to supervise and maintain continuing education (WHO, 2008). The success hitherto observed in Uganda might not be realized on a national scale and that observed in Burkina Faso might have been attributed to the presence of the research team. In addition, the strategy is challenged by the inability to sustain CHWs (Kironde and Klaasen, 2002). Although, in theory, CHWs have worked as volunteers, there has been a growing demand and concerns for incentives. In some projects this has been provided in the form of self payment through cost recovery of the drugs they dispense and performance based incentives, especially, when working with vertical programmes (Soeters and Griffiths, 2003). However, this modality might not be sustainable on a large national level scale. This led to some researchers to conclude that improving access within hospitals and clinics should be a major priority (Smith et al., 2009).

1.7.3 Adherence to treatment schedule

Prompt access alone is not enough, caretakers have to adhere to a treatment schedule in order to achieve cure (Brugha et al., 1999). In addition to the need for increasing prompt access, policy change to ACTs also poses a challenge to adherence to treatment. The limited subsidy that limits availability, complex dosing and high drug efficacy that causes dramatic cessation of symptoms, might prompt caretakers to discontinue treatment and save the remaining drugs for future use (Hinton et al., 2007, Makanga et al., 2006). Failure to adhere to the treatment schedule would lead to resistance to ACT, the last in the armaments of antimalarials for treating uncomplicated malaria.

Few community based studies have been conducted on adherence to ACTs in the African countries; this is partly because the drug has been adopted quite recently. Nevertheless, quite high levels of adherence were reported (Ajayi et al., 2008b, Beer et al., 2009, Kabanywany et al., 2010). Some of the factors deterring caretakers' adherence to previous antimalarial treatment included *emic* local perception about the disease (Nsungwa-Sabiiti et al., 2004), lack of basic education (Beer et al., 2009, Fogg et al., 2004) and understanding the importance of adhering to a treatment schedule (Yeung and White, 2005); and caretakers' forgetfulness (Beer et al., 2009). Non-adherence to antimalarials has been associated with provision of inadequate doses (Yeung and White, 2005) and low drug efficacy (Chuma et al., 2009, Yeung and White, 2005). Providing information and education to caretakers on correct drug use (Okeke, 2010), use of pictorial instruction (Fogg et al., 2004) and pre-packaged tablets with proper labelling (Agyepong et al., 2002, Ansah et al., 2001) have been associated with adherence to treatment.

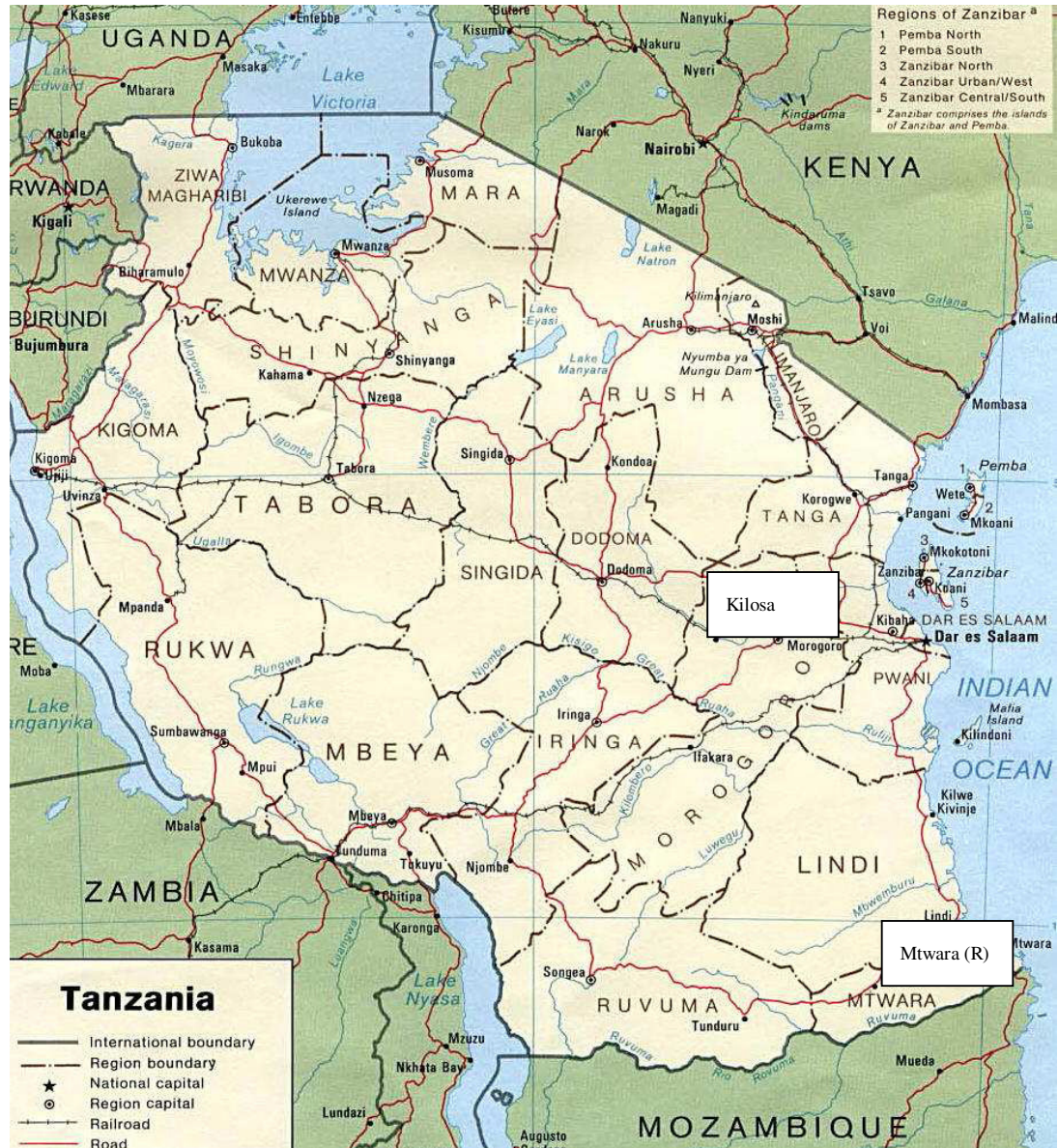
1.7.4 Adherence to referral advice

Normally, patients are expected to start treatment at a lower level of service delivery to be cost-effective (Segall, 2003). However, while in urban areas there is overuse of referral facilities, in rural areas there is inadequate use (Kalter et al., 2003). Children with severe malaria need to be treated at higher level facilities or hospital (Simoes et al., 2003) where parenteral treatment can be administered (Gomes et al., 2008, WHO, 2010a). However, many of the children die before reaching referral facilities or soon after (de Savigny et al., 2004) if appropriate treatment is not obtained within 24 to 48 hours (Breman, 2001). Since most children with severe symptoms in rural remote areas are at more risk of dying, the WHO recommended pre-referral treatment with rectal artesunate and RDTs for home based management of malaria, where feasible (WHO, 2010a). The success of this strategy, however, depends on adherence to referral advice which is challenged by the weak referral system in malaria endemic areas (de Savigny et al., 2004, Font et al., 2002, Petterson et al., 2004). Failure to adhere to referral advice might lead to delay in identification and treatment of other different or overlapping febrile conditions (Gomes et al., 2008, Kallander et al., 2004). Some factors reported to influence adherence to referral advice include severity of the illness, need for permission to make the journey to the clinic and the associated costs. Other factors included household chores, perceived quality of hospital care and health workers' communication skills (de Zoysa et al., 1998, Kalter et al., 2003).

1.8 TANZANIA COUNTRY PROFILE

The United Republic of Tanzania was formed by a union of two states, Tanzania mainland and Zanzibar and is one of the five countries in East Africa; others are Kenya, Uganda, Rwanda and Burundi. The country is located between longitude 29⁰ and 41⁰ east and latitude 1⁰ and 12⁰ south and it is bordered by the Indian Ocean in the east, the Democratic Republic of Congo, Rwanda and Burundi in the west; Kenya and Uganda in the north and Zambia, Malawi and Mozambique in the south. The country's population is estimated to be over 44 million (National-Bureau-of-Statistics, 2006) and spreads over an area of about 945,000 sq. km. making it larger than all the other East African countries put together. It is divided into 21 regions and 137 districts, recently three regions were added, see Figure 2.

Figure 2: A map of Tanzania showing study sites (I-IV)



1.8.1 Economic characteristics

With a GDP per capita of 542 USD (IMF, 2010) and a quarter (25%) of the people living below the poverty line, Tanzania is classified as one of the least developed countries (World Bank Report 2007). The level of poverty is higher in rural areas where over one-third (37%) of the people live below the poverty line compared to urban areas (18%) (National-Bureau-of-Statistics, 2002). The majority (85%) of the population lives in rural areas and depends on agricultural activities as their main source of income.

1.8.2 Demographic characteristics

The demographic characteristics in Tanzania are typical of a low income country with a growth rate of 2.9% (National Census) and total fertility rate (TFR) of 5.4 births per woman, see Table 2 (National-Bureau-of-Statistics, 2010). TFR is almost twice as high in rural areas (6.1) compared to urban areas (3.7). The rate has not changed from that estimated in 1996. The life expectancy at birth for a Tanzanian is 52 years. The infant mortality rate and the under five mortality rate have been declining since 1996 despite the HIV/AIDS epidemic that started in the country in 1983. The country has unfavourably high maternal mortality rates which have remained high throughout the period (Table 2). About 70% of the population lives in rural areas and 25% of the women and 10% men have not attended school (National-Bureau-of-Statistics, 2010).

Table 2: Tanzania demographic indicators (Source TDHS)

Indicator	1996	1999	2004	2009
Under five mortality rate (deaths/1,000 live births)	137	147	112	81
Infant mortality rate (deaths/1,000 live births)	88	99	68	51
Neonatal mortality rate (deaths/1,000 live births)	32	36	32	26
Children under weight (%)	30	29	22	21
Stunting (%)	44	44	38	35
Total fertility rate (number of children women bear in lifetime)	5.8	5.6	5.7	5.4
Maternal mortality ratio per 100,000 live-births	529	...	578	454
HIV Prevalence (%)	7	6
Children under five with fever last 2 weeks (%)	28.1	35.0	16.8	23.0
Children under five with cough accompanied with fast breathing last 2 weeks (%)	13.0	13.8	6.1	4.0
Children under five with diarrhoea last 2 weeks	13.7	12.0	7.4	15.0

1.8.3 Health care system

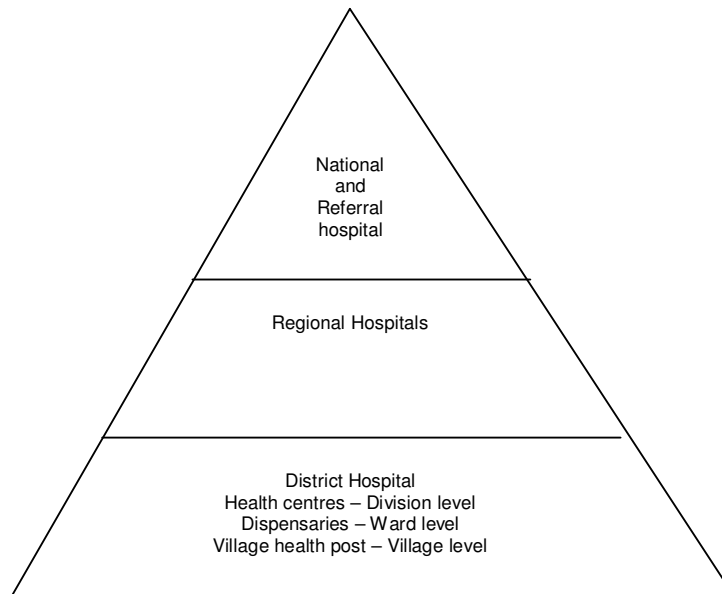
Structure and organisation of the health care system

There are 5,178 dispensaries, 737 health centres and 420 hospitals (MoH&SW, 2008a). Of these 67% of the facilities are government owned. There are more than 8,000 drug shops in the country (Goodman et al., 2009) which are now in the process of being transformed to ADDO. Ordinary shops, those selling household merchandize, also stock and sell drugs such as analgesics.

The health care systems in the country are organised in a hierarchy from the community to the national level (Figure 3). The health care system is decentralised at the district level where a four level tier system operates. At the community level there is a village health post supposed to be run by CHWs. Many of them function on an ad hoc basis. There are two CHWs per village, one male and another female. At the ward level there is a dispensary that caters for about 3-5 villages with a catchment population of about 10,000 people. A dispensary is normally run by one assistant clinical officer and one public health nurse. At the level of division, there is a health centre that serves

a catchment population of about 50,000 people. In addition to outpatient services offered at the dispensary level, health centres also offer laboratory and in-patient services. They are staffed by 3-5 clinical officers, several enrolled nurses and medical attendants. There is a district hospital that serves as a referral facility for the dispensaries as well as the health centres.

Figure 3: Organisation structure of the health system in Tanzania



Policy context

The history of health services in Tanzania starts from the colonial period where the private providers of health services, mainly religious organisations, provided most of the services (MOH&SW, 1994). The Arusha declaration in 1967, reformed the country into a state planned economy where health services were to be provided free of charge at all levels (Semali, 2003). Private facilities and practice was banned, unless operating under the auspices of religious organisations. Even before the Alma Ata declaration in 1978 the country reshaped the health services with a focus to the rural areas, building and equipping dispensaries in villages, putting emphasis on preventive services and community participation (Semali, 2003). The coming of the Alma Ata with the PHC saw the introduction of the VHWs programme in the country. Two VHWs were selected by community leaders in each village to provide preventive care as well as treating minor illnesses. The structural adjustment policies that came in the 1990s, following a change in the economic set-up, from state planned to free market economy, saw the lifting on the ban of private practice (MOH&SW, 1994). This was followed by health sector reforms in which cost sharing was gradually introduced and other alternative mechanisms for health care financing initiated, that is CHF and NHIF (MOH&SW, 1994). As a consequence of the structural adjustment programme, the health sector faced a period of stagnation. Due to severe under funding of health services, health facilities were faced with severe shortages of essential drugs,

equipment and supplies. Staff retrenchment that came with the economic reforms, severely affected the health sector and has not recovered, to date.

Since the turn of the century, a number of policy decisions have been made and strategies formulated, that shaped the direction of health care services in the country, as shown in Table 3.

Table 3 Policy decisions and strategies that influence the provision of health services in Tanzania

Strategy	Year	Focus on	Target
Vision 2025	2000	-high quality of livelihood -access to quality primary health care for all	Become a middle income country by 2025
MKUKUTA	2005	-improve the quality of life and social well being -reduce disparities in access to and use of social services between the better-offs and the poor and between urban and rural population and -operational and effective service delivery agreements	-Reduce basic need poverty from 38.6% in 2000/01 to 24% in 2010 with a focus on rural areas -Reducing IMR from 95 in 2002 to 50 in 2010 and <5 MR from 154 to 79 per 1000 live births
<i>The National Health Policy</i>	2000	-providing primary health care using essential health care package through a decentralised health system devolved to the Councils -having a well-planned, trained and deployed workforce, remunerate and support health workers adequately -incorporate other financing mechanisms such as user-fees, insurance and community health fund	
<i>Health Sector Reform (HSR): Plan of Work</i>	1997	-improve access, quality and efficiency in health services -strengthening decentralised district health services -ensuring basic health services are available and accessible to all	
<i>The Primary Health Care Service Development Programme (MMAM)</i>	2007	Accelerating provision of primary health care for all by 2017.	Rehabilitating and constructing new health facilities to have a dispensary in each village and a health centre in each ward
<i>The Health Sector Strategic Framework (HSSP III):</i>	2009	-strengthening; referral system and district health services -increasing accessibility to health services -maximize effective utilization of human resource for health; -partnership with the private sector -disease prevention and control of priority diseases that includes malaria, TB and HIV/AIDS -universal access to intervention	

Governance

National level

The Ministry of Health and Social Welfare (MoH&SW) is responsible for policy making, monitoring, supervision and reinforcement of technical issues related to health in the country. The day to day management of activities is decentralised to the districts, called Councils, answerable to the Prime Minister's Office for Regional Administration and Local Government (PMORALG). This sometimes creates a lack of clarity regarding the authority boundaries between these two policy making bodies (MoH&SW, 2007a).

Performance monitoring is conducted effectively at the national level through joint annual joint reviews that involve stakeholders from government, NGO and development partners. The joint reviews are preceded by technical reviews, conducted by consultants, which give an independent opinion of the health situation in the country. Periodically, joint evaluations are conducted with the involvement of external consultants. Compiled indicators include milestone to MDG, MKUKUTA, MTEF, PER, performance at the Council level and human resources issues. These are disseminated to stakeholders annually and used during review meetings to discuss progress in the performance of the health sector. These mechanisms raise the level of accountability and transparency at the national level.

District level

Each district, township, municipality and city has a health team known as the Council Health Management Team (CHMT) led by the Council (District) Medical Officer (DMO). The CHMT is responsible for planning, organising and monitoring delivery of health care services in the district. The CHMTs work under the Council Health Service Boards (CHSB), whose membership is derived from the community. The heads of departments, including the DMO, reports to the District Executive Director (DED) who is the overall in-charge of all sectors. The DED in turn is accountable to the District Council which comprises of Counsellors elected by the people.

The role of the district is to implement health interventions as outlined in the policy guidelines. The districts prepare Comprehensive Council Health Plans and implement them after endorsement by the Councils. Accountability is through quarterly Council, CHSB and CHF Board meetings. It is however, reported that the functioning of accountability structures are weak (MoH&SW, 2007a). With the exception the Council, board meetings are irregular or by-passed (MoH&SW, 2007a). The discussions during Council meetings lack mechanisms for accountability and transparency as rigorous as those at national level, where evidence based information compiled by independent reviewers is used as the basis for discussions by key stakeholders.

Health facility level

The health boards are mandated through by-laws to oversee health care provision in the respective districts. At the primary health facility level, there are Health Facility

Governing Committees, with representation from the community, whose responsibility is to oversee the provision of health services in the respective health facilities. While these structures have been formed to ensure accountability through community representations they are sometimes by-passed by technical staff in the decision making processes (MoH&SW, 2007a).

Financing the health care

National level

There has been an increase in government funding in the health sector which has increased from 3.5 USD per capita in 1993 during the structural adjustment policy (MoH&SW, 2007a) to 11.2 USD in 2009 (MoH&SW, 2009a). Adding the contribution from development partners, the per capita expenditure is 15 USD (MoH&SW, 2009a). The increase however, is still lower than the optimum WHO's estimated per capita spending on health of 34 USD per capita. Measured as a share of total Government spending on health, there has been a slight increase from 9% in 2000 to (MoH&SW, 2008a) about 10% (MoH&SW, 2009a), which is lower than 15% commitment made in Abuja by African countries in 2005.

The government is the largest source of public spending on health; however, external resources are significant, accounting for up to 37% of the total expenditures. User fee revenues, although a relatively small proportion of the contribution, are an important source of funding in the facilities where it is collected and spent. The proportion of development expenditure, largely contributed to by the development partners has increased from about 20% in 2004/05 to about 45% of estimates in 2008/09. Although most funds from development partners were previously channeled through the basket fund, the ratio has reversed from 5:1 in 2004 to 1:2 in 2007 (MoH&SW, 2009a). Disbursing a large share of the fund outside the basket fund distorts the Ministry and Council plans and might contribute to the reported slow pace in reaching some of the targets.

District level

Provision of health services at the district level is financed through 13 different sources (MoH&SW, 2007a). Block grant from the central Government to the Council accounts for 47% of the health budget; about 80% is for salaries and other employee's benefits, leaving merely 20% for other costs. Health Basket Fund (HBF) contributed by development partners is the second major source of fund accounting for 14.4% of the district health budget. User fees have been charged in hospitals since 1993, the fees have been introduced gradually in primary health facilities, where patients pay one USD for a disease episode. User fees apply only as a parallel payment system for non-members where CHF has started. A waiver policy has been instituted by the MoH&SW, among others, services provided to children under five. About half (72/137) of the districts have started CHF since its commencement in 1998. Operating on a voluntary basis for rural households, only 6% of the population in the country were enrolled in by 2008 (MoH&SW, 2009a). This is unlike the National Health Insurance Fund (NHIF) which is mandatory for public servants. In 2007/8 the

fund was able to collect over 50 million USD of which, only 15% were used for refund (MoH&SW, 2007a). Decentralisation to the district is compromised by the fact that more than half of the health budget is controlled at the MoH&SW headquarters (MoH&SW, 2007a). The large number of funding sources also increases bureaucracy making accountability and transparency more cumbersome.

Human resources for health crisis in the country

The human resource workforce was 29,000 staff in 2006 with almost half of them untrained staff (MoH&SW, 2008a). Staff shortages started with staff retrenchment in 1994 followed by a 10-year freezing of staff recruitment which was part of a structural adjustment programme. Only 35% of the required work force was in place in the country, in 2006 (MoH&SW, 2007a). A wide variation exists between regions, with the highest having almost seven times staff population ratio compared to the lowest region, in 2006. This reflects differences in the ability to retain recruited staff with more advantage in urbanized areas. Although there has been an increase in the number of students enrolled in health training institutions and those posted to Councils, there has been no noticeable increase in staff numbers, because, this has only enabled the replacement of staff as a result of normal attrition (MoH&SW, 2009a). Recruited staffs are not retained due to delays in receiving their first salary; this favours staff retention in urban areas, where there are alternative means of survival.

Staffing is complicated by the number of stakeholders involved that includes local governments that recruit; the PMORALG dealing with career development including promotion, MoH&SW for technical health issues, Department of Human Resource of the Presidents Office for human resource planning and the Ministry of Finance for paying salaries and other benefits. Staffing problems are compounded by deficiencies in accountability, absenteeism and productivity (MoH&SW, 2009a). A result based bonus scheme and pay on performance basis advocated by MoH&SW, with priority to rural areas, is yet to be implemented at the district level. Some of the challenges to implement include an inadequate routine information system and supervision necessary for a fair and transparent performance measurement and reward.

Drug procurement and distribution

The Medical Stores Department (MSD), an autonomous Government agency under the Ministry procures and distributes drugs and supplies to government and FBO facilities based on a list of essential drugs. Drug distribution has been changed from kit 'push' to indent system 'pull' where facilities order drugs according to their requirements. Despite the initiatives, stock outs of essential commodities are common and sometimes accompanied by expiry of excess stocks (MoH&SW, 2009b, MoH&SW, 2009a). This indicates an inadequate logistics information system as well as inadequate supportive supervision. While facilities are allowed to purchase drugs whenever there is a shortage, using funds collected through user fees and CHF, lengthy bureaucracy in accessing funds and procuring drugs undermines the system. Drugs supplied through vertical programmes, including ALu, are allowed to bypass the bureaucratic system, hence, shortages rarely occur (MoH&SW, 2007a).

Drug shops are the commonest source of drugs, but these are mostly located in urban and semi-urban areas. Although they are supposed to sell over-the-counter drugs only, prescription drugs can also be obtained (Viberg, 2009). Currently the MoH&SW is rolling out nationwide the ADDOs where drug shops are allowed to sell a selected number of prescription-only drugs including ALu after training on good pharmaceutical practice (Moon et al., 2009). Ordinary shops that sell household goods also sell drugs, and are often the only source of drugs in rural remote areas (Goodman 2004)

1.8.4 Malaria control in Tanzania - Mainland

Malaria burden

In the Tanzania Mainland, malaria is the leading cause of morbidity and mortality (MoH&SW, 2008a). With 93% of the population at risk of malaria, approximately 16 million clinical malaria cases occur, accounting for about 30% of outpatient attendances. Malaria deaths are estimated to be 60,000 and accounts for approximately 15% of deaths among children admitted in hospitals. Over 80% of malaria occurs among children under five years of age (National-Bureau-of-Statistics, 2005). A decline in the percent of children under five reported to have had fever in the past two weeks from 35% in 1999 to 23% in 2009 is seen in Figure 2 (MoH&SW, 2009a) with a stagnation between 2004 and 2009. The burden of malaria was higher in rural areas (19.7%) compared to urban areas (8.1%), in 2007 (MoH&SW, 2008b). Compared to the Mainland, Zanzibar has made great achievements in controlling malaria. With all 1.2 million people in Zanzibar (100%) at risk of getting malaria (National-Bureau-of-Statistics, 2006), the prevalence has declined from 40.3% in 1996 to 0.8% with a slide of <5%, in 2007-08 (National-Bureau-of-Statistics, 1996, Tanzania Commission for AIDS (TACAIDS) et al., 2008). Zanzibar is now in the pre-elimination phase (WHO, 2009). The success has been attributable to the cumulative high coverage in the implementation of ITN, IRS and IPTp.

Malaria control strategies

The National Malaria Control Programme (NMCP) through its second National Malaria Medium Term Strategic Plan (NMMTSP) seeks to reduce the burden of malaria by 80% between 2007 and 2013 (MoH&SW, 2007b). In order to achieve this, the NMCP adopted the WHO-recommended strategies. As regards to effective case management, the NMCP plans to 1) increase coverage of malaria parasitological diagnosis through the introduction of RDTs where microscopes are unavailable; 2) increase access to ACTs through subsidy in the private sector; and: 3) improve the quality of care for severely ill patients; and 4) improve monitoring and evaluation. This thesis addresses the second strategy, that is, improvement of prompt access to ACTs (I), for those who get access, to determine factors influencing caretaker's adherence to treatment (II). The thesis also addresses the third strategy, which is, improving quality of care for severely ill children at community level through the innovative strategy of pre-referral treatment with rectal artesunate followed by a referral to a health facility for definitive care (III, IV).

In the recent Tanzania Demographic Health Survey (TDHS), three-quarters of households in the Tanzania, Mainland owned some type of mosquito net. Household ownership of at least one ITN increased from 23 percent in 2004-05 to 64 percent in 2010, and almost the same percentage of children under five slept under ITN the night before the survey. Approximately, one-third of the children under five had access to ACTs and prompt access was 26.7%. Compared to the Mainland, nearly 90% of household in Zanzibar owned a bed-net and about 80% owned ITNs. Since 2006, IRS coverage in Zanzibar has been over 95% compared to 4% in the Mainland (Tanzania Commission for AIDS (TACAIDS) et al., 2008). However, access to ACTs was considerably lower for children in Zanzibar (15%) and prompt access was only 4%.

Funding of malaria control activities

Tanzania depends on outside sources to finance malaria activities. The main funding agency is the GFATM, see Table 4. Concerns have been raised among development partners regarding the government budget allocation to malaria reduction from \$5.2 million in 2006-2007 to \$2.8 million in 2007-2008 (USAID, 2009).

Table 4: Major External Sources of Funding for Malaria Control Mainland
(Source: President's Malaria Initiative year five financial year 2010/11 Malaria Operational plan (MOP), Tanzania. November 13, 2009)

Source	Amount	Period	What is covered
GFATM Round 4	54.2	Jun 05 – May 07	Provision of ACTs
GFATM Round 7	52.5	2008 – 2013	-Improved malaria diagnosis using RDTs; -Access to ACTs in the private sector; -Improved quality of care in severe malaria; - Monitoring and evaluation.
GFATM RCC*	59.8	2008 – 2011	Support pregnant woman voucher; LLIN catch-up campaign for under fives; behaviour communication change; and monitoring and evaluation
GFATM Round 8	113.3	2009 - 2014	Attain universal coverage of LLINs Strengthen regional malaria IMCI focal persons
World Bank	25	Jul 07 – Dec 09	Under-five LLIN catch-up campaign
Italian Cooperation 2	1.3	Jan 08 – Dec 09	Activities not yet determined.
Swiss Development Corporation	1.5	Sep 08 – Aug11	ITN Cell within NMCP
Japanese International Cooperation Agency	1	Jan 07 – Dec 09	Establishment of acute paediatric care units tertiary and regional hospitals

*Global Fund – AIDS, Tuberculosis and Malaria - Rolling Continuation Channel

Malaria treatment policy in Tanzania

Following *Plasmodium falciparum* resistance to SP three years after its introduction (Eriksen et al., 2005, Mubyazi and Gonzalez-Block, 2005), Tanzania changed the drug policy for treatment of uncomplicated malaria from SP to ALu in 2006 (MoH&SW, 2006). However, the implementation of the policy change started in January 2007. The change was anticipated because of the increasing resistance from the time it was introduced (Mubyazi and Gonzalez-Block, 2005). Blood tests for malaria parasites are prepared in health centres and hospitals where microscopes and trained personnel are available. The NMCP is currently rolling out RDTs for malaria country-wide through the training of health workers at all levels, especially, at dispensary level.

Antimalarial supply

Government and PNF health facilities provide ALu procured through MSD with funding support from GFATM. Tanzania has been invited to benefit from the AMFm, a strategy introduced with the intent to reduce the cost of ALu at the manufacturer level so as to ensure availability of the drugs at an affordable price, in the private sector (Moon et al., 2009).

1.9 EVIDENCE GAP AND RATIONALE FOR THE STUDIES

Effective innovations exist supported with high level international commitment and financing (RBM-Partnership, 2008a). However, these efforts do not seem to commensurate with the slow pace towards attaining universal access to ACTs as evidenced by the low prompt access to ACTs, ranging between zero and 28% (Gitonga et al., 2008, Tipke et al., 2009, WHO, 2009). Studies are required to understand factors influencing the low uptake. In the absence of an alternative in the near future, the world community is facing a challenge to rapidly increase ACTs coverage while at the same time, preserve the drug effectiveness by avoiding irrational use, in order to avoid losing the few antimalarials to resistance. Studies on factors influencing prompt access to ACTs are necessary to inform policy decisions in the process of resolving this delicate balance.

Most African countries adopted the ACTs between 2004 and 2006 (WHO, 2009). Thus experience of factors influencing adherence to ACTs treatment is mostly based on studies conducted in Asia (Gomes et al., 1998, Yeung and White, 2005), where the social and cultural context is different from Africa. Studies performed in Africa were mostly based on CQ (Agyepong et al., 2002, Ansah et al., 2001, Fogg et al., 2004), yet, ACTs are characteristically different from previous antimalarials in terms of access and its use. The few community-based studies performed on adherence to ACTs in Africa, have shown quite high adherence rates. This was contrary to the fear that dramatic cessation of symptoms due to high ACTs efficacy might prompt caretakers to discontinue treatment and save the remaining drugs for future use (Hinton et al., 2007, Makanga et al., 2006). Studies in different contexts, such as in rural remote areas where the malaria burden is highest and access to recommended drugs is poor (Gitonga et al., 2008, Tipke et al., 2009, WHO, 2009), are necessary to inform policy implementation.

Since 2006, the WHO recommended the use of pre-referral rectal artesunate suppository for children who could not take orally, followed by an immediate referral to a health facility (WHO, 2006). The policy recommendation is yet to be adopted by most member countries in Africa, including Tanzania, despite evidence of significant reduction in malaria mortality and central nervous system complications (Gomes et al., 2008). A formative study reported the treatment modality was acceptable by members of the community (Warsame et al., 2007). Generating information on factors influencing caretakers' decisions to adhere to referral advice after pre-referral rectal artesunate dose will, in addition to improving practice, add to information necessary to inform decision makers to expedite the adoption of this life saving strategy into the national malaria treatment policy guidelines.

2 AIMS AND OBJECTIVES

Aim

To study the factors influencing prompt access to effective antimalarials and adherence to treatment schedule as well as referral advice among children aged under five in rural areas in Tanzania.

Specific objectives

1. To determine the magnitude of, and identify factors influencing prompt access to ACTs among under five children in rural settings (I)
2. To determine the degree of adherence to ALu treatment and its influencing factors in real life situations in under five children in a rural district (II).
3. To determine the factors influencing parents' decisions to adhere with advice to go to a health facility following pre-referral treatment (III)
4. To understand caretakers' decision making on whether or not to adhere to the referral advice after their child had been given pre-referral treatment with rectal artesunate, using qualitative methods (IV)

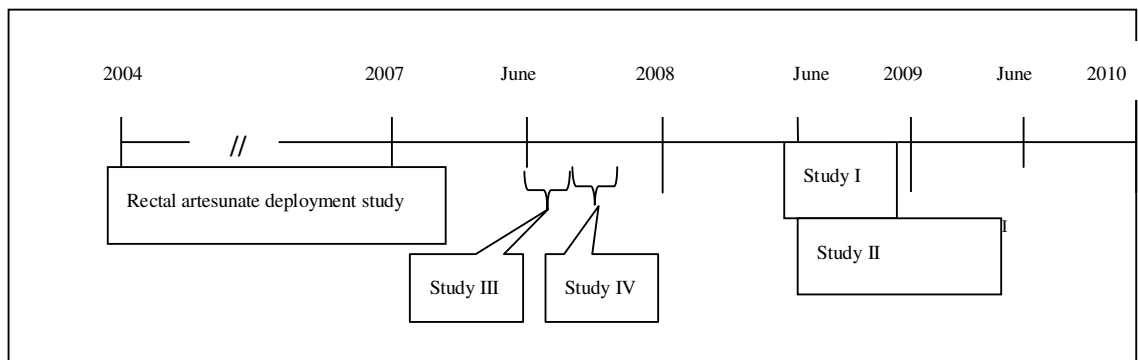
3 STUDY SETTINGS

Studies I and II were conducted in Kilosa district while studies III and IV were conducted in Mtwara rural districts, see Figure 4.

Kilosa district was selected for studies I and II because it is one among the highly malaria endemic districts in the country. The studies started 18 months since the commencement of the implementation of ACTs drug policy change in January 2007. While study (I) took four months to complete data collection, study II took 12 months (Figure 4). Data collection for study I and II started in Kilosa district, simultaneously, in June 2008.

Mtwara rural district was selected for the studies because studies III and IV were nested on a rectal artesunate deployment study which started in 2004 (Figure 4). This enabled us to take advantage of the experience and rapport already created with the district authorities and the population at large. Study III was the first to start so as to minimise the recall period from the end of the deployment study to the present studies, followed by study IV a month after.

Figure 4 showing study periods (I-IV)



Kilosa district is one of the six districts in Morogoro region located about 300 km west of Dar es Salaam, the biggest business city in Tanzania, along the central railway to Kigoma and highway to Rwanda and Burundi (Figure 2). The district is bordered by Mvomero district in the south, Kilombero district in the west, Mpwapwa district in the north and Handeni district in the east. It has a population of about half a million people (Projections from the National Census, 2003) living in 260 villages (District Annual Report, 2008). About a third of the population lives below one dollar per day; a figure that includes both rural and urban areas, thus the poverty level is likely to be higher in the rural areas. There were 61 dispensaries, 7 health centres, 3 hospitals 152 drug shops of which 92 had been converted to ADDOs. Of these, Faith Based Organisation (FBO) owned nine dispensaries, one health centre and two hospitals. There were no private-for-profit health facilities in the district. Malaria is one of the leading causes of out-patient attendance and admissions in the district accounting for more than half (55.5%) of the total outpatient attendance, and 60% of the total deaths among under-fives admitted to the hospitals (District Annual Report, 2008). Kilosa district reported the highest

percent of outpatient cases attributed to malaria in the country in 2008 (MoH&SW, 2009a).

Mtwara rural district is one among five districts in Mtwara region which is located south of Dar es Salaam (Figure 2). It is bordered by the Indian Ocean in the east, Mozambique in the south, Tandahimba district in the west and Lindi region in the north. The district has a population of about 212,000 and 112 villages. About one third of the population lives below the poverty line (District Council Annual Report, 2006). There were 30 dispensaries and four health centres and no hospital. Patients from dispensaries and health centres are referred directly to the regional hospital. During the deployment study, all 67 villages located 5 km or more from a nearby health facility were selected for the study; one health facility was built later. Malaria is also the leading cause of out-patient attendances and admissions in the district (MoH&SW, 2008a)

4 MATERIAL AND METHODS

4.1 STUDY DESIGN AND SAMPLE POPULATION

A mixed methodological approach was used in this thesis with minimal interference on the day to day activities in the study areas in order to obtain data that reflected the real life situation as much as possible. This practical approach allowed addressing practical policy issues likely to act as a barrier to access ALu promptly and adhere to the treatment schedule as well as to referral advice. While quantitative methods were useful in determining the magnitude of the problem and its determinants, the qualitative method was employed in order to get a better understanding and the linkages between the various independent factors reported to influence the dependent variables studied in this thesis. Quantitative studies were started first based on the fact that the topics were generally known from studies previously performed on CQ and SP (Eriksen et al., 2005, Nsimba et al., 2002).

Rural villages were purposely selected because of the high malaria burden which is higher in these settings, prevalence of 20% compared to urban (7%) (Tanzania Commission for AIDS (TACAIDS) et al., 2008). In addition, caretakers in these settings are relatively poor compared to those in semi and urban settings (National-Bureau-of-Statistics, 2002), thus, they are more prone to marginalization to access ALu (I) and health facilities (I and III).

Studies in this thesis were community based, so as to obtain information from the end users of the services, a strategy that was more likely to gather information that reflects the real situation. In a setting where not all disease episodes are taken to a health facility, community-based studies are more likely to capture the views of the those who could not otherwise be reached (Marsh, 1998).

Study I was prospective in nature in which under five children were followed up for six months. Those reported to have fever suspected to be malaria were recruited. The prospective method has the advantage of dealing with active cases hence minimising recalls period and bias (Kroeger, 1985). The method also has the advantage of establishing a time relationship between dependent and independent variables. The method is however limited by slow progress in recruiting cases when the event of interest occurs infrequently. In study I, it took 6 months to recruit the required number of children when the plan was to accomplish data collection within a period of four months. Study II was also prospective in nature. All children under the age of five, in five villages, were followed up at home and those found to have malaria, confirmed using RDT and treated with the correct dose of ALu, were enrolled, for a period of 12 months.

Study III was retrospective in design, nested in a rectal artesunate deployment intervention study (Gomes et al., 2008). A randomly selected number of under five children were followed up at home to determine factors likely to have influenced caretakers' action, to adhere to referral advice or not, after pre-referral treatment with rectal artesunate. Retrospective study is the one in which the event of interest has

already occurred at the time of the study. In this approach, selection of subjects using random sample is easy, which allows making inference over the study population (Bowling, 2002). However, the method depends on recall which, in addition to reducing the quality of data, it is also likely to result in bias if there is a difference in recall between the groups being compared.

Study IV was qualitative, conducted after study III to allow for preliminary analysis that gave an opportunity to develop relevant questions to make the interview guide focused. Focus group method was employed, taking advantage of opening up discussions without personalizing opinions and also obtaining a community perspective on the issues discussed (Corell, 1995).

4.2 SAMPLING AND SAMPLE SIZE

Stratified sampling was performed in study I and II, in which, 161 rural villages were selected out of 260 villages in Kilosa district (National Census, 2003). Villages were grouped into four geographical climatic zones namely; wet-lowland, wet-highland, dry-lowland and dry-highland. In study I, villages were grouped according to whether they had a health facility or not, for each of the four zones. Using EPI-Info software (version 6; WHO, Geneva) one village was randomly selected from the group of villages with health facilities, and two, from villages without, making a total of 12 villages. Random sampling was performed to select the names of children under the age of five from an updated village register using the same software. Proportionate sampling of village's size was used. In study II, villages in the wet-lowland area were purposively selected because of high malaria transmission throughout the year. Villages were grouped into those with and without a health facility, as in study I, and all children in the three villages (2,351) were followed up. Two semi-urban villages, headquarters of the three selected villages, were later added for the purpose of comparison, making a total of 3,618 children followed-up.

The deployment study, in which studies III and IV were nested, was aimed at testing the feasibility of community health workers and selected mothers to administer pre-referral rectal artesunate to children who could not take orally, before referring them to a health facility. The study was conducted in 67 rural villages that were 5 km or more from a nearby health facility in which 2,281 were involved. Caretakers were followed up about two weeks later, to establish the action taken after the referral advice, and for those reporting to have gone to a health facility; information was confirmed using health facility records. In study III stratified sampling was performed in which all the children enrolled in the deployment study were grouped according to the action taken by caretaker after the pre-referral dose of rectal artesunate, that is, those who i) went to health facilities ii) went to drug shops iii) went to traditional healers and iv) took no further action.

Sample sizes for studies I-III were calculated using the formula for independent observations assuming a maximum length of a 95% confidence interval to be +/- 5%. In study I and III, the assumed proportion of 50% was used due to large variations reported in literature and in study III acceptance of referral from the deployment study was not yet known. In study II, the proportion of caretakers adhering to treatment was

assumed to be 24% (Nsungwa-Sabiiti et al., 2005). Finally, adding 10% for possible loss to follow-up and appropriate correction factor for clustering effect (ICC=0.01). In study I, the sample size came to 591 (approximated as 600). Assuming the incidence of 6% in two weeks (Hetzl et al., 2008), 1,200 children were followed-up in order to obtain the sample size in four months. However, it took six months to obtain the required number and 35 children dropped out and were replaced using random selection method. In study II, the sample size was 399 (approximated as 400). Assumption was made that 80% of the febrile children will be attended at a health facility (de Savigny et al., 2004), thus the study was planned to take four months. But it took 12 months to recruit the required number of children, because, during data collection many children in the remote villages were reported to be treated by drug vendors. In study III, the sample size was 800, thus the aim was to have 200 children from each of the four strata. However only those who went to a health facility had more than 200. Therefore 286 children were randomly selected from those taken to health facilities (in total 1810) and all children who went to a traditional healer (in total 52), drug shops (in total 202) and took no further action (in total 201).

In the qualitative study (IV), focus group discussions (FGDs) were conducted in three villages. The decision on the number was determined by saturation and geographical representation. When selecting the next village priority was given to a different geographical area, that is, coastal and inland areas. One FGD was conducted per day in order to allow time for reflection. In each village, FGDs were held with a male and a female group of caretakers, separately; whose children had pre-referral treatment and those who did not, making a total of four FGDs in each village, adding up to 12 FGDs. Female and male group discussions were performed to give an opportunity to each group to express themselves freely. The caretaker at the time the child was sick was invited in the treated groups, with the support from CHWs who knew them. Each FGD comprised of 6-10 participants. Selection was made to represent people of different social characteristics. A total of 84 participants were involved with a male to female ratio 1:1. Participants were small scale farmers, half of them with primary level education.

4.3 DATA COLLECTION METHODS

Research assistants (RA) for study I were CHWs in the respective villages, supervised by members of the research team recruited from the research group, working at the study site in Kilosa, and the Principal Investigator (PI). In study II research assistants experienced in blood sampling from children were recruited. RAs were initially trained by the principal investigator on questionnaire administration and by a pharmacology technician in blood sampling. They were then involved in a pilot study that aimed at refining data collection instruments and giving them practical exposure to taking blood samples and data collection. In study III research assistants were from six leavers also working at one of the research sites in Mtwara district. These were supervised by a member of the research team, and the PI.

Structured interviews

Structured interviews have the advantage of being easy to conduct and to obtain data hence they are a commonly used technique in health systems research where data are often required to feed on implementation policy/ programme (Varkevisser et al., 1991). However, the method is limited by the subjectivity of responses especially when the topic in question is sensitive. The method also limits detailed explanation of an event. Structured interviews were conducted in studies I-III. A questionnaire was prepared based on literature review and pilot tested to validate the questions. Face-to-face interviews were held with the caretakers at their homes to obtain socio-economic and demographic data, knowledge about malaria and other variables thought to influence the outcome variables. Interviews were conducted in Kiswahili, the language spoken by the majority of Tanzanians, about one week from the time of the event in study I and II. In study III and IV, the recall period was longer, between 3 months and 3 years.

Direct observation

Observation of events has the advantage of capturing first hand information on an ongoing event hence no recall is involved (Robson, 2003). However, the method is limited by the risk of the person under observation altering behaviour so as to conform to what is desirable (Hawthorn effect). In study III, community drug dispensers observed child symptoms and recorded them on a form before administering the initial dose and referring the caretaker to a health facility using a referral form. Adherence to referral advice was confirmed by checking records at the respective health facilities where the caretaker had reported to have taken the child.

Laboratory methods

Laboratory methods produce more reliable findings compared to self reporting; however, the method is only available for some types of studies and often expensive. In study II, blood samples were collected to determine lumefantrine concentration levels using a field adapted method (Ntale et al., 2008). The use of filter paper method ensured that a small amount of blood was taken and easily handled during transportation with no need of refrigeration. This method is thus well adapted in tropical settings (Bergqvist et al., 1987). High Pressure Liquid Chromatography was used to measure blood lumefantrine concentration as described by Ntale et al (Ntale et al., 2008).

Focus group discussions

FGD is a method for collecting data in qualitative studies. The method has the advantage of allowing participants to share ideas in responding to research questions (Cresswell, 2007). The method works well if the research topic is not sensitive. The disadvantage of the method is that social norms might not allow some people to contribute effectively in the discussion and it requires a good moderator to guide and obtain relevant information from participants (Cresswell, 2007). FGDs were performed in study IV where detailed information was collected on factors influencing adherence to referral advice and how the factors interrelated to each other. The main questions

were pre-tested in one village and the interview guide modified. Discussions were held in a quiet place or village government office after participants had signed a written consent form. Discussions were moderated by a Tanzanian male social scientist and took about one and a half hours. The moderator was assisted by two male research assistants, one took notes and another made observations. Discussions were conducted in Kiswahili and were tape-recorded.

Triangulation

Triangulation means the use of one or more methods with the purpose to cross-check data credibility/validity in a study (Cresswell, 2007). There are several types of triangulation (Todd, 1979), these include *method triangulation* the use of different methods to study the same objective/phenomenon. This was achieved in study III and IV where the objective in both studies was to establish factors influencing adherence to referral advice using quantitative methods in study III and qualitative in study IV. *Data triangulation*, where a different type of data is collected to answer the same question was performed in study IV where the same questions were asked to male and female caretakers whose children had pre-referral treatment and those who did not. The experience of caretakers whose children had pre-referral treatment was triangulated with those whose children were not treated. The caretakers of non-treated children were taken as independent observers, as relatives or neighbours of a treated child, in a rural community where people interact closely. *Investigators' triangulation* where multiple researchers of different disciplines interpret the same data was achieved in study IV through the participation of a social scientist, health systems and malaria researchers, some with local and other with international experience. Other methods include *theoretical triangulation* where more than one theoretical framework is used to interpret a phenomenon.

4.4 DATA ANALYSIS

Quantitative data was double entered and validated using – EpiData software (EpiData Association, Odense, Denmark) and analysed using Stata version 10 software (Stata Corp., College Station, TX, USA). The unit of analysis was individual child in studies I-III. In order to avoid overrepresentation by those with more episodes, only first episode was taken for analysis in study I and II. The primary outcome variable for study I was prompt access to ALu, and the secondary was source of care. No child received ALu more than once in one episode, this avoided confusion in classifying children in the outcome variable. History of fever was used as diagnosis for presumptive malaria, as this was the recommended definition of malaria at the time the studies were conducted (MoH&SW, 2006, WHO, 2006) and had been used in several other studies (Gitonga et al., 2008, Malenga et al., 2005, Tipke et al., 2009). Weighted analysis over the strata was used to obtain unbiased estimates. In study II, the outcome variable was, reported adherence to ALu treatment. Caretaker's report was used as the basis for defining adherence to treatment (see definitions). Analysis of blood lumefantrine concentrations by explanatory variable was limited by the lack of a clear cut-off point. In study III, the outcome variable was adherence to referral advice defined as action taken by caretakers following pre-referral treatment with rectal artesunate. Those who went to health facilities were regarded as adherent and this

information was verified at the respective facilities. Analysis included data collected at the time the child was sick and merged with those collected in study III. Both pooled analysis and analysis by strata were performed after finding significant differences between strata on the outcome variable

Measurements

Descriptive statistics were presented as means, median and proportion in studies I-III. Contingency tables were made and analysed using Chi square test. P values of 5% were taken as the cut-off point for significance testing. Logistic regression analysis was performed in studies I-III. Explanatory variables likely to influence outcome variables, and had no values of more than 90% in one attribute were introduced in a stepwise (manual) regression analysis using a 10% cut-off point for the p-values to obtain a parsimonious model.

Wealth status calculation using Principal Component Analysis (PCA)

Wealth index was calculated using principal component analysis (PCA). The method is useful in situations where income data is difficult to obtain (Filmer and Pritchett, 2001). The method applies the concept of using the first principal component that contains the most important aspect of data in terms of variance. Using 19 household assets adopted from the TDHS 2004/5, PCA was performed by introducing variables that had no attribute with more than 90% subjects. Each asset was assigned a weight loading by scoring with the first principal component before dividing wealth status into quintiles. Quintiles were then grouped into better-off (quintile 3-5) and poor (quintile 1 and 2)

Qualitative - Qualitative content analysis was conducted in study IV. Transcription of tape recorded information was performed together with the notes taken during FGDs and were translated back into English. Latent qualitative content analysis (Graneheim and Lundman, 2004) taking advantage of its ability to take into consideration variations in opinions among participants was performed. Manual analysis was conducted by coding the information and assigning categories. While the main author initiated the coding and category assignments, others went through them identifying areas of discrepancies and discussions were held until consensus was reached. Comparison was made between codes and between categories (Graneheim and Lundman, 2004). Comparisons were also made between treated and non-treated; and male and female groups and little difference was found. The unit of analysis was a group and not individuals; this was performed in order to retain the context of the FGD. Relevant statements were extracted and presented verbatim. Preliminary results were discussed in a researchers' forum where critical comments were obtained and addressed.

4.5 ETHICAL CONSIDERATIONS AND CLEARANCE

Ethical concern in study I, III and IV was in the use of participants' time when they could be doing other personal productive work. However, participation in the research had a benefit to a larger community thus outweighing personal loss of time or inconvenience. A minimum number of questions were asked, necessary to answer the objectives, in order to maximise the use of time. The topics raised during the interviews were not sensitive and were thus less likely to interfere with or disturb the caretakers'

personal emotions. Confidentiality was another issue likely to be of concern. This was ensured by using code numbers instead of names to identify children and blood samples. Only the principal investigator had the key to the codes. Study II, involved blood sampling; where a drop of 100 μ L was obtained through a finger prick after caretakers' consent. A total of 18 caretakers refused to take blood samples from their children and were excluded. Blood samples drawn from children cause pain and have a risk of cross-infection if not properly performed. Special paediatric prickers were used, that in addition to minimizing pain, ensured an optimum drop of blood was obtained. Research assistants wore plastic gloves and cleaned the site with spirit to prevent cross-infection. The blood drop was spotted on a filter paper and dried before storage in plastic envelopes, thus further minimising cross-infection.

Informed consent was administered to caretakers in Kiswahili, a language spoken by most Tanzanians. Caretakers signed a written informed consent form on behalf of their children. Those who did not know how to read and write, the information was read in the presence of a witness and then thumb-printed and the witness countersigned. Caretakers were made aware of their freedom to refuse entering in the studies (I-IV) as well as withdrawing, in the course of the studies, without negative consequences. Although some caretakers required additional information prior to signing, there was no refusal. Ethical approval, for all the studies (I-IV), was obtained from the Muhimbili University College of Health Science. Permission to conduct studies was obtained from the relevant authorities at the regional, district and village level before commencing data collection.

4.6 SUMMARY OF METHODS

Sub-study	Objectives	Subjects and sample size	Design and Method	Analysis	Year of field work
I	To determine the magnitude of, and identify factors influencing prompt access to ACTs among under five children in rural settings	600 under fives reported to have fever	Follow up study using structured questionnaire interviews	Descriptive, multiple logistic regression	2008
II	To determine the degree of adherence to ALu treatment and its influencing factors in real life situations in under five children in a rural district.	400 Under fives diagnosed to have malaria using RDT and treated with artemether-lumefantrine	Follow up study using structured questionnaire interviews and blood sample taken for lumefantrine concentration	Descriptive, multiple logistic regression	2008-2009
III	To determine the factors influencing parents' decisions to adhere with advice to go to a health facility following pre-referral treatment	587 under fives treated with rectal artesunate	Retrospective study nested in an intervention study. Caretaker of children followed up at home and interviewed using structured questionnaire	Descriptive, multiple logistic regression	2007
IV	To understand caretakers' decision making on whether or not to adhere to the referral advice after their child had been given pre-referral treatment with rectal artesunate, using qualitative method	12 Focus group discussions	Qualitative study, nested in an intervention study using FGDs	Qualitative content analysis	2007

5 RESULTS

5.1 PROMPT ACCESS TO ARTEMETHER-LUMEFANTRINE (I)

A total of 1,200 children were followed up for a period of six months and 35 of them were replaced because of attaining the age of five or shifting residence, making the total number of children followed 1,235. In total 957 episodes of fever were recorded of which 607 were first episodes, these were used as the basis of the analysis.

Table 5 shows that, less than half of the febrile children were taken to government facilities. Those who were taken elsewhere, nearly half of them (44.6%; 153/343) went to ordinary shops and only a third were taken to FBO facilities and ADDOs; which was less than 20% of all the children (114/607).

Table 5: General information on type of care sought and received by caretakers

Source of care	Number	Percent
Children who received care from government facilities	264/607	44.8*
Children who received care from ordinary shops	153/343	44.6
Children who received care from FBO facilities and ADDOs	114/343	33.2
Access to artemether-lumefantrine	Number	Percent
Children treated with any antimalarials	374/607	66.3*
Children treated with ALu	268/607	45.8*
Children treated with ALu at government facilities	220/264	83.3
Children treated with ALu at FBO and ADDOs	41/114	37.0.
Prompt access to artemether-lumefantrine	Number	Percent
Children who had prompt access to ALu	223/607	37.6*
Children who had prompt access to ALu in government facilities	185/264	70.1
Children who had prompt access to ALu in FBO facilities	27/86	31.4
Children who had prompt access to ALu in ADDOs	6/28	21.4

* Weighted data - weighted analysis over the strata was used to obtain unbiased estimates. Analysis within sub-samples was not weighted.

Two-thirds (66.3%) of the children were treated with any antimalarial while nearly half (45.8%) of all children were treated with ALu. The majority (>80%) of the children treated with ALu were those taken to government facilities. Despite having subsidized ALu, FBO facilities and ADDO contributed less than 10%% (41/607) of the children who accessed the drug. Approximately, one third of the febrile children had prompt access to ALu; which was higher in government facilities (70%) compared to FBO facilities and ADDOs where less than one-third had prompt access.

Caretakers who sought care from FBO facilities reported paying for drugs more (median expenditure Tsh 2,500) compared to other sources of care; followed by ADDOs (median expenditure Tsh. 1,600). About 10% (26/264) of caretakers who

sought care from government facilities reported paying for drugs (median expenditure – zero). The median expenditure on drugs was higher among the poor (median expenditure Tsh. 500) compared to the better-offs (median expenditure - Zero).

Table 6 shows that children whose caretakers sought care from government facilities were 17-times more likely to have prompt access to ALu compared to those taken elsewhere. Lack of prompt access was highly attributed to not getting ALu (>80%). The median distance to the government facility was shorter (2 km) for children who had prompt access to ALu compared to those who did not (5 km). Caretakers from better-off household and those who had knowledge on the recommended treatment for uncomplicated malaria were 2-3 times more likely to access government facilities than the poor and those without knowledge.

Table 6: Determinants of prompt access to artemether-lumefantrine and accessing care from government health facilities for children under five

Factors influencing prompt access to ALu in all strata n= 607	Unadjusted OR		Adjusted OR	
	OR	95% CI	OR	95% CI
Children whose caretakers sought care at government health facility	17.7	10.55 - 29.54	16.87	10.06-28.28
Children from better-offs households (Quintile 3+)	2.1	1.39 - 3.28		
Children whose caretakers knew that <i>dawa mseto</i> (ALu) is the recommended drug for the treatment of <i>malaria ya kawaida</i> (uncomplicated malaria)	2.04	1.36 - 3.07	1.26	0.76-2.09
Factors influencing seeking care from government health facilities in all strata n=607				
Children from better-offs households (Quintile 3+)	3.22	2.10 - 4.92	2.56	1.63-4.01
Children whose caretakers knew that <i>dawa mseto</i> (ALu) is the recommended drug for the treatment of <i>malaria ya kawaida</i> (uncomplicated malaria)	2.55	1.71 - 3.81	2.07	1.35-3.16

Caretakers from the better-off households were found to live closer to government facilities (average 2 km) compared to the poor (average 5 km). The better-offs were 4-times more knowledgeable about the recommended treatment for uncomplicated malaria than the poor and were approximately 3-times more likely to own a radio.

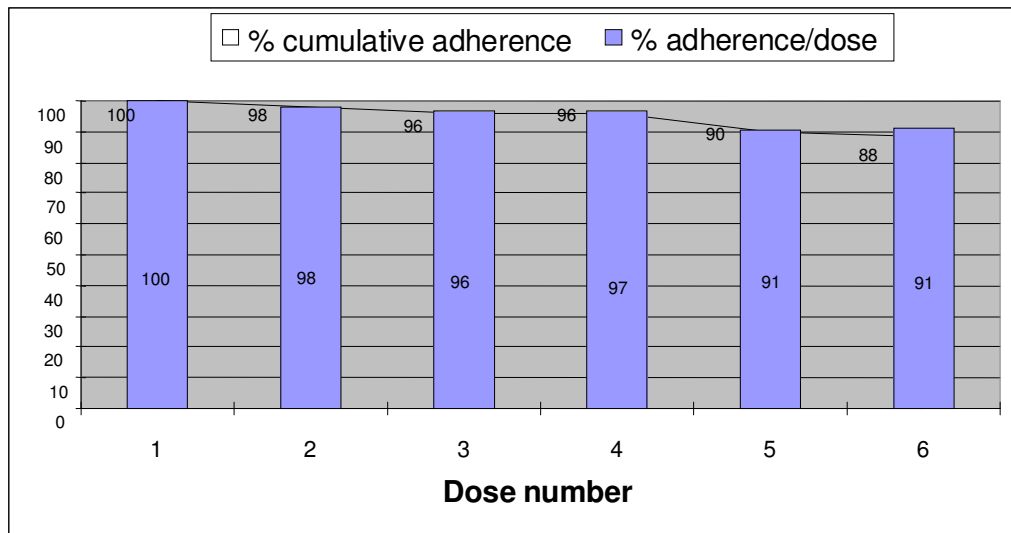
5.2 ADHERENCE TO ARTEMETHER-LUMEFANTRINE TREATMENT (II)

A total of 544 eligible children were identified at the health facilities, of which, 467 (85.8%) were traced at home on day 7. Loss to follow up was attributed mainly to the caretaker not being at home on the day of the visit. Repeat follow up on the next day could not be performed because the visits were specifically targeted for day 7. The relatively high follow up rate was due to the low numbers of children followed-up per

day (0-3). With the use of a motorcycle, RAs could trace caretakers who were not at home but within a reachable distance, up to 10 km. Blood samples could not be collected from 21 children because caretakers refused (18) or RA failed to draw blood (3); and two caretakers could not remember the details on drug administration. Thus, complete data was available for 444 children.

Of the 444 children, 392 (88.3%) were reported by caretakers to have received ALu according to the recommended schedule. Non-adherence was attributed mainly to off-schedule dosing (untimely) rather than missing doses. Non-adherence was higher with the last dose, as indicated by a drop in the reported adherence (Figure 5).

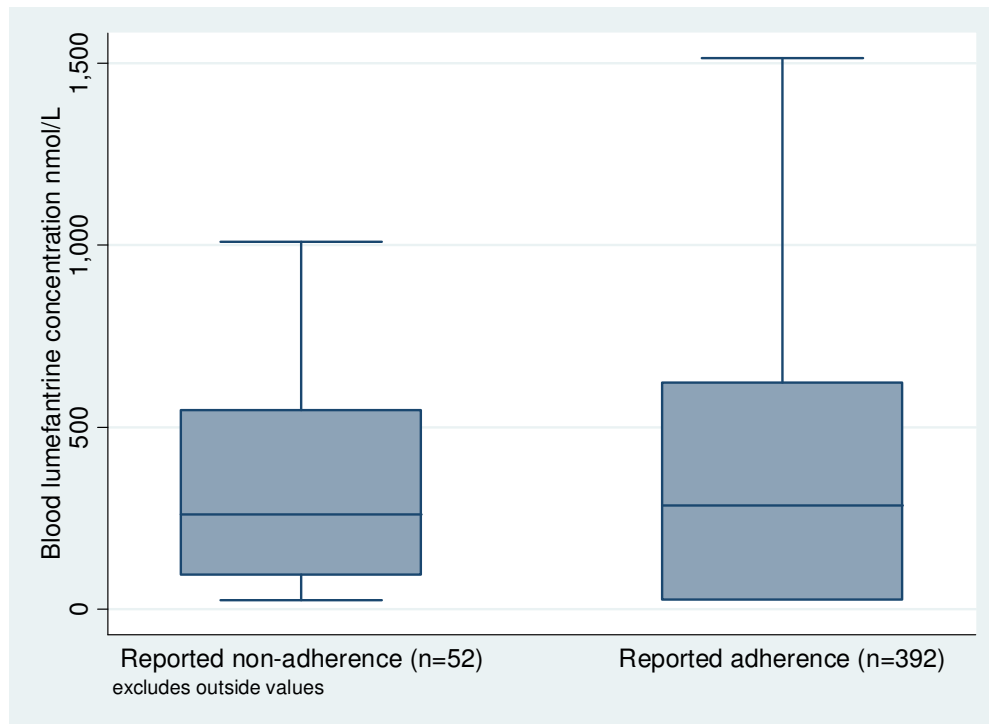
Figure 5: Bar chart showing percent adherence as reported by caretakers for each dose and cumulative adherence from dose 1 to 6 (n=444)



The odds for children from better-off households to adhere to ALu treatment was 2-times larger compared to the poor, after adjusting for confounding factors (OR 2.45; 95% CI 1.35-4.45; adjusted OR 2.23; 95% CI 1.20-4.13). While more than 90% of the caretakers reported correct knowledge about the frequency and duration of administration of the drug, basic primary level education was not found to influence the reported adherence to treatment schedule.

No significant difference in mean blood lumefantrine concentrations was found between children whose caretakers reported adherence and non-adherence, respectively. The corresponding median levels were 286 nmol/L and 261 nmol/L (Figure 6). There was however a wide variation in blood lumefantrine concentration ranging from 25 nmol/L, which was the limit of quantification, to 9,318 nmol/L for the total group, and 25 nmol/L to 1382 nmol/L for those with reported non-adherence and 25 nmol/L to 9318 nmol/L for those with reported adherence. Extreme values (outliers) are not shown in Figure 6.

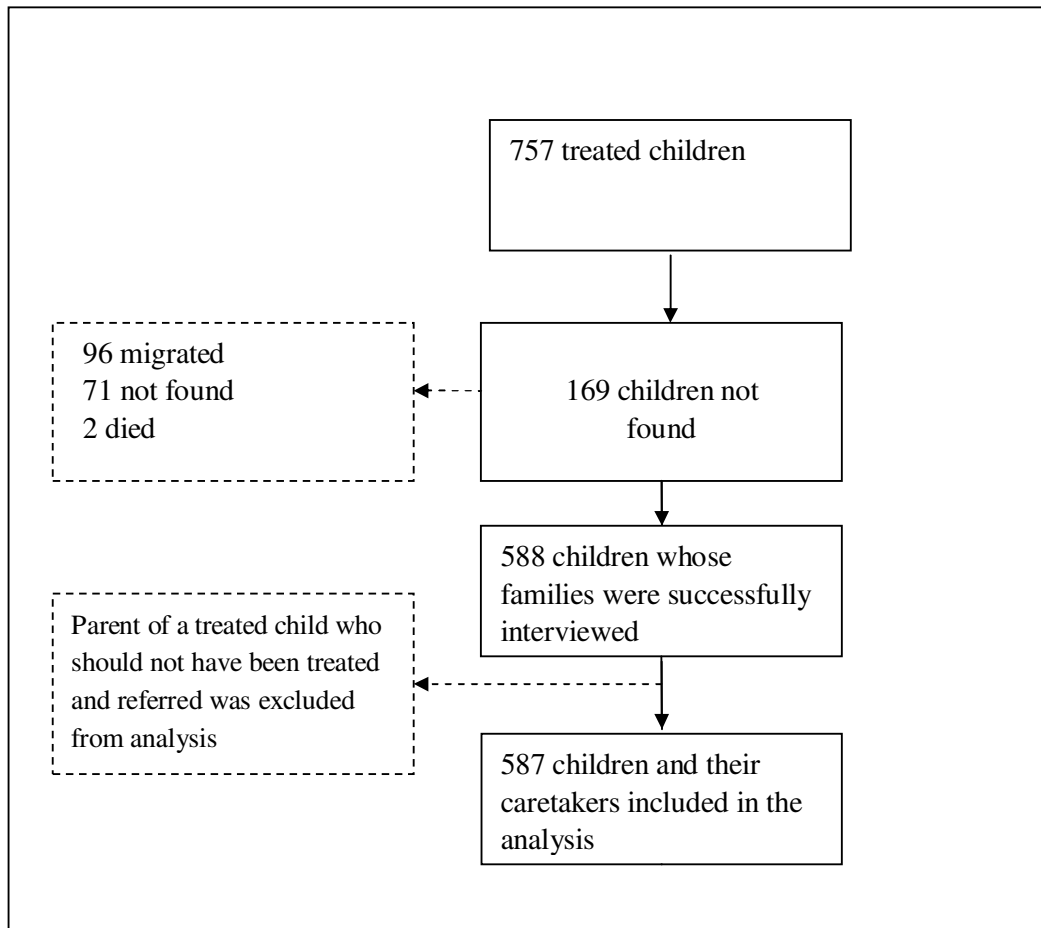
Figure 6: The distribution of lumefantrine blood concentration levels of study children by reported adherence status (n=444). Outliers not shown in box-plot.



5.3 ADHERENCE TO REFERRAL ADVICE (III)

A total of 757 children were traced at home, of these, 588 (78%) were found and their caretakers interviewed. The loss to follow up was attributed mainly to shifting place of residence or not found at home after three follow up visits as shown in Figure 7. One of the children excluded from the analysis was found to have not met the criteria for inclusion; hence, analysis was based on 587 children. Loss to follow up was higher among those who went to traditional healers (38.5%) compared to other groups (19-23%).

Figure 7: Flowchart: The number of children whose caretakers were traced and interviewed and those not traced



Nearly a third of the children (31%; 182/587) had altered consciousness and / or convulsions at the time of pre-referral treatment; and the majority were taken to the health facility (56.4%; 102/181) compared to those taken to traditional healers (7.2%; 13/181).

Table 7 shows the results from pooled analysis of action taken after pre-referral treatment with rectal artesunate (see analysis section). Children with altered consciousness and or convulsion (severe symptoms) were 3 -times more likely to adhere to referral advice compared to those with less severe symptoms (OR 3.47, 95% CI 2.52–5.17, $P < 0.0001$). Further analysis by strata showed varying odds ratio between health facilities-traditional healers comparison (OR 1.53; CI 0.73–3.19) and health facilities- no action comparison (OR 4.0 2.43–6.60). Over 90% of the caretakers reported to have been told to go to a health facility after the pre-referral dose of rectal artesunate. Those reporting knowledge on when and why they should have gone to a health facility were twice more likely to adhere than those who did not, OR 2.19, 95% CI 1.48–3.23 and OR 1.77, 95% CI 1.07–2.95, respectively.

Table 7: Factors affecting adherence to referral advice after pre-referral dose of rectal artesunate, with adjusted odds ratio (OR) from logistical regression analysis, (n=587)

Seeking care from health facility vs. all other actions (pooled results)	OR	95% CI	P-value
Children presenting with altered consciousness or convulsion	3.26	2.24-4.74	0.000
Children whose caretaker had knowledge about cause of malaria	0.52	0.36-0.76	0.001
Children whose caretaker reported being advised on when to go to a health facility	2.21	1.53-3.18	0.000
Children whose caretaker reported being advised on why should go to a health facility	1.66	1.02-2.68	0.040

About 21% (124/587) of the caretaker reported paying at the health facilities, of these, the majority (79%; 98/124) resided in villages served by a PNFP facility. A small proportion (5.5%; 26/445) of the caretakers residing in villages served by government facilities reported paying for services. Caretakers residing in a catchment area of facilities that charged for services and reported paying for laboratory and consultation services were 4-5 times less likely to adhere to referral advice, Table 8. In this area, severity of symptoms did not influence adherence to referral advice.

Table 8: Factors influencing adherence to referral advice in government and non-government catchment areas

Government health facilities catchment villages	OR	95% CI	P-value
Children presenting with altered consciousness and convulsion	3.90	2.35-6.45	0.000
Children whose caretakers paid for consultation	0.86	0.36-2.09	0.744
Children whose caretakers paid for drugs	1.10	0.70-1.74	0.680
Children whose caretakers paid for laboratory tests	2.36	0.28-19.81	0.430
Faith-based health facilities catchment villages			
Children presenting with altered consciousness and convulsion	1.05	0.39-2.87	0.92
Children whose caretakers paid for consultation	0.13	0.02-0.73	0.021
Children whose caretakers paid for drugs	6.48	1.48-28.32	0.013
Children whose caretakers paid for laboratory tests	0.17	0.04-0.73	0.018

Although charges for services at NGO facility deterred adherence to referral advice, SES was found to have no influence. The distance to and the perceived quality of care at the health facility as well as caretaker's basic education did not influence adherence to referral advice in all settings.

5.4 ADHERENCE TO REFERRAL ADVICE (IV)

Caretakers' decisions to referral adherence or not, after pre-referral treatment with rectal artesunate dose, fell under four groups. There were:-

Caretakers whose child condition *improved* and they *did not* proceed to a health facility.

'Just after doing the suppository insertion the fever went down. So we decided not to go to the dispensary (Male participant of a child treated with rectal artesunate)

There were caretakers whose child condition *improved* and they *adhered* to referral advice but *without clearly understanding* the rationale for doing so.

'... because when a child gets high fever, you will hear the mother saying next morning 'today I am just going to the hospital, but with that medicine they inserted into my child it helped him/her. So I am going just for the sake of it'. (Female participant of a child not treated with rectal artesunate)

There were those caretakers whose child's condition *improved* and they *adhered* to referral advice with a *clear understanding* of the reasons.

'... .. now you see it is better to go to the hospital and see the doctor because he uses medical equipment...he can examine him and tell how many malaria parasites the child has' (Female participant of a child not treated with rectal artesunate).

The last group was of caretakers whose child condition *did not improve* and they mostly reported to *adhere* to referral advice.

'After inserting the drug degedege (convulsions) and quivering stopped but I still went to the health facility because the child was still sick' (Female participant of a child treated with rectal artesunate)

The different standpoints were a result of misunderstanding the information about when to go to a health facility, and why, as reported by different participants in the FGDs.

Caretakers' whose children had pre-referral treatment with rectal artesunate, especially those whose child condition improved, were faced with a dilemma to decide on whether or not to adhere to referral advice. In decision making, caretakers seemed to weigh the condition of the child after pre-referral treatment, against other competing priorities, difficulties in reaching the health facility and perceived quality of care. Some of the obstacles met at the health facilities included a few staff, negative attitude of providers to the caretakers, drug shortages and informal payments. When the child condition did not improve, caretakers would tend to adhere to referral advice irrespective of these constraints. But these constraints become a concern to adherence if the child condition is seen to have improved

"Going to the health facility does not-need transport costs. One can walk even to town (30 km) if he/she has a sick child". (Male participant of a child not treated with rectal artesunate)

There was also a gender perspective on adherence to referral advice where male parents reported to be involved when the child condition was critical, or money was needed or when care-seeking required travelling far away or during the night.

'... We (male parents) contribute a lot to this problem. We have a lot of other plans and activities. It is only when the condition has become critical that is when we act ... So after having the first aid (suppository treatment) the father would say, 'but the kid is playing now! Why don't I go and do my things. Meanwhile, the child's condition might be getting worse (Male participant of a child treated with rectal artesunate)

This was confirmed by female participants who reported that, in general, the responsibility for seeking care rests upon them when the child's condition is perceived as not being life threatening.

6 DISCUSSION

Caretakers with children who had altered consciousness and convulsions were 4-times more likely to adhere to referral advice than those with less severe symptoms, such as lethargy, failure to feed and vomiting (III). Caretakers whose children did not improve after the initial pre-referral dose were also more likely to adhere to referral advice than those who improved (IV). In addition, the caretakers' practice of taking children with convulsion to health facilities was quite high (III) contrary to previous reports where they were taken to traditional healers (Makemba et al., 1996, Winch et al., 1996). Rectal artesunate has been reported to significantly reduce malaria mortality and central nervous system complications in African settings (Gomes et al., 2008) and that the rectal application was acceptable to community members (Warsame et al., 2007). The WHO recommended its use for children with malaria who were unable to take oral medication, followed by referral where treatment was not available, since 2006. Studies III and IV were nested in the rectal artesunate deployment study; these thus contribute some knowledge in the information gap necessary to inform policy decisions for the adoption and implementation of this life saving strategy.

This thesis has shown that once a child had access to ALu, caretakers were likely to adhere to treatment schedule (II); and to referral advice, if child had severe symptoms or not improved after pre-referral treatment (III, IV). This conforms to the pre-referral rectal artesunate strategy that aims at reducing deaths resulting from severe malaria. These finding suggests that strategies to increase the low prompt access found in study I should be of high priority. Moreover, a wide coverage in prompt access to ALu will reduce the need for rectal artesunate strategy (Gomes et al., 2008). The few studies conducted before policy change to ACT (Krause and Sauerborn, 2000, Nsungwa-Sabiiti et al., 2005) that addressed most of the steps in the pathway to survival, reported weaknesses in almost all the stages (Claeson and Waldman, 2000). Lower levels of prompt access to ALu, compared to findings in study I, have been reported in several African countries (Gitonga et al., 2008, Tipke et al., 2009, WHO, 2009). An important question addressed in the following discussion is, why there was low prompt access to ALu in rural remote areas, where the malaria burden is known to be high, when there is a high level of political commitment with pro-poor policies, and huge financing at national and international levels?

Studies in this thesis were conducted from a caretakers' perspective, thus shedding more light on the immediate and some of the underlying factors influencing access to ALu, as well as health facilities, for those who were referred. Thus, further analysis on the underlying factors likely to influence the outcomes (UNICEF, 1998) was performed using the existing data from literature in order to enrich the discussion.

6.1 PROMPT ACCESS TO EFFECTIVE MALARIA TREATMENT

6.1.1 Prompt access to treatment in governmental facilities

The immediate factor influencing the low prompt access to ALu was, overwhelmingly, the source of care (I); where, caretakers seeking care from government facilities were about 17-times more likely to have prompt access, compared to those who went

elsewhere (I). However, less than half went to government facilities where prompt access to ALu was found to be high (I). Not receiving the recommended drug was the main contributing factor (>80%) to lack of prompt access (I). Studies on factors influencing access to antimalarials in Africa are mostly based on previous antimalarials, that is, CQ and SP (Chuma et al., 2009, Holtz et al., 2003, Kazembe et al., 2007, Nsungwa-Sabiiti et al., 2004, Rutebemberwa et al., 2009a). In these studies, most of the factors found in studies I and IV were reported. However, the finding in study I, that the source of care was the only factor influencing prompt access to ALu after controlling for confounders, was new. The underlying reasons for accessing government facilities were distance to government facility, SES and knowledge of malaria treatment. Half of the caretakers who had prompt access to ACT resided within 2 km from government facilities compared to those who did not (median 5 km). In study IV, caretakers reported to be deterred to adhere to referral advice by the informal payments, poor provider-caretaker interaction, characterized by negative attitudes to caretakers by some of the health workers, and drug shortages in government facilities. Similar findings have been reported to influence access to government facilities in previous studies (Goodman et al., 2009, Rutebemberwa et al., 2009c). However, in study I, drug shortages were uncommon due to the vertical logistic supply of ALu that allows such programmes to by-pass the routine logistic system (MoH&SW, 2007a). In addition, the international support through the MMSS ensures adequate availability of the drug in the country (Roll-Back-Malaria-Partnership, 2005).

In order to further understand the underlying reasons, there is a need to answer the pertinent question, why caretakers did not seek care from government facilities, where services are supposed to be free? In study IV, caretakers raised concerns on the few numbers of health workers at health facilities in which one facility could be served by only one clinical officer for a catchment of 4-5 villages, each having between 3,000 and 5,000 people (IV). Inadequate provider performance has been reported to be associated with high workload, due to severe staff shortages, unskilled staff, lack of motivation and support supervision from the district (MoH&SW, 2007a, MoH&SW, 2009a). In Tanzania, like in many other African countries, human resources for health are in a crisis and threaten efforts to reach the MDG goals (Gerein et al., 2006, Jong-wook, 2003a, Narasimhan et al., 2004, Riley et al., 2005). With a staffing gap of over 60% (MoH&SW, 2009a), providers lack adequate time to communicate effectively to caretakers (Riley et al., 2005). The problem is experienced more in rural facilities, due to poor communication, infrastructure and social amenities and lack of opportunities for extra income from private practice or attending workshops; making the attrition rate in these settings higher (Riley et al., 2005). In one of the study facilities (II), a trained nurse was observed to prescribe, dispense, provide antenatal and child health care as well as mobile services to neighbouring villages, during the whole year of study period.

Health workers in rural remote areas also lack regular supportive supervision from the district managers (MoH&SW, 2009a). Where supervision occurs, the quality of supervision is inadequate, partly due to the criteria of measuring supervisor performance through number of visits instead of outputs (MoH&SW, 2004). Incentives for performance improvement are lacking and salaries are meagre thus hampering performance (Manongi et al., 2006). Salaries for health workers in Tanzania are no different from other African countries ranging between 70 – 300 USD per month

(Buchan and Sochalski, 2004, Friedman, 2004); the lowest being among rural health staff (Gerein et al., 2006, McCoy et al., 2008). Thus, a health worker with an average family of 6 dependents (National-Bureau-of-Statistics, 2010) will have an income less than the poverty line of 1.25 USD per person. Since their income does not correspond to the cost of living, most health workers utilise their working hours to earn a living through other income generating activities such as seminars and workshops (Roenen et al., 1997, Rowe et al., 2005) while others resort to soliciting informal payments (IV). Improvement in salaries and incentives is made difficult by the low countries GDP per capita (Schiavo–Campo et al., 1997). In addition, because there is no link to performance, due to inadequate supervision and routine health information system, increase in payment might not necessarily lead to improved health services (MoH&SW, 2004, Simba and Mwangu, 2005). Efforts by international agencies to improve country health systems through the Health Metric Network (WHO, 2010b) are yet to reach the caretaker-providers level. As a result of the huge workload and low pay, staff does not have enough time and motivation to offer user friendly services. In this context, the performance of the provider is driven by a personal sense of duty, more than the checks-and-balances that should be inbuilt within the system.

6.1.2 Prompt access to treatment in formal private drug outlets

Study I showed that faith-based organisations (FBO) facilities charged caretakers a relatively higher cost for drugs compared to other facilities. These fees deterred caretakers from adhering to referral advice (III). It also undermined the advantages that FBO facilities have in being located in rural remote areas where organisations that serve the vulnerable and poor are required. The fees are defended as being necessary in order for the FBOs to meet operational costs (Njau et al., 2006). Although the government gives grants to designated hospitals and subsidies to some FBO hospitals, this arrangement leaves out FBO health centres and dispensaries (MoH&SW 2009),

The national policy is to provide free medical services to children. But those residing in areas served by FBO facilities do not always benefit. Although the new HSSP III recommends that local governments contract out services to the private sector, especially where government services are not available or inadequate, these policies have yet to be implemented (MoH&SW, 2009a).

The transformation of drug shops to ADDOs aimed at improving access to patients of some essential drugs that were permitted to be sold through prescription only, including ALu. However, most ADDOs are situated in urban and semi-urban areas hence they have contributed little to prompt access in rural and remote areas (I). Owners of ADDOs are unlikely to operate in rural remote areas where the logistics costs are high due to poor transportation networks and sales are low because of a scattered population with low purchasing power. Consequently, it is only the ordinary shopkeeper who finds it profitable to add antimalarial drugs as one among other profitable commodities being sold in the shop

6.1.3 Prompt access to treatment in ordinary shops

About half of the children who were not taken to government facilities were taken to ordinary shops (I) where no subsidised ALu were available. The private sector is

reported to be preferred over the government sector due to the user-friendly services offered, being closer, faster, offering more convenient opening hours, the availability of drugs all the time and the provision of a cheaper source of drugs because they do not have to pay formal and informal fees (Amin et al., 2003, Brieger et al., 2001, Rutebemberwa et al., 2009b, Williams and Jones, 2004). Although the private sector accounts for a large proportion of antimalarials dispensed in Tanzania (Goodman et al., 2009), in remote rural villages, it is the ordinary shops, which sell rice and other household commodities, that also sell medicine, (Patouillard et al., 2010). Thus most studies reporting the advantages of the private sector base their findings on the formal private sectors comprised of registered drug shops which are supposed to be regulated through regular inspection and supervision (Hongoro and Kumaranayake, 2000). However, the majority of those utilising the private sector in study I, sought care from ordinary shops where they received non-recommended drugs. The underlying factors for caretakers utilizing ordinary shops was the distance to government facilities and ADDOs that were primarily located in semi-urban areas (I) and the relatively high cost of drugs charged at FBO facilities (I).

In study II, the level of adherence to ALu treatment was shown to be quite high and non-adherence was primarily attributed to untimely administration of the drug, rather than taking a fewer number of doses. The Affordable Medicine Facility for malaria policy aims to reduce ALu prices to a level equivalent to previous antimalarials (SP and CQ), by applying subsidies at the manufacturer level, so that the drugs can be affordably accessed through the private sector (Moon et al., 2009, RBM-Partnership, 2007a). The strategy is likely to improve access to ALu in remote rural areas, even through the ordinary shops. However, this might compromise the high level of adherence found in study II and elsewhere (Beer et al., 2009, Kabanywanyi et al., 2010) because study I showed that a large proportion of caretakers of febrile children in remote rural areas sought care from ordinary shops. Although the AMFm strategy might enable caretakers to afford a full course of ACT, drug sellers are reported to sell drugs according to patients' demands and under-dosing is common due to low purchasing power (Viberg, 2009), and inadequate knowledge about the importance of taking a full course (Hongoro and Kumaranayake, 2000). A study in Asia reported non-adherence to ACTs due to inadequate doses provided in private facilities (Yeung and White, 2005). While these studies were conducted in urban areas, the problems are likely to be more manifest in rural areas, where the purchasing power and knowledge is relatively lower.

Studies in Kenya reported improvements in the uptake of antimalarials and in the behaviour of the members of the community through training of shopkeepers (Goodman et al., 2006, Marsh et al., 1999). However, the success observed was on a small scale and under the influence of the research team which might not be realized on a national scale implementation because the regulatory bodies in many low income countries are so weak to even regulate practice in registered drug shops (Goodman et al., 2007, Kumaranayake et al., 1997). Unlike previous antimalarials, there is no immediate alternative to ACT in the near future. Thus resistance to ACT might be catastrophic in an African setting (Trape, 2001, Zucker et al., 2003). Moreover, the WHO recommends diagnosis of malaria based on microscopy or RDT. It is not clear whether RDT use will be practical when applied by the shopkeeper, and reinforcing

safety in blood handling on a nation-wide scale might overstretch the capacity of the regulatory bodies to monitor its safety in a community where HIV/AIDS is still a major problem.

In the absence of an alternative to ACTs in the near future, strategies to improve prompt access, in a setting where a substantial proportion of caretakers seek care from ordinary shops, should be accompanied with efforts to preserve drug efficacy the existing high level of adherence to treatment (II), in order to avoid the development of drug resistance. Resistance to ALu will lead caretakers to seek alternative treatment thus reducing prompt access to the recommended drug (ALu), thus creating a potential for non-adherence, forming a vicious cycle, spiralled by the lack of an alternative effective antimalarial. Measures to contain the emergence of resistance includes increasing access to ALu in rural communities where the burden is high, and ensuring adherence to a treatment schedule (Marsh, 1999). Through public-private partnerships advocated in the national health policy and strategies, the formal private sector should be allowed to continue providing services to people who can afford it, mostly in urban areas, while government efforts are directed towards rural remote areas. Strong government regulations and oversight will still be required to maintain adequate quality services provided by the private sector.

6.1.4 Prompt access to treatment by community health workers

Community drug dispensers were involved in the provision of a pre-referral dose of rectal artesunate to children reported to have malaria but unable to take oral medication, with success (III, IV). The involvement of CHWs has been reported to be one of the practical strategies for improving access to care in rural areas (Haines et al., 2007, Onwujekwe et al., 2007, Pagnoni, 2009). CHWs are much closer to caretakers and offer services all the time (Haines et al., 2007). Entrusting CHWs with the responsibility to diagnose malaria using RDTs, treat uncomplicated malaria with ALu and provide pre-referral rectal artesunate to children, where the option for parenteral treatment does not exist, could be cost-effective and holistic. The WHO, currently advocates the integration of malaria treatment with pneumonia and diarrhoea through the integrated community case management (iCCM) strategy (WHO, 2010a).

Studies have reported the feasibility of CHWs to perform all these functions effectively (Ajayi et al., 2008b, Mubi et al., 2010, Mukanga et al., 2010). Tanzania was among the pioneers in African countries where a country-wide Village Health Workers Programme was implemented in the 1980s (Heggenhougen et al., 1987). The main lesson from the failed programme was lack of sustainability that led to a high drop out rate. Recently, there have been some success stories in some countries, although the implementation scale was small (Haines et al., 2007, Onwujekwe et al., 2007, Pagnoni, 2009).

While operational research might be required to inform the decision making process (Pagnoni, 2009), a number of issues have to be considered prior to the re-introduction of CHWs. Integration of CHWs into the health-care system, improvement of their scope of work, incentives, technical support and career development are important (Hermann et al., 2009). The current Tanzania national health policy recognises the

position and role of village health workers as providers of health services at the village health post, but it does not provide them with salaries (MoH&SW, 2002). Although the Primary Health Care Service Development Programme (MMAM) strategy aims to train multipurpose CHWs (MoH&SW, 2007c), there are no suggestions about how they should or will be supported, remunerated and integrated as part of the workforce for the provision of health services. Although the policy document recommends local governments to introduce CHWs where feasible, many of them fail to start. To a large extent, local governments depend on central government for the financing of district health services, including the salaries and personal emoluments for health workers (MoH&SW, 2007a).

6.2 CARETAKERS' UNDERSTANDING OF INFORMATION GIVEN BY PROVIDERS

In study II, adherence to ALu was found to be quite high compared to studies implemented during the chloroquine era; and contrary to fears that rapid cessation of symptoms might lead caretakers to discontinue treatment and retain the remaining tablets for future use (Hinton et al., 2007). Such high levels of adherence have been reported in other community based studies conducted in Kilombero/Ulangu in Tanzania, Mainland and in Zanzibar (Beer et al., 2009, Kabanyanyi et al., 2010). The underlying factors to the high level of adherence to ALu treatment in the present study could partly be due to better understanding, by the majority of caretakers (>90%), of the information given by providers on how to administer the drug (Okeke, 2010). The pre-packaged pills in packets with pictorial instructions (Agyepong et al., 2002, Ansah et al., 2001), that were used in study II, also added to the understanding on drug administration by caretakers (Piola et al., 2005). High drug efficacy has also been reported to influence adherence to treatment (Chuma et al., 2009, Yeung and White, 2005).

In addition, caretakers were faced with a dilemma to adhere to referral advice by having to weigh the severity of child condition against the magnitude of obstacles in accessing care at the health facilities (IV) leading to delay in taking the appropriate action. Knowledge regarding the urgency and rationale for adhering to referral advice might have tipped the balance in favour of adherence to referral advice. Caretakers who understood the rationale for the adherence and its urgency were more likely to persevere and overcome the obstacles compared to those with less understanding. Likewise, knowledge about the recommended treatment for uncomplicated malaria, was found to be in favour of caretakers' decisions to seek treatment and care from government facilities (I).

Contrary to expectations, caretakers' basic (primary level) education, provided for 7 years, was not found to influence any of the outcomes studied in this thesis (I-III). Hence their understanding of the reasons why their child should be given the full treatment for ALu and the reasons for urgent hospital care determined their adherence behaviour. Some studies reported that secondary level education influenced adherence to a treatment schedule (Beer et al., 2009). In studies I-IV, caretakers reported to having secondary level education were too few (<10) to allow analysis. Was the type of education offered at this level not adequate to prepare caretakers to seek or become

exposed to appropriate information through written media? Further research on this might be required.

6.3 POVERTY AS A BARRIER TO ACCESSING CARE AND ADHERING TO TREATMENT

Poverty was one of the underlying factors found to influence almost all the outcome variables in this thesis (I-IV). Children whose caretakers were poor were less likely to seek care from government facilities (I) and to adhere to an ALu treatment schedule (II). Although in study III no statistically significant association was found between SES and adherence to referral advice, the cost of services, where charges were levied, was found to be a deterrent. This is an indication that poverty, in a way, did influence adherence to referral advice. Several studies have reported the influence of SES on accessing care for febrile children (Rutebemberwa et al., 2009a). Interestingly, in study IV, caretakers reported that cost was not a deterrent to adherence to referral advice, if the child had severe symptoms or had not improved after the pre-referral dose of rectal artesunate. Caretakers from low SES were found to be less likely to own a radio and to have knowledge about malaria treatment (I). This puts them at a disadvantage in the opportunity to acquire the knowledge necessary for decision making, faced with a febrile child. Ownership of radios might also have facilitated caretakers' adherence to administration of ALu doses according to the schedule, through following up the timing from radio programmes.

The barriers likely to be met when accessing care from a government facility or adhering to referral advice might have an impact on a caretaker, a family and their daily survival. Caretakers in study III were drawn from villages that were 5 km away from a nearby government facility. Caretakers, therefore, had to walk for 10 km to access care. Adding the long waiting time at the facility, this might mean spending half of the day seeking care for the child. Since the majority of caretakers in rural areas are poor (National-Bureau-of-Statistics, 2002) the opportunity cost to access care might be high, thus compelling them to weigh the risk between the child's condition and the time involved in accessing care. Policies stipulating free medical care for children were not known by some of the caretakers (IV). Even if they knew, the informal payments reported to be solicited by some providers (I, III, IV) might deter them from not seeking care from a government facility. Apparently, the national policy and international organisations' strategies aim at not making cost a barrier to accessing malaria interventions (MoH&SW, 2002, Roll-Back-Malaria-Partnership, 2005) and reaching the poor in rural remote areas high in the priorities (GFATM, 2010, Jongwook, 2003b, MoH&SW, 2002, USAID, 2009). Efforts to reduce the costs and reaching children in rural remote areas need to consider strategies to contain such informal payments.

6.4 METHODOLOGICAL CONSIDERATION

Design -Selection bias favouring the poorer –Studies were conducted in rural villages (1) and rural villages that were more than 5 km from a nearby health facility (III). This was purposely done in order to identify barriers in places where the burden of malaria is the highest. However, this excluded children from semi-urban and urban areas where people are less poor. The focus on the poorest increased homogeneity of the study

population and thus reduced the likelihood of detecting a difference if it existed in behaviour between rural and urban households or in different income classes in the rural areas.

Study power - In the design of studies I and III stratified sampling was conducted in order to capture diversity in geographical location and type of action taken in the respective studies. However, in the calculation of sample size we did not consider analysis within the stratum. This might have compromised the power of the studies (I, III) to detect a difference within stratum, if it existed.

Study generalization – Random selection was performed in all studies (I-IV) to ensure generalization of the study findings. However, Study II enrolled children who attended health facilities thus reducing the probability of recruiting those not utilizing care from health facilities. Since the study aimed at determining adherence to ALu and the drug was available only in health facilities, generalization to the whole population was not intended.

Loss to follow up – In Study III, loss to follow up was higher among those who went to traditional healers. This reduced the ability of the study to analyse data using this population group.

Self reporting and recall- Self reporting has the advantage of obtaining responses in a direct and versatile way (Denzil and Lincoln, 2000). However, it has the disadvantage of being subjective and demonstrates problems concerned with recall (Nwanyanwu et al., 1996, Roberts et al., 1996) especially for topics that are sensitive and stretch over a long period. The issue of accessing care and administration of drugs are less sensitive. The outcome variable in study I, and to some extent study II, was determined through caretakers' report. The accuracy of measurements in these studies therefore depended on the ability of the caretaker to recall events. In studies I and II the questionnaire was administered within an average period of one week in order to minimise the recall period to enable the collection of detailed data. It has however been argued that two weeks is optimal because it balances between extracting unnecessary detail and forgetting the necessary detail (Freij et al., 1977). The fact that less than 10% of the febrile children in study I were taken for care outside home shows that they were serious enough to require attention. In study II details about how drugs were administered was needed and this required a shorter recall period than two weeks (Roberts et al., 1996). When interviewing caretakers there is usually an urge on their side to provide socially desirable responses. We tried to minimize this by making clear to the caretakers the objectives of the studies prior to the interviews. Recalling detailed information about how the drug was administered after seven days, might result in data inaccuracy as some details might be forgotten. While in study I and II caretakers were asked to recall events that occurred in the past seven days, in study III the ranges were wider, that is, between 3 months and three years. The amount of detail required was more in study II where caretakers were expected to recall information on food intake between one to six days prior to interview. However, caretakers are reported to pay more attention to a sick child than other members of the household, this might have improved the recall of events. Recall was minimized in study III by using some of the data collected during the disease episode such as symptoms and action taken; and

adherence to referral advice verified using facility records. The fact that rectal administration of modern medicine is a rare event in the community might also have contributed to better recall by caretakers.

Use of community health workers in data collection

CHWs were used in data collection in study I. Since the majority had 7 years basic education, this might have compromised data accuracy. This limitation was compensated by training them for one-week followed by another week of pilot study. The weekly meeting with supervisors were also utilised to discuss and improve data quality.

7 CONCLUSIONS AND RECOMMENDATIONS

7.1 CONCLUSIONS

- Despite the high level of international and national level commitment and large funding coupled with pro-poor policies and strategies, prompt access to artemisinin-based combination therapy (ACTs) was quite low in rural remote areas where the burden is highest (I). Seeking care from a government facility was the overwhelming factor in accessing ALu promptly. Lack of prompt access was mainly attributed to receiving non-recommended drugs.
- The contribution of formal private facilities that had subsidized ALu was low because they were not easily reached by caretakers due to the relatively high cost of drugs at FBO facilities and most ADDOs were located in semi-urban areas (I).
- Since the majority of caretakers who sought care from the private sector went to ordinary shops, efforts to improve the low prompt access (I) should be made with caution, lest the high levels of adherence, hitherto attained (II), are compromised.
- Caretakers of children with altered consciousness and or convulsions and children who had not improved after pre-referral dose of rectal artesunate were more likely to adhere to referral advice (III), and less likely to go to traditional healers. Better caretakers' understanding about urgency and rationale for referral advice helped to overcome obstacles in accessing care from government facilities (I, III, IV).

7.2 RECOMMENDATIONS AND POLICY IMPLICATIONS

There is a need to prioritize, realign and reinforce implementation of pro-poor policies such as waiver for under fives, and improve access to government facilities to remote rural areas, in line with integrated Community Case Management (iCCM). Improving prompt access to ALu should be the first priority in the control of malaria because in addition to curing uncomplicated malaria this strategy reduces the number of cases of severe malaria. Most of the potential providers have several inadequacies in improving access to ALu in rural settings, including government facilities. However, the government, as the duty bearers for the health of the people, needs to strengthen its services to reach remote rural areas. The Government should also consider meeting operational costs for FBO facilities, especially, those located in areas where no government facility is accessible.

The government strategy to reach remote rural areas through MMAM strategy that aims at having a dispensary in each village is unlikely to be accomplished before 2017, given the severe shortage in the health workforce. Yet, the RBM Partnership malaria control goals of universal coverage with ACTs and reducing malaria mortality to near zero, have to be attained by 2015. Mainstreaming CHWs as a cadre in the health system will not only be a temporary solution to reaching rural communities, but will also serve

as a long term solution to linking the formal health care services with the community, thus fostering community participation in preventive services, which was the primary goal of introducing CHWs. Reintroduction of CHWs should be preceded with an outlining mechanism for their career path, technical support and remuneration, which have been the major problem in their sustenance. Their scope of work should be matched to that of integrated Community Case Management (iCCM) where CHW are trained to treat three major killer diseases that is malaria, pneumonia and diarrhoea.

Given that ordinary shops are second to government facilities as a major source of drugs in remote rural areas, efforts to increase prompt access to ALu in these settings should be matched with efforts to curb indiscriminate distribution and dispensing of the drug. This is on the understanding that once resistance sets in, it will compromise prompt access thus forming a vicious cycle. Regulatory bodies should be supported to improve capacity to reach drug outlets in the whole country and should also be challenged by the government to apply sanctions where regulations are breached, through a checks-and-balance system.

While there is need to urgently introduce rectal artesunate as a strategy to reduce malaria mortality, the challenge will be to deal with some caretakers whose children had less severe symptoms prior to or improved after pre-referral treatment. Since no further care was sought by caretakers once the child improved, this might indicate that the fever was self limiting, perhaps of viral origin. Nevertheless, there will still be a need to address the misunderstanding and misconceptions on the reasons for referral and its urgency through a strong and sustained communication strategy to ensure peoples' understanding on the rationale for referral.

8 ACKNOWLEDGEMENTS

The production of this thesis will not have been possible if not for the support of a number of people who contributed in various ways to make it happen. Since the space does not allow mentioning all of them in person, I wish to convey my sincere gratitude to each one of them for the part they played in the course of pursuing research work until the final stage.

I wish to thank all the children, their mothers and fathers who volunteered their precious time to participate in the group discussions and individual interviews that formed the basis of this research work.

I wish to convey special thanks to my supervisors: Max Petzold, for the guidance you gave me to the last minute of constructing this thesis. Through your assistance I was able to design the studies and perform all the necessary statistical analysis in my PhD work. Thank you Goran Tomson, for bringing me on board this PhD journey; and always reminding me of my position 'on the driver's seat'. Your critical and encouraging comments based on your vast experience on health systems research at a global level, are behind the success of this work. I wish to thank Zul Premji, for also bringing me on board and giving me the necessary support at the most opportune time, when options seemed to be exhausted. Your extensive knowledge and experience in malaria research helped to shape this thesis. Thank you Marian, for enduring your tight working schedules to accommodate my constant demands for timeliness. Thank you for being instrumental from the inception of my PhD work, especially with the referral and prompt access to artemisinin-based combination therapy studies, and for all the guidance you provided me in the malaria context. To all the supervisors, I say thank you, together, we have made it.

I wish to thank my mentor: Amos Massele, for giving me all the logistic and administrative support I needed in the course of my PhD studies. Your fatherly approach in dealing with contentious issues is worth emulating.

Thank to Sida/SAREC for sponsoring my PhD study, including travelling and living expenses while in Sweden and for the support to the Muhimbili University / Karolinska Institutet Malaria Project on which my studies were based. Thanks also to the Muhimbili University for giving me this study opportunity and supporting me financially while pursuing my studies.

I wish to thank my co-authors; Deodatus C. V. Kakoko, Melba Gomes, Omari Kimbute, Zena Machinda, Eva Johansson, Zakayo Mrango, Lars L. Gustafsson and Margarita Mahindi to whom we shared great moments in the scientific ups and downs which made research work quite interesting. Special thanks to Melba Gomes for your contribution in the design of the referral studies and assisting me to the end of my PhD thesis.

I wish to convey my heartfelt gratitude to Annika Janson for being ready to share with me your ideas from the initial design of my studies. With your on the ground

experience, I was able to avoid, to a great extent, learning through mistakes. I will always remember the tour you took me on around Stockholm historical sites.

Thank you Anita Osborn and Said Aboud, for always being around to help me with accommodation arrangements in Stockholm, during difficult moments.

Thanks to my fellow team members in the Malaria group at MUHAS, to whom I shared some of the ideas in these studies; Marcelina Mubi, Billy Ngassala and Omari Minzi; to the drivers, who took us through the rough terrains of Uponera, Lumbiji and Berega; Nico Peter and Omari; to data collectors for a job well done Mpunga, Daudi Katopola, Salum, Fransis Mulokozi, Joseph Shishira, Peter Mponeja, and Malekela; and to data entrants for your diligent work; Godfrey Mwakabole and Zabibu Mohammed.

Thanks to Andreas Martensson and Jaran Eriksen for your critical comments during my pre-defence and for reminding me of important issues to add in my thesis.

Thanks to my colleagues at the Department of Community Health who persevered with my absence during the course of my studies; David Urassa, Anna Kessy, Felix Kisanga and Gernard Msamanga; not forgetting the supporting staff Teemba, Jamila and Mtimbila.

Thanks to Members of staff at IHCAR, members of the Health Systems Research groups and colleagues at IHCAR for sharing ideas during formal meetings and informal encounters.

Thanks to my Dear wife Sara for enduring my absence even when I was at home, and my family, for your understanding on the rationale for my quest for further studies; Kalunde, Baraka, Amani and Hariri and not to forget; Zabibu, Ana-Maria, Joseph who are part of my extended family.

Thanks to my friends in Dar es Salaam, with whom, we turned dull moments interesting; Mkanga, Amina, Rogelius, Blandina, Elizabeth, Jerome, Katarina, Don and not forgetting my friends in Sweden who made my weekend enjoyable; Martin, Freddy, Kamala, Ngaimisi and Hizza.

Lastly, thanks to my parents Hadija (Kalunde), Hadija (Biti Abdallah) and Omari (the late) and Juma Daudi (the late) for the inspiration bestowed on me that took me to this stage. For the deceased, I say *Inna lillahi fainna Ilahi raajiuun*.

9 REFERENCES

- A/RES/55/2 (2000) United Nations Millennium Declaration: resolution adopted by the General Assembly. 55/2. Sept 18, 2000.
- Abdulla, S., Sagara, I., Borrman, S., D'Allesandro, U., Gonzalez, R., Hamel, M., Ogutu, B., Martensson, A., Lymo, J. & Maiga, H. (2008) Efficacy and safety of artemether-lumefantrine dispersible tablets compared with crushed commercial tablets in African infants and children with uncomplicated malaria: a randomised, single blind, multicentre trial. *Lancet*, 372, 1819-1827.
- Abeku, T., Kristan, M., Jones, C., Beard, J., Mueller, D., Okia, M., Rapuoda, B., Greenwood, B. & Cox, J. (2008) Determinants of the accuracy of rapid diagnostic tests in malaria case management: evidence from low and moderate transmission settings in the East African highlands *Malaria Journal*, 7, doi:10.1186/1475-2875-7-202.
- Agyepong, I., Ansah, E., Gyapong, M., Adjei, S., Barnish, G. & Evans, D. (2002) strategies to improve adherence to recommended chloroquine treatment regimes: a quasi-experiment in the context of integrated primary health care delivery in Ghana. *Social Science & Medicine*, 55, 2215-2226.
- Ajayi, I., Browne, E., Bateganya, F., Yar, D., Happi, C., Falade, C., Gbotosho, G., Yusuf, B., Boateng, S., Mugittu, K., Cousens, S., Nanyunja, M. & Pagnoni, F. (2008a) Effectiveness of artemisinin-based combination therapy used in the context of home management of malaria: A report from three study sites in sub-Saharan Africa. *Malaria Journal*, 7, doi:10.1186/1475-2875-7-190.
- Ajayi, I., Browne, E., Garshong, B., Bateganya, F., Yusuf, B., Agyei-Baffour, P., Doamekpor, L., Balyeku, A., Munguti, K., Cousens, S. & Pagnoni, F. (2008b) Feasibility and acceptability of artemisinin-based combination therapy for the home management of malaria in four African sites. *Malaria Journal*, 7.
- Amin, A., Marsh, V., Noor, A., Ochola, S. & Snow, R. (2003) The use of formal and informal curative services in the management of paediatric fevers in four districts in Kenya. *Tropical Medicine and International Health*, 8, 1143-1152
- Ansah, E., Gyapong, J., Agyepong, I. & Evans, D. (2001) Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. chloroquine syrup. *Tropical Medicine and International Health*, 6, 496-504.
- Awad M, Alkadru A, Behrens R, Baraka, O, & Eltayib, I. (2003) Descriptive study on the efficacy and safety of artesunate suppository in combination with other antimalarials in the treatment of severe malaria in Sudan. *American Journal of Tropical Medicine and Hygiene*, 68, 153-158.
- Barnes, K., Durrheim, D., Little, F., Jackson, A., Mehta, U., Allen, E., Dlamini, S., Tsoka, J., Bredenkamp, B. & Mthembu, D. (2005) Effect of artemether-lumefantrine policy and improved vector control on malaria burden in KwaZulu-Natal, South Africa. *PLoS Medicine*, 2, e330.
- Becerra-Posada, F., Berwick, D., Bhutta, Z., Chowdhury, M., de Savigny, D., Haines, A., Lavis, J., Lumbiganon, P., Mills, A., Mshinda, H., Narayan, R., Oxman, A., Sanders, D., Sewankambo, N., Tomson, G. & Victora, V. (2004) Informed choice for attaining the Millennium Development Goals: towards an international cooperative agenda for health systems research. *Lancet*, 364, 997-1003.
- Beer, N., Ali, A., Rotllant, G., Abass, A., Omari, R., Al-mafazy, A., Bjorkman, A. & Ka'llander, K. (2009) Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. *Tropical Medicine and International Health*, 14, 766-774.
- Bell, D., Wootton, D., Mukaka, M. & Montgomery, J. (2009) Measurement of adherence, drug concentrations and the effectiveness of artemether-lumefantrine, chlorproguanil-dapsone or sulphadoxine-pyrimethamine in the treatment of uncomplicated malaria in Malawi. *Malaria Journal*, 8, doi:10.1186/1475-2875-8-204.
- Bergqvist, Y., Hjelm, E. & Rombo, L. (1987) Sulfadoxine assay using capillary blood samples dried on filter paper - suitable for monitoring of blood concentration in the field. *Therapeutic Drug Monitor*, 9 203-207.

- Bjorkman, A. & Bhattarai, A. (2005) Public health impact of drug resistant Plasmodium falciparum malaria. *Acta Tropica*, 94, 163-169.
- Bjorkman, A. & Martensson, A. (2010) Risk and benefits of targeted malaria treatment based on Rapid Diagnostic Test results. Editorial commentary. *Clinical Infectious Disease*.
- Bowling, A. (2002) *Research Methods in Health*, Buckingham, Philadelphia, University Press.
- Breman, J. (2001) The ears of hippopotamus: manifestations, determinants, and estimates of the malaria burden. *American Journal of Tropical Medicine and Hygiene* 64, 1-11.
- Brieger, W., Sesay, H., Adesina, H., Mosanya, M., Ogunlade, P., Ayodele, J. & Orisasona, S. (2001) Urban malaria treatment behaviour in the context of low levels of malaria transmission in Lagos, Nigeria. *African Journal of Medical Science*, 30, 7-15.
- Bruce-Chwatt, L. (1986) *Chemotherapy of malaria*, Geneva, World Health Organization.
- Brugha, R., Chandramohan, D. & Zwi, A. (1999) Viewpoint: management of malaria - working with the private sector. *Tropical Medicine and International Health*, 4, 402-406.
- Buchan, J. & Sochalski, J. (2004) The migration of nurses: Trends and policies. *Bulletin of the World Health Organization*, 589.
- Chuma, J., Abuya, T., Memusi, D., Juma, E., Akhwale, W., Ntwiga, J., Nyandigisi, A., Tetteh, G., Shretta, R. & Amin, A. (2009) Reviewing the literature on access to prompt and effective malaria treatment in Kenya: implications for meeting the Abuja targets. *Malaria Journal*, 8, doi:10.1186/1475-2875-8-243.
- Corell, J. (1995) Group interview methods in community health research. *Medical Anthropology*, 16, 193-210.
- Cresswell, J. (2007) *Qualitative inquiry and research design: choosing among five approaches*, California, Sage.
- d'Acremont, V., Malila, A., Swai, N., Tillya, R., Kahama-Marro, J., Lengeler, C. & Genton, B. (2010) Withholding antimalarials in febrile children who have a negative result for a Rapid Diagnostic Test. *Clinical Infectious Diseases*, 51, 000-000.
- de Savigny, D., Mayombana, C., Mwangeni, E., Masanja, H., Minhaj, A., Mkilindi, Y., Mbuya, C., Kasale, H. & Reid, G. (2004) Care-seeking patterns for fatal malaria in Tanzania. *Malaria Journal*, 3, doi:10.1186/1475-2875-3-27.
- de Zoysa, I., Bhandari, N., Akhtari, N. & Bhan, M. (1998) Care-seeking for illness in young infants in an urban slum in India. *Social Science and Medicine*, 47, 2101-14.
- Debas, H. (2010) Global Health: priority agenda for the 21st Century. http://www.un.org:80/wcm/content/site/chronicle/lang/en/home/archive/issues2010/achieving_global_health/. Accessed 28 October 2010
- Denzil, N. & Lincoln, Y. (2000) *Handbook of qualitative research*, London and New Delhi.
- Dondorp, A., Yeung, S., White, L., Nguon, C., Day, N., Socheat, D. & von Seidlein, L. (2010) Artemisinin resistance: current status and scenarios for containment. *Nature Reviews Microbiology*, doi:10.1038/nrmicro2331.
- Drakeley, C. & Reyburn, H. (2009) Out with the old, in with the new: the utility of rapid diagnostic tests for malaria diagnosis in Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 103, 333-337.
- Eriksen, J., Nsimba, S., Minzi, O., Sanga, A., Petzoid, M., Gustafsson, L., Warsame, M. & Tomson, G. (2005) Adoption of the new antimalarial drug policy in Tanzania - a cross-sectional study in the community. *Tropical Medicine and International Health*, 10, 1038-1046
- Filmer, D. & Pritchett, L. (2001) Estimating Wealth Effects without Expenditure Data - or Tears: An application to educational enrolments in states of India. *Demography*, 38, 115-132.
- Fogg, C., Bajunirwe, F., Piola, P., Biraro, S., Checchi, F., Kiguli, J., Namiro, P., Musabe, J., Kyomugisha, A. & Guthmann, J. (2004) Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated

- plasmodium falciparum malaria in Uganda. *American Journal of Tropical Medicine and Hygiene*, 71, 525-530.
- Font, F., Quinto, L., Masanja, H., Nathan, R., Ascaso, C., Memnendez, C., Turner, M., Schellenberg, J. & Alonso, P. (2002) Paediatric referrals in rural Tanzania: the Kilombero District study - a case series. *BMC International Health and Human Rights*, 2.
- Freij, L., Nystron, L. & Walls, S. (1977) Exploring child health in ecology. *Scandinavian Journal of Social Medicine*, 12, 1-9.
- Friedman, E. (2004) An action plan to prevent brain drain: Building equitable health systems in Africa. A report by physicians for human rights. <http://www.phrusa.org/publications/aids.html#braindrain>. Accessed 22 October 2010.
- Gerein, N., Green, A. & Pearson, S. (2006) The implications of shortages of health professionals for maternal health in Sub-Saharan Africa. *Reproductive Health Matters*, 14, 40-50.
- GFATM (2010) [http://www.theglobalfund.org/en/pressreleases/?pr=pr_101005c]. Accessed on 22 October 2010.
- Gitonga, C., Amin, A., Ajanga, A., Kangwana, B., Noor, A. & R, S. (2008) The use of artemether-lumefantrine by febrile children following national implementation of a revised drug policy in Kenya. *Tropical Medicine and International Health*, 13, 487-494.
- Gomes, M., Faiz, M., Gyapong, J., Warsame, M., Agbenyega, T. & Babiker, A. (2008) Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. *Lancet*, 373, 557-566.
- Gomes, M., Wayling, S. & Pang, L. (1998) Interventions to improve the use of antimalarials in South-East Asia: an overview. *Bulletin of the World Health Organisation*, 76, 9-19.
- Goodman, C., Kachur, P., Abdulla, S., Bloland, P. & Mills, A. (2007) Drug shop regulation and malaria treatment in Tanzania—why do shops break the rules, and does it matter? *Health Policy and Planning*, doi:10.1093/heapol/czm0331.
- Goodman, C., Kachur, S., Abdulla, S., Bloland, P. & Mills, A. (2009) Concentration and drug prices in the retail market for malaria treatment in rural Tanzania. *Health Economics*, 18, 727-742.
- Goodman, C., Kachur, S., Abdulla, S., Mwangeni, E., Nyoni, J. & Schellenberg, J. (2004) Retail supply of malaria-related drugs in rural Tanzania: risks and opportunities. *Tropical Medicine and International Health*, 9 655-663.
- Goodman, C., WM., M., Baya, E., Willetts, A. & Marsh, V. (2006) The cost-effectiveness of improving malaria home management: shopkeeper training in rural Kenya. *Tropical Medicine and International Health*, 276-88.
- Graneheim, U. & Lundman, B. (2004) Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Education Today*, 24, 105-112.
- Guerra, C., Gikandi, P. & Tatem, A. (2008) The limits and intensity of Plasmodium falciparum transmission: implications for malaria control and elimination worldwide. *PLoS Medicine*, 5, e38.
- Haines, A., Sanders, D., Lehmann, U., Rowe, A., Lawn, J., Jan, S., Walker, D. & Bhutta, Z. (2007) Achieving child survival goals: potential contribution of community health workers. *Lancet*, 369, 2121-31.
- Hamer, D., Ndhlovu, M., Zurovac, D., Fox, M., Yeboah-Antwi, K., Chanda, P., Sipilinyambe, N., Simon, J. & Snow, R. (2007) Improved diagnostic testing and malaria treatment practices in Zambia. *Journal of American Medical Association*, 297, 2227-2231.
- Haque, N. & Aziz, J. (1998) The quality of governance: “second-generation” civil service reform in Africa, Washington, DC, USA: International Monetary Fund, 1998. <http://www.imf.org/external/pubs/CAT/doctext.cfm?docno=WPIEA1641998> Accessed 22 October 2010.
- Heggenhougen, K., Muhondwa, E. & Rutabanzibwa-Ngaiza, J. (1987) *Community Health Workers The Tanzanian Experience*, Oxford University Press.

- Hermann, K., Van-Damme, W., Pariyo, G., Schouten, E., Assefa, Y., Cirera, A. & Massavon, W. (2009) Community health workers for ART in sub-Saharan Africa: learning from experience--capitalizing on new opportunities. *Human Resource for Health*, 9, 31.
- Hetzel, M., Alba, S., Fankhauser, M., Mayumana, I., Lengeler, C., Obrist, B., Nathan, R., Makemba, A., Mshana, C., Schulze, A. & Mshinda, H. (2008) Malaria risk and access to prevention and treatment in the paddies of the Kilombero Valley, Tanzania. *Malaria Journal* 7.
- Hetzel, M., Msechu, J., Goodman, C., Lengeler, C., Obrist, B., Kachur, P., Makemba, A., Nathan, R., Schulze, A. & Mshinda, H. (2006) Decreased availability of antimalarials in the private sector following the policy change from chloroquine to sulphadoxine-pyrimethamine in the Kilombero Valley, Tanzania. *Malaria Journal*, 5, doi:10.1186/1475-2875-5-109.
- Hildenwall, H., Rutebemberwa, E., Nsabagasani, X., Pariyo, G., Tomson, G. & Peterson, S. (2007) Local illness concepts-implications for management of childhood pneumonia in eastern Uganda. *Acta Tropica*, 101, 217-224.
- Hinton, R., Auwun, A., Pongua, G. & Davis, M. (2007) Caregivers' acceptance of using artesunate suppositories for treating child malaria in Papua New Guinea. *American Journal of Tropical Medicine and Hygiene*, 76, 634-640.
- Holtz, T., Kachur, S., Marum, L., C., M., N., C., Roberts, J., Macheso, A. & Parise, M. (2003) Care seeking behaviour and treatment of febrile illness in children aged less than five years: a household survey in Blantyre District, Malawi. *Transaction of the Royal Society of Tropical Medicine and Hygiene*, 97, 491-497.
- Hongoro, C. & Kumaranayake, L. (2000) Do they work? Regulating for-profit providers in Zimbabwe. *Health Policy and Planning*, 15, 368-77.
- Hopkins, H., Kambale, W., Kanya, M., Staedke, S., Dorsey, G. & Rosenthal, P. (2007) Comparison of HRP2- and pLDH-based rapid diagnostic tests for malaria with longitudinal follow-up in Kampala, Uganda. *American Journal of Tropical Medicine and Hygiene*, 76, 1092-1097.
- Hsu, E. (2006) Reflections on the 'discovery' of the antimalarial qinghao. *British Journal of Clinical Pharmacology*, 61, 666-70.
- IMF (2010) International Monetary Fund Website. <http://www.imf.org/external/> Accessed 03 November 2010.
- Jones, K., Donegan, S. & Lalloo, D. (2007) Artesunate versus quinine for treating severe malaria (Review). *Cochrane Database of Systematic Reviews*, 4, Art. No.: CD005967. DOI: 10.1002/14651858.CD005967.pub2.
- Jong-wook, L. (2003) Global health improvement and WHO: shaping the future. *Lancet*, 362, 2083-88.
- Kabanywanyi, A., Lengeler, C., Kasim, P., King'eng'ena, S., Schlienger, R., Mulure, N. & Genton, B. (2010) Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania. *Malaria Journal*, 9, doi:10.1186/1475-2875-9-48.
- Kallander, K., Nsungwa-Sabiiti, J. & Peterson, S. (2004) Symptom overlap for malaria and pneumonia-policy implications for home management strategies. *Acta Tropica*, 90, 211-214.
- Kalter, H., Salgado, R., Moulton, L., Nieto, P., Contreras, A., Egas, M. & Black, R. (2003) Factors constraining adherence to referral advice for severely ill children managed by the Integrated Management of Childhood Illness approach in Imbabura Province, Ecuador. *Acta Paediatrica*, 92, 103-110.
- Karamagi, C., Lubanga, R., Kiguli, S., Ekwaru, P. & Heggenhougen, K. (2004) Health providers' counselling of caregivers in the Integrated Management of Childhood Illness (IMCI) Programme in Uganda. *African Health Science*, 4, 31-29.
- Kazembe, L., Appleton, C. & Kleinschmidt, I. (2007) Choice of treatment for fever at household level in Malawi: examining spatial patterns. *Malaria Journal*, 6, doi:10.1186/1475-2875-6-40.
- Kironde, S. & Klaasen, S. (2002) What motivates lay volunteers in high burden but resource-limited tuberculosis control programmes? Perceptions from the Northern Cape province. *South Africa. International Journal of Tuberculosis and Lung Disease*, 6, 104-110.

- Krause, G. & Sauerborn, R. (2000) Comprehensive community effectiveness of health care. A study of malaria treatment in children and adults in rural Burkina Faso. *Annals of Tropical Paediatrics*, 20, 273-282.
- Kroeger, A. (1985) Response errors and other problems of health interview surveys in developing countries. *World Health Statistics Quarterly*, 38, 15-37.
- Kumaranayake, L., Hongoro, C., Lake, S., Mujinja, P. & Mpenbeni, R. (1997) Coping with private health markets - regulatory effectiveness in sub-Saharan Africa [Unpublished].
- Kurowski, C., Wyss, K. & Abdulla, S. (2004) Human resources for health: requirements and availability in the context of scaling up priority interventions in low-income countries. Case studies from Tanzania and Chad. HEFP Working Paper 01/04. London7 London School of Hygiene and Tropical Medicine.
- Lefèvre, G., Looareesuwan, S., Treeprasertsuk, S., Krudsood, S., Silachamroon, U., Gathmann, I., Mull, R. & Bakshi, R. (2001) 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*, 64, 247-256.
- Lienert, I. & Modi, J. (1997) A decade of civil service reform in sub-Saharan Africa. Washington, DC, USA: International Monetary Fund, 1997.
<http://www.imf.org/external/pubs/cat/longres.cfm?sk=2453.0>. Accessed 22 October 2010.
- Lindstrand, A., Bergstrom, S., Rosling, H., Rubenson, B., Stenson, B. & Tylleskar, T. (2006) *Global Health: An introductory textbook*, Narayana Press.
- Lubell, Y., Reyburn, H., Mbakilwa, H., Mwangi, R., Chonya, K., Whitty, C. & Mills, A. (2007) The cost-effectiveness of parasitologic diagnosis for malaria-suspected patients in an era of combination therapy. *American Journal of Tropical Medicine and Hygiene*, 77, 128-132.
- Makanga, M., Premji, Z., Falade, C., Karbwang, J., Mueller, E., Andriano, K., Hunt, P. & De Palacios, P. (2006) Efficacy and safety of the six-dose regimen of artemether-lumefantrine in pediatrics with uncomplicated plasmodium falciparum malaria: a pooled analysis of individual patient data. *The American Society of Tropical Medicine and Hygiene*, 74, 991-998.
- Makemba, A., Winch, P., Makame, V., Mehl, G., Premji, Z., Minjas, J. & Shiff, C. (1996) Treatment practices for degedege, a locally recognized febrile illness and implications for strategies to decrease mortality from severe malaria in Bagamoyo District, Tanzania. *Tropical Medicine and International Health*, 1, 305-313.
- Malaria-Website (2010) http://www.malariasite.com/malaria/history_control.htm. Accessed 28 October 2010.
- Malenga, G., Palmer, A., Staedke, S. & Kazadi, W. (2005) Antimalarial treatment with artemisinin combination therapy in Africa. *British Medical Journal*, 331, 706-707doi:10.1136/bmj.331.7519.706.
- Manongi, R., Marchant, T. & Bygbjerg, C. (2006) Improving motivation among primary health care workers in Tanzania: a health worker perspective. *Human Resources for Health*, 4, doi:10.1186/1478-4491-4-6.
- Marsh, K. (1998) Malaria disaster in Africa. *Lancet*, 352 924-925.
- Marsh, V., Mutemi, W., Muturi, J., Haaland, A., Watkins, W., Otieno, G. & Marsh, K. (1999) Changing home treatment of childhood fevers by training shop keepers in rural Kenya. *Tropical Medicine and International Health*, 4, 383-9.
- Mayxay, M., Newton, P., Yeung, S., Pongvongsa, T., Phompida, S., Phetsouvanh, R. & White, N. (2004) Short communication: An assessment of the use of malaria rapid tests by village health volunteers in rural Laos. *Tropical Medicine and International Health*, 9, 325-329.
- McCoy, D., Bennett, S., Witter, S., Pond, B., Baker, B., Gow, J., Chand, S., Ensor, T. & McPake, B. (2008) Salaries and incomes of health workers in sub-Saharan Africa. *Lancet*, 371, 675-81.
- MOH&SW (1994) Tanzania health sector reforms: Proposal.
- MoH&SW (2002) Tanzania national health policy.
- MoH&SW (2004) Tanzania quality improvement framework (TQIF).

- MoH&SW (2006) Tanzania national guidelines for malaria diagnosis and treatment 2006. Malaria control series 11.
- MoH&SW (2007a) Joint external evaluation: the health sector in Tanzania, 1999-2006. Dar es Salaam.
- MoH&SW (2007b) Tanzania national malaria medium term strategic plan (NMMTSP).
- MoH&SW (2007c) Tanzania primary health services development programme-MMAM 2007 – 2017.
- MoH&SW (2008a) Annual health statistical abstract: Tanzania mainland 2008.
- MoH&SW (2008b) Tanzania health sector performance profile 2008.
- MoH&SW (2009a) Tanzania health sector performance profile report 2009 Update: Mainland Tanzania July 2008 – June 2009.
- MoH&SW (2009b) Tanzania joint annual health sector review: Technical review September 2009. HSSP III and CCHP Planning 2010.
- Moon, S., Casas, C., Kindermans, J., de Smet, M. & von Schoen-Angerer, T. (2009) Focusing on quality patient care in the new global subsidy for malaria medicines. *PLoS Medicine*, 6, e1000106.
- Mubi, M., Janson, A., Warsame, M., Mårtensson, A., Källander, K., Petzold, M., Ngasala, B., Gustafsson, L., Masseur, A., Tomson, G., Premji, Z. & Björkman, A. (2010) Malaria rapid diagnostic testing by community health workers is effective and safe for targeting artemisinin-based combination therapy: a community-based randomised cross-over trial in rural Tanzania. *Submitted*.
- Mubyazi, G. & Gonzalez-Block, M. (2005) Research influence on antimalarial drug policy change in Tanzania: case study of replacing chloroquine with sulfadoxine-pyrimethamine as the first-line drug. *Malaria Journal*, 4, doi:10.1186/1475-2875-4-51.
- Mukanga, D., Tibenderana, J., Kiguli, J., Pariyo, G., Waiswa, P., Bajunirwe, F., Mutamba4, B., Counihan, H., Ojiambo, G. & Kallander, K. (2010) Community acceptability of use of rapid diagnostic tests for malaria by community health workers in Uganda. *Malaria Journal*, 9.
- Narasimhan, V., Brown, H., Pablos-Mendez, A., Adams, O., Dussault, G., Elzinga, G., Nordstrom, A., Habte, D., Jacobs, M., Solimano, G., Sewankambo, N., Wibulpolprasert, S., Evans, T. & Chen, L. (2004) Responding to the global human resources crisis. *Lancet*, 363, 1469-1472.
- National-Bureau-of-Statistics (1996) Tanzania demographic health survey 1996. Dar es Salaam.
- National-Bureau-of-Statistics (2002) Household budget survey. In President's Office (Ed.), National Bureau of Statistics, Tanzania.
- National-Bureau-of-Statistics (2005) The Tanzania demographic and health survey (TDHS) 2004-05
- National-Bureau-of-Statistics (2006) Tanzania national projections Vol. XII based of 2002 Census. National Bureau of Statistics – Mainland and Chief Government Statistician – Zanzibar. Nov 2006.
- National-Bureau-of-Statistics (2010) Tanzania demographic and health survey 2010. Preliminary report.
- Ngasala, B., Mubi, M., Warsame, M., Petzold, M., Masseur, A., Gustafsson, L., Tomson, G., Premji, Z. & Björkman, A. (2008) 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*, 7, doi:10.1186/1475-2875-7-199.
- Njama-Meya, D., Clark, T., Nzarubara, B., Staedke, S., Kamya, M. & Dorsey, G. (2007) Treatment of malaria restricted to laboratory-confirmed cases: a prospective cohort study in Ugandan children. *Malaria Journal*, 6.
- Njau, J., Goodman, C., Kachur, S., Palmer, N., Khatib, R., Abdulla, S., Mills, A. & Bloland, P. (2006) Fever treatment and household wealth: the challenge posed for rolling out combination therapy for malaria. *Tropical Medicine and International Health*, 11, doi:10.1111/j.1365-3156.01569.x.
- Noedl, H., Se, Y., Schaefer, K., Smith, B., Socheat, D. & Fukuda, M. (2008) Evidence of Artemisinin-Resistant Malaria in Western Cambodia. *The New England Journal of Medicine*, 359, 2619-2620.

- Nsimba, S. E., Massele, A. Y., Eriksen, J., Gustafsson, L. L., Tomson, G. & Warsame, M. (2002) Case management of malaria in under-fives at primary health care facilities in a Tanzanian district. *Tropical Medicine and International Health*, 7, 201-9.
- Nsungwa-Sabiiti, J., Kallander, K., Nsabagani, X., Namusisi, K., Pariyo, G., Johansson, A., Tomson, G. & Petersen, S. (2004) Local fever illness classifications: implications for home management of malaria strategies. *Tropical Medicine and International Health*, 9, 1191-1199.
- Nsungwa-Sabiiti, J., Peterson, S., Pariyo, G., Ogwal-Okenga, J., Petzold, M. & Tomson, G. (2007) Home-based management of fever and malaria treatment practices in Uganda. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 101, 1199-1207.
- Nsungwa-Sabiiti, J., Tomson, G., Pariyo, G., Ogwal-Okeng, J. & Peterson, S. (2005) Community effectiveness of malaria treatment in Uganda - a long way to Abuja targets. *Annals of Tropical Paediatrics*. 25, 89-98.
- Ntale, M., Ogwal-Okenga, J., Mahindi, M., Gustafsson, L. & Beck, O. (2008) A field-adapted sampling and HPLC quantification method for lumefantrine and its desbutyl metabolite in whole blood spotted on filter paper. *Journal of Chromatography B*, doi:10.1016/j.jchromb.2008.11.002.
- Nwanyanwu, O., Redd, S., Ziba, C., Luby, S., Mount, D., Franco, C., Nyasulu, Y. & Chitsulo, L. (1996) Validity of mother's history regarding antimalarial drug use in Malawian children under five years old. *Transaction of the royal society of tropical medicine and hygiene*, 90, 6648.
- Nyamongo, I. (1999) Home case management of malaria: an ethnographic study of lay people's classification of drugs in Suneka Division, Kenya. *Tropical Medicine and International Health*, 4, 736-743.
- Okeke (2010) Improving malaria recognition, treatment and referral practices by training caretakers in rural Nigeria. *Journal of Biosocial Sciences*, 42, 325-339.
- Onwujekwe, O., Uzochukwu, B., Ojukwu, J., Dike, N. & Shub, E. (2007) Feasibility of a community health worker strategy for providing near and appropriate treatment of malaria in southeast Nigeria: An analysis of activities, costs and outcomes. *Acta Tropica*, 101, 95-105.
- Pagnoni, F. (2009) Malaria treatment: no place like home. *Trends in Parasitology*, 25, 115-119.
- Pagnoni, F., Convelbo, N., Tiendrebeogo, J., Cousens, S. & Esposito, F. (1997) A community-based programme to provide prompt and adequate treatment of presumptive malaria in children. *Transaction of the royal society of tropical medicine and hygiene*, 91, 512-517.
- Patouillard, E., Hanson, K. & Goodman, C. (2010) Retail sector distribution chains for malaria treatment in the developing world: a review of the literature. *Malaria Journal*, 9, doi:10.1186/1475-2875-9-50.
- Petterson, S., Nsungwa-Sabiiti, J., Were, W., Nsabagasani, X., Magumba, G., Namboozee, J. & Mukasa, G. (2004) Coping with paediatric referral-Ugandan parents' experience. *Lancet*, 363, 1955-1956.
- Piola, P., Fogg, C., Bajumirwe, F., Biraro, S., Grandessa, F., Ruzagira, E., Babigumira, J., Kigozi, I., Kiguli, J., Kyomuhendo, J., Ferradini, L., Taylor, W., Checchi, F. & Guthmann, J. (2005) Supervised versus unsupervised intake of six-dose artemether-lumefantrine for treatment of acute, uncomplicated Plasmodium falciparum malaria in Mbarara, Uganda: a randomized trial. *Lancet*, 365, 1467-73.
- Price, R., Uhlemann, A., van, V., Brockman, A., Hutagalung, R., Nair, S., Nash, D., Singhasivanon, P., Anderson, T., Krishna, S., White, N. & Nosten, F. (2006) Molecular and pharmacological determinants of the therapeutic response to artemether-lumefantrine in multidrug-resistant Plasmodium falciparum malaria. *Clinical Infectious Disease*, 42, 1570-1577.
- RBM-Partnership (2007) Affordable Medicines Facility – malaria (AMFm) technical design. <http://rbm.who.int/partnership/tf/globalsubsidy/AMFmTechProposal.pdf>. Accessed 02 November 2010.

- RBM-Partnership (2008a) The global malaria action plan. Roll Back Malaria, 2008. <http://www.rbm.who.int/gmap/gmap.pdf>. Accessed 28 October 2010
- RBM-Partnership (2008b) RBM Partnership operating framework. RBM/BOA/2008/DEC.2. New Delhi.
- Reyburn, H., Mbakilwa, H., Mwangi, R., Mwerinde, O., Olomi, R., Drakeley, C. & Whitty, C. (2007) Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial. *British Medical Journal*, 334.
- Ricketts, T. & Goldsmith, L. (2005) Access in health services research: The battle of the frameworks. *Nursing Outlook*, 53, 274-280.
- Riley, P., Anderson, B., Noguchi, L. & Vindigni, S. (2005) Caring for global caregivers: a call to action. *Journal of midwifery and women's health*, 50, 265-268.
- Roberts, R., Bergstralh, E., Schmittz, L. & Jacobson, S. (1996) Comparison of self-reported and medical records healthcare utilization measures. *Journal of Clinical Epidemiology*, 48, 989-95.
- Robson, C. (2003) *Real world research: a resource for social scientists and practitioner researchers*, Oxford Blackwell Publishers.
- Roenen, C., Ferrinho, P., Van Dormael, M., Conceicao, M. & Van Lerberghe, W. (1997) How African doctors make ends meet: an exploration. *Tropical Medicine and International Health*, 2, 127-35.
- Roll-Back-Malaria-Partnership (2005) Global strategic plan Roll Back Malaria 2005-2015.
- Roll-Back-Malaria-Partnership (2008) The global malaria action plan for a malaria free world.
- Rowe, A., De-Savigny, D., Lanata, C. & Victoria, C. (2005) How can we achieve and maintain high-quality performance of health workers in low-resource settings? *Lancet*, 366, 1026-1035.
- Rutebemberwa, E., Kallander, K., Tomson, G., Peterson, S. & Pariyo, G. (2009a) Determinants of delay in care-seeking for febrile children in eastern Uganda. *Tropical Medicine and International Health*, 14 472-479.
- Rutebemberwa, E., Nsabagasani, X., Pariyo, G., Tomson, G., Peterson, S. & Kallander, K. (2009b) Use of drugs, perceived drug efficacy and preferred providers for febrile children: implications for home management of fever. *Malaria Journal*, 8, doi:10.1186/1475-2875-8-131.
- Rutebemberwa, E., Pariyo, G., Peterson, S., Tomson, G. & Kallander, K. (2009c) Utilization of public or private health care providers by febrile children after user fee removal in Uganda. *Malaria Journal*, 8, doi:10.1186/1475-2875-8-45.
- Sabot, O., Mwita, A., Cohen, J., Ipuge, Y., Gordon, M., Gordon, M., Bishop, D., Odhiambo, M., Ward, L. & Goodman, C. (2009) Piloting the global subsidy: the impact of subsidized artemisinin-based combination therapies distributed through private drug shops in rural Tanzania. *PLoS ONE*, 4, e6857. doi:10.1371/journal.pone.0006857.
- Schellenberg, J., Victora, C. & Mushi, A. (2003) Inequities among the very poor: health care for children in rural southern Tanzania. *Lancet*, 361, 561-66.
- Schiavo-Campo, S., de Tommaso, G. & Mukherjee, A. (1997) Government employment and pay in global perspective: a selective synthesis of international facts, policies and experience, World Bank Policy Research Working Paper 1806. 1997. <http://www.worldbank.org/html/dec/Publications/Workpapers/WPS1700series/wps1771/wps1771.html> Accessed 22 October 2010.
- Segall, M. (2003) District health systems in neo-liberal world: a review of five key policy areas. *International Journal for Equity in Health Policy and Planning*, 18, S5-26.
- Semali, I. (2003) Understanding stakeholders' roles in health sector reform process in Tanzania: the case of decentralizing the immunization program. Thesis. Universität Basel.
- Shillcutt, S., Morel, C., Goodman, C., Coleman, P., Bell, D., Whitty, C. & Mills, A. (2008) Cost-effectiveness of malaria diagnostic methods in sub-Saharan Africa

- in an era of combination therapy. *Bulletin of the World Health Organization*, 86, 101-110.
- Simba, D. & Mwangu, M. (2005) Quality of a routine data collection system for health: case of Kinondoni district in the Dar es Salaam region, Tanzania. *South African Journal of Information Management*. On line journal. <http://www.sajim.co.za> Accessed 17 October 2010
- Simoës, E., Peterson, S., Gamaie, Y., Fs., K., Mukasa, G., Nsungwa-Sabiiti, J., Were, M. & Weber, M. (2003) Management of severely ill children at first level health facility in sub-Saharan Africa when referral; is difficult. *Bulletin of the World Health Organisation*, 75, 43-53.
- Smith, L., Jones, C., Meek, S. & Webster, J. (2009) Review: Provider practice and user behavior interventions to improve prompt and effective treatment of malaria: Do we know what works? *Tropical Medicine and Hygiene*, 80, 326-335.
- Snow, R. W. & Guerra, C. A. (2005) The global distribution of clinical episodes of *Plasmodium falciparum* malaria. *Nature*, 434, 214-7.
- Soeters, R. & Griffiths, F. (2003) Improving government health services through contract management: a case from Cambodia. *Health Policy and Planning*, 18, 74-83.
- Swarthout, T., Counihan, H., Senga, R. & van Broek, I. (2007) Paracheck-Pf accuracy and recently treated *Plasmodium falciparum* infections: is there a risk of over-diagnosis? *Malaria Journal*, 6.
- Tanzania Commission for AIDS (TACAIDS), Zanzibar AIDS Commission (ZAC), National Bureau of Statistics (NBS), Office of the Chief Government Statistician (OCGS) & Macro International Inc (2008) Tanzania HIV/AIDS and malaria indicator survey 2007-08. Dar es Salaam.
- Tipke, M., Louis, V., Ye, M., De Allegri, M., Beiersmann, C., Sie, A., Mueller, O. & Jahn, A. (2009) Access to malaria treatment in young children of rural Burkina Faso. *Malaria Journal*, 8, doi:10.1186/1475-2875-8-266.
- Todd, J. (1979) Mixing qualitative and quantitative methods: triangulation in action. *Administrative Science Quarterly*, 602-11.
- Trape, J. (2001) The public health impact of chloroquine resistance in Africa. *American Journal of Tropical Medicine and Hygiene*, 64, 12-17.
- Travis, P., Bennett, S., Haines, A., Pang, T., Bhutta, Z., Hyder, A., Pielemeier, N., Mills, A. & Evans, T. (2004) Overcoming health-systems constraints to achieve the Millennium Development Goals. *Lancet*, 364, 900-906.
- UNDP (2008) <http://undp.org/en/reports/global/hdr2007-2008/> Accessed on 23 September 2010.
- UNICEF (1998) The state of the world's children 1998. Geneva.
- UNICEF (2010) The state of the world's children - special edition. Celebrating the 20 years of the convention of the rights of the child, UNICEF. Geneva.
- USAID (2009) President's Malaria Initiative. Year five. Financial year 2010. Malaria Operational Plan (MOP), Tanzania.
- van Vugt, M., Ezzet, F. & Phaipun, L. (1998) The relationship between capillary and venous concentrations of lumefantrine (benflumetol). *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 92, 564-5.
- van Vugt, M., Wilairatana, P., Gemperli, B., Gathmann, I., Phaipun, L., Brockman, A., Luxemburger, C., White, N., Nosten, F. & Looareesuwan, S. (1999) Efficacy of six doses of artemether-lumefantrine (benflumetol) in multidrug-resistant *Plasmodium falciparum* malaria. *American Journal of tropical Medicine and Hygiene*, 60, 936-942.
- Varkevisser, C., Pathmanathan, I. & Browiee, A. (1991) *Designing and conducting health systems research projects*, Ottawa.
- Viberg, N., Mijinja, P., Kalala, W., Kumaranayake, L., Vyas, S., Tomson, G. and Lundborg, S. (2009) STI management in Tanzania private drug stores - practices and roles of drug sellers. *Sexually Transmitted Infections*, doi:10.1136/sti.2008.032888
- Victora, C., Hanson, K., Bryce, J. & Vaughan, P. (2004) Achieving universal coverage with health interventions. *Lancet*, 364
- Warsame, M., Kimbute, O., Machinda, Z., Ruddy, P., Melkisedick, M., Peto, T., Ribeiro, I., Kitua, A., Tomson, G. & Gomes, M. (2007) Recognition,

perceptions and treatment practices for severe malaria in rural Tanzania: implications for accessing rectal artesunate as a pre-referral. *PLoS ONE*, 2, e149.

- White, N., van Vugt, M. & Ezzet, F. (1999) Clinical Pharmacokinetics and Pharmacodynamics of artemether-lumefantrine. *Clinical Pharmacokinetics*, 37, 105-125.
- WHO (2000) The world health report 2000. World Health Organisation. Geneva.
- WHO (2003) The world health report 2003 - shaping the future. World Health Organisation. Geneva.
- WHO (2006) Guidelines for the treatment of malaria, World Health Organisation. Geneva.
- WHO (2008) World malaria report 2008. World Health Organization, WHO/HTM/GMP/2008. (<http://www.who.int/malaria/wmr2008/malaria2008.pdf>). [Accessed 26 October 2010]
- WHO (2009) World malaria report. Geneva.
- WHO (2010a) Guidelines for the malaria treatment, second edition. Geneva.
- WHO (2010b) The WHO agenda. <http://www.who.int/about/agenda/en/index.html> Accessed 28 October 2010
- Williams, H. & Jones, C. (2004) A critical review of behavioral issues related to malaria control in sub-Saharan Africa: what contributions have social scientists made? *Social Science and Medicine*, 59, 501-23.
- Winch, P., Makemba, A. & Kamazima, S. (1996) Local terminology for febrile illnesses in Bagamoyo district, Tanzania and its impact on the design of a community-based malaria control programme. *Social Science and Medicine*, 42, 1057-1067.
- World-Bank (2008) World Bank development indicators 2008. <http://go.worldbank.org/5V41Z1WRL0> Accessed 23 September 2010.
- World-Bank (2010) <http://www1.worldbank.org/hnp/CHPS/chpsdefpvtctr.asp>. Accessed 22 October 2010.
- Yeung, S. & White, N. (2005) How do patients use antimalarial drugs? A review of the evidence. *Tropical Medicine and International Health*, 10, 121-138.
- Zeng, M., Lu, Z. & Yang, S. (1996) Determination of benflumetol in human plasma by reversed-phase high-performance liquid chromatography with ultraviolet detection. *Journal of Chromatography and Biomedical Application*, 681, 299-306.
- Zucker, J., Ruebush, T., Obonyo, C., Otieno, J. & Campbell, C. (2003) The mortality consequences of the continued use of chloroquine in Africa: experience in Siaya, western Kenya. *American Journal of Tropical Medicine and Hygiene*, 68, 386-390.