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

TARGETING MALARIA ELIMINATION:

AN ASSESSMENT OF MALARIA CONTROL INTERVENTIONS FOR CHILDREN IN ZANZIBAR

Netta Beer

Karolinska Institutet

Stockholm 2012

Cover photo: Khaalidat Mwinyi Msellem demonstrating how to use a long-lasting insecticidal net (not a study participant)

Published by Karolinska Institutet.
Printed by Larserics Digital Print AB

ISBN 978-91-7457-850-8

"Oh Mama Africa

so much love, so much spite;

so much happiness, so much sadness;

so rich, so poor;

so honest, so corrupt;

so much life, and yet so much death.

You are indeed extreme, but you hold our hearts…"

Judi Palmer (after the Zanzibar ferry accident, September 2011)

ABSTRACT

Background: After decades of neglect, a renewed global focus on malaria was initiated in the 90s, followed by global financial support in the early 2000s. Zanzibar has been in the forefront of these renewed efforts: Case management and vector-control interventions have been implemented and scaled-up rapidly, resulting in markedly reduced malaria transmission and the targeting of malaria elimination.

Aim: The overall aim of this thesis was to assess caretakers' uptake of malaria control interventions for under-five children in Zanzibar, an area where malaria transmission has rapidly decreased.

Methods: In Study I, a follow-up survey of 210 caretakers was performed to assess caretaker adherence to Artemisinin-based Combination Therapies (ACTs), where caretakers were interviewed in their homes four days after receiving the three-day treatment for their children. In Studies II & III, an assessment of the effective coverage of vector control interventions was carried out in two community-based surveys in 2006 and 2009, with 509 and 560 caretakers, respectively. Both surveys were done in North A and Micheweni districts. In the 2006 survey, the system effectiveness of a targeted free mass distribution of long-lasting insecticidal nets (LLINs) was also assessed, and in the 2009 survey, caretaker perceptions of the malaria situation in Zanzibar and of vector control interventions, were evaluated. Perceptions of malaria and vector control interventions were further explored by conducting in-depth interviews with 19 caretakers (Study IV).

Results: Moderate adherence of 77% to Artesunate-Amodiaquine (AsAq) was documented, and was mostly due to misunderstanding or forgetting the correct dose regimen. Factors associated with adherence were caretaker's education exceeding 7 years and receiving the exact number of pills to complete the treatment regimen, while administering the first dose at the health facility resulted in complete adherence (I). System effectiveness of the targeted mass distribution had increased in the distribution scale-up in North A district as compared to the pilot distribution in Micheweni. This resulted in high (87%) and equitable effective coverage of LLINs in under-five children in the North A district. Effective coverage was associated with receiving an LLIN and thinking that LLINs were better than conventional nets (II). Effective coverage of LLINs in under-fives in the 2009 survey was also equitable and relatively high (70%) following an un-targeted mass distribution, while effective coverage of IRS was as high as 95%, resulting in almost perfect effective coverage (98%) of at least one vector control intervention (III). Seasonality was found to interrupt continuous adherence to bed-nets (III & IV). Low risk perceptions of malaria (III & IV) were not significantly associated with effective coverage (III), although the higher perceived risk for children is in line with the finding that children were prioritized for use of bed-nets (III & IV). Vector control interventions were generally well accepted (II-IV), and caretakers appreciated the importance of their continued use as malaria further declines (III).

Conclusions: Findings of this thesis indicate that caretaker uptake of malaria control interventions for children remains high in Zanzibar in the face of declining malaria burden. ACTs, freely provided at public health facilities, were relatively well adhered to, and the high effective coverage of IRS, together with satisfactory effective coverage of LLINs, provided an almost perfect effective coverage of vector control interventions. This high effective coverage elevates the prospects of achieving malaria elimination in Zanzibar.

Key words: Zanzibar; malaria; elimination; bed-nets; long-lasting insecticidal nets; LLIN; indoor-residual spraying; IRS; effective coverage; adherence; access; artesunate; amodiaquine; artemisinin-based combination therapies; ACT

LIST OF PUBLICATIONS

I. Beer N, Ali AS, Rotllant G, Abass AK, Omari RS, Al-Mafazy AW, Björkman A, Källander K (2009) Adherence to artesunate-amodiaquine combination therapy for uncomplicated malaria in children in Zanzibar, Tanzania. Tropical Medicine & International Health 14:766-74.

II. Beer N, Ali AS, de Savigny D, Al-Mafazy AW, Ramsan M, Abass AK, Omari RS, Björkman A, Källander K (2010) System effectiveness of a targeted free mass distribution of long lasting insecticidal nets in Zanzibar, Tanzania. Malaria Journal 9:173 (9 pp).

III. Beer N, Ali AS, Shakely D, Elfving K, Al-Mafazi AW, Msellem M, Björkman A, Källander K. High effective coverage of vector control interventions in children after achieving low transmission in Zanzibar, Tanzania. Submitted (2012).

IV. Beer N, Ali AS, Eskilsson H, Jansson A, Abdul-Kadir FM, Rotllant-Estelrich G, Abass AK, Wabwire-Mangen F, Björkman A, Källander K. A qualitative study on caretakers' perceived need of bed-nets after reduced malaria transmission in Zanzibar, Tanzania. Accepted for publication in BMC Public Health (2012).

CONTENTS

LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AL	Artemether-Lumefantrine
AMFm	Affordable Medicines Facility - malaria
AsAq	Artesunate-Amodiaquine
BCC	Behavior Change Communication
DDT	Dichloro-diphenyl-trichloro-ethane
DHMT	District Health Management Team
EIR	Entomological Inoculation Rate
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
GMEP	Global Malaria Eradication Program
IEC	Information, Education and Communication
IMCI	Integrated Management of Childhood Illnesses
IPTi	Intermittent Presumptive Treatment in infants
IPTp	Intermittent Presumptive Treatment in pregnant women
IRS	Indoor-residual Spraying
ITN	Insecticide-treated Nets
LLIN	Long-lasting Insecticidal Net
MDG	Millennium Development Goals
MEEDS	Malaria Early Epidemic Detection System
MoH	Ministry of Health
*Pf*PR	*Plasmodium falciparum* Parasite Rate
PHCC	Primary Health Care Center
PHCU	Primary Health Care Unit
PMI	President's Malaria Initiative
RBM	Roll Back Malaria
RDT	Rapid Diagnostic Test
RTI	Research Triangle Institute
SP	Sulfadoxine-pyrimethamine
SSA	Sub-Saharan Africa
USAID	US Agency for International Development
WHO	World Health Organization
ZAMRUKI	Zanzibar Malaria Research Unit Karolinska Institutet
ZMCP	Zanzibar Malaria Control Program

DEFINITIONS

Malaria control: Reducing the disease burden to a level at which it is no longer a public health problem [1].

Malaria elimination: Interruption of local mosquito-borne malaria transmission in a defined geographical area, i.e. zero incidence of locally contracted cases, although imported cases will continue to occur. Continued intervention measures are required [1].

Malaria eradication: Permanent reduction to zero of the worldwide incidence of malaria infection [1].

Effective coverage: The proportion of the population in need of an intervention who are using an effective intervention (Paper II).

System effectiveness: The accumulated proportion of success in all steps of an intervention (Paper II).

PREFACE

I first came to Zanzibar in 1996, with the opportunity to live there for three months. It didn't take long for me to fall in love with the island. I loved its peaceful nature, the long beaches, the endless ocean, the narrow streets of stone town, the markets, the rich culture, the language, the music, the fruits, the spices, the calmness, the liveliness… and the people. What struck me the most about Zanzibar was the way in which people lived in such solidarity, as if they were one big family.

I remember being amazed at the way mothers, when boarding a *dala-dala* (public transportation), would hand over their small children to any random person, who would seat the child on their lap or hold them, sometimes for the entire journey. No one refused this task and, although keeping very cool and calm, I could see that they were happy and honored to help. I also remember admiring the way that, on Fridays, the elderly people would go around the different shops and stands to collect money from the shopkeepers and vendors. Also here, no one ever refused to share the little they had.

I returned to Zanzibar in 2005 for malaria research, and again I had the opportunity to live on the island. This time I was less naive, and I also became more aware of the difficulties and challenges. But despite the shortcomings, I have always felt so fortunate to be able to live and work in such a unique and wonderful place. Landing in ZNZ airport was always a breathtaking moment, not just because of the heat-wave that strikes you as you inhale that first breath of hot and humid air (☺), but because it always felt like coming back home.

Mathematical models have assessed Zanzibar's ability to reach malaria elimination. The predictions are that it is possible, but extremely challenging. It will require decades of strong will and commitment to the cause. In addition to strong political commitment by the Zanzibar government and international partners, community participation was stressed as one of the vital condition for success. Here, Zanzibar has a secret advantage; the strong solidarity and team spirit that are inherent in the Zanzibari culture can and should be used to win this battle against malaria.

As the Bongo Flava artists shout out to the crowd at the Old fort:

Tuendelee ama tusiendelee

(Shall we continue/carry on or not?)

The crowd responds, together, united:

Tuendelee

(Let's continue/carry on)

BACKGROUND

Malaria

In 2010, 3.3 billion people worldwide were at risk of contracting malaria. The malaria burden has been difficult to estimate since most cases and deaths are never properly diagnosed and reported. However, revised estimates of the malaria burden indicate that there were approximately 216 million cases, and 655,000 deaths, due to malaria in 2010. These figures remain high, despite the 26% reduction in mortality and 17% reduction in morbidity and incidences per population at risk in the past decade. The burden is highest in the African region, where 81% of cases and 91% of malaria deaths occur, with children under five years of age and pregnant women being the most vulnerable [2].

Malaria is a parasitic disease caused by the protozoan *Plasmodium*. There are five species that cause human malaria: *P. falciparum*, *P. malariae*, *P. ovale*, *P. vivax* and *P. knowlesi*. *P. falciparum* is the most common species in Sub-Saharan Africa (SSA) and is also the most pathogenic species, responsible for the majority of malaria deaths. The vector is a female *Anopheles* mosquito, and there are over 30 *Anopheles* species that are able to transmit *Plasmodium* [2, 3].

Plasmodium has a complex life-cycle that takes place in both the vector and the human host. During a blood meal, the mosquito takes up female and male *Plasmodium* gametocytes from an infected human host. The gametocytes create zygotes in the mosquito gut. The zygotes develop into oocysts that, in turn, form sporozoites which migrate to the salivary glands. When the mosquito takes another blood meal, she inoculates another human with the sporozoites. The sporozoites travel through the human blood stream into the liver cells where they multiply and are again released into the blood as merozoites. In the blood stage, the merozoites attack red blood cells and transform into trophozoites. The trophozoites then multiply into merozoite cells within a blood cell, until it bursts and the released merozoites continue to infect more blood cells. During the blood stage some merozoites develop into female and male gametocytes, which the mosquito again takes up during a blood meal [4].

In *P. falciparum* infections, the symptoms usually appear 9-14 days after being bitten by an infected mosquito, when the parasites are in the blood stage. Symptoms of uncomplicated malaria include fever, headache, vomiting and other flu-like symptoms. If the infection is not treated promptly, severe forms of malaria may develop. These include conditions such as severe anemia and, the most life-threatening complication, cerebral malaria [3].

Epidemiology

Malaria endemicity has historically been classified by splenomegaly (enlargement of the spleen) or parasitemia rates as follows: over 75% is holo-endemic; 51-75% is hyper-endemic; 11-50% is mesoendemic; and 10% or less is hypoendemic [3].

Another classification of *P. falciparum* endemicity is by *P. falciparum* parasite rate (*Pf*PR) and *P. falciparum* annual parasite incidence (*Pf*API) [5] (Figure 1).

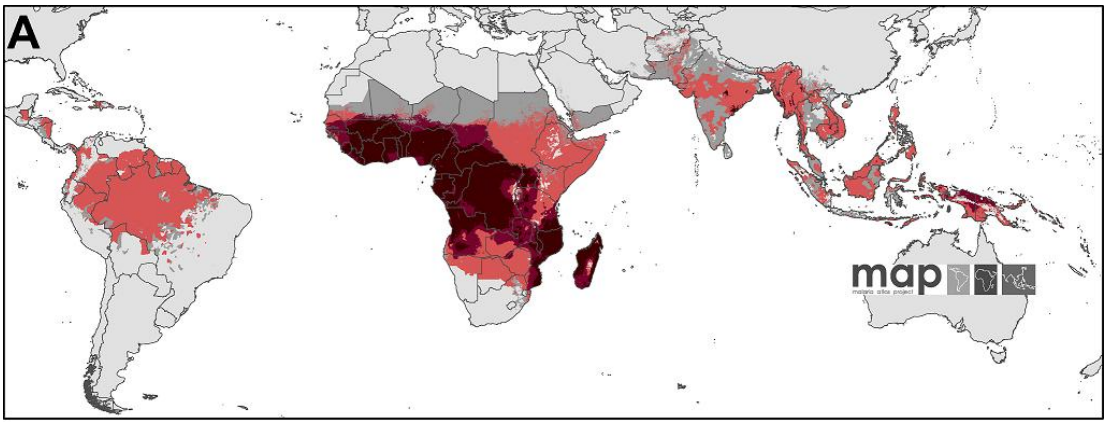


Figure 1: The Spatial distribution of Plasmodium falciparum malaria $PfPR_{2-10}$ in 2010 stratified by endemicity class

Source: Gething et al. Malaria Journal 2011, 10:378 [5]

An additional classification is vector-based and relies on the entomological inoculation rate (EIR), i.e. the number of infected bites per person per year. According to this classification, when malaria is stable, the population is continuously exposed to a high rate of malaria inoculations, with an EIR of over 10 per person per year. Un-stable malaria is characterized by fluctuating inoculation rates over seasons and years, with EIRs usually between 1 to 5 per person per year [6].

Malaria transmission, or the spread of malaria, is measured by the basic reproduction rate. This is the number of new malaria cases generated by a single case. Reproduction rate is an expression of the efficiency of the mosquito vector (vectorial capacity) and the magnitude of infective parasite pool in humans [1].

In high transmission settings, the population develops acquired immunity after being exposed to *Plasmodium* several times. In these areas, the vulnerable groups are children under the age of five who have not developed immunity yet, and pregnant women whose immunity is compromised [7].

Malaria control

Case management

Malaria control highly relies on early diagnosis and prompt appropriate treatment, within 24 hours of onset of symptoms. This is crucial because although uncomplicated malaria is easily curable with efficacious drugs, delaying treatment, especially in vulnerable groups such as children, may lead to severe forms of malaria. Case fatality rates for children hospitalized with severe malaria are 10-50% [3].

The gold standard for malaria diagnosis has been microscopy. A blood drop taken from the patient's finger is smeared on a slide, and Giemsa staining is then used to highlight the parasite and make it more visible under the microscope. However, due to weak health systems and inadequate facilities in resource-poor settings, most malaria diagnoses have been presumptive and rely solely on symptoms. Integrated Management of Childhood Illnesses (IMCI) is a simple tool developed by the World Health Organization (WHO) which is designed to improve management of childhood illnesses in resource-poor settings. Since the most common symptom of malaria is fever, IMCI guidelines state that all febrile cases in malarious areas should be treated with antimalarials [8]. More recent developments in diagnosis are the rapid diagnostic tests (RDTs) which are based on antigen detection. Blood from a finger prick is placed in a plastic cassette and spreads on a filter paper with an antibody strip that changes its color if antigens adhere to it. The recent scale-up of RDTs has made malaria diagnosis easier and more accessible, and it is now recommended that malaria diagnosis, using either microscopy or RDTs, should always precede treatment with antimalarials [6]. However, there have been concerns about the validity and reliability of RDTs. For example, antigens can stay in the blood up to two weeks after infection and thus give a false-positive result. An additional concern is the cost-effectiveness of using RDTs, especially in high-transmission areas.

For several decades, treatment of uncomplicated malaria has relied on two inexpensive and widespread drugs, namely chloroquine and Sulfadoxine-pyrimethamine (SP). However, the abundance of these drugs and their misuse has led to resistance [9]. The first evidence of chloroquine-resistant *P. falciparum* in Africa arose in 1979, and by the late 80s reports of resistance were extensive, with drug failure rates varying between 10% and 90% [10]. However, it was only in the late 90s that the harsh implications of antimalarial resistance were realized and this was followed by an outcry within the scientific community [11, 12]. Antimalarial resistance had a major public health impact in SSA with a notable increase in malaria cases and deaths. Most affected were young children under the age of five, and in the 90s malaria-specific mortality rose in this age group [13-15], accounting for approximately a third of all under-five deaths [13]. Other negative effects of resistance included the increase of other related health conditions such as anemia [16], an increased burden on the health systems, as well as social and economic consequences [17].

Artemisinin-based combination therapies (ACTs) were identified as the most appropriate replacement for treatment of uncomplicated malaria, and have been recommended by WHO since 2001 [18, 19]. Artemisinin and its derivatives are highly efficacious, leading to rapid reduction of the parasite (including reduction of gametocytes) and resolution of clinical symptoms, with few adverse events and with no reported resistance at that time [11, 18]. The purpose of combining artemisinin derivatives with a partner drug was to prevent the emergence of resistance. Additionally, combination with a drug that has a longer half-life ensured shorter dose regimens with higher cure rates and less possibility for recrudescence [11].

The two most used ACT combinations in SSA are either Artemether-Lumefantrine (AL) or Artesunate-Amodiaquine (AsAq). AL is currently adopted as the first-line

antimalarial by 22 malaria endemic countries and AsAq is the first line treatment in 13 countries, while 9 countries are using both [20].

Prevention

Malaria prevention mostly relies on vector control interventions; mainly bed-nets and indoor-residual spraying (IRS). Bed-nets have been used in different cultures since ancient times to protect against insect bites [21]. They are especially useful in preventing malaria due to the fact that *Anopheles* mosquitoes are active from dusk till dawn. Thus, a physical barrier that protects people when they sleep is an effective way to prevent malaria. In the past two decades there has been renewed interest in bed-nets and especially in insecticide-treated nets (ITNs) which were revitalized in the mid 80s. In addition to the physical barrier, the insecticide repels, inhibits or kills the mosquitoes and thus provides not only a better individual protection to those sleeping under the net, but also have a community effect [7]. Insecticide-treated nets have been found to be efficacious, and in randomized control trials they reduced overall under-five mortality by 18% [22]. Despite the worry that the high ITN efficacy would not be translated into effectiveness under routine conditions [23], it has been show that the scale-up of ITNs result in 23-27% reduction in child mortality [24-26].

WHO started recommending and endorsing ITNs as the leading malaria prevention intervention in the late 90s [27]. However, due to low re-treatment rates of ITNs, the long-lasting insecticidal nets (LLINs) were developed [28]. LLINs do not require treatment or re-treatment by the consumer, as they are pre-treated in the factory with an insecticide that is embedded in the fabric and can remain effective for 4-5 years. ITNs and LLINs are normally treated with pyrethroids [29].

In 2006, the WHO also started recommending the scale-up of IRS as an additional control intervention [30]. IRS is the application of residual insecticides on the inner walls and roofs of dwellings, where many of the *Anopheles* species tend to rest after taking a blood meal [2, 30]. Although there is a general lack of evidence on the health impact of IRS from formal trials, especially in stable malaria settings [31], IRS with dichloro-diphenyl-trichloro-ethane (DDT) was the main vector control strategy in the 1940s-60s and was responsible for malaria elimination in many unstable transmission areas. Today, in addition to DDT, other insecticides used for IRS belong to 3 chemical groups: pyrethroids, organophosphates and carbamates [30].

Although ITNs seem to be more effective than IRS in areas with high endemicity [32-34], both interventions are often scaled up simultaneously. Combining IRS and ITN has previously shown to have an additive effect [35, 36]. However, achieving an additive effect is thought to be highly dependent on the insecticides used, coverage and vector characteristics [37].

Additional vector control interventions, such as larva control in breeding water bodies, fogging or area spraying and environmental management, are also available. Though they are not being scaled up, they are still used to some extent, especially in densely populated urban settings [38].

Other prevention interventions include preventive therapies for malaria. Intermittent presumptive treatment for pregnant women (IPTp) is the most widespread intervention of this type. With IPTp, all pregnant women in malaria endemic areas are provided with at least 2 doses of malaria treatment during their pregnancy. IPT can also be given to infants (IPTi), although this intervention has not been adopted as national policy and scaled up as of yet [2]. Seasonal malaria chemoprevention (SMC) is now also being considered in areas with seasonal transmission [2].

History of malaria control

Malaria was historically controlled mainly through environmental management even prior to the discovery of the malaria transmission mechanisms in the end of the 19th century. Later, the development of the residual insecticide DDT in the 1940s and the growing evidence of its effectiveness prompted the initiation of the Global Malaria Eradication Program (GMEP) [39].

When the GMEP was initiated by the WHO in 1955, eradication efforts focused on IRS with DDT, antimalarial treatment with chloroquine, and surveillance. While the program had succeeded in eliminating malaria from areas with temperate climates and seasonal malaria transmission, such as Europe and North America, there were no major successes in areas with tropical climate and high and stable transmission, such as in SSA. The failure was attributed to several reasons, and especially to technical challenges and the development of resistance to DDT. Thus, the program was finally abandoned in 1969 [39, 40].

In the post-eradication era, during the 1970s-90s, there was little global support for malaria control. However, a better understanding of the social, economic and cultural dimensions of malaria was achieved, and advances were made on malaria control tools such as ITNs. With the realization that there was no "magic bullet" for malaria control, an integrated approach which included the combination of several interventions, was adopted. The goals became less ambitious, and instead of eradication the new aim was for malaria control [40].

Despite the overall reduction in child mortality during the 1980s and 1990s in most regions of the world, malaria specific mortality increased in Africa. The increase was largely due to drug resistance, emerging resistance to insecticides used for vector control and the general deterioration of primary health services [41]. This led to a renewed global focus on malaria, and in 1992 malaria was re-established as a global health priority at the Conference of Ministers of Health in Amsterdam, and in 1993 WHO started formulating a global strategy for malaria control [42, 43].

In 1998, the Roll Back Malaria partnership (RBM) was launched with the goal of halving the global burden of malaria by 2010, and by 75% by 2015 [44] (Table 1). In 2000, African heads of state signed the Abuja declaration, where they committed themselves to the RBM goal through implementation of several strategies including prompt access to effective treatment, prevention with ITNs, prevention and control in pregnant women and strengthening the malaria epidemic and emergency response [7, 45].

Global financial support for up-scaling malaria control interventions were made available through the initiation of several organizations, including: Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) in 2002; The US President's Malaria Initiative (PMI) in 2005; and the World Bank's Booster Program for Malaria Control in Africa in 2005.

Due to the recent advances in malaria control in SSA, malaria elimination and even eradication is again "back on the table" following a plea by Bill and Malinda Gates [1, 40, 46, 47]. The Global Malaria Action Plan (GMAP), formulated in 2008 by RBM, explicitly mentions eradication as a long-term target [48]. The GMAP provides a guideline on how to achieve elimination by first controlling malaria through scaling-up for impact (SUFI) of interventions and then sustaining control over time to prevent its resurgence. In areas of stable high transmission a "consolidation period" should be introduced, where achievements are sustained, health services adapt to the new clinical and epidemiological situation, and surveillance systems are strengthened. When the incidence rate is decreased to five or less new cases per 1000 population at risk per year (with the proxy measure of having a monthly slide positivity rate of less than 5% in febrile cases), the low case load allows intensive follow-up of new cases which is required by an elimination program. At this stage, the country can start the pre-elimination phase, and move into the elimination phase when incidence rates are below 1 per 1000 population at risk per year. After reaching elimination, measures should continue to be in place to prevent re-establishment of transmission [1, 48]. The steps from control to elimination are illustrated in Figure 2.

The Millennium Development Goals (MDGs), which were initiated after the Millennium Summit in 2000, have been used to guide strategic plans in low and middle income countries. The RBM global strategic plan 2005-2015 states that "Six out of eight Millennium Development Goals can only be reached with effective malaria control in place" [49]. This is due to malaria's direct and indirect associations with child mortality, maternal health, poverty, education and access to antimalarials, in addition to the malaria-specific target (MDG 6c) of halting and beginning to reverse the incidence of malaria by 2015 (Table 1) [49, 50].

Table 1: Goals and targets for malaria control

Targets for 2005	Targets for 2010	Targets for 2015
	Reduce global malaria deaths from 2000 levels by 50% *[48]* Reduce global malaria cases from 2000 levels by 50% *[48]*	Reduce global malaria deaths to near zero [51] Reduce global malaria deaths from 2000 levels by 75% [52] Reduce global malaria cases from 2000 levels by 75% *[51, 52]* MDG 6: Have halted and begun to reverse the incidence of malaria and other major diseases [53]
At least 60% of those at risk of malaria particularly pregnant women and children under five years of age, benefit from the most suitable combination of personal and community protective measures *[45]* At least 60% of all pregnant women who are at risk of malaria, especially those in their first pregnancies, have access to chemoprophylaxis or presumptive intermittent treatment *[45]*	Achieve universal coverage for all populations at risk of malaria using locally appropriate interventions for prevention and case management [48] 80% of people at risk from malaria are protected, thanks to locally appropriate vector control methods such as insecticide-treated nets (ITNs), and, where appropriate, indoor residual spraying (IRS) and, in some settings, other environmental and biological measures *[49, 52]* At least 80% of pregnant women receive intermittent preventive treatment in areas where malaria transmission is stable *[49, 52]*	Achieve universal access to and utilization of prevention measures: By end 2013, in countries where universal access and utilization have not yet been achieved, achieve 100% access to and utilization of prevention measures for all populations at risk with locally appropriate interventions *[51]* Sustain universal access to and utilization of prevention measures: By 2015 and beyond, all countries sustain universal access to and utilization of an appropriate package of preventive interventions *[51]*
At least 60% of those suffering from malaria have prompt access to and are able to use correct, affordable and appropriate treatment within 24 hours of the onset of symptoms *[45]*	80% of malaria patients are diagnosed and treated with effective antimalarial medicines, e.g. artemisinin-based combination therapy (ACT) within one day of the onset of illness [49, 52]	Achieve universal access to case management in the public sector: By end 2013, 100% of suspected cases receive a malaria diagnostic test and 100% of confirmed cases receive treatment with appropriate and effective antimalarial drugs *[51]* Achieve universal access to case management, or appropriate referral, in the private sector: By end 2015, 100% of suspected cases receive a malaria diagnostic test and 100% of confirmed cases receive treatment with appropriate and effective antimalarial drugs *[51]* Achieve universal access to community case management (CCM) of malaria: By end 2015, in countries where CCM of malaria is an appropriate strategy, 100% of fever (suspected) cases receive a malaria diagnostic test and 100% of confirmed uncomplicated cases receive treatment with appropriate and effective antimalarial drugs, and 100% of suspected and confirmed severe cases receive appropriate referral *[51]*
		Accelerate development of surveillance systems: By end 2015, all districts are capable of reporting monthly numbers of suspected malaria cases, number of cases from all public health facilities, or a consistent sample of them [51]

Source: WHO World Malaria Report 2011 [2]

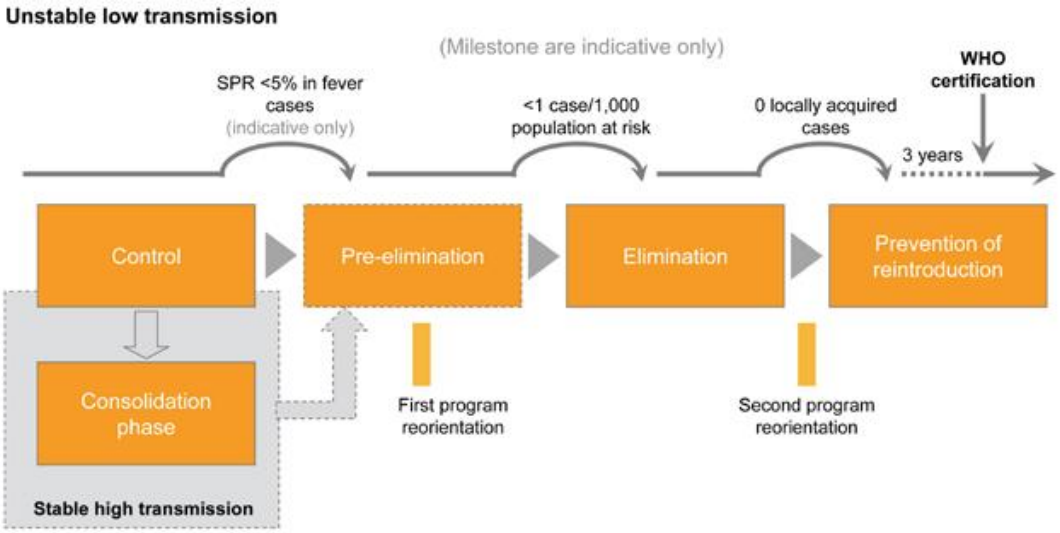


Figure 2: Epidemiological milestones from control to elimination
Source: The Global Malaria Action Plan, 2008 [48]

Although malaria control programs have usually been vertical "stand-alone" initiatives [54], it has increasingly been recognized that malaria control efforts should be integrated and coordinated with other health activities within the existing health systems [40]. Thus, there is now more emphasis on general health system strengthening and capacity building, in addition to implementation of malaria-specific interventions [48, 49].

From efficacy to effectiveness

Highly efficacious control interventions are available to combat malaria. Efficacy describes the effect of an intervention under optimal conditions, such as those achieved under randomized control trials. Effectiveness in real-life conditions, also known as "community effectiveness", is often considerably lower due to different barriers. The steps from efficacy to "community effectiveness" could include: access, diagnostic accuracy, provider compliance and consumer adherence [55, 56].

Efficacy

Malaria control currently relies heavily on a limited number of efficacious tools, in particular artemisinin derivatives for therapy and pyrethroids for vector control. However, their high efficacy is threatened by development of parasite and vector resistance [1, 2], especially in light of their wide-spread use.

Emergence and increase of *P. falciparum* artemisinin resistance has been identified at the Cambodia-Thailand border from 2002 [57, 58]. Evidence of resistance has so far been constrained to limited areas in Southeast Asia [59]. In 2011, the WHO released the Global Plan for Artemisinin Resistance Containment (GPARC), with the aim of halting the spread of resistance [59].

Pyrethroids are now the most commonly used insecticides for ITNs and LLINs. It is also one of the insecticides used for IRS. Resistance to pyrethroids is emerging in SSA [60, 61], compromising the efficacy of vector control interventions.

Given the above, research and development of new highly efficacious antimalarials and insecticides to replace current tools that will inevitably become resistant are major necessities. These new agents should ideally be from new classes, and different agents with different modes of action should be combined to delay development of resistance [1]. Although maintaining efficacy is crucial, this thesis will focus on the implementation of currently available efficacious tools.

Access

Access to timely and appropriate treatment can be hampered by many different factors inside and outside the home. When a child is sick, the immediate caretaker, usually the mother, is responsible for recognizing the illness and seeking care. Health-seeking behavior is complex and is influenced by geographical, financial and cultural factors. Mothers' low access to financial resources and lack of decision making power is often an obstacle for timely treatment-seeking [62-64]. Local beliefs and disease perceptions often drive the choice of treatment, be it biomedical ("western") or traditional medicine [65, 66].

When biomedical treatment is chosen, the type of facility, whether it is a public health facility, private health facility, pharmacy or normal shop, will greatly affect the access to appropriate drugs. The high cost of ACTs may influence their accessibility, especially in the private health sector. In public health facilities, even if ACTs are the antimalarial of choice, they might not be available due to stock-outs. At the health facility level, diagnostic accuracy and provider compliance to national guidelines, which was often observed to be low [67, 68], may further reduce the patient's access to an efficacious treatment.

Access to ITNs and IRS is largely influenced by health system delivery strategies. While IRS has been implemented through the public health sector and provided free of charge, there has been debate as to which delivery system is most efficient in scaling up ("catch-up") and sustaining ("keep-up") ITN coverage [69, 70]. Available strategies range from social marketing [71] and voucher schemes [72], to free mass distributions [73].

Socio-economic inequity is also an important factor which hampers access. Access to good medical care or preventive measures tends to vary inversely with the need of the population served [74]. Thus, the poor, who are often more exposed to mosquitoes and malaria, are often less likely to access anti-malarial treatment [75] and to own or use bed-nets [7, 76, 77].

Adherence

Adherence can be influenced by attitudes and beliefs, as well as social, economic and emotional factors. In an attempt to better understand health-related behavior and the determinants of adherence to health interventions, a number of theoretical models have

been proposed, including the Health Belief Model (HBM) which is widely used. The HBM states that individuals will take a health related action to prevent, diagnose or treat a health condition if they have a desire to avoid an illness or get well and if they believe that a specific health action will, in fact, prevent the illness or improve their condition. The model includes six elements: 1) **Perceived susceptibility** of the individual to the condition; 2) **perceived severity** of the condition as having serious medical and social consequences; 3) **perceived benefits** of taking the health action in reducing the disease threat as well as other additional benefits; 4) **perceived barriers** to taking the health action, which should not overweigh the benefits. These four perceptions are elements that determine the readiness to take action. They are activated by: 5) **Cues to action** that trigger readiness and 6) **self efficacy,** which is the conviction that one can successfully execute the health behavior. Although the HBM is one of the most widely used models, it has been criticized for solely focusing on individuals' attitudes and beliefs without taking into account other factors that may also influence health-related actions. Additionally, there is dispute as to which of the HBM components have more influence on health-behavior and what the relationship is between these components [78, 79].

Adherence to ACTs is vital, since non-completion of the standard regimens can result in treatment failure and promote resistance development [80, 81]. Ensuring consumer adherence is important since most antimalarials for uncomplicated malaria are administered at home. Previous studies on adherence to a full treatment course of ACTs have shown varying results, ranging from 39% to 97% [82, 83]. Factors found to influence adherence to antimalarials include education level [84-86], drug packaging and dosing [87, 88], speed of symptom relief [89], duration of treatment [89, 90] and communication with the health worker [84, 91, 92].

Adherence to ITNs is also crucial in maintaining its effectiveness since it is up to community members to cover themselves and their children with bed-nets every night. ITN adherence was previously shown to vary by seasonality [93, 94], age [94, 95] and gender [96, 97]. Education of the head of the household was found to affect adherence in Nigeria, but not in Kenya [94, 98]. Non-adherence due to disruption of sleeping arrangements, temporary migrations and difficulties in mounting the nets was reported [94, 99-101]. Fear of toxicity and safety of ITNs, which was mentioned in early distributions, were reduced with time [97, 99]. Partial effectiveness of the nets, due to perceived additional causes of malaria, as well as use of other protective measures against malaria was also found to impede adherence to bed-nets [97, 99, 102]. However, perceived additional advantages of bed-nets, such as providing protection against mosquitoes and other insects and pests, was found to uphold their use [99, 100].

IRS, on the other hand, does not require continuous adherence from community members after the initial agreement to have the house sprayed. Community acceptance of IRS was previously impeded by increase in bedbug infestation, insecticide smell, mess left by the sprayers, inconvenience of having to remove furniture from the house, perceived ineffectiveness and side effects [103-105]. Additionally, effectiveness can be reduced by re-plastering and washing the walls after they have been sprayed [104, 106].

System effectiveness and effective coverage

System effectiveness and effective coverage are both outcomes that describe how well an intervention had been implemented. Although there are different definitions for these terms in the literature [107-109], in this thesis, the following definitions are used:

Effective coverage: The proportion of the population in need of an intervention who are using an effective intervention.

System effectiveness: The accumulated proportion of success in all steps of implementing an intervention.

Both system effectiveness and effective coverage are relevant outcomes in assessing the overall success of an intervention implementation, and both outcomes encompass, and are influenced by, programmatic issues that affect access as well as caretakers' adherence to the intervention. While each step of the implementation must be measured and accumulated in order to compute system effectiveness, effective coverage can more easily be evaluated by measuring the final outcome of the implementation, regardless of success rates in each step. Thus, system effectiveness and effective coverage measure the effectiveness of the implementation of an intervention rather than the effectiveness of the intervention itself.

Zanzibar

Zanzibar is an archipelago off the coast of mainland Tanzania. It was united with Tanganyika in 1964 to form the United Republic of Tanzania. However, Zanzibar remains semi-autonomous and has its own government, the Revolutionary Government of Zanzibar. Zanzibar consists of two large islands, Unguja and Pemba, and numerous small islands. Unguja is approximately 1,464 km^2 and Pemba is smaller with 864 km^2. Zanzibar is divided into 5 regions and 10 districts; 6 in Unguja and 4 in Pemba. The districts are sub-divided into constituencies and shehias. A shehia is the smallest administrative unit and is composed of several communities or villages, and is led by a Sheha [110].

The projected total population of Zanzibar in 2011 was over 1.3 million with approximately 64% in Unguja and 36% in Pemba Island. The under-five children comprise around 18% of the total population [111]. Approximately 60% of the population is rural and the main livelihood is subsistence farming and fishing. In 2002, the annual population growth rate was 3.1% [112], and in 2010 the population density was more than 10 times greater than on Tanzania's mainland, with 518 persons per km^2 [113]. The literacy rate in 2002 was around 73%. The population is mostly Muslim and the spoken language is Kiswahili.

The climate is tropical and humid, with two distinct rainy seasons; the long or heavy rains (Masika) from March/April to May/June and the short rains (Vuli) from October to December. There is also a seasonal classification by temperature, whereby the cool season occurs between June and November and the hot season occurs between December and March.

Health

Zanzibar's Ministry of Health (MoH) is under the direct jurisdiction of the Zanzibar government and is independent from the Tanzanian Ministry of Health. The MoH provides free health care through public health facilities. Health services are also provided through the private sector, which is largely concentrated in the urban areas and include hospitals, clinics pharmacies and "over the counter" drug shops. In addition to the for-profit facilities, there are not-for-profit and non-governmental organizations as well [110].

The public health system in Zanzibar is provided at three levels. The primary level includes 1st and 2nd line primary health care units (PHCU and PHCU+) that provide outpatient services, and primary health care centers (PHCCs), also known as "cottage hospitals", which provide basic inpatient services. The primary health facilities should have at least one staff member providing out-patient services (medical assistant or nurse practitioner A), at least one staff member providing reproductive and child health services (midwife or public health nurse B) and a health promotion person (environmental health officer). Some also have a laboratory technician and a pharmaceutical assistant that dispenses medicines. The secondary level includes district hospitals that serve as referral points for primary level facilities. The tertiary level includes the referral hospital Mnazi Mmoja which is located on Unguja Island. Mnazi Mmoja also has two specialized wings for maternity and mental health [110].

Overall, there are more than 130 PHCUs, four PHCCs and four hospitals in Zanzibar, resulting in high geographical access whereby over 95% of the population is living within five kilometers of a health facility [110]. However, population density is high, and although population coverage per health facility should ideally be between 4,000-8,000 people it is sometimes up to 4-folds higher, especially in the Urban and West districts (personal communication with Sharifa Awadh Salmin, GF portfolio Coordination –ZMCP, 2012). This, in addition to financial constraints and shortage of human resources, which hampers the quality of health services on the one hand, and the high infectious diseases burden on the other, has resulted in generally poor health of the population [110, 114] (Table 2).

Table 2: Zanzibar health indicators

	2002	**2010**
Life expectancy	57 years*	59.5 years**
Total fertility rate	6.2*	5.1***
Infant mortality rate per 1,000 live births	89*	54***
Under-five mortality rate per 1,000 live births	141*	73***

Sources: * *2002 census: Analytical report [112]*
** *Tanzania in Figures 2010 [113]*
*** *Tanzania Demographic and Health Survey [115]*

In 2001 the MoH started the health sector reform which aimed at improving health and well being, especially of vulnerable groups including children. To achieve this aim, structural and management changes with emphasis on decentralization are taking place. Two Zonal Health Offices, one in Unguja and one in Pemba island, are meant to serve as a link between the districts and the MoH headquarters, and are responsible for supervising and monitoring the health services and the channeling of operational funding to the districts within their zones. On the district level, the District Health Management Teams (DHMTs) are responsible for planning and management of health care services provided in their respective districts. An additional organizational goal of the health sector reform is to integrate the different vertical programs. The Zanzibar Malaria Control Program (ZMCP) is one of these vertical programs, which functions under the director of preventive services and health education [110, 114].

The MoH also aims to improve access to high quality health care services, with emphasis on primary care. This is done by reducing the patient crowding through increasing human resources and out-patient services as well as introducing community level health workers that will assist the health facilities, especially with health education. On the referral level, existing PHCC and district hospitals will be upgraded.

Malaria

The main malaria vectors on Zanzibar belong to the *Anopheles gambiae* complex. *Plasmodium falciparum* is the predominant malaria species which constitutes over 95% of all malaria infections, while less than 5% are due to *Plasmodium malariae* [116].

Historically, Zanzibar was classified as an area with high and stable malaria transmission. In the mid 20s till mid 50s, malaria prevalence was as high as 68%, despite control efforts which included environmental management, chemical and biological larviciding, quinine distribution and the use of mosquito nets [117].

Zanzibar attempted malaria elimination twice. It was one of the areas that achieved satisfactory malaria reduction during the GMEP, using IRS and mass drug distributions [118]. By the late 1960s malaria transmission was low, and malaria prevalence was below 5%, but interrupted transmission was not achieved due to technical and operational problems. Within a few years after the GMEP was abandoned, the malaria burden increased again, and reached prevalence rates of 40% in the late 1970s. The second attempt was the Zanzibar Malaria Control Project, which was an aggressive program led by the US Agency for International Development (USAID) in 1984-1989. Strategies included IRS and chloroquine administration. However, this program was also not successful, and malaria re-emerged once more [117, 119].

Although the malaria burden in Zanzibar did not return to its historical hyper-holoendemicity, it was still considered to have high and stable transmission, with peaks during and right after the rainy seasons. In 2001, malaria was the most common illness in Zanzibar, constituting more than 40% of all diagnoses at the health facilities and was the leading cause of morbidity and mortality [120]. However, with the renewed fight against malaria, and with heavy reliance on external funding, Zanzibar has made enormous advances through case management and preventive interventions.

Case management

In 2000 it was established that the therapeutic efficacy of chloroquine had been grossly reduced in Zanzibar and the treatment failure rates exceeded 60% [120]. As a result, Zanzibar was one of the first nations in Africa to change their malaria treatment policy to ACTs in May 2002. Zanzibar opted for AsAq combination for 1st line treatment and AL as 2nd line treatment of uncomplicated malaria. Quinine was the 3rd line treatment and drug of choice for severe malaria. SP was recommended for IPTp and treatment of uncomplicated malaria in pregnancy [120].

ACTs were deployed to all public health facilities by May 2003, where they were to be given free of charge to all malaria diagnosed patients. Until 2006, the artesunate and amodiaquine pills were dispensed in four different dose-specific sachets for the different age-groups (<1 year, 1-6 years, 7-13 years, >14 years). From 2006 to 2010, the AsAq was dispensed in the form of a co-blistered package (Falmal®) (Cipla Ltd., India), which had 2 packs; one for "children" (0-6 years) and one for "adults" (over 7 years) [121]. The children pack consisted of 3 tablets of As (50 mg) and 3 tablets of Aq (100 mg) and included two dose regimens; the "infant dose" for children under 1 year or weighing under 10 kg and the "child dose" for children between one and six years or weighing 10-20 kg. In 2010, co-formulated AsAq tablets, which came in four dose-specific packs, was adopted.

New national guidelines for malaria diagnosis and treatment were introduced in 2010, the 1st line drug remaining AsAq while AL was an alternative drug in case of intolerance, and parenteral quinine remained the preferred drug for severe malaria, followed by ACTs for completion of treatment. SP is still recommended for IPTp, however treatment for uncomplicated malaria in pregnancy in the 1st trimester is now oral quinine, while AsAq is used in the 2nd and 3rd trimesters [122].

Although ACTs have been dispensed free of charge in the public sector, they were expensive and largely unavailable in the private sector until 2010, when Zanzibar, together with Tanzania, was chosen for the pilot phase of Affordable Medicines Facility - malaria (AMFm), that provide subsidised ACTs at an affordable cost [123].

Diagnostics were scaled-up in 2006 and currently every public health facility has RDTs (82%), microscopes (4%), or both (14%). Initially, the Paracheck® RDTs, which only detect *P.falciparum*, were deployed. However, they have now been replaced by SD Bioline® RDTs that can detect all *Plasmodium* species. ACTs and RDTs are funded through GFATM and PMI.

Prevention

Malaria prevention in Zanzibar, as in most SSA countries, relies mainly on vector control and prevention in pregnancy. The ZMCP started information, education and communication (IEC) activities regarding bed-nets in the early 90s. A cost recovery scheme was implemented from 2003 to 2005, whereby nets provided by UNICEF were sold at a reduced price at antenatal clinics. Other efforts included small scale social marketing efforts and re-treatment campaigns. However, coverage remained low, and in May 2005 the overall ITN use in children under five in Zanzibar was

documented at 40%, with Micheweni district having the lowest under-five ITN use of less than 10% [124]. As a result, retreatment campaigns were carried out in Micheweni district during 2005, and continued being carried out sporadically in different districts till 2009.

Additionally, the GFATM and PMI supported the ZMCP in carrying out a targeted free mass distribution of LLINs to all pregnant women and children under five. The campaign took place from August 2005 till February 2006 in nine of the 10 districts of Zanzibar (excluding the Urban district). The distributed nets were blue rectangular Olyset® nets, which were made of polyethylene and had a mesh size of 4×4 mm. Micheweni district was chosen as the site for trial implementation in August 2005. The distribution scale-up in the other districts followed in January 2006. For details on the 2005-2006 distribution see the Methods section in Paper II.

After the mass distribution, there was an attempt to start up a voucher system through antenatal clinics, whereby pregnant women could purchase LLINs at a reduced price. This attempt was unsuccessful and was terminated within a few months. Since 2009, UNICEF has been providing PermaNet® LLINs for free distribution in antenatal clinics; however these provisions are not consistent and rely on irregular availability of nets.

The second free mass distribution of LLINs took place from 2008 till 2009 in seven out of the 10 districts, as well as in some shehias of the Urban district. In this distribution all households were to receive two LLINs, except for households with a single resident, who received only one LLIN. The majority of LLINs that were distributed were the same blue rectangular Olyset® nets which were distributed in 2006, but some were white PermaNet® LLINs that cannot be easily distinguished from conventional nets. The LLINs supply was funded by GFATM.

A third mass distribution, the Zanzibar universal coverage campaign, took place in 2012. In this distribution, all households of all districts received one to three nets per household, according to the universal coverage method of one net for every two people. For this distribution, Olyset® nets were donated by the UK Department for International Development (DIFID), while Yorkool® LLINs were funded by GFATM. The distribution was carried out with technical support from the Red Cross.

IRS rounds started in 2006 with support from PMI and the Research Triangle Institute (RTI). Three biannual rounds with the synthetic pyrethroid lambda-cyhalothrin (ICON) were implemented in 2006-2007. In December 2008 an ICON formulation, with a residual effect that ranges between 9-12 months, was used, followed by two rounds in March 2010 and January 2011. The rounds included all districts of Zanzibar but excluded houses in Stone Town. Due to indications of *Anopheles* resistance to pyretheroids in 2011, in the spraying rounds of 2012 carbamate insecticide, which lasts for 4-6 months, is being used. These rounds are being done in selected areas, "hotspots", based on epidemiology and potential for transmission.

Other vector control interventions, although not scaled-up nationally, have also been used in the past years. Since Stone Town was not covered by IRS, area spraying with

pyretheroids was done irregularly to reduce mosquito burden when needed. Additionally, larvaciding was done on several ocasions in urban areas whenever chemicals were available and where there was a high increase in mosquitoe density. ZMCP now plans to regulate the larvaciding activities in the Urban district where IRS is not implemented. (personal communication with Juma Hassan Mcha, Head of Vector Control Unit – ZMCP, 2012). Environmental management has been advocated by ZMCP as a method of malaria control, but these efforts rely on the communities, who are responsible for carrying out these activities.

Since 2002, all pregnant women are recommended to receive at least two doses of IPTp with SP during the 2nd and 3rd terms of pregnancy. From 2004, the IPTp is given as part of the routine antenatal care services.

Additionally, ZMCP established a Malaria Early Epidemic Detection System (MEEDS) in 2008. The MEEDS relies on mobile-phone weekly reporting of malaria indicators from public health facilities. The surveillance data is forwarded to central server and can be viewed by ZMCP through a secure website. From January 2012, all public and three private health facilities in Zanzibar participate in weekly reporting. When a sudden increase in transmission occurs, a team sets out to confirm and investigate the outbreak. Activities to halt outbreaks have included focal distribution of LLINs and IRS (personal communication with Abdul-Wahid H. Al-mafazy, Head of Surveillance Monitoring and Evaluation Unit – ZMCP, 2012). This system is financially supported by PMI and technically supported through RTI.

In December 2005, PMI supported ZMCP in launching the "Kataa malaria" (Reject malaria) campaign. The campaign provided information, education and communication /behavior change communication (IEC/BCC) support for the malaria control interventions that were conducted in Zanzibar, including mass media activities, through TV and radio, billboard messages, as well as the production of pamphlets, posters, teacher's guides, etc. [125]. Since 2010, IEC/BCC activities are implemented under the "Maliza malaria" (Eliminate malaria) campaign, which, up to date, is supported by PMI.

Due to the intensive abovementioned malaria control efforts, Zanzibar has been successful in dramatically reducing malaria transmission and maintaining low transmission rates in the past decade [126, 127] (Figure 3).

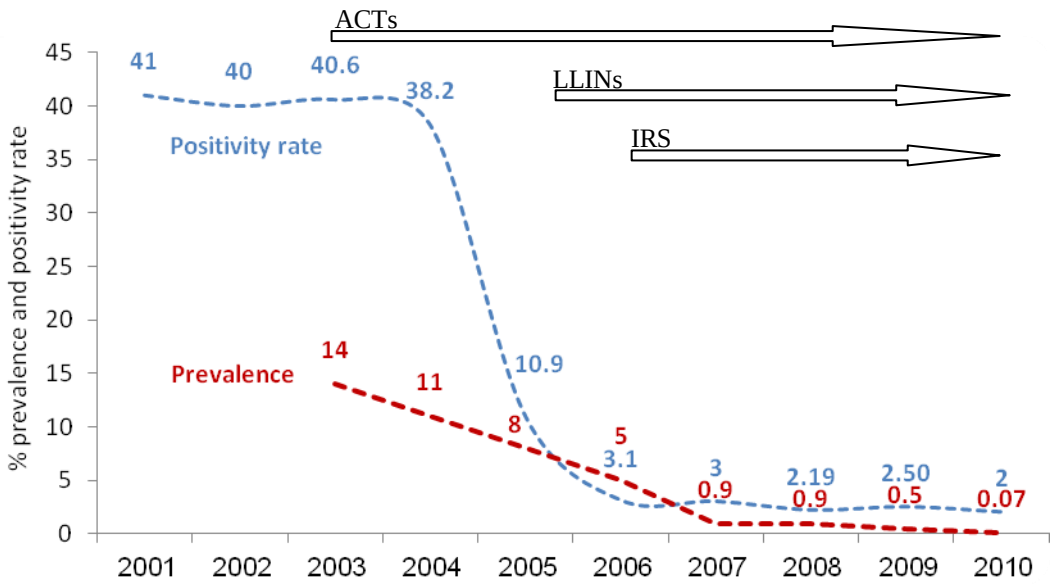


Figure 3: Prevalence (in the general population) and positivity rates (in suspected cases who are tested at the public health facilities) of malaria in Zanzibar in the past decade.
Source: Zanzibar Malaria Control Program (ZMCP, 2012)

Inspired by this success, one of the specific objectives in the 2007-2012 Zanzibar strategic plan was to assess the potential for sustainable malaria elimination [116]. Consequently, a feasibility assessment was done in 2009 and the conclusion of the report was that it would be feasible to reach and maintain malaria elimination with currently available tools. However, it was acknowledged that it would be extremely challenging, both operationally and financially [117]. Yet, since this report was published, Zanzibar has been targeting elimination and is one of the 39 "elimination countries" [128].

Rationale

Zanzibar has been in the forefront of the renewed fight against malaria. In 2002 it was one of the first nations to adopt ACTs, and vector-control interventions have been implemented and scaled-up rapidly. These efforts have markedly reduced the malaria burden in Zanzibar and have moved the country closer to the goal of malaria elimination.

AsAq was adopted in 2007 as a first-line drug by 16 SSA countries including Zanzibar. In Zanzibar, AsAq was not co-formulated at the time and was not delivered in age or weight specific blister-packs, factors that could reduce correct health worker prescribing and dispensing practices as well as consumer adherence. Since low adherence to drugs have both personal and public health consequences, it was considered important to establish adherence levels and identify reasons for non-adherence (Study I).

In 2005-2006 Zanzibar implemented a stand-alone targeted free mass distribution of LLINs. This mass delivery strategy was one of the first of its kind in SSA, and assessing the process of such a distribution would allow for identification of barriers in the health system that can be improved in order to achieve high and equitable coverage in future distributions (Study II).

Despite the rapid decline in malaria transmission in Zanzibar, sustaining high effective coverage of vector control interventions is crucial for achieving elimination and for avoiding malaria resurgence. Therefore, assessing effective coverage and identifying its associated factors is a key step in recognizing barriers to effective coverage and estimating the prospects for elimination (Studies II & III). Exploring caretaker perceptions of vector control interventions and the intention to continue their use when malaria burden further declines, was considered important in order to assess the prospect for sustained use of these interventions as Zanzibar approaches elimination (Studies III & IV).

AIM AND OBJECTIVES

Overall aim

To assess caretaker uptake of malaria control interventions for under-five children in an area where malaria transmission has rapidly decreased.

Specific objectives

1. To assess caretaker adherence to ACTs freely dispensed at public health facilities.

2. To evaluate the system effectiveness of a free mass distribution of long-lasting insecticidal nets (LLINs).

3. To assess the effective coverage of vector control interventions.

4. To explore caretaker perceptions of malaria and vector control interventions.

METHODS

Overall study design

The overall aim and specific objectives were achieved by conducting three quantitative surveys and one qualitative study (Figure 4).

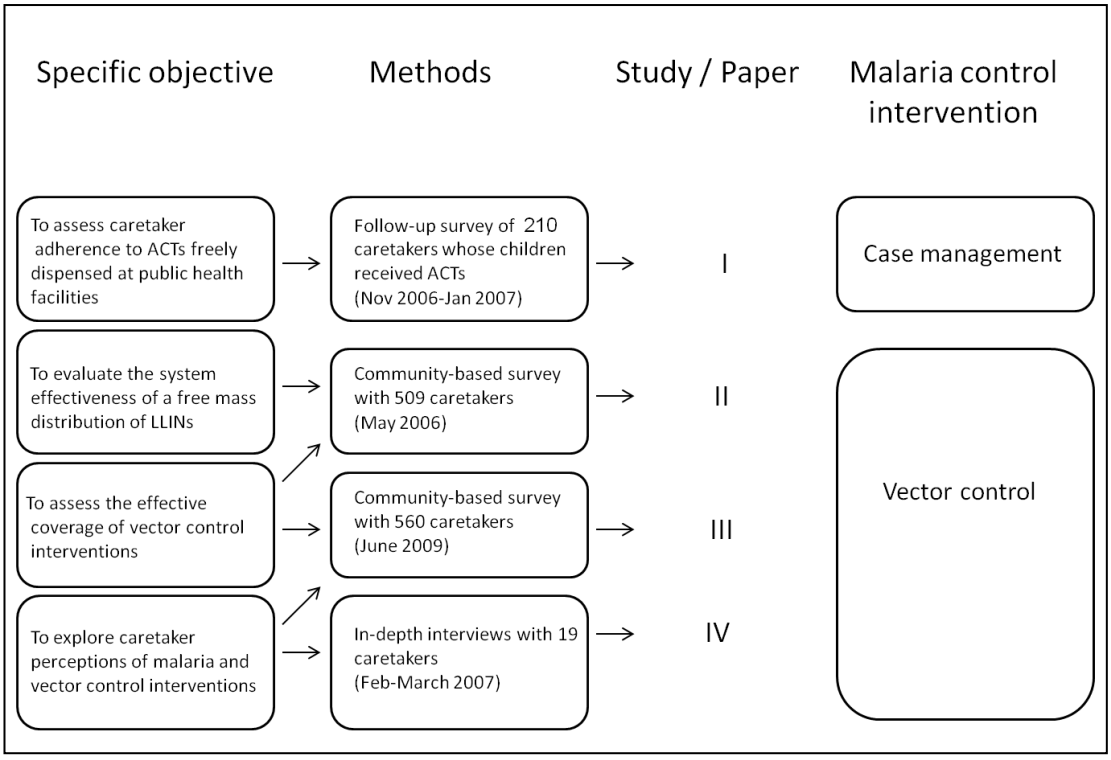


Figure 4: Overall study design

The studies were conducted over a course of three years, assessing the uptake of different malaria control interventions that were being routinely implemented by ZMCP. Figure 5 illustrates the timing of each study in relation to the different program implementations.

Study I, which assessed caretaker adherence to AsAq regimens, was carried out in Nov 2006 till Jan 2007. This was approximately 3 years after Zanzibar had implemented AsAq as the first-line treatment for uncomplicated malaria, and about 6 months after starting to use the "Falmal" co-blistered packaging.

Study II evaluated the different steps and outcomes of the targeted free mass distribution campaign of LLINs. It was done in May 2006 during the peak of the heavy rains season, nine and four months after the distribution in Micheweni and North A districts, respectively.

Study III, which assessed the effective coverage of vector control and intention to continue to use malaria prevention methods, as well as caretakers' perceptions of malaria and vector control, was done in June 2009 at the end of the heavy rains season.

This was around seven months after the second free mass distribution in Micheweni district, right after the distribution in North A district, and about six months after a round of IRS.

Study IV explored caretaker perceptions of malaria and bed-nets, and was conducted in Feb-March 2007. This was approximately one year after the targeted mass distribution was carried out, and 2-3 months after the second round of IRS was implemented.

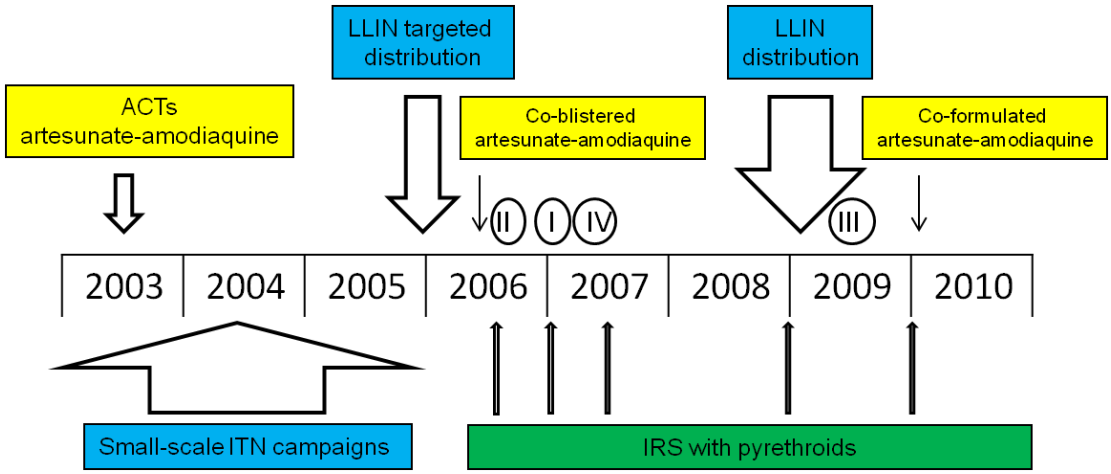


Figure 5: The timing of the studies (numbered in circles) in relation to the different major malaria control interventions (in boxes).

Study settings and participants

Study I was conducted in 8 of the 10 districts of Zanzibar. North A and Wete districts were excluded since, at the time of the study, all health facilities in these districts were engaged in piloting RDTs. It was likely that the routine prescribing and dispensing habits in these health facilities would be affected by the extensive training and supervision they had undergone. Studies II & III were done in the predominantly rural North A and Micheweni districts, as part of the annual malaria surveys that routinely took place in these districts. Study IV was carried out only in the North A district (see Figure 6).

All participants of the studies were caretakers of under-five children, most of them mothers. In Study I, the caretaker who was responsible for administering the medicine to the child was interviewed. In Studies II & III an available caretaker was interviewed, and priority was given to mothers. In Study IV, female and male caretakers whose under-five children had received an LLIN during the targeted distribution were purposefully chosen.

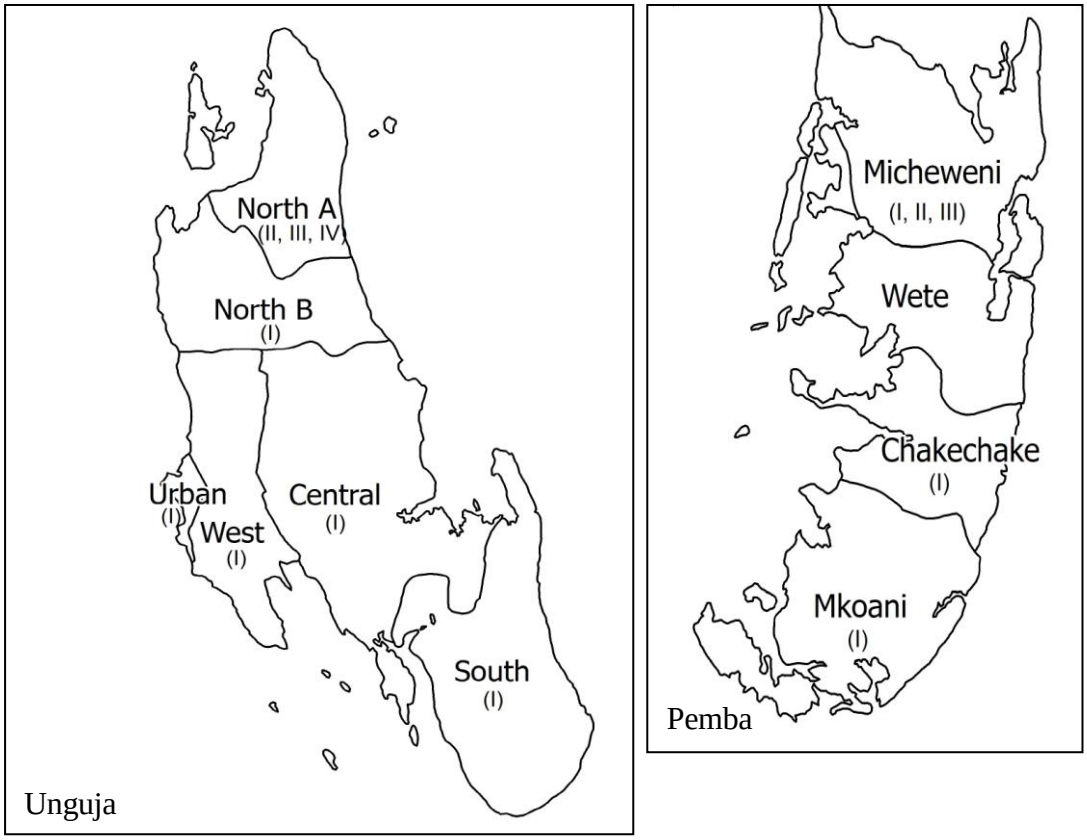


Figure 6: Zanzibar districts, and locations of the different studies (I-IV)

Study design, sampling and data collection

Study I

Adherence to the "Falmal" child package was assessed using a cross-sectional follow-up survey, where caretakers of under-five children who had received AsAq treatment for uncomplicated malaria at public health facilities were followed up in their homes four days after receiving the three-day treatment. A two-stage cluster sampling [129] was used to select the caretakers from 21 health facilities. The health facilities included 15 PHCUs that were randomly selected from the complete list of PHCUs in the districts. All three PHCCs, two district hospitals and the referral hospital were purposefully selected. Caretakers were randomly selected from a register of all children who had received AsAq treatment for uncomplicated malaria.

The caretaker who was responsible for administering the medicine to the child was interviewed in their homes using a structured questionnaire. Closed and open ended questions were asked on characteristics of the child and caretaker, instructions and drugs received at the health facility, laboratory tests made, amount of drugs dispensed, administration of drugs, vomiting of drugs, types and reasons for non-adherence, and opinions about the drugs.

Prescription at the health facility was determined by reviewing the patient book while drug dispensing was determined by caretaker reporting in combination with

examination of the remaining pill package, when available. Caretakers' adherence was assessed by the caretaker's self report in combination with pill count.

Studies II & III

Uptake of vector control interventions was assessed in two cross-sectional community-based surveys, where caretakers of under-five children from North A and Micheweni districts were interviewed in their homes. Two stage cluster sampling was used [129], whereby caretakers were randomly chosen from pre-selected Shehias. The caretaker was interviewed using a structured questionnaire with closed and open ended questions. In Study II, the caretakers were asked about bed-net ownership and use, experiences with the LLIN distribution, perceptions on LLINs and other bed-nets, as well as household characteristics. The interviewers also asked to see the nets reported and to document whether the nets were hanging above a sleeping space. In Study III, the caretakers were asked about their perceptions and beliefs on the malaria situation in Zanzibar and vector control interventions provided, household characteristics, use of bed-nets and IRS, and their intention to continue using vector control interventions as the malaria burden further declines.

Sample size calculations (Studies I, II & III)

The desired sample size was calculated in relation to the main study outcome. Thus, sample sizes were estimated according to caretaker adherence (Study I), and children under-five sleeping under an LLIN (Studies II & III). In all studies, calculations were done with the assumption that the proportion of the outcome was 50%, as this would result in the most conservative sample size. The calculations also accounted for a cluster effect of 2, an absolute precision of ±10% and 95% CI. These calculations resulted in a desired sample size of minimum 192 participants in the three studies.

Study IV

In-depth interviews with female and male caretakers were conducted to explore perceptions of malaria and bed-nets. The informants were all North A residents who were caretakers of children and had received at least one LLIN during the targeted distribution. They were purposefully selected by their ability to provide extensive answers in the open-ended questions of Study II. The interviews were carried out using interpreters and following an interview guide, which was based on the HBM framework. They were asked about perceived susceptibility and severity of malaria, benefits and barriers to bed-net use, self-efficacy in using bed-nets and cues to action.

Following each interview, the translated transcripts were reviewed to assess whether more interviews needed to be scheduled or whether saturation was achieved, as suggested by Dahlgren et al., 2007 [25]. After 19 interviews, it was felt that saturation had been reached.

Data management

Data from the quantitative studies (Studies I, II & III) were single entered in CSPro. The data was transferred to Excel where it was cleaned and checked for errors and inconsistencies. Open-ended questions were reviewed and coded. The data was then imported to STATA software, where recoding and generation of new variables continued. For example, some continuous variables, such as age and years of education, were re-coded into categorical variables.

The recorded in-depth interviews (Study IV) were transcribed verbatim and translated from Kiswahili to English by the study interpreters.

Data analysis

Univariate, bivariate and multivariate analysis (Studies I, II & III)

Data analysis was done using STATA software. Univariate analysis included presentation of frequencies and proportions of different categorical variables, and means and medians of continuous variables. Bivariate analysis was performed by using chi-square or bivariate logistic regression for dichotomous outcomes. Multivariate analysis (MVA) was done on all variables that were at the significance level of $p \leq 0.25$ in the bivariate analysis. Variables considered for MVA were checked for colinearity before being entered to the multivariate model. Variables that remained significant in the MVA were checked for interactions. P-values and confidence intervals in bivariate and MVA were adjusted for cluster effects using STATA svy command. The cluster effect was adjusted on the health facility level (Study I), household and shehia levels (Study II), and the shehia level (Study III).

Adherence definitions (Study I)

1. *Caretaker adherence* was defined as caretaker reporting giving the correct daily dosage of one of the two recommended AsAq regimens for the first 3 days from receiving the treatment, with the pill count not contradicting this report.
2. *Perfect caretaker adherence* was defined as, in addition to the above mentioned adherence criteria, the child not having vomited the drugs within half an hour, or caretaker having re-administered a vomited dose.

System effectiveness analysis (Study II)

Success in the four steps of the distribution process were assessed for all eligible children who were above one year old, to avoid including children who were not yet born at the time of registration. The four steps were:

1. Being registered to receive an LLIN.
2. Arriving at the distribution point.
3. Receiving an LLIN.
4. Sleeping under an LLIN.

Three measurements were used to assess each step, as proposed by Krause et al. [130]:

1. *Unconditional proportion* (UP) – The proportion of children who successfully completed a certain step out of all eligible children.
2. *Conditional proportion* (CP) – The proportion of children who successfully completed a certain step out of those who succeeded in previous steps.
3. *Accumulated proportion* (AP) – The proportion of children who successfully completed all steps up to and including a certain step out of all eligible children. The overall systems effectiveness was calculated as the AP of all distribution steps.

Equity analysis (Studies II & III)

An asset index was created by principal component analysis (PCA) as suggested by Filmer and Pritchett [131]. In Study II, assets which were used in the final model were type of floor, walls and roof, sources of water, and owning a mat, cupboard, sofa, clock, iron, phone, radio, motorcycle, car, TV and fridge. In Study III, the index was based on all socio economic variables and included type of floor, walls and roof, source of water and light, type of toilet and cooking facilities, and owning 20 different assets. The households were then divided into socio-economic quintiles based on their asset index.

In Study II, the difference in proportions of success of each distribution step between the poorest and least poor quintiles was checked for significance using chi-square. The equity effectiveness was calculated as the ratio of system effectiveness in the least poor and poorest quintiles.

In Study III, effective coverage of IRS and LLINs in different socio-economic quintiles was compared and the difference between the poorest and least poor quintiles was checked for significance using bivariate logistic regression.

Deductive content analysis (Study IV)

The HBM served as the main framework of Study IV and its elements (i.e. perceived susceptibility, perceived severity, perceived benefits, perceived barriers to bed-net use, cues to action and self efficacy) served as categories. Therefore, a deductive (directed) approach was applied whereby the categories were pre-determined according to the theory used [132, 133]. Meaning units were copied into a matrix where they were condensed and assigned a code [134], which was then placed under an HBM category.

Ethical considerations

All studies have been ethically approved by the appropriate authorities in Zanzibar. Studies I, II & IV were approved by the Zanzibar Medical Research Task Force and Study III was approved by the Zanzibar Medical Research Ethical Committee (ZAMEC).

District and local leaders (Shehas) were informed about all studies, and in Study I the health facility staff was also informed. Written consent was obtained from all participants before starting the interviews.

RESULTS

Adherence to ACTs (Study I)

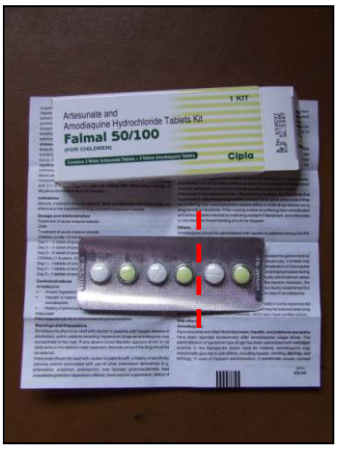
Caretaker adherence to AsAq was 77% (134/174) (95% CI: 67%–87%). Non-adherence resulted in under-dosing in 30 of the 40 non-adherers, and was most often a combination of mistakes such as giving the wrong daily doses (48%; 19/40) or not completing the 3-day treatment (30%; 12/40), as well as initiating treatment late or skipping pills. The main reasons for non-adherence were misunderstanding or forgetting the correct dose regimens (53%; 21/40). Other reasons included forgetting to give some of the pills, stopping treatment due to improvement in the child's health, difficulty in administering the medicine and thinking the treatment was too strong for the child.

The infant dose regimen was in most cases (59%; 39/66) dispensed with an inexact number of pills to complete the treatment regimen by cutting off the last 2 pills, and providing 2 As and 2 Aq pills, when in fact only 1.5 pills of As and Aq are required (Figure 7). This resulted in half pills being left over beyond three days, and although not considered as non-adherence, 9 caretakers continued and 20 intended to continue the treatment.

Predictors of adherence were caretaker's education exceeding 7 years (OR = 5.08, p=0.008) and receiving the exact number of pills to complete the treatment regimen (OR = 4.09, p=0.006). Additionally, all caretakers of children who were administered the first dose at the health facility had adhered to the treatment.

The majority of caretakers had positive opinions about the drugs. Negative opinions included complaints that the drugs were too strong and that they weaken or drowse the child, cause loss of appetite and are too bitter. Having positive or negative opinions about AsAq was not found to be associated with adherence.

In total, 19% (38/195) of the children vomited at least one dose within half an hour of drug intake. Perfect caretaker's adherence was therefore reduced to 63% (110/174) (95% CI: 54%–73%) after 24 caretakers, who were otherwise adherent, did not re-administer a vomited dose.



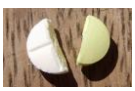
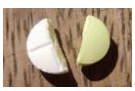
	Day 1	Day 2	Day 3
'Infant' dose regimen (<12 months or <10Kg)			
'Child' dose regimen (1-6 years or 10-20 Kg)			

Figure 7: Treatment instructions for 50/100 mg Falmal Package

Although the objective of the study was to assess caretaker's adherence, health worker's poor adherence to the national guidelines was found, as 11% (21/195) of the caretakers were excluded from adherence analysis due to receiving inappropriate prescribing and/or dispensing of drugs. Additionally, there was a large variance in adherence according to the health facility that dispensed the drug (29% to 100%). Caretakers who received the AsAq from PHCUs were significantly more likely to adhere (82%; 108/131), compared to those who received the medicine from hospitals and PHCCs (60%; 26/43) (p=0.03) (data from Study I).

System effectiveness of a targeted free mass distribution of LLINs (Study II)

The system effectiveness (AP) of the free mass distribution, in children 1 to 5 year old, was higher in the North A (87%) than in the Micheweni (49%) district. This was a result of higher conditional proportions of success in every one of the distribution steps. Effective coverage of the distribution (UP of the final step), was higher than the system effectiveness, at 88% in North A and 58% in Micheweni (Figure 8).

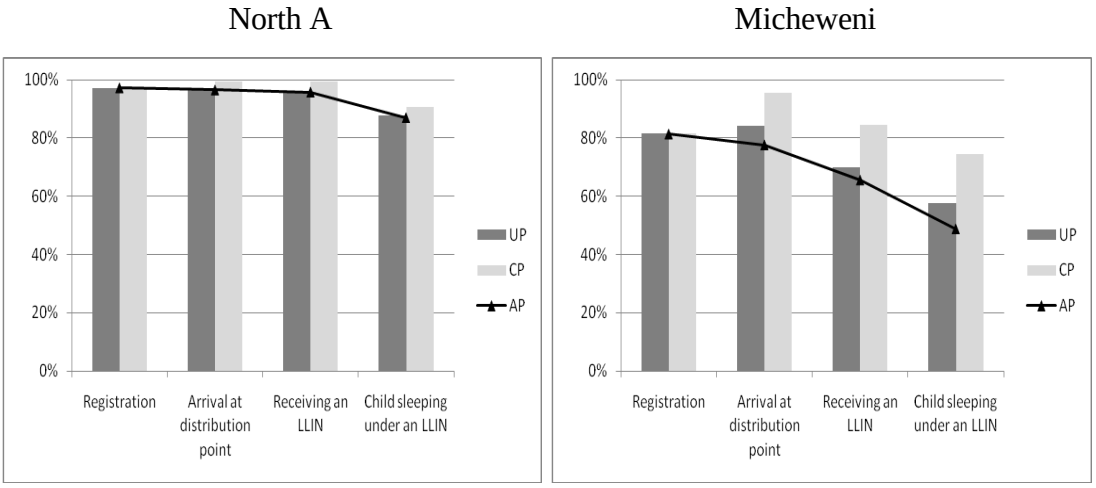


Figure 8: Unconditional Proportion (UP), Conditional Proportion (CP) and Accumulated Proportion (AP) of the LLIN distribution process in North A and Micheweni districts.

When comparing the proportions of success in each distribution step between the poorest and the least poor quintiles, equity was maintained in all distribution steps in North A district, resulting in an equity ratio of 1. In Micheweni district, system effectiveness was 1.5 times higher in the least poor compared to the poorest, with the greatest inequity occurring in the registration step (Table 3).

Table 3: Conditional Proportion (CP), Unconditional Proportion (UP) and Accumulated Proportion (AP) of the distribution steps in the poorest and least poor quintiles.

		Registered	Arrived at distribution point	Received an LLIN	Child sleeping under an LLIN	System effectiveness (AP)	Least poor: poorest equity effectiveness ratio	
Micheweni								
Least poor n = 50	CP	48/50 (96%)	48/48 (100%)	43/48 (90%)	32/43 (74%)	64%	1.5	(Pro-rich)
	UP	48/50 (96%)	48/50 (96%)	43/50 (86%)	32/50 (64%)			
Poorest n = 54	CP	38/54 (70%)	36/38 (95%)	32/36 (89%)	24/32 (75%)	44%		
	UP	38/54 (70%)	43/54 (80%)	37/54 (69%)	32/54 (59%)			
P-value	CP	0.0019	0.24	0.93	0.95	0.076		
	UP	0.0019	0.019	0.044	0.65			
North A								
Least poor n = 67	CP	65/67 (97%)	65/65 (100%)	64/65 (98%)	58/64 (91%)	87%	1	(Equitable)
	UP	65/67 (97%)	65/67 (97%)	64/67 (96%)	59/67 (88%)			
Poorest n = 45	CP	43/45 (96%)	43/43 (100%)	43/43 (100%)	39/43 (91%)	87%		
	UP	43/45 (96%)	43/45 (96%)	43/45 (96%)	39/45 (87%)			
P-value	CP	0.69	-	0.43	0.99	0.99		
	UP	0.69	0.69	0.99	0.82			

Effective coverage of vector control interventions (Studies II & III)

The overall effective coverage of LLINs in all under-five children in Study II was also assessed, as was the effective coverage by other types of bed-nets. In Study III, the effective coverage of under-five children to both LLINs and other types of nets, as well as IRS, was evaluated (Table 4). Effective coverage of LLINs and IRS in under-five children was equitable between the poorest and least poor quintiles.

Data on household coverage is also available, and in 2006 96% (375/392) of the under-five children in Micheweni district were living in a house with at least one bed-net, and 86% (336/392) were living in a house with at least one LLIN. In North A district, 99% (393/395) of the under-five children were living in a house with at least one bed-net, and 97% (383/395) were living in a house with at least one LLIN (data from Study II). In 2009, 99% (683/693) under-five children were living in a house with at least one bed-net, and 96% (663/693) were living in a house with at least one LLIN. However, only 64% (446/693) of the under-fives were living in a house where there was at least one bed-net per two persons, and 45% (311/692) were sleeping in a household where there was at least one LLIN per two persons (data from Study III).

Table 4: Effective coverage of vector control interventions in children under-five in North A and Micheweni districts in 2006 and 2009.

	2006			2009		
	North A	**Micheweni**	**Total**	**North A**	**Micheweni**	**Total**
LLINs	87% (338/389)	57% (216/380)	72% (554/769)	71% (241/338)	68% (218/322)	70% (459/660)
Conventional treated nets	5% (19/389)	27% (102/380)	16% (121/769)	8% (26/338)	6% (18/322)	7% (44/660)
Conventional untreated nets	5% (18/389)	4% (15/380)	4% (33/769)	9% (31/338)	8% (25/322)	9% (60/660)
Total treated nets (ITNs)	92% (357/389)	84% (318/380)	88% (675/769)	79% (267/338)	73% (236/322)	76% (503/660)
Total bed-nets	96% (375/389)	88% (333/380)	92% (708/769)	89% (301/338)	81% (262/322)	85% (563/660)
IRS				95% (324/342)	94% (314/333)	95% (638/675)
Both interventions (LLINs and IRS)				68% (225/329)	64% (201/314)	66% (426/643)
At least one of the interventions (LLINs and IRS)				98% (321/329)	98% (307/314)	98% (628/643)
Both interventions (ITNs and IRS)				75% (248/329)	70% (219/314)	73% (467/643)
At least one of the interventions (ITNs and IRS)				98% (324/329)	98% (307/314)	98% (631/643)

In 2009, effective coverage of the total population was lower than that of under-fives at 66% for ITNs (2,094/3,170) and 60% for LLINs (1,905/3,170), while IRS coverage remained high at 95% (3,266/3,455). While 57% of the population (1,776/3,095) was covered by both interventions, effective coverage by at least one vector control intervention was high at 97% (3,004/3095) (data from Study III).

In 2006, factors that were found associated with LLIN effective coverage of under-five children, in both districts, were a child receiving an LLIN and caretakers thinking that LLINs were better than conventional nets.

Bed-net usage patterns (Studies I, II & III)

Seasonality (Studies III & IV)

Interrupted bed-net usage in adults was common, whereby 33% of caretakers (171/514) reported to be using the bed-nets seasonally (data from Study III), while in under-five children seasonal usage was less common and was reported by 25% of the caretakers (125/508) (Study III). In Study IV, seasonality was seen to have an effect on different HBM elements and varied due to temperatures and rainfall. The heat caused by sleeping under the bed-net was considered as a barrier in the hot season, while in the cool season it was considered as a benefit. In the rainy season mosquito density was perceived to be higher, which affected both perceived malaria burden and mosquito nuisance. The mosquito nuisance affected the perceived added benefit of the bed-nets as protection against mosquito bites. The change in malaria burden might have an effect on the perceived susceptibility to malaria and the perceived benefit of using the net as protection against malaria, although these associations were not explicitly mentioned (Figure 9).

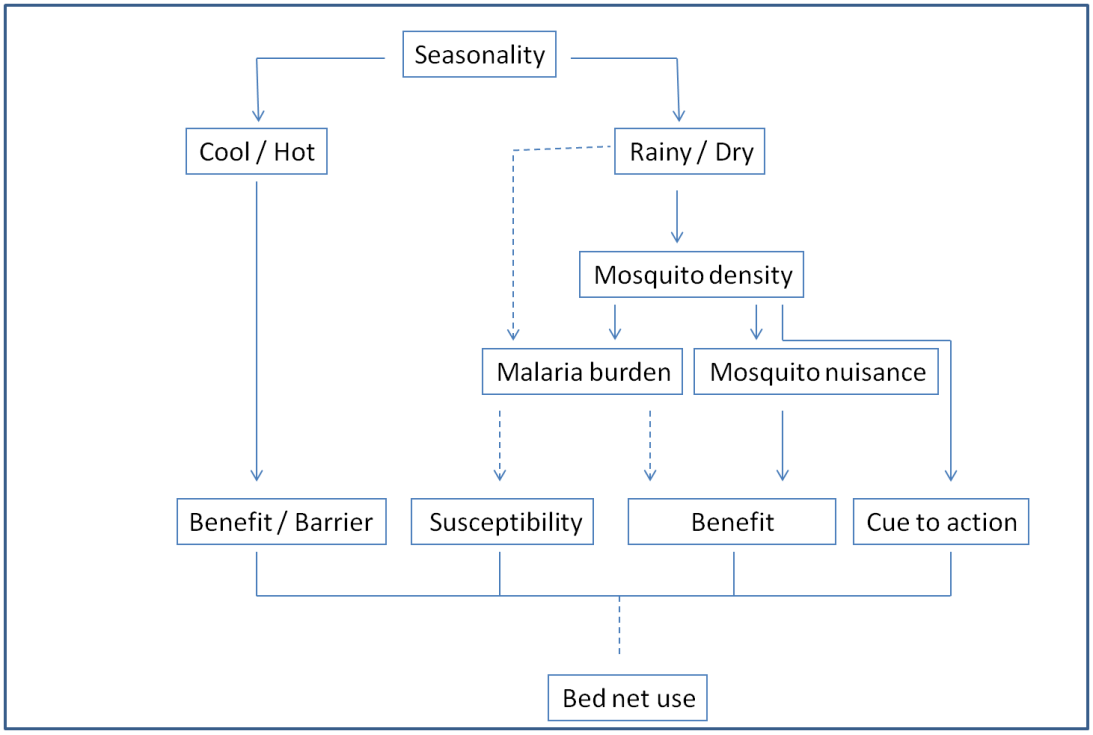


Figure 9: The effect of seasonality on elements of the Health Belief Model

Prioritizing children and bed-net sharing (Studies II, III & IV)

Under-five children were prioritized when it came to bed-net usage (Studies III & IV). This is evident from the higher reported continuous usage in children, mentioned above, as well as from the significantly higher overall proportion of children under-five sleeping under bed-nets as compared to over-fives. LLIN usage was especially higher in under-five children (70%; 459/660) than in over-fives (58%; 1,446/2,510) (Figure 10) (data from Study III).

In Study II it was found that of the 1,307 nets that were in use (excluding 127 that were not being used), 54% (701/1,307) were used by a single person while 40% (519/1,307) were shared by two people, 6% (83/1,307) were shared by three people, and four nets were shared by 4 people. While 45% (292/642) of the under-fives used a net by themselves, the others shared a net with one older household member (36%; 229/642), two older household members (9%; 56/642) or other under-fives (6%; 41/642) (data from Study II).

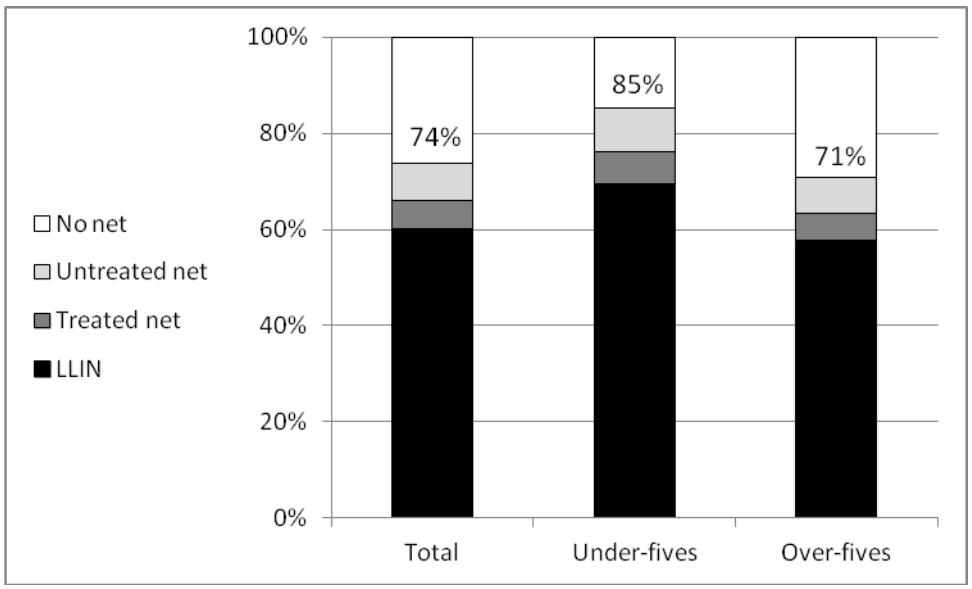


Figure 10: Under-five children and Over-fives sleeping under different types of bed-nets (data from Study III)

Caretaker perceptions on malaria and vector control (Studies II, III & IV)

Risk perceptions

Awareness of malaria among the caretakers was high but risk perceptions were low as the illness was seen as easily curable and uncommon (Study IV). The majority of caretakers (65%; 363/560) did not currently see malaria as a serious health problem (Study III). However, perceived susceptibility was strongly linked to mosquito density (Study IV) and was also considered higher in children (Study III & IV). A majority of caretakers believed that children were most at risk of contracting malaria (83%; 467/560), and most at risk of developing malaria complications (80%; 450/560) (Study III). One father explained:

> *"I pity the child because an adult can at least hit it [the mosquito] and it will leave, but a child is not able to do that….A child's health is delicate so he can get infected quickly"* 27 year old father (Study IV).

No association was found between different risk perceptions and LLIN effective coverage in under-five children (Study III).

Benefits and barriers

Caretakers spontaneously attributed the malaria reduction in Zanzibar mainly to bed-nets (41%; 231/560) and IRS (37%; 206/560). Malaria prevention methods mentioned by caretakers were bed-nets (75%; 414/560), environmental cleanliness (30%; 167/560) and IRS (18%; 100/560) (Study III).

Bed-nets were highly appreciated by caretakers and the majority of caretakers agreed to the statement that bed-nets were useful in preventing malaria and mosquito bites (Study III). The added benefit of bed-nets as protection against mosquito nuisance was also highlighted and seasonal and overall increase in mosquito burden was the main cue to action of using a bed-net (Figure 9).

> *"I think it is good [to use a bed-net] because the mosquitoes cannot penetrate. During the night I just enter into it and sleep well. If you do not cover yourself with a bed-net, you will not be able to sleep. You will have to chase the mosquitoes away here and there, they bite you sometimes, but if you sleep with it you will get a very nice sleep without problems."* 44 year old mother (Study IV)

Study IV also points to high self-efficacy of female caretakers, who are mainly responsible for covering the children with bed-nets.

Although some characteristics of LLINs were more appreciated (i.e. its color, strength, and ability to keep mosquitoes away), while others were considered problematic (i.e. large mesh size and insufficient height), satisfaction with these specific characteristics were not significantly associated with under-five use of LLINs (Study II).

The only major barrier to bed-net use was heat, as explained in more detail above under seasonality. Additionally, a barrier to bed-net ownership was the increasingly high cost of bed-nets (Study IV).

IRS was also perceived to be useful in preventing malaria and mosquito bites, though to a lesser extent than what was reported for bed-nets. Advantages of IRS that were spontaneously mentioned by caretakers included mosquito reduction (48%; 269/560) and insect reduction (41%; 230/560), while malaria reduction was mentioned by only 19% (104/560) of the caretakers (Study III). IRS shortcomings included the perceptions that their effect is temporary and specific only to malaria-carrying *Anopheles* mosquitoes (Study IV). Other disadvantages of IRS were mentioned by 20% (112/550) of the caretakers, and included side-effects such as itching and increased mosquito and insect populations (especially of bed-bugs) (Study III).

Study III indicates that most caretakers (85%, 456/536) found it useful to combine several preventive measures together, and over twenty percent of the caretakers (114/555) reported using additional means of malaria prevention, such as environmental cleanliness, canned insecticide, coils and other devices.

Sustainability

The importance of sustaining bed-net usage after malaria had declined was stated by 93% (502/537) of the caretakers, mainly because of the continued mosquito prevention and also because of continued malaria protection. For the same reasons sustained IRS after malaria reduction was acknowledged by 87% (487/546) of the caretakers. The majority of caretakers (95%; 500/524) mentioned that they would continue using preventive measures for their under-five children (Study III).

However, there was also an indication of strong dependency on the government and health workers to provide vector control interventions (Study IV). This is in line with the finding that in 2006 the proportion of nets that were reported to have been received for free was 63% (890/1,404), with 55% (791/1,435) being freely distributed LLINs (data from Study II). In 2009, the proportion of freely distributed nets increased and of those who slept under bed-nets, less than 20% (458/2,332) slept under a bed-net that was bought, while 77% (1,795/2,332) were sleeping under a freely distributed LLIN (data from Study III).

DISCUSSION

Discussion of main findings

In this thesis, the uptake of three malaria control interventions was assessed: Artemisinin-based combination therapies (ACTs), bed-nets and indoor-residual spraying (IRS). These three interventions are essential in reducing the malaria transmission (basic reproduction rate). Once the basic reproduction rate is below one, malaria elimination can be achieved. While the vector control interventions (i.e. bed-nets and IRS) reduce the efficiency of the mosquito vector (vectorial capacity), the infective parasite pool in humans or duration of infectivity is reduced by prompt and appropriate case management [1].

Vector control

Vector control interventions have an important role to play in reducing malaria transmission during malaria control, interrupting malaria transmission to achieve malaria elimination and preventing the re-establishment of malaria transmission after elimination had been achieved.

Effective coverage

Findings from Zanzibar demonstrate high and equitable effective coverage of vector control interventions following free mass distributions of long-lasting insecticidal nets (LLINs) and IRS campaigns (Studies II & III). One of the indicators that is commonly used to assess different insecticide-treated nets (ITN) delivery mechanisms is ITN use, especially by the vulnerable groups (i.e. pregnant women and under-five children). In this thesis the term ITN effective coverage is used in the same way as ITN use; both terms encompass access and adherence to ITNs.

Bed-net delivery mechanisms

With the aim of improving access to ITNs, a wide range of delivery mechanisms have been implemented since the late 90s. These included public sector, private sector, mixed public-private and community-based deliveries, that provided free, partially subsidized or unsubsidized ITNs to the public [135].

While private sector approaches did not normally result in high or equitable effective coverage [136, 137], mixed public-private sector delivery generally yielded better outcomes. The KINET project in Tanzania involved a social marketing program as well as a voucher scheme targeting pregnant women and mothers of small children. This project resulted in an increase in ITN effective coverage of children under-five and pregnant women. However, although equity had increased, socio-economic inequities were still present [71, 138, 139]. The national voucher scheme in Tanzania also demonstrated a steady increase in ITN effective coverage in pregnant women and under-five children, though it did not achieve equity [140, 141].

Since 2003, it was increasingly recognized that ITNs should be distributed free of charge in order to rapidly achieve high and equitable coverage [48]. Targeted distribution of free ITNs and LLINs to under-five children in conjunction with

immunization campaigns were shown to achieve these goals, with effective coverage in under-five children ranging from 46% in Senegal and Zambia to 81% in Madagascar, with improved equity [142-147]. Stand-alone targeted mass distribution campaigns of LLINs for under-five children, which were not in conjunction with other health activities, such as the one conducted in Zanzibar in 2005-2006, have also been implemented in Kenya and Tanzania [148, 149]. In Tanzania, the mass distribution resulted in under-five usage of LLINs at 64% [149]. In Zanzibar, following the targeted mass distribution, effective coverage of the distributed LLINs was high and equitable in the North A district, which is representative of the distribution scale-up, at 87%. ITN effective coverage in North A district was higher at 92% (Study II). These findings demonstrate that free targeted mass distribution of bed-nets, either through stand-alone campaigns or integrated with other health interventions, are an effective delivery strategy to increase equitable effective coverage in the targeted population.

Although targeting and prioritizing the under-five children and pregnant women has been a useful way of providing personal protection to these vulnerable groups, it has become increasingly recognized that high coverage levels of the entire population would utilize a community protective effect. This protective effect would increase the benefit to the entire population, including the vulnerable groups [150]. This is especially relevant since children above the age of five and adults comprise a large portion of the population, and are more attractive to mosquitoes, and thus they represent a large reservoir of parasites [95, 151, 152]. Additionally, as malaria transmission is reduced the entire population becomes vulnerable to malaria as they lose their acquired immunity. For countries targeting elimination, universal coverage is important due to the vital role that vector control plays in interrupting malaria transmission [46]. Due to the above-mentioned reasons, Roll-Back Malaria (RBM) shifted its target in 2008 from covering vulnerable groups to achieving universal coverage of one LLIN for every two people [48]. Accordingly, the mass distribution technique had changed and mass distributions were no longer targeting only the vulnerable groups. In Sierra Leone, an un-targeted distribution resulted in under-five effective ITN coverage of 73%, and in Nigeria under-five use was at 62% of those living in households that own at least one ITN [98, 153]. In Zanzibar, after two LLINs were distributed per household, overall under-five ITN effective coverage was at 76%, and LLIN effective coverage was at 70% and equitable (Study III). These findings show that effective coverage of under-five children with LLINs remained relatively high, even after the change in the distribution strategy from a targeted mass distribution to an un-targeted one.

Perhaps more relevant in assessing advances towards the elimination goal in Zanzibar is the overall effective coverage in the entire population. In 2009, the ITN effective coverage of the entire population was 66% and LLIN effective coverage was 60% (Study III). According to the elimination feasibility assessment, 60% is the minimal vector control coverage required for reaching the basic reproduction rate of less than one and, consequently, achieving elimination. It is predicted that achieving elimination with 65% effective coverage would take approximately two decades [117].

While free mass distributions have led to equitable and rapidly increased coverage [148], and are probably the most efficient "catch-up" strategy available, sustaining high

coverage would benefit from complementary routine interventions ("keep-up"). Therefore, different delivery strategies should be used to complement each other [154-157]. In Zanzibar, however, periodical mass distributions in 3-year intervals have been carried out (2006, 2009, 2012). This strategy might create gaps in the effective coverage due to population growth and in-migrations. Perhaps the establishment of "keep-up" strategies, including reinforcement of continuous LLIN delivery through the antenatal care services, as well as finding additional routine delivery strategies, such as provision of LLINs during immunizations or through schools, would elevate the effective coverage and make elimination more feasible.

Integrated vector control

In 2009, the 95% effective coverage with IRS was found to be much higher than that of LLINs and bed-nets in general (Study III). This is probably due to that fact that spraying one house effectively covers all of its inhabitants, while effective coverage of LLINs is still regarded as an individual intervention. Additionally, IRS does not require continuous adherence by community members beyond their initial agreement to have the house sprayed.

Together, IRS and ITNs effectively covered 98% of under-five children, and 97% of the total population (Study III). Although the use of ITNs and IRS simultaneously have the potential of producing an additive effect, it is more likely to achieve such an effect when different types of insecticides are used for IRS and ITNs. It was specifically recommended that when pyrethroid treated bed-nets are used, the IRS insecticide should have a different mode of action [37]. The fact that in 2009 pyrethroids were used as insecticides for both LLINs and IRS in Zanzibar does not optimize the potential of combining these two vector control interventions. Nevertheless, even when additive effects are not considered, the effective coverage to a vector control intervention was elevated. With such high effective coverage of vector control, the prospects of achieving elimination rise, and it has been predicted that with 100% effective coverage, elimination could be achieved in less than 5 years [117].

Access

Access to bed-nets can be assessed by measuring household ownership. In Tanzania, household ownership of at least one bed-net had increased from 37% to 73% during three years of an intense social marketing efforts in the KINET project [138]. Three years of the national voucher program in Tanzania resulted in a bed-net ownership increase from 44% to 65% [140]. Targeted free mass distributions to under-five children have resulted in ITN household ownership ranging from 94% in households with under-fives [144] to 63% in all households [145]. In Zanzibar, after the targeted mass distribution of LLINs, 96% of the children in Micheweni and 99% of the children in North A were living in a house that owned at least one bed-net, and 86% and 97% of children were living in a house with at least one LLIN, respectively (Study II). The un-targeted mass distribution in Zanzibar has resulted in 99% of the under-five children living in a house with at least one bed-net, and 96% living in a house with at least one LLIN (Study III). Other un-targeted distributions have also resulted in high access to bed-nets, where household ownership of at least one bed-net in Sierra Leone reached 88% [153] and 70% in Nigeria [98].

However, ownership of one bed-net per household does not indicate how much access an individual within that household has to a bed-net. Intra-household access can be better determined by measures that are in line with the universal access definition of 'one bed-net per two people'. According to this definition, in Zanzibar, although 99% and 96% of under-fives were living in a house with at least one bed-net and LLIN, respectively, only 64% and 45% were living in a house that reached universal coverage of bed-nets and LLINs (Study III). Similarly, in Sierra Leone, the 88% household coverage was reduced to 36% households with universal coverage [153]. High intra-household access was previously found to be the strongest determinant of use [98], and specifically for under-five use [158].

A more specific assessment of LLIN access can be achieved by reviewing the three first steps of the targeted mass distribution in the system effectiveness analysis. Due to the fact that the different steps are not mutually exclusive, those who were not registered could have still arrived at the distribution point and have ended up receiving an LLIN, and even those who did not arrive at the distribution point could have still received a net from a health worker at a different occasion. Therefore, the unconditional proportion (UP) of the third step is most appropriate to describe the overall access of an eligible child to an LLIN. In Micheweni district 70%, and in North A district 96% of the eligible children received an LLIN. In North A access to an LLIN was also equitable between the poorest and least poor. The higher access in North A district, as compared to Micheweni district, was especially attributed to incomplete registration of children and insufficient amount of LLINs for distribution during the pilot distribution in Micheweni. However, even children who did not personally receive an LLIN during the distribution could still have accessed and slept under an LLIN, most likely by using one that was distributed to another family member or sharing a net with family members who had received an LLIN in the same distribution (under-five siblings or pregnant mothers) (Study II).

Assessments of success in different steps of a delivery system were also done in order to evaluate a voucher scheme in Tanzania [141] and Ghana [159]. However, the voucher scheme in Tanzania, mostly due to the fact that the women had to treat their own nets with packaged insecticide, resulted in a low (30%) and inequitable cumulative rate of success [141]. In Ghana, the voucher scheme resulted in even lower success rates, mainly due to women not being offered a voucher and women not using the voucher to purchase a net. This type of detailed assessment, similar to the system effectiveness analysis in Study II, is important in order to find the specific barriers in the health system that can be improved [108].

In Zanzibar, access to LLINs highly depends on the government delivery strategies, since they are normally not available in the local market and private shops. In 2006, all LLINs identified in the survey were deployed through the targeted mass distribution, and in 2009 the vast majority of LLINs in Zanzibar were freely distributed nets (less than 6% were either bought or delivered through the short-lived voucher system).

Adherence

Adherence to LLINs was assessed in the system effectiveness analysis in Study II, as the conditional proportion of the final step of having a child sleep under an LLIN. This figure represents the caretaker's adherence to the LLIN intervention, as it signifies the proportion of children sleeping under an LLIN out of all the children who have received an LLIN. Adherence was at 74% in Micheweni district and at 91% in North A district (Study II). The higher adherence in North A district as compared to the pilot distribution in Micheweni district could be due to, among other factors, the emphasis on information, education and communication / behavior change communication (IEC/BCC) strategies in the distribution scale-up. However, although adherence was improved in the distribution scale-up, it still remained the weakest step compared to the preceding steps that determine access. The problematic gap between bed-net ownership and bed-net use has also been highlighted in several other studies [160, 161].

Seasonality

One factor that has been hampering continuous bed-net adherence is seasonality. The seasonal fluctuations interrupted regular use of bed-nets due to changes in perceived mosquito density, and possibly perceived malaria burden, as well as the discomfort of sleeping under a bed-net during the hot seasons (Study IV), as has previously been suggested by Winch et al. [93]. Seasonal usage was evident already from the early randomized control trials where bed-net adherence was found to increase in the wet and cold seasons as compared with the dry and hot seasons in Kenya and Ghana [94, 162, 163]. This trend continued throughout the years, and an increase in bed-net use was often observed during the cool, rainy seasons [100, 145, 146, 161, 164]. In Zanzibar, 33% of the caretakers and 25% of the under-five children were reported to be using bed-nets seasonally (Study III). Since heat was found to be the only major barrier to bed-net use (Study IV), delivery of LLINs with larger mesh size to allow for ventilation, could possibly improve bed-net use in the hot season.

Intra-household adherence

In Zanzibar, there was a strong indication of prioritizing children when it came to bed-net usage (Studies III & IV), and in 2009, even after an un-targeted distribution, children under-five were still more likely to use bed-nets (Study III). Age has previously been shown to be a determinant for adherence to bed-nets. Early experiences during a randomized control trial in Kenya indicated that adherence to bed-nets was higher in adults who were prioritized in using bed-nets due to their role as income providers. Under-fives were also less likely to sleep under a bed-net as it was perceived to be too hot or disrupt sleeping arrangements [94, 99]. Adult males were also found to be more likely to use bed-nets in a study done in Burkina Faso [96]. However, in a review of household surveys conducted from 1991 till 2001, it was shown that children's use of bed-nets increases with ownership, and that bed-net use was equal or higher in children as compared to adults in most settings, excluding findings from Zimbabwe, Kenya, Rwanda and Burkina Faso [164]. As delivery strategies focused more on targeting the vulnerable populations through targeted subsidies, free distributions and the accompanying IEC/BCC efforts, these groups were increasingly prioritized. Targeted delivery strategies to pregnant women resulted in an increase in

bed-net use in women and their children [165-167]. Similarly, following the targeting of under-five children, studies covering a wide-range of settings in Sub-Saharan Africa (SSA) have demonstrated a trend of prioritizing under-five children throughout the past decade [95, 97, 160]. Prioritizing children has continued even when distributions are no longer specifically targeting under-five children [98, 153].

In Zanzibar, under-five children most commonly shared a bed-net with one older household member (Study II). Sleeping arrangements influence who in the household uses the bed-net. In addition to targeting pregnant women, mothers' habit of sleeping with their young children also resulted in the overall observed advantage of females in the reproductive age when it comes to bed-net use [97, 98, 153]. When both parents share a sleeping space with their children, they are both protected under a bed-net, and this could explain the rise in bed-net use in the 20-44 age group that was shown in 18 SSA countries [95].

Risk perceptions

Risk perceptions of malaria in Zanzibar were low, with low perceived susceptibility and severity (Studies III & IV). Theoretically, according to the Health Belief Model (HBM), perceived susceptibility to a disease would influence an individual's readiness to engage in a health prevention action [78]. Reduction in perceived susceptibility has previously been shown to lower adherence to preventive measures, as in the case of childhood vaccinations, that become less appreciated for their benefits and, instead, more attention is given to their side-effects, after incidence of illnesses are reduced [168, 169]. While seasonal reduction in bed-net usage due to lower perceived risk of mosquitoes and malaria in the dry seasons was previously reported [93], reduction in bed-net use due to overall reduction in malaria burden has rarely been explored. One exception is a qualitative study done in Vanuatu where bed-net use was maintained in areas of low perceived risk of malaria [170]. High community acceptance of IRS has also been maintained in Southern Africa despite its success in dramatically reducing malaria burden [171]. These findings are in line with findings in Zanzibar, where despite the low risk perceptions, effective coverage of vector control interventions remained high (Study III). High perceived vulnerability of children is consistent with the prioritizing of children when it comes to bed-net use; although this perception was not found to be significantly associated with LLIN use (Studies III & IV).

Perceptions of vector control interventions

Bed-nets and IRS were highly appreciated by caretakers and were recognized as the main causes of malaria reduction in Zanzibar. In addition to the benefit of malaria reduction, both interventions, and especially bed-nets, were appreciated as protection against mosquito nuisance (Studies III & IV). This added benefit of bed-nets was previously documented in several countries [99, 100, 172, 173], and was most likely the main reason for continued use after malaria burden was reduced in Vanuatu [170]. Thus, it can be assumed that as long as there is need for protection against mosquito nuisance, bed-nets will remain desirable. However, different perceptions of bed-nets were not found to be significantly associated with LLIN use (Study III).

IRS was slightly less valued in comparison to bed-nets (Study III), as was documented in Mozambique [174]. While it was as well appreciated for general

insect reduction (Study III), it was also blamed for mosquito and insect increase (Studies III & IV). Bed-bug increase was previously reported from studies where dichloro-diphenyl-trichloro-ethane (DDT) was used for IRS [105]. Other disadvantages of IRS, which have also been observed in Mozambique [174], included its short lived effect of the insecticide and the belief that it affects only *Anopheles* mosquitoes (Studies III & IV). Reported side effects of IRS, such as itching (Study III), were also in line with previous findings [103]. However, despite these shortcomings, IRS was still well accepted, and community members had agreed to the spraying (Study III). This is in line with findings from Mozambique, where acceptance of IRS relied more on socio-political factors than on perceptions [174, 175].

Simultaneous use of bed-nets and IRS was highly acceptable, and caretakers valued the combination of several interventions (Study III). There was also no indication that IRS would be considered as a replacement for bed-nets, given its perceived disadvantages (Study IV). This is in contrast to previous findings indicating that additional protective measures would substitute rather than complement bed-nets [97, 102].

Sustained adherence

Studies II, III & IV indicate that sustained adherence to malaria control interventions by caretakers, in the face of declining malaria-transmission, is possible. This is supported by high effective coverage rates after malaria burden has markedly declined (Studies II & III), and by the reported intentions for their continued use after the malaria burden is further reduced (Study III). However, as malaria burden further declines and malaria becomes a rare disease, the community may experience "elimination fatigue" [48]. Community members might not be motivated to continue using or accepting preventive measures and may also relax the prompt treatment seeking behaviour associated with malaria. Therefore, it is necessary to engage the community in malaria elimination efforts and ensure that the community is aware of the continued risk of malaria resurgence and re-introduction [48]. It was previously found that involving the community in all stages of the IEC/BCC activities, from early planning [176] to the implementation stages [177], were vital for their success. Community-directed interventions, where the communities themselves direct the planning and implementation of intervention delivery, were found to be effective in bed-net interventions [177, 178].

Case management

Case management is important in treating malaria patients and reducing malaria morbidity and mortality. In addition to being a curative measure, it also has preventive traits as it reduces the duration of infectivity in humans and thus leads to reduction of malaria transmission. In the context of malaria elimination it is extremely important to identify and properly treat people infected with malaria as soon as possible to avoid onward transmission.

Adherence

Caretakers' adherence to Artesunate-Amodiaquine (AsAq) was shown to be moderate at 77% (Study I). However, the outcome could be considered quite good taking into account the facts that the drug was not co-formulated or optimally packaged, and that the health workers' dispensing practices were not optimal. It was difficult to compare the adherence level with other ACT adherence studies due to differences in ACTs used, methodologies and adherence definitions. Adherence in other studies varied from 39% to 97% for Sulfadoxine-pyrimethamine and artesunate combination [84, 179], Artemether-Lumefantrine (AL) combination [82, 83, 85, 86, 180-182], and AsAq combination [83, 183, 184]. These drug combinations all differ in dose regimens, formulation and packaging. In some studies the health workers were given special training before the assessment [83, 184], while others assessed adherence under routine conditions following a policy change [182]. Additionally, definitions of adherence vary across studies. While in some studies adherence is assessed by looking at the number of tablets left over when the treatment was supposed to be completed [184], others followed a more strict definition and took into account the reported timing and amount of each dose intake [85]. No recommended standard definition or methodology for adherence could be identified. The approach in Study I was to study adherence to AsAq under routine conditions and taking into consideration intake of correct daily dose during the three-day treatment.

In Study I, non-adherence mostly resulted in under-dosing. Sub-optimal drug levels can have implications on treatment failure [80], on the development of resistance to the antimalarial drug [81], and on infectivity. The major reasons given for non-adherence were caretaker misunderstanding or forgetting the correct dose regimens (Study I), as was also found previously in other studies [180, 183]. These obstacles could potentially be resolved by improving instructions either through better communication with the health worker [84, 91, 92, 185] or through providing simple pictorial inserts [185] that can be understood even by illiterate caretakers. Simplifying instructions are especially important given the finding that low education level was associated with non-adherence, as was previously shown in Zambia and Uganda [84-86].

One factor associated with non-adherence was the health worker's practice of dispensing inaccurate number of pills to complete the dose regimen. This practice also allowed for continuation of the regimen beyond the three-day-treatment. In 2010 (after Study I was done), a co-formulated AsAq tablet, packaged in four dose-specific packs was introduced in Zanzibar. This new co-formulated and blister-packed drug has likely improved adherence to AsAq, as there is evidence that age or weight specific blister-packs enhance both caretaker's [87, 88, 92, 186] and health workers' [187] adherence.

Administering the first dose at the health facility, which was also associated with adherence (Study I), is yet another intervention that can be reinforced at the health facility level. This practice would also be beneficial in avoiding late initiation of treatment and create an opportunity for re-administration of a vomited dose. Although this is a general treatment guideline [188], it is a practice that is rarely carried out [84, 92, 187].

Access

Although access to ACTs was not assessed in this thesis, achieving high access to efficacious malaria treatment is necessary for all malaria infected individuals. Access to malaria treatment depends, first of all, on health seeking behavior. The importance of seeking timely and appropriate treatment should therefore be highlighted and reinforced.

While ACTs are freely distributed at the public health facilities to all patients who are diagnosed with uncomplicated malaria, stock-outs and expired drugs sometimes hinder their availability. General efforts are being made in Zanzibar to improve the delivery of drugs and other supplies to the health facilities by employing the "pull" system. With the "pull" system, health facilities are responsible for requesting the supplies, while in the "push" system supplies are being delivered on the basis of forecasts that predict the quantities that would be needed (Personal communications with Mwinyi Msellem, Medical Laboratory Scientist –ZMCP, 2012). However, even when drugs are available, health care provider's non-compliance with national guidelines can hamper caretakers' access to appropriate treatment regimens. Findings from Study I indicate that in 11% of the cases health care providers prescribed and/or dispensed an incorrect dose regimen.

Making ACTs available in the private sector is pursued through the Affordable Medicines Facility - malaria (AMFm) program. AMFm, which has been implemented in Zanzibar since 2010, aims to ensure affordable drugs in the private sector through provision of heavily subsidized ACTs. Free and widespread availability of efficacious antimalarials are seen as a priority as Zanzibar approaches elimination. Since it is imperative that infected persons clear infection as soon as possible to avoid onward transmission, barriers to access and adherence should be removed [117].

Malaria elimination in Zanzibar

Massive financial and operational support that came with the world's renewed interest in malaria reduction has enabled Zanzibar to scale-up their efforts against malaria and achieve marked reductions in the malaria burden. After conducting an elimination feasibility assessment [117], Zanzibar has made the decision to target malaria elimination. Although Zanzibar is not an ideal candidate for elimination, it has several advantages that elevate its prospects for elimination: First, malaria transmission has been reduced in recent years [128, 189] to a point where it complies with the WHO epidemiological criteria for entering the pre-elimination phase [46]. Second, Zanzibar is an isolated archipelago [189] and thus has less importation risk by the vector and by infected humans [128]. Third, Zanzibar is a small nation with a manageable population size [189].

On the other hand, disadvantages include the fact that Zanzibar has a historical high innate transmission risk [117]. Being a low-income nation with generally poor health and a weak health system will make it challenging to keep a low burden disease at a high priority, although being a low-income country does have the advantage of being eligible for financial aid [189]. Also, its proximity to the mainland and the substantial daily incoming traffic of visitors, migrants and returning residents maintains the risk of importation [117].

The prospects for achieving and maintaining elimination highly depends on the vulnerability and receptivity of an area. Vulnerability is elevated with "either proximity to malarious areas or resulting from the frequent influx of infected individuals or groups and/or infective anophelines" [46]. Once parasites are imported, local transmission can be re-established due to high receptivity. Receptivity is "the abundant presence of anophline vectors and the existence of other ecological and climatic factors favoring malaria transmission" [46]. Zanzibar has high receptivity, evident by its high innate risk of transmission, and high vulnerability, due to the risk of importation by infected individuals. Thus, the greatest challenge to reaching elimination and then maintaining a malaria-free status, is to avoid the resurgence and re-establishment of malaria [117]. In order to achieve and maintain malaria elimination in Zanzibar, it will be necessary to uphold a high level of:

Surveillance – To quickly identify a high proportion of new malaria infections. This can be done by upgrading the current Malaria Early Epidemic Detection System (MEEDS) passive detection and expanding it to include all public and private health facilities. Once a positive case is reported, surveillance officers should follow up the case and screen family members and surrounding households through re-active case detection. Pro-active case detection may also be considered for the screening of those who are considered to be at high risk of malaria [117].

Case management – Once a malaria infected person is identified, efforts should be made to clear parasitemia as soon as possible. In addition to the personal benefit of promptly curing a person from malaria, the public health effect of reducing the duration of infectivity to reduce possibility of onward infection is especially vital when approaching malaria elimination [46].

Vector control interventions – To further avoid onward transmission by an infected individual, vector control efforts should be in place to reduce vectorial capacity. Reduction of the mosquitoes' daily survival rate is possible with IRS, and to a lesser extent by ITNs. A reduction of feeding frequency by disrupting human-vector contact is also achieved with ITNs [1] .

Community involvement – Just as community involvement was seen as an important component in malaria control [190], full collaboration from the community is believed to be needed in order to achieve and maintain elimination. This includes participation in all stages of the elimination efforts, from planning to implementation [117]. IEC and BCC activities should encourage community members to go for malaria testing with each febrile illness, and to accept and adhere to treatment regimens and preventive measures.

Commitment by the government and international donors – Leadership and strong political will is needed when embarking on the long and costly elimination goal. It is expected to become increasingly challenging to continue prioritizing an illness that is becoming rare when other illnesses are inflicting high burdens of morbidity and mortality. Additionally, it will become harder to maintain the external development partner's financial support. Targeting elimination is more costly than maintaining

controlled low-endemic malaria, mainly due to higher expenditures on surveillance and diagnosis, as well as management costs [117, 191].

The decision to target elimination rather than continuing with sustained control has programmatic, operational and financial consequences. In a highly vulnerable and receptive area like Zanzibar, these include maintaining extremely high levels of malaria control, emphasis on surveillance and case detection, ensuring continued commitment and leadership and high community participation, as well as measures to reduce importation risk and capacity building [117].

Methodological considerations

Study design

A great strength, but also a weakness, of the studies presented in this thesis is the fact that they assessed implementation of malaria control interventions carried out by a national control program. The strength was that following the Zanzibar experience was an opportunity to assess implementations under routine conditions. That, and the fact that this work was done in strong collaboration with the ZMCP, allowed us to identify and consequently address operational barriers in real-time. However, this was also a weakness since it was challenging to identify all the different details that may have affected the intervention outcomes. Since the interventions were not implemented simultaneously or in the same manner in all districts, the differences observed between districts were sometimes difficult to interpret (Studies II & III).

The three quantitative studies that were conducted were cross-sectional surveys. Therefore, although associations can be made through bivariate and multivariate analysis, the temporal relationships between the dependent and independent variables cannot be established [192]. For example, when finding an association between a perception and LLIN use, it should not be assumed that a certain perception is a determinant of LLINs use, when another plausible explanation could be that using LLINs has led to that perception (as was done in Study II).

External validity

External validity and generalizability are the extent to which a study's results can be relevant or applicable to other people or settings [192]. In general, while lessons learned from Zanzibar can be applicable to other SSA settings, Zanzibar is unique in several ways, and this should be considered before generalizing findings from Zanzibar to other SSA countries. First, Zanzibar is an archipelago, and thus its islands are separated and isolated from the African continent, which makes malaria elimination more feasible. Additionally, Zanzibar is small in area and population size, and is thus easier to manage and access.

External validity within the Zanzibar setting can also be affected by ways in which participants were selected in the different studies, and whether they are representative of the total population [192]. In Study I, adherence to ACTs was only assessed in caretakers who obtained the treatment at public health facilities. Assessing adherence in those who received treatment from the public sector might not be representative of those who received treatment from the private sector. However, ACTs in the private

sector were scarce at the time, as they were expensive and unaffordable to the majority of the population.

In Studies II & III, the sampling was done from a list of households provided by the Shehas. As a result, only households registered by the Shehas were included in the surveys. Since LLIN distributions and IRS spraying are also done through registration with Shehas, there is a possibility that community members who are not registered, and therefore also lack access to control interventions, were not represented. Additionally, Studies II & III were conducted as part of yearly cross-sectional malaria surveys that are routinely done in Micheweni and North A districts. Assessing effective coverage of vector control interventions in 2006 and again in 2009 was an opportunity to compare and evaluate changes over time. However, the repeated yearly interviews may have cause conditioning-effects, whereby behavior and reporting patterns are affected by the repeated interactions with the interviewers, as well as "research fatigue" or exhaustion [193]. To mitigate these effects, each year a random sampling within the pre-selected Shehias is done, so that the same households were not necessarily approached every year.

In Study IV, caretakers who gave extensive responses in a previous survey were prioritized. Therefore, more empowered and outspoken individuals participated in the study. This may have led to an overestimation of the high self-efficacy and decision making power of the female interviewees, and thus affect the transferability of the findings.

Internal validity and reliability

Internal validity refers to how well a study succeeded in measuring what it was intended to measure and how confident one can be in the results interpretation and conclusions, while reliability is the consistency or repeatability of the findings [194].

The way in which the information was collected may affect the internal validity of the studies. In Study II, bed-net usage was asked in a general manner rather than asking specifically about usage in the previous night, which is in line with the core RBM indicator. This way of asking about bed-net use may have resulted in an overestimation of usage. However, the interviewers viewed the bed-nets, and less than 5% (31/612) of the nets that were reported to have been used by under-five children were not seen hanging above a sleeping area at the time of the interview. Nevertheless, the fact that the nets were hanging does not necessarily mean they were being properly used to cover the individuals sleeping under them. Asking about bed-net usage in this way also makes it problematic to compare the study findings with findings of other studies, including Study III.

In Study III, some questions that are qualitative in nature were asked as closed-ended questions with dichotomous "yes"/"no" answers. This may have led, on some occasions, to answers that were not well thought out, and thus may have affected the reliability of the study. Perhaps a better way of asking these questions would have been using a Likert-like scale. However, in some instances, the closed-ended question would be followed by an open ended question in which the respondent was asked to elaborate on the dichotomous answer given.

Recall limitations may compromise the validity of the responses [193]. Limitations in recall may have affected the way in which caretakers reported on drug administration to their children in Study I. In order to minimize this limitation, interviews were conducted on the fourth day of receiving the medicine, only one day after the three day dose-regimen was supposed to have been completed.

In Studies II & III, detailed information from the distribution process may have been affected by recall limitations, as the distribution had taken place up to 9 months prior to the survey.

Social desirability bias is when respondents take social norms into account when responding to verbal interviews [193, 195]. This bias may have been enhanced due to the fact that interviewers of quantitative surveys were all health professionals, and also due to the fact that in the consent form it was mentioned that the ZMCP was involved conducting the survey. Thus, caretakers may have felt compelled to over-report adherence to malaria control measures such as correct intake of ACTs (Study I) or use of bed-nets (Studies II & III). In Study I, desirability bias was mitigated by confirming the self-reported adherence with pill count. In Study II, an assessment of self-report error was done by verifying that the reported nets were in fact hanging above a sleeping space.

In Study IV, the interviews were conducted by foreign researchers using interpreters. This may have affected the trustworthiness of this study by increasing social desirability aspects, as well as the possible impact that the interpreter may have on the findings [196]. This was mitigated by training the interpreters on the interview guide and considering only the dialogue between the interpreter and informant when analyzing the data.

Triangulation refers to combining different data collection methods or disciplines to address a research question [197]. The thesis includes both qualitative (Studies I, II & III) and quantitative methods (Study IV), and Study IV involved researchers from the fields of public health and psychology. In this thesis, findings from the different studies are combined to present a comprehensive picture of patterns in malaria control uptake and its implications on malaria elimination.

Ethical considerations

Although ethical clearance was granted, in Study I there was an ethical dilemma related to the follow-up of caretakers in their homes without their initial approval. However, since malaria is not a stigmatized illness, it is believed that obtaining informed consent upon arrival to the household was sufficient.

CONCLUSIONS AND IMPLICATIONS

Findings of this thesis indicate that caretaker uptake of malaria control interventions for children remains high in Zanzibar in the face of declining malaria burden. ACTs, freely provided at public health facilities, were relatively well adhered to, and the high effective coverage of IRS with the satisfactory effective coverage of LLINs, together provided an almost perfect effective coverage by vector control interventions. This high effective coverage elevates the prospects of achieving elimination in Zanzibar.

Adherence to ACTs was found to be relatively good, taking into consideration the fact that the drug was not co-formulated or ideally packaged. Sub-optimal adherence to ACTs compromises curing the patient, has implications on resistance and prolongs the duration of infection, thus increasing opportunities for onward transmission. The findings suggest that providing dose-specific blister packs (which were adopted in 2010), as well as improvements in health workers' prescribing and dispensing practices, would improve adherence.

ACTs are provided free of charge through the public sector, and efforts are being made to expand their access in the private sector by providing affordable ACTs through AMFm. Also, in addition to elevating caretaker adherence, improving health workers' prescribing and dispensing practices will also improve access to correct dose regimens.

Vector control interventions are currently highly dependent on delivery by the government through the support from external funders. IRS application requires highly skilled and professional staff, and therefore it is necessary that they are implemented under the management and control of health services. LLINs and ITNs, one the other hand, may be delivered through complementary delivery strategies to elevate their access. However, the possibility of community members to obtain LLINs and ITNs independently is impeded by increasingly high costs. Access to LLINs, for example, may be enhanced through the private sector by providing affordable and highly subsidised nets, similar to the way ACTs are provided through the AMFm.

Community acceptance of IRS and adherence to bed-nets have a substantial effect on the overall effective coverage of these interventions. Findings in this thesis suggest that IRS is well accepted while sub-optimal adherence levels to LLINs compromise their effectiveness. Therefore, there should be emphasis on the importance of LLINs in order to increase the adherence levels.

Community members' perceptions of the malaria control interventions were generally positive, while risk perceptions of malaria were low. Although there was no evidence of these perceptions' actual influence on adherence, it is important to maintain positive attitudes towards malaria control interventions. This can be done through different IEC/BCC activities, and it is important that these activities engage the community from the early stages of planning and implementation. Thus, ways of engaging the community in the elimination process should be pursued.

Recommendations

1. Improving health workers' prescribing and dispensing practices would enhance access to correct dose regimens according to the national guidelines, in addition to having a positive effect on caretaker adherence.

2. Since high effective coverage by vector control is mainly upheld by high IRS coverage, scaling back IRS should be reconsidered until a higher effective coverage of LLINs is obtained.

3. Although mass distributions of LLINs can achieve satisfactory and equitable effective coverage, the establishment of a continuous delivery strategy should be considered for maintaining high effective coverage.

4. Affordable LLINs should be made available in parallel to the free mass distributions in order to elevate their access and complement the governmental delivery strategies.

5. Raising the adherence to LLINs is necessary in order to achieve high effective coverage. IEC/BCC activities should therefore focus on elevating positive attitudes towards LLINs to increase adherence.

6. Emphasis should be placed on efforts which increase community participation and ownership in order to ensure community engagement and acceptance of malaria elimination efforts.

ACKNOWLEDGEMENTS

I thank all those who supported me throughout my PhD studies:

My supervisors and mentor
Karin – My brilliant main supervisor, for being supportive, available, sharp and attentive. Your ability to multitask, excel at a wide range of fields, and your remarkable writing and editing skills have always amazed me.

Anders – for taking me on for the wonderful Zanzibar project, for support and constructive criticism during manuscript and kappa writing.

Fred – especially for your kindness during my stay in Uganda.

Asli – My mentor, for listening and giving good advice. Sometimes your peaceful, gentle presence was enough. You are an exceptional woman.

In Zanzibar
I thank the Zanzibari caretakers for allowing us to enter their homes and for sharing their time and thoughts, and the shehas for welcoming, assisting and introducing us to their communities.

The wonderful ZMCP staff, thank you for welcoming me and making me feel at home right from the start. It was great working with such a group of committed and dedicated individuals. *Hongera* (congratulations) on your success in reducing malaria and saving lives!

At ZMCP I thank
First, Manager (Abdullah), for believing in me and for being a wonderful collaborator throughout all the different stages of the studies. Thank you for sharing the Zanzibar success story with me.

Abdul, for being a great colleague and a good friend throughout the years. Thank you for your invaluable help in a very wide range of tasks, from data management to providing useful information, helping me with *pikipiki* issues… I could always count on you.

Mwinyi, fellow student and friend, thank you for welcoming me into your home and giving me a chance to meet your beautiful family, and also for last minute assistance with kappa issues.

Ali and Rahila, for being great team leaders and making field work as smooth as possible.

My *madada* at ZMCP: Bi-Lucie, Safia, Ghanima, Amina(s), Hasna**,** Mgeni, Fatma and Jokha.

Others from ZMCP, especially Bakari, Dr.Shija, Dr. Moddy, Hashim, Mcha, Mkanga, Mohamed, Mwinyi, Sharifa and Zulfa.

At ZAMRUKI I thank
Guida, the former manager for being supportive and understanding, a great boss and friend.

Juma and Labani for protecting me, Raphael for driving me, Rose for caring for me.

Ilu, for everything! Translating, data entering, giving good advice, listening, supporting, and being excellent company.

Others from Zanzibar
All interviewers and study teams, especially Mdungi, Mzee Rajab, Faiza, Zuhura and Fatma.

Dr. Mahdi and Fabrizio, Patrick and Peter, for supporting and inspiring.

Bai, my Zanzibari mother. Thank you for taking good care of me and always welcoming me home.

ZNZ friends: Caludia, Judi and Masoud, Rashidi, Yahya and Muna, Mahsin, David and Sulla.

In Uganda
Colleagues from Mkerere and Iganga/Mayuge DSS in Uganda. Especially Suzanne, Josephine, Rosett, Najib, Jane, Dorean, Aloysius, Anne, Sabrina and George.

Ugandan Israelis, especially Rona, Boaz and Dorit, for friendship, help and holidays.

Little Light children and staff, especially Qasasa, Resti, Dr. Anna and little Betty, for making my stay in Uganda meaningful.

My family in Uganda: Qasasa (My Hero!) and all the kids you care for, including: David, Arafat, Linet, Baron, Trevor, and Auma Margret. You all hold a very special place in my heart.

At IHCAR
Birgitta, for all your support, and for helping me qualitatively.

Stefan, for providing me with research assistant positions in Uganda, and for your kindness and support.

Marie and Lucie, for that great kappa seminar.

Others from IHCAR: Hans, Vinod, Cecilia and Goran.

The HSP research group, for listening and providing helpful insights.

The kind and helpful administrative staff, especially Bo, Gun-Britt, Elisabeth, Kersti, Marie and Amina.

All of IHCAR's past, present and future students, for making IHCAR such a pleasant place to come to every day: Anna B, Anna T, Anastasia, Ashish, Ayesha, Charlotte, Chris, Cuong, David, Edith, Elin, Elizeus, Galit, Gorrette, Grethe, Hamideh, Hanani, Hassan, Helena, Helle, Herve, Hoa, Jaran, Jesca, Jessica, Jesper, Jill, Jolly, Krushna, Ketkesone, Linus Lisa, Marie, Meena, Mira, Mohamed, Mohammadi, Mohsin, Nina, Owolabi, Patricia, Peter, Rachel, Romano, Saima, Samina, Senia, Simba, Tam, Tazeen, Ziad
And my pregnant mothers cohort: Abela, Hana, Linda and Lotta.

Helena, Birger, Anastasia, Asli, Klara, Berty, Linda, Hana, Senia, Lotta and Yair, for advice and assistance with kappa issues.

Yanga! Thank you for lovely times.
Klara! For so many things…Can't quite imagine my time in Sweden without you.

At the malaria lab
Akira, Andreas, Berit, Pedro G. and Lisa, for good times.

The fun bunch of students at the malaria lab: Sabina, Christin, Johan(s), Pedro, Isabel, Isa, Ilomo, Maja, Aminatu, Billy, Mubi, Irina et al.

Deler and Kristina for making such a fun team in the Zanzibar 2009 X-sectional.

Family and friends
Sanja and Imba – for being my dadas in Zanzibar and beyond.
Sandra – for helping me out so many times with accommodation in Sweden and for all the other great things you do...
Lenka – for your friendship and helping me figure out statistics every now and again.
Batia – for providing me with a good solid base through my MPH training.
Maayan – for all the wonderful things you do, and especially for helping me out with Adam.

For friendship and support I thank: Alia and Yosef, Anat, Awadalla, Danit, Dotan, Gal, Niina and Madi, Sadik, Sigal(s), Yahya, Yair and Yiftach.

I thank my family: Ema and Broz for all the love and support, and Aba also for English editing, proof-reading and loads of morfaring.

My men – Ibra and Adam.
I am truly blessed to have you with me.
Am bogonyi chalaaaak!

REFERENCES

1. WHO: **Global Malaria Control and Elimination: Report of a technical review.** 17-18 January, 2008. Geneva.
2. WHO: **World Malaria Report 2011.** 2011. Geneva.
3. Warrell DA and Gilles HM (Ed.). **Essential Malariology**, 4th edition. London: Arnold; 2002.
4. CDC: **Malaria - Biology.** In *http://wwwcdcgov/malaria/about/biology/*; 2010.
5. Gething PW, Patil AP, Smith DL, Guerra CA, Elyazar IR, Johnston GL, Tatem AJ, Hay SI: **A new world malaria map: Plasmodium falciparum endemicity in 2010.** *Malar J* 2011, **10:**378.
6. WHO: **Guidelines for the Treatment of Malaria, 2nd edition.** 2010, Geneva.
7. WHO: **Africa malaria report 2003.** *WHO/CDS/MAL/20031093;* 2003.
8. WHO: **IMCI chart booklet for high HIV settings.** 2008.
9. Bjorkman A, Phillips-Howard PA: **Drug-resistant malaria: mechanisms of development and inferences for malaria control.** *Trans R Soc Trop Med Hyg* 1990, **84:**323-324.
10. Bjorkman A, Phillips-Howard PA: **The epidemiology of drug-resistant malaria.** *Trans R Soc Trop Med Hyg* 1990, **84:**177-180.
11. White NJ, Nosten F, Looareesuwan S, Watkins WM, Marsh K, Snow RW, Kokwaro G, Ouma J, Hien TT, Molyneux ME, et al: **Averting a malaria disaster.** *Lancet* 1999, **353:**1965-1967.
12. Trape JF, Pison G, Spiegel A, Enel C, Rogier C: **Combating malaria in Africa.** *Trends Parasitol* 2002, **18:**224-230.
13. Snow RW, Trape JF, Marsh K: **The past, present and future of childhood malaria mortality in Africa.** *Trends Parasitol* 2001, **17:**593-597.
14. White N: **Antimalarial drug resistance and mortality in falciparum malaria.** *Trop Med Int Health* 1999, **4:**469-470.
15. Trape JF: **The public health impact of chloroquine resistance in Africa.** *Am J Trop Med Hyg* 2001, **64:**12-17.
16. Bjorkman A: **Malaria associated anaemia, drug resistance and antimalarial combination therapy.** *Int J Parasitol* 2002, **32:**1637-1643.
17. Bjorkman A, Bhattarai A: **Public health impact of drug resistant Plasmodium falciparum malaria.** *Acta Trop* 2005, **94:**163-169.
18. WHO: **Antimalarial Drug Combination Therapy: Report of a WHO Technical Consultation.** 4-5 April 2001. Geneva.
19. WHO: **The use of antimalarial drugs: Report of a WHO informal consultation.** 13 - 17 November, 2000. Geneva
20. WHO: **Country antimalarial drug policies: by region: African region.** http://www.who.int/malaria/am_drug_policies_by_region_afro/en/; 2012.
21. Lindsay SW, Gibson ME: **Bednets revisited- old idea, new angle.** *Parasitol Today* 1988, **4:**270-272.
22. Lengeler C: **Insecticide-treated bed nets and curtains for preventing malaria.** *Cochrane Database Syst Rev* 2004**:**CD000363.
23. Lengeler C, Snow RW: **From efficacy to effectiveness: insecticide-treated bednets in Africa.** *Bull World Health Organ* 1996, **74:**325-332.
24. Lim SS, Fullman N, Stokes A, Ravishankar N, Masiye F, Murray CJ, Gakidou E: **Net Benefits: A Multicountry Analysis of Observational Data Examining Associations between Insecticide-Treated Mosquito Nets and Health Outcomes.** *PLoS Med*, **8:**e1001091.
25. Schellenberg JR, Abdulla S, Nathan R, Mukasa O, Marchant TJ, Kikumbih N, Mushi AK, Mponda H, Minja H, Mshinda H, et al: **Effect of large-scale social marketing of insecticide-treated nets on child survival in rural Tanzania.** *Lancet* 2001, **357:**1241-1247.
26. Eisele TP, Steketee RW: **African malaria control programs deliver ITNs and achieve what the clinical trials predicted.** *PLoS Med*, **8:**e1001088.

27. RBM: **Guidelines on the Use of Insecticide-treated Mosquito Nets for the Prevention and Control of Malaria in Africa.** 1997.
28. Guillet P, Alnwick D, Cham MK, Neira M, Zaim M, Heymann D, Mukelabai K: **Long-lasting treated mosquito nets: a breakthrough in malaria prevention.** *Bull World Health Organ* 2001, **79:**998.
29. WHO: **Insecticide-treated Mosquito Nets: A WHO Position Statement.** 2007. Geneva.
30. WHO: **Indoor residual spraying: Use of indoor residual spraying for scaling up global malaria control and elimination.** 2006. Geneva.
31. Pluess B, Tanser FC, Lengeler C, Sharp BL: **Indoor residual spraying for preventing malaria.** *Cochrane Database Syst Rev***:**CD006657.
32. Chitnis N, Schapira A, Smith T, Steketee R: **Comparing the effectiveness of malaria vector-control interventions through a mathematical model.** *Am J Trop Med Hyg*, **83:**230-240.
33. Yukich JO, Lengeler C, Tediosi F, Brown N, Mulligan JA, Chavasse D, Stevens W, Justino J, Conteh L, Maharaj R, et al: **Costs and consequences of large-scale vector control for malaria.** *Malar J* 2008, **7:**258.
34. Curtis CF, Maxwell CA, Finch RJ, Njunwa KJ: **A comparison of use of a pyrethroid either for house spraying or for bednet treatment against malaria vectors.** *Trop Med Int Health* 1998, **3:**619-631.
35. Kleinschmidt I, Schwabe C, Shiva M, Segura JL, Sima V, Mabunda SJ, Coleman M: **Combining indoor residual spraying and insecticide-treated net interventions.** *Am J Trop Med Hyg* 2009, **81:**519-524.
36. Kleinschmidt I, Torrez M, Schwabe C, Benavente L, Seocharan I, Jituboh D, Nseng G, Sharp B: **Factors influencing the effectiveness of malaria control in Bioko Island, equatorial Guinea.** *Am J Trop Med Hyg* 2007, **76:**1027-1032.
37. Okumu FO, Moore SJ: **Combining indoor residual spraying and insecticide-treated nets for malaria control in Africa: a review of possible outcomes and an outline of suggestions for the future.** *Malar J*, **10:**208.
38. WHO: **Vector control for malaria and other mosquito-borne diseases: report of a WHO study group.** In *WHO Technical Report Series*. 1995. Geneva.
39. Najera JA, Gonzalez-Silva M, Alonso PL: **Some lessons for the future from the Global Malaria Eradication Programme (1955-1969).** *PLoS Med*, **8:**e1000412.
40. Tanner M, de Savigny D: **Malaria eradication back on the table.** *Bull World Health Organ* 2008, **86:**82.
41. WHO: **The world malaria report 2005.** 2005.
42. WHO: **A Global Strategy for Malaria Control.** 1993. Geneva.
43. WHO: **Implementation of the global malaria control strategy. Report of a WHO Study Group on the Implementation of the Global Plan of Action for Malaria Control 1993-2000.** *World Health Organ Tech Rep Ser* 1993, **839:**1-57.
44. Nabarro DN, Tayler EM: **The "roll back malaria" campaign.** *Science* 1998, **280:**2067-2068.
45. WHO: **The Abuja Declaration and the Plan of Action.** 2000.
46. WHO: **Malaria Elimination: A field manual for low and moderate endemic countries.** 2007. Geneva.
47. Roberts L, Enserink M: **Malaria. Did they really say ... eradication?** *Science* 2007, **318:**1544-1545.
48. RBM: **The Global Malaria Action Plan.** 2008.
49. RBM: **Global Strategic Plan, Roll Back Malaria 2005-2015.** 2005.
50. UN: **Millennium Development Goals.** In http://wwwunorg/millenniumgoals/; 2000.
51. RBM: **Refined/Updated GMAP Objectives, Targets, Milestones and Priorities Beyond 2011.** 2011.
52. WHO: **Resolution WHA58.2. Malaria control.** Fifty-eighth World Health Assembly, Geneva, 16-25 May 2005; 2005.
53. UN: **Official list of MDG indicators.** 2008.

54. Atun R.A BS, Duran A: **Policy Brief: When do vertical (stand-alone) programmes have a place in health systems?** (Policies WROfEOoHSa ed.; 2008.
55. Tanner M. LC, Lorenz N.: **From the efficacy of disease control tools to community effectiveness.** *Trans R Soc Trop Med Hyg* 1993, **87:**518-523.
56. Tugwell P, de Savigny D, Hawker G, Robinson V: **Applying clinical epidemiological methods to health equity: the equity effectiveness loop.** *BMJ* 2006, **332:**358-361.
57. Phyo AP, Nkhoma S, Stepniewska K, Ashley EA, Nair S, McGready R, Ler Moo C, Al-Saai S, Dondorp AM, Lwin KM, et al: **Emergence of artemisinin-resistant malaria on the western border of Thailand: a longitudinal study.** *Lancet*.
58. WHO: **Global Report on Antimalarial Drug Efficacy and Drug Resistance: 2000-2010.** 2010. Geneva.
59. WHO: **Global Plan for Artemisinin Resistance containment.** 2011. Geneva.
60. Munhenga G, Masendu HT, Brooke BD, Hunt RH, Koekemoer LK: **Pyrethroid resistance in the major malaria vector Anopheles arabiensis from Gwave, a malaria-endemic area in Zimbabwe.** *Malar J* 2008, **7:**247.
61. Nwane P, Etang J, Chouaibou M, Toto JC, Kerah-Hinzoumbe C, Mimpfoundi R, Awono-Ambene HP, Simard F: **Trends in DDT and pyrethroid resistance in Anopheles gambiae s.s. populations from urban and agro-industrial settings in southern Cameroon.** *BMC Infect Dis* 2009, **9:**163.
62. Tolhurst R, Nyonator FK: **Looking within the household: gender roles and responses to malaria in Ghana.** *Trans R Soc Trop Med Hyg* 2006, **100:**321-326.
63. Vlassoff C, Garcia Moreno C: **Placing gender at the centre of health programming: challenges and limitations.** *Soc Sci Med* 2002, **54:**1713-1723.
64. Tanner M, Vlassoff C: **Treatment-seeking behaviour for malaria: a typology based on endemicity and gender.** *Soc Sci Med* 1998, **46:**523-532.
65. Nsungwa-Sabiiti J, Kallander K, Nsabagasani X, Namusisi K, Pariyo G, Johansson A, Tomson G, Peterson S: **Local fever illness classifications: implications for home management of malaria strategies.** *Trop Med Int Health* 2004, **9:**1191-1199.
66. Comoro C, Nsimba SE, Warsame M, Tomson G: **Local understanding, perceptions and reported practices of mothers/guardians and health workers on childhood malaria in a Tanzanian district--implications for malaria control.** *Acta Trop* 2003, **87:**305-313.
67. Eriksen J, Tomson G, Mujinja P, Warsame MY, Jahn A, Gustafsson LL: **Assessing health worker performance in malaria case management of underfives at health facilities in a rural Tanzanian district.** *Trop Med Int Health* 2007, **12:**52-61.
68. Font F, Alonso Gonzalez M, Nathan R, Kimario J, Lwilla F, Ascaso C, Tanner M, Menendez C, Alonso PL: **Diagnostic accuracy and case management of clinical malaria in the primary health services of a rural area in south-eastern Tanzania.** *Trop Med Int Health* 2001, **6:**423-428.
69. Curtis C, Maxwell C, Lemnge M, Kilama WL, Steketee RW, Hawley WA, Bergevin Y, Campbell CC, Sachs J, Teklehaimanot A, et al: **Scaling-up coverage with insecticide-treated nets against malaria in Africa: who should pay?** *Lancet Infect Dis* 2003, **3:**304-307.
70. Lines J, Lengeler C, Cham K, de Savigny D, Chimumbwa J, Langi P, Carroll D, Mills A, Hanson K, Webster J, et al: **Scaling-up and sustaining insecticide-treated net coverage.** *Lancet Infect Dis* 2003, **3:**465-466; discussion 467-468.
71. Schellenberg JR, Abdulla S, Minja H, Nathan R, Mukasa O, Marchant T, Mponda H, Kikumbih N, Lyimo E, Manchester T, et al: **KINET: a social marketing programme of treated nets and net treatment for malaria control in Tanzania, with evaluation of child health and long-term survival.** *Trans R Soc Trop Med Hyg* 1999, **93:**225-231.
72. Hanson K, Nathan R, Marchant T, Mponda H, Jones C, Bruce J, Stephen G, Mulligan J, Mshinda H, Schellenberg JA: **Vouchers for scaling up insecticide-**

treated nets in Tanzania: methods for monitoring and evaluation of a national health system intervention. *BMC Public Health* 2008, **8:**205.
73. Teklehaimanot A, Sachs JD, Curtis C: **Malaria control needs mass distribution of insecticidal bednets.** *Lancet* 2007, **369:**2143-2146.
74. Hart JT: **The inverse care law.** *Lancet* 1971, **1:**405-412.
75. Schellenberg JA, Victora CG, Mushi A, de Savigny D, Schellenberg D, Mshinda H, Bryce J: **Inequities among the very poor: health care for children in rural southern Tanzania.** *Lancet* 2003, **361:**561-566.
76. Bernard J, Mtove G, Mandike R, Mtei F, Maxwell C, Reyburn H: **Equity and coverage of insecticide-treated bed nets in an area of intense transmission of Plasmodium falciparum in Tanzania.** *Malar J* 2009, **8:**65.
77. Matovu F, Goodman C, Wiseman V, Mwengee W: **How equitable is bed net ownership and utilisation in Tanzania? A practical application of the principles of horizontal and vertical equity.** *Malar J* 2009, **8:**109.
78. Glanz K, Lewis FM, Rimer BK (Eds.): **Health behavior and health education: Theory, research, and practice**. San Francisco: Jossey-Bass; 1997.
79. Shumaker SA, Ockene JK, Riekert KA (Eds.): **The Handbook of Health Behavior Change**, 3rd edition. New York: Springer Publishing Company; 2009.
80. Oyakhirome S, Potschke M, Schwarz NG, Dornemann J, Laengin M, Salazar CO, Lell B, Kun JF, Kremsner PG, Grobusch MP: **Artesunate--amodiaquine combination therapy for falciparum malaria in young Gabonese children.** *Malar J* 2007, **6:**29.
81. White NJ, Olliaro PL: **Strategies for the prevention of antimalarial drug resistance: rationale for combination chemotherapy for malaria.** *Parasitol Today* 1996, **12:**399-401.
82. Lemma H, Lofgren C, San Sebastian M: **Adherence to a six-dose regimen of artemether-lumefantrine among uncomplicated Plasmodium falciparum patients in the Tigray Region, Ethiopia.** *Malar J*, **10:**349.
83. Ajayi IO, Browne EN, Bateganya F, Yar D, Happi C, Falade CO, Gbotosho GO, Yusuf B, Boateng S, Mugittu K, et al: **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.** *Malar J* 2008, **7:**190.
84. Depoortere E, Guthmann JP, Sipilanyambe N, Nkandu E, Fermon F, Balkan S, Legros D: **Adherence to the combination of sulphadoxine-pyrimethamine and artesunate in the Maheba refugee settlement, Zambia.** *Trop Med Int Health* 2004, **9:**62-67.
85. Fogg C, Bajunirwe F, Piola P, Biraro S, Checchi F, Kiguli J, Namiiro P, Musabe J, Kyomugisha A, Guthmann JP: **Adherence to a six-dose regimen of artemether-lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Uganda.** *Am J Trop Med Hyg* 2004, **71:**525-530.
86. Cohen JL, Yavuz E, Morris A, Arkedis J, Sabot O: **Do patients adhere to over-the-counter artemisinin combination therapy for malaria? evidence from an intervention study in Uganda.** *Malar J*, **11:**83.
87. Gomes M, Wayling S, Pang L: **Interventions to improve the use of antimalarials in south-east Asia: an overview.** *Bull World Health Organ* 1998, **76 Suppl 1:**9-19.
88. Qingjun L, Jihui D, Laiyi T, Xiangjun Z, Jun L, Hay A, Shires S, Navaratnam V: **The effect of drug packaging on patients' compliance with treatment for Plasmodium vivax malaria in China.** *Bull World Health Organ* 1998, **76 Suppl 1:**21-27.
89. McCombie SC: **Treatment seeking for malaria: a review of recent research.** *Soc Sci Med* 1996, **43:**933-945.
90. Nshakira N, Kristensen M, Ssali F, Whyte SR: **Appropriate treatment of malaria? Use of antimalarial drugs for children's fevers in district medical units, drug shops and homes in eastern Uganda.** *Trop Med Int Health* 2002, **7:**309-316.
91. Agyepong IA, Ansah E, Gyapong M, Adjei S, Barnish G, Evans D: **Strategies to improve adherence to recommended chloroquine treatment regimes: a**

quasi-experiment in the context of integrated primary health care delivery in Ghana. *Soc Sci Med* 2002, **55:**2215-2226.
92. Conteh L, Stevens W, Wiseman V: **The role of communication between clients and health care providers: implications for adherence to malaria treatment in rural Gambia.** *Trop Med Int Health* 2007, **12:**382-391.
93. Winch PJ, Makemba AM, Kamazima SR, Lwihula GK, Lubega P, Minjas JN, Shiff CJ: **Seasonal variation in the perceived risk of malaria: implications for the promotion of insecticide-impregnated bed nets.** *Soc Sci Med* 1994, **39:**63-75.
94. Alaii JA, Hawley WA, Kolczak MS, ter Kuile FO, Gimnig JE, Vulule JM, Odhacha A, Oloo AJ, Nahlen BL, Phillips-Howard PA: **Factors affecting use of permethrin-treated bed nets during a randomized controlled trial in western Kenya.** *Am J Trop Med Hyg* 2003, **68:**137-141.
95. Noor AM, Kirui VC, Brooker SJ, Snow RW: **The use of insecticide treated nets by age: implications for universal coverage in Africa.** *BMC Public Health* 2009, **9:**369.
96. Okrah J, Traore C, Pale A, Sommerfeld J, Muller O: **Community factors associated with malaria prevention by mosquito nets: an exploratory study in rural Burkina Faso.** *Trop Med Int Health* 2002, **7:**240-248.
97. Baume CA, Marin MC: **Intra-household mosquito net use in Ethiopia, Ghana, Mali, Nigeria, Senegal, and Zambia: are nets being used? Who in the household uses them?** *Am J Trop Med Hyg* 2007, **77:**963-971.
98. Ye Y, Patton E, Kilian A, Dovey S, Eckert E: **Can universal insecticide-treated net campaigns achieve equity in coverage and use? the case of northern Nigeria.** *Malar J*, **11:**32.
99. Alaii JA, van den Borne HW, Kachur SP, Shelley K, Mwenesi H, Vulule JM, Hawley WA, Nahlen BL, Phillips-Howard PA: **Community reactions to the introduction of permethrin-treated bed nets for malaria control during a randomized controlled trial in western Kenya.** *Am J Trop Med Hyg* 2003, **68:**128-136.
100. Frey C, Traore C, De Allegri M, Kouyate B, Muller O: **Compliance of young children with ITN protection in rural Burkina Faso.** *Malar J* 2006, **5:**70.
101. Galvin KT, Petford N, Ajose F, Davies D: **An exploratory qualitative study on perceptions about mosquito bed nets in the Niger Delta: what are the barriers to sustained use?** *J Multidiscip Healthc*, **4:**73-83.
102. Wiseman V, Scott A, McElroy B, Conteh L, Stevens W: **Determinants of bed net use in the Gambia: implications for malaria control.** *Am J Trop Med Hyg* 2007, **76:**830-836.
103. Rodriguez AD, Penilla RP, Rodriguez MH, Hemingway J, Trejo A, Hernandez-Avila JE: **Acceptability and perceived side effects of insecticide indoor residual spraying under different resistance management strategies.** *Salud Publica Mex* 2006, **48:**317-324.
104. Govere J, Durrheim D, la Grange K, Mabuza A, Booman M: **Community knowledge and perceptions about malaria and practices influencing malaria control in Mpumalanga Province, South Africa.** *S Afr Med J* 2000, **90:**611-616.
105. Rafatjah H: **The problem of resurgent bed-bug infestation in malaria eradication programmes.** *J Trop Med Hyg* 1971, **74:**53-56.
106. Mnzava AEP, Ntuli MV, Sharp B, Mthembu DJ, Ngxongo S, le Sueur D: **House replastering as a reason to shift from DDT spraying to synthetic pyrethroids.** *S Afr Med J* 1998, **88:**1024-1028.
107. Shengelia B, Tandon A, Adams OB, Murray CJ: **Access, utilization, quality, and effective coverage: an integrated conceptual framework and measurement strategy.** *Soc Sci Med* 2005, **61:**97-109.
108. The malERA Consultative Group on Health Systems and Operational Research **A research agenda for malaria eradication: health systems and operational research.** *PLoS Med*, **8:**e1000397.
109. WHO: **Background paper for the Technical Consultation on Effective Coverage of Health Systems.** 27-29 August, 2001**.** Rio de Janeiro, Brazil; 2001.

110. Zanzibar MoHSW: **Zanzibar Health Sector Reform Strategic Plan II 2006/7-2010/11.** 2006.
111. Zanzibar MoH: **Zanzibar Health Management Information System (ZHMIS).** In *http://417320142/hmisnews/*; 2011.
112. Tanzania National Bureau of Statistics: **2002 census: Analytical Report.** 2006.
113. Tanzania National Bureau of Statistics: **Tanzania in Figures 2010.** 2011.
114. Zanzibar MoHSW: **Zanzibar Health Sector Reform Strategic Plan I: 2002/2003-2006/2007. 2002**.
115. Tanzania National Bureau of Statistics: **Tanzania Demographic and Health Survey 2010.** 2011.
116. Zanzibar MoHSW: **Assessing the Potential for Elimination: Zanzibar Strategic Plan for Malaria Control 2007-2012.** 2007.
117. ZMCP: **Malaria Elimination in Zanzibar: A Feasibility Assessment.** *http://wwwmalariaeliminationgrouporg/sites/default/files/MalariaEliminationZanzibarpdf*; 2009.
118. Curtis CF, Mnzava AE: **Comparison of house spraying and insecticide-treated nets for malaria control.** *Bull World Health Organ* 2000, **78:**1389-1400.
119. Schwartz E, Pener H, Issa SM, Golenser J: **An overview of the malaria situation in Zanzibar.** *J Community Health* 1997, **22:**33-44.
120. Zanzibar Roll Back Malaria Programme: **National Guidelines for Malaria Diagnosis and Treatment in Zanzibar** 2002.
121. Zanzibar MoHSW: **Dawa za kutibu malaria artesunate na amodiaquine zilizofungwa pamoja (co-blister pack).** In *WAUJ/DMU/1/6*; 2006.
122. Zanzibar MoHSW: **National Guidelines for Malaria Diagnosis and Treatment in Zanzibar.** 2010.
123. Zanzibar MoHSW: **Annual Report Zanzibar Malaria Control Programme.** 2010.
124. ZMCP: **Roll Back malaria evaluation report.** 2005.
125. PMI: **Malaria Operational Plan (MOP) Tanzania.** 2006.
126. Bhattarai A, Ali AS, Kachur SP, Martensson A, Abbas AK, Khatib R, Al-Mafazy AW, Ramsan M, Rotllant G, Gerstenmaier JF, et al: **Impact of artemisinin-based combination therapy and insecticide-treated nets on malaria burden in Zanzibar.** *PLoS Med* 2007, **4:**e309.
127. Aregawi MW, Ali AS, Al-mafazy AW, Molteni F, Katikiti S, Warsame M, Njau RJ, Komatsu R, Korenromp E, Hosseini M, et al: **Reductions in malaria and anaemia case and death burden at hospitals following scale-up of malaria control in Zanzibar, 1999-2008.** *Malar J*, **10:**46.
128. Feachem RG: **Shrinking the Malaria Map, a guide on malaria elimination for policy makers.** The Malaria Elimination Group; 2009.
129. Levy PS, Lemeshow S: **Two-stage cluster sampling; clusters sampled with equal probability.** In *Sampling of populations: Methods and applications. Volume* 3rd Ed. Edited by Groves RM, Kalton G, Rao JNK, Schwarz N, Skinner C. New York: John Wiley & Sons, Inc.; 1999
130. Krause G, Borchert M, Benzler J, Diesfeld HJ: **From diagnosis to drug taking: staff compliance with guidelines and patient compliance to prescriptions in Burkina Faso.** *Int J Qual Health Care* 2000, **12:**25-30.
131. Filmer D, Pritchett LH: **Estimating wealth effects without expenditure data--or tears: an application to educational enrollments in states of India.** *Demography* 2001, **38:**115-132.
132. Hsieh HF, Shannon SE: **Three approaches to qualitative content analysis.** *Qual Health Res* 2005, **15:**1277-1288.
133. **Qualitative content analysis** *http://www.qualitative-research.net/index.php/fqs/article/view/1089/2385#g4*
134. Graneheim UH, Lundman B: **Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness.** *Nurse Educ Today* 2004, **24:**105-112.
135. Webster J, Hill J, Lines J, Hanson K: **Delivery systems for insecticide treated and untreated mosquito nets in Africa: categorization and outcomes achieved.** *Health Policy Plan* 2007, **22:**277-293.

136. Noor AM, Omumbo JA, Amin AA, Zurovac D, Snow RW: **Wealth, mother's education and physical access as determinants of retail sector net use in rural Kenya.** *Malar J* 2006, **5:**5.
137. Hamel MJ, Odhacha A, Roberts JM, Deming MS: **Malaria control in Bungoma District, Kenya: a survey of home treatment of children with fever, bednet use and attendance at antenatal clinics.** *Bull World Health Organ* 2001, **79:**1014-1023.
138. Nathan R, Masanja H, Mshinda H, Schellenberg JA, de Savigny D, Lengeler C, Tanner M, Victora CG: **Mosquito nets and the poor: can social marketing redress inequities in access?** *Trop Med Int Health* 2004, **9:**1121-1126.
139. Mushi AK, Schellenberg JR, Mponda H, Lengeler C: **Targeted subsidy for malaria control with treated nets using a discount voucher system in Tanzania.** *Health Policy Plan* 2003, **18:**163-171.
140. Hanson K, Marchant T, Nathan R, Mponda H, Jones C, Bruce J, Mshinda H, Schellenberg JA: **Household ownership and use of insecticide treated nets among target groups after implementation of a national voucher programme in the United Republic of Tanzania: plausibility study using three annual cross sectional household surveys.** *BMJ* 2009, **339:**b2434.
141. Marchant T, Schellenberg D, Nathan R, Armstrong-Schellenberg J, Mponda H, Jones C, Sedekia Y, Bruce J, Hanson K: **Assessment of a national voucher scheme to deliver insecticide-treated mosquito nets to pregnant women.** *CMAJ*, **182:**152-156.
142. Thwing JI, Perry RT, Townes DA, Diouf MB, Ndiaye S, Thior M: **Success of Senegal's first nationwide distribution of long-lasting insecticide-treated nets to children under five - contribution toward universal coverage.** *Malar J*, **10:**86.
143. Grabowsky M, Farrell N, Hawley W, Chimumbwa J, Hoyer S, Wolkon A, Selanikio J: **Integrating insecticide-treated bednets into a measles vaccination campaign achieves high, rapid and equitable coverage with direct and voucher-based methods.** *Trop Med Int Health* 2005, **10:**1151-1160.
144. Grabowsky M, Nobiya T, Ahun M, Donna R, Lengor M, Zimmerman D, Ladd H, Hoekstra E, Bello A, Baffoe-Wilmot A, Amofah G: **Distributing insecticide-treated bednets during measles vaccination: a low-cost means of achieving high and equitable coverage.** *Bull World Health Organ* 2005, **83:**195-201.
145. Wolkon A, Vanden Eng JL, Morgah K, Eliades MJ, Thwing J, Terlouw DJ, Takpa V, Dare A, Sodahlon YK, Doumanou Y, et al: **Rapid scale-up of long-lasting insecticide-treated bed nets through integration into the national immunization program during child health week in Togo, 2004.** *Am J Trop Med Hyg*, **83:**1014-1019.
146. Thwing J, Hochberg N, Vanden Eng J, Issifi S, Eliades MJ, Minkoulou E, Wolkon A, Gado H, Ibrahim O, Newman RD, Lama M: **Insecticide-treated net ownership and usage in Niger after a nationwide integrated campaign.** *Trop Med Int Health* 2008, **13:**827-834.
147. Kulkarni MA, Vanden Eng J, Desrochers RE, Cotte AH, Goodson JL, Johnston A, Wolkon A, Erskine M, Berti P, Rakotoarisoa A, et al: **Contribution of integrated campaign distribution of long-lasting insecticidal nets to coverage of target groups and total populations in malaria-endemic areas in Madagascar.** *Am J Trop Med Hyg*, **82:**420-425.
148. Noor AM, Amin AA, Akhwale WS, Snow RW: **Increasing coverage and decreasing inequity in insecticide-treated bed net use among rural Kenyan children.** *PLoS Med* 2007, **4:**e255.
149. Bonner K, Mwita A, McElroy PD, Omari S, Mzava A, Lengeler C, Kaspar N, Nathan R, Ngegba J, Mtung'e R, Brown N: **Design, implementation and evaluation of a national campaign to distribute nine million free LLINs to children under five years of age in Tanzania.** *Malar J*, **10:**73.
150. Hawley WA, Phillips-Howard PA, ter Kuile FO, Terlouw DJ, Vulule JM, Ombok M, Nahlen BL, Gimnig JE, Kariuki SK, Kolczak MS, Hightower AW: **Community-wide effects of permethrin-treated bed nets on child mortality**

and malaria morbidity in western Kenya. *Am J Trop Med Hyg* 2003, **68:**121-127.
151. Killeen GF, Smith TA, Ferguson HM, Mshinda H, Abdulla S, Lengeler C, Kachur SP: **Preventing childhood malaria in Africa by protecting adults from mosquitoes with insecticide-treated nets.** *PLoS Med* 2007, **4:**e229.
152. Ross A, Killeen G, Smith T: **Relationships between host infectivity to mosquitoes and asexual parasite density in Plasmodium falciparum.** *Am J Trop Med Hyg* 2006, **75:**32-37.
153. Bennett A, Smith SJ, Yambasu S, Jambai A, Alemu W, Kabano A, Eisele TP: **Household possession and use of insecticide-treated mosquito nets in sierra leone 6 months after a national mass-distribution campaign.** *PLoS One*, **7:**e37927.
154. Grabowsky M, Nobiya T, Selanikio J: **Sustained high coverage of insecticide-treated bednets through combined Catch-up and Keep-up strategies.** *Trop Med Int Health* 2007, **12:**815-822.
155. Lengeler C, Grabowsky M, McGuire D, deSavigny D: **Quick wins versus sustainability: options for the upscaling of insecticide-treated nets.** *Am J Trop Med Hyg* 2007, **77:**222-226.
156. Khatib RA, Killeen GF, Abdulla SM, Kahigwa E, McElroy PD, Gerrets RP, Mshinda H, Mwita A, Kachur SP: **Markets, voucher subsidies and free nets combine to achieve high bed net coverage in rural Tanzania.** *Malar J* 2008, **7:**98.
157. Lengeler C, deSavigny D: **Programme diversity is key to the success of insecticide-treated bednets.** *Lancet* 2007, **370:**1009-1010.
158. Eisele TP, Keating J, Littrell M, Larsen D, Macintyre K: **Assessment of insecticide-treated bednet use among children and pregnant women across 15 countries using standardized national surveys.** *Am J Trop Med Hyg* 2009, **80:**209-214.
159. Webster J, Kweku M, Dedzo M, Tinkorang K, Bruce J, Lines J, Chandramohan D, Hanson K: **Evaluating delivery systems: complex evaluations and plausibility inference.** *Am J Trop Med Hyg*, **82:**672-677.
160. Vanden Eng JL, Thwing J, Wolkon A, Kulkarni MA, Manya A, Erskine M, Hightower A, Slutsker L: **Assessing bed net use and non-use after long-lasting insecticidal net distribution: a simple framework to guide programmatic strategies.** *Malar J*, **9:**133.
161. Atieli HE, Zhou G, Afrane Y, Lee MC, Mwanzo I, Githeko AK, Yan G: **Insecticide-treated net (ITN) ownership, usage, and malaria transmission in the highlands of western Kenya.** *Parasit Vectors*, **4:**113.
162. Nevill CG, Some ES, Mung'ala VO, Mutemi W, New L, Marsh K, Lengeler C, Snow RW: **Insecticide-treated bednets reduce mortality and severe morbidity from malaria among children on the Kenyan coast.** *Trop Med Int Health* 1996, **1:**139-146.
163. Binka FN, Kubaje A, Adjuik M, Williams LA, Lengeler C, Maude GH, Armah GE, Kajihara B, Adiamah JH, Smith PG: **Impact of permethrin impregnated bednets on child mortality in Kassena-Nankana district, Ghana: a randomized controlled trial.** *Trop Med Int Health* 1996, **1:**147-154.
164. Korenromp EL, Miller J, Cibulskis RE, Kabir Cham M, Alnwick D, Dye C: **Monitoring mosquito net coverage for malaria control in Africa: possession vs. use by children under 5 years.** *Trop Med Int Health* 2003, **8:**693-703.
165. Tami A, Mbati J, Nathan R, Mponda H, Lengeler C, Schellenberg JR: **Use and misuse of a discount voucher scheme as a subsidy for insecticide-treated nets for malaria control in southern Tanzania.** *Health Policy Plan* 2006, **21:**1-9.
166. Guyatt H, Ochola S: **Use of bednets given free to pregnant women in Kenya.** *Lancet* 2003, **362:**1549-1550.
167. Tsuang A, Lines J, Hanson K: **Which family members use the best nets? An analysis of the condition of mosquito nets and their distribution within households in Tanzania.** *Malar J* 2010, **9:**211.

168. Gust DA, Woodruff R, Kennedy A, Brown C, Sheedy K, Hibbs B: **Parental perceptions surrounding risks and benefits of immunization.** *Semin Pediatr Infect Dis* 2003, **14:**207-212.
169. Gangarosa EJ, Galazka AM, Wolfe CR, Phillips LM, Gangarosa RE, Miller E, Chen RT: **Impact of anti-vaccine movements on pertussis control: the untold story.** *Lancet* 1998, **351:**356-361.
170. Atkinson JA, Fitzgerald L, Toaliu H, Taleo G, Tynan A, Whittaker M, Riley I, Vallely A: **Community participation for malaria elimination in Tafea Province, Vanuatu: Part I. Maintaining motivation for prevention practices in the context of disappearing disease.** *Malar J*, **9:**93.
171. Mabaso ML, Sharp B, Lengeler C: **Historical review of malarial control in southern African with emphasis on the use of indoor residual house-spraying.** *Trop Med Int Health* 2004, **9:**846-856.
172. Ng'ang'a PN, Jayasinghe G, Kimani V, Shililu J, Kabutha C, Kabuage L, Githure J, Mutero C: **Bed net use and associated factors in a rice farming community in Central Kenya.** *Malar J* 2009, **8:**64.
173. Dye TD, Apondi R, Lugada ES, Kahn JG, Smith J, Othoro C: **"Before we used to get sick all the time": perceptions of malaria and use of long-lasting insecticide-treated bed nets (LLINs) in a rural Kenyan community.** *Malar J* 2010, **9:**345.
174. Munguambe K, Pool R, Montgomery C, Bavo C, Nhacolo A, Fiosse L, Sacoor C, Nhalungo D, Mabunda S, Macete E, Alonso P: **What drives community adherence to indoor residual spraying (IRS) against malaria in Manhica district, rural Mozambique: a qualitative study.** *Malar J*, **10:**344.
175. Montgomery CM, Munguambe K, Pool R: **Group-based citizenship in the acceptance of indoor residual spraying (IRS) for malaria control in Mozambique.** *Soc Sci Med*, **70:**1648-1655.
176. Minja H, Schellenberg JA, Mukasa O, Nathan R, Abdulla S, Mponda H, Tanner M, Lengeler C, Obrist B: **Introducing insecticide-treated nets in the Kilombero Valley, Tanzania: the relevance of local knowledge and practice for an information, education and communication (IEC) campaign.** *Trop Med Int Health* 2001, **6:**614-623.
177. Panter-Brick C, Clarke SE, Lomas H, Pinder M, Lindsay SW: **Culturally compelling strategies for behaviour change: a social ecology model and case study in malaria prevention.** *Soc Sci Med* 2006, **62:**2810-2825.
178. TDR: **Community-directed interventions for major health problems in Africa. A multi-country study Final Report.** 2008.
179. Kachur SP, Khatib RA, Kaizer E, Fox SS, Abdulla SM, Bloland PB: **Adherence to antimalarial combination therapy with sulfadoxine-pyrimethamine and artesunate in rural Tanzania.** *Am J Trop Med Hyg* 2004, **71:**715-722.
180. Depoortere E, Salvador ET, Stivanello E, Bisoffi Z, Guthmann JP: **Adherence to a combination of artemether and lumefantrine (Coartem) in Kajo Keji, southern Sudan.** *Ann Trop Med Parasitol* 2004, **98:**635-637.
181. Lawford H, Zurovac D, O'Reilly L, Hoibak S, Cowley A, Munga S, Vulule J, Juma E, Snow RW, Allan R: **Adherence to prescribed artemisinin-based combination therapy in Garissa and Bunyala districts, Kenya.** *Malar J*, **10:**281.
182. Simba DO, Kakoko D, Tomson G, Premji Z, Petzold M, Mahindi M, Gustafsson LL: **Adherence to artemether/lumefantrine treatment in children under real-life situations in rural Tanzania.** *Trans R Soc Trop Med Hyg*, **106:**3-9.
183. Gerstl S, Dunkley S, Mukhtar A, Baker S, Maikere J: **Successful introduction of artesunate combination therapy is not enough to fight malaria: results from an adherence study in Sierra Leone.** *Trans R Soc Trop Med Hyg*, **104:**328-335.
184. Asante KP, Owusu R, Dosoo D, Awini E, Adjei G, Amenga Etego S, Chandramohan D, Owusu-Agyei S: **Adherence to Artesunate-Amodiaquine Therapy for Uncomplicated Malaria in Rural Ghana: A Randomised Trial**

of Supervised versus Unsupervised Drug Administration. *J Trop Med* 2009, **2009:**529583.
185. Okonkwo PO, Akpala CO, Okafor HU, Mbah AU, Nwaiwu O: **Compliance to correct dose of chloroquine in uncomplicated malaria correlates with improvement in the condition of rural Nigerian children.** *Trans R Soc Trop Med Hyg* 2001, **95:**320-324.
186. Ansah EK, Gyapong JO, Agyepong IA, Evans DB: **Improving adherence to malaria treatment for children: the use of pre-packed chloroquine tablets vs. chloroquine syrup.** *Trop Med Int Health* 2001, **6:**496-504.
187. Zurovac D, Njogu J, Akhwale W, Hamer DH, Snow RW: **Translation of artemether-lumefantrine treatment policy into paediatric clinical practice: an early experience from Kenya.** *Trop Med Int Health* 2008, **13:**99-107.
188. WHO: **Model IMCI handbook: Integrated management of childhood illnesses.** 2005.
189. Feachem RG, Phillips AA, Hwang J, Cotter C, Wielgosz B, Greenwood BM, Sabot O, Rodriguez MH, Abeyasinghe RR, Ghebreyesus TA, Snow RW: **Shrinking the malaria map: progress and prospects.** *Lancet*, **376:**1566-1578.
190. RBM: **Community involvement in rolling back malaria.** 2002.
191. Sabot O, Cohen JM, Hsiang MS, Kahn JG, Basu S, Tang L, Zheng B, Gao Q, Zou L, Tatarsky A, et al: **Costs and financial feasibility of malaria elimination.** *Lancet*, **376:**1604-1615.
192. Gordis L: *Epidemiology.* 3rd edition. Philadelphia: Elsevier Saunders; 2004.
193. Kroeger A: **Response errors and other problems of health interview surveys in developing countries.** *World Health Stat Q* 1985, **38:**15-37.
194. Fraser MW, Richman JM, Galinsky MJ, Day SH : *Intervention Research.* New-York: Oxford university press; 2009.
195. Bowling A: **Mode of questionnaire administration can have serious effects on data quality.** *J Public Health (Oxf)* 2005, **27:**281-291.
196. Wallin AM, Ahlstrom G: **Cross-cultural interview studies using interpreters: systematic literature review.** *J Adv Nurs* 2006, **55:**723-735.
197. Patton M: **Qualitative Research and Evaluation Methods,** 3rd edition, Los Angeles; Sage Publication; 2002.