Malaria control dynamics in rural Tanzania: Evaluation of implementation of Artemisinin based Anti-malarial Combination Therapy

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Acknowledgements

I have reached a point that reminds me a swahili song *hayawi hayawi sasa yamekuwa* that I used to overhear at wedding festivals more than twenty years ago when I was a small village boy. This song literally means that hopes of success that used to be ridiculed as mere daydream have finally materialized. I have ultimately reached what even three years ago I perceived to be the climax of academic ladder. However, I always believe that the world is too big to be conquered by whatever level of a single skill or whatever volume of a single thesis. That aside, finalizing a PhD program is a long journey that does not start when one joins the University that provides that program. The chapter begins on day one of beginning ones education. To me, it was in 1973 at a school within the walking distance from our home at a remote village in Africa. It comes at its last end this year in 2009 at the University of Basel in Switzerland at the heart of Europe. It is obvious that it has taken many healthy life years for me up to the point of writing this acknowledgement. This could not be possible was it not for the almighty God who has given me life and good health for the whole that period.

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SUMMARY

Malaria is the most important parasitic disease caused by protozoans of the genus plasmodia that are transmitted by female anophelene mosquitoes. Plasmodium falciparum is the most important species owing to its distribution, virulence and pathogenicity. World-wide some 500 million infections, 200-300 million episodes and about 1 million malaria-related deaths occur every year amounting to a burden of some 45 million DALYs (Disability Adjusted Life Years) [1]. At least 80% of this intolerable burden is concentrated in Sub-Saharan Africa with young children bearing the biggest share. In Tanzania, malaria accounts for not less than 30% of the country's burden of disease [2].

Malaria can be cured if it is diagnosed and treated rapidly with effective drugs. Delay in diagnosis and treatment leads to the progression of disease and eventually death. Chloroquine and salfudoxine-pyremethamine (SP) had for a long time been the first-line treatment of choice for most endemic African countries but these drugs are no longer effective for treating patients in many parts owing to the development of resistance [3]. Artemisinin based Combination Therapy (ACT) is now widely recommended as the first-line treatment of choice owing to its efficacy, safety profile and the fact that no resistance has, so far, been described.

Regarding prevention of malaria infections, Insecticide Treated Nets (ITNs) play the key role, while Indoor Residual Spraying (IRS) and elimination of mosquito breeding sites using larvicides are additional tools for integrated malaria control that can be applied dependant on local conditions.

As a reaction to the growing resistance of malaria parasites to Chloroquine and SP, and when ACTs were being considered for first-line treatment, the Interdisciplinary Monitoring Project for Anti-malarial Combination Therapy for Tanzania (IMPACT-Tz) was designed to evaluate the effectiveness of ACT

introduction and application in the Rufiji, Kilombero and Ulanga districts within the Coast and Morogoro Regions of Southern Tanzania.

The present thesis was undertaken within the frame of IMPACT-Tz from 2001-2006 with the following aims:

(i) Describing patients' adherence to ACT

(ii) Following the dynamics of parasite prevalence during ACT promotion and use

(iii) Analyzing the project's impact on health facility use, and ITN coverage and its concomitant delivery strategies within the study areas of IMPACT-Tz .

The present studies were based on the demographic surveillance systems which have been well established within the studied districts for many years. We conducted the study assessments using questionnaires to members of sampled households, key informant interviews and analyzed blood specimens that we concurrently collected during the interviews. Follow up visits to the homes of patients who had been treated with ACT at health facilities was the main method that we used to analyze patients' adherence.

Patients' adherence to ACT showed very promising results with 75% reaching complete adherence as established by self-reporting and tablet counts. These results were substantially better than reported elsewhere and compared favorably with former intervention studies to optimize adherence to chloroquine.

ITN coverage continuously increased through mixed delivery strategies involving free distribution during an immunization campaign combined with social marketing and a voucher system. All delivery mechanisms, especially sale of nets at full market price, tended to under-serve the poorest. Voucher-subsidized and freely distributed nets did not appear to create inequalities. In 2005, overall

net use reached 62.7% and that among infants 87.2%. Thirty percent of all nets had been treated six months prior to the interview.

The parasite prevalence declined over the study period and was clearly related to the interventions. In 2001, parasite prevalence was 26% in the general population of Rufiji and 18% in Ifakara. Following the deployment of ACT in 2003, there was a sharp decline of malaria prevalence from 29% in 2002 to 19% in 2004 in Rufiji. It remained the same in 2005 and decreased to 15% in 2006. The respective estimates for Ifakara were 22% in 2002, 25% in 2004, 11% in 2005 and 14% in 2006. The prevalence of anaemia (Hb<8g/dl) measured from 2004 to 2006 showed a drop from 23% in 2004 to 16% in 2005 and 2006 in Rufiji. Respective values for Ifakara were 12%, 18% and 10%. Use of any nets increased from 18% in 2001 to 63% in 2006 in Rufiji and from 69% to 86% in Ifakara.

Treatment-seeking also changed with the introduction of AC. Starting with 31-35% of febrile episodes seen at health facility level at the beginning of the study, an increase to up to 45% was observed as a consequence of ACT introduction. Treatment seeking in the comparison district where SP was still used as first-line treatment as stipulated in the national policy, treatment-seeking showed fluctuations but remained basically unchanged. Young children were those most seen with febrile episodes. The least poor showed higher health facility usage than the poorest segments of the population.

Our study suggests that ACT first-line therapy is an accepted and feasible approach that can reduce both the burden of disease and transmission when ACT is offered at health facility level. ACT was effective as part of an integrated approach that also entailed the promotion of ITNs. The study further demonstrated that high levels of adherence to ACT can be reached provided treatment is preceded by sufficient health worker training together with innovative information, education and communication. Provision of ACT at health facilities

improves the use of health facilities in a broad sense. Achieving and sustaining broad access to ACTs will require other strategies for ACT delivery that include all providers of services and may include home-based management in order to reach all segments of a population and, thus, to achieve equitable access.

There are additional other important issues that need to be investigated further such as how ACTs can be effectively made available to all possible health service providers in a given area, also including possible home management strategies to achieve broad and equitable access to rapid diagnosis and treatment. Finally we need to understand to what extent synergies are created when different sets of malaria control interventions are implemented concomitantly and/or sequentially with different time-space dynamics of coverage. Such information is critical for tailoring strategies to different endemic settings and for moving from control towards elimination.

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Zusammenfassung

Malaria ist die wichtigste parasitäre Erkrankung, welche durch die Protozoen der Gattung Plasmodia verursacht wird. Die Plasmodien werden durch die weiblichen Moskitos der Gattung Anopheles übertragen. Plasmodium falciparum ist die wichtigste Spezies aufgrund ihrer Verbreitung, Virulenz und Pathogenität. Weltweit gibt es geschätzte 500 Millionen Infizierte, wobei etwa 200-300 Millionen Episoden und 1 Million Tote jedes Jahr durch Malaria verursacht werden, was 45 Millionen DALYs (Disability Adjusted Life Years) entspricht. Mindestens 80% von dieser Krankheitslast konzentriert sich auf Afrika südlich der Sahara und dort wiederum insbesondere auf junge Kinder. In Tansania ist Malaria für nicht weniger als 30% der gesamten nationalen Krankheitslast verantwortlich.

Malaria kann geheilt werden, wenn die Krankheit rechtzeitig diagnostiziert und mit wirksamen Medikamenten behandelt wird. Verzögerungen in der Diagnose oder Behandlung können zu einem Fortschreiten der Krankheit und letztlich zum Tod führen. Chloroquine und Salfudoxine-Pyremethamine (SP) waren lange Zeit in den meisten endemischen Ländern in Afrika als Erstbehandlung vorgesehen, sind aber heute aufgrund von zunehmenden Resistenzen vielerorts nicht mehr wirksam. Wegen ihrer Wirksamkeit, ihres Sicherheitsprofils und bisher noch nicht aufgetretenen Resistenzbildungen wird deshalb heutzutage die so genannte Artemisinin-based Combination Therapy (ACT) als Erstbehandlung empfohlen. In Bezug auf die Prävention spielen Insecticide Treated Nets (ITN) eine Schlüsselrolle. Indoor Residual Spraying (IRS) sowie das Eliminieren von Moskitobrutstätten mit Larviziden sind zusätzliche Massnahmen für eine lokal angepasste, integrierte Malariakontrolle.

Als Reaktion auf die zunehmende Resistenz der Malaria-Erreger gegenüber Chloroquine und SP wurde der Einsatz von ACT als neue Methode der Erstbehandlung in Betracht gezogen. Um die Wirksamkeit von ACT im Rufiji,

Kilombero und Ulanga Distrikt in der Küsten- und der Morogoro-Region im Süden von Tansania zu evaluieren, wurde das Interdisciplinary Monitoring Project for Anti-malarial Combination Therapy for Tanzania (IMPACT-Tz) konzipiert.

Die vorliegende Doktorarbeit wurde im Rahmen von IMPACT-Tz zwischen 2001 und 2006 durchgeführt und beabsichtigte innerhalb des IMPACT-Tz Studiengebietes (i) die Befolgung der ACT durch die Patienten zu beschreiben, (ii) die Dynamik der Parasiten-Prävalenz während der ACT Förderung und Anwendung zu beschreiben, (iii) den Einfluss des Projekts auf die Nutzung von Gesundheitseinrichtungen und ITNs unter Berücksichtigung von deren Verfügbarkeit und Belieferungsstrategien zu analysieren. Die Studien stützten sich auf die seit einigen Jahren in den Studiengebieten etablierten Demographic Surveillance Systems (DSS). Zur Durchführung der Studien befragten wir Mitglieder von ausgewählten Haushalten mit Hilfe von Fragebogen, führten Interviews mit Key Informants und analysierten Blutproben, welche gleichzeitig mit den Interviews eingesammelt wurden. Hausbesuche bei Patienten, welche in den Gesundheitseinrichtungen mit ACT behandelt wurden, waren die grundlegende Methode um die Befolgung der Therapie durch die Patienten zu beschreiben.

Die Resultate zur Befolgung der ACT-Therapie durch die Patienten waren viel versprechend. Gemessen an den Aussagen der Patienten und dem Auszählen der Tabletten befolgten 75% der Patienten die Therapie vollständig. Diese Resultate waren deutlich besser als anderswo und auch besser als Resultate von früheren Interventionsstudien zur Optimierung der Befolgung von Chloroquine-Behandlungen.

Der Deckungsgrad mit ITNs stieg kontinuierlich dank einer gemischten Belieferungsstrategie, welche eine Gratis-Verteilung während Impfkampagnen mit Massnahmen des Social Marketing und einem Gutschein-System kombinierte. Alle Belieferungsmechanismen und insbesondere der Verkauf von ITNs zu

Marktpreisen tendierten dazu die Ärmsten unterzuversorgen. Durch Gutscheine subventionierte und gratis verteilte Netze schienen am wenigsten Ungleichheiten zu erzeugen. Gesamthaft erreichte der Anteil von Netzbenutzer im Jahr 2005 62.7% und sogar 87.2% bei Kindern. Dreissig Prozent aller Netze wurde in den letzten sechs Monaten vor dem Interview mit Insektizid behandelt.

Die Parasiten-Prävalenz war eindeutig mit den Interventionen verbunden und nahm im Verlauf der Studien ab. 2001 betrug die Prävalenz 26% in der allgemeinen Bevölkerung von Rufiji und 18% in Ifakara. Nach dem Start der ATC-Anwendung 2003 sank die Malaria-Prävalenz in Rufiji von 29% im Jahr 2002 auf 19% im Jahr 2004 deutlich, blieb im Jahr 2005 konstant und sank schliesslich noch einmal auf 15% im Jahr 2006. Dieselben Schätzungen für Ifakara sind 22% 2002, 25% 2004, 11% 2005 und 14% 2006. Die Anaemie-Prävalenz (Hb<8g/dl) in Rufiji sank von 23% 2004 auf 16% 2005 und 2006. Dieselben Werte für Ifakara liegen bei 12%, 18% und 10%. In Rufiji nahm die Anwendung von Moskitonetzen aller Art von 18% im Jahr 2001 auf 63% im Jahr 2006 zu und in Ifakara von 69% auf 86%.

Durch die Einführung von ACTs änderte sich auch das so genannte Treatment-Seeking. Als Konsequenz der Einführung von ACTs stieg der Anteil Fieberepisoden, welche auch zu den Gesundheitseinrichtungen gelangten, von 31-35% auf 45% im Verlauf der Studien. Treatment-Seeking in einem Vergleichsdistrikt, wo gemäss der nationalen Strategie immer noch SP als Erstbehandlung verwendet wurde, zeigte zwar Fluktuationen, blieb aber im Wesentlichen unverändert. Im Zusammenhang mit Fieberepisoden wurden am häufigsten junge Kinder festgestellt. Die reichsten Bevölkerungssegmente benützten die Gesundheitseinrichtungen häufiger als die ärmsten.

Unsere Studien zeigen, dass ACT als Erstbehandlung in Gesundheitseinrichtungen ein akzeptierter und realisierbarer Ansatz ist, der sowohl die Krankheitslast als auch die Krankheitsübertragung einschränken kann.

ACT war wirksam als ein Teil eines integrierten Ansatzes, der auch die Förderung von ITNs beinhaltete. Die Studien zeigen auch, dass eine gute Befolgung der ACT erreicht werden kann, wenn den Behandlungen ein ausreichendes Training des Gesundheitspersonals und innovative Informations-, Aufklärungs- und Kommunikationsmassnahmen vorangehen. Die Bereitstellung von ACT in Gesundheitseinrichtungen verbessert die Nutzung dieser Einrichtungen in vielerlei Hinsicht. Zur Erreichung und Gewährleistung eines breiten Zugangs zu ACTs sind aber auch andere Abgabestrategien nötig, welche alle Anbieter von Gesundheitsleistungen mit einschliessen und für die bessere Erreichbarkeit und Zugangsgerechtigkeit auch heimbasierte Behandlungen zulassen.

Dementsprechend gibt es wichtige Probleme, welche weitere Forschungsanstrengungen benötigen. Wie zum Beispiel können ACTs wirksam und unter Berücksichtigung sowohl aller Anbieter von Gesundheitsleistungen in einem bestimmten Gebiet als auch aller Möglichkeiten der heimbasierten Behandlung zur Verfügung gestellt werden, so dass ein möglichst breiter und gerechter Zugang zu schnellen Diagnosen und Behandlungen erreicht werden kann? Zudem sollten wir Synergien, welche entstehen, wenn verschiedene Malariakontrollinterventionen begleitend und/oder einander nachfolgend in unterschiedlichen Zeit-Raum-Dynamiken der Abdeckung implementiert werden, besser verstehen. Diese Informationen sind entscheidend um massgeschneiderte Strategien für verschiedene endemische Situationen zu entwerfen und um einen Schritt von der Malariakontrolle hin zur Malariaelimination zu machen.

MUHTASARI

Ugonjwa wa malaria huambukizwa na vimelea vya aina ya *P.Falciparum*. Vimelea hivi huenezwa na mbu wa kike wa aina ya anophelene. Vimelea hivi vya *P.Falciparum* vina usumbufu wa kipekee kwa vile vipo maeneo mengi na vinazaliana haraka haraka na kuzaa ugonjwa mbaya. Kila mwaka wata wapatao millioni 500 humbukizwa vimelea ambapo wagonjwa baina ya millioni 200 mpaka 300 huugua ugonjwa wa malaria na kiasi ya wagonjwa millioni moja hufa kote duniani. Jumla ya maisha ya binadamu inayopotea kutokana na vifo na kuugua ugonjwa huu inakadiriwa kufikia miaka millioni 45. Kiasi ya asilimia thamanini ya hasara hii hupatikana katika bara la Africa na wanaoathirika zaidi ni watoto wadogo wadogo. Nchini Tanzania kiasi ya asilimia thelathini ya hasara iletwayo na magonjwa husababishwa na malaria.

Ugonjwa wa malaria unaweza kutambulika na kutibika kwa haraka kwa dawa imara. Ugonjwa huu hugeuka kuwa hatari sana na kusababisha vifo vingi ikiwa matibabu yake yatacheleweshwa. Dawa za Chloroquine na salfadoxine-pyremethamine (SP) ambazo kwa muda mrefu zilikuwa zinatumika kutibia ugonjwa huu katika nchi za Africa zenye kuambukizwa zaidi, sasa hivi hazifanyi tena kazi kwa sababu ya usugu wa vimelea. Dawa za mseto zenye mchanganyiko wa artemisinin (ACT) sasa hivi zinapendekezwa zaidi kutokana na kuthibitika uimara na usalama na kwa vile kwa sasa hakuna matokeo ya usugu wa vimelea uliotolewa taarifa. Pamoja na hayo, Ugonjwa wa malaria unakingika kwa kutumia vyandarua vyenye viatilifu (ITN), dawa za kunyunyiza majumbani na kuuwa mayai ya mbu kwa kutumia dawa katika mazalia ya mbu.

Katika kipindi ambapo dawa za Chloroquine na SP zilikuwa zinashindwa kwa kasi kubwa kuponesha ugonjwa wa malaria, mradi wa kutathmini dawa mseto za malaria (IMPACT-TZ) ulibuniwa na ulifanya tathmini ya dawa mseto katika wilaya za Rufiji, Kilombero na Ulanga zilizopo mikoa ya Pwani na Morogoro nchini Tanzania.

Kitabu hiki cha uhitimu wangu wa shahada ya udaktari wa falsafa katika fani ya epidemiology kinatokana na utafiti uliofanywa chini ya muavuli wa mradi wa IMPACT-Tz kati ya mwaka 2001 mpaka 2006. Madhumuni yake ni (i)kutathmini jinsi wagonjwa wa malaria waliotibiwa kwa dawa mseto walivykuwa wakitumia dawa hizo kwa usahihi; (ii) kufuatilia uwepo wa vimelea vya malaria katika kipindi ambacho dawa mseto zilihamasishwa na kutumika; na (iii) kutafiti athari ya utekelezaji wa mradi huu kwa matumizi ya vituo vya tiba na pia matumizi ya vyandarua vyente viatilifu na mikakati mbali mbali ya kuvisambaza katika vijiji vilivyokuwa kwenye mradi. Tathmini hizi zilifanywa katika vijiji vilivyo kwenye mpango wa kufuatilia taarifa zinazohusu uhamiaji, uhamaji, vizazi na vifo (DSS sites) katiak sehemu za Rufiji na Ifaka zilizo chini ya Taasisi ya Utafiti wa afya ya binadamu ya Ifakara (IHI). Utaratibu huu wa DSS ulishakuwepo kwenye vijiji hivyo kwa muda mrefu. Tulifanya utafiti huu kwa njia ya mahojiano na wanakaya wa kaya ambazo zilichaguliwa kwa bahati nasibu na kwa kuhakiki matone ya damu yaliyokuwa yakichukuliwa wakati wa mahojiano. Katika kuangalia matumizi ya dawa mseto kwa usahihi, tulikuwa tunawazungukia wagonjwa waliokuwa walishatibiwa kwa dawa mseto katika vituo vya tiba majumbani mwao na kuwadodosa jinsi walivyokuwa wametumia dawa hizo.

Jumla ya wagonjwa 253 walifuatiliwa majumbani mwao kuulizwa maswali baada ya masaa 24 na 48 tokea kwenda kituoni kupata matibabu. Ilionekana kuwa asilimia 75 ya wagonjwa waliofuatiliwa baada ya masaa 48 walitumia dawa mseto kiusahihi. Haya yalipimwa kwa kukehasabu idadi ya vidonge vilivyokuwa vimebaki na taarifa za mgonjwa mwenyewe walipotembelewa majumbani mwao na kudododswa na wahojaji. Kwa kweli majibu haya ya wagonjwa kutumia dawa mseto kiusahihi yalikuwa bora kuliko majibu yaliyokuya yamepatikana huko nyuma katika tathmini ya dawa za Chloroquine

Matumizi ya vyandarua vyenye viatilifu yalikuwa yanaongezeka kutokana na vyandaraua hivyo kusambazwa kwa kutumia njia mseto ambazo zilijumuisha

ugawaji wa vyandarua vya bure siku ya chanjo na kwa njia ya soko na hati punguzo. Njia zote hizo hasa ile ya kuviuza vyandarua dukani haikuwanyanyua sana watu maskini sana. Vyandarau vilivyotolewa bure na vile vilivyouzwa kwa hati punguzo havikuonekana kuleta kutokuwepo na usawa. Katika mwaka 2005, matumizi ya kila aina ya chandarua yalifikia silimia 63 na kwa watoto wachanga peke yao yalifikia asilimia 87. Asilimia thelathini ya vyandarua vilikuwa vimewekwa viatilifu kipindi cha miezi 6 kabla ya mahojiano.

Ama katika tathmini ya vimelea vya malaria katika jamii, tuliona kuwa mwaka 2001 uwepo wa vimelea ulikuw asilimia 26 ya watu wote katika DSS upande wa Rufiji ikilinganishwa na asilimia 18 katika upande wa Ifakara. Uwepo wa vimelea ulipungua hadi kufikia asilimia 19 mwaka 2004 kwa upande wa Rufiji baada ya kanzishwa matibabu ya dawa mseto mwaka 2003. Katika mwaka 2002 uwepo wa vimelea huko ulikuwa 29%. Baadae kiwango hicho cha mwaka 2004 huko Rufiji kilibaki hivyo kwa mwaka 2005 na kushuka kufikia asilimia 15 mwaka 2006. Tathmini ya Ifakara ilionesha kuwa uwepo wa vimelea ulikuwa 22% mwaka 2002, 25% katika mwaka 2004, 11% mwaka 2005 na 14% mwaka 2006. Kwa upande wa upungufu wa damu mwilini , tathmini yetu iliyofanywa mwaka 2004 mpaka 2006 katika upande wa Rufiji ilionesha kuwa upungufu ulipungua kutoka asilimia 23 mwaka 2004 hadi 16% mwaka 2005 na 2006. Upande wa Ifakara hali ilikuwa 12% mwaka 2004, 18% mwaka 2005 na 10% mwaka 2006. Matumizi ya vyandarua yaliongezeka huko Rufiji kutoka asilimia 18% mwaka 2001 na kufikia asilimia 63 mwaka 2006. Na huko Ifakara matumizi yalikuwa asilimia 69 mwaka 2001 na kuongezeka kuwa asilimia 86 mwaka 2006.

Katika tathmini yetu ya kujua matumizi ya vituo vya matibabu kwa wale waliosema waligua homa au malaria wiki mbili kabla ya mahojiano tuligundua kwamba matumizi ya chanzo hicho yalikuwa 31% na 35% kwa mika ya 2001 na 2002 huko Rufiji. Hii ni miaka kabla ya kuanza kutibu malaria kwa kutumia dawa mseto katika vituo vya afya sehemu hiyo. Matumizi yaliongezeka kufikia 45% katika mwaka 2004, mwaka mmoja baada ya kuanza dawa hizo katika vituo vya

afya peke yake. Matumizi hayo yalipungua kidogo na kufikia 41% mwaka 2005. Yalianguka zaidi mwaka 2006 kwa kufikia 30% tu. Kwa upande wa Ifakara ambako wagonjwa waliendelea na sera ya serikali kwa nchi nzima ya matibabu ya dawa isiyo ya mseto ya SP wakati ule , wagonjwa waliopata matibabu yao kutoka vituo vya Afya yalikuwa 27% kunako mwaka 2001 na 33% katika mwaka 2002. Hali ilishuka na kufikia 29% kunako mwaka 2004 na kuongezeka kufikia 36% katika mwaka 2005 na kutokuwepo na mabadiliko katika mwaka 2006. Katika kuhusisha matumizi haya ya vituo vya afya na rika za watu, watoto chini ya miaka 5 walikuwa wanatumia vituo hivyo mara nyingi zaidi kuliko wenye umri zaidi yao kutoka zote za Rufiji na Ifakara. Aidha, wale wenye unafuu wa maisha walikuwa na fursa zaidi ya kutumia vituo vya matibabu kwa zaidi ya 50% ya wale waliokuwa wanaishi maisha ya chini zaidi kutoka katika sehemu zote.

Kwa ujumla, utafiti wetu umeonesha kuwa matumizi ya dawa mseto yanaweza kupunguza maambukizi ya vimelea vya malaria na mzigo wa maradhi katika jamii hata kama dawa hizo zitakuwa zinapatikana kutoka vituo vya afya peke yake. Dawa mseto zilikuwa na umadhubuti kama sehemu ya mkakati wa pamoja ambao pia ulihusisha uhamasishaji wa vyandarua vyenye viatilifu. Utafiti wetu pia umegundua kuwa kuna fursa nzuri kwa wagonjwa wa malaria kutumia dawa mseto kwa usahihi ikiwa wafanyakazi wa afya wataelimishwa na kutakuwa na elimu kwa wagonjwa kabla ya kuanzishwa mpango wowote wa dawa mseto. Matibabu ya dawa mseto kwenye vituo vya matibabu huboresha matumizi ya vituo hivyo kwa upana wa namna yake. Ufanikishaji wa kuongeza upatikanaji wa dawa mseto na udumishaji wake unahitaji mikakati mengine ya kutibu kwa dawa mseto kwa njia nyengine kama vile njia za upatikana ji dawa majumbani ili wagonjwa wa kila uwezo azipate na kwa namna hiyo kufikia lengo la usawa wa upatikanaji wa dawa.

Kuna mambo mengine muhimu ambayo inabidi yatafitiwe zaidi kama vile namna gani dawa mseto zinaweza kupatikana zaidi kwa kuwahusisha watowaji matibabu wengine katika eneo husika ikiwemo mikakati ya kuzitowa dawa katika

njia zisizo rasmi ili kuwafikishia wagonjwa dawa na vipimo karibu zaidi bila kuleta tofauti kati ya watu wa vipato mbali mbali. Mwisho inabidi tuelewe namna gani njia mbali mbali za kudhibiti malaria zinaweza kuchangishana matokeo bora zitakapotumika kwa pamoja.

PART I: BACKGROUND

CHAPTER 1: Introduction

Malaria transmission

Malaria is a protozoan infection caused by four major species of *Plasmodium*. They are *P. Falciparum, P. Vivax, P. Ovale and P. Malariae*. The most virulent, most prolific, most unpredictable and most lethal is *P. Falciparum*. This work will focus on this species as it is one of the leading health risks in sub-Saharan Africa. The parasite is capable of reproducing both sexually in the mosquito and asexually in the human body. The life cycle of P. Falciparum begins when mosquitoes feed on human blood infected with gametocytes. When feasting on their blood meal, mosquitoes simultaneously ingest the parasites at this stage of their life cycle. Once reaching the mosquito's body, gametocytes split into male and female gametes and glue themselves in the gut. They then fertilise to produce zygote that elongates to form ookinete. Ookinete penetrates the mosquitoes' gut lining and multiply into oocysts. Oocysts grow up in the gut wall and ultimately rupture to release thousands of sporozoites that migrate to the salivary glands of mosquitoes. Each oocyst multiplies into 10,000 sporozoites. This process normally takes 9-30 days depending on ambient temperature. At 30^{o}C it can take exactly 9 days, 10 days if temperature falls to 25^{o}C and 23 days at 20^{o}C (Beier 1998). Evidence so far suggests that sporozoites can not be developed in the mosquito body below 16-18^{o}C.

Asexual reproduction of P. Falciparum in the human body begins when infected mosquitoes bite a human being for their blood requirement. While mosquitoes tap the human blood, they simultaneously inject the sporozoites into the human body. Within half an hour after reaching the human body, sporozoites move to the liver where they multiply into thousands of schizonts in the human liver cells. This development takes between 6-15 days. Each schizont divides itself into 30,000 merozoites. The merozoites rupture their host cells in the liver and migrate into blood stream. They attach to specific erythrocyte surface receptors and penetrate into red blood cells. Upon entering red blood cells, each merozoite splits again

into trophozoites and back into schizonts. The invaded red blood cells swell and burst, releasing the next batch of merozoites. When in the blood, each schizont multiplies into 16-32 merozoites. Several such multiplications occur, giving rise to simultaneous waves of merozoites escaping and infecting red blood cells. The pathogenicity resulting from the parasite infection appears in different ways. First when red blood cells rupture due to pressure of increased merozoites, parasite toxin is released which precipitates a complex network of cytokines and effectors that causes fever. Second after red blood cells are destroyed they sequester into blood vessels, the combination of this sequestration and toxin cause tissue damage. Third when red blood cells are destroyed by different level of parasite multiplications, anaemia comes into being (Winstanley 2000). Some of the merozoites change themselves into male and female gametocytes and circulate freely in the human blood ready to be picked up by mosquitoes for another turn of sexual reproduction. However, parasite progression in the human body into a form that is disastrous to human health is influenced by a number of factors. For instance, it has been observed that sickle cell and other traits that alter red blood cell structure can limit parasite multiplication within red blood cells (Allison 1954). It has also been shown that hereditary ovalocytosis, glucose-6-phosphate dehydrogenase deficiency, spectrin, Lewis and Kid Is (a) red cell mutations in the gene for red blood cell membrane protein can also reduce parasite efficiency (Luzzatto 1979). Frequency of the class 1 major histocompatibility complex molecule HLA-B53 has equally been found to have an impact on immunity on liver stage of parasite (Hill et al. 1991)

Mosquitoes are crucial in malaria parasite transmission cycle. Female *anopheles gambiae* complex sensu strictois mosquito species is the most effective in transmitting malaria in Africa. They are the predominant malaria vector in the continent. They badly need human blood for egg maturation. They prefer breeding in small and large collection of sun-exposed still water under very humid environments. These conditions are more likely to occur in tropical areas with heavy rainfall. Mosquitoes can not survive at temperature below 18^{o}C.

Temperatures of above 32°C have been reported to cause high vector population turnover, weak individuals and high mortality (Craig 1999). A number of studies have demonstrated the association between *An. gambiae s.l.* abundance and rainfall (Charlwood et al. 1995; Molineaux and Gramiccia 1980). *Anopheles gambiae s.l.* is seen to breed more prolifically in temporary and turbid water bodies, such as ones formed by rain. It has been shown that the ideal climatic conditions for stable malaria transmission are temperatures between 22-32^{o}C with monthly rainfall of about 80mm for not less than five months per year (Craig et al. 1999) The vectors preferential biting time is midnight when most people in sub-Saharan Africa especially in rural areas are dead asleep. It has been recently observed that they can even feed in late afternoon or early morning. Some of these mosquitoes can bite throughout the day. They are exquisitely adapted to living around humans and adapt to changing human mosquito preventing habits. Just one bite from an infected mosquito can cause disease. Some studies have shown that mosquitoes do not just bite any human. They have preferences. Their biting choice is determined by some form of smell containing kairomone, a chemical substance that is secreted in certain parts of the body by individuals with certain characteristics. It is this odor that helps them detect their human preys. It has been observed that people with big bodies like pregnant women and smelly regions of the body like feet and ankles are very much associated with this odor and therefore are most attractive to mosquitoes (De Jong and Knols 1995; Dekker 1998; Haddow 1942). It has also been shown that A. gambiae becomes hungrier to multiple blood meals when infected by parasites than when they are not infected (Koella et al. 1998).

Thus, the presence of sporozoite infected female mosquitoes is the necessary condition for malaria transmission. However, this process is so complex that it entails a dynamic causal web of factors related to humans, malaria parasites and mosquitoes.

Figure 1: The life cycle of malaria parasites in the human host and anopheline mosquito vector

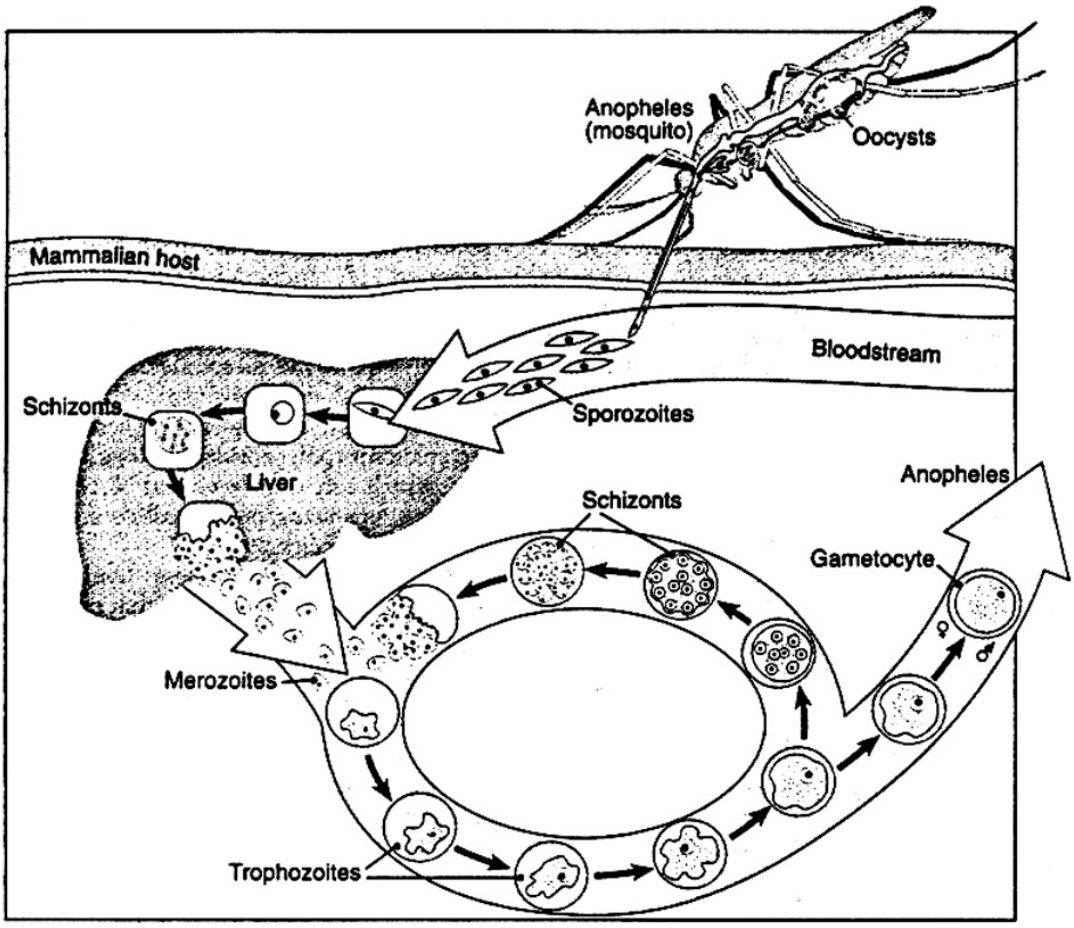
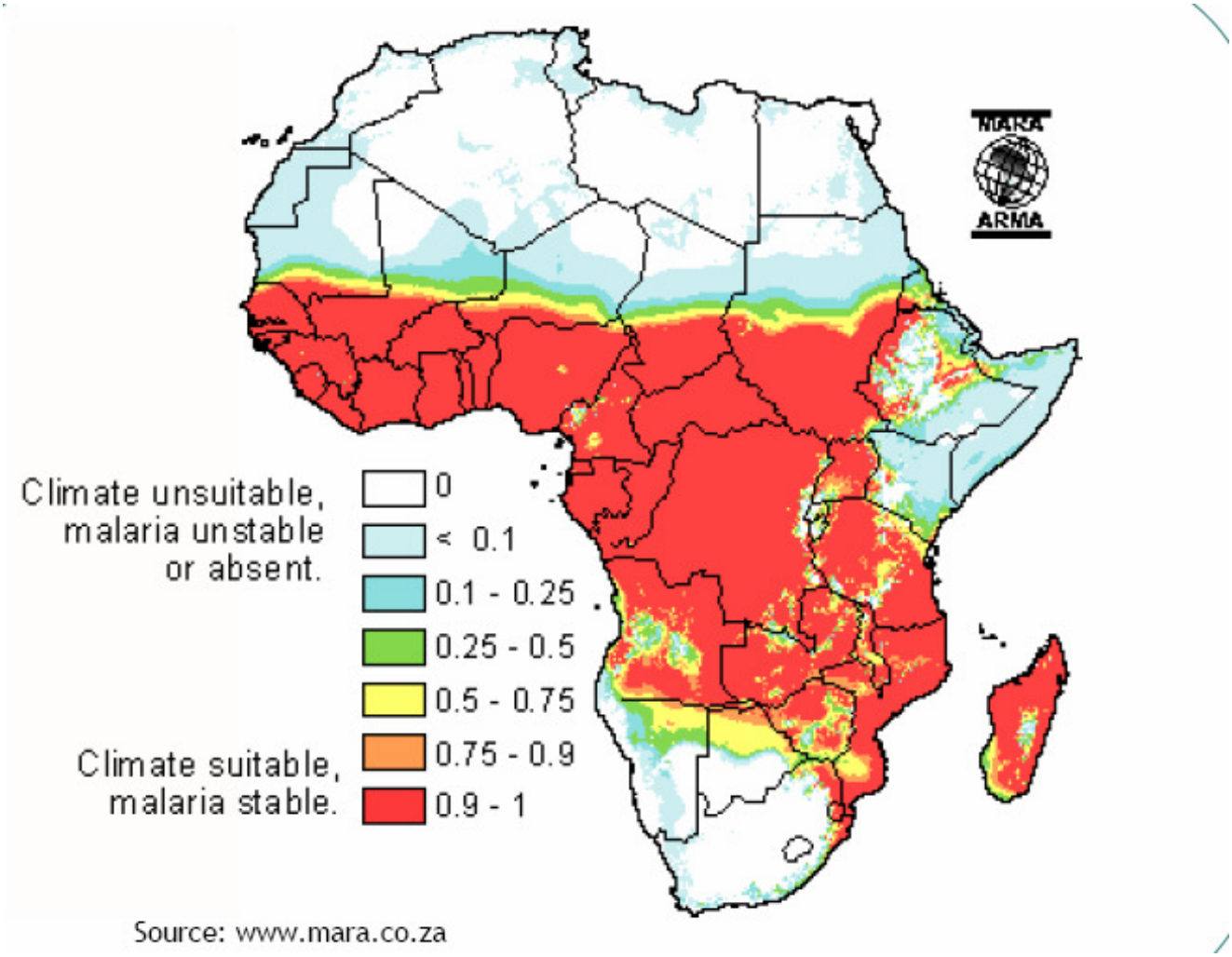


Figure 1: Map showing distribution of malaria intensity in Africa



Malaria burden in Africa

It is obvious that such enormous resources invested for malaria control in Africa can be reasonably justified if we describe a brief assessment of the magnitude of health problems caused by this disease. However, estimating malaria burden in Africa is a subject for discussion and in some ways may be controversial. This is the case due to the fact that these estimates are based on health facility records of malaria patients attending these facilities. It is argued that in areas that malaria

transmission is endemic; the majority of the infections are asymptomatic (Breman et al. 2001). But the fact is that substantial percentage of them have parasitaemia at any one time and children less than five years of age may have 4-9 or more febrile episodes each year (Breman et al. 2001). Different research studies have shown that above 70% of malaria illnesses in Africa are treated outside health facilities. Consistent to this, treatment seeking pattern and similar amount of deaths are suspected to occur at home. Poor documentation for health facility records makes reporting even for cases presented to health facilities unreliable. In their article published in Lancet on the scandal of invisibility, Setel and his co-authors argue that most people in Africa and Asia are born and die without leaving a trace in any legal record or official statistic (Setel et al. 2007).

Malaria burden estimates in Africa are also criticized for deriving their numbers from only malaria direct effects. They overlook such effects like malaria-induced acute and chronic anaemia, maternal pathology (including low birth weight babies that increases risk of death in the first month of life, hypoglycemia and long term neuropsychologic-development sequelae. It is urged that malaria-induced anaemia causes more deaths than any other manifestations of malaria infection (Murphy et al. 2001). The highest prevalence of anaemia occurs toward the end of the child's first year (Crawley 2004). It has been shown that in areas with stable and intense malaria transmission, more than 80% of the infants 10 months of age are anaemic, and approximately one third have haemoglobin level <8g/dl (Crawley 2004). These numbers do not include malaria's enhancement of the severeness of childhood illnesses (Breman et al. 2004). People infected with HIV are especially at risk of malaria.

These weaknesses aside, available estimates suggest that there are 515 million clinical attacks due to *P. falciparum* worldwide. The majority of these events, 70%, are concentrated in Africa (Snow et al. 2005). Malaria kills between 1 and 3 million people each year. Between 80-90% of these deaths occur in Africa (Guinovart et al. 2006). African children younger than five years have been

shown to be the biggest victims of malaria related deaths. They are responsible for 65-75% of all malaria deaths occurring on the continent (Breman et al. 2004; Snow et al. 1999). Other effects include impaired growth and development for small children that have an effect on their learning capability, low birth weight for babies born to parasitimic mothers and anaemia. Malaria is responsible for 3% of worldwide life years lost due to just premature deaths and sufferings. Africa accounts for more than 10% of this burden (Hay et al. 2004). Table 1 shows estimates for 2008 of all deaths occurring globally, proportion of malaria deaths and their distribution by different geographic regions. Africa suffered lower all cause mortality than Southeast Asia or Western Pacific but was responsible for more than four fifths of all malaria specific mortality. Simple interpretation of these numbers is that when talking of deaths in Africa, you talk of malaria deaths. Measures designed to reduce mortality on the continent must target malaria.

Table 1: Deaths and malaria-related deaths (,000s)

	Population	All deaths (%)	Malaria deaths (%)
World	6,436,826	58,772	889
Africa	737,536	11,249(19.2)	806(90.6)
Americas	874,380	6,158(10.5)	2.2(0.2)
Eastern Mediterranean	519,688	4,307(7.3)	39(4.4)
Europe	883,311	9,493(16.2)	0
Southeast Asia	1,671,904	15,280(26.0)	36.5(4.1)
Western Pacific	1,738,457	12,191(20.8)	5.5(0.6)

WHO, 2008 report

Table 2 has summarized global disability-adjusted life years lost due to illnesses and premature deaths from malaria parasites for the year 2008. Of 1523,259,000 life years lost due to sufferings and premature deaths from all health problems, 376,525,000 years were lost due to malaria.

Table 2: Disability-adjusted life years (DALYs, 000s), all cause and malaria-related

	DALYs from all causes (%)	DALYs from malaria deaths (%)
World	1,523,259	33,976
Africa	376,525(24.9)	30,928(91.1)
Americas	143,232(9.5)	89(0.3)
Eastern Mediterranean	141,993(9.4)	1,412(4.2)
Europe	141461(9.4)	4(0.01)
Southeast Asia	442,979(29.3)	1,341(4.0)
Western Pacific	264,772(17.5)	169(0.5)

WHO, 2008 report

Table 3 presents under-five mortality in Africa distributed by each manifestation of malaria parasite infection. It is shown that total under-five deaths due to malaria represents 65% of all malaria related deaths on the continent. The majority of these deaths occur as a result of low birth weight babies during delivery. Many studies have shown that malaria in pregnancy is a very important factor for low birth weight deliveries in Africa which is an exposure to increasing infant mortality observed on the continent.

Table 3: Deaths from malaria in Africa in children less than five years of age

Cause of death	Range of deaths in children <5 years old
Cerebral malaria	110,000 (no range)
Severe malarial anemia	190,000–974,000
Respiratory distress	110,000 (no range)
Hypoglycemia	153,000–267,000
Low birth weight	62,000–363,000
Deaths	625,000–1,824,000
All malaria deaths in Africa[†]	962,000–2,806,000

[†] Children <5 years of age represent 65% of all deaths in Africa as per Snow and others (Breman et al. 2004)

Despite the sufferings and deaths that could be translated into billions of US dollars, malaria in Africa is similarly responsible for direct costs of expenditure on prevention and treatment. Households spend their money on preventive measure such as mosquito coils, aerosol sprays, bed nets and mosquito repellents. Malaria related treatment seeking expenses include out-of-pocket expenditures for consultation fees, drugs, transport and the cost of subsistence at a distant health facility. It has been demonstrated that a monthly per capita household expenditure on malaria prevention ranges between US$0.24 per household in rural Malawi and US$15 in urban Cameroon. Associated costs related to treatment per month per household were US$1.88 in rural Malawi and US$26 in urban Cameroon (Mills 1998). It is estimated that direct costs of malaria treatment amount to 28% of households' income amongst very low income households, and 2% amongst the rest (Ettling et al. 1994). Around 20-40% of outpatient visits in sub-Saharan Africa are meant for fever (Chima et al. 2003). The average total cost per malaria outpatient ranges between US$1.54 and US$4.49, and per inpatient admission between US$3.05 and US$21.29 in Tanzania (1999). Inpatient treatment for severe paediatric malaria cost US$68 per admission in the district hospital in Kenya (Kirigia et al. 1998). The opportunity cost of healthy household members' time spent treating or attending to the malaria patients or accompanying them for treatment in Africa is enormous. It is estimated that the average time lost per malaria episode for a sick adult ranges from 1 to 5 days (Chima et al. 2003). In Ethiopia 71% of adult cases were attended by a carer who stopped performing his or her own work (Cropper 1999). In Malawi the indirect cost of malaria amounted to 2.6% of annual household income (Ettling et al. 1994). Total annual value of malaria related productivity loss was 2-6% of GDP in Kenya and 1-5% in Nigeria (Leighton and Foster 1993). Malaria treatment and prevention expenses directly shouldered by African governments account for 40% of all public expenditures on health (Chima et al. 2003). Malaria is estimated to cost African countries about US$12 billion each

year in lost GDP (RBM 2003). The disease could be controlled for a fraction of that sum.

Global public health initiatives in the fight against malaria

Growing evidence of malaria devastation in Africa inspired commitments and initiatives from African governments and their international development partners. Roll Back Malaria (RBM) was the first of these initiatives on which all other frameworks that followed have been built. RBM was adopted in 1998 under the leadership of World Health Organization. The momentum had been built by commitments shown by African heads of states and governments at their meeting one year earlier in Abuja, the capital of Nigeria. At its beginning RBM laid down target of halving morbidity and mortality from the disease between 2005 and 2010 and reducing it by additional 15% by 2015. RBM's long term aspiration is total worldwide elimination of the disease. This commitment is supported by other important malaria control partners such as Bill & Melinda Gates Foundation and WHO.

Malaria control efforts are equally shared by the Millennium Development Goals (MDGs). This is the poverty eradication programme initiated by the United Nations at its millennium assembly in 2000. It calls for a halt in the growing incidence of malaria by 2015 and a reversal thereafter. Goal 6 of the programme specifically categorise malaria control as one of its priority. However, even achieving goals 4 and 5 on reduction of under-five and maternal mortality especially for Africa require substantial gains in malaria control. Malaria infection is the biggest risk for under-five mortality in Africa. Equally important, malaria in pregnancy significantly contributes to maternal mortality.

Application of combination of all malaria control strategies has been identified by all malaria control initiatives to be the cornerstone of malaria control goals. These are prompt recognition of symptoms and early treatment with effective medicines,

Insecticide treated nets (ITN), Indoor residual spraying, Intermittent Presumptive treatment during pregnancy and other vector control strategies. For interventions providing individual protection such as ITN, prompt recognition and early treatment with effective medicines and IPTP RBM has set a target of 80% coverage to population groups most vulnerable to transmission. These initiatives are largely funded through grants from Global Fund to fight AIDS, Tuberculosis and Malaria, Bill and Melinda Gates Foundation, US President's Malaria Initiative (PMI) and the World Bank Malaria Booster Program.

Key malaria control interventions

In the preceding section I have stated that global malaria control initiatives have identified a combination of malaria control interventions for achieving the targets and overall control of the disease. In this section I will introduce each of these strategies

Prompt diagnosis and early treatment with effective medicines

This is the primary malaria control strategy. Therapeutic measures are the only way that can clear parasites from humans. There is little evidence showing that malaria can be transmitted in any way other than sporozoite infective bites of mosquitoes. Sexual reproduction of malaria parasites that result in the presence of sporozoites in the mosquito salivary glands can only happen when this mosquito ingests gametocyte infected blood of human. Hence the logic is simple. Anti-malarial drugs that are strong enough to eliminate parasites in human body will starve mosquitoes of gametocytes that they need for malaria transmission to humans. Effective implementation of this strategy is undermined by many and complex challenges.

In malaria endemic settings, transmission to most people other than under-five children and pregnant women is asymptomatic. People are infected but they do not become sick and they do not seek treatment. Hence the benefits of medicines, of whatever effectiveness, do not reach them. Some studies have

shown that untreated adults are significant sources of gametocytes in their community (Githeko et al. 1992). However, other approaches consider silent infection as an advantage in the fight against malaria. It is seen to be an immunity that inhibits parasite multiplication and hence prevents the progression to severe disease and leads to resolution of fever and other symptoms (Day et al. 1996; White 2004). Like other medicines, anti-malarial drugs can only reach their potential of parasite clearance if its toxic concentration reaches its optimal blood levels (Bloland et al. 2000). Patients need to observe full recommended dosing regimen. However, the need for timely malaria treatment has encouraged African government to adopt policies that have led to widespread availability of anti-malaria drugs. Because access to health facilities in Africa is not so good, a significant number of people who perceive their conditions to be malaria and warrant malaria treatment their preferred source of medicines are retail outlets and left over medicines from family members and nearby friends (Deming et al. 1989; McCombie 1996; Ruebush et al. 1995). These retail outlets encompass pharmacists, drug shop staff with minimal medical qualifications, and shopkeepers and street vendors with no medical training (Deming et al. 1989; Ejezie et al. 1990; Hamel et al. 2001; Ndyomugyenyi and Magnussen 1999; Yeneneh et al. 1993) (Hamel et al. 2001; Molyneux et al. 2002; Ndyomugyenyi and Magnussen 1999). Hence health facilities are visited as an alternative and not the preferred choice for malaria treatment. Some estimates suggest that more than 70% of malaria cases are initially treated through this string of retailers (Amexo et al. 2004; Bloland 1999b). Breman has equated this condition with showing up of hippopotamus's ears with largest and most dangerous part resting below water (Breman et al. 2001). It has been observed that self treatment for malaria is an exposure to inappropriate use of medicines in Africa (McCombie 1996; Ruebush et al. 1995; Slutsker et al. 1994). These observations justify the conclusion that self treatment of malaria in Africa reduces medicine ability to clear parasite even for symptomatic malaria cases and hence preventing malaria chemotherapy from reaching their potential. An improper practice to malaria management in Africa is not limited to malaria patients who treat themselves at

home. Again, many governments in sub-Saharan Africa are not able to equip most of their peripheral health facilities with diagnostic equipments and sufficiently trained personnel. Along this problem, presumptive treatment of malaria patients is very common at these clinics. As a result some illnesses that share similar clinical symptoms with malaria are treated as malaria cases (Amexo et al. 2004; Redd et al. 1992). Under this confusion the risks of mistreating both malaria and non malaria cases and subsequent treatment failure are high. Given the familiarity of malaria the most likely scenario seems to treat non-malaria cases as malaria. This scenario can pose three risks. First, patients whose problems do not warrant anti-malarial drugs are given these drugs. It is argued that this practice is dangerous as people are exposed to selective drug pressure unnecessarily. This is especially the case when they remain at high risk of subsequent exposure to malaria while their drug levels are declining (Bloland et al. 2000). Second, problems that are responsible for health facility attendance are not appropriately managed and they remain the same. Sometimes lives are lost or the illness is unnecessarily prolonged with subsequent loss of income or productivity (Amexo et al. 2004). When the illness is cured through non-conventional means (such as traditional practices- which is a common option in Africa) trust in modern health practices is eroded. Third, unnecessary prescription of anti-malaria drugs is one of the factors contributing to persistent stock outs at health facilities, a factor mentioned to scare away malaria patients from this encouraged source of treatment (McCombie 1996a). This situation poses a big challenge to ending malaria in Africa for whatever medicines that will be deployed.

Life threatening symptoms of malaria such as convulsions, severe anaemia, respiratory distress, splenomegaly, dehydration, coma and impaired consciousness in African communities are confused with illnesses that according to many customs require traditional management. These symptoms are most common among children below five years. They may arise due to many factors. They include delayed treatment, inappropriate management at home or at the health facilities, treated with parasite resistant or substandard drugs or

inadequate dosage. These symptoms have widely been shown to be an exposure to hospital based treatment (McCombie 1996a; Mwenesi et al. 1995). As I have stated it also occurs that the illness deteriorates into this condition after failure of treatment obtained from health facilities. A study in Ifakara, Kilombero district, found that 60% of mothers and guardians had to visit traditional healers after visiting the hospital (Muela et al. 1998). Hence treatment seeking for malaria is a complex process, but poses a big challenge to control interventions.

Loss of anti-malarial medicines to parasite resistance is another problem undermining the effectiveness of malaria control using case management as an intervention of choice. Inappropriate treatments of malaria due to reasons that have been reported are largely responsible for the development and spread of parasite resistance to important malaria medicines. Chloroquine was the first line treatment for uncomplicated falciparum malaria throughout Africa. It was safe, efficacious, simple and affordable. Widespread parasite resistance to Chloroquine forced many countries to replace it with sulfadoxine pyremethamine (SP). Apart from sharing all the advantages of Chloroquine, SP is given as a single doze treatment. It has now suffered the same fate of Chloroquine. The emergence of parasite resistance to every single drug has heralded a disaster for malaria control in Africa. Drug resistance is the single largest challenge facing malaria community. It is reported that resistance to drugs has contributed substantially to the resurgence of malaria over the past 30 years (Baird 2000)

Vector Control measures

I have shown that mosquitoes are the necessary exposure to malaria transmission. Malaria transmission intensity is measured in terms of average mosquito sporozoite infectious bites a person receives for a specified period of time (Winkler et al. 1999) . In entomological terms, this phenomenon is called entomological inoculation rate (EIR). Areas experiencing 1 average bite per year are considered to be low transmission settings and those with 100 average bites high transmission settings (Geissbuhler 2008) Hence when measures are taken

to reduce or remove these bites, malaria can definitely be reduced or eliminated. Different strategies have been found to achieve this goal. They include environmental measures that deny mosquitoes of their habitat.

There are many successes that have been documented arising from implementing this measure (Hay et al. 2004). Environmental management through draining of swampland combined with improved housing and modern infrastructures have eliminated malaria in rich developed countries (Kitron and Spielman 1989). Another strategy that has proven to reduce EIR is an indoor residual spraying of insecticides. Widespread use of dichlorodiphenyltrichloroethane (DDT) following malaria eradication program in the 1950s towards the end of 1960s is associated with massive malaria reduction in those areas that the program was implemented (Kitron and Spielman 1989; Sharma 2003). Reported vectors resistance to DDT and its subsequent adverse outcome to environment resulted to its abandonment (UNEP). Insecticide Treated Nets (ITN) is the latest and biggest technology that has revived hopes of malaria control initiatives. Its efficacy, safety and effectiveness have well been documented (Abdulla et al. 2001; Binka et al. 1996; Lengeler 2004; Schellenberg et al. 2001b). ITN reduces malaria transmission by preventing mosquito and human contact, repelling them from households that residents sleep under these nets and killing them if they at all dare to land on the nets (Abdulla et al. 2005; Binka et al. 1998 ; Gimnig et al. 2003; Hawley et al. 2003; Howard et al. 2000; Killeen and Smith 2007; Maxwell et al. 2003). These characteristics of ITN have been shown to provide individual, household and community protection against infective mosquito bites (Abdulla et al. 2005; Gimnig et al. 2003; Killeen et al. 2007). These multiple benefits of ITN are the main reasons that this intervention has emerged as the popular malaria preventive tool for Africa (Schellenberg 2001). The biggest challenge for ITN is on how it can be translated into a protection for those most at risk of malaria transmission. This issue has incited a hot debate among malaria control stakeholders on the continent. A large-scale social marketing program of ITNs in rural Tanzania demonstrated that promotion

and distribution of ITN and insecticides involving both public and private sectors with subsidies targeted to pregnant women and young children can achieve high and sustainable ITN coverage for these biologically vulnerable groups that can save them from malaria related morbidity and mortality (Abdulla et al. 2001; Mushi et al. 2003; Schellenberg et al. 2001b; Schellenberg et al. 2003). Some arguments encourage free distribution of ITNs and insecticides to all at risk of transmission as the only way that can realise quick benefits of the technology (Curtis et al. 2003; Teklehaimanot et al. 2007). These arguments are concerned by costs that will hinder the ITNs full potential. Other arguments counter that frees distribution may kill market for ITNs and insecticide (Lines et al. 2003). A study in another rural part of Tanzania has demonstrated that voucher subsidies, commercial market and free distribution can collectively achieve sufficient and equitable ITN coverage without endangering one another (Khatib et al. 2008). Insecticide re-treatment was another setback to realization of full potential of ITNs. Insecticide that was available could be effective only for a certain period. Users have to retreat the nets once the previous one expires. Many studies observed that net re-treatment was low in many places in Africa. Development of technology that will make nets pre-treated at source with insecticide that can be effective during net's life time may ultimately provide a solution to this problem. Many net manufacturers now produce long lasting insecticide treated nets. Another potential challenge for ITN intervention is the reported threat of mosquitoes resistance to most insecticides developed to kill them. Some studies are concerned by the long-term effects of reducing malaria transmission in case ITN realize its full potential (Snow et al. 1997). If countries succeed to eliminate malaria through massive ITN use, they would find it impossible to sustain (Feachem and Sabot 2008). Reduced malaria transmission has been associated with a suppression of immunity in areas that malaria transmission is endemic. This condition called rebound effects of malaria elimination has been observed in several studies of malaria chemoprophylaxis in children (Coulibaly 2002; Greenwood et al. 1995; Menendez et al. 1997; Saarinen et al. 1988; von Seidlein and Greenwood 2003).

Intermittent Treatment of malaria in pregnancy

Pregnant mothers are at particular risks of malaria transmission. The acquired immunity resulting from persistent malaria attacks in endemic areas is suppressed during this period. Their condition is more worrying as their infections can endanger their health and the health of their babies. Parasitimic pregnant mothers are associated with abortion, still birth, severe anaemia and delivery of low weight babies. It has been shown that low birth weight is an important risk for infant mortality. Severe anaemia is an exposure to delivery complications including death of a mother or a baby. This is why Millennium Development Goals 4 and 5 of reducing under-5 and maternal mortality rates by two-thirds by 2015 can only be achieved if malaria in pregnancy is properly addressed. Intermittent preventive treatment (IPT) of pregnant women with a therapeutic course of an anti-malarial drug has shown a potential of protecting them against the adverse consequences of malaria. It has been observed that IPT use during pregnancy in high transmission areas can reduce placental parasitaemia and anaemia (Eijk et al. 2004; Parise 1998; Rogerson et al. 2000; Schultz et al. 1994 ; Shulman 1999). Thus, this strategy has been identified as another priority intervention for malaria control in Africa (Greenwood and Mutabingwa 2002; Parise 1998; Shulman 1999; Verhoeff et al. 1998). Pregnant mothers in endemic transmission areas are required to be administered with IPT during their antenatal (ANC) clinics during pregnancy. The treatment need to be administered during second and third trimesters of pregnancy to achieve the potential of the intervention. Poor attendance to ANC visits are widely reported in Africa (Nydomugyenyi et al. 1998; Okonofua et al. 1992). Plenty of reasons have been raised to explain this behavioral pattern. They range from persistent drug stock outs, user fees charged for the services, long distance to health facilities, delays in clinic openings, long waiting time, unwelcome behavior of health workers and adverse reactions of the medicines (Mubyazi and Gonzalez-Block 2005; Nydomugyenyi et al. 1998). Whatever the reasons, however, if pregnant women do not make regular visits to clinics during their pregnancy there is little chance

that they can benefit from the intervention. Some studies have shown that the effectiveness of this strategy is also compromised by late clinic attendance. It is estimated that 25% of women attend ANCs for the first time during third trimester (WHO/UNICEF 2003). In this circumstance it is difficult for women to take all the required two doses of protection. Very high client to staff ratios and inadequate supervision have bee also cited as other significant barriers to effective delivery of IPT in Africa (Hill and Kazembe 2006). In Malawi, providers in some clinics may attend up to 75 pregnant women daily, resulting in poor quality of care, minimal (if any) counseling and long waiting times (Hill and Kazembe 2006). Another important challenge facing this program is emerging threat of parasite resistance of the commonly used drugs.

Intermittent Treatment of malaria in infants

Randomized Controlled Trials have demonstrated that this intervention strategy is as effective as ITN in its ability to protect young children from malaria transmission (Chandramohan et al. 2005; Schellenberg et al. 2006; Schellenberg et al. 2001a). It has been shown that it can be delivered through integration with the existing child health programs with limited additional costs It has not yet promulgated as a policy, but has a strong appeal to large part of malaria control community and is seriously considered to be included in malaria control armoury.

Malaria control in Tanzania

Tanzania lies just south of the equator between the great lakes Victoria, Tanganyika and Nyasa on one hand and the Indian Ocean on the other. With land area of about 945,000 square kilometers, Tanzania is the biggest country in East Africa. Its size is the same as Nigeria, bigger than California and a little smaller than France and Spain combined. Except for a narrow belt along the 900 kilometers coast, most of Tanzania's land lies above 200 meters altitude and much of the country is higher than 1,000 meters above sea level. Woodland, bush land and wooden grasslands, are the predominant types of vegetation. The

main climatic feature is the long dry spell from May to October, followed by a period of low rainfall, which is often concentrated into relatively few days of heavy showers. The main rainy season on the coast of the country is from March to May but there is a second season from October to December. Total rainfall increases towards the north. Around Lake Victoria rainfall is well distributed throughout the year but there is a peak during March to May.

By 2008 estimates Tanzania has a population of about 49.7 million. The population density is 39 people per square kilometre. The majority of the population are highly scattered in rural areas. Poor road network is a serious problem to access to public services including malaria treatment and ANC attendance for pregnant women. The country has over 100 ethnic groups, each one with its unique ethnic language. However, Kiswahili is the country's only national language. Tanzania has a per capita income of US$.428. Its economy is dominated by subsistence farming of food and cash crops.

Tanzania is characterized by endemic malaria transmission across the country. The number one infectious agent is *Plasmodium falciparum*. It accounts for 96% of all infections in the country (PMI 2007). However, there are some variations in the degree of indemnicity. Unstable seasonal malaria transmission characterizes approximately 20% of the country, while stable malaria with seasonal variation occurs in another 20%. The remaining malaria endemic areas in Tanzania (60%) are characterized as stable perennial transmission. The principal transmission vector is *Anopheles gambiae* (PMI 2007).

An estimated 100,000 malaria deaths occur annually in the country, of which 80% are in children under five years of age. Approximately 14-18 million clinical malaria cases each year are reported by public health services. Over 40% of all outpatient attendances are attributable to malaria. Prevalence of very high malaria transmission intensity is the main reason that Tanzania has been an important research site for a plenty of important malaria intervention evaluation

studies in Africa (PMI 2007). However, results from HIV and Malaria indicator survey conducted in the country in 2008 suggest that point prevalence of malaria parasitaemia is low as 0.4% in regions with low indemnicity and as high as 49% in areas with perennial and stable transmission (NBS 2008).

Malaria control activities in Tanzania are coordinated by National Malaria Control Program (NMCP). It is a vertical program under the department of preventive services in the ministry of health and social welfare. NMCP – Tanzania strategies for malaria control are those adopted from RBM. The goal of medium-term strategic plan for malaria in Tanzania (2008-2012) is reduction of all mortality and morbidity due to the disease by 80% by 2012. Strategies outlined to achieve this goal are: 1) appropriate management of febrile episodes in homes and health facilities 2) protecting pregnant women against malaria by using IPT; 3) vector control which includes encouraging populations at risk to sleep under ITNs and efforts to implement indoor residual spraying (IRS) in epidemic-prone areas; and 4) prompt recognition and response to epidemics.

Over fifty years the key malaria control strategy in Tanzania had been management of cases with Chloroquine (Mshinda 2000). It was safe, effective affordable and acceptable. It succumbed to similar challenges that have been reported under malaria control strategies. Parasites responded to pressures of those challenges by developing resistance that was reported throughout the country. Widespread resistance to Chloroquine made it worthless and was abandoned in 2001. SP was officially adopted to replace ill fated Chloroquine in 2001. All acute uncomplicated malaria cases were required to be treated with SP. This drug could not last long in Tanzania. Pockets of its resistance had already been reported in some parts of the country even before its official use (Ronn et al. 1996; Warsame et al. 1999). Its introduction was like monitoring its increasing resistance. In 2007, the government replaced SP with anti-malarial combination (ACT) composed of co-formulated artemether-lumefantrine (Arlu). The new policy discourages availability of Arlu in informal retail outlets. It is a measure taken to

address the risks of development and spread of parasite resistance. The government is promoting Accredited Drug Dispensing Outlets (ADDOs) to make up for the shortfall arising from restricted availability measures. It has been observed that about 40% of malaria patients in Tanzania are getting their treatment from informal retail outlets. The government is also getting ready to introduce rapid diagnostic tests (RDT) as a popular parasitological examination intervention aimed at reducing unnecessary treatment with anti-malarial drugs. This technology will serve two purposes. One, it will reduce the use of Arlu which is very expensive. We have seen that due to the lack of microscopes in most primary health facilities in Africa, malaria treatment is treated presumptively. Treatment that depends on clinical symptoms has been shown to be an important factor of high use of anti-malarial drugs in Africa. For very expensive drugs like Arlu, syndromic treatment will increase the risks of persistent stock outs. Two, reduction of unnecessary prescription of ACT will inherently shrink anti-malarial drug pressure in the community which has been shown to be an important exposure to drug resistance. In all, RDT and ADDOs will help protect resources and life of ACT.

The National Malaria Control Program is promoting ITNs as its key vector control strategy. Apart from its compliance with RBM, the program's adoption of ITN has been encouraged by the fact that Tanzania has been a testing ground for both efficacy and effectiveness of the technology (Magesa 1991; Schellenberg et al. 2001b). Tanzania embrace of ITN is responsible for government's removal of string of taxes on netting materials which has turned the country into a hub of mosquito net industry in Africa. The government has also been encouraged by huge financial support it is getting from Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM), Unites States President's Malaria Initiative (PMI) and other multilateral and bilateral donors. In response to observations that had shown that Tanzania was not on trek to achieve RBM or PMI targets, NMCP and other malaria control partners introduced pregnant women and infant ITN vouchers and under-five catch-up campaigns. These strategies had worked

elsewhere in increasing and sustaining equitable high ITN coverage to malaria vulnerable groups in Africa. In 2008, NMCP will implement nation-wide free distribution of long lasting insecticide treated nets and insecticide treatments. This program will be financed by US$ 59.8 million grant from GFATM (NATnets 2008). This implementation will target all sleeping sites used by under-five children and pregnant women. Concerns are lingering over this operation on future market, long-tern availability of ITNs and future control of malaria.

We have seen that preventive malaria treatment in pregnancy is another intervention that has been identified for malaria control consistent with RBM strategies. As a policy, every expectant mother is required to be administered with one dose of SP during his second trimester and another one in the third semester when attending ANC visits. Tanzania Demographic and Health Survey (TDHS) has shown that IPTP coverage is still low in Tanzania (Tanzania 2005). It has been observed that one third of women do not make ANC visits until their sixth month or later. These figures suggest that there is little chance that these women can complete the required dosage of IPTP. It is shown that only 22% of pregnant women complete the two dose regimen of SP in Tanzania.

Artemisinin-based Anti-malarial Combination Therapy: Potential and challenges

The increasing loss to parasite resistance of anti-malarial mono-therapeutic drugs is an important risk to malaria control. This is more serious to Africa which bears the brunt of malaria burden. An experience from South East Asia has demonstrated that an approach that combines artemisinin derivatives and another anti-malarial drug can offer the solution (Bloland et al. 2000; Nosten et al. 2000; Winstanley 2001). This strategy is based on a theory that the two chemotherapeutic agents have independent mechanisms of action and hence the probability that the parasites could confer resistance to both medicines simultaneously is very low (White 1998). This theory had been validated in the

treatment of tuberculosis, cancer, and HIV (Bloland et al. 2000). A randomized clinical trial conducted in Gambia, a single dose of sulphudoxine-pyremethamine combined with six dose regimen of artesunate taken for three days showed to resolve clinical symptoms and gametocytaemia (von Seidlein et al. 2000a). Another one carried out in Uganda involving similar course regimen of artesunate and amodiaquine demonstrated high activity against parasitaemia (Yeka et al. 2005). Evaluations being conducted in Zanzibar and KwaZulu-Natal, South Africa, following implementation of multiple malaria control interventions demonstrated a dramatic decline of malaria transmission partly associated with adoption of artemisinin based anti-malarial combination therapy (ACT) (Barnes et al. 2005; Bhattarai et al. 2007). The collateral benefit that has been widely reported for artemisinin based ACT to malaria control is its strong action on gametocytes (Hallett et al. 2004; Price et al. 1996; Targett et al. 2001). This treatment targets the malaria parasite at the stage that its risks to continued cycle of transmission begins. This means that even if a parasite has survived the double action of the drugs, the probability that it will be transmitted is low. This impact on gametocyte carriage has not been shown from administration of monotherapeutic agents (Gogtay et al. 1999).

All these are good reasons for malaria control movement to recommend the rolling out of artemisinin based anti-malarial combination therapy in Africa. However, there are serious concerns that the benefits of combination treatment could not be extrapolated to the whole of the continent (Bloland et al. 2000). First, malaria transmission intensity in Africa is different from those reported success stories. South-East Asia is a low transmission setting and people infected by malaria in such environment become symptomatically ill with no difference across age groups and are therefore more likely to seek some form of treatment (Alles et al. 1998; Luxemburger et al. 1996; Price et al. 1996). This condition increases the probability of most infections being treated with combination treatment. In Africa, where malaria transmission is largely stable and intense, most *falciparum* infected people especially older children and adults are asymptomatic and hence

they have little reason to seek treatment (Bloland et al. 2000). The majority of treatment seekers are young children and pregnant women whose immunity to malaria transmission is comparable to low transmission areas of South-East Asia. Older children and non pregnant adults comprise the bulk of the population and hence they could not only contribute to the maintenance of intense malaria transmission by acting as reservoirs of gametocytes but could also perpetuate resistance through the inappropriate use of medicines (Githeko et al. 1992).

Second, in South-East Asia and even in South Africa, public health care delivery is very strong. Access to health care facilities is very high and treatment provision is strictly subject to microscopic examination (Bloland et al. 2000). Malaria treatment in most parts of Africa is largely based on clinical signs and symptoms of the disease that have been found to overlap with other illnesses. Consequently, people visiting health facilities are over- diagnosed and as a rule fever is treated as malaria (Font et al. 2001; Reyburn et al. 2007). It has been demonstrated that laboratory based diagnosis can reduce the use of anti-malarial drugs. It has been explained that this weakness can be a risk factor for development and intensification drug resistance in any strategy of malaria therapy (Bloland et al. 2000). Limited access to health facilities and cultural beliefs and practices about malaria in Africa encourage treatment seeking practices that create conditions that are also conducive to emergence, intensification and spread of drug resistance. It is argued that poor practices about drug use result in inappropriate dosing that provides increased opportunity for parasites to be exposed to sub-optimal blood levels of either drug in the combination (Bloland et al. 2000).

This study reports some findings of the evaluation that was conducted in Southern Tanzania to address those concerns.

Implementation and evaluation of ACT in rural Tanzania

We implemented ACT in one rural district in Southern Tanzania. Our evaluation involved another rural district with similar conditions. All health facilities in this district replaced SP monotherapy with SP+Art combination for routine malaria treatment. We first of all, evaluated health workers and patients' compliance with the treatment regimen. This was even important for combination treatment and in the setting that we conducted our implementation. The implementation would replace the then ongoing SP monotherapy which was a single dose regimen with the combination of SP+Artesunate whose regimen was composed of two separate drugs with many tablets, to be taken twice per day for three days. Artemisinin derivatives had been shown to resolve fever symptoms more quickly than SP (Nosten et al. 1994; Williams et al. 1999). So, there was a concern that quick fever disappearance before a regimen was completed would prompt the perception of being cured on the part of the patient and treatment would be stopped and the remaining drug would be saved for later use (McCombie 1996a) Hence compliance with treatment regimen was a legitimate outcome measure of the evaluation. This evaluation could also help the implementers to identify the risks of poor compliance and they would take measures to address them.

The project was implemented in a way that the appropriate use of the combination would be maximized and their potential benefits would be realized. In that case their availability was limited to health facilities. I have already dwelt on the risks of retailers on misuse of medicines and subsequent development and spread of parasite resistance. However, we have seen how manifestations of malaria are perceived in many endemic transmission settings in Africa. And how these perceptions translated into treatment seeking. There was an understanding between the project and all health facilities providing this treatment that malaria treatment would be provided for free. Therefore, direct costs were not a barrier to treatment. However, several studies have demonstrated an association between delays in seeking malaria treatment from health facilities and physical distance between one's residence and the health facility (McCombie 1996a). It was

interesting for the project to investigate whether that availability for free of effective medicines in the midst of other factors that were beyond our subject area had affected the choice of sources of treatment.

This evaluation has provided an opportunity to observe long term trend for malaria parasitaemia across the population and anaemia prevalence for under-five children in the two study sites. We thought that in documenting this dynamic, malaria community would have an opportunity to see the changes for the important indicators for malaria morbidity as a result of implementation of SP+Art combination for malaria treatment and rolling out insecticide treated nets. Our data also provide an opportunity to report on the effects of the implementation of ACT on treatment seeking pattern. The report will better inform the delivery strategies for ACT at the time that most countries in Africa are looking for right ways to take this medicine to scale. When ACT implementation was in progress in Rufiji district in 2004, the Tanzanian Red Cross implemented an ITN catch-up campaign for under-fives during the child vaccination period. It is widely believed that this is very important for achieving ITN coverage targets in Africa (Grabowsky et al. 2005; Grabowsky M 2007). Since the campaign occurred during the time that ITN voucher subsidies for pregnant women and market operation were already in place in the district, it provided an opportunity for our subsequent surveys to evaluate the potential of multiple ITN distribution systems for achieving high and equitable ITN coverage. It has been argued that the promised impact of ACT in Africa can only be established through detailed evaluation that includes an evaluation of INT coverage (Kachur et al. 2001a). This is the case because persistent malaria transmission due to lack of ITN protection is a potential risk exposure to an evolution of drug resistance (Hastings and D'Alessandro 2000; Molyneux et al. 1999). The next chapter will present malaria transmission intensity in the two study sites and major malaria control interventions in existence in each one of them. This will include the introduction of ACCESS project which is implemented in Kilombero/Ulanga site in order to

identify and address most important risks to prompt and appropriate malaria treatment in the area (Hetzel et al. 2007a; Hetzel et al. 2007b; Hetzel et al. 2006).

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PART II: OBJECTIVES AND METHODS

Chapter 2: Goal and Methodology

Goal of the study

This study was conducted to measure the impact of introduction of artemisinin based combination therapy (ACT) in health facilities for routine treatment at a district scale on parasite resistance and malaria transmission in African communities.

Objectives of the study

1. Assess the changes in the prevalence of malaria parasitaemia before and after the introduction of ACT
2. Describe and analyse the changes in treatment seeking practices for malaria episodes before and after the introduction of ACT
3. Evaluate malaria patients' adherence to ACT provided at the health facilities
4. Describe and analyse the contextual factors other than ACT that could influence malaria transmission.

Study area

The basic evaluation for this study was conducted within the frame of the Rufiji and Ifakara Demographic Surveillance System sites (Mwageni E 2002; Schellenberg 2001) in southern Tanzania between 2001 and 2006. However, the district-wide implementation of SP and Artesunate was conducted only in Rufiji district between 2003 and 2006.

The Rufiji DSS site operates in Rufiji District, Coast Region about 178 kilometres south of Dar es Salaam - Tanzania's commercial centre. The site covers a land area of 1,813 square kilometers in the flood plain of Rufiji River. There are

80,842 people in the sites residing in 17,287 households in 31 registered villages. Ifakara DSS site covers Kilombero and Ulanga Districts in Morogoro Region. It covers the flood plain of Kilombero River which about 460 kilometres south west of Dar es Salaam. The Ifakara DSS site has a population of 74,200 individuals and 17,050 households in 25 registered villages. Households in both sites are highly scattered with estimated population density of 25 people/km^2. The area is characterized by a poor road network; there are no paved roads, and some villages are cut off for parts of the year as a result of flooding. There is limited opportunity for mixing of population between the two DSS sites due to the presence of the Selous Game Reserve along their common border. Most local houses have mud walls and thatched roofs, but up to one-third have brick walls and corrugated iron roofs. Most families have a second house known as a *shamba* house (farmhouse), in Rufiji they call them *Dungus* (traditionally built shelters on stilts that suit the flooding conditions), where they stay during the planting and harvesting seasons. The most common sources of water are shallow wells, open wells, and rivers. During the time of our surveys the sites had no telephone service, and most houses had no electricity. The sites have an overall mean altitude of less than 500 meters. Their vegetation is mainly formed of tropical forests and grassland. They are characterized by hot weather throughout the year and two rainy seasons; short rains (October to December) and long rains (February to May). The average annual precipitation in the area is between 800 to 1000 millimeters.

Figure 2: A map of Tanzania showing the location of the study areas

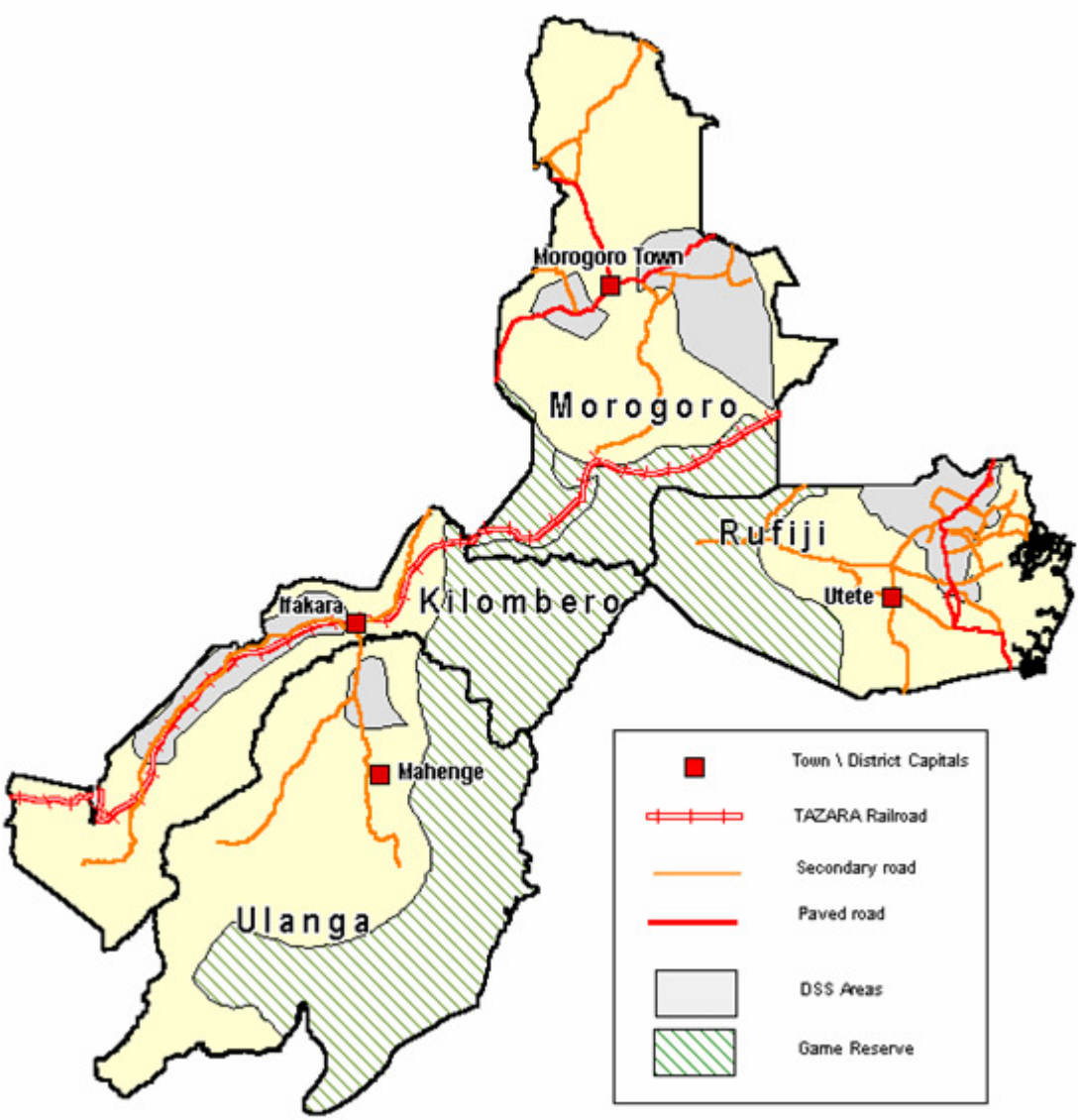

Figure 3: DSS sites of Ifakara and Rufiji

The population in the study area has a wide mix of ethnic groups. The largest ones are Wandamba, Wapogoro, Wabena, Wambunga, and Wahehe in Ifakara and Wandengereko, Wamatumbi, Wanyagatwa, and Wamakonde in Rufiji. Muslims constitute the majority of Rufiji population followed by Christians and the opposite is the case for Ifakara. Like the rest of Tanzania, Kiswahili is the lingua franca in the area. People are predominantly peasants who are largely growing rice, maize, bananas, vegetables and cassava. Some residents are involved in fishing while others in small-scale commercial activities such as selling wood products (e.g. timber, furniture and carvings).

Malaria endemnicity

The study site is characterized by essential features for intense and perennial malaria transmission with some seasonal fluctuation. It reaches its peak during the season of long rains during the months of May and June. Malaria related mortality accounts for most deaths reported by the health system and in the community (De Savigny et al. 2008; Schellenberg et al. 1999). The main parasite specie is *Plasmodium falciparum*. *An. gambiae* complex and *An. funestus* are the prime vectors involved in the transmission cycle. The estimates in the area for 1990s suggest that there were 200 – 300 infective mosquito bites per person per year (Schellenberg et al. 1999). Of late, there has been a sharp decline to 42 and 120 bites thanks to increased ITN use (Smithson 2009). However, like any area with stable endemnicity, young children and pregnant women have the highest risks of malaria transmission in the study site.

Interventions other than IMPACT that would have affected malaria situation in the study area

As outlined in chapter one there are other major interventions that had been and are still being implemented in the study area. These interventions are outlined in the following sections.

Tanzania Essential Health Interventions Project (TEHIP)

It essentially strengthened the Council Management Team (CHMT) in Rufiji District to develop health plans that would respond to priority local health needs. The principle behind this intervention was that health status among poor communities could be improved by redirecting resources to cost effective programs that addressed health problems that matter most in those communities.

Based on health needs assessment conducted by the project, it was discovered that in the district malaria claimed virtually a third of life years lost due to premature deaths and disability. Two thirds of the burden was shouldered by children less than five years. This evidence together with the tools developed by TEHIP, led to a more effective approach in health planning through an intervention addressable disease-burden based approach of priority setting and resource allocation. More specifically, it convinced the CHMT to subsequently increase financial allocation for malaria in their plans from 5 to 25% (De Savigny et al. 2008) . Furthermore, much more interventions that were implemented targeted to malaria and children less than five years such as IMCI (Schellenberg et al. 2004b). This development could obviously make a difference in malaria control efforts in Rufiji district including the DSS area.

ACCESS

It is a program that was designed to identify and address factors that were important for malaria patients' access to appropriate and effective treatment in Kilombero and Ulanga Districts. Previous studies had demonstrated that timely treatment seeking for malaria had been undermined by common local perceptions that associated symptoms of severe malaria with an illness not amenable to chemotherapy (Hetzel et al. 2007). In one of its surveys, ACCESS found out that more than three quarters of malaria cases in the community was being treated with recommended anti-malarial medicines (Hetzel et al. 2008b). An important challenge to malaria case management was poor adherence with the recommended dose by patients regardless of medicine delivery source (Hetzel et al. 2008b). The program was introduced during the time that malaria patients in the study area were being routinely treated with sulfadoxine-pyrimethamine consistent with the national policy for malaria treatment in Tanzania that existed at the time.

Several research studies have associated informal drug outlets with the rising loss of malaria medicines to parasite resistance (Bloland et al. 2000). The government confronts this risk exposure by limiting drug availability to formal delivery points. ACCESS had observed that that restriction had denied access to appropriate treatment to the poorest of the poor and malaria patients from the remote hamlets of the villages (Hetzel et al. 2008a). Interventions carried out by ACCESS targeted these important risk factors to access to prompt and appropriate malaria treatment. Important elements of the intervention were a) strengthening knowledge and awareness of malaria and promote prompt and appropriate treatment seeking from reliable sources; b)capacity building on the part of health workers in order to be able and willing to deliver quality malaria treatment; and c) supporting efforts to introduce and build capacity for Accredited Drug Dispensing Outlets (ADDO) (Hetzel et al. 2007) .

Integrated Management of Childhood Illnesses (IMCI)

The IMCI strategy was initially implemented only in Rufiji and Morogoro rural districts (1997 – 1998) due to TEHIP. It was then extended to Ulanga and Kilombero districts (2002 onwards). The program was designed to improve child health and development through combined delivery of essential child health interventions by addressing leading causes of childhood mortality in the area such as pneumonia, diarrhea, malaria, measles, and malnutrition. These conditions were responsible for more than three quarters of post-perinatal deaths for under-fives (Schellenberg et al. 2004b). Its elements were improvements in case management, improvement in health systems and improvements in family and community practices.

Kilombero Insecticide Treated Nets program (KINET)

KINET implemented a large-scale social marketing program of insecticide-treated nets in Ifakara DSS site between 1997 and 2000 (Schellenberg et al. 1999). The program identified and promoted *Zuia Mbu* (a Kiswahili name which means

preventing mosquitoes) for all treated bed nets and insecticide sachets that it supplied. Prices for *Zuia Mbu* products were subsidized by the program and they were targeted to under-five children and pregnant women. In parallel to distribution of subsidized insecticide treated nets and insecticide sachets, the program implemented an extensive information, education and communication campaign intended to create, expand and sustain community demand for this malaria control intervention. The commodities were supplied through both public and private sales agents. Following KINET and based on its impact and experience, a national program aimed at going to scale introduced voucher subsidies targeting pregnant women and their newly born babies in some areas of the country such as Rufiji district between 2004 and 2006. Free distribution to small children was also implemented during the vaccination campaign in 2005 by the Red Cross (Khatib et al. 2008). ITN use increased to 36% in Ifakara and 30% in Rufiji across all ages (chapter 5)

Methodology

The detailed description of data collection and analysis are described is found in each chapter. At this stage, only the broad approaches are outlined below:

Household surveys

The primary sampling units for the study were households. They were sampled from a database of households compiled and updated by each of Ifakara and Rufiji DSS sites. The questionnaires were administered to each individual who had been listed in the sampled households. The respondents were equally asked to provide drops of blood which was used for examining malaria parasitaemia status and hemoglobin level for children less than five years. Household socio-economic status was estimated using indicator variables administered to heads of households or their substitutes. The interviews were conducted subject to informed consent obtained from the study participants or caretakers of small children.

The questionnaires were originally written in English but were translated in Kiswahili and then back translated in English. They were comprehensively pretested. The translation was necessary as all interviews were conducted in Kiswahili, the lingua franca in the study community. These same questionnaires were used for data collection in all survey years of the study. They were 2001, 2002, 2004, 2005 and 2006.

The interviewers were recruited from the local community. They were form four leavers at minimum and most of them had been involved in data collection activities conducted by DSS in the area. They were trained for seven days on how to administer the questionnaire and collecting blood specimens. After the training, they were initially asked to pilot among themselves. They were then sent to the field to practice the questionnaires for couple of days. Interviewers who could not pass all these tests were dropped. Most interviewers who participated in the initial survey were recruited again in the subsequent survey years.

Adherence study

Patients' adherence with sulfadoxine-pyrimethamine combined with artesunate was assessed in 2003 in the Rufji DSS site. Consecutive outpatients diagnosed with uncomplicated malaria and prescribed SP plus AS were approached for enrollment at the under 5 clinic and the general outpatient clinic before arriving at the dispensing unit to receive treatment. Patients residing in a catchment area of nine census-enumerated villages surrounding the health facility were considered eligible and provided consent for enrollment.

Two data collectors were recruited among form four leavers from the local community. They were identified from the team that the project used for household surveys. They were trained on all procedures to do this job. These ata collectors observed encounters between dispensing health workers and all study patients in the dispensing unit and recorded key health worker behaviors on a

structured observation checklist. This included noting the exact number of tablets delivered under direct observation for the
first dose and the number dispensed to the patient for follow-up doses on the second and third days. In addition, they noted what counseling advice dispensing health workers provided. Data collectors also recorded demographic data and any additional diagnoses other than malaria. Before being discharged home, detailed information about the household location
was obtained from all enrolled patients. Enrolled participants were randomly assigned to three study arms: observation of dispensing encounter with no follow- up; observation of dispensing encounter with follow-up at home after 24 hours; and observation of dispensing encounter with follow-up at home after 48 hours.

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PART III: ARTICLES

CHAPTER 3: Adherence to antimalarial combination therapy with sulfadoxine/ pyrimethamine and artesunate in rural Tanzania.

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On January 26, 2003 at 0958h Shomari Jumanne was the first person in Rufiji District to receive SP+Artesunate

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ABSTRACT

Artemisinin-containing antimalarial combination therapies are recommended to confront drug resistant *P. falciparum* malaria. Among the questions surrounding whether these complex multi-dose treatments will be practical is to what extent patients complete the recommended doses. Combination therapy through coadministration of sulfadoxine/ pyrimethamine plus artesunate was introduced as first-line treatment for uncomplicated malaria in one district. Interventions to optimize correct use were implemented as well. We observed 453 patient encounters at one health facility and recorded key practices as health workers dispensed the combination. A total of 253 patients were followed up at 24 or 48 hours. Complete adherence measured at 48 hours reached 75.0%, based on self-report and tablet counts. This is substantially better than reported elsewhere and compares favorably with intervention studies to optimize adherence to chloroquine. Counseling about what to do if a patient vomits appears to have been an independent risk factor for nonadherence.

INTRODUCTION

Antimalarial drug resistance undermines efforts to reduce the public health burden nearly everywhere malaria transmission occurs. Chloroquine, once highly effective against the parasites that cause the disease, has become compromised as drug-resistant *P. falciparum* parasites have become increasingly prevalent in recent decades (Bloland et al. 1998). Resistance to other drugs including sulfadoxine-pyrimethamine, mefloquine, and quinine, has followed closely behind. In 2 refugee camps in Thailand, the use of an artemisinin-containing combination treatment (ACT) with artesunate and mefloquine has been linked to halting the progression of antimalarial drug resistance(Price et al. 1997) and reducing malaria transmission (Nosten et al. 2000). Advocates of this approach(White et al. 1999) and international organizations (World Health Organization 2001) have recently called for ACT strategies to be deployed without delay across Africa,

where the greatest burden of malaria-related morbidity and mortality occurs. Although there are limited data and experience to guide the introduction of ACTs in Africa, there is consensus evolving that the threat of unchecked resistance to the currently used drugs is too urgent to delay their deployment. At least two large-scale evaluations are underway to document the effect of ACTs in African settings (Kachur et al. 2001b). However, these research outcomes may be years away and potential short-term advantages of ACTs are already evident from *in vivo* efficacy studies on the continent (Adjuik et al. 2002; International Artemisinin Study Group 2004; von Seidlein et al. 2000b). So far, the cost of artemisinin-containing drugs, (Snow et al. 2003) their limited global supply, (Duffy and Mutabingwa 2004) and some lingering concerns about safety, (Bloland et al. 2003b) have slowed their wide-spread deployment. As unprecedented resources for malaria control start to become available,(World Health Organization and UNICEF 2003) these barriers, too, are being lowered.

When chloroquine was efficacious, patterns of drug use evolved that were often far from ideal. Because it was relatively affordable and safe, health officials widely recommended chloroquine for anyone who might have malaria (World Health Organization 1986). Over decades the drug became pervasive - used with or without diagnostic confirmation, obtained easily from formal health facilities as well as unregulated sources in the community, and taken with little or no attention to complete, appropriate dosing. As a result, a number of studies in Africa documented that health workers' and consumers' adherence to recommended indications and doses were poor, (McCombie 1996b) and may have contributed to the intensification and spread of resistant parasites (Basco 2004). More recently, efforts to improve the use of chloroquine have demonstrated promise. Providing the drug through trained community health workers, (Kidane and Morrow 2000; Pagnoni et al. 1997) training shopkeepers (Marsh et al. 1999b) and wholesalers, (Tavrow et al. 2003) and dispensing prepacked unit doses (Yeboah-Antwi et al. 2001) with improved labeling, (Agyepong et al. 2002) have

all been shown to enhance the proportion of patients who receive and complete the recommended dose.

Before ACTs are widely deployed in Africa, it will be useful to revisit experiences gained with chloroquine and other monotherapies and carefully consider how the new treatments can be used judiciously. Health officials will have to balance the need to make ACTs widely accessible with concerns about minimizing their inappropriate use (Bloland et al. 2003b). In particular, it may be possible to adapt approaches used to improve complete adherence with chloroquine to the more complex combination regimens. As part of a multidisciplinary evaluation of ACT, the Rufiji District Council Health Management Team (CHMT) introduced sulfadoxine-pyrimethamine (SP) plus artesunate (AS) as first line treatment for confirmed or suspected malaria at all registered health facilities in the district. Shortly after introducing the new treatment, we undertook a follow-up study to assess patient adherence.

MATERIALS AND METHODS

This study was completed as part of the Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania.[*] The objective of this study was to measure adherence shortly after introduction of SP + AS for routine treatment of malaria and to assess factors that might influence this proportion. Informed consent was obtained from all adult participants and from parents or legal guardians of minors. The study protocol was reviewed and approved by the institutional review boards of the US Centers for Disease Control and Prevention

[*]The Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania (IMPACT-Tz) is a multiyear implementation research evaluation project that rests on a collaborative platform comprising the US Centers for Disease Control and Prevention, Ifakara Health Research and Development Centre, the National Institute for Medical Research, Muhimbili University College of Health Sciences, the London School of Hygiene and Tropical Medicine (UK), and the Tanzanian Ministry of Health, including its National Malaria Control Programme, the Tanzania Essential Health Interventions Project, the Adult Morbidity and Mortality Project, and the Council Health Management Teams of Rufiji, Morogoro, Kilombero and Ulanga Districts. IMPACT-Tz is primarily supported by funding from the United States Agency for International Development.

(CDC) and the Ifakara Health Research and Development Centre (IHRDC). In addition, this research has been approved by the National Medical Research Coordinating Committee of the Tanzania Commission on Science and Technology.

The study was completed in Rufiji District, a rural community in Tanzania's Coast Region. *Plasmodium falciparum* malaria transmission is intense and perennial with some seasonal fluctuation (Mwageni et al. 2002). The district population of 203,102 (National Bureau of Statistics United Republic of Tanzania 2002) is served by 56 hospitals, health centers, and dispensaries operated by the government of Tanzania, or officially registered non-governmental organizations. One of these, Ikwiriri Health Centre was chosen for this evaluation because of its central location and high utilization.

Beginning in January 2003, 2 to 5 senior health workers from each of the 56 health facilities in the district were invited to participate in one-day training workshops conducted by the Rufiji District CHMT. These participatory training workshops introduced the principle of ACT and informed health workers to prescribe SP+AS as first-line treatment for confirmed or suspected cases of uncomplicated malaria in all patients 2 months of age or older. The trainers adopted four age-stratified 3-day dosing regimens that had been validated elsewhere(International Artemisinin Study Group 2004) and are illustrated in table 1.

Table 1. Age-specific dosing schedule for sulfadoxine-pyrimethamine (SP) plus artesunate (AS), Rufiji District, 2003

Age group	SP tablets[§] at time 0	AS tablets[†] At time 0	AS tablets[†] at 24 hours	AS tablets[†] at 48 hours
2 to 11 months	0.5	0.5	0.5	0.5
1 to 5 years	1	1	1	1
6 to 13 years	2	2	2	2
14 years and older	3	4	4	4

[§]SP tablets contain sulfadoxine 500 mg and pyrimethamine 25 mg.
[†]AS tablets contain artesunate 50 mg

The training employed simple job aids including a dosing guide, wall chart, and dispensing envelopes with age-appropriate dosing instructions written in Swahili and illustrated for illiterate clients. Participants were trained to administer the first dose of SP+AS under direct observation and to counsel patients and their caretakers about how to take the remaining 2 days of AS to complete the course of therapy. They were also trained to counsel patients and caretakers on how to prevent malaria and when to return if treatment failed or the patient developed additional symptoms. The training methodology included lecture as well as participatory question and answer sessions and clinical case studies. Health workers left the training workshops with supplies of drugs and supporting materials and were directed to train the remaining workers at their respective facilities. This cascade training approach is commonly used to introduce new clinical guidelines and other health system innovations.

Following introduction of SP+AS at all health facilities in the district, we enrolled patients treated with this combination at Ikwiriri Health Centre between 4 February and 27 March 2003. Consecutive outpatients diagnosed with uncomplicated malaria and prescribed SP+AS were approached for enrollment at the under 5 clinic and the general outpatient clinic before arriving at the dispensing unit to receive treatment. Patients residing in a catchment area of 9 census-enumerated villages surrounding the health facility were considered eligible and offered consent for enrollment. Patients with severe or complicated infections, those requiring inpatient treatments, individuals with known sensitivity

to sulfa drugs, pregnant women, and infants less than 2 months of age were excluded from receiving the combination and were ineligible for the study.

Two data collectors were recruited from the local community. These data collectors observed encounters between dispensing health workers and all study patients in the dispensing unit and recorded key health worker behaviors (identified in Table 5) on a structured observation checklist. This included noting the exact number of tablets delivered under direct observation for the first dose and the number dispensed to the patient for follow-up doses on the second and third days. In addition they noted what counseling advice dispensing health workers provided. Data collectors also recorded demographic data and any additional diagnoses other than malaria. Before being discharged home, detailed information about the household location was obtained from all enrolled patients.

Enrolled participants were randomly assigned to three study arms: observation of dispensing encounter with no follow-up; observation of dispensing encounter with follow-up at home after 24 hours; and observation of dispensing encounter with follow-up at home after 48 hours. This design was selected to minimize 2 sorts of bias that might be expected to affect participants' behavior. Including a no follow-up group introduced some uncertainty, so that patients and caretakers may have been less prone to social desirability bias. Including the follow-up at 24 hours, before the treatment should have been completed, allowed us to characterize practices such as completing the entire course ahead of time, which might be overlooked by assessing adherence only once, at or beyond 48 hours. Data collectors, patients, caretakers, and health workers were blinded to the study arm on the day of enrollment.

At the end of each enrollment day, data collectors reviewed the random assignment of patients, identified those selected for follow-up visits, and planned these visits for the following days. If one of the data collectors observed the dispensing encounter with a patient or caretaker the other data collector was

assigned to visit that household in follow-up. With the assistance of local leaders, they visited patients at home on the selected follow-up day and completed a standardized questionnaire. The follow-up questionnaire included questions about household education, construction and ownership of specific assets. These were included to characterize each household's relative socioeconomic status. Knowledge of the recommended dose was determined by structured interviews with patients themselves or their primary caretaker for patients under 12 years of age. Adherence with recommended follow-up doses was assessed by self-report and corroborated by physically counting the remaining number of tablets available at the time of the visit.

Data entry forms were checked in the field by a single investigator (RAK). Forms were then sent to the central data processing unit. Data were double-entered using MicroSoft FoxPro (Seattle, USA). Data managers developed automated routines to identify discrepancies and execute some simple consistency and range checks and these were resolved with reference to the original data forms. The investigators cleaned and analyzed data using Stata, version 7 (College Station, USA).

We defined adherence by self-report as any case where the patient stated they had taken all of the tablets as recommended by the time of the follow-up visit at either 24 or at 48 hours. Adherence based on tablet counts was defined as any case where the expected number of remaining tablets was physically counted. Cases in which the health worker dispensed an incorrect number of tablets to begin with were excluded. Finally a composite assessment of adherence was made using information from both the self-report and tablet counts. Cases where tablet counts were correct but where the reported timing of doses was incorrect and cases where the reported timing of the doses was correct but did not match tablet counts were considered non-adherent using this composite measure. Complete adherence was assessed by this composite measure only for patients visited at 48 hours. Patients randomized to the 24-hour follow-up arm were not

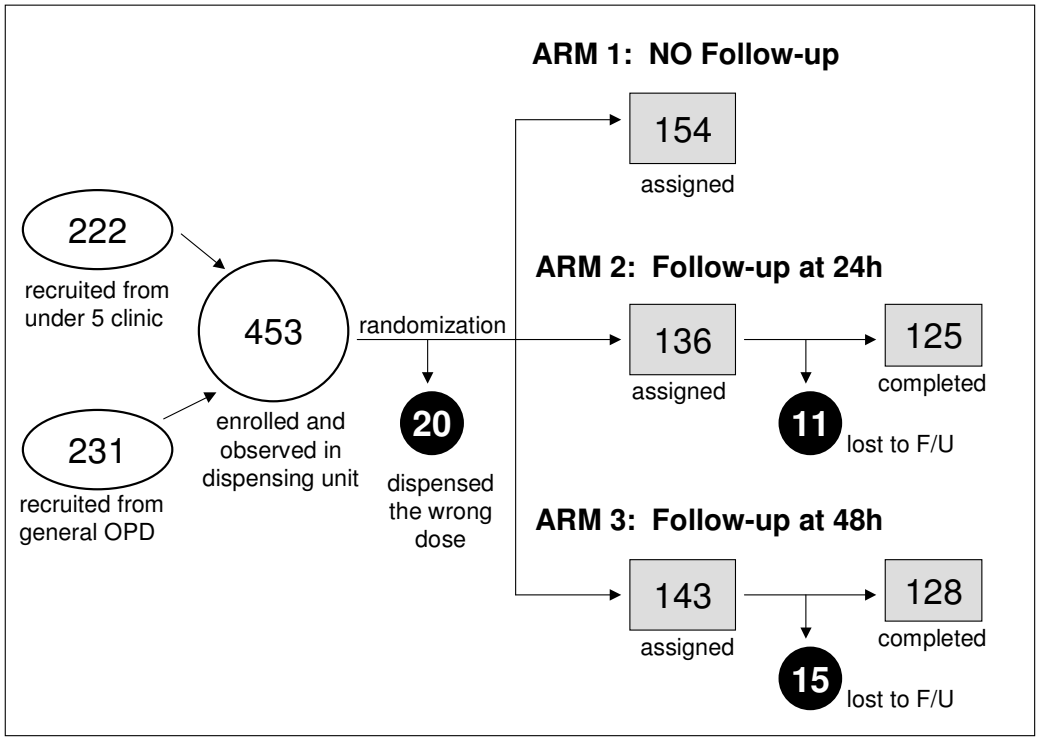
considered in calculating complete adherence, but are presented for comparison and were included in the analysis of factors associated with adherence (on the basis of the composite measure).

An index of socioeconomic status was derived from a list of 42 household asset variables using principal components analysis. This technique has been validated in a previous cross-sectional survey in the study area (Armstrong-Schellenberg et al. 2003). Statistical comparisons across 2 variables were made using the chi square or Fisher exact test as appropriate. The chi square test for linear trend was used to examine statistical associations between the asset index and outcome variables. Multivariate logistic regression analyses were performed to examine the simultaneous influence of multiple potential predictors on patient knowledge and adherence outcomes. Findings with $P < 0.05$ were considered statistically significant.

RESULTS

Figure 1 illustrates the enrollment, randomization and follow-up of study patients. A total of 453 consenting patients were enrolled: 222 from the under 5 clinic and 231 from the general outpatient clinic. Among these 20 (4%) were excluded from further analysis because the health worker dispensed an incorrect number of tablets. Seventeen of these patients were dispensed too few tablets and only 3 received more than the recommended number. Table 2 includes information on the patients assigned to each of the study groups. There were no statistically significant differences observed between the study groups with respect to age, gender, or the likelihood of receiving the correct number of tablets. Although additional diagnoses other than malaria were rare, participants enrolled in the 48-hour follow-up arm were significantly more likely than other participants to have been diagnosed with a respiratory infection.

Figure 1: Enrollment, assignment and follow-up of patients in SP+AS adherence study, Rufiji District, 2003



Two hundred fifty-three (90.7%) of the participants randomized to receive a follow-up visit were successfully identified in the community and completed the study. There was no statistically significant difference in loss to follow-up between the study arms. The 29 patients lost to follow-up did not differ significantly from those who completed follow-up visits with respect to age, gender, additional diagnoses, nor village of residence.

Household Asset Index. Of the 42 household asset ownership questions asked, 15 were eliminated from further analysis because they were reported too frequently or too infrequently to adequately characterize variation in the sample. The analysis retained 27 principal components. The first principal component explained 21% of the variability in these variables and gave the greatest weight to households constructed with cement walls (0.30), using electric lighting (0.30),

having a dirt floor (-0.29) or relying on locally made oil lamps (-0.29). An overall index of socioeconomic status was generated using these weights for each of the 27 principal components. One common way of using this information is to divide the participants into wealth quintiles based on their asset index scores. Comparing wealth quintiles between participants followed up at 24 hours and at 48 hours produced a chi-square test for linear trend of 0.02, which demonstrates no statistically significant difference in socioeconomic status between participants assigned to the 24 and 48 hour follow-up study arms (see Table 2).

Table 2. Characteristics of clients enrolled in SP+AS adherence study, by study arm, Rufiji District, 2003

	No visit n=162	**24-hour visit n=143**	**48-hour visit n=148**
Point of recruitment			
Under 5 clinic	76 (46.9%)	74 (51.7%)	81 (54.7%)
General OPD	86 (53.1%)	69 (48.3%)	67 (45.3%)
Gender			
Male	64 (39.5%)	58 (39.2%)	57 (39.9%)
Female	98 (60.5%)	90 (60.8%)	86 (60.1%)
Additional diagnoses			
Respiratory Infection	9 (5.6%)	10 (7.0%)	18* (12.6%)
Gastroenteritis	5 (3.1%)	7 (4.9%)	4 (2.7%)
Skin Infection	0	3 (2.1%)	4 (2.7%)
Dispensed the correct number of SP and AS tablets for age	154 (95.1%)	136 (95.1%)	143 (96.6%)
Completed follow-up visit	Not applicable	125 (91.9%)	128 (89.5%)
Socioeconomic status by wealth quintile			
Most poor		22 (19.8%)	24 (21.8%)
Very poor		20 (18.0%)	23 (20.9%)
Poor		27 (24.3%)	17 (15.5%)
Less poor		23 (20.7%)	21 (19.1%)
Least poor	Not applicable§	19 (17.1%)	25 (22.7%)

*Differs significantly from no visit and 24-hour follow-up arms ($O^2_{df=1}$=3.92, p=0.05).

§Socioeconomic data were not collected from patients randomized to the no follow-up study arm.

Patient knowledge and adherence. Nearly all patients or caretakers in both study groups accurately reported knowledge of the correct dose (Table 3). Adherence was measured by self-report, tablet counts, and a composite of the two, as defined above. In general adherence was higher among patients visited at 24 hours compared with those in the 48-hour follow-up group. This difference was statistically significant. The most restrictive measure of complete adherence is that from the composite measure in the 48-hour group: 75.0%. Among the 45 patients who were non-adherent in either study arm, a reason for this could be assessed in 42 cases (see Table 4). Finishing all the tablets in fewer than 48 hours was the most common reason for non-adherence and 12 of the 16 cases to which this applied were children.

Table 3. Patient/caretaker knowledge and adherence to SP+AS by self-report, tablet counts, and composite measure at 24 and 48 hours, Rufiji District, 2003 (n=253)

Parameter	At 24 hours	At 48 hours
Total number completing follow-up	125	128
Patient/ caretaker knowledge of correct dose	118 (94.4%)	115 (89.8%)
Adherent by self-report only	115 (92.0%)	98∞ (76.6%)
Adherent by tablet count only	113 (90.4%)	105 (82.0%)
Adherent by composite measure of self-report & count	112 (89.6%)	96‡ (75.0%)

∞Differs significantly from estimate at 24-hour follow-up, ($O^2_{df=1}$=11.79=0.001).

‡*Complete adherence*. This estimate differs significantly from the comparable estimate at 24-hour follow-up, ($O^2_{df=1}$=9.48, p=0.002).

Table 4. Reasons for non-adherence to SP plus artesunate, Rufiji District, 2003. (n=45)

Reason for non-adherence	Frequency (percent)
Finished total course of doses in fewer than 48 hours	16 (35.6%)
Discontinued prematurely because the patient's condition improved	12 (26.7%)
Skipped one dose	6 (13.3%)
Intended to take the dose later in the day	5 (11.1%)
Took too few tablets with one or more dose	3 (6.7%)
No reason identified	3 (6.7%)

Predictors of adherence. In bivariate analyses, adherence was not associated with patient's age, gender, or home village. As noted above, adherence was

slightly but significantly higher among patients visited at 24 hours. There was also a statistically significant association between adherence and knowledge of the correct dose. Adherence was not statistically associated with the education of the patient's head of household or with socioeconomic status as defined by household wealth quintiles. All of the patients diagnosed with gastroenteritis were adherent, and those patients diagnosed with a skin infection were less likely to adhere to the recommended doses. There was no statistical association with adherence for those diagnosed with acute respiratory illness or for those with no diagnosis other than malaria.

During their training, health workers learned to use simple job aids for prescribing and dispensing the SP+AS and for counseling patients and their caretakers on how to complete the dose. As part of the study, data collectors observed the encounter between each patient and the dispensing health worker and recorded key behaviors (see Table 5) in order to examine whether any were associated with patient adherence. At one extreme, none of the observed dispensing health workers mentioned that the treatment was for malaria, informed the patient about possible side effects, or advised the patient to sleep under an insecticide treated net. On the other hand, in nearly all interactions, the health worker dispensed the correct number of tablets (96.5%), gave the first dose under direct observation (98.9%) and correctly advised the patient how to take the remaining AS tablets at 24 and 48 hours (98.9%). These behaviors occurred either too frequently or too infrequently to be evaluated effectively as predictors of adherence. Among the behaviors that were observed more intermittently, most were not statistically associated with adherence. Paradoxically, only health workers' advice about what to do if the patient vomited was associated with adherence ($O^2_{df=1} = 5.28$, $P < 0.022$), and this association was negative.

Table 5: Potential factors associated with adherence to SP+AS, Rufiji District, 2003

Potential factor	Adherent n=208	nonadherent n=45	Odds ratio	Adjusted OR
Demograhic factors				
Patient's age < 5 years	110 (52.8%)	25 (55.6%)	0.90 (0.47, 1.72)	1.11 (0.54, 2.28)
Male patient	82 (39.4%)	18 (40.0%)	0.98 (0.50, 1.89)	dropped
Assigned to the 48-hour study arm	96 (46.2%)	32 (71.1%)	0.35 (0.17, 0.70)	0.38 (0.18, 0.80)
Patient / caretaker knowledge of correct dose	207 (99.5%)	26 (57.8%)	151.27 (11.81, 1937.21)	not included
Socioeconomic status				
Head of household has had formal education	119 (65.4%)	20 (51.3%)	1.79 (0.89, 3.63)	--
Household asset index in the poorest 2 quintiles	73 (35.2%)	16 (35.6%)	0.98 (0.50, 1.92)	--
Household asset index in the least poor 2 quintiles	75 (36.1%)	13 (28.9%)	1.39 (0.68, 2.81)	--
Household asset index as a continuous variable	--	--	--	1.05 (0.92, 1.20)
Additional diagnoses				
Acute respiratory illness	16 (7.7%)	6 (13.3%)	0.54 (0.20, 1.48)	dropped
Gastroenteritis	11 (5.3%)	0	undefined	not included
Skin infections	3 (1.4%)	4 (8.9%)	0.15 (0.03, 0.71)	dropped
None	179 (86.1%)	36 (80.0%)	1.54 (0.67, 3.55)	dropped
Dispensing health worker behaviors				
Told the patient the drugs were intended to treat malaria	0	0	undefined	not included
Told the patient about possible side effects	0	0	undefined	not included
Advised the patient to sleep under an insecticide-treated net	0	0	undefined	not included
Told the patient the names of the drugs	1 (0.5%)	0	undefined	not included
Advised the patient to return if condition worsened	1 (0.5%)	3 (6.7%)	0.07 (0.01, 0.67)	dropped
Asked if the patient had questions	1 (0.5%)	1 (2.2%)	0.21 (0.01, 3.51)	dropped
Told the patient what to do if he/she vomits after a dose	9 (4.3%)	6 (13.3%)	0.29 (0.10, 0.87)	0.29 (0.09, 0.90)
Used the wall chart or dosing guide to explain dose	58 (27.8%)	13 (29.0%)	0.95 (0.47, 1.95)	dropped
Told the patient the drugs were for one person only	79 (38.7%)	19 (42.2%)	0.84 (0.43, 1.61)	dropped
Told the patient to take the medicines with food or water	88 (42.3%)	18 (40.0%)	1.10 (0.57, 2.12)	dropped
Dispensed tablets with the age appropriate dosing envelope	188 (90.4%)	39 (86.7%)	1.45 (0.54, 3.85)	dropped
Told the patient to take 2 daily doses of artesunate at home	207 (99.5%)	45 (100.0%)	undefined	not included
Gave the first dose under direct observation	207 (99.5%)	45 (100.0%)	undefined	not included

We fitted logistic regression models to examine the influence of various predictive factors associated with knowledge of the correct dose and with adherence. Because patient knowledge and adherence were closely correlated ($O^2_{df=1}$ = 86.08, $P < 0.001$), we modeled each outcome individually and did not include knowledge as a predictor of adherence. Models developed for patient or caretaker knowledge was similar to those developed for adherence outcomes and are not presented here. Independent variables included at the start of the stepwise logistic regression included demographic characteristics such as age and gender; the household asset index as a continuous variable; additional diagnoses of acute respiratory illness, skin infections, or none but malaria; and 6 of the dispensing health worker behaviors that occurred with enough frequency to be assessed as predictors of adherence. Diagnosis of acute respiratory infection was dropped for colinearity. The health worker behaviors included in the modeling process were counseling the patient about what to do if he/she vomited a dose, advising them to return if the condition worsened, asking if the patient had questions, recommending that the medications be taken with food or water, advising that the medications were for one person only, using the dosing wall chart, and dispensing the medicines in the age-appropriate dosing envelope. Most of these along with gender and the additional diagnosis variables were eliminated in fitting the multivariate model.

Because they were related to the study design, variables for age less than 5 years and study follow-up arm were retained at each step. In the final fitted model only being counseled about what to do if the patient vomited was an independent risk factor for nonadherence. Being randomized to the 48-hour follow-up arm was also statistically associated with nonadherence. Socioeconomic status as measured by the household asset index approached statistical significance in the multivariate model despite no observable trend in bivariate analysis. Interaction terms between socioeconomic status, follow-up arm, age less than 5 years and being counseled about vomiting were tested but did not achieve significance nor improve the fit of the model.

DISCUSSION

This study provides useful information about how complex multi-dose combination therapy regimens for malaria may be delivered in ways that can optimize adherence and appropriate drug use. Because patients observed at 24 hours may not have gone on to complete their third dose, we estimated complete adherence only among the patients randomized to the 48-hour follow-up arm. Based on a composite of self reports and tablet counts, 75.0% of patients were completely adherent to the recommended regimen. This is substantially higher than the only other published follow-up study of patients treated with SP+AS, in which only 39% of patients were considered adherent based on a similar definition combining tablet counts and caretaker's history.(Depoortere et al. 2004) This estimate is also encouraging because it comes immediately after the intervention was introduced at health facilities and can be expected to improve as health workers and their clients become more familiar with and confident in the new treatment. It is equally possible, however, that after the new treatment becomes routine, health workers and consumers may eventually feel comfortable enough to stray from recommended practices and adherence could decline.

While there is clearly room for improvement, this estimate also compares favorably with data from studies examining adherence to 3-day regimens of chloroquine monotherapy in Africa. Without interventions to improve complete adherence, cross sectional studies have demonstrated that only a small fraction of children received adequate doses of chloroquine. Estimates of the proportion of children who received complete treatment with chloroquine ranged from 30% in Togo, (Deming et al. 1989) to 12% in western Kenya,(Ruebush et al. 1995) and 7% in Malawi (Slutsker et al. 1994). These cross-sectional estimates can be difficult to compare across studies and are quite dissimilar from the methodology employed in our assessment. We found one published study of adherence to chloroquine that used a design similar to ours, with observation at the dispensing unit and follow-up at home. This study in Uganda showed that among children

who were dispensed a correct dose of chloroquine, complete adherence after 3 days was only 38% (Nshakira et al. 2002).

Intervention studies to improve adherence with chloroquine are more numerous. In one Nigerian study complete adherence reached 73.3% after introducing a combination of illustrated dosing instructions and health worker counseling (Okonkwo et al. 2001). In Ghana, complete adherence reached 91% after an intervention promoting prepackaged tablets (Ansah et al. 2001). Also an intervention based on training shopkeepers in coastal Kenya improved the proportion of children treated with an adequate dose of chloroquine to 65.2% (Marsh et al. 1999b). We achieved comparable results after introducing counseling and packaging innovations alongside the new SP+AS combination therapy. We have no estimate of what complete adherence might have been without these additional intervention elements in place.

It is disappointing that few of the observed health worker behaviors could be evaluated as independent factors predicting adherence. In general, dispensing health workers provided recommended doses very accurately but failed to adopt many of the other training elements related to counseling or advising patients. It is not possible from this data to say if this is a trend throughout the district or if it is limited to the small number of health workers observed at this one health facility. The senior health workers who took part in the CHMT's training workshops are primarily responsible for diagnosis and prescribing, and their activities were not directly observed. By conducting the study at the dispensing unit we were able to observe only the practices of more junior dispensing health workers. From their observed behavior, the training cascades appear to have been only partially effective at this site. Busy supervisors may have abbreviated the training or dispensing health workers may have interpreted their role narrowly and opted to leave discussion of diagnosis and potential side effects to their senior colleagues. The project team plans to reemphasize these elements in future training workshops that will include dispensing health workers as well as

prescribers. Additional studies are planned to observe prescribers' encounters with patients and document dispensing health workers' behavior at other sites in the coming months.

The surprising association between counseling about what to do when a patient vomits and nonadherence is difficult to explain. Perhaps health workers only emphasized this issue to patients who appeared more ill or complained of vomiting and who were less likely to complete the follow-up doses for those reasons. Alternatively, in the absence of any information about side effects, patients and caretakers may have been less likely to complete the follow-up doses if they feared the medicine might cause them to vomit. None of the participants reported vomiting after taking the SP+AS. More information about community perceptions of the SP+AS is needed and qualitative assessments are currently underway in Rufiji District to assess these.

One particularly concerning practice was identified in 16 cases, 12 of them children. These patients took all their follow-up doses but were considered non-adherent because they or their caretaker reported having taken the entire course of treatment in fewer than 48 hours. In dose-finding studies for artesunate monotherapies, the same dose was more effective delivered over 5 days compared with 3 days (Li et al. 1994) and still more effective delivered over 7 days compared to 5.(Bunnag et al. 1991) Indeed, 3 dose artesunate monotherapy has been considered insufficiently efficacious to recommend, and when used in combination with other antimalarial drugs, a minimum of 2.5 days has been demonstrated efficacious.(Barradell and Fitton 1995) This is particularly important because the SP+AS combination may be only partially effective if the total dose is compressed into fewer than 48 hours. Even if the immediate clinical outcome is unaffected, shortening the duration of therapy may increase the theoretical potential to select for SP-resistant parasites.

Our findings regarding socioeconomic status, as measured by the household asset index, as a predictor of adherence, are also equivocal. In a previous study that included parts of the same district, Armstrong-Schellenberg, *et al.*(Armstrong-Schellenberg et al. 2003) demonstrated that children from relatively poorer households were taken to health facilities less promptly and were less likely to receive appropriate care than children from wealthier households. However, they also demonstrated that once the children received treatment, adherence was not affected by socioeconomic status.

Our study has several other important limitations that should be considered. First of all, the study was completed at a single health facility over a relatively brief period. It may not be representative of the situation in the rest of the district or at other times of year. More importantly, simply enrolling patients in a follow-up study may alter their adherence to treatment. We attempted to minimize this by including an arm with no follow-up and by blinding the clients, data collectors, and health workers to the randomization on the day of enrollment. We also visited participants only once, so that a visit at 24 hours would not affect a participant's behavior at or before 48 hours. It is still possible that social desirability bias may have led us to overestimate adherence. It is equally possible that some patients would have taken their 24- and 48-hour follow-up doses later in the day but had not done so by the time the investigators arrived at their homes. Indeed 6 of 45 nonadherent patients indicated that they intended to complete the recommended dose later that same day. In this way we may have underestimated adherence. In the future we plan to assess adherence retrospectively through population-based studies that will provide more representative data that may be less prone to these biases.

Admittedly, self-report and tablet counts are imperfect measures of adherence. A measure based on drug levels in biological samples would be more robust. Unfortunately such an approach would be more invasive as well. Because the first dose of SP+AS was given under direct observation, there would be little

point measuring blood levels of the sulfa component. Furthermore, blood levels of the artemisinin compounds would be difficult to interpret without accurate information about the timing of the follow-up doses and the samples, which would make such a study more difficult to execute in a rural African community where timepieces are not commonplace. In addition, such assays require expensive equipment and reagents that may be unsuitable for field conditions.(Edwards 1994)

Nonetheless, these findings were immediately useful to the project team and contributed to efforts to improve the coverage and delivery of SP+AS combination therapy in Rufiji District. They directly led to development of a health communication campaign in the district, which emphasizes the need to take the tablets once a day for 3 days in a row, even if patients feel better before then. These findings also prompted us to revise our training and supervision plans for health workers in facilities throughout the district. As the SP+AS combination therapy becomes more widely used in Rufiji District and experience with it accumulates, we are hopeful that adherence will improve further. Repeat assessments are planned in early 2004.

The findings have relevance beyond our study site as well. At the very least they reinforce some of the lessons learned about how to improve malaria treatment during the chloroquine era. Interventions such as health worker training, simple job aids, patient counseling, directly observed therapy, and unit dose packaging with illustrated instructions can be easily adapted to combination therapies for malaria. By carefully introducing these elements along with the SP+AS, we were able to achieve reasonable levels of adherence right from the first weeks. This will be particularly important as other ACTs become more broadly used throughout the region. Public health officials, pharmaceutical regulatory bodies, and manufacturers should begin now to make sure these simple interventions are incorporated as new drugs are deployed in both the public and private sectors.

Artemisinin-containing combination therapy has yet to be shown to reduce transmission or stall resistance in African settings; it will be an expensive and ambitious undertaking to extend this approach where resources and infrastructure are badly constrained; but the strategy may represent the best hope for confronting the crisis facing malaria treatment in the region. Whether this hope has a chance of being realized will depend on optimizing the delivery of and adherence to these new treatments. Our findings demonstrate that it is possible to achieve reasonably high levels of adherence to a 3 day treatment with SP+AS delivered through existing health systems. More experience measuring adherence is needed so that practical, standardized approaches that will facilitate comparisons across different settings can be devised.

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CHAPTER 4: Markets, voucher subsidies and free nets combine to achieve high bed net coverage in rural Tanzania

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Abstract

Background

Tanzania has a well-developed network of commercial ITN retailers. In 2004, the government introduced a voucher subsidy for pregnant women and, in mid 2005, helped distribute free nets to under-fives in small number of districts, including Rufiji on the southern coast, during a child health campaign. Contributions of these multiple insecticide-treated net delivery strategies existing at the same time and place to coverage in a poor rural community were assessed.

Methods

Cross-sectional household survey in 6,331 members of randomly selected 1,752 households of 31 rural villages of Demographic Surveillance System in Rufiji district, Southern Tanzania was conducted in 2006. A questionnaire was administered to every consenting respondent about net use, treatment status and delivery mechanism.

Findings

Net use was 62.7% overall, 87.2% amongst infants (0 to1 year), 81.8% amongst young children (>1 to 5 years), 54.5% amongst older children (6 to 15 years) and 59.6% amongst adults (>15 years). 30.2% of all nets had been treated six months prior to interview. The biggest source of nets used by infants was purchase from the private sector with a voucher subsidy (41.8%). Half of nets used by young children (50.0%) and over a third of those used by older children (37.2%) were obtained free of charge through the vaccination campaign. The largest source of nets amongst the population overall was commercial purchase (45.1% use) and was the primary means for protecting adults (60.2% use). All delivery mechanisms, especially sale of nets at full market price, under-served the poorest but no difference in equity was observed between voucher-subsidized and freely distributed nets.

Conclusions

All three delivery strategies enabled a poor rural community to achieve net coverage high enough to yield both personal and community level protection for

the entire population. Each of them reached their relevant target group and free nets only temporarily suppressed the net market, illustrating that in this setting that these are complementary rather than mutually exclusive approaches.

Background

It is estimated that malaria is responsible for 515 million clinical attacks worldwide, 70% of these events are concentrated in Africa (Snow et al. 2005). Young African children and pregnant women bear brunt of the burden and at least 18% of childhood mortality on the continent is due to malaria (WHO/UNICEF 2005). More encouragingly, the fact that insecticide-treated nets (ITN) prevent malaria has been irrefutably documented (Fegan et al. 2007; Lengeler 2004). The Roll Back Malaria Partnership and Millennium Development Goals (MDG), therefore, aim to achieve 80% ITN use amongst pregnant women and children below five years of age in Africa, while the US President's Malaria Initiative (PMI) is even more ambitious, aiming for 85% use amongst these same population categories (2006; MillenniumProject 2005; RollBackMalariaPartnership 2005). However, there is growing consensus that this important intervention will only achieve its full potential to prevent malaria if at least one third of the entire population sleeps under ITN, as well as the vast majority of the most vulnerable groups such as pregnant women and young children (Binka et al. 1998; Hawley et al. 2003; Killeen et al. 2007b; Maxwell et al. 2002; WHO 2007). This is because residents are protected by not only personal use of ITNs but also by the community-wide effect that their neighbours nets have on mosquito populations. Much as there is increasing call for rapid and sustained achievement of high ITN coverage targeting entire populations (Hawley et al. 2003; Howard et al. 2000; Killeen et al. 2007b; Maxwell et al. 2002), including non-vulnerable adults and older children, delivery mechanisms by which this noble goal can be achieved are still actively debated [14-16]. Until recently, public debate has largely focussed upon the comparative merits of free and market-based strategies for deploying ITNs (Magesa 1991; Magesa et al. 2005; Schellenberg et al. 2001b; Skarbinski et al.

2007). While spirited debate over such a potentially important public health issue is welcome (Roberts 2007), it carries a risk that policy makers and donors will perceive a false dichotomy between free and market-based strategies for promoting ITNs. If so, they may overlook an important opportunity to implement complementary strategies for rapidly increasing and maintaining high levels of ITN ownership and use.

Tanzania has been a front-line country for testing the efficacy (Magesa et al. 1991) and effectiveness (Schellenberg et al. 2001a) of ITNs , and has developed a nationwide implementation strategy based on in-country experience (Magesa et al. 2005). Notably, it was also the first country in which a large-scale cost-sharing scheme for distributing subsidized ITNs was evaluated and shown to improve child survival under programmatic conditions (Schellenberg et al. 2001a). When Tanzania first decided to take ITNs to scale, mosquito nets were almost exclusively supplied through commercial retailers bundled with insecticide-treatment kits subsidized by the public sector (Magesa et al. 2005). In 2004, the National Malaria Control Programme (NMCP) introduced a voucher subsidy for pregnant women as part of a nation-wide programme to prevent malaria by enhancing coverage of pregnant women and the young children who share their sleeping spaces during and after the pregnancy. In addition to this national programme, NMCP also assisted a small number of districts including Rufiji on the south-central coast to distribute free bundled nets to under-fives through a child health campaign in mid-2005 with support from partner organizations including UNICEF and the Tanzanian Red Cross (Skarbinski et al. 2007).

The Interdisciplinary Monitoring Project for Anti-malarial Combination Therapy (IMPACT) had been implementing and evaluating effects on drug resistance of sulphadoxine-pyrimethamine (SP) combined with artesunate (SP+Art) for routine treatment of malaria in Rufiji district southern Tanzania between 2000 – 2006 (Fuller and Lurry 1977). Annual household surveys, which included net ownership, use and source, were conducted as a routine part of this study. The

coincidence of the unsubsidized market, voucher subsidies and free distribution happening at the same time and place created an opportunity to evaluate the interactions between these major and apparently inconsistent ITN delivery strategies – the primary focus of the ongoing debates. This paper presents results from this assessment and show that these combined strategies complemented rather than competed with each other.

Methods

Study area and population

Rufiji district lies in southern Tanzania about 178 km south of Dar es Salaam, the country's primary commercial centre and biggest city (Figure 1). The Demographic Surveillance System (DSS) site in which this survey was conducted is composed of 31 villages with an area of 1,813 km^2 and population of about 85,000 people (Mwageni E 2002). It is low-lying (<500 m above sea level) and most of its surface area lies within the fertile flood plain of Rufiji river. Rufiji typically experiences a long rainy season between February and May and a shorter, less intense one from October to December. The majority of the population in this area belongs to Ndengereko tribe. Other important ethnic groups include the Matumbi, Nyagatwa, Ngindo, Pogoro and Makonde. Islam is the predominant religion in the community and commonest language spoken in the area is Kiswahili, consistent with the rest of the country. The main economic activity is subsistence farming of crops such as rice, cassava, oranges, mangoes, cashews, papayas and coconuts. Farms are often located some distance from the family home and rely on periodically flooded alluvial soils. Residents often stay in seasonal makeshift dwellings at farms, especially during rice growing season of February to July. A significant number of people are also engaged in artisanal fishing, charcoal burning, logging, carpentry and small scale trading. All study villages are located on the northern side of Rufiji River along Dar-es-salaam – Kilwa highway (Figure 1). Most of these villages are quite isolated in

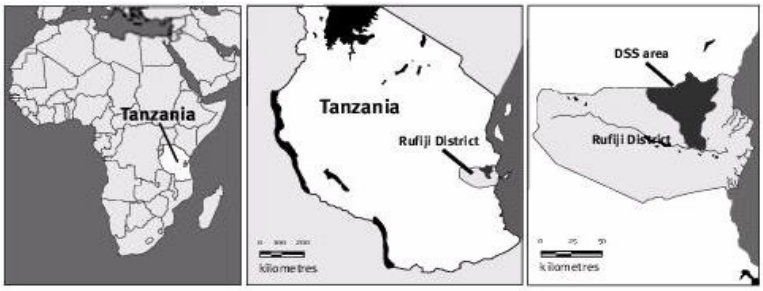
the interior of the district and are connected to the highway by unpaved roads that are often impassable during long rains. Most houses have wood-framed mud walls with thatched or corrugated roofs. Common water supplies are communal boreholes, natural spring or river water, and hand-dug wells.

Malaria is among the biggest health problem in the area reported by health system and perceived by local community (Schellenberg et al. 2004b). It is caused largely by *Plasmodium falciparum*, primarily transmitted by *Anopheles gambiae*, *Anopheles arabiensis* and *Anopheles funestus* vector mosquitoes. Transmission in this area is categorized as intense and perennial (Mwageni E 2002). Prompt recognition and timely treatment with sulphadoxine-pyrimethamine (SP) combined with artesunate and the distribution of ITNs to young children and pregnant women in particular were the two priority malaria control measures in the district at the time.

Nets have been available in most retail shops existing in these villages for more than a decade, typically bundled with insecticide. Residents use these retailers to buy their nets and insecticide as they do for other household goods. The normal retail price for a 6 foot x 6 foot net at the time of the study was 6,000 Tanzanian shillings (equivalent to US$ 4.65) and a sachet of insecticide sold at TShs 500 (equivalent to 40 US cents). A voucher subsidy for nets to be used by pregnant women and their newly born babies was introduced under the Tanzania National Voucher Scheme (TNVS) in the study area at the end of 2004. The value of the voucher was fixed at TShs 3,250 (equivalent to US$ 2.5) and vouchers were issued to pregnant mothers attending clinic by Reproductive and Child Health staff. The voucher recipient was then entitled to purchase an insecticide treated net at reduced cost by presenting the voucher and paying the price difference to the contracted retailers. Distribution of nets free of charge to under-five children was implemented through the national child vaccination campaign in July 2005 lasting for three days. Every child below five years presenting for vaccination against measles, treatment of helminths and vitamin A supplementation received

a free bed net bundled with an insecticide treatment sachet. Additionally, a small number of interviewees received nets at no cost from a variety of sundry sources, including small-scale donations, relatives and friends.

Figure 1. Location of the study area.



Study design and data collection

A survey on which this paper is based was conducted between June and August 2006. A total of 2,000 households were randomly selected from DSS Household Registration Books (HRB), of which 1,752 were completed with 6,331 respondents. In each visited household, every registered and consenting member who was available on the day of the visit was interviewed using a structured questionnaire written in Kiswahili. The questions were pre-tested in 30 households before being finalized and deployed. Data collectors had been used before for similar activities conducted by the project in 2001, 2002, 2004 and

2005, but were nevertheless retrained for three days for this particular survey. Questions written in the questionnaires included date of interview, sex of the respondent, net ownership, whether respondent had slept under net the night preceding the interview, how was the net obtained, whether the net had been treated before, and when was it last treated together with characteristics of houses and households including asset ownership. Dates of birth of household members were already available in the DSS data base. Each completed questionnaire was inspected by the study supervisor who selected a sample of forms from each week's for authentication in the field. Ethical approval for the study was obtained from Centres for Disease Control and Prevention (CDC) of the USA and the Ifakara Health Research and Development Centre, the Medical Research Coordination Committee of the National Institute for Medical Research and Tanzania Commission on Science and Technology of Tanzania.

Data management and analysis

All completed forms were sent to a central data processing unit and double entered using Microsoft (Redmond, WA) FoxPro® software. Data managers developed automated routines to identify discrepancies and executed some simple consistency and range checks which were resolved by referring to original data forms. All data were cleaned and analysed using STATA Version 9.0 (STATA Corporation). This programme was used in computing frequencies, in doing Chi square tests and calculating 95% Confidence Intervals for examining the existence of real differences in net use, sources used to get the nets and treatment of nets for different population groups described in this paper. A wealth index was constructed using principal component analysis for each household based on members owned assets and housing characteristics as described in detail elsewhere (Fuller and Lurry 1977). Concentration curves were plotted and concentration indices calculated by assigning these asset index scores to their respective households' members (Fuller and Lurry 1977; Kakwani et al. 1997; Wagstaff 2005) using Microsoft Excel software.

Results

Net use varied across population age groups (Pearson X^2 (d.f. =12) = 839.9253; P<0.001) with excellent targeting of high coverage to the most vulnerable groups (Table 1). Infants (0-12 months) had the highest proportion of net use in the study area, with >85% using any net the previous night, exceeding the targets of the Millennium Development Goals (MDG), Roll Back Malaria (RBM) and the US President's Malaria Initiative (PMI) for ITN use (2006; MillenniumProject 2005; RollBackMalariaPartnership 2005). It is true that these targets have only been exceeded in terms of any net and that approximately half of these were not recently treated. However, long-lasting insecticide formulations (Kiszewski et al. 2007; Teklehaimanot et al. 2007) for factory pre-treatment or bundling with all nets made in Tanzania were introduced as of March 2007 so these documented levels of coverage with any net should practically translate such achievements into *de facto* ITN coverage. Coverage of young children exceeded the MDG and RBM targets but not the PMI target for protection of under-fives with usage rates exceeding 80% (2006; MillenniumProject 2005; RollBackMalariaPartnership 2005). While coverage of adults and older children was lower than that of the vulnerable groups that were targeted with the bulk of the subsidies, overall coverage of the entire population as a whole was more than sufficient to achieve major communal reduction of malaria transmission (Hawley et al. 2003; Killeen et al. 2007b) if new long lasting treatments could make most nets insecticidal for their lifetime. Although only short-lived insecticide formulations were available at the time, approximately one third of the population used a recently treated net in 2006 so appreciable communal suppression is likely to have been achieved (Killeen and Smith 2007; Killeen et al. 2007b). It is expected that such invaluable community-level benefits to be improved upon by the superior ITN technologies which are now available (Bates et al. 2004; Sachs and Malaney 2002) and further gains in coverage as these delivery systems become better established.

Table 1. Net usage the previous night in Rufiji District during 2006 household survey by age group.

Usage category	Infants	Young children	Older children	Adults	Overall
N	484	732	2024	3098	6338
Proportion use (% (95% CI))					
No nets	12.8 (10.1, 16.1)	18.3 (15.7, 21.3)	45.6 (43.4, 47.7)	40.4 (38.6, 42.1)	37.4 (36.2, 38.6)
Untreated nets[a]	38.2 (34.0, 42.6)	42.0 (38.4, 45.6)	30.0 (28.0, 32.0)	31.0 (29.4, 32.7)	32.5 (31.3, 33.7)
Recently treated nets[b]	49.0 (44.5, 53.4)	39.8 (36.3, 43.4)	24.5 (22.7, 26.4)	28.6 (27.1, 30.3)	30.2 (29.0, 31.3)
Any net[c]	87.2 (83.9, 89.9)	81.8 (78.7, 84.3)	54.5 (52.3, 56.6)	59.6 (57.9, 61.4)	62.7 (61.4, 63.8)

[a] Untreated nets are defined as nets that were not treated at all or were not treated within six months of the interview date

[b] Recently treated nets means nets that were treated within the last six months since the day of interview

[c] Any net means nets including both untreated and recently treated nets.

It is noteworthy that proportional contribution of various net delivery systems varied across age groups (Pearson X^2 (d.f. =20) = 844.8122; P<0.001) and each delivery system appears to have supported its appropriate target group (Table 2). The majority of nets used by infants were obtained through the national voucher scheme, indicating this important vulnerable group is effectively targeted by this system for delivering heavily subsidized nets through commercial distributors. Nets provided at no charge to the user during the child vaccination campaign supported half of the net coverage achieved amongst young children and over a third of coverage amongst older children. The commercial market, with no subsidy other than bundled insecticide, was the biggest source of nets in the population as a whole. Nets obtained at full market price accounted for almost two thirds of use by older children and adults who must be covered if community-level suppression of transmission is to be achieved (Killeen et al. 2007b). Clearly

this mix of delivery mechanisms reaching different segments of the population demonstrates that all three delivery tactics are complementary rather than competitive. Rapid attainment of high net coverage for the vulnerable population was achieved through the combined contributions of the product provision campaign and voucher subsidy while broad coverage for the rest of the community resulted largely from nets purchased on the open market at full price (Magesa et al. 2005). Viewed in this integrated manner, these data provide clear evidence that commercial markets, voucher subsidies and free net distribution are not mutually exclusive choices and can complement each other effectively to make the most of limited subsidy.

Table 2. Sources of nets used the previous night in Rufiji District during 2006 household survey by age group.

Bed net source	Infants	Young children	Older children	Adults	Overall
n	*422*	*598*	*1102*	*1848*	*3970*
Proportion use (% (95% CI))					
Voucher	41.5 (36.9, 46.2)	10.0 (7.9, 12.7)	4.0 (3.0, 5.3)	14.9 (13.3, 16.6)	14.0 (12.9, 15.1)
Free-Vaccine	27.0 (23.0, 31.5)	50.0 (45.8, 53.8)	37.3 (34.5, 40.2)	15.8 (14.2, 17.5)	28.1 (26.7, 29.5)
Free-Other	5.9 (4.0, 8.6)	12.7 (10.3, 15.6)	19.2 (16.9, 21.6)	8.9 (7.7, 10.3)	12.0 (11.0, 13.1)
Commercial market	24.0 (20.1, 28.2)	26.3 (22.9, 29.9)	37.9 (35.1, 40.8)	60.2 (58.0, 62.4)	45.1 (43.5, 46.6)
Unknown source	1.7 (0.8, 3.4)	1.2 (0.6, 2.4)	1.6 (1.0, 2.6)	0.2 (0.1, 0.5)	0.9 (0.6, 1.2)

Free-other means all nets that a user obtained it as a gift from a relative or a friend

Unknown source means all nets that the respondent could not identify its source

Figure 2 shows the number of nets in use during the 2006 survey by source and time of acquisition. The distribution of nets at no cost to the recipients through the vaccination campaign in the third quarter of 2005 caused a clear surge in net acquisition. It is interesting to note that a concomitant surge was observed for nets obtained through sundry other sources, suggesting significant redistribution within families and communities. Over 16% of all nets reported for this period were obtained through this mechanism. It therefore seems likely that under-five children who already had a net and received another through free distribution from the campaign may have passed on the existing or additional net. This suggests that every additional net supplied contributes to both personal and communal protection in the population as a whole, regardless of any leakage or exchange. While the number of nets procured on the unsubsidized market or through the voucher for pregnant women declined shortly after the free distribution in mid-2005, within a year these market-based sources of nets appear to have rebounded to levels equal to or in excess of their levels before the campaign. Provision of nets at no cost through the public sector did not compromise the viability of either the voucher scheme or the commercial market, presumably because this limited full subsidy was targeted toward a previously unsubsidized population group and was not of sufficient volume to compete with established demand for nets in the entire population. Such hybrid approaches represent an excellent mix of strategies for catching up and keeping up coverage when subsidies are not adequate for mass distribution to entire populations (Grabowsky M 2007; Lengeler et al. 2007). This suggests that a number of options are available to NMCPs and that diverse tactics can be astutely combined to achieve the RBM, MDG and PMI targets rapidly and sustainably, even with only partial subsidies.

Figure 2. Reported sources and time of acquisition of nets used in Rufiji District at the time of the 2006 household survey. Note that the voucher programme was launched in late 2004 and the free distribution occurred at the start of the third quarter in 2005. The household survey did not capture complete data for the second quarter of 2006 because this is when the household surveys began.

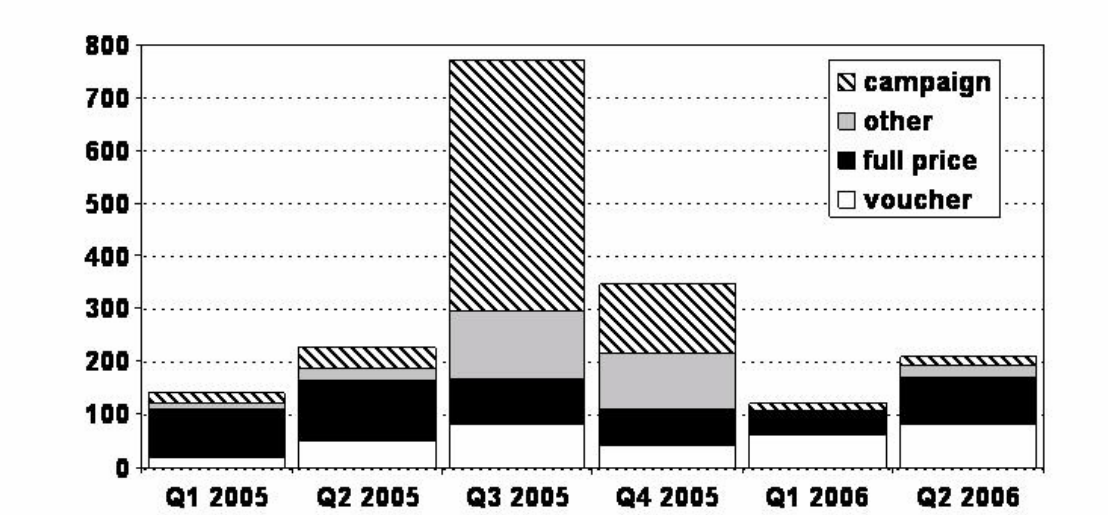


Table 3 demonstrates that contributions of various delivery mechanisms to net use vary by socio-economic status (Pearson X^2 (d.f. =20) = 844.8122; P<0.001). Net coverage was far higher for the least poor with more than four fifths of this better off quintile using a net. Over half obtained their net from commercial market at full price. The concentration index of inequality was the highest for nets obtained from this almost completely unsubsidized distribution mechanism (Table 3) and the concentration curve for these nets lies below the line of perfect equity (Figure 3). This confirms favouritism of the unsubsidized market towards those who are better off and can readily pay for nets. Nevertheless, unsubsidized commercially sold nets were the most important for net coverage achieved by all other socio-economic groups except for the poorest where this source was matched but not exceeded by those obtained for free from the child vaccination

campaign. Indeed, the contribution of the unsubsidized commercially-obtained nets towards net coverage achieved by the poor exceeded that of nets obtained with assistance of the voucher subsidy, demonstrating that even the poorest invested in nets for non-target groups when no subsidy was available (Table 2).

Table 3: Sources of nets used the previous night in Rufiji District during 2006 household survey by socioeconomic status

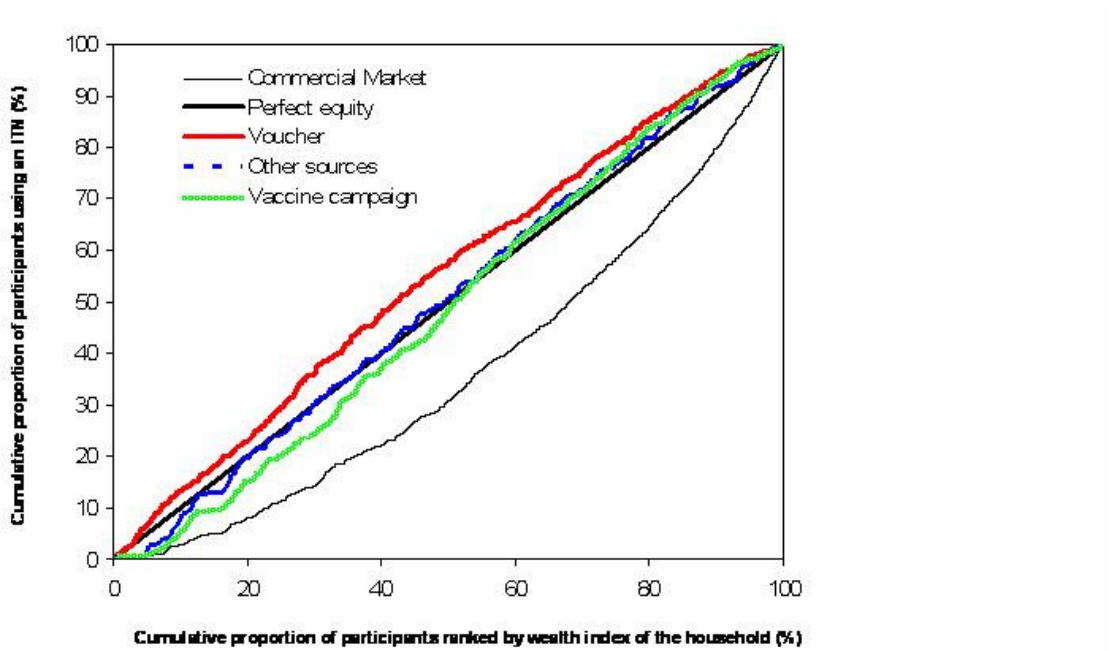
Bed net source	Most poor	Very poor	Poor	Less poor	Least poor	Concentration Index
N (6323 overall)[a]	985	1249	1398	1357	1334	
Proportion use (% (95% CI))						
No net	66.8 (63.8, 69.7)	42.5 (39.8, 45.3)	36.6 (34.1, 39.2)	30.1 (27.8, 32.6)	19.0 (17.0, 21.2)	-0.214 (-0.335, -0.093)
Voucher	5.8 (4.5, 7.4)	8.3 (6.9, 10.0)	9.4 (8.0, 11.0)	10.6 (9.1, 12.4)	8.9 (7.4, 10.5)	0.067 (-0.027, 0.161)
Free-Vaccine	11.2 (9.3, 13.3)	19.6 (17.5, 21.9)	20.7 (18.7, 23.0)	20.2 (18.1, 22.4)	14.4 (12.6, 16.4)	0.015 (-0.129, 0.159)
Free-Other	6.2 (4.8, 7.9)	8.6 (7.1, 10.3)	8.1 (6.8, 9.6)	7.1 (5.9, 8.6)	7.1 (5.8, 8.6)	-0.005 (-0.074, 0.064)
Commercial market	9.8 (8.0, 11.8)	20.4 (18.3, 22.7)	24.1 (21.9, 26.4)	31.6 (29.2, 34.1)	50.3 (47.6, 53.0)	0.254 (0.119, 0.389)
Unknown source	0.3 (0.1, 0.9)	0.6 (0.3, 1.2)	1.1 (0.6, 1.8)	0.3 (0.1, 0.8)	0.4 (0.2, 0.9)	-0.045 (-0.295, 0.205)
Any source[b]	33.3 (30.3, 36.1)	57.5 (54.7, 60.2)	63.4 (60.8, 65.9)	69.9 (67.3, 72.1)	81.1 (78.8, 83.0)	0.127 (0.021, 0.234)

[a] Do not add up to 6338 (see tables 1) because data on households' assets and housing characteristics were collected in forms that were separate from those used for other variables. These two sets of forms were merged using household registration numbers that were supposed to be identical for forms that were related. Some of these related forms were erroneously filled with different numbers that could not be rectified and therefore the study participants had to be dropped for this analysis as they could not be assigned their rightful economic status.
[b] Proportion of nets obtained from all shown net sources

Conventional interpretation of concentration indices, comparing coverage of the poorest with that of the least poor, might suggest that all forms of subsidized delivery (voucher and free product provision) are completely equitable (Table 3).

Similarly, uncritical interpretation of Figure 3 might confirm this observation with all these forms of subsidized delivery approximating the line of perfect equity. Closer examination of Table 3, however, indicates that the least poor may not be a representative group with which to compare the poorest because this group appears to underutilize subsidized delivery mechanisms and relies more heavily upon the open market, presumably for reasons of choice and convenience. Comparing the poorest with the three intermediate wealth quintiles shows that the former do suffer substantial inequities relative to the latter, regardless of what system is used to deliver subsidized nets. While coverage of the three intermediate wealth quintiles is relatively even, coverage of the poorest is consistently and substantially lower for both voucher-subsidized and freely distributed nets. Nevertheless, population-wide net coverage for the most poor approaches the levels at which community level protection may be achieved (Killeen et al. 2007b) when the reported long lasting net treatment technologies(Yates et al. 2005) will make all the nets insecticidal. It also should be noted that the poorest are typically intermingled with neighbours from better socioeconomic strata and, therefore, share the communal protection delivered by the coverage of these groups which is typically twice as high.

Figure 3: Degree of inequality for net distribution strategies for different wealth status. The concentration curve below the line of perfect equity indicates that net use obtained from that source is concentrated among higher socio-economic groups. The concentration curve above the line of equity indicates that net use obtained from that source is concentrated among the poor. When the curve lies along the line of perfect equity, then there is no wealth related inequity for that distribution strategy.



Discussion and conclusions

This study has reported how commercial markets, free product distribution through mass campaign and voucher subsidy can work together to achieve high rapid and sustainable ITN coverage in a poor rural African community exposed to intense and perennial malaria transmission. Some recent publications have advocated that ITN coverage targets can only be achieved through mass distribution at no cost to the end user (Magesa 1991; Magesa et al. 2005; Schellenberg et al. 2001b). While these arguments are based largely on opinion, this study provides empirical data showing that direct product distribution through mass campaigns can accelerate attainment of coverage in target groups if

astutely integrated with market based approaches which similarly target subsides to the neediest. Vouchers and free products both clearly succeeded in targeting their respective subsidies to different biologically vulnerable population groups they were intended to support (Table 2) with insecticide treatment rates being highest in the vulnerable groups (Table 1). Not only did both approaches bias coverage of nets and insecticide treatment to the young (Table 2), in combination they enabled a largely unsubsidized private sector to flourish, resulting in high coverage of the non-vulnerable majority of the population. This latter point is crucially important for achieving community-wide suppression of transmission (Hawley et al. 2003; Killeen et al. 2007b; WHO 2007) and represents a step forward relative to recent studies in Kenya and Ghana which focused exclusively on coverage of infants and young children (Grabowsky M 2007; Noor et al. 2007). When data for infants and young children are pooled, use of any net for under-fives observed in this study is higher 1020/1216 (83.9%) than that reported from Kenya (80.3%) (Noor et al. 2007) and in Ghana (72.6%) (Grabowsky M 2007). Use of recently treated nets shown amongst under-fives appears to be lower in this study (43.4%; 528/1216) than that achieved in Kenya 67.3% and Ghana 59.6%. Nevertheless, it is suggested that the issue of net treatment rates will become less challenging as NMCPs increasingly prioritize the exclusive promotion of long-lasting insecticidal nets and treatments (WHO 2007).

Importantly, largely unsubsidized nets were available to everyone able and willing to pay for them through the commercial market which was actively promoted through the voucher scheme (Magesa et al. 2005). Indeed, the majority of all nets used in our study area were obtained at full market price reflecting the contribution of the community itself to the cost of high population-wide coverage under current circumstances in which global public subsidies for malaria control amount to only 20% of the true full cost (Kiszewski et al. 2007). Although use of unsubsidized nets was greater amongst the least poor (Table 3), recently voiced concerns about the potential inequities associated with market-based delivery of subsidies (Noor et al. 2007; Teklehaimanot et al. 2007) appear to apply just as

much to free product delivery, with approximately equivalent inequity resulting from both voucher discounts and fully subsidized distribution of nets through vaccination campaigns.

Our study has shown that overall net use in Rufiji district was far higher than most other parts of Africa. This data provides further definitive evidence that net delivery strategies other than fully subsidized mass distribution to entire populations can achieve net coverage high enough to provide community level benefits. Achieving high ITN coverage for non-pregnant adults and older children is just as important as comprehensive personal protection of vulnerable groups for three reasons. First, they are the majority in the population and more attractive to mosquitoes [36-38] so reasonably high but not necessarily comprehensive net coverage is essential to deliver the mass effect of ITNs (Hawley et al. 2003; Killeen et al. 2007b; Maxwell et al. 2002). Second, they are the only source of labour for economic productivity required to support the population as a whole and dependent children in particular, so the impacts of malaria illness and associated costs trickle down to every one (Sachs and Malaney 2002). Third, many people living with HIV may be biologically vulnerable to severe malaria in a manner similarly to small children and pregnant women (Bates et al. 2004; French et al. 2001). Here it is demonstrated that high net coverage for adults and older children has been achieved in our study area, largely through purchase of unsubsidized nets at market prices. This study supports the view that high and broad ITN coverage including older children and adults is important for effective malaria control (Hawley et al. 2003; Killeen et al. 2007b; Maxwell et al. 2002) but show here that market-based cost-sharing strategies utilizing voucher-targeted subsidies can also help achieve this goal (Teklehaimanot et al. 2007). However, unlike previous reports from other parts of Tanzania (Killeen et al. 2007a), this is evidence that such targets can be achieved very rapidly by augmenting voucher-stimulated “keep-up” mechanisms with complementary “catch up” campaigns directly distributing products at no cost to the end user.

One limitation of this study is that our survey did not distinguish between pregnant and non-pregnant adult females so coverage in this key target group could not be directly assessed. Nevertheless, high net usage by infants, largely supported by the voucher scheme, presents an informative proxy for net use by pregnant women because mothers of newborns tend to share sleeping sites with their offspring in this area. All in all, Tanzania may be a uniquely informative site for a study of this kind. It was the site of initial experimental hut trials and ITN efficacy studies (Magesa et al. 1991) and it is where such innovations as do-it-yourself treatment and social marketing were pioneered (Schellenberg et al. 1999). Moreover, the combination of both a socialist past and more recent reforms to enable a market-based economy may have elevated many of the national and local policy makers above the ideological considerations that have too often characterized discussions about how to deliver ITNs. The open market and subsidized voucher programme were relatively mature at the time the free distribution was undertaken in Rufiji District and this may not be a unique situation. Market-based delivery systems for ITNs are operational in many countries and present a valid option for attaining high coverage without comprehensive subsidies. As donor support for mass distribution of free nets become more widely available, and it is sincerely hoped that this will be viewed as potentially complementary rather than disruptive to market-based distribution and promoted as a means for rapidly expanding coverage, particularly amongst vulnerable groups. Unlike the development and implementation of the voucher programme (Magesa et al. 2005), the decision to undertake a mass distribution in Rufiji District was not achieved by broad national consensus and was more opportunistic in its origins. Instead, the mix of strategies employed in Rufiji District represents the pragmatic efforts of local and national health officials to sensibly deploy scarce resources offered by partners with competing ideologies. In that sense, it is expected that Tanzania and Rufiji District will not remain an historic exception. If, decades after the life-saving value of this intervention has been firmly established (Lengeler 2004), ITN advocates, no matter their stripe,

can agree that broad community coverage is a priority, then there is promise that diverse approaches can be simultaneously applied in an imperfect but constructive and complementary manner. It is time to step away from the ideological debates about how to deliver ITNs and engage constructively with the local and national authorities to confronting this challenge through whatever means are practical.

Authors' contributions

RAKH contributed to the design of the study, supervised the field surveys, analysed and interpreted the data, and wrote the manuscript in consultation with the other authors. GFK contributed to the analysis and interpretation of the data and to the drafting and editing of the manuscript. EK, PDM and AM contributed to the analysis and interpretation of the data and to the editing of the manuscript. RPMG assisted in the design of the study, execution of the field surveys, interpretation of the data and editing of the manuscript. SMKA and SPK oversaw all aspects of the study, including design and execution of the field work, analysis and interpretation of the data and drafting of the manuscript.

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CHAPTER 5: Artemisinine-based combination deployment and high bed net coverage both contribute to decline of malaria transmission in rural communities of Tanzania

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Abstract

Background: Artemisinine-based combinations have been associated with reduced malaria transmission in areas with low to moderate transmission. To investigate whether this effect is also measurable in highly endemic areas, we performed a longitudinal study based on repeated cross-sectional surveys in two communities of Tanzania, one where ACT was deployed (Rufiji) and one where standard treatment with conventional monotherapy was maintained (Kilombero/Ulanga).

Methods: Community-based cross-sectional surveys were performed regularly from 2001-2006 in two highly endemic areas under continuous demographic surveillance system. Households were randomly selected and a finger prick blood sample was taken from every available person for parasitological assessment by blood slide microscopy and from every child less than 5 years for parasitaemia and haemoglobin measurement. A questionnaire was also administered to these households for documenting households' characteristics, asset ownership and individual net use. The combination of sulfadoxine/pyrimethamine (SP)+artesunate(AS) was deployed in 2003 in Rufiji concurrently with the national roll out of insecticide treated nets (ITNs). ITNs had been introduced earlier in Kilombero/Ulanga where SP treatment continued to be used throughout the study period.

Findings: In 2001, parasite prevalence was 26% in the general population of Rufiji versus 18% in Kilombero/Ulanga. Following the deployment of ACT, there was a sharp decline of malaria prevalence from 29% in 2002 to 19% in 2004 in Rufiji. Then the level decreased to 15% in 2006. The respective estimates for Kilombero/Ulanga were 22% in 2002, 25% in 2004, 11% in 2005 and 14% in 2006. The anaemia prevalence (Hb<8g/dl) measured from 2004 to 2006 showed a drop from 23% in 2004 to 16% in 2005 and 2006 in Rufiji. Respective values for Kilombero/Ulanga were 12%, 18% and 10%. Use of any nets increased from 18% in 2001 to 63% in 2006 in Rufiji and from 69% to 86% in Kilombero/Ulanga

Conclusion: The findings show that malaria transmission and prevalence of anaemia were generally decreasing overtime in both study sites, although there were fluctuations that may be the result of moving from stable to unstable malaria transmission. The sharp decline observed in Rufiji one year after deployment for ACT suggests that the introduction of the new

combination may have contributed to the decrease in malaria transmission. However, a well conducted ITN program reached similar effects in Kilombero/Ulanga without introduction of an ACT. While it was not possible to distinguish a direct contribution of one intervention over the other- or from climatic trends- our findings support current efforts to scale up effective case management and vector control interventions in highly endemic communities.

Background

Malaria is still one of the biggest public health concerns in Africa and its control has become an issue of international urgency. As a result of this increasing global interest, health and development resources invested for malaria have been sharply increased. However, community-based information highlighting evidence of progress arising from this investment is still limited.

Between 2003 and 2006, the Interdisciplinary Monitoring Project for Anti-malarial Combination Therapy in Tanzania (IMPACT-Tz)[1] implemented sulfadoxine-pyrimethamine (SP) + artesunate (AS) combination treatment at all health facilities in Rufiji District as the routine treatment for uncomplicated malaria. This separately formulated combination was a precursor to co-formulated products such as artemether + lumefantrine (Arlu) combination whose implementation is currently under way nationwide in Tanzania. At that time, official first line treatment for malaria in other parts of the country was SP mono-therapy. IMPACT's primary objective was to evaluate the potential of SP+AS combination in reducing emergence and spread of malaria parasite resistance and transmission of malaria (Kachur et al. 2004; Njau et al. 2006) . The project conducted annual cross-sectional household surveys over this period to assess several endpoints in Rufiji, as an intervention district, and Kilombero and Ulanga Districts (Kilombero valley), as comparators. The collection of blood samples to screen for parasitaemia and to measure

[1] The Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania (IMPACT-Tz) is a collaborative implementation research platform resting on: Ifakara Health Institute, U.S. Centers for Disease Control and Prevention, London School of Hygiene and Tropical Medicine, and the Ministry of Health and Social Welfare including its National Malaria Control Programme, the Tanzania Essential Health Interventions Project and the Council Health Management Teams of Kilombero, Rufiji, and Ulanga Districts. Financial support for IMPACT-Tz comes primarily from CDC, the U.S. Agency for International Development and Wellcome Trust.

hemoglobin concentration in children less than five years provided an opportunity to look at trends and patterns of malaria indicators by age and socio-economic status over this period between these two study sites.

Approaches & Methods

Study area and population

Data were collected in villages lying along the flood plains of the Rufiji and Kilombero rivers in southern Tanzania whose detailed description is available elsewhere (Kachur et al. 2004; Njau et al. 2006; Schellenberg et al. 1999). In this paper, we have used Rufiji District to refer to the area of study located in the Valley of Rufiji River and Kilombero valley for villages lying in the Valley of Kilombero River which are spread in Kilombero and Ulanga Districts. The last census conducted in 2002 shows that these three districts have a total population of 706,892. The inhabitants belong to several ethnic groups but the biggest are Ndengereko, Matumbi, Nyagatwa, Ngindo, Pogoro, Ndamba and Hehe. More than four fifths of the population is either Muslims or Christians. Major economic activities in the area are small holder farming, fishing and carpentry. The main crops grown are rice, maize, cassava, fruits and plantains. Most local houses have mud walls and thatched roofs. The health services in the area is composed of network of hospitals, health centres and dispensaries operated by the government of Tanzania and religious non-governmental organizations.

Malaria is still a major health problem recorded at the health facilities. Its transmission is intense and stable. All health facilities in all areas of the study currently manage malaria episodes based on the national malaria treatment policy that require the use of Arlu as the first line treatment for uncomplicated malaria. As we stated at the beginning, at the time of our surveys malaria patients attending the health facilities in Rufiji were treated with SP+AS combination while those from Kilombero received SP monotherapy consistent with the nation-wide policy at the time. As a policy, all pregnant women attending ante-natal clinics during their second and third trimesters were required to be administered SP as Intermittent Preventive Treatment (IPT). It was and is still applied in both study sites much as it is the policy for the rest

of the country. Kilombero Valley was the site where a social marketing program of treated nets and net treatment for malaria control was implemented and evaluated in the late 1990s (Schellenberg et al. 1999). This and other ITN delivery strategies that were subsequently implemented as part of the national plans for taking ITN to scale (Khatib et al. 2008; Skarbinski et al. 2007; Smithson 2009) were able to increase net use in Kilombero to more than 80% for under-fives by 2006 (Table 1). Concentrated efforts to roll out ITN to vulnerable groups in Rufiji started in 2005 with the introduction of pregnant women vouchers that enabled pregnant women to buy nets and insecticide sachets at a substantially subsidized price for their protection and their newly born babies (Hanson et al. 2008). That initiative was complemented by free distribution of ITN to under-fives during the measles vaccine campaign introduced the same year. By 2006 net use for under-fives in Rufiji had also been pushed up to more than 80% (Table 1).

We have shown data on rainfall in the study sites in figure 1. It is indicated that Kilombero/Ulanga experienced average higher rainfall for all years than Rufiji. However, it reached its highest point in 2002 and the lowest measurement in 2003. The highest rainfall reading to be recorded in Rufiji was in 2004 and the smallest one was measured in 2003. In the months between June and September, the period that our surveys were conducted, average rainfall was generally very low compared to the rest of the year. The situation between the study sites during this season was quite the same. However, the first two surveys were conducted during times periods that were wetter than the last three.

Study design and procedures

Households were randomly selected from demographic surveillance databases of the two study sites. Repeated cross-sectional household surveys were conducted over 5 years (2001 – 2006). Separate samples from the same population were selected for each of the survey years. All surveys were conducted immediately after the long rainy season in the study areas, between June and September where malaria is reported to be at its peak. A questionnaire was administered to the head of the households that provided information on household asset ownership and their characteristics. A

composite index of socioeconomic status was generated using this questionnaire as outlined below and in (Kachur et al. 2004). Study participants were visited at home and they signed written consent on their own. For children less than 12 years it was obtained from their parents or guardians. A finger prick blood sample was taken from every member of the household available on the day of the visit. Haemoglobin concentration for under-five children was measured on site by trained field workers using HemoCue system (HemoCue, Angelholm, Sweden). A child was classified anaemic if his/her hemoglobin concentration (hb) was <8g/dl as this is the level that has been associated with mortality (Stoltzfus 1997) and is consistent with earlier study in Tanzania (Skarbinski et al. 2007; Smithson 2009) and is recommended as an indicator of effective malaria control (MERG 2003). Blood slides were being sent to reference laboratory where the smears were stained with Giemsa and read using standard procedures by trained microscopists. Only *P. falciparum* asexual stage infections were considered positive for the analysis of parasitaemia prevalence as they were found to consist of more than 98% of malaria parasite infections in the study area. Parasites were shown whether present and their densities were quantified by counting number of asexual forms per number of leucocytes. Five per cent of slides read by each microscopist were read again by senior laboratory technician for ensuring the reliability of results and it was found out that the disagreement was consistently less than 14%.

Ethical approval

We obtained ethical approval for the study from the institutional review boards of Ifakara Health Research and Development Centre (IHRDC), now Ifakara Health Institute (IHI), the US Centres for Disease Control and Prevention (CDC), and from the National Tanzanian Medical Research Co-ordinating Committee.

Data analysis

Data were entered using Microsoft FoxPro software (Redmond, WA). We then transferred them into STATA version 10 software (Stata Corp., college station,

TX) for merging, cleaning and performing analyses. An index of socio-economic status was generated using Principal Component Analysis for household characteristics and asset ownership as described in detail elsewhere (Kachur et al. 2004). Statistical comparisons between outcome of interest and the assumed explanatory variables were made using Chi-square test. All statistical tests presented are based on the STATA.svy commands to control for clustering of findings at the household level.

Results

Table 1 shows the frequency distribution of study participants for all survey years in both study sites by age group, net use pattern and health facility use for febrile illnesses. Age group distribution was similar for all survey years for both Rufiji and Kilombero/Ulanga. Adults constituted the majority of the sample for each year and site. Children aged 1-5 years comprised approximately 20% of the sampled persons.

Table1: Characteristics of study population in both Rufiji and Kilombero/Ulanga study sites

	2001	2002	2004	2005	2006
Rufiji					
Households, n	1036	996	1380	1724	1739
Infants (< 1y), n(%)	46 (1.2%)	91 (2.5%)	124 (2.5%)	148 (2.3%)	237 (3.7%)
Young children (1-5 y), n(%)	285 (7.4%)	532 (14.7%)	808 (16.2%)	1107 (16.9%)	993 (15.5%)
School age children (5-15 y), n(%)	602 (15.6%)	1099 (30.3%)	1581 (31.7%)	2026 (31%)	2044 (31.9%)
Adults (>15 y), n(%)	2938 (75.9%)	1902 (52.5%)	2477 (49.6%)	3252 (49.8%)	3252 (48.8%)
No net use	1563 (82.5%)	2974 (82.3%)	3985 (79.9%)	4035 (61.8%)	2387 (37.3%)
use of untreated net*	278 (14.7%)	545 (15.1%)	506 (10.1%)	1068 (16.4%)	2090 (32.7%)
use of treated net*	53 (2.8%)	96 (2.7%)	499 (10%)	1428 (21.9%)	1923 (30.1%)
use of any net*	331 (17.5%)	641 (17.8%)	1005 (20.1%)	2496 (38.9%)	4013 (62.8%)
use of medicine from health facility for recent fever/malaria**	680 (28.7%)	375 (34.9%)	456 (45.2%)	857 (41%)	691 (30%)
Kilombero/Ulanga					
Households, n	1155	1380	1483	1626	1774
Infants (<1 y), n(%)	51 (0.5%)	118 (2.5%)	185 (3.6%)	261 (4.4%)	203 (3.2%)
Young children (1-5 y), n(%)	240 (2.6%)	742 (15.7%)	778 (15.1%)	944 (16%)	960(15.2%)
School age children (5-15 y), n(%)	555 (5.9%)	1378 (29.2%)	1626 (31.5%)	1838(31.1%)	1989 (31.5%)
Adults (>15 y), n(%)	8564 (91%)	2486 (52.7%)	2574 (49.9%)	2860(48.5%)	3172 (50.2%)
No net use	579 (31.2%)	1420 (30.1%)	1213 (23.5%)	1112 (18.9%)	903 (14.3%)
use of untreated net*	1095 (59%)	2809 (59.5%)	2587 (50.2%)	2751 (46.7%)	3165 (50.1%)
use of treated net*	181 (9.8%)	491 (10.4%)	1357 (26.3%)	2034 (34.5%)	2253 (35.6%)
use of any net*	1276 (68.8%)	3300 (69.9%)	3944 (76.5%)	4785 (81.2%)	5418 (85.7%)
use of medicine from health facility for recent fever/malaria**	553 (26%)	657 (33.3%)	507 (28.2%)	560 (35%)	545 (34.5%)

* During the previous night

** The demonstrated denominator is all people who were interviewed

Table 1 also summarizes the contextual factors that could influence trend for malaria parasitaemia and anaemia in the implementation and comparison sites. Kilombero/Ulanga participants reported higher use of any net than did Rufiji participants during each survey period. Bed net use in Rufiji increased from 18% in 2001 to 63% in 2006 (insecticide-treated use rose from 3% to 30%). Respective estimates for Kilombero/Ulanga were from 69% to 86% (ITNs from10% to 36%). The increase over the entire period was therefore more striking for Rufiji which was able to bridge the difference with Kilombero/Ulanga in the last survey year. The data suggest that about a third of the population slept under insecticide treated nets in 2006 in both Rufiji and Kilombero/Ulanga. Getting medicines for fever or malaria from formal health facilities was low but equal in both sites during the first two years. Not more than a third of the respondents reported obtaining health facility treatments for their recent febrile illnesses. In 2004, after the introduction of SP+AS in Rufiji, health facility use increased significantly. Almost half of the respondents reported utilizing health facilities when getting sick with malaria. The rate remained flat in 2005 and declined to 30% in 2006. In Kilombero/Ulanga the trend dipped in 2004, then moved up in 2005 and leveled out during the last survey period.

Figure 1: Rainfall pattern between Rufiji and Kilombero/Ulanga during the study period.

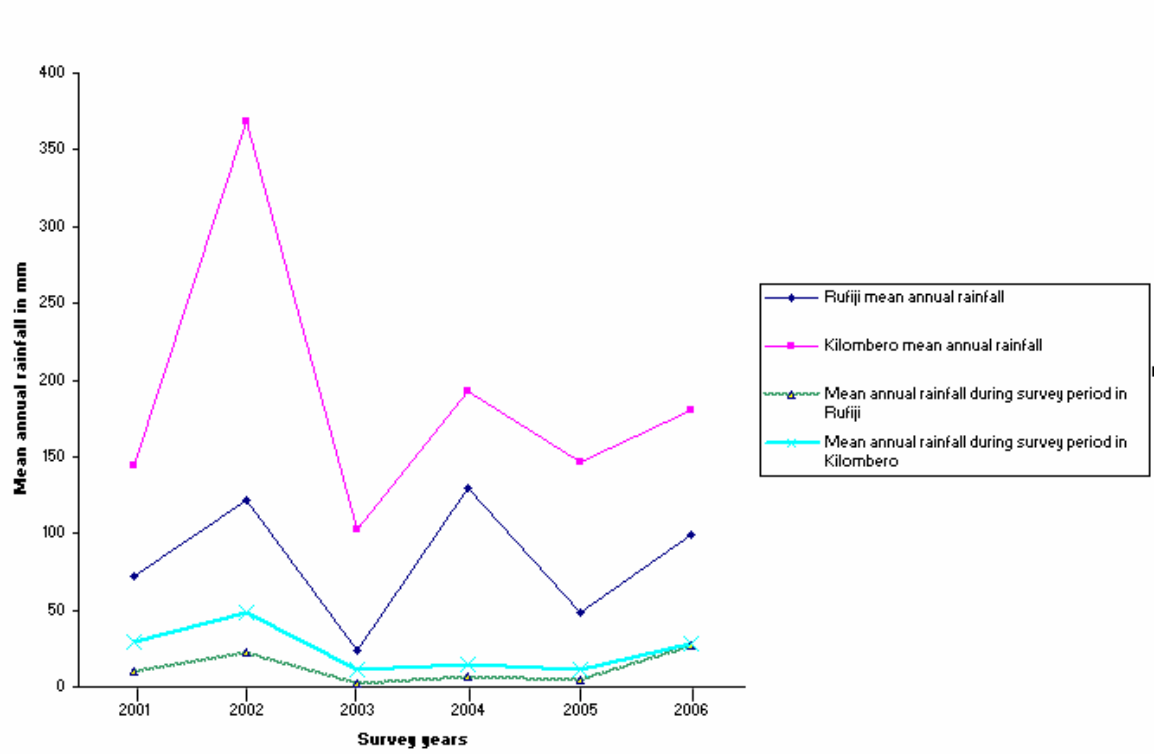


Figure 2 compares annual trends for malaria parasite prevalence between the two study sites for all survey years and highlights the interrelated dynamics. In the first two surveys (2001-2002) Rufiji was characterized by higher parasitaemia than Kilombero/Ulanga. A quarter of the Rufiji population was infected with malaria parasites compared to a fifth of that in Kilombero/Ulanga. However, a sharp decline was observed in Rufiji from 2004 onwards. Compared to 2002, parasite prevalence in Rufiji dropped by about 46% in 2006. In contrast, in Kilombero/Ulanga, malaria prevalence only declined in 2005 where it reached its lowest point, with a 56% decrease when compared to 2004. Prevalence were almost equivalent (15 and 14%) in both districts in 2006.

Figure 2: Trend in malaria parasitaemia in Rufiji and Kilombero/Ulanga (Ifakara) and their respective ITN coverage from 2001 to 2006, as established by repeated cross-sectional household surveys

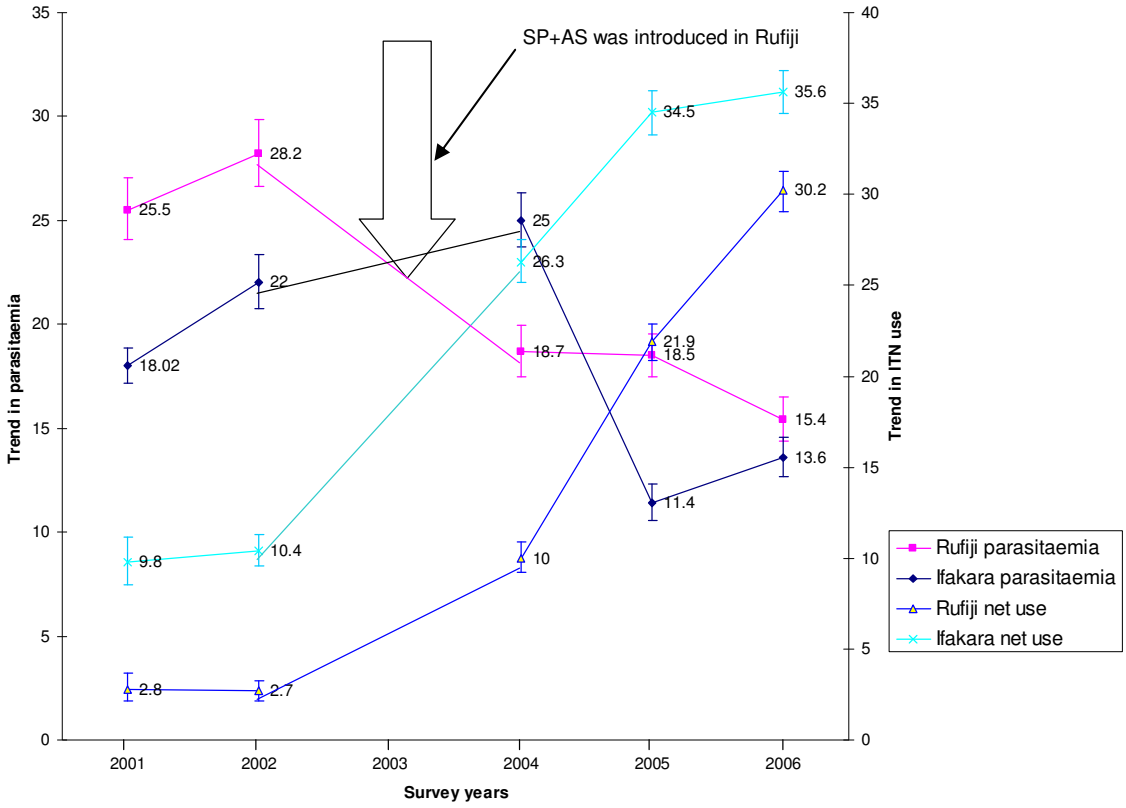


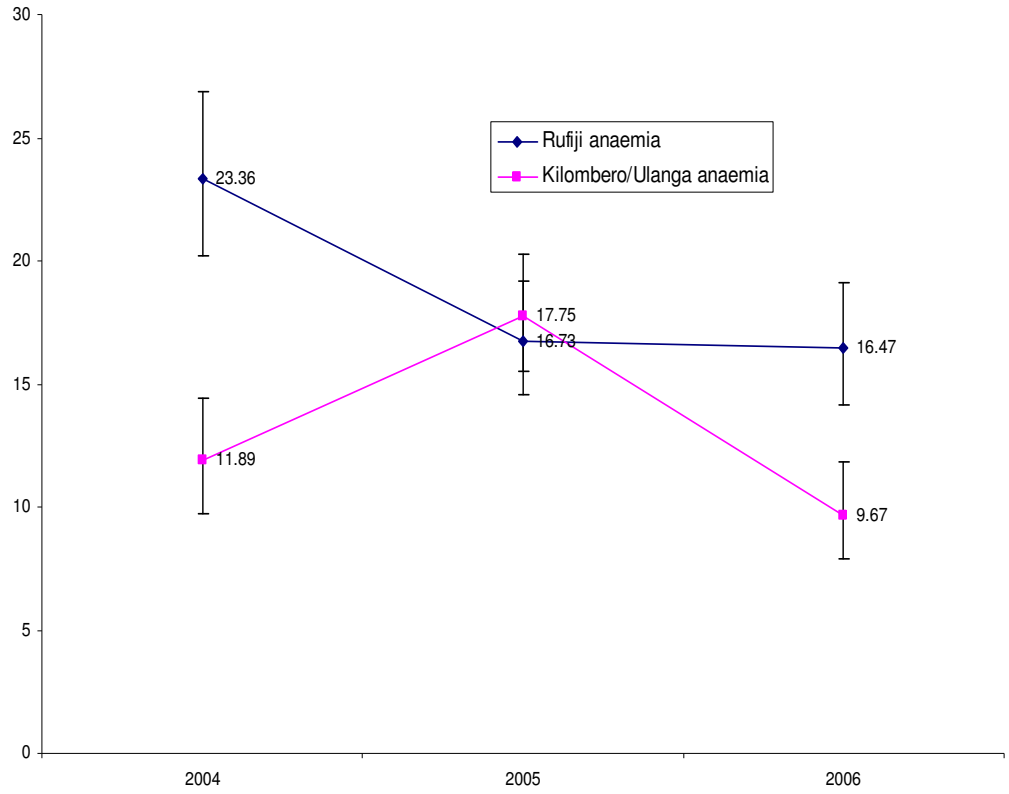
Table 2 presents the distribution of parasitaemia prevalence by age groups and socio-economic status. Parasite prevalence is shown to be significantly higher for young and school aged children than infants and adults in both Rufiji and Kilombero/Ulanga. According to results shown in table 2, infants and adults had equal rates of parasitaemia in Kilombero/Ulanga but in Rufiji the former had more than double of the parasitaemia prevalence of the latter ($p<0.001$). This study confirms that poverty increases vulnerability to malaria as parasite prevalence was much more common among the poorest group compared to the least poor in both study sites. In both sites malaria parasitaemia prevalence among the poorest was almost twice as that among the least poor.

Table 2: Parasite and anaemia prevalence between Rufiji and Kilombero/Ulanga by age and asset index

	Rufiji		Kilombero/Ulanga	
Parasitaemia by age	Proportion	%(95% CI)	Proportion	%(95% CI)
Infants (<I year)	116/512	22.81(19.4-26.66)	77/665	11.53(9.3-14.2)
Young childre (1-5 years)	1076/3007	35.9(34.2-37.6)	835/3124	26.6(25.08-28.2)
School age children (5-15 years)	1736/5754	30.2(29.1-31.4)	1736/5982	28.9(27.74-30.0)
Adults (>15 years)	1117/10000	10.7(10.1-11.3)	1947/16000	11.9(11.37-12.4)
Parasitaemia by asset index				
Most poor	458/2127	21.6(19.9-23.4)	536/2620	20.4(18.85-21.9)
second poor	476/2599	18.3(16.9-19.8)	464/2752	16.8(15.5-18.2)
third poor	501/2856	19(17.6-20.5)	501/2856	17.5(16.1-18.9)
fourth poor	520/2943	17.7(16.4-19.1)	451/3002	15(13.7-16.3)
Least poor	357/2864	12.5(11.3-13.8)	345/3051	11.3(10.2-12.4)
Anemia by age				
Infants	97/364	26.7(22.4-31.4)	80/490	16.4(13.3-19.9)
Young children	353/2091	16.9(15.4-18.6)	269/2115	12.7(11.4-14.2)
Anaemia by asset index				
Most poor	83/343	24.2(20.0-29.0)	86/448	19.2(15.8-23.1)
Second poor	90/477	18.9(15.7-22.7)	71/539	13.2(10.6-16.3)
third poor	117/569	20.6(17.5-24.1)	68/549	12.4(9.9-15.4)
fourth poor	106/578	18.4(15.4-21.7)	60/545	11(8.7-14.0)
Least poor	54/480	11.3(8.8-14.5)	62/516	12.1(9.5-15.2)

Figure 3 similarly shows trends for anaemia for children younger than five years in the study sites for 2004-2006. In 2004, anaemia prevalence in Rufiji was twice that of Kilombero/Ulanga (23% vs 12%). It dropped steeply in 2005 and remained the same in 2006 (16%). In Kilombero/Ulanga the prevalence increased considerably from 2004 to 2005 (12% to 18%) and dropped to its lowest level in 2006 (10%), significantly lower than in Rufiji. When anaemia was compared between infants and young children as shown in table 2 the former were more anaemic than the latter in Rufiji. Little more than one quarter of infants were anaemic compared to a sixth of young children. The difference was statistically significant ($p=0.027$). In the Kilombero Valley on the other hand, anaemia prevalence was not much different between both categories of children. In terms of socio-economic status as measured by household wealth index demonstrated in table 2, anaemia prevalence observed in Rufiji was highest for children from poorest households and lowest for the least poor. Almost a quarter of poorest children were anaemic in Rufiji but less than one sixth of the least poor qualified for that status ($p<0.057$). In Kilombero/Ulanga there was no statistically significant difference in anaemia prevalence between different socio-economic categories but again the poorest had the highest level of anaemia when compared to the other groups.

Figure 3: Trend in anaemia prevalence in Rufiji and Kilombero/Ulanga from 2004 to 2006, as established by repeated cross-sectional population based surveys



(Hb <8g/dl) in children < 5years

Discussion

Our findings demonstrate that malaria parasitaemia prevalence in the community dropped significantly over a period of five years both in Rufiji District and Kilombero Valley in the South Eastern Tanzania. The decline presents evidence of progress towards achieving targets defined by international health initiatives (Anonymous; MillenniumProject 2005; RollBackMalariaPartnership 2005). It brightens hope for those involved in implementing malaria control interventions in Africa. Our findings have included coverage achieved for health facility utilization in malaria treatment and use of bed nets. ACT implementation in Rufiji district from 2003 increased health facility utilization for malaria from 17% in 2001 to 45% in 2004. The trend slightly declined thereafter. Anti-malarial treatment combining SP+AS was theoretically expected to reduce both asexual parasitaemia and also partly gametocytaemia (Bloland et al. 2000).

Hence increasing use of medicines containing artemisinin derivatives for febrile episodes may have played an important role in the sharp decline in malaria parasitaemia prevalence observed in Rufiji District especially between 2002 and 2004 when coverage of ITNs remained low. Indeed, we report elsewhere the high levels of health facility workers' and patients' adherence with recommended usage requirements with SP+AS combination (JI Thwing et al. 2009; Kachur et al. 2004). Also, during the same period parasitaemia prevalence actually increased in the adjacent Districts Kilombero/Ulanga where SP alone continued to be used as first line treatment for uncomplicated malaria. The potential beneficial effect of ACT on malaria transmission in Rufiji cannot be readily separated from the possible impact of increased use of insecticide-impregnated bed nets (from 3 to 10%) during the period 2001-2004. However, this slight increase in bednet use is unlikely to be the major contributor to the 46% decrease of parasitaemia observed during this period.

The lower overall parasitaemia prevalence in Kilombero/Ulanga is likely to be due to the long-term impact of the social marketing program for insecticide treated nets that had been ongoing since 1997 (MillenniumProject 2005). This intervention and later schemes of voucher subsidies for insecticidal nets carried out in the area led to a much higher overall coverage in Kilombero/Ulanga than in Rufiji. The initial increasing trend in parasitaemia prevalence from 2001 to 2004 in Kilombero/Ulanga in spite of increasing use of bed nets illustrates possible fluctuations of malaria transmission to be expected in the transition from stable to unstable malaria. ITN has long been demonstrated to substantially reduce exposure to malaria transmission. Based on this evidence it is widely recommended as life saving intervention for reaching global public health goals and the overall lower malaria parasitaemia in the community reported for Kilombero/Ulanga in this study can partly be a result of this achievement. The increased use of every status of nets in Rufiji in the final years of our surveys may be similarly responsible for the additional fall of parasitaemia in this site shown for this period. Overall trend of decreasing malaria burden in sub-Saharan Africa in recent years is not unique to our study. Similar trends have been reported for overall Tanzania (Smithson 2009) and particularly for the Ifakara town area, where

the infection rate for infants fell from 9.1% in 1996 to 3.5% in 2001, and similarly dropped from 17% in 1996 for older children to 8.5% in 2001(Schellenberg et al. 2004a). An even more dramatic fall of malaria parasitaemia and malaria related mortality was also observed in Zanzibar (Bhattarai et al. 2007). At the African level, WHO reported a 64% decline of malaria cases and 66% decrease of mortality among small children between 2005 and 2007 in Rwanda (Chambers et al. 2008). In Ethiopia malaria related deaths went down by 51% and cases fell by 60% over the same period (Chambers et al. 2008). It is reasonable to assume that this progress could be achieved thanks to wide availability and integrated use of the common malaria control interventions; particularly the promotion of ITNs and the early diagnosis and treatment with ACTs.

The fact that the level of anaemia also declined supports earlier studies associating anaemia in children in malaria endemic areas with malaria parasitaemia (Bhattarai et al. 2007; Bloland et al. 2000; Schellenberg et al. 2004a; Thwing et al. 2009). It suggets the validity of anaemia as a measure of malaria burden in Africa and/or of impact of malaria control interventions. The study has shown that children in Rufiji were generally more anaemic than in Kilombero/Ulanga (table 1), which corresponds to the overall higher parastaemia rates. The difference was statistically significant only in 2004 and 2006 probably as the decline in anaemia prevalence that was achieved in Rufiji in 2005 compared to 2004 was maintained well up to 2006. In contrast, the anaemia prevalence worsened in Kilombero/Ulanga in 2005 compared to 2004 and then improved to 2004 levels when it reached 2006. The reason for a higher prevalence of anaemia in Kilombero/Ulanga in 2005 when compared to 2004, in spite of a sharp decrease of parasitaemia is not fully understood as we could not investigate possible other interrelated causes in the area.

The malaria burden observed in our study matches the well-know pattern of high endemic areas with prevalence highest among young and school aged children reflecting the development of semi-immunity (Perlmann and Troye-Blomberg 2002) and a short protection after birth owing to the transfer of maternal antibodies (Hviid and Staalsoe 2004).

Variation in parasite prevalence between the most poor and the least poor in our study reflects similar variation in the use of malaria control interventions between different socio-economic categories. Many studies seeking to evaluate the effectiveness of delivery strategies for these interventions in sub-Saharan Africa have shown that coverage is influenced by socio-economic status (Bloland 1999a; Hviid and Staalsoe 2004; Njau et al. 2006; Skarbinski et al. 2007). The least poor tend to benefit most from these malaria control tools vis-à-vis the most poor. So, the benefits of malaria control interventions are not equally shared between different socio-economic categories.

This study has shown that infants were more anaemic than older children. Similar observations have been reported elsewhere (Breman et al. 2001; Kitua et al. 1997; Menendez et al. 1997; Schellenberg et al. 2004a) and reflect pattern of anaemia prevalence in areas of intense malaria transmission where higher parasite density prevail in infants compared to older children (Bloland 1999a; Kitua et al. 1997). In addition, infants tend to be more anaemic owing to maternal iron deficiency and anaemia that can lead to impaired fetal development and iron deficient and anaemic babies (Sweet et al 2001; Singla et al 1996; Singla et al 1997; Jaime-Prez et al 2000). Our surveys were conducted during the main farming season in the study areas. As an overwhelming majority of adults including lactating mothers spend the whole day on their fields often far from the villages, it is possible that most infants are also not sufficiently breastfed during this time. Finally, we could not investigate to what extent the dynamics of the HIV epidemic might also have contributed to the anaemia pattern, maybe would have affected it differently in the two sites.

Our study was conducted during the peak of malaria transmission in the study area. Hence, the levels of parasite infections and anaemia are probably the highest during the year in the study area. The fact the last survey year was least parasitaemic and anaemic in both study sites gives hopes for malaria control and elimination efforts in Africa. It may demonstrate evidence that this progress was not based on a single intervention. It shows the effect of an integrated use of curative, early diagnosis and treatment with ACTs, and preventive, the promotion of ITNs, approaches. Besides achieving the

effectiveness of integrated control approaches, these data also indicate that more needs to be done with regards to equity effectiveness. There is still a higher malaria burden among the poorest segments in the study populations. Adding active mass treatment strategies to the existing measures in place may help address the problem through increasing access for all population groups (Menendez et al. 1997).

Finally the study highlights the burden of malaria profile at community level in rural districts in Tanzania (Breman et al. 2001) and underlines the importance of combining the routine data collection with community-based data to design public health strategies that, certainly for the case of malaria, need to be of integrated nature when one aims at achieving the elimination of malaria as public health burden or, eventually, elimination of malaria from certain areas at all.

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CHAPTER 6: Effects of introduction of Antimalarial Combination Therapy for malaria on health facility utilization for febrile illness in rural Tanzania

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Abstract

Background: Appropriate use of antimalarial drugs within 24 hours on the onset of illness has for a long time been an important component of malaria control. Implementation of home management is seen as integral for achieving this goal in Africa where access to health services is limited. Concerns for inappropriate treatment associated with this strategy prompted a call for its reconsideration when the continent moved towards artemisinin based combination therapy. This factor and other important challenges encouraged provision of combined sulfadoxine-pyrimethamine (SP) + artesunate (AS) only in health facilities at the time when the Interdisciplinary Monitoring Project of Anti-malaria Combination Therapy (IMPACT) implemented and evaluated the drugs in rural Tanzania. This approach of implementation created an environment to evaluate changes in health facility utilization for malaria treatment in our study.

Methods: Population-based cross-sectional surveys were performed annually from 2001-2006 in Rufiji and Kilombero/Ulanga demographic surveillance system sites. In Rufiji, official malaria treatment was available in health facilities only and in Kilombero/Ulanga the medicine had broader unrestricted access also through private providers. Households were randomly selected and their members were interviewed about recent febrile episodes, sources of treatment, medicine use and socio-economic characteristics

Findings: Treatment seeking for people reporting recent febrile episodes was 31% and 35% in 2001 and 2002 respectively in Rufiji site before the implementation of combination treatment in health facilities. The use increased to 45% in 2004, one year after the implementation of combination treatment in health facilities only. It declined slightly to 41% in 2005 and dropped further to 30% in 2006. In the Kilombero/Ulanga site, 27% and 33% of febrile respondents obtained their treatment from the health facilities in 2001 and 2002 respectively. The trend declined to 29 % in 2004, picking up to 36% in 2005 and levelled out at 35% in 2006. In relation to age, under-fives

had been consistently more likely than other age categories to get treatment from health facilities in both study sites. In addition, the least poor had higher facility use by at least 50% than the poorest in both study areas.

Conclusion: Implementation of combination treatment in health facilities increased treatment seeking from this source of care in Rufiji District. However, as the years extended, the difference between prior and after implementation periods were not significant. This scenario raises concerns that limiting ACT to health facilities will not achieve the level of treatment access that is enough for better public health outcome.

Introduction

Prompt recognition and appropriate treatment with effective drugs is a key component of any malaria control strategy. The Roll Back Malaria Initiative (RBM) has set a target of achieving 80% treatment of malaria patients with effective medicines within twenty four hours of the onset of illness in sub-Saharan Africa. Home-based management of malaria has been identified as an important strategy for achieving this target (Pagnoni et al. 2005; Were 2004). It involves the use of drugs available at community level without prescription. The strategy to provide malaria treatment early and at the periphery, eg households, is conceptually simple but is associated with a series of problems in a real health system setting such as inapropriate advise and poor compliance with dose regimens for drugs requiring more than one single dose (Bloland et al. 2003a). There is also the risk of over-dispensing of antimalarials, as often all fevers are treated without differential diagnosis and the quality of antimalarials on the market is poor or doubtful in many areas (D'Alessandro et al. 2005; Marsh et al. 1999a). These problems not only prevent effective treatment of those suffering but also - alone or in combination – contribute to the development of drug resistance owing to the highly prevalent levels of sub-therapeutic drug levels in the population. This is of particular relevance in the light of reports of lower sensitivity to ACTs in SE-Asia (Hyde 2005; Wongsrichanalai and Meshnick 2008) . Consequently, any national policy must take these factors into account for all health service

providers and must also aim at gaining the involvement of the informal sector (Were 2004).

It is within this context that the Interdisciplinary Monitoring Project for Anti-malarial Combination Therapy, Tanzania (IMPACT-Tz) piloted in Rufiji District in southern Tanzania the co-administration of SP+AS for the treatment of uncomplicated malaria (Bloland et al. 2000). This treatment was made available only in the health facilities to avoid the potential complexities associated with the informal drug outlets. Here we report trend in health facility utilization for malaria treatment after the introduction of ACT in rural Tanzania.

METHODS

Study area and population

This study was conducted as part of the Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in southern Tanzania (IMPACT-Tz)*. The study area took place in two Demographic Surveillance System (DSS) sites. One site is located in Rufiji District, Coast Region, covering 31 villages with 73,839 people and another one is in Kilombero and Ulanga Districts, Morogoro Region comprising 25 villages with 66,503 people. Common ethnic groups in Rufiji are Ndengereko, Matumbi, Pogoro and Makonde. Dominant tribes in Kilombero and Ulanga are Ndamba, Pogoro, Hehe and Bena. Swahili, the national language in Tanzania, is lingua franca in these multi-tribal communities. The main religions in the area are Islam and Christianity. Major economic activities are subsistence farming, artesnal fishing, animal husbandry, carpentry, charcoal making and small-scale informal trading. Main crops grown are rice, maize, cassava, plantains, cashews and fruits. Short rains are normally between October and December and the long rains span between February and May. A detailed description of the study areas is found elsewhere (de Savigny et al. 2004; Schellenberg et al. 1999)

Malaria is the leading public health problem in the area. The infection is commonly caused by *Plasmodium falciparum*. Transmission is intense and

perennial with some seasonal fluctuation. It is most frequent between April and September (Smithson 2009; Tanner et al. 1991). The health care system in these districts is based on a network of hospitals, health centres, dispensaries, pharmacies and drug stores both government, private not for profit and private for profit. Getting medicines for febrile episodes from general retail outlets is also common like other places in the country. A cost sharing scheme is already in place in public health facilities in Kilombero and Ulanga Districts while its implementation has not yet started in Rufiji. In August 2001 malaria treatment policy shifted from Chloroquine to salfudoxine-pyremethamine (SP) which continued to December 2006. However, IMPACT introduced combination treatment with SP and Artesunate (AS) for treatment of uncomplicated malaria in Rufiji District in 2003. The combination was made available only in hospitals, health centres and dispensaries. Since January 2007 the new, national first malaria treatment policy has changed to combination of Artesunate and Lumefantrine (Arlu) (2007)

Study design and data collection

This paper is based on five household surveys that were conducted between May and September in 2001, 2002, 2004, 2005 and 2006. Between 1300 and 2000 households were selected at random from the DSS databases for each survey. Each member who was available and willing on the day of the interview from every selected household was asked questions on whether they were sick with fever or malaria two weeks prior to the interview, whether they sought treatment from any source and what medicines they obtained from every source of medicines they visited. Questionnaires for young children were administered to their caretakers. There were also questions addressing household characteristics and asset ownership that were directed to heads of households.

Interviewers were recruited from people who were familiar with study communities. More individuals had been invited for the training than those who were finally selected for the assignment. The questionnaires were prepared in English and translated to Swahili and back translated. The interviewers were rigorously acquainted with these questionnaires and pre-tested them among themselves and in the field. All questionnaires were

administered in Kiswahili. Each selected household was visited not more than three times in case some of its members had not been available during the first and second visits. The interviewers were given consent forms to read them to the study participants and only when these participants were satisfied and had agreed to take part then the interview could start. The interviewers submitted the completed forms each week to one of the study investigators who undertook a standardized quality control for completeness, consistency and coherence. Problems that interviewers could not clarify were solved through an additional field visit in the following days. In addition, the principal investigator randomly selected a sample of 5 forms from each 30 forms that were returned during the week's rounds and took them back to the field to verify whether the households had actually been visited and interviewed.

Data management and analysis

All completed forms were brought to the central data processing unit. Data were double entered using Microsoft (Redmond, WA) FoxPro® software. Data managers developed automated routines to identify discrepancies and executed some simple consistency and range checks and these were resolved with reference to original data forms. The study investigators moved all data into Stata Version 8 software using Stata Transfer (Stata Corp., College station, TX). Data were cleaned again, all modules linked and finally analysed in the same Stata version. Analyses have been corrected for clustering both between individuals in the same household and within study sites and weighted to adjust for population sampling fractions.

Results

Table 1 shows that there was no statistically significant difference in health facility use for malaria treatment at baseline years, 2001 and 2002, between Rufiji and Kilombero/Ulanga DSS sites. In 2004, one year after the introduction of ACT in all health facilities in Rufiji District and SP monotherapy remained the same in Kilombero/Ulanga; health facility visits for febrile episodes were higher at 45.2% in Rufiji compared to Kilombero/Ulanga where the visits were 28.5%. The difference was statistically significant different (X^2 = 28.94; p<0.005). In 2005, the visits between the two study sites were still

statistically different between the two DSS sites. More people obtained their treatment from health facilities in Rufiji than in Kilombero/Ulanga (X=3.91, p=0.048). There was no difference that was observed between the two sites in 2006.

Table 1: Health facility use for malaria treatment by district and survey years

	Rufiji			Kilombero/Ulanga			
	n	%	95% CI	n	%	95% CI	*p*
2001	341	30.5	25.6:35.4	268	26.9	21.6:32.2	0.33
2002	375	34.9	30.1:39.8	657	33.3	29.7:36.9	0.6
2004	456	45.2	40.6:49.7	509	28.5	24.6:32.4	<0.005
2005	859	41	37.7:44.3	573	35.8	31.9:39.7	0.048
2006	691	30	26.5:33.4	545	34.5	30.5:38.5	0.089

In a next step, 2002 was taken as the baseline and subsequent health facility visits for fever and/or malaria were compared in the two study sites between 2004, 2005 and 2006 (table 2). As table 2 reveals, there was an increase of 53% for febrile episodes that were treated with drugs from the health facilities in Rufiji DSS site in 2004 compared to a survey that was conducted one year before the implementation of ACT in the site (95%CI: 1.16; 2.03). The increase slowed to 29% in 2005 (95%CI: 1.01; 1.66). The upward trend reverted to nil in 2006.

Table 2: Change in health facility use before and after implementing ACT in health facilities in Rufiji using 2002 as baseline

	Rufiji			Kilombero/Ulanga		
	OR	95% CI	*p*	OR	95% CI	*p*
2002			comparison			
2004	1.53	1.16:2.03	0.003	0.8	0.62:1.02	0.08
2005	1.29	1.01:166	0.05	1.11	0.88:1.41	0.37
2006	0.8	0.61:10	0.1	1.05	0.83:1.34	0.67

Table 3 suggests that under-five children used health facility for medicines meant for febrile episodes more frequently than school aged children or adults from both study sites. From Rufiji DSS site, under-fives were more likely by 40% than school aged children to get medicines from health facilities (95%CI: 0.48; 0.75). They were more likely by 62% than adults to get medicines from health facilities (95%CI: 0.4:0.57). The pattern was the same for Kilombero/Ulanga. Under-fives were similarly more likely than both school aged children and adults to get treatment from health facilities. The odds were higher against adults by 73% than by school aged children at 68%.

Table 3: Association between health facility use and age groups for malaria treatment in the study sites using under-fives as baseline

	Rufiji			Kilombero/Ulanga		
	OR	95% CI	*p*	OR	95% CI	*p*
under fives			comparison			
4-15 years	0.6	0.48:0.75	<0.005	0.42	0.34:0.53	<0.005
over15	0.48	0.4:0.57	<0.005	0.37	0.30:0.44	<0.005

Table 4 demonstrated that socio-economic status is an important factor in the choice of health facilities for fever treatment in both sites. Febrile study participants from the least poor socio-economic category were 50% more likely than the poorest to get treatment from health facilities from Rufiji (95%CI: 1.11; 2.03). From Kilombero/Ulanga DSS site, this relatively better off group was more likely by 99% than the poorest to use medicines from health facilities (95%CI: 1.43; 2.77). Gender was a risk for health facility utilization only in Rufiji where males were more likely by 55% than females to get medicines from the health facilities. However, this was not observed in the Kilombero/Ulanga area.

Table 4: Association between health facility use and socio-economic status in the study sites using most poor as baseline

	Rufiji			Kilombero/Ulanga		
	OR	95% CI	*p*	OR	95% CI	*p*
most poor			comparison			
more poor	0.7	0.51:0.96	0.025	1.11	0.77:1.6	0.588
poor	1	0.74:1.35	0.998	1.26	0.88:1.79	0.211
Least poor	1.33	0.987:1.79	0.061	1.23	0.88:1.72	0.232
Least poor	1.5	1.11:2.03	0.008	1.99	1.43:2.77	<0.005

Discussion

Health facility use for malaria investigated in this study is based on individuals who reported febrile episodes in the previous fourteen days. This is the standard procedure for identifying fever prevalence at household level (Njau et al. 2006) . Fever is an important component of clinical diagnosis of malaria but is confounded by the large body of non-malaria fevers which is also prevalent. For this study, we did not apply additional methods to distinguish

malaria-related fevers at health facility level from fevers due to other illnesses. Hence, health facility use for malaria observed in this study may have been overstated. Despite this potential limitation, the study is helpful for next steps of the introduction of ACTs.

Our study did not reveal any difference in the frequency of visits to health facilities for treatment of fever and/or malaria between the two DSS sites during survey years before the implementation of SP+AS combination in Rufiji district in 2003. The pattern changed significantly in 2004 and 2005. Rufiji experienced more health facility visits than Kilombero/Ulanga during the period. This difference can be associated with the introduction of the ACTs as it was the only relevant intervention that distinguished the two sites. It is also true that health facility use showed important improvement in Rufiji during the implementation period compared to pre-implementation phase. Again, this development was not observed in Ifakara. These differences in treatment seeking between the two sites suggest that availability of effective anti-malarial medicines in only health facilities can strengthen dependence on formal sources for malaria treatment. This is a desirable outcome as it is true that health facility delivery of therapeutic intervention against malaria is more conducive to optimal use. Some studies have demonstrated that parasite resistance to ACT was not seen in South East Asia because it has been administered under professional supervision in the formal health sector (Bloland et al. 2000). There were concerns that this benefit could not be replicated in Africa because of widespread use of drugs at community level (Ajayi et al. 2008). Many countries in Africa had already adopted SP as the first line malaria treatment. Unlike SP which was a single oral dose, ACT, particularly artemether-lumefantrine, entails six doses over three days. Hence, home management of malaria with insufficient information could be a potential risk for incomplete treatment. ACT is more expensive than SP, so tight household budgets could prevent purchasing the full course in case of getting the medicines from the informal sector. All these are potential risks associated with treatment available from sources other than health facilities which in turn can undermine ACT effectiveness in Africa. And these are some of the arguments raised in favour of adopting ACT as a prescription only medicine.

The highest health facility use for all survey years was observed in Rufiji in 2004, even so we could discovered that only 45% of febrile patients obtained their medicines from the health facilities. Consequently, more than half of the patients still obtained their treatment from informal sources. Hence, the availability of ACT at health facility level did not prevent / reduce the use of other sources of treatment. We have also observed that, health facility use in Rufiji sharply increased at the beginning but decreased as the years went on. These trends must be followed and studied carefully in order to understand the underlying reasons, particularly to what extent ACTs "lost their role" as incentive to seek treatment at health facility level owing to the broad offer of ACTs and/or artemisinin monotherapies in the private and informal sector. The careful study of the factors that govern access and use in different health systems settings are of crucial importance for the broad introduction and promotion of ACTs in other endemic areas (Greenwood 2008).

The experience from the present study suggests that informal sources have and will have a role in implementing ACT in Africa. In addition, more efforts need to be made to define the diagnostic strategy for the different endemic areas in order to assure the appropriate use of the ACTs at the different levels of care (D'Acremont et al. 2009; Whitty et al. 2008). While in an areas of high malaria endemnicity, malaria treatment is based on a clinical diagnosis (Pagnoni et al. 2005) and is encouraged by the adoption of Integrated Management of Childhood Illnesses strategies, the diagnostic strategies for areas of lower endemicity and areas where successful control leads to a decline of malaria need to be adapted to prevent mis- and overuse of precious drugs potentially resulting in early drug resistance (D'Acremont et al. 2009; Reyburn et al. 2004) Finally, the re-thinking of the diagnosis and treatment strategies should also take into account that studies showed that specificity of diagnosis of malaria in children performed at home by their caretakers is comparable with that at the health facilities (D'Acremont et al. 2009; Dunyo et al. 2000; Whitty et al. 2008).

The fact that health facility use for malaria treatment was significantly more common by under-fives than for other age groups is consistent with the situation of a highly endemic area (Bloland et al. 2000). Since young children

are more likely to seek treatment increased health facility use therefore favoured under-fives much more than other ages in the population. Consequently, efforts to develop ACT formulations that are appropriate and acceptable for young children are of crucial importance for any introduction of ACTs. Recently, progress was made by the development of infant and children formulations for artemether-lumefantrine (Abdulla et al. 2008).

Our findings may also have implications for policy discussion intent on addressing the issue of equity for ACT access through health facilities. The study has demonstrated that the least poor were more likely than the poorest to obtain their malaria treatment from the health facilities from both study sites. It should be noted that ACT implemented in health facilities in Rufiji district was provided to patients for free consistent with the operating government policy in the area. Hence, the user fee problems which have long been shown to be important barrier to access to malaria treatment for the poor had been resolved. Hence, there are still additional challenges to health facility utilization in malaria treatment for the poor other than direct financial payments and availability of effective medicines. Some studies have shown that people from wealthier households have higher chances to seek appropriate malaria treatment when getting sick compared to the poorest families because better off individuals appear more informed and/or knowledgeable of danger signs of the disease and their access to a health facility is more likely to be shorter (Schellenberg et al. 2003). Our study did not explore population knowledge of danger signs of the disease in question, but could establish that wealthier families lived in areas with easier physical access to health care facilities. Understanding these factors helps us to become more cost- and equity-effective in introducing ACTs in Africa.

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PART IV: Discussion and Conclusions

CHAPTER 7: Discussion and conclusions

This section synthetically discusses the major findings presented in different chapters of this thesis. It also highlights the methodological issues of the different studies/approaches pursued. Finally it aims at defining the further research needed in the area of artemisinin based combination therapy (ACT) as well as the evidence established and the lessons learnt that could be directly translated into public health action.

Methodological issues

The studies presented in this thesis are based on data collected from a series of repeated annual cross sectional surveys at household and health facility level; conducted by the Interdisciplinary Monitoring Project for Anti-malaria Combination Therapy (IMPACT) in Tanzania between 2001 and 2006. The samples for the surveys were selected from the databases of Household Registration Books (HRB) compiled and updated four months a year by the demographic surveillance systems (DSS) of Rufiji and Kilombero/Ulanga (Mwageni E 2002; Schellenberg 2001). The choice of study sites was linked to the availability of DSS infrastructures and did not have to rely on the civil registration system that still lacks completeness in Tanzania. Thanks to the availability of HRBs, it was not necessary for the project to conduct a full census in the study site. Selected households had DSS numbers that guided our interviewers to their locations. Households' members had been listed according to their respective households, their dates of birth, sex and education together with their members' numbers called permanent identification numbers (permanent ID). The permanent IDs were crucial for merging individual information collected in separate data collection tools. It was easy for our study to use dates of births to determine individual's age, something that could be very difficult to figure out in communities that lack useful birth registration. This basic approach firmly grounded on the DSS ensured high quality and completeness of the data collected. Problems arising such as missing households or for those that were no longer occupied, wrong sex or odd dates of birth could usually be resolved with the DSS teams. This was further facilitated by the fact that the DSS sites started to equip their field interviewers with tablet PCs based on experiences from southern Tanzania

(Shirima et al. 2007). Data collection for this study was conducted using the same tools in all survey years; hence the questions remained the same in all surveys. This feature, and the fact that we sampled our study subjects from the same population, further strengthened the quality and validity of the data. The field interviewers remained largely the same during the entire study period and this also reduced the possibility of between-observer biases. Having the same team in the field doing interviews to largely the same people for so many years in the community that had been overstudied might, of course, expose our study to a high risk of unresponsiveness and "data cooking". However, the implementation of several public health interventions in these communities played a very important role in reducing these concerns (de Savigny et al. 2004; Schellenberg et al. 2004b; Schellenberg 2001). Our research centre's policy of recruiting the interviewers and intervention implementers from these communities has also created a perception that that these studies are important for their livelihood. As part of our responsibility as researchers to the community and as a component of our formal ethical responsibility for our study we also used to ask every study participant found, who was ill, to seek treatment from the facility of their choice with full expenses paid by the project. There was also a concern that interviewers' over familiarity might encourage "cooking of data". We introduced a control for this justified concern of repeat follow-up visits to a random sample of households that had been interviewed. This was a routine practice in our study every week on the basis of the forms returned by the interviewers. Concluding the methodological considerations, we feel that the data collected is of a very high quality, i.e. does not entail major systematic errors/biases that might seriously affect the evidence generated and our conclusions drawn.

Malaria parasitaemia before and after the introduction of ACT

ACT for malaria is highly efficacious and is the current policy for first-line treatment in Africa (Hallett et al. 2004; NMCP 2006; Omari et al. 2004; PMI 2007; White 2004). This development is the only strategy to overcome the ever-growing and intensifying parasite resistance to drugs that had once been efficacious, affordable, and acceptable and had long been used in most malaria endemic settings. ACTs had already had a great impact when

adopted for large-scale use in South-East Asia where treatment failure against falciparum malaria had previously been alarming (Bloland et al. 2000). The issue that dominated policy discussion for sub-Saharan Africa following intolerable parasite resistance to chloroquine and sulfadoxine-pyrimethamine was whether the success from South-East Asia could be replicated in Africa; i.e. the transmission dynamics in Asia and Africa are different – Africa having large areas of intense perennial transmission – and also with marked differences in the public health approaches to malaria and in the health system's characteristics (Bloland et al. 2000).

In highly endemic areas of Africa, the older children and adults who constitute the majority of the population at any time are less likely to fall sick when infected with malaria (White and Pongtavornpinyo 2003). Infants, young children and pregnant mothers form the population groups at highest risk. This age-pattern of malaria is reflected in the health seeking behaviour reported in our study (chapter 6). This observation raises concerns for malaria control initiatives that shift from control to elimination (AfricanUnion 2007; Feachem and Sabot 2008). It means that small children fall sick quickly when they are infected and the severity of symptoms encourage their caretakers to seek treatment for them, mostly from health facilities (chapter 6). Hence it is critical for the health care facilities to sustain continuous availability of ACTs in order to make sure that the lives of these young children are saved. But because these children are similarly vulnerable to common illnesses other than malaria, but with overlapping symptoms, it is important that the treatment is guided by parasitological examination. This is especially important during the period of lower parasitaemia when fevers may not be due to malaria and malaria fevers are non-specific (D'Acremont et al. 2009; Rafael et al. 2006). It is why the current discussions on the introduction of rapid diagnostic tests at peripheral health facility levels in many areas of Africa are a welcome development for improved treatment outcome for these children, and especially when malaria control debates are moving towards elimination (AfricanUnion 2007; D'Acremont et al. 2009; English et al. 2009; Feachem and Sabot 2008; Greenwood 2008; Rafael et al. 2006). However, innovative approaches need to be developed to ensure that the existing effective drugs have an impact on the parasitaemia carried by adults in those endemic

settings. This is despite it being increasingly likely that as malaria loses further ground, many more adults will lose their existing semi-immunity to malaria and thus, their risk of disease will be no different than that of small children.

The strategy and efficiency of early diagnosis followed by treatment has important implications on the rational use of ACTs, and the prevention of the development of resistance, besides the economic considerations (Bloland et al. 2000; Bloland et al. 2003c). In addition, poor access to health care facilities and/or the poor quality of services offered encourages care seeking practices outside the formal health care system (McCombie 1996a). In addition, it has invariably been reported that informal drug outlets in sub-Saharan Africa form an important risk for poor drug use and the consequent emergence and spread of parasite resistance (Bloland et al. 2000). On the basis of these facts IMPACT was designed and implemented in Tanzania. The project was actually one of the first two large scale ACT effectiveness evaluations in Africa (chapter 3). It responded to arguments raised in the discussions that preceded final decisions to recommend ACT as a malaria treatment in Africa (Bloland et al. 2000). The evidence generated and experience obtained from IMPACT can certainly contribute to the effective use of ACTs in many other parts of Africa. The data shows a substantial decline of malaria parasitaemia in the community after the introduction of ACTs as a routine first line treatment in the health facilities (chapter 3). The decline also observed in the comparison site where patients continued to be treated with the failing SP treatment, appears, however, clearly linked to the high and widespread ITN coverage as expected from the experience on ITN effectiveness in the specific comparison area and other places in Africa (Lengeler 2004). Use of insecticide treated nets in Ifakara had consistently been higher, throughout the study years, than Rufiji (chapter 5). Our study highlights that were it not for the use of ACT for malaria treatment parasite prevalence would always have been higher in Rufiji than in Kilombero/Ulanga. This fact is supported by another study conducted in Zanzibar and KwaZulu-Natal, South Africa, where multiple implementations of several malaria control interventions, including treatment of malaria patients with ACTs, achieved substantial achievements in the area of malaria control (Barnes et al. 2005; Bhattarai et al. 2007).

Moreover, benefits arising from parasitaemic patients' use of ACTs have been demonstrated to extend beyond the direct users (Garner and Graves 2005). Artemisinins and thus also ACTs have been shown to be gametocytocidal. Hence, gametocyte free individuals are an impediment to the spread of malaria parasites in the population. Consequently, it is reasonable to assume that the introduction of ACTs has - besides reducing parasitaemia - also had an impact on transmission. However, our findings should not conclude that these developments from our study and their impact on malaria are unique, as significant progress has been reported in other several places in Tanzania and elsewhere in sub-Saharan Africa (Hommel 2008; Smithson 2009). The distribution of parasitaemia among the different age-groups largely represented the pattern of highly endemic areas. Interestingly, the pattern of parasitaemia and its decline was not reflected in the levels of anemia observed which can partly be explained by the multifactorial nature of anaemia in these rural African areas (Menendez et al. 2000).

Treatment seeking practices for malaria episodes before and after the introduction of ACT

ACT was only delivered through health facilities in this study. A comprehensive program ought to, in general, include home management strategies, an area in which much development is still required, particularly for the effective use of ACT (Pagnoni et al. 2005; RBMAMFm 2008). Despite this limitation, our program provided an opportunity to evaluate to what extent the availability of effective drugs in health facilities governs treatment seeking practices; The data shows that getting malaria treatment from health facilities increased significantly after the introduction of ACT (Chapter 6) and should be considered when one discusses a possible restriction of ACT to health facilities only, i.e. without home management practices that include ACT (D'Alessandro et al. 2005). Based on our data we cannot disentangle to what extent the increased use of health facilities was due to the availability and/or perceived effectiveness of the new drugs. In this respect it is noteworthy that another study in Tanzania documented the influence of sufficient drug supply (de Savigny et al. 2004). Although this has played a role in our study, the results from the focused group discussions conducted by another team of our

study revealed that members of the community perceived the ACT to be superior in alleviating their febrile illness problems (unpublished results from IMPAC-Tz). Our project provided the medicines at no cost to the patients, compared to charges of around USD 5 when they obtained them from commercial drug outlets. Assuming that a higher price reflects the superiority of the commodity might also have swinged the public opinion in favour of combination treatment and has also contributed to the increased use of health facilities following the introduction of ACT.

Several studies have associated the majority of inappropriate use of anti-malarial drugs in Africa to informal care providers (Bloland 2003; D'Alessandro et al. 2005). Like the patients, the informal sector is not well informed on the correct use of the drugs. In addition there is an economic motive. The guiding principle of the informal sector is also maximization of the highest margin for every cent invested. The risks could be higher for separately formulated and packaged SP and Artesunate which was the ACT used for our study (RBMAMFm 2008). Naturally, they would also serve customers who would not buy both drugs (RBMAMFm 2008). While these factors played a role in the present study, they are now overcome with the particularly unique use of co-formulated ACT and the fact that most national control programmes are run as integrated programmes (Pagnoni et al. 2005; Sirima et al. 2003) that include the informal sector as an important provider of care (NMCP 2006; PMI 2007).

Besides the distribution of the risk of infection and disease explained by the transmission pattern, the perceived importance and risks of spells of illness that also show age-differentials have also contributed to the observed health seeking behaviours (Bloland et al. 2000). As stated in chapter 6, illness perceptions and the perception of the quality of care provided are the main drivers of health seeking dynamics. Finally, and as also documented in other studies (Barat et al. 2004; de Savigny et al. 2004; Njau et al. 2006; Schellenberg et al. 2003; Uzochukwu et al. 2008), we have observed that higher health facility utilization was most beneficial to higher socio-economic groups. This apparent inequality might partly have been contributed to by the existing standards used to measure socio-economic status in epidemiological

studies in poor rural communities. The Principal Component analysis generates scores for household asset ownership which gives bigger weight to assets that are more common in the population centres. Health facilities are predominantly concentrated in these settlements which give an access advantage to their inhabitants. This emphasizes the importance of community based approaches that will expand ACT access to remote settlements and will therefore help to overcome inequities in access to treatment and general health care. Once one shift from control to elimination particular importance should be paid to marginal areas and populations, as inadequacy in service provision could leave remaining foci/pockets of transmission. Accredited drug dispensing outlets (ADDOs) have shown a good potential for addressing some of these important issues in Tanzania, but this strategy needs additional evaluation and larger-scale validation when it is scaled up in the country (Mbwasi and Mlaki 2008; Samarasekera 2008).

Malaria patients' adherence to ACT provided at the health facilities

In studying care-seeking patterns for fatal malaria in Tanzania, de Savigny et al (de Savigny et al. 2004) found out that treatment seeking practices for malaria has shifted to "modern"/Western health care. The majority of children who died of malaria and whose families they followed up for verbal autopsy had used medicines from modern health care facilities. The previous studies that had predominantly associated treatment seeking for malaria with cultural beliefs and practices that encouraged the choice of traditional treatments in Africa seem largely to have no more relevance in Tanzania (Hausmann-Muela and Ribera 2003; Makemba et al. 1996; McCombie 1996a; Minja et al. 2001; Mwenesi et al. 1995; Tarimo et al. 2000; Winch et al. 1997). Consequently, demand creation for ACTs should not be overwhelming, but we should still be sensitive by such concerns. The new challenge for malaria case management strategies is to identify issues related to health systems factors that encompass both patient adherence and providers' appropriate practices. This challenge is more important for treatments that are more expensive and their dosing regimen is more complex than the previously used single treatments.

Thus, the real challenge is, besides knowing the efficacy of a drug established through randomized control trials, to learn how under specific health and social systems factors, a given efficacy of an intervention will be translated into community effectiveness, say the cure rate of a drug provided through the different layers of the health system (Tanner 1990; Tanner and Vlassoff 1992). Finally it is of primary interest to know to what extent social, ethnic and gender strata have equal access and are equally covered by the intervention and what is captured in the term "equity effectiveness of an intervention" that has recently been introduced (Tanner 2005a; Tanner 2005b). It is therefore important to understand qualitatively and quantitatively as many elements of the complex pathways of health interventions in a given health and social systems context to identify why and where they can lose traction (Tanner 2005a; Tugwell et al. 2006) Provider compliance and patient adherence have been singled out as key determinants for effectiveness in ACT programs. Chapter 3 shows that patients who had been treated with the combination treatment and followed up at home achieved 75% complete adherence. This was an encouraging observation for an assessment that was carried out not more than three months since the treatment had been introduced. This very satisfactory level of patient adherence has certainly been translated into the decreasing levels of overall parasitaemia observed in the community (chapter 5). When infected individuals obtained an efficacious treatment from the appropriate source of care and are adherent to treatment which is also gametocytocidal, their risk to contribute to ongoing transmission is substantially reduced. The decline of parasitaemia in the study area after the introduction of ACTs is a good indicator of the success of our programme in particular and sort of the proof of concept for ACT introduction in general.

Scaling up the intervention, i.e. nationwide deployment remains the next challenge to overcome. The Tanzanian malaria control programme with support of the Global Fund to fight AIDS, TB and Malaria (GFATM), the World Bank and United States President's Malaria Initiative (PMI) is currently on its way towards the sustainable use of ACTs (Na et al. 2003; NMCP 2006; PMI 2007; Smithson 2009; Turell et al. 2002). However, it should be noticed that this progress was achieved following massive investments in developing and deploying information, education and communication tools and training health

workers before and after the drugs had been brought to the forefront of health workers desks.

Factors other than ACT that could influence malaria transmission

Our study had been comparing public health outcome in the Rufiji DSS site where District-wide ACT deployment was introduced and the Kilombero/Ulanga DSS site where health care facilities continued with the then ongoing policy of SP use for first line treatments. As described above, the decrease in the Rufiji area appears mainly due to the introduction of ACT while the reduction of parasitaemia prevalence in Kilombero/Ulanga is clearly related to the very successful introduction of ITNs.

It is against this background that our project investigated ITN use throughout the study period and a particularly good other opportunity came with the Red Cross distributing free insecticide treated nets to under-fives in the middle of our study in Rufiji District. There was a big difference in ITN use between Rufiji and Kilombero/Ulanga at the beginning of the study which was no longer seen by the end of the study (see chapter 5). The experience from Tanzania on ITN promotion and use shows that it is no longer relevant to discuss which should be the single effective strategy (Curtis et al. 2003; Lengeler and desavigny 2007; Teklehaimanot et al. 2007). Best results are obtained when a combined strategy is based on the local realities, i.e. campaigns with long-term promotion and social marketing with free-distribution linked to a local private sector committed to producing the ITNs (Curtis et al. 2003; Lengeler and desavigny 2007; Teklehaimanot et al. 2007). Rufiji's experience documents this, as the implementation of free distribution of ITNs to children under five within Rufiji's DSS site went in parallel with the continued presence of ITNs sold in the retail commercial outlets and - additionally - vouchers that subsidized the price for pregnant women and their infants were able to equitably achieve high ITN coverage that could bridge its substantial gap with Kilombero/Ulanga.

The way forward for malaria control in Tanzania and elsewhere

Our study was started during the time when ACT had not yet been generally promoted as a malaria control policy for Africa and when co-formulated products were only about to be introduced. The debates at the start of IMPACT entailed with the primary aim to prevent early resistance to ACTs: Which combination therapy (non-fixed/co-blistering, [chloroquine+artesunate; SP+artesunate; amodiaquine+artesunate; mefloquine+artesunate) versus fixed co-formulation, fixed [artesunate+lumefantrine)], type of delivery strategies, costs, outlets and compliance etc.

Our experience with the co-blistered SP and artesunate, although we have now moved towards co-formulated ACTs – anyhow inspired - and can still (do so) other countries in Africa on the strategies for wide-scale first-line use of ACT. The dispensing envelopes with age-appropriate dosing instructions written in Swahili and illustrated for illiterate patients were adopted by malaria control programmes in Zaire and Zanzibar when they introduced ACT and the current large-scale use of artesunate-lumefantrine carefully considered during the IMPACT experience (Leonard et al. 2003; Na et al. 2003; NMCP 2006; PMI 2007; Smithson 2009). Particular emphasis was placed on the information and communication strategies to allow smooth transitions in order not to repeat the problems and confusions caused when SP was first introduced as the first-line treatment (Leonard et al. 2003; Na et al. 2003; NMCP 2006; PMI 2007).

The decline of malaria parasitaemia at the community level demonstrated in our study (chapter 5) echoes the general trend observed for the rest of the country (Smithson 2009). Of late there has been encouraging reports of malaria decline in several countries in sub-Saharan Africa (Bhattarai et al. 2007; Nyarango et al. 2006; Okiro et al. 2007; Otten et al. 2009). Many important factors including secular trend may have a role for this decline. But it is important to note that all these countries have experienced expanded and sustained coverage of a package of malaria control interventions, thanks to availability of unprecedented funding for malaria control (Feachem and Sabot 2008; Grabowsky 2008; Hommel 2008). This progress brings hope to debates

dominating malaria elimination in Africa (Feachem and Sabot 2008; Grabowsky 2008; Hommel 2008).

However, while acknowledging these positive developments, it is equally important to reflect on important challenges brought by the observed development related to malaria control in Tanzania. The study demonstrated that the majority of malaria patients who use health care facilities are small children (chapter 6). The majority of older children and adults are getting their treatment from the retail and informal sector. The malaria control program needs to expand the availability of ACTs to this important source of treatment. It is true that drugs need to be dispensed and used appropriately. There are concerns that the private sector can encourage continued use of single drugs in contrast to the official policy of ACT use (RBMAMFm 2008). The introduction of ADDOs in some areas of Tanzania has shown the potential to improve access and effective treatments so long as official regulatory oversight is in place (Mbwasi and Mlaki 2008; Samarasekera 2008). It is also encouraging that the Global Fund is to introduce Affordable Medicines Facility for malaria (AMFm), the strategy that will likely reduce the costs for ACTs in the private sector. The high price of ACTs in the private sector has often been blamed as a main reason why artemisinin monotherapies are still wide-spread in Africa (Laxminarayan and Gelband 2009).

Even the highest net coverage we have observed in our study (chapter 6) is still below the latest declared targets. The African Ministers of Health who met in Johannesburg in 2007 replaced the Abuja target with universal access to every malaria control intervention including ITNs (AfricanUnion 2007). They agreed on a 50% reduction of malaria morbidity and mortality by 2010 (AfricanUnion 2007). It has been demonstrated that if coverage for these interventions reaches a reasonable level (as it has been resolved by the ministers), mortality could be reduced by 60% (Tanner 2005b). Since 2008 the Tanzania National ITN program (NATNETS) coordinated by the ITN cell of the National Malaria Control Program with a technical support from the Swiss Tropical Institute has been conducting the under-fives Long Lasting Insecticidal Nets (LLIN) coverage campaign throughout Tanzania (Mwita 2009). This campaign will be followed by the universal coverage campaign

targeting every population group. It is likely that these programs will expand ITN coverage to more sleeping sites and replace worn-out nets, hence making all untreated nets insecticidal. Similar campaigns had substantial impact on ITN coverage in Zanzibar and in Kenya (Bhattarai et al. 2007; Lengeler and desavigny 2007). A new push is needed to ensure that the nets are used at all times as it has been shown that in some parts of Africa they are only used during the cold season (Gunasekaran et al. 2009; ter Kuile et al. 2003; Toé et al. 2009) . Anopheles mosquitoes can become infected with malaria parasites all year round and thus transmission is perennial (Beier et al. 1999). The risks posed by changing the feeding habits of mosquitoes in response to increasing levels of ITN coverage is real and could be countered by programs to spray all households with IRS or larvicidal interventions at the potential breeding sites of mosquitoes (Killeen et al. 2006). The present project, as well as previous work, has emphasized that only integrated approaches to malaria control and elimination will have substantial effects and long-term success (Utzinger et al. 2002).

Further key research areas

It has been demonstrated in chapter 5 that additional decline of the community based malaria burden was observed in Rufiji after expanded ITN coverage. In Zanzibar, it was reported that the introduction of ACTs after extended use of ITNs accelerated the decline of malaria (Bhattarai et al. 2007). These results from two study areas with similar levels of malaria endemicity can generate a hypothesis that integrated implementation of combined malaria interventions can have synergistic effectiveness. This important finding will have great significance for malaria control if different combinations of malaria control interventions will be compared to find out which one of these combinations is the best one for achieving the most substantial results. For example, a research study could select a study area A with a high coverage of ITNs and ACTs and compare it with study area B using IRS and ACTs and area C using a larviciding program, high ITN coverage and ACT and follow them up over a period of time to document some important outcome measures.

As discussed earlier, the potential efficacy of drugs demonstrated in clinical trials is often lost when introduced in a large scale operation (Whitty et al. 2008). This is an important concern, especially for malaria control in which a substantial amount of money is continuously invested in R&D of new drugs while far too little is invested in understanding the determinants of effectiveness in different health system settings. Poor access to drugs, especially for the poorest people in remote corners of areas with endemic malaria transmission, is reported to be an important factor in this problem (chapter 6) (Whitty et al. 2008). Drugs are often delivered through modern and public health care facilities, which in sub-Saharan Africa are normally concentrated in the demographic centres overwhelmed by people who are relatively well-off (chapter 6). This health care delivery strategy not only bears the risk of creating health inequities but also stifles the promise of the drugs. A comprehensive approach would entail inclusion of all providers in the strategy for delivery of treatments. In Tanzania, one important response has been the introduction of ADDOs which have demonstrated promising results at the beginning (Samarasekera 2008). Yet, because ADDOs can only be sustained if run by individuals with basic business skills and knowledge of rules and bureaucratic procedures, it is difficult to envision how they would be maintained in areas predominantly inhabited by illiterate poor peasants. In this case, it is important to design and implement a research study that will evaluate different strategies of ACT delivery involving all types and levels of providers, particularly the public, private and NGO/charity sectors. A carefully defined set of such operational research will help us to better understand the determinants for access to and sustainability of ACTs, particularly also for the most disadvantaged segments of the population (Hopkins et al. 2007).

Conclusion

The present thesis has presented the dynamics of malaria in rural Tanzania following the introduction of artemisinin based antimalarial combination therapy. The delivery of ACT through modern health facilities contributed to substantial decline in the malaria burden on the community. Multiple ITN distribution strategies were shown not only to be complementary (and not mutually exclusive) in the rural endemic setting of Africa but to have achieved

significant coverage, resulting in an accelerated decline of malaria transmission. The effective treatment available only at health facilities achieved a high level of patient adherence and increased treatment-seeking within the public health facilities. However, if ACTs will continue to be available in public health facilities only, a substantial number of malaria patients will not have optimal access to new and effective approaches for malaria control. A broader approach that includes the design of ACT [deployment?] strategies in all types and levels of health care providers is necessary to sustain the success of malaria control and possibly eventual elimination of malaria in Tanzania (Feachem 2009).

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