PHARMACO-EPIDEMIOLOGY OF ARTEMISININ-BASED COMBINATION THERAPY IN THE CONTEXT OF IMPACT EVALUATION OF ARTEMETHER-LUMEFANTRINE ON MALARIA MORBIDITY AND MORTALITY DURING PROGRAMMATIC IMPLEMENTATION IN RURAL TANZANIA

INAUGURALDISSERTATION

zur
Erlangung der Würde eines Doktors der Philosophie
vorgelegt der
Philosophisch-Naturwissenschaftlichen Fakultät
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von

Abdunoor Mulokozi Kabanywanyi

aus
Muleba, Kagera Tanzania

Basel, Februar 2012

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Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von Prof. Dr. Blaise Genton, Prof. Dr. Marcel Tanner und Prof. Dr. Zul Premji.

Basel, den 16. November 2010

Prof. Dr. Martin Spiess

Dekan

Dedicated to my late mother she strived to make my dreams realized

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LIST OF ABBREVIATIONS

ACPR	Adequate Clinical and Parasitological Response
ACT	Artemisinin-based Combination Therapy
ADDO	Accredited Drug Dispensing Outlets
AE	Adverse Event
AL	Artemether-Lumefantrine
ALIVE	Artemether-Lumefantrine In Vulnerable patients: Exploring health Impact
AMFm	Affordable Medicines Facilities for malaria
AS+AQ	Artesunate plus Amodiaquine
CI	Confidence Intervals
CQ	Chloroquine
DALYs	Disability Adjusted Life Years
DDT	Dichloro-Diphenyl-Trichloroethane
DSS	Demographic Surveillance System
EANMAT	East African Network for Monitoring Anti-malaria Treatment
ETF	Early Treatment Failure
GDP	Gross Domestic Products
HIV	Human Infection Virus
IHI	Ifakara Health institute
IHRDC	Ifakara Health Research and Development Centre
IMCI	Integrated Management of Child Illness
IMPACT	Interdisciplinary Monitoring Project of Anti-malaria Combination Therapy
INDEPTH	international Network for the Demographic Evaluation of Populations and their Health in developing countries
INESS	INDEPTH Effectiveness and Safety Studies of anti-malarial drugs in Africa
IRR	Incidence Relative Rate
IRS	Indoor Residual Spraying
ITN	Insecticide Treated mosquito bed-Net
K/U	Kilombero and Ulanga Districts
KINET	Kilombero Net Social marketing programme
LCF	Late Clinical failure
LLITN	Long Lasting Insecticide Treated Nets

LPF	Late Parasitological Failure
MDG	Millennium development Goals
NATNETS	Tanzania National Insecticides Treated Nets programme
NMCP	National Malaria Control Programme
PCR	Polymerize Chain Reaction
RDT	Rapid Diagnostic Test
PHC	Primary Health Care system
SADC	Southern African Development Community
SAE	Serious Adverse Event
SMS	Short Mobile phone Message
SPD	Sentinel Panel of Districts
TB	Tuberculosis
TFDA	Tanzania Food and drug Authority
U5	Under five years child
UNICEF	United Nations Children's Fund
UPT	Urine Pregnancy Test
USA	United States of America
WBC	White Blood Cells
WHO	World Health Organization

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SUMMARY

In sub-Saharan Africa previous efforts to control malaria have proved less successful mostly due to prolonged use of less efficacious mono-therapy drugs to which *Plasmodium falciparum* has developed drug resistance. In most parts of malaria endemic regions chloroquine (CQ) was found to be poorly effective for several decades but it was still being prescribed until recently. In Tanzania, for instance, P.f*alciparum* was already resistant to CQ in more than 60% of all P*. falciparum* positive patients back in the late 80's but was still used until when it was possible to replace it by sulfadoxine-pyrimethamine (SP) in 2001. SP is anti-folate sulfa based anti-malaria drug that was adopted as an interim first line drug by many malaria endemic countries as there was no affordable immediate alternative to CQ. Elsewhere in sub-Saharan Africa Zambia was the first African country to embrace policy change with efficacious anti-malaria combination therapy using Artemisinin-based Combination Therapy (ACT) back in 2004 after support from global funds.

Until 1990, the past three decades have had a sustained global focus on malaria control strategy with the aim of intensifying developing intervention tools. This was preceded by specific eradication efforts of the 1940s, which were intensified in most parts of Southern Europe and America. It was during this period that the global focus on malaria sustained a great deal of change. In that same period therefore, the main focus was on technical issues as well as research and development for new tools, that could lead to advances in drug and vaccine development alongside vector control strategies. There were medium term gains during this period but at the same time some challenges were recorded. Key among these challenges was the fragmented global efforts, whereby there was total loss of a broad based global focus to a joint strategy on the fight against malaria. This resulted in little global support with no clear roadmap for developing states, mostly in Sub Saharan Africa, to establish adequate health systems and primary health care for comprehensive malaria management. These challenges resulted in to overuse of ant-malaria mono-therapies that were cheaply available in most of these countries and led to development of parasite resistance to drugs with far reaching consequences. Towards the mid of 1990s, the combination of a worsening malaria situation and emerging positive technical developments led to renewed global focus on malaria control. It is for the same reason that in 2000 the global head of states developed a joint position to address the global disease burden most affecting developing countries as

part of the Millennium Development Goals (MDG) of global programme on development to be achieved by 2015. Two goals were developed to improved health for the Under Five (U5e.i, MDG4 and MGD6. MGD4 sets target to reduce child mortality by two third by 2015 while MGD6 aims at combating malaria and other major infectious diseases (HIV and TB) by year 2015 as compared to baseline 1990.

As the results of the launch of these global initiatives, a number of new strategies and tools against malaria have been developed and existing ones sharpened to better address the problem. Not later than beginning of last decade, Artemisinin-based Combination Therapy (ACT) emerged as potential therapeutically efficacious proven tool to combat malaria. In the face of growing anti-malarial drug resistance due to the use of mono-therapies, ACT has placed itself as a novel treatment for malaria treatment. Use of insecticide Treated Mosquito bed-Nets (ITN) has also been advocated. With the support of Global Health Partners, ITN have been made available to the vulnerable persons within endemic communities. Support to control malaria has exceeded $ 1000 million a year but malaria still exerts a threat to the U5 and expectant mothers.

In Tanzania ACT as the first line anti-malaria drug was introduced in late 2006, scaled for country wide use in 2007. The ACT implementations in Tanzania bear some similarities with approaches in other African countries but there are still major differences. Tanzania has a homogenous health system that facilitated the rolled out of the malaria control programme as part of the primary Health Care (PHC) system. This was also supported by the evidence generated from the North-South research collaborations that informed policy makers. Government and non-state collaboration within Tanzania was key in informing the above process. In some cases cross boarder collaboration among economic blocks of East Africa and Southern African Development Community (SADC) have provided insights into the control of malaria in the continent.

Some of the novel implementation tools developed and tested in Tanzania have been applied in the rest of Sub-Saharan malaria endemic states and often supported the global campaign against malaria. In Tanzania, political stability and peace for over four decades has also made it easy for quick policy change and scale up of control interventions using ACT this could have been different in neighboring nations like Uganda, Sudan, Mozambique and Democratic republic of Congo which have experienced civil strife during this period. Tanzania has

emerged as one of the few African countries that provided the ground to test some of the most successful malaria control interventions for the rest of the world to up-scale.

The Kilombero River basin in Ifakara Tanzania is a known cradle for malaria endemicity. Several novel interventions have been tested for efficacy and then evaluated for impact during roll out as programmes. Most findings presented in this thesis have been largely derived from the Ifakara Demographic surveillance system among other study sites in Tanzania. This work has provided major insights into the policy change for ACT and its implementation at the national scale.

The aim of the PhD work presented here was to contribute to a better understanding of the impact of the ACT introduction on malaria morbidity and mortality in rural Tanzania and to monitor its long-term safety when used at country wide.

Availability of baseline efficacy profile, mobilization of stakeholders including participating communities and preparedness among researchers accelerated policy implementation in most part of Tanzania right from the on-set of policy inception. Findings from the Interdisciplinary Monitoring Project of Anti-malaria Combination Therapy (IMPACT) and East African Network for Monitoring Anti-malaria Treatment (EANMAT) programmes as described in this thesis have provided evidence that informed policy. The *invivo* studies have shown that artemether-lumefantrine (AL) was nearly 100% efficacious after controlling for re-infection by Polymerase Chain Reaction (PCR) in children U5 years in the years prior policy change. We have also shown that in real life situation it is possible to build comprehensive researchers-policy makers-pharmaceutical industry partnership to implement strategies for monitoring safety and proper use of anti-malaria drugs as reported in the programme Artemether-Lumefantrine In Vulnerable patients: Exploring health Impact (ALIVE). We were able, for the first time in the ALIVE project to describe a compliance of more than 95% using a complex six-dose regimen for AL in a randomized study conducted at community level. We have report the establishment of a pharmacovigilance system in a rural community that also tested for the first time the use of mobile phone technology with SMS to report anti-malarial serious adverse events (SAE). The ALIVE project provided an assessment of the impact of ACT and other malarial interventions on child mortality as well as on malaria transmission. It demonstrated that for every 10% increases in ITN coverage, there was a 48% reduction in the annual community parasitaemia [IRR=0.52; 95% CI=0.38 to 0.73]. It also showed that, compared to a period

when anti-malaria first line was SP, ACT was responsible for nearly 11% annual decreases in under five mortality when adjusted for other key factors [IRR= 0.89; 95% CI=0.79 to 1.0]. ALIVE also showed the relationship of key contextual factors with malaria interventions and U5 child mortality. Food security was major determinant of under five child mortality; notably the rice yields was responsible for nearly 36% reduction in annual mortality [IRR=0.64; 95% CI=0.54 to 0.75]. As far as malaria transmission is concerned, we observed parallel a 65% reduction of parasite prevalence in asymptomatic community members of study area as compared to baseline in 2006 before ACT was introduced in the study population.

Lastly, these effects are likely to be sustainable since the efficacy of AL, as evaluated with an *invivo* study conducted one year after implementation has remained above 96% in the Kilombero valley in spite of its wide scale use. The findings of this thesis attest the importance of policy change in malaria control supported by evidence gathered from operational researches. The lessons learned from this work will be relevant to similar interventions locally and on a global scale in most malaria affected communities. We have also learnt that safety and compliance issues of medicinal products that are deployed at large scale such as ACT should be monitored and managed by strong partnership involving the Ministry of Health and it allied departments, the pharmaceutical industries when possible, the researchers and most importantly with full participation and support of local leadership and communities. We, recommend that this partnership gain support from other global health partners to ensure safety of drugs through rigorous monitoring of its use and long life span. Capacity building of market and policy implementers is another critical aspect that should be given priority. We also recommend that resources be made available to strengthen the health system (human resource, Health Information System and Infrastructure) in order to gain sustained results in malaria control. This will further create enabling environment and a critical mass of scientists and public health experts to spearhead anti-malaria policy implementations properly and monitor it on timely basis.

As outlined in this work, a successful campaign against malaria can be realized through combining efforts of researchers, policy makers, global health development partners and communities. This partnership has lead to real life time achievements related programmes, such as the 1940s malaria elimination campaign in Sardinia Island of Italy.

ZUSAMMENFASSUNG

In Subsahara-Afrika haben sich die bisherigen Bemühungen zur Bekämpfung von Malaria als wenig erfolgreich erwiesen, da vor allem auf eine Mono-Medikamente-Therapie gesetzt wurde, gegen welche *Plasmodium falciparum* inzwischen Resistenzen entwickelt hat. Obwohl sich Chloroquin (CQ) in den letzten Jahrzehnten in den meisten Malariagebieten als nur teilweise wirksam erwies, wurde es noch bis vor kurzem eingesetzt.
Bereits in den späten 1980er Jahren wurden beispielsweise in Tansania in über 60% der P.*falciparum*-positiven Patienten Resistenzen gegenüber CQ festgestellt. Trotzdem wurde CQ erst im Jahre 2001 durch Sulfadoxin-Pyrimethamin (SP) ersetzt. SP ist ein Malaria-Medikament, das in vielen Malaria-endemischen Ländern als Zwischenlösung eingeführt wurde, da noch keine erschwingliche Alternative zu CQ zur Verfügung stand. Etwa zur selben Zeit erlebte Sambia als erstes afrikanisches Land einen Politikwandel und führte 2004 mithilfe globaler Fördermittel die effizientere Artemisinin-based Combination Therapy (ACT) ein.

Zwischen 1960 und 1990 wurde der Fokus auf eine nachhaltige Malaria-Kontroll-Strategie gelegt, die zum Ziel hatte, die Interventionsstrategien der Entwicklungsländer zu fördern. Vorangegangen sind in den 1940er Jahren spezifische Maßnahmen zur Ausrottung, wobei der Schwerpunkt auf technische Fragen sowie auf die Forschung und Entwicklung von neuen Werkzeugen gelegt wurde, die zu Fortschritten in der Medikamenten- und Impfstoffentwicklung, sowie in der Vektorkontrollstrategie hätten führen sollen. Es gab mittelfristig einige Errungenschaften, gleichzeitig entstanden aber in diesem Zeitraum auch neue Herausforderungen. Eine Hauptherausforderung lag in den globalen Bemühungen, die eine fokussierte, breit angelegte Strategie zur Bekämpfung von Malaria erschwerte. Dies war auch der Grund, weshalb es den Ländern südlich der Sahara nicht gelang, eine angemessene Gesundheitsversorgung aufzubauen. Sie waren deshalb immer noch von veralteten Mono-Therapien abhängig, die zwar in den meisten Ländern zu günstigen Preisen zur Verfügung standen, aber wegen deren chronischen Überbeanspruchung zur Entwicklung von Resistenzen beitrugen. Mitte der 1990er Jahre führte die verschlechterte Situation bezüglich Malaria zusammen mit den sich abzeichnenden positiven technischen Entwicklungen dazu, dass die Kontrolle von Malaria wieder in den globalen Fokus rückte.

Aus dem gleichen Grund versuchten im Jahr 2000 verschiedene Staatschefs eine gemeinsame Position bezüglich der Strategie zur Bekämpfung der wichtigsten Krankheiten zu finden. Zwei Ziele wurden in Form der Millennium Development Goals (MDG) konkret formuliert und sollten bis 2015 erreicht werden. Das MGD 4 bestand darin die Kindersterblichkeit bezogen auf das Jahr 1990 um zwei Drittel zu senken, während MGD 6 darauf abzielte die Bekämpfung von Malaria und anderen schweren Infektionskrankheiten (z.B. HIV und TB) bezüglich der Situation in 1990 deutlich zu verbessern.

Diese globalen Initiativen vermochten einige bereits bestehenden Interventionsstrategien gegen Malaria zu verbessern und halfen zur Entwicklung einer Reihe neuer Instrumente und Strategien bei. Erst zu Beginn des letzten Jahrzehnts kam die „Artemisinin-based Combination Therapy“ (ACT) als eine Alternative zu den Mono-Therapien auf, welche wegen der wachsenden Resistenz immer mehr an Wirksamkeit einbüsste. Des Weiteren wurde auch für den Einsatz von „insecticide treated mosquito bed-nets“ (ITNs) plädiert. Dank der Unterstützung von Global Health Partnern, konnten die ITNs nun für viele in Malaria-endemischen Gebieten lebende Personen zugänglich gemacht werden. Obwohl bisher jährlich über 1000 Millionen US$ für die Bekämpfung von Malaria ausgegeben wurden, stellt Malaria weiterhin eine grosse Bedrohung vor allem für Kinder unter 5 Jahren und für schwangere Frauen dar.

ACT wurde als Haupt-Malaria-Medikament in Tansania gegen Ende 2006 eingeführt und 2007 auf das ganze Land ausgeweitet. Die Realisierung dieses Projekts hatte einige Ähnlichkeiten mit Ansätzen in anderen afrikanischen Ländern, jedoch gibt es nach wie vor grosse Unterschiede. Das homogene Gesundheitssystem in Tansania im Allgemeinen und das „Primary Health Care“ (PHC) System im Speziellen erleichterten die Realisierung dieser Malaria-Programme erheblich. Auch die Erkenntnisse, die im Rahmen der Nord-Süd-Forschungskooperationen gewonnen wurden, die Kollaborationen zwischen NGOs und der Regierung, sowie die Bereitstellung der erforderlichen Nachweise durch die politischen Entscheidungsträger, führten schliesslich zu einer erfolgreichen Umsetzung. Zusätzlich ermöglichte die Zusammenarbeit zwischen den wirtschaftlichen Blöcken Ostafrikas und der „Southern African Development Community“ (SADC) neue Einblicke in die grenzüberschreitende Kontrolle von Malaria.

Einige dieser in Tansania neu entwickelten und praxis-erprobten Instrumente wurden auch in anderen Staaten südlich der Sahara angewandt und dabei oft von globalen anti-Malaria Kampagnen unterstützt.

Die politische Stabilität und der Frieden in Tansania während mehr als vier Jahrzehnten haben ein schnelles Umdenken in der Politik und die landesweite Ausdehnung der ACT-Kontrollstrategie überhaupt erst ermöglicht. Viele benachbarte Länder wie Uganda, Sudan, Mozambique und die Demokratische Republik Kongo erlebten im gleichen Zeitraum viele Unruhen. Tansania hat sich als eines der wenigen afrikanischen Länder nicht gescheut sich dem Rest der Welt für Grossversuche der heute erfolgreichsten Interventionen gegen Malaria zur Verfügung zu stellen.

Der Kilombero River Basin in Ifakara Tansania wird als Wiege von Malaria bezeichnet. Etliche neue Interventionen wurden auf ihre Wirksamkeit getestet und evaluiert. Die in dieser Arbeit präsentierten Ergebnisse wurden hauptsächlich aus verschiedenen Studienzentren in Tansania zusammengetragen, wobei der grösste Teil aus dem „Ifakara Demographic Surveillance System“ stammt. Die vorliegende Arbeit gewährt Einblicke in das von Tansania verfolgte Programm zur landesweiten Umsetzung der ACT.

Das Ziel der Doktorarbeit ist es, einen Beitrag zum besseren Verständnis der Auswirkungen, welche die Einführung der ACT auf die Malaria Morbidität und Mortalität hatte, beizutragen und die langfristige Sicherheit im landesweiten Einsatz zu überwachen.

Die erfolgreiche Einbindung der Akteure, insbesondere der teilnehmenden Communities, sowie die grosse Bereitschaft unter den Forschern beschleunigten die Umsetzung der neuen Richtlinien von Beginn an. Die auf Beweisen basierten Erkenntnisse, die aus dem “Interdisciplinary Monitoring Project of anti-malaria Combination Therapy” (IMPACT) und dem “East African Network for Monitoring anti-malaria Treatment” (EANMAT) gewonnen wurden, werden in die Entwicklung von neuen Richtlinien einfliessen. Die *in vivo* Studien haben gezeigt, dass Artemether-Lumefantrin (AL) nach Kontrolle der Reinfektion durch Polymase Chain Reaction (PCR) bei Kindern unter fünf Jahren nahezu 100% wirksam war. Wir haben ebenfalls bewiesen, dass es durch eine intensive Zusammenarbeit zwischen Forschung, Politik und der pharmazeutischen Industrie möglich ist, auch unter Realbedingungen Strategien für die Überwachung der Sicherheit und dem sachgemäßen Gebrauch von Anti-

Malaria-Medikamenten umzusetzen. Das „Exploring Health Impact“ Programm (ALIVE) war als erstes Programm überhaupt in der Lage, in einem randomisierten Beurteilungsdesign auf Community-Level eine Compliance von mehr als 95% zu einer komplexen 6 Dosen Therapie von Artemether-Lumefantrin (AL) aufzuzeigen. In Kapitel 5 wird berichtet, dass „ALIVE-pharmacovigilance“ afrikaweit die erste community-based Pharmakovigilanz-Studie ist, welche auch die Verwendung von SMS als Überbringer von schweren Nebenwirkungen untersucht. Das Projekt ALIVE gewährt sowohl einen Einblick in die Auswirkungen von ACT und anderen Interventionen auf die Kindersterblichkeit und die Prävalenz. ALIVE hat gezeigt, dass eine Erhöhung der ITN Abdeckung um 10% eine Verringerung von 48% jährlicher Malaria-bedingten Parasitämie auf kommunaler Ebene erzielt [IRR=0.52; 95% CI=0.38 to 0.73]. Es wurde ebenfalls gezeigt, dass im Vergleich zu der Zeit, als in erster Linie noch SP verwendet wurde, ACT für ungefähr 11% der jährlichen Reduktion der Mortalität verantwortlich war, wenn man für andere wichtige Faktoren stratifiziert [IRR = 0,89, 95% CI = 0,79 bis 1,0]. Des Weiteren wurde beobachtet, dass die Erhöhung der Ernährungssicherheit, insbesondere der Reiserträge, für fast 36% der Reduktion der jährlichen Mortalität von Kindern unter 5 Jahren verantwortlich war [IRR = 0,64, 95% CI = 0,54 - 0,75]. Hinsichtlich der Übertragung von Malaria wurde parallel eine Parasiten-Prävalenz Reduktion von 65% bei asymptomatischen Community-Mitgliedern im DSS in Ifakara aufgezeichnet, im Vergleich zum Ausgangswert im Jahr 2006 als ACT eingeführt wurde.

Darüber hinaus wurden diese Auswirkungen als nachhaltig beurteilt, da die Wirksamkeit von AL, wie anhand einer *in vivo* Studie ein Jahr nach Umsetzung gezeigt, im Kilombero-Tal bei über 96% liegt.
Die Ergebnisse dieser Arbeit unterstreichen die Bedeutung des politischen Wandels in der Malariabekämpfung. Dazu gehört die Forschung als systematischer Weg, um das Gesundheitssystem zu stärken und sich in der Malaria Bekämpfung innerhalb eines endemischen Entwicklungslands zu engagieren. Die Erfahrungen aus dieser Arbeit werden relevant sein für Malaria-betroffene Gebiete vor Ort und auf globaler Ebene. Wir haben auch gelernt, dass die Sicherheit und Compliance von Arzneimitteln, die, wie ACT, im großen Maßstab eingesetzt werden überwacht und verwaltet werden muss. Dabei sollten das Gesundheitsministerium und verwandte Fachbereiche sowie die pharmazeutische Industrie und Forschungspartner, als auch die örtliche Führung miteinbezogen werden. Wir empfehlen, dass diese Partnerschaft von globalen Gesundheitsorganisationen unterstützt wird. Die

rigorose Überwachung der ordnungsgemässen Verwendung von Medikamenten würde zu einem besseren Verständnis betreffend der Fragen der Sicherheit von Arzneimitteln führen, sowie deren Lebensdauer verlängern. Ein weiterer kritischer Aspekt, welcher den Vorrang eingeräumt werden sollte, ist der Aufbau von Kapazitäten. Wir empfehlen, dass Ressourcen zur Verfügung gestellt werden um das Gesundheitssystem in Malaria-endemischen Gebieten zu stärken (human resources, Health Information und Infrastruktur), um nachhaltige Ergebnisse in der Malariabekämpfung zu erreichen. Damit werden günstige Rahmenbedingungen geschaffen um eine wirksame, regelmässig überwachte, Anti-Malaria-Politik zu implementieren.

Wie in dieser Arbeit erläutert, kann eine erfolgreiche Kampagne gegen Malaria durch die Bemühungen der Forscher, politischer Entscheidungsträger, globaler Entwicklungs-Partnern und der lokalen Gemeinden realisiert werden. Eine solche Partnerschaft hat bereits Erfolge erzielt, wie das Beispiel in den 1940er Jahren der Malaria Eliminationskampagne in Sardinien, Italien zeigt.

MUHTASARI

Juhudi za kupambana na malaria katika Afrika Kusini mwa jangwa la Sahara zimeonyesha kuwa na mafanikio madogo kutokana na matumizi ya muda mrefu ya madawa yenye ufanisi hafifu yasiyo mseto ambayo wadudu wa malaria wamejenga usugu. Katika sehemu nyingi zinazo athiriwa na malaria, dawa ya chloroquine ilionekana kutofanya kazi vizuri kwa miongo kadhaa, lakini bado iliendelea kutolewa kwa ajili ya matibabu ya malaria mpaka katika siku za karibuni. Kwa mfano katika Tanzania, vijidudu vya malaria vilikuwa tayari vimejijenga usugu kwa dawa ya chloroquine kwa zaidi ya 60% kwa wagonjwa wengi waliokuwa na malaria katika miaka ya mwishoni mwa 1980 hivi lakini iliendelea kupewa wagonjwa mpaka pale ilipowezekana kupata mbadala na kuanza kutumika dawa ya SP (sulfadoxine-pyrimethamine) katika mwaka 2001. SP ni dawa ya kutibu malaria inayotokana na salfa iliyotumika kama dawa ya mstari wa mbele kutibu malaria katika kipindi cha mpito katika nchi nyingi zinazoathiriwa na malaria kwa kuwa hakukuwa na dawa yenye gharama nafuu mbadala wa chloroquine. Kwingineko katika Afrika Kusini mwa Sahara, Zambia ilikuwa nchi ya mwanzo ya Afrika kubadili mkakati kwa kutumia dawa ya malaria ya mseto yenye Artemisini tangu mwaka 2004 kwa msaada kutoka mfuko wa dunia.

Mpaka mwaka 1990, miongo mitatu iliyopita ilikuwa na mikakati yenye kuendelea katika kupambana na malaria ambapo mpango kamambe ulikuwa kutafuta na kendeleza mbinu mpya za kupambana na malaria. Hii ilitanguliwa na mpango wa kuondoa kabisa malaria ya miaka ya 1940 iliyokuwa na nguvu sana sehemu za kusini mwa Ulaya na Marekani. Katika kipindi hicho ndipo mikakati ya ulimwengu ya kupambana na malaria ilipata mabadiliko na chachu kubwa. Kwa hivyo, katika kipindi hicho hicho nguvu kubwa ilielekezwa kwenye mambo ya kiufundi na utafiti na ugunduzi wa zana mpya ambazo zinapelekea maendeleo zaidi katika kupambana na malaria kwa kupata dawa bora na chanjo sambamba na kupata mbinu za kuua na kujikinga na mbu. Mafanikio ya muda yalipatikana na pia kulikuwepo na changamoto zilizorekodiwa. Changamoto kubwa kabisa ilikuwa ni kukosekana juhudi za pamoja za kiulimwengu, ambapo mwelekeo, mkakati na nguvu za pamoja vilikosekana katika kupambana na malaria. Matokeo yake yalikuwa uwepo wa uungwaji mkono hafifu ulimwenguni na kutokuwepo mwelekeo na mipango thabiti hasa kwa ajili ya nchi zinazoendela hasa Afrika kusini mwa Sahara kuweza kuimarisha miundo mbinu na afya ya msingi kwa ajili ya kudhibiti malaria kiujumla wake. Changamoto hizi zilipelekea kuendelea

kwa matumizi makubwa ya dawa zisizo mchanganyiko zinazopatikana kwa kiurahisi katika nchi nyingi za Afrika kusini mwa Sahara iliyopelekea vijidudu vinavyosabisha malaria kujijenga usugu kwa dawa na kusababisha madhara makubwa. Kuelekea miaka ya 1990 hivi, mjumuiko wa hali mbaya ya malaria na kuibuka kwa maendeleo chanya ya kiufundi yalipelekea kuwepo kwa nguvu mpya ya kiulimwengu katika kuelekeza nguvu katika kupambana na malaria. Na kutokana na sababu hizo hizo, mwaka 2000 wakuu wa nchi wa ulimwengu walitengeneza mkakati wa pamoja kutatua matatizo makubwa ya magonjwa ulimwenguni hasa yanayoathiri nchi zinazoendelea unaoitwa mkakati wa Milenia unaotakiwa kufikiwa 2015. Katika malengo yaliyomo, mawili yanaelekeza nguvu kuimarisha afya ya watoto chini ya miaka mitano (Lengo 4 na 6). Lengo namba 4 linapanga kupunguza vifo vya watoto kwa 2/3 mpaka 2015, wakati lengo namba 6 linalenga kupambana na malaria na magonjwa mengine ya kuambukiza (Malaria na Ukimwi) ifikapo 2015 ukilinganisha na kiwango cha kuanzia cha 1990.

Matokeo ya kuanzishwa kwa malengo ya Milennia ya kiulimwengu, imepelekea mikakati mingi mipya ya kupambana na malaria imebuniwa na ile iliyokuwepo kutengenezwa vizuri kuweza kufanya kazi vizuri zaidi kupambana na tatizo la malaria. Sio kipindi kirefu katika mwanzo wa mwongo uliopita ambapo dawa mseto yenye Artemisinin (ACT) imeibuliwa na kuwa tegemeo kubwa na inayofanya kazi vizuri kupambana na malaria. Katika hali ya kukua kwa usugu wa madawa ya malaria kutokana na kutumia dawa zisizo za mseto, ACT imekuwa ugunduzi mpya na mzuri katika kutibu malaria. Matumizi ya vyandarua vyenye viuatilifu (vilivyowekwa dawa) pia vinatiliwa mkazo. Kwa kuungwa mkono na msaada wa Kiulimwengu wa kiafya, vyandarua vyenye dawa vimewezeshwa kupatikana kwa watu walio kwenye hatari zaidi katika jamii zinazoathiriwa zaidi na malaria. Msaada katika kupambana na malaria imefikia zaidi ya $1000 milioni kwa mwaka lakini malaria bado ni tatizo kubwa kwa watoto chini ya miaka mitano na akina mama wajawazito.

Katika Tanzania ACT kama dawa ya mstari wa mbele katika kutibu malaria ilianza mwishoni mwa mwaka 2006, na utekelezaji wake ulienea mwaka 2007. Utekelezaji wa matumizi ya ACT unafanana na ule wan chi nyingine za Afrika ingawa kuna utofauti. Miundo mbinu ya afya ya Tanzania ni ya aina moja katika wilaya zote ambayo inawezesha utekelezaji kuenezwa kama sehemu ya afya ya msingi. Hii ilisaidiwa na ushahidi uliotokana na utafiti wa kiumoja wa nchi za Kaskazini- Kusini (utafiti wa ushirika wa nchi zilizoendelea za kaskazini na zinazoendelea za Kusini) ambapo majibu yake yaliwafikia na kuwasaidia watunga sera. Ushirikiano wa Serikali ya Tanzania pamoja na mashirika yasiyo ya kiserikali yalisaidia sana kufahamisha na

kuwezesha utekelezaji wa sera kama ilivyoelezwa hapo mwanzoni. Wakati mwingine, ushirikiano wa umoja wan chi mbalimbali katika masuala ya kiuchumi kama Jumuiya ya Afrika Mashariki na ile ya nchi za kusini mwa Africa imesaidia kutoa mwanga na mwelekeo katika juhudi za kudhibiti malaria katika bara la Afrika.

Baadhi ya mbinu mpya za utekelezaji zilizobuniwa na kufanyiwa majaribio nchini Tanzania zimefanyiwa pia majaribio pia katika nchi nyingine Afrika kusini mwa Sahara zenye tatizo la malaria na kusaidiwa na harakati za kilimwengu za kupambana na malaria. Katika Tanzania, hali ya utulivu wa kisiasa katika miongo minne imesaidia kurahisisha kubadilisha sera na kueneza utekelezaji wa kutumia ACT suala ambalo lingekuwa na ugumu katika nchi za jirani kama Uganda, Sudani, Msumbiji na Kongo ambazo zimekuwa na matatizo ya vita vya wenyewe kwa wenyewe katika kipindi hicho. Tanzania imetokea kuwa ni sehemu chache muhimu katika nchi za Afrika ambapo majaribio ya mikakati ya kudhibiti malaria imefanyika kisha kunakiliwa sehemu nyingine duniani.

Bonde la Mto Kilombero lililopo Ifakara Tanzania linajulikana kwa kuathiriwa sana na malaria. Mbinu mpya nzuri zimejaribiwa kuangalia ufanyaji kazi katika uangalizi maalumu na baadaye kufanyiwa tathimini zaidi ya kufanya kazi katika hali ya kawaida ya utekelezaji mkubwa. Sehemu kubwa ya matokeo ya kitabu hiki cha kazi ya masomo ya juu ya philosofia yametokana na shughuli za ufuatiliaji wa kuendelea wa maisha ya watu ya kila siku katika bonde la Ifakara ambayo ni moja ya ufuatilia unaoendelea Tanzania. Kazi imeonesha mabadiliko ya sera ya ACT na utekelezaji wake katika ngazi ya kitaifa.

Lengo la kazi hii ya kwa ajili ya shahada yangu ya philosofia inayoelezwa hapa ni kuchangia uelewa wa matokeo ya matumizi ya dawa ya ACT katika kupunguza kuugua na vifo vinavyotokana na malaria katika maeneo ya vijijini katika nchi ya Tanzania na kufuatilia matokeo yake ya kiusalama katika muda mrefu inapotumika katika nchi nzima.

Upatikanaji wa taarifa za awali za ufanyaji kazi wa dawa katika hali ya uangalizi wa kitaalam, kuwaleta pamoja washika dau mbalimbali wakiwemo wanajamii wanaoshiriki, hali ya maandalizi inayofanywa na watafiti imerahisisha utekelezaji sera katika sehemu nyingi za nchi ya Tanzania pale tu mabadiliko ya sera ya matumizi ya dawa ya ACT kwa malaria ilipofanyika. Matokeo ya utafiti wa malaria mkubwa wa Tanzania (The Interdisciplinary Monitoring Project of Anti-malaria Combination Therapy-(IMPACT) na nchi za Africa Mashariki (East African

Network for Monitoring Anti-malaria Treatment –EANMAT programmes) kama ilivyoelezewa katika kitabu hiki cha kazi, imesaidia kutoa takwimu na taarifa kwa wakati kwa ajili ya utungaji sera. Matokeo ya utafiti wa mwanzoni wa dawa kwa matumizi ya binadamu (*invivo* studies) yameonyesha kuwa dawa ya ACT inafanya kazi vizuri sana karibu 100% ukishaondoa tatizo la kurudiwa kupata maambukizi mapya kwa watoto wa chini ya miaka mitano katika kipindi cha miaka kabla ya kubadilisha sera.

Vilevile tumeweza kuonesha kuwa katika maisha ya kawaida inawezekana kujenga kundi la umoja imara unaojumuisha watafiti, watunga sera na watengenezaji dawa kutekeleza mikakati ya kufuatilia usalama na matumizi sahihi ya dawa za kudhibiti malaria kama kwenye utafiti uliojulikana kama ALIVE (Artemether-Lumefantrine In Vulnerable patients) ulioangalia afya za makundi maalumu katika jamii. Kwa mara ya kwanza, tuliweza katika mradi wa ALIVE kuona kwamba kutumia dawa kwa wakati kwa 95% kwa dawa yenye kutumika mara sita katika utafiti uliotumia uchaguzi wa kaya kwa bahati nasibu katika jamii ya vijijini.

Tumetoa taarifa ya kuanzisha mtandao wa kufuatilia matumizi ya dawa katika jamii ya vijijini kwa ujumla (pharmacovigilance system) ambayo pia imefanya majaribio ya mwanzo ya matumizi ya simu za mkononi kwa kutuma ujumbe mfupi kutoa taarifa iwapo kuna maafa katika kutumia aina yoyote ya dawa (SAE). Mradi wa ALIVE umetoa nafasi ya kutathmini matokeo ya matumizi ya ACT na pia matumizi ya aina nyinginezo za mikakati ya malaria katika kupunguza vifo vya watoto wadogo na uambukizaji wa malaria. Imeonywsha kuwa kila matumizi ya vyandarua vilivyowekwa dawa yanapoongezeka kwa 10%, maambukizo ya malaria katika jamii yanapungua kwa 48% kwa mwaka [IRR=0.52; 95% CI=0.38 hadi 0.73]. Pia tumeonyesha kuwa, ukilinganisha na kipindi cha matumizi ya dawa ya SP kama dawa ya mstari wa mbele kutibu malaria, ACT imepunguza malaria kwa karibu 11% kwa mwaka kwa watoto chini ya miaka mitano baada ya kuzuia athari za sababu nyinginezo [IRR= 0.89; 95% CI=0.79 hadi 1.0]. ALIVE pia imeonyesha uhusiano wa mambo mengineyo yanayoathiri vifo vya watoto chini ya miaka mitano. Upatikanaji wa chakula imeonekana una mchango mkubwa katika vifo vya watoto chini ya miaka mitano; hasa mchele ulichangia karibu 36% kupunguza vifo kwa mwaka [IRR=0.64; 95% CI=0.54 hadi 0.75]. Kuhusu uambukizaji wa malaria, tumeona kuwa kuna usambamba wa kupunguza maambukizo kwa 65% ya malaria katika jamii kwa malaria iliyotambuliwa kwa homa tu ukilinganisha na taarifa za awali za mwaka 2006 kabla ya kuanza matumizi ya ACT katika jamii iliyofanyiwa utafiti.

Mwisho, matokeo haya yanawezakuwa endelevu kwani ufanisi wa ALU, kama ulivyofanyiwa tathmini kwa kutumia study ya *invivo* uliofanyika mwaka mmoja uliopita baada ya utekelezaji,umebakia juu ya 96% katika bonde la Kilombero licha ya matumizi ya kiwango kikubwa.

Matokeo ya kazi hii yameonesha umuhimu wa badiliko la sera ya kudhibiti malaria yakitiwa nguvu na ushahidi kutoka tafiti zinazoendeshwa. Mafunzo yaliyotokana na kazi hii yatafaa katika hatua za ndani ya nchi na kwa kiwango cha kimataifa katika jamii nyingi zinazoathirika na malaria.
Tumejifunza pia kwamba usalama na kukubalika kwa bidhaa za dawa ambazo zinatumika kwa kiwango kikubwa kama vile MSETO/ACT hazina budi kufuatiliwa na kudhibitiwa kwa ushirikiano thabiti unaojumuisha Wizara ya Afya na idara zake shirikishi,viwanda vya madawa itakapowezekana, watafiti na muhimu zaidi kwa ushiriki kamili na msaada wa viongozi wa ndani ya nchi na jamii.

Tunapendekeza kwamba, ushirikiano huu upate kuungwa mkono na washirika wengine wa afya kuhakikisha usalama wa dawa kupitia ufuatiliaji mkali wa kisheria wa matumizi yake na muda mrefu wa maisha/matumizi.Ujengaji uwezo wa soko na watekelezaji sera ni kipengele muhimu cha kupewa kipaumbele.Tunapendekeza pia kwamba rasilimali ziwepo tayari kuimarisha mfumo wa afya (rasilimali watu,Mfumo wa Taarifa za Afya na Miundombinu) ili kupata matokeo endelevu katika udhibiti wa malaria.Hii itazalisha zaidi mazingira ya uwezeshaji na umma makini wa wanasayansi na wataalamu wa afya ya umma kuongoza kikamilifu utekelezaji wa sera dhidi ya malaria na kuufuatilia kwa muda maalum.

Kama ilivyoanishwa katika kazi hii, kampeni yenye mafanikio dhidi ya malaria inaweza kupitia kuunganisha juhudi za watafiti,watunga sera,washiriki wa maendeleo/uendelezaji afya wa kimataifa na jamii.Ushirikiano huu umewezesha mafanikio ya maisha halisi yanayohusiana na mipango,kama vile kampeni ya kuondoa malaria katika kisiwa cha Sardinia Italia, katika miaka ya 1940.

PART I: BACKGROUND

CHAPTER 1: INTRODUCTION

1.1.0 Global burden of malaria

Beginning of current decade, African continent inhabits nearly 11% of the global population and yet contributes to nearly 19% of the global mortality. A great chunk of the global mortality due to malaria 87% (963,000/1,124,000) and its consequences is happening in Africa and this is 17% part of the globally overall cause mortality putting Africa to the most vulnerable continent of malaria disease burden (WHO ; Zucker, Lackritz et al. 1996).

Depending on the geopolitical presentation in Sub-Saharan Africa, most of the disease burden (94-72%) is occurring in rural setting where the poorest of the world population resides. It is estimated that nearly 58% of this population are at most risk to this burden due to them being the least population group receiving the worst health care as a result of poor health care infrastructures in their settings (Breman, Alilio et al. 2004). In sub-Saharan Africa, malaria is too a leading cause of outpatient and inpatient admission (Maegga, Cox et al. 2005) and malaria due to Plasmodium *falciparum* is an important cause of fatal illness and disability in most vulnerable population groups. It is estimated that almost 3% of disability adjusted life years (DALYs) are due to malaria mortality globally whereas 10% of similar DALYs stands for Africa (Breman, Alilio et al. 2004).

1.1.1 Global initiatives to combat malaria burden

The 20th century witnessed comprehensive programmes that led to not only reduced malaria vectors but the eliminations of plasmodium parasites in most invaded Southern European states. Sardinia Island in Italy in mid 1940s eradicated malaria encounter through massive campaign ranging from vector control to sustaining vigilance at malaria detection and management for long term eradication campaign in the island (Tognotti 2009). Today, more than half century after Sardinia achievements, most malaria endemic countries are still struggling on how to best come to common terms in order to address malaria eradication programme globally. Lack of common approach to address malaria burden in most endemic states has been due to various genuine bottlenecks. During the past two decades in the aftermath of 1940s eradication in years 1969-1991 the global focuses on malaria was mainly on technical issues as well as research and development for new tools, that could lead to advances in drug and

vaccine development alongside vector control strategies. It is during the same period also that better understandings of the natural variation on experience among different malaria endemicity in a variety of epidemiological settings have been developed. However, because this period was short of a joint global focus on region-wide based plan to fight malaria, there was as a result little global support and clear roadmap provided for the malaria endemic but also newly emerged independent states of Africa. These states at that time were struggling to establish adequate health systems and primary health care (PHC) system. As a result of these hurdles, reliance on use of historical anti-malaria monotherapies that were cheaply available in most of these countries was rampant and resulted in to development of drug resistance. Towards the mid of 1990s, the combination of a worsening malaria situation and emerging promising technical developments led to renewed global focus on malaria control (Tanner and de Savigny 2008). It is for the same reason that, in 2000 the global head of states forged a scheme of goals that can best address the global diseases burden most affecting developing countries to be achieved by 2015 and these goals are known as; eight Millennium Development Goals (MDG) (Nations 2010). Among these goals two that aim to improve health reflect under five (U5) survival and combat malaria illness; MDG4 and MGD6. MGD4 set target to reduce child mortality by two third during 2015 while MGD6 aims at combating malaria and other major infectious diseases (HIV and TB) by year 2015 as compared to baseline 1990. To date as the results of these global initiatives a number of new strategies and tools against malaria have been developed and existing ones sharpened to better address the problem. Not later than beginning of last decade artemisinin based combination therapies (ACT) emerged as potential therapeutically efficacious proven tool among the key other existing in the fight against malarial. Use of insecticide mosquito bed-net (ITN) have also been advocated and where possible funding for their availability for free distribution to vulnerable persons within endemic countries have been developed within current funding mechanism from global health financing partners. Global support to control malaria has exceeded 1000 billion US Dollar to date, but malaria still exerts a threat to the U5 and pregnant women (Snow, Guerra et al. 2008; Perry 2010). Another parallel key tool in the fight against malaria that was successfully implemented in the past with better outcome is indoor residual spraying (IRS) with insecticide. IRS was the best tool ever shown good results in the past century before it was intermittently abandoned following environmental campaign against the use of [dichloro-diphenyl-trichloethane]-DDT as well as the shift in the global focuses to malaria control strategies. IRS has proven to be a major tool for vector control alongside ITN, in place

where it has been jointly implemented with bed-net and chemotherapy has resulted in to tremendous achievements (AFM 2008).

Country like South Africa in the KwaZulu-Natal province were all measures were implemented jointly we do observe a reduction in malaria related outpatients and mortality cases by 99% and 97% respectively (Barnes, Durrheim et al. 2005). In Zambia and parts of Ethiopia following massive deployment of ACT in areas where ITN use and IRS were underway a reduction in overall and malaria specific mortality has gone down to the level close to the MGD bench marks (Barnes, Chanda et al. 2009). Despite the low pace to implement key tools for malaria combating strategies, Tanzania is in the right direction towards addressing MGDs goals. Over the past 5-10 years Tanzania has reduced infant mortality from 100 in 1995-1999 to 68 deaths per 1000 live births in 2004 [Tanzania National Bureau of statistics & Macro International Inc. Calverton,2005] (Masanja, de Savigny et al. 2008). Key to these strategies includes the use of efficacious anti-malarial in the first line policies for therapies and chemoprophylaxis and improving financing the health system. Use of vector control strategies such as insecticide treated mosquito bed nets and indoor residual spraying strategies in combination with ACT has rendered Zanzibar; part of united republic of Tanzania a territory close to malaria elimination (AFM 2008).

1.1.2 Use of artemisinin based combinations ant malarial chemotherapy

The legacy of inadequate global translations of achievements gained in years post 1940s eradication campaigns in Europe, America and Northern Africa has accounted for huge impedance in the fight against malaria today in sub-Saharan Africa and South-Eastern Asia. Major among impedance, were the use of failing anti-malaria therapy as a result of consistent use of non-efficacious but cheaply available first line monotherapy drugs. In place of inadequate monitoring programme to advocate to the change of treatment policies on timely bases has resulted to subjecting available mono-therapies to high drug pressures (Mutabingwa 2005). Beyond control however, it has been unavailability of real time efficacious anti-malarial drug alternatives as well as insufficient knowledge of health care staff to promptly diagnosis and management of malarial illness in some parts of malaria endemic regions (Nosten, McGready et al. 2007). In most part of malaria endemic regions chloroquine was found unfit nearly quite long ago. In Tanzania for instance P.*Falciparum* was already resistant to chloroquine in more than 60% of all P*. Falciparum* positive slides towards the end of the last decade

(Hatz, Abdulla et al. 1998) . Despite the obvious failure of chloroquine to such magnitude there was little effort to change policy to a more efficacious first line until in 2001. The emergence and rapid spread of resistance to anti-malarial drugs over the past recent years has led to the intensification of search for new efficacious anti-malarial alternatives by researchers and pharmaceutical companies (MMV 2009) as well as emergence of concerted global initiatives. In late nineties for instance the World Health Organization (WHO) launched a Roll Back malaria campaign whereas by then malarial vector control strategy was high on agenda in many malaria endemic countries. During the same period the uptake and strategy to make available of most efficacious anti-malarial therapy in many endemic countries was very slow. In the aftermath of ACT availability at scale in the beginning of the current decade, a cluster sampling surveys in most sub-Saharan African countries, Tanzania inclusive was done. It was evident that in more than 53% of under five children with febrile illnesses who sought health care were being treated with Chloroquine despite of it being inadequate to treat P. *falciparum* (Breman, Alilio et al. 2004). Thanks to an article that was published in the Lancet in 2004 by prominent scientists with criticism on lack of policy change at the global level, 2004 became the turning point resulting in many endemic countries changing their policy to ACT (White, Nosten et al. 2004). Thanks to increasing availability of fixed-dose ACT options by 2009, nearly 77 of 81 *P. falciparum* malaria-endemic countries and territories had adopted ACTs for use in their national drug policies (WHO). WHO is monitoring the global supply of and demand for the ACT fixed-dose and to date artemether-lumefantrine (AL) fixed-dose combination as part of the requirements of the Memorandum of Understanding signed with the manufacturer, Novartis Pharma AG, Basel Switzerland, in 2001, to make Coartem® available at cost price for distribution in the public sector of malaria-endemic developing countries AL has reached more than 78 million treatment courses in 2008 (WHO).

1.1.3 Insecticide treated bed-nets

Insecticide treated mosquito bed net is another very important vector control tool that has not only demonstrated effect on individual using it directly but also the community at large in places where high coverage is achieved in a given malaria endemic community (Maxwell, Msuya et al. 2002; Hawley, Phillips-Howard et al. 2003). By the year 2008 nearly 31% of African household was estimated to own at least an insecticide-treated bed net (ITN) or a long lasting insecticidal treated Mosquito net (LLITN). More children aged less than 5 years were also sleeping under ITN on an average of 24% as compared to 17% in the previous 2 years (WHO). In some countries

in African region where high coverage of ITNs has been achieved a fall of malaria cases and deaths by more than 50% has been reported (Nations 2010). Such developments are encouraged and may suggest that overall attainment of MGD to reduce child mortality by two third ahead of the target 2015 in some countries is possible (WHO ; Barnes, Chanda et al. 2009).

It is worth mentioning here that a good coverage of vector control in some part of the continent has resulted from funding commitments for malaria control from Global Fund, the World Bank and other international donor communities. The main challenge in the future will therefore remain to be the sustaining public funding by endemic countries at the time of weaning this global support.

Now that ACT is widely available and in many areas a combination of malaria control tools have been implemented widely and widely supported by global health partners, there is an ample need to assess the impact of these interventions. In general this has to be assessed by individual health authorities with commitments to strengthen their health system that have to be scaled up in the framework of these assessments. Full implementation of ACT is fundamental and routine monitoring and surveillance for the safe use of these drugs as well as emergence of resistance signals is too vital to mirror out the intended impact overtime.

1.1.4 Tanzania country specific initiatives to combat malaria burden

The Tanzania Mainland has an estimated population of 40 million for the year 2008 as projected from the 2002 population Census (nbs 2002). It has an annual population growth rate of 2.9% and total fertility rate of 5.5 children per woman. The national crude death rate and infant mortality rate stands at 12.9 and 100.3 deaths per 1000 persons per year respectively (in 2000). Only 23% of the population resides in urban areas whereas the majority (77%) of population is rural dwellers. On average 35.7% of the population is below the poverty line with Gross Domestic Product (GDP) per capita of US$280 (in 2000). Malaria in Tanzania is a leading cause of outpatients' attendances and a leading cause of deaths in children less than five years old.

In 1993 the Tanzanian government approved the health sector reform act that gave rise to the adoption of the current nationwide health reforms. The main focus of this reform is to address burden of disease existing in a particular local setting with evidence based tools and strategies. This approach is in line with requirement laid forward by World Bank report in 1993 that emphasized on: (a) the suggestion to look

beyond the health sector for the answers to many of the problems of disease (b) the identification of certain challenges for the future: HIV, malaria, child mortality, fertility rates, and ageing populations (c) the recommendation to create a cost-effective national public health package and a national clinical services package (WORLD-BANK 1993). As the results, in 1999 at the time when global malarial control initiatives were at revival, Tanzania ministry of health defined and launched the National Package of Essential Health Interventions. This package addresses communicable diseases among other diseases that burden Tanzania and emphasized on control and management of common diseases such as malaria. It encouraged the use of locally available evidence on interventions and funding mechanisms at district level to facilitate the decentralization of health management structure as key to strengthen health system.

Aimed at supporting evidence based interventions at district level for guiding to policy, Ifakara Health Institute in collaboration with other local and international health partners has consistently maintained the implementation of several key interventions to address the burden of malaria at the district level in Kilombero and Ulanga (K/U) Districts. In late nineties and early 2000 most of the interventions that were implemented in K/U Districts have mainly focused on improving child health. These programmes include; the integrated management of childhood illness (IMCI) that introduced a set of guidelines for management of sick children seen at different level of health care facilities country-wide beginning of 1996 and up scale of WHO and UNICEF expanded IMCI strategy later in K/U 2002.

In 1997 a project that socially-marketed subsidized Insecticide Treated Mosquito bed-nets in K/U Districts (KINET) was implemented (Schellenberg, Abdulla et al. 1999). The KINET project was implemented until 1999 and achieved a community ITN ownership of nearly 37% by the year 2000. Through this programme the coverage of ITN for infants in the area rose from less than 10% at baseline to more than 50% 3 years later (Schellenberg, Abdulla et al. 1999; Schellenberg, Abdulla et al. 2001) . The ITN model has been up-scaled nationwide in the programme named after-NATNETS (Tanzania National Insecticide Treated Net).

The KINET project did set the grounds for the Ifakara Health Demographic Surveillance System (IHDSS) that was initiated in 1996 (Armstrong Schellenberg, Adam et al. 2004) The DSS infrastructure is being used to assess different intervention at community level. Another intervention in the area that has been implemented through support of the IHDSS infrastructure is the ACCESS programme. The ACCESS was launched in

K/U Districts to addresses programmatic issues of improving access to effective malaria treatments since 2003 (http://www.novartisfoundation.org/page/content/index.asp: Cited on 21 July). This project was integrated in the community and local health system structure with a set of interventions including: A social marketing campaign that aimed at sensitizing community for more effective health care seeking. The other component of ACCESS was training of public health care staff on key guidelines of IMCI and the up-scaling Accredited Drug Dispensing Outlets (ADDOs) in collaboration with other partners-Tanzania Food and Drug Authority. The ACCESS project has witnessed an increase of 87% coverage of anti-malarial retails outlet as compared to 71% at baseline and number of anti-malaria dispensation to increase by 78% (Alba, Hetzel et al.).

It is therefore imperative to note here that during the implementations of all the above mentioned initiatives the ministry of health of the Tanzania mainland at the same time has gone through a period of succession for two anti-malarial first line treatment policy changes. It is during the same period that the national level up scaling most of interventions that were confirmed efficacious in research settings has been implemented. In 2001, Tanzania switched the first line anti-malarial policy from CQ to SP and later at the end of 2006 from SP to AL. The use of SP for prevention of malaria during pregnancy was also launched as policy in mid 2001. In 2002 the nation-wide social marketing campaigns on ITN began whereby subsidized ITNs to pregnant women and children under five years through a Swahili connoted voucher scheme "HATI PUNGUZO" was implemented. Alongside this implementation, a free distribution long lasting ITN pilot scheme was introduced in some areas where the most poor social economical quartile in Tanzania belongs; namely Rufiji District, Mtwara and Lindi regions in the South Eastern coast of Tanzania. In the K/U Districts both periods of first line policy transition; first with SP and later with AL have been under successions of two research programmes of impact assessment. In 2001 the policy change was monitored by the **IMPACT** (**I**nterdisciplinary **M**onitoring **P**roject for **A**rtemisinin **C**ombination **T**herapy) –as a byproduct of comparative assessment of a pilot implementations of ACT in Rufiji district and K/U districts were considered as non-implementation comparator districts. In that set-up Rufiji district was being compared to the National first line policy with SP in K/U. As second phase of assessment beginning in 2007 during the aftermath of ACT introduction countrywide, in K/U the policy was privileged again to be closely monitored by a community based study **ALIVE**

[**A**rtemether-**L**umefantrine **I**n **V**ulnerable patients: **E**xploring health Impact] project that is implemented in the region toward the end of 2011

The next two chapters of this thesis state the overall goal, main objectives and details of methodologies to address most questions regarding first line policy with ACT implementation in Tanzania. Beginning from the fourth chapter the thesis sheds light on plans and research activities that were implemented ahead of the policy uptake and it gives insight on further steps undertaken to monitor ACT when the policy was implemented. Chapter 4 describes the assessment of safety and efficacy of ACT as the means of accumulating evidence to prepare a room for evidence based policy change. The fifth chapter describes the extension of assessment strategies to include policy monitoring strategies during the implementation period. The sixth chapter looks closely at the descriptive parameters of medium term impact of the first line anti-malarial policy on morbidity and mortality in children under five years. The seventh chapter describes programmatic issues of the patients' acceptability and compliance to the treatment policy. Finally in chapter eight a general discussion and conclusion is articulated whereas at the end of the discussion key message and recommendations from the thesis are made hence future research agenda is set forwards.

PART II: GOAL AND OBJECTIVES

CHAPTER 2: OBJECTIVES

2.1.1 Goal

To assess the impact of ACT introduction on malaria morbidity and mortality in rural Tanzania and to monitor its long-term safety when used at country scale.

2.1.2 General objective

To evaluate the impact of the introduction of AL on i) malaria transmission (in two districts of rural Tanzania) and ii) mortality of children under five years

2.1.3 Specific objective

1. To evaluate efficacy of ACT in children under five years before implementation as first line policy in Tanzania.
2. To monitor efficacy of AL one year after the introduction of AL as first line anti-malarial policy in Tanzania.
3. To evaluate the feasibility of using demographic surveillance system framework to record early anti-malarial drug exposure during pregnancy.
4. To monitor safety of AL using a programmatic pharmacovigilance system in rural endemic population in Tanzania.
5. To assess the impact of anti-malarial first line policy on malaria transmission and under five mortality in rural area with high ITN coverage in Tanzania
6. To describe programmatic issues of the proper use of AL as 1st line anti-malarial treatment in Tanzania.

PART III: METHODOLOGY

CHAPTER 3: METHODS

3.0 Methodology

3.1 Thesis framework

This thesis describes the before and after strategies that were implemented to prepare the room for first line anti-malarial policy with ACT and thereafter outlines research activities that were implemented to monitor its impact. Data that has been used in this thesis include datasets collected prospectively in three projects. Two projects were implemented in a period before the introduction of ACT in years 2004-2006. The reminder project was implemented during the introduction of ACT as first line anti-malarial policy. The three projects are **E**ast **A**frican **N**etwork for **M**onitoring **A**nti-malarial **T**reatment (**EANIMAT**), the IMPACT project implemented before policy and ALIVE project that was implemented thereafter. The major components of evaluation completed before the introduction of ACT include; *invivo* studies conducted in 2004/5 under EANMAT .Community surveys that assessed asymptomatic carrier of malaria parasites and mortality in children under five years in rural Tanzania was conducted under the IMPACT project for which this thesis uses surveys that were conducted between 2004-2006 as baseline. In the same framework we assessed safety of anti-malarial in pregnant women at community level. The ALIVE study that was implemented in 2007 in the aftermath of the ACT introduction countrywide evaluated the ACT post implementation strategies and gave platform for further assessment of the impact of ACT in three years after the first line policy adaptation as compared to 1st line policy with SP during the IMPACT project.

3.2 Design of studies involved and study population

3.2.1 invivo efficacy studies

EANMAT platform represent a sub-regional anti-malarial efficacy monitoring that was founded in 1998 to provide reliable and current estimates of malaria treatment efficacy representative to Eastern Africa region. The network is composed mainly of staff from national malaria control programmes (NMCPs) of participating sub-regional ministries of health. EANMAT started with three member countries: Kenya, Tanzania (mainland) and Uganda. Rwanda joined the network in 1999, Burundi and Zanzibar; a semiautonomous region within the United Republic of Tanzania, both joined in 2001 (2003). Each country in the network decides which treatments should be monitored, according to their respective anti-malarial first line drug policies. The WHO *invivo* test

protocol was adopted for this monitoring as the central tool of all networks whereas 28 days follow up studies were being conducted in children under five years that were being recruited from outpatient department of involved health facilities. In Tanzania IHI is one of the NMCP technical country member of the EANMAT and was mandated to lead assessment of anti-malarial at two NMCP/EANMAT sentinel sites; Ipinda in the Kyela District in Mbeya region and Mlimba in the Kilombero District in Morogoro all in the South-Eastern and Southern Tanzania respectively. It is through this framework that AL was assessed as a candidate ACT for the Tanzania first line anti-malaria policy. Details of this invivo assessment are given in Chapter 4.1 of this thesis.

3.2.2 Safety of anti-malarial monitoring in pregnant women

This is a pilot study that evaluated the possibility for the conduct of pregnancy test at household level to evaluate safety of anti-malarials that were reported to be used during pregnancy. This methodology was implemented in the Ifakara Health Demographic Surveillance system (IHDSS) in 2006 during the IMPACT project. The IMPACT project was implemented in K/U and Rufiji Districts beginning of 2001 towards 2006 to evaluate the impact of SP plus artesunate; an artemisinin drug on the prevention and reduction of malaria transmission and the spread of resistance (Malisa, Pearce et al.). SP plus artesunate was introduced to pilot ACT policy implementation in Rufiji District while in Kilombero river valley SP was used as a comparator. During the lifespan of the IMPACT project, cross-sectional household surveys in the Rufiji and IHDSS were periodically conducted in May-August after every each year and malaria indicators were collected throughout. During these survey level of anaemia among under five children and community parasitaemia in all age groups were being assessed. Alongside these, mortality data were collected using verbal autopsy and a questionnaire listing the use of anti-malaria in the previous two weeks was applied. Ascertainment of pregnancy status and further assessment of anti-malarial drug safety was introduced in this set up in 2006 in the IHDDS. In this study women who reported exposure to anti-malarial while pregnant and those who were not certain if they were pregnant when exposed were identified and offered a (rapid) urinary pregnancy test (UPT) to confirm presence of pregnancy. A professional IHDSS field interviewer was trained on how to perform UPT and to give to women the test results. Pregnancy outcome among women who tested positive were followed up through the IHDSS framework. The DSS field interviewers were used to document pregnancy outcomes and the survival of the woman child pair in the subsequent IHDSS household visits that

occurs at home during periodic surveys after every four months. Details of this evaluation are given in chapter 4.2 of this thesis.

3.2.3 ACT policy with AL implementation; monitoring of policy and assessment of its impact- The ALIVE study.

The ALIVE study is a prospective, community-based, longitudinal surveillance study including demography and morbidity surveillance systems. The primary objective of this project is to assess the impact of the introduction of AL on all-cause mortality in infants/children ≥ 3 months [and > 5 kg] and < 5 years of age in a rural area of southern Tanzanian Districts (Kilombero and Ulanga) in comparison with historical data when SP was used. Key indicators of ALIVE are being collected within the existing demographic surveillance system (DSS) and the ACCESS project. The secondary objectives are to assess the impact of the introduction of AL on malaria-specific mortality in infants/children using 'verbal autopsy' reports, all-cause health facility attendance rate of patients overall, malaria-related health facility attendance rate of patients. In particular the level of haemoglobin concentration in children under five years and parasitaemia in the general population are collected annually during a community household survey at the peak of malaria transmission in May-August of every year beginning 2008. In addition, patient satisfaction and drug adherence was conducted in March - April 2008. Furthermore, safety assessments of anti-malarial at the moment of country-wide deployment in the community have been introduced since September 2007.

Given the good efficacy of AL as first line and policy it is expected that AL should be more effective than SP to treat clinical malaria and clear *Plasmodium* parasites, and hence should ultimately reduce the incidence of severe malaria and death among the most at risk for malaria; children under five years. Furthermore it is expected that occurrences of malaria attack could be less frequent and eventually transmission dwindle with time thanks to the effect of AL on gametocytes clearance in the community. The expectation is therefore to observe a lower overall mortality and morbidity in Tanzania from 2007 onwards, when compared to the previous period of 2002-2006 when SP was used as standard anti-malarial first line treatment during the IMPACT project. Details of this evaluation are given in chapter 5, 6 and 7 of this thesis

3.3 Statistical methods

Most of findings presented in this xx are descriptive of disease burden and percentage coverage of most applied intervention in the region. For drug efficacy studies, clinical

and molecular failure or efficacy rates are presented. Most of the data were managed on a tailored Visual FoxPro version 9 programme in Ifakara whereas analysis was performed using Sata programme versions 8-11.

PART IV: EVALUATION OF EFFICACY AND SAFETY OF *ACT* BEFORE THE INTRODUCTION OF AL AS FIRST LINE POLICY IN TANZANIA

CHAPTER 4.1: Efficacy and safety of artemisinin-based anti-malarial in the treatment of uncomplicated malaria in children in Southern Tanzania

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4.1.1 Summary

Background

Tanzania switched the anti-malarial first line to sulphadoxine-pyrimethamine (SP) in 2001 from ineffective chloroquine (CQ). By 2003 higher levels of SP resistance were recorded, prompting an urgent need for replacing the first line drug with ACT, as currently recommended by the World Health Organization. Despite this recommendation country-specific evidence-based data to support efficacy and safety profile of ACT is still limited. A study on the efficacy and safety of artesunate plus amodiaquine (AS+AQ) and artemether plus lumefantrine (Coartem®) was carried out in 2004 with the view of supporting the National Malaria Control Programme in the review of the policy in mainland Tanzania.

Methods

An i*nvivo* efficacy study was conducted at Ipinda and Mlimba health facilities between May and November 2004. The study recruited children aged 6-59 months presenting with symptoms of uncomplicated malaria, history of fever or an axillary temperature ≥37.5^{o}C; mono infection with *Pasmodium falciparum* (2,000-200,000 parasites/µl). Patients were randomized to receive either SP or amodiaquine monotherapy or treated with standard doses of AS+AQ in Mlimba and Coartem in Kyela and followed-up for 28 days to assess treatment responses. This study reports results of the combination therapies.

Results

A total of 157 children (76 in Mlimba and 99 in Kyela) who were enrolled in to the study and treated with either Coartem or AS+AQ were successfully followed-up. Both combinations were tolerated and effected rapid fever and parasite clearance. The crude ACPRs were 80 (87 %) and 41 (63%) for Coartem and AS+AQ respectively. However, after PCR adjustments the corresponding figures raised to 100% (n=86) and 93.8% (n=45) in Coartem and AS+AQ groups, respectively. The mean haemoglobin improved moderately from day 0 to day 28 by 1g/dl in Coartem and 0.4g/dl in AS+AQ treatment group and was statistically significant ($p<0.001$ both).

Conclusion

These findings provide substantial evidence that Coartem is highly efficacious in areas of high resistance of SP and supported the country's decision to switch from SP monotherapy to Coartem.

4.1.2 Background

The emergence and spread of *Plasmodium falciparum* resistance to commonly used anti-malarial such as chloroquine (CQ) and sulphadoxine/pyrimethamine (SP) has posed major challenges to malaria control in sub-Saharan Africa. In the face of escalated resistance to these widely used and long utilized anti-malarial l the World Health Organization (WHO) currently recommends the use of artemisinin combination therapies (ACTs) as the first line treatment of malaria in sub-Saharan Africa (WHO 4-5 April 2001; WHO/UNICEF 2003; Koram, Abuaku et al. 2005). Several countries in the region have started implementing the use of ACTs as the first line drug. Despite these recommendations, country specific evidence-based data to support anti-malarial l first line treatment policy change to ACTs is still limited(Coleman, Morel et al. 2004).

In 2001, the Tanzanian Ministry of Health and Social Welfare switched its first line drug from CQ to SP Prior to this change, CQ has remained in use as the first line drug for over 45 years and had recorded day 14 parasitological cure rates of 10.3%(Hatz, Abdulla et al. 1998). A number of lessons were, therefore, learnt after this policy revision. Some of these include, poor acceptability of the new policy as health services providers and the general public at large were short of preparedness to adopt the new policy(Eriksen, Nsimba et al. 2005; Mubyazi and Gonzalez-Block 2005). In addition, there were very few efficacious, safe and cheap drugs to be considered for first line. At the same time efficacy and safety data on the few available drugs were missing. In the aftermaths of interim policy inception, several major steps were taken including conducting *invivo* studies on efficacy of SP and other newly registered anti-malarial geared to increase choices and preparedness should the need for policy revision arise (Tarimo, Minjas et al. 2001; Mugittu, Ndejembi et al. 2004; Hetzel, Msechu et al. 2006). In this framework, therefore, an *invivo* study was carried out on the efficacy of some ACT drugs with a view of supporting the National Malaria Control Programme (NMCP) in reviewing the anti-malarial l drug treatment policy in Tanzania.

4.1.3 Methods

Study site and design

The study was conducted within the *invivo* efficacy testing framework of the Tanzania NMCP/East African Network for Monitoring Anti-malarial (EANMAT).Two health facilities took part in the study; Ipinda in Kyela District at the border with Malawi and Mlimba in Kilombero District in South-eastern Tanzania. This study was conducted in

2004 between January - June and March - October at Ipinda and Mlimba health facilities, respectively. At both sites malaria transmission is perennial and peaks between May and July, after the long seasonal rainfall.

The WHO standardized protocol for the assessment of therapeutic efficacy of anti-malarial drugs (WHO 2000) was used and the study included sick children who were 6-59 months age if they presented with history of fever in the past 24 hours or axillary temperature of ≥ 37.5℃, and mono-infection of *P. falciparum* count of 50-5,000/200 white blood cells (WBC) assumed to be 2,000-200,000parasites/µl. Patients were excluded from the study if they present with repeated convulsion, inability to take anything orally, severe anaemia i.e. Hb≤5gm/dl, difficulty in breathing or patient with signs consistent with renal failure and patient's parent/guardian unwillingness to participate.

Intervention

The patients were randomized to receive either monotherapy or the ACT according to the NMCP schedule of sentinel testing. At Ipinda sentinel site SP and amodiaquine were used as the monotherapies and artemether/lumefantrine (Coartem®) was used as the ACT while Artesunate and Amodiaquine (AS+AQ) in an *ad-hoc* as ACT and the same monotherapies were given at Mlimba. This study reports only the outcome of both combination therapies. Coartem was given to children according to bodyweight as follows 20/120 mg tablet to those weighing 5-14kg and two tablets 40/240 mg to children with 15-24 kg. The full course of treatment for all study patients in this group consisted of 6-doses of Coartem that was given at 0, 8 and 16 hours, the remaining doses were given at 12-hourly intervals for a total of three days. At Mlimba sentinel site AS+AQ was given at a dose of 4mg/kg and 10mg/kg body weight respectively. AS+AQ was given on day 0, 1 and 2 with only amodiaquine's dose reduced to 5mg/kg body weight on day 2. All treatments were supervised by study nurse and patients were observed for 30 minutes in the aftermath of drug intake. All patients who vomited within 30 minutes intervals were re-administered another full dose of the same medicine. All treated patients were followed for 28 days to assess clinical and parasitological responses. Patients that did not turn up for scheduled dose were visited at home by the study nurse on the same day. Treatment outcomes were classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical and parasitological responders using the (WHO 2003) guidelines. Clinical therapeutic outcomes were adjusted by genotyping the *P. falciparum* merozoite surface

protein 2 (*msp2*) and glutamate rich protein (*glurp*) on admission (Day 0) and any day of infection recurrences (Day 7, 14, 21 or 28). Recrudescence was differentiated from new-infections as described by Mugittu et al 2006 (Mugittu, Adjuik et al. 2006) only for patients who received ACTs due to cost limitation. Under this assessment, only parasitaemia that was confirmed by PCR as recrudescence was considered as treatment failure and conversely, was considered as new infection and counted as the ACPR.

Clinical and laboratory procedures

Patient follow up were scheduled on days 1, 2, 3,7,14, 21 and 28. On each visit, including day 0 under which patient were enrolled. Clinical, parasitological and haematological examinations were performed. Haemoglobin level (Hb) was assessed using HemoCue® (Angelholm, Sweden) and the Hb of ≤5g/dl was considered as severe anaemia. Parasitological examinations involved preparation of thick and thin blood smears from each patient and examined by specialized microscopist from Ifakara Health Research and Development Centre (IHRDC). Parasitaemia was expressed as count per 200 WBC of blood assuming a normal leucocytes level of 8,000/µl.

Analysis

Data generated in patient's case record forms were entered on FoxPro® database software version 7 (Microsoft Corporation, Redmond USA 2001) at Ifakara Health Research and Development Centre (IHRDC). Data analysis was performed using STATA® statistical analysis software package version 8 (Stata corporation, Collage Station TX, USA, 2003). Descriptive analysis was done and differences in proportions of treatment outcome were compared using chi square test for proportions. Student's t-test was applied for continuous variables. Data on patients that were excluded for different reasons and those that were loss to follow up were not considered in the final analysis.

4.1.4 Results

Study profile and patient's records

A total of 99 and 76 patients were enrolled at Ipinda and Mlimba health facilities, respectively. Table 1.4 summarizes patient's mean age, body weights, clinical and haematological parameters at admission/enrollments. There were 18 patients who

were loss to follow up; 7/99 (7%) in Ipinda and 11/76 (14.5%) in Mlimba. Overall 92/99 (92.9%) patients in Ipinda (Coartem arm) and 65/76 (85.5%) in Mlimba (AS+AQ arm) were available for the assessment of therapeutic endpoints.

Table1.4: Mean age, temperature, parasite density and haemoglobin on the day of enrollments

Sentinel site	Measured parameters –Means (Standard Deviations [SD])				
	Age in years	Body weight in Kg	Temperature in ℃	Hb in g/dl	Parasites/µl
Ipinda (n=99)	2.3 (1.2)	11.9 (2.7)	38.9 (0.98)	9.7 (1.4)	43114.5 (40130.4)
Mlimba (n=76)	2.1 (1.2)	11.3 (2.5)	38.2 (1.2)	8.7 (1.7)	49347.8 (48194.1)

Treatment outcome

Both drugs were tolerated; there was no report of significant Adverse Drug Reaction (ADR).Table 2.4 shows crude and PCR corrected treatment rates of the test drugs. The crude ACPRs were 80/92 (87 %) and 41/65 (63%) for Coartem and AS+AQ, respectively. After PCR adjustment however, the corresponding figures rose to 100% (86/86) and 93.8% (45/48) in Coartem and AS+AQ respectively. Most of the recurrent infections at both sites were due to LPF. Interestingly, after genotyping all these were found to be due to new infection. The study recorded only two recrudescent infection, both of which in the AS+AQ. No recrudescence was observed in the Coartem arm. Moreover, a total of 10 recurrent infections (six in Coartem and four in AS+AQ) could not be unresolved even after repeated DNA extraction and PCR amplification. When these 10 recurrent infections were assumed to be recrudescence in the final analysis together with the PCR corrected ones however, the ACPRs were 93.3% (83/89) in Coartem and 87.1% (54/62) in AS+AQ.

Table 2.4: Clinical and parasitological therapeutic outcome

End points	Coartem (Ipinda site)			AS+AQ (Mlimba site)		
		After PCR corrections			After PCR corrections	
	Before PCR corrections	With unresolved PCR	Without unresolved PCR	Before PCR corrections	With unresolved PCR	Without unresolved PCR
ETF	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.5)	1 (1.6)	1 (2.0)
LCF	1 (1.0)	1 (1.1)	0 (0.00)	4 (6.1)	3 (4.8)	2 (4.2)
LPF	11 (12.0)	5 (5.6)	0 (0.00)	19 (29.2)	4 (6.5)	0 (0.00)
ACPR	80 (87.0)	83 (93.3)	86 (100)	41 (63.2)	54 (87.1)	45 (93.8)
Total	92	89	86	65	62	48

The mean haemoglobin improved moderately from day 0 to day 28 by 1g/dl in Coartem and 0.4g/dl in AS+AQ treatment groups. The mean haemoglobin recovery after day 28 was statically significant in both groups ($p<0.001$ both).

4.1.5 Discussion

The main goal of this *invivo* ACT efficacy study was to support the establishment of evidence-based results that can be used to change malaria treatment policy in Tanzania. This study has demonstrated high therapeutic efficacy and tolerability for a six dose regimen of Coartem and a 3-day course of AS+AQ in southern Tanzania. Both crude and PCR-corrected ACPRs for Coartem (87% and 100%) were higher than those recorded in the AS+AQ (63.2% and 93.8%) arm. The Coartem crude and PCR-corrected cure rates are more or less similar to those recorded in Muheza Tanzania in 2005 (79% and 97.2%), (Mutabingwa, Anthony et al. 2005) and in mult-country (Tanzania inclusive) Coartem efficacy study (86.5% and 93.9%) (Falade, Makanga et al. 2005).

The testing of each drug independently for each site was due to the arrangements in place that required testing each individual drug as part of anti-malarial I nationwide drug testing allocation. This allows accumulation of evidence of the performance of the ACT in different settings. It can be argued that there are differences from place to place

related to the response to treatment that is observed but treatment policies are formulated at regional or sub-regional level hence the need to get regional summary estimates. The sentinel system is a good approach toward addressing that need. Secondly it will be very difficult to sample all possible places where variation is being expected and under the current malaria transmission intensity in Tanzania, it is hard to follow up enough patients for all treatment groups in a single site during the same transmission year(Schellenberg, Menendez et al. 2004).

An interpretation of the comparative efficacy of the two drugs was not considered in our analysis. The reasons for this approach are; first this study was not designed to measure the differences between two test drugs but only to get point estimates of the efficacy which also allows monitoring of their performance overtime. Second, both ACT drugs have high efficacy profiles in the region that in principal would require huge sample size to be able to show a comparative difference(Adjuik, Agnamey et al. 2002; Mutabingwa, Anthony et al. 2005). For this same reason the direct comparison of the two ACTs in a randomized trial is not an optimal approach of monitoring drug efficacy in the programme's implementation setting and the reliance of sentinel sites in a country therefore becomes an efficient solution.

4.1.6 Conclusion

According to the current malaria treatment policy revision guidelines (changing policy at >10% failure rate), both Coartem and AS+AQ would be considered suitable drugs for first line purpose since both recorded high PCR-corrected efficacies i.e. 100% and 93.8%, respectively. However, it was more rational to adopt Coartem as its efficacy is far above the cut-off point, whereas AS+AQ efficacy is just 3 units higher from the policy revision cut-off point and its useful therapeutic life might be compromised sooner following widespread use. In addition, the policy revision process took into account the suggestion that apart from reasonably high efficacies of partner drugs, an effective combination therapy should comprise of drugs that have not been deployed previously in the area for use as monotherapies (Watkins, Sibley et al. 2005). Prior to the 2006 policy change AQ was being used as a second line anti-malarial drug in Tanzania. Finally, Coartem was highly recommended based on its extra privileges such as being the only co-formulated ACT at the time of policy change and good effectiveness

parameters in the country(Mulligan, Mandike et al. 2006). All these experience have paved the way for adoption of Coartem as the first line anti-malarial drug in Tanzania.

Authors' contributions

AM was responsible for the protocol development, study design, field trial set up data analysis and developing of the manuscript. SA was responsible for study design, training research assistants and developing of the manuscript. KM participated in manuscript development and for comments on the earlier version. DS participated in molecular genotyping of recurrent infections. RM & AM were responsible for study design.

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CHAPTER 4.2 Using a Demographic Surveillance System to evaluate the feasibility of pregnancy testing for recording early pregnancy with anti-malarial drug exposure

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4.2.1 Summary

Background: The risk of malaria infection and its severity tends to increase during pregnancy and for this reason WHO recommends the use of anti-malarial for case management and intermittent prevention of malaria during pregnancy. Coverage of recommended programs is still low in sub-Saharan Africa. Anti-malarial self treatments is common hence exposure in early periods of pregnancy despite the absence of infrastructure to monitor drug safety.

Methods and findings: A list of women of child bearing age who were exposed to anti-malarial s, with or without knowing they were pregnant four weeks preceding household surveys was generated from the Ifakara health demographic surveillance system (IHDSS) database in 2006. Women who reported exposure to anti-malarial s while pregnant were offered a urinary pregnancy test. This test was performed by a female, none-medical, professional IHDSS field interviewer trained on testing and to give test results. Pregnancy outcome among women who tested positive was followed up through the IHDSS framework. The IHDSS field interviewers documented pregnancy outcomes and the survival of women in the regular household surveys.

Overall 268 women were identified and almost 98% reported use of one or two types of anti-malarial drug in the two to four weeks prior to the interview. Nearly all agreed to undergo urinary pregnancy tests. The test showed 38 women were pregnant at any early gestation age. 26% of positive cases thought they were not pregnant before the test was done. Thirty seven women had a live birth; one woman had a non-live birth.

Conclusions: This assessment has provided useful information on the feasibility of monitoring early drug exposure in pregnancy. The methodology can be further extended to include a close follow-up of pregnancy and newborns. Detailed information about pregnancy status and subsequent offspring developmental safety milestones can be recorded through extended form of pharmacovigilance reporting system.

4.2.2 Introduction

The risk of malaria infection and its severity tends to increase during pregnancy and for this reason the frequency of anti-malarial exposure during pregnancy also tends to increase (Steketee and Nahlen 2001). It is for this reason that the World Health Organization (WHO) currently recommends a three-pronged approach for the management of malaria during pregnancy: use of insecticide-treated mosquito bed nets, use of intermittent preventive treatment of malaria and proper malarial case management (World Health Organization. WHO Regional Office for Africa 2004). The last two approaches require the use of anti-malarial drugs.

Despite these recommendations, the coverage of these programs is still very low and in sub-Saharan Africa, where malaria is highly endemic, anti-malarial self treatment is common (Ndyomugyenyi, Neema et al. 1998). The occurrence of new malaria episodes in an endemic setting tends to increase with transmission intensity and therefore correlates with a significantly high number of anti-malarial exposures (Hetzel, Alba et al. 2008). Of all population groups pregnant women have a reduced immunity to malaria infection and, in the rural setting, they are frequently exposed to malaria vectors and therefore often self-medicate with anti-malarial drugs (Ndyomugyenyi, Neema et al. 1998). It is therefore expected that in sub-Saharan Africa anti-malarial exposure in the early critical periods of pregnancy, and untoward pregnancy outcome, is likely to account for most of the unrecorded drug exposures in the absence of an adequate infrastructure to monitor and efficiently record drug safety assessments (Dellicour, Ter Kuile et al. 2008). This problem is likely to be even more acute following the use of different new anti-malarial products that are easily available in private pharmaceutical outlets (Goodman, Kachur et al. 2004; Hetzel, Dillip et al. 2008).

To understand these challenges, we piloted a procedure on how to identify and monitor early drug exposure during pregnancy in women of reproductive age in the Kilombero river valley where the Ifakara Health Institute (IHI) runs a Demographic Surveillance System (IHDSS). The IHDSS is a longitudinal health- and population- based surveillance system that records vital demographic information including births, migration, death and causes of deaths through verbal autopsy. Details of the IHDSS are given elsewhere in the literature (Schellenberg, Abdulla et al. 2001; Kabanywanyi, Macarthur et al. 2008).

4.2.3 Methods

Ascertainment of women exposed to anti-malaria.

A list of women of child bearing age who were exposed to anti-malarial, with or without knowing they were pregnant, in the four weeks preceding subsequent household surveys was generated from the Ifakara health demographic surveillance system (IHDSS) database in 2006. Women who reported exposure to anti-malarial drugs while pregnant, and those who were not certain if they were pregnant, were both identified and were offered a urinary pregnancy test

Procedures

Details of these women, including demographic parameters and morbidity status of their household, were routinely recorded during preceding household surveys. In addition, women were asked about their current reproductive status and if they had used any anti-malarial drugs in the two to four weeks prior to the date of interview. Women who reported being pregnant was asked to ascertain the actual gestation age and all women were offered confirmatory pregnant tests. Pregnant women with gestation age above two months at the moment of drug exposure also were offered a test, but were not included in the subsequent follow-up. All eligible women were asked for informed consent to undergo urinary pregnancy tests. A female, none-medical professional IHDSS interviewer was initially trained on how to perform the test. She could then provide respondents with the test results. All women unaware of their pregnancy status were given the results of the confirmatory test. For those women who were pregnant the estimated date of conception was ascertained by the reported last date of menstrual cycle. Test results were kept confidential between the interviewer and the women tested, unless a request was made for the results to be disclosed to other household members.

Ethics consideration.

All of the data presented in this paper was obtained as part of the IHDSS initial surveys that obtained ethical approval from the Ifakara Health Institute's Institutional Ethics Committee. This study was implemented in the same framework of these surveys that record vital demographic parameters (births, deaths out migration and in migration). For each participant in this study we obtained a verbal consent that was sought after detailed explanation about the aim of the study.

4.2.4 Results

Overall, 268 women were identified with nearly 98% of them reporting use of one or two types of anti-malarial drug in the two to four weeks prior to the interview. More than half (n=166) used sulfadoxine-pyrimethamine (SP), 38 (14%) used amodiaquine, 29 (11%) used quinine, 9 (3%) used SP plus quinine, while 11 (4%) used SP plus amodiaquine. Fifteen women could not clearly state which type of anti-malarial drug they used. Nearly all agreed to undergo urinary pregnancy tests. The test revealed that 38 women were pregnant and had been exposed to an anti-malarial during their early period of pregnancy. Another three women in whom the test result was positive had been exposed to an anti-malarial at a late gestation stage. In about 26% positive result cases the women had not thought they were pregnant before the test was made.

It had been planned in this pilot study to follow up pregnancy outcome at the time of delivery, but woman-child pair follow-ups were not included in the plan of assessment. In women that were identified as pregnant during this survey all gave birth to live offspring with the exception of one stillbirth. The long-term survival and health status of the 37 children born to the women who were exposed to anti-malarial drugs whilst pregnant was not systematically assessed during subsequent surveys.

4.2.5 Discussion

The methodology in the study provides new important information on the feasibility of performing urinary pregnant tests among reproductive age group women at household level. In addition, this approach shows how this methodology can be used to record any untoward teratogenic medical outcome attributable to early medical inadvertent exposure in pregnancy.

This pilot study was designed to identify the risks of anti-malarial exposure during early pregnancy and describe the usefulness and practicability of urinary pregnancy tests in the routine household surveys. IHDSS has the potential for follow-up of pregnant women through its routine longitudinal household visits, where vital demographic parameters (birth, migration, death and cause of death through verbal autopsy) are routinely documented.

This study was not designed to record the occurrence of rare, adverse events, but, rather to test the hypothesis that a urine pregnant test could be done that was acceptable at community level. It was also designed to asses any untoward pregnancy outcome in all women who were exposed to anti-malarial drugs in early pregnancy. It is important to note here that this approach allows early drug exposure during critical

stages of pregnancy to be tracked with follow-up pregnancy outcome for recording safety signals. This type of follow-up, however, is not routinely implemented at Reproductive and Child Health clinics. One of the major reasons for the failure of these clinics to implement this follow-up could be the late antenatal booking that is routine practice in most sub-Saharan settings (Fekede and A 2007; Ouma, van Eijk et al. 2007).

Drug exposure during pregnancy is based on information supplied by pregnant women. This presents limitations to the findings on the association of drug exposure and pregnancy outcome as there was no attempt to quantify this source of information. Another limitation is that this study was only able to follow up on hard outcomes such as birth or abortion at the end of pregnancy. This type of follow-up does not take account of the incidence of short-term, mild to moderate adverse drug reactions experienced whilst the embryo is developing. It is for this reasoning that short-term symptoms and problems that regress with gestation age might have gone undetected through our surveys.

Although this study applied a close follow-up plan of pregnancy outcome, the actual set up was less stringent than would be applied in a clinical controlled trial. This study has provided the research community with ample evidence that in places where DSS exists, a longitudinal monitoring platform for health status in the community can further be utilized to include drug safety follow-up and can generate useful real time information.

4.2.6 Conclusion

This assessment has provided useful information on the feasibility of monitoring early drug exposure in pregnancy. This methodology can be further extended to include a close follow-up of pregnant women and their newborns after birth. Such an extension has the potential to reveal detailed information about pregnancy status and subsequent offspring developmental safety milestones and could serve as a comprehensive pharmacovigilance reporting system.

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close supervision. We extend our gratitude to all women in the study area who participated in the study and interviewed.

Competing interests

The author(s) declare that they have no competing interests.

PART V: EVALUATION OF EFFICACY AND SAFETY OF *ACT* AFTER THE INTRODUCTION OF AL AS FIRST LINE POLICY IN TANZANIA

CHAPTER 5.1 In vivo efficacy of artemether-lumefantrine one year after the implementation of first line anti-malarial treatment policy in Tanzania

A working paper

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5.1.1 Summary

Background. The emergence and rapid spread of resistance to anti-malarial drugs over the past two decades has led to most malaria endemic countries to abandon most historically used anti-malarial in the past. The increased availability of fixed-dose ACT by 2009 has led to nearly 77 out of 81 *P. falciparum* malaria-endemic countries and territories to adopt ACTs for use in their national drug policies.

Mainland Tanzania replaced sulfadoxine-pyrimethamine with artemether-lumefantrine (AL) in 2006. Following this change in Tanzania, a study that monitored the performance of AL in the invivo set-up was conducted in 2008.

Method. The monitoring study was conducted using the WHO invivo assessments protocol in the framework of pharmacogenetic/kinetic project. This study took place from March to May 2008 at the Kibaoni Health Centre in Ifakara town

Results.

There were 13 (9%) and 9 (7%) patients who were lost to follow-up until day 28 and day 42 respectively and therefore not included in the final analysis. There was no early treatment failures and crude ACPR were 125 (95.4%) at day 28 and 122 (96.7%) at day 42. During the 28 day follow-up (FUP) there were 2 (1.5%) LCF and 4 (3.1%) LPF failure rates while during the 42 day FUP there were only 4 LPF (3.3%). The mean haemoglobin improvement of 1.1 and 1.6 g/dl from baseline-day 0 to day 28 and day 42 follow-up was statically significant in both groups ($p<0.001$ both).

Conclusion. The excellent efficacy of AL one year after country-wide policy implementation suggests that combination therapies with effective drugs can potentially be used over a long period of time.

5.1.2 Introduction

The emergence and rapid spread of resistance to anti-malarial drugs over the past two decades has led most malaria endemic countries to abandon the most historically widely used anti-malarial chloroquine (WHO 2009). (Hatz, Abdulla et al. 1998; Breman, Alilio et al. 2004). This followed an intense search for new safe and efficacious anti-malarial alternatives by researcher community and pharmaceutical companies (Falade, Makanga et al. 2005; Makanga, Premji et al. 2006). During the last decade, several options of fixed combinations of anti-malarials have gone through series of clinical trial testing their efficacy and safety parameters before market authorization (Makanga,

Premji et al. 2006). Few among these new therapies have passed international requirements for post marketing large scale up-scaling in to national malaria first line policies of several malaria endemic countries. Despite ACT to be proven efficacious in the beginning of last decade, global adoption of new anti-malaria policy was slow with little support from WHO. Thanks to prominent scientists that criticized the n lack of policy change at the global level, 2004 became the turning point resulting in many endemic countries changing their policy to ACTs (Attaran, Barnes et al. 2004; White, Nosten et al. 2004). Despite the Global Fund to support the free availability of ACT in most malaria endemic countries, during the early phase wide-ACT implantation it wasn't readily accessible due to various hurdles in health systems in most malaria endemic countries. In the aftermath of ACT availability at scale at the beginning of the current decade a cluster sampling surveys in most sub-Saharan African countries indicated that less than 15% of children under five with febrile illnesses who sought health care were being treated with ACT (WHO 2009).

The increased availability of fixed-dose ACT by 2009 has led to nearly 77 of 81 *P. falciparum* malaria-endemic countries and territories to adopt ACTs for use in their national drug policies (WHO). In 2008, artemether-lumefantrine (AL) fixed-dose combination has reached more than 78 million treatment courses (WHO). In the United republic of Tanzania, Zanzibar changed its first line anti-malarial treatment from ineffective chloroquine to amodiaquine and artesunate since September 2003 whilst in Mainland Tanzania AL replaced sulphadoxine-pyrimethamine (SP) with AL in 2006 (Kabanywanyi, Mwita et al. 2007).

Following the adoption of ACT with AL as the anti-malaria first line policy in late 2006 and its subsequent implementation in 2007 country wide, a new *in vivo* study was conducted to compare the efficacy of AL one after implementation with that before implementation. This study was part of a broader assessment of the pharmacogenetic-kinetic of AL and took place in a health facility in the Kilombero river valley (Hodel, Kabanywanyi et al. 2009).

5.1.3 Methods

Study site and design. The study was conducted from March to May 2008 at in the Kilombero river valley at the Kibaoni Health Centre located six kilometers outside of the old Ifakara town. In this part of the country malaria transmission is perennial and peaks between May and July, after the long seasonal tropical rainfall.

The WHO standardized protocol for the assessment of therapeutic efficacy of anti-malarial drugs (WHO 2000) was used. The study included sick children who were 6-59 months old / of age and presented with history of fever in the past 24 hours or axillary temperature of ≥ 37.5℃, and mono-infection of *P. falciparum* count of 50-5,000/200 white blood cells (WBC) assumed to be 2,000-200,000 parasites/µl. Patients were excluded from the study if they presented with repeated convulsion, inability to take anything orally, severe anaemia i.e. Hb≤5gm/dl, difficulty in breathing or patients with signs consistent with renal failure and patient's parent's/guardian's unwillingness to participate.

Intervention. The patients were allocated to a standard dose of AL [Coartem®, Novartis], a fixed combination of 20 mg of artemether and 120 mg of lumefantrine) that was given to children according to bodyweight as follows: One tablet (i.e. 20 mg artemether /120 mg lumefantrine) to those weighing 5-14kg and two tablets (i.e. 40 mg / 240 mg) to children with 15-24 kg. The full course of treatment for all study patients consisted of 6-doses that was given at 0, 8 and 16 hours; the remaining doses were given at 12-hourly intervals for a total of three days. All morning treatments were supervised by study nurse and patients were observed for 30 minutes following the drug intake. All patients who vomited within 30 minutes intervals were re-administered another full dose of the same medicine.

Patients were followed for 28 days to assess clinical and parasitological responses and those that did not turn up for scheduled dose were visited at home by the study nurse on the same day. A patient was considered lost to follow-up if at the moment of scheduled visit he or she did not turn up and could not be found at home after three home visit attempts within one week of follow-up. An intention-to-treat analysis was planned for a follow-up extension to include day 42 end points. All patients who were available for this extension were followed up to day 42. Treatment outcomes were classified as early treatment failure (ETF), late clinical failure (LCF), late parasitological failure (LPF) and adequate clinical and parasitological responders (ACPR) using the guidelines (WHO 2003).

Clinical and laboratory procedures. Patient follow-up was scheduled on days 1, 2, 3,7,14, and 28 or day 42. On each visit, (including day 0 under which patient were enrolled) clinical, parasitological and haematological examinations were performed. Haemoglobin level (Hb) was assessed using HemoCue® (Angelholm, Sweden) and Hb

of ≤5 g/dl was considered as severe anaemia. Parasitological examinations involved assessment by rapid diagnostic tests with *Parahit*© (Span Diagnostics Limited, India) and microscopic assessment by thick and thin blood smears from a research microscopist of the Ifakara Health Institute (IHI). Parasitaemia was expressed as count per 200 WBC of blood assuming a normal leucocytes level of 8,000/µl.

Analysis. Data generated in patient's case record forms were entered into FoxPro® database software version 7 (Microsoft Corporation, Redmond USA 2001) at IHI. Data analysis was performed using STATA® statistical analysis software package version 11 (Stata corporation, Collage Station TX, USA, 2007). Descriptive analysis was done and differences in proportions of treatment outcome were compared using Chi square test for proportions. Student's t-test was applied for continuous variables. Data on patients that were excluded for different reasons and those that were lost to follow-up were not considered in the final analysis.

5.1.4 Results

Study profile and patient's records. A total of 389 malaria confirmed patients who attended the outpatient department of the Kibaoni health centre between March-May 2008 were screened for eligibility into the study. A total of 131 and 122 children were eligible for invivo efficacy study and hence included in the final analysis for days 28 and 42 endpoints respectively. There were 13(9%) patients who were lost to follow-up before day 28 and therefore not included in the final analysis. Similarly there were an additional 9 (7%) patients who were lost to follow-up during the day 42 extension and therefore not included in the final analysis.

Treatment outcome. There was no early treatment failure in all patients that met inclusion criteria and could be followed up until day 28 at least. Crude ACPR were 125 (95.4%) and 122 (96.7%) for day 28 and day 42, respectively. During the day 28 follow-up there were 2 (1.5%) LCF and 4 (3.1%) LPF failure rates while in day 42 there were only 4 (3.3%).

For the 6 failures samples after day 28 and the 4 after day 42 discrimination analysis of recrudescence versus re-infection using PCR could not be performed. Indeed, the filter papers were misplaced during the renovation of the laboratory unit of the Ifakara Health Institute in Ifakara.

The mean haemoglobin improved moderately from 10.3 g/dl on day 0 to 11.5 g/dl on day 28 and to 12.0 g/dl on day 42 follow-up. The mean haemoglobin recovery after day 28 was statically significant in both groups ($p<0.001$ both).

5.1.5 Discussion

One year after its implementation as first line anti-malarial policy in Tanzania, the level of efficacy of AL was still high and consistent with what had been observed three years prior to the policy change back in 2004. As a matter of fact, the day 28 ACPR estimate of 95% that has been recorded in this paper was even higher than that recorded before implementation at 87% (Kabanywanyi, Mwita et al. 2007). This finding is likely to be due to chance. Other factors may have played a role. For example, at present AL is used countrywide and is distributed free of charge through public health care facilities which implies that any malaria case seen at most health facilities is readily promptly treated (Alba, Dillip et al. ; Alba, Hetzel et al.) with anti-malaria. This results into cutting down the potential community biomass of asexual parasitaemia that could resulted in to sexual form of parasites reservoir that account for transmission intensity. It can be argued that, the higher coverage of insecticide treated net (ITN) in the area has contributed to the extended protection against malaria 42 days after AL treatment. It is acknowledged that the implementation of complementary strategies leads to better outcomes.

This study did not evaluate the nature of parasites found in 9% of all slides of patients that were considered either LCF or LPF. Failure to analyze these samples is not a major issue considering the low number of clinical and parasitological failures. Our estimate of an efficacy of 95% is quite conservative since we assume that all parasite recurrences are recrudescence. The efficacy could have been even higher, should molecular analyses been available. Indeed, in the same study in 2004 (Kabanywanyi, Mwita et al. 2007), it was shown that in areas with intense perennial malarial transmission the majority of patients that were classified as failure rates after blood smear analysis, were then found to be new infections by PCR analysis and subsequently classified as ACPR.

Conclusion. The current crude clinical efficacy rates of AL one year after country-wide policy implementation suggest that AL is still highly efficacious to treat malaria. These findings provide substantial evidence that combination therapies with effective drugs can potentially be used over a long period of time.

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.Conflict of interest: Abdunoor M Kabanywanyi and Blaise Genton have received funding from Novartis Pharma to assess the impact of the introduction of artemether-lumefantrine in Tanzania and travel grants to present results at international conferences.

CHAPTER 5.2: Experience of safety monitoring in the context of a prospective observational study of artemether-lumefantrine in rural Tanzania: lessons learned for pharmacovigilance reporting

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5.2.1 Summary

Objectives

To identify and implement strategies that help meet safety monitoring requirements in the context of an observational study for artemether-lumefantrine (AL) administered as first-line treatment for uncomplicated malaria in rural Tanzania.

Methods

Pharmacovigilance procedures were developed through collaboration between the investigating bodies, the relevant regulatory authority and the manufacturer of AL. Training and refresher sessions on the pharmacovigilance system were provided for healthcare workers from local health facilities and field recorders of the Ifakara Health Demographic Surveillance System (IHDSS). Three distinct channels for identification of adverse events (AEs) and serious adverse events (SAEs) were identified and implemented. Passive reporting took place through IHDSS and health care facilities, starting in October 2007. The third channel was through solicited reporting that was included in the context of a survey on AL as part of the ALIVE (**A**rtemether-**L**umefantrine **I**n **V**ulnerable patients: **E**xploring health impact) study (conducted only in March-April 2008).

Results

Training was provided for 40 healthcare providers (with refresher training 18 months later) and for six field recorders. During the period 1st September 2007 to 31st March 2010, 67 AEs were reported including 52 under AL, five under sulphadoxine-pyrimethamine, one under metakelfin, two after antibiotics; the remaining seven were due to anti-pyretic or anti-parasite medications. Twenty patients experienced SAEs; in 16 cases, a relation to AL was suspected. Six of the 20 cases were reported within 24 hours of occurrence.

Discussion

Safety monitoring and reporting is possible even in settings with weak health infrastructure. Reporting can be enhanced by regular and appropriate training of healthcare providers. SMS text alerts provide a practical solution to communication challenges.

Conclusion

Experience gained in this setting could help to improve spontaneous reporting of AEs and SAEs to health authorities or marketing authorization holders.

5.2.2 Background

Spontaneous reporting of suspected adverse drug reactions (ADRs) utilizing post-marketing surveillance or pharmacovigilance techniques during drug therapy is less applicable in many sub-Saharan African countries (Edwards 1998). Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem (WHO). Pharmacovigilance plays a key role in ensuring that patients receive safe drugs. The knowledge of a drug's adverse effects can be increased by various means, including spontaneous reporting, intensive monitoring and database studies (Harmark and van Grootheest 2008). Post-marketing surveillance - which is often used synonymously for pharmacovigilance (Cobert and Biron 2002) and will be used throughout this article - is an important component of safety monitoring for drugs after they have been licensed for use. Detailed data on adverse events (AEs) are collected during the controlled clinical trials that are required for licensing, but however rigorous this process, the information collected cannot be regarded as entirely comprehensive due to the relatively restricted number of patients involved (Edwards 1998) and the exclusion criteria that are frequently applied, for example to omit pregnant women, young children, or elderly patients (Gough 2005). Accordingly, post-marketing surveillance, especially in the context of observational studies, can be a valuable source of additional safety data within a large patient population in a real-world setting.

The main factors limiting the implementation of pharmacovigilance in resource-limited settings include limited access to healthcare facilities, availability of most prescription drugs from the informal market, poor labeling of medications, high levels of illiteracy,

poor record-keeping, a shortage of qualified healthcare professionals and a lack of awareness among healthcare workers of the need to identify and report suspected ADRs that occur during drug therapy. Post-marketing surveillance, including monitoring of anti-malarial drugs, is currently not undertaken in most sub-Saharan countries. A few countries in the region, including Tanzania, have managed to introduce a system of yellow cards, but this reporting process is still inefficient. Therefore, the benefits of pharmaco-epidemiological studies with planned, protocol-mandated collection of safety data may be particularly relevant in this region. However, careful attention must be paid to strategies that help to achieve effective safety monitoring during such studies.

Failure to properly assess the safety of a widely used drug such as a first-line anti-malarial treatment could result in public misperception and lead to problems with acceptability. This was seen in recent years with sulphadoxine-pyrimethamine (SP) (Mubyazi, Bloch et al. 2005). Concerns about SP-related serious adverse skin reactions (e.g. Stevens-Johnson syndrome) led to unnecessary delays in the process of policy change in several African countries (Mubyazi and Gonzalez-Block 2005). At the time, it was difficult for Ministries of Health to provide evidence-based information to the media and the public, and as a result public suspicion lingered for a long time.

Since then, following recommendations from the WHO that artemisinin-based combination therapy (ACT) be used as first-line treatment of uncomplicated malaria (WHO), artemether-lumefantrine (AL, Coartem®, Novartis Pharma AG, Basel, Switzerland) has been widely adopted throughout sub-Saharan Africa as first-line treatment for uncomplicated *Plasmodium falciparum* malaria. The efficacy and safety of AL have been extensively documented in clinical trials (Falade, Makanga et al. 2005; Koram, Abuaku et al. 2005; Martensson, Stromberg et al. 2005; Mutabingwa, Anthony et al. 2005; Dorsey, Staedke et al. 2007; Zongo, Dorsey et al. 2007), but safety data for AL are currently limited when deployed on a large scale outside controlled clinical trials.

In November 2006, Tanzania adopted AL as first-line anti-malarial therapy as part of its national policy. Following this decision, the ALIVE (**A**rtemether-**L**umefantrine **I**n **V**ulnerable patients: **E**xploring health impact) study was initiated to evaluate the impact of implementing AL as first-line malaria treatment in a rural, malaria-endemic region of the country. ALIVE is an observational study undertaken by the Ifakara Health Institute (IHI) and the Swiss Tropical and Public Health Institute, and sponsored by Novartis Pharma AG and the Novartis Foundation for Sustainable Development. As for any

study of this type, specific requirements for safety monitoring were specified in the protocol, but the challenges in meeting these requirements were recognized.

This paper describes how the pharmacovigilance requirements of the ALIVE study were being addressed through innovative initiatives that included dedicated training of relevant healthcare workers and community longitudinal demographic surveillances recorders. The use of short message service (SMS) text alerts was also encouraged. This may provide a potential model to ensure compliance with safety reporting requirements in other observational studies or more general post-marketing surveillance programmes.

5.2.3 Methods

The ALIVE study

ALIVE is a prospective, observational, community-based, longitudinal, demographic surveillance study in adults and children, undertaken to assess the impact of AL on malaria morbidity and mortality in a rural, malaria-endemic area of Tanzania when used as first-line treatment for uncomplicated malaria. Since first-line use of AL was adopted in Tanzania as national treatment policy in late 2006, it has been distributed to health facilities for use twice daily for three days to all patients' ≥3 months of age with a clinical diagnosis of uncomplicated malaria. The first dose is administered under supervision at the health facility.

The primary objective of the study is to assess the effect of AL on all-cause mortality in infants and children aged ≥3 months (and >5kg) and <5 years old compared to historical data using SP. Secondary objectives include the assessment of overall and malaria-related health facility attendance rate in children and in adults. This study also provided a framework for assessment of patient satisfaction, adherence to the AL regimen in both children and adults using a structured questionnaire, and safety monitoring of AL (Kabanywanyi, Lengeler et al.).

The study is taking place over a five-year period (2007-2011) in two rural districts of Tanzania (Ulanga and Kilombero). The ALIVE study population comprises the population of the Ifakara Health Demographic Surveillance System (IHDSS) in the Ulanga and Kilombero Districts, which numbered approximately 82,000 at the start of the study. The study area is characterized by monsoon tropical rains that fall from December to May, leading to an average annual rainfall of 1,200 mm. Malaria

transmission ranges from intense to moderate and transmission is perennial, peaking after the period of long rains with little seasonal variation (Smith, Charlwood et al. 1993). Across the study area there are 25 villages and 25 health facilities that include health posts, dispensaries, health centres and hospitals, with varying quality of care.

The ALIVE study is conducted in compliance with the Declaration of Helsinki following approval by the institutional review board of IHI and the Tanzanian National Institute for Medical Research (NIMR).

Ifakara Health Demographic Surveillance System

The IHI runs a well-established demographic surveillance system covering parts of the Ulanga and Kilombero districts in the ALIVE study, whereby standardized information on pregnancies, births, deaths and migrations are collected every four months by trained field recorders who visit each of the approximately 19,000 households in the surveillance areas of the two districts (Schellenberg, Abdulla et al. 2001). A complete household survey is performed annually to update the IHDSS database with socioeconomic and other key indicators. The IHDSS is being used to collect selected outcomes data in the context of the ALIVE study. The IHDSS unit is part of the Indepth-Network, a global network of 37 field sites in Africa and Asia focused on health and population research .

Pharmacovigilance monitoring

In the context of this study, an AE is defined as *'unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study'*. A serious adverse event (SAE) is defined as *'an undesirable sign, symptom or medical condition which is fatal or life-threatening, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, constitutes a congenital abnormality or a birth defect, is medically significant, or may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously'*. A suspected causality assessment is defined as follows: '*The temporal relationship of the clinical event to trial drug administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event'*.

The protocol included three channels through which AEs and/or SAEs can be identified and reported (Figure 1.5), to ensure that reporting is compliant with the regulations of the Tanzanian Food and Drugs Authority (TFDA) and with standard operating procedures of Novartis, the manufacturer of AL and the study sponsor. Of these, the first two channels (IHDSS and health facilities) employ passive pharmacovigilance while the third (patient satisfaction/adherence survey) actively solicits information on AEs and SAEs. Standard reporting forms from the TFDA were used to collect data on AEs. Standard Novartis SAE forms were, in addition, used to report SAEs.

Safety data from patients of all ages were reported.

1. *IHDSS (Level I).* Field reporters in the IHDSS (who are permanent residents in the area) have been instructed that for any AL-associated AE (regardless of seriousness) spontaneously brought to their attention, they should complete a TFDA form, and recommend to the reporter/patient that the event be reported to the health facility. The TFDA form is delivered to the local health facility, where additional details are added if possible. In the event of an SAE, a Novartis SAE form is additionally completed, and the SAE is assessed for causality by the physician and forwarded to Novartis. Additionally, in the event of an SAE being identified by IHDSS reports, IHDSS interviewers are trained to advise the patient to attend the local health facility immediately.

2. *Health facilities (Level II).* Health professionals working in health facilities (i.e. medical officers, pharmacists, clinical/maternal and child health nurses, or laboratory staff) have also been instructed to complete a TFDA form for any spontaneously reported AL-associated AE, regardless of seriousness. In the event of an SAE, a Novartis SAE form is additionally completed. Assessment of causality by the treating physician is undertaken. If AL is administered during pregnancy, a specific Novartis pregnancy form is completed.

3. Patient satisfaction/adherence survey (Level III). During the patient satisfaction/adherence survey that involved 552 malaria patients and was conducted between March-April 2008, information was actively solicited on AEs and SAEs, and recorded on the TFDA form (AEs) and the Novartis SAE form (Kabanywanyi, Lengeler et al.). If an SAE is suspected after assessment by a treating physician, the form is submitted to Novartis.

The TFDA forms are collected monthly from health facilities and transmitted to the TFDA safety desk in Dar es Salaam by postal mailing.

From Ifakara, all SAE forms are transmitted to the local East African Novartis safety office, by fax or email. All data are entered to a specific ALIVE safety database held at the IHI. The ALIVE safety coordinator also actively follows up the patients for verification and assessment and, if necessary, the safety coordinator refers the patient to a health facility for further assessment and management. In the event of incomplete information from the relevant healthcare providers, the ALIVE coordinator may visit the patient and complete all necessary forms on site. All TFDA and Novartis SAE forms are also forwarded to the TFDA (Figures 1.5 and 2.5).

The TFDA form requires standard reporting information (e.g. patient demographics, description of the event, suspected and concomitant drug(s), management and outcome of the event etc). The Novartis SAE form, which was field-tested by IHDSS and was found to be consistent with the TFDA report form, requires information on the diagnosis and description of the event, how the event met criteria for classification as a SAE, treatment doses at or before onset of the SAE, therapy dates, past medical history, relevant concomitant drugs, relevant laboratory values, investigator's causality assessment (i.e. suspected [possibly or probably related to study drug] or not suspected) and outcome. If a causality assessment is missing when an SAE is reported either at a health facility or during the patient satisfaction/adherence survey, the SAE form is sent to Novartis for provisional reporting.

SMS reporting

In order to ensure timely reporting of AEs and SAEs, IHDSS field recorders or health facility staff were encouraged to send a mobile telephone SMS text alert to the ALIVE safety coordinator immediately when an AE or SAE is identified, prior to submitting the physical reporting form. The SMS includes a summary of patient demographics, date and type of event. Using this information, the safety coordinator then uses SMS texting to alert the local East African Novartis safety office and as necessary sends a fax or scanned copy of the initial report by email. Reminders to IHDSS field reporters and staff at health facilities that completed forms are required within the proscribed time frame (i.e. initial report within 24 hours of event and follow-up report not later than 15 days after the initial report) are also sent through SMS alerts.

Training for healthcare workers

In October 2007, a one-day training session was provided for healthcare providers from health facilities located in the two districts in which the ALIVE study was undertaken. Participants were divided in to two groups, each trained separately once during each of the two consecutive training days. Each session comprised at least 35 persons, from both of the districts that host IHDSS (Kilombero and Ulanga). This training was conducted jointly by facilitators from the investigating bodies (IHI and the Swiss Tropical and Public Health Institute), the regulatory authority (TFDA) and the drug manufacturer (Novartis Pharma AG). Trainees were designated as focal persons for their health facilities after training. During the training session, delegates were instructed on how to identify AEs and SAEs, procedures for completing the relevant forms, and the reporting channels (Table 3.5). All reporting forms were presented and delegates were shown how to complete each one in a step-by-step process. Plenary presentations were followed by small-group breakout sessions in which case studies provided an insight into the identification and handling of AEs and SAEs and how to report them in a timely manner in compliance with the requirements of TFDA and Novartis. Delegates received training materials, handouts and copies of all relevant reporting forms.

Eighteen months later (April 2009) another very similar training session was undertaken by experts from Novartis Pharma AG, Swiss Tropical and Public Health Institute, IHI and TFDA. This training included more details and emphasis on expedited reporting and causality assessments.

A similar package of training materials was also provided to IHDSS field recorders individually in the field by the ALIVE safety coordinator. In addition, a retraining session was provided for IHDSS field recorders, again undertaken by IHI with materials developed jointly by the Swiss Tropical and Public Health Institute, the TFDA and Novartis. The session covered the definition of safety terms (AEs, ADRs and SAEs), explained the reporting forms, and described the reporting procedures.

5.2.4 Results

The first training session, in October 2007 was attended by 40 healthcare providers from health facilities in the study districts. The second training session was attended by 35 healthcare providers, of whom more than half had not attended the first training

course because they had recently been relocated from facilities outside the ALIVE study area or returned from college. Six IHDSS field recorders attended the IHDSS training session and all IHDSS field recorders received reporting materials.

Pharmacovigilance activity from 1st September 2007 to 31st March 2010 is described in the following sections. Within this period, 67 AEs were reported across the total patient population, of which seven were identified through Level I (passive surveillance), 59 through Level II (passive surveillance) and the remainder through Level III (active surveillance). Among the 59 AEs that were reported through Level II, nearly 24% were exposure to AL during pregnancy. Eleven exposures occurred during the second trimester and the remaining three occurred in the third trimester. One of the three AEs that took place in the third trimester was a stillbirth, which occurred four weeks after AL exposure during the 34th week of pregnancy with no suspected relationship with AL. The other exposures were not associated with any adverse pregnancy outcome. The reporting rate peaked shortly after the first training course, subsequently declining until after the second training course in April 2009 (Figure 3.5).

Of the 67 AEs reported, 52 occurred after AL therapy, five after SP, one after metakelfin, and another one after amodiaquine and paracetamol. Of the other AEs, one occurred after penicillin injection, two after paracetamol, four after ivermectin and one after administration of amoxicillin. During the same period (1st September 2007 to 31st March 2010), a total of 181,609 patients with suspected malaria reported to health facilities in the ALIVE study area and received AL as first-line treatment for malaria. The reporting rate of AL-associated AEs was therefore 28.6 per 100,000 AL-exposed patients. The AEs that were recorded after AL included vomiting (5 cases), itching and/or rash (21 cases); difficulty breathing, convulsion and headache occurred in 12 cases. The other 14 AEs recorded after AL administration, which occurred alone or in combination, were high fever (2), dyspnoea (2), fatigue (3), dizziness (2), paraplegia (1) and a swollen eyelid (1). Others were insomnia (1), stiffness of joints and neck (1) and dysuria (1). In all cases occurrences were reversible and regressed with malaria symptoms. The five AEs that occurred after SP were mild erythematic skin lesions that did not progress to Stevens-Johnson syndrome. The AEs seen following treatment with penicillin and amoxicillin were both rashes.

A total of 20 patients were reported who experienced SAEs during September 2007 to March 2010 (Table 4.5). In 16 cases, a relation to AL was suspected. All but two patients recovered; in the two cases where the patient died and the one in which a

stillbirth occurred, the SAE was not classified as having a suspected relation to AL. Of the 20 patients with SAEs, 6 cases were notified to the ALIVE safety database within 24 hours of occurrence. Twelve of these cases were detected at the health facilities and seven at home through IHDSS surveys (passive surveillance). Only one case was detected at home during the patient satisfaction/adherence survey (active surveillance) by a research field interviewer and was thus reported directly to the safety coordinator in Ifakara. Two patients died. One was a 4-year-old child who died in hospital on the third day after admission. The patient was diagnosed with malaria at a secondary health care facility and given two tablets of AL, then referred to the tertiary health care facility where severe malaria was diagnosed on the day of referral, together with symptoms of convulsion and cough. AL was stopped and the patient put on quinine injection. Two days later, the patient died in the hospital, with the verbal autopsy giving the cause of death as difficulty in breathing. The second death occurred in an infant of five months, who was initially treated with AL and amoxicillin at a secondary health care facility one day before death. On the next day the infant's condition deteriorated and AL discontinued, and the infant was then treated at the nearby primary health care facility as a case of severe malaria and pneumonia using quinine and penicillin injection. The patient was not referred to hospital on time and as a result died at home due to severe respiratory distress.

5.2.5 Discussion

Observational studies such as ALIVE offer the opportunity to obtain safety data on marketed drugs in settings that extend beyond the relatively small and selected populations that are assessed in randomized, controlled clinical trials. Undertaking a prospective observational study, however, requires careful consideration of how to meet the protocol-specified safety monitoring requirements of the relevant health authorities and the manufacturer. Particular challenges are faced in establishing pharmacovigilance monitoring in many rural areas of sub-Saharan Africa, where existing health services and patient access are often limited and often coupled with low awareness and motivation of healthcare staff about the need to report potential safety problems that occur during drug treatment.

The current paper describes how a training programme for healthcare personnel, accompanied by provision of training and reporting materials and the use of SMS text

alerts, was adopted to support the safety monitoring for a large-scale prospective observational study of the use of AL for uncomplicated *P. falciparum* malaria in a rural area of Tanzania. The benefits of training were demonstrated by the increased AE reporting rate observed after both initial and follow-up training sessions, and by the appropriate nature of the events reported and adequacy of data provided. The decline in reporting during the 18-month interval between the initial and follow-up training highlights the critical nature of repeated training and reminders. The upsurge in AE reporting and subsequent downturn eight months later is a significant cause for concern, especially for a programme that has to be incorporated into the routine health service delivery system. In particular, the type of training session conducted in this study may not be sustainable within the standard health service given the inherent costs and time burden for the already overstretched system. In the ALIVE study, however, this approach was adopted because there was no efficient and cheaper comparable alternative. The view of the authors is that pharmacovigilance reporting must be included in the curricula of medical schools and be part of the job description of health care workers. Where possible, it should be included in the health information management system in the set up of developing countries to maximize capture of AEs. This work provides a solid basis for a recently planned project to establish pharmacovigilance reporting in eight sites in Burkina Faso, Ghana, Mozambique and Tanzania: the INDEPTH Phase IV Safety and Effectiveness Studies Platform (INESS) .

For each AE reported, minimum reporting requirements were met, i.e. an identifiable reporter, an identifiable patient, a suspected product, and an AE. SAEs were reported in 20 patients, of whom five were given intravenous quinine after referral to tertiary health facilities and subsequently recovered, suggesting a missed diagnosis of complicated malaria for which AL was not the appropriate treatment (Bronzan, McMorrow et al. 2008). Rash, as reported here in 21 cases, is a recognized and frequent AE associated with artemesinin-based combination therapy (Lefevre, Looareesuwan et al. 2001; Falade, Makanga et al. 2005; Makanga, Premji et al. 2006; Ibrahium, Kheir et al. 2007). There were 14 cases of AL treatment reported in pregnant women during the period described. For the single case of stillbirth that occurred during AL exposure, medical records were sparse which made the cause of stillbirth difficult to establish. The mother may have been HIV-positive. In addition, she was given quinine at week 32 of pregnancy, followed four days later by vaginal bleeding and then stillbirth, suggesting that quinine may have played a causative role.

A markedly lower reporting rate is routinely observed in observational post-marketing studies that use passive pharmacovigilance monitoring (whereby AEs are only reported spontaneously by patients or carers to health professionals) compared to clinical trials in which data on AEs are collected actively, even in countries with well-established spontaneous reporting systems (Gough 2005; Hazell and Shakir 2006). In some sub-Saharan African countries, the challenge of capturing safety data may be even more profound: in a recent observational study of first-line AL use in rural Ethiopia, not a single AE was reported spontaneously over a two-year period despite over 200,000 individuals presenting with suspected malaria (Lemma, Byass et al.). Reporting rates of AEs in the ALIVE study – which mainly relied on passive pharmacovigilance – were higher than in the Ethiopian study; however, they were still low taking into account that over 180,000 AL treatments were administered during the observation period. This may be partly explained by the good overall safety profile of AL, with most of the AEs observed in clinical trials being related to malaria itself rather than to AL exposure (Makanga, Premji et al. 2006; Abdulla, Sagara et al. 2008). Most of the AEs occurring after AL exposure in the current study are similar in nature to those that were observed in the pre-registration clinical trials of the drug (Makanga, Premji et al. 2006; Mueller, van Vugt et al. 2006).

Most of the reports of AEs made under the ALIVE pharmacovigilance programme reported in this paper were captured through the passive surveillance route, but it should be borne in mind that passive pharmacovigilance systems have various limitations. Passive pharmacovigilance can be particularly challenging in poorly educated, remote communities some distance from the nearest health facility and with a low number of trained healthcare workers. These factors are likely to have been an important cause contributing to low reporting rates in this study as well. Other passive monitoring initiatives, such as the promotion of ‘yellow cards’ in a rural area of Mozambique (Sevene, Mariano et al. 2008) and a malaria pharmacovigilance programme in South Africa (Mehta, Durrheim et al. 2007) have also shown low reporting rates (of ADRs), underscoring the challenge of effective safety data collection during anti-malarial therapy in Africa outside the context of clinical trials.

The use of active surveillance, with prospective follow-up of the treated population, is ideal but unrealistic on a large scale due to cost and manpower requirements. In this study, however, active surveillance was applied only during a survey that investigated the feasibility and acceptability of AL during March-April 2008. The depth of information

that was obtained during the survey may not be representative of standard pharmacovigilance reporting as considered in this article, due to the short duration of the survey. Notably, the aim of the ALIVE feasibility study was primarily to assess the adherence to and acceptability of AL, and results showed that patients believed AL to be a good drug (Kabanywanyi, Lengeler et al.). This could have biased their judgment such that they did not report minor AEs that might have occurred because this conflicted with their belief that the drug was excellent. Using passive reporting it has been suggested that reporting rates could be improved by providing non-financial incentives to community members and healthcare workers and ensuring confidentiality (Bukirwa, Nayiga et al. 2008). It has also been proposed that the lack of local expertise in pharmacovigilance could be tackled through developing exchange programmes with the major drug regulatory agencies and sharing of best practice, with the long-term goal that each country should establish its own national pharmacovigilance system that would contribute to a global database such as that held by the Uppsala Monitoring Centre (Pirmohamed, Atuah et al. 2007).

The pharmacovigilance monitoring established for this study had the advantage of being a joint initiative between the investigators, the relevant drug regulatory authority and the sponsor (here, as in many instances, the drug manufacturer) – an approach which has recently been advocated (Pirmohamed, Atuah et al. 2007; Bukirwa, Nayiga et al. 2008). This resulted in a valuable combination of local knowledge, utilization of an existing healthcare and technical infrastructure, regulatory skills, funding, and experience of safety monitoring and data management. Additionally, training and the provision of materials spanned all levels of healthcare personnel although the decline in AE reporting during the 18-month delay between initial training and follow-up training may indicate that more frequent repetition of training, with regular reminders, could have increased the number of events reported. Prompt training of new healthcare staff would also be beneficial. Lastly, use of SMS texts to notify the ALIVE safety database coordinator at the time an AE was identified ensured prompt data capture and guaranteed that the event would not be lost during its progress through the subsequent reporting channels.

In the ALIVE pharmacovigilance system reported here, it was observed that most AEs resolved in parallel with improvement in the treated clinical malaria. However, the relatively short half-life of artemether indicates that if an AE were related to the drug, drug clearance would have coincided with clearance of parasites (and host-response

inflammatory markers) (Ezzet, Mull et al. 1998; Djimde and Lefevre 2009). Lumefantrine, in contrast, has an extended half-life of approximately 33 hours (White, van Vugt et al. 1999). Because this study included neither measurement of artemether or lumefantrine plasma concentration nor ascertainment of parasitaemia at recovery, it is likely that these AEs were related to malaria but the contribution of treatment cannot be excluded.

In conclusion, this article presents a practical model for pharmacovigilance monitoring during a prospective observational study that is applicable for rural community settings in sub-Saharan Africa or other developing regions. Training of healthcare workers at all levels to support protocol-mandated safety monitoring requirements was straightforward to undertake and showed a positive impact on the identification and safety reporting, but more frequent refresher courses and reminders are required to optimize and sustain reporting levels over time. Use of SMS texts is a pragmatic solution to communication challenges and helps to avoid lost or delayed reports. Finally, a collaborative approach involving all major participants – investigators, sponsor and regulatory authorities – from the outset offers a valuable template for future studies and facilitates sensitization of healthcare workers to the need for safety reporting. It is the authors' view that these strategies could support the achievement of safety monitoring requirements during an observational study. Moreover, they could contribute to improvements in ongoing spontaneous reporting of AEs to health authorities, marketing authorization holders and the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre) (WHO) in regions with limited experience of pharmacovigilance monitoring and in which local resources are restricted.

Conflicts of interest

BG and AMK have received honoraria and travel grants from Novartis Pharma to present study findings at various international conferences. RS and NM are employees of Novartis. CM is an employee of the Tanzania Food and Drugs Authority. CL and AM have no conflicts of interests. A medical writer assisted with editing of a draft manuscript prepared by AMK.

Authors' contributions

AMK contributed to study design, was a study investigator and drafted the manuscript for input by the other authors. NM acted as the safety reporting advisor to the project and facilitated the training of safety reporting staff. CM provided input and advice from the TFDA and acted as focal person for communication between the TFDA and the project. AM undertook data collection and facilitated the training of safety reporting staff. RS contributed to study design and provided input to the manuscript. CL participated in data interpretation and provided input to the manuscript. BG contributed to study design, facilitated the training of safety reporting staff and contributed to the writing of the manuscript.
All authors read and approved the final manuscript.

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Figure 1.5: Reporting channels for adverse events (AE).

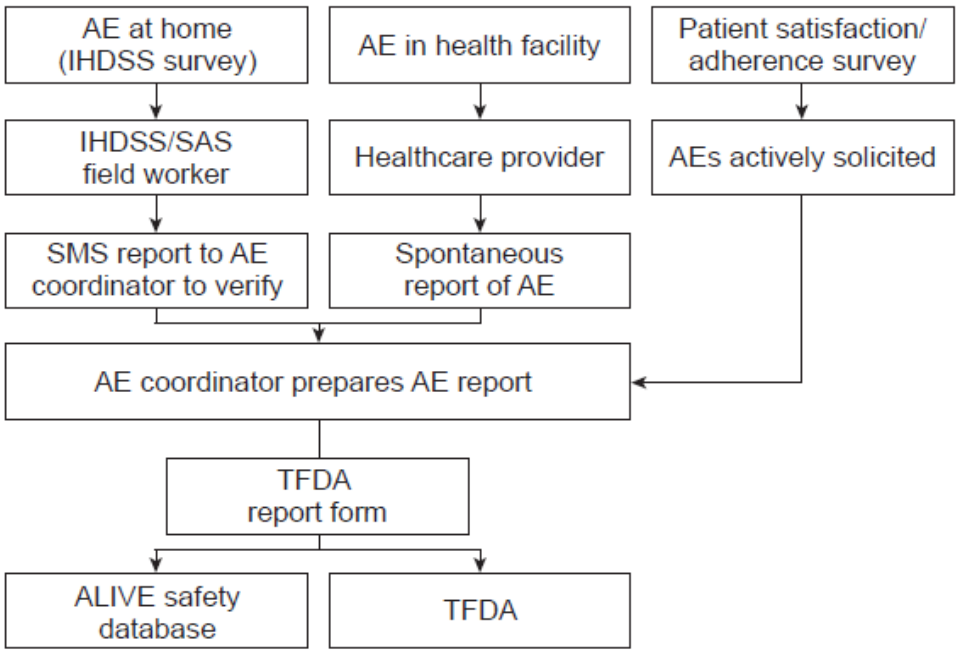

Figure legend: IHDSS, Ifakara Health Demographic Surveillance System; TFDA, Tanzanian Food and Drugs Authority; HH, Household; HF, Health Facility; SAS, Satisfaction/Adherence Survey

Figure 2.5: Reporting channels for serious adverse events (SAE).

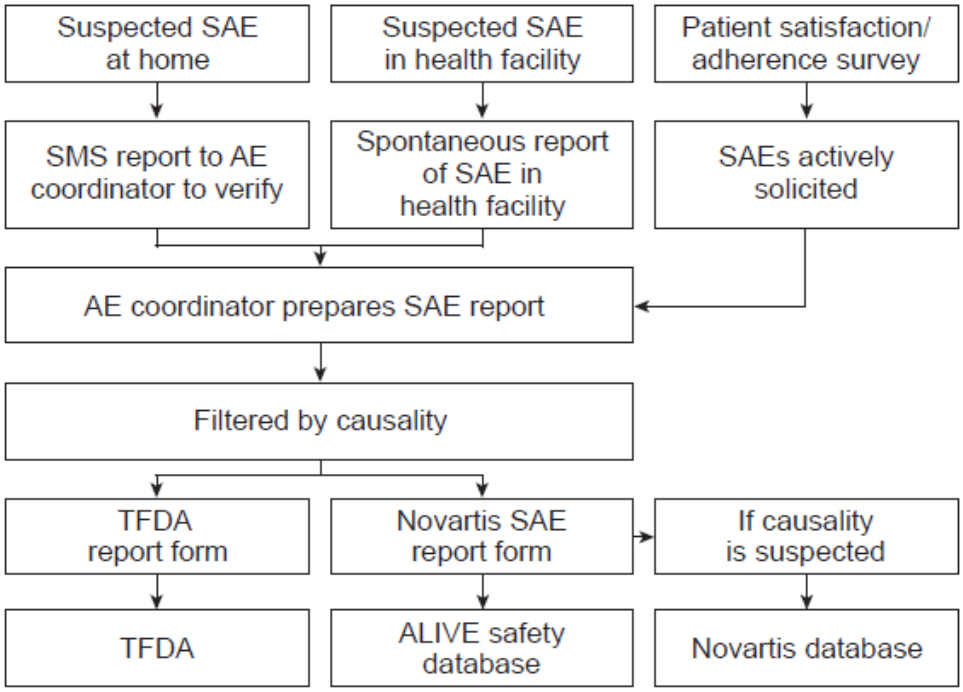

Figure legend: IHDSS, Ifakara Health Demographic Surveillance System; TFDA, Tanzanian Food and Drugs Authority; HH, Household; HF, Health Facility; SAS, Satisfaction/Adherence Survey

Figure 3.5: Number of adverse events (AEs) reported per month during 1st September 2007 to 31st March 2010.

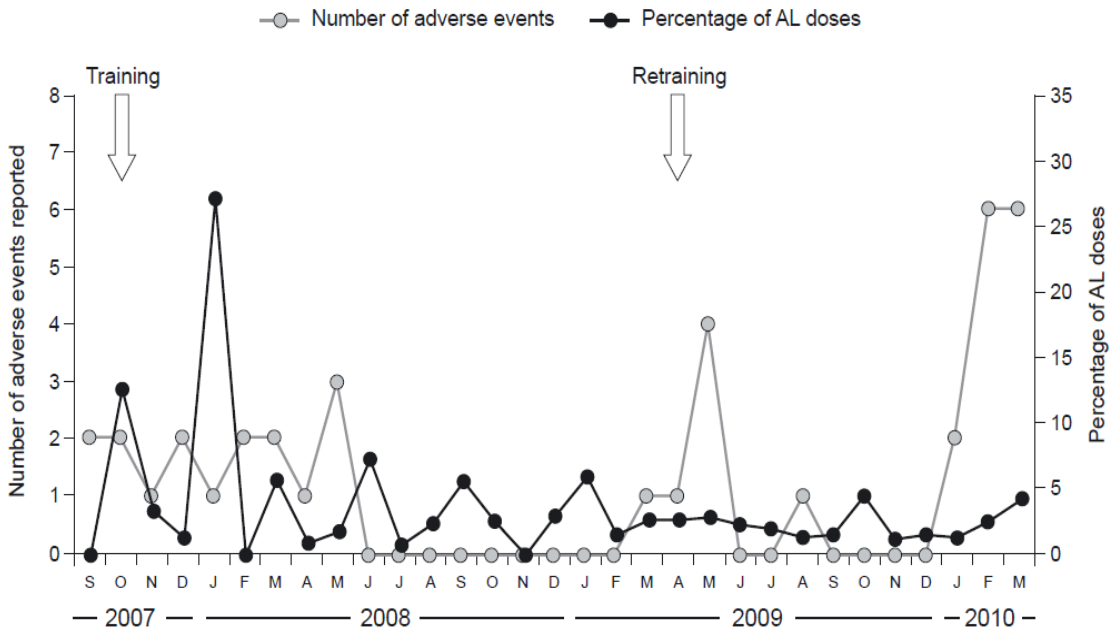

Figure legend: From 1st September 2007 to 31st March 2010 indicated on the left-hand y-axis. The right-hand y-axis indicates the percentage of AL tablets prescribed per month, with the total number of AL tablets during 1st September 2007 to 31st March 2010 as the denominator.

Table 3.5: Content of training programme for healthcare workers at health facilities

Topic	Content
Study drug (AL)	Indications and dosage Contraindications Drug interactions Use in pregnancy/lactation Common ADRs (frequency >10%) Special precautions
Study objectives	Primary and secondary objectives of the observational study (ALIVE)
ADRs, AEs & SAEs	Minimum reporting requirements Definitions of ADRs, AEs & SAEs (including congenital abnormalities & birth defects) Detection and recognition of ADRs, AEs & SAEs
Reporting of AEs & SAEs	Data collection requirements TFDA reporting form Novartis SAE reporting form

Table legend: ADR = adverse drug reaction; AE = adverse event; AL = artemether-lumefantrine; ALIVE=**A**rtemether-**L**umefantrine **I**n **V**ulnerable patients: **E**xploring health impact; SAE = serious adverse event; TFDA = Tanzanian Food and Drugs Authority. ADRs were defined as 'all noxious and unintended responses to a medicinal product related to any dose. The responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility i.e. the relationship cannot be ruled out'

Table 4.5: Patient characteristics, type, timing and outcomes of serious adverse events (SAEs) reported during 1st September 2007 to 31st March 2010.

Sex	Age (years)	SAE[a]	Interval between event and recording	Outcome	Level of reporting
Female	37	Severe headache & vomiting	1 days	Recovered	II
Female	12	Dyspnoea & vomiting	1 day	Recovered	II
Male	2	Twitching	1 days	Recovered	II
Female	4	Severe vomiting	4 days	Recovered	II
Female	2	Generalized itching/rash[b]	>60 days [a]	Recovered	II
Female	1	Respiratory distress	3 days	Died; not classified as suspected in Novartis safety database	III
Female	4	Convulsion	9 days	Died; not classified as suspected in Novartis safety database	II
Female	46	Dyspnoea	1 day	Recovered	II
Male	38	Generalized rash[b]	7 days	Recovered	II
Female	47	Generalized rash[b]	1 day	Recovered	II
Male	13	Dyspnoea & swollen eyelids	1 day	Recovered	II
Male	7 months	Skin rashes	20 days	Recovered	I
Female	17	Paraplegia	>60 days	Recovered	I
Female	5	Joint stiffness	>60 days	Recovered	I
Male	10	Dizziness & headache	30 days	Recovered	I
Female	32	Skin rashes & amnesia	>60 days	Recovered	I
Female	11	Skin rashes	60 days	Recovered	I

Male	7	Skin rashes	60 days	Recovered	I
Female	47	Skin Rashes	10 days	Recovered	II
Female	34 weeks (gestational age)	Stillbirth	>60 days	Stillbirth; not classified as suspected in Novartis safety database	II

All events were recorded following AL treatment and were classified as SAEs by presenting with any or all of the following: (a) fatal or life-threatening (b) prolonging hospitalization (c) resulting in persistent or significant disability/incapacity (d) may jeopardize the subject or (e) may require medical or surgical intervention to prevent one of the previous outcomes.

[a] Report was initially misplaced at the health facility and not made available to safety coordinator on time

[b] Skin depigmentation for an extended period, which was considered to constitute significant incapacity

Level of reporting: Level I, IHDSS; Level II, health facilities; Level III, patient satisfaction/adherence survey

PART VI: IMPACT OF ANTI-MALARIAL FIRST LINE POLICY ON MALARIA TRANSMISSION AND UNDERFIVE MORTALITY IN TWO RURAL DISTRICTS OF TANZANIA-

A working paper

CHAPTER 6: Impact of artemther-lumefantrine as first line policy on malaria transmission and under five mortality in a rural area with high ITN coverage in Tanzania

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6.1.1 Summary

Introduction. Wide use of artemisinin-based combination therapy (ACT) in addition to other vector control measures is recommended in the fight against malaria. To date, there is scanty evidence on the contribution of ACT to reduce malaria transmission and overall U5 mortality in most endemic settings. Little has been documented on the effect of artemether-lumefantrine (AL) on malaria prevalence and there is no direct evidence that ACTs reduce mortality in Africa.

As part of the ALIVE [Artemether-Lumefantrine In Vulnerable patients: Exploring health Impact] project, we assessed the impact of the introduction of AL as first line treatment for uncomplicated malaria on parasite prevalence, anaemia and under five mortality in rural Tanzania.

Methods. Parasite and anaemia prevalence were obtained by repeated cross-sectional surveys conducted in two rural districts (Kilombero and Ulanga) in Tanzania during the period when the national first line anti-malarial therapy was sulfadoxine-pyrimethamine (SP) (2005 & 2006), and when it was AL (2008, 2009 and 2010). Mortality rates were obtained using a Demographic Surveillance System (DSS) that covers a dynamic expanding population of about 90,000 in both districts. Changes in mortality rates of children under five years were compared between both anti-malarial first line policy periods. The contributions of key interventions to control malaria introduced in the region were adjusted using Poisson regression model.

Results. A total of 26,396 persons were assessed during annual surveys in 2004, 2005, 2006, 2008 and 2009. On average the under five children that participated in the survey were always nearly 22% of the total population. Asymptomatic parasite prevalence in the whole population was 25% in 2004, 11.4%in 2005, 13.6% in 2006, 11.0% in 2008, and 4.6% in 2009. The coverage of any net was kept at above 91% throughout the period. The mean U5 child mortality over the period was 21.9 (95%; 20.9 to 22.9). Under five mortality rate per 1000 person-years decreased by 33% from baseline in 2005 compared to 2009. ITNs were associated with reduction in community parasitaemia. For every 10% increases in ITNs coverage, there was nearly a 48% reduction in the annual community parasitaemia [IRR=0.52; 95% CI=0.38 to 0.73]. ACT was responsible for 11% annual decrease in under five mortality when adjusted for other key factors IRR= 0.89; 95% CI=0.79 to 1.0). Food security was the only other main contributor of malaria decrease over the studied period. One unit (tone of rice/ha) annual increase in food security, notably the rice yields, was responsible for nearly 36% reduction in annual under five child mortality (IRR=0.64; 95% CI=0.54 to 0.75).

Discussion. After 3 years of ACT implementation wit AL in Tanzania, there was a considerable decline in child mortality and parasite prevalence but no change in anaemia prevalence. ACT contributed to this change but to a lesser extent than ITNs and contextual factors such as food security. High coverage of ITNs has shown an impact on community parasitaemia.

Conclusion. Timely change of anti-malarial first line policy with efficacious ACT in areas with high coverage of malaria vector control programmes is an impetus to key malaria elimination milestone. In the period when malaria elimination/eradication will be attained, food security in rural community will be key to sustain a healthy malaria free under five children who initially were vulnerable to fatal malaria.

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6.1.2 Introduction

Deployment of highly efficacious anti-malaria drugs such as artemisinin-based combination therapy (ACT) and other malaria control measures have the potential to reduce malaria transmission and the overall U5 mortality. In addition to their potential to cure asexual *P.* f*alciparum* parasite, ACTs have also unique advantage of reducing malaria transmission by suppressing sexual parasites carriage rates (Barnes, Durrheim et al. 2005). Evidence from South-East Asia indicated that ACTs reduce malaria transmission by curbing the number of gametocytes in the person with the disease. On the north-western border of Thailand for instance, there was a 47 per cent reduction in the incidence of *P. falciparum* infections one year after the use of ACTs containing artesunate and mefloquine. There was a further improvement of a six fold reduction in malaria transmission(Barnes and Abdulla 2005).

In sub-Saharan Africa previous efforts to control malaria have proved less successful mostly due to long use of poorly efficacious drugs which *P.falciparum* has manifested drug resistance. In most part of malaria endemic regions chloroquine (CQ) was found poorly effective for several decades but it was still being prescribed until most recently. In Tanzania for instance P.f*alciparum* was already resistant to chloroquine in more than 60% of all P*. falciparum* positive patients in the late 80ies (Hatz, Abdulla et al. 1998)and was replaced by sulfadoxine-pyrimethamine (SP) only in 2001 after demonstrating consistent high failure rates (Mutabingwa, Maxwell et al. 2001; Mugittu,

Abdulla et al. 2005). Elsewhere in sub-Saharan Africa in Zambia for instance, during the same period it was recorded that the day 28 chloroquine failure rates were already at 40% (Barat, Himonga et al. 1998). SP is anti-folate sulfa based anti-malaria drug that was adopted as an interim first line policy by many malaria endemic countries as there was no cheap immediate alternative to CQ.

The emergence and rapid spread of resistance to most ant malarial drugs including SP over the past few years has led to the intensification of search for new efficacious anti-malarial alternatives (Mugittu, Ndejembi et al. 2004). These efforts went parallel with global initiatives to combat malaria illness. In the 90s the World Health Organization (WHO) launched a Roll Back malaria campaign that advocated the use of more efficacious anti-malaria as one of the intervention tool. Despite the urgency call from this initiative there were few countries in malaria endemic region that were willing to adopt new anti-malaria policy with the use highly efficacious combination therapies such as ACTs due to overwhelming high cost imposed by ACT (Mutabingwa 2005). Until after 2004 nearly all malaria endemic countries were still using either SP or CQ in their first line Anti-malarial policies. The year 2004 became the turning point resulting in many endemic countries changing their policy to ACT thanks to the advocacy by prominent scientists and to the launch of initiatives such as the Global Fund for AIDS Tuberculosis and Malaria, ACT became available as fixed-dose at cheap price. Beginning of current decade many global health partners such as Global Malaria Initiatives (GMP), Medicine for Malaria Venture (MMV) and others have joined forces to new initiatives on fight against malaria illness. Thanks to increasing commitments and funding from global health partners and further availability of new fixed-dose ACT by 2009, nearly 77 of 81 *P. falciparum* malaria-endemic countries and territories had adopted ACTs for use in their national drug policies (WHO 2009). At present for instance WHO is monitoring the global supply of and demand for the ACT fixed-dose and to date artemether-lumefantrine (AL) fixed-dose combination as part of the requirements of the Memorandum of Understanding signed with the manufacturer, Novartis Pharma AG, Basel Switzerland, in 2001, to make Coartem® available at cost price for distribution in the public sector of malaria-endemic developing countries. It is through these initiatives that AL has reached more than 78 million treatment courses in 2008 (WHO 2009). These initiatives and the recently new others like Affordable Medicines Facilities for Malaria (AMFm) will be key especially in the malaria elimination phase.

The other mainstay tool to fight against malaria is insecticide treated mosquito bed nets (ITN). This tool has not only shown a directly effect on the individuals using ITN but

also on the community at large when high coverage is achieved in that community (Binka, Hodgson et al. 2002; Binka and Akweongo 2006). By the year 2008 nearly 31% of African household was estimated to own at least one ITN or one long lasting insecticidal treated Mosquito net (LLITN). More children aged less than 5 years were also sleeping under ITN on average of 24% in 2008 as compared to 17% in the previous 2 years. In several countries in the African region where high coverage of ITNs has been achieved, Tanzania included, a fall of malaria cases and deaths by more than 50% have been reported. In some malaria endemic countries and territories such as Zambia, South Africa and Zanzibar a territory in United republic of Tanzania the uptake of indoor residual spraying (IRS) of mosquito insecticides has gained significant coverage as compared to other nations. Such developments are encouraged and may suggest that overall attainment of initiatives such as Millennium Development Goals 4 & 6 (MDG) to reduce child mortality by two third ahead of the target time i.e., 2015 and combat malaria and other infectious diseases are possible (Barnes, Chanda et al. 2009; WHO 2009).

Deployment of combined strategies such as ACT with vector control measures such as ITN and IRS is an important strategy to reduce malaria transmission and overall under five mortality (WHO 2009). To date most malaria endemic countries have realised the need to implement a combination of all available strategies to combat malaria as recommended by global health authorities. As part of the ALIVE [Artemether-Lumefantrine In Vulnerable patients: Exploring health Impact] project, we assessed the impact of the introduction of AL as first line treatment for uncomplicated malaria on parasite prevalence, anaemia and under five mortality in a malaria endemic region in rural Tanzania where ITN coverage was already high before implementation of ACT. This paper presents dynamic changes in uptake of several interventions aimed to address the burden of malaria and trends in achievements recorded over time in reduction of malaria transmission and overall under five mortality in the years before (SP era) and after ACT implementation (AL era).

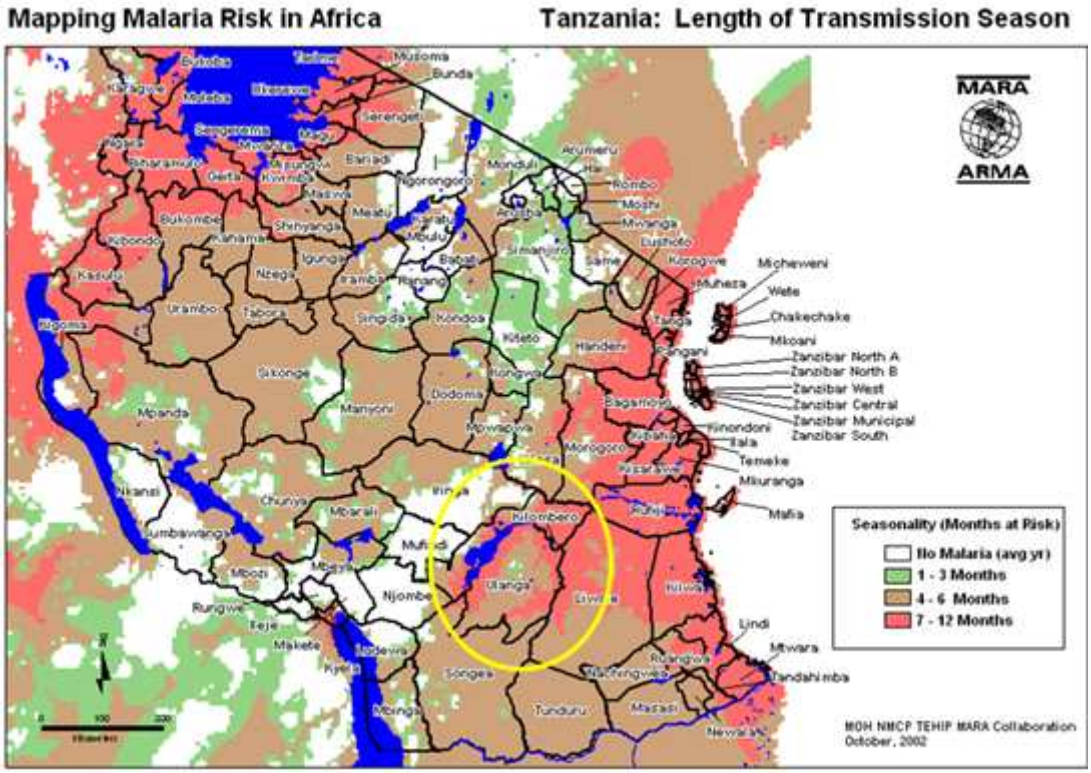
6.1.3 Methodology

The study site for the impact assessment of the introduction of ACT in Tanzania is a rural area in South-Eastern Tanzania in the Kilombero river valley where two rural administrative districts lie side by side. Malaria transmission is intense and perennial in both districts. There are two main rainy seasons, October-December the short rainy season and February May the long rainy season. The area is inhabited by a mix of

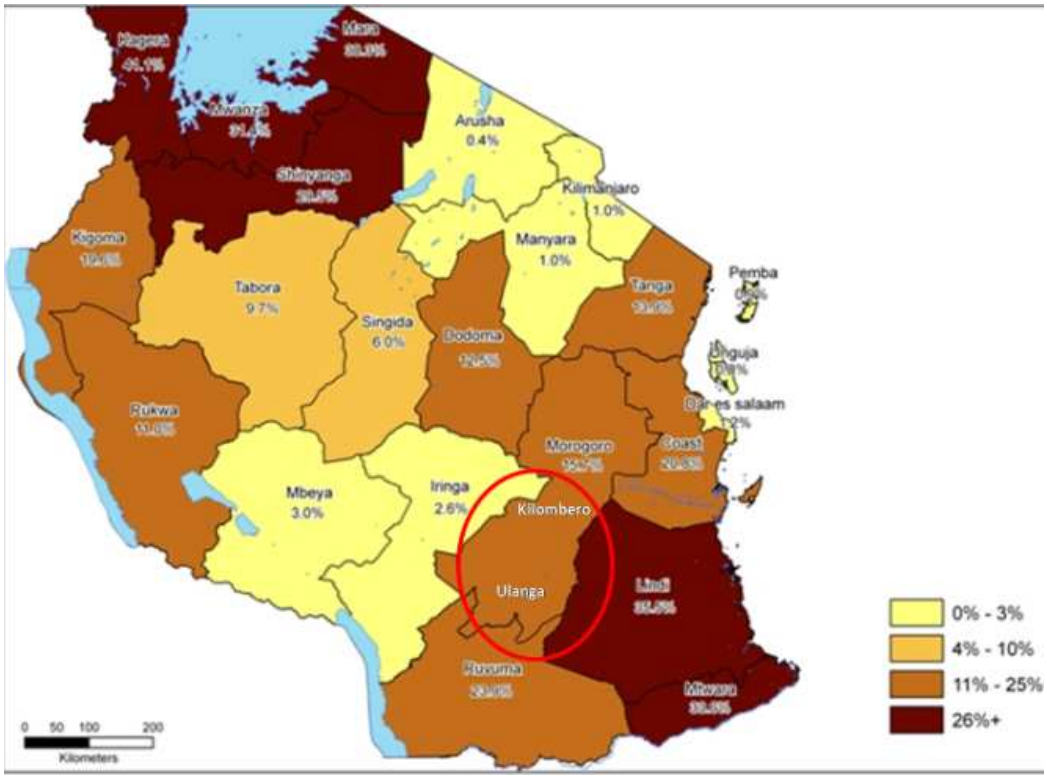
mainly indigenous subsistent farmers and few recently immigrated pastoralists communities from the North of the country. Farming is set at a more distance from family homestead in the race farming fields of the Kilombero river bank plains traditionally know as *Shamba.* These satellite farming fields are characteristic to malaria transmission as majority of individuals normally live in semi constructed huts during farming activities periods that includes; cultivation, weeding and harvesting periods at the peak of malaria transmission. This area is characterized by malaria and waterborne diseases such as cholera and diarrhea. This area was chosen for it its potential of hosting a longitudinal population based demographic surveillance system (DSS) that monitors vital demographic parameters such as in and out-migration, pregnancies and deliveries, births and deaths and special household surveys that record malariariometric indicators and morbidity. This system was launched in 1996 and operates in two districts Kilombero and Ulanga and covers nearly 18000 households and a population of about 95000 individuals (Schellenberg, Abdulla et al. 1999; Armstrong Schellenberg, Bryce et al. 2004). This area was chosen also due to its potential to host key efficacious anti-malarial interventions and implementation programmes that ranged from health system support to social marketing of key malaria interventions for nearly 14 years back. At the beginning of ALIVE in 2007 there was no action plan in the region to implement other vector control strategy such as IRS and others alike.

Figure 4.6: Maps of Tanzania depicting malaria risk: (a) before and (b) after the introduction of ACT. ALIVE study area is circled in a marked selection on both maps. (a) Before ACT introduction

(a) Before ACT introduction

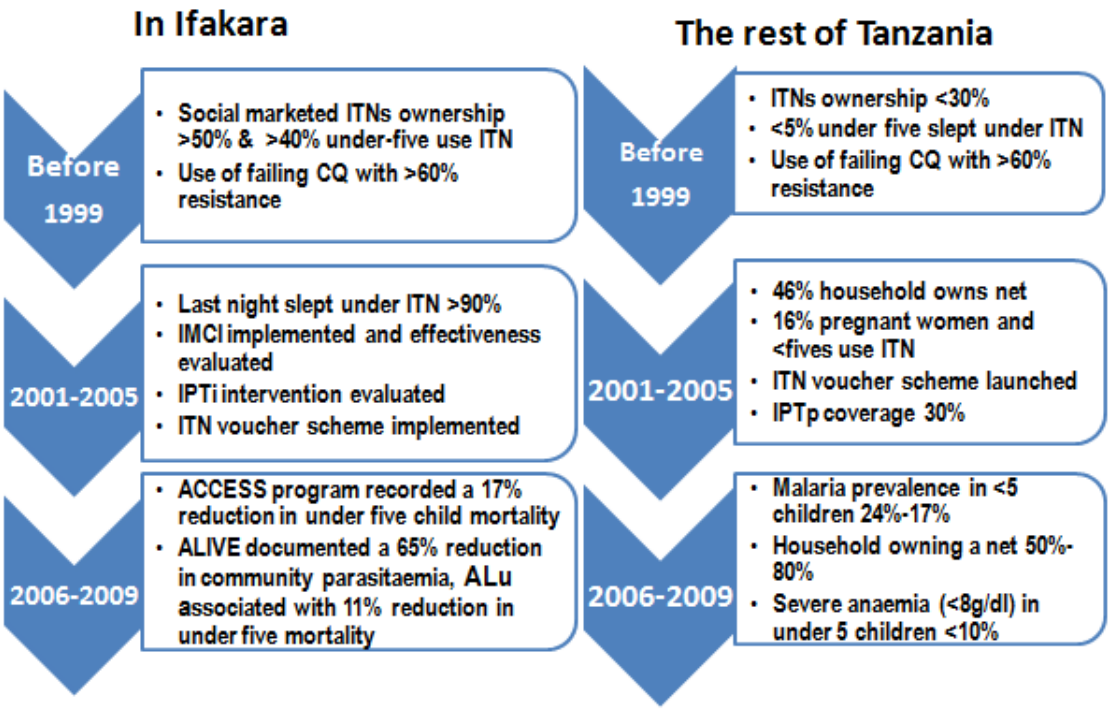


(b) After ACT introduction



Indeed several malaria intervention programmes have been implemented in the region starting of late 1990s. These programmes include; the integrated management of child illness (IMCI) that introduced a set of guidelines for management of sick children seen at primary health care facilities beginning of 2002 (Armstrong Schellenberg, Bryce et al. 2004). In 1997 to 1999 a project that socially-marketed subsidized Insecticide Treated Mosquito bed-nets in K/U Districts (KINET) was implemented (Schellenberg, Abdulla et al. 1999). The ITN model has been up-scaled nationwide in the programme named after-TNVS (Tanzania National Voucher Scheme). Another intervention that has been implemented in the region which anchors its activities to the IHDSS is ACCES programme. A schematic diagram in included in (figure 5.6) below that shows timeframe of these interventions.

Figure 5.6: Schematic representation of malaria interventions in Ifakara region and Tanzania with their medium term effects.



Study design

The ALIVE project was initiated to evaluate the impact of implementing AL as first-line malaria treatment in a rural, malaria-endemic region of the country. ALIVE is a prospective, observational, community-based, longitudinal, demographic surveillance study in adults and children, undertaken to assess the impact of AL on malaria morbidity, transmission and mortality in a rural, malaria-endemic area of Tanzania when used as first-line treatment for uncomplicated malaria. The primary objective of the study was to assess the effect of AL introduction on all-cause mortality in children aged <5 years old compared to historical data when SP was used. Secondary objectives include the assessment of overall and malaria-related health facility attendance rate in children and in adults. This study also provided a framework for assessment of patient satisfaction, adherence to the AL regimen in both children and adults using a structured questionnaire with AL safety monitoring indicators. This study relied on a before and after design covering a period of three years during SP use (2004-6) and three years of AL use (2008-2010) as first line national policy. The present paper presents results on data collected up until end of 2009.

Ascertainment of mortality

The Ifakara health demographic surveillance system (IHDSS) operates all year around whereas field based recorders operate at a house level by registering all vital demographic parameters; death, births, migration and pregnancy. Special questions are introduced that interviewers administer routinely as per research need quarterly in planned surveys to a sample of household in each round. Alongside field based IHDSS interviewers the system has identified in each hamlet a reporter who is a member of that particular hamlet to initially make an enquiry about each death that took place in the hamlet to the field based reporters. Hamlet reporters are vital to maximize the capture of all events and therefore a modest payment is made on monthly bases for every event reported. Based on this initial report, a list of deceased individual that contains name, date of birth, sex and date of death is populated in the Ifakara database and a printout is made available monthly to field based reporters to facilitate a full verbal autopsy interview with bereaved family members.

Verbal autopsy interviews are scheduled at least 40 days later after the death and this period is considered minimum for the traditional mourning period. Most preferred respondents are family member who taken care the deceased during terminal period. Verbal autopsy is adopted as the simplest cause of death ascertainment in the INDEPTH network (INDEPTH 2010) where vital registration system is not in place. This process involved IHI DSS interviewers who interviewed close relatives of the deceased using a structured questionnaire that was adopted from. In the questionnaire account of sequelaes and events that led to deaths were recorded. All causes of deaths were collated to a large database where the final diagnosis of the cause is arrived after three physicians' panel that review the codes of disease adopted from the international classification of Disease and related health problems. For each death, at least two clinicians independently assigned a primary or underlying morbidity that resulted to death. In case of discordant results a third physician was asked to code the cause of death independently. In the event that there is discordant from three physicians the cause was then assigned an undetermined cause. These codes are then compared using a custom written programme in FoxPro [Visual Studio FoxPro Inc, Microsoft Cooperation, and California USA]

An annual cross-sectional survey to measure parasite prevalence in the whole population and anaemia (haemoglobin<5 g/dl) in children under five years was conducted among all consenting members of a random sample of 2000 households in

2008, 2009 and 2010, approximately 18 months, 30 and 42 months after countrywide AL introduction. These surveys always were being conducted at the same time point every year during May-September at the end of long seasonal rainfalls that correspond to a peak of malaria transmission. A questionnaire with information on fever in the past two weeks and health care seeking attempts, ITN ownership and use IPTp in pregnancy was applied. A drop of blood from a finger prick was collected on Hemacue cuvettes and examined for anaemia only in children less than 5 years old using Hemacue® machine (Angelhom Sweden). Thick blood smear on a glass slide was investigated for the presence of parasite by specialized microscopist from IHI and rapid diagnostic test for malaria (RDT) was used to confirm malaria infection that was diagnosed by microscope on blood slide from all household members. When the RDT was positive, a treatment of AL was offered on the spot. Results from these three surveys were compared with those obtained during the SP era 2004, 2005 and 2006 when SP was used as nation first line anti-malarial.

Data management and analysis

Data management was made on a tailor-made Visual FoxPro 7 (Microsoft Corporation, Redmond USA 2001) at Ifakara Health Institute (IHI). Data analysis was performed using Intercooler STATA® statistical analysis software package Stata (Stata corporation intercooled version 11, Collage Station TX, USA, 2007)

Descriptive analysis was done to quantify reported fever in the past two weeks, prevalence of community parasitaemia anaemia in children and ownership of ITN. Under five (infant and <5 years) mortality was calculated as rates per 1000 person-years of exposure. The effect of first line anti-malaria drug policy on malaria parasitaemia and under-five children mortality was assessed separately by Poisson models. Key factors such as ITN ownership, mean annual rainfall, agricultural yields were independent variables that were used in univariate analysis to explore the association with mortality and parasitaemia. For the year 2007 in which no survey was conducted estimates from preceding year was inferred to represent values for 2007. For multivariate Poisson model, we fitted two models: one with parasitaemia as dependent (intermediate predictor of mortality), the second with mortality rate as dependent parameter. All factors were included into the models using a backward stepwise removal for predictors that exceeded 15% point of significance. We considered food yields as a proxy of food security to represent malnutrition in place of food shortage. Anti-malarial policy was dichotomized as 0 values to present a period with SP as first line in 2004-2006 and 1 represented first line as AL in 2007 to 2010.

6.1.4 Results

A total of 26,396 persons were assessed during annual surveys in 2004, 2005, 2006, 2008 and 2009. On average the under five children that participated in the survey were always nearly 22% of the total population. Asymptomatic parasite prevalence in the whole population was 25% (95% CI; 22.3 to 27.7) in 2004, 11.4% (CI; 8.4 to 13.7) in 2005, 13.6% (CI; 11.1 to 16.3) in 2006, 11.0% (CI; 8.4 to 14.1) in 2008, and 4.6% (CI; 2.7 to 7.5) in 2009. The coverage of any net was kept at above 91% throughout the period. Details of six years surveys are presented on table 5.6. The mean U5 child mortality rate per 1000 person-years over the period was 21.9 (95%; 20.9 to 22.9). Table 6.6 and figure 6.6 presents mortality profile going back to 1997.

After 3 years of AL implementation, there was a considerable decline in parasite prevalence but no change in anaemia prevalence. Figure 7.6 represents prevalence of anaemia in children less than five years during the evaluation period. On average gametocyte carriage rate has remained < 1% throughout the period. Mortality in children <5 years decreased with maintenance of a downturn trend that was sustained from preceding periods. In the Poisson univariate analysis, malaria interventions that were found to be independently associated with community parasitaemia hence under five child mortality was coverage of ITNs and use of ACT. Food security and rainfall were the only contextual (non-intervention) factor that showed a strong relationship with decrease in parasite prevalence as well as a downturn in under five child mortality. In a multivariate analysis of all interventions with community parasitaemia, ITNs was the only intervention that was associated with parasitaemia. For every 10% increases in ITNs coverage, there was nearly a 48% reduction in the annual community parasitaemia [IRR=0.52; 95% CI=0.38 to 0.73]. Table 7.6 shows results from the univariate and multivariate Poisson model on parasitaemia and table 8.6 on U5 child mortality. In the multivariate analysis between U5 child mortality and all other factors rice yields and ACT were the only factors that were associated with decrease in mortality. ACT was responsible for nearly 11% annual decreases in under five mortality when adjusted for contextual factors [IRR= 0.89; 95% CI=0.79 to 1.0]. A unit annual increase in food security; notably the rice yields was also responsible for nearly 36% reduction in annual under five child mortality [IRR=0.64; 95% CI=0.54 to 0.75.

Table 5.6: Characteristics of surveyed individuals and contextual factors in the ALIVE surveys (2008 &2009) as compared to IMPACT surveys in (2004-2006).

	2004 (N=4,044) n (%)	2005 (N=4,902) n (%)	2006 (N=5,223) n (%)	2008 (N=4773) n (%)	2009 (N=7454) n (%)
Median age in yrs (interquartile range)	15 (5-35)	15 (5-33)	15 (6-34)	15 (5-33)	12 (5-29)
Age groups					
<1 year old	156 (4%)	207 (4%)	163 (3%)	41(1%)	51 (1%)
1-4 years old	652 (16%)	820 (17%)	781 (15%)	963 (20%)	1,777 (23%)
5-15 years old	1201 (30%)	1473 (30%)	1629 (31%)	1429 (30%)	2,409 (33%)
>15 years old	2035 (50%)	2402 (49%)	2618 (50%)	2338 (49%)	3208 (43%)
Bed-net use previous night					
Used untreated net	(91%)	(92%)	(92%)	(91%)	(92%)
Uses insecticide treated net	(26%)	(34%)	(36%)	(44%)	(47%)
Use of other anti-malarial					
Mean annual rice yields (tone/h)	1.9	1.9	1.9	2.5	2.5
Mean annual rainfall (in mm)	1520.1	1287.1	1611.1	1556.7	2401.5
Malaria burden [n]	[4044]	[4902]	[5223]	[4533]	[7401]
Asexual parasitaemia	1013 (25%)	559 (11%)	698 (13%)	506 (11.1%)	341 (4.6%)
Gametocytemia	73 (2%)	14 (<1%)	25 (<1%)	11(0.24%)	53(0.43%)

Table 6.6: Under five mortality case, rates and computed persons years (pyr)

Year	Deaths	pyrs	Annual rate
1997	284	8.95149	31.72655
1998	249	8.87911	28.04333
1999	246	8.67338	28.36264
2000	298	10.07777	29.57003
2001	284	11.26623	25.20807
2002	345	11.96768	28.82764
2003	392	12.16668	32.21913
2004	307	12.59317	24.37829
2005	346	12.82348	26.98177
2006	318	13.73179	23.15794
2007	325	14.65734	22.17319
2008	299	15.79292	18.93254
2009	297	16.6297	17.8597

Table 7.6: Effect of malaria control interventions and other key factors on malaria prevalence as determined from Poisson regression model between years (2004-2009)

Attributes	Univariate model IRR (95% CI)	p-value	Multivariate model IRR (95% CI)	p-value
1st Line anti-malaria policy				
SP (2004-2006)	1			
ALu (2007-2009)	0.56 (0.36; 0.89)	0.015		
ITN ownership (10% rise in coverage)	0.52 (0.38; 0.73)	<0.001	0.52 (0.38; 0.73)	<0.000
Contextual factors				
Rice yields (tone/ha)	0.27 (0.11; 0.71)	<0.001		
Rainfall (total annual rainfall in mm)	0.98 (0.91; 1.05)	0.505		

Table 8.6: Effect of malaria control interventions and other key factors on annual under five child mortality as determined from Poisson regression model between years (2004-2009)

Attributes	Univariate model IRR (95% CI)	p-value	Multivariate model IRR (95% CI)	p-value
1st Line anti-malaria policy				
SP (2004-2006)	1			
ALu (2007-2009)	10.79 (0.72; 0.86)	<0.001	0.89 (0.79; 1.0)	0.080
ITN ownership (10% rise in coverage)	0.84 (0.79; 0.89)	<0.001		
Contextual factor				
Rice yields (tone/ha)	0.64 (0.54; 0.75)	<0.001	0.73 (0.58; 0.92)	0.007
Rainfall (total annual rainfall in mm)	0.98 (0.96; 0.99)	0.001		

Figure 6.6: Trends of under five mortality rates going back to 1997 (Adopted from Alba et al.)

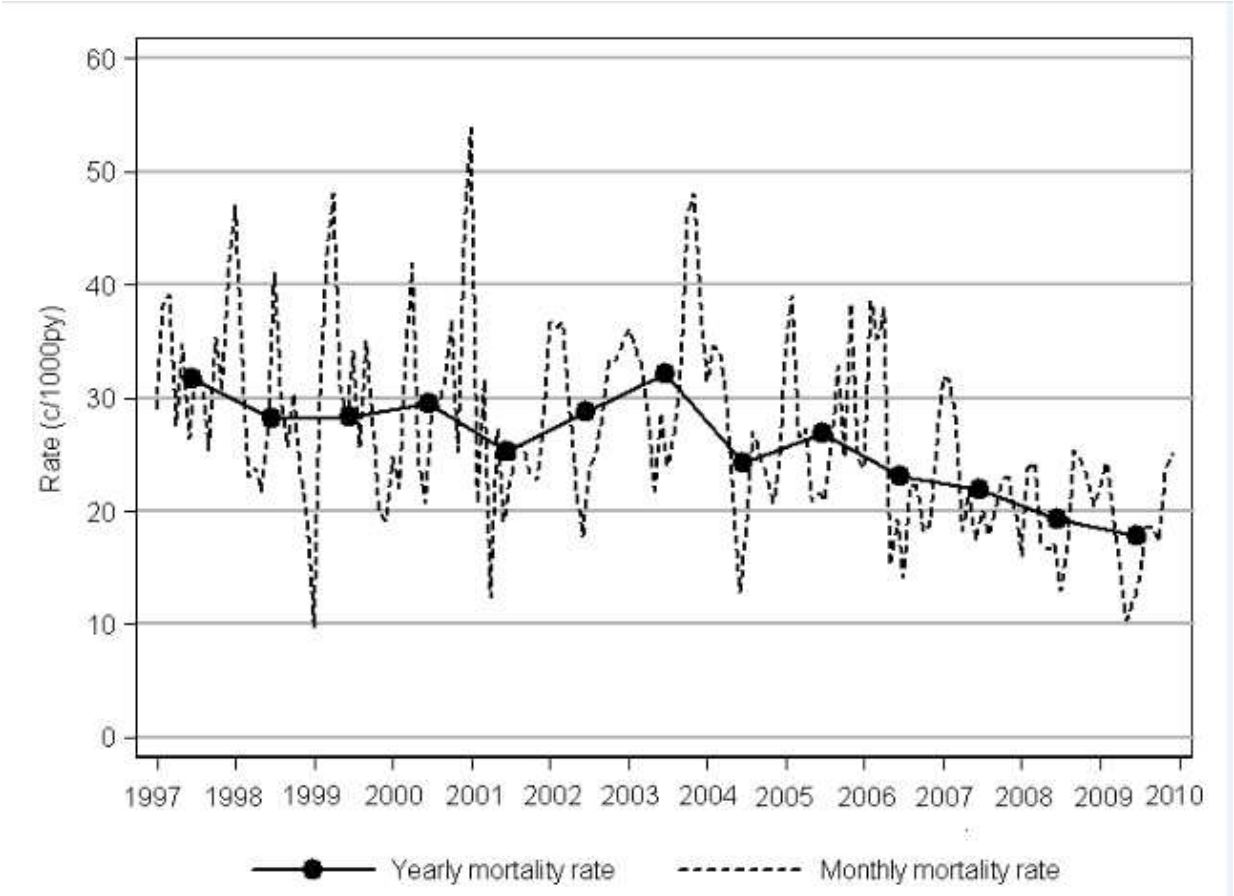
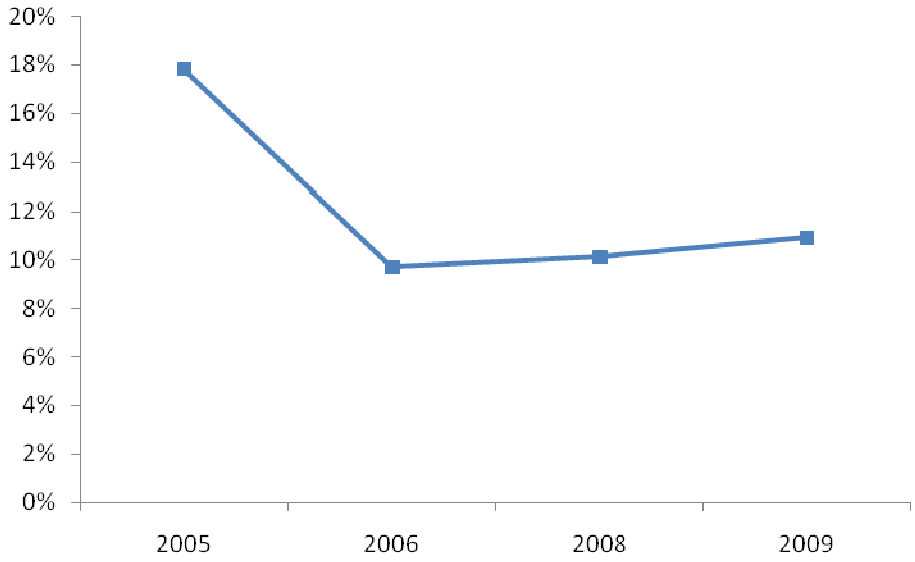


Figure 7.6: Prevalence of anaemia in children under five years during evaluation period.



6.1.5 Discussion

Two years after the implementation of anti-malarial first line policy in Tanzania in the Kilombero river Valley the ALIVE project has documented a sharp downturn of malaria parasitaemia from 11% (698/5223) in 2006 to 4.6%(341/7401) in the community among asymptomatic individuals. There is also a consistent reduction in all-cause U5 child mortality from annual 23.2 cases/1000py in 2006 to nearly 17.9 cases/1000py in 2009. Both reductions in malaria transmission and mortality that were observed under ALIVE can be attributed In part to ACT. On one hand the mortality changes documented have to be seen as a trend in the downturn that goes back to mid 1990 which can be extrapolated to a secular trend in the framework of several other interventions that were put in place since mid last decade. On the other hand the sharp downturn in malaria parasite prevalence in asymptomatic individuals in the DSS community as documented in 2009 when compared to the pre-ACT era is strong evidence that the introduction of AL has had an impact on malaria transmission in Tanzania, whereas ITNs coverage has remained high over the whole observation periods (pre- and post-AL era).

The introduction of AL as the first line treatment of malaria in Tanzania and in the Kilombero river valley in particular was privileged to coincide with a number of achievements on the ground. First AL was introduced in Kilombero at the time when SP had already attained good accessibility coverage in both private and public outlets (Hetzel, Msechu et al. 2006). Second AL was introduced in the region at a time Tanzania was up-scaling ITN with bundled or LLITN programme countrywide through-NATNET Scheme. It can therefore be argued that despite the significant failure rate of SP in the general community at the time policy transition was being implemented with AL as first line, much of AL good performance have been backed-up by the former interim SP policy. This is due to the fact that SP was readily accessible in two years preceding AL introduction through strategies implemented by the ACCESS project that resulted in to increased channels of anti-malarial availability in the region (Alba, Hetzel et al.). This could mean that most malaria fevers at the moment of ascertainment were being treated with anti-malarials on time and resulted in a reduction of the overall community malaria transmission [Alba et al, fever paper]. Several other factors may have played a role in the transmission and mortality downturn that was recorded. It is imperative to note here that the improvement in health care seeking behavior and gain

in food yields in particular were contributing factors behind this surge (Alba, Dillip et al. ; Alba, Hetzel et al.). Food security is key to sustain gains in child mortality obtained with implementation of effective malaria control interventions.

Introduction of ACT did not seem to have impacted on malaria transmission in the multivariate Poisson analysis as it did in the Poisson model on mortality. This is not readily explained since it would be expected that the reduction of overall mortality that is due to the reduction of malaria, thanks to ACT introduction, would parallel affect malaria transmission. In fact, it is more likely, from our observations, that the effect of ACT on mortality is due to the direct benefit of ACT on level of cure, namely on the number of patients who were successfully treatment and do not go into severe disease and death.

Limitations.

Our findings are prone to various limitations as follows. First, the before after design; has sliced three years before and three years after ACT introduction. The timeframe might be too short to have sufficient confidence that the observed downturn in U5 mortality is due to the change in ACT policy. The same applies to the absence effect of ACT on malaria transmission, although the modest reduction was seen in mortality during the same period of ACT introduction. Also, many other factors than those analyzed may have influenced mortality and were not taken into account (vitamin A distribution, IPTp, IMCI etc.). Third, there have been some hurdles in ACT distribution in the region, and as it is now the delivery system is still imprecise to account for good coverage of ACT accessibility by rural community in need of it.

Despite these limitations our findings are still valid and consistent with similar assessments that were conducted elsewhere. Similar studies elsewhere in Sub-Saharan Africa, Kwa Zulu Natal province in South Africa for instance in 2003 showed that malaria-related deaths decreased by 97% over two years after a combined strategy of implementation of ACT and other intervention such as ITN and IRS (Barnes, Chanda et al. 2009). Our findings on the effect of ITNs on malaria transmission are consistent with results from the Cochrane review synthesized evidence from randomized trials on bed-net in Sub-Saharan Africa that showed a 17% protective efficacy of ITN in area where coverage is near to 60% (Lengeler 2000).

Conclusion Three years after ACT implementation wit AL in Tanzania, there was a considerable decline in U5 child mortality, and ACT introduction has contributed to this decline. Malaria parasite prevalence declined to more than 65% over the entire period but no change in anaemia prevalence was observed. Key malaria interventions such as ITN and contextual factors such as food security have contributed greatly to these changes. Timely change of anti-malarial first line policy with efficacious ACT in an area of Ifakara DSS with high coverage of malaria vector control programmes has demonstrated key findings to malaria elimination milestone. In the future malaria elimination/eradication period, food security in rural community will to be key to sustain healthy malaria free U5 children who initially were vulnerable to fatal malaria.

PART VII: DESCRIPTION TO PROGRAMMATIC ISSUES OF PROPER USE OF AL AS 1ST LINE ANTI-MALARIAL IN TANZANIA

CHAPTER 7: Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania

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7.1.1 Summary

Background: Controlled clinical trials have shown that a six-dose regimen of artemether-lumefantrine (AL) therapy for uncomplicated *Plasmodium falciparum* malaria results in cure rates >95% with good tolerability.
Materials and methods: A prospective study was carried out to document the adherence to and acceptability of AL administration. This was undertaken in the context of the ALIVE study, a prospective, community-based, observational study in a rural, malaria-endemic area of Tanzania. Following microscopic confirmation of *P. falciparum* infection, the first AL dose was taken under supervision, with the subsequent five doses taken unsupervised at home. Patients were randomized to receive a home-based assessment close to the scheduled time for one of the unsupervised doses, but were blinded to which follow-up visit they had been allocated. A structured questionnaire was administered by trained staff and AL consumption was confirmed by inspection of blister packs.
Results: A total of 552 patients were recruited of whom 352 (63.8%) were <13 years old. The randomization process allocated 112, 109, 110, 100 and 111 patients to a follow-up visit after doses 2, 3, 4, 5 and 6, respectively. For dose 2, 92.0% of patients (103/112) correctly took AL at 8±1 hours after dose 1. The remaining doses were taken within 4 hours of the correct time in 87-95% of cases. Nine patients (1.7%) missed one dose. Blister packs were available for inspection in 548 of cases (99.3%) and confirmed patient-reported data that the previous dose had been administered. Nearly all patients took AL with water (549/552 [99.5%]). Two patients (0.4%) took the drug with food. The dosing pictogram and clustering of tablets within the blister packs was considered helpful by 91.8% and 100.0% of patients, respectively. Overall, 87.1% of patients (481/552) found AL easier to take/administer than sulphadoxine-pyrimethamine (SP) and 87.7% (484/552) believed that AL was more effective than SP.

Discussion: Factors contributing to adherence were likely to be helpful packaging, pictorial dosing instructions and patients' conviction that AL is effective.

Conclusion: Adherence to the dosing regimen and timing of AL administration was very good.

7.1.2 Background

Malaria is the leading cause of outpatient and inpatient admissions in most sub-Saharan African countries, including Tanzania, and continues to exert a high burden in terms of mortality [1-3], morbidity [1, 4] and health expenditure [5, 6]. The use of anti-malarial drugs for chemotherapy and chemoprophylaxis is a critical component in the fight against malaria, but *Plasmodium falciparum* resistance to conventional anti-malarials, such CQ and sulphadoxine-pyrimethamine (SP), is high [1, 7-10]. It is for this reason that the World Health Organization (WHO) has been recommending artemisinin-based combination therapy (ACT) as first-line therapy to replace failing anti-malarial drugs [11].

The ACT artemether-lumefantrine (AL, Coartem®), combines the short-acting artemisinin derivative artemether with long-acting lumefantrine. Giving the second dose of AL eight hours after the first dose quickly achieves and maintains the blood concentration of artemether above the minimum effective concentration [12] to help ensure that malaria parasites are exposed to high levels during the middle third of their life cycle, when they are most susceptible to anti-malarial agents [13]. AL has demonstrated a high level of efficacy and a good tolerability profile [14-18]. As a result, the national treatment policy of Tanzania was revised in November 2006 to adopt AL as first-line treatment for uncomplicated malaria.

AL is administered as a six-dose regimen over a period of three days [19]. Controlled trials using this regimen have demonstrated cure rates of over 95% [20-23], consistent with recommendations from WHO that cure rates for uncomplicated *P. falciparum* malaria should be at least 90% and preferably exceed 95% [11]. Evidence regarding the adherence to the AL dosing regimen and feasibility of its use in programmatic conditions remains limited [24-29]. Nevertheless, proper evaluation of adherence and acceptance outside the context of controlled clinical studies is important as AL is widely deployed throughout malaria endemic sub-Saharan countries.

Following the inclusion of AL within the national Tanzanian treatment policy, the ALIVE ('artemether-lumefantrine in vulnerable patients: exploring health impact') study was undertaken in a rural, malaria-endemic area of the country with the aim of evaluating the impact of introducing AL as first-line malaria treatment on malaria-related morbidity and mortality. As part of ALIVE, a prospective study was conducted under routine

conditions to document the adherence to and acceptability of AL drug administration in this setting.

7.1.3 Methods

The ALIVE study

ALIVE is a prospective, observational, community-based, longitudinal, demographic surveillance study taking place in two rural districts of Tanzania (Ulanga and Kilombero). The primary objective is to assess the effect of AL on all-cause mortality in infants and children aged ≥3 months (and >5kg) and <5 years old, using historical data based on the former first-line treatment with SP as comparator. Secondary objectives include assessment of adherence to the AL regimen, knowledge of correct AL intake and patient satisfaction

The conduct of the ALIVE study complies with the Declaration of Helsinki. The study protocol was approved by the institutional review board of the Ifakara Health Institute (IHI), which implements the ALIVE study, and the Tanzanian National Institute for Medical Research (NIMR).

Administration of AL

As per the instructions from the manufacturer (Novartis Pharma AG, Basel, Switzerland), AL is dosed according to body weight: 5 to <15kg, 1 tablet per dose; 15 to <25kg, two tablets per dose; 25 to <35kg, three tablets per dose; ≥35kg, four tablets per dose. The first two doses of AL are to be given eight hours apart on day 1. On days 2 and 3, AL is to be given twice daily, 12 hours apart; with the morning dose being administered 24 hours after the first dose was taken.

In this study, the first dose of AL was taken under supervision at the health facility, with the subsequent five doses taken unsupervised at home. Dosing and time of taking/administering the drugs was explained and the time was clearly marked on the AL blister packs by the dispensing healthcare provider. Patients or caregivers were advised to ensure AL was not taken/given on an empty stomach.

Assessment of adherence and acceptability

Assessment of adherence to and acceptability of AL was conducted within the context of the ALIVE study and was undertaken at the Mlimba Health Center in the Kilombero

District during the period March to April 2008, i.e. approximately one year after the new treatment policy was introduced in Tanzania (January 2007). Patients living in villages no further than six kilometers from the Mlimba Health Center were eligible to take part in the assessment if they had no clinical signs of complicated malaria and *P. falciparum* infection was confirmed by blood smear. Informed consent was obtained from all patients.

A computer-generated randomization list was used to allocate eligible patients to a home visit for one of the five doses of AL to be taken after the initial, supervised dose. It was planned that all patients be visited at home at a time close to the scheduled time of AL administration. In the event those patients were due to be visited late in the evening or at night following an evening dose, visits were scheduled for the following morning. Patients or caregivers were informed that there would be a follow-up visit but were blinded as to which of the five possible follow-up visits they had been allocated.

Each visit was undertaken by one of two IHI field workers or three local field assistants, after appropriate training based on standard AL training materials provided by the drug manufacturer (Novartis) which had been field tested by researchers from IHI in Ifakara. For patients younger than 13 years, the patient's caregiver was interviewed instead of the patient.

Questionnaire

A structured questionnaire (see Additional file 1) was developed by researchers from IHI and the Swiss Tropical Institute and Novartis, after which it was field tested by researchers from IHI in Ifakara, and then administered to the patient or caregiver at each visit. This included questions on the number of doses to be administered, the number of tablets per dose, the exact time at which the last dose was given, reason for any missed doses, appropriate action if a dose was vomited, consumption of concomitant food or drink at the time of AL dosing, and how patients/caregivers remembered that AL doses should be taken. Additional questions included whether the instructions/drawing on the AL pack were considered useful, how patients/caregivers perceived the clustered doses in the blister packs, how easy it was for them to take/administer AL, how effective they judged AL as compared to SP (the previous first-line therapy for uncomplicated malaria in Tanzania), and their preference for AL over other treatments (antibiotics, analgesics/antipyretics, quinine injection, herbs from

traditional healer or remedy from witchdoctor). Consumption of the dose was confirmed by inspection of the AL blister packs.

7.1.4 Results

Patient population

A total of 552 patients met the eligibility criteria and were recruited for the study (Table 9.7). The majority of patients (352/552 [63.8%]) were aged less than 13 years. All included patients had come to the medical facility to seek medical attention for fever. Almost all patients (544/552, 98.6%) were reported to be unwell or moderately unwell at the time of presentation to the health facility.

The randomization process allocated 112, 109, 110, 100 and 111 patients to a follow-up visit after doses 2, 3, 4, 5 and 6, respectively.

Adherence to AL

AL was dispensed at the Mlimba Health Center in all cases. When asked, 100% of patients/caregivers reported that they had received an explanation of how to use AL. Results of the questionnaire confirmed that all patients/caregivers understood the number of doses required, and the number of tablets that should be taken or administered per dose (Table 10.7). All but one patient responded that five doses in total were to be taken, an answer that was correct when referring only to the doses for which they were responsible (the first dose was given by the healthcare provider). AL was taken at the correct time in approximately 90% of cases for each dose (Table 10.7). For dose 2, 92.0% of patients (103/112) took AL at 8±1 hours after dose 1. The remaining doses were taken within four hours of the correct time in 87-95% of cases. In total, nine out of 522 patients (1.7%) reported missing a single dose of AL. In two out of these nine cases, the patient had forgotten to take the final dose. One patient used the intended dose to replace a dose vomited previously, and one patient ceased to take the drug after vomiting. In the remaining five patients there was no apparent reason for missing prescribed doses. AL blister packs were available for examination at the randomized visit in 548 cases (99.3%), and the reported number of doses taken corresponded with actual pill count at each visit. No patient missed more than one dose, and no patient missed dose 2. In case of a dose being vomited, the majority of patients correctly understood that they should return to the health facility for a replacement dose (316/552, 57.3%). However, a relatively high proportion of patients

(42.7%) incorrectly believed that a replacement dose could be taken from the existing blister pack or that no action was required.

Nearly all patients took AL with water (549/552 [99.5%]). Two patients (0.4%) took the drug with food. The most frequently reported factor that positively influenced adherence to the timing of AL dosing was the impact of the current illness (Table 10.7).

Acceptability of AL

Almost all patients (91.8%) found the dosing pictogram helpful, and all patients reported that clustering of tablets within the blister packs was useful (Table 11.7). In total, 87.1% of patients (481/552) found AL easier to take/administer than SP and 484/552 (87.7%) believed that AL was more effective than SP (Table 11.7). Approximately 90% of patients (495/552) would not have preferred other medications than AL to treat the current illness, although 5.6% (31 patients) would have chosen quinine injections. Two patients would have preferred to receive herbs from a traditional healer.

7.1.5 Discussion

Adherence to the standard AL regimen was very good in this population of patients in a rural area of sub-Saharan Africa. The full six-dose regimen was taken by 98% of patients, with the dose being taken at a satisfactory time in ~90% of cases. These results were obtained without any additional training for staff at the dispensing health center beyond the standard National Malaria Control Programme training initiative, and no special guidance was given to patients other than that which is routinely offered by the local healthcare personnel. The proportion of patients taking all five unsupervised doses was consistent with other reports for ACT in general [24, 25] and AL in particular [26, 27, 28, 29]. This is, however, the first study to provide data related to the timing of AL administration, and the first to apply a randomized study design to the assessment of AL adherence.

Although multiple doses of AL are required, there is no need for individual dose calculations according to body weight; instead, complete treatment packages are available for each body weight group. Thus, AL is simpler to prescribe than SP, the previous first-line therapy, which requires weight-adjusted dosing. However, patients need to take five doses of AL unsupervised over a three-day period compared to a single dose of SP. Our findings, however, indicate that adherence to the AL regimen is

very good following standard instructions from the dispensing healthcare provider, as confirmed by pill counts at the randomized visits. According to the patient responses to the questionnaire, the clustering of tablets for each dose within the AL blister packets is likely to have contributed to the correct number of tablets being taken, and the pictogram shown on the packaging was considered as a helpful supplement to the instructions provided by healthcare workers. The pictogram made the timing of drug administration clear in this rural area where few individuals have a clock or wrist watch [30]. Care should be taken, however, that dispensing staff explain that the 'sun' and 'moon' symbols refer to daytime and night-time, and not sunrise and sunset as believed in a few isolated cases among our study population. Finally, the wide-held response that AL is effective may also have played a role in supporting adherence to the regimen.

It was notable that responses indicated that AL was virtually never taken with food, despite the fact that health providers emphasized that AL works better if not taken on an empty stomach. Based on responses to the question about timing of tablet intake, it appears that some patients may have eaten shortly before or after taking the AL dose and did not consume additional food at the time of dosing, but specific information was not collected. It is encouraging, however, that a recent analysis of data from a large-scale study of AL in five African countries found that although concomitant food intake increased lumefantrine absorption in children with malaria, there was no tendency for lower food intake in the few patients in whom treatment failure was recorded [31]. Indeed, all 37 patients who were unable to eat food with any dose achieved PCR-corrected cure at day 28. Nevertheless, food consumption, or resuming food consumption as soon as possible, at the time of AL dosing remains advisable in order to maximize effectiveness, in view of the observed association between lumefantrine exposure and clinical and parasitological outcomes [23]. This can, of course, be challenging since initially patients may be reluctant to eat due to symptoms of nausea and vomiting during the acute phase of malaria.

Fewer than 60% of patients or caregivers understood the need to return to the health clinic for a replacement if a dose was vomited. Although the number of patients in whom a dose was reported to have been vomited was low (n=2), the findings that more than 40% of patients or caretakers did not know what to do if this happens is of concern.

The current findings provide detailed evidence of the timely intake of AL under programmatic conditions. Other analyses of unsupervised adherence have all involved home visits after the three-day course was completed [26-29]. Encouragingly, however, no study has reported fewer than 90% of patients taking all six doses by the end of the three-day treatment period, based on pill counts. In our case, we were able to validate oral information about pill administration in over 99% of cases, and found no difference between reported consumption and the remaining number of pills. Such validation is essential given the known limitations of self-reporting [32]. Our findings concur with those described recently by Bell *et al*, based on a study in Malawi in which children or adults with uncomplicated *P. falciparum* malaria were randomized to receive AL or chorproguanil-dapsone [29]. Of the patients randomized to receive AL, 100% reported correct pill consumption during oral interviews. However, in a subpopulation of 87 patients in whom pills were dispensed from an electronic pill container that recorded the time of opening, Bell *et al* found that the rate of adherence was only 92%. Thus, the adherence rate obtained using this different measurement approach was the same as that observed in our study population (92%), where we assessed adherence by randomized, scheduled visits shortly after each dose was due to be taken. Clinically, the high adherence rates observed when AL is self-administered after the first dose have been shown to result in excellent efficacy rates irrespective of whether the drug is given supervised or unsupervised [23].

Certain aspects of the study design merit consideration. The study was undertaken in the context of routine use of AL therapy in a rural area of sub-Saharan Africa. The healthcare providers who dispensed AL did not receive any special training in addition to the standard training provided through the National Malaria Control Program when first-line treatment with AL was introduced, approximately one year prior to our assessment. Also, the randomization approach helped ensure comparability of groups for each AL dose assessed, and minimized the influence of interviews by avoiding expected or repeated visits. However, we are aware that responses may be due to the phenomenon that patients or caregivers provided answers they thought would be expected or desired by the interviewer. Whether or not a pill had been removed from the blister pack could be checked through pill counts, but other questions – e.g. those in which the acceptability of AL was compared to other treatment options – could not be validated. Furthermore, responses for children under 13 years were given by parents or caregivers, not by the patient. Therefore, the views expressed in cases of children under 13 are those of their parents/guardians and may not necessarily reflect

the patient's perspective. We also recognize that the questions posed could be refined, particularly those which resulted in 100% or near-100% responses, such as 'Was the clustering of AL doses useful to remember how to take the drug?'. Moreover, there is a need to standardize questionnaires that assess adherence and acceptability to improve the quality and subtlety of the information gained and to improve comparability between studies.

In conclusion, adherence to the AL regimen as standard first-line treatment of uncomplicated *P. falciparum* malaria was high among this rural study population. Patients adhered closely to the dosing regimen, partly due to effective packaging and pictorial dosing instructions and to patients' conviction that AL is effective. These results may be helpful for future training of healthcare providers by National Malaria Control Programmes in sub-Saharan Africa before and during implementation of ACT therapy as first-line anti-malarial treatment.

Conflicts of interest

Funding for this study was provided from Novartis Pharma and Novartis Foundation for Sustainable Development. A M Kabanywanyi, B Genton and C Lengeler received honoraria and travel expense reimbursement from Novartis Pharma to present study findings at various international conferences. R Schlienger and N Mulure are employees of Novartis Pharma. P Kasimu and S King'eng'ena have no conflicts of interest. A medical writer, funded by Novartis Pharma, provided editorial support based on the draft manuscript prepared by A M Kabanywanyi.

Authors' contributions

AMK contributed to study design, was a study investigator and drafted the manuscript for input by the other authors. CL participated in questionnaire design, data interpretation and writing of the manuscript. PK and SK undertook data collection. RS contributed to study and questionnaire design and provided input to the manuscript. NM contributed to questionnaire design and acted as the medical advisor to the project. BG contributed to study and questionnaire design and provided input to the manuscript. All authors read and approved the final manuscript.

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Table 9.7: Patient characteristics (n=522)

Attribute	N (%)
Age	
<13 years	352 (63.8)
≥13 years	200 (36.2)
Female gender	319 (57.8)
Level of education of patient/caregiver	
None	63 (11.4)
Primary school	421 (76.3)
Secondary school	68 (12.3)
College	0 (0)
Occupation of patient/caregiver	
Employed	22 (4.0)
Self employed	77 (13.9)
Farmer	369 (66.9)
Other	84 (15.2)
Age	
3 months – 3 years	270 (48.9)
3 – 8 years	62 (11.2)
8 – 12 years	39 (7.1)
>12 years	181 (32.8)
Patient condition on presentation at health facility	
Very unwell	0 (0)
Unwell	399 (72.2)
Moderately unwell	145 (26.3)
Moderately well	2 (0.4)
Well	1 (0.2)
Perfectly well	5 (0.9)

[a] Dose used to replace vomited dose 2 (n=1), dose not taken due to stomach ache (n=1)

[b] Dose delayed (n=1), tablets lost (n=1)

[c] No reason given (n=1), dose not taken due to excessive vomiting (n=1), admitted to hospital due to

asthma, treated with quinine (n=1)

[d] Forgot to take dose (n=1)

[e] Refers to morning dose (results were similar for evening dose)

[f] Not specified

Table 10.7: Assessment of adherence to the AL dosing regimen, as evaluated by questionnaire (n=522)

	N (%)
How many doses in total to be administered for a complete course of treatment	
1	0
2	0
3	0
4	0
5	551(99.8)
6	1 (0.2)
Number of tablets per dose to be taken?	
1 tablet	270/270 (100)
2 tablets	62/62 (100)
3 tablets	40/40 (100)
4 tablets	180/180 (100)
AL dose taken at correct time (i.e. ± 1 hours for dose 2, ±4 hours for doses 3-6)	
Dose 2	
Dose 2	103/112 (92.0)
Dose 3	103/109 (94.5)
Dose 4	100/110 (91.0)
Dose 5	96/110 (87.0)
Dose 6	99/111 (89.2)
Number of missed doses	
Dose 2	0/122 (0)
Dose 3[a]	2/109 (1.8)
Dose 4[b]	2/110 (1.8)
Dose 5[c]	3/100 (3.0)
Dose 6[d]	2/111 (1.8)
Action to be taken if tablets are vomited	
Go back to health facility for replacement dose	316 (57.3)
Give another dose	209 (37.8)
Do nothing	27 (4.9)
Don't know	0 (0)
With what was AL taken/given?	
Nothing	0 (0)
Water only	549 (99.4)
Food	2 (0.4)
Beverage	1 (0.2)
Other	0 (0)

Timing of tablet intake when administered with food?	
Before meal	171 (31.0)
During meal	2 (0.4)
After meal	379 (68.6)
What acted as a reminder to take tablets?[e]	
The dispenser's instructions	231 (41.8)
The pictograms	309 (55.9)
Illness	12 (2.2)
Other[f]	12 (2.2)

Table 11.7: Acceptability assessments (n=552)

	N (%)
Were the instructions (drawings) in the AL pack useful?	
Yes	507 (91.8)
No	34 (6.2)
Don't know	11 (2.0)
Was the clustering of AL doses useful to remember how to take the drug?	
Helpful	552 (100)
Confusing	0 (0)
Not important	0 (0)
How do you or your child feel now?	
Very unwell	6 (1.1)
Unwell	5 (0.9)
Moderately unwell	3 (0.6)
Moderately well	47 (8.5)
Well	486 (88.0)
Perfectly well	9 (0.9)
How do you find AL to administer/take?	
Easier to take than SP	481 (87.1)
Less easy than SP	2 (0.4)
Same as SP	32 (5.8)
Don't know	37 (6.7)
Do you find that AL works?	

Yes	549 (99.5)
Better than SP	484 (87.7)
Same as SP	32 (5.8)
Don't know	35 (6.5)
No	3 (0.6)
Would you or your child prefer to have anything else than AL for this particular illness?	
No	495 (89.7)
Yes	57 (10.3)
No specific choice	21/57(36.8)
Antibiotics	1/57 (1.8)
Analgesics/antipyretics	2/57 (3.5)
Quinine injection	31/57 (54.4)
Herbs from traditional healer	2/57 (3.5)

PART VIII: DISCUSSION

CHAPTER 8: DISCUSSION

This chapter provides discussion of the main findings gathered from different parts of the work presented in this thesis as reflected from main objectives (Chapter 2), namely anti-malarial policy issues with respect to preparedness to policy adoption and the monitoring of its implementation. Subsequently the chapter also provides recommendations and considerations for future researches on anti-malarial therapy and treatment policy. In-depth discussion is given below under sub-thematic sections as outlined in the main thesis.

8.1 Enabling environment for health policy changes in the treatment of uncomplicated malaria with ACT before and after the introduction of AL as first line policy in Tanzania

In 2001 when most malaria endemic countries in sub-Saharan African were at the cross-road of adopting ACT, Tanzania implemented SP as an interim first line anti-malarial policy. At the same time, researchers at the Ifakara Health Institute (Ifakara Health Research and Development Centre, by then) and elsewhere in the country were already in the process of researching for ACT candidates' drugs to be used as anti-malarial new first line policy (Mutabingwa, Nzila et al. 2001; Adjuik, Babiker et al. 2004; Kabanywanyi, Mwita et al. 2007; Abdulla, Sagara et al. 2008). The change from chloroquine to SP was an interim measure taken by the ministry of health in Tanzania to pave the way for a smooth transition to ACT once enough evidence on candidate ACT drugs of choice as well as funding mechanism were properly established. The first line policy with ACT was adopted in late 2006 and full implementation took place in 2007. In Tanzania, ACT policy adoption by policy makers and uptake by the public at large was fast due to preparedness that was put in place based on experience accumulated during implementation of SP policy in the past (Mubyazi and Gonzalez-Block 2005; Hetzel, Msechu et al. 2006; Kabanywanyi, Mwita et al. 2007). It is important to note here that, in 2001 the time when the country was moving from CQ to SP things went somehow bitter resulting in several outcries particularly related to safety issues of SP. These concerns resulted in poor policy uptake by the public (Mubyazi and Gonzalez-Block 2005). Based on the lessons learnt in the past effective measures were put in place in order to allow for a smooth transition to ACT policy implementation in Tanzania. The gained experience was useful not only to researchers in the field whose studies provided evidence for policy change, but also policy-makers. For these

reasons research findings should be linked to advocacy in order to affect any required translation of results to policy (Mubyazi and Gonzalez-Block 2005). This experience is particularly important for researchers in the field who often propose novel interventions but face opposition and delay from policy-makers to uptake the gained research evidence on time. The outcry from scientific community in 2004 on the need to avail and upscale ACT attests to the frustrations and problems associated with delay in policy implementation (Duffy and Mutabingwa 2004; White, Nosten et al. 2004).

The call for global action by the research community and the general acceptance by African heads of states through the Abuja declaration in 2000 to support global initiatives for up-scaling malaria intervention programmes is the best ever recorded example worthy of emulation (WHO 2000). The Abuja declaration laid down several bench-marks to be attained by the year 2010. Major among the bench marks were: at least 60% of those suffering from malaria have prompt access to treatment within 24 hours of onset of symptoms, at least 60% of those at risk of malaria, particularly children under five years of age and pregnant women access preventive tools such as ITN, at least 60% of all pregnant women who are at risk of malaria have access to chemoprophylaxis or presumptive treatment. The political will shown by most African heads of states to commit themselves to the Abuja declaration is one of the major steps that have led to a positive region-wide adoption and scaling up of several effective malaria interventions like ACT and ITN in the beginning of the decade.

Surprisingly enough in most endemic African countries, ten years after the Abuja declaration the desirable target of improvement in most bench-marks is still far to reach. It is worth noting here that despite the Abuja political commitment and excelled support from donor communities to scale up several malaria interventions, political leaders in Africa still believe malaria must always be fought with support from abroad. Because the Abuja declaration was a political statement that was neither legally binding nor supported by any rigorous enforcement, researchers and the donor community have another task; i.e., to advocate a bridge of research knowledge-to-policy by helping build capacity of most health system in Africa. It is expected that most of the remaining gaps to addressing benchmarks of the Abuja declaration could be realized through implementing the MDGs that re-addresses untouched issues in the Abuja declaration (UN 2010). It must be emphasized that that political will alone is not enough but has to be followed by appropriate mechanisms to put the will of the politicians in a real life meticulous process. Because ten years after the Abuja

declaration hundreds of thousands of young African children are still dying due to malaria and there is equally similar a number of avoidable still birth babies that are occurring in many parts of malaria endemicity (WHOSIS 2009), there is therefore enough evidence to convince most African heads of states to be more proactively committed to live up on their promises.

Malaria management scheme in the post independence era in Sub-Saharan Africa and South East Asia as noted earlier in this thesis have a lot in common in terms of geopolitical landscape and epidemiology of the post-independence newly emerged malaria endemic states. In Tanzania for instance, the national malaria control programmes differs from the rest of Sub-Saharan Africa countries basically due to various reasons. Tanzania has a homogenous health system that facilitated the roll out malaria control programme as part of the primary Health Care (PHC) system. This was supported by evidence-based research emerging from the North-South research collaborations. Government and non-state collaborations within Tanzania was key in informing the above process. In some cases cross boarder collaboration among economic blocks of East Africa and Southern African Development Community (SADC) have also provided insights into the control of malaria across nations. Some of the novel implementation tools developed and tested in Tanzania, have been applied in the rest of Sub-Saharan malaria endemic states and often supported the global campaign against malaria. Political stability and peace for over four decades has also made it easy for quick policy change and scale up of control interventions using ACT, which could have been different in neighboring nations like Uganda, Sudan, Mozambique and Democratic republic of Congo which have experienced civil strife during this period. Due to these reasons, Tanzania has emerged as one of the few African countries that provided the ground to test some of the most successful malaria control interventions for the rest of the world to up-scale.

As part of a long term malaria related research agenda in Tanzania, social marketing of ITN and its resultant effect on child anaemia and mortality have been proven effective (Schellenberg, Abdulla et al. 2001; Abdulla, Gemperli et al. 2005). Tanzania is also one among few countries in Africa together with South American-Peru and Asia that evaluated the effectiveness of IMCI (Armstrong Schellenberg, Bryce et al. 2004). Malaria management in children through a novel intermittent preventive treatment in infancy strategy was initially tested in Tanzania (Schellenberg, Menendez et al. 2001; Schellenberg, Menendez et al. 2005). These are just few on the list of many key malaria intervention that have taken place in Ifakara in Tanzania.

Ifakara is an area that was initially home to intense perennial malaria endemicity but quite opposite today. Malaria in this region is on the decline and transmission has changed significantly (Russell, Lwetoijera et al.). It is worthy to note that, malaria endemic Ifakara and Tanzania at large has provided the venue for developing new malaria intervention tool and a fertile environment for global anti-malarial policy transitions.

8.2 Impact of anti-malarial first line policy on malaria transmission, morbidity and under five mortality in rural two districts in Tanzania.

Not long after the launch of a special initiative for Africa to control malaria by the United Nations secretary general in 1995, the Kilombero river Valley mosquito bed-net social marketing programme (KINET) was launched in Ifakara, in 1996. This launching was facilitated by researchers from Ifakara Health Institute, London School of Tropical medicine and Hygiene and Swiss Tropical Institute (Schellenberg, Abdulla et al. 1999). The social marketing campaign started to focus on distribution of net to the most vulnerable to malaria population groups; pregnant women and children under five years, and subsequently assessed the medium term impact of the programme in later years (Marchant, Schellenberg et al. 2002). This programme in the long-term was enhanced by the regional strategies that were being implemented at the national level such as the Roll Back Malaria in 1998 that was also supported by the Abuja Declaration in 2000. The introduction of KINET project in Ifakara and subsequent launching of DSS was a turning point to succession of upcoming other intervention programmes that took place in the region (Schellenberg, Abdulla et al. 1999; Schellenberg, Abdulla et al. 2001). It is therefore imperative to note here that, this succession of interventions and their resultant medium term changes in transmission intensity in Ifakara today stems from past efforts dating fourteen years (Russell, Lwetoijera et al.).

It is therefore a fact that consistent reduction in malaria transmission and all-cause U5 child mortality that we witness today in Ifakara started to emerge soon after the implementation of socially marketed ITNs in the region and support regional achievements that have been accumulated through various implementation platforms (Russell, Lwetoijera et al.; Marchant, Schellenberg et al. 2002; Armstrong Schellenberg, Bryce et al. 2004; Abdulla, Gemperli et al. 2005; Masanja, Schellenberg et al. 2005). On one hand this has to be seen as a secular trend in downturn which is

likely due to effect of several interventions that have taken place since mid of last decade. On other hand however, the recent sharp decrease in parasite prevalence in asymptomatic individuals and the consequential decrease in mortality documented in 2009 as mentioned in the results section of chapter six of this thesis was influenced through the introduction of ACT using AL. The ALIVE study demonstrated that ACT was responsible for 11% annual decreases in U5 mortality when adjusted for other interventions like ITN and contextual factors (rainfall and food yields). Additionally since its introduction in 2007, ACT with AL has consistently kept the sexual form of malaria parasitaemia below 1%.

The introduction of AL as the first line treatment of malaria in Tanzania and in the Kilombero river valley in particular coincided with a number of valuable achievements on control worthy emulating in similar settings. First AL was introduced in Kilombero at a time when SP was readily available in both private and public outlets made possible under the community-based social marketing programme for access of malaria interventions-ACCSESS project (Hetzel, Msechu et al. 2006). Future malaria programmers should pay attention to the accessibility of ACT for better treatment outcome (Alba, Hetzel et al.). The social marketing programme of ACCESS programme contributed to the timely accessibility of AL, resulting in comparatively fewer cases of fever compared to those before the implementation of ACT policy (Khatibu et al., person communication) (Alba, Dillip et al. ; Alba, Hetzel et al.). It is crucial to note that during the past three years of ACT policy implementation in Ifakara, most malaria fevers at the moment of ascertainment were promptly treated with anti-malarial on time (Alba, Dillip et al.). Prompt treatment of malaria related fevers with efficacious ACT that could result in severe form of malaria had they been delayed or treatment with non-efficacious mono-therapies underlines achievements realized under ALIVE. ACT was responsible for nearly 65% reduction in community parasitaemia as compared to the baseline in 2006. Secondly AL was introduced in a time Tanzania was up-scaling ITN together with bundled or LLITN programme countrywide through-NATNETS scheme and ITN coverage in Ifakara has gone beyond global MDGs benchmarks (Schellenberg, Abdulla et al. 2001; Kabanywanyi, Macarthur et al. 2008; WHO Abuja declaration, 2000). As reported in chapter six of this thesis, it can therefore be argued that a good performance of ACT in similar other malaria endemic settings will depend on timeliness of implementations and proper monitoring of parallel interventions.

The consequence of this achievement to the overall health care system at large is an exercise that should always attract the attention of several health care partners including MDGs scheme evaluators. Because it has been historically acknowledged that malaria accounts for a significant majority of outpatient attendances (Maegga, Cox et al. 2005) the current positive achievements in the region is likely to be of a major health sector importance especially to the local districts health management authorities and the overall global extrapolation to the ongoing MGDs scheme. A recent completed study on ACCESS to treatment in the Kilombero river valley (2005-08) estimated a high coverage (86% to 96%) of fever treatment with anti-malaria in the public health facilities and timely high use of anti-malarial (80% to 93-97%) treatments taken within 24 (Alba, Dillip et al.). These findings are peculiar to Tanzania and have never been released in other malaria endemic setting in Sub-Saharan Africa. These findings imply that with minimal staff, effective interventions including newly introduced malaria rapid diagnostic tests could reduce malaria morbidity and mortality considerably and such interventions are highly needed in rural Africa (D'Acremont, Lengeler et al. ; d'Acremont, Malila et al.).

Another very important consideration in this regard, is the overall implication of the impact achieved at the country or regional level especially in the era of malaria eradication/elimination. Consistently successions of malaria intervention programmes in Ifakara have resulted from integrated research agenda in the region. Because these researches sought to address the burden of malaria at the district level in order to inform policy, it can be argued that similar outcomes elsewhere are possible through defined commitment. High coverage of efficacious interventions with exceeding impact has started to project an image of malaria elimination phase in Zanzibar. The same implies that similar achievements may happen elsewhere in malaria endemic setting given availability of good coverage of political will. Another similar example of positive uptake of efficacious interventions is the scaling up of the Tanzania countrywide bed nets-NATNETS programmes and voucher scheme (Magesa, Lengeler et al. 2005; Mulligan, Yukich et al. 2008).

Attainment of good coverage of impact interventions is not only due to a long term arrangements. A short term focused programmes can also be successful as the one in Bioko island of Equatorial Guinea. In Bioko, it was shown that an integrated malaria control programme resulted in to major reduction in entomological indices of malaria

transmission prompting to transit to an elimination phase just 4 years after the programme (Kleinschmidt, Schwabe et al. 2009; Kleinschmidt, Schwabe et al. 2009).

In general terms, what has been achieved in Ifakara may have already been coming along the path in similar localities in the country or elsewhere in the continent. What remains is to mobilize available tools, resources and knowledge in order to replicate achievements in different regions of Africa and other malaria endemic countries.

8.3 To describe programmatic issues and their implication for anti-malarial first line policy and impact assessments

The contribution of AL as first line policy to the reduction of malaria morbidity and mortality in children U5 years in the K/U area is described in chapter 6 of this thesis under ALIVE study. This is consistent with any success story drawn from the Kilombero river valley. In a conventional applicable definition; a programme success may be defined as gain in intervention coverage and in health impact under real world conditions when intensity of its implementation is lower than in efficacy trial (Habicht, Victora et al. 1999). The Tanzania country-wide ACT introduction with AL as first line could be considered as a continuum of a more secular programmatic stepwise phase that started back in 2001. The equivalence of policy implementation and subsequent evaluation in the framework of Kilombero valley in the IHDSS in particular has different picture i.e., regional programmatic evaluation under ALIVE study that is referenced here. Although the country-wide policy implementation by itself is not ecological in nature but the Ifakara regional assessment by itself is the case. Malarial intervention programmes in Ifakara region date back to the mid 1990s with subsequent phasing out of two malaria first line policy; first with CQ in 2001 and later with SP in 2006. Ifakara has experienced crucial achievements with respect to malaria morbidity, mortality and evidence of changes in malaria transmission. Because changes in malaria transmission intensity as documented from asymptomatic individuals in household surveys and reduction in children U5 mortality in this area have occurred concurrently with anti-malarial policy transitions, the introduction of ACT policy attests to the contribution of this effect. The association of less efficacious anti-malarials with child mortality in the past during the CQ era was presumed to confound the impact of IMCI intervention on mortality in the intervention districts in Tanzania back in 2003. This happened despite the fact that IMCI is an efficacious intervention strategy against most child health problem (Armstrong Schellenberg, Adam et al. 2004). This particular

finding is a crucial background to our findings and supports our extrapolation that ACTs have contributed to reduction of U5 child mortality.

Availability of baseline efficacy profile and intensive campaign by stakeholder and preparedness among researchers accelerated policy implementation in most part of Tanzania (Alba, Dillip et al. ; Kabanywanyi, Mwita et al. 2007). The ACT policy in Tanzania was highly acceptable as compared to the SP policy (Kabanywanyi, Lengeler et al.). This phenomenon can be explained by consistent stock-outs of AL in most public health facilities for a considerable extended period during the early phase of implementation that resulted from high uptake of the drug (Alba, Hetzel et al.). The experience of mass public campaigns has also contributed to an increase in the improvement of most health seeking-parameters (de Savigny, Mayombana et al. 2004). A better understanding about causes of malaria among community members in Ifakara (from 62% to 84%), an increase in health facility attendance as first treatment option for patients older than five years (27% to 52%), higher treatment coverage with anti-malarial [86% to 96%) and more timely use of anti-malarial (80% to 93-97% treatments taken within 24 hrs] (Alba, Dillip et al.) are among important programmatic issues that supported ACT policy in K/U.

Monitoring the efficacy and safety of anti-malarial first line policy before and after its full implementation is a programmatic aspect that must always be considered as important in any successful policy implementation. The richness of evidence that was available before the policy with AL when introduced is a good example of worthy emulation in similar policy preparedness (Falade, Makanga et al. 2005; Makanga, Premji et al. 2006; Kabanywanyi, Mwita et al. 2007). In the past it was even difficult for policy makers to confidently convince the public that the untoward consequences of treatment with SP as compared to treatment with failing anti-malarials were much lower than an occurrence of adverse event in one person out of a thousand successfully handled patients (Newman, Parise et al. 2003; Mubyazi and Gonzalez-Block 2005). The introduction of a safety monitoring framework in the K/U region is another practical important step towards gaining local experience to the establishment of a full large scale pharmacovigilance reporting system in the region. A good coverage of similar experiences in other parts of the country and at the regional level is needed to maximize capture of safety information on ACT and other medications in use. Failure to properly assess the safety of anti-malarias in use or new ones that are entering the market could result in public misperception and lead to problems with acceptability (SP)

(Mubyazi, Bloch et al. 2005). Concerns about SP-related serious adverse skin reactions (e.g. Stevens-Johnson syndrome) led to unnecessary delays in the process of policy change in several African countries (Mubyazi and Gonzalez-Block 2005). It is also equally important for the relevant drug regulatory authorities to assume more responsibility in monitoring drug safety and put in place useful arrangements with local regulatory agencies to allow hospitals and pharmacies to enquire more information on drug safety and keep vigilance to all drugs that are in use. This will eventually ensure accumulation of relevant information on drug safety and increase trust between drug users and health authorities or programme authorization holders.

Partnership between the ministry of health, researchers, pharmaceutical industry and communities as documented under the ALIVE project in chapter 5 and 7 of this thesis is a unique novel example worthy of emulation in similar polices in the future. A combination of research experience from IHI and Swiss TPH research communities, the local contextual community as well as policy implementation skills from the ministry of health in Tanzania and technical expertise plus funding opportunities form Novartis Pharma/Novartis Foundation for Sustainable Development has provided a unique partnership for programme implementation. This partnership is the first of its kind in Sub Saharan Africa. A long time rooted research partisanship and trust between these three institutions represented a novel model of health system partnerships. Safety and compliance issues of medicinal products that are deployed at large scale like ACT for instance should not and will neither be the responsibility of drug authorizations holder nor pharmaceutical industries alone. It is therefore imperative that global health partners at present should forge a comprehensive and trustworthy partnership among interested parties to implement and upscale anti-malarial drug policies. Lessons on partnership and networking from our experience in malaria, reported in this thesis could be replicated for other diseases of developing countries.

Capacity building of market and policy implementation holders is very crucial and must be considered seriously. Today the Global Fund to fight AIDS, Tuberculosis and Malaria and other malarial global partners have massively increased their support for malaria treatment and diagnosis. Investments should also be made towards capacity building in order to strengthening health sectors of institutions in malaria endemic countries. This will further create enabling environment and a critical mass of scientists and public health experts to spearhead anti-malaria policy implementations properly and monitor their performance on timely a basis.

8.4 Implications

(a) Practical

Isolated success in some benchmarks of the Abuja declarations for 2010 have been realized in Ifakara some years ahead of the 2010 target. It is true that not all part of Tanzania Mainland has reproduced similar coverage and indicators of success. A bigger countrywide and notably continental picture replicated by emulating regional based success to a larger scale by undertaking similar implementation strategies in other endemic but still lagging behind regions is needed.

Partnership between the ministry of health, researchers and pharmaceutical industry as experienced and documented under the ALIVE project of this thesis is a unique example worthy of emulation in future policy implementations.

Safety and compliance issues of any medicinal product which is deployed in a large scale like the ACT should be the responsibility of several responsible but also interested parties.

Capacity building of market and policy implementation holders is another critical aspect that should be taken seriously. This will further create an enabling environment and a sustainable critical mass of scientists and public health experts to spearhead and monitor policies for anti-malaria.

(b) Research related

At present, in most endemic settings the untoward outcome due to malaria today could be avoided because all potential tools to fight malaria such as LLITN and ACT are available.

What is thus needed for the entire community involved is to streamline the thinking and to somehow merge the approaches that are at hand very carefully.

In ALIVE programme it has been demonstrated that with high ITNs coverage deployment of efficacious drug has the potential to decrease U5 mortality, conversely high ITNs coverage with efficacious drug has lowered malaria transmission. This attests the argument that deployments of complimentary anti-malarial interventions together at a scale produce a huge effect. For Tanzania it can be expected that, since

there is a countrywide distribution of LLTN through NATNETs, then similar assessment that will include a large area with different ecological setting notably; different districts in order to gain a broad understanding of the actual effect in different administrative setting is needed. For this assessment, Tanzania and few other African countries at present are well positioned to undertake it through the ongoing formation of the Sentinel Panel of Districts (SPD) where the unit of assessment is the district itself and not the classic assessment through interventions or programmes. This can also be carried out at the continental level with the aim of assessing the health system of individual countries on their ability to scale up malaria interventions by including various units of measurements for the health system such as governance, human resources, services, mechanism of basket funding, intervention delivery infrastructures etc of the individual or group of countries. Similar assessment once applied will be a unique opportunity for MDGs evaluation since it will provide more granulations on what is happening at the regional level for different malaria endemicity and a more complex analysis of malaria/HIV synergetic untoward effect on the health system.

It can thus be hoped that through similar arrangements and sharing experience the malaria fighting community truly succeed in the fight that could read to malaria eliminations (Perry 2010).

8.5 Recommendations.

Public-private partnerships as exemplified in the ALIVE model of researches represent a classical option for the malaria community today. It is therefore recommended here that; global health partners at present be able to forge a comprehensive and trustworthy partnership for proper anti-malarial policy implementation. It is also recommended that global health financing partners should allocate funds through existing funding mechanism tin for capacity building in order to strengthen health sectors of institutions in malaria endemic countries.

8.6 Future work

Where possible in developing countries to include in medical collage's some syllabuses on key issues like safety reporting and policy-based programme implementation. Also on job capacity building scheme for programmers and policy implementation holders in

order to create enabling environment and a critical mass of scientists and public health experts to spearhead anti-malarial policy implementation.

Revival of regional anti-malarial monitoring platforms such as EANMAT is critical now at the moment of establishing of efficacy profile of anti-malarial with ACT taking in to serious consideration of the emergence of ACT drug resistance in South Eastern Asia.

8.7 Conclusion

This work has provided evidence that a successful campaign against malaria can be realized through combining efforts of researchers, policy makers, global health development partners and communities. This partnership has lead to real life time achievements in past programmes such as that recorded in the 1940s malaria eradication campaigns in Europe.

8.8 Key message

I. Preparedness for policy inceptions and timely implementation of real time focused based operation researches and emulating them in a real practical life as outlined in order to address resurgences of global anti-malaria drug resistance.

II. Evidence accumulation before and after policy inception is crucial for long life-span of the new anti-malaria drug policy.

III. Isolated success gained on the impact of well implemented malaria interventions in some malaria endemic settings are good examples to emulate in other regions. It is moreover crucial that are critically analyzed before extrapolations to other regions as it will be crucial to take account of heterogeneous nature of health systems in different regions.

IV. Global partnership as exemplified in the ALIVE study represents a classical option for malaria combating community today.

V. Capacity building of regulatory and policy decision-makers is a critical aspect that should be looked seriously and where possible reasonable part of available

global funds be invested to strengthening health sector of most institutions in malaria endemic countries.

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Appendix

Curriculum vitae

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Name: Abdunoor Mulokozi KABANYWANYI

Date of birth: 24 June 1967

Nationality: Tanzanian

Profession: Research scientist -Clinical Epidemiologist

Current employment and status

1. Clinical coordinator & Institutional Intervention thematic group reading scientist, Ifakara Health Institute (IHI)

2. Site leader Dodoma Blanch for IHI

3. PhD student, University of Basel, Switzerland

Terminating responsibilities

1. Principal Investigator MiPPAD study (EDCTP/EU funded project)

2. Clinical coordinator ALIVE study in Tanzania [Novartis Foundation funded project]

3. Pharmacovigilance coordinator for the project of monitoring antimalarial adverse drug reactions in four rural Tanzanian districts (Rufiji, Ulanga Kilombero and Morogoro rural).

4. Clinical coordinator efficacy studies of antimalarial combination therapy for Interdisciplinary Monitoring Project of Antimalarial Combination Therapy (IMPACT) project [USAID/PMI funded projects].

Other work experiences

1. 2010 Consultancy work: Leading consultant on feasibility of the implementation of HPV vaccine in Tanzania-SDC (Completed)

2. 2009 Consultancy work: Leading consultant on impact evaluation of PMTCT in refugee camps in western Tanzania-UNICEF (Completed)
3. 2004-todate-Clinical coordinator various field epidemiological study at IHI

4. 2002-2003 Part-time physician at St Francis Designated district hospital-Kilombero

5. October 2002-March 2006: Clinical coordinator Antimalarial efficacy studies under [IMPACT, EANMAT, MoHSW/NMCP projects] at various sentinel sites in Tanzania.

6. 2007-To date: Project leader

   I. (Artemether/Lumefantrine In Vulnerable Patients: Exploring health impact)-ALIVE project.

   II. Malaria in Pregnancy Prevention with Alternative drugs-MiPPAD

Education & Qualifications

2009 **Certificate of Good Clinical Practice** (GCP) for Investigators, Maputo, **Mozambique**

2006 **(MSc) Masters Degree in Clinical Epidemiology**, Erasmus Medical Centre-Erasmus University, Rotterdam **The Netherlands**

2003 **Certificate of Clinical Trial and Bioethics**. Noguchi Memorial Institute for Medical Research, Accra **Ghana**

2002 **Certificate of Clinical drug and Vaccine Research**, Vienna school of Medical Research, Vienna **Austria**

2001 **Certificate of Internship**, Muhimbili National Hospital, **Tanzania**

1999 **(MD) Bachelor degree in Medicine**, Volgograd Medical academy, **Russia**

1999 **(BA) Bachelor of Arts**-Teacher of Russian Language, Volgograd Medical academy, **Russia**

Publications

1. Efficacy and safety of artemisinin-based antimalarial in the treatment of uncomplicated malaria in children in Southern Tanzania:
http://www.malariajournal.com/content/6/1/146
Abdunoor M Kabanywanyi, Alex Mwita, Deborah Sumari, Renata Mandike, Kefas Mugittu, Salim Abdulla

2. **Malaria in pregnant women in an area with sustained high coverage of insecticide-treated bed nets**: http://www.malariajournal.com/content/7/1/133
Abdunoor M Kabanywanyi, John R MacArthur, Wilma A Stolk, J Dik F Habbema, Hassan Mshinda, Peter B Bloland, Salim Abdulla, S Patrick Kachur

3. **Residual Antimalarials in Malaria Patients from Tanzania – Implications on Drug Efficacy Assessment and Spread of Parasite Resistance**
http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0008184
Eva Maria Hodel, **Abdunoor Mulokozi Kabanywanyi**, Aggrey Malila, Boris Zanolari, Thomas Mercier, Hans-Peter Beck, Thierry Buclin, Piero Olliaro, Laurent Arthur Decosterd, Blaise Genton

4. **Adherence to and acceptability of artemether-lumefantrine as first-line anti-malarial treatment: evidence from a rural community in Tanzania**
http://www.malariajournal.com/content/9/1/48
Abdunoor M Kabanywanyi, Christian Lengeler, Prudensiana Kasimu, Said King'eng'ena,
Raymond Schlienger, Nathan Mulure, Blaise Genton,

5. Experience of safety monitoring in the context of a prospective observational study of artemether-lumefantrine in rural Tanzania: lessons learned for pharmacovigilance reporting http://www.malariajournal.com/content/9/1/205
Abdunoor Mulokozi Kabanywanyi**, Nathan Mulure, Christopher Migoha, Aggrey Malila, Christian Lengeler, Raymond Schlienger, Blaise Genton**

Submitted Manuscripts

1. Using demographic surveillance system to record early inadvertent exposure of antimalarial during pregnancy.

Abdunoor M Kabanywanyi, Aggrey Malila, Mathew Alexander, Honesta Mzyangizyangi, Honorati Masanja and Salim Abdulla*

International Meeting and Conferences Presentations

1. November 2009, Using demographic surveillance system to record early inadvertent exposure of antimalarial during pregnancy, American Society of Tropical Medicine and Hygiene**, Washington USA**
[*Oral presentation*]

2. November 2009, Adherence and safety of artemether/lumefantrine(Coartem®) as first-line treatment for uncomplicated malaria in Tanzania, 5th International conference for Multilateral Initiative on Malaria (MIM), **Nairobi Kenya** [*Oral presentation*]

3. December 2008, Training and implementation of pharmacovigilance in rural sub-Saharan setting in Tanzania, American Society of tropical medicine and hygiene-**New Orleans USA** [*Oral presentation*]

4. October 2008 Adherence to artemether/lumefantrine(Coartem®) as first-line treatment for uncomplicated malaria in Tanzania, 17th International Congress for Tropical Medicine and Malaria, **Jeju South Korea**
[*Oral presentation*]

5. November 2007, Risk factors in pregnant women without IPTp protection, American Society of tropical medicine and hygiene-Philadelphia, **Pennsylvania USA** [*Oral presentation*]

6. November 2006, Data Management and statistical issues for Malaria Clinical Trials, AMANET workshop of clinical Investigators, **Kilifi Kenya** [*Lecture*]
www.amanet-trust.org/ext/reports/workshops/2006/AMAWS1106.pdf

7. November 2002, Surveillance of antimalarial adverse events, 3rd International conference for Multilateral Initiative on Malaria (MIM), **Arusha Tanzania** [*Poster presentation*]

Languages

	Speak	***Read***	***Write***
Swahili	Mother tongue	Excellent	Excellent
English	Good	Good	Good
Russian	Good	Good	Good

Referees

1**. Dr Salim Abdulla**
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