INFLUENCE OF HEALTH SYSTEMS IN MALARIA CASE MANAGEMENT AS PART OF MALARIA CONTROL IN TANZANIA

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Prof. Dr. Jörg Schibler

Dekan

To my parents: Naomi and Daniel E. MASANJA

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Summary

The World Health Organization report in 2007, declared that, it will not be possible to achieve national and international health goals without greater investments in health systems. It is a known fact that today, the advancement in science has led to a better understanding of etiologies and risk factors of most diseases burden in the world. However, the capacity to deliver these innovations to the population that needs them the most is severely handicapped by fragile and poor health systems, particularly in developing countries. The differing diseases burden spectrum between and within countries, underscores the complexity and the need for context specific measures to address disease burdens and major causes of poor ill health in respective societies.

Today, malaria continues to be a public health problem and important cause of morbidity and mortality in countries with ongoing transmission. In Tanzania, malaria is among the leading causes of hospital attendance and mortality in prevalent areas. Efficacious interventions to combat malaria have advanced such that endemic regions are seeing a decline in malaria related deaths and morbidity. These gains however, are threatened with the emergency of drugs and insecticide's resistance, environmental, vectors and hosts' related challenges. Despite these challenges, malaria is a preventable disease and historically the disease, once prevalent in the North, was successfully eradicated. This provides hope for elimination and possible eradication of malaria in endemic regions in future if efficacious interventions are adopted in scale.

The current malaria control strategies in Tanzania can broadly be categorized as; vector control activities which includes use of treated bed nets, indoor residual praying and environmental management; chemoprevention to specific vulnerable groups; and prompt, effective treatment of cases. Health care provision in the country is facing many bottlenecks such as shortage of qualified workforce, lack of appropriate technologies and frequent stock-out of essential medicines. In addition, reports of poor providers'

compliance to treatment recommendations undermine the effectiveness of the health system.

Through a phase four platform of effectiveness and safety studies of antimalarials (INESS), we assessed the quality of malaria case management in the study areas. The goal was to understand factors influencing treatment outcomes in real world settings, with focus in diagnostic accuracy and provider's compliance for malaria treatment. This work involved a pair of cross-sectional health facility surveys that interviewed patients, providers and inventoried health facilities for availability of products related to malaria treatment. Complimentary data were obtained from the IMPACT-Tz project which introduced artemisinin based combination therapy (ACT) in similar study areas, before the national adoption of ACT for malaria treatment.

Findings from this work demonstrated that, increased use of malaria rapid tests (RDTs) for routine care reduced over-treatment with ACT during high malaria transmission period from 45.8% in a pre-RDT area to 20.9% in a post-RDT area. Conversely, correct treatment with ACT was higher in the post-RDT area 85.9% as compared to pre-RDT area 58.3%. This implies that, having appropriate technology in place improves targeting of resources and facilitates providers' compliance. Further assessment on correct dosing revealed that age based dosing were more prone to errors. The proportion of patients receiving correct dosing as per national guideline was lower in middle aged groups; 42% for 9-12 years old and 50% for 3-9 years old patients. Analysis of health facility data from 2002 to 2010 showed that presence of parasitemia at health facility was generally declining to children below 5 and increasing to above 5 years. However, significant intra-group's differences were observed. While children below age of 2 showed a declining trend, those above 2-5 years had an increasing trend ($p<0.001$). This was in contrary to the findings from population based surveys.

This work also described health workers' specific factors that influences correct treatment of malaria and showed that, work experience does influence quality of care. Providers with 3 or more years of work experience had higher of odds of giving a correct

treatment than otherwise [aOR: 2.6 (1.2-5.6)]. In the same pattern, lower cadre health workers [aOR: 4.2 (1.5-11.7)] and having a confirmatory test [aOR: 2.6 (1.2-5.8)] were significant predictors of correct treatment. Furthermore, this work revealed that provider's attitudes towards treatment recommendations have little influence in their personal practices; a good proxy indicator of their general practice. Factors like type of patients, place of work and level of health care, had more influence in their personal use of treatment recommendation.

Findings from this work underscore the multidisciplinary nature of health problems. Concentrating in only certain aspects of the health system than others may lead to undesirable consequences. Addressing a common health problem requires looking at the problem holistically, with systems thinking approach. Understanding the complexity nature of systems is the underlying principle of systems thinking. The problems highlighted here in relation to malaria case management may constitute a small part of disease burden in Tanzania, but provides important lessons for harmonization of technical and organizational challenges that hinders progress to better health outcomes with the right pace.

This work made evident the need to advocate transparency and harmonization of health system actors, towards a common goal; empower policy makers and health managers to understand and adopt systems thinking approach in their daily endeavours as well, provide more scientific evidence for what does or doesn't work, to guide policy making decisions.

Unless we change the status-quo, health systems performance will remain sub-optimal and an impediment for moving the malaria (and other diseases) elimination agenda forward.

Zusammenfassung

Der Bericht der Welt Gesundheits Organisation des Jahres 2007 sagt aus, dass es nicht ohne grössere und effizientere Investitionen in Gesundheitssystemen und -Dienstleistungen möglich ist, nationale und internationale Gesundheitsziele zu erreichen. Der Fortschritt in der Wissenschaft führt zu einem besseren Verständnis von Ätiologie und der Risikofaktoren von den meisten Krankheiten. Die Fähigkeit, diese Innovationen der Bevölkerung in Entwicklungsländern, welche sie am meisten benötigt, zur Verfügung zu stellen, wird durch anfällige und schlechte Gesundheitssysteme untergraben. Die unterschiedlichen Krankheitsbelastungen in einem Land und im Vergleich zu anderen Ländern unterstreichen die Komplexität und das Bedürfnis nach gezielten Massnahmen gegen Krankheitsbelastungen und den schlechten Gesundheitszustand in den genannten Völkern.

Heutzutage ist Malaria weiterhin ein bekanntes Gesundheitsproblem und führt in den 99 betroffenen Ländern zu steigender Morbidität und Letalität durch kontinuierliche Übertragung. In Tansania ist Malaria einer der Hauptgründe für Spital-Einweisungen und Tod in infizierten Regionen. Getroffene Gegenmassnamen waren insofern wirksam, als dass in endemischen Gegenden die Morbidität und Letalität zurück ging. Diese positive Entwicklung wird jedoch durch Medikament- und Insektizid Resistenz zusammen mit Umwelteinflüssen und deren Vektoren und Überträger, erschwert. Trotz diesen bekannten Bedrohungen kann Malaria verhindert werden, historisch belegt durch die Ausrottung im Norden. Dadurch entsteht die Hoffnung, dass Malaria auch in den endemischen Gebieten in naher Zukunft ausgerottet werden kann, sofern effiziente Massnahmen zur Anwendung kommen.

Die aktuelle Malaria-Strategie kann grob in folgende Kategorien unterteilt werden. Erstens: Vektorbezogene Massnahmen, wie der Gebrauch von Behandelten Netzen über dem Bett, Spray-Anwendung im Haus und Umweltmanagement. Zweitens: Chemo prävention in gefährdeten Bevölkerungsgruppen und drittens: Schnelle und effektive behandlung von Malaria. Die gesundheitsvorsorge in Tansania hat einige engpässe wie

wenige, qualifizierte Arbeitskräfte, fehlende, angemessene Technologien und zu wenig Medizin für Patienten zu bewältigen. Zusätzlich schwächt die Nichteinhaltung von Behandlungs-Vorschriften die Effektivität des Systems.

Im Rahmen eines Phase 4-Trial Programms von Indepth Network Effectiveness and Safety Studies of antimalarials (INESS) untersuchten wir die Qualität von behandlung in den Studiengebieten. Das Ziel war es, faktoren zu verstehen, welche in der praxis behandlungsergebnisse beeinflussen, wobei der fokus bei der diagnostikgenauigkeit und der zustimmung der anbieter für malaria behandlung. Die arbeit enthielt ein paar von cross-sectional Gesundheitszentren umfrage in der regen- und der trockenzeit. Im rahmen dieser Studien wurden Patienten, Anbieter und involvierte Gesundheitszentren über die Verfügbarkeit von Produkten für die Malariabehandlung befragt. Zusätzliche Daten erhielten wir vom Interdisciplinary Monitoring Project of Antimalarial Combination Therapy in Tanzania (IMPACT-Tz), welches vor der nationalen Einführung von ACT für Malariabehandlung artemisinin based combination therapy (ACT) in ähnlichen Studiengebieten einführte.

Zusammenfassend zeigten die Resultate dieser Studien, dass die anwachsende Anwendung von malaria schnelltests “rapid tests“ (RDTs) für Routineuntersuchungen die Übertherapie mit ACT während Perioden mit hoher Malariaübertragung von 45.8% (37.2-54.6) in einem pre-RDT Gebiet zu 20.9% (14.7-28.8) in einem post-RDT gebiet reduzierte. Dies impliziert, dass das Vorhandensein von geeigneten Technologien das Targeting von Ressourcen und die Zustimmung der Anbieter verbessert. Weitere Untersuchungen zur korrekten Dosierung von ACT für das behandlung von unkomplizierter Malaria zeigten, das altersabhängige Dosierung fehleranfälliger war. Der Anteil von Patienten, welche eine korrekte Dosis nach nationalen Richtlinien erhielten, war in der Gruppe der älteren Kinder kleiner; 42% für 9-12 Jahre alte Kinder und nur 50% für 3-9 Jahre alte Patienten. Auch in der multivariaten Datenanalyse zeigte sich ein signifikanter Zusammenhang mit einem tieferen chancen für korrektes Dosieren ($p<0.05$). Die Analyse von gesundheitszentren-daten aus den Jahren 2002 bis 2010

zeigte, dass die präsenz von parasitemia in einem Gesundheitszentrum über die Jahre zurückging für Kinder unter fünf Jahren und anstieg für Kinder über fünf Jahre. Allerdings wurden signifikante Unterschiede innerhalb der Gruppen festgestellt. Während Kinder unter zwei Jahren einen abnehmenden trend für die Präsenz von parasitemia in einem Gesundheitszentrum zeigten, hatten diejenigen Kinder zwischen zwei und fünf Jahren einen zunehmenden trend ($p<0.001$). Diese Funde stehen im Widerspruch zu Ergebnissen von Bevölkerungsbasierten Untersuchungen.

Diese Arbeit beschreibt unter anderem spezifische faktoren von fachkräften im gesundheitswesen, welche die richtige Behandlung von malaria beeinflussen. Es war interessant zu sehen, dass die arbeitserfahrung der fachkräfte im gesundheitswesen die behandlungsqualität beeinflusst. Dienstleistende, welche schon 3 oder mehr jahre arbeitserfahrung vorweisen konnten, hatten einen höheren odds die richtige behandlung durchzuführen, als dienstleistende mit weniger als 3 jahren Arbeitserfahrung. Genauso waren lower cadre health workers und der besitz eines bestätigungstest signifikante einflusswerte für eine richtige malariabehandlung. Weiter zeigt diese arbeit, dass die einstellung der dienstleistenden gegenüber behandlungsempfehlungen wenig einfluss auf ihre eigene praxis hat. Dies stellt ein guter proxy-indikator der allgemeinen praxis dar. Mehr einfluss auf den persönlichen gebrauch von behandlungsempfehlungen hatten faktoren wie patientenkategorien, wie zum beispiel kinder vs. erwachsene, schwangere vs. nicht-schwangere, oder wie arbeitsplätze, wie zum beispiel öffentliche vs. private arbeitsplätze oder auch level der gesundheitsversorgung wie zum beispiel spital vs. krankenhausapotheke.

Resultate dieser Arbeit betonen den multidisiplinären Charakter der Strategien zur Krankheitsbekämpfung. Den Schwerpunkt auf nur einen Gesundheitsaspekt zu legen, könnte führen zu unerwünschten folgen. Harmonisierung der verschiedenen Funktionen des Systems auf eine gemeinsame Gesundheits-Problems erfordert das Problem suchen ganzheitlich, mit Systemen denken Ansatz. Das Verständnis der Komplexität der Natur von Systemen ist das zugrunde liegende Prinzip des Systemischen Denkens.

Die probleme hier in Bezug auf malaria behandlung hervorgehoben darstellen kann einen sehr kleinen teil in der karte der krankheitslast in Tansania, sondern bietet wichtige Lehren für die harmonisierung der technischen und organisatorischen herausforderungen, die den fortschritt behindert, bessere gesundheitliche ergebnisse mit dem richtigen tempo.

Solange der aktuelle Zustand nicht geändert wird, wird die Leistungsfähigkeit des Gesundheitssystems suboptimal bleiben und stellt somit im Vorantreiben der Beseitigung von Malaria und anderen Krankheiten ein Hindernis dar.

Abbreviations:

<5	Children less than 5 years of age
>5	Children or adults above 5 years of age
ACT	Artemisinin-based combination therapy
ADDO	Accredited Drug Dispensing Outlet
ADR	Adverse Drug Reaction
AIDS	Acquired Immunodeficiency Syndrome
AL (ALU)	Artemether-Lumefantrine
AMO	Assistant Medical officer
aOR	adjusted Odds Ratio
BS	Blood smear
CDC	Centers for Disease Control and Prevention
CHMT	Council health management team
CMO	Chief Medical Officer
CO	Clinical officer
cOR	crude Odds Ratio
DHA	Dihydroartemisinin
DMO	District Medical Officer
HDSS	Health and Demographic Surveillance System
HF	Health facility
HIS	Health information system
HIV	Human Immunodeficiency virus
HMIS	Health management information system
HRP2	Histidine Rich Protein 2
HW	Health worker
i.e.	that is
IHI	Ifakara Health Institute (formally known as IHRDC)
IHRDC	Ifakara Health research and Development Center
IMCI	Integrated Management of Childhood Illness

IMPACT-Tz	Interdisciplinary Monitoring Programme for Antimalarial Combination Therapy in Tanzania
INESS	Indepth Network for Effectiveness and Safety Studies of antimalarials
IRB	Institution ethical Review Board
K/U	Kilombero/ Ulanga
LGA	Local Government Authority
LSHTM	London School of Hygiene and Tropical Medicine
M&E	Monitoring and Evaluation
MO	Medical officer
MOHSW	Ministry of Health and Social Welfare
mRDT	Malaria RDT
NBS	National Bureau of Statistics
NCDs	Non-communicable diseases
NIMR	National Institute for Medical Research
NMAIST	Nelson Mandela African Institute of Science and Technology
NMCP	National malaria control program
PCR	Polymerase Chain Reaction
PMO	Prime Minister's Office
POPC	President's Office Planning Commission
QA	Quality Assurance
RBCs	Red Blood Cells
RALG	Regional Administrative and Local Government
RBM	Roll Back Malaria
RDT	Rapid diagnostic tests
RHMT	Regional health management team
RMO	Regional Medical Officer
SP	Sulphadoxine -Pyrimethamine

TDHS	Tanzania Demographic and Health Survey
TEHIP	Tanzania Essential Health Interventions Project
THMIS	Tanzania HIV/AIDS and Malaria Indicator Survey
TN	Trained Nurse
USAID	United States Agency for International Development
WBCs	White Blood Cells
WHO	World Health Organization

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PART I: BACKGROUND

Chapter 1: Introduction

1.1 Malaria:

Malaria has been and still is an important cause of human morbidity and mortality. The disease is caused by members of the phylum *Apicomplexa*, genus *Plasmodium*. *Plasmodium* species exhibit a heteroxenous life cycle involving a vertebrate host and the anthropod vector. Five Plasmodium species are responsible for human infection; *P. falciparum, P. vivax, P. ovale, P. malariae and P. knowlesi (WHO, 2011; Figtree M 2010)*. The species differ in their morphology, details of their life cycles and clinical manifestations. Malaria due to *P. falciparum* is the most deadly and it predominates in Africa.

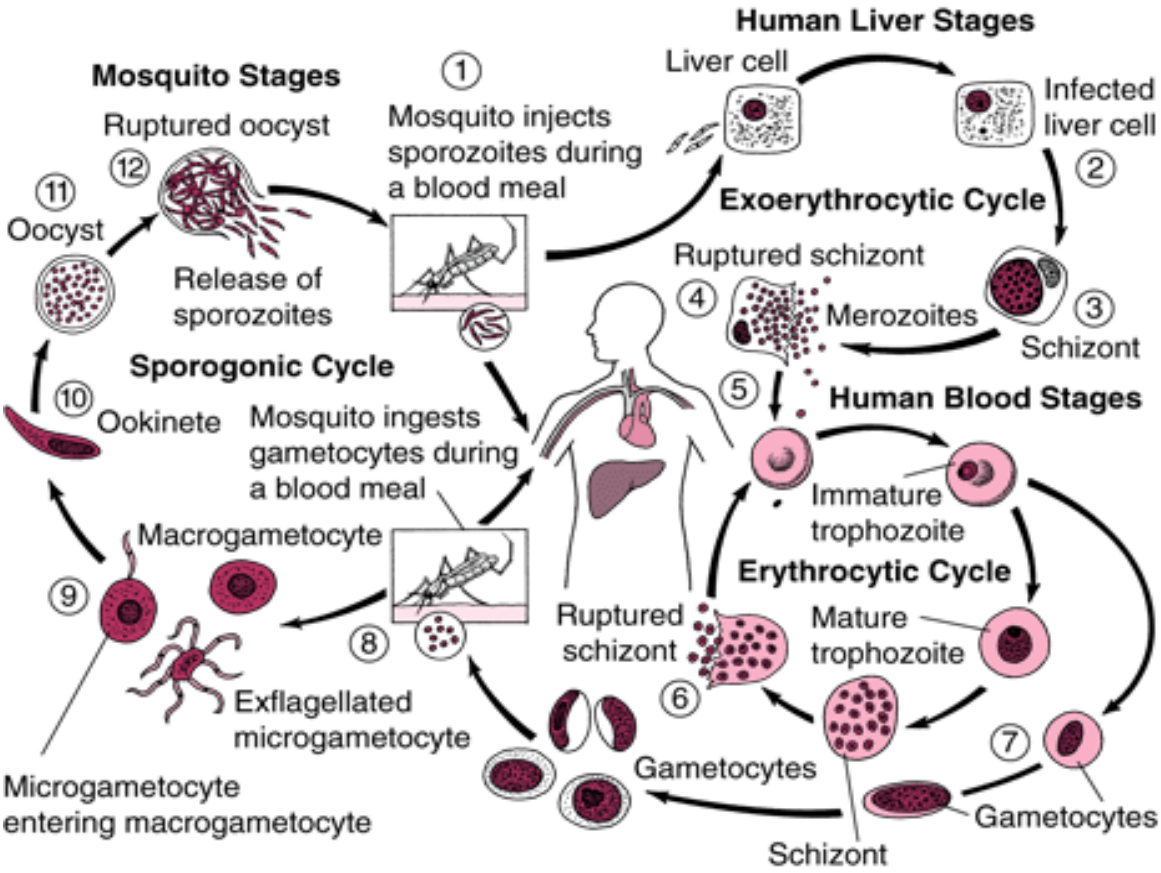
Pathogenesis and Transmission of malaria:

Malaria infection in humans is transmitted through the bite of female infected anopheline mosquitoes. Sporozoites injected during mosquito feeding, enter the circulatory system, and within 30-60 minutes will invade a liver cell (figure 1). In the hepatocyte (exoerythrocytic cycle), the parasite undergoes asexual replication, often called pre-erythrocytic cycle (schizogony) (Kakkilaya, 2011; Vaughan AM et al., 2008) . During this replicative process, merozoites are released into the circulation following rupture of hepatocytes. In *P. vivax* and *P. Ovale* infections, some sporozoites do not undergo asexual replication, entering a dormant phase known as hypnozoite. Hypnozoites can reactivate on a later stage causing a relapse (Cogswell, 1992). While relapse in malaria refers to a reactivation of infection through hypnozoites, recrudescence describes a situation where parasites fall below a detectable level and later, increases to a patent detectable parasitemia.

As alternative to schizogony, some parasites undergo a sexual cycle and differentiate into gametocytes (Vaughan AM et al., 2008). Gametocytes do not cause pathology in the human host, but once taken up by mosquito, they go into a sexual stage in the mosquito gut and produce sporozoites (sporogony cycle) that carry on malaria

transmission (figure1). Merozoites released from infected liver cells invade erythrocytes (erythrocytic cycle). The pathology associated with all malaria species is related to rupture of infected red blood cells (RBCs) (Cogswell, 1992; Cowman A.F and Crabb B.S, 2006); erythrocytes, releasing parasite materials, metabolites, hemozoin (malaria pigment) and cell debris. This corresponds to malaria paroxysm, which is the main clinical stage of malaria. During this stage, there are increased activities of the reticuloendothelial system, particularly in the liver and spleen, resulting in their enlargement. Destruction of RBCs results in anemia. The destroyed RBCs and along with toxins, sequestrate into blood vessels causing tissue damage. Of all the species, *P.falciparum* infection is associated with severe clinical manifestation.

Figure 1: Life Cycle of malaria parasite. Source: merckmanuals.com



Clinical manifestation of malaria:

The clinical manifestation of malaria is almost exclusively due to the asexual erythrocytic stage. All malaria species present non-specific prodromal symptoms before a febrile attack. These symptoms includes; headache, slight fever, muscle pain, anorexia, nausea and lassitude (Kakkilaya, 2011). The symptoms tend to correlate with increasing parasite counts. The prodromal period is followed by febrile attacks known as paroxysm, which shows periodicity of 48 to 72 hours depending with the *Plasmodium* species. In *P. falciparum* infection, the paroxysms may be irregular, exhibiting periods of continuous fever, daily or irregular attacks. Patients may also present with splenomegally, hepatomegally with slight jaundice and hemolytic anemia.

The paroxysm is usually followed with onset of chills (with rigorous shivering) where a patient experiences cold despite having elevated temperature. The cold stage is immediately followed by the hot stage, where a patient feels intense heat, severe headache, fatigue, dizziness, anorexia, myalgia and nausea. The next stage is characterized by profuse sweating and the decline of fever. The patient feels weak and exhausted but does not exhibit other symptoms until the next paroxysm (Kakkilaya, 2011). Among the serious disease complications is cerebral malaria. Cerebral malaria is commonly characterized by impaired consciousness (Molyneux ME, 1989); severe headache, convulsions, drowsiness, confusion and coma. These neurological manifestations are believed to be due to manifestation of infected erythrocytes in microvasculature.

The burden of malaria:

Malaria is a public health problem with ongoing transmission in 99 countries (WHO, 2011). In 2010, there were estimated 216 million episodes of malaria of which approximately 81% were in the African region (WHO, 2011). Estimates in early 21st century describe the annual global burden of malaria as deaths, 1.12 million, 300-500 million clinical cases and disability-adjusted life years (DALYs) 34.0 million (WHO, 2001). Murray and colleagues in 2012, reported higher malaria mortality burden,

especially in the adult population, than previously estimated or reported by the WHO (Murray CJL et al., 2012). More than 90% of malaria disease burden falls in sub-Saharan Africa where *P. falciparum* infection is most prevalent (WHO, 1999). The most vulnerable groups in malaria are children below age of 5, mainly due to their less developed compensatory and immune mechanisms as well as pregnant women because of their increased circulatory demands and pregnancy induced immune-suppression.

Malaria is among the leading causes of hospital attendance and mortality where the disease is prevalent. The national malaria medium term strategic plan (NMMTSP 2008-13) reports that malaria accounts for up to 40% of all out-patient-department (OPD) attendances in health facilities (PMI, 2008). The WHO world malaria report, 2012 describes a significant reduction in malaria burden since 2000, with 52% of cases averted and 58% lives saved from the 2000 estimates (WHO, 2012b). The number of cases is estimated to have decreased globally from 244 million in 2005 to 225 million in 2009 to 219 million in 2010. Likewise, deaths due to malaria have decreased from 985,000 in 2000 to 781,000 in 2009 to 660,000 in 2010 (WHO, 2010b; WHO, 2011; WHO, 2012b). Africa continues to bear the biggest burden of malaria with 91% of all malaria deaths reported from (WHO, 2011). The disease is also a major cause of school absenteeism and loss of productivity, hence a huge impact in the countries' economy.

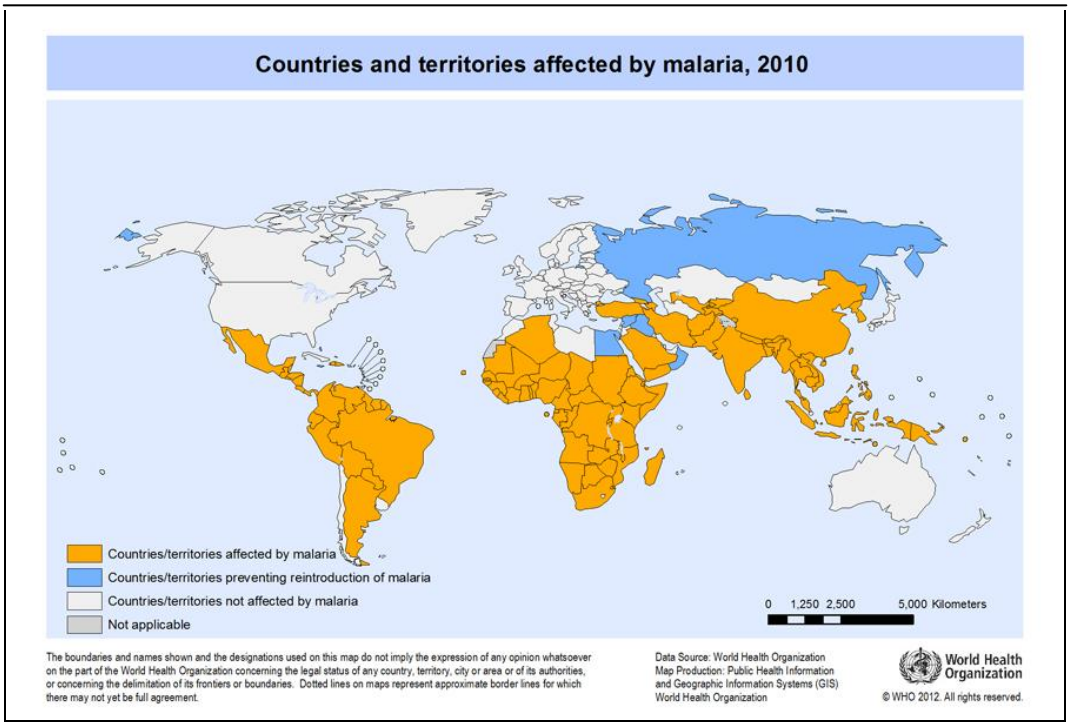
1.2 Malaria epidemiology:

Malaria is mainly a disease of the tropics, sub-tropics and hot humid regions of Africa, Asia, South and Central America. In the past, malaria was also found in temperate areas including Europe and North America, but it has been eliminated. Literature shows that, the ideal environmental conditions for malaria transmission are rainfall about 80mm for not less than five months per year and temperature between 22-32°C (Craig MH et al., 1999). These conditions are favourable for the existence of *Anopheles gambiae s.I.* mosquito that transmits malaria (Charlwood JD et al., 1995). *Anopheles*

gambiae complex are complimented with *Anopheles funestus* group that feeds almost exclusively indoor at nigh (Killeen et al., 2006).

The epidemiology of malaria can be described according to its transmission intensity, clinical features, etc. In terms of transmission, we have areas with stable malaria which implies persistency of high prevalence of malaria infection with minimal seasonal fluctuation; where as in areas with unstable malaria, there are variability of malaria infection in place and time. In terms of parasitemia we can have hypo-endemic (intermittent transmission) with <10% parasite prevalence among 2-9 years old, meso-endemic (regular/ seasonal transmission) with 11-50% prevalence in 2-9 years old age group, hyper-endemic (intense but with periods of no transmission) with >50% parasite prevalence and holoendemic (all year long transmission) with >75% parasite prevalence in infants (WHO, 1951).

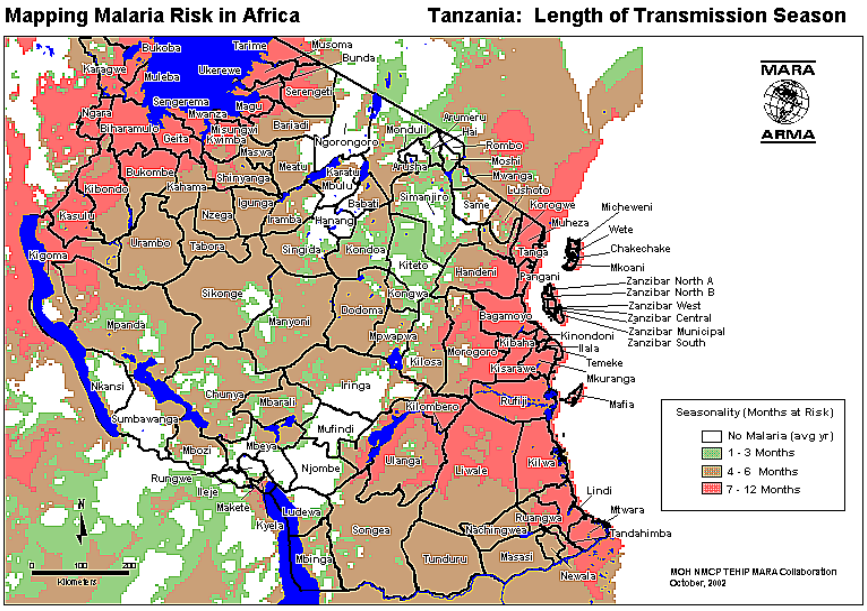
Figure 2: World Malaria distribution. Source World Health Organization



Epidemiology of malaria in Tanzania:

Malaria in Tanzania remains a major public health problem, and a leading cause of morbidity and mortality (NMCP, 2003c). The disease is endemic in all parts of the country but with variation in endemicity levels caused by differing rainfall patterns, altitude and temperature. In early 2000, a programme of mapping malaria risk in Africa (MARA) described Tanzania, to have different malaria transmission patterns (figure 4). There were areas with unstable seasonal malaria with transmission, not exceeding three months a year which included areas at high altitude above 2000 Meters above sea level and semi-arid along the Rift Valley (NMCP, 2003c). Areas with stable, seasonal malaria have about 3-6 months of intense transmission; where as stable perennial transmission occurs along the coastal areas extending as far as 160-240 Km inland.

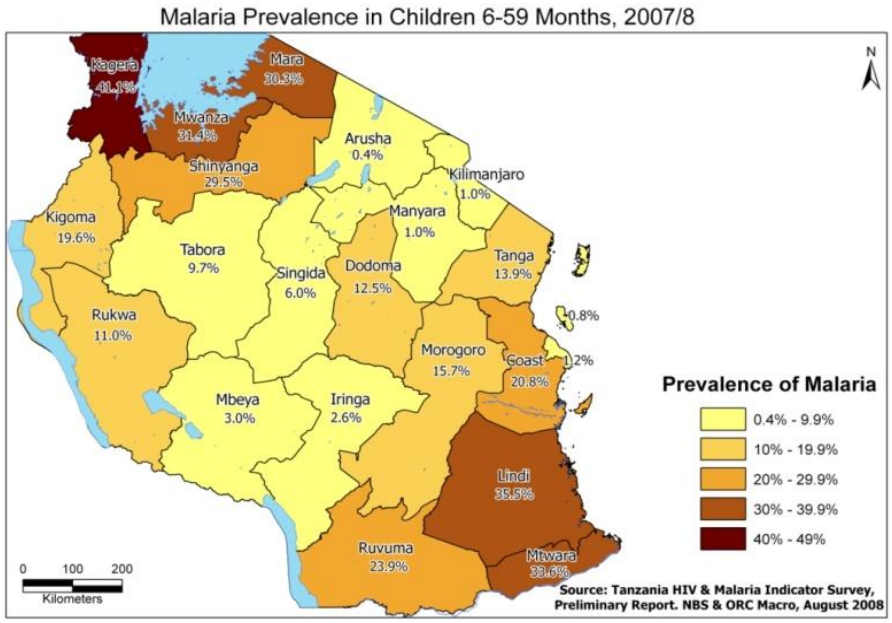
Figure 3: Malaria Transmission pattern in Tanzania (2002)



Data from the country's statistics indicates that malaria prevalence is on the decline. Abstracts from National health management information system in early 2000, estimated 14-18 million cases and mortality ranging between 140-165 per 100,000 population (NMCP, 2003c). The community household surveys of the countrywide

representative sample commonly known as Tanzania Demographic and Health survey (TDHS) have shown a steady decline of fever prevalence in children below age of five. Fever as the commonest malaria indicator averaged 35.1% in 1999, to 24.4% in 2004 to 22.9% in 2010 (NBS, 1999; NBS, 2004/5; NBS and Macro ICF, 2011). Likewise, the Tanzania HIV/AIDS and Malaria Indicator Survey report a decline in malaria positivity from 18.1% in mainland Tanzania in year 2007/8 to 9.5% in 2012 by rapid test or 4.5% by microscopy, with a wide rural-urban difference, whereby urban has persistently lower malaria prevalence than rural areas (THMIS, 2007/8; THMIS, 2012). This rural-urban difference is also seen in the TDHS reports.

Figure 4: Variations in malaria prevalence, Tanzania (2007/8)



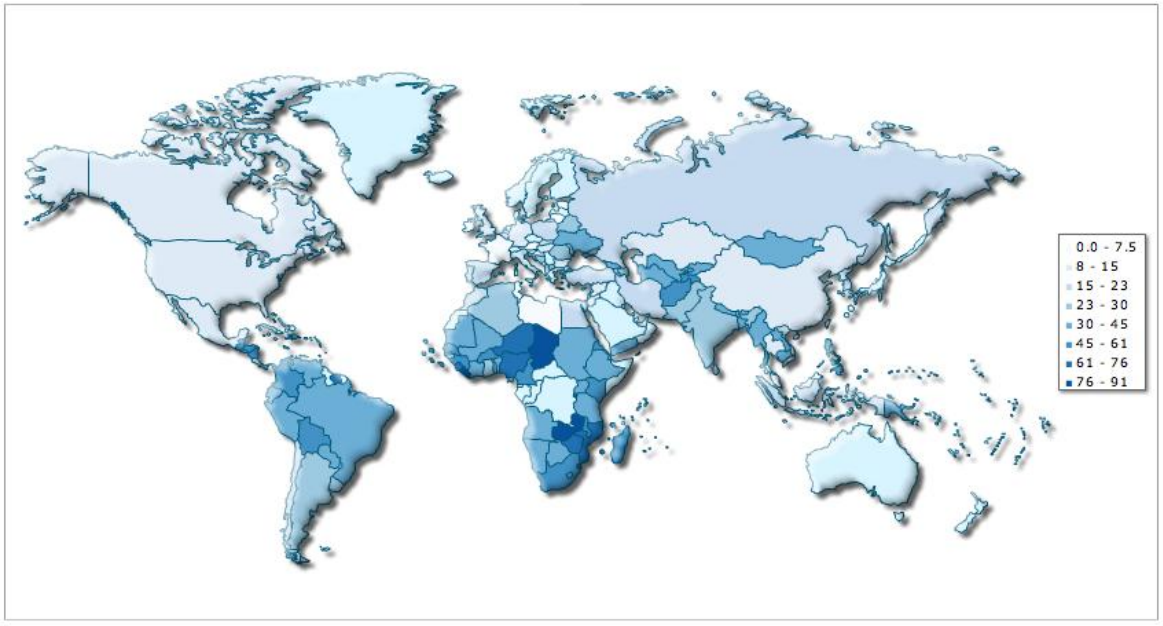
Malaria and poverty:

Malaria and poverty has been a topic of interest for many years. The disease is almost always referred to as the disease of poverty. While the disease is largely determined by environment, host and vector factors; there is a striking correlation between global burden of malaria and poverty (figure 2- malaria, figure 5- poverty below). The indirect

and direct costs of malaria are related to loss of income and productivity and expenditure related to the disease prevention measures and treatment.

Although the relationship between malaria and poverty has long been recognized, its paths and mechanisms are not clear. Studies suggest that causality works both ways; trapping communities in cycles of poverty. This underscores the need for malaria control efforts to include poverty reduction strategies (Teklehaimanot A and Mejia P, 2008).

Figure 5: World Poverty map: Percent of population living below poverty line. Source: Econosystemics.com



1.3 Malaria control strategies in Tanzania and beyond:

Malaria is an entirely preventable and treatable disease, provided that recommended interventions are properly implemented (WHO, 2011). The major preventive mechanism for control of malaria infection relies on avoiding contact with vector that transmits malaria, chemoprevention and effective treatment of infected cases.

Vector control:

The goals for malaria vector control are to protect people against infective mosquito bites and reduce intensity of local malaria transmission, by reducing longevity, density and human-vector contacts. The most common interventions targeting vector control includes environmental management (EM), use of insecticide treated bed-nets (ITNs), preferably long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS). Environmental management (EM) through larva control is advisable in minority of settings including urban to complimenting IRS and LLINs. Historically, EM has brought important achievements in overall malaria control and improvements in health conditions that was evident with the construction of Panama canal and Zambia copper belt as good examples (Keiser et al., 2005; Castro et al.). In Tanzania, EM activities were done during the colonial period and shortly after independence, but were discontinued due to country's adverse economic conditions (Castro et al.). During 2005-07, the partnership between Japan International Cooperation Agency (JICA), the National Malaria Control Programme (NMCP) and the Urban Malaria Control Programme (UMCP) planned and implemented a pilot intervention of community-based EM of *Anopheles* breeding sites in Dar es Salaam (NMCP, JICA 2004). This programme reported a significant reduction in malaria infection during the post-cleaning period, but as well recommended a need for multidisciplinary coordination of integrated vector management for malaria control (Castro et al.).

Indoor residual spraying, involves application of residual insecticides to the inner surface of dwellings where many species of anopheles mosquito rest after taking a blood meal. It remains one of the main interventions for reduction and interruption of malaria transmission in all epidemiological settings (WHO, 2011). Currently there are 12 insecticides recommended by WHO pesticide evaluation scheme (WHOPES) for IRS (WHO, 09), of which selection of use depends on resistance data, residual efficacy, costs, safety and the surface to be sprayed. The Dichloro-Diphenyl-Trichloroethane (DDT), has a long residual efficacy (6+ months), and is allowed to use for IRS, as long

as appropriate guidelines are followed. IRS activities in Tanzania mainland are carried out in epidemic prone areas since 2009 (PMI, 2011). The early IRS implementation in Muleba district was associated with a 56% reduction in hospital admissions and a 75% reduction of deaths attributable to malaria (PMI, 2011).

Insecticide-treated nets are among the key malaria control interventions that have shown tremendous success in the fight against malaria. The use of insecticide treated bed-nets provides physical and other barriers against mosquito bites. The effectiveness of ITNs for malaria prevention has been demonstrated in several African countries such as Ghana and Tanzania, in late 20th century (Binka et al., 1998; Abdulla et al., 2005; Abdulla et al., 2001). Furthermore, use of ITNs have been reported to provide both individual and community protection against infective bites (Abdulla et al., 2005; Killeen et al., 2007). The need to extend ITNs benefits to malaria risk groups, led to exploration of different delivery strategies through both public and private sectors. There is now more evidence to suggest that, delivery of ITNs through different mechanisms including social marketing, free distribution, etc, significantly increases coverage of ITNs to the communities (Abdulla et al., 2001; Schellenberg et al., 2001; Khatib et al., 2008; Curtis C et al., 2003).

One of the challenges reported in the early use of ITNs was the low level of net re-treatment. This was a major setback to the fully realization of ITNs impact to sustainable malaria control efforts. However, availability of long lasting insecticide nets (LLINs) has provided a solution to the re-treatment challenge, at least to the life span of the net. Another challenge to vector control for the control of malaria is related to changes in behaviour of the vector populations. Russell and colleagues, reported an increase in proportion of outdoor feeding among residual malaria vector populations following increased use if ITNs in rural Tanzania (Russell TN et al., 2011).

Chemoprevention:

There are other effects of malaria that are not always directly linked to the disease. Scientists have long documented that, malaria causes some indirect effects especially related to pregnancy outcomes and growth of the fetus. In malaria endemic regions, pregnant women are at risk of infection due to the decreased immunity. Malaria in pregnancy is associated with abortions, stillbirths, anemia and delivery of low birth weight babies. Birth weight has been shown to be a significant predictor of child's survival and growth (Greenwood et al., 1992). In order to reduce the consequences of malaria in pregnancy and child survival, the intermittent preventive treatment in pregnancy (IPTp) is recommended to women living in endemic areas. In IPTp, a therapeutic course of antimalarial is taken, and had shown to reduce placental parasitemia (Newman et al., 2003; van Eijk et al., 2011). Despite of the benefits reported, uptake of the second IPTp dose has been a major setback (WHO, 2011).

Another vulnerable group to the hazardous effects of malaria is infants. Many children in malaria endemic African countries die due to malaria. The World Health Organization reported that about 86% of all malaria deaths in 2010 were in children below the age of five (WHO, 2011). The fact that newborns and younger children have underdeveloped immunity plays a huge role in malaria pathogenesis to this group. Randomized clinical trials (RCTs) have demonstrated that, providing antimalarial preventive treatments as intermittent preventive treatment to infants (IPTi), protects children and significantly reduce the negative health consequences of malaria in this age (Schellenberg et al., 2006). WHO now recommends IPTi with Sulphadoxine Pyrimethamine (SP) in countries with moderate to high malaria transmission, where levels of parasite resistance to SP are low (WHO, 2011).

Development of other tools for malaria control is still ongoing. This includes malaria vaccines for African children and other malaria endemic countries. A phase 3 trial of candidate malaria vaccine RTS,S/A S01 conducted in seven African countries brought new hope for an efficacious vaccine of malaria in future. In this trial, RTS, S/A S01

provided protection against both clinical and severe malaria in African children (The RTS, S Clinical Trial Partnership). Initial results provided by the study team, published in the New England Journal of Medicine in October, 2011 shows that, the RTS,S vaccine provided protection against clinical and severe malaria in both per- protocol and intention-to-treat analysis (RTSS/AS01, 2011).

Malaria case management:

Prompt and effective treatment of malaria cases is advocated for control of the disease. The emergency and widespread of resistance to insecticides and commonly used antimalarials medicines such as Chloroquine and Sulphadoxine-Pyrimethamine (SP), makes appropriate treatment very challenging to poor countries. The current global efforts to improve malaria treatment are on use of artemisinin based combination therapy (ACTs) for malaria treatment. Artemisinins are still effective even against Chloroquine resistant parasites and are being used for treatment of both severe and uncomplicated forms of malaria. Tanzania changed her malaria treatment guidelines twice within a decade. First, in early 2001, Chloroquine was replaced by SP for management of uncomplicated malaria and in late 2006, artemether-lumefantrine (ALu) which is an artemisinin based combination treatment, replaced SP. Quinine continued to be a treatment of choice for severe malaria, newborns below 2 kg of weight and pregnant women in their first trimester. In 2012, the country is reviewing malaria treatment guidelines to introduce artesunate injection as first line medicine for treatment of severe malaria.

Studies in rural Tanzania have shown that, malaria patients seek care and obtained antimalarial medicines from informal retail outlets (Goodman et al., 2004; Kachur et al., 2006; Hetzel et al., 2008). In the move to increase accessibility of antimalarial medicines, the Government of Tanzania (GoT) piloted and started to implement a revised pharmaceutical criterion, allowing ACTs to be stocked in private Accredited Drug Dispensing Outlets (ADDOs). During the pilot phase, ADDOs demonstrated an improvement in availability of malaria treatment in study areas (Quick JD et al., 2005).

Tanzania also bans the use of artemisinin based monotherapy, in order to reduce development of drug resistance. In addition, GoT introduced malaria rapid diagnostic tests (mRDTs) for routine use to all levels of care, to complement microscopy services wherever available. Introduction of mRDTs in routine health care system is expected to improve quality of care given to malaria suspected patients, limit the use of ACTs to true malaria patients and provide accurate estimates of the disease burden in the country. Despite good prospects for using mRDTs in routine care, bottlenecks in the health system may limit obtaining the full value of this tool in malaria control (Masanja et al., 2011).

1.4 Health systems

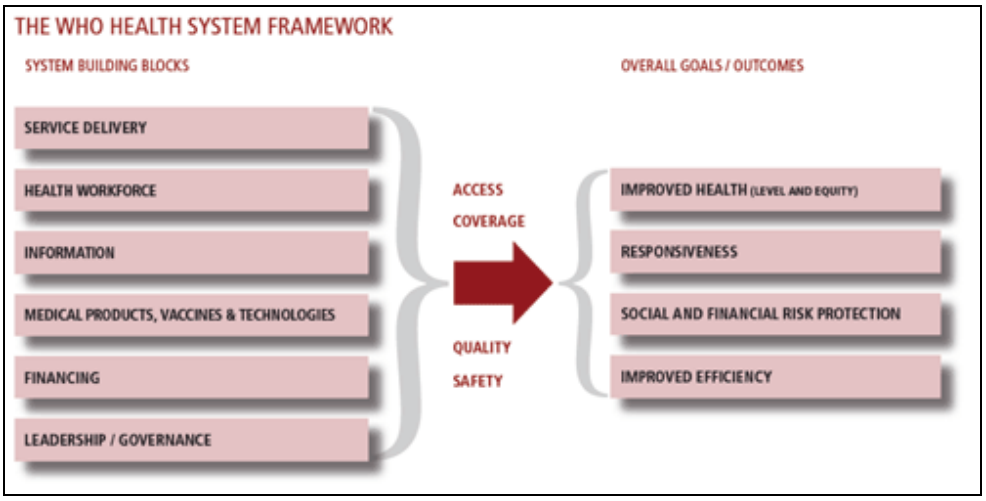
The WHO defines health system as all organizations, people and actions whose primary intent is to promote, restore or maintain health (WHO, 2007). But, the description of health system performance goes beyond assessment of health care services indicators such as immunization coverage, number of hospital beds, maternity care etc (Olafsdottir AE, 2011). It needs to include wider determinants of health including governance and its relation to health and health equity, human resources for health, availability of supplies and products, etc. The WHO health system framework describes health system in terms of six core interconnecting building blocks; finances, health workforce, information, governance, medical products and technologies as well as service delivery (figure 6) (WHO, 2008).How this framework depends on substantial inter-linkage and interactions among the blocks such that, they all contribute to the strengthening of the health systems in different ways, was clarified by de Savigny and Adam in 2009 (De Savigny D and Adam T, 2009).

Health systems building blocks:

While governance provides a cross-cutting role in health systems performance, financing, human resources, information, medicines and technologies for health are major inputs for production of health, whereas service delivery reflects the immediate

outputs of the health system (WHO, 2008). All of the six blocks have unique strengths to influence performance of the entire health care system in respective countries (Kaufmann D, 2008). Assessment of governance in health requires ensuring appropriate policies and strategies are in place, and effectively implemented or enforced (Mikkelsen-Lopez et al., 2011).

Figure 6: The WHO Health systems framework: The six building blocks



Financing in health systems requires raising of sufficient funds to run the system through revenue collection and external sources; but also to provide financial risk protection to the population, avoiding catastrophic expenditures in health through a proper mix of financing policies; weighing between regressive and progressivity as well as providing efficiency use of resources, in order to avoid wastes and corruption.

The information sub-system is the basis for decision making and policy development. Information may be of little value if it lacks accuracy, completeness and not be available in timely manner and in appropriate formats to meet the needs of multiple users. One big challenge related to health information systems is the existence of different methods of data collection, multiple data sources and multiple indicators. Many reports have highlighted the challenges of fragmentation, untimely availability and incompleteness of data from routine health care systems in resource poor countries (Smith M et al., 2008).

Now, information technology experts are thinking of ways to simplify the complexity of health information system (HIS) through enterprise architecture (EA) (Mwanyika H, 2011), e-health and the Health Metrics Network framework (WHO, 2012a).

Human resources for health are known to have a big influence in delivery of quality health services. Studies have shown a positive link between number of health workers and population health outcomes (Anand S and Barnighausen T, 2007). The critical shortages of health workers in sub-Sahara African countries are known to have many contributing causes, including inadequate skill mix, mal-distribution (Maestad, 2006; Leon BK, 2010; Kurowski C et al., 2003), death, retirement as well as career change and out-migration. Brain drain and health workers attrition is an all too common phenomenon much reported in literature (Kurowski C et al., 2003; Pang T, 2002).

Provision of quality service requires available products and technologies in place. In order to ensure availability of medical products, vaccines and technologies, an effective and accountable local and national procurement and drug management system is needed. This is unfortunately not always practical in resource poor countries and may leave way for leakages and corruption. New health system technologies may improve the situation. Such programmes as use of short text messages (Barrington et al., 2010) to assess stocking levels of products and act accordingly, brings new hope for ensuring availability of necessary medical products for improving quality of health care.

Service delivery block is the most visible component of the health system. Health services can be promotive, preventive, curative or rehabilitative services and may be delivered at home, community, and workplace or in health facilities. Effective service delivery depends on having resources in place; including staff, medicines, supply chain, etc, that are timely accessible to people. Any improvement in the provision of health care is most likely to improve the livelihood of people in the respective communities. With respect to malaria, studies have shown that, improving access to recommended treatment also improved malaria treatment and treatment seeking behavior, with an impact in the disease morbidity and mortality (Alba, 2010).

Health systems strengthening and global health systems:

The WHO report in 2007 (Everybody's Business); declares that it will be impossible to achieve national and international health goals without greater and more effective investments in health systems and services (WHO, 2007). Among the challenges facing health systems in developing world has to do with failing health systems, failure of scaling-up effective interventions and resources constraints. The facts that the spectrum of disease burden differs across communities and countries, and countries differs in economic, social-cultural and political contexts; makes it extremely difficult to have common measures of action for health systems improvement globally. The WHO reports that, threats posed by new epidemics such as the avian or human pandemic influenza, demands response from all countries rich and poor (WHO, 2007); which further illustrates the severity of challenges faced.

The recognition of the need to strengthen health systems has resulted a growth in country's domestic budgets and donors support, particularly in low and middle income countries (WHO, 2007). The patterns of disease, risk factors and treatments recommendations also keep changing, posing differing demands in time and place. In many developing countries, the poorest quintile is the hardest to reach by interventions that seem to be working well for the majority of people. This brings the issue of inequity and inequality of services, and ethical concerns for human rights to access quality health care and efficiency of health systems. Despite these challenges and complexity of addressing them in context, the WHO now advocates a 'systems thinking' approach to guiding response to health systems challenges as described in several reports including its 2009 publication; Systems Thinking for Health Systems Strengthening (De Savigny D and Adam T, 2009).

The Tanzanian Health System:

Tanzania is one of the low income countries that have a well defined national health strategy and health care delivery structure. As described in the Ministry of Health and Social Welfare government website (www.tanzania.go.tz/health.html),

village/community health services are the lowest level of health care delivery in the country (www.tanzania.go.tz/health.html). They essentially provide preventive services which can be offered at home. Dispensaries are the second stage, and cater for 6,000 to 10,000 people, as well as supervising all village health posts in its ward. Health centers (3rd level) are expected to cater for 50,000 people, which is approximately a population of one administrative division. The fourth level is the district hospitals followed by regional hospitals. These two levels, offer similar services, but regional hospitals may have specialists in some fields, offering additional service. The highest level of hospital services in Tanzania is referral/ consultant or specialized hospitals. These hospitals are also used for teaching purposes.

In the past, health services in Tanzania have been largely a prerogative of the state with only a limited number of private-for-profit health services available in major towns (www.tanzania.go.tz/health.html). The importance of private sector in health care delivery was further recognized with the amendment to the Private Hospitals (Regulatory) Act, in 1977 (www.tanzania.go.tz/health.html). Administratively, each higher level of care has the mandate to supervise services provided at their respective lower level categories. In addition, the District Medical Officer (DMO) is the senior health manager in the district and the Regional Medical Officer (RMO) served the region. The DMO works hand in hand with the Council Health Management Team (CHMT) to plan, implement and supervise health related activities in their district. Each health facility in turn, have a committee made of members from the Village Government, who, among other tasks, have the mandate to monitor daily running of the health facility in their respective areas. The distribution of health facilities has a heavy rural emphasis since more than 70% of population lives in rural areas (www.tanzania.go.tz/health.html).

Among the major challenges facing the Tanzania health system are the shortage of human resources for health with a small and inequitable distribution (Leon BK, 2010; Kurowski C et al., 2003), incomplete and inaccurate data (Smith M et al., 2008) as well as frequent stock-outs of medical supplies. This has resulted in low standard of care,

particularly in public sector and in-appreciation of the value of user fees in public health facilities. The total government expenditure in health is low, hence, running of the system is highly dependent on donor funding and driven by disease specific programmes. The process of decentralization by devolution, adds a layer of complexity on the country's health system performance by stretching the roles and managerial ability of staff at the Ministry of Health and Social Welfare (MOHSW) and the Prime Minister's Office-Regional Administration and Local Government (PMO-RALG) (Musau S et al., 2011)

1.5 Health systems influence in malaria case management

The 20th century was faced with many challenges in malaria control. Countries that were close to moving from control to malaria elimination status were stalled and even backsliding. The increased burden of malaria morbidity and mortality was primarily due to growing resistance of malaria parasite to anti-malarias medicines and insecticides in use, changing in weather patterns (e.g. the El-Nino rains), human migration as well as deteriorating health systems. The global consensus to move to the use of ACTs for malaria treatment aimed at curbing anti-malarial drug resistance. Most malaria endemic countries adopted the use of ACTs for management of uncomplicated malaria; following WHO recommendations (WHO, 2010a) and increased use of rapid tests for malaria confirmation. The use of long lasting insecticide-treated nets (LLINs) was emphasized, as well as IRS and environmental management for vector control. Another important step was the recognition of the need to invest greater efforts to health systems strengthening. There is now increased donor funding to support malaria control activities in endemic countries, both from funders through global coordinated efforts such as the Global Fund to fight Malaria, TB and HIV; and from individual developed-nation's support, through bilateral agreements with endemic countries.

These efforts have lead to a significant reduction of malaria prevalence in many areas where malaria has been a major public health problem for decades. One good example is the achievement of the Zanzibar Island (Tanzania) where prevalence of malaria has

stayed consistently low to a point that the government is declaring moving the malaria control status to the elimination stage. In Mainland Tanzania, prevalence of fever reported through country representative household surveys, has also declined from 35.1% in 1999 to 22.9% in 2010 (NBS, 1999; NBS and Macro ICF, 2011). Despite these gains, there are still striking rural-urban differences as well as persistent of variation in transmission intensities in various areas of the country. The global malaria mortality also shows a similar trend. Murray et al, reported a decline of mortality due to malaria in the past decade, from 1,817,000 in 2004 to 1,238,000 in 2010 ; but surprisingly reported more deaths due to malaria in individuals aged 5 years and above, than has been previously estimated (Murray CJL et al., 2012).

Health Systems Effectiveness

Prompt and effective treatment of malaria can only be achieved through good access to health care and presence of appropriate personnel, technology and medicines. Inappropriate use of available effective treatment will not provide effective cure and is known to foster development of drug resistance. Studies from Tanzania and elsewhere found that clinicians continued to prescribe anti-malarials to patients whose test did not provide evidence of the presence of malaria parasites, hence no malaria (Makani et al., 2003; Reyburn et al., 2007; Opoka RO et al., 2008). Ideally, a good provider's compliance to treatment recommendation should be coupled with better patients' adherence to prescribed medicine, for maximum treatment benefits. This means that effectiveness of the treatment recommendation is a shared responsibility among individuals, families, communities and health care providers.

Development of medicines follows a defined pipeline from exploration of the possible chemical combinations to field trials. The candidate treatment formulation is again subjected to a series of clinical trials (phase 1 to 3), before being approved for human use. This process may take years to be completed, followed by registration of the product for routine use in clinical settings. In countries with well developed health systems, the registered medical products continue to be monitored routinely to ascertain

any delayed adverse reactions. These are commonly known as phase 4 trials and occur in real world settings. The importance of phase 4 platforms relies on a fact that humans live in very diverse conditions environmentally, socio-culturally, politically and in very different health systems.

1.6 Rationale of systems effects in health care

Health systems researchers have hypothesized the links between drug's efficacy and health systems effectiveness. A drug with very high efficacy may not provide desired benefits when subjected to real life routine use. This decay in drug's apparent efficacy may be influenced by other system factors which have a role in achieving provision of care. These may include poor access to treatment, inappropriate provider's behavior such as poor prescription practices, patients' non-adherence of prescribed treatment or dosing scheme, in-availability of medicines hence use of a substitute or poor quality product, etc. This is where the need to understand factors influencing treatment outcomes, becomes of paramount importance. In the schematic presentation below, treatment effectiveness is shown to be not only a result of efficacy, but also a product of access, diagnostic accuracy, provider's compliance and patient's adherence which are characteristic elements of the health system delivering the service.

Figure 7 Health systems factor that can lead to a decay of drug efficacy once introduced in real world health systems. Source: The malERA Consultation Group (malERA, 2011)

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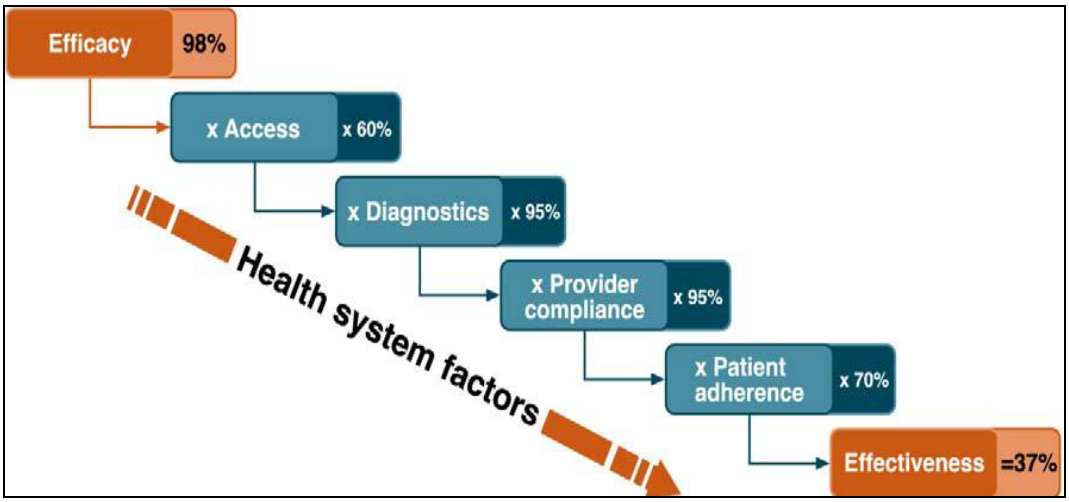


The present work was conducted to understand the influence of health system factors in malaria control strategies by assessing the quality of malaria case management as determined by diagnostic accuracy and provider's compliance. The assessment analyzes health system factors in the framework of the existing Tanzanian health care system and currently available resources without much influence in the system performance. The work was carried out in a phase 4 platform of effectiveness and safety studies of antimalarials in Africa, named INESS: Indepth Network for Effectiveness and Safety Studies of antimalarials in Africa (INESS). These studies therefore address the following research questions:

1. What systems factors (e.g. health workers characteristics, availability of products, etc) are associated with appropriate management of uncomplicated malaria?
2. Does availability of malaria diagnosis technology improve providers' compliance?
3. What are the predictors of malaria parasitemia in patients seeking care at formal health sector (to facilitate diagnostic accuracy)?

PART II: OBJECTIVES AND METHODS

Chapter 2: Objectives and Methods

2.1 Goal of the study

The goal of this work was to determine health systems factors which influence appropriate malaria case management in Tanzania.

2.2 Specific Objectives

1. To determine the influence of malaria diagnostics to guide appropriate targeting of antimalarial treatment for uncomplicated malaria;
2. To assess determinants of correct dosing for treatment of uncomplicated malaria by health workers in rural Tanzania;
3. To assess health workers factors that predict providers' compliance with treatment recommendations for uncomplicated malaria;
4. To assess health workers attitudes and personal use of recommended antimalarial treatment;
5. To assess predictors of parasitemia in patients seeking care in the formal health sector of rural Tanzania.

2.3 Methods

Description of project:

The INDEPTH Effectiveness and Safety Studies of Antimalarials (INESS) project undertakes Phase 4 comparative safety and effectiveness studies of new combination therapies for malaria in seven INDEPTH Network Demographic Surveillance System (DSS) sites in four countries in Africa. In Tanzania, the project is implemented in Rufiji District (Pwani Region) and Kilombero/ Ulanga districts (Morogoro Region). These DSS sites are managed by the Ifakara Health Institute (IHI). The project creates the missing final section of drug development pipeline in Africa. In order to reach its objectives, INESS work is organized into separate modules that answer a particular objective

(http://indepth-network.org/iness/) (INESS). Additional data to assess trends in some outcome measures (objective 4 and 5) were collected from the IMPACT-Tz project (Interdisciplinary Monitoring Project for Antimalarial Combination Therapy in Tanzania); a multiyear implementation research evaluation project implemented in same study area as INESS (Kachur et al., 2004).

Study design and study period:

In INESS, we conducted repeated cross-sectional cluster surveys in all health facilities within the HDSS area. These were government, private and other non-government health facilities. A cluster was defined as all patients consultations performed in a health facility on one day during regular working hours, i.e. 8am to 5pm. The surveys were conducted during March 2010 (coinciding with the rainy season) and October 2010 (during dry season) in order to capture the high and low malaria transmission seasons, respectively.

Study area:

The INESS study (and IMPACT-Tanzania) was implemented in Rufiji and Ifakara Health and Demographic Surveillance Systems (HDSS). The Ifakara HDSS extends to include part of Kilombero and Ulanga districts (figure 8 below). The Rufiji HDSS has been operating since 1998 and has registered about 85,000 people (Mwageni E et al.). The Ifakara HDSS started in 1996 with a population of about 99,000 population extending to include part of the Kilombero and Ulanga districts (Ifakara HDSS).

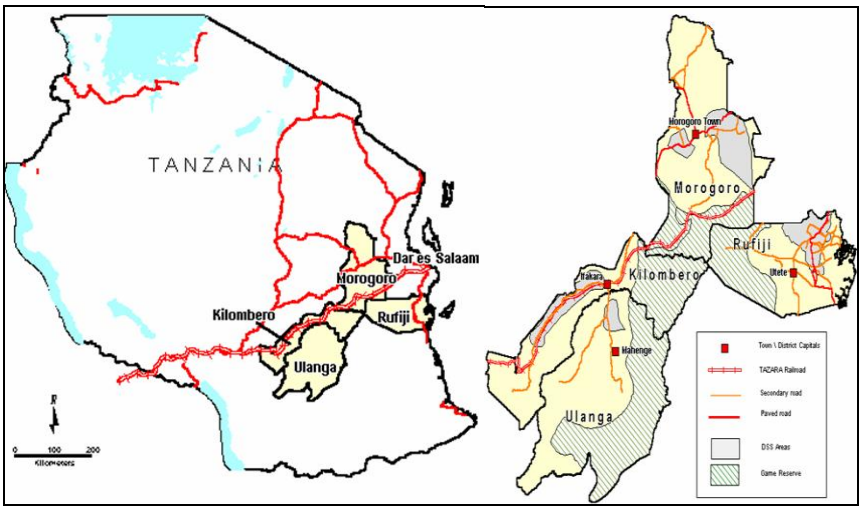
Study participants:

The health facility module collected information from three areas:

a) Health facilities: Any public or private health facility serving in the HDSS area that provides curative care in the outpatient settings. These were referred to as ACT providers.
b) Health workers: Any health worker who performs consultations with the sick patients in outpatient settings of an eligible ACT provider

c) Patients: All patients who came for initial consultation, seeking care for any illness in outpatient department of an eligible ACT provider, during regular working hours, Monday to Friday (except public holidays).

Figure 8: Map of the study sites (adopted from IMPACT Tanzania project 2000-2005):



Sampling:

The final sample size calculated was 1,537 patients for both sites, presenting for initial consultation to estimate a 50% +/-10% fever prevalence for targeting accuracy with a 95% confidence, accounting for clustering with a design effect of two. We worked with assumptions that: 50% of patients presenting to health facilities will have fever, and 20% of them will have malaria parasites. 70% of patients with fever and parasitemia will receive any ACT and 10% of patients without fever will get ACT.

Training of data collectors

Field workers were trained for two days on the survey procedure and blood slide collection procedure in a classroom setting and then practiced in the test health facility outside the HDSS area.

Data collection and field procedures:

One team of two to three field workers visited the health facility to collect data. The assumption was that, 15 patients were to be enrolled per health facility per day, then the survey needed to include 48 health facilities-survey days per round. Procedures at the health facility included:

a) Dates of survey visit were not announced in advance to health facility staff. On a survey day, the team arrived before working hours with a letter from the DMO specifying the nature and purpose of the assessment. The teams meet with facility staff to introduce themselves and introduce the survey purpose. In addition, they created a list of health workers who perform outpatient consultation and conduct health worker's interviews to obtain information about their training, supervision and knowledge of malaria case management.

   The survey team also obtained agreement from the laboratory to obtain an extra blood smear for study purposes.

b) As ill patients arrive into the facility, presence of the study team was announced in the waiting area to alert patients. Patients were assessed for their eligibility at the waiting area. These eligibility criteria required a person to be attending a facility for initial illness consultation, not a follow-up visit from a recent illness, ascertained by a series of three questions. All eligible patients who gave their consent were included in the study and provided with identification number and card. The laboratory personnel used this identification number to label an extra slide.

   When the patient was ready to leave the facility, the surveyor interviewed the patient and collected a blood smear if this patient was not send to a laboratory as part of routine service. The interview was used to determine if the patient understood information provided by the provider, as well all prescribed and provided medications

were recorded. At the end of the interview, or end of the day, information from patient's record was extracted.

c) The team remained at the facility until regular closing time. After the facility closure, one surveyor conducted an inventory of facility equipment and drug stocks. One surveyor conducted interviews with the facility staff to obtain information on the health workers' training, supervision and knowledge of malaria case management.

Before leaving the facility, interviewers reviewed all data forms to ensure completeness.

Laboratory procedures

If the patient was not sent to a laboratory and an extra slide was not collected, the field worker performed a finger prick and took a blood smear after completing patient interview, before the patient leave the facility. All blood smears were stained with Giemsa stain. Two independent laboratory technicians read all films. A third microscopist read discordant results. Parasite density was calculated by counting asexual stage parasites per 200 white blood cells (WBCs) assuming 8000 WBCs/ dl of blood. Smears were considered negative if no parasites were found after counting 200 fields. Results were available approximately one week after the survey and were sent to the facility, where participants could pick up their results.

Data management and analysis

Data was double entered in EPI Data. Entry screens were optimized with data checks and skip patterns to ensure consistency. Patient's results from slide readings were merged with data from exit interview. Analysis was done in STATA 11 (STATA Corporation, College Station, USA) accounting for clustered nature of the data. Pregnant women were excluded in the analysis. Both Univariate and multivariate analysis were performed in order to assess relation of outcome variables and various predictors.

Ethical considerations

Written informed consent was sought from patients and caretakers of children. Consent forms were translated into Swahili and back translated into English to for validation. Unaccompanied minors (person <18 years) were not included in the survey since they were unable to provide informed consent. Permission to carry out the surveys was obtained from the district health authorities. Additional verbal consent was sought for health workers interview. In order to maintain confidentiality, participants personal data such as names, were not collected, instead code numbers and HDSS permanent identity numbers were used. No cost was incurred by study participants.

INESS project was granted national (August 17, 2009) and institutional ethical approval number IHI/IRB/No.67-2009, in June 20, 2009. As well, IMPACT-Tz project received both institutional and national ethical clearance in year 2000.

Collaboration with IMPACT project and access to data:

The INESS project involves international collaborations with technical expertise from Swiss TPH, the US Center for Disease Control and Prevention (CDC), University of Ghana, etc. In the Swiss TPH, collaboration is with the Health Systems Research and Dynamic Modeling (HSRDM) unit, with lead from Professor Don de Savigny and Dr Irene Kuepfer. INESS collaboration in CDC, it is within the Malaria branch with Dr Jacek Skarbinski and Dr Patrick Kachur as health facility module leaders.

The IMPACT – Tanzania project was also a collaborative effort between the Ifakara Health Institute (Tanzania), the CDC, Malaria branch and other local and international collaborators as described at a footnote in Kachur et al, 2004 (Kachur et al., 2004). In both INESS and IMPACT-Tanzania programmes I supervised activities under the health facility surveys. As a senior researcher, I have publishing access to the modules' data.

PART III: SERVICE DELIVERY FOR MALARIA TREATMENT

Chapter 3: Malaria Diagnostics

Increased use of malaria rapid diagnostic tests improves targeting of anti-malarial treatment in rural Tanzania: Implications for nationwide rollout of malaria rapid diagnostic tests.

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Abstract:

Background: The World Health Organization recommends parasitological confirmation of all malaria cases. Tanzania is implementing a phased rollout of malaria rapid diagnostic tests (RDTs) for routine use in all levels of care as one strategy to increase parasitological confirmation of malaria diagnosis. This study was carried out to evaluated artemisinin combination therapy (ACT) prescribing patterns in febrile patients with and without uncomplicated malaria in one pre-RDT implementation and one post-RDT implementation area.

Methods: A cross-sectional health facility surveys was conducted during high and low malaria transmission seasons in 2010 in both areas. Clinical information and a reference blood film on all patients presenting for an initial illness consultation were collected. Malaria was defined as a history of fever in the past 48 h and microscopically confirmed parasitemia. Routine diagnostic testing was defined as RDT or microscopy ordered by the health worker and performed at the health facility as part of the health worker-patient consultation. Correct diagnostic testing was defined as febrile patient tested with RDT or microscopy. Over-testing was defined as a febrile patient tested with RDT or microscopy. Correct treatment was defined as patient with malaria prescribed ACT. Over-treatment was defined as patient without malaria prescribed ACT.

Results: A total of 1,247 febrile patients (627 from pre-implementation area and 620 from post-implementation area) were included in the analysis. In the post-RDT implementation area, 80.9% (95% CI, 68.2-89.3) of patients with malaria received recommended treatment with ACT compared to 70.3% (95% CI, 54.7-82.2) of patients in the pre-RDT implementation area. Correct treatment was significantly higher in the post-implementation area during high transmission season (85.9% (95%CI, 72.0-93.6) compared to 58.3% (95%CI, 39.4-75.1) in pre-implementation area (p = 0.01). Over-treatment with ACT of patients without malaria was less common in the post-RDT implementation area (20.9%; 95% CI, 14.7-28.8) compared to the pre-RDT

implementation area (45.8%; 95% CI, 37.2-54.6) ($p < 0.01$) in high transmission. The odds of overtreatment was significantly lower in post- RDT area (adjusted Odds Ratio (OR: 95%CI) 0.57(0.36-0.89); and much higher with clinical diagnosis adjusted
OR (95%CI) 2.24(1.37-3.67)

Conclusion: Implementation of RDTs increased use of RDTs for parasitological confirmation and reduced over-treatment with ACT during high malaria transmission season in one area in Tanzania. Continued monitoring of the national RDT rollout will be needed to assess whether these changes in case management practices will be replicated in other areas and sustained over time. Additional measures (such as refresher trainings, closer supervisions, etc.) may be needed to improve ACT targeting during low transmission seasons.

Keywords: Malaria rapid diagnostic tests, ACT, HDSS, INDEPTH network, Tanzania

3.1 Background

The World Health Organization (WHO) recommends that clinically suspected malaria be confirmed parasitologically prior to treatment (WHO, 2010a). Diagnosis based on signs and symptoms has varied sensitivity and specificity depending on clinical features present, age, and transmission-associated acquired immunity (O'Dempsey TJ et al., 1993). Microscopic analysis of blood films for malaria parasites has been the most commonly used method for parasitological confirmation of malaria infection. However, due to reports of poor quality malaria microscopy (Payne, 1988; Bell et al., 2006) and the logistical, personnel and financial resources required to increase coverage of quality microscopy services, many endemic countries in sub-Saharan Africa have opted to use malaria rapid diagnostic tests (RDTs) to expand the use of parasitological-based malaria diagnosis (Zurovac et al., 2008a; Harvey SA et al., 2008).

Tanzania mainland introduced the use of artemether-lumefantrine (AL), an artemisinin-based combination therapy (ACT), as a first line treatment for uncomplicated malaria in 2006 (NMCP, 2006). In early 2009, a phased rollout of RDTs was initiated in all levels of care to complement microscopy services for parasitological confirmation of malaria prior to treatment (National guideline for the use of rapid malaria diagnostic tests in Tanzania, 2007, National Malaria Control Programme, Dar es Salaam, Tanzania: unpublished). This roll-out is expected to cover the entire country before end of year 2012. Since the adoption of RDT policy and increased rollout of this strategy in sub-Saharan Africa, there has been limited evidence of the performance of RDTs in routine use and their impact on case management practices, on a wider scale, outside research settings.

Using a pair of cross-sectional health facility surveys conducted in two areas of Tanzania in 2010, this study assessed the impact of RDTs by comparing malaria case management practices in a post-RDT implementation area with a pre-RDT implementation area. The assessment aimed on determining ACT targeting accuracy, i.e. the proportion of patients presenting to ACT provider for initial illness consultation with fever or history of fever in the last 48 h who were prescribed AL; and provider compliance, i.e. the proportion of patients presenting to an ACT provider for initial illness consultation with fever or history of fever in the last 48 h and blood slide confirmed malaria parasitaemia, who were prescribed AL.

In the post-RDT implementation area, Rufiji Health and Demographic Surveillance System (HDSS) located in Rufiji District, RDTs were introduced for routine use in November 2009 as part of the national rollout. In the pre-RDT implementation area, Ifakara HDSS located in Kilombero and Ulanga Districts, RDT were not introduced as part of the national roll-out, but were available in seven health facilities (out of 79 health facilities in Kilombero and Ulanga districts) as part of small scale research study; the ACCESS programme, since 2008 (ACCESS Project).

3.2 Methods

INDEPTH Network Effectiveness and Safety Studies of Antimalarial Drugs in Africa platform (INESS) operates in HDSSs in Rufiji District, Coast Region, and in Kilombero and Ulanga Districts, around the town of Ifakara, Morogoro Region, Tanzania (INESS). The platform assesses safety and community effectiveness of anti-malarial drugs in real life health systems. As part of this effort, INESS conducts assessments of the quality of malaria case management using a series of health facility surveys to evaluate ACT prescribing patterns among febrile patients with and without parasitological confirmed uncomplicated malaria.

Study area

The study was conducted in health facilities located in the Rufiji and Ifakara HDSS areas, in March and October 2010 corresponding to high and low malaria transmission seasons respectively at those sites. The Rufiji HDSS has been operational since 1998 and contains a population of approximately 85,000 people (Rufiji DSS). Malaria rapid tests were available on a limited scale as part of demonstration project in 12 health facilities in the Rufiji HDSS since 2007 (Masanja et al., 2010) and in all facilities after the national RDT rollout in 2009. Ifakara HDSS has been operational since 1996 and contains a population of approximately 99,000 people (Ifakara HDSS). Early in 2008, the ACCESS project introduced RDT in seven (out of 79) health facilities in Kilombero and Ulanga districts; four out of these seven facilities are within the HDSS area (ACCESS Project). Although use of RDTs under ACCESS project was under research settings, health workers received training and guidelines similar to those provided in the rollout areas for routine case management. These were modified versions of the generic guides provided by the WHO. The two areas differ in terms of support supervision and stock supply for RDTs. In Rufiji, supervision and acquisition of supplies was to follow routine practices in existing health system; those under ACCESS project were assessed

by project investigators who were also responsible for replenishing facility supplies of RDTs.

Health facility surveys

Cross-sectional health facility cluster surveys were conducted in March and October 2010. A cluster was defined as all outpatient consultations in a health facility conducted in one day during regular working hours. All government and non-government health facilities that provide outpatient care to the HDSS population were included (16 in Rufiji HDSS and 14 in Ifakara HDSS). Each facility was visited for two to three days with the goal to collect data on 720 patients per HDSS per year in order to estimate the proportion of patients with uncomplicated malaria correctly treated with ACT with 10% confidence, assuming 20% of all patients present with uncomplicated malaria, 75% of patients with uncomplicated malaria are treated with ACT, and a design effect of 2 for cluster sampling

All outpatients presenting for initial illness consultation on a day of a survey, and who consented to participate in the survey, were interviewed prior to leaving the health facility. Using standardized questionnaires developed in English and translated into Kiswahili, information on history of fever, health worker's diagnoses, laboratory tests, medications prescribed and counselling messages were collected. In addition, a reference blood film for malaria microscopy was collected on every patient. Patients with severe malaria were excluded from the survey. Moreover, interviews were carried out with health workers providing outpatient consultations and collected information on pre-service training, work experience, in-service training and receipt of supervision. Assessment of the level of staffing, availability of diagnostics, medications and other medical supplies was done at the health facility.

Laboratory procedure

Blood films were stained with 10% Giemsa and thick and thin films were examined by study microscopists at centralized locations in Rufiji and Ifakara HDSS sites. A second reading was conducted by a reference laboratory technician at the Ifakara Health Institute Bagamoyo Research and Training Unit. Parasite densities were calculated by counting the number of asexual stage parasites per 200 white blood cells (WBCs) and assuming an average of 8,000 WBC per micro-litre of blood. A blood film was considered negative if no parasites were found after counting 100x high power fields. Blood film results were made available to the respective health facilities between five to seven days after the day of survey.

Definitions

National malaria treatment guidelines and clinical information from the exit interview were used to determine when diagnostic testing was indicated, and the same plus study blood film results to determine when prescription of ACT was indicated. In the treatment guidelines, malaria diagnostic testing was indicated for patients with febrile illness (history of fever in the last 48 h), and this was assessed through exit interviews. Malaria was defined as a patient with febrile illness as determined by exit interview, and reference blood film positive for malaria parasites. Routine diagnostic testing was defined as RDT or microscopy ordered by the health worker and performed at the health facility as part of the health worker-patient consultation. Correct diagnostic testing was defined as febrile patient tested with RDT or microscopy. Over-testing was defined as a febrile patient tested with RDT or microscopy. Correct treatment was defined as patient with malaria prescribed ACT. Over-treatment was defined as patient without malaria prescribed ACT. ACT stock out referred to absence of all types of AL blister packs.

Data management and analysis

Data were double entered in EPIDATA (version 3.1, EPIDATA Association, Odense,

Denmark) and analysed using STATA (version 11.0, STATA Corporation, College Station, USA) using survey procedures that account for clustering. An alpha level of 0.05 was used for all significance tests. Pregnant women (N = 60) were excluded from the analysis as quinine rather than ACT is the recommended treatment of malaria in the first trimester. Descriptive analysis was performed to derive proportions for different outcome measures. Logistic regression was done to identify the impact of diagnostics on prescription of AL and overtreatment to patients receiving AL.

Ethical clearance

All components of the INESS platform were reviewed by the Tanzanian National Institutes of Medical Research and IHI's Ethical Review Boards (IHI/IRB/No.A67-2009), Dar es Salaam, Tanzania.

3.3 Results

A total of 1,531 patients were interviewed (742 in Rufiji HDSS and 789 in Ifakara HDSS) and 1,471 non-pregnant patients with complete data were included in the analysis. Almost half of all patients in both areas were children age <5 years (Table 1). Use of insecticide treated bed nets, availability of ACT and diagnostic testing (RDT and microscopy) differed significantly between the two areas. In particular, more patients in Rufiji HDSS (post-RDT implementation area) were seen in a health facility with ACT in stock (93.8%) or with any diagnostic capacity (RDT or microscopy) (74.2%) compared to the Ifakara HDSS (pre-RDT implementation area) where, 42.8% were seen in a health facility with ACT in stock and 32.6% seen in a health facility with diagnostic capacity. Moreover, the prevalence of uncomplicated malaria varied significantly between Rufiji HDSS (high season 19.2% and low season 7.2%) and Ifakara HDSS (high season 9.4% and low season 4.2%), respectively.

Results in Table 2 describe the use of RDTs between the two areas. More patients in the post- RDT area received a diagnostic test 62.1% (95%CI: 50.3- 72.6) as compared

to a pre-RDT area 46.5% (95%CI: 36.3- 57.1) (p=0.05). Use of RDTs was significantly higher in post-RDT area whereas microscopy use was more common in the pre-RDT area. Overall correct testing and over-testing did not differ significantly between two areas.

Table 1: Characteristics of patients in health facility surveys conducted in pre- and post-RDT implementation HDSS areas

	Ifakara HDSS (pre-RDT implementation) (N=761)		**Rufiji HDSS (post-RDT implementation) (N=710)**		**P-value**
Characteristic	**n/N**	**% (95%CI)**	**n/N**	**%(95%CI)**	
Female	441/761	58.0 (54.7-61.1)	347/710	48.9 (44.9-52.9)	<0.01
Child aged <5 years	352/761	46.3 (41.8-50.8)	349/710	49.2 (44.4-53.9)	0.56
Used insecticide-treated bed net previous night	575/761	75.6 (71.3-79.4)	344/710	48.5 (40.9-56.1)	< 0.01
Used anti-malarial prior to health facility visit	37/761	4.9 (3.2-7.3)	20/710	2.8 (1.5-5.3)	0.14
Seen in high transmission season (March 2010)	384/761	50.5 (40.2-60.7)	375/710	52.8 (39.7-65.5)	0.78
Seen in low transmission season (October 2010)	377/761	49.5 (39.3-59.8)	335/710	47.2 (34.5-60.3)	
Seen in HF with ACT in stock	326/761	42.8 (30.9-55.7)	666/710	93.8 (86.9-97.2)	0.01
Seen in HF with RDT or BS in stock	248/761	32.6 (21.4-46.1)	527/710	74.2 (61.1-84.1)	<0.01
Seen in HF with a RDT in stock	132/761	17.4 (10.6-27.6)	343/710	48.3 (35.2-61.7)	<0.01
Seen in a HF with BS in stock	242/761	31.8 (22.0-43.5)	397/710	55.9 (41.9-69.1)	0.28
Fever prevalence	627/761	82.4 (78.3-85.8)	620/710	87.3 (83.3-90.5)	0.06
Uncomplicated malaria prevalence	54/761	7.1 (5.1-9.8)	96/710	13.5 (10.3-17.6)	<0.01
High transmission season	36/384	9.4 (6.2-13.9)	72/375	19.2 (14.3-25.3)	<0.01
Low transmission season	16/377	4.2 (2.5-7.2)	24/335	7.2 (4.2-12.0)	0.21

Table 3 shows ACT prescriptions to malaria patients as categorized by use of diagnostic tests (RDT and microscopy) or clinically. In both areas, most RDT-positive patients received ACT, but only about half microscopy-positive patients received ACT.

RDT-negative patients were significantly less likely to be treated with ACT in the post-RDT implementation area than the pre-RDT implementation area. The proportion of patients receiving ACT based on clinical diagnosis alone did not differ between the two sites. In the multivariate analysis (table 4), the odds of febrile patients receiving ACT were highest with clinical diagnosis (adjusted OR 95%CI: 2.24(1.37-3.67).

Table 2: Use of diagnostics to patients with and without fever in pre- and post-RDT implementation HDSS areas

	Ifakara HDSS (pre-RDT implementation area)		**Rufiji HDSS (post-RDT implementation area)**		**P-value (site)**
Characteristic	**n/N**	**%(95%CI)**	**n/N**	**%(95%CI)**	
All patients tested by either RDT or microscopy	354/761	46.5 (36.3-57.1)	441/710	62.1 (50.3-72.6)	0.05
RDT	132/761	17.4 (11.0-26.2)	309/710	43.5 (32.4-55.4)	< 0.01
Microscopy	242/761	31.8 (28.5-35.2)	132/710	18.6 (15.8-21.7)	0.05
Correct testing: Patients with fever tested either RDT or microscopy	314/627	50.1 (38.9-61.2)	400/620	64.5 (51.8-75.5)	0.09
RDT	123/627	19.6 (12.4-29.6)	282/620	45.5 (33.3-58.2)	< 0.01
Microscopy	210/627	33.5 (29.8-37.3)	118/620	19.0 (16.0-22.3)	0.04
Over-testing: Patients without fever tested with either RDT or microscopy	40/134	29.9 (16.5-47.9)	41/90	45.6 (32.9-58.8)	0.15
High season	5/60	8.3 (3.6-18.0)	26/56	46.4 (33.2-60.2)	<0.01
Low season	35/74	47.3 (24.0-71.9)	15/34	44.1 (22.0-68.9)	0.86

Overall ACT use and correct treatment of malaria were about similar in the two areas, except during high transmission season (Table 5) but over-treatment of non-malaria patients with ACT was significantly higher in the pre-RDT area (39.1%; 95%CI 31.0-47.8) compared to the post-RDT area (24.7%; 95%CI 18.4-32.2), adjusted OR(95%CI) 0.57 (0.36-0.89); Table 6. Seasonal differences were noted in malaria prevalence (Table 1), testing rate (Table 2), correct treatment and over-treatment (Table 5)

Table 3: ACT† prescription according to tests results, and clinical malaria* in pre- and post-RDT implementation areas

	Ifakara HDSS (pre- RDT implementation)		Rufiji HDSS (post- RDT implementation)		P-value
	n/N	%(95% CI)	n/N	%(95% CI)	
RDT positive	22/30	73.3 (53.1-87.0)	79/95	83.2 (69.2-91.6)	0.32
RDT negative	28/104	26.9 (16.4-40.9)	17/217	7.8 (4.7-12.7)	<0.01
Microscopy positive	62/110	56.4 (41.5-70.1)	15/36	41.7 (22.1-64.3)	0.28
Microscopy negative	7/135	5.2 (2.1-12.1)	5/96	5.2 (2.3-11.6)	0.99
Clinical diagnosis of malaria and no diagnostic test performed	165/313	52.7 (42.9-62.4)	99/220	45.0 (34.3-56.2)	0.33
No clinical diagnosis of malaria and no diagnostic test performed	7/94	7.5 (2.9-15.8)	2/49	4.1 (1.1-14.4)	0.45

* Clinical diagnosis of malaria based on presence of fever in patients who did not receive a malaria diagnostic test †= Artemether lumefantrine

Table 4: Multivariate analysis of ACT† prescription according to tests results, and clinical malaria* for all febrile patients in pre- and post-RDT implementation areas

Variable	Crude Odd ratio	95%CI	p-value	Adjusted Odd ratio	95%CI	p-value
Type of diagnosis						
mRDT	Ref					
Microscopy	0.59	0.37-0.93	0.02	0.61¥	0.38-1.01	0.054
Clinical diagnosis	1.29	0.87-1.91	0.21	1.30¥	0.87-1.95	0.201
Season						
High season	Ref					
Low season	0.64	0.43-0.97	0.036	0.67Ɨ	0.45-1.00	0.048
Site						
Ifakara HDSS (pre-mRDT)	Ref					
Rufiji HDSS (post-mRDT)	0.74	0.49-1.12	0.15	0.72‡	0.48-1.10	0.127

¥: adjusted for season and site

Ɨ: adjusted for type of diagnosis and site

‡: adjusted for type of diagnosis and season

Table 5: Prescription of ACT for all patients in post- and pre-RDT implementation areas with ACT in stock at health facility

	Ifakara HDSS (pre-mRDT implementation)		Rufiji HDSS (post-mRDT implementation)		P-value (site)
Characteristic	**n/N**	**%(95% CI)**	**n/N**	**%(95% CI)**	
All patients treated with ACT (overall)	241/587	41.1 (33.4-49.2)	217/666	32.6 (26.5-39.4)	0.10
High transmission season (March 2010)	155/332	46.7 (38.9-54.6)	119/349	34.1 (27.9-40.9)	0.02
Low transmission season (October 2010)	86/255	33.7 (22.6-47.0)	98/317	30.9 (20.7-43.4)	0.74
Correct treatment: Patients with uncomplicated malaria treated with ACT (overall)	26/37	70.3 (54.7-82.2)	76/94	80.9 (68.2-89.3)	0.22
High transmission season (March 2010)	14/24	58.3 (39.4-75.1)	61/71	85.9 (72.0-93.6)	0.01
Low transmission season (October 2010)	12/13	92.3 (54.2-99.2)	15/23	65.2 (36.2-86.1)	0.11
Over treatment: Patients without uncomplicated malaria treated with ACT (overall)	215/550	39.1 (31.0-47.8)	141/572	24.7 (18.4-32.2)	0.01
High transmission season (March 2010)	141/308	45.8 (37.2-54.6)	58/278	20.9 (14.7-28.8)	<0.01
Low transmission season (October 2010)	74/242	30.6 (19.6-44.3)	83/294	28.2 (18.2-41.1)	0.78

Table 6: Multivariate description of ACT over-treatment for all patients in post- and pre-RDT implementation areas

Variable	Crude Odd ratio	95%CI	p-value	Adjusted Odd ratio	95%CI	p-value
Type of diagnosis						
mRDT	Ref					
Microscopy	1.20	0.72-1.98	0.48	1.05¥	0.60-1.84	0.856
Clinical diagnosis	2.54	1.56-4.12	0.00	2.24¥	1.37-3.67	0.001
Season						
High season	Ref					
Low season	0.89	0.57-1.38	0.587	0.82 Ⱨ	0.54-1.23	0.328
Site						
Ifakara HDSS(pre-mRDT)	Ref					
Rufiji HDSS(post-mRDT)	0.50	0.32-0.8	0.004	0.57‡	0.36-0.89	0.014

¥: adjusted for season and site Ⱨ: adjusted for type of diagnosis and site
‡: adjusted for type of diagnosis and season

3.4 Discussion

Parasitological confirmation of all malaria diagnoses is recommended by WHO and there is increasing evidence supporting the use of RDTs for clinical management of fever and malaria cases (D'Acremont V et al., 2011; Ishengoma DS et al., 2011; Faucher J et al., 201). Many of these findings are based on operational research that assessed performance and accuracy of RDT use in clinical care as part of a pilot or research projects. This study evaluated the implementation of RDTs for routine use in the Tanzanian health system, under "real world" conditions. Most importantly, in the post-RDT implementation area correct treatment of malaria remained high (80.9%) and over-treatment of non-malaria patients was low (24.7%). This suggests that the routine use of RDTs might improve malaria case management.

Tanzania began and phased introduction of RDTs for routine malaria case management in 2008 and plans to achieve nationwide coverage by 2011 [National guideline for the use of rapid malaria diagnostic tests in Tanzania, 2007, National Malaria Control Programme, Dar es Salaam, Tanzania: unpublished]. The scaling up of health interventions is a complex undertaking and simply increasing coverage might not translate into an impact on the larger population (Manham LJ and Hanson K, 2010; Gilson L and Schneider H, 2010). By comparing the post-RDT implementation area to the pre-RDT implementation area, the impact of RDT roll-out in malaria case management can be assessed. First, the post-RDT implementation area had much higher availability of malaria diagnostic testing capacity; 74% of patients were seen in a health facility that had either RDTs or microscopy available compared to 32.6% of patients seen on the pre-RDT implementation area. However, availability of diagnostics alone does not improve malaria case management. In particular, more patients were tested for malaria in the post-RDT implementation area (62.1%) than the pre-RDT implementation area (46.5%), and more patients were correctly tested.

Despite the improvement seen in proportion of febrile patients receiving a test, this achievement is far from optimal. The reason could be associated with the much too frequent stock out of medical products affecting the Tanzania health system, including timely in-availability of testing materials/ devices. However, results show that over-testing in post implementation area is also high. Over-testing may be associated with wasted resources as patients who do not meet clinical criteria for malaria diagnostic testing are tested. Although we did not assess reasons for over-testing, one may think that the problem may be contributed by lower understanding of case selection for the test, probably resulting from lack of experience in using the tests, unclear guideline, supportive supervision not focusing on the topic or even patient pressure to get tested. Post-implementation care quality improvement efforts should focus on ensuring that only persons who have clinical signs and symptoms of malaria such as a history of fever are tested.

Another important consideration for RDT implementation is assuring the diagnostic test performance. In this study, sensitivity and specificity of RDTs in the post-implementation area was adequate (>85%). The continued monitoring of RDT performance post-implementation is critical as poor malaria microscopy performance has been documented throughout sub-Saharan Africa. For the time being, RDTs appear to have better sensitivity and specificity than routine microscopy and might be critical in improving the overall quality of malaria diagnostic capacity in routine settings.

In addition, this study suggests that adherence to RDT results is reasonably high with 83.2% of RDT-positive patients receiving ACT and only 7.8% of RDT-negative patients receiving ACT. Adherence to diagnostic test results is critical if the implementation of RDTs is expected to reduce over-treatment. Unlike previous studies, this study suggests that health workers do adhere to RDT results, even after routine implementation of RDTs. In addition, findings from this study also confirm reports from previous studies in Tanzania, that RDT introduction can lower anti-malarial drug

consumption (D'Acremont V et al., 2011) and may help reduce the problem of anti-malarial drug stock-outs. This may imply that once a policy of malaria diagnostic confirmation expands to the entire country, the availability of ACT in the Tanzanian health sector might be significantly improved.

This study showed that only about a third of fever patients actually received ACT in the post RDT implementation area, despite the fact that most of the patients (94%) were seen in a facility with ACT in stock. As the use of the rapid tests increase once introduced, health workers' performance is likely to improve since there will be an added tool in the line of care that provides more job and client satisfaction (Williams et al., 2008). Some community studies in Tanzania and elsewhere indicate that community members are willing to receive and pay for a laboratory test prior to malaria treatment (Rennie W et al., 2009). Moreover, some studies reported that clients' demand for a malaria confirmatory test before treatment (Chandler CIR et al., 2008) and having a malaria test increased patient satisfaction with clinical care provided (Williams et al., 2008; Rennie W et al., 2009).

Rapid tests seemed to be performing better than microscopy. It is important to become conscious of the possibility for over-estimation of positivity rate that might result from use of RDTs. In particular, this is likely to be a problem with the use of Histidine rich protein-2 based RDT devices for detecting *Plasmodium falciparum* infection, as they may continue to test positive weeks after parasite clearance. In this case, training on RDTs should stress the need for assessing other disease conditions despite a positive test for malaria, and referral to higher level of care for a microscopic examination of malaria. This is particularly important for providing quality care of malaria patient in the changing malaria transmission patterns, with a downward trend observed in many malaria endemic countries. It as well, supports present efforts to obtain accurate information about the disease burden in the population.

There are several limitations to this evaluation. First, this survey was carried out in established health facilities where both the providers and patients were aware of the presence of the study team. This may have inadvertently influenced prescription behaviour of the providers. Care was taken to use field interviewers who were local residents of the survey area. Response bias was minimized by using survey tools that recorded what was done on the survey day without longer recall periods, except for provider's experience and training. Secondly, the survey was limited to health facilities within the HDSS areas and since the HDSS conducts many health interventions and research studies, this may render the population more health conscious than the general population. Third, the presence of RDTs in the pre-RDT implementation area and some RDT stock-outs in the post-RDT implementation area, may have underestimated the true impact of rolling out RDTs. Methodologically, a 'before and after' design would have provided a better measure of RDT impact in case management, but the purpose of this evaluation was to assess performance of health care system with all the bottlenecks associated with it such as stock outs of medicines, diagnostics and other medical products. In addition, prescription practices may differ from one area of practice to another due to common experiences and governing principles. This may affect the true measure of impact of RDT implementation between the study areas. Lastly, ACT stock out was another limitation that might have affected the true impact of the programme.

3.5 Conclusion:

In conclusion, the implementation of RDTs increased use of RDTs for parasitological confirmation and reduced over-treatment with ACT during high malaria transmission season in one area in Tanzania. Continued monitoring of the national RDT rollout will be needed to assess whether these changes in case management practices will be replicated in other areas and sustained over time. Additional measure such as refresher trainings, closer supportive supervisions, etc, may be needed to improve ACT targeting during low transmission seasons. The need to extend parasitological confirmation of

malaria in the context of integrated community case management is becoming apparent and needs to be addressed.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

IMM was responsible for the field supervision, analysis and preparation of first draft. MS and DK undertook statistical analysis and review of subsequent manuscript. BA was responsible for field supervision and review of subsequent manuscripts. RK, SPK, JS designed the study and reviewed the manuscripts. All authors have read and approved the final manuscript.

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Additional files

Additional files provided in this paper: sup1-3.doc, 37K
http://www.malariajournal.com/imedia/2123671188751411/supp1.doc

Additional file 1: Performance of facility malaria diagnostic tests in pre- and post-RDT implementation HDSS areas (table 7 below).

Table 7: Performance of facility malaria diagnostic tests in pre- and post-RDT implementation HDSS areas

	Malaria rapid diagnostic tests (RDT)				
	Ifakara HDSS (pre- RDT implementation)		**Rufiji HDSS (post- RDT implementation)**		**P-value**
	n/N	**% (95%CI)**	**n/N**	**% (95%CI)**	
Sensitivity	4/14	28.6 (10.2–58.4)	58/65	89.2 (79.3 - 94.7)	<0.01
Specificity	94/120	78.3 (70.0- 85.0)	210/247	85 (79.6 - 89.2)	0.51
Predictive value positive	4/30	13.3 (4.4- 34.0)	58/95	61.1 (48.7-72.1)	0.01
Predictive value negative	94/104	90.4 (83.0- 94.8)	210/217	96.8 (94.1-98.3)	0.05
	Microscopy				
	Ifakara HDSS (pre- RDT implementation)		**Rufiji HDSS (post- RDT implementation)**		**P- value**
	n/N	**% (95%CI)**	**n/N**	**% (95%CI)**	
Sensitivity	7/10	70(19.1 - 95.8)	10/13	76.9 (47.9 - 92.4)	0.18
Specificity	132/235	56.2(39.6-71.4)	93/119	78.2 (68.7 - 85.3)	0.05
Predictive value positive	7/110	6.4 (2.6-14.8)	10/36	27.8 (12.4- 51.2)	0.49
Predictive value negative	132/135	96.9 (90.8-99.0)	93/96	96.9 (90.8-99)	0.32

Chapter 4: Correct Dosing of ACT

Correct dosing of artemether-lumefantrine (AL) for management of uncomplicated malaria in rural Tanzania: do facility and patient characteristics matter?

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Abstract:

Introduction: Poor adherence and inappropriate use of recommended treatment may contribute to drug resistance. Use of artemisinin-based combination therapy (ACT) such as artemether-lumefantrine (AL) requires a strict dosing schedule that follows the drugs' pharmacokinetics properties. The quality of malaria case management was assessed in two areas with health and demographic surveillance systems to ascertain patients' characteristics and facility-specific factors that influence correct dosing of AL for management of uncomplicated malaria in rural Tanzania.

Methods: Exit interviews were conducted with all patients attending for initial illness consultation at health facilities at each site. Information about health workers' training and supervision visits was collected. As well, health facilities were inventoried for capacity and availability of medical products related to care of malaria patients. The outcome was correct dosing of AL based on age and weight. Logistic regression was used to assess health facility factors and patient characteristics association with correct dosing of AL by weight.

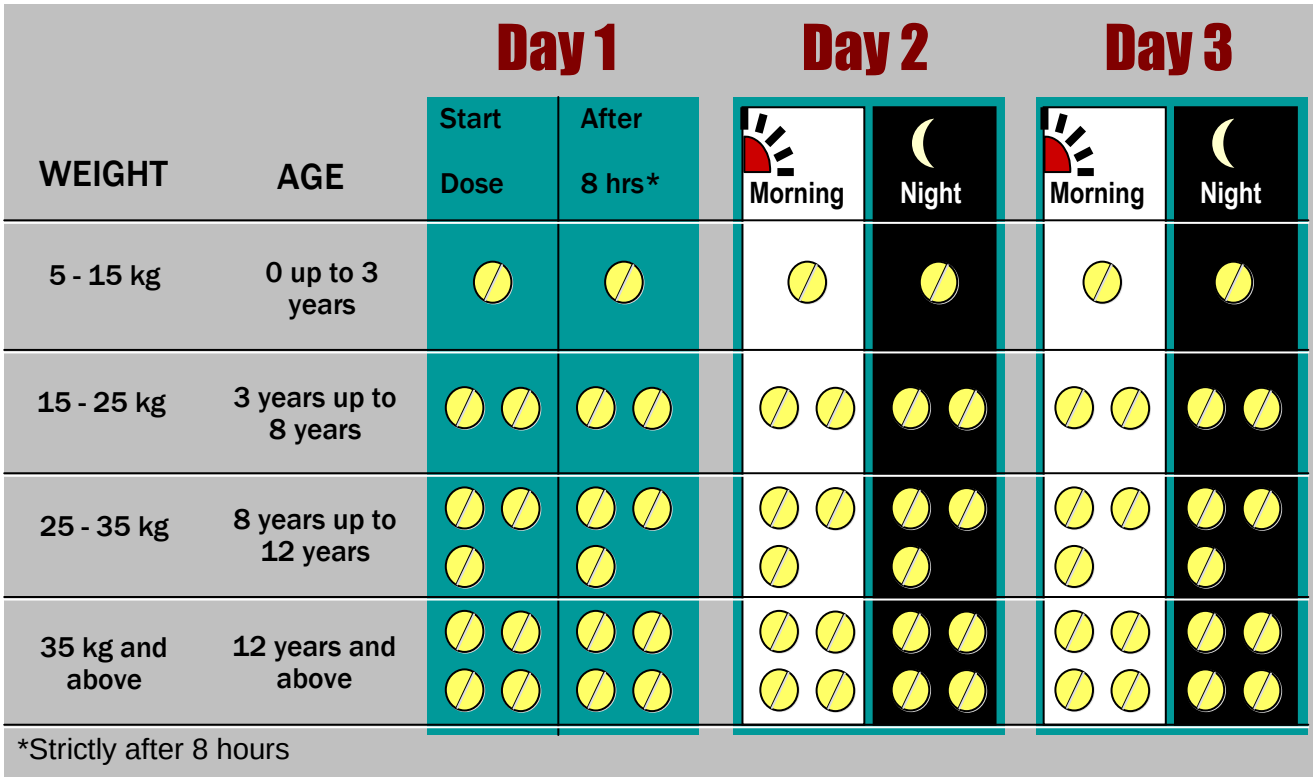
Results: A total of 1471 patients were interviewed but only 503 (34.2%) patients who received AL were assessed for correct dosing. Most patients 430 (85.5%) were seen in public health facilities, 383 (76.1%) in a dispensary and 458 (91.1%) in a facility that had AL in stock on the survey day. Overall, 395 (78.5%) patients received correct dosing by age and 430 (85.5%) by weight. The proportion of patients receiving correct dose of AL as per national guideline was lower for middle aged groups; 42.4% for 9-12 years and 50.0% for 3-9 years age group. As well only 50.0% of patients weighing 25-35 and 60.9% of patients weighing 15-25kg received appropriate AL dosing ($p<0.001$). In multivariate analysis, weighing between 15-35 kg was significantly associated with incorrect dosing of AL ($p<0.05$) compared to those above 35kg.

Conclusion: Although malaria treatment guidelines indicates AL dosing can be prescribed based on age or weight of the patient; findings from this study shows that age based dosing is more prone to errors. Patients' age groups predispose them to

varying odds of incorrect dosing of AL. The use of weight-based prescriptions is emphasized.

(Key words: AL dosing, uncomplicated malaria, Tanzania)

AL dosing instruction chart provided to guide AL prescriptions



4.1 Introduction

The World Health Organization (WHO) declares that much of the ill health, disease, premature death and suffering we see are needless, since efficacious and affordable interventions for prevention and treatment are available. It is further noted that, these effective interventions are not matched with the power of the health systems to deliver them to those in greatest need, in a comprehensive way and on an adequate scale (WHO, 2007). This well appreciated fact raises the significance of assessing and addressing health systems bottlenecks, in order to improve health outcomes and the quality of health care services.

Following wide spread resistance of malaria parasites to commonly used antimalarials such as chloroquine and sulphadoxine-pyrimethamine (SP); there was a global to move to use artemisinin-based combination therapy (ACT) for malaria treatment (Bosman A et al., 2001). This requires the artemisinin derivatives with shorter half-life be combined with a longer half-life partner drug, to enhance therapeutic efficacy and reduce treatment durations (Bosman A et al., 2001). Currently, the artemisinin derivatives used for malaria combination treatment include; artesunate, artemether and dihydroartemisinin (DHA). ACTs such as artemether-lumefantrine (AL) have become a first-line medicine for management of uncomplicated malaria in many malaria endemic countries including Tanzania (NMCP, 2006).

Poor adherence and inappropriate use of recommended treatments have long been linked to development and spread of drug resistance. Use of ACTs for malaria treatment requires a strict dosing schedule that follows the drugs pharmacokinetics (Morris CA et al., 2011). AL dosing is based on four pre-defined weight bands or age groups. According to manufacturers, an 8-hour interval between the first and the second doses of AL is critical for appropriate parasite clearance and clinical cure. In addition, manufacturers recommend completing the doses at defined time intervals and taking AL with a fatty meal for better absorption of the drug to enhance its bioavailability. These recommendations, if followed thoroughly, will optimize therapeutic response.

Unfortunately many studies have reported that clinical guidelines are not always adhered to for various reasons (Zurovac et al., 2004; Dodoo ANO, 2009; Zurovac et al., 2008c), and especially when they are ambiguous (Rowe et al., 2009).

Packaging of AL medicines for public sector use in Tanzania is customized for each dosing band and incorporates illustrated instructions for low-literate patients and caretakers. However, appropriate patient counseling is mandatory for optimal adherence. This study was carried to assess the quality of malaria case management under real world settings. It included, among other things, assessment of ACT dosing schedule and health facility factors related to care of malaria patients. Understanding of the factors influencing correct dosing will help disease control programme and local health management teams to plan effective malaria related supportive supervision, knowing specific areas that requires emphasis.

4.2 Methods

Study design and study area*:* Data was collected through pair of cross-sectional health facility surveys in the Rufiji and Ifakara Health and Demographic Surveillance Systems (HDSS) area, in March and October, 2010. This work was completed as part of the large phase four platform of the INDEPTH Network to assess effectiveness and safety of antimalarial drugs called INESS- Indepth Network Effectiveness and Safety Studies of antimalarial drugs (INESS).

Data collection: All out-patients presenting for initial illness consultation on the day of a survey, were approached for inclusion in the study. Information was collected by means of questionnaires through interviews with patients or caretakers. Information on the patients' complaints, provider's diagnosis, dosing instructions and counselling messages were recorded. As well, patient's clinical notes were later reviewed and recorded, and patients were measured weight and asked for a blood smear for independent assessment of presence of malaria parasites. Information of providers training, work experience and supervision visits were also recorded. The facility was

inventoried for availability of medicines, diagnostics and reference materials related to malaria treatment.

Data entry and analysis: Data was entered in EPIDATA Entry version 3.1 (EpiData Association, Odense, Denmark) by two independent entry clerks. Analysis was performed in STATA 11 (StataCorp, College Station, Texas). Descriptive analysis was undertaken after merging health facility, health worker and patient datasets, clustered by health facility consultation days. Analysis was performed at patient level, in order to assess effect of care to patients seen. Pearson Chi-squared test was used to draw proportions of patients who received correct AL dose based on age or weight by different patients' characteristics and facility factors. Logistic regression was carried out to assess association of health facility factors and patients' characteristics with correct dosing of AL, clustered by facility consultation days. An alpha level of 0.05 was used for all significance tests.

Definition of correct dosing of AL: Correct dosing of AL was assessed based on four criteria: a patient is prescribed AL; an appropriate number of AL tablets per dose given either based on patient's age or body weight; the appropriate number of doses per day and appropriate total number of days, which were always 2 and 3, respectively. Any dosing instruction below these criteria was considered inappropriate.

Additional information on the study area and study population are presented by Masanja and colleagues (Masanja et al., 2012).

4.3 Results

A total of 1471 patients were interviewed, but only 503 (34.2%) who received AL will be included in the analysis (figure 1).

Results in Table 1 shows that, majority of patients were seen in dispensaries 383 (76.1%) and public health facilities 430 (85.5%). Most patients who received AL were seen in a facility that had AL in stock of the day of a survey 458 (91.1%) but only 280

(55.7%) were seen in a facility with malaria testing capacity on the survey day. Although 366 (73%) of patients were seen in a facility that had a functioning weighing scale, less than half, 167 (33.2%) had their weigh assessed and recorded during a provider- patient interaction, compared to 95.6% (481) who had their age assessed and recorded during clinical consultation. Very few patients were seen by a health worker who had received a supervision visit in the past 6 months (21.7%) and who had training on the use of ACT (44.1%). Most patients reported fever or history of fever 489 (97.2%).

Figure 1: Distribution of study participants

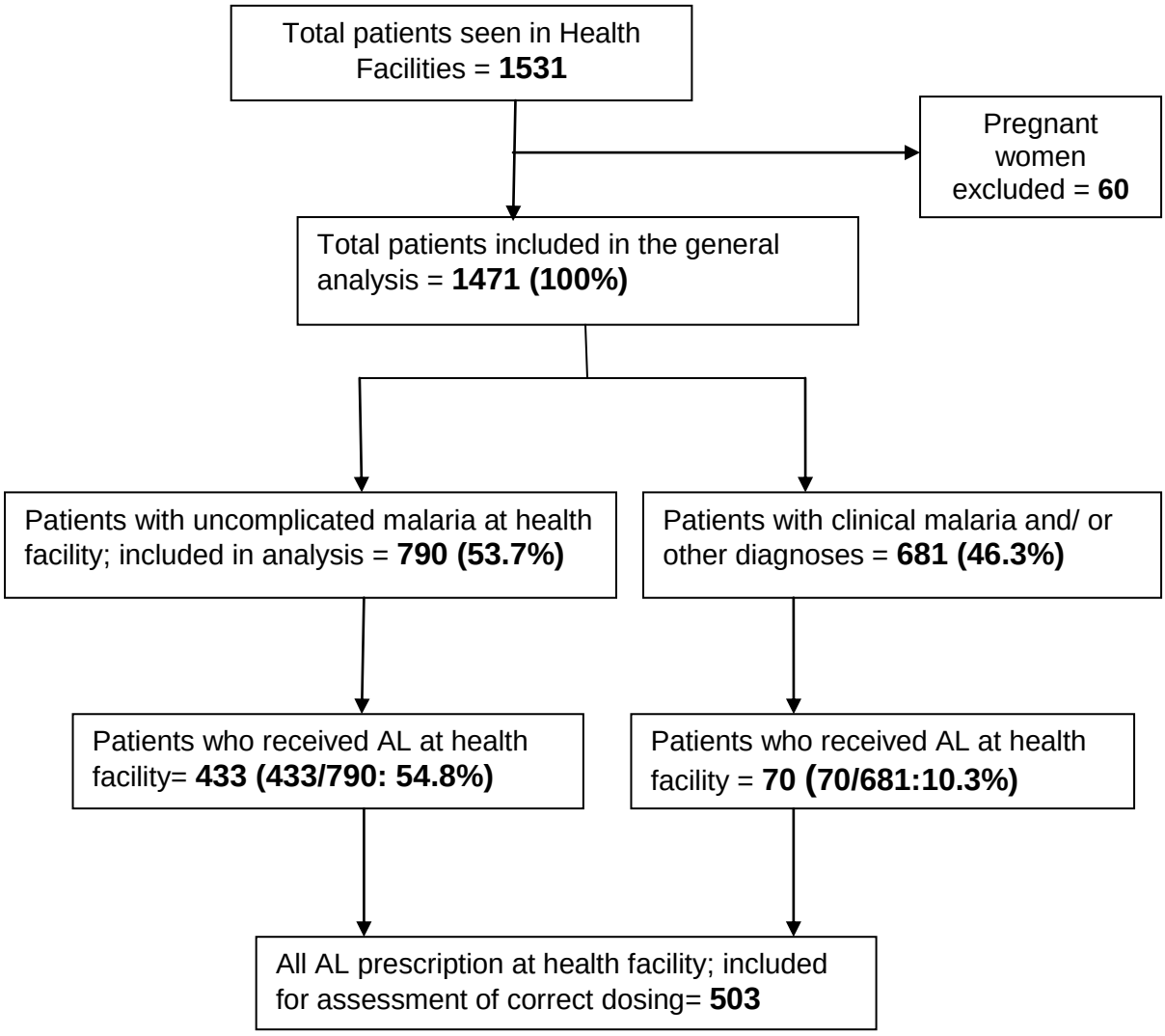


Table1: Characteristics of patients who received AL during the survey (N=503)

Category	Health facility and patients characteristic	n (%)
Type of health facility:	Patients seen in Dispensary	383 (76.1)
	Patients seen in Health Centers	113 (22.5)
	Patients seen in Hospitals	7 (1.4)
Facility ownership:	Patients seen in Public HFs	430 (85.5)
	Patients seen in Non-public HFs	73 (14.5)
Availability:	Seen in HF with ALu in stock	458 (91.1)
	Seen in HF with RDT &/or functional microscopy	280 (55.7)
	Seen in HF with any scale	366 (72.7)
	Patients who had their weight assessed / recorded	167 (33.2)
	Patients who had their age assessed/ recorded	481 (95.6)
Other characteristics for malaria case management:	Seen HW who had supervision in last 6 months	109 (21.7)
	Seen by HW who had training on ACT	222 (44.1)
	Seen in HF with ACT guideline/reference	412 (84.7)
Patients characteristics:	Children <3 years	178 (35.4)
	3-12 years	177 (35.2)
	Above 12 years	148 (29.4)
	Had fever/ history of fever in past 48 hours	489 (97.2)
	Had fever and a malaria test performed at HF	175 (34.8)
	Patients who slept under net the previous night	312 (62.0)

The proportion of patients who had correct AL dosing by age was 78.5% (395), lower than those who had correct dosing by weight 85.7% (431), table 2. Correct dosing by age was low in age group 3-9 years (50.0%) and much lower in age group 9-12 years (42.4%; p<0.00). As well, patients weighing between 15-25 kg and 25-35 kg, had low proportions of correct dosing than marginal groups (p<0.001) - table 2.

A multivariate analysis was taken to assess predictors of correct AL dosing by weight and age. The middle weighing patients between 15-35 kg had significantly lower odds of correct dosing than those above 35 kg, in the unadjusted analysis, table 3. When AL dosing was based on age, these middle aged patients groups (3-9 and 9-12 years) has

lower odds of correct dosing compared to children below age of 3, in both crude and adjusted analysis (p<0.005). Having diagnostics seem to decrease the odds of correct dosing by weight in unadjusted analysis. Supervision, and training on ACT also showed lower odds of correct dosing in the adjusted model- table 3.

Table 2: Proportion of patients who received correct dosing of AL according to age and weight as per national treatment guideline [N(age)=395; N(weight)=430; N(overall)=503]

Category	**Health facility and patients characteristic**	**Correct dose by age: n (%)**	**P-value (age)**	**Correct dose by weight: n (%)**	**P-value (weight)**
Overall	Correct dosing: n/N (%)	395/503 (78.5)		431/503 (85.7)	
Type of health facility:	Patients seen in Dispensary	296 (74.9)		332 (77.0)	
	Patients seen in Health Centers	92 (23.3)	0.244	93 (21.6)	0.505
	Patients seen in Hospitals	7 (1.8)		6 (1.4)	
Facility ownership:	Patients seen in Public HFs	336 (85.0)	0.606	368 (85.6)	0.871
	Patients seen in Non-public HFs	59 (15.0)		63 (14.6)	
Availability:	Seen in HF with ALu in stock	37 (9.4)	0.527	391 (90.7)	0.520
	Seen in HF with either RDT or functional microscopy	217 (55.0)	0.529	235 (54.5)	0.207
	Seen in HF with any scale	297 (75.2)	0.019	314 (73.0)	0.911
Patients age categories	<3 years (N=178)	172 (96.6)			
	3- <9 years (N=144)	72 (50.0)	<0.001	NA	
	9- <12 years (N=33)	14 (42.4)			
	12 years and above (N=148)	137 (92.6)			
Patients weight categories	5 -15 kg (N= 242)			215 (89.6)	
	>15 -25 kg (N=87)	NA		64 (73.6)	<0.001
	>25- 35 kg (N= 24)			15 (62.5)	
	>35 kg (N= 150)			137 (91.3)	
Other characteristics:	HW who had reference materials	161 (40.8)	0.606	176 (40.9)	0.565
	HW who had supervision in last 6 months	85 (21.5)	0.875	90 (20.9)	0.294
	HW trained on AL	174 (44.0)	0.942	186 (43.3)	0.279

Table 3: Multivariate analysis of health facility factors and patients characteristics associated with correct dosing of AL by weight (and age): N=501

	Correct dosing by weight			
Health Facility Factors	**Crude OR (95%CI)**	**p-value**	**Adjusted OR (95%CI)**	**p-value**
Type of health facility:				
Hospitals	Ref		Ref	
Health Centers	0.92 (0.21-4.17)	0.923	0.85 (0.17-4.22)	0.850
Dispensaries	1.30 (0.32- 5.20)	0.706	0.68 (0.15-3.21)	0.633
Type of ownership:				
Public HFs	Ref		Ref	
Non-public HFs	0.94 (0.48- 1.84)	0.860	0.58 (0.20-1.68)	0.316
Products availability:				
HF with functioning scale for all age	1.34 (0.67-2.67)	0.399	1.21 (0.57-2.52)	0.614
HF with AL in stock	0.64 (0.36- 1.14)	0.128	0.75 (0.23-2.39)	0.626
HF with RDT or functional microscopy	0.51 (0.29- 0.92)	0.026	0.66 (0.33-1.33)	0.244
Supporting materials/supervision:				
HF with supervision visit past 6 months	0.71 (0.38-1.33)	0.286	0.39 (0.20-0.74)	0.005
HW who had training on ACT	0.65 (0.37- 1.16)	0.145	0.50 (0.25-1.02)	0.058
HW who had reference materials	0.96 (0.53- 1.73)	0.895	0.63 (0.33- 1.21)	0.166
Patients weight:	**Correct dosing by weight**			
5 -15 kg	1.39 (0.92- 2.11)	0.116	3.39 (0.71-16.1)	0.124
>15 -25 kg	0.47 (0.26-0.84)	0.012	1.76 (0.32- 9.80)	0.512
>25- 35 kg	0.30 (0.13- 0.72)	0.007	0.69 (0.15- 3.03)	0.623
>35 kg	Ref		Ref	
Patients age:	**Correct dosing by age**			
<3 years	Ref			
3- <9 years	0.08 (0.05-0.15)	<0.001	0.05 (0.02- 0.11)	<0.001
9- <12 years	0.05 (0.02- 0.15)	<0.001	0.02 (0.00- 0.06)	<0.001
12 years and above	0.44 (0.25- 0.76)	0.004	0.09 (0.02- 0.41)	0.002

Table 4 describes the direction of inappropriate dosing. Most incorrect dosing was towards less pill counts than recommended, especially for age based prescriptions.

Table 4: Description of inappropriate dosing by pill count according to patients' age and weight (N=501)

Age categories	Less number of tablets	Appropriate number of tablets	More number of tablets	Missing/ in-determinate count	Total patients
<3 years	1	164	6	7	178
3 to 9 years	58	68	10	8	144
9 to 12 years	15	15	1	3	33
Above 12 years	7	138	0	1	146
Total (%)	81 (16)	385 (76.8)	18 (3.5)	19(3.7)	501(100%)
Weight categories					
<15 kg	1	206	24	10	241
15 to 25 kg	16	59	7	5	87
25 to 35 kg	5	15	2	2	24
Above 35 kg	9	134	3	2	148
Total (%)	31 (6.2)	414 (82.8)	36 (7.2)	19(3.8)	500(100%)

4.4 Discussion

This study gives a snapshot of facility and patient characteristics associated with correct dosing of artemether-lumefantrine for management of uncomplicated malaria in rural Tanzania, 4 years after AL introduction as a first line treatment. As expected, most patients were seen in dispensaries, which are the lowest level of formal health care provision in the country. It was of interest to record that, some patient characteristics are significantly association with lower odds of correct dosing of AL. In particular, older children and young adults, i.e. 3-12 years; are more likely to be subjected to inappropriate dosing of AL especially, if dosing is based on age, than younger children or adults. Malaria treatment guidelines in Tanzania allow for both age and weight based AL dosing, following manufacturers' recommendations (NMCP, 2006).

This is not a first study to report inappropriate dosing of malaria treatment for children. A study from Kenya showed more similar findings, where infants were more likely to receive appropriate treatment than older children (Zurovac et al., 2004). The authors in the Kenya study thought that health workers were being more careful with the younger

age group, which seems like a logical explanation for the observation. As well, concerns of incorrect dosing of malaria drugs have been reported in other settings (Zurovac et al., 2008c; Zurovac and Rowe, 2006; Rowe et al., 2009). Correct dosing with AL in our study was better with weight than age based categories. This may reflect a problem of poor correlation for the age-weight profiles used. Probably the local age-weight profile differs with the available nutrition profiles, due to poor nutrition or living conditions in the studied population.

Basically two very similar conclusions can be drawn following these findings. First, AL dosing by weight was frequently more correct than dosing by age or AL doses prescribed to patients on the basis of their weight is more often correct than given based on age. Judging from results presented in table 1, it more reasonable to suggest that, AL prescriptions in this survey was more often based on age than weight; because of the low proportion of patients who had their weight assessed as compared to age (33.2% versus 95.6%). Whichever way one looks at, it signifies the importance of stressing the use of weight based prescription to ensuring appropriate amount of medicine is delivered in the system. Where age-weight profiles differ, it may practically be difficult to have guidelines that comply with age-weight indices for every given population. This fact should be emphasized during trainings.

The fact that some patients received inappropriate dosing levels of ACT in the study areas, if dosing is based on age; implies that adequate parasite clearance may not be achieved. As a consequence, this provides opportunities for drugs' selection pressure and continued disease transmission in the community. Results have shown that, inappropriate dosing was more likely to happen to older children and young adults who are physically active and moves from place to place e.g. school or outdoor activities; increasing the likelihood of contact with malaria vectors and other infected or susceptible individuals. Understanding predictors of appropriate care for malaria patients will assist health managers to plan for resources and supportive supervision aiming at quality improvement and disease control.

During treatment policy change, it is customary to train health workers on the new guideline and provide reference materials for in-depth referencing after training. In this assessment, health workers training on ACT, possession of reference materials and supervision did not seem to improve the odds of correct dosing of AL. The most logical explanation for these findings could be related to a fact that, few patients were seen by providers who had training on ACT (44%) and fewer by a provider who had supervision visit in the past few months (21.7%). Moreover, we neither had information on the contents of the training provided on ACT nor did we have details of the supervision visits happening in relation to malaria case management. The role of supervision visits in improving quality of case management (in malaria) has provided inconsistent conclusions (Zurovac et al., 2004; Trap B et al., 2001; Osterholt et al., 2006) in other settings. This finding is alarming and requires further understanding of the role, schedule and contents of supervision visits for case management and its impact in clinical practices.

Limitations:

We did not collect information on total number of patients attended by a provider to assess the caseload but, we included all patients and provider's on the day of survey, hence patient's sample is self weighing on the basis of utilization for the days surveyed, assuming survey days were typical for the rest of the year. The importance of caseload assessment has been described (Zurovac et al., 2004; Rowe et al., 2009; Nyandigisi et al.).

4.5 Conclusions:

A good clinical practice should stress the use of weigh based dosing and support infrastructure for having weighing scales available at health facilities. The correct dosing of AL in health facilities in the study areas was better when based on weight than age. Patients' characteristics, such as age and weight seem to be associated with the odds of correct dosing of AL. This needs to be addressed in order to improve treatment outcomes for management of uncomplicated malaria in rural Tanzania.

Conflict of interest:

The study was carried as part of the phase 4 platform for evaluation of antimalarials effectiveness and safety in Africa, called INESS. INESS project was primarily funded y the Bill and Melinda Gated foundation. No conflict of interest is declared.

Authors contributions:

MIM trained and supervised field workers, analysis, prepared the first draft; MS and DK assisted in training of field workers, performed statistical analysis, revision of first and subsequent drafts; RK and BA supervision of field work and revision of draft manuscripts, IK, DDS, SPK and JS; study design, technical support and revision of subsequent manuscripts.

Disclaimer:

The conclusions reached in this work are those of the authors and do not reflect the stand of their institutions and funders.

Chapter 5: Age as a Predictor of parasitemia

Relationship between age and presence of malaria parasites in the out-patients' clinical settings, rural south-eastern Tanzania: analysis of data from 2002 to 2010.

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This manuscript is submitted for review at CDC, Atlanta, GA

Abstract:

Background: The relationship between age, severity and patterns of malaria transmission has long been reported in literature. Most of these works were done in relation to severely ill patients and young children below age of 10. In this report, data collected through health facility surveys from 2002-2010, was analysed to assess relationship between age and presence of malaria parasitemia at out-patient clinical settings.

Methods: Cross sectional health facility surveys were conducted in Rufiji (2002-2010), Kilombero/ Ulanga (2002, 2004 and 2010) and Morogoro rural districts in 2002. Information was collected during exit interviews and blood smears were taken to assess presence of malaria parasitemia. Data was entered in fox-Pro for 2002-2006 and EPIDATA for 2010, but analysis was performed in STATA 11. Graphs showing trends were computed using Microsoft excel and multivariate linear regression was used to quantify the relation between presence of parasitemia and age.

Results: Higher proportion of parasitemic patients were seen at dispensaries (48.5%) compared to other levels of care. About 4% of positive blood smears had gametocytes. Children aged 1-5 had higher prevalence of parasitemia. Overall, parasitemia was declining in children below 5 years, showing similar trends as population based surveys; but, significant differences were observed within this age group. While children below 2 years showed a decreasing trend ($p<0.001$), those aged 2-5 years had an increasing trend for malaria parasitemia ($p<0.001$), contrary to population based findings. Adults generally showed a declining trend for presence of parasitemia. Presence of parasitemia at health facility declined with a 5 years increase in patient's age; in both crude and adjusted linear regression models ($p<0.001$).

Conclusion: Age of parasitemic patients significantly increased with decrease in malaria transmission intensity. The disease burden shifted to 2-5 years and older children up to 15 years of age. Broad age categorization to below and above 5 years; masks important intra-groups' effects. Older children should also be among the priority

target groups for malaria control interventions in the wake of decreasing malaria transmission.

5.1 Background

Assessing the impact of malaria control strategies requires more robust and reliable measures. Rowe and colleagues suggested the use of experimental designs for assessing changes in malaria morbidity and mortality, but acknowledges that such evaluations would be less feasible in evaluating real- world programmes (Rowe AK et al., 2009). Other studies have reported changes in transmission patterns, transmission intensity, decreased malaria parasite prevalence in population surveys and a decrease of malaria specific mortality, as indicators of changing malaria burden in respective areas (Smith T et al., 2004; Okiro EA et al., 2007; Hay SI et al., 2008; Ceesay SJ et al., 2008; Otten M et al., 2009; Khatib RA et al., 2012). To provide accurate estimates of changing malaria transmission in the community, other scientists have used serological markers (Stewart L et al., 2009) and age (Marsh K and Snow RW, 1999; Smith T et al., 2004; Carneiro I et al., 2010).

The relationship between age and severity of malaria infection has long been reported (Marsh K and Snow RW, 1999; O'Meara WP et al., 2008; Carneiro I et al., 2010). It is now understood that, as malaria transmission declines, the age of clinical malaria attacks also shifts to older children (Aponte JJ et al., 2007). This has mainly been documented with relation to severe malaria using inpatients data and, or, blood smear results in population bases surveys (O'Meara WP et al., 2008; Ceesay SJ et al., 2008; Okiro EA et al., 2007; Schellenberg D et al., 2004; Bodker et al., 2006). In a typical clinical setting in rural Tanzania, severe cases of malaria are normally first seen at outpatient department (OPD) before admission. It is now widely agreed that understanding of disease trends in the respective communities, helps appropriate resources allocations for its control. The same can be concluded in relation to patients' management. Knowledge of the local patterns of the disease is useful to guide clinical judgment during patient's care.

Efforts to combat malaria in endemic countries have resulted in a steady decline of malaria prevalence. The World Health Organization (WHO) world malaria reports a reduction of malaria cases globally from 244 million in 2005 to 216 million in 2010 (WHO, 2010b). Likewise, the Tanzania HIV/ AIDS and malaria indicator survey reports a decline in malaria positivity from 18.1% in 2007/8 to 4.5% (by microscopy) or 9.5% (by rapid tests) in 2012 (THMIS, 2007/8; THMIS, 2012). This decline however, is not very apparent at the health facility level. Patients with malaria like signs and symptoms constitute majority of patient seen in Tanzanian hospitals (NMCP, 2003b). The situation is particularly challenging in areas where malaria parasitological confirmation is not readily available. As a result, clinicians attending these patients may continue to consider malaria diagnosis where the likelihood of the disease is minimal, missing opportunities to treat other similar life-threatening conditions. In this situation, a description of patient demographic characteristics as a possible indicator of the increased likelihood to have the disease will be well appreciated to facilitate initial screening for a confirmatory test.

Here, findings from the retrospective analysis of data collected from health facility surveys between year 2002 and 2010, is presented to assess the relationship between age and presence of parasitemia in out-patients during clinical consultation in endemic areas, sub-Saharan Africa. During this study period, some of these areas witnessed the introduction of artemisinin based combination therapy (ACTs) for malaria treatment, first under pragmatic evaluation (Kachur et al., 2001) and later as a country policy (NMCP, 2006).

5.2 Methods

This work analyzed data from two major projects conducted in south- east of Tanzania. First was the Interdisciplinary Monitoring Programme for Antimalarial Combination Therapy in Tanzania (IMPACT-Tz) as described in (Kachur et al., 2001; Njau et al., 2008; Khatib RA et al., 2012) and second, the Indepth Network Effectiveness and

Safety Studies (INESS) of antimalarial drugs in Africa (INESS), as reported in (Masanja et al., 2012b).

Study area

Both IMPACT-Tz and INESS were operating in the Rufiji district in Pwani region, Kilombero and Ulanga districts in Morogoro region and the latter also collected data from Morogoro rural district, Morogoro region in its early years (Masanja et al., 2012a). Kilombero and Ulanga were treated as a single unit (K/U) in both studies, because of the high population interactions between the two districts. Morogoro rural was included in the IMPACT-Tz baseline assessments, but was dropped from the evaluation after it was divided into two districts; Morogoro rural and Mvomero in 2003. Likewise, the INESS programme also operated in K/U and Rufiji districts, but its work is mainly focused within the Health and Demographic Surveillance System (HDSS) areas (Masanja et al., 2012b).

Health facilities selection and procedures

During the IMPACT-Tz programme, OPD surveys were conducted in 1 hospital, 1 health center and 3 dispensaries from each district (most of them within the HDSS area); for several days until the required sample size was reached. In INESS surveys, all health facilities serving within the HDSS areas were visited for 2-3 days to achieve the required sample size. In both studies, sampled patients at the health facility were requested for their consent to participate. Upon acceptance, an exit interview was conducted, their clinical notes reviewed and few drops of blood were collected for assessing the presence of malaria parasites. IMPACT-Tz also assessed haemoglobin levels of all patients enrolled in the survey.

Patients included in the survey during IMPACT-Tz study were of all ages (above and below 5 years), excluding trauma patients and severe cases; where as in INESS surveys, patients recruited for the study were all patients who came for initial illness consultation on the survey day, excluding severe cases. During IMPACT-Tz, data was

collected in K/U, Rufiji and Morogoro rural in February- March, year 2002 (as baseline survey), then in Rufiji and K/U only in March, year 2004 after Rufiji had started using ACT- artesunate plus Sulphadoxine-pyrimethamine (AS+SP), as part of the programme implementation. In year 2006- March, health facility survey was conducted only in Rufiji. INESS facility surveys were done in March and October, 2010 only.

Laboratory procedure

In both IMPACT-Tz and INESS studies, thick and thin blood smears were stained with 10% Giemsa stain and asexual parasites were counted per 200 white blood cells (WBCs) assuming average of 8,000 WBC per blood microlitre. Gametocytes were quantified in reference to 500 WBCs. In IMPACT-Tz, 5% of all slides that were read by each microscopist were read again by a senior laboratory technician, for quality control. Discordant readings were consistently less than 14%; where as in INESS all slides were sent for a second reading and discordant results harmonized by a third reader.

Data management and analysis

IMPACT-Tz data was entered in FoxPro software (Redmond Washington, USA), and INESS data were entered in EPIDATA (version 3.1, EPIDATA Association, Odense, Denmark) programme. All data were converted to, and analyzed in STATA version 11 (STATA Corporation, College Station, USA). The four datasets (2002, 2004, 2006 and 2010) were combined (appended) for this analysis. Because of differences in variables collected throughout the years with slightly different protocols, this analysis only dealt with age (in years and months), type of health facility, district, year and month of survey, gender, parasite counts, gametocyte counts and type of Plasmodium species.

Analysis started with frequency distribution of different characteristic variables. Pearson chi squared was used to assess relation between presence of parasitemia by different patients or facility characteristics. Multivariable linear regression was run to assess relationship between parasitemia and age, district or year of study. Graphs were constructed using Microsoft Excel (Microsoft Office Excel 2000) to show trends in level

of parasitemia with age over the years. Results were considered statistically significant at a p-value of <0.05. In order to better describe the distribution of study participants in the univariate and bivariate analysis, and in trend graphs, age was grouped into categories; first, only two categories were invented (below and above 5 years); second, 6 categories were created; below 1 year of age, 1-2 years of age, >2-5 years, >5-15 years, >15 to 25 years and above 25 years. This grouping was considered important for discussing public health implications of the findings. Likewise, parasite count was also presented into 4 groups (less than or equals to 50parasites/200 WBCs, 51-500, 501-5000 and >5000/200WBCs).

The Tanzania HIV/AIDS and Malaria Indicator surveys (THMIS) collects population based data related to HIV and Malaria control activities in the country. As well the Tanzania Demographic and Health Surveys (TDHS), collect health related indicators in the population. Both THMIS and TDHS draw nationally representative samples in their surveys. Malaria in TDHS is estimated by the proportion of children below age of 5, who had fever two weeks preceding the survey, but since 2007/8 the THMIS performs parasitological tests to children below 5 in order to estimate prevalence of malaria parasitemia. Data from TDHS 2004/5, THMIS 2007/8 and THMIS 2011 (collectively referred to as THMIS in this paper), were plotted against graphs of patients below age of 5, i.e. against 2004, 2006 and 2010, respectively; in order to compare trends between health facilities and population based surveys (NBS, 2004/5; THMIS, 2007/8; THMIS, 2012).

Morogoro rural had only one data point, therefore excluded in the multivariate analysis.

Ethical review

Both IMPACT- Tz and INESS programme received ethical approval from national and institutional ethical review boards.

5.3 Results

A total of 9,740 patients' records were included in the analysis. Results in table 1 show a similar distribution of age in the five of the six groups; except adults of above 25 years. Female constituted about 58% of study population. As expected, there were more participants in the first survey (2002) due to inclusion of Morogoro rural. Parasite counts showed comparable proportions in the first three groups, with fewer patients recording very high levels of parasitemia (4.1%)

Table 1: Characteristics of patients seen during survey(s) period

Main category (N)	Sub-category	n	(%)
Age categories (9,514)	Less than 1 year	1,354	14.2
	1 to 2 years	1,546	16.3
	2 to 5 years	1,457	15.3
	5 to 15 years	1,464	15.4
	15 to 25 years	1,319	13.9
	More than 25 years	2,374	24.9
Prevalence of parasitemia (1,876)	Less than 1 year	224	12.0
	1 to 2 years	428	22.9
	2 to 5 years	491	26.3
	5 to 15 years	353	18.9
	15 to 25 years	178	9.5
	More than 25 years	194	10.4
Gender (9,723)	Male	4,102	42.2
	Female	5,621	57.8
District (9,740)	K/U	3,177	32.6
	Rufiji	5,211	53.5
	Morogoro	1,352	13.9
Facility type (9,728)	Hospital	2,409	24.8
	HC	2,829	29.1
	Dispensary	4,490	46.1
Year of interview (9,740)	2002	4,206	43.2
	2004	2,715	27.9
	2006	1,348	13.8
	2010	1,471	15.1
Parasite counts/200 WBCs (1,892)	</= 50	591	31.2
	51 to 500	594	31.4
	501 to 5000	630	33.3
	>5000	77	4.1
Other clinical characteristics	BS checked	8,237/9,721	84.7
	P. falciparum	1,628/ 1,715	95.0
	Gametocytes	96/1,892	5.1
	Parasite positive	1,876/9,721	19.3

Assessment of the characteristics and distribution of parasitemic patients (n=1,892) in table 2 showed that, higher parasite count was most common to children below 5 years (p<0.001). Dispensaries recorded highest proportion of patients with malaria parasitemia (48.5%; p<0.001). Malaria prevalence was higher in 2002 with a decline in the following 2 surveys, but indicating a slight increase in 2010. *P. falciparum* species accounted for about 95% of all infections and gametocytes was recorded in 4% of all parasitemic individuals, especially in n low parasite densities.

Table 2: Characteristics and distribution of parasitemic patients (Parasitemia count/ 200 WBCs)

Parameter (N)	Sub-group	</ = 50 (n; %)	51-500 (n;%)	500-5000 (n;%)	>5000 (n;%)	Total (n; %)	p value
Gender (1,885)	Male	261 (44.3)	287 (48.4)	291 (46.5)	43 (55.8)	882 (46.8)	0.201
	Female	328 (55.7)	306 (51.6)	335 (53.5)	34 (44.2)	1,003(53.2)	
Age (1,868)	<5 years	259 (44.7)	364 (62.2)	457 (73.0)	63 (81.8)	1143 (61.2)	<0.001
	<5 years	321 (55.3)	221 (37.8)	169 (27.0)	14 (18.2)	725 (38.8)	
Age in categories (1,868)	<1 years	70 (12.1)	69 (11.8)	80 (12.8)	5 (6.4)	224 (12.0)	<0.001
	1-2 years	86 (14.8)	151 (25.8)	162 (25.9)	29 (37.7)	428 (22.9)	
	2-5 years	103 (17.8)	144 (24.6)	215 (34.3)	29 (37.7)	491 (26.3)	
	5-15 years	127 (21.9)	109 (18.6)	108 (17.2)	9 (11.7)	353 (18.9)	
	15-25 years	87 (15.0)	54 (9.1)	36 (5.7)	1 (1.3)	178 (9.5)	
	>25 years	107 (18.4)	58 (9.9)	25 (4.1)	4 (5.2)	194 (10.4)	
Type of health facility (1,891)	Hospital	142 (24.0)	94 (15.8)	147 (23.4)	10 (13.0)	393 (20.8)	0.001
	Health centers	184 (31.1)	187 (31.5)	189 (30.0)	20 (26.0)	580 (30.7)	
	Dispensaries	265 (44.9)	313 (52.7)	293 (46.6)	47 (61.0)	918 (48.5)	
Year of survey (1,892)	2002	330 (55.8)	354 (59.6)	337 (53.5)	13 (16.9)	1034 (54.7)	<0.001
	2004	158 (26.7)	187 (31.5)	229 (36.3)	39 (50.6)	613 (32.4)	
	2006	69 (11.7)	13 (2.2)	10 (1.6)	0	92 (4.9)	
	2010	34 (5.8)	40 (6.7)	54 (8.6)	25 (32.5)	153 (8.0)	
Plasmodium species (1,694)	Pf	528 (96.5)	503 (93.9)	527 (94.4)	50 (98.0)	1608 (94.9)	0.09
	Non Pf	19 (3.5)	35 (6.5)	31 (5.6)	1 (2)	86 (5.1)	
Gametocytes carriage (1,648)	Yes	28 (5.3)	24 (4.6)	15 (2.7)	0	67 (4.0)	0.073
	No	502 (94.7)	498 (95.4)	530 (97.3)	51 (100)	1,581 (96)	

Assessment of trends of parasitemia by age groups over the survey years shows that, overall presence of parasites in children below 5 years was declining, but that of older children and adults were on the rise (figure 1). This decline was also evident in population based surveys (THMIS). Further analysis with smaller age groups revealed intra-group variations with differing patterns; where babies below 1 year and 1-2 years generally had a decreasing trend (figures 2a, 2b), those aged 2-5 years old showed an increase in proportion parasitemic (figure 2c), contrary to the population based picture (THMIS). Similarly, the group of age above five years, showed an increasing trend in parasitemia (figure 1) but, intra-group analysis revealed that the increase was only in the older children group (5-15 years; figure 2d), but the adults generally showed a declining trend (figures 2e, 2f).

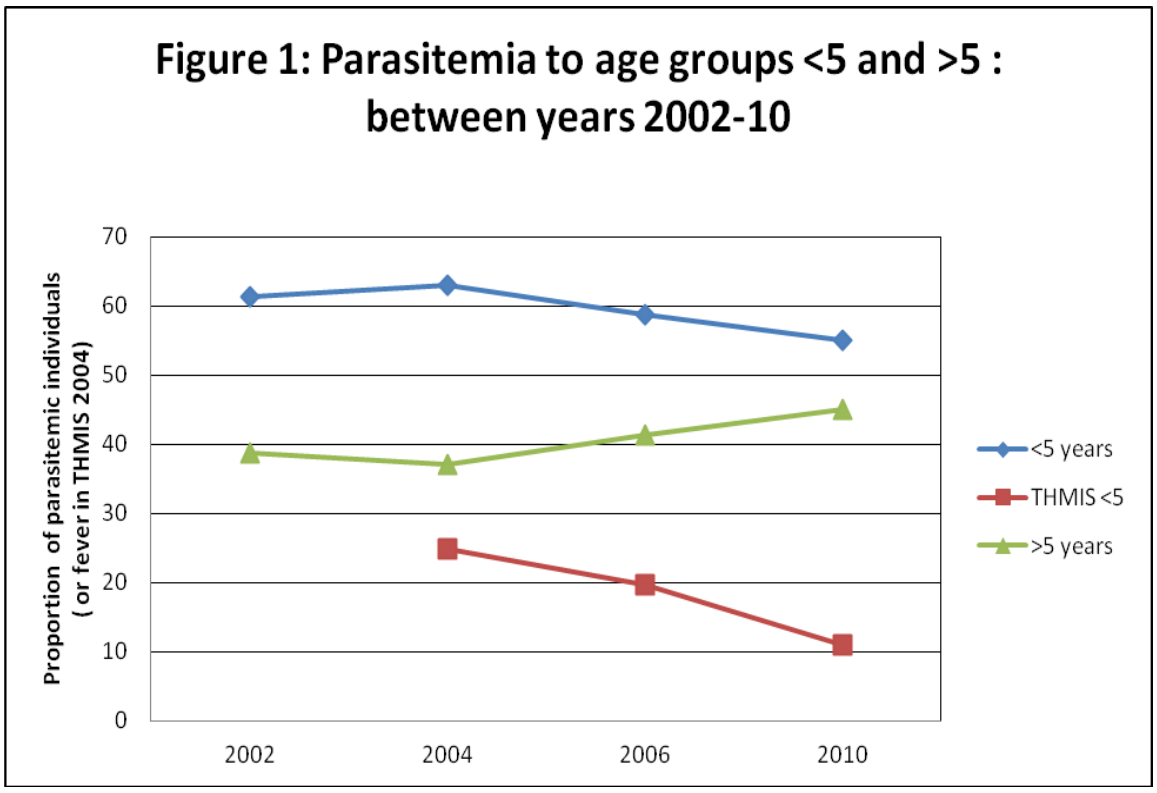


Figure 2a: Parasitemia in <1 year old: 2002-10

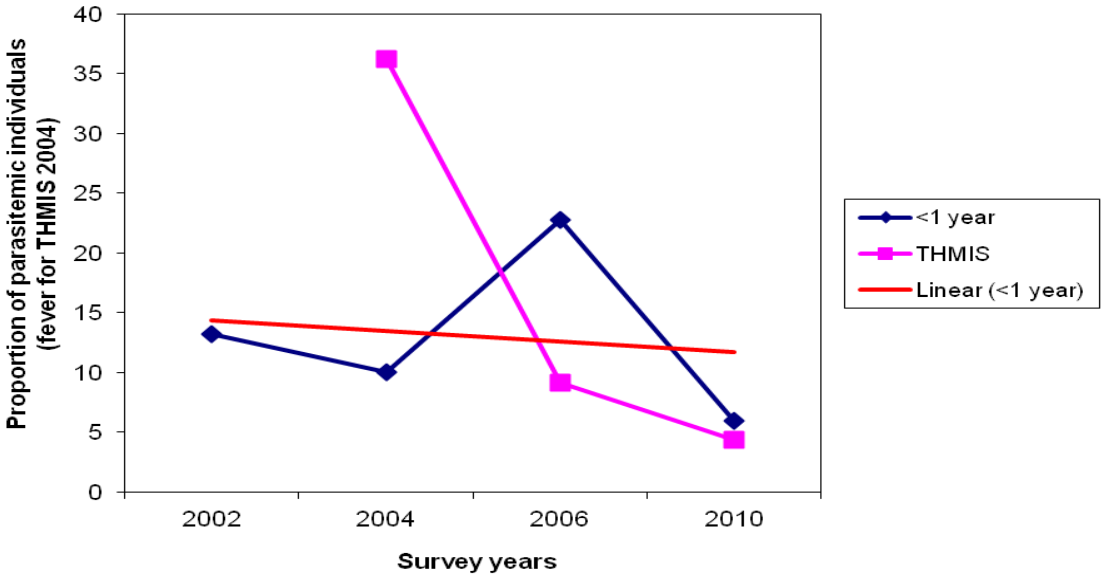


Figure 2b: Parasitemia in 1-2 years old: 2002-10

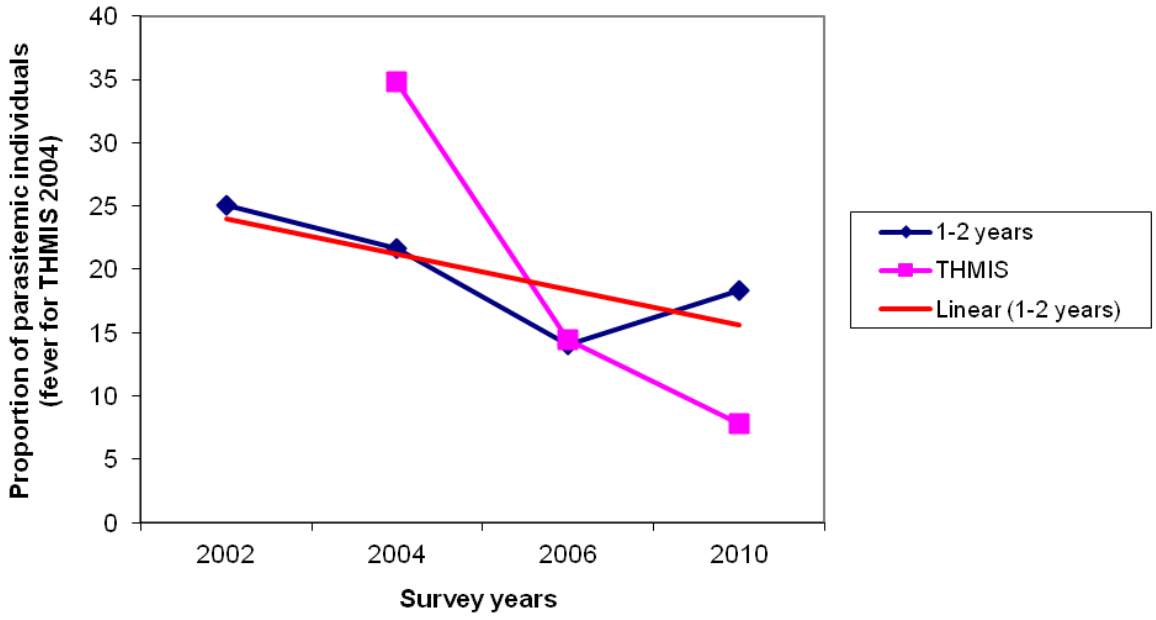
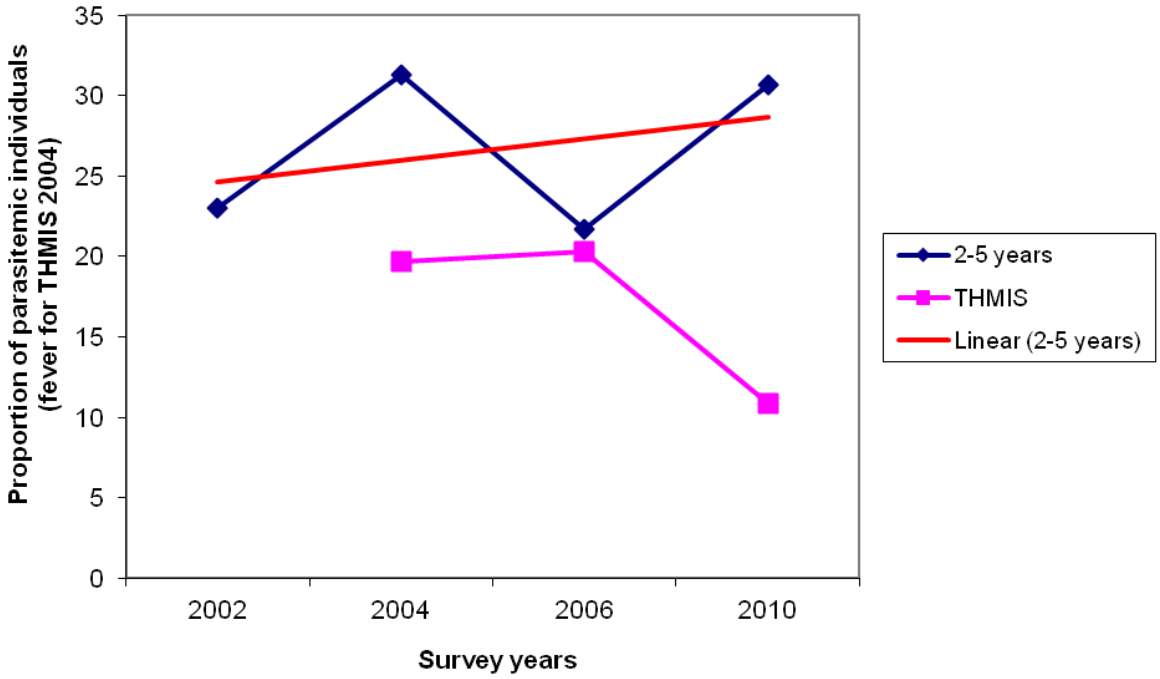
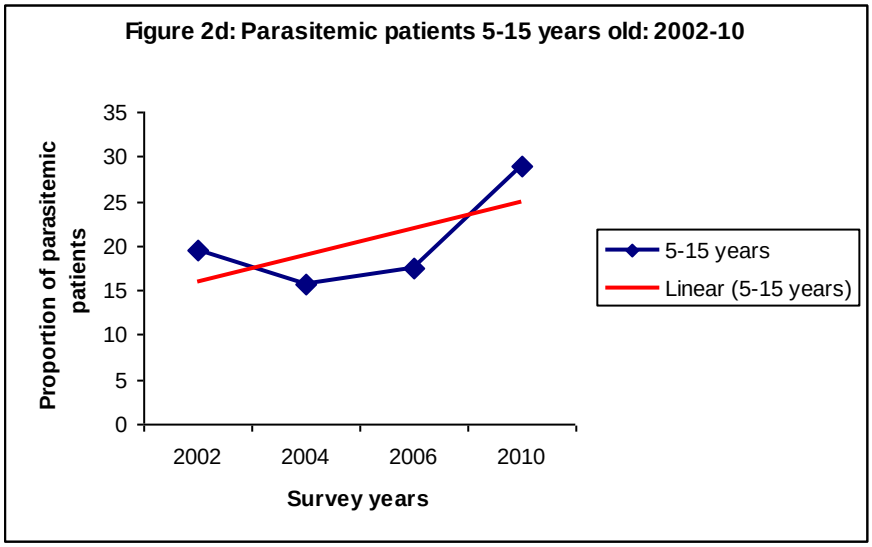
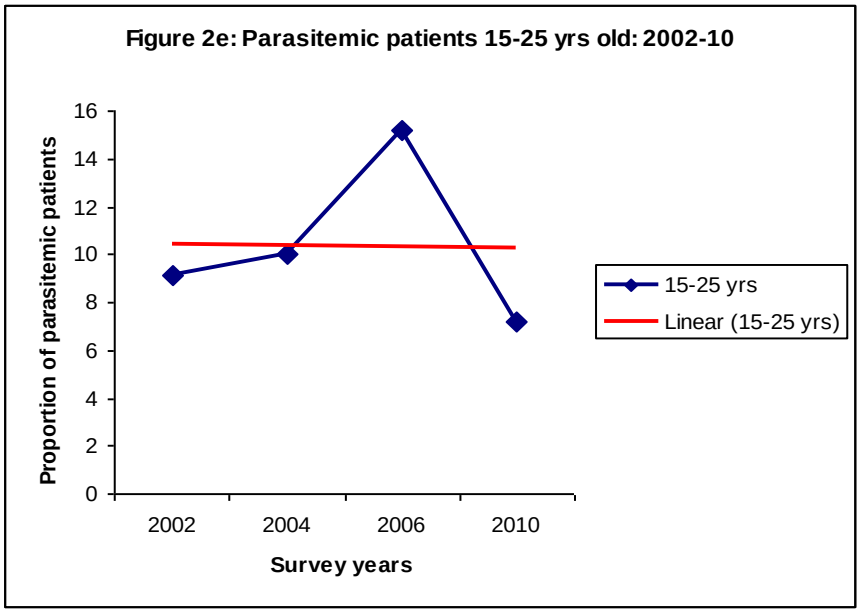
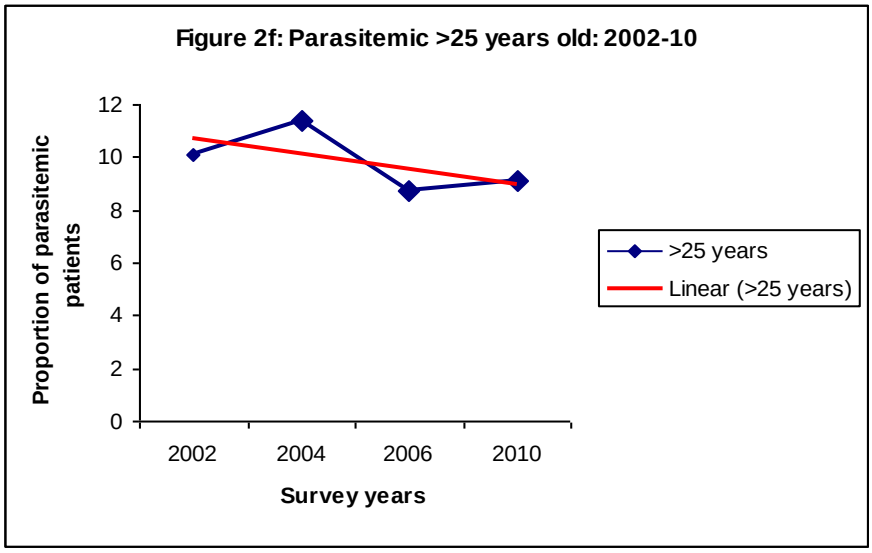


Figure 2c: Parasitemia in 2-5 years old: 2002 -10









In the multivariate analysis, presence of parasitemia was negatively related to age in both crude and adjusted analysis. On average, parasitemia decreases with 5 to 6 years increase in age (table 3). Parasitemia was mostly concentrated at lower age (right skewed) with the arithmetic mean parasite count higher than the median parasite count (table 3). A strong negative relation was seen between Rufiji and K/U where Rufiji seem to have lower parasitemia with increasing patient's age. However, no significant relation was observed between the two districts over the years, table 3.

Table 3: Relationship between parasitemia, age and district

Parasitemia in relation to:	Regression coefficient (95%CI)	p value
Age of patients:		
Age (unadjusted)	- 5.59 (-6.51 to -4.68)	<0.001
Age (adjusted by year)	- 5.72 (-6.63 to -4.80)	<0.001
Age (adjusted by district)	- 5.56 (-6.48 to -4.65)	<0.001
Age (adjusted by year & district)	- 5.74 (-6.66 to -4.82)	<0.001
District (Rufiji/ KU only with K/U as reference):		
District (unadjusted)	- 59.04 (-97.91 to -20.17)	0.003
District (adjusted by age)	- 49.01 (-88.44 to -9.58)	0.015
District (adjusted by year)	- 8.78 (-50.07 to 32.50)	0.677
District (adjusted by age & year)	3.32 (-19.69 to 35.52)	0.877

Arithmetic mean parasite count = 916/ 200 WBC; Median = 234/ 200 WBCs and Geometric mean= 172.7/ 200WBCs

5.4 Discussion

Findings from this analysis show a negative relation between presence of parasitemia and patients age in an area where malaria prevalence is declining. These results aligns with what is already known in literature; that decline in malaria transmission leads to changes in the age group most affected with malaria (Marsh K and Snow RW, 1999; O'Meara WP et al., 2008). In the studies that assesses effects to children under five; it is customary to group the affected age as below 5 and above 5, mainly because malaria is known to affect the former more severely than the latter. Likewise, this work demonstrates that parasitemia decreases with a 5-6 years age intervals. Despite this broader categorization, this work described the specific age most affected within these two broad categories and what happens in the light of changing malaria prevalence.

The decline in malaria burden in the study areas; K/U and Rufiji has been reported previously. Schellenberg and colleagues reported the changes in malaria epidemiology in Ifakara town (in K/U) between years 1995 to 2000. The mean age of malaria admissions changed from1.55 years in 1995 to 2.33 years in 2000, p<0.001 (Schellenberg D et al., 2004). Recently, Khatib et al published the measured and modelled decline in asexual parasitemia prevalence within HDSS areas in Rufiji and

K/U (Khatib RA et al., 2012). These findings are supported by country-wide representative surveys that reports fever prevalence to children below age of five, in the past two weeks preceding the survey during the national demographic and health surveys (TDHS) and parasite prevalence through the HIV/AIDS and malaria indicators surveys. Fever prevalence was 35.1% in 1999 and 22.9% in 2010 (NBS, 1999; NBS and Macro ICF, 2011), where as malaria prevalence declined from 18.1% in 2007/8 to <10% in 2011 (THMIS, 2012).

These achievements can be credited to the malaria control strategies already in place including use of ACTs for case management (AS+SP during IMPACT-Tz and artemether-lumefantrine (AL) country wide, from late 2006), increased use of treated nets (especially in K/U site) as shown by Khatib et al (Khatib RA et al., 2012) and community based or health facility based interventions to address malaria. However, the proportion of patients who were found to have malaria parasite in this analysis was still higher than population based estimates. This is not surprising, as study participants were people who attended facilities seeking for care. This is among the limitations of using facility based data to assess disease trends (Rowe AK et al., 2009). To a large extent, health facility malaria prevalence can be influenced by treatment seeking practices in the respective communities, such that frequencies reported, may not reflect a true picture of trends in the population. Despite this fact, findings in this work did show significantly appreciable trends in age of parasitemic patients managed at health facilities within the study areas.

Focusing on the children below age of five who are most vulnerable to effects of malaria; this work shows that, as malaria burden decrease, the burden shift to children between 2-5 years and older children up to 15 years of age. It wouldn't come as a surprise because the two to five years olds are at the critical growth stage learning to walk, run and play with peers. On the other hand, the group of 5-15 years old are older children, most likely, school going, thereby most likely to be active, e.g. playing out late evening. These activities would render them susceptible to outdoor biters of malaria

transmission (Russell TN et al., 2011). In addition, sleeping arrangements in a typical African family may replace an older baby in one sleeping space when a new born arrives, or considered “old enough” to sleep separately from the parents (Alaii JA et al., 2003). This implies that, probably newborns and breastfeeding mothers will almost always get a net if one is available. Following the success of pregnant and infants’ treated-net provision schemes; these age groups (2-5 and 5-15) should also be additional target groups of the current catch-up and keep-up strategies for increasing net ownership and use.

It is anticipated that, as the decline in malaria transmission continues in the same or accelerated pace, a shift of parasitemia prevalence to older age group will become more obvious. The older children will be burdened with other malaria associated morbidities as well, such as anemia as previously reported (Schellenberg D et al., 2003), bringing public health concerns in respective communities. The time to strengthen the use of routinely health facilities surveillance data to monitor trends and act is now. At a point of care, clinicians should be made aware of these shifts in age patterns to understand local disease profile and enhance appropriate identification of patients in need of effective treatment. It is especially important during malaria elimination phase as the decrease in natural acquired immunity will render the population more susceptible to malaria infection. In fact, as malaria endemic countries are heading towards elimination and eradication phases, and population loose natural immunity against malaria, even lower parasite densities may become fatal. This work, only assessed presence of parasitemia, and did not attempt to relate parasite density and other factors.

Limitations:

In these surveys, it is possible that some patients found to have malaria parasitemia did not have any malaria related signs and symptoms, resulting to overestimation of the reported facility based malaria prevalence. However, a fact that they were attending facilities for clinical management of illnesses increase our suspicion that, majority of

parasitemic patients were true malaria cases. Second, we are aware that microscopic or blood smear analysis of malaria parasites may miss sub-microscopic infections of malaria in endemic areas as compared to Polymerase Chain Reaction (PCR) (Okell LC et al., 2009); which may lower the reported parasite positivity counts. The relevance of these sub-microscopic parasitemia levels into development of a clinically relevant infection is known to be very low, except for vulnerable groups such as pregnant women.

5.5 Conclusion

Following the decline in malaria transmission in K/U and Rufiji districts, there was a significant age shift of parasitemic patients presenting at health facilities. Presence of malaria parasites declined in children less than 2 years old, but increased in those above 2 years of age, contrary to population based surveys. Adults (above 15 years) generally showed a decline in presence of malaria parasites at health facilities. These findings underscore the need to include older children as another priority group in malaria control activities, such as the catch-up and keep-up campaigns for increasing treated net ownership and usage.

Competing interests

Conclusions reached in this work are those of the authors, they do not relate in any way with their institution and/ or study funders. IMPACT-Tz was primarily funded by the US Agency for International Development (USAID) where as INESS was funded by the Bill and Melinda Gates Foundation.

Author's contribution

IMM supervised data collection in INESS, data analysis and writing first draft, RAK supervised data collection in IMPACT-Tz, review of first and subsequent manuscripts, JS, DDS and SPK involved in protocol development and study design of INESS and

reviewed subsequent draft manuscripts. SPK and SA developed IMPACT-Tz protocol (with investigators from other institutions) and reviewed subsequent manuscripts.

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PART IV: HEALTH WORKERS INFLUENCE IN CORRECT TREATMENT

Chapter 6: Providers' factors associated with correct use of ACT

Health worker factors associated with correct prescribing of artemisinin combination therapy for uncomplicated malaria in rural Tanzania

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This manuscript is undergoing CDC clearance

Abstract:

Background: Improving malaria case management is partially dependent on health worker compliance with clinical guidelines. We assessed health worker factors associated with correct antimalarial prescribing practices at two sites in rural Tanzania.

Methods: We conducted repeated cross-sectional health facility surveys and collected information on patient consultations and health worker characteristics. Using logistic regression, we assessed health worker factors associated with correct prescription for uncomplicated malaria defined as prescription of artemisinin based combination therapy (ACT) for patients with fever and *P. falciparum* asexual parasitemia based on blood slide according to official policy guideline.

Results: In this analysis, we included 685 patients with uncomplicated malaria who were seen in a health facility with ACT in stock and 71 health workers practicing in 30 health facilities. Overall, 58% of malaria patients were correctly treated with an ACT. Health workers with 3 or more years of work experience were significantly more likely than others to prescribe correctly (adjusted odds ratio (aOR) 2.6; 95% confidence interval (CI) 1.2-5.6; p=0.021). Clinical officers (aOR 3.1; 95% CI 1.2-8.0; p=0.019), health workers of the nurse aide or lower cadre (aOR 4.2; 95% CI 1.5-11.7; p=0.007) were more likely to correctly prescribe ACT than medical officers; diagnosed by mRDT (aOR 2.6; 1.2-5.8) were more likely to correctly prescribe ACT than microscopy. Training on ACT use, supervision visits, and availability of job aids were not significantly associated with correct prescription.

Conclusion: In this analysis, 58% of malaria patients were correctly treated. Years of working experience, health worker cadre and use of mRDT diagnosis were associated with correct ACT prescription for uncomplicated malaria. Targeted interventions to improve health worker performance are needed to improve overall malaria case management.

Keywords: Uncomplicated malaria, correct prescription and Artemisinin Combination Therapy

6.1 Background

Effective treatment of patients with malaria illness is a cornerstone of global control efforts to reduce malaria morbidity and mortality. However, effective malaria case management depends on early recognition of symptoms and signs as requiring malaria diagnosis and treatment, as well as the clinical skills of the health worker. In most malaria endemic areas, management of malaria patients is determined by the clinical presentation and where possible, diagnostic confirmation (NMCP, 2006). Many countries use evidence-based clinical practice guidelines to help health workers assess, diagnose and treat patients with malaria. To implement guidelines, a common strategy is to provide health workers with in-service training, printed copies of the malaria treatment guidelines, and wall charts and other job aids. Despite these trainings and aids, health workers have often been reported not to follow recommended guidelines (Nicholas DD et al., 1991; Kelly JM, 2001; Naimoli J et al., 2006).

Improving health worker's compliance to treatment guidelines remains critical to the success of any new drug policy. However, results from health facility surveys conducted elsewhere, have shown that health workers (HW) frequently do not comply with treatment guidelines (Rowe AK et al., 2001). Different types of treatment error have been reported, each with different assumed clinical consequences (Rowe AK et al., 2003). For example, treatment with an antimalarial drug that is effective but not recommended by the guideline has been used as an error (Rowe AK et al., 2003). Other scholars have documented that clinical practices can be influenced by factors other than treatment recommendations, such as age of the patient and suspected concurrent conditions (Dodoo ANO, 2009).

In Tanzania, as in many sub-Saharan countries, effective implementation of clinical guidelines is a critical challenge– especially for malaria, which is a leading cause of child morbidity and mortality (RBM:). This challenge is particularly relevant today because new policies are being implemented that recommend artemisinin-based combination therapies (ACTs), parasitological confirmation with mRDTs and blood slide. Artemisinin based combination therapies are more expensive and have more complex dosing regimens than previously used antimalarials. However, there are relatively few reports on the quality of clinical practice following implementation of ACT policy in Africa (Zurovac et al., 2007; Zurovac et al., 2008b), particularly those focusing on factors specific to health workers.

In recognition of the fact that new drug policies will need better implementation strategies in the health facility setting, the need for improving health workers performance cannot be overly emphasized (Rowe AK et al., 2005). Yet little is known about the health worker factors associated with correct prescribing of ACTs for uncomplicated malaria. This study therefore, present findings from an assessment of health worker factors associated with correct prescription of ACT for management of uncomplicated malaria patients in rural health facilities in Tanzania.

6.2 Methodology

Study area:

The study was conducted in Rufiji and Ifakara Health and Demographic Surveillance System (HDSS) sites. Rufiji HDSS situated in Coast Region, the eastern part of Tanzania with a catchment population of approximately 85,000 people living in 16,000 household (Rufiji DSS). Ifakara HDSS is situated in, and covers parts of Kilombero and Ulanga Districts in Morogoro Region. Ifakara HDSS site constitutes more than 99,000 people, living in 28,000 scattered rural households (Ifakara HDSS). The two HDSS sites have high malaria transmission during the high rainfall season, between March and June annually.

Study design and data collection

This was a cross-sectional cluster survey conducted in March and November 2010, where a cluster was defined as all patient consultations performed in a health facility on the one day of survey during regular working hours. The survey was conducted in all health facilities licensed to prescribe the ACT of interest, Artemether-Lumefantrine (ALU) within the Rufiji and Ifakara HDSS.

Twenty interviewers and two supervisors were trained together on survey procedures and blood slide collection in a classroom setting and then practiced these activities in test health facilities. At health facilities, all health workers performing patient consultation on the day of survey were given an identification number. All outpatients presenting for initial illness consultation on a day of a survey, and who consented to participate in the survey, were interviewed prior to leaving the health facility. Patients eligible to participate in the survey were asked to provide informed consent. All patients who consented were included in the survey and given a study identification card with their study identification number. The health workers seeing a consented patient noted their initials and health worker identification number on the patient's study identification card as well the patient's medical record (file) number. In the laboratory, the patient identification number on the study identification card was used to label any extra blood slides they made for patient.

When the patient was ready to leave the health facility after visiting the laboratory and pharmacy as needed, the surveyor interviewed the patient and collected a blood slide (if not already done in the laboratory). The interview was used to determine if patients had understood the information provided by the health worker regarding diagnosis, referral, treatment, follow-up, and home care. All information and prescribed medications were recorded on a standardized questionnaire.

At the end of the survey day all health workers who had performed patient consultations were interviewed to collect information on their demographics, cadre, pre-service and in-service training, work experience, access to national guidelines and wall charts, and exposure to supervision in the preceding six months. Finally, a health facility assessment was undertaken to record the availability of ALU and other antimalarials on the survey day and in the past three months, the presence of functional weighing scales, thermometers, malaria diagnostics, and any displayed case-management wall charts.

Definitions

Uncomplicated malaria used in this analysis was defined as either presence of fever and blood slide positive for malaria parasitemia or clinical diagnosis of malaria according to IMCI classification.

Correct prescription of ACT defined as prescription of artemisinin based combination therapy (ACT) for patients with fever and *P. falciparum* asexual parasitemia based on blood slide positive at health facility or clinical confirmed according to IMCI classification.

Data Processing:

Data were double entered into EPIDATA version 3.1 (Odense, Denmark, 2004) and validations were conducted for checking completeness and consistency. All analyses were performed using STATA Version 11.0 (StataCorp: 2009, College station, TX) procedures that account for survey design by identifying different probabilities of selection (sampling weights), clustering and stratification. Thus, all percentages and odds ratios reported are population-average estimates which have been adjusted to take into account the clustering and sampling weights of the study design. Descriptive analysis was done after merging health facilities, health worker and patient datasets and clustered by patient consultation days.

Logistic regression was used to assess health worker factors associated with correct prescribing of ACT for uncomplicated malaria. The outcome variable in this analysis was patients with uncomplicated malaria correctly prescribed an ACT and the determinant/ explanatory variables were health worker's factors: health worker cadre; in-service training; having 3 or more years of working experience; supervision visit in past six months; type of malaria diagnostic and availability of job aids. In-service training was classified into two groups: first; health worker trained on either, malaria case management, Integrated Management of Childhood Illness (IMCI), or use of new anti-malarials, and second; health workers' who are not trained on either of the above 3 categories. Availability of job aids includes possession of the national malaria treatment guideline and wall chart that described the current treatment recommendations.

To identify health worker factors associated with correct prescribing practices, treatment practices were analyzed at all health facilities with the availability of ALU during the survey, a binary response outcome 1 indicates that a patient with uncomplicated malaria was correctly prescribed an ACT and 0 indicates that, the patient with uncomplicated malaria has not been prescribed an ACT. Health worker factors suspected to be associated with correct prescription of ACT for uncomplicated malaria were identified in the multivariate model. Pregnant women, patients without uncomplicated malaria and patients with uncomplicated malaria seen in a health facility without ACT in stock were excluded from the analysis. An alpha level of 0.05 was used for all tests of significance.

Ethical Approval

Ethical approval for this study was received from the Ifakara Health Institute ethical review board (IHI/IRB/No.A67-2009) and National ethical clearance after having met the criteria for ethical considerations.

6.3 Results

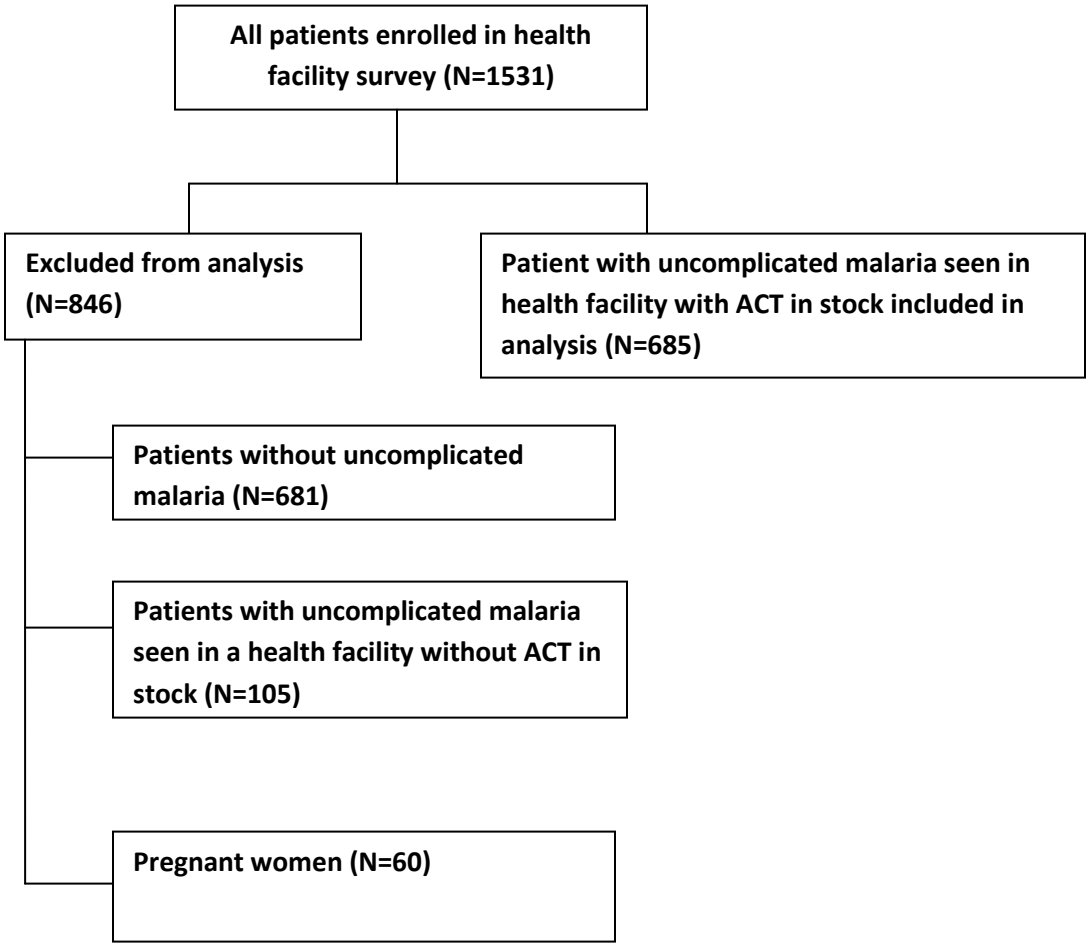
Patient Characteristics

Data were collected from 31 health facilities and analysis is based on 685 patients with uncomplicated malaria seen in 30 health facilities with ACT in stock (figure 1) by 71 health workers (table 2). A total of 846 patients were excluded from analysis (figure 1). More than half (54%) of the patients seen at the health facilities were children under five and 55 % were females (table 1). 34% were diagnosed by either microscopy or mRDT while 66% were clinically diagnosed.

Malaria treatment received by patients

Overall, only more than half (58%) of patients with uncomplicated malaria seen in health facilities with ACT in stock received an ACT (table 1). Quinine a second line treatment for uncomplicated malaria was given to 10% of all patients. Only 1% received SP as the first line treatment and 31% of malaria patients did not receive any anti-malarial drug. Parasitological diagnosis was available in 82% health facilities and 34% of patient with uncomplicated malaria were diagnosed by microscopy or mRDT (table 2). The national malaria treatment guidelines recommend presumptive treatment of a fever with ACT when malaria tests are not available, but only half (51%) of patients who were clinically diagnosed were prescribed ACT (table1).

Figure 1: Inclusion of patients in the analysis



Health facility and Health worker characteristics

Few health facilities had both malaria diagnostic microscopy and mRDT (20%) and 60% of the health facilities surveyed had only mRDT diagnostic in stock (table 2). At the time of the survey, most of the health facilities reported that they had anti-malarial drugs in stock and field staff verified that ACT was in stock in 94% of health facilities surveyed. 71% of the patients with uncomplicated malaria seen in health facility with ACT in stock were seen by Medical Assistant/Clinical Officer/ Clinical Assistant, and only 5% of patients were seen by medical officer; 67% were seen by health workers (HW) who had

received in-service training (which includes either training in malaria case management and/or integrated management for child illness, or use of new anti-malaria). 77% of patients were seen by health worker having three or more years of working experience. Few patients (22%) were seen by health workers who had received at least one supervision visit in the last six months and 42% of patients were seen by health workers who had job aids in possession (table 2).

Table 1: Patient Characteristics included in analysis

Patient Demographic	**N=685 n/N**	**%**	**95%CI**
Patient age			
Mean age (range)	11		(0-80)
Children under 5	370/685	54.0	50.3-57.8
5 and above	315/685	46.0	42.3-49.7
Patient gender			
Female	373/685	54.5	51.0-57.9
Male	312/685	45.5	42.2-49.0
Type of malaria diagnostic			
Patient diagnosed by microscopy	115/685	16.8	10.8-25.2
Patient diagnosed by MRDT	114/685	16.6	11.1-24.3
Patient diagnosed by clinical	456/685	66.6	56.6-75.2
Patient treatment			
Patient prescribed ACT	398/685	58.1	51.9-64.1
Under 5	219/370	59.2	51.9-66.1
5 and above	179/315	56.8	49.6-63.8
Patient prescribed ACT by type of diagnostic			
Diagnosed by microscopy	70/115	60.9	48.5-72.0
Diagnosed by mRDT	95/114	83.3	72.9-90.3
Clinical diagnosed	233/456	51.1	42.8-59.4
Patient prescribed with Non-ACT	287/687	41.9	35.9-48.2
SP	5/685	0.7	0.3-2.1
Quinine	71/685	10.4	7.4-14.3
Other anti-malaria	1/685	0.1	0.02-1.1
Not prescribed with any anti-malaria	210/685	30.7	27.2-34.3

Table 2: Health facility and health worker characteristics

Distribution of facility and health workers factor	n/N	%	95%CI
Availability of malaria diagnostic and ACT			
HF with microscopy	6/30	20.0	7.7-38.6
HF with mRDT	18/30	60.0	40.6-77.3
Bothe microscopy and mRDT	6/30	20.0	7.7-38.6
Health workers			
Medical officer	6/71	8.4	3.2-27.5
Clinical officer	40/71	56.3	44.0-68.1
Nurse aide and lower cadre	25/71	35.2	24.2-47.5
Patient seen by health worker (cadre, experience, training and job-aides)			
Patient seen by a medical officer	32/685	4.7	2.4-9.0
Patient seen by a clinical officer	488/685	71.2	60.5-80.0
Patient seen by nurse aide or lower cadre	165/685	24.1	15.9-34.8
Patient seen by HW with 3 or more years of experience	525/685	76.6	68.0-83.5
Patient seen by HW who had supervision visit in the last 6 month	153/685	22.3	15.0-32.0
Patient seen by HW who received in-service training in malaria case management*	458/685	66.9	55.4-76.6
Patient seen by HW who owns a malaria case management job aid**	289/685	42.2	30.7-54.5

*In-service training includes malaria case management, Integrated Management of Childhood Illness (IMCI), or use of new antimalarials **Job aids include possession of the national malaria guideline and wall chart

Health worker factors associated with correct prescription of ACT

In the univariate analysis, patients seen by nurse aide or lower cadre, patients diagnosed by mRDT, and a health worker with three or more years of work experience had higher odds ratio of receiving ACTs (OR=2.8, 95%CI: 1.4-5.7, p=0.008,OR=3.2, 95%CI: 1.5-7.1, p=0.004, and OR 2.7, 95%CI: 1.3-5.6 p=0.008) respectively (table 3). These variables remained statistically significant in multivariate model with odds ratios of 4.2, 2.6 and 2.6 respectively (table 4).

Patients seen by a clinical officer and nurse or lower cadre health worker had significantly higher odds of getting an ACT than patients seen by medical officer (table

4). Health workers with three or more years of work experience had significantly higher odds of correctly prescribing ACT (adjusted OR=2.6, 95%CI: 1.2-5.6). Indicating that a health worker with more working experience had about three times higher the odds of prescribing ACTs compared to one with less work experience. In-service training, supervision visit, type of malaria diagnosis used and availability of job aids for health workers were not associated with prescribing ACT at 5% significance level. The analysis shows that the patients who were diagnosed by mRDT rather than microscopy were more likely to be prescribed ACT (adjusted OR=2.6, 95%CI: 1.2-5.8) (see table 4).

Table 3: Univariate analysis for health worker factors associated with correct prescription of ACT (N=685)

Variable	Odds ratio	95%CI	P-value
Health worker cadre			
Seen by medical officer	Ref		
Seen by a clinical officer	1.9	0.99-3.63	0.051
Seen by a nurse aide or lower cadre	2.8	1.41-5.73	0.004
Working experience, supervision visit, in-service and job aids			
Seen by HW with 3 or more years of work experience	2.7	1.30-5.65	0.008
Seen by HW who had supervision visit in the last 6 month	0.8	0.42-1.48	0.460
Seen by HW who received in-service training in case management	1.3	0.77-2.09	0.343
Seen by HW who owns a malaria case management job aids	1.3	0.79-2.09	0.313
Type of malaria diagnostic			
Diagnosed by microscopy	Ref		
Diagnosed by mRDT	3.2	1.46-7.07	0.004
Clinical diagnosed	0.7	0.36-1.25	0.206
Age of patients			
Less than 5	Ref		
5 and above	0.9	0.67-1.22	0.520
Site			
Rufiji	Ref		
Kilombero/Ulanga	0.97	0.58-1.61	0.906
Season			
High transmission season	Ref		
Low transmission season	0.46	0.29-0.72	0.001

Table 4: Multivariate analysis for health worker factors associated with correct prescription of ACT (N=685)

Variable	Odds ratio	95%CI	P-value
Health worker cadre			
Seen by medical officer	Ref		
Seen by a clinical officer	3.1	1.21-8.00	0.019
Seen by a nurse aide or lower cadre	4.2	1.49-11.65	0.007
Working experience, supervision visit, in-service and job aids			
Seen by HW with 3 or more years of work experience	2.6	1.16-5.63	0.021
Seen by HW who had supervision visit in the last 6 month	1.2	0.57-2.70	0.580
Seen by HW who received in-service training in case management	1.0	0.58-1.87	0.892
Seen by HW who owns a malaria case management job aids	1.1	0.60-1.82	0.873
Type of malaria diagnostic			
Diagnosed by microscopy	Ref		
Diagnosed by mRDT	2.6	1.22-5.76	0.014
Clinical diagnosed	0.6	0.30-1.10	0.095

6.4 Discussion

This study aimed to assess a limited range of health workers' factors that seemed possibly associated with correct ACT prescribing practices at health facilities. Our findings provide some explanations that help understanding correct prescription of ACT for uncomplicated malaria. ACT was more commonly prescribed by clinical officers and nurse aides or lower cadres than medical officers. This finding was similar to what was observed during the era of SP policy in Kenya (Zurovac et al., 2004) and Chloroquine policy in Benin (Rowe AK et al., 2003). Several reasons may explain these results. First, there are always more lower level cadres health workers (clinical officers, nursing aide and lower cadre) in rural health facilities who interface with most patients with minor

illnesses compared to doctors or medical officers. Medical officers are always involved in administrative work and when the conditions are severe. Second, clinical officers and nursing aides or lower cadres may not know how to prescribe second-line drugs or other anti-malarials and therefore avoid using them. Third, clinical officers and nursing aides or lower cadres may be better at following clinical algorithms because they have less of a 'medical vocabulary' of alternative diagnoses and treatments that might interfere with the simple 'fever = malaria' concept upon which the guideline is based. Fourth, medical officers and, to a lesser extent, clinical officers, may have been taught that their clinical judgment can and ought to override guidelines. Indeed, they may view guidelines as suggestions, rather than rules that should be followed systematically. Furthermore, our findings reveal that health workers with lower cadre commonly perform consultations and follow recommended guidelines than higher cadres (Zurovac et al., 2004) in rural areas of formal health system, although they are not allowed to do so. This is because the health sector is facing a serious human resource (HR) crisis that is negatively affecting the ability of the sector to deliver quality health services. There is a severe shortage of HR at all levels which is more severe in rural districts (Musau S et al., 2011).

There is great need to improve the quality of malaria case management for uncomplicated malaria in rural Tanzania, with a greater emphasis on health worker to comply with clinical guidelines. ACT prescribing for uncomplicated malaria was considerably below the RBM target of 80% of uncomplicated malaria treated with ACT. In Kenya and Zambia poor quality treatment practices were observed at public and mission facilities soon after ACT was introduced as first-line, though subsequent studies up to five years later show improvements in the proportion of patients that are prescribed and receive ACT (Zurovac et al., 2007; Zurovac et al., 2008b; Juma and Zurovac, 2010). As found elsewhere, the proportion of patients that were prescribed or received an ACT seems low given the availability of ACT at health facilities (Zurovac et

al., 2004; Zurovac et al., 2008b; Juma and Zurovac, 2010; Wasunna et al., 2008; Zurovac et al., 2008c; Uzochukwu BSC et al., 2010).

Improved access to mRDT malaria diagnosis was statistically more likely to correctly prescribe ACT in the health facilities with ACT in stock. This is due to accuracy of malaria rapid diagnosis test is high, parasitological confirmation of all malaria diagnoses is recommended by WHO and increased evidence supporting the use of mRDTs reduce overtreatment with anti-malarials (Trap B et al., 2001; Uzochukwu BSC et al., 2010; Naimoli J et al., 2006; Zurovac and Rowe, 2006; Loevinsohn BP et al., 1995; Zurovac et al., 2011; Ishengoma DS et al., 2011).

Health workers who had three or more years of working experience were statistically more likely to correctly prescribe ACT in health facilities with ACT in stock. Several reasons may explain why having more working experience for caring patients was associated with correct prescribing of ACTs. First, the relationship may have been confounded by a factor that was studied. For example, the health worker experienced in caring for patients has been more involved in training on malaria case management which included the use of new antimalarials and more likely for health workers to provide correct prescribing of ACTs of interest during the survey. Indeed, theoretically, the working experience might improve health worker performance, but still might have had enough impact to overcome differences between well-performing health workers who were not having three or more years of caring patients and poorly performing health workers with less three years of working experience. Second, it is possible that health workers who have been more experienced in caring for patients comply with the national malaria treatment guidelines. And third, perhaps through years of experience they came to trust the recommended medicine for management of uncomplicated malaria after having seen other patients getting good clinical response following its use. Finally they have had several supervision visits in the course of their practice, and hence more confidence with prescribing drugs.

Common interventions such as in-service training, regular supervision visits, and availability of job aids were not associated with correct prescribing of ACTs for uncomplicated malaria at health facility where ACT was in stock (table 4). This result has been observed in other settings; not all routine in-service initiatives to improve clinical management practices have had positive effects on treatment practices (Zurovac et al., 2004; Naimoli J et al., 2006; Zurovac and Rowe, 2006). In this study perhaps the most important observation was that workers having supervision visits in the previous six months were more likely to prescribe ACT to patients with uncomplicated malaria compared to health workers who do not receive any supervision visit. Although few studies have examined the independent effect of supervision on health care worker performance, small studies in Africa and the Philippines have suggested an association between supervision and improved knowledge, planning, the clinical skills and improve health workers' case management practices (Loevinsohn BP et al., 1995; Zurovac et al., 2011; Trap B et al., 2001).

The lack of association of in-service training and correct prescribing ACTs is consistent with other studies (Rowe AK et al., 2003; Reyburn et al., 2007; Paredes P et al., 1996) and there are several possible explanations. First, the quality of training may have been poor. Although we have no evaluation of the courses, we know they used adult teaching methods and were mostly of an adequate duration. Perhaps the short time dedicated to clinical practice diminished the training's effectiveness. Secondly, the health workers who were trained in-service training may have been too few to detect an important difference; however, this explanation is unlikely because the estimated odds ratio was substantially higher than one. A third possible explanation for the lack of association between in-service training and correct prescribing ACTs treatment is that training improves knowledge, but knowledge is not sufficient to improve clinical performance. Our failure to find an association between in-service training and correct prescribing

ACTs is consistent with other studies showing that correct knowledge does not translate into correct behavior (Paredes P et al., 1996; Rowe et al., 2000).

Finally, better prescribing of ACTs practices could not be attributed to any routine ACT implementation activities (in-service training, guidelines, wall charts). The reviews of previous studies with similar design, as well as systematic reviews of other interventional trials on the use of medicines in developing countries, commonly reported a mixed association between in-service training and health worker performance, and sometimes, as in this study, no association was found with in-service training (Rowe AK et al., 2005).

Limitations

This study had several important limitations. First, not all potential factors were included in analysis, such as the complexity of the guideline for health workers. Second, the method of directly observing health workers may have influenced their performance either making them anxious or motivating them to perform better than usual. As one study found that most health workers reported the presence of observers either had a small positive effect or had no effect on their performance (Rowe AK et al., 2002), we were less concerned that observation had introduced a large bias. Third, we had only limited details on evaluation of training that had no baseline performance measurement, and our evaluation of the quality of supervision was not very detailed. Finally, we did not assess over-prescription of ACTs to patients without malaria in this analysis.

6.5 Conclusions

Health worker's having three or more years on caring malaria patients; health worker cadre and use of mRDT diagnosis were associated with correct prescribing ACTs treatment. While in-service training, supervision visit, and availability of job aids were not associated with correct prescribing ACTs. We do not mean to imply that training,

supervision visit and job aids are useless components of the health worker performance; we are concerned by the scarcity of evidence from well-designed study that supports these commonly used interventions. Targeted interventions to improve health worker performance are needed to improve overall malaria case management. Interventions above and beyond in-service training, supervision, job aids, etc will need to be tailored to the specific needs of newly qualified providers(less than three years working experience) and medical doctors. Improving malaria case management will be required to reach Roll Back Malaria goal of “near zero” malaria deaths by 2015. Recommendation on further intervention research to explore new approach to improve health worker performance such as use of text messaging to health workers is needed.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MS wrote the manuscript first draft, MIM field supervision and revised the paper and contributed to the discussion. MS, MN and DK analyzed data, revised manuscript and contributed to the discussion. MA, RK, JS, SA and SPK revised the paper and contributed to discussion. All authors read and approved the final manuscript.

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Chapter 7: Providers' attitudes and practices

Do health workers' preferences influence their practices? Assessment of providers' attitude and personal use of new treatment recommendations for management of uncomplicated malaria, Tanzania

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Abstract:

Background: Due to growing antimalarial drug resistance, Tanzania changed malaria treatment policies twice within a decade. First in 2001 chloroquine (CQ) was replaced by sulfadoxine-pyrimethamine (SP) for management of uncomplicated malaria and by late 2006, SP was replaced by artemether-lumefantrine (AL). We assessed health workers' attitudes and personal practices following the first treatment policy change, at six months post-change and two years later.

Methods: Two cross-sectional surveys were conducted in 2002 and 2004 among healthcare workers in three districts in South-East Tanzania using semi-structured questionnaires. Attitudes were assessed by enquiring which antimalarial was considered most suitable for the management of uncomplicated malaria for the three patient categories: i) children below 5; ii) older children and adults; and iii) pregnant women. Practice was ascertained by asking which antimalarial was used in the last malaria episode by the health worker him/herself and/or dependants. Univariate and multivariate logistic regression was used to identify factors associated with reported attitudes and practices towards the new treatment recommendations.

Results: A total of 400 health workers were interviewed; 254 and 146 in the first and second surveys, respectively. SP was less preferred antimalarial in hospitals and private health facilities ($p<0.01$) in the first round, and the preference worsened in the second round. In the first round, clinicians did not prefer SP for children below age of 5 and pregnant women ($p<0.01$), but two years later, they did not prefer it for all patient scenarios. SP was the most commonly used antimalarial for management of the last malaria episode for health workers and their dependants in both rounds, in the public sector ($p<0.01$). Health workers in the dispensaries had the highest odds of using SP for their own treatment [adjusted OR- first round: 6.7 (95%CI: 1.9-23.4); crude OR- second round: 4.5 (1.5-13.3)]

Conclusion: Following changes in malaria treatment recommendations, most health workers did not prefer the new antimalarial drug, and their preferences worsened over

time. However, many of them still used the newly recommended drug for management of their own or family members' malaria episode. This indicates that, other factors than providers' attitude may have more influence in their personal treatment practices.

Key words: health workers, attitude, practices, new treatment guidelines, malaria

7.1 Background:

In early 2000, malaria was a leading cause of death (NMCP, 2003c) and hospital attendances in Tanzania, particularly among children under the age of five and pregnant women (NMCP, 2000). During that time, Tanzania recorded a range of 14-18 million clinical malaria cases yearly, with a mortality rate of 140-165 per 100,000 people and approximately 70,000 to 100,000 deaths among children under-five (NMCP, 2000; NMCP, 2003c). Malaria was endemic in almost all parts of the country but with varying endemicity levels (NMCP, 2003a). Current malaria control activities in the country involve prompt diagnosis and treatment of cases, intermittent preventive treatment for pregnant women (IPTp), promoting the use of insecticide treated bed-nets (ITNs), indoor residual spraying (IRS), monitoring and managing epidemics as well as environmental management for vector control. However, the emergence and spread of insecticide and antimalarial drugs resistance may undermine the disease control strategies already in place.

The pace at which malaria parasites develop resistance to antimalarial drugs is alarming and necessitates investigating ways to prolong the lifespan of efficacious antimalarials (WHO, 1996; Snow RW et al., 1999). The fact that drug resistance is a natural and expected process, stresses the need for cost-effective strategies to delay development of resistance, while continuing to provide effective treatment to those in need. Fear that resistance will develop to drugs in use, is justifiable and may provide a significant challenge to policymaking decisions, initiating endless cycles of drug replacement.

Towards the end of 2006, mainland Tanzania introduced Artemisinin-based combination therapy (ACTs) for routine management of uncomplicated malaria (NMCP, 2005). This was a second change of malaria treatment policy within a decade. The first change occurred in August 2001 when chloroquine (CQ) was replaced by sulfadoxine-pyrimethamine (SP) as the first line treatment of uncomplicated malaria (NMCP, 2000). The changes were necessary due to growing resistance of malaria parasites to CQ (Mubyazi and Gonzalez-Block, 2005). At the time of change, SP was a second line drug for treatment of malaria while quinine (QN) was reserved for severe malaria. SP was one of the few inexpensive and relatively safe antimalarial drugs that was still effective against chloroquine-resistant malaria (Mugittu et al., 2004). SP was introduced on interim basis due to the fact that resistance to SP had already been recorded in some parts of the country (Gorissen E et al., 2000; Ronn A.M et al., 1996; Schellenberg D et al., 2002). Moreover, SP is known to be susceptible to resistance if used on a wide scale.

During the SP era, treatment guidelines indicated that uncomplicated malaria should be treated with SP (sulfadoxine 500mg with pyrimethamine 25mg) as a single dose based on age (above two months) and weight (above 5 kg) (NMCP, 2003a). Furthermore, the policy document explained how to recognize and manage non-response to SP, contraindications, administration and adverse effects of SP. In addition, the guideline explained that SP should not be used in late pregnancy (36 weeks and above) and for lactating mothers whose children are below two months of age. Contraindications for use of SP as stated in the guideline included history of sulfadoxine hypersensitivity, premature babies and children below two months who were to receive QN. The policy also explained when and how to use the second line antimalarial drug, amodiaquine (AQ), for management of uncomplicated malaria, including indications, contraindications, adverse reactions and dosage regimen (NMCP, 2003a). At all levels of care, severe malaria was to be managed with QN and where possible referred to a higher level of care after a pre-referral quinine shot (intra-muscular). Non responses to QN were to receive Artemisinin derivative along with QN (Gorissen E et al., 2000).

The introduction of SP for management of uncomplicated malaria in Tanzania was received with fear and negative perceptions from both community and health care workers (Nsimba SE, 2006). Fear of side effects related to sulphur content of the SP, was exacerbated by newspaper reports of suspected victims of adverse drug reactions (ADR) following use of SP. There was a chance that these fears may have affected health provider's acceptance of the new treatment recommendations and behave inappropriately, since it is well understood that health workers' performance can influence effectiveness of treatment policies. Their actions may be a result of their own perceptions of treatment efficacy. If a recommended treatment is perceived to be effective, it is more likely to be used as stipulated in the guideline whereas treatment recommendations that do not measure up to their expectations may be less utilized.

Contrary to expectations that health providers with more training will more likely abide by evidence based guidelines, Zurovac and colleagues reported that more qualified health workers such as clinical officers and nurses made more errors as compared to nurse aides by using non-recommended antimalarials in treating uncomplicated malaria at government health facilities in Kenya (OR 25.4; 95% CI 2.9-217.3 and OR=7.1 95% CI 1.1-44.5 respectively) (Zurovac et al., 2004). In Ghana, Dodoo et al. concluded that although first line treatment recommendations may change, clinical practice can still be influenced by factors other than the decision or ability to diagnose malaria (Dodoo ANO, 2009). Based on a longitudinal non-intervention study to monitor adverse events, they found that age of the patient, diagnostic confirmation and suspected concurrent conditions all had significant influence in clinical practice.

Human beings tend to demand and use what perceive to be the best available option at a given time. Clinicians and health workers would want to use the best available treatment when managing their own illnesses and their loved ones. Accurate information on this practice may shed a light on how health providers' preferences influence their practices. The need to assess if providers' attitude does influence their practices was particularly high following introduction of SP since; first, the change was

not well received by providers and the general population, and second, the change was on an interim basis whilst evaluating other efficacious treatment options. Understanding of this behavior would assist policy making decisions for future treatment changes in Tanzania and beyond.

7.2 Materials and methods:

Study design: This study was completed as part of the Interdisciplinary Monitoring Project for Antimalarial Combination Treatment in Tanzania (IMPACT-TZ). Data presented here were collected in two cross sectional surveys aimed at evaluating health workers' understanding and utilization of new treatment recommendations for use of SP as first line treatment for management of uncomplicated malaria. The evaluation was conducted in two steps: i) First survey in February 2002 (approximately 6 months post-change to SP) and ii) second survey in March 2004, two years after the first survey. In both phases, semi-structured questionnaires were used to assess health workers' attitudes and practices related to the new recommendations.

Site description: The districts involved in the evaluation were Rufiji, Morogoro Rural, Kilombero and Ulanga. For the purpose of this evaluation, Kilombero and Ulanga (K/U) were treated as a single unit because population movement between these two districts is high. Rufiji and Morogoro rural are isolated from each other and movement between them is limited by the Selous game reserve and the long distances required to by-pass the game reserve (additional file 1). The three districts are similar in terms of urban, peri-urban and rural population proportions and predicted intensity and duration of malaria transmission. Based on data modeled by the Mapping Malaria Risk in Africa (MARA) project, the three districts have a range of 7-12 months of malaria transmission season (additional file 2).

The Health and Demographic Surveillance Systems (HDSS) were in place since 1998 in Rufiji and since 1996 for Ifakara DSS (which covers the districts of Kilombero and Ulanga). In the first survey, data were collected from three districts Morogoro Rural,

Rufiji and K/U. Two years later Rufiji district had started using ACT, as part of the IMPACT-TZ project evaluation and was hence excluded in the comparison between rounds.

Sample selection: In each district, one hospital, one or two health centers and three to four dispensaries that record a high number of malaria cases were selected to participate. The health facilities were purposively chosen based on type, ownership, utilization rates and geographical location. Selection of these facilities was done by the research team in collaboration with the District Medical Officer (DMO) using district health statistics and maps.

Eligibility criteria: Health workers from each selected facility were included in this study if they were involved in prescribing and caring for malaria patients. Interviews were conducted to eligible health workers who were present and could spare time for an interview (even after working hours), on a day of visit. In both survey rounds, the same health facilities were included, but no attempt was made to match respondents between the two surveys.

Data collection: Information was collected through face-to-face interviews using questionnaires. Questionnaires were originally developed in English and translated into Swahili, then back translated to ensure accuracy. Trained local field workers performed interviews in Swahili and later that day, transcribed the responses into English. The field guides had two parts: first were semi-structured and open-ended questions while the second section had case scenarios. The section with semi-structured questions asked about health workers' understanding, attitudes and practices relating to the new treatment guidelines and needed a mention of antimalarial drug from the interviewee as a response. The open-ended questions enquired about challenges and problems faced during the implementation of the new treatment policy while the case scenarios were knowledge-based questions where a patient scenario was described and required the health worker to narrate how that case would be managed. Data analyzed in this report

were from the semi- structured part of the tool. Responses from the open-ended and case scenario parts will be presented elsewhere.

Attitudes: Questions to assess attitudes asked which antimalarial drug was thought to be most suitable for management of uncomplicated malaria for: i) children below 5, ii) children above 5 years/adults and iii) pregnant women. *Practices:* Health workers' practices were assessed by asking what antimalarial they or their dependants used the last time they suffered malaria.

Data entry and analysis: Data were entered into EPI Info 2000 (CDC, Atlanta) by a project statistician and verified by the project supervisor through range and consistency checks for all variables within each dataset separately. Original questionnaires were referred to whenever inconsistency, outliers or errors were encountered. Data from the two surveys were stored in separate databases. Analysis was done using STATA 10 (Stata Corporation, Texas). The outcome variables for this paper were attitude and practice and risk factors were type of health worker, type of health facility, facility ownership and district.

Definitions: Health workers were grouped into 5 categories; first were physicians with a minimum of a medical degree or advanced diploma in medicine, second were clinical officers (CO's) with a diploma in medicine, third were trained nurses (TN) which included all nurses with more than two years of training i.e. registered and enrolled nurses such as nurse midwives and nurse officers. All other nurses, particularly with training of less than two years (nurse assistants and nurse auxiliaries) were grouped as "other nurses". Other health workers e.g. laboratory assistant, who sees malaria patients only when it is necessary, were termed as "other cadres".

Attitudes towards the national malaria treatment guidelines were assessed by comparing what health workers considered the most appropriate antimalarial for the three patient scenarios. If the response corresponded to the recommendation in the guidelines it was scored as "1" and "0" if not. Practice was assessed from the reported

antimalarial used by health workers themselves or their family members in their last malaria episode. Again, if the response corresponded to the recommendation on the guideline it was scored as “1” and “0” if not. Percentages were drawn and stratified by district, type of health facility and type of health worker.

Percentages were used to describe the variables and characteristics of study participants. For each of the three scenarios, crude analyses of the associations between the various risk factors and the outcomes (attitude and practice) were performed. In the univariate analysis, cross tabulations and chi square tests were conducted to identify possible confounders. Logistic regression was used to build multivariate models to identify factors independently associated with each outcome. The group with the higher number of respondents was regarded as a reference in the multivariate analysis. Both crude and adjusted odds ratios are presented.

Ethical approval: Ethical clearance for the IMPACT- Tanzania project was granted by the Ifakara Health Institute Review Board and Tanzanian National Institute of Medical Research (NIMR), in 2000.

7.3 Results:

Characteristics of study participants:

In the first survey, 23 health facilities were visited in the 3 districts and 254 health workers were interviewed, whereas in the second survey 16 health facilities within 2 districts were visited and 146 health workers were interviewed (table 1). There were fewer respondents during the second survey, due to the exclusion of Rufiji district. As shown in table 1, K/U generally had the highest percentage of participants in both phases. In the first survey, a higher percentage of participants were from non-public facilities (59%). In both rounds, hospitals had the majority of study participants compared to dispensaries and health centers (table 1). The proportion of physicians and ‘other’ cadres was small in both surveys.

Attitudes towards recommended treatment

Results in table 2 shows that, in the first round, 44.1% of providers reported to prefer SP for management of uncomplicated malaria in children below five, 68% preferred SP for older children and adults and 51.6% preferred SP for pregnant women. Health workers in health centers and dispensaries were more likely to report preferring SP than in hospitals ($p<0.05$) and more providers from public facilities were in favor of SP than from non-public health facilities; particularly for children and pregnant women; $p<0.001$ (table 2).

Table 1: Characteristics of study participants for survey rounds 1 and 2

Characteristic variable	Category	Round 1		Round 2	
		n	%	n	%
	Total	254	100	146	100
District	Morogoro	73	28.7	59	40.4
	Rufiji	85	33.5	-	-
	K/Ulanga	96	37.8	87	59.6
Health facility ownership	Public	105	41.3	79	54.1
	Non-public	149	58.7	67	45.9
Health facility type	Hospital	171	67.3	90	61.6
	Health center	45	17.7	22	15.1
	Dispensary	38	15	34	23.3
Cadre of health worker	Physicians	6	2.4	8	5.4
	Clinical Officers	51	20.1	26	17.8
	Trained nurses	70	27.5	55	37.7
	Other nurses	118	46.5	55	37.7
	Others	9	3.5	2	1.4

During the second round, preference for SP treatments was very low in all categories; with only 6.2% reporting to prefer SP for management of uncomplicated malaria in children below five, 5.5% preferred SP for older children and adults, and only 4.1% preferred SP for pregnant women (table 3). There were no statistically significant differences in reported preferences in almost all patients' scenarios and by different providers' characteristics (table 3).

Table 2: Proportion of health workers who thought SP was appropriate treatment for uncomplicated malaria, year 2002

Character variable	Category	Children<5 n (%)				Older children/ adults n (%)				Pregnant women n (%)			
	(N=254)	SP: n=112 (44.1)	*Other drug: n=139 (54.7)	DK/ Missing: n=3 (1.2)	p-value	SP: n=173 (68)	*Other drug: n=79 (31.1)	DK/ Missing: n=2 (0.8)	p-value	SP: n=131 (51.6)	*Other drug: n=116 (45.7)	DK/ Missing: n=7 (2.7)	p-value
District	Morogoro (73)	33 (45.2)	39 (53.4)	1 (1.3)		48 (65.8)	25 (34.2)	-		27 (36.9)	44 (60.3)	2 (2.7)	
	Rufiji (85)	38 (44.7)	45 (52.9)	2 (2.3)		64 (75.3)	19 (22.4)	2 (2.3)		53 (62.4)	30 (35.3)	2 (2.3)	
	K/Ulanga (96)	41 (42.7)	55 (57.3)	-	0.662	61 (63.5)	35 (36.5)	-	0.085	51 (53.1)	42 (43.7)	3 (3.1)	0.032
Health facility type	Hospitals (93)	39 (34.5)	53 (64.3)	1 (1.2)		103 (60.2)	66 (38.6)	2 (1.2)		72 (42.1)	92 (53.8)	7 (4.1)	
	Health Centers (45)	27 (60.0)	17 (37.8)	1 (2.2)		37 (82.2)	8 (17.8)	-		31 (68.9)	14 (31.1)	-	
	Dispensaries (38)	26 (68.4)	12 (31.6)	-	<0.001	33 (86.8)	5 (13.2)	-	0.049	28 (73.7)	10 (26.3)	-	<0.001
HF owners hip	Public (176)	92 (52.3)	82 (46.6)	2 (1.1)		126 (71.6)	49 (27.8)	1 (0.6)		113 (64.2)	59 (33.5)	4 (2.3)	
	Non-public (78)	20 (25.6)	57 (73.1)	1 (1.3)	<0.001	47 (60.3)	30 (38.5)	1 (1.3)	0.189	18 (23.1)	57 (73.1)	3 (3.8)	<0.001
Cadre of health worker	Physicians (6)	0	6 (100)	-		5 (83.3)	1(16.7)	-		-	6 (100)	-	
	Clinical Officers (51)	22 (43.1)	29 (56.9)	-		38 (74.5)	13 (25.5)	-		24 (47.1)	27 (52.9)	-	
	Trained nurses (70)	25 (35.7)	45 (64.3)	-		43 (61.4)	27 (38.6)	-		30 (42.9)	38 (54.3)	2 (2.8)	
	Other nurses (118)	63 (53.4)	54 (45.8)	1 (0.8)		84 (71.2)	33 (27.9)	1 (0.9)		74 (62.7)	40 (33.9)	4 (3.4)	
	Other cadres (9)	2 (22.2)	5 (55.6)	2 (22.2)	<0.001	3 (33.3)	5 (55.6)	1 (1.1)	0.01	3 (33.3)	5 (55.6)	1 (11.1)	0.007

*Other drugs includes: Chloroquine, Amodiaquine, Artemisinins, Quinine or any combination of these P-value: Chi squared test

Practices related to new recommended malaria treatment:

Most health workers who had malaria episodes in the recent past had used SP for treatment in both rounds; 55% in round one and 60% in round two; indicating that, the proportion of health workers who had used SP for managing their own illnesses were higher in second survey than the first; but fewer in absolute numbers. The exception was to health workers in non-public facilities (table 4). However, SP use for health workers dependants declined in the second round. Only providers working in dispensaries, public facilities and clinical officers recorded higher proportions of SP usage among family members (table 4).

Table 3: Health workers who thought SP was appropriate treatment for uncomplicated malaria year 2004

Characteristic variable	Category	Children<5 n (%)			p-value	Older children/ adults n (%)			p-value	Pregnant women n (%)			p-value
	(N =146)	SP; n=9 (6.2)	*Other drug; n=135 (92.5)	DK/ Missing; n=2 (1.3)		SP; n=8 (5.5)	*Other drug; n=138 (94.5)			SP; n=6 (4.1)	*Other drug n=126 (86.3)	DK/ Missing n=14 (9.6)	
District	Morogoro (59)	1 (1.7)	58 (98.3)	0		1 (1.7)	58 (98.3)			1 (1.7)	56 (94.9)	2 (3.4)	
	K/Ulanga (87)	8 (9.2)	77 (88.5)	2 (2.3)	0.08	7 (8.1)	80 (91.9)		0.09	5 (5.7)	70 (80.5)	12 (13.8)	0.04
Health facility type	Hospitals (90)	9 (10.0)	79 (87.8)	2 (2.2)		8 (8.9)	82 (91.1)			6 (6.7)	73 (81.1)	11 (12.2)	
	H/Centers (22)	0	22 (100)	0		0	22 (100)			0	21 (95.5)	1 (4.5)	
	Dispensaries (34)	0	34 (100)	0	0.11	0	34 (100)		0.07	0	32 (94.1)	2 (5.9)	0.18
HF ownership	Public (79)	4 (5.1)	75 (94.9)	0		4 (5.1)	75 (94.9)			3 (3.8)	71 (89.9)	5 (6.3)	
	Non-public (67)	5 (7.5)	60(89.5)	2 (3.0)	0.24	4 (5.9)	63 (94.1)		0.81	3 (4.5)	55 (82.1)	9 (13.4)	0.33
Cadre of health worker	Physicians (8)	0	8 (100)	0		0	8 (100)			0	8 (100)	0	
	Cl/ Officers (26)	0	26 (100)	0		0	26 (100)			0	23 (88.5)	3 (11.5)	
	Trained nurses (55)	5 (9.1)	48 (87.3)	2 (3.6)		5 (9.1)	50 (90.9)			5 (9.1)	43 (78.2)	7 (12.7)	
	Other nurses (55)	4 (7.3)	51 (92.7)	0		3 (5.5)	52 (94.5)			1 (1.8)	50 (90.9)	4 (7.3)	
	Other cadres (2)	0	2 (100)	0	0.56	0	2 (100)		0.48	0	2 (100)	0	0.41

*Other drugs includes: Chloroquine, Amodiaquine, Artemisinins, Quinine or a combination of these P-value: Chi squared test

Table 4: Personal and/ or family member use of SP for management of uncomplicated malaria in 2002 and 2004.

Characteristic variable	Category	Self use N=247(%) – (2002) SP; n=135 (54.7)	*Other drug; n=112 (45.3)	p-value	Self use N=81(%) – (2004) SP; n=49 (60.5)	*Other drug; n=32 (39.5)	p-value	Own child/family N= 207(%)-(2002) SP; n=124 (59.9)	*Other drug; n=83 (40.1)	p-value	Own child/family N=84 (%) (2004) SP; n=37 (44)	*Other drug; n=47 (55)	p-value
District	Morogoro	41 (56.2)	32 (43.8)		22 (66.7)	11 (33.3)		35 (47.9)	26 (35.6)		12 (40.0)	18 (60.0)	
	Rufiji	43 (50.6)	38 (44.7)		-	-		48 (56.5)	23 (27.0)		-	-	
	K/Ulanga	51 (53.1)	42 (43.8)	0.48	27 (56.2)	21 (43.8)	0.34	41 (42.7)	34 (35.4)	0.41	25 (46.3)	29 (53.7)	0.57
Health facility type	Hospitals	86 (50.3)	81 (47.4)		22 (50.0)	22 (50.0)		68 (39.8)	67 (39.2)		16 (32.0)	34 (68.0)	
	Health Centers	24 (53.3)	18 (40.0)		12 (66.7)	6 (33.3)		26 (57.8)	12 (26.7)		6 (50.0)	6 (50.0)	
	Dispensaries	25 (65.8)	13 (34.2)	0.16	15 (78.9)	4 (21.1)	0.08	30 (78.9)	4 (10.5)	<0.001	15 (68.2)	7(31.8)	0.01
HF ownership	Public	99 (56.3)	72 (40.9)		35 (71.4)	14 (28.6)		100 (56.8)	52(29.6)		30 (58.8)	21 (41.2)	
	Non-public	36 (46.2)	40 (51.3)	0.30	14 (43.7)	18 (56.3)	0.01	24 (30.8)	31 (39.7)	<0.001	7 (21.2)	26 (78.8)	0.001
Cadre of health worker	Physicians	3 (50.0)	3 (50.0)		2 (100)	0		2 (33.3)	2 (33.3)		0	3 (100)	
	Clinical Officers	26 (51.0)	25 (49.0)		10 (83.3)	2 (16.7)		21 (41.2)	13 (25.5)		8 (66.7)	4 (33.3)	
	Trained nurses	34 (48.6)	34 (48.6)		18 (56.3)	14 (43.7)		28 (40.0)	29 (41.4)		11 (40.7)	16 (59.3)	
	Other nurses	69 (58.5)	45 (38.1)		19 (54.3)	16 (45.7)		66 (55.9)	38 (32.2)		18 (43.9)	23 (56.1)	
	Other cadres	3 (33.3)	5 (55.6)	0.48	0	0	0.19	7 (77.8)	1 (11.1)	0.01	0	1 (100)	0.21

*Other drugs includes: Chloroquine, Amodiaquine, Artemisinins, Quinine or a combination of these

The multivariate analysis (table 5) shows that, compared to providers at hospitals, working at dispensaries and health centers were significant predictors of SP preference for older children and adults in the first round; adjusted OR (aOR; 95% confidence interval) = 6.3 (1.8-22.2) for dispensaries and aOR = 4.9 (1.7-14.0) for health centers (table 5). Poor SP preference was recorded in non-public facilities with respect to management of uncomplicated malaria to pregnant women aOR= 0.2 (0.07-0.4) when

compared to the public facilities. Non-public facilities had consistently lower odds of SP preferences both in a crude and adjusted analysis (table 5). In terms of use, only providers at dispensaries had statistically significant higher odds of using SP in the last illness episode of a family member than those working in the hospitals aOR= 6.7 (1.9-23.4).

Table 5: Health-workers attitude and personal (or/and family) use of SP for management of uncomplicated malaria, 2002

Characteristic variable	Category	Children<5: OR (95%CI)		Older children/ adults: OR (95%CI)		Pregnant women: OR (95%CI)		Self use: OR (95%CI)		Own child/family use: OR (95%CI)	
	(N=254)	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
District	K/Ulanga (96)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Morogoro (73)	1.1 (0.6-2.0)	1.5‡ (0.6-3.6)	1.1 (0.6-2.1)	0.9 ‡ (0.3-2.2)	0.5 (0.3-0.9)	0.9‡ (0.3-2.1)	0.9 (0.5-1.8)	1.1‡ (0.5-2.4)	0.9 (0.5-1.8)	0.7‡ (0.3-1.6)
	Rufiji (85)	1.1 (0.6-1.9)	1.4‡ (0.7-2.9)	1.7 (0.9- 3.3)	2.0‡ (0.9-4.4)	1.4 (0.8 -2.6)	2.9‡ (1.3-6.3)	0.9 (0.5-1.7)	0.9‡ (0.5-1.9)	1.4 (0.7-2.8)	1.3‡ (0.6-2.7)
Health facility type	Hospitals (93)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Health Centers (45)	2.8 (1.4-5.6)	2.1 ŧ (0.9-4.7)	3.1 (1.3-6.9)	4.9 ŧ (1.7-14.0)	3.0 (1.5-6.1)	2.1 ŧ (0.9-4.9)	1.2 (0.6-2.6)	1.2 ŧ (0.5-2.6)	1.7 (0.8-3.6)	1.8 ŧ (0.6- 2.7)
	Dispensaries (38)	4.1 (1.9-8.7)	2.4 ŧ (0.9-6.1)	4.3 (1.6-11.7)	6.3 ŧ (1.8-22.2)	3.8 (1.7-8.4)	2.3 ŧ (0.8-6.6)	1.5 (0.7-3.3)	1.3 ŧ (0.5-3.4)	5.4 (1.8-16.1)	6.7 ŧ (1.9-23.4)
HF ownership	Public (176)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Non-public (78)	0.3 (0.2-0.6)	0.8 ¥ (0.4-1.7)	0.6 (0.3-1.0)	0.9 ¥ (0.4-2.1)	0.1 (0.09-0.3)	0.2¥ (0.07-0.4)	0.6 (0.4-1.1)	0.7 ¥ (0.3-0.5)	0.6 (0.3-1.1)	1.2¥ (0.5-2.7)
Cadre of health worker	Other nurses (118)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Physicians (6)	-	-	2.0 (0.2-17.9)	3.8§ (0.4-36.4)	-	-	0.6 (0.1-3.2)	0.8§ (0.1-4.5)	0.9 (0.2-5.4)	1.3§ (0.2-8.2)
	Clinical Officers (51)	0.7 (0.3-1.3)	0.8 § (0.4-1.6)	1.2 (0.5-2.5)	1.6§ (0.7-3.6)	0.5 (0.3-1.0)	0.7§ (0.3-1.4)	0.6 (0.3-1.2)	0.6§ (0.3-1.3)	1.3 (0.6-2.9)	1.7§ (0.8-3.7)
	Trained nurses (70)	0.5 (0.3-0.9)	0.8§ (0.4-1.7)	0.6 (0.3-1.2)	1.2§ (0.6-2.4)	0.4 (0.2-0.8)	1.0§ (0.5-2.2)	0.6 (0.3-1.2)	0.8§ (0.4-1.5)	0.7 (0.3- 1.2)	0.9 § (0.5-1.9)
	Other cadres (9)	0.2 (0.04-1.2)	0.1§(0.03-0.8)	0.2 (0.05-0.8)	0.07§ (0.02-0.4)	0.3 (0.07-1.2)	0.1§ (0.02-0.6)	0.5 (0.1-1.9)	0.4§ (0.1-1.7)	3.8 (0.4-31.5)	3.1§ (0.3-27.1)

‡Adjusted for type of health facility, health facility ownership and health worker cadre.
ŧ Adjusted for district, health facility ownership and health worker cadre
¥ Adjusted for district, type of health facility and health worker cadre
§ Adjusted for district, type of health facility and health facility ownership

In the second round (table 6), only providers from dispensaries showed higher odds of using SP for management of their own [cOR= 5.5 (1.9-15.6)] or family member illness episodes [cOR= 4.5 (1.5-13.3)] in un-adjusted analysis, compared to providers from the hospitals. As well staff of non-public facilities showed lower odds of SP use that those working in the public facilities, in the crude analysis cOR =0.3 (0.1-0.5) for self use and 0.2 (0.06-0.5) for family member.

Table 6: Health workers attitude and personal use (or/and family use) of SP for management of uncomplicated malaria, 2004

Characteristic variable	Category	Children<5: OR (95%CI)		Older children/adults: OR (95%CI)		Pregnant women: OR (95%CI)		Self use: OR (95%CI)		Own child/family use: OR (95%CI)	
	n=(146)	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
District	Morogoro (59)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	K/Ulanga (87)	5.8 (0.7-48.3)	3.4 ‡ (0.3-35.2)	5.1 (0.7-42.4)	2.7‡ (0.2-29.9)	3.5 (0.4-31.1)	2.4‡ (0.2-30.7)	1.2 (0.5-2.2)	0.5 ‡ (0.1-1.8)	1.2 (0.5-3.2)	2.1‡ (0.5-7.8)
Health facility type	Hospitals (90)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	H/Centers (22)	-	-	-	-	-	-	1.6 (0.6-4.4)	0.7 ɬ (0.1-3.9)	2.1 (0.6-7.6)	0.8 ɬ (0.1-4.1)
	Dispensaries (34)	-	-	-	-	-	-	5.5 (1.9-15.6)	1.2 ɬ (0.2-8.0)	4.5 (1.5-13.3)	3.0 ɬ (0.5-17.6)
HF ownership	Public (79)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Non-public (67)	1.5 (0.4-5.8)	0.5¥ (0.1-2.7)	1.2 (0.3-4.9)	0.4¥ (0.08-2.3)	1.2 (0.2-6.0)	0.5¥ (0.07-3.5)	0.3 (0.1-0.5)	0.2¥(0.05-1.2)	0.2 (0.06-0.5)	0.2¥ (0.06-1.1)
Cadre of health worker	Other nurses (55)	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	Physicians (8)	-	-	-	-	-	-	1.2 (0.2-5.5)	2.6§(0.5-13.5)	-	-
	Clinical Officers (26)	-	-	-	-	-	-	1.9 (0.7-5.4)	1.4§ (0.6-3.4)	0.8 (0.3-2.3)	1.3§ (0.4-4.1)
	Trained nurses (55)	1.2 (0.3-5.0)	0.8§ (0.2-3.7)	1.7 (0.4-7.6)	1.0§ (0.2- 5.4)	5.4 (0.6-47.8)	3.6§ (0.3-34.9)	1.1 (0.4-2.8)	1.8§ (0.6-5.4)	2.5 (0.6 -9.8)	3.1§ (0.4-14.2)
	Other cadres (2)	-	-	-	-	-	-	-	-	-	-

‡Adjusted for type of health facility, health facility ownership and health worker cadre.
ɬ Adjusted for district, health facility ownership and health worker cadre
¥ Adjusted for district, type of health facility and health worker cadre
§ Adjusted for district, type of health facility and health facility ownership

7.4 Discussion:

This study provided an opportunity to assess the influence of health workers' attitude to the usage of new malaria treatment recommendations. Overall, results showed variations in health workers attitudes and practices regarding new treatment recommendations in terms of type of health facility, ownership and type of health worker at six months post changes and two years later. There was less variation of provider's attitudes and personal use of new recommended antimalarial between districts. Dispensaries and health centers showed higher preferences for SP than hospitals. Similarly, public facilities reported higher preference for SP than non-public ones. Most providers were not comfortable with the use of SP for children below age of 5 and for pregnant women. Personal use of SP for their malaria episodes was high in both rounds, with some exceptions in the second round.

The introduction of SP as a first line treatment of uncomplicated malaria in Tanzania was not well received (Nsimba SE, 2006). It is therefore not surprising that from the first survey (baseline), preference to SP as appropriate treatment for management of uncomplicated malaria was low among health workers in the surveyed districts. Their dissatisfaction of treatment recommendation could have influenced their perceptions, attitudes and practices. This attitude may be based on their daily experiences in the clinical management of patients as became evident when we assessed providers' preferences by type of health facility. In many areas especially rural Tanzania, hospitals are expected to be receiving referal cases. For malaria, these could mean patients who did not respond well to first line treatment at lower level of care, i.e. dispensary or health center, hence sent to hospitals for further management including laboratory assessment and in-patients' service. This may explain the significant findings of providers from dispensaries and health workers appreciating SP use better than hospitals.

Many studies have assessed users' perceptions of new treatments when changes occur. Several authors explored community perceptions to malaria treatment and other aspects of health services in Tanzania and elsewhere (Tarimo DS et al., 2001; Wakgari

D et al., 1999; Okolo SN and Ogbonna C, 2002). Likewise, most studies of health workers' knowledge, perceptions, attitudes and understanding have been conducted in relation to health services and health problems other than malaria (Olowookere SA, 2009; Ignacio LL and DeArango MV, 1989; Wasunna et al., 2008). The introduction of ACTs in most African countries received considerable attention, with researchers evaluating the process of change and performance of health workers on new policies. Some of these evaluations were on artemether-lumefantrine in Kenya, Uganda, and Zambia as well as on artesunate plus amodiaquine in Ghana (Dodoo ANO, 2009; Zurovac et al., 2008c; Zurovac et al., 2007; Zurovac et al., 2008a). These evaluation assessed providers' use of new treatment recommendations for malaria case management, with no focus on personal preferences and personal use.

The difference in providers' preferences for SP for management of uncomplicated malaria may also be related to performance of the health facilities governing committees. A fact that public providers were more comfortable with SP than those in the non-public sector may be linked to a closer supervision of health management teams. Intrinsically health workers do assess clinical progress of their patients. Results in this survey indicate that most providers were skeptical using SP for children under 5, and pregnant women; probably because they perceived it too strong for children below age of 5 as previous studies from Tanzania reported (Tarimo DS et al., 2001).This preference worsened over time suggesting that providers were not satisfied with experiences of using SP. This finding is in contrary to what one would expect; that providers need time to appreciate, accept and comply with new treatment policies. An important lesson here is that, when there is a failing drug in the system, health care providers will, without doubt, notice it and may provide initial indication of the drug resistance in the population.

Despite poor attitudes to the new drug for first line management of uncomplicated malaria, many providers indicated that they had used SP in their last illness episode of malaria. In the first round, it was difficult to assess if SP was used before or after the

change, since we did not specify the duration of illness prior the survey, but in the second round we gave a time frame; i.e. we inquired for a malaria episode in the past three months preceding the survey. Also, we did not seek additional clinical information; therefore couldn't assess if it was correctly used. Interestingly, compared to hospitals, providers' from the dispensaries were more likely to have used SP for their illness episode or their family members. This finding was observed in both survey rounds. One possible explanation for this observation may be related to a fact that, hospitals are a higher level of care, therefore more likely to see referal cases of malaria; i.e. non response to first line treatment and/or severe form of the disease. But also, dispensaries do not have a wider range of treatment choices and services available, hence more likely to follow treatment guidelines presented.

Also, it is more likely that, knowing this is the only available treatment option for them, dispensaries strives to have medications available in stock; hence availability of the drugs facilitated it being used by a staff or staff's family member. This may not be a case for higher levels of care, given a wider choice of drugs available. The same may apply for public providers, with good health management team supervision, public facilities are more likely to abide by the new treatment recommendations, but this cannot be said for non-public facilities, hence significantly less use of SP for last malaria episodes was observed from non-public providers in this study. SP was available as a single dose and its price was not as high as other antimalarials available at the time of survey. During time, other antimalarials available in private sector included amodiaquine, chloroquine (the outgoing medicine), artemisinin mono-therapy, quinine, etc. All of these products require more than a single dose to finish a course of treatment, therefore more likely to cost more than SP. A possibility of financial gain for using other treatment recommendations than SP cannot be ruled-out in the private sector.

Study limitations:

We did not account for the clustering of health facilities in the analysis. This may have affected the magnitude of the measured effect. Ideally, this clustering effect should be taken into account because there may be similarities between individuals working in the same health facility, such that, on average they are more similar to each other than to individuals in other health facilities, due to many factors such as training received at facility level and experiences acquired through everyday's practices. However, we worked with the assumption of independence between the observations, since we were assessing individuals' attitudes, through their preferences and personal use of treatment recommendations. These variables are more likely to be related to personal understanding and beliefs.

However, it is acknowledged that personal preferences can be influenced by many factors such as training, work experience and for the case of malaria treatment; availability of medicines and appropriate technologies to assist in clinical care of patients e.g. diagnostics for malaria confirmation, as well as presence of policy briefs and documents for referencing. These factors were not assessed and therefore limit our conclusions with regards to the role they play to shape health workers preferences and personal use of new treatment recommendations for management of uncomplicated malaria in the surveyed area.

Third, a fact that the criteria used to obtain interviewee was not random, implies that results from this evaluation cannot be generalized for all health workers in Tanzania. However, we are confident that, this study provided additional information on predictors of preferences and practices among health care providers toward SP, which complimented previous reports of poor community and provider's perceptions towards SP when it was introduced for management of uncomplicated malaria in Tanzania; as well, it provides a clue on what happens to the health system when there is a failing drug.

Although we did not match respondents in the two surveys, the fact that we interviewed health workers from the same health facilities, increased our confidence that the

differences reported in preferences and practices reflect a general picture for providers with similar experiences.

Fourth, not being able to assess clinical information when assessing practices towards recommended treatment through personal/family use, might have led to a biased estimation of SP use. It is possible that there were good reasons for not using SP to some cases that may be due to, for example, a diagnosis of severe malaria, non-response to SP or history of hypersensitivity reaction to sulphur- containing medicines.

Fifth, it is possible that some health workers reported what was considered appropriate rather than what they would actually do, or actually did, leading to courtesy bias. Furthermore, recalling what happened in terms of treating malaria in the past may have been difficult for some participants, introducing a recall bias. These biases could have affected measures of effect estimated. In this respect, we limited the recall for up to the past three months in the second survey.

Lastly, the relatively small sample for some sub-groups of explanatory variables e.g. physicians; made it difficult to detect associations between some potential risk factors and the outcomes studied.

7.5 Conclusion:

Following changes in malaria treatment guidelines, health workers in Morogoro Rural, Rufiji and K/U districts showed variations in attitude towards new recommendations. Health workers generally showed poor attitudes towards the new recommended first line treatment, but many used it in their last malaria episode or their dependants'. Clinicians did not to totally accept the recommendation after the change, and this attitude worsened over time. Poor attitude to and lower use of SP for self-treatment was more apparent in hospitals and non-public health facilities. These findings indicate that other factors than provider's attitude may play important role in providers' practices and acceptance of new treatment recommendations. Such things as experience acquired through observation of clinical response to treatment, having a range of available

treatment choices and patients' characteristics may have more influence in clinical practices.

The need for close monitoring of implementation of new treatment policies is emphasized including assessment of training and sensitization needs for different health worker cadres and facility type, particularly early in the change process. Training should involve refresher trainings, especially in contents that seem not to be well adhered to.

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Some of these data was used to fulfill requirements for a Master's of Science (Epidemiology) degree, at the London School of Hygiene and Tropical Medicine, 2009.

Authors' contribution: IM- Tool translation, data collection, analysis, preparation of first draft; AML- Statistical analysis and review of draft manuscript; RAK- Supervision of data collection, review of subsequent draft manuscript. All authors read and agreed the final version of the manuscript.

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The authors declare that, conclusions reached in this paper do not reflect the opinion of the funders, their institution(s) or other non-authors from IMPACT- Tanzania study team.

Additional Files: Two additional files were provided with this publication:

Additional file1 (figure 8 in chapter 2): Map of Tanzania showing study sites: Morogoro Rural, Rufiji, Ulanga and Kilombero districts (Source: IMPACT- Tanzania protocol).doc

Additional file 2 (figure 3 in chapter 1): Patterns of Malaria Endemicity in Tanzania, 2002 (adopted from Tanzania Essential Health Interventions Project – TEHIP).doc

PART V: GENERAL DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

Chapter 8: General Discussion, Conclusions and Limitations

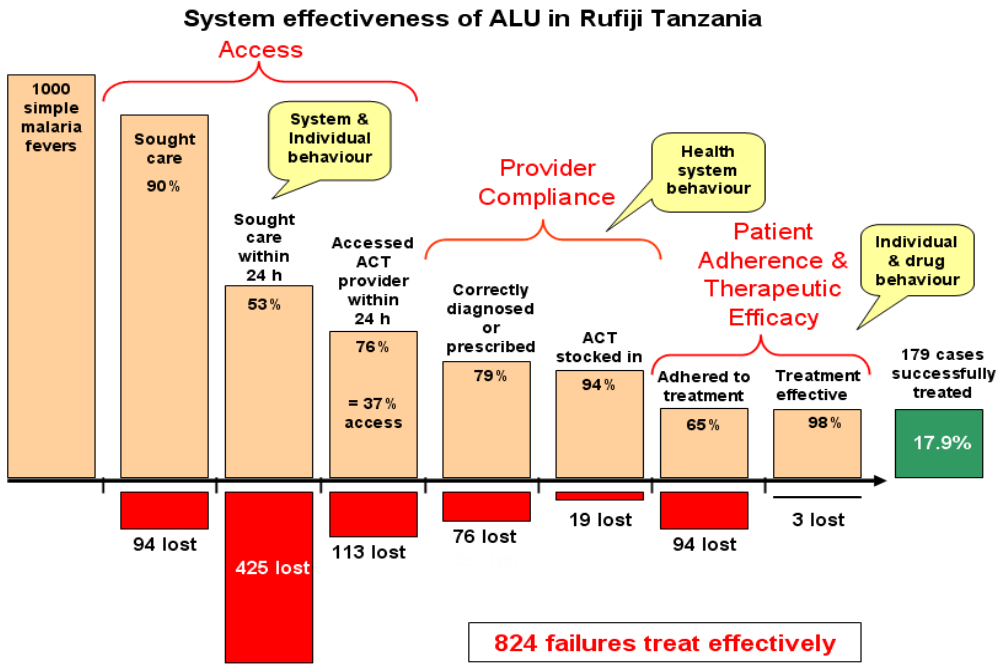
8.1 General discussion:

Effective malaria case management requires efficacious antimalarial medicines in place. The global move to use ACTs for malaria treatment in early 2000, contributed to a tremendous decline in malaria prevalence in many endemic areas (WHO, 2006; WHO, 2012b). These achievements cannot be attributed to use of ACTs alone, but also scale-up of other malaria control interventions such as vector control measures as use of ITNs, IRS, larviciding, intermittent preventive treatments for vulnerable population groups and the increased use of diagnostics for routine care. However, the full potential of ACTs to clear malaria infection and halt the disease progression can be realized if the medicines are delivered and used as intended, e.g. in the controlled environment. This is not possible because medicines need to be used for routine care within the health systems using existing channels to procure, deliver, store, distribute and prescribe the drugs for patients use; termed “systems effectiveness”.

The complexity of systems effectiveness is a result of the multi-disciplinarily nature of the actors. In the case of malaria control as investigated through INESS platform, health system factors played important role in the decay of ACT efficacy (in Rufiji). Major losses of systems effectiveness were observed in relation to poor or delayed access to care, poor providers compliance to treatment policies which lead into poor patients adherence (INESS report to Gates foundation:2011). In the INESS reports, only 37% of all fever cases had access to an ACT provider within 24 hours (figure 1, Chapter 8). Further decay was due to unavailability of medicines at health facilities, providers’ behaviour and patients’ adherence to treatment, resulting to effectiveness of about 18% (figure 1, below). Indepth assessment of factors associated with poor providers’ compliance during INESS surveys is the primary focus of this work. Here an abstract of important findings from the five papers above (chapter 3,4,5,6 and 7) is presented and its implication for the control of malaria and other diseases within the context of a similar health system structure in the region and elsewhere is discussed; with particular

emphasis in service delivery, health workforce, availability of technology and products as well as governance. Based on these findings, recommendations are put forward to guide appropriate use of resources to maximize systems' performance for better health outcomes.

Figure 1: Systems effectiveness of ALU in Rufiji Tanzania, 2010-2011. Source: INESS report (unpublished data)



8.2 Quality of services delivered:

This work demonstrated that having a malaria confirmatory test before treatment, significantly reduced over-treatment of malaria (during high transmission season) in one area that this policy was implemented (Chapter 3: tables 5 and 6 ; (Masanja et al., 2012b). Introduction of malaria rapid tests for routine care in Rufiji increased the chances of fever patients being seen in a facility with malaria confirmatory capacity (chapter 3: table 1). Having the tests in the facility also improved correct testing, i.e. testing patients with fever to rule out malaria, complying with testing algorithms provided during training of the new policy. Unfortunately, having tests was also associated with

higher over-testing, i.e. non febrile patients sent for a malaria confirmatory test, indicating poor case selection (chapter 3: table 2). However, the gain achieved by prescribers complying with test results, benefits both the patients and the system. Improvements in malaria case management following introduction of rapid tests for routine use have been reported in other settings as well (D'Acremont V et al., 2011; Ishengoma DS et al., 2011)

Assessment of the quality of malaria treatment revealed that some patient groups are prone to inappropriate dosing of ACT (chapter 4: tables 2 and 3). AL dosing by age for older children between 3-12 years of age, showed more than 50% of target group received inappropriate AL dosing ($p<0.05$). Weight based prescriptions provided a better indicator for dosing, but were less practiced as evident by the lower proportion of patients (33.2%) who had their weight assessed during provider- patient interaction (chapter 4: table 1). These findings have important implications for malaria control, as sub-therapeutic doses of antimalarial chemicals may lead to resistant strains of the parasite and lower the drug's gametocidal function. In addition, poor providers' behaviour is one precursor of poor patients' adherence to treatment. If a patient is prescribed incorrect or inappropriate dosing, and took the treatment faithfully as prescribed, in the end this person did not complete a recommended treatment without his/her awareness or intentions of doing so.

It is further very unfortunate because results in chapter 5 demonstrate that, as malaria prevalence declines in population surveys (NBS and Macro ICF, 2011), the burden shifts from infants and toddlers to children and young adults. Analysis of data collected from 2002-2010 in out-patient settings within the study areas (Rufiji and K/U) shows that over the years, children between age of 2-5 years and older children from 5-15 years have an increased prevalence of malaria parasitemia at health facilities (chapter 5: table 2 and figure 2c, 2d); contrary to population based findings to the former. These findings bring a public health concern in relation to malaria prevention policies and strategies. The respective age group is likely to be school children who are actively involved in

outdoor activities. A fact that, the same group is prone to receiving inappropriate dosing of ACT when infected (chapter 4) implies that adequate parasite clearance may not be achieved, hence a significant morbidity burden and continued malaria transmission in the community.

8.3 Availability of products and technology:

Products availability is known to have influence on care. Indeed, patients diagnosed with RDT in INESS surveys, had higher odds of getting a correct treatment of ACT (Chapter 6: table 3 and 4) where as clinical diagnosis of malaria lowered the odds of correct treatment (chapter 6: table 3 and 4); and increased the odd of over-treatment (chapter 3: table 4 and 6). The frequent stock-out of life saving malaria commodities in the study settings threatens quality of care of malaria patients. Innovations like “SMS for Life” provide a better means of assessing stock levels of medical products in ones administrative area (Barrington et al., 2010). SMS for Life, has further shown to guide reallocation of resources in rural health facilities in Kenya in order to reduce the problem of stock-outs of medical products (Githinji et al., 2013). This is the current best alternative strategy for insuring availability of medical products in health facilities. In the Kenya study, up to 73% of stock-out alerts were resolved by district managers through redistribution. As a tool to monitor stock levels, too much reliance shouldn’t be put on emergency stock replenishing platform. This dependence will lead to expensive unscheduled field trips for re-stocking or re-distribution, which has resource implications and may divert attention from other prior planned activities. However, the platform can be useful to plan for activities during supervision visits, or raise important discussions points during planning meetings.

With regards to improving products availability, the need to reassess the original plan of medical products procurement, ordering and distribution act has become more obvious. After experience gained in the first 2-3 years of implementing “SMS for Life”, implementing partners should now analyze the stocking trends and see how stock management can be improved at the facility and national levels. The procedure of

products forecasting may need to be revised to take into account real time data available through “SMS for Life”. It may be necessary to revise the requisition and ordering formulas or use mathematical modeling to account for morbidity patterns, population growth (USAID | DELIVER PROJECT, 2011), seasonality, utilization rate, changes in weather patterns, availability of diagnostics, resultant epidemics as well as other unforeseen factors e.g. increased utilization due to closure of the nearby facility for social or administrative reasons, etc. Lately, there have been reports of the national medical store department (MSD) delivering products directly from the national level to the health facilities. This may be a good initiative to improve availability and stock levels of essential medical supplies at the point of care in rural areas.

8.4 Health workforce:

An assessment of personnel’s factors affecting provider’s compliance revealed that, work experience significantly improved the odds of giving a correct treatment of malaria (p=0.02). As well, providers of lower cadres were more likely to comply with treatment recommendations (chapter 6: tables 3 and 4); a similar observation to what has been reported from neighboring countries (Zurovac et al., 2004; Rowe AK et al., 2003). Regular support supervision would be useful to improve compliance in this aspect. In chapter 7, this work showed that, providers attitude may have less influence to their practices regarding treatment recommendations (Masanja et al., 2012a) than other system components; chapter 7: tables 3,4,5 and 6). Such factors as the type of provider served and availability of recommended medicines at their respective work areas may have more effect in their practices. These findings have practical implications to health management teams; that, having the recommended treatment products available in health facilities facilitates provider’s compliance. It is possible that, the act of prescribing medications that are not in stock frustrates providers, particularly in rural settings where this work was carried out, as there aren’t many drug selling outlets and purchasing power of the community members is very low. Nevertheless, inadequate health workers

performance has been long recognized as widespread problem which required multifaceted approaches to address (Rowe AK et al., 2005).

8.5 Financing and Access to care:

The poor quality of services may be one of the major factors for poor access to formal health care. The proportion of people who had fever and accessed care within 24 or 48 hour of fever onset, to a recognized ACT provider in INESS survey was very low (INESS report to Gates Foundation). Barriers to prompt access to care reported in other settings included acceptability, availability and affordability, mentioning a few (Hetzel MW et al., 2007; Chuma J et al., 2010). The frequent stock out of medicines in nearby health facility discourages prompt attendance to facilities, especially when the problem at hand is perceived to be minor, such as fever at its initial onset. The indirect costs of medical care, such as transport, food etc, complicates affordability issue. In addition, problems with the organization structure of the health system such that a facility can stay closed on days when it should have been functional (e.g. due to human resources crisis, e.g. because a provider had to travel to district headquarters, humanitarian reasons, etc), brings about undesirable consequences. These, including other factors described by health financing scientists (Mtei G and Mulligan J, 2007), may be among the reasons for low enrolment of community health insurance schemes in rural Tanzania.

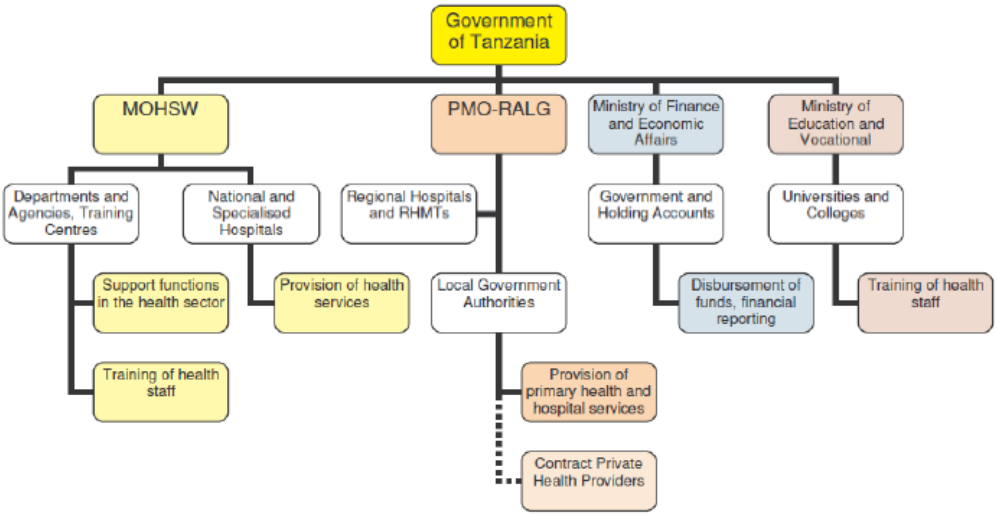
8.6 Governance:

On the other hand, problems of providers' compliance with treatment recommendations and availability of medical products would have been significantly improved if district health management teams perform supportive supervisions as required. In this work, very few health workers reported to have had a supervisory visit within the six months preceding the surveys (chapter 5: table 1, 2 and chapter 6: table 2). As a result, we couldn't record any meaningful effect supervision visits have had on quality of care. In fact, the role of supervision on improving provider's performance have led to

contradictory findings in the last decade, but seem to, at large, be associated with improved health workers performance (Loevinsohn BP et al., 1995; Trap B et al., 2001). This finding underscores the need for district health management teams and other supervisory bodies to adhere to supervision plans in order to get a common ground for discussion of challenges facing health care provision in provider's working areas at different levels of care.

However, the main hindrances to achieving the required level of supervision activities in many resources poor settings are multifaceted and require support from responsible leaders as well as investigating cost-effective ways to implement quality supervision activities (Rowe AK et al., 2010). Understanding that health policy or health systems studies implies broader range of methods (Bennett S et al., 2011); not only limited to hypothesis testing and proving causal pathways, etc (Gilson L et al., 2011); an assessment of the context where reported providers' practices occurs was done. This lead to an in-depth analysis of stakeholder's contributions to malaria control efforts in the country and realized that the administrative structure of the Tanzanian health system leaves room for improvement. The fact that health services are managed by different Ministries at different levels of care (figure 2, chapter 8), can be complimentary or can lead to contradictory responsibilities between the actors.

Figure 2: **Administrative organization of the Tanzanian health system** [adopted from the World Bank report: (World-Bank, 2011)



Source: Tanzania, MoHSW 2008, 12
Notes: MOHSW = Ministry of Health and Social Welfare; PMO-RALG = Prime Ministers Office, Regional Administration and Local Government; RHMT = regional health management team.

8.7 Health services and organization structure:

Partnership between various Ministries is encouraged because health issues are cross-cutting and affected by all aspects of life, such as environment, infrastructure, gender, education, water and sanitation, etc. For mutual benefits and understanding, a clear, transparent and accountable collaboration between actors is needed. For example, there are seven divisions (with 6 directorates) working under the Chief Medical Officer at the MoHSW (Figure 3, chapter 8 below).

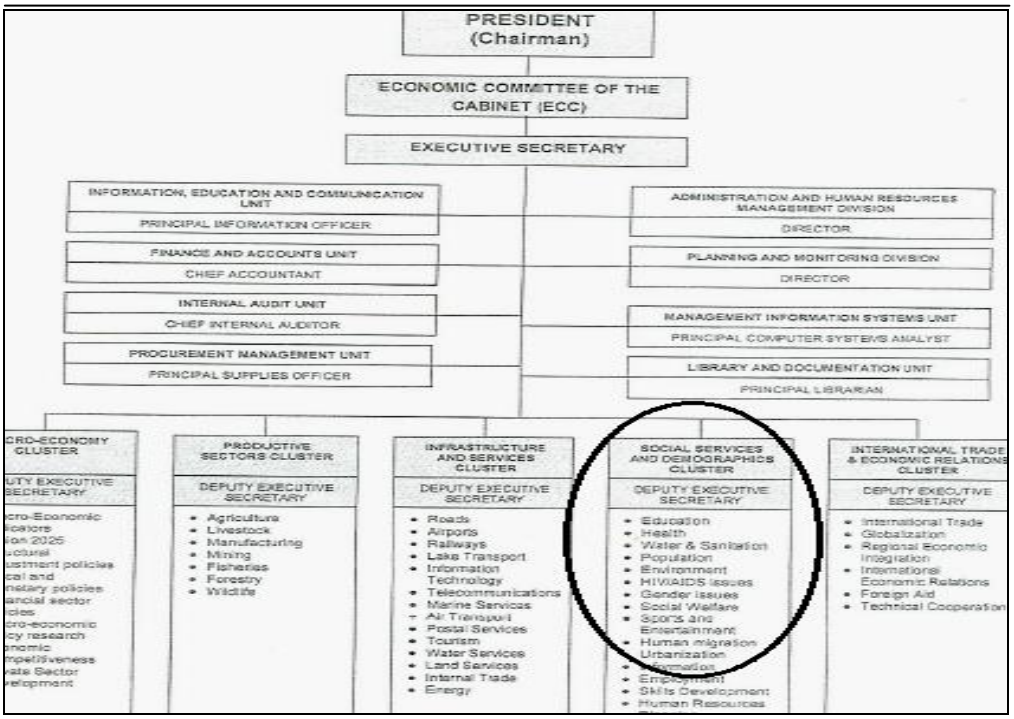
The CMO coordinates all health services delivery in the country, including quality assurance of services and budgetary allocation of funds to various health services. It is worth to remember that, funding matters for the central government (e.g. Ministries) are coordinated at the Ministry of Finance and Economic affairs (figure 2 above). Other units within the Ministry of health include: Information and communication technology which is responsible for e-health, m-health, Tele-health, health management information systems, etc; Legal services; Financing & Accounting; Internal Audit; Procurement management and Government communication unit (MoHSW-webpage).

Figure 3: Directorates under the Chief Medical Officer [summarized from the Ministry homepage (MoHSW-webpage)]

Office of the Chief Medical Officer, MoHSW Tanzania	Preventive Services (directorate)	Epidemiology and Disease control Reproduction and Child health Environmental, hygiene & sanitation Health education & Promotion Nutritional Services
	Curative Services (directorate)	Public & Private Health services Diagnostic and Technical services Traditional & Alternative medicine Oral Health NCDs, Mental health& Substance abuse
	Human Resources development (directorate)	Health human resources planning Allied health services training Nursing services training Continued Education & Post-graduate Social Welfare staff development
	Health Quality Assurance (directorate)	Pharmaceutical Services Health Services inspectorate & QA Emergency preparedness & response Nursing Services
	Social Welfare (Commissioner)	People with disabilities & elderly Family, child welfare & early childhood Juvenile Justice services
	Administrative matters and Human Resources management (directorate)	Administration Human Resources management
	Policy and Planning (directorate)	Policy Section Planning Section (& budgetary) M&E and Performance reporting

In additional to the Ministry of Health, Ministry of Education and Vocational Training and Prime Minister's Office; health matters are also featured at the President's Office Planning Commission (POPC) under the Social Services Demographic Cluster. The cluster deals with monitoring and advisory role in many population services and social development issues in the country.

Figure 4: Section of the Organization structure of the Planning Commission
(available at http://www.mipango.go.tz/documents/POPC_orgnization%20structure.pdf last accessed on 10th April, 2013)



In all these areas (ministries and POPC), units/sections have specific goals and description of their work, which demarcates them from other sections/ units. A simplified relationship of country's administrative health actors is such that, the MoHSW supervises formulation of health policy and guidelines, coordinates health services provision and monitors quality of services, whereas the local government authorities (LGA) under the Prime Minister's Office (PMO- RALG) delivers these services to people and the social services cluster monitors, analyses and advises accordingly. Unless there are deliberate measures to coordinate processes and outputs across different sections working towards a common goal, every section will be concentrating on what they are expected to do, in the usual classical, linearized approach.

Systems' thinking requires working in dynamical, inter-connectedness approaches between different system components, or actors. Understanding the complex nature of systems is the underlying principle of systems thinking approach (Adam T and De

Savigny D, 2012). Health problems have multiple, on-going causality and require multidisciplinary actions to mitigate them. No single actor can work alone to control, eliminate or eradicate a health problem. This is why health systems are categorized as complex adaptive systems (CAS) (Pain L and Peters DH, 2011). The effect of malfunctioning of one part of the system can result to adverse consequences to the other component, or on the system as a whole. A good example as was evident in this work is the trickledown effect of poor provider's compliance to treatment recommendations leading to poor patients' adherence (and probably poor treatment outcomes) decreasing systems effectiveness of ACTs.

8.8 Challenges facing health systems actors

Scientists have gone further to describe the relationship between health systems building blocks and its actors, such that the systems building blocks represent "systems hardware" while the interconnectedness and relations between them as "systems software" (Sheikh K et al., 2011). Unfortunately, the software part of the health systems is often neglected (Bigdeli M et al., 2012). Furthermore, health systems actors, just like health systems researchers are too fragmented; based on their expertise, experiences, current responsibilities and knowledge. Gilson and colleagues describes this knowledge paradigm to be responsible for framing understanding of reality, functions and nature of research in relation to health policy and systems (Gilson L et al., 2011). This clash of knowledge paradigms may lead into communication barriers that discourage interdisciplinary collaborations (Gilson L et al., 2011; Bennett S et al., 2011). In such situation, investing in smothering actors' interactions (the systems software side) may prove to be more beneficial.

On an equal note is the need to foster international partnership and learn from others. Although health systems problems occur in local contexts, some expertise may not be available locally. The problem of inadequate dosing to older children described in chapter 4 can be used to illustrate this point. Tanzania do not manufacture AL (ACT for malaria treatment), and therefore cannot modify manufacturers dosing instructions

provided to guide clinical use. It is appropriate to conclude that manufacturers' uses internationally recognized profiles with known credible/ confidence intervals to guide dosing. This implies that the target population may fall anywhere in these intervals. In this case, a consensus is needed to clarify what patient characteristic (e.g. age vs weight) provides a good basis for better clinical outcomes based on the drugs' pharmacokinetics and pharmacodynamics properties. Both age and weight based prescriptions have a role in clinical pharmacology particularly in pediatric dosing; age as an indicator of maturity e.g. internal organs – for drug metabolism and weight as indicator of surface area for drugs' distribution.

8.9 Limitations:

There are several limitations to this work that made it not possible to make reliable conclusions on some aspects of care. First; no detailed assessment was made on the effect of staff shortages on provider's compliance. In reality, two facilities that provide similar level of health services but with an appreciable gap of total number of health workers with the right mix of expertise (e.g. a dispensary with one health worker versus that with three staff), may have differing levels of care quality. Our study was not structured to assess the implication of this disparity in quality of malaria case management. Second; many studies have reported the difference in quality of health care services provided between public and private providers (Basu S et al., 2012). Our surveys were not powered to assess these differences therefore could not demonstrate appreciable findings regarding the influence of providers' type on quality of care. In fact, there were very few private providers in the areas we worked, and in the country as a whole.

Chapter 9: General Conclusions and Recommendations

9.1 General Conclusions:

The quality of malaria case management in rural Tanzania needs improvement. Four years after the introduction of ACT (AL) for management of uncomplicated malaria, provider's practices are still sub-optimal, stock-out of medical products to facilitate case management is rampant, support supervision occur less frequent, correct dosing of ACT for uncomplicated malaria is low to some group of patients - especially when prescription was age-based, etc. All these challenges affect the quality of malaria case management, especially in rural Tanzania. Despite of these deficiencies, this work showed that investing in health system does have a positive effect. The policy of malaria confirmation prior to treatment seems to improve correct treatment, although the strategy is handicapped by stock-out of testing devices. As well work experience had positive impact in correct treatment of malaria, but support supervision rarely happens.

These observations demands integrated efforts to reverse the possible negative consequences resulting from poor provider's compliance. Some of the possible factors for this behaviour, as demonstrated here, could be outside the provider's capacity. Issues of stock-outs may, sometimes, need to be dealt at a higher administrative level, that is, district, regional or national stakeholders involved in the procurement policy. The problem of inadequate dosing may require stakeholder's involved in health workers training to refine existing guidelines and provide recommendations for improvement e.g. do refresher trainings, etc. A fact that work-experience improves the odds of correct prescription, demands closer support to new employees in their work areas.

Another complexity may be related to levels of supervision responsibility between the various ministries involved in provision of health services (chapter 8: figure 2) and implementers. Who is required to provide resources for what kind of supervision support, at what level of care, requires more transparency. This is another area to look

into deeply and provide practical guidelines. It is possible that the guidelines referred here do exist; but they seem not to be complied with very well. If this is the case, then, there is a need to fine-tune management procedures and hold responsible actors accountable for consequences.

9.2 Recommendations:

The complexity of issues demonstrated here speaks to the need to adopt a systems thinking approach in the health sector. The problems discussed in this thesis touch a small area of health care services in Tanzania, yet highlight challenges and major areas of concern. Currently, health systems' strengthening is on the global health agenda and there is adequate will to seize the momentum and act. Several guidelines are now available for use by policy makers to analyze and integrate systems components for better health system performance (Lavis JN et al., 2012; Bosch-Capblanch X et al., 2012; Lewin S et al., 2012; Bosch-Capblanch X, 2011). What is needed now to benefit from the advances in systems knowledge are the practical methodological steps that are context specific to a respective health system. Failure to do this means business will continue as usual, and it will take a very long time to see small positive changes in health systems' performance in the developing world.

Here, three recommendations are put forward to address and progress the health systems strengthening agenda, in Tanzania. The aim is not to overhaul the system, but rather to provide trouble-shooting mechanisms in areas not working well by smoothening interactions between actors and performing technical adjustments wherever needed.

1. First is to improve stewardship in the health sector to ensure health policies are implemented effectively. This may require a use of internal "Health Diplomacy" as a strategy to employ "systems thinking" for stakeholders' management of health system's strengthening agenda. This implies, taking time to understand the complexity of challenges facing different aspects of care, and finding sensitive,

effective ways of harmonization geared towards a common goal. This strategy can be very useful if applied at a higher level of administrative hierarchy. Say, in the ministry of health having a small team of 2-3 technical staff (with the right mix of expertise; e.g. in financing, pharmaceuticals, clinical work, policy analysts, etc) to work for systems strengthening, with "systems thinking" approach. Ideally this team should work under the CMO in either Quality Assurance or Policy and Planning directorates. The main objective of the team should be to analyze challenges in different programmes/ units/ sections, and work together for solutions, i.e. strengthening the "system software" aspect. When there are conflicting interactions between units, the team could act as outsiders to assess the situation and advice accordingly.

A possibility of having this team positioned at the POPC, which is higher ranked than within the MoHSW, should be encouraged. It is envisaged that, at POPC, the team will have better power to assess and provide useful recommendations taking into considerations the existing state of affairs; even at ministerial levels. Ideally this organ should connect and be able to work with all actors in health sector, from all governmental departments. The assumption for having this team placed at POPC is a possibility of getting classified information on resources available and approval to divert them to the challenged endeavor. Another advantage of placing this team outside the Ministry with a primary responsibility for health matters is to avoid animosity among work colleagues.

2. The second recommendation is based on knowledge creation and training. Understanding the nature of complex adaptive systems such as health systems, and the possible interactions amongst its components, will help officials make better and more informed decisions regarding their actions. This recommendation suggests training at two levels; first: is to deal with executives. Here, a programme is advised for executive officers and programme officers/ managers. This will provide grounds for sharing experiences, learning from one another and working for a common goal

between actors within and outside the similar areas of work. Ideally the courses could be week-long international or local courses with participants from diverse work environment.

The second part of the training recommendation is a long term strategy that will involve introducing health systems block courses to health related trainings. This can begin at undergraduate level, e.g., in nursing or medical related trainings, management courses; and at postgraduate level, e.g. masters programmes for public health and health administration, etc. Already this concept is happening in some institutions such as the Swiss TPH, NMAIST (under IHI) is planning a more similar course, etc.

3. A third recommendation is the need for more evidence on health systems interventions. Scientists and researchers need to study innovative concepts for improving systems performance which address various components of health systems in the right mix. One review has raised a concern on lack of evaluations which addresses multiple systems building blocks (Adam T et al., 2012). This should be regarded as a call to increase evidence for system wide interventions that work. In the same manner as the criteria for scientific evidence stands, all forms of intervention studies, from randomized control trials (RCTs) to case controls and quasi- experimental studies should be undertaken for this course.

   This recommendation does not intend to down-play exploratory, descriptive and social science studies, but rather, employ them onboard, to monitor the change of paradigm. Descriptive studies will be very useful to highlight the change and highlight future directions, where as qualitative studies will provide in-depth understanding of the contexts.

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PUBLICATIONS:

1. *Irene M. Masanja*, Angelina M. Lutambi, Rashid A. Khatib. **Do health workers' preferences influence their practices? Assessment of providers' attitude and personal use of new treatment recommendations for management of uncomplicated malaria, Tanzania**. BMC Public Health 2012, 12:956
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9. *I.M. Masanja,* E.G.S. Mumghamba. **Knowledge on gingivitis and oral hygiene practices among secondary school adolescents in rural and urban Morogoro, Tanzania.** International Journal of Dental Hygiene November 2004 Volume 2: Issue 4: 172 – 178.
10. *M.I. Masanja*, B.M. Kalyanyama, E.N.M. Simon. **Salivary Glands Tumors in Tanzania.** East African Medical Journal Aug 2003; Volume 80 No. 8:429-433.