Understanding and improving malaria diagnosis in health facilities in Dar es Salaam, Tanzania

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Summary

In Tanzania, as in most settings of sub-Saharan Africa, malaria is the first reported cause of attendance in health facilities. The National Bureau of Statistics estimates that a total of 16 million cases and 100,000 deaths (mainly in children) are due to malaria each year. In Dar es Salaam, the main city, approximately 3 million attendances are recorded, of which about one third are due to fever, mostly considered as presumptive malaria. Recent data show that transmission intensity is much lower in urban settings than in rural lowland areas. This is especially true for Dar es Salaam where only a small fraction of all fever episodes in children and adults are actually associated with *Plasmodium* parasitaemia.

Clinical presentation of malaria is largely unspecific. No reliable clinical predictor that allows including or excluding the diagnosis of malaria has been identified. In this context, and in the absence of diagnostic test, WHO recommended in the past all fever episodes to be treated with antimalarials. Such blanket treatment leads first to substantial over-treatment with malaria drugs (in Dar es Salaam up to 95% of all treatments are unnecessary) and second to increased risk of missing alternative diagnoses with potentially fatal outcome. To address this issue of high public health relevance, we undertook a project called IMALDIA (Improving Malaria Diagnosis) aimed at improving the management of febrile patients in health facilities in Dar es Salaam, mainly through the implementation of Rapid Diagnostic Tests for malaria (*m*RDT). The project had 3 major components:

(1) *Evaluating the safety of withholding antimalarials in febrile children* with a negative *m*RDT living in a moderate and a highly endemic area

(2) *Introducing laboratory diagnosis for malaria in the routine management of fever cases,* using mRDT. The focus of this operational research was to document how feasible and effective the introduction of these tests is in the context of the routine management of fever cases.

(3) *Understanding the aetiologies of fever cases in children* by screening a group of 1000 children with detailed clinical assessments and a range of laboratory tests in order to better identify the diversity of the causes of fever in small children living in an urban and a rural area.

The overall aim of the IMALDIA project was to improve the diagnostic approach and management of fever cases in health facilities in Dar es Salaam, contribute to a more efficient and effective health sector, and help Tanzania on its way to reducing infant and child mortality.In a first step, we assessed the diagnostic performance of *m*RDT when used by health workers in routine practice. For this purpose, a quality assurance system both at central and peripheral level was set up. This system did not detect major problem and showed that the final result of *m*RDT by health workers was reliable.

The purpose of the second step was to better estimate the pre-test probability of malaria in populations targeted by *m*RDT (febrile patients of all age groups attending a health facility of any type). To this end we undertook a systematic review of the studies giving the proportion of patients with associated *P. falciparum* parasitemia (PFPf) in Sub-Saharan Africa. We found that the median PFPf was 35%, and that it had decreased by half when comparing the period before with the period after the year 2000 (44% versus 22%). This relatively low pre-test probability nowadays is another reason to implement *m*RDT in Africa. In Dar es Salaam the PFPf was very low (below 10%) hence it was even more urgent to start using a reliable malaria test. Microscopy was available in almost all public health facilities of the city but its performance was extremely low, with an overall sensitivity of 71% and a specificity of only 47%.

On the request of several Tanzanian stake-holders, in particular clinicians working routinely with patients, we assessed the safety of withholding antimalarials in children under five years with a negative malaria test. We did not observe any complication or death due to a missed diagnosis of malaria in our cohort of 1000 children, of which 60% were negative by *m*RDT. We concluded that the strategy of withholding antimalarials in negative children is safe and does not expose the child to an increased risk.

The results of the systematic review coupled with the findings of the safety study led us to question the appropriateness of the previous WHO recommendation of treating all fevers with antimalarials in children less than five years living in highly endemic areas. WHO has now changed its policy, confirming that the IMALDIA findings were very relevant to the changed situation of many African countries, including Tanzania.

The core of this thesis, and the main objective of the IMALDIA project, was to investigate the feasibility and value of implementing *m*RDT in the management of fever episodes in an urban malaria setting. Using 2 different designs and 2 independent data sources, we found a three quarter reduction in antimalarial consumption following RDT implementation. This massive reduction was due to the higher accuracy of routine *m*RDT compared to routine microscopy (that led to a dramatic reduction in the number of positive patients) and to the confidence of health workers in *m*RDT results (the proportion of negative patients treated with antimalarials dropped from 53% to 7%). The impact was maintained up to the end of the observation period (18 months). Not surprisingly, *m*RDT implementation increased the prescription of antibiotics by 50% and unfortunately did not have a major impact on the quality of the medical consultation.

We took the opportunity of our near-to-program implementation of *m*RDT to perform a cost-saving analysis in a real situation and in a setting representative of many moderate endemic places in Africa. The conclusion was that costs can be saved on drugs, from both the provider and from the client's perspective. For this reason, the overall expenditure for the patient was lower in health facilities using *m*RDT (by 0.31 USD per patient). However, the overall expenditure for the health

system was higher (by 1.31 USD per patient) when using *m*RDT instead of routine microscopy, mainly because of the relatively high price of the device.

The aim of the last study was to explore the other causes of fever (beside malaria), in order to generate evidence for a revision of the existing clinical decision-charts for the management of patients, in particular the Integrated Management of Childhood Illness (IMCI). Half of the fever episodes in children were due to acute respiratory infections (ARI), of which 2/3 were probably of viral origin. Only 5% of all ARI were documented pneumonia. Gastroenteritis contributed to 9% of all fevers, of which at least 1/3 were due to a virus. In 1/5 of the children, no aetiology of high probability could be found but most of them recovered without treatment. Most of the children with acute fever thus do not need to receive an antibiotic. Based on these findings, we proposed a limited series of modifications to the IMCI chart and concluded that new point-of-care laboratory tests for the main infectious diseases are urgently needed.

In conclusion, the IMALDIA project provided a deep insight into many aspects of the implementation of *m*RDT in near-to-programme conditions in Tanzania. Our findings show that the introduction of *m*RDT is safe, feasible and useful for the routine management of fever cases in all age groups and at all levels of the health system. Implementation at large scale will require flexibility on the part of the health care provider in order to be able to change his/her behaviour and a strong commitment of all persons involved. As malaria diagnosis is only one aspect of the management of patients presenting with fever, this will not solve all obstacles for making a proper differential diagnosis and prescribing the appropriate treatment for fever episodes. To really improve the quality of care it will be essential to develop new improved guidelines for clinicians. These decision charts should be based on the new available evidence and could include novel point-of-care tests for the key diseases, once these become available.

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Muhtasari

Katika Tanzania, kama zilivyo sehemu nyingi kusini mwa jangwa la sahara, malaria ni ugonjwa unaoripotiwa zaidi kwa mahudhurio kwenye vituo vya kutoa huduma za afya. Tume ya takwimu ya Taifa, inakadiria kuwa jumla ya wagonjwa milioni kumi na sita na vifo laki moja (wengi wao wakiwa ni watoto) vinatokana na ugonjwa wa malaria. Katila jiji la Dar es Salaam,inaripotiwa takribani watu milioni tatu huorodheshwa kuhudhuria matibabu na theluthi moja kati yao hutokana na homa na hivyo kutibiwa kama malaria isiyothibitishwa. Takwimu za hivi karibuni zinaonyesha kuwa kiwango cha maambukizi ya malaria kimepungua zaidi maeneo ya mijini kuliko maeneo tambarare ya vijijini. Hali hii inaonekana zaidi katika jiji la Dar es salaam ambako idadi ndogo sana ya matukio ya homa kwa watoto na watu wazima inathibitika kuwa ni kutokana na uambukizo wa vimelea wa ugonjwa wa malaria.

Kwa kiasi kikubwa muonekano wa dalili za ugonjwa wa malaria sio mahususi. Hakuna viashiria wala dalili zilizokwisha gunduliwa zinazoweza kuthibitisha au kukanusha kuwa mtu ana ugonjwa wa malaria. Kwa sababu hii na kutokana na uhaba wa vipimo vya kugundua ugonjwa wa malaria, shirika la afya duniani (WHO) limeridhia kutoa dawa za malaria kwa wagonjwa wote wenye homa. Matibabu ya jumla kama haya kwanza, husababisha matumizi makubwa ya dawa za kutibu ugonjwa wa malaria (katika jiji la Dar es salaam, takribani ailimia 95 ya matibabu ya malaria siyo ya lazima), na pili, husababisha uwezekano mkubwa wa kushindwa kugundua magonjwa mengine yanayosababisha homa yanyoweza kusababisha vifo.

Ili kutangaza ujumbe huu, tulianzisha mradi wa kuboresha ubainishaji wa ugonjwa wa malaria unaoitwa IMALDIA, unaolenga kuboresha matibabu na huduma kwa wagonjwa wenye homa katika vituo vya kutolea huduma za afya jijini Dar es salaam kwa kuanzisha matumizi ya vipimo vya haraka vya kubainisha malaria (*m*RDT)

Mradi ulikua na sehemu kuu tatu.

(1) Kutathmini kama kuna usalama kwa kutokutoa dawa za malaria kwa mtoto mwenye homa aliyethibitishwa kua hana vimelea vya malaria (*m*RDT hasi).

(2) Kuanzisha utaratibu wa kubainisha ugonjwa wa malaria kwa njia ya maabara kwa matibabu ya kila siku ya homa kwa kutumia kipmo cha haraka cha malaria (*m*RDT). Utafiti huu ulilenga kutathmini ufanisi na uwezekano wa kutumia vipimo hivi vya haraka kwa matibabu ya homa ya kilasiku.

(3) Kutambua vyanzo mbalimbali vya homa kwa watoto, na kuawafanyia uchunguzi wa kina wa kitabibu watoto wapatao elfu moja na kuwafanyia vipimo mbalimbali vya maabara ili kuweza kubaini vyanzo anuai vya homa kwa watoto wadogo mjini na vijijini.

Lengo kuu la mradi huu wa IMALDIA, ni kuboresha utaratibu wa kubainisha na kutibu wagonjwa wenye homa katika vituo vya huduma za afya mkoa wa Dar es salaam na kuchangia kuboresha sekta ya afya na kuiunga mkono Tanzania katika juhudi zake za kupunguza vifo vya watoto.

Hatua ya kwanza tulitathmini iwapo ufanisi wa kipimo ulizingatiwa na wafanyakazi wa afya wakati wa kuwapima wagonjwa. Kwaajili hii, mfumo wa kudhibiti ubora wa kipimo kuanzia ngazi ya juu hadi vituoni ulianzishwa. Hakuna mapungufu makubwa yaliyobainika, na ianaonesha kuwa wafanyakazi wa afya walitumia vipmo kwa ufanisi.

Hatua ya pili ilikua kukadiria uwezekano wa majaribio ya malaria kwa walengwa wa kipimo cha *m*RDT (wagonjwa wenye homa wa rika zote wanaohudhuria vituo vya huduma za afya vya ngazi zote). Tulipitia tafiti mbalimbali, hatua kwa hatua ili kupata uwiano wa wagonjwa wenye vimelea vya malaria aina ya P.falciparum (PFPf) kusini mwa jangwa la Sahara. Tulikuta kua wastani wa PFPf ni asilimia 35 nao ulikua umepungua kwa nusu ukilinganisha na kipindi kilichopita na baada ya mwaka 2000 (aslimia 44 dhidi ya 22). Kiwango hiki kidogo cha uwezekano wa majaribio, ni sababunyingine ya kuanzisha matumizi ya kipimo cha *m*RDT barani Africa kwa sasa. Kutokana na kiwango kidogo sana cha PFPf (chini ya asilimia kumi), Dar es salaam, matumizi ya kipimo hiki yalihitajika kwa haraka. Pamoja na kua hadubini zilikuwepo katika vituo vyote vya jiji la Dar es salaam, ufanisi wake ulikua ni wa kiwango cha chini sana chenye kipima hisi (sensitivity) asilimia 71, na specificity 47%.

Kwa maombi ya washika dau Tanzania hususan waganga katika vituo mbali mbali vya huduma za afya, tulitafiti kuona kama ni salama kutowapa dawa za malaria watoto wenye umri chini ya miaka mitano ambao wana kipimo hasi cha malaria. Katika utafiti huo, hatukuona madhara yoyote wala vifo kutokana na kukosea bainisho la malaria katika utafiti huu wa watoto elfu moja ambao kati yao asilimia 60 walikua na *m*RDT hasi. Tulihitimisha kua ni salama kutokutoa dawa za malaria kwa mtoto mwenye majibu hasi ya kipimo cha malaria. Matokeo ya tafiti zilizopita yalilandana na matokeo ya tafiti hii tuliyofanya, jambo ambalo lili sababisha tuhoji usahihi wa muongozo wa shirika la afya duniani (WHO) unaoamuru kuwapatia dawa za malaria watoto wote wenye umri chini ya miaka mitano wenye homa katika maeneo yenye malaria kwa wingi. Kufuatia hoja zetu, shirika la afya duniani (WHO) limeridhia kubadilisha sera yake, na hii ina maana matokeo ya utafiti wa IMALDIA yalipewa kipaumbele kutumika katika hali ya malaria ya nchi za kiafrika ikiwemo Tanzania.

Kiini cha tasnifu (thesis) hii na lengo kuu la mradi wa IMALDIA, lilikua ni kuchunguza uwezekano na thamani ya kuanzisha matumizi ya kipimo cha haraka cha malaria kwa matibabu ya homa kwenye miji yenye malaria. Kwa kutumia mifumo miwili tofauti na vyanzo viwili vya taarifa vilionyesha kua matumizi ya dawa za malaria yalipungua kwa kiasi cha robo tatu ya kiwango cha awali. Hii ilitokana na usahihi wa kipimo cha haraka cha malaria (*m*RDT) dhidi ya hadubini (idadi ya wagonjwa wenye majibu chanya ya malaria ilipungua kwa kiasi kikubwa) pia iliwajengea wafanyakazi wa afya kujiamini na hivyo kiwango cha wasio na malaria wanaopewa dawa za malaria kilishuka toka asilimia 53 hadi asilimia 7. Mafanikio haya yalizingatiwa hadi mwisho wa kipindi cha utafiti cha miezi 18. Kwa bahati mbaya matumizi ya *m*RDT, yamesababisha kuongezeka kwa matumizi ya vijiua sumu (antibiotics) kwa asilimia 50 na haikubadilisha ubora wa huduma inayotolewa na wahudumu wa afya.

Tulitumia nafasi ya kuwa karibu na mradi (near-to-program implementation) kuainisha gharama itkayopungua (cost-saving analysis) katika mazingira halisi yanayowakilisha maeneo yenye

maambukizi ya wastani ya malaria katika bara la Afrika. Hitimisho lilikua kwamba gharma inaweza kupungua kwenye matumizi ya dawa kwa mtazamo wa pande zote mbili, yaani mtoa huduma na mgonjwa pia. Gharama kwa mgonjwa zilikua ndogo pia (kwa TsH 383 kwa mgonjwa). Hata hivyo, gharama za mfumo wa huduma za afya, zilikua kubwa (kwa TsH 1'607 kwa mgonjwa) mtawalia iwapo kipimo cha haraka cha malaria kitatumiwa badala ya hadubini kutokana na gharama kubwa ya kipimo cha *m*RDT.

Utafiti wetu wa mwisho ulidhamiria kuchunguza sababu nyingine zinazosababisha homa kwa watoto (mbali na malaria) ili kutoa ushahidi wa kupitia upya majedwali ya matibabu ya wagonjwa hususan mpango wa jumla wa kutibu magonjwa ya watoto (IMCI). Nusu ya matukio ya homa kwa watoto yanasababishwa na maambukizi kwenye njia ya hewa (ARI), na theluthi mbili (2/3) kati ya hao huenda ni kutokana na virusi. Ni asilimia tano (5%) tu kati ya hao (ARI) ilirekodiwa kuwa ni kutokana na kichomi (pneumonia). Asilimia tisa (9%) katika matukio yote ya homa ilitokana na kuharisha na kutapika (gastroenteritis) na kati ya hao, theluthi moja ilisababishwa na virusi mbalimbali. Chanzo cha homa kwa sehemu moja ya tano (1/5) ya watoto wote hakikufahamika, ingawa wengi kati ya hao walipona bila matibabu. Kwa hiyo, watoto walio wengi wenye homa hawahitaji kiua vijasumu (antibiotics). Kutokana na matokeo haya, tulipendekeza marekebisho mabalimbali na kuhitimisha kua vipimo vipya vya ki maabara vya kupima maambukizi ya magonjwa makuu, vinahitajika haraka katika vituo vya kutoa huduma za afya.

Kuhitimisha, mradi wa IMALDIA umetoa ufahamu wa kina kwa sura mbalimbali za kutekeleza matumizi ya kipimo cha haraka cha malaria RDT. Matokeo yetu yanaonesha kuwa ni muhimu, ni salama na inawezekana kutumia RDT kwa matibabu ya homa kwa wagonjwa wa rika zote katika ngazi mbali mbali za mfumo wa utoaji wa huduma za afya. Kupanua wigo wa matumizi ya kipimo hiki unahitaji kuwa makini ili kuweza kubadilisha tabia na hamasa kwa mtoa huduma ya afya na wote wanaohusika. Kuboresha bainisho la malaria (malaria diagnosis) na matumizi ya kipimo, haitatatua mapungufu yote yaliyo katika utaratibu wa kuainisha magonjwa mbalimbali (diferential diagnosis) na kutoa tiba sahihi, kwa kuwa ni sehemu tu ya mfumo mzima wa matibabu kwa watu wenye homa. Ni muhimu kuandaa miongozo mipya ya matibabu au kuboresha majedwali ya utaratibu wa matibabu ili kuweza kuboresha kiwango cha huduma inayotolewa kwa wagonjwa. Majedwali ya matibabu yahusishe kikamilifu ushahidi uliopo (evidence based) na ikiwezekana kuhusisha vipimo vipya vya magonjwa makuu mara vinapopatikana au kugunduliwa.

List of abbreviations

ACT	Artemisinin *Combination* Therapy
ALu	Artemether/Lumefantrine (trade name: Coartem®)
ARI	Acute Respiratory Infection
CMOH	City Medical Office of Health
DMO	District Medical Office
GFATM	Global Fund to fight AIDs TB and Malaria
HF	Health Facility
HRP2	Histidine-Rich Protein II
IHI	Ifakara Health Institute
IMCI	Integrated Management of Childhood Illness
IPTp	Intermittent Preventive Treatment for pregnant women
IPTi	Intermittent Preventive Treatment for infants
ITN	Insecticide Treated Net
LR	Likelihood ratio
LR(+)	Likelihood ratio for a positive test
LR(-)	Likelihood ratio for a negative test
*m*RDT	Malaria Rapid Diagnostic Test
NMCP	National Malaria Control Program
pLDH	*Plasmodium* Lactate Dehydrogenase
PMI	President Malaria Initiative
SP	Sulfadoxine/Pyrimetamine
Swiss TPH	Swiss Tropical and Public Health Institute
*ty*RDT	Typhoid Rapid Diagnostic Test
URTI	Upper Respiratory Tract Infection
WHO	World Health Organization

1. Background

1.1 Clinical diagnosis of malaria

In Tanzania, as in most settings in sub-Saharan Africa, malaria is the first cause of attendance in health facilities. Unfortunately, the clinical presentation of malaria is one of the least specific of all the major diseases, with a large clinical overlap with other serious conditions, especially with acute respiratory infections (ARI) (O'Dempsey *et al*. 1993; English *et al*. 1996). For example, respiratory distress is a common occurrence in severe malaria (K Marsh *et al*. 1995). In the absence of any laboratory tests (the rule in most health facilities in Sub-Saharan Africa) the dual treatment for malaria and pneumonia of febrile children is the standard of care in the frame of the Integrated Management of Childhood Illness (IMCI) advocated by WHO and UNICEF. In a study in Uganda, over 30% of children presenting with fever at basic health facilities received this dual treatment (Källander *et al*. 2004).

There have been numerous attempts to develop clinical algorithms to improve the discrimination between malaria and ARI but none has proven to be sufficiently reliable to justify withholding one or the other treatment on this basis (Chandramohan *et al*. 2002). With existing algorithms, the risk of missing a malaria case on clinical presentation alone is increasing with increasing transmission levels, while the risk of over-diagnosis and hence drug wastage is increasing as the transmission level decreases. Settings with highly seasonal malaria transmission such as cities in the Sahel belt are moving each year from one of these extremes to the other (Olivar *et al*. 1991).

1.2 Malaria over/misdiagnosis

Magnitude of over-diagnosis of malaria in Tanzania

The strategy of presumptive treatment for malaria was primarily designed for the population (children under 5 years) and area (rural Africa) bearing the highest burden of the disease. However, there has been a clear tendency to apply this strategy to children older than 5 years and even adults, and also in settings with very low transmission of malaria. This strategy was initially introduced because of the lack of diagnostic facilities in most settings. Unfortunately, it has been clearly shown that even when microscopy is available, results are systematically disregarded by the clinician, for a number of reasons (Zurovac *et al.* 2006).

The end result is a massive over-diagnosis, resulting in a massive over-treatment of malaria. In Tanzania, five studies are available which confirm that the over-diagnosis is extremely high in urban settings and low-transmission areas: 95% in Dar es Salaam (Wang *et al*. 2006a), 96% in the highlands (Reyburn *et al*. 2006); it is still important in rural areas, even during the rainy season: 41% in Rufiji district (Rooth & A Björkman 1992); 43% and 76% in less than five years and older children/adults respectively in Kilombero district (Font *et al*. 2001); 62% in Kibaha district (Nsimba *et al*. 2002). In all these studies, more than 95% of all febrile patients received an antimalarial

treatment, which means that the wastage of drugs was almost of the same magnitude as the over-diagnosis.

Consequences of over-diagnosis of malaria

This massive over-diagnosis was bearable as long as cheap and safe drugs such as chloroquine or sulfadoxine/pyrimethamine (SP) were efficient against the parasite. A new paradigm is emerging now with the introduction of artemisinin-combination therapies (ACT) as first line treatment in more than 50 African countries, including Tanzania. In this new context, the fact that over-diagnosis is at least 40% and much higher in urban and low-transmission settings implies that implementing reliable diagnosis of malaria has become indispensable. It is indeed impossible to justify engaging considerable financial resources for the large-scale introduction of a costly drug knowing that more than half of the tablets will be wasted.

This massive over-diagnosis has a second deleterious consequence: misdiagnosis of febrile patients, in whom other causes of fever are not looked for. In two Tanzanian studies dealing with severe malaria cases, a higher mortality rate was found in the group of patients without malaria (having possibly bacterial infections left untreated) than in the group having documented malaria (Makani *et al*. 2003; Reyburn *et al*. 2004).

1.3 Malaria diagnosis using Rapid Diagnostic Tests (*m*RDT)

Quality of routine microscopy in Tanzania

In Tanzania, like in the majority of Sub-Saharan countries, the quality of malaria diagnosis made by microscopy, when available, has been generally of poor quality. This is due to poor training and skill of personnel, inadequacy of equipment and reagents, absence of supervision and the fact that it is a time-consuming technique in a high patient load environment. A recent study performed in the Tanga region, aimed at assessing the quality of malaria diagnosis in 35 laboratories, showed that this worrying situation has not improved at all (Magesa *et al*. 2005). In the highlands, the sensitivity and specificity of hospital routine microscopy were only 50% and 96% respectively (Reyburn *et al*. 2006). It is thus clear that, even if the human resources were available, implementing microscopic diagnosis in health facilities all over Tanzania is unlikely to be a practical solution.

WHO recommendation regarding malaria diagnosis

In view of the increasing experience with *m*RDT, WHO convened a Technical Consultation in 2004 to determine whether parasitological diagnosis could provide benefits and cost-savings in areas of intense malaria transmission, and to evaluate the operational feasibility of large-scale deployment of the currently available tests (WHO 2004). The recommendations were intended to provide guidance on the appropriate use of parasitological diagnosis of malaria in areas of stable transmission, with specific focus on *m*RDT use in countries implementing ACTs.

The meeting concluded the following: “A prompt and accurate diagnosis of malaria is the key to effective disease management. It guides the management of febrile patients and reduces the unnecessary use of anti-malarial drugs. High sensitivity of malaria diagnosis is important in all settings, and it is essential for the correct management of the most vulnerable population groups in which malaria infection produces an acute illness, which can rapidly progress to death. Microscopy and rapid diagnostic tests (*m*RDT) are the currently recommended methods for parasitological confirmation of malaria. In all settings laboratory services providing malaria microscopy should be strengthened. Where microscopy is not possible, *m*RDT should be introduced. Well conducted field studies and large-scale operational experiences have shown that *m*RDT can be effectively used by trained health workers at the periphery, including community health workers. To ensure reliable results, appropriate systems for quality assurance of microscopy and *m*RDTs should be implemented and maintained.”

Performance of mRDT

For more than 20 years in travellers in industrialized countries and almost 10 years in semi-immune population in South Africa, *m*RDT have been used with great success (Figure 1). The performance of *m*RDT devices has been extensively studied. A meta-analysis of studies including 7’396 tests performed in non-immune travellers (having generally much lower parasitemia than semi-immune patients) showed that their performance to detect *Plasmodium falciparum* was excellent and very consistent: sensitivity ranged from 88 to 99% and specificity from 95 to 100% (Marx *et al*. 2005). In order to be able to exclude malaria in a patient, the key characteristic of performance is the likelihood ratio (LR) for a negative result (reflecting mainly sensitivity). In this meta-analysis, it was 0.05 for the last generation of HRP2 detecting *P. falciparum* tests, which is excellent (close to zero).

Figure 1: Content of a kit for *m*RDT

In semi-immune patients, where parasites appear generally before symptoms, giving thus higher parasite density at the time of diagnosis, the sensitivity of *m*RDT is even better. A meta-analysis including 48 studies from endemic areas has clearly shown that *m*RDT are largely good enough for clinical management of patients. A comparison between four different malaria diagnosis technologies using a statistical method that avoids defining a gold standard demonstrated that *m*RDT are at least as sensitive as microscopy (Ochola *et al*. 2006).

The overall sensitivity of *m*RDT when used in the field has progressively improved along the new generations of tests (Marx *et al*. 2005) and is now often better than that of expert microscopy. Indeed between 60% and 92% of the patients with a positive *m*RDT but a negative microscopy were positive by PCR (Dal-Bianco *et al*. 2007; Bell *et al*. 2005; Stauffer *et al*. 2009). As all malaria tests, *m*RDT cannot detect parasite densities below a certain threshold (considered to be 50-100 parasites/µl for *m*RDT). But, for clinical management of patients living in endemic areas, sensitivity is less a problem as it is well known that the probability that a fever is due to the current parasites ('true malaria') is strongly dependant on their density. A very low parasitemia that would be undetected by an *m*RDT is very unlikely to be the cause of the fever. A good case selection for testing (clear history of fever or temperature ≥ 38°C) is the way forward since the likelihood that a certain parasite density would be reached is much higher.

The specificity of *m*RDT used in endemic areas is likely to be lower than in non-endemic areas, because of two problems:

1) *m*RDT detect persisting antigens for up to 4 weeks after an infection, even if it has been cured. This phenomenon will thus tend to increase the prevalence of parasitemia found in community surveys (Bell *et al*. 2005). The practical implication for patients is that *m*RDT cannot be used for follow-up of a treated episode of malaria (Mayxay *et al*. 2001; Iqbal *et al*. 2004). However, for the differential diagnosis of fever on day 0 the problem due to persisting antigens is not an issue. As mentioned before, most of the patients that are *m*RDT positive but microscopy negative [because the density is just under the microscopy threshold of detection but antigens are circulating (Bell *et al*. 2005)] are in fact infected and thus in need for treatment.

2) *m*RDT, at least those based on the detection of pLDH, detect also gametocytemia (Mueller *et al*. 2007), although, pure gametocytemia in the general population is rather rare: it was only 1.3% in a cross-sectional survey in the Kilombero/Ulanga Districts in Tanzania (a high endemicity area) in 2008 (Mulokosi, *unpublished data*). The real prevalence of gametocytemia based on PCR detection is much higher (Shekalaghe *et al*. 2007), but most of these submicroscopic densities would probably not be detected by *m*RDT. Anyway, the small treatment wastage that a test positive due to gametocytemia would imply is nothing compared to the wastage in the present situation.

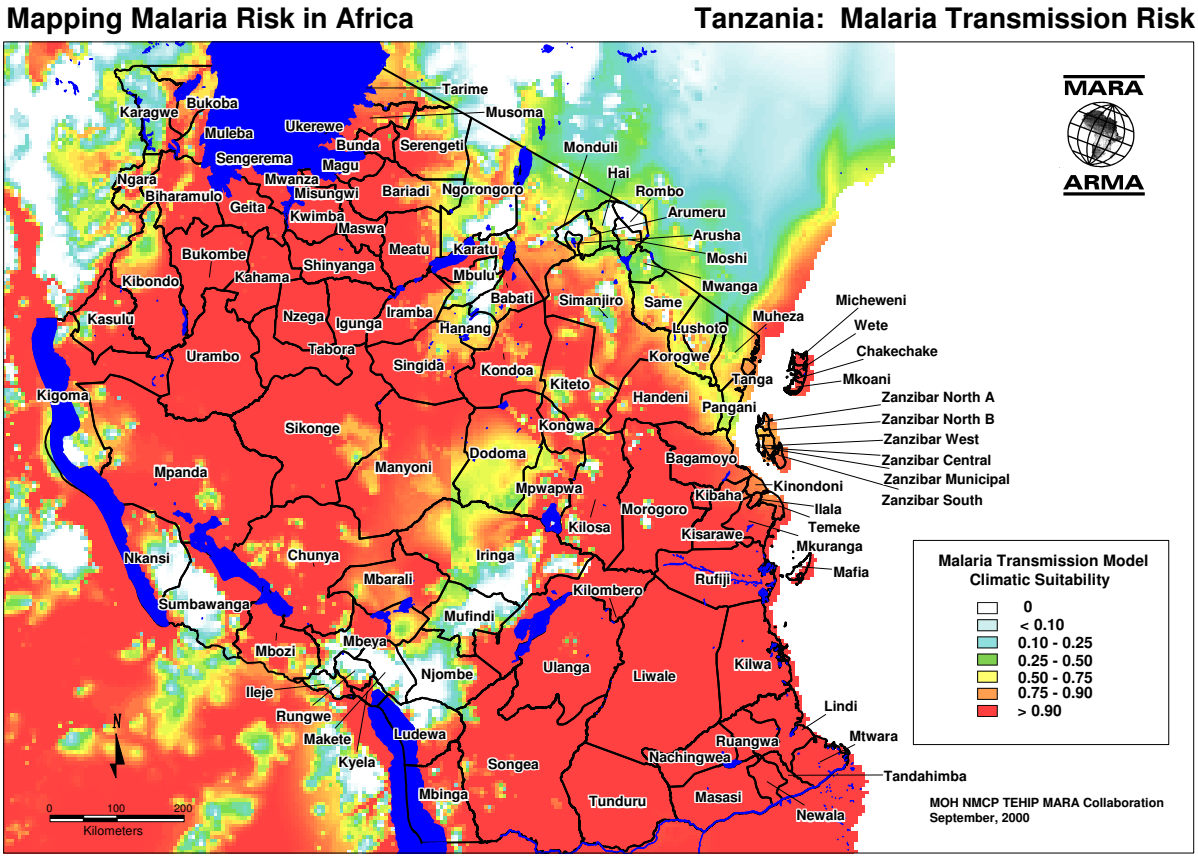
An important issue is that the quality of the tests is variable from one brand to the other and this has recently been assessed in detail by a multilateral initiative (WHO/FIND/CDC/TDR 2008). For the

brands most widely used in the world, more than 95% of the lots tested between 2007 and 2009 by the WHO reference laboratories fully passed the quality control procedure (WHO Technical Consultation on parasitological confirmation of malaria diagnosis, Geneva, 6-8 Oct 2009).

1.4 Malaria in Tanzania

In Tanzania malaria is a major public health problem. Malaria is endemic in almost all parts of the country (Figure 2) and is thus a treat for an estimated 32 million people (94% of the population). It is estimated that about 16 million cases occur every year, resulting in about 100'000 deaths, of which 39'000 are among children less than five years (National Bureau of Statistics, Tanzania and Macro International Inc. 2007). It is the leading cause of outpatient attendance for children less than five years (38%) and for all other patients (32%) (Ministry of Health and Social Welfare 2002). About 65% of these episodes are treated in public or faith-based health facilities and 35% are treated outside the public health sector in private outlets (National Malaria Control Program 2005). These data are based on reported malaria that is essentially not laboratory documented, and thus represent the burden of fever episodes rather than that of malaria. Indeed, in Tanzania, about 83% of public health facilities do not provide laboratory services. Therefore, only 12-20% of the malaria cases are confirmed parasitologically (National Malaria Control Program 2005).

Figure 2: Distribution of malaria endemicity in Tanzania (MARA/ARMA 2002, www.mara.org.za)

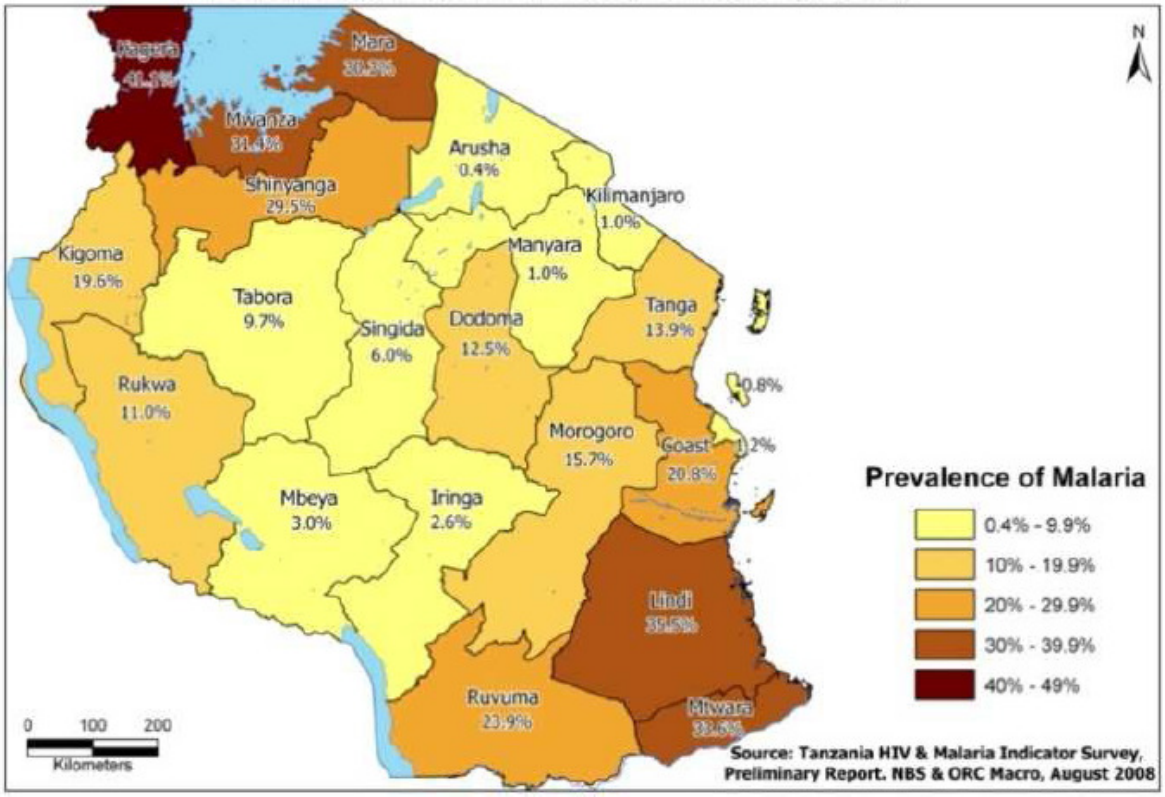


An estimated 65 million US$ is spent on the prevention and treatment of malaria in Tanzania each year, which amounts to 39% of all health expenditures and just under 1.1% of the Gross Domestic Product (Jowett & Miller 2005). More recently, a Global Fund for fight AIDS TB and Malaria (GFATM) proposal financial analysis indicated amounts varying from 43-154 millions per year, depending on the timing of the different interventions implemented (http://www.theglobalfund.org/grantdocuments/8TNZM_1766_0_full.pdf).

Malaria epidemiology in Tanzania

In 2007/8, 18% of children less than five years were positive for malaria (TACAIDS, ZAC, NBS, OCGS & Macro International 2008). Prevalence in rural areas was more than double that in urban areas, and there were huge variations across regions (Figure 3).

Figure 3: Malaria prevalence in Children 6-59 months. Source THMIS 2007/8



Data from previous surveys and studies indicated that malaria prevalence in Tanzania has roughly halved over the past decade (Smithson 2009). There has been a decline of similar timing and magnitude in malaria transmission, severe anemia, fever incidence, malaria inpatient admissions and the proportion of fever cases positive for malaria. All-cause under-five mortality has declined by nearly 40% since 1999. The evidence suggests that malaria-related deaths have declined by a similar extent.

Malaria control strategy in Tanzania

A range of complementary malaria control measures have been implemented, commencing in the late 1990s. After two decades of growing drug resistance, the first line therapy for clinical malaria was changed – first from chloroquine to sulfadoxine/pyrimethamine (SP) in 2002, and later to artemether/lumefantrine (ALu) in 2007. The use of SP for prevention of malaria in pregnancy was introduced in 2001/2, and continues to-date. Insecticide Treated Net (ITN) social marketing at national scale began in 2000 and subsidized ITNs have been provided to pregnant women and infants through the "Hati punguzo" voucher scheme since 2004 (Magesa *et al*. 2005). Free distribution of long-lasting ITNs for under-fives took place in the entire country in 2009 and on the islands of Zanzibar in 2006. Zanzibar also benefited from indoor residual spraying, as did certain areas on the mainland (Muleba Municipality, Kagera Region). Meanwhile, additional interventions at pilot stage were deployed in limited localities, including Intermittent Preventive Treatment for infants (IPTi; Mtwara and Lindi) and larviciding (Dar es Salaam). The ownership and use of mosquito nets has grown steadily, from less than 30% of households in 1999 to over 60% in 2009. Urban net ownership has consistently outpaced net ownership in rural. ITN use by children less than 5 years and pregnant women has risen from nearly zero in 1999 to more than 35% in 2008. The proportion of pregnant women receiving preventive treatment (IPTp, 2+ doses) rose from 22% in 2004/5 to 30% in 2007/8.

The reduction in malaria transmission, prevalence and morbidity corresponds closely to the increase in use of nets and ITNs. The protection afforded by nets extends beyond individual users to benefit the community as a whole. The fact that multiple malaria interventions have been implemented at the same time makes it difficult to assign causation to any one particular control measure.

1.5 Malaria epidemiology in Dar es Salaam

Currently over a quarter of all Africans live in urban centres and this proportion will increase to half by 2025 (Keiser *et al.* 2004). There are an estimated 25-103 million cases of urban malaria each year. If truly the large majority of these cases are not actually malaria but have another cause, this represents a major public health challenge. Urban malaria has been the subject of a few studies in recent years, with a focus on describing existing malaria control practices and the over-diagnosis of malaria (Robert *et al.* 2003; Caldas de Castro *et al*. 2004; Wang *et al*. 2005a; Donnelly *et al*. 2005; Othnigué *et al*. 2006).

Dar es Salaam has a hot and humid tropical climate with two rainy seasons, a main one during the months of March-May, and a short one occurring in November-December. Originally it was an area with endemic and perennial malaria. As a result of urbanization and malaria control activities it is now an area of low endemicity: the Entomological Inoculation Rate (EIR) was 1.3 in 2009 (Geissbühler *et al*. 2009). A study by Wang *et al.* could demonstrate that the level of endemicity in Dar es Salaam was actually lower than expected (Wang *et al.* 2006a). Most importantly, this work demonstrated that

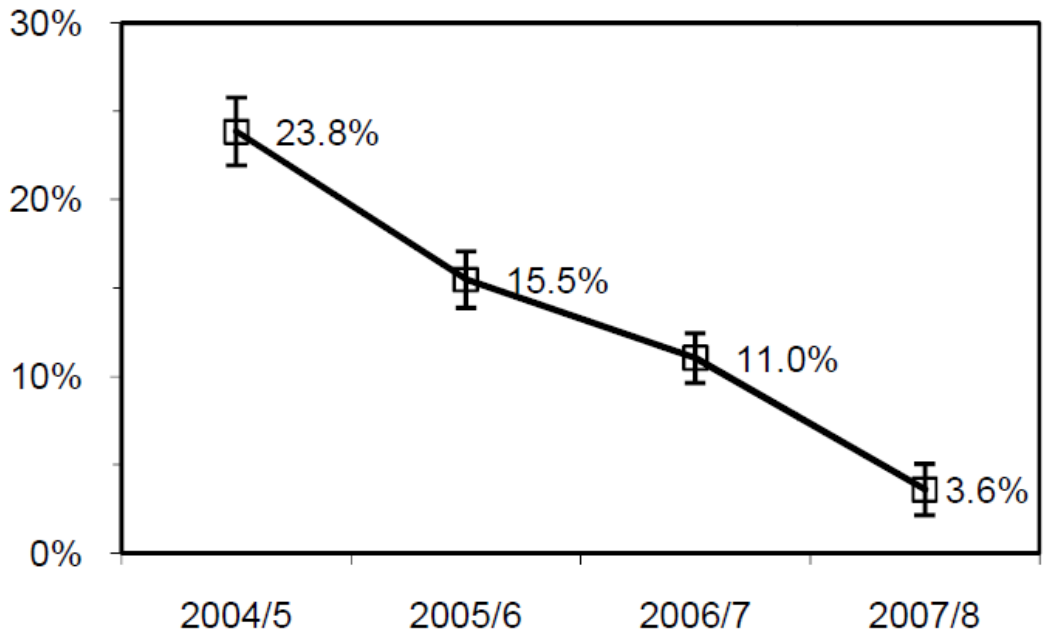
the malaria-attributable fraction among fevers ranged from 2 to 7%, indicating that between 93% and 98% of all treatments were unnecessary (Table 1).

Table 1: Proportion of fevers due to malaria in 4 African cities, by age groups (Wang *et al.* 2005a)

	0-1 year	1-5 years	6-15 years	>15 years
Abidjan (Yopougon)	23%	43%	44%	26%
Cotonou	0	7%	0	1%
Dar es Salaam	2%	7%	7%	4%
Ouagadougou	12%	26%	37%	18%

In Dar es Salaam, the reduction in (all-age) malaria prevalence in the community has indeed been dramatic – from 24% in 2004 to just 4% in 2008 (Figure 4). It is quite variable from one sector of the city to the other, with prevalence in school-children ranging from 0.8% in the centre to 3.7% in the rural peripheral areas of the town (Wang *et al.* 2006a).

Figure 4: All-age malaria prevalence in Dar es Salaam, 2004-8 (Smithson 2009)**.**



From 1990 until 2002 the Swiss Tropical and Public Health Institute (Swiss TPH - ex-Swiss Tropical Institute) was the executive agency of the Dar es Salaam Urban Health Project (DUHP), which

rehabilitated existing infrastructure and improved management practices (Wyss *et al*. 2000). As a result, there is a longstanding and very good relationship between the Swiss Swiss TPH and the City Medical Office of Health (CMOH). Malaria control has a long history in Dar es Salaam (Caldas de Castro *et al*. 2004). The Dar es Salaam CMOH together with the Ifakara Health Institute (IHI), the Swiss TPH and other institutions have implemented an urban malaria control program in 2002. While diagnosis and treatment remain the most important malaria control strategy, the use of preventive measures such as insecticide-treated nets is also high, with over 80% of the population of Dar es Salaam using regularly a mosquito net. In addition, larval control has been introduced in some areas in Dar es Salaam since March 2006 (Chaki *et al*. 2009).

1.6 Management of fever episodes in Africa

As mentioned above, because of the lack of diagnostic tools in Africa, patients presenting to health facilities with fever have usually been denied the usual aetiology finding process inherent to any medical consultation (Zurovac *et al*. 2006b). In Tanzania, as in many other countries, the official management schedule for children less than five years is the Integrated Management of Childhood Illness (IMCI) (Ministry of Health and Social Welfare, Tanzania *et al*. 2004; Armstrong Schellenberg *et al*. 2004), in which no laboratory test is proposed. To improve this situation, the first step is the introduction of malaria diagnosis in the routine management of fever cases. This, however, opens a new problem that is a major challenge to clinicians: what should be done when the malaria test is negative?

Strangely, the aetiology of non-malaria fevers has never been studied in a systematic way in sub-Saharan Africa. As a result, there is no way to guide clinicians with an evidence-based strategy. The IMCI decision-chart, although it does at present not include any laboratory test, is an excellent tool developed on the basis of the scarce evidence existing in the mid-1990s. Unfortunately, very few studies have seriously addressed this question since and we still have an insufficient evidence base. Disease-specific studies have been carried out in a few settings, for example for arboviruses on the Kenyan Coast (Morrill *et al*. 1991), Dengue in Somalia (Botros *et al*. 1989), Mycoplasms and Rickettsia sp. in Somalia (Nur *et al*. 1999). However, no comprehensive study to assess the respective contribution of each disease has ever been undertaken in resource-poor, high infectious disease burden countries. This hinders any attempt to improve the present IMCI decision chart.

The reason for the scarce data is that investigating systematically all fevers in inpatients and outpatient clinics is a major enterprise that needs rigorous methodology, highly skilled clinicians, and laboratory culture facilities. In addition, sophisticated molecular techniques are necessary to investigate the fevers with aetiologies still unknown after routine laboratory tests and cultures. This lack of knowledge has recently been acknowledged by the international science community and several studies are ongoing in different parts of the world. A similar attempt has already been conducted to improve knowledge on the aetiology of fevers in returning travellers and migrants. This

study has led to the publication of clear guidelines endorsed by the international scientific community (D'Acremont *et al*. 2003) and the construction of a web site (www.fevertravel.ch) aimed at helping primary care physicians to deal with such cases (Ambresin *et al*. 2007).

2. Goals and objectives

Goal

To improve the evidence-based management of fever cases seen in outpatient clinics in malaria endemic countries, through the implementation and assessment of accurate malaria diagnosis, and through an improved understanding of the main causes of fever in children.

Objectives

The IMALDIA project had 3 different but closely related objectives:

1. To evaluate the safety of withholding antimalarials in febrile children with a negative *m*RDT living in a moderate and a highly endemic area
2. To investigate the feasibility and value of implementing *m*RDT in the management of fever episodes in an urban malaria setting
3. To describe systematically the aetiologies of fever in children living in an urban and a rural environment of Tanzania

3. Methodology for the main components of IMALDIA

The general approach was to conduct operational research to assess the impact of *m*RDT implementation on antimalarial consumption in close to real conditions of large-scale deployment

For the safety of *m*RDT in children, we worked in conditions between that of a clinical trial (the intervention being to force clinicians not to give antimalarials in children with a negative test) and operational research (all other conditions were those encountered in routine practice). For the study on aetiologies of fever we moved towards more basic clinical research in fully controlled conditions.

3.1 Study design

3.1.1 Safety of *m*RDT use in children less than five years

We conducted a prospective two-arm longitudinal study in areas of moderate and high endemicity of Tanzania. Children with a history of fever were managed routinely by resident clinicians of two health facilities, except that no antimalarials were prescribed when the *m*RDT was negative. Children were followed up at home on day 7 for health outcomes

Sample size
300 children aged 6 months to 10 years in Dar es Salaam (moderately endemic setting) and 700 children aged 2 months to 5 years in Signal (highly endemic setting)

Primary outcome
Rate of complications (admissions and deaths) in children *m*RDT negative at inclusion, with a positive *m*RDT during the follow-up period (*m*RDT positive children at inclusion were followed up for the same outcomes for indirect comparison).

3.1.2 Feasibility of implementing malaria *m*RDT for the management of fever

Intervention
Introduction of *m*RDT in 9 health facilities in Dar es Salaam. Implementation involved: i) training of health care providers and laboratory staff; ii) regular supply of *m*RDT kits and; iii) regular supervision of their performance. Three comparable health facilities (HF) without *m*RDTs were selected randomly as matched controls.

Method of evaluation
We used two different data collection tools:

1) Routine health statistics from health facilities registers of all types collected for 33 months (period before and period after *m*RDT introduction)

2) Two cross-sectional surveys in all health facilities, one before and one 18 months after *m*RDT introduction, investigating consultation processes (direct observation of clinicians).

With both sources of data, we evaluated the impact of *m*RDT implementation on antimalarial prescription using two different analyses:

1) Comparing data from the period before with the period after *m*RDT implementation in the 9 intervention health facilities (before-and-after analysis)

2) Comparing data from 6 intervention and 3 matched control health facilities 18 months after *m*RDT introduction (cluster-randomized analysis).

For the before-and-after analysis, changes in practice were likely to be large and could reasonably be attributed to the intervention in the frame of a plausibility design (Habicht *et al*. 1999). To improve confidence in our assessment, we added a cluster randomized controlled study. We matched 3 primary care control health facilities with 6 primary care intervention health facilities and undertook a comparative study at baseline and after the intervention. Unfortunately, suitable controls did not exist for the 3 district hospitals, as they were all included in the study.

Main outcome measures

1) Using data of health facilities registers: routine statistics (called MTUHA books), laboratory registers, ledger books and dispensing books of pharmacies

- change or difference in the number of antimalarials issued by the pharmacy
- change or difference in the number of antibiotics issued by the pharmacy
- change or difference in the number of malaria tests (*m*RDT and blood slides) performed per month
- change or difference in the number of malaria diagnoses

2) Based on the observation of clinicians' consultation (using a standard questionnaire)

- change or difference in the proportion of patients receiving antimalarials
- change or difference in the proportion of patients receiving antibiotics
- change or difference in the proportion of patients tested for malaria (by *m*RDT or blood slide)
- change or difference in the proportion of patients tested for other diseases

Study population and sample size (for the consultation's observation)

Patients of any age coming for a first consultation for the present problem, not having a severe illness requiring immediate admission or referral. 100 consultations per health facility for each survey (total: 2400)

3.1.3 Aetiologies of fever in children less than five years

A systematic investigation of the aetiology of fever was carried out in all children presenting at the outpatient department of one of the three municipal hospitals in Dar es Salaam (Amana hospital) and of the district hospital of Kilombero (S^{t} Francis hospital) and fulfilling the inclusion criteria.

Study population and sample size

1000 consecutive children (500 in each site) aged 2 months to 10 years presenting with axillary temperature ≥ 38°C were included.

Procedures

All study procedures were derived from IMCI. A very detailed medical history, as well as a thorough clinical examination was performed on each child.

- The first step was to identify those illnesses that are reliably diagnosed on clinical ground only.
- All patients underwent venepuncture to estimate full and differential blood cell count, measurement of liver and kidney function tests, *m*RDT, Giemsa stained thick film for malaria and borrelia, Rapid Diagnostic Test for typhoid (*ty*RDT) and nasal swab.
- Children with key-symptoms or signs that should lead to specific laboratory investigations (based on a pre-defined algorithm) were then identified.
- A series of pre-defined criteria were used to attribute an aetiology with high (= 'documented diagnosis'), intermediate or low probability.
- All children without a 'documented' diagnosis (on clinical grounds or by the laboratory tests performed on the spot) at that stage, were further investigated by blood, urine or stool culture during the following days. PCR of respiratory viruses were performed for each child. Further molecular techniques and serologies will be done on the children with no clear aetiology.

3.2 Study area and setting

Study area in Dar es Salaam

Dar es Salaam is the economic and political capital city of the United Republic of Tanzania, on the East coast of Africa. The current surface area is 1'393 sq. km and the population was estimated to be about 2'500'000 in 2002. As many other sub-Saharan African cities, Dar es Salaam has grown rapidly over the last decades (growth rate 4.3%).

Dar es Salaam is governed by a political structure consisting of three levels: region, district and division. Table 2 shows the administrative levels in the city.

Table 2: Dar es Salaam political and administrative structure

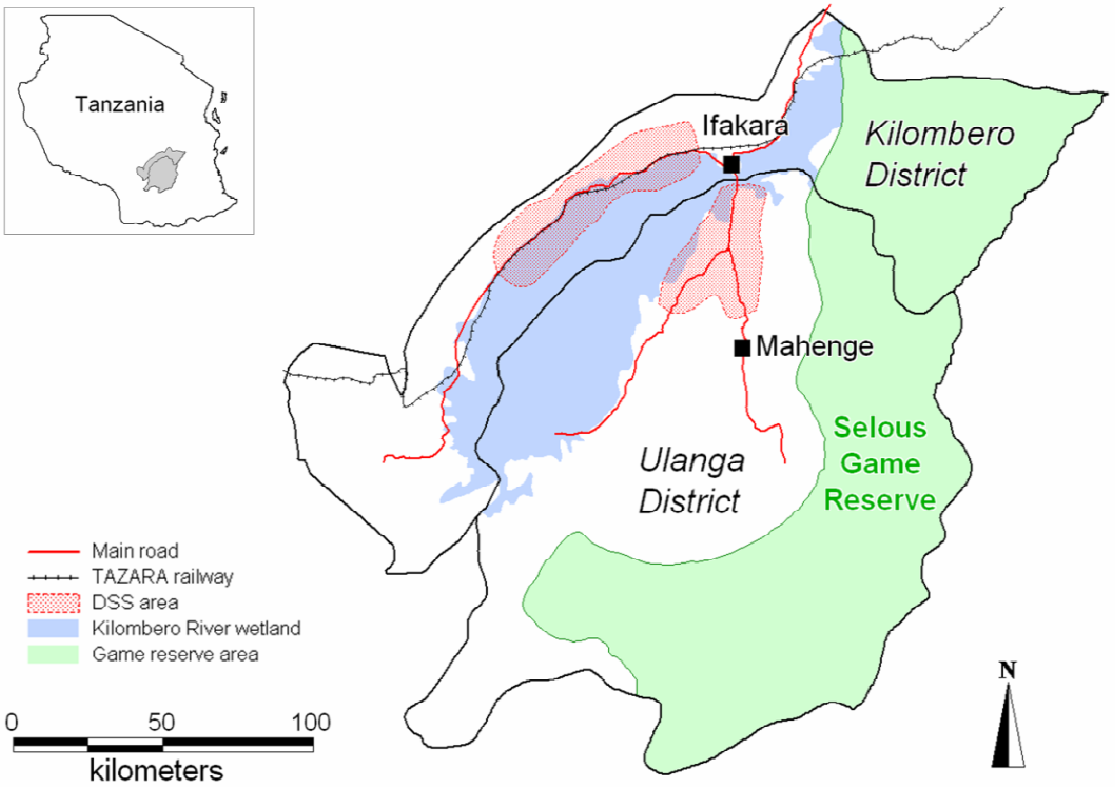
District or municipal area	Divisions	Wards	Subwards *Mtaa*	Population (2002)
Ilala	3	22	65	637'573
Kinondoni	4	27	113	1'088'867
Temeke	3	24	97	771'500
Total	10	73	275	2'497'940

The three municipals (Kinondoni, Temeke and Ilala) are headed by commissioners. Alongside the political structure are the administrative and executive structures. The administrative structure of Dar es Salaam has four levels: city, municipality, ward (*Kata*) and subward (*Mtaa*). The highest level is the Dar es Salaam City Council. Below the City Director are three municipal directors, corresponding to the three political districts. The health sector is organized under the City Medical Office of Health (CMOH). Each of the three urban District Medical Offices (DMO) is responsible for and manages one municipal district hospital, one or two health centres and 13-14 dispensaries. In addition, there are non-government health facilities and a thriving private practitioners sector.

Study area in Kilombero and Ulanga districts

The Kilombero River separates the two districts of Kilombero and Ulanga districts that are both situated in the Morogoro region of the South-East of Tanzania (Figure 5).

Figure 5: Map of Kilombero and Ulanga districts showing Ifakara town



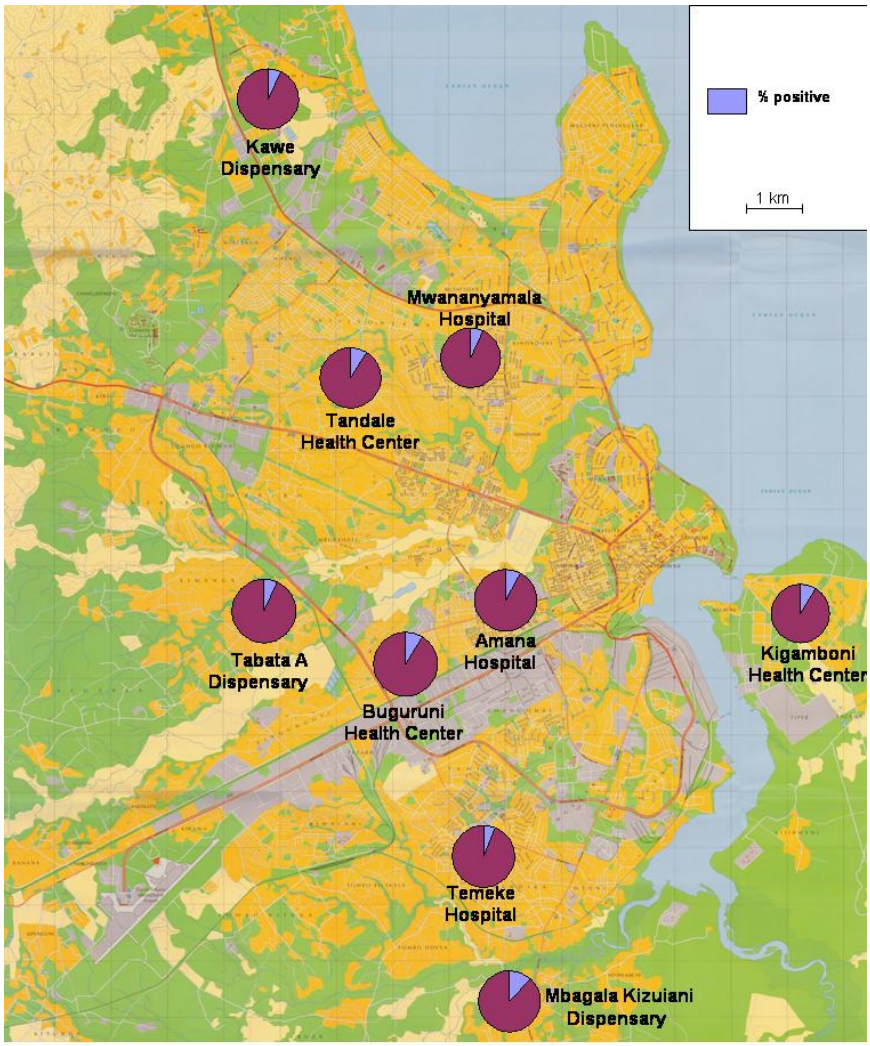
Large parts of the Kilombero Valley are flooded during the rainy season which usually lasts from November to May. In 2002, there were 517'000 people living in the 109 villages of the 2 districts. Ifakara, the administrative capital of Kilombero, is the major settlement in the valley with a population of approximately 46'000.

Malaria transmission in the area is intense and perennial with important differences between the rural and semi-urban settings. Overall transmission has been however declining over the past 10 years. A study conducted between 2001 and 2003 reported an entomological inoculation rate of 349 infective bites per person per year (Killeen *et al*. 2007), but according to recent data it has declined to 81 (Russell *et al*, *unpublished data*). In Ifakara, the transmission rate is about a log order smaller than in the surrounding rural areas (Drakeley *et al*. 2003)

Study setting

The intervention of introducing *m*RDT in routine management of fevers took place in 9 health facilities with outpatient departments in Dar es Salaam (figure 6): the 3 municipal hospitals (Mwananyamala, Amana and Temeke) and 6 primary care health facilities (Kawe and Tandale in Kinondoni municipal, Buguruni and Tabata A in Ilala municipal, Kigamboni and Mbagala kizuiani in Temeke municipal).

Figure 6: Health facilities included in the IMALDIA project.
The pie charts show the malaria positivity rate by *m*RDT (Kahama-Maro, *in preparation*)



The health facilities were selected in collaboration with the DMO staff according to their size and willingness to participate. In addition, three additional primary care health facilities (Sinza in Kinondoni municipal, Vingunguti in Ilala municipal, Mbagala rangi tatu in Temeke municipal) were selected as control health facilities.
The study on safety of using *m*RDT in children less than five years took place in Buguruni health centre in Dar es Salaam and Signal dispensary situated North-East of Ifakara (Ulanga district).
The study on aetiologies of fever took place in the outpatient departments of Amana hospital in Dar es Salaam and in S^{t} Francis hospital in Ifakara (Kilombero/Ulanga districts).

3.3 System of quality assurance for *m*RDT used in IMALDIA

The reliability of *m*RDT needs to be monitored when used by health workers (laboratory technicians as well as clinicians) in the real conditions of managing a patient. For this purpose, a quality assurance system, both at central and peripheral level, was set up for the project.

Three different brands of mRDT were used during the project [Paracheck (Orchid biomedical system, India), ParaHit (Span Diagnostics, India) and ICT malaria test (ICT diagnostics, South Africa)], depending on which one was attributed to us by the National Malaria Control Program of Tanzania.

The quality assurance took place at 3 levels:

- To make sure that the lots we used were of good quality, a specimen of each new consignment of *m*RDT was sent to a WHO reference laboratory (Muntinlupa City, Philippines and Bagamoyo, Tanzania) for lot-testing. All of them passed.
- In the central pharmacy of Amana hospital, where our consignments were stored, as well as in all different storage places of each health facility, we organized every 3 months an check that included: 1) check of the minimum and maximum temperatures recorded in the place; 2) blind-testing of 4 devices with 3 blood samples known to be either negative, or positive with a moderate or a high parasite density.
- Observations of 12 pre-defined steps of the *m*RDT performance on a real patient for each health worker present on the day of the survey were also undertaken every 3 months (Figure 7).

Figure 7: Laboratory technician showing the result of *m*RDT to a patient

3.4 Ethics

Informed consent and treatment of the participants

Informed consent was obtained from every study participant after explaining the purpose, the risks and the benefits of the study.

For the cross-sectional surveys in the feasibility study of *m*RDT implementation, as well as the study on safety of *m*RDT in children less than five years (where the patient is managed as usual), consent was first asked to the clinician in charge, who asked for oral consent from the patient or caretaker. For each patient, the study clinician observing the consultation then signed on the questionnaire to testify that informed consent was obtained.

For the study on aetiologies of fever, written informed consent was obtained. This study was carried out by fully-trained and experienced physicians and health workers, strictly following current best practices for clinical care in Tanzania. We ensured that an appropriate treatment was offered to each child for a disease that was diagnosed within our investigation on fevers. As the Tanzanian National Treatment Guidelines had not been updated since 1997, the hospital directors asked us to rather prescribe the treatment recommended by the WHO manual for hospital care (WHO 2005a). If for any

reason the child could not get that treatment through the usual health care system, the investigators provided a treatment that was available in the country and this for the duration of the project.

Human Immunodeficiency virus in the study on etiologies of fevers

Originally, we had decided not to test the HIV status of the study children because of the low prevalence of HIV in this age group and the ethical and practical issues involved. The currently estimated rate of HIV positivity in children aged 1-9 years in Dar es Salaam is below 2% (Dar es Salaam City Medical Office of Health, unpublished) and the likelihood that a given fever episode is caused by HIV positivity is extremely low in this age group. For comparison, the measured HIV positivity rate in pregnant women was 11% in Dar es Salaam in 2003/4 (National Bureau of Statistics, Tanzania and Macro International Inc. 2007).

On the other hand we used the IMCI clinical criteria to detect a possible case of HIV/AIDS, so that we could counsel the caretaker to bring the child to Voluntary Counseling and Testing, available in the hospitals we were working in. We did not actively trace the result of the HIV test if it was done and left the decision of bringing us back the result at the discretion of the caretaker. Clinical management and anti-retroviral therapy for HIV positive adults and children were available free of charge in government health facilities of Dar es Salaam and at S^{t} Francis hospital in Ifakara.

4. Reduction in the proportion of fevers associated with *Plasmodium falciparum* parasitemia in Africa: a systematic review

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4.1 Abstract

Background

Malaria is almost invariably ranked as the leading cause of morbidity and mortality in Africa. There is growing evidence of a decline in malaria transmission, morbidity and mortality over the last decades, especially so in East Africa. However, there is still doubt whether this decline is reflected in a reduction of the proportion of malaria among fevers. The objective of this systematic review was to estimate the change in the Proportion of Fevers associated with *Plasmodium falciparum* parasitaemia (PFPf) over the past 20 years in sub-Saharan Africa.

Methods

Search strategy

In December 2009, we searched publications from the National Library of Medicine database using the combination of 16 MeSH terms.

Selection criteria

Inclusion criteria: studies 1) conducted in sub-Saharan Africa, 2) patients presenting with a syndrome of 'presumptive malaria', 3) numerators (number of parasitologically confirmed cases) and denominators (total number of presumptive malaria cases) available, 4) good quality microscopy.

Data collection and analysis

The following variables were extracted: parasite presence/absence, total number of patients, age group, year, season, country and setting, clinical inclusion criteria. To assess the dynamic of PFPf over time, the median PFPf was compared between studies published in the years ≤2000 and >2000.

Results

39 studies conducted between 1986 and 2007 in 16 different African countries were included in the final analysis. When comparing data up to year 2000 (24 studies) with those afterwards (15 studies), there was a clear reduction in the median PFPf from 44% (IQR 31-58%; range 7-81%) to 22% (IQR 13-33%; range 2-77%). This dramatic decline is likely to reflect a true change since stratified analyses including explanatory variables were performed and median PFPfs were always lower after 2000 compared to before.

Conclusions

There was a considerable reduction of the proportion of malaria among fevers over time in Africa. This decline provides evidence for the policy change from presumptive anti-malarial treatment of all children with fever to laboratory diagnosis and treatment upon result. This should insure appropriate care of non-malaria fevers and rationale use of antimalarials.

4.2 Background

Currently, the global target for malaria control is to provide prompt and effective treatment as well as insecticide-treated nets (ITNs) to 80% of the people at risk of malaria by the end of 2010 (Roll Back Malaria 2008; Rugemalila *et al*. 2006). The greatly increased malaria control effort since 2000 has been supported by global initiatives such as the Global Fund to fight AIDS, Tuberculosis and Malaria, the World Bank Malaria Booster Programme and the US Presidential Malaria Initiative. By the end of 2008, more than 50 African states had adopted artemisinin-combination therapies (ACTs) and the number of ITNs distributed had increased more than 10 times in 14 African states (Roll Back Malaria 2005). There is evidence now of reduced malaria transmission, morbidity and mortality in locations where these strategies have been massively deployed (O'Meara *et al*. 2008; WHO 2008). There is also a documented decline in Africa of *Plasmodium falciparum* prevalence rates in children aged 2-10 years from 37% before the year 2000, to 17% after 2000 (Guerra *et al*. 2008). This decline is further evidenced in recent Demographic and Health Surveys (DHS) in malaria endemic countries of sub-Saharan Africa: 11 of the 12 national surveys conducted since 2004 showed declines in underfive mortality estimates over the previous five years (declines of 5% to 30%, median 23%) (de Savigny 2007).

Theoretically, a reduction of malaria transmission, and hence parasitaemia, should translate into a decline of the proportion of fevers due to malaria, but the relationship between these two parameters is not straightforward. In part, this is due to the fact that the pattern of other causes of fever found in each area or patient population is not uniform and influence therefore the magnitude of the effect. Annual episodes of fever among African children have been estimated to be as high as 870 million (Robert W Snow *et al*. 2003). For those patients who reach clinics across the continent, a presumptive diagnosis of malaria is done in 30–40% of the cases (Chima *et al*. 2003a). Malaria thus appears to be the number one cause of fever in Sub-Saharan Africa, as well as the leading cause of mortality, at least in children (Rowe *et al*. 2006). However, these data might be largely overestimated nowadays due to the lack of specificity of a purely clinical diagnosis. Assigning malaria as a cause of fever in the absence of laboratory diagnosis is based on clinical experience but also on an understanding of the underlying epidemiology of the disease. Unfortunately, current practice by health care providers largely ignores the declining trend of *P. falciparum* parasite prevalence observed in community surveys and the proportion of fevers attributed to malaria does not seem to change. This question is of great practical relevance to correctly estimate the burden of disease due to malaria and for tracking progress in malaria control.

The objective of the present project was, therefore, to review the available evidence on the proportion of fevers due to malaria over the last 20 years in sub-Saharan Africa, to identify trends and to quantify the magnitude of expected changes. This assessment has obvious implications for optimizing recommendations concerning the management of fever cases in children under five years of age who live in highly endemic areas.

4.3 Methods

Criteria for considering studies for this review

*Type of studies: o*bservational studies or diagnostic studies

Inclusion criteria were i) study conducted in an area of sub-Saharan Africa where *P. falciparum* is the dominant species, ii) including patients (or a clear subset of patients) presenting at a health facility with a syndrome of 'presumptive malaria', either considered as such by the health worker in charge, or defined on clinical criteria by the investigators, iii) numerator (number of parasitologically-confirmed cases) and denominator (total number of presumptive malaria cases) available or possible to calculate from text, tables, or obtained after request to the authors, iv) good quality microscopy (reference centre or research laboratory), v) no obvious selection bias of patients.

Exclusion criteria were: i) studies using a parasite density threshold for malaria case definition, ii) intervention studies and studies aimed at evaluating the incidence of malaria episodes, iii) studies including < 100 patients, or those focusing on inpatients only and severe malaria.

The reasons for excluding these studies are as follows: i) defining a parasite threshold leads to a patients population that has lower proportion of malaria than when presence/absence of parasitaemia is used to define a case, ii) messages given to subjects in interventions studies ('attend as soon as possible in case of any symptom') lead to a patients population that is likely to be biased towards milder cases, and hence potentially lower prevalence of parasitaemia (undetectable parasitaemia because of low density), iii) studies with < 100 patients would have lacked precision (more than +/- 10% in the prevalence estimate) and be at higher risk of bias and confounding because of the limited sampling.

Type of participants

Patients of any age

Type of outcome measures

Proportion of Fevers associated with *Plasmodium falciparum* parasitemia (PFPf)

Search method for identification of studies

All relevant published studies of human medicine, regardless of language were searched for. In the COCHRANE reviews, 'malaria' as search term was used. In MEDLINE, a combination of several MeSH terms was used in the following way: malaria AND Africa AND (diagnosis OR parasitemia OR microscopy) AND (epidemiology OR sensitivity and specificity OR prevalence OR seasons OR transmission OR cross-sectional studies OR predictive value of tests) AND (aetiology OR fever OR algorithms OR case management). Titles and abstracts to be reviewed were listed. On the basis of abstract reading, full papers were selected, reviewed and those that matched the selection criteria were retained. Then, abstracts of the related articles of this first

series of papers were explored, reviewed and eventually the full paper was read if deemed appropriate. All references of the retained papers were also examined. This process was performed iteratively until no new suitable study could be found.

Databases

Cochrane Infectious Diseases Group Specialized Register (up to 15th December 2009), MEDLINE (through 15th December 2009).

Researchers and organizations

The following authors were contacted for clarifications on entry criteria of patients or for additional information on proportion of malaria among their sample: Pedro Alonso, Patrick Kachur, Christoph Hatz, Sophie Yacoub, Babacar Faye, Thomas Mschana and Nadjitolnan Othingué.

Reference lists

The reference lists of all studies identified by the above methods was checked.

Methods of the review

Study selection

One author (VdA) independently applied the inclusion criteria to all identified studies. All studies selected were checked by a second author (BG) for appropriateness. For studies for which there were doubts about inclusion, the second author assessed them fully and potential differences were discussed until consensus was reached.

Data extraction

Besides the proportion of fevers with associated *Plasmodium falciparum*, eight variables were extracted from each paper: year, season [rainy versus dry; when season was not mentioned it was searched on the CIA website (www.cia.gov) using dates of beginning and end of recruitment], country, setting (urban versus rural), health facility type (hospital versus primary care), age group (<5 years, 5-15 years, adults), clinical inclusion criteria used and total number of patients.

Data analysis

As it was not possible to obtain the original databases of all studies, essentially a descriptive analysis on aggregated data was performed. The proportion of fever or presumptive malaria cases associated with *P. falciparum* documented by high quality microscopy, hereinafter referred to as proportion of fevers due to malaria (PFPf), was retrieved or calculated from each study. To assess the trend of PFPf over time, the median PFPf including all studies (pooled analysis) was compared for the period up to the year 2000, and for that from 2001 onwards. This threshold was chosen since large-scale interventions started around this time thanks to a massive increase in funding for control measures (Waddington 2004). That cut-off is also consistent with the analysis by Guerra *et al* for parasitaemia (Guerra *et al*. 2008). No formal multivariate analysis was possible since individual records for each study were not available.

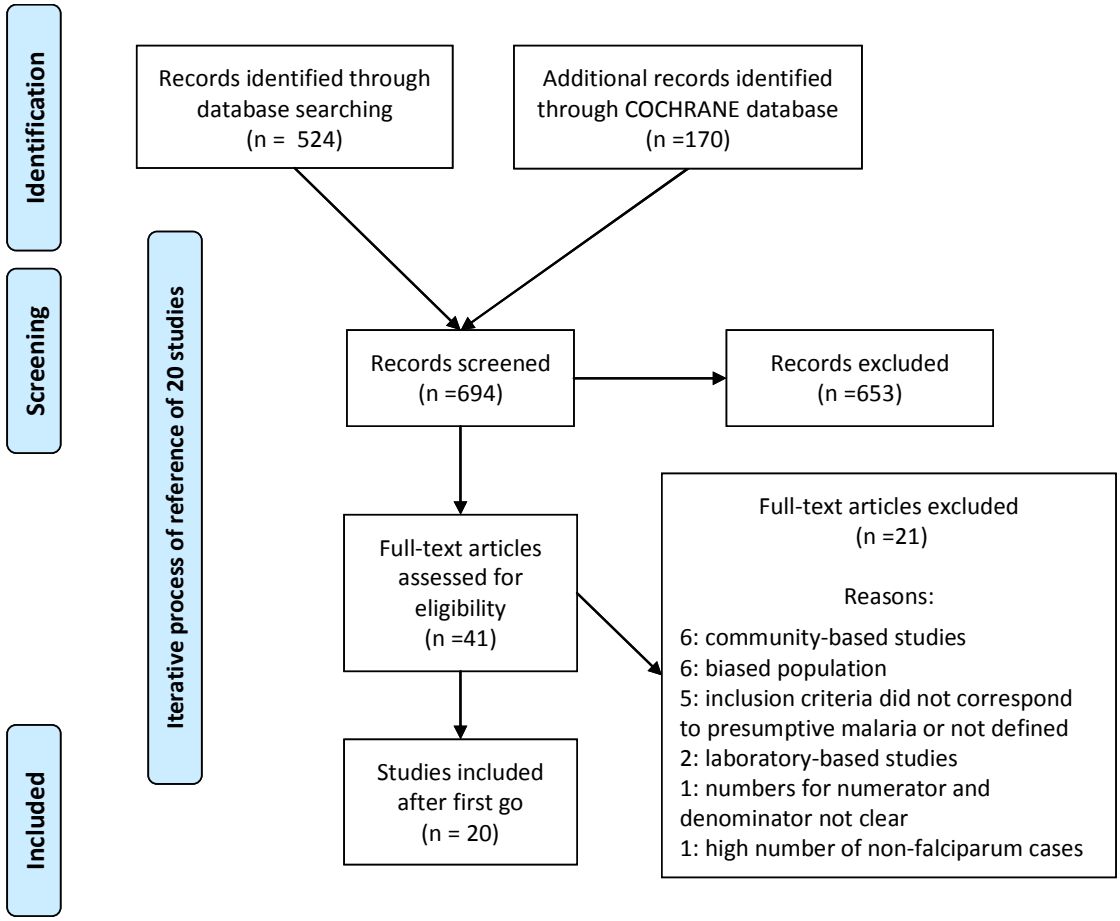
However, to investigate potential confounding factors, a stratified analysis by age group (<5 and ≥5 years), season (rainy and dry), setting (rural and urban), type of health facility (primary care and hospital) was performed using data from studies where such information was available. These parameters are known to have an effect on malaria fevers and the categories are standard to describe the epidemiology of malaria.

4.4 Results

Description of studies

Up to 15th December 2009, 170 titles were extracted from the COCHRANE database, but none was relevant for this review. From MEDLINE, 524 titles were identified and extracted, all abstracts were reviewed and 41 papers were selected in the first round. Based on the reading of the full article, 20 met all inclusion criteria and were retained. After iterative cross-referencing of these 20 articles, 19 additional articles meeting all inclusion criteria were found (see Figure 8). The 39 studies included in the final analysis were conducted between 1986 and 2007 and published between 1989 and 2009. The total number of patients included was 42,979 (median: 576; range: 149 to 7713). All relevant details of the included studies are described in Table 3.

Figure 8: Flow chart of the MEDLINE articles search



Time frame

24 studies were conducted up to the year 2000 and 15 from 2001 onwards.

Location

The included studies were conducted in 16 different African countries. 21 studies took place in East Africa, mainly Tanzania (12 studies), 16 studies in West Africa, 1 in Central Africa (Chad) and 1 in the Northern region (Sudan) (Figure 9).

Age group

Fifteen studies included children only (age <5 years, n = 8; age <9 years, n = 6; age <12 years, n = 1). One study included only adults older than 18 years and one study only patients older than 5 years. The remaining 22 studies included patients of all ages.

Level of endemicity and transmission season

Studies on clinical management of malaria have been done mainly in highly endemic areas and a period of the year with peak transmission, and this is reflected in the included studies. Patients were recruited during the rainy season only, the rainy and the dry seasons and the dry season only in 19, 16 and 4 studies, respectively.

Setting and level of health care

Twenty one studies were conducted in a rural area of Africa (54%), while the remaining took place in urban areas. Also, 21 studies were undertaken at primary care level and the rest at hospital level.

Overall proportion of parasitaemia among fever cases (PFPf)

The proportion of parasitaemia among fever or presumptive malaria cases (PFPf) varied considerably between studies and sub-groups of patients within the same study. Taking each study as a unit, the median PFPf was 35% [inter-quartile range - IQR: 20-54%; range 2-81%).

Variation of PFPf according to key stratification parameters

Age group-specific PFPf

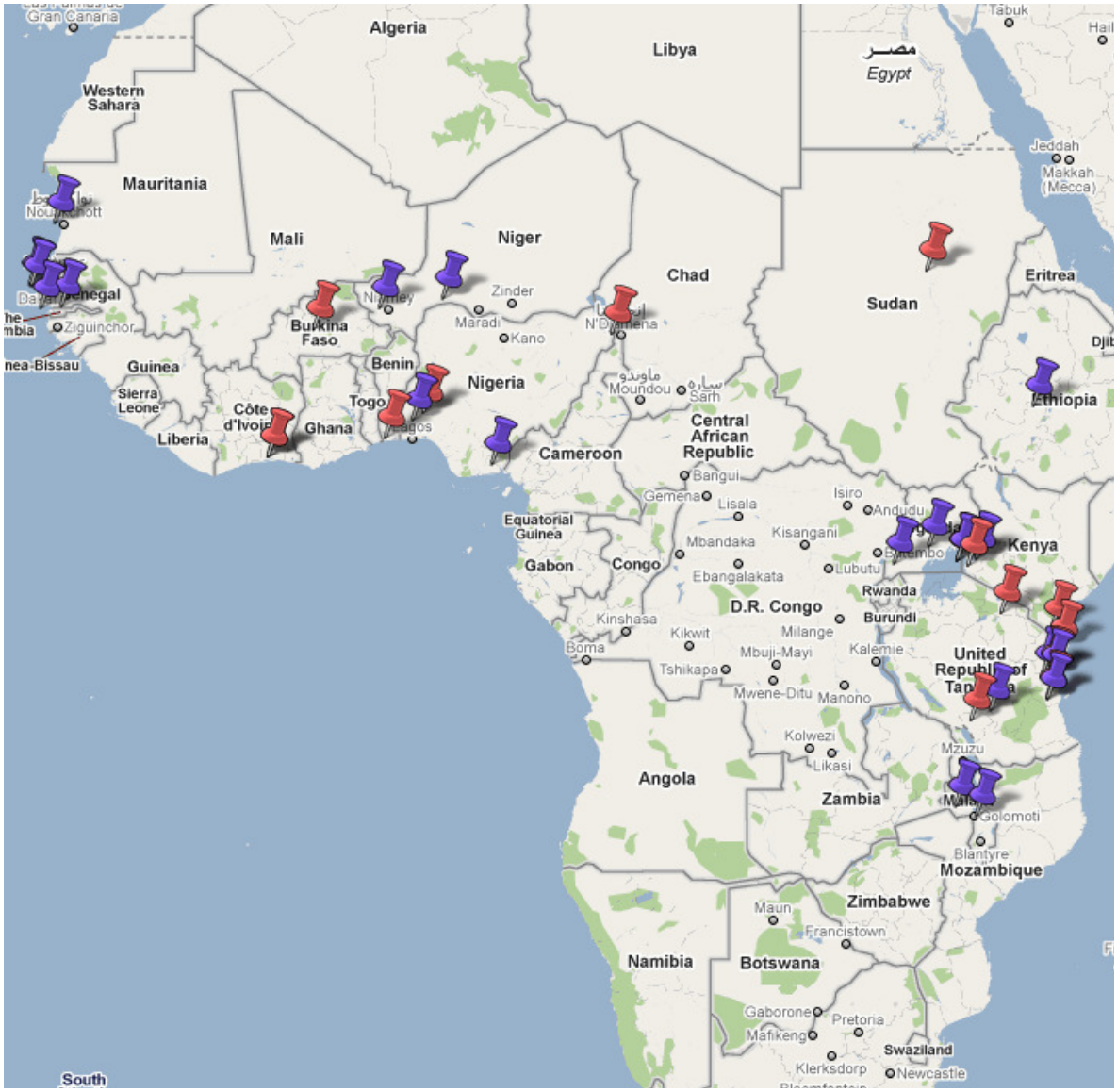
Taking into account all studies where data were stratified by age or those that included only one defined age group, overall median PFPf was 36% (IQR 21-60%; range 4-77%) for children under five years (25 studies) and 26% (IQR 13-33%; range 1-53%) for those above five years (18 studies). In the 16 studies providing stratified values of PFPf in both age groups, median PFPf in children under five years of age (32%; IQR 18-55%) was not significantly different from that in the group above five years (27%; IQR 19-34%). When using only the 10 studies providing details for the older age groups, the median PFPf was 27% (IQR 20-50%) for the group under 5 years, 40% (IQR 22-48% for the age group of 5-15 years, and 24% (IQR 11-27%) in adults above 15 years.

Season-specific PFPf

The overall median PFPf was 37% (IQR 30-60%; range 4-77%) in the rainy season versus 5% (IQR 4-12%; range 0-28%) in the dry season. Among all factors studied, this was the most dramatic

difference observed. This difference remained when restricting the analysis to the 7 studies providing stratified value of PFPf for both the rainy and dry seasons: 35% (IQR 25-57%) versus 5% (IQR 4-9%).

Figure 9: Geographical distribution of sites of included studies (blue pins are for studies ≤ year 2000 and red pins > year 2000)



Setting-specific PFPf

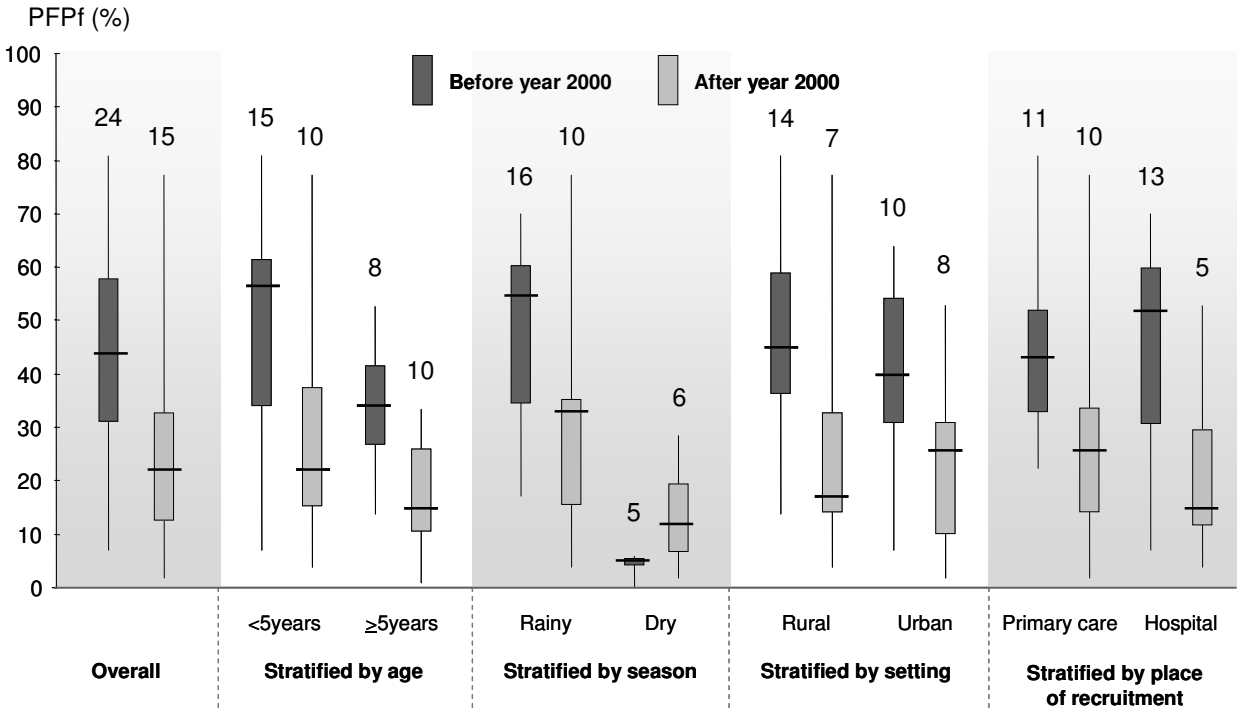
Urban/rural There were 21 studies conducted in rural areas and 18 in urban areas (as defined by investigators). The overall median PFPf was 38% (IQR 22-57%; range 4-81%) in rural areas versus 31% (IQR 19-50%; range 2-64%) in urban settings.

Level of health care 21 studies were conducted in primary care facilities and 18 in the outpatient department of a hospital. The overall median PFPf was 35% (IQR 22-44%; range 2-81%) in primary care settings versus 40% (IQR 16-56%; range 4-70%) in hospitals.

PFPf up to the year 2000 and afterwards

When comparing PFPf from studies conducted up to the year 2000 (24 studies) with those done afterwards (15 studies), there was a clear reduction in the median PFPf from 44% (IQR 31-58%; range 7-81%) to 22% (IQR 13-33%; range 2-77%) (Figure 10).

Figure 10: Comparison between the Proportions of Fevers associated with *Plasmodium falciparum* parasitemia (PFPf) in years ≤2000 and >2000, stratified by baseline characteristics



This dramatic decline is likely to reflect a true change since all variables listed above and which were shown to have an effect on PFPf were well balanced between the two groups of studies. For studies before and after 2000 respectively, 17.5/24 (73%) and 9.5/15 (63%) studies were conducted during the rainy season (when a study took place during both the rainy and the dry season, the count was 0.5 study for each of the season) (p = 0.45); 14/24 (58%) and 7/15 (47%) studies were conducted in a rural setting (p = 0.53); and 11/24 (46%) and 10/15 (67%) were conducted at primary care level (p = 0.32).

In the 11 studies from Tanzania (considered mostly as a highly endemic area), PFPf in children under five years during the rainy season decreased from 81% in 1986-88 (Rooth & A Björkman 1992) to 57% in 1995 (Font *et al*. 2001), 38% in 1997 (Nsimba *et al*. 2002) and 21% in 2005 (Reyburn *et al*. 2007).

To further check for potential confounding factors, a stratified analysis was conducted including each of the variables listed above. The reduction of PFPf over time was confirmed since median PFPfs were almost always lower for the years after 2000 compared to the years ≤2000 (see Figure 10). There was one exception in the case of the data collected during the dry season.

4.5 Discussion

This systematic review demonstrates a 50% reduction of PFPf for the period after year 2000 when compared to that of ≤2000 (22% versus 44%). This decrease by half of the proportion of malaria cases among fever episodes is likely to be due to a reduction of malaria transmission. It mirrors the reduction observed in parasite prevalence rates collected from community cross-sectional surveys in sub-Saharan Africa during the same time periods (17% after year 2000 versus 37% before) (Guerra *et al*. 2008). A decrease in malaria is now observed in many settings across sub-Saharan Africa, mainly because of the large scale implementation of effective control measures following a drastic increase of funding since the year 2000 (Waddington 2004). Recently, Okiro & Snow demonstrated the clear linear relashionship between the risk of infection among febrile children and parasite prevalence in the community (Okiro & Snow 2010).

An inherent difficulty with systematic reviews is that they look at studies which may not be comparable. In the present review, the most recent studies report a lower proportion of malaria attributable fevers, but some of these later studies have been conducted in areas of lower endemicity than those performed previously. This is especially true for some studies in Tanzania, a country largely represented in this systematic review. In part, this was due to the fact that some of the recent studies were conducted in urban and peri-urban settings, whereas old ones were traditionally done in rural places, where transmission of malaria is usually higher. Part of the reduction in the proportion of malaria among fevers may thus be ascribed to selection biases. To address this problem, stratified analyses for variables known to have an effect on PFPf were performed. These analyses confirmed the reduction of PFPf over time when controlling for these different factors. The only exception was for dry season and this is easily explainable by the fact that the median PFPf was always rather low, irrespective of the period. Whe data are available, such as in Tanzania for example, the substantial reduction of PFPf parallels closely the decline of incidence of malaria episodes and overall mortality in children under five observed in the same areas over the last fifteen years (Schellenberg *et al*. 2004; Masanja *et al*. 2008; Khatib *et al*, unpublished data).

Although the reduction of PFPf was considerable, it is unclear how representative these data are at this point in time. Data are over-represented in sites with research institutions or special situations

and it would be a great importance to confirm such trends in other settings, especially in the largest malarious countries on the continent, the Democratic Republic of the Congo and Nigeria. Also, within a country or region, the reductions are not necessarily uniform. There are still a number of places that harbour PFPf over 50%, especially so in areas where healthcare is not readily accessible.

On the other hand, there is no doubt that malaria control is very successful in many countries (WHO 2009b) and these trends are expected as a result of greatly improved preventive activities. In any case, the immediate practical implication of the changing epidemiology of fever episodes is the much increased need for a systematic laboratory diagnosis of every case before initiating treatment for malaria (Chapter 6).

4.6 Conclusions

This systematic review demonstrates a considerable reduction of PFPf in sub-Saharan Africa between the periods before the year 2000 and from 2001 onwards (44% versus 22%). With only around a fifth of all fever episodes being associated with malaria parasitaemia, this review provides strong evidence to support the new WHO policy of laboratory-based diagnosis and treatment upon result (WHO 2010). This should insure appropriate care of non-malaria fevers and rationale use of anti-malarials. The relative cost effectiveness and value of introducing diagnosis for febrile children will obviously depend on infection prevalence in the community.

4.7 Financial disclosure

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Authors' contributions

VdA did the literature search, the analyses, and wrote the first draft of the manuscript.
BG counterchecked the selection of articles and contributed to the manuscript writing.
CL contributed to the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Table 3: All 39 included studies showing the Proportions of Fevers associated with *Plasmodium falciparum* parasitemia (PFPf)

Reference	Start of the study	Country	Urban / rural area	Place of recruit-ment	Clinical inclusion criteria	Total number of patients	Overall PFPf	Age groups	Season	PFPf
Rooth & A Björkman 1992	1986	Tanzania	Rural	Primary care	History of fever	596	81%	≤ 9 years	Both seasons	81%
Rougemont *et al.* 1991	1987	Niger	Rural	Primary care	Temp ≥37.5°C	285	57%	≤ 9 years	Rainy season	57%
Salako *et al.* 1990	1987	Nigeria	Urban	Hospital	History of fever or elevated temp	7713	55%	< 5 years	Both seasons	61%
								5-18 years		60%
								> 18 years		41%
Ejezie & Ezedinachi 1992	1988	Nigeria	Urban	Hospital	Presumptive malaria	1188	45%	≤ 9 years	Both seasons	45%
Gaye *et al.* 1989	1988	Senegal	Urban	Primary care	Temp ≥38°C	353	31%	≤ 9 years	Rainy season	28%
								10-14 years		35%
								> 14 years		33%
Olivar *et al.* 1991	1989	Niger	Urban	Primary care	Temp >38°C	576	35%	< 5 years	Rainy season	62%
									Dry season	5%
Lubanga *et al.* 1997	1992	Uganda	Urban	Hospital	History of fever	435	64%	≤ 5 years	Rainy season	64%
Meremikwu *et al.* 1995	1993	Nigeria	Urban	Hospital	Temp ≥37.5°C	225	63%	< 5 years	Rainy season	63%
Redd *et al.* 1996	1993	Malawi	Rural	Hospital	Presumptive malaria	1124	60%	< 5 years	Rainy season	60%
Olaleye *et al.* 1998	1993	the Gambia	Rural	Primary care	History of fever or temp ≥37.5°C	407	59%	≤ 9 years	Rainy season	59%
Weber *et al.* 1997	1993	the Gambia	Urban	Hospital	Presumptive malaria	440	7%	< 5 years	Rainy season	17%
									Dry season	4%
Gaye *et al.* 1997	1994	Senegal	Urban	Hospital	History of fever	762	31%	All ages	Rainy season	59%
									Dry season	5%
								< 5 years	Both seasons	14%
								> 5 years		36%
Font *et al.* 2001	1995	Tanzania	Rural	Primary care	History of fever or temp >37.5°C	641	44%	< 5 years	Rainy season	57%
								> 5 years		24%
Tarimo *et al.* 1998	1996	Tanzania	Urban	Hospital	Presumptive malaria	400	52%	All ages	Both seasons	52%
Cooke *et al.* 1999	1996	the Gambia	Rural	Hospital	History of fever or elevated temp	398	36%	All ages	Rainy season	36%
Muhe *et al.* 1999	1996	Ethiopia	Rural	Primary care	History of fever or temp ≥38°C	2490	22%	< 5 years	Rainy season	30%
									Dry season	6%
Cortes *et al.* 2003	1996	Mauritania	Urban	Hospital	History of fever	416	19%	All ages	Both seasons	19%
Oster *et al.* 2000	1996	Tanzania	Rural	Hospital	History of fever or temp ≥37.5°C	168	14%	Adults	Rainy season	20%
									Dry season	0%
Nsimba *et al.* 2002	1997	Tanzania	Rural	Primary care	Presumptive malaria	449	38%	≤ 5 years	Rainy season	38%
Akim *et al.* 2000	1997	Tanzania	Rural	Primary care	History of fever	6580	43%	≤ 6 years	Both seasons	57%
								7-15 years		44%
								> 15 years		27%
Arness *et al.* 2003	1998	Kenya	Rural	Primary care	Presumptive malaria	2796	29%	< 5 years	Both seasons	32%
								5-15 years		35%
								≥ 15 years		23%

Tarimo *et al.* 2001	2000	Tanzania	Rural	Hospital	Malaria based on IMCI criteria	395	70%	≤ 5 years	Rainy season	70%
Guthmann *et al.* 2002	2000	Uganda	Rural	Hospital	Presumptive malaria	742	57%	< 5 years	Rainy season	64%
								≥ 5 years		52%
Gouagna *et al.* 2003	2000	Kenya	Rural	Primary care	Presumptive malaria	3754	47%	< 5 years	Both seasons	55%
								5-15 years		57%
								> 15 years		36%
Raharimalala *et al.* 2002	2001	Madagas-car	Rural	Primary care	Presumptive malaria	149	35%	< 15 years	Rainy season	37%
								≥ 15 years		29%
Assoumou *et al.* 2008	2001	Ivory Coast	Urban	Hospital	Temp ≥37.5°C	902	29%	< 5 years	Both seasons	31%
								5-15 years		27%
Othnigué *et al.* 2006	2002	Chad	Urban	Primary care	Presumptive malaria	712	30%	All ages	Rainy season	35%
									Dry season	12%
								< 5 years	Both seasons	19%
								5-14 years		50%
								≥ 15 years		27%
Zurovac *et al.* 2006b	2002	Kenya	Rural	Primary care	Sent for malaria test by clinician in charge	261	13%	≥ 5 years	Rainy season	13%
Malik *et al.* 2005	2002	Sudan	Urban	Hospital	History of fever	655	12%	< 5 years	Dry season	11%
								5-16 years		13%
Wang *et al.* 2006c	2002	Ivory coast	Urban	Primary care	History of fever or temp ≥37.5°C	429	35%	≤ 5 years	Rainy season	36%
								6-15 years		44%
								> 15 years		26%
Wang *et al.* 2005b	2002	Burkina	Urban	Primary care	History of fever or temp ≥37.5°C	560	22%	≤ 5 years	Dry season	22%
								6-15 years		37%
								> 15 years		18%
Wang *et al.* 2006a	2003	Tanzania	Urban	Primary care	History of fever or temp ≥37.5°C	717	5%	≤ 5 years	Dry season	5%
								6-15 years		7%
								> 15 years		4%
Wang *et al.* 2006b	2003	Benin	Urban	Primary care	History of fever or temp ≥37.5°C	379	2%	≤ 5 years	Dry season	4%
								6-15 years		0%
								> 15 years		1%
Yacoub *et al.* 2005	2003	Zanzibar	Rural	Primary care	History of fever or temp >37.5°C	207	77%	≤ 5 years	Rainy season	77%
Ogungbamig be *et al.* 2007	2004	Nigeria	Urban	Hospital	Temp ≥37.5°C	646	53%	≤ 9 years	Rainy season	62%
									Dry season	28%
Kachur *et al.* 2006	2004	Tanzania	Rural	Primary care	History of fever	769	31%	< 5 years	Rainy season	43%
								≥ 5 years		23%
Reyburn *et al.* 2007	2005	Tanzania	Rural	Hospital	Sent for malaria test by clinician in charge	2397	15%	< 5 years	Rainy season	21%
								5-15 years		17%
								> 15 years		8%
Reyburn *et al.* 2006	2005	Tanzania	Rural	Hospital	Sent for malaria test by clinician in charge	214	4%	All ages	Rainy season	4%
Mens *et al.* 2008	2007	Kenya	Rural	Primary care	History of fever or temp ≥37.5°C	650	17%	≤ 12 years	Rainy season	17%

5. Withholding antimalarials in febrile children who have a negative result for a Rapid Diagnostic Test

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Key words: rapid diagnostic test, malaria, safety, children, diagnosis

Summary

Presumptive treatment for malaria is widely used, especially in children. Withholding antimalarials in febrile children with negative RDT*m* was safe, even in a highly endemic area. This study provides evidence for treatment recommendations based on parasitological diagnosis in children underfives.

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5.1 Abstract

Background

The availability of a Rapid Diagnostic Test for malaria (*m*RDT) allows accurate diagnosis at all levels of health facilities. The objective of the present study was to evaluate the safety of withholding antimalarials in febrile children with a negative test result.

Methods

We conducted a prospective 2-arm longitudinal study in areas of Tanzania that are moderately and highly endemic for malaria. Children with a history of fever were managed routinely by resident clinicians of 2 health facilities, except that no antimalarials were prescribed if the *m*RDT was negative. Children were followed up at home on day 7. The main outcome was the occurrence of complications in children with negative *m*RDT results; children with positive *m*RDT results were followed up for the same outcomes for indirect comparison.

Results

One thousand children (median age, 24 months) were recruited. Six hundred three children (60%) had a negative *m*RDT result. Five hundred seventy-three (97%) of these children were cured on day 7. Forty-nine (8%) of the negative *m*RDT results spontaneously visited the dispensary before day 7, compared with 10 (3%) of the children with positive *m*RDT results. All children who had negative initial results had negative results again when they were tested either at spontaneous attendance or on day 7 because they were not cured clinically, except for 3 who gave positive results on days 2, 4 and 7 respectively but who did not experience any complication. Four children who had negative initial results were admitted to the hospital subsequently, all with negative results for malaria tests upon admission. Two of them died, of causes other than malaria.

Conclusions

Not giving antimalarial drugs in febrile children who had a negative *m*RDT result was safe, even in an area highly endemic for malaria. Our study provides evidence for treatment recommendations based on parasitological diagnosis in children <5 years old.

5.2 Introduction

The number of episodes of fever among African children could be as high as 870 million per year (Snow *et al*. 2003). Among children who reach outpatient clinics across the continent, a presumptive diagnosis of malaria is given in 30–40% of these cases (Chima *et al*. 2003b). Malaria appears therefore to be the number one cause of fever, as well as the leading cause of mortality, in children in Sub-Saharan Africa (Rowe *et al*. 2006). In 2006, the World Health Organization (WHO) published the following treatment recommendation: *'In areas of high stable malaria transmission, the prior probability of fever in a child being caused by malaria is high. Children <5 years of age should therefore be treated on the basis of a clinical diagnosis of malaria. There is as yet no evidence to show that the benefits of parasitological diagnosis in this highly vulnerable group outweigh the risks of not treating false negatives*.' (WHO 2006). Obviously, the prime reason for this recommendation of blanket antimalarial treatment is to save lives. It takes into account the lack of sensitivity and lack of specificity of the clinical diagnosis of malaria (Chandramohan *et al*. 2002).

Although this recommendation was probably sound at the time of its formulation, it should now be reviewed because of the steady decline in malaria transmission that is occurring all over Sub-Saharan Africa. This decrease is due to large-scale control (WHO 2008; Guerra *et al*. 2008) and the availability of reliable, inexpensive and easy-to-use malaria diagnostic tools (Chris Drakeley & Reyburn 2009). One consequence of the falling transmission rates is that the blanket approach to treatment is not as safe as it was a decade ago, because the malaria-attributable fraction of fevers is now significantly lower and therefore the relative likelihood of missing other potentially fatal diseases has become higher (Chapter 6). To support a change to this recommendation, WHO looks for convincing evidence on the safety of treating children <5 years old who live in areas endemic for malaria on the basis of a malaria test result.

The few studies that have looked at the outcome of treating febrile children who live in areas endemic for malaria on the basis of a malaria laboratory test suggest that this strategy might be safe (Njama-Meya *et al.* 2007; Ngasala *et al.* 2008; Msellem *et al.* 2009). To our knowledge, our study is the first prospective study in an area that is highly endemic for malaria that took place under routine implementation conditions with the aim of evaluating the safety of withholding antimalarials in febrile children who have a negative result for a rapid diagnostic test for malaria (*m*RDT). Our primary interest was the clinical outcome of the children, namely the rate of complications and deaths, irrespective of any other consideration (eg, parasitemia). The *m*RDT testing by health care workers in both of our study settings was found to be reliable in a previous study (Kahama-Maro *et al*. 2008).

5.3 Methods

Study areas

This work is part of a larger project on the introduction of mRDT in Tanzania and the evaluation of its impact on health outcomes, drug prescriptions, consultation processes, patient and health worker satisfaction, and cost saving (IMALDIA: Understanding and improving malaria diagnosis in Tanzania). The present study was performed first in an area of moderate endemicity and then in an area of high endemicity. This stepwise design was chosen to ensure the safety of the patients. If the strategy of withholding antimalarials in febrile children with a negative malaria test were shown to be not safe in an area of moderate endemicity, the second part of the study in an area of high endemicity area would be canceled.

Dar es Salaam: Buguruni Health Center of Ilala Municipality in the city center of Dar es Salaam, Tanzania was chosen as a place of recruitment because of its characteristics typical of the urban setting. This area is moderately endemic for malaria, with parasite rates in the community at ~ 1%-4% (Wang *et al*. 2006a) and with only 5%-10% of febrile patients being parasitemic (Chapter 7).

Signal: Signal is a remote village in the Kilombero Valley (south-central Tanzania). The local health facility was chosen because of the ready availability of *m*RDT, the high percentage of febrile patients having parasites (~50%) and the sufficiently high average number of patients attending daily (30), compared with the characteristics of the other remote dispensaries in the Kilombero Valley. *m*RDT had been introduced in 7 health facilities in the area 1 year previously, with a 1-day initial training of all health care workers, a 2-month follow-up of general performance, and a routine quality assurance of the *m*RDT (including lot testing at a WHO reference laboratory) every 3 months. No further training was conducted in the Signal health facility in the frame of the present study.

Study subjects

Inclusion criteria were as follows:

- 1. Children were aged from 6 months to 10 years in Dar es Salaam and from 2 months to <5 years in Signal.
- 2. Children attending the health facility for the first time for the present problem.
- 3. There was a history of fever in the last 48 hours or axillary temperature of $\geq$37.5°C at the time of consultation.
- 4. There was an absence of severe illness that required specific treatment or referral
- 5. The main complaint was neither injury nor trauma.

Study procedures

Oral informed consent was obtained from the parent or guardian. Patients were managed at the discretion of the clinicians, except that the latter were asked to perform an *m*RDT (ParaHit-f

cassette; Span Diagnostics) and to not prescribe antimalarials if the result was negative. A blood slide was also prepared as back-up for retrospective investigation of complicated cases. Patients were asked to come back to the same health facility in case of any problem. In Dar es Salaam, parents and guardians were informed that they would be visited at home after 7 days (+/- 1 day) to assess whether the child was cured. In Signal, we asked them to come back on day 7 for the same reason. If they had not returned on the due day before 2:00 PM, they were visited at home on the same or on the following day. At each home, the clinician would ask the parent or guardian about the status of the child (cured, not improved or condition worsened) and whether they had gone to another health facility in the meantime.

If the child were ill between day 0 and day 7 or not cured on day 7, a new consultation was performed by the usual clinician of the health facility, and the patient was tested again with either an *m*RDT (if the test was negative on inclusion) or by microscopy (when the initial *m*RDT test result had been positive). Patient management was again left to the discretion of the clinician, and antimalarials were again withheld if the test was negative. The child was then visited at home on day 14 to check his or her status.

Children who had positive *m*RDT were treated with the recommended first-line antimalarial (artemether-lumefantrine [Coartem]) and followed up in the same way as children who had negative *m*RDT results. For obvious reasons, they did not represent a proper control group, because they represented a clinically very different group of children. Consequently, no tests of significance were performed to compare the 2 groups.

We calculated that a sample of 500 malaria-negative children was required to estimate an adverse event rate of 5% with a precision of ± 2%. This risk was estimated on the basis of the sensitivity of routine *m*RDT (90%) combined with a 50% risk of complication (defined as hospital admission or death) due to delayed diagnosis and therefore absence of timely treatment.

The study protocol and related documents were approved by the Ethikkommission beider Basel (EKBB) in Switzerland and by the National Institute for Medical Research Review Board in Tanzania. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration.

5.4 Results

Status at inclusion

In Buguruni health centre (Dar es Salaam), 300 children with a median age of 28 months (range: 3 - 120 months, with 256 [86%] being $\leq$5 years old) were included in May-June 2007. One hundred forty-three (48%) were female. All had a history of 'homa', the Swahili word for fever, although this was the main complaint in only 205 (68%) of the cases. The axillary temperature was $\geq$37.5°C in 118 (39%) of the children. At inclusion, 41 (14%) of the 300 children had a positive *m*RDT result. All 41

children with positive results were treated with an antimalarial: 35 (85%) received artemisinin-lumefantrine and the rest received oral quinine. Thirteen children with positive results (32%) also received an antibiotic. Except for one child, all children with negative results received an antibiotic (cotrimoxazole, amoxicillin, and injectable penicillin were mostly used).

In the Signal dispensary (Kilombero), 700 children with a median age of 24 months (range, 2-59 months) were included from September 2008 through February 2009. Three hundred forty-one (49%) were females. They all had a history of homa, which was the main complaint in 604 (86%) of the cases. The axillary temperature was $\geq$37.5°C in 404 (58%) of the children. At inclusion, 356 (51%) of the 700 children had a positive *m*RDT result. All children with positive results were treated with an antimalarial: 342 (96%) with artemisinin-lumefantrine and the rest received injectable or oral quinine. Sixty-four (18%) of the 356 children with positive results also received an antibiotic. Three hundred twelve (91%) of the 344 children with negative results received an antibiotic.

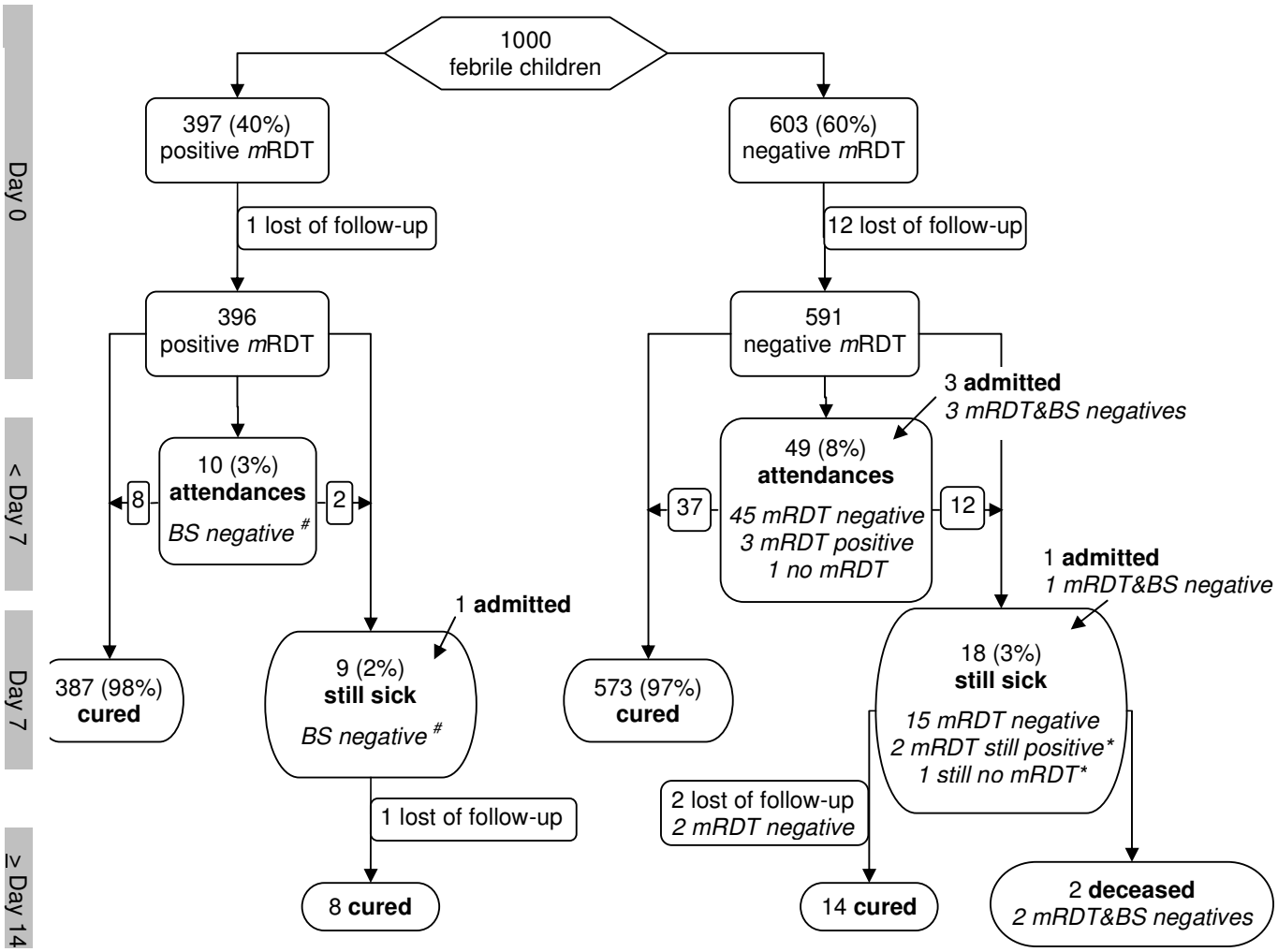
Spontaneous attendance before day 7

In total, 59 (5.9%) of the 1000 children consulted spontaneously before day 7, the majority of them (45 [76%]) visiting the same facility that they visited for the initial consultation. Among the 603 children who had a negative *m*RDTresult at inclusion, 49 (8%) (representing 31 [12%] of 259 in Dar es Salaam and 18 [5%] of 344 in Signal) attended before day 7 (median, 3 days after inclusion), with persisting fever in 37 children (despite antibiotics prescribed at first place in 35 of them). Among the 397 children who had a positive *m*RDT result at inclusion, 10 (3%) attended spontaneously before day 7 (median, 4 days after inclusion), with persisting fever in 5 children (4 of them had received an antibiotic at inclusion in addition to the antimalarial) (Figure 11).

Outcome on day 7 and 14

Thirteen (1.3%) of the 1000 children included were lost to follow-up, either because they had moved or the address was not sufficiently precise. Among the 591 children who had a negative *m*RDT result, 573 (97%) were cured on day 7. For the remaining 18 children, 15 were examined before or on day 7 because of fever, 2 because of diarrhea and one because of a headache. Of these 18 children, 14 were cured on day 14, 2 died (see below), and 2 were lost to follow-up after day 7 (both had negative *m*RDT results on day 7). Among the 396 children who had a positive *m*RDT result, 387 (98%) were cured on day 7 (38 [95%] of 40 in Dar es Salaam and 349 [98%] of 356 in Signal). Eight children were still febrile (all had a negative blood slide results) and 1 had asthma. All these children were cured on day 14 (1 was lost to follow-up after day 7) (Figure 11).

Figure 11: Flow chart of patients in a study of withholding antimalarials in febrile children who have a negative result for a rapid diagnostic test in Tanzania. BS, [result of] blood slide for malaria; RDTm, [result of] rapid diagnostic test for malaria.



* same patients as under attendances

only patients still complaining of fever were tested

Complications

Among the 603 children who had a negative *m*RDT result at inclusion, 4 (1 in Dar es Salaam and 3 in Signal) were hospitalized: 1 on day 2 because of severe sepsis with exanthema, 1 on day 4 because of severe pneumonia, 1 on day 7 because of gastroenteritis with severe dehydration, and 1 on gay 7 because of severe anaemia without fever. These 4 children had an *m*RDT and an expert microscopy for malaria performed upon admission at the hospital and all gave negative results. Two children died (1 with severe sepsis died on day 6, and 1 with severe pneumonia died on day 8). Among the 397 children who had a positive *m*RDT result at inclusion, 1 was hospitalized on day 7, because pneumonia had not responded to the first-line intravenous antibiotic treatment (Figure 11).

Subsequent *m*RDT results of the children with negative initial results who consulted before day 7 or who were not cured on day 7

Among the 603 children who had negative *m*RDT result at inclusion, 55 consulted spontaneously before day 7 or were not cured on day 7 when we visited them at home. Of these 55 children, 51 had negative *m*RDT results; one had positive results on day 4 and two on day 7 (all living in Signal, the area of high endemicity), and one could not be tested but recovered on day 14 after receiving erythromycin prescribed in another health facility. Among the 3 newly positive results, 1 child was likely to have had coincidental low-density parasitemia. Indeed, he had positive results on day 4 and did not respond to the antimalarial treatment given on that day, but he responded to an antibiotic given on day 7. Another child had dysuria at inclusion, received amoxicillin, and recovered, but he became feverish again at day 5 with dysuria; he had positive test results at day 7 and was treated with intramuscular quinine and cotrimoxazole and was cured on day 14. He had either a coincidental or a new infection. The last child had vomiting on day 0 and was treated with cotrimoxazole; then, because of persisting fever, he attended another dispensary on day 2 where he was not tested for malaria but received oral quinine. He was cured on day 7 but had positive results by *m*RDT. He might have experienced a malaria episode that was not diagnosed on day 0 because of clinical symptoms that appeared before patent parasitemia

5.5 Discussion

To our knowledge, our study is the first to provide strong evidence that withholding antimalarial treatment in children with fever who have a negative *m*RDT result in a setting highly endemic for malaria is safe and does not expose the child to an increased risk of complication or death. Because the present study was conducted with programmatic conditions that were reasonably close to routine, we believe that the results are applicable more generally.

Complications or deaths

In this cohort of 1000 feverish children, 60% had a negative *m*RDT result at inclusion and were not treated with an antimalarial. We did not observe any complication or death due to malaria among these children. In total, 4 children (0.7%) were admitted to the hospital and 2 (0.4%) died; malaria test results on admission were negative for all 4. Our study provides strong evidence that the strategy is safe, irrespective of the level of endemicity of malaria. To our knowledge, the only other study with a follow-up of fever episodes in untreated children with negative tests results (tested by expert microscopy rather than by *m*RDT) was the study by Njama-Meya *et al* in Kampala, Uganda (Njama-Meya *et al*. 2007). That study, designed primarily to assess the efficacy of antimalarial drugs, was performed in a highly controlled setting and included children with danger signs. No complication or death due to the withholding of antimalarial treatment in children with negative results occurred.

Although the absence of a proper control group did not allow us to know the usual rate of complications in the absence of any reliable malaria test, the lack of admissions and/or deaths due to

malaria following *m*RDT use certainly suggested that this approach is safe. One (0.3%) of the 397 children in the malaria group and 4 (0.7%) of the 603 children in the nonmalaria group were admitted after first consultation. There was no death among the malaria group and 2 deaths in the nonmalaria group. We know that these complications in nonmalaria patients were not due to undetected malaria parasites, because we had performed ≥3 malaria tests on each of these children and none had positive results.

On the basis of 2 previous studies on severe malaria conducted in Tanzania, we knew that the rate of adverse outcomes is higher in nonmalaria patients, compared with the rate in malaria patients, because diseases such as pneumonia, typhoid or meningitis have a fatality rate at least as high as that of malaria and because severely ill febrile patients are often misdiagnosed as having malaria and therefore do not receive appropriate antibiotics (Makani *et al*. 2003; Reyburn *et al*. 2004). Such a trend was also found in our study which included less severe cases. Therefore, accurate diagnosis is essential even at outpatient level to prevent the further occurrence of complications and deaths. This is especially true now, because of the regular decrease in malaria transmission in many endemic settings of endemicity (WHO 2008; Ceesay *et al*. 2008; O'Meara *et al*. 2008), and therefore the relative increase of fevers due to other treatable causes in many places in Africa.

Outcome on day 7

In our study, the percentage of children not cured on day 7 was very low in both groups (2% in the malaria group versus 3% in the nonmalaria group). The 9 malaria patients who were still sick after 1 week all had a negative result for a follow-up blood slide. Therefore, it is very likely that they were suffering from another fever cause, with parasitemia being coincidental. For the nonmalaria cases, 17 of the 18 children who were not cured on day 7 had received an antibiotic, which suggests that they had either a viral disease with prolonged fever or a bacterial disease resistant to the first-line antibiotic. In these 2 areas, we know that nonmalaria fevers are composed of 56% acute respiratory infections, 10% gastroenteritis, 6% urinary infections, 3% typhoid, 3% other documented infections and 22% fever of unknown origin. Furthermore, 68% of acute respiratory infections and 31% of gastroenteritis are associated with documented viruses (Chapter 9) that obviously do not respond to antibiotics and that therefore tend to persist longer than malaria episodes treated with an effective drug. For nonmalaria fevers due to bacteria, the high rate of resistance to first-line antibiotics in Tanzania also leads to prolonged episodes (Blomberg *et al.* 2007).

Outcome of children with negative initial results and positive subsequent results

There are several reasons for which a malaria test can yield negative initial results and positive subsequent results within a few days: (1) coincidental low-density malaria fluctuating around the threshold of detection of a malaria test; (2) symptoms and signs appearing before parasites can be detected in the blood by conventional tests, especially in non-immune infants or young children; (3) new infections; and (4) failure of the test (negative test result in the presence of normal density parasitemia). Coincidental or new infection is the most likely explanation for 2 out of the 3 patients

with initial positive results and positive subsequent results. In an area of high endemicity, it is expected to have some children presenting with new parasitemia every day. We found in our sample of children from Signal an incidence of malaria in the 7 days after a negative test result of 0.45 episodes per child per year, which is lower than expected. This rate is close to the one reported by Njama-Meya *et al* (0.42 episodes per child per year) (Njama-Meya *et al*. 2007) and found by using microscopy instead of *m*RDT. It is also similar to the incidence of malaria episodes in infants (0.43 episodes per infant per year) found by using passive-case detection in the main town of Kilombero District in the year 2000 (Schellenberg *et al*. 2004). Failure of the *m*RDT to detect parasitemia of a density high enough to be detected by conventional test did not occur in our study, because all 3 patients who had negative *m*RDT results at inclusion also had negative results by expert microscopy. In Njama-Meya's study (Njama-Meya *et al*. 2007), this happened for 2 children diagnosed with expert microscopy. False negative results do exist with *m*RDT but possibly at a lower rate than with expert microscopy, as demonstrated by Ochola *et al* (Ochola *et al*. 2006) and Bell *et al* (Bell *et al*. 2005).

5.6 Conclusions

In 2 Tanzanian settings (1 urban and 1 rural), the strategy of *m*RDT-based diagnosis and treatment proved to be safe, with no case missed by a negative initial *m*RDT result ending in complication or death. The sample size of our study allowed us to say with 95% confidence that the probability of such an unfavourable event was between 0% and 0.5% (rule of three) (Eypasch *et al*. 1995). Although our study does not provide the definite answer in this matter, it contributes important evidence towards a change in policy in malaria diagnosis and treatment, and thus towards a better management of fever in countries endemic for malaria.

5.7 Acknowledgments

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Potential conflicts of interests. All authors: no conflicts.

6. Time to move from presumptive malaria treatment to laboratory confirmed diagnosis and treatment in African children with fever

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Background to the debate: Current guidelines recommend that all fever episodes in African children be treated presumptively with antimalarial drugs. But declining malarial transmission in parts of sub-Saharan Africa, declining proportions of fevers due to malaria, and the availability of rapid diagnostic tests mean it may be time for this policy to change. This debate examines whether enough evidence exists to support abandoning presumptive treatment and whether African health systems have the capacity to support a shift toward laboratory-confirmed rather than presumptive diagnosis and treatment of malaria in children less than five.

In this Viewpoint, Blaise Genton and colleagues argue in favour of abandoning presumptive treatment for under-fives. Mike English and colleagues present the opposing Viewpoint in a related article:
English M, Reyburn H, Goodman C, Snow RW (2009) Abandoning presumptive antimalarial treatment for febrile children aged less than five years—A case of running before we can walk? PLoS Med 6(1): e1000015. doi:10.1371/journal.pmed.1000015

This paper has been published in *Plos Medicine* 2009; 6(1): e252

Malaria has long been the number one cause of fever and the leading cause of child mortality in sub-Saharan Africa. As a result, the World Health Organization (WHO) recommends treating any fever episode in African children with antimalarial drugs to save lives. However, this approach may not be as safe as it was 20 years ago for two major reasons. Firstly, the proportion of fevers due to malaria has become significantly lower, even in highly endemic areas, and hence the relative likelihood of missing other potentially fatal diseases has become higher. Secondly, we now have new reliable rapid diagnostic tests (*m*RDT) to allow proper diagnosis of malaria at all levels of the health system.

Evidence of Decreased Malaria Transmission in Sub-Saharan Africa, and Declining Proportion of Fevers Due To Malaria

There is growing evidence documenting a substantial decline in malaria transmission, morbidity, and mortality in more than 13 African countries where malaria control interventions have been implemented at scale. This reduction is also observed in areas with previously high levels of transmission (e.g., WHO, Geneva 2008). Although available data are not always spatially congruent, and therefore cannot necessarily be viewed as representing secular changes, the sharp decline in sub-Saharan Africa of the Plasmodium falciparum prevalence rate in children aged two to ten years—from 37% in the years 1985–1999 to 17% in 2000–2007—clearly documents this trend (Guerra *et al*. 2008). This decrease implies that many of the areas previously defined as “high stable malaria transmission” have changed, or will soon change, into “moderate to low transmission” areas.

The lower the transmission, the lower the probability that a fever episode will be due to malaria. In Tanzania, a high endemicity country, only one to four out of ten under-five patients with fever are parasitaemic in the rural settings (Kabanywany 2007 and D’Acremont 2008, personal communications; (Wang *et al*. 2006a). With a decline in malaria’s prevalence, the hazard of misdiagnosis of many children becomes significant. When giving an antimalarial, the health worker is less likely to look for another treatable cause of fever, and this leads to higher morbidity and mortality due to delay in giving appropriate treatment, as suggested by studies that showed higher case fatality rates among non-malaria fevers compared to malaria fevers (Reyburn *et al*. 2004).

Availability of *m*RDT for Malaria

The shift from symptom-based diagnosis to parasite-based management of malaria requires that clinicians have a reliable, easy-to-use, and inexpensive diagnostic test. It should have good sensitivity, require minimal training and equipment, and retain accuracy even after extensive storage under tropical conditions. All these characteristics are met by the new generation of *m*RDT. Two meta-analyses have clearly shown that the performance of *m*RDT is comparable to that of expert microscopy (Marx *et al*. 2005; Ochola *et al*. 2006). Appropriate action taken on the basis of the test result is now the key element for the successful introduction of *m*RDT. Unfortunately this has not

always been achieved in the implementation of *m*RDT so far, partly because the training was insufficient to change the clinician's perception of malaria risk (Hamer *et al*. 2007). In addition, the ambiguous messages from WHO and national guidelines stating that malaria should be considered even in the presence of a negative test have added to the confusion (D'Acremont *et al*. 2007).

At present risk levels, the risk of missing a malaria case due to a false-negative test is substantially smaller than the risk of the patient dying due to another severe disease because of the focus on malaria. The risk of a false-negative test and its potential consequences have recently been evaluated thoroughly in Uganda (using microscopy) (Njama-Meya *et al*. 2007) and in Tanzania (using *m*RDT; Chapter 7), and the safety of not treating malaria-negative children confirmed.

Other compelling arguments for systematic testing are listed in Box 1 (Lubell *et al*. 2007; Shillcutt *et al*. 2008).

Box 1. Additional Arguments for a Shift from Presumptive Malaria Treatment to Laboratory-Confirmed Diagnosis and Treatment According To Test Results in Children Under Five with Fever

- Treating all fever patients with antimalarials leads to a huge drug wastage, and hence potential for drug shortage
- Inappropriate use of antimalarials leads to unnecessary adverse drug reactions
- Irrational use of antimalarial drugs leads to increased parasite resistance
- Potential mistrust on the part of the public on the real efficacy of artemisinin-based combination therapies (ACTs) due to use for inappropriate indications (viral or bacterial disease)
- Parasitological diagnosis and treatment with ACTs according to test results versus presumptive treatment with ACTs is costeffective in all current malaria-endemic situations (as long as test result is taken into account)

Caveat

A switch from presumptive treatment to laboratory-confirmed diagnosis and treatment is now urgent but needs to be carefully planned. Large-scale deployment of *m*RDT is a great challenge that requires theoretical and practical training, regular supervision, and sustained financial mechanisms to ensure constant availability. It is crucial that quality assurance is implemented at all steps.

Also, introduction of reliable diagnosis implies that clinicians need to be trained to manage the "negative syndrome" (patients with a negative malaria test). This is challenging after years of upholding the notion that fever equals malaria and requires substantial change in the behaviour of clinicians and caretakers. This is now a great opportunity to update and re-strengthen the Integrated Management of Childhood Illnesses to promote improved case management of African children.

Conclusion

The recent trend of malaria decline in Africa calls for a shift from presumptive treatment to laboratory-confirmed diagnosis and treatment in all areas, regardless of age and level of malaria transmission. Such a move is especially relevant with the new momentum towards elimination and is now realistic thanks to reliable *m*RDT. As part of renewed malaria control efforts, it is time to improve clinical management and abandon irrational use of drugs, i.e., antimalarial treatment for no malaria and no treatment for other potentially fatal causes of fevers.

7. Massive reduction of antimalarial prescriptions after Rapid Diagnostic Tests implementation in Dar es Salaam, Tanzania

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Key words: rapid diagnostic test, malaria, antimalarial, drugs, diagnosis, compliance

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7.1 Abstract

Background: Presumptive treatment of all febrile patients with antimalarials leads to massive over-treatment, especially in areas with low malaria endemicity. We aimed to assess the effect of implementing malaria rapid diagnostic tests (*m*RDT) on the prescription of antimalarials and case management.

Methods: After training of health workers, *m*RDTs were introduced in Dar es Salaam in all 3 district hospitals and 6 primary care facilities. Three comparable health facilities (HF) without *m*RDTs were selected randomly as matched controls. We used two different data collection tools: (1) routine statistics of antimalarial prescription recorded in ledger books before and after intervention (total 33 months), and (2) repeated cross-sectional surveys in all HF, investigating consultation processes. We evaluated the impact of *m*RDT implementation on antimalarial prescriptions with three independent designs: (1) comparing drug consumption data before and after *m*RDT implementation (2a) comparing consultations processes before and 18 months after intervention, and (2b) comparing contemporaneously consultations processes in 9 intervention and 3 matched control HF (cluster-randomized analysis).

Findings: Based on routine statistics, the amount of artemether-lumefantrine blisters used post-intervention was reduced by 68% (95%CI 57–80) in intervention and 32% (9–54) in control HF. For quinine vials, the reduction was 63% (54–72) in intervention and an increase of 2.49 times (1.62–3.35) in control HF. Repeated cross-sectional surveys before-and-after *m*RDT implementation showed a similar decrease of 77% (from 75% to 20%) in the number of patients receiving antimalarial treatment (RR 0.23, 95%CI 0.20–0.26). The cluster-randomised analysis showed a considerable difference of antimalarial prescription between intervention HF (22%) and control HF (60%) (RR 0.30, 95%CI 0.14–0.70). Adherence to test result was excellent since only 7% of negative patients received an antimalarial.

Interpretation: Programmatic implementation of *m*RDT in a moderately endemic area reduced drastically over-treatment with antimalarials. Properly trained clinicians with adequate support complied with the recommendation of not treating patients with negative results.

7.2 Introduction

One essential component of the global malaria strategy is prompt diagnosis and treatment (within 24 hours of onset of illness) with an effective drug (WHO 2006). Because of the scarce availability of laboratory facilities and the high mortality of malaria in young children, presumptive treatment in case of fever was seen as the only practical solution to improve child survival. This strategy thus became part of the Integrated Management of Childhood Illness (IMCI) decision chart. The strategy of presumptive treatment was easily and rapidly adopted by health workers to such an extent that it started also to be applied: 1) to children older than 5 years and even adults; 2) in low endemicity

areas; and 3) in setting where laboratory diagnosis was actually available (Zurovac *et al*. 2006b). This led to a situation in which the principle of proper diagnosis prior to treatment became an exception rather than the rule. Whatever the medical history (when taken) and irrespective of the clinical examination (if done at all), the same treatment is prescribed: an antimalarial drug, possibly supplemented by an antipyretic. When the patient returns with persistent fever a second-line antimalarial drug is given, sometimes intravenously. This may go on until either the spontaneous recovery of the patient from his/her (often viral) illness or up to a deterioration of the patient's condition due to an unrecognized bacterial infection. The strategy of presumptive treatment of all fevers with antimalarials lead clinicians to believe that all fevers are due to malaria, resulting in a massive over-diagnosis (Masika *et al*. 2006; Chapter 7), and more importantly to ignoring non-malaria causes of fever that have similar, or even higher case fatality rates than malaria (Makani *et al*. 2003; Reyburn *et al*. 2004).

The availability of reliable, easy-to-use and affordable rapid diagnostic tests (*m*RDT) allows now a realistic switch from presumptive treatment to laboratory-confirmed diagnosis and treatment upon result (Chapter 6). This is especially important considering the trend of malaria decline in Africa, which leads to a strong reduction in the proportion of fevers due to malaria. There is now solid consensus that diagnosis should be part of fever case management everywhere and WHO is about to change its previous recommendation on this (R. Newman, personal communication). Hence, the discussion is now no more on whether laboratory diagnosis for malaria should be deployed (English *et al*. 2009) but on how best to effect it. Zambia was the first Sub-Saharan country to deploy *m*RDT at the national scale in 2004. Since then, several countries have adopted laboratory-confirmed diagnosis, even in highly endemic areas. However, the implementation of *m*RDT at scale poses also many challenges. Rigorous procedures to train and supervise clinicians, to strengthen procurement systems and to ensure quality assurance need to be established. Strong monitoring and evaluation plans need to be put in place. The impact of large-scale implementation of *m*RDT needs to be carefully assessed in different settings and health systems to ensure that it actually reduces over-diagnosis, wastage of antimalarial drugs and prevents patient suffering.

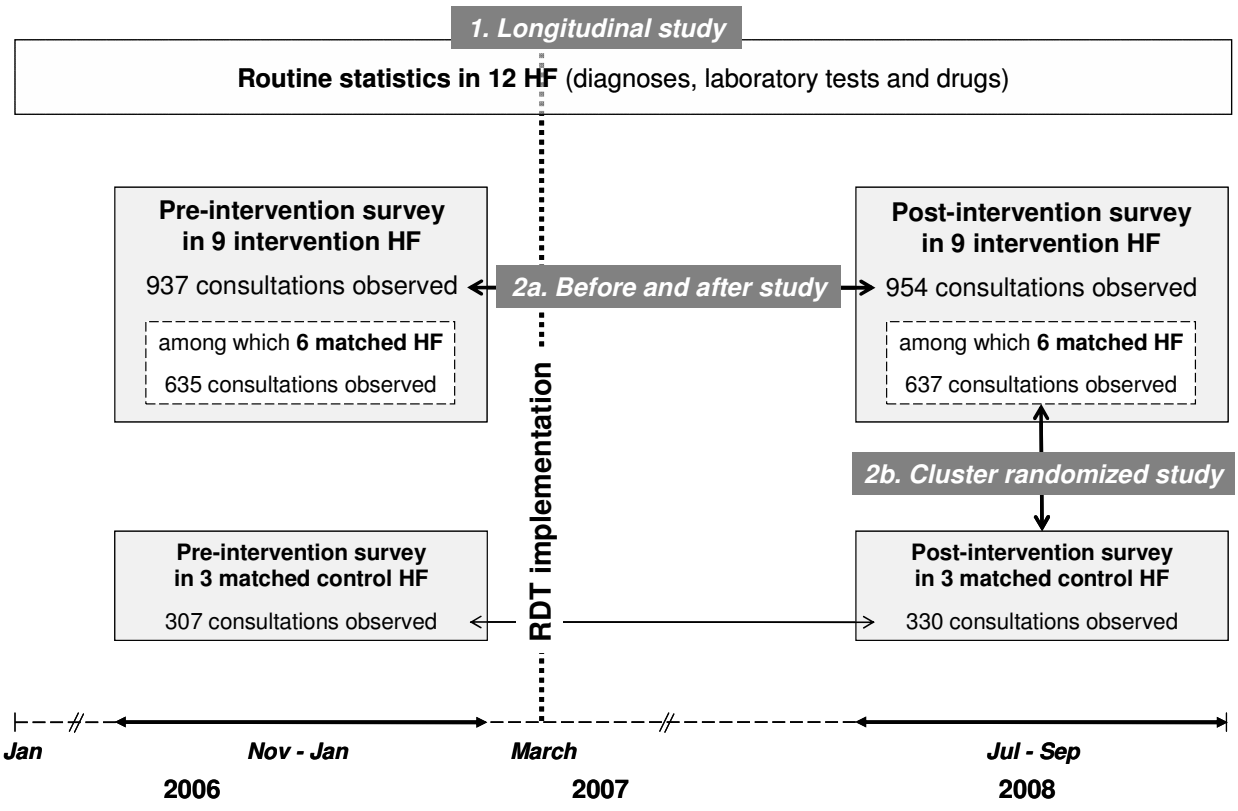
In order to evaluate the impact of *m*RDT implementation on antimalarial use and fever case management, we conducted a large study under near-programme conditions in an urban setting of Tanzania with low to moderate malaria endemicity. Our primary objective was to measure the change in overall antimalarial prescription at different levels of the health system. Secondary objectives were to assess the effect of *m*RDT implementation on the number and type of patients tested and/or treated for malaria, the number of non-malaria laboratory tests performed and the number of antibiotic prescriptions. To ensure robustness in our findings, we used data from two independent sources and evaluated the effects of *m*RDT implementation with three different designs, including a randomized cluster analysis.

7.3 Methods

Study setting and population

The study took place from January 2006 to September 2008 in Dar es Salaam, the economic capital of Tanzania, with an estimated population of over 3'000'000 inhabitants. Dar es Salaam has 3 municipalities with a public health system organized in 3 levels (district hospital, health centres and dispensaries). We included all three district hospitals (Mwananyamala, Amana and Temeke hospitals), 4 health centres (HC) among the existing 6, and 5 dispensaries (D) among the existing 10 in the urban zone of the town. In each municipality we created a trio of similar HC/D (9 in total) on the basis of the following criteria: availability of microscopy, accuracy of the general registers (called MTUHA books) and laboratory registers, socio-economic status of the catchment population, quality of governance of the health facility (HF) and willingness of the staff to participate. We then randomly assigned one HC/D in each trio to be the control HF by picking pieces of paper with the names of the HF out of a hat. We thus ended up with 6 intervention HF (2 HC/D per municipality) and 3 control HF (one HC/D per municipality), as well as the three hospitals in which the intervention was also implemented but for which we could obviously not find controls (Figure 12).

Figure 12: Study methodology with 3 different evaluation methods: (1) longitudinal routine statistics collection, (2a) repeated cross-sectional surveys on consultations processes with a before-and-after comparison and (2b) cluster randomized comparison of consultation processes. HF = Health facilities



Intervention

In February 2007, after a sensitization meeting with the persons in charge of the 9 intervention HF, the City Medical Officer of Health (who was also one of the investigators) and representatives of the Municipal Medical Offices of Health, we organized 5 one-day training sessions attended by a total of 116 clinicians, 31 laboratory technicians, 31 nurses and 3 pharmacists. The training included one hour on the situation of malaria in Tanzania, half an hour on malaria diagnosis in Africa and in Dar es Salaam, one hour on the clinical use of each type of malaria tests, one hour practical in which participants performed a *m*RDT on each other, and finally 2 hours of group work on 5 clinical case studies. The guidelines for the use of *m*RDT were the following: 1) only patients complaining of fever should be tested; 2) no antimalarials should be prescribed when the result of the *m*RDT is negative, regardless of the age of the patient; 3) for non-malaria problems, IMCI guidelines should be followed in children less than five years. Feedback from the health workers on the training was very positive, although they would have liked to learn more on how to manage non-malaria fevers.

We then went to each HF to discuss *m*RDT implementation using a standard check-list to be filled in by the focal person for *m*RDT. Between mid- and end of March 2007, we brought the first consignment of *m*RDT and did a supervision visit 3 days later in each HF. Thereafter, supervision took place 1, 2, 5, 10 and 15 months after *m*RDT introduction. Specific problems in 4 HF were addressed by one or two additional on-site meetings. No incentives were given to any health worker. Control HF were given *m*RDT after 18 months (November 2008), after training their clinical staff.

Project design

In order to come to robust conclusions we collected data with two complementary tools, and assessment our outcomes with three different designs (Figure 12).

1) Routine statistics from ledger books

A longitudinal study based on the continuous monitoring of routine statistics (MTUHA books) was conducted for a period of 15 months before (including one long and one short rainy season) and 18 months after *m*RDT implementation (including two long and one short rainy season). We collected all MTUHA books from the years 2006 to 2008 to get monthly information on the following: number of new attendances, number of specific diagnoses, number of laboratory tests, number of malaria tests and their results. We also collected for each health facility the number of antimalarials and antibiotics dispensed per month from ledger books in the pharmacies. To get the monthly consumption for each drug we counted the total number of tablets, vials or blisters (for artemether-lumefantrine - ALu) issued by the main store to the different departments of the HF, excluding the drugs issued to another HF. To get the monthly number of ALu dispensed to patients, we counted the number of patients receiving one of the 4 types of blisters from the books used at the dispensing windows.

2) Cross-sectional surveys of consultation processes

We also conducted two cross-sectional surveys, one that took place 2-5 months before and the other 15-18 months after *m*RDT implementation in the 9 intervention and 3 control HF (Figure 12). In each

HF survey 100 consultations were observed at the Outpatient Department. In order to lessen the influence of season, 50 consecutive consultations were observed in each HF in a first week and an additional 50 consultations were observed 6 weeks later. The targeted sample size for each of the two surveys (before and after) was thus 1200 consultations. The inclusion criteria for attending patients were: 1) first consultation for the present problem; 2) absence of severe illness requiring immediate admission or referral; 3) main complaint not being an injury or trauma. As clinicians in Dar es Salaam tend to consider the diagnosis of malaria even in the absence of fever (Zurovac *et al*. 2006b), we did not have fever/history of fever as an inclusion criteria. A standardized questionnaire in Swahili language was used by the research clinicians while observing the consultation process.

A first consent to participate was requested from the observed clinician after explaining him/her the aims of the study and the conditions of observation (confidentiality, anonymity and no interference). Informed consent was then requested by the observed clinician from each of his/her patients. The following were observed: complaints mentioned spontaneously by the patient, questions asked by the clinician and the corresponding answers by the patient, signs looked for and laboratory tests ordered by the clinician, tests results, diagnoses, drugs and advice given by the clinician.

This cross-sectional information was analyzed using two designs: (1) comparing antimalarial prescriptions between pre-intervention and 18 months post-intervention surveys in the 9 intervention health facilities (thereafter called before-and-after analysis) and (2) comparing antimalarial prescriptions between 6 intervention and their 3 matched controls contemporaneously, during the post-intervention survey (cluster-randomized analysis) (Figure 12).

Statistical analyses

For the routine statistics data, the unit of analysis was the HF rather than the patient, in order to give the same weight to each HF. Linear models were fitted to the monthly number of antimalarial or antibiotic doses issued and the number of performed diagnostic tests, and results were expressed as a percentage of the pre-intervention mean. Random effects allowed accounting for differences between health facilities. The results were finally expressed as the ratio of numbers post- over pre-intervention (PP). From this, the percentage reductions could be calculated as (1-PP) * 100. For drug variables, 95% confidence intervals (CI) could not be calculated for the individual HF, because of the auto-correlated structure of the data, reflecting month-to-month variations in issuing of drugs. For instance, when large drug volumes were issued from the main store on a certain month, there could be a compensatory reduction the next month. Data were entered in Microsoft Excel 2002 and analysed using the STATA version 10 xtreg command.

For the cross sectional studies (before-and-after and cluster randomized analyses), the unit of analysis was the patient. Since the number of consultations observed in each facility was almost the same, the weight given to each HF was almost identical and this allowed a direct comparison with the longitudinal study. Comparison of proportions was done by calculating odds ratios using a multilevel mixed-effects logistic regression model to account for clustering. Risk ratios (RR) were

calculated from the fitted values for each cell of the 2 by 2 tables. P-values (2-sided) were calculated using Pearson κ^2 statistics. Data were entered in Epi Info version 3.5.1 and analyzed in STATA version 10.

The level of agreement between results given by the two different sources of data (the routine statistics and the repeated cross-sectional surveys) was measured by the Lin concordance-correlation coefficient (Lin 1989).

Role of the funding body

The sponsor of the study (Swiss National Science Foundation) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

7.4 Results

1. Routine statistics from ledger books – longitudinal study

Nearly all required data could be retrieved from the MTUHA books with a few exceptions: among a total of 3960 monthly data points to be collected (10 variables measured in 12 HF during 33 months), only 36 were missing. For the monthly drug quantification, missing data were replaced by the mean of all data of the corresponding pre- or post intervention period. Missing monthly numbers of consultations were replaced by the mean of the value from the month before and the month after.

Impact of mRDT implementation on antimalarial consumption

The number of ALu blisters issued by the main store of the 9 intervention HF decreased from 20'660 per month to 7'933 per month after *m*RDT implementation. It decreased in each of the 9 HF with PP ranging from 0.04 to 0.63 (Table 4). When using HF as a unit the overall PP was 0.32 (95% CI 0.20–0.43) corresponding to an overall decrease of 68%. The impact of *m*RDT was stronger in dispensaries than in health centres or hospitals (PP 0.26 versus 0.35 and 0.34). There was also a clear trend when analyzing the data by municipality (PP 0.32, 0.22 and 0.41 for Municipality 1, 2 and 3 respectively). When only looking at the last 6 months of the study to assess the sustainability of *m*RDT implementation the results were even better (PP 0.25, 95% CI 0.13–0.37). In the 3 control HF, the overall PP using the whole period was 0.68 (95% CI 0.46–0.91) (Table 4).

Table 4: Routine statistics of ledger books: average monthly number of patients positive by *m*RDT, and ALu blisters & quinine vials issued by the main store, before and after *m*RDT implementation, in intervention and control health facilities.

Health facility	Patients positive by *m*RDT Number per month *(SD)*	ALu blisters [£] Before RDT initiation* Blisters per month n	ALu blisters [£] After RDT initiation[#] Blisters per month n	ALu blisters [£] Post-intervention blisters as a proportion of pre-intervention PP (95% CI)	Quinine vials [&] Before RDT initiation[$] Vials per month n	Quinine vials [&] After RDT initiation[#] Vials per month n	Quinine vials [&] Post-intervention vials as a proportion of pre-intervention PP (95% CI)
Intervention health facilities							
Hospital 1	495 [¢]	4560	1326	0.29	3205	1503	0.47
Hospital 2	323	1500	307	0.20	5049	549	0.11
Hospital 3	335	3100	1608	0.52	1747	1048	0.60
Health centre 1	329	3000	1890	0.63	830	272	0.33
Health centre 2	209	1430	268	0.19	553	86	0.16
Health centre 3	93	1540	360	0.23	177	92	0.52
Dispensary 1	43	650	25	0.04	59	26	0.44
Dispensary 2	101	770	202	0.26	245	85	0.35
Dispensary 3	210	4110	1947	0.47	303	111	0.37
Total of 9 HF[₸]				0.32 (0.20 - 0.43)			0.37 (0.28 - 0.46)
Total of 6 matched intervention HF[₸]				0.30 (0.15 - 0.46)			0.36 (0.24 - 0.48)
Control health facilities							
Control 1	N.A	1900	1952	1.03	280	766	2.73
Control 2	N.A	3410	1353	0.40	209	151	0.72
Control 3	N.A	4180	2617	0.63	217	871	4.01
Total of 3 matched control HF[₸]				0.68 (0.46 - 0.91)			2.49 (1.62 - 3.35)

[£] One blister of ALU is needed for one antimalarial course, whatever the age or weight of the patient, [&] Between 2 and 6 vials are used per antimalarial course, * observation period of only 3 months because ALu only introduced in Tanzania in January 2007, [#] observation period of 18 months, [$] observation period of 15 months, [₸] allowing for random-effect.

Figure 13 shows the monthly consumption of ALu over time, with the contribution of each HF. The four weight categories of ALu blisters were included, with one blister counting as one antimalarial treatment course. There was a marked decrease in ALu consumption just after *m*RDT initiation and then a further decrease 4 months later. The initial 4 months of the intervention period was used to identify and rectify operational problems (use of microscopy instead of *m*RDT, lack of trust in laboratory technicians, conflict of interest with private laboratories, and reshuffle of staff) in the 4 HF where little impact was observed during the first 4 months.

We found a similar reduction of injectable quinine consumption in each of the 9 intervention HF (average PP 0.37, 95% CI 0.28–0.46) (Table 4). For quinine there was also a longer period of observation before *m*RDT initiation (15 months) compared to ALu which was only introduced in the country in January 2007. In the 3 control HF, there was a marked increase in quinine use over the same period (PP 2.49, 95% CI 1.62–3.35).

Figure 13: Number of artemether-lumefantrine (ALu) treatments and quinine vials issued monthly in each of the 9 intervention health facilities. Pre-intervention follow up times vary because ALu was only introduced in January 2007.

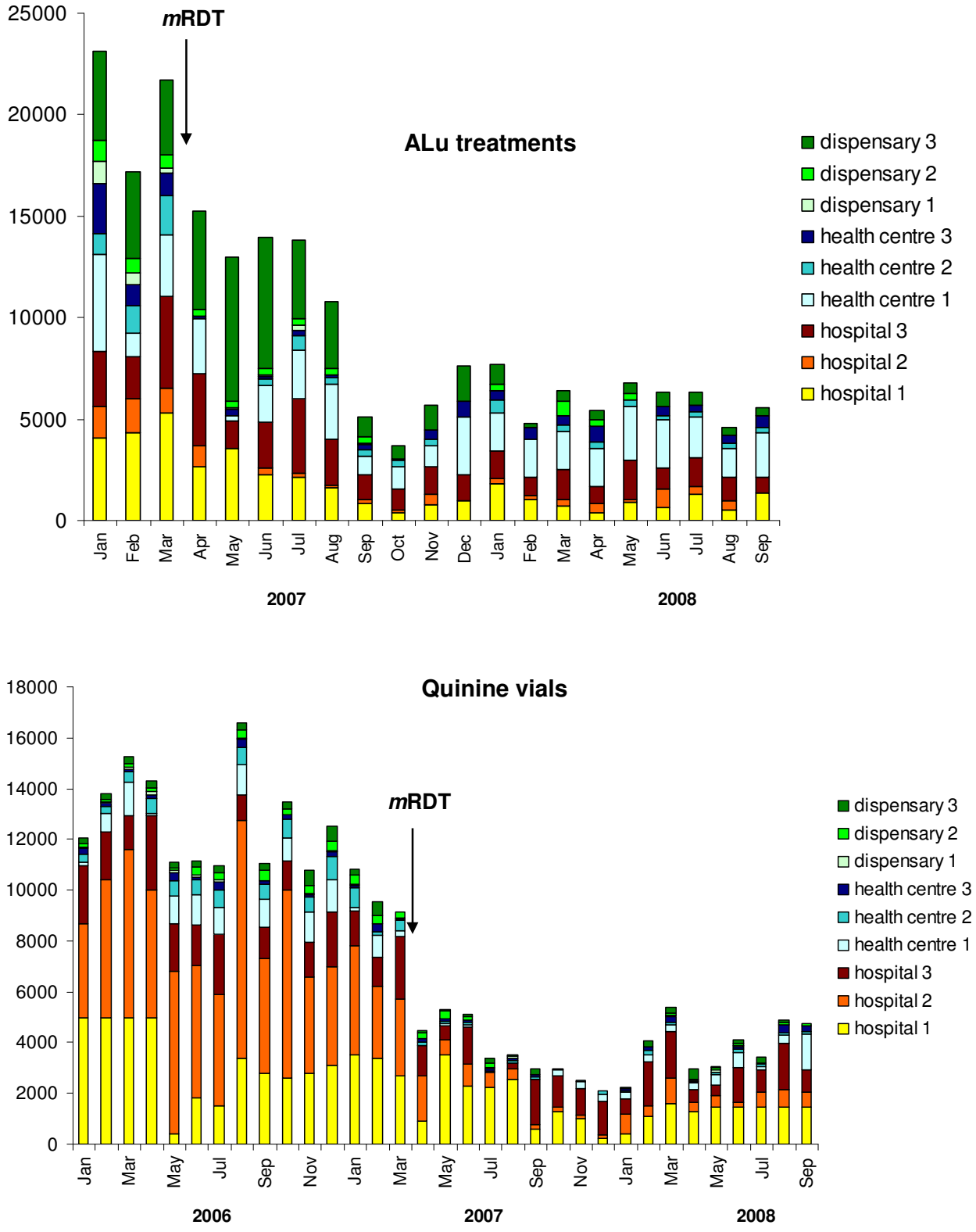


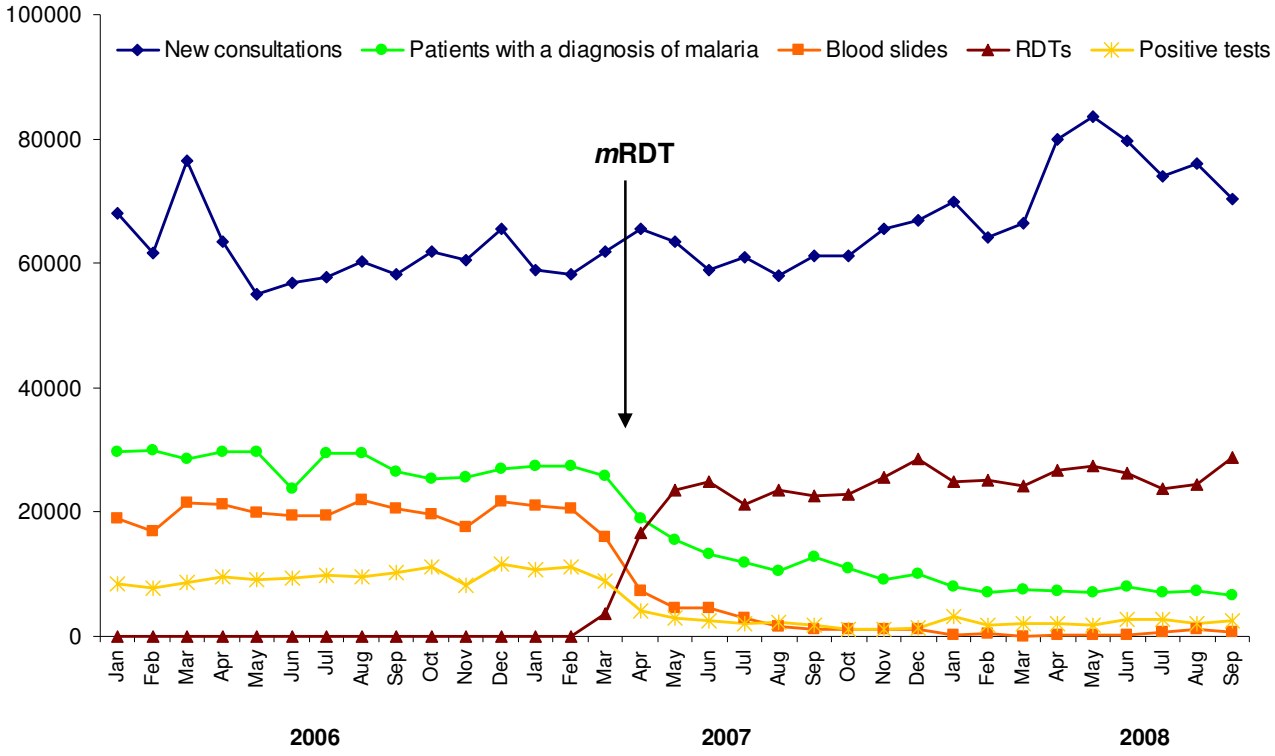
Table 4 shows that in some HF, the number of issued ALu blisters was much higher than the actual number of positive patients (median excess: 168%). These amounts represent the quantities 'consumed' by the HF and not necessarily the numbers of blisters received by patients. When looking at data from dispensing books between 6 and 12 months after *m*RDT implementation this excess was confirmed (data not shown). "Mishandling" of drug stocks is likely to be the main reason for the over-consumption of antimalarials after *m*RDT implementation (although at a much lower level than before).

Impact of mRDT implementation on malaria testing

In the 9 intervention HF, from January 2006 to March 2007 (before *m*RDT initiation) a total of 20'143 blood slides were performed on average per month. After *m*RDT initiation, 27'398 *m*RDT and 768 blood slides were performed on average per month (Figure 14). Microscopy was thus almost entirely replaced by *m*RDT as first-line malaria test, except for a few special cases (admitted patients, persisting fever in outpatients with malaria, during short periods of *m*RDT stock out).

The number of patients attending the 9 intervention HF for a new consultation increased slightly over time (61'642 before and 68'065 after *m*RDT implementation on average per month). The proportion of patients tested for malaria increased when *m*RDT were introduced (PP 1.21) and thereafter the proportion of patients tested was stable up to the end of the project (Figure 14).

Figure 14: Number of new consultations, blood slides and *m*RDTs performed, patients with a diagnosis of malaria and positive malaria tests, over time, in the 9 intervention health facilities.



Impact of mRDT implementation on diagnoses

The total number of patients with a diagnosis of malaria given by the clinicians was 27'693 per month before and 9'920 after *m*RDT initiation. This represents a 3-fold decrease (PP 0.33, 95% CI 0.28–0.38) (Figure 14). By contrast, for the diagnoses of acute respiratory infection, pneumonia, diarrhoeal diseases and urinary tract infections there was no change or even an increase after *m*RDT implementation (PP 1.02, 1.29, 1.15, 1.46, respectively). The number of "ill defined syndrome" as well as of "other diagnoses" increased much more (PP 2.14 and 2.36, respectively). In the 3 control HF, there was no change in the number of patients with a diagnosis of malaria (PP 1.03, 95% CI 0.82–1.24), while acute respiratory infections, pneumonia, diarrhoeal diseases and urinary tract infections increased after *m*RDT implementation (PP 1.59, 1.30, 1.55 and 2.12, respectively).

Impact of mRDT implementation on malaria positivity rate

At the time of microscopy, the positivity rate of the routine malaria tests in the 9 HF was very high: 51% (range 13 - 88%) and it was similar in the 3 types of HF: 41% in hospitals, 49% in health centres and 65% in dispensaries. After intervention, the positivity rate of routine *m*RDT was only 8% (range 6 – 12%; Figure 14), which is in line with what had been shown in previous studies using expert microscopy in Dar es Salaam (Wang *et al*. 2006a). A baseline assessment performed in the 12 HF included in our study had shown that the quality of routine microscopy was poor, with very low sensitivity (71%) and specificity (47%) (Kahama-Maro *et al*. 2008). Conversely, the performance of routine *m*RDT evaluated in one health centre was excellent (97% sensitivity, 97% specificity) and the quality assurance results for *m*RDT testing done all along the study showed excellent results (not shown). In control HF that kept on using microscopy, the positivity rate dropped only slightly after the intervention in the other HF: from 73% before to 60% after.

Impact of mRDT implementation on antibiotics consumption

The total consumption of oral antibiotics did not change after *m*RDT implementation (PP 1.02, 95% CI 0.92–1.13). In control HF, the total consumption of all oral antibiotics increased a bit more (PP 1.26, 95%CI 1.00–1.52) than in the matched intervention HF (PP 1.14, 95% CI 1.00–1.28). In general, the amounts of antibiotics consumed by HF were very high: about 38% of newly attending patients received an oral antibiotic after *m*RDT implementation versus 40% before.

Impact of mRDT implementation on laboratory tests other than malaria

The number of urine analysis and direct stool examination increased slightly after *m*RDT implementation (PP 1.18 and PP 1.23 respectively) in intervention HF. In control HF, both type of investigations increased more (PP 1.66 and 1.74 respectively).

2. Cross-sectional surveys: before-and-after analysis

The before-and-after analysis was based on the repeated cross-sectional observation of consultations before and after intervention in 9 intervention HF (Table 5). The proportion of children

were similar in the pre- and the post-intervention surveys (52 versus 53%), while slightly more female patients were included in the pre-intervention survey (60 versus 54%, p<0.02).

Impact of mRDT implementation on antimalarials consumption

Consultation observations performed before-and-after *m*RDT implementation revealed a decrease of 77% (from 75% to 20%) in the total number of patients receiving an antimalarial treatment (Table 5). This decrease (RR 0.23, 95% CI 0.20–0.26) was more pronounced in the subgroup of patients not complaining of fever (RR 0.16) than in the group complaining of fever (RR 0.25). This reduction was mainly due to a drastic change in the adherence of clinicians to test results. At the time of microscopy, 53% (95% CI 47–60) of negative patients were treated with antimalarials while this proportion was only 7% (95% CI 4–11) with *m*RDT.

Table 5: Before-and-after analysis based on repeated cross-sectional surveys investigating the consultation process: effect of *m*RDT implementation on the main outcomes

	Before *m*RDT implementation *Total patients = 937*			After *m*RDT implementation *Total patients = 954*			Risk ratio (accounting for clustering)		*p-value*
	n*	%	(95% CI)	n*	%	(95% CI)	RR	(95% CI)	
*Effect of mRDT implementation on **antimalarial treatment***									
Patients treated with antimalarials									
All patients	894	75%	(72-78)	912	20%	(17-22)	0.23	(0.20 - 0.26)	< 0.001
Patients complaining of fever	755	81%	(79-84)	682	24%	(20-27)	0.25	(0.22 - 0.29)	< 0.001
Patients not complaining of fever	139	42%	(33-50)	230	7%	(4-11)	0.16	(0.10 - 0.27)	< 0.001
*Effect of mRDT implementation on **adherence to malaria test result***									
Patients treated with antimalarials									
Patients with a positive malaria test	370	99%	(99-100)	126	99%	(98-100)	1.00	(0.98 - 1.01)	0.8
Patients with a negative malaria test	215	53%	(47-60)	628	7%	(5-9)	0.09	(0.06 - 0.13)	< 0.001
*Effect of mRDT implementation on **selection for malaria testing***									
Patients tested for malaria									
All patients	937	68%	(65-71)	954	83%	(81-85)	1.26	(1.19 - 1.33)	< 0.001
Patients complaining of fever	782	71%	(68-74)	717	91%	(89-93)	1.31	(1.25 - 1.36)	< 0.001
Patients not complaining of fever	155	49%	(41-57)	237	58%	(52-65)	1.21	(0.99 - 1.48)	0.06
*Effect of mRDT implementation on **antibiotic treatment***									
Patients treated with antibiotics									
All patients	894	49%	(46-53)	912	72%	(69-75)	1.47	(1.37 - 1.59)	< 0.001
Patients complaining of fever	755	49%	(45-52)	682	73%	(69-76)	1.50	(1.38 - 1.63)	< 0.001
Patients not complaining of fever	139	52%	(43-60)	230	71%	(65-77)	1.38	(1.16 - 1.65)	< 0.001
Patients with a positive malaria test	370	37%	(32-42)	126	35%	(26-43)	0.91	(0.68 - 1.21)	0.5
Patients with a negative malaria test	215	54%	(47-61)	628	78%	(75-81)	1.45	(1.28 - 1.65)	< 0.001
*Effect of mRDT implementation on **other laboratory tests than malaria***									
Patient tested for urinary infection	937	7%	(6-9)	954	13%	(11-15)	1.74	(1.31 – 2.31)	< 0.001
Patient tested for typhoid (Widal)	937	2%	(1-2)	954	1%	(1-2)	0.76	(0.36 – 1.63)	0.5
Patient tested for stool parasites	937	6%	(5-8)	954	7%	(6-9)	1.13	(0.81 – 1.59)	0.5

* numbers differ from total sample size because of the variables applying to different subpopulations of patients (and for drugs because a few patients who did not come back from laboratory to get treatment).

Impact of mRDT implementation on malaria testing

The overall proportion of patients tested for malaria increased by 26%, from 68% to 83%, RR 1.26 (95% CI 1.19–1.33) after *m*RDT initiation. This increase was mainly seen in patients complaining of fever (from 71% to 91%). In patients without fever, a high proportion was still tested after *m*RDT implementation (49% before versus 58% after, p=0.06).

Impact of mRDT implementation on antibiotics consumption

The overall prescription of antibiotics increased after *m*RDT initiation by 47%, from 49% to 72%, RR 1.47 (95% CI 1.37–1.59). This increase was slightly more important in patients complaining of fever (RR 1.50) than in those not complaining of fever (RR 1.38) and was seen in malaria negative patients but not in positive ones. As a result, the vast majority [78% (95% CI 75–81)] of negative patients were treated with an antibiotic after the introduction of *m*RDT.

Impact of mRDT implementation on laboratory tests other than malaria

*m*RDT implementation did not dramatically increase the request for alternative laboratory tests by clinicians, which remained generally low.

Convergence of results between the longitudinal and the before-and-after evaluations

Although the variability between HF was high, there was a strong intra-health facility convergence of the main outcome result (reduction of antimalarial use) between the longitudinal routine data assessment and the cross-sectional before-and-after assessment (Lin concordance- correlation coefficient: ρ_c =0.91) (Figure 15). This is a strong confirmation of the robustness of the data.

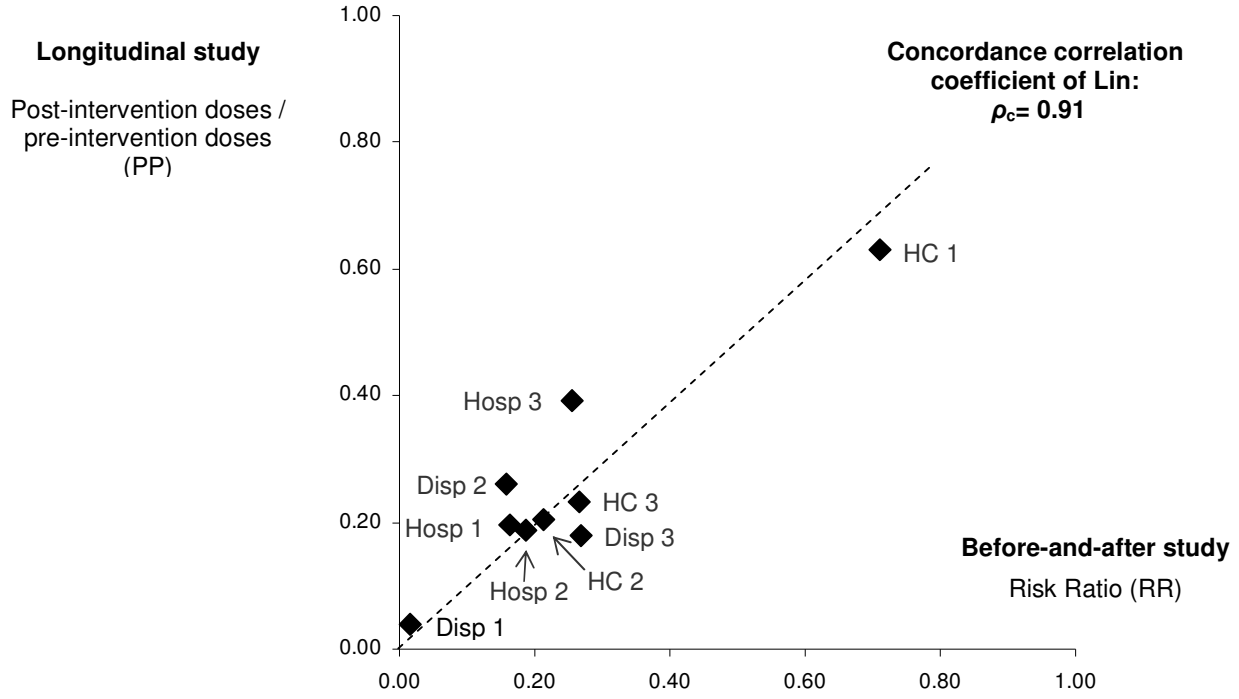
3. Cross-sectional surveys: cluster randomized analysis

The contemporaneous, post-intervention cluster-randomized comparison of patient consultations was carried out in 6 intervention versus 3 control HF (Table 6). Key population characteristics (age, gender) and outcome results were similar in intervention and control HF (p>0.05) (results not shown).

Impact of mRDT implementation on antimalarials consumption

There was a considerable difference between the two groups in the proportion of patients that were prescribed antimalarials: 22% in intervention versus 60% in control HF (from a baseline in both of 79%) (RR 0.30, 0.14–0.70) (Table 6). The difference was more pronounced in non-febrile than in febrile patients since only 9% of non-febrile patients received an antimalarial in intervention HF compared to 38% in control HF (RR 0.23, 95% CI 0.10–0.55). The reasons for the low antimalarial prescription in intervention HF were multiple: better selection of patients for malaria testing, better specificity of *m*RDT compared to microscopy and better adherence to *m*RDT result. On the other hand, in control HF the lower antimalarial prescriptions in post- versus pre-intervention survey was only due to a better trust in malaria test result (negative patients treated with antimalarials decreased from 43% to 25%), even if it was still based on microscopy.

Figure 15: Association between the measures for first-line antimalarials consumption reductions by two independent assessments: (1) health facility routine statistics based on ledger books, and (2) cross-sectional surveys using a before-and-after analysis.



Hospital 1, Hospital 3 and Dispensary 3 had difficulties at the start of *m*RDT implementation that could be solved with one additional training/meeting. Therefore, their ALU consumption further dropped after the 5th month of *m*RDT use. For these 3 HF we thus used the data of the last 13 months (instead of the whole period of 18 months).

Differences between intervention and control HF regarding antibiotic prescriptions

The proportion of patients that were prescribed antibiotics was higher in intervention HF than in controls: 71% versus 53% respectively (from a baseline of 50 and 51%) (RR=1.34, 95% CI 1.08–1.70). There was, however, no significant difference by category of patients (with/without fever; with positive/negative result), which confirmed that the overall difference in antibiotic prescription was almost only due to the higher number of negative patients and not to a behavioural change of clinicians.

Impact of mRDT implementation on laboratory tests other than malaria

The proportions of patients tested for urine, stool or the Widal test did not increase after *m*RDT implementation in both the intervention and control HF ($p > 0.05$).

Table 6: Cluster randomized analysis based on the post-intervention cross-sectional survey investigating the consultation process: comparison between 6 intervention and 3 control health facilities.

	Intervention health facilities N=637			Control health facilities N=330			Risk ratio (accounting for clustering)		
	n*	%	(95% CI)	n*	%	(95% CI)	RR	(95% CI)	*p-value*
*Effect of mRDT implementation on **antimalarial treatment***									
Patients treated with antimalarials:									
All patients	618	22%	(19-25)	318	60%	(54-65)	0.30	(0.14 - 0.70)	0.007
Patients complaining of fever	473	26%	(22-30)	253	65%	(59-71)	0.31	(0.16 - 0.67)	0.004
Patients not complaining of fever	145	9%	(4-14)	65	38%	(26-51)	0.23	(0.10 - 0.55)	0.001
*Effect of mRDT implementation on **adherence to malaria test result***									
Patients treated with antimalarials:									
Patients with a positive malaria test	96	100%	(100-100)	155	100%	(100-100)	1		N.A
Patients with a negative malaria test	412	7%	(5-10)	128	25%	(17-33)	0.09	(0.01 - 0.79)	0.03
*Effect of mRDT implementation on **selection for malaria testing***									
Patients tested for malaria:									
All patients	637	82%	(79-85)	330	89%	(86-92)	0.93	(0.86 – 1.04)	0.2
Patients complaining of fever	487	90%	(88-93)	263	95%	(93-98)	0.95	(0.91 - 0.99)	0.03
Patients not complaining of fever	150	57%	(49-65)	67	64%	(52-76)	0.91	(0.69 – 1.26)	0.5
*Effect of mRDT implementation on **antibiotic treatment***									
Patients treated with antibiotics:									
All patients	618	71%	(67-74)	318	53%	(48-59)	1.34	(1.08 - 1.70)	0.006
Patients complaining of fever	473	71%	(67-76)	253	52%	(46-58)	1.44	(1.09 – 1.94)	0.008
Patients not complaining of fever	145	68%	(61-76)	65	58%	(46-71)	1.17	(0.94 – 1.49)	0.2
Patients with a positive malaria test	96	32%	(23-42)	155	28%	(21-36)	1.14	(0.77 - 1.66)	0.5
Patients with a negative malaria test	412	77%	(73-81)	128	74%	(67-82)	1.05	(0.91 – 1.26)	0.5
*Effect of mRDT implementation on **other laboratory tests than malaria***									
Patient tested for urinary infection	637	9%	(7-11)	330	11%	(8-15)	0.73	(0.34 – 1.58)	0.4
Patient tested for typhoid (Widal)	637	2%	(1-3)	330	8%	(5-11)	0.29	(0.04 – 1.97)	0.2
Patient tested for stool parasites	637	7%	(5-9)	330	5%	(3-8)	1.27	(0.50 – 3.29)	0.6

* numbers differ from total sample size because of the variables applying to different subpopulations of patients (and for drugs because a few patients who did not come back from laboratory to get treatment).

7.5 Discussion

Our pilot implementation of *m*RDT for malaria in 9 health facilities in Dar es Salaam in near-programme conditions showed a dramatic reduction in antimalarials consumption. This was confirmed in all three methods of evaluation with two independent data sets: the longitudinal analysis of routine statistics (PP of 0.32 for ALu and 0.37 for injectable quinine), the before-and-after study based on pre- and post-intervention surveys (RR 0.23 for the first line treatment and 0.35 for injectable quinine) and the cluster-randomized analysis comparing matched intervention and control

health facilities (RR 0.26 for the first line treatment and 0.43 for injectable quinine). The high level of convergence of the results gives a strong robustness to the findings. The two main reasons for this decrease were illuminated by our observations of patient-provider interactions in the repeated cross sectional surveys. Firstly, the higher accuracy of routine *m*RDT compared to routine microscopy led to a dramatic reduction in the number of positive patients. Secondly, as health workers trusted *m*RDT results, the proportion of negative patients treated with antimalarials dropped from 53% to 7%. The impact was maintained up to the end of the observation period (18 months) and even increased after the initial 4 months thanks to targeted programmatic actions in poor-performing HF. In the control HF there was a moderate decrease in ALu consumption (PP 0.68), but a corresponding increase in quinine consumption and in the number of patients diagnosed with malaria.

The repeated cross sectional surveys showed that 1.49 *m*RDTs were needed to save one malaria treatment course. This was, however, at the cost of an additional 0.41 antibiotic treatment courses. If clinicians had been fully adherent to both patients selection for *m*RDT testing and treatment upon *m*RDT result, only 1.22 *m*RDTs would have been required. Our post-intervention survey took place just after the rainy season, when 18% of patients complaining of fever were positive by *m*RDT. If the malaria prevalence had been 5% (the lowest monthly rate observed in Dar es Salaam), clinicians would have needed 1.05 *m*RDTs per antimalarial treatment saved. From the longitudinal study, in which wastage of drugs between the main store and the dispensing window was important, we found that 2.15 *m*RDTs were necessary to save one ALu blister and half a vial of quinine. These observations show clearly how circumstances shape the effectiveness of *m*RDT implementation.

An interesting observation was the “contamination” of the control HF with some of the key messages passed on during our training activities. This was mainly due to health workers from intervention HF being shifted to work in control HF during the study period. Our message that the incidence of malaria in Dar es Salaam was much lower than commonly thought was clearly passed on to control HF. This helped clinicians to withhold antimalarials when the result of microscopy was negative and presumably also the microscopists to refrain from giving so many false positive results.

Routine statistics were considered meaningful because of the reasonable quality of registers in Dar es Salaam. Besides giving a robust confirmation that clinicians’ behaviour changes took place, this gave for the first time a unique measure of the amount of antimalarial drug that could be saved following *m*RDT implementation: 12’727 ALu blisters and 6’061 quinine vials per month in 9 HF, including the 3 district hospitals. The analysis of these routine statistics also identified another important source of drug wastage: the mishandling of drug stocks that were either lost, diverted or got expired between the main store and the patients. Initiatives aimed at reducing drug wastage should thus not only target clinicians’ prescription behaviour but also drug management more generally.

To our knowledge there are currently 7 studies that looked at the impact of *m*RDT on antimalarial prescription or clinicians’ adherence to *m*RDT result (Skarbinski *et al*. 2009; Hamer *et al*. 2007). One

Kenyan study was inconclusive because adherence to test result was already very high prior to any intervention (Skarbinski *et al*. 2009); two studies from Tanzania and Burkina Faso showed no effect of *m*RDT at all (Reyburn *et al*. 2007; Bisoffi *et al*. 2009); three studies from Zanzibar, Tanzania mainland and Uganda showed a strong impact (RR 0.42 and 0.29 for antimalarial prescription and RR 0.29 for over-prescription) (Msellem *et al*. 2009; Hopkins *et al*. 2008). A Zambian survey, conducted one year after deployment of *m*RDT at national scale, showed intermediate results (RR 0.62 for negative patients treated with antimalarials) but was underpowered because of an unexpected low number of patients tested for malaria (Hamer *et al*. 2007). All these studies are very heterogeneous in terms of setting, design and type of training and it is therefore difficult to draw conclusions on the reasons for failure or success. These studies were all different from ours in several ways: they took place in rather controlled conditions (except the Zambian study), used consultation observations only, and were conducted shortly after the start of *m*RDT implementation (with or without a baseline survey). The reasons given by the authors of the two studies showing no impact was the insufficient training on *m*RDT given to clinicians in the Tanzanian one and artemisinin-combination therapy not being available in the Burkina Faso one (Reyburn *et al*. 2007; Bisoffi *et al*. 2009). In Zambia, the very first experience of *m*RDT use in Africa outside South-Africa, the main problem was probably the assumption that clinicians would act upon *m*RDT result without problem (Hamer *et al*. 2007). By contrast, the successful Ugandan study put a strong emphasis on training and on giving straightforward messages (Hopkins *et al*. 2008). The Zanzibar study used a weekly cross-over design where nurses received a financial incentive to participate in the study and adhere to specific instructions on *m*RDT (Msellem *et al*. 2009). It is thus difficult to know if their success would be reproducible in a less controlled setting. The Tanzanian mainland study was also successful although no direct incentive was given, but a study staff member was physically on-site during the entire study period and all facilities were visited regularly by the supervisory staff (Williams *et al*. 2008).

Based on our observations and on the feed-back given by clinicians, we think that the major determinants for the positive results of our programme were the following: (1) the study was presented to clinicians as the pilot phase of a planned national deployment of *m*RDT; (2) as one of the main investigator of the study was the City Medical Officer of Health, health workers considered this assessment not just as an isolated research project but rather as the new guidelines for malaria management in the city; 3) the training was appreciated by the target audience for the following reasons: provision of strong evidence on malaria prevalence, on bad quality of routine microscopy and on performance of *m*RDT (from meta-analyses and data acquired locally), and effort to target their own reality with cases studies. The fact that the mutual mistrust between laboratory staff and clinicians around malaria test result could be spoken out and that *m*RDTs were presented as a tool to overcome this issue was probably also helpful. Clear take-home messages were given avoiding ambiguous messages (D'Acremont *et al*. 2007). We believe that our experience should be reproducible in the context of a well planned programmatic deployment of *m*RDT in the public health

system. Indeed our project is feasible when deployed at scale [short training (one-day), limited supervision (once quarterly) and absence of financial incentive].

Knowing the difficulty of clinicians to identify other causes of fever than malaria, we expected a potentially higher prescription rate of antibiotics. In the cluster-randomized study, we found that the overall proportion of patients treated with antibiotics increased by one third in intervention HF, while it did not change in control HF. This increase was mainly due to the increased number of negative patients, who were more often treated with antibiotics. This clearly highlights the necessity of integrating *m*RDT training in a broader training on management of fevers (IMCI or others).

Limitations of the study

In the longitudinal study, the impact of *m*RDT on antimalarials consumption might have been underestimated. Indeed the ALu decrease was less pronounced in the first 4 months post *m*RDT initiation than in the following months. This was related to problems at the start of the implementation that could be solved. Also the total number of attendances slightly increased over time, while our data for tests and drugs were not corrected by the total number of patients. The pre-intervention period was rather short for ALu (3 months), which reduces the strength of the assessment. However, the impact measured on the consumption of quinine vials, which was based on a much longer pre-intervention period (15 months), was quite similar to that of ALu. Also, the high intra-health facility convergence between these results and those of the before-and-after repeated cross-sectional study speaks for strong robustness of the findings.

7.6 Conclusions

When deployed appropriately (official support of the new tool by senior health authorities, high quality training, regular routine supervision and monitoring after implementation), *m*RDTs lead to a considerable saving of oral and injectable antimalarial drugs at all levels of the health system, including in hospitals. *m*RDT also prevent patients from misdiagnosis and adverse events of unnecessary antimalarial treatments. The potential of antimalarial saving through *m*RDT use could be maximized if other causes of drug wastage were tackled as well, i.e. drug procurement mechanisms based on the number of confirmed malaria patients, rigorous and dynamic management of stocks, similar diagnostic and treatment strategies in the private sector including pharmacies and drug shops. The downside of *m*RDT implementation is the shift from antimalarial wastage to antibiotic wastage due to insufficient knowledge and training on other causes of fever. Deployment of *m*RDT should therefore move hand in hand with strategies aimed at reducing irrational use of antibiotics at outpatient level, for example through updated IMCI decision charts promoted by innovative approaches for teaching and communication.

7.7 Authors' contribution

VDA, BG and CL designed the study. VDA and JKM led the project in the field with facilitation of DM. NS helped with the training and supervision of health workers. VDA analysed the data and wrote the manuscript. BG, CL and JKM contributed to the manuscript. All authors commented on the paper and agreed on the content.

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8. Cost-savings from Rapid Diagnostic Tests for malaria in low transmission areas? – evidence from Dar es Salaam

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8.1 Abstract

Rapid Diagnostic Tests (*m*RDTs) for malaria may help rationalize anti-malarial use; however, the economic effects of these tests may vary. Data on costs were collected from 259 patients in 6 health facilities using exit and in-charge interviews plus record reviews during a trial of *m*RDT roll-out in Dar es Salaam, Tanzania. *m*RDTs lowered patient expenditure on drugs (savings: USD 0.36; p=0.002) as well as provider drug costs (savings: USD 0.43; p=0.034) compared to control facilities. However, *m*RDT introduction did not significantly reduce patients' overall expenditure (USD 1.02 (0.76 – 1.36) vs. USD 1.33 (0.99 – 1.77)) and may increase total provider costs (USD 3.63 (3.40 – 3.89) vs. USD 2.32 (1.99 – 2.69)) when compared to control facilities. Clinician's compliance with test results was higher with *m*RDTs than with routine microscopy (95% vs. 82%; p=0.002). *m*RDTs reduced drug costs in this setting but did not offset the cost of the tests, though they also brought non-monetary benefits including improved management of patients and increased compliance with test results.

8.2 Introduction

Within African public health facilities, malaria is largely diagnosed on clinical grounds alone, and fever cases are routinely treated without laboratory confirmation (WHO 2009b). Malaria microscopy, when available, is often of poor quality (Mundy *et al*. 2000; Kahama-Maro *et al*. 2008). However, with the high costs of the new generation artemisinin combination therapy (ACT), as well as concerns about the development of drug resistance due to drug overuse, many donors and health system managers are searching for ways to improve the rational use of drugs for malaria treatment. Additionally, in many endemic areas, intense malaria control activities and rapid urbanization have led to falling clinical malaria incidence rates. As a consequence, the malaria-attributable rates in fever episodes have been falling, further increasing the need for improved diagnostic strategies (Chapter 6).

The modern generation of HRP2 antigen based rapid diagnostic tests (*m*RDTs) have been shown in trials to have high sensitivity and specificity for the diagnosis of *P. falciparum* infection among clinical patients in Africa (Bell & Peeling 2006; Ochola *et al*. 2006). Several studies have shown that the sensitivity of *m*RDTs can be higher than expert microscopy and thus far more accurate than routine microscopy. (Bell *et al*. 2005; Dal-Bianco *et al*. 2007; Stauffer *et al*. 2009).

There are potential drawbacks to the use of *m*RDTs for routine malaria diagnosis, including the persistence of the target antigen in the blood stream for up to several weeks after an infection has been treated, hence *m*RDTs cannot be used to measure treatment success (Mayxay *et al*. 2001; Iqbal *et al*. 2004; Swarthout *et al*. 2007). Additionally, such tests cannot determine parasite load and their specificity may vary with the setting (Bell & Peeling 2006).

While more accurate laboratory diagnosis may help to rationalize anti-malarial drug use at health facilities in Africa, there is also a clear possibility that any cost savings made from the reduction of anti-malarial prescriptions may be outweighed by increases in prescription of antibiotics or other

drugs to treat test-negative patients (Hume *et al*. 2008). Additionally, *m*RDTs add cost to case management which is not inversely proportional to the number of patients tested, as is the case for microscopy, and which could outweigh cost-savings from reduced anti-malarial consumption (Lubell *et al*. 2007). The effects of diagnostic changes will also depend on the adherence of clinicians to the diagnostic result, the frequency with which they request a test, as well as on the prevalence of parasitemia among the clinical population (Zurovac *et al*. 2006a; Lubell *et al*. 2008a).

There is a sizable body of literature which has examined the implications of improving malaria diagnostic methods, including both empirical and modelling studies. The results of the empirical studies have shown that there is a possibility to reduce average cost per patient as well as household costs through improved malaria diagnosis - and that such interventions could be implemented in a highly cost-effective manner (Jonkman *et al*. 1995; Zikusooka *et al*. 2008).

Modelling studies have helped to confirm and highlight the myriad factors which could influence both the cost-effectiveness and the overall cost-saving potential of improved diagnosis. The main factors which influence the desirability of one testing strategy over another relate to the proportion of febrile cases which are parasite positive, the sensitivity and specificity of the new method and its alternatives, the costs of the tests, clinicians' adherence to test results as well as the cost of the drug regimens prescribed to parasite-positive and parasite-negative patients (Shillcutt *et al*. 2008).

Since the potential for cost savings appear to be highly situation dependant it is necessary to evaluate the economic implications of the decision to shift to *m*RDTs locally and at specific levels of the health care system. While models can be used to explore these implications, there is still a strong rationale to assess alternatives and validate models empirically in representative settings (Lubell *et al*. 2008b). This paper describes a study of the economic implications of the implementation of diagnosis with *m*RDTs in a low-endemicity urban African setting in Dar es Salaam, in the United Republic of Tanzania.

8.3 Materials and Methods

Study area. Dar es Salaam is the economic capital of the United Republic of Tanzania. It is a large urban area (population approximately 3 million) with highly heterogeneous land use, including commercial districts, industrial districts, residential districts, urban slums, and areas with high levels of urban agriculture (Dongus *et al*. 2009). As a result there is high variability in the number of *Anopheles sp.* breeding sites and hence adult mosquito densities across the city. As of 2009 it is considered a low but stable malaria transmission area: EIR ≈ 1.3 (Geissbühler *et al*. 2009), with low parasite prevalence (less than 10% in the general population). All of the health facilities included in the costing exercise are located in densely populated low-income areas, though one facility's catchment area (Kawe Dispensary) also includes some peri-urban and higher income areas.

Twelve public health facilities were selected for inclusion in a trial of *m*RDT rollout three hospitals and 9 primary health care facilities The 3 hospitals were assigned to receive the *m*RDT intervention while the 9 primary care facilities were randomly assigned to either receive the *m*RDT intervention

(experimental) or not (control) (Chapter 7). Of these, six primary health care facilities were included in the costing exercise. Four primary care facilities were experimental facilities in which *m*RDTs replaced routine microscopy for the diagnosis of malaria. Two primary care health facilities, remained as controls with only routine microscopy. These six were selected because this evaluation was targeted at the primary care level and these facilities were the most comparable in terms of patient population, size and numbers of monthly consultations. Sample size was calculated using EpiInfo 3.4.1 (StatCalc Module) (U.S. Centers for Disease Control and Prevention, Atlanta, GA, USA) with the aim of being able to measure a 25% difference in arithmetic mean patient costs between *m*RDT and control facilities with 95% significance and 80% power.

Collection of patient and facility costs and resource use. Costing was conducted both from the patient and provider perspectives. A large survey examining the effects of *m*RDT introduction on health worker practices and patient response was used as a platform for collecting patient-specific and facility costs. This survey was the second in a pre- post cross-sectional survey evaluation of the *m*RDT intervention (that consisted in training of health workers in February 2007, initiation of *m*RDT use at the end of March 2007 and supervision on site 1, 2, 5, 10 and 15 months after *m*RDT introduction) and conducted 15 to 18 months post intervention from July through September of 2008. Within the six selected facilities the inclusion criteria were the following: (1) first consultation for the present complaint (not a follow-up visit), (2) absence of severe disease, and (3) main complain not trauma related. Eligible patients or caretakers of young patients were included if they gave oral informed consent to participate. Their consultation was then passively observed by a survey worker with clinical training. These patients or caretakers were questioned during an exit interview, which included questions relating to their perceptions of the clinical and laboratory consultation, as well as episode-related expenditures and any previous treatment seeking and related expenditures. The questionnaire also probed travel time and costs, time spent accessing the facility and missed work or lost income due both to the attendance at the facility and/or any time taken to care for the patient at home.

All patients or caretakers who participated in the exit interview (and therefore had costing questions) were requested to return to the same health facility one week later for a follow-up interview. They were also provided with a small incentive to cover transportation costs. At follow up, all patients or caretakers were administered a second questionnaire which solicited information on their current health status and any treatment seeking activity or expenditure during the intervening week, as well as lost income and time taken to care for the patient at home. They were also asked about the previous consultation and any associated expenditures, mainly as a check on consistency, as well as to potentially garner information about informal payments. If in-person follow-up was not possible we attempted a shortened follow-up interview via mobile telephone. All follow-up patients who reported at a health facility were tested with an HRP2 based *m*RDT in order to check for missed infections, as well as to identify false negatives or positives in the control facilities given the persistence of the HRP2 antigen in treated patients. Persistence of the antigen was low (<33%) in previously *m*RDT

positive and appropriately treated patients and as such results for the second *m*RDT were not of use for determining numbers of correct diagnoses. For the patients who tested positive by *m*RDT during follow-up it was ascertained whether they had received appropriate first line treatment, and whether their condition had improved. If this was not the case we ensured that they were subsequently treated for malaria at the health facility.

In order to assess treatment costs to the provider a health facility survey was conducted in the six facilities participating in the cost study to identify per patient resource use at the facility level. In-charge interviews and a health facility level data survey instrument were used to collect information on the number of outpatients and malaria cases seen at the facility over the past three years, as well as numbers of blood slides and *m*RDT tests performed. Additionally, we collected information on numbers and grades of staff and estimated effort dedicated to outpatients. We also collected additional information used to calculate overhead and patient visit costs, including the facility's spending on electricity, water, other overhead costs, and the numbers of capital items in the facility – including microscopes and other clinical equipment. Facility records were also utilized to collect information on the use of consumables including laboratory books, Giemsa stain, blood slides, lancets, syringes and other consumables. We measured resource use at each of the six facilities through a questionnaire administered to the in-charge of health facility, as well as the collection of routine data on facility use, numbers of outpatients treated, numbers of malaria test performed, and records of consumables used. Additionally, we conducted data collection at the central offices of the City Medical Office of Health to estimate the costs of construction of health facilities and other costs which we could not obtain directly from the health facilities themselves, including salary ranges for various grades of health workers.

Valuation of resource use. Costs of resource inputs were determined for the provider costs on the basis of (1) the Tanzania pharmaceutical and supply price list for 2008, and (2) interviews with the appropriate financial managers of the Dar Es Salaam City Medical Office of Health. Information on drug prices was obtained from the International Drug Price Indicator Guide database published by Management Sciences for Health (MSH) or from a WHO-AFRO database of indicator drug prices (Management Sciences for Health 2009; WHO Regional Office for Africa 2003). Patient costs were valued according to patients reported expenditures and lost income.

Costs for the initial implementation of *m*RDTs, including training and quarterly supervisory visits were calculated based on reported expenditure and activities, excluding specific research costs. Costs were reported in the local currency (TSH), U.S. Dollars (USD), or Swiss Francs (CHF). All costs were converted to USD using official exchange rates for the year in which the cost occurred and adjusted into a common year (2008) using the U.S. GDP deflator (U.S. Bureau of Economic Analysis). Capital costs were discounted and annualized using a 3% discount rate and assumed lifetimes for equipment based on expert opinion and past literature. All costs attributable to *m*RDT implementation were then divided by the estimated total number of *m*RDT tests performed in the nine experimental (from the full trial) health facilities (328,000 – 435,000) over the entire duration of the

project (approximately two years) to calculate an average implementation cost per test. The number of tests was estimated in two ways: the first and lower number was the number of *m*RDTs performed according to facility records, and the second and larger number referred to the number of *m*RDTs delivered to the facilities according to project records. This range had little effect on the cost of implementation per test (excluding the cost of the test itself).

For provider costs all costs were related to their allocation to outpatient services (as opposed to maternal and child health services) and then related to the number of out-patients seen at the facility during the period under which their consumption could be measured (between 2005 and 2008). Because some resource usage could not be measured at each facility due to missing records (26% of requested records were missing) these costs have been estimated using the mean values per patient from the facilities where information could be collected. Prices of drugs have been adjusted to account for transport costs and wastage according to the following assumptions. Drugs costs were inflated 20% over actual costs to adjust for wastage, then an additional 10% for local transport, and finally an additional 10% for international transport where CIF (Cost, insurance and freight) prices were not available.

Statistical analysis. We tested the differences in patient expenditure and provider costs using two different statistical tests. We first applied the Kruskal-Wallis test for equality of populations. We used this test because, as is typical of expenditure data, the distribution of both patient specific provider costs and patients expenditures was highly non-normal, due both to a significant right skew and a large zero-mass. Thus performing significance testing with a non-parametric method was necessary. Additionally, we used non-parametric bootstrapping to estimate confidence intervals for each expenditure value. This approach was adopted due to the fact that alternative non-parametric methods do not compare arithmetic mean costs, transformation of the data to a log scale would result in comparison of geometric means, and furthermore, such transformation did not result in a normal expenditure distribution. Methodological studies and reviews have suggested this methodology to appropriately deal with the need to compare arithmetic means and generate confidence intervals on such data (Barber & Thompson 1998; Nixon *et al*. 2010).

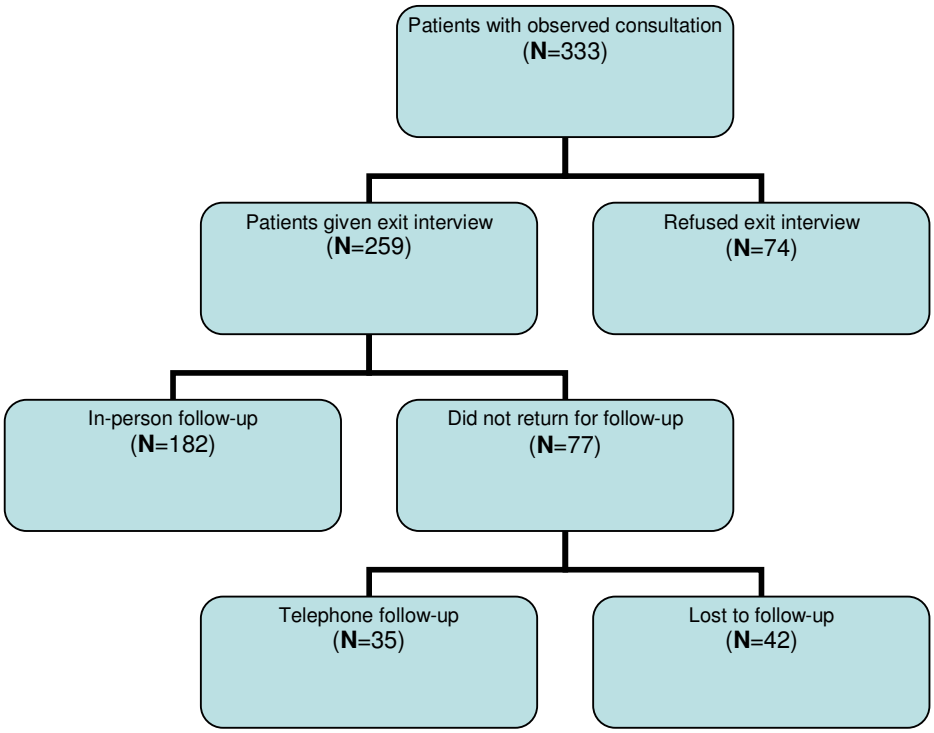
Total time for patient visits to the health facility was normally distributed and thus amenable to standard parametric tests. Data was entered in EpiInfo 3.4.1 (US CDC), and analyzed in STATA 9.2 (Stata Corporation, College Station, TX).

Ethical approval: The protocol and related documents were approved by the National Institute for Medical Research Review Board in Tanzania.

8.4 Results

General results. 333 patients were recruited during consultation at each of the six selected facilities for exit interviews. 259 patients were successfully administered an exit interview. The final rate of follow-up (for patients participating in the full costing study) was 84%, and is illustrated in Figure 16. No patients or clinicians refused the initial consultation observation. At the 5% significance level, patients in *m*RDT facilities were no more likely to attend the exit interview than those in control facilities; after stratifying by the portion of the patient population over age five differences were less significant.

Figure 16: Losses to follow-up during the study



Patients who were lost to follow-up were not significantly different from those who were successfully re-interviewed based on several demographic measures (Tables 7a and 7b). No significant differences were found for age distribution, patient sex, method of travel to and from the health facilities or the occupation of the patients' head of household (details not shown). Additionally, we found no significant differences on the same set of measures between facilities which offered *m*RDTs and those facilities which did not offer *m*RDTs (Tables 7a and 7b). Unfortunately, patients who were over five years of age were significantly more likely (29% vs. 15%) to leave the health facility before completing the exit interview.

Table 7a: Comparability of control and experimental populations, and those lost to follow-up

	N	Estimate	95% confidence interval	*p*-value
Proportion of patients age five years and older				
Control facility	81	51.9	41.0 – 62.7	0.49*
*m*RDT facility	178	47.2	39.9 – 54.5	
Lost to follow up	42	59.5	44.7 – 74.4	0.12*
Not lost to follow up	217	46.5	39.9 – 53.2	
Proportion of patients who were female				
Control facility	81	55.6	44.7 – 66.4	0.87*
*m*RDT facility	178	54.5	47.2 – 61.8	
Lost to follow up	42	54.8	39.7 – 69.8	0.99*
Not lost to follow up	217	54.8	48.2 -61.5	

**p*-values are based on Pearson's χ^2 test with d.f.(1)

Table 7b: Comparability of control and experimental populations, and those lost to follow-up

Patients method of travel to health facility (proportion)

	Lost to follow up (N=42)	**Not lost to follow up** (N=214)	***m*RDT facility** (N=175)	**Control facility** (N=81)
Walking	61.7	60.8	61.7	61.7
Mini-bus	33.3	35.5	34.9	35.8
Other	0.0	3.7	3.4	2.5
p-value	0.529**		1.000**	

***p*-values based on Fischer's Exact Test

Of the 259 patients who were administered exit interviews 178 were interviewed at experimental facilities (with *m*RDTs) and 81 were patients at control facilities (no *m*RDTs). Within the *m*RDT facilities, patients were significantly less likely than in control facilities to receive results for a laboratory test for malaria (84% vs. 95%; p=0.009 Fischer's exact), a difference that was also significant in patients five years and older (86% in *m*RDT facilities vs. 98% in control facilities; p=0.04) but not for children less than five years (82% in *m*RDT facilities vs. 92% in control facilities; p=0.13). Patients in *m*RDT facilities were also significantly less likely to test positive for malaria parasites (14% vs. 43%; p<0.001). While in both control and *m*RDT facilities large fractions of all patients received laboratory diagnosis, clinicians in the *m*RDT facilities appeared to be more parsimonious in their use of tests, at least among adults.

Adults were significantly more likely than children less than five years to test positive for malaria in control facilities, but not in *m*RDT facilities (55% vs. 28% in control facilities; p=0.016 and 15% vs. 13% in *m*RDT facilities; p=0.69). These results clearly confirm the problem with microscopic examination, and indeed the low quality of routine microscopy was confirmed in more detailed studies in the same facilities (Kahama-Maro *et al*. 2008).

Patients within *m*RDT facilities were significantly less likely to receive the first line anti-malarial drug ALU (artemether-lumefantrine, Coartem^{TM}) compared to patients in control facilities. This was seen when the analysis was restricted to patients who left the facility with any drug prescription as well as among all patients observed: 12% vs. 52% $p<0.001$ (with any prescription); 10% vs. 48% $p<0.001$ (all patients). This difference remained highly significant regardless of the age of the patient.
Patients in *m*RDT facilities were also more likely to receive ALU in correct correspondence with the results of their diagnosis. When only patients with a laboratory diagnosis were examined, those in *m*RDT clinics received ALU in correspondence with the laboratory diagnosis 95% of the time vs. 82% in control facilities ($p=0.002$). Since a related study has shown that most positive blood slide results in the control facilities are false positives (Kahama J and others, unpublished data), it follows that high clinician compliance with microscopy results leads to overuse of anti-malarial drugs. Patients under the age of five years appeared no more likely to be correctly prescribed ALU than those over five years of age (93% less than five vs. 88% five and older; $p=0.17$). Differences remained statistically insignificant when restricted within either *m*RDT facilities or within control facilities (details not shown).

Implementation costs of *m*RDT program (provider). Cost data on implementation was collected over a 14 month period. During this 14 month period approximately 435,400 *m*RDTs were issued to implementing facilities and usage data indicated that approximately 330,000 *m*RDTs for malaria had been performed. Due to this high volume of tests, the cost of implementation training and support for *m*RDT roll-out was relatively low when considered per test. The total cost of the *m*RDT intervention over this period (not including the test kits themselves) was estimated to be $16,946 in 2008 USD, or $1,883 USD per implementing facility. Thus we estimated that the cost of implementation per *m*RDT test (excluding the test kits themselves) was between 0.04 USD and 0.05 USD. The test kits themselves were estimated to cost USD 0.66 each. When calculating the cost per patient in *m*RDT clinics we include the cost of *m*RDT implementation.
The bulk of the expenses went to staff salaries for the implementation of the *m*RDT rollout (72%) and for training and quality control at the implementing facilities (22%). The only other substantial line item cost was transport, which accounted for 3% of the total cost of implementation.

Patient perspective – direct costs (expenditure). Patient costs consist of two main parts: direct costs due to expenditure on medicines, transport, diagnostics or other health services, and indirect costs, such as lost productivity or the opportunity cost due to time spent seeking care. We attempted to measure both direct and indirect costs.
Patient expenditures were directly reported by patients. Table 8 shows arithmetic mean expenditure per patient in *m*RDT or control facilities arising before and during the first consultation, as well as after the first consultation for the subset of patients with follow-up. Expenditures have been subdivided into several categories, and are reported here in Tanzanian Shillings and USD.

Table 8: Patient expenditures. HF=Health Facility. Totals are different than sum of means because of varying sample sizes for each group

Type of Expenditure		N	Mean cost per patient		Standard Deviation (TSH)	Significance+
			TSH	USD		
Care pre-HF	*m*RDT	178	89	0.07	630	0.506
	Control	81	46	0.04	298	
Drugs at HF	*m*RDT	178	464	0.38	1060	0.002
	Control	81	902	0.74	1407	
Out-patient charges	*m*RDT	125	79	0.06	117	0.347
	Control	56	104	0.08	129	
Lab fee at HF	*m*RDT	122	245	0.20	411	0.841
	Control	56	252	0.21	431	
Post visit	*m*RDT	126	198	0.16	1008	0.956
	Control	56	70	0.06	447	
Travel	*m*RDT	178	362	0.30	897	0.779
	Control	81	270	0.22	440	
Total	*m*RDT	122	1247	1.02	2021	0.033
	Control	56	1630	1.33	1826	

+significance results are based on Kruskal-Wallis tests

Table 8 shows that significant differences in reported expenditure were found between patients at *m*RDT clinics and those at control clinics. Patients' mean total expenditures were lower in *m*RDT clinics (USD 1.02) compared to control clinics (USD 1.33), and were significantly different using the Kruskal-Wallis test for equality of populations. Patients' mean expenditure on drugs was 0.36 USD lower in *m*RDT clinics than in control clinics.

Table 9 shows bootstrapped means and bias corrected confidence intervals for each of the parameters shown in Table 8. Each estimate is based on 10,000 re-samples of the observed data. Arithmetic mean patient expenditures, when reduced into smaller component parts, failed to show significant differences in all but the line item expenditure for drugs at the first health facility visit, which was highly significantly different in *m*RDT clinics (using the Kruskal-Walis test: TSH 464 (USD 0.38) vs 902 (USD 0.74); p=0.002). Bootstrapped confidence intervals showed, however, that the difference was only close to significance.

The similarity of expenditure across the two types of facilities helped to support our assumption that the populations of patients in control and *m*RDT facilities were similar since the cost of transportation and actions taken before attending the health facility would not be expected to be significantly different between the two groups. Further, it supports the argument that effects on patient expenditures were largely limited to those on drug purchases.

Expenditures on drugs at the health facility accounted for the largest single component of patient expenditure, followed by laboratory fees and travel costs.

Table 9: Results of non-parametric bootstrap for confidence interval estimation of patient expenditures. Totals are different than sum of means because of varying sample sizes for each group

Type of Expenditure		Mean cost per patient	95% Bias Corrected C.I.
		2008 USD	TSH
Expenditure for care pre-HF	*m*RDT	0.07	0.02 – 0.18
	Control	0.04	0.01 – 0.12
Drug expenditure at HF	*m*RDT	0.38	0.27 – 0.53
	Control	0.74	0.52 – 1.03
Out-patient charges	*m*RDT	0.06	0.05 – 0.08
	Control	0.08	0.06 – 0.12
Lab fee at HF	*m*RDT	0.20	0.15 – 0.27
	Control	0.21	0.13 – 0.32
Post visit expenditure	*m*RDT	0.16	0.04 – 0.34
	Control	0.06	0.00 – 0.22
Travel expenditure	*m*RDT	0.30	0.21 – 0.43
	Control	0.22	0.15 – 0.31
Total expenditure	*m*RDT	1.02	0.76 – 1.36
	Control	1.33	0.99 – 1.77

Patient perspective – indirect costs. Additionally, patients incurred indirect costs through lost income, reduced productivity, and the opportunity cost of lost time due to attending the facility either as patients or as caretakers of patients. One hundred-eight (42%) patients or caretakers reported missing work to attend the health facility; of that group, 85% reported lost income as a result. Neither result was significantly different at the 10% level between *m*RDT and control facilities: p=0.16; d.f.(1) and p=0.66; d.f.(1). Among those reporting lost income, mean lost income was reported as 7175 TSH (5.87 USD) a figure which was not significantly different between control and *m*RDT groups (Kruskal-Wallis p=0.16). This figure is significantly larger than patients' expenditures on all other categories. For patients who lose income to attend the facility, the opportunity cost of facility attendance is far larger than the direct costs of health care and such large opportunity costs might prevent significant numbers of people from accessing care.

Total time per visit, including transportation time was measured by adding estimates of time at which the patients or caretakers left their home or work place to attend the facility to the time they spent at the health facility (determined by the time of the start of their exit interview), with an additional time factor added for their estimated time to return home. In control clinics mean time per visit was estimated to be 4.7 hours, while in *m*RDT clinics it was estimated at only 4.0 hours (t=2.8703; p=0.005). Hence, being a patient in an *m*RDT clinic in our sample was associated with approximately 42 minutes shorter total visit time. Though a certain amount of this variation can be attributed to slightly shorter travel times to *m*RDT facilities (mean travel time 35 minutes) compared to control facilities (44 minutes; p=0.058) resulting in a mean difference of approximately 9 minutes of travel in each direction, or 18 minutes total. Reduced waiting times and total visit times might help to reduce

the opportunity costs of facility attendance and thus could improve access to care, though the reductions seen here are small (~10%) in relation to total visit time.

Provider perspective. In this analysis we focus on gross provider economic costs and not net costs, which would account for the collection of user fees by health facilities. Table 10 lists the costs which were included in the analysis.

Table 10: Costs included in provider perspective analysis

Recurrent Costs	Capital Costs
Clinical staff salaries	Building and furnishings
Lab technician salaries	Microscopes
Support staff salaries	Other equipment
Consumables	
Drug costs	
Diagnostics	
Electricity	
Water	
Communication	

Table 11 shows the results of the provider perspective analysis for the *m*RDT and control facilities. The table shows the results of non-parametric tests for each of three sub-divisions of total provider costs. They are analyzed either within control or experimental facilities. “Drug costs” represent the cost to the provider of all drugs and prescription provided to a given patient. “Facility cost” is the cost of the commodities whose usage is measured at the facility level but not linked to specific patients (overhead, staff costs, equipment and general consumables, excluding drug costs), thus there are only six observations corresponding to the number of facilities in our study. “Total costs” include drug costs, facility costs and other marginal costs including *m*RDTs and consumables which are patient specific rather than general consumables used for all patients. Significant differences were found for all costs except facility cost, though the latter result is compromised by the extremely small sample size.

When patients who attended *m*RDT clinics were compared to patients who attended control clinics, drug costs were significantly lower for patients from *m*RDT clinics (USD 1.28 vs. USD 1.71; p=0.014). However, total provider costs were higher for patients from *m*RDT clinics USD 3.63 vs. USD 2.32; p<0.001 for total cost.

Table 11: Provider costs per patient. Totals include drug costs, facility level costs and other patient specific marginal costs.

Type of cost (per patient)	Group	N	Arithmetic mean		Standard Deviation	Significance
			TSH	USD	TSH	
Drug cost	*m*RDT facility	178	1567	1.28	1799	0.014[+]
	Control facility	81	2095	1.71	1938	
Facility cost	*m*RDT facility	4	1926	1.58	903	0.161[*]
	Control facility	2	720	0.59	424	
Total cost	*m*RDT facility	178	4440	3.63	2019	<0.001[+]
	Control facility	81	2833	2.32	1978	

[+]Kruskal-Wallis based *p*-values
[*]t-test based *p*-values

Again we were confronted with results which were highly non-normally distributed, including in some cases a large zero mass and in all cases a significantly right-skewed distribution. Hence we estimated confidence intervals using non-parametric re-sampling (bootstrapping) with 10,000 re-samples for each outcome, excepting facility cost (Table 12).

Table 12: Results of non-parametric bootstrap for confidence interval estimation of provider economic costs. Cost values in 2008 USD.

		All Ages		Under Five		Over Five	
Type of cost (per patient)	**Group**	**Mean cost**	**95% bias corrected C.I.**	**Mean cost**	**95% bias corrected C.I.**	**Mean cost**	**95% bias corrected C.I.**
Drug cost	*m*RDT facility	1.28	1.07 – 1.50	1.19	0.90 – 1.53	1.38	1.10 – 1.68
	Control facility	1.71	1.40 – 2.08	1.08	0.74 – 1.57	2.29	1.82 – 2.79
Total cost	*m*RDT facility	3.63	3.40 – 3.89	3.59	3.11 – 3.95	3.69	3.36 – 4.03
	Control facility	2.32	1.99 – 2.69	1.72	1.37 – 2.22	2.87	2.39 – 3.38

Bootstrapped confidence intervals generally confirm the results of the Kruskal-Wallis tests. However important differences do exist between the two results. The confidence intervals for drug costs between *m*RDT and control facilities show a large overlap when analyzed for all age groups. However, when the sample is stratified by over and under five years of age a significant difference exists for patients five years of age and older. This may be the result of a combination of high rates of ALU prescription in control facilities and the higher cost of this drug for adults in relation to other adult drugs. Once facility costs are included, the total cost of treating a patient including all provider costs is significantly higher in *m*RDT facilities than in control facilities.

Summary of all results. The results indicate that in the presence of *m*RDTs, drug cost savings are likely to accrue to patients, and may also accrue to the providers, especially for adults. However, whether these savings translate into overall cost savings is more in doubt.

For patients, it appears likely that there is some reduced overall spending when *m*RDTs are available. However, the savings is small (USD 0.36) and it represents only a small component of the total economic costs to patients.

For providers the drug cost savings is of a similar order (USD 0.43) as a result of *m*RDT introduction. Unfortunately, these savings appear to be too small to offset the entire cost of *m*RDT introduction and use. In fact, it appears that *m*RDTs may increase the cost of treatment per patient in public facilities, despite reducing anti-malarial drug usage and creating drug cost savings for the health system. Additionally, the cost savings arise largely from reduced anti-malarial usage among adults who are most likely to be charged a user fee for drugs. Hence, the resulting reduction in user fee revenue due to reduced patient drug expenditure will reduce the financial incentives for *m*RDT implementation.

8.5 Discussion

This study was conducted under routine conditions in health facilities and sampled patients were taken from six different health facilities. As there is likely to be a tendency towards similar prescribing practices within facilities, the results should be adjusted for clustering within health facilities (Rowe *et al*. 2002). Unfortunately, because of the small sample size and small number of health facilities included in the study, we were unable to formally account for this in most of the statistical analysis. Nevertheless we believe that these results are likely to be robust, although the extent to which they are generalizable depends on how representative these facilities are of typical Tanzanian facilities or more widely of other sub-Saharan African health systems.

These results are of course sensitive to the relative prices of malaria drugs and antibiotics (ALU: USD 0.41 to USD 1.60 depending on dosage; antibiotics USD 0.20 to USD 3.50 depending on drug, dosage and formulation) as well as any other drugs used to treat test-positive and test-negative patients. It is possible that given changes in drug prices our results could change. One of the most expensive drugs commonly in use among this type of patients is artemisinin combination therapy for malaria. Much of the drug cost savings seen in this study, both to the patients and to providers, is due to reduced anti-malarial usage in *m*RDT facilities. Hence, a reduction in the price of anti-malarial drugs may erase the drug cost savings seen here. Currently a global subsidy scheme for antimalarials is at an advanced stage and a virtually free drug at country level might prove to be a disincentive to testing for malaria (Gelband & Seiter 2007). Subsidized provision of malaria *m*RDTs should be considered in parallel to help overcome this problem.

Additionally, we chose to focus on gross provider costs, this could affect our results because it excludes health facility receipts for user fees. However, based on the evidence from the patients perspective the primary effect of *m*RDTs was likely to have been a reduction in user fees due to

reduced prescriptions of drugs and no changes in laboratory or general fees. Thus shifting the perspective to net costs at the facility level would have likely made *m*RDTs appear even more costly than microscopy as they reduce the primary source of HF user fee revenue.

It has been postulated in several studies that *m*RDTs could produce cost savings to health facilities in low transmission settings (Zikusooka *et al*. 2008; Shillcutt *et al*. 2008). Here we show based on empirical data from six health facilities in Dar Es Salaam that indeed significant drug cost savings and reductions in anti-malarial drug usage appear to be achievable in such settings. In addition, there was a large reduction in false positive malaria test results due to good specificity of routine *m*RDT. Clinicians' compliance with test results was also significantly better when *m*RDTs were in use, and this is likely to have contributed to the drug cost savings seen here (Lubell *et al*. 2008a). Increased compliance by providers may be a result of high quality training or their perception of the increased accuracy of *m*RDTs compared to their routine laboratory diagnostic methods.

However, despite demonstrable drug cost savings we did not see overall cost savings due to the use of *m*RDTs and in fact provider costs appeared to significantly increase in the presence of *m*RDTs. Though some of this increase is likely due to higher fixed costs within the set of facilities selected for this study, the drug cost savings that we observed (USD 0.43) were not likely to be large enough to offset the cost of the *m*RDTs themselves when a high percentage (84%) of the patients at the facility have the test administered. Further, reduced patient expenditure on drugs leads to falling revenue from user fees, which might make the intervention appear economically less attractive at the facility level. Other considerations such as reduced effort at the laboratory level may partially compensate this loss.

Our results show that for a significant proportion of all individuals seeking treatment, the indirect costs of lost productivity far outweigh the direct costs of transportation and treatment. When averaged over all the patients observed, lost income accounted for approximately two-thirds of all costs. Other studies have come to mixed conclusions about the balance of direct and indirect costs of uncomplicated malaria morbidity. There is, however, general consensus that the indirect costs of morbidity form an important part of the economic burden of malaria (Chima *et al*. 2003b). Our results are consistent with a number of studies, both from Africa and also from other locations, which showed that the indirect costs of malaria can outweigh the direct costs of treatment for uncomplicated episodes (Ettling & Shepard 1991; Sauerborn *et al*. 1991; Gatton & Cho-Min-Naing 2004; Morel *et al*. 2008).

Unfortunately, in the context of this study it was not possible to measure differences in health outcomes between the groups of patients, nor to assess whether patients were truly malaria infected using expert microscopy. Thus, it was not possible to assess the cost-effectiveness of the intervention, either per health outcome or per additional correct diagnosis. An in-depth analysis of case management practices will determine if *m*RDTs improved compliance with standard treatment guidelines and improved case management (Chapters 7 and 10.1). That information could also be

used to calculate a cost per additional correct treatment, as has been done in previous diagnostic costing studies (Lubell *et al*. 2007).

An additional benefit is that with a more reliable laboratory test it becomes more realistic to monitor malaria trends on the basis of routine data. Though it is unclear what monetary value such a benefit would have for the health system, substantially improved knowledge of malaria incidence rates could lead to efficiencies in other health care domains. Distribution of malaria prevention and treatment resources could potentially be more efficiently allocated to high incidence areas. Alternatively, more accurate measures of malaria incidence could enhance the responsiveness of health systems to malaria epidemics (Abeku *et al*. 2004). Finally, reduction of unnecessary anti-malarial over-use is important to limit the development of resistance to ACTs (Wongsrichanalai *et al*. 2007).

Our results show significant savings on drug expenditure to patients and on drug costs to providers in the presence of *m*RDTs. However, the savings are outweighed by other fees and charges and lost income for patients - or the cost for *m*RDTs and higher facility costs for providers.

Clinicians' compliance with test results was higher when *m*RDTs were in use, showing that they trusted this new technology. It is also likely that the use of such tests accrues significant other benefits, including improved case management, more rational anti-malarial use, and reductions in development of resistance to ACTs. While valuation of such benefits is outside of the scope of this work they are highly important from a public health perspective. While *m*RDTs are likely to bring significant benefits to the health system in areas like Dar es Salaam, these benefits may not be fully paid for through drug cost savings, but require additional investment.

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9. Etiology of fever in children from urban and rural Tanzania

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Working paper *(Results of molecular analysis and serologies will be added in the final version of the paper and discussion amended accordingly)*

9.1 Abstract

Background: Several studies have looked at the proportion of either malaria, pneumonia, diarrhoea or bacteraemia among fever cases in Africa but none of them has looked at the overall spectrum of aetiologies. We aimed at investigating the precise cause of fever episodes in children attending an outpatient clinic in urban (Dar es Salaam) and rural settings (Ifakara) in Tanzania.

Methods: All consenting children aged 2 months - 10 years with an axillary temperature >38C were recruited, except for those that required immediate supportive treatment. A detailed medical history and clinical examination were done to identify obvious foci of infection. A blood sample was taken to perform rapid tests for malaria and typhoid, blood culture as well as serological and molecular analyses. All had a throat and nasal swab taken for molecular investigation of respiratory pathogens. Urine was taken when no obvious cause of fever was found on clinical examination and a stool sample when diarrhoea was present. A chest X-ray was performed when IMCI criteria for clinical pneumonia were met. Each diagnosis was assigned a probability level (high, moderate, low) on the basis of pre-defined criteria.

Results: 1010 children were recruited, 510 in DSM and 500 in Ifakara. Preliminary results (prior to molecular analysis or serologies on blood) on the causes of fever (of high probability only) were as follows: 50% had acute respiratory infection (ARI) [31% URTI, 18% LRTI (4% bronchiolitis, 12% non-documented pneumonia and 3% pneumonia confirmed by X-ray)], 11% malaria, 9% gastroenteritis (3% Rotavirus, 1% *Salmonella/ Shigella* and 5% unknown), 5% urinary tract infection, 3% typhoid, 1% skin infection, 1% occult bacteraemia, 1% other infections and 20% still unknown at this stage. Only 13% had more than one diagnosis (high probability).

In severe children, the 3 leading aetiologies were ARI (38%), malaria (36%) and gastroenteritis (8%).

A virus in the nasopharyngeal swab was isolated in 68% of the children with ARI, 55% with unknown disease and 44% with documented disease other than ARI. When Picornaviruses were excluded, these rates dropped to 39%, 18% and 13% respectively.

Conclusion: These results provide for the first time an accurate picture of the respective causes of fever in African children. As expected, ARI contribute to the largest burden of disease, most of them being URTI. Malaria confirmed to be lower than generally thought. There was a sizeable proportion of fevers due to typhoid documented by the rapid test for most of them. Results of molecular analyses provided further insight on the contribution of respiratory viruses, a critical issue for appropriate management of fever and rational use of antibiotics.

9.2 Introduction

Because of the lack of diagnostic tools in Africa, patients presenting to health facilities with fever have often been denied the usual aetiology finding process inherent to any medical consultation (Zurovac *et al*. 2006b). Moreover, based on the fact that malaria was highly prevalent and a deadly disease, all fever episodes tended to be considered as malaria and treated as such. With the decreasing transmission of malaria in Africa following the implementation of efficient control strategies (Chapter 4) and the increasing awareness that non-malaria fevers could be life-threatening (Makani *et al*. 2003; Reyburn *et al*. 2004), an effort has recently be done to introduce, even in highly malaria endemic areas, reliable malaria test in the routine management of fever. Thanks to the reliability and ease of use of Rapid diagnostic Tests for malaria, this is now becoming a reality in several countries if Africa. But this important step opens a new problem that is a major challenge to clinicians: what should be done when the malaria test is negative? The aetiology of non-malaria fevers has never been studied in a systematic way. We are thus presently not able to give a precise answer to this question and to guide the clinician with an evidence-based strategy. The Integrated Management of Childhood Illness (IMCI) decision-chart, although it does not include any test because of the risk of their unavailability, is an excellent tool developed on the basis of the scarce evidence existing in the mid-1990s. Disease-specific studies have been carried out in a few settings - for example for urinary tract infections (Rabasa & Gofama 2009) or acute otitis media (Alabi *et al*. 2009) in Nigeria, for arboviruses on the Kenyan Coast (Morrill *et al*. 1991) or Dengue in Somalia (Botros *et al*. 1989) and for *Mycoplasms* and *Rickettsia spp.* in Somalia (Nur *et al*. 1999). However, no comprehensive and systematic study to assess the respective contribution of each disease has ever been undertaken in Sub-Saharan African, and even elsewhere. A list of the proportion of patients with some specific diseases is sometimes given in studies not primarily designed for this purpose (Njama-Meya *et al*. 2007; Yacoub *et al*. 2005; Animut *et al*. 2009). However the way of establishing the diagnosis was not systematic and left at the discretion of the clinician. Also a very limited number of investigations were undertaken. Some studies have looked specifically at bacteraemia in severe hospitalized patients (Okwara *et al*. 2004; Ayoola *et al*. 2005; James A Berkley *et al*. 2005; Bronzan *et al*. 2007), but no link was done with the aetiology of the fever episode. The same drawback is found in one study that has looked at bacteraemia at outpatient level, but was aimed as assessing the incidence of invasive bacterial disease in the sick general population (Brent *et al*. 2006).

Evidence on the aetiology and the prevalence of each non-malaria disease causing fever in children is urgently needed to improve management of patients in Africa. Information is essential not only for severe cases but also for mild episodes managed at outpatient level. This is necessary to be able to update the IMCI decision-chart and hence ensure good health outcome as well as rational use of antimalarial and antibiotic drugs at health facility level. Also more and more point-of-care diagnostic tools for all kind of diseases are appearing on the market. To know the potential of these tests in

African children but also to avoid their irrational use, the first step is to document which diseases are existing in a specific setting, what are their respective prevalence as well as their clinical predictors if any. This is why we designed a study aimed at assessing the precise aetiology of fever episodes in children attending an outpatient health facility in a rural as well as an urban setting in Tanzania. To avoid subjective diagnosis by the clinician or by the investigators, we used pre-defined algorithms to decide for investigations and pre-defined criteria to establish the final diagnosis. The aim was to combine precise clinical information with relevant investigations of high quality and as broad as possible (in the frame of infectious diseases producing fever).

9.3 Methods

Study setting and population

The study took place from April to August 2008 at Amana hospital in Dar es Salaam, the economic capital of Tanzania, and from end of June to beginning of December 2008 at St-Francis hospital in Ifakara, Kilombero district, situated in the centre of Tanzania. Dar es Salaam (DSM) is a moderately endemic for malaria, with parasite rates in the community around 1-4% (Wang *et al*. 2006a) and only 5-10% of febrile patients being parasitaemic (Chapter 7). Kilombero Valley is considered as a highly endemic area with a parasites rate in the community of 10% in 2008 (Mulokozi, *unpublished data*) and about 35% of febrile patients being parasitaemic (Tillya *et al*. 2009). However in Ifakara town where St Francis hospital is situated, only 7% of febrile patients are parasitaemic nowadays (Tillya *et al*. 2009). Patients were recruited at the outpatient department of these two district hospitals. The vast majority of them originated from the neighbourhood and attended because it was the nearest health facility while a small proportion was referred from the surrounding health centres and dispensaries.

The Expanded Program on Immunization in Tanzania includes BCG, Diphteria-Tetanos-Pertussis, Polio, Hepatitis B and Measles and has reached a high coverage (90% in 2007) in the country (www.who.int/immunization_monitoring). Outside a few specific research studies, vaccines against *Hemophilus influenzae b* and *Pneumococcus* were not used up to the time of the study. In Dar es Salaam, a measles outbreak response vaccination campaign was organized from 22 to 24 September 2006, resulting in an estimated coverage of almost 100% for the targeted age group (6 months through 14 years) (Goodson *et al*. 2009). A three-day national integrated campaign of measles vaccines, vitamin A supplementation, de-worming tablets and long-lasting insecticide treated bed nets also took place in August 2008 (www.unicef.org/infobycountry/tanzania_45503.html). These two interventions probably stopped measles transmission in Dar es Salaam and the Kilombero Valley for the period during which the study took place. In 2007, a Rift Valley fever outbreak took place in Kilombero district but it had subsided at the time of study start (WHO 2007).

The standard diagnosis and treatment for children less than five years is the Tanzanian version of IMCI (Ministry of Health and Social Welfare, Tanzania *et al*. 2004). The first-line treatment for malaria is arthemeter/lumefantrine (ALu) since January 2007. The first-line antibiotic for pneumonia, acute ear infection and dysentery is cotrimoxazole.

Study subjects

All consecutive patients aged 2 months to 10 years, categorized as P2 or P3 WHO categories by the triage (not requiring immediate live saving procedures) (WHO 2005b), without severe malnutrition and with an axillary temperature of ≥ 38°C were further assessed for possible inclusion in the study. The caretaker of the child was then asked about the other inclusion criteria, namely: 1) first consultation for the present problem; 2) fever lasting for one week or less; 3) main complaint was not an injury or trauma and; 4) no antimalarials or antibiotic drug taken in the last week. If all inclusion criteria were met, the research clinician asked written informed consent to the caretaker after explaining in detail the purpose, risks and benefits of the study.

Study procedures

Assessment of the patient

To record the medical history and child examination findings, the research clinician used a questionnaire where all relevant items for a febrile case were listed and had to be checked one by one. The main complaint, 23 symptoms with their respective duration, a travel history, sick persons in the neighbourhood and chronic conditions were asked for. 49 physical signs were looked at (Figure 17). The clinician had then to list again all positive items to help her deciding about the working diagnosis. A nasal and a throat sample as well as a blood sample of 5 ml (venepuncture) were taken for each child. Based on predefined algorithms (see below), the clinician selected the appropriate investigation(s) to be done.

Once the clinician had received the results of all immediately available investigations, she decided about the final diagnosis(ses) based on the same predefined algorithms. For clinical findings that were not included in the algorithms, she would list an additional diagnosis based on her clinical judgment. Thereafter she ticked for the absence or presence of each of 28 acute diseases defined by a precise constellation of symptoms and/or signs and/or investigation results. If a diagnosis not mentioned in this list was recorded, the items on which it was based had to be described precisely. Co-morbidities were also listed. Finally, the IMCI clinical criteria for a suspected HIV infection were assessed and if present, the caretaker was advised to bring his child to HIV voluntary testing. The clinician mentioned that he/she was free to bring back the result to her afterwards.

Figure 17: Physical examination of a patient

The clinician then decided if the child had to be admitted in the paediatric ward or could be managed as outpatient. Based on the standard treatment procedures [following the last WHO recommendations for hospital care (WHO 2005a)] given next to the 28 diagnoses listed, she prescribed the necessary drugs and advised the mother on how to take them. In the absence of a diagnosis or if the diagnosis was not documented by a laboratory investigation or a chest X-ray, the caretaker was asked to bring back the child after 7 days for follow-up. His/her phone number was recorded to be able to call him/her in case a blood, stool or urine culture would turn positive and a further treatment was needed.

At day 7, as well as when the child was brought back to the hospital in-between, the clinician assessed the patient for any new complain or new sign. In case of persisting fever, a full assessment similar to the one done at day 0 was performed again. In all cases a blood sample was taken for storage. Haemoglobin was measured, not for study purposes but for the direct benefit of the child (treatment of chronic anaemia). Finally, based on the new findings, if any, the clinician decided about the final diagnosis(ses) for the fever episode and the complementary treatments.

Choice of investigations based on pre-defined algorithms

To avoid performing investigations in children with a very low pre-test probability for a specific disease, we developed 7 decision charts starting with a specific symptom or sign and then conditions that would justify such or such investigation (see Annex 2). These decision charts, that were not mutually exclusive (except for the last one), had the following entry points: 1) neck stiffness or bulging fontanel; 2) non-vesicular rash; 3) black spot; 4) cough or difficult breathing; 5) {Pharyngeal redness and enlarged tonsils} OR {tonsil exsudate}; 6) diarrhoea with ≥ 3 stools per day; 7) no confirmed infection (either clinically or by a laboratory test).

A full blood cell count, a rapid test for malaria, a thick film for malaria parasites and borrelia bacteria examination, a rapid test for typhoid, liver (ALT) and kidney (creatinine) function tests were performed in all children. Plasma and serum as well as a nasal and a throat swabs were stored for all children. Based on the algorithms, the following investigations could be asked for: a cerebral spinal fluid (CSF) direct examination; CSF culture; a skin aspiration for *Rickettsia*; a rapid test for *Streptococcus* in the throat; a direct stool examination for amoeba; a rapid test for adenovirus and rotavirus in the stool; a stool culture; a urine dipstick; a urine culture; a blood culture (available only for the DSM site) and a chest X-ray.

Definitive diagnosis(ses) given by the investigators based on pre-defined criteria

Using the known diagnostic performance of each clinical condition and laboratory test (from available international guidelines or systematic reviews), we established beforehand the criteria necessary to diagnose a certain disease (see Annex 3). We also defined the additional criteria necessary to decide about the level of probability (low, intermediate or high) for this disease to be the aetiology of the acute fever episode. For diagnoses corresponding to different spectrum of the same type of disease (for example tracheo-bronchitis and pneumonia being both an acute respiratory infection), the criteria were established so that only one of them could be given to a certain child (see Annex 3).

The designation of ‘severe’ was added to the diagnosis when the child fulfilled the WHO criteria for the corresponding group of diseases (for example the criteria for severe/very severe pneumonia were applied to all ARI) (WHO 2005a). Whatever the diagnosis, the presence of severe anaemia (as defined for malaria: Hb <5 g/dl) would put the child in the severe category, as bacteraemia is the strongest predictor (just before malaria) for severe anaemia in African children (Calis *et al*. 2008).

Once the diagnoses with their respective levels of probability had been attributed to each patient, a ranking of the diagnoses (if more than one) was established using the following strategy: 1) the diagnosis with the highest probability was put at first level; 2) if a child had more than one diagnosis of the same level of probability, the most documented one (based on the respective levels of performance of the clinical, laboratory or radiological test used) was put at first level; 3) if a child had no diagnosis of high probability at all, a diagnosis called ‘unknown’ was put at first level and the diagnosis of intermediate or low probability at second level.

Based on all criteria mentioned above, the final diagnoses were generated by a computer program to ensure consistency and eliminate subjectivity.

Laboratory analyses

Beside blood cultures performed at the research laboratory of Muhimbili University College of Health Science, Tanzania and the PCR on respiratory samples performed at the Laboratory of Virology, University Hospital, Geneva, Switzerland, all investigations were done on site [at the routine laboratory of Amana hospital in DSM and the research laboratory of IHI in Ifakara].
Rapid diagnostic tests for malaria [ParaHit-f (Span Diagnostics, India)], for typhoid [TyphiRapid IgM (Malasian Bio-Diagnostics research)], for adenovirus and rotavirus [VIKIA Rota-Adeno (BioMérieux, France)] and for *Streptococcus* [QuickVue In-Line Strep A test (Quidel, USA)], as well as the urine dipstick [Urilab H10 (Urilab systems Diagnostics,)], were performed following manufacturer's instructions. Thick blood films were stained with 10% Giemsa solution and *P. falciparum* asexual parasites were counted against 200 white blood cells (WBC). The parasite density was calculated using the white cell count of the patient. A slide was considered negative if no trophozoites were seen after 200 high power fields were examined. Discrepant results between the Rapid Diagnostic Test for malaria (*m*RDT) and the blood slide were reread by a second microscopist whose result was considered the final one. Urine and stool cultures were performed using the procedures described in the 'Medical Laboratory Manual for Tropical Countries' (Figure 18).

Figure 18: Culture at the laboratory of Amana hospital

Between 1 and 2 ml of blood were collected in BACTEC PedsPlus culture bottles and incubated in a BACTEC 9050 blood culture system for 4 days (Becton Dickinson, BD Biosciences, San Jose, CA, USA). We cultured positive samples on blood agar, chocolate agar, and cysteine, lactose, and electrolyte deficient agar. We used API biochemical galleries (API, Biomerieux, Durham, NC, USA), or serology, or both, to confirm the presence of suspected pathogens.
Nasal and throat swabs were immediately put in phosphate-buffered saline containing 40 U/mL RNase-inhibitor (Roche, Basel, Switzerland). Real-time TaqMan reverse transcription polymerase chain reaction (RT-PCR) assays for the detection of influenza A, B and C, respiratory syncytial virus (RSV) A and B, parainfluenza virus (PIV) 1, 2, 3 and 4, human rhinovirus (HRV), enterovirus and Human metapneumovirus were then performed as described previously (Regamey *et al*. 2008).

Radiology

Chest X-ray were performed on site and read by a paediatric radiologist in Switzerland who classified the radiographic findings according to the WHO Pneumococcal Trialist Ad Hoc Committee recommendations (WHO Pneumonia Vaccine Trial Investigators Group 2001; Cherian *et al*. 2005). The diagnosis of documented pneumonia was applied to children with a chest X-ray showing a 'primary endpoint pneumonia'. The diagnosis of non-documented pneumonia was applied to children with other findings on the X-ray or with a negative, unclear or unavailable X-ray. The diagnosis 'clinical pneumonia' is used for children with IMCI criteria for pneumonia, i.e. with documented or non-documented pneumonia.

Statistical analyses

Simple proportions were used. For analyses over time, as inclusion of patients in Ifakara took place only during 3 days in June and 3 days in December, these few patients were grouped under the next/previous month. Data were entered in Epi Info version 3.5.1 by the first author and analyzed in STATA version 10.

Role of the funding body

The sponsor of the study (Swiss National Science Foundation) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

9.4 Results

Between April and December 2008, 1010 febrile children were recruited (none refused), 510 in DSM and 500 in Ifakara. 5 patients (3 in DSM and 2 in Ifakara) were excluded from the study because caretakers of 2 children (complaining respectively of fever and cough and fever only) withdraw their consent at the moment of blood puncture, blood withdrawal failed in one child having pneumonia and

2 children did not have the right age. The 1005 children included had a median age of 18 months (20 months in DSM and 16 months in Ifakara) (see Table 13 for basic characteristics).

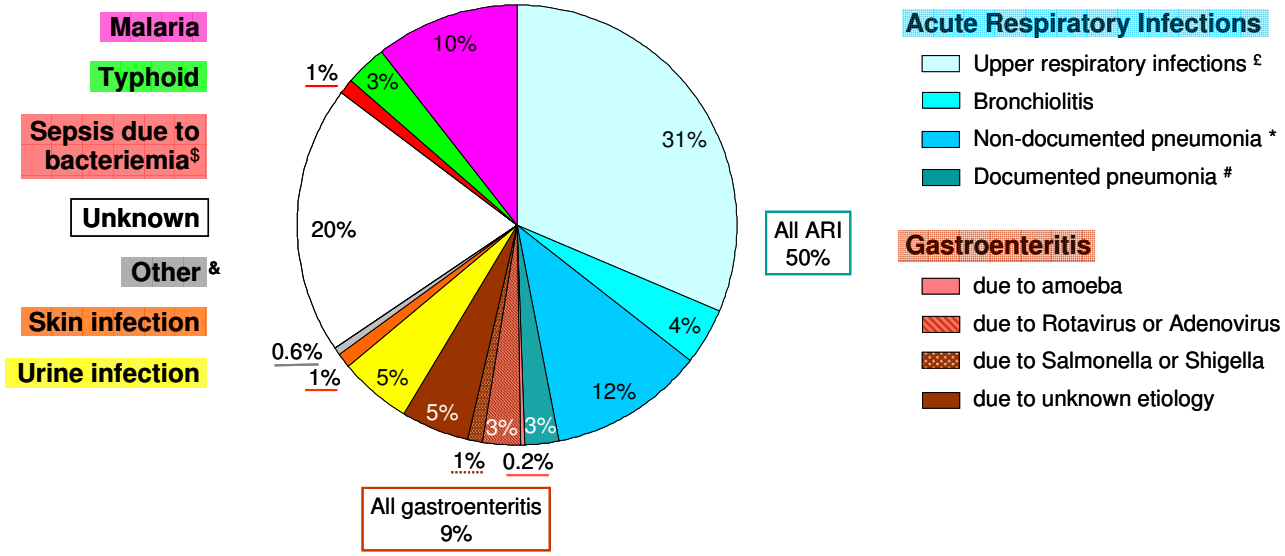
Table 13: Basic characteristics of patients by study site

	Dar es Salaam study site *Total patients = 507*		Ifakara study site *Total patients = 498*	
	n	(%)	n	(%)
Female	237	(46.8)	250	(50.2)
Age				
2 -<12 months	150	(29.6)	177	(35.5)
12 -<36 months	228	(45.0)	226	(45.4)
36 - <60 months	75	(14.8)	85	(17.1)
5 years - <8 years	36	(7.1)	8	(1.6)
8 years - <11 years	18	(3.6)	2	(0.4)
Temperature				
38 - <39°C	382	(75.4)	398	(79.9)
39 - <40°C	107	(21.1)	81	(16.3)
≥ 40°C	18	(3.6)	19	(3.8)
Main complain				
fever	313	(63.0)	354	(71.5)
cough	56	(11.3)	47	(9.5)
vomiting	47	(9.5)	28	(5.7)
diarrhoea	33	(6.6)	22	(4.4)
Abdominal pain	15	(3.0)	19	(3.8)

Aetiology of fever in all patients

The first diagnosis (as defined in the methodology) found in the 1005 children is shown in Figure 19. 498 (49.6%) children had an Acute Respiratory Infection (ARI) (31.3% URTI, 4.1% bronchiolitis, 11.5% non-documented pneumonia and 2.6% pneumonia documented by X-ray), 105 (10.4%) malaria, 90 (9.0%) gastroenteritis, 54 (5.4%) urinary tract infections (UTI), 33 (3.3%) typhoid, 26 (2.6%) other infections and 199 (19.8%) an unknown disease.

Figure 19: Diagnosis of high probability at first level in 1005 febrile children



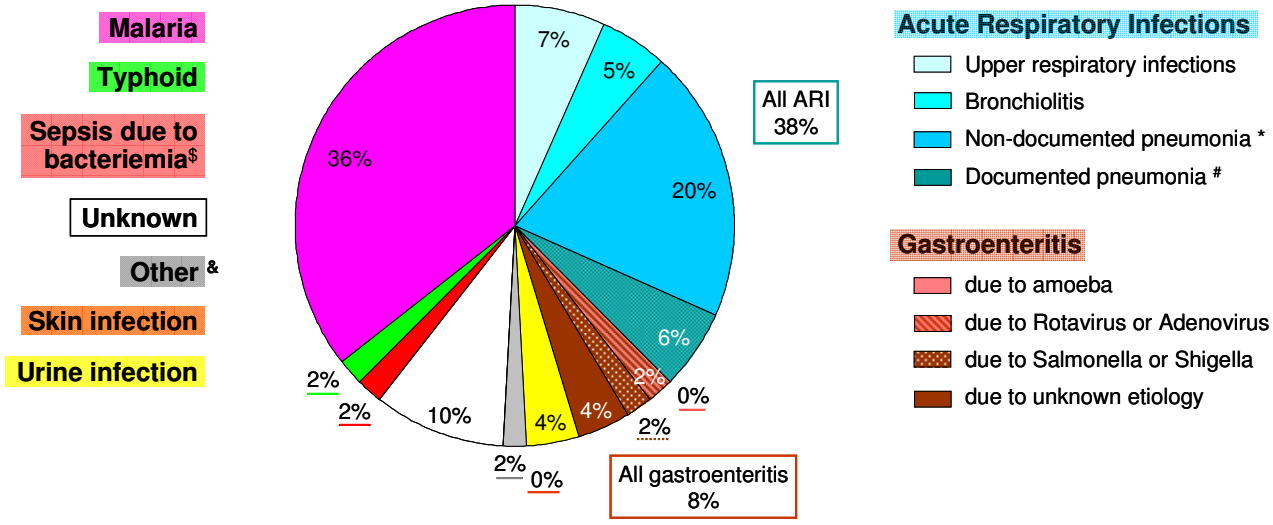
$ Blood cultures could not be performed in Ifakara; * Pneumonia based on IMCI criteria, chest X-ray was normal; # Pneumonia confirmed by chest X-ray; £ URTI: 180 tracheobronchitis, 106 rhinitis, 19 acute otitis media and 10 non-streptococcal tonsillitis. & Other diagnoses: 2 meningitis (with clear CSF), 1 mumps, 1 dental abscess, 1 chickenpox and 1fifth disease.

Aetiology of fever in severe patients

Among the 1005 children included (patients in need for life-savings procedures having been excluded before inclusion) 78 (7.8%) were admitted to the paediatric ward. Based on WHO criteria (WHO 2005a), 104 (10.3%) patients had a severe disease: 39 (37.5%) severe ARI, 37 (35.6%) severe malaria, 10 (9.6%) severe sepsis of unknown aetiology, 8 (7.7%) gastroenteritis with severe dehydration, 8 (7.7%) severe sepsis with documented infection and 2 meningitis (see Figure 20). 7 patients were admitted although they did not have a severe disease (by WHO definition): 3 because of near to severe anaemia (Hb between 5 and 6 g/dl), 2 because of vomiting in uncomplicated malaria and 2 because of bad general condition. 3 children died: one of severe malaria+typhoid, one of severe sepsis due to *Hemophilus influenzae* and one of meningitis in the context of HIV/AIDS.

The reasons for being classified as severe were (more than 1 reason per child was possible): 29 had respiratory distress (with chest indrawing in 27, nasal flaring in 16 and grunting in 5), 20 and 7 had jaundice in the context of severe malaria and severe sepsis respectively, 15 had convulsions, 14 had severe anaemia (Hb <5 g/dl), 13 were lethargic, 9 had severe dehydration, 4 had pre-choc, 2 had meningeal irritation, 2 had hypoglycaemia and 1 had cardiac failure.

Figure 20: Diagnosis of high probability at first level in 104 febrile children with severe disease

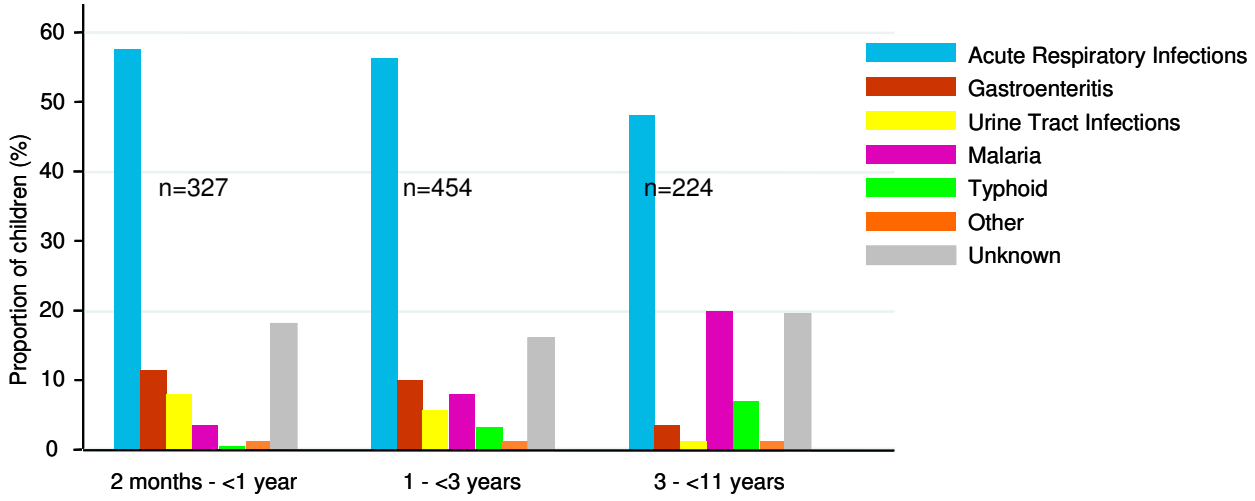


$ Blood cultures could not be performed in Ifakara; * Pneumonia based on IMCI criteria, chest X-ray was normal; # Pneumonia confirmed by chest X-ray; & Other diagnoses: 2 children with meningitis

Diseases by age groups

Figure 21 shows the distribution of diseases by age groups. Gastroenteritis as well as UTI is essentially a disease of infants and small children while typhoid prevalence increases with age. Malaria is found much more in older children as expected in moderately endemic areas. ARI is frequent in all age groups but tend to decrease slightly with building immunity.

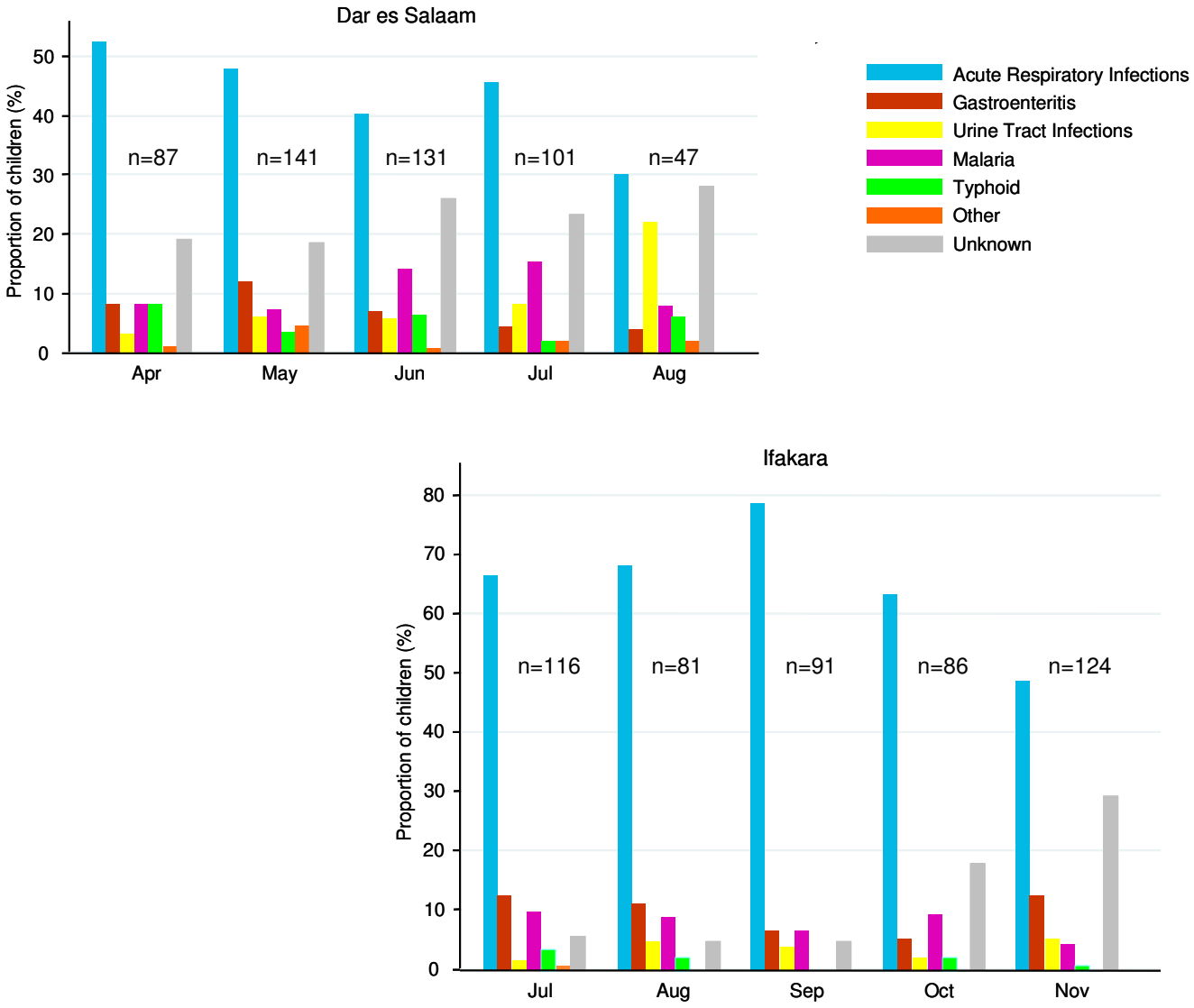
Figure 21: Proportion of 1005 febrile children with each diagnosis of high probability at first, second or third level over age groups



Seasonality and geographical distribution of diseases

Figure 22 shows the proportion of children with the main diseases by month of inclusion for the 2 different sites. In DSM, malaria peaked in June/July just after the rainy season, while gastroenteritis peaked in May. ARI decreased over time and was replaced by UTI and unknown diseases. Typhoid did not shown any trend. In Ifakara, compared to DSM, there was more ARI but less typhoid and gastroenteritis. In Ifakara, ARI and gastroenteritis show a reverse trend with a peak for ARI and a nadir for gastroenteritis in September. Unknown diseases increased strongly towards the end of the year, corresponding probably to undiscovered epidemic. Malaria and typhoid did not show any clear trend.

Figure 22: Proportion of 1005 febrile children with each diagnosis of high probability at first, second or third level over time by study site



Diseases of bacterial origin

Blood culture was performed in 424 (84%) of the 507 children included on the DSM site. 18 (4.2%) of the blood cultures were positive: 5 for a Gram positive cocci (3 *Staphylococcus aureus*, 1 *Streptococcus pneumonia* and 1 *Streptococcus spp*) and 13 for a Gram negative rod (4 *Salmonella typhi*, 2 for *Escherichia coli*, 2 for *Acinetobacter spp*, 1 *Salmonella non-typhi*, 1 *Shigella flexneri*, 1 for *Hemophilus influenzae*, 1 for *Aeromonas spp*, 1 *for Pseudomonas aeruginosa*). 20 (4.7%) of the blood cultures grew for a contaminant. For the 18 children with a significant bacteraemia, 4 had typhoid (already diagnosed by the rapid test for 2 of them), 3 had an already diagnosed focal infection (2 UTI due to E. coli and one gastroenteritis due to Shigella) being clearly the origin of the bacteraemia, 6 had a focal infection unrelated to the bacteraemia and 5 had no focal infection at all. Among the latter 11 children, 1 was admitted and died a few hours later of *Hemophilus influenzae* severe sepsis, while the others were managed as outpatient without receiving an antibiotic in 7 cases. All were cured at day 7 except one who had persistent fever at day 5 and then recovered with antibiotics. Bacteraemia was thus occult in 9 children among the 18.

Urine culture was performed in 144 children and was significantly positive (one bacteria with $\geq 10^4$ colonies) in 59 (41%) of them, for the usual gram-negative bacteria in most of the children. Stool culture was performed in 54 children and was positive for *Salmonella* or *Shigella* (no other bacteria was looked for) in 12 (22%) of them (11 for *Shigella flexnerii* and 1 for *Salmonella typhi*).

If we consider that, on top of the documented bacterial diseases [by laboratory as described above or clinically (for example purulent skin infections)], all pneumonia documented by X-ray were of bacterial origin, it means that 157 (16%) of the 1005 children had a bacterial infection as first, second or third diagnosis.

Diseases of viral aetiology

Among the 622 children diagnosed with ARI as first, second or third diagnosis, a positive PCR for at least one virus was found in 424 (68.2%) of them: 274 (66.5%) of the 412 children with an URTI, 31 (68.9%) of the 45 children with bronchiolitis, 102 (76.1%) of the 134 children with non-documented pneumonia and 17 (54.8%) of the 31 children with documented pneumonia (see Table 14). Regarding diarrhoea, rotavirus was found in 28 (27.7%), adenovirus in 1 and both viruses in 2 of the 101 children with gastroenteritis.

If, on top of the viral diseases mentioned above, we consider that all URTI, bronchiolitis or non-documented pneumonia were of viral origin and that the children with an unknown diagnosis (97% had recovered at day 7 while only 19% had received an antibiotic) had a viral infection, the overall proportion of children with a disease of viral aetiology as first diagnosis would be 71.2% (716/1005).

Table 14: Proportion of febrile children with respiratory viruses detected in the nasal and throat swabs by diagnostic category

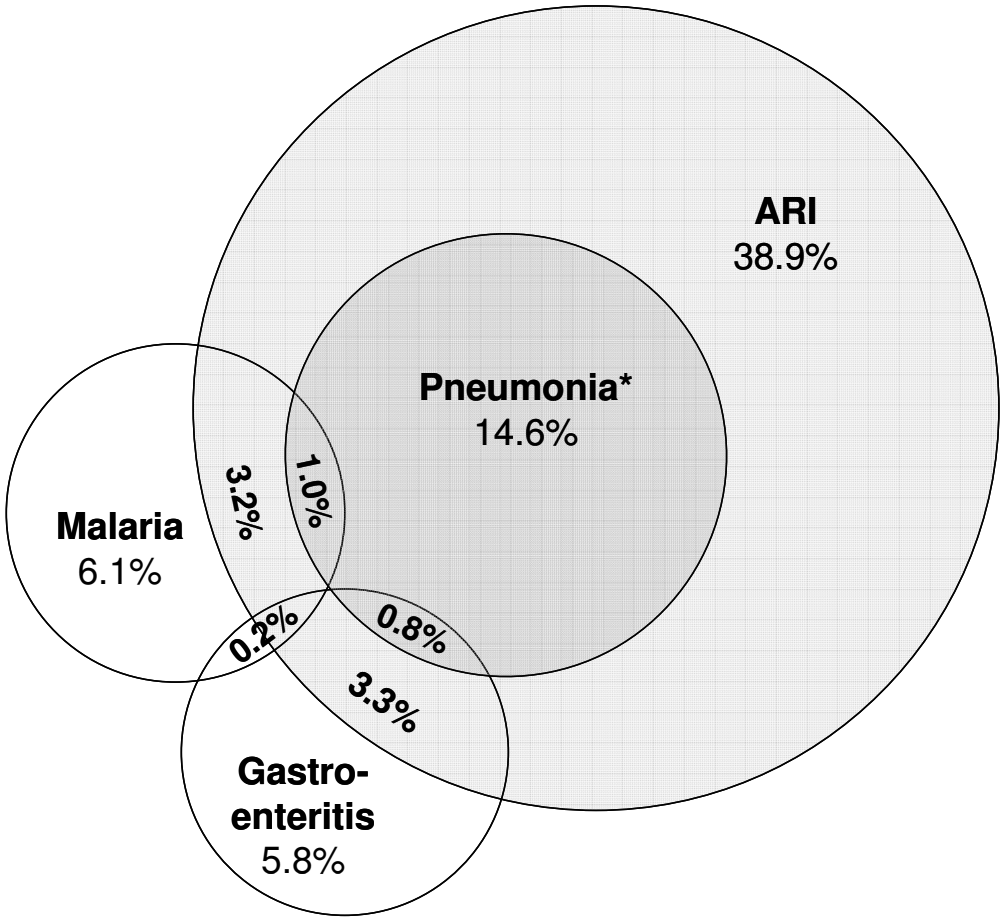
	Total number of children	At least one respiratory virus*	At least one respiratory virus except picornavirus*	Influenza A	Influenza B	RSV	human meta-pneumo virus	Para-influenza 1 and 3	Picorna virus
Children with an Acute Respiratory Infection #									
Any type of ARI	622	68%	39%	12%	14%	7%	2%	5%	38%
URTI	412	67%	37%	11%	16%	5%	2%	5%	37%
Bronchiolitis	45	69%	49%	24%	4%	13%	2%	9%	33%
Pneumonia with normal X-ray	134	76%	44%	13%	12%	10%	4%	7%	44%
Documented pneumonia	31	55%	23%	6%	6%	13%	0%	0%	35%
Children with a fever of unknown aetiology #									
Unknown	199	55%	18%	4%	9%	4%	1%	2%	38%
Children with a documented disease and no ARI #									
Any disease	184	44%	13%	2%	3%	7%	1%	1%	34%
Malaria	62	44%	6%	0%	2%	3%	2%	2%	39%
Gastroenteritis	59	44%	14%	3%	3%	5%	2%	0%	34%
Typhoid	19	47%	26%	0%	16%	5%	0%	5%	21%
UTI	40	45%	15%	3%	0%	13%	0%	0%	33%
Other disease	13	31%	15%	0%	0%	15%	0%	0%	23%

* One child can have more than one virus; # Diagnosis at first, second or third level

Co-diagnoses

253 (25.2%) children had more than one diagnosis (240 had 2 diagnoses and 13 had 3 diagnoses) of any level of probability. 131 and 3 children had respectively 2 and 3 diagnoses of high probability. The overlap of the 3 main causes of fever with high level of probability is presented in Figure 23. Looking in more detail at co-diagnosis in malaria patients, we found that, among the 105 children with any parasite density, 56 (53%) had at least another diagnosis (45 of high, 3 of intermediate and 8 of low level of probability). The 3 most frequent co-diagnoses of high level of probability with malaria were: URTI in 22 children, pneumonia (documented by chest X-ray or not) in 10 children and typhoid in 4 children. For the 15 children who had a parasite density <2000 parasites/µl, exactly the same proportion (53%) had at least one other diagnosis of any level of probability. Malaria patients (with any parasite density) were twice less likely to have a pneumonia (documented or not) and 3 times less likely to have a documented pneumonia than non-malaria patients. The probability of having typhoid was however the same in malaria and non-malaria patients.

Figure 23: Proportion of 1005 febrile children with Acute Respiratory Infections (ARI), malaria and gastroenteritis of high probability as first, second or third level
*Pneumonia as defined in IMCI (documented or not by chest X-ray)



9.5 Discussion

Using a thorough clinical work up, a broad range of laboratory investigations, chest X-ray and precise pre-defined criteria for diagnoses and their level of probability, we managed to establish the aetiology of fever in 80% of 1005 children attending one rural and one urban outpatient health facility in malaria moderately endemic areas in Tanzania. Half of the children had an acute respiratory infection (high or low), of which only 5% were confirmed to be pneumonia by chest X-ray. Malaria and gastroenteritis represented only 10% and 9% of the fevers, which is much less than generally thought for a traditional African setting. Indeed the transmission of malaria is declining in many countries (WHO 2009b; Chapter 4) and the sanitary conditions and knowledge have probably improved in the last 10 years. The latter also explains the limited number of typhoid fevers that were still found more in urban DSM (5.3%) than in rural Ifakara (2.0%). Urinary tract infections

documented by culture were few (4%) as expected in a healthy population of children [14% was found in hospitalized children in Nigeria (Rabasa & Gofama 2009)]. Many clinicians in Africa perceive UTI as a frequent cause of non-malaria fever; this is due to the unavailability of urine culture and the very low specificity of the test used instead (microscopy) to document UTI (the same is happening for typhoid). Bacteraemia was found in 4.2% of the 424 children with blood culture, which is double than what was found (2.0%) in the outpatient Kenyan study (Brent *et al*. 2006). The proportion of occult bacteraemia was 50% in our study and 27% in the Kenyan study. Regarding the 20% of all children in whom no diagnosis could be establish, PCR and serologies on the blood samples are ongoing and should allow us to know more about the aetiology. As the vast majority of these children recovered without antibiotic, they were probably suffering from a viral illness. In 55% of these 199 children, a respiratory virus was found in the nasoharyngeal sample and is probably the origin of the fever for most of them (except for picornavirus).

Children with severe disease

In severe patients, the major change in the distribution of diseases concerns malaria (36% versus 10% in non-severe patients) and ARI that were shifted towards the more severe forms of the disease (pneumonia). The proportion of children with an unknown diagnosis was half compared to the whole group. Bacteraemia was documented rarely (3.8%) in severe cases, but was still 2 to 3 times more likely than in non-severe cases. A respiratory virus was found at the same rate than in non-severe cases (63% and 61% respectively) and was clearly the aetiology of the severe disease in several of them (for example, human metapneumovirus, which is known to produce severe ARI, was overrepresented in severe cases). Even if the documentation of a bacterial origin in severe cases was still low, the management is totally different than in non-severe patients. Antibiotics should always be given immediately whatever is the working diagnosis. Indeed diagnostic tools that can reliably exclude invasive bacterial infection or confirm with certainty a viral aetiology do not yet exist. It is clearly stipulated in IMCI that ‘severe fever’ should receive iv antibiotics immediately but in the WHO guidelines for hospital care for children, only one page is devoted to severe sepsis and no clear statement on the necessity of treating all febrile children with severe features is given. Therefore clinicians are not aware that almost all features that apply to severe malaria are part of the definition of severe sepsis due to bacteraemia, and they tend to give quinine and withhold antibiotics, even if the malaria test is negative. The consequence is that presently in Africa the mortality is higher in non-malaria than in malaria cases (Makani *et al*. 2003; Reyburn *et al*. 2004).

Co-diagnosis

In these moderately endemic areas for malaria, the overlap between malaria, gastroenteritis (defined as ≥ 3 stools/day) and clinical pneumonia (defined by the presence of fast-breathing) was minimal. This highlight the fact that the overlap classically described in highly endemic areas might be due to the presence of incidental parasitemia in children with pneumonia or diarrhoea rather than a synergic co-infection. It is important to keep this in mind when deciding on the strategy of malaria testing for

low-endemic areas: it is probably reasonable to withhold malaria testing in a child with pneumonia, diarrhoea or skin infection. However, the overlap between URTI and all the other diseases was significant, showing that children often harbour an URTI that is probably not the origin of the acute fever episode. Therefore malaria testing should probably not be withheld in children with URTI, even in low transmission areas.

Aetiology of acute respiratory infections

Only 5% of all ARI were confirmed to be pneumonia by chest X-ray. This may mean that 95% of these ARI were probably of viral origin and did not need to be treated with antibiotics. Moreover, especially in preschool age infants and children, pneumonia are often of viral origin (Brodzinski & Ruddy 2009a; Cevey-Macherel *et al*. 2009), which means that even a higher proportion of all ARI were of viral origin. Primary end point pneumonia as defined by WHO has shown to be associated with a bacterial aetiology (Enwere *et al*. 2007) in contrast to ARI with other types of chest X-ray abnormalities or with normal X-ray. However the proportion of children with end point pneumonia and bacteraemia was still only 12.6%. In our study we found that 69% of the children with URTI, bonchiolitis and non-documented pneumonia had a virus in the nasopharyngeal sample and also 55% of the children with documented pneumonia. It is known that all respiratory viruses, including rhinoviruses (Peltola *et al*. 2008), can produce pneumonia even severe. It is clear that this virus might not be the only aetiology of the ARI but rather a co-factor with a bacteria (Cevey-Macherel *et al*. 2009; Nakayama *et al*. 2007). This is why we are presently testing these samples for *Pneumococcus* and *Hemophilus influenzae* type b by PCR, knowing the limitation of the result due to the impossibility to distinguish commensal from pathogenic bacteria. Whatever the contribution of bacteria in low respiratory tract infections, this affected only a very limited number of children and at least 95% of these ARI did not need to be treated by antibiotic. Based on the IMCI criteria, 27% of these children would have received an antibiotic treatment, which is much more than 5% but much less than the current habit of many clinicians to treat almost all ARI with antibiotics (Chapter 7).

Respiratory viruses isolated in children without ARI

A respiratory virus was found in 55% of children with a fever of unknown aetiology and 44% of children with a documented disease of high probability other than ARI (Table 14). These proportions are close to that of children with ARI (68%). When looking at the same data but removing picornaviruses, the differences between these 3 categories of children was bigger (39% for ARI, 18% for unknown fevers and 13% for other documented diseases). This suggests that part of the picornaviruses retrieved were not related to the present fever episode. Indeed small children are constantly infected by new strains of respiratory viruses, in particular picornaviruses (rhinoviruses) that take a few days to weeks (depending on the type of virus) to clear from the respiratory tract (Peltola *et al*. 2008). Therefore, at the onset of a new fever episode, whatever the cause (ARI, unknown or other documented infections), children can still harbour some viruses from a recent episode of URTI that is on the road to recovery. Part of the picornaviruses, and probably most of the

other viruses, might still represent the cause of the fever for the children with unknown aetiology [in particular for influenza that can present without respiratory symptoms in small children (Calvo Rey *et al*. 2005)] or a co-infection in children with malaria, typhoid or any other disease.

Typhoid fever

Among 37 children with documented typhoid, 32 (86%) had a mild presentation. 5 children did not receive any antibiotic and cured spontaneously. As we have no way to know which children with mild typhoid will get complications later on, it is still desirable to detect them as early as possible. There is no good clinical predictor that is sensitive enough to exclude typhoid on clinical grounds (in our study, abnormal abdominal palpation had an OR of 8.5 but was still only found in 19% of the cases). Therefore a point-of-care laboratory test is highly desirable, especially in Africa where blood culture is unavailable and Widal test performed widely despite its very low specificity. A few brands of Rapid Diagnostic Tests for typhoid (*ty*RDT) had shown good sensitivity, although with some variation when performed in the field (Naheed *et al*. 2008). In our study, we used a new generation of *ty*RDT based on the detection of specific IgM that had not yet been tested in real conditions. The sensitivity was much higher than blood culture, even early in the course of the disease (the median duration of fever mentioned by caretakers was only 2 days). Beside its actual price that is too high, the main problem is the necessity to test all febrile children to be able to detect the few existing cases. Age-specific prevalence of typhoid might help to better select those should be tested. In any case, *m*RDT will be deployed in many settings where the prevalence of typhoid is possibly close to that of malaria. The benefit of using *ty*RDT in Africa is thus worse being evaluated carefully.

9.6 Conclusion

In Dar es Salaam and Kilombero/Ulanga, half of the aetiologies of fever episodes in children were ARI, of which 2/3 were probably of viral origin based on clinical and microbiological criteria. Only 5% of all ARI were pneumonia (based on WHO criteria for chest X-ray interpretation). Gastroenteritis contributed to 9% of all fevers, of which at least 1/3 were due to a virus. In 1/5 of the children, no aetiology could be documented with certainty but most of them recovered without treatment. Most of the children with acute fever thus do not need to receive an antibiotic. Malaria (defined by any parasite density) contributed for only 10% of all episodes meaning that few children are in need for antimalarial treatment. It is important for clinicians and other actors of the health system to know these different pre-test probabilities to realize that the systematic provision of dual treatment (antimalarial and antibiotic) is no long appropriate. It expose the patient to unnecessary adverse events and the community to accelerated development of micro-organisms' resistance to drugs. The diversity of febrile causes, of which most cannot be diagnosed on clinical grounds, calls for new point-of-care laboratory tests that should be included in an evidence-based clinical decision chart. The ultimate goal being to prevent death, there is a need to think of new approaches that would help clinicians to detect early in the course of the disease children who are likely to develop complications,

whatever is the underlying infection. Beside validated clinical predictors, new biomarkers of inflammation predictive of the outcome that could be measured at point-of-care using simple devices would thus be invaluable tools.

9.7 Authors' contribution

VDA and BG designed the study. VDA led the project in the field, analyzed the data and wrote the manuscript. MK, EK and SP enrolled and did the full assessment of the patients. JKM and WS contributed to the design and the conduct of the study. LA analyzed the chest X-rays. PC and LK led the PCR analyses for respiratory viruses. BG contributed to the manuscript. CL contributed to the design and revised the manuscript.

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10. Complementary important findings from IMALDIA

Important findings from IMALDIA that are crucial to understand the effects of *m*RDT implementation but not included in the preceding chapters, will be presented below.

10.1 Impact of *m*RDT implementation on the consultation process

Background

The quality of the consultation performed by clinicians is often poor in Africa (Zurovac *et al*. 2006b; Reyburn *et al*. 2008). One of the reasons is the absence of reliable malaria diagnosis that drives the clinician to consider almost all patients as malaria cases and to omit to look for other causes of fever. Implementation of *m*RDT should trigger clinicians to spend more time on history taking and physical examination when the result is negative in order to identify symptoms or signs specific for another disease.

Objective

To assess the effect of *m*RDT implementation on the quality of the consultation preformed by clinicians in public health facilities.

Methodology

Cross-sectional surveys before and 18 months after mRDT implementation in 9 public health facilities in Dar es Salaam (see details of methodology in Chapter 7.3). Observation of consultation process by independent clinician.

Results (Table 15)

The quality of the history taken by clinicians did not improve after *m*RDT implementation. 40% of patients before and 31% after *m*RDT initiation were not asked about any complaint beside those they had mentioned spontaneously. Danger signs (as defined in IMCI) were still not assessed in children less than five years. There was improvement on one point only: previous drug intake was more often asked for (31% increase).

Physical examination remained very poor, if non-existent, in most of the patients. It even became worse with a 2-fold decrease in the proportion of patients examined for at least one sign (42% before versus 21% after). The respiratory rate was still almost never measured (1% of patients before and after) and chest auscultation was less often performed (22% before versus 7% after).

Counselling about the necessity to come back to the health facility in case of ‘persisting fever’ or ‘getting sicker’ was rare (in 4% and 21% of the patients respectively) at the time of microscopy but was done in about half of the patients after *m*RDT implementation.

The median duration of consultation remained extremely short after *m*RDT implementation and even decreased slightly (from 6 to 5 minutes, $p<0.001$). The time spent by patients to wait for the laboratory results was however shortened by more than half (92 before versus 39 minutes after *m*RDT initiation).

Table 15: Effect of *m*RDT implementation on the consultation process: before-and-after analysis. *SD* = standard deviation

	Before *m*RDT implementation *Total patients = 937*		After *m*RDT implementation *Total patients = 954*		Risk ratio	*p-value*
	n	% (95% CI)	n	% (95% CI)		
History taking						
Patient asked about at least one symptom	937	60% (57-63)	954	69% (66-72)	1.14	< 0.001
Patient asked about duration of symptoms	937	85% (83-88)	954	75% (73-78)	0.88	< 0.001
Patient asked about previous drug intake	937	43% (40-47)	954	57% (54-60)	1.31	< 0.001
Underfive patients asked about danger signs	486	7% (5-10)	501	9% (6-11)	1.16	0.5
Physical examination						
Patient examined for at least one sign	937	42% (39-46)	954	21% (18-23)	0.49	< 0.001
Temperature measured	937	3% (2-4)	954	4% (3-6)	1.68	0.04
Respiratory rate measured	937	1% (0-2)	954	1% (0-1)	0.71	0.5
Stethoscope put on chest	937	22% (20-25)	954	7% (5-8)	0.30	< 0.001
Counselling about when to return to health facility						
In case of fever / persisting fever	888	4% (3-5)	909	42% (39-46)	10.78	< 0.001
In case of getting sicker	888	21% (19-24)	909	56% (53-59)	2.61	< 0.001
Time spent by the patient at the health facility						
Median duration of consultation	866	6 min (3-9)	834	5 min (3-7)	1.17	< 0.001
Median time spent by the patient at the lab	574	92 min (64-127)	671	39 min (21-65)	0.42	< 0.001

Discussion

Unfortunately, *m*RDT implementation did not in itself improve the quality of the medical consultation, except for advising patients about when to return to the health facility. During the training, we mentioned the importance to take a short and well targeted history and to look for a few key signs (such as proposed by IMCI) to guide the request for additional specific laboratory analyses or treatment choice. We insisted that a full assessment from head to toe was not necessary and that the time to get the few key elements needed was short. The absence of improvement in clinicians procedures could mean that they were considering history taking and physical examination only for the purpose of trying to guess who had malaria or not, and not for the purpose of doing a differential diagnosis. The mistake of considering the usefulness of symptoms and signs mainly for deciding about the final diagnosis, which could thus be advantageously replaced by modern technology, is widespread in industrialized countries. The fact that symptoms and signs are rather essential to assess the pre-test probability of diseases and hence to choose the appropriate investigations (that will make this probability jump to a useful level for treatment decision) is not yet clear for many clinicians in Africa, but also in Europe and elsewhere.

Conclusion

Training focused on *m*RDT use is not enough to motivate clinicians to look for other causes of fever and thus improve the quality of the consultation. Teaching modules on malaria diagnosis should go hand in hand with training on the clinical management of fever cases. The new evidence-based approach of medical care, using probabilities and likelihood ratio concepts, needs to be taught to clinicians from the start, already at pre-graduate level.

10.2 Improvement of the IMCI algorithm based on evidence

Background

The development by WHO in the mid-1990s of an evidence-based algorithm for the management of acute medical conditions in children was an initiative that provided clinicians with a practical tool of high quality. Although originally designed for remote dispensaries working without laboratory facilities, it remains up to now the best integrated practice guidelines available for the management of an acute medical condition in outpatients at any level of the health system. The evidence on aetiologies of fevers was scarce in the mid-1990s and not much has been added since, mainly because studies are always disease specific and not aimed at assessing the respective contribution of each disease in a comprehensive and systematic way. In our study to investigate the causes of fever (Fever study), the proportion of each disease in febrile children living in urban Dar es Salaam and rural Ifakara was determined (Chapter 9). For each medical condition, it was also possible to calculate the performance of the clinical and laboratory predictors. These findings, although specific for the setting where the study was conducted, can be a starting point for improving the IMCI decision chart. Indeed, the present algorithm is probably very safe: 100% of malaria cases and around 80% of bacterial diseases are treated (Factor *et al*. 2001) but it recommends treatment with antimalarials and antibiotics for too many children.

Objective

To assess the robustness of the actual IMCI decision chart, evaluate the existing WHO proposals to improve these recommendations and articulate suggestions for an update of the IMCI algorithm dealing with acute conditions.

Methodology

We first compared the list of clinical conditions included in IMCI with the frequency of the aetiologies found in the Fever study. For each of the 10 most frequent conditions, we then assessed the appropriateness of including them in the IMCI decision chart and the best way to consider them based on the likelihood ratios (LR) that we calculated (Deeks & Altman 2004). We only assessed the management of acute conditions, ignoring treatment follow-up, chronic conditions and preventive measures.

The need to protect children from complications was weighted against the need to protect antimicrobials from micro-organisms' resistance. The concepts of "threshold for testing" and

"threshold for treatment" according to the probability of diagnosis (Grimes & Schulz 2005) were used to help in this decision.

Results

When comparing the results of our fever study with the content of IMCI, it appears that the medical conditions included in the latter do not match entirely the reality. On the other hand, the basic structure and flow of IMCI is still relevant, i.e. first assessing danger signs, then considering different predictors for specific conditions in parallel, and then deciding about treatment and action based on a combination of the post-test probability and the level of dangerousness of the disease. However, some predictors used as entry points and some clinical or laboratory tests need to be updated. The aetiologies found in our study were (in descending order of frequency): URTI (31.3%, including 2.5% acute otitis media), documented and non-documented pneumonia (14.1%), malaria (10.4%), gastroenteritis (8.9%), urinary tract infection (5.4%), bronchiolitis (4.1%), typhoid (3.3%), sepsis due to bacteraemia (1.0%) and skin infection (1.0%). The four most frequent conditions are all tackled by IMCI, which is good news, but the next five conditions are not addressed at all. Measles is a disease that appears in several branches of IMCI, but we did not observe any case in the fever study; thanks to the recent vaccination efforts the incidence of measles is now low in many African settings (WHO 2009a).

An unexpected observation from the Fever study was that the overlap between the 3 main diseases (malaria, pneumonia and gastroenteritis) has considerably decreased compared to the data available in the 1990's (O'Dempsey *et al*. 1993). This does not question the need for considering aetiologies in parallel (without mutual exclusion) as this overlap will never be zero, but it is one more reason to stop systematic double treatment for malaria and pneumonia.

Pertinence of IMCI according to our findings in severely ill children

With regard to severe disease, the first important finding is that the three leading causes of severe disease are still malaria (36%), pneumonia (based on IMCI criteria: 26%) and gastroenteritis (8%). For severe malaria, the algorithm for the use of *m*RDT (see Annex 1) needs to be integrated into the IMCI. In any case, severely ill patients should be given antimalarials without testing to avoid delay in referral. At hospital level, the patient should be tested by both *m*RDT and microscopy to increase sensitivity, and treated upon result. For severe pneumonia, an antibiotic should obviously be given and for severe gastroenteritis, beside re-hydration, an antibiotic should be given as soon as there is suspicion of fever, because the child then fulfils the criteria for severe sepsis (Lever & Mackenzie 2007). For sepsis with bacteraemia without a focus of infection (including typhoid), blood culture is an insensitive procedure (Mancini *et al*. 2010) and as a result it is difficult to know the actual number of children affected. Looking at the findings of the Fever study, it is probably between the 6% we found in Dar es Salaam (blood culture was not available in Ifakara) and 20% (proportion of children with an unknown aetiology or an URTI that cannot in itself explain the severe disease). In addition some of the children with a documented viral or parasitological disease (thus a priori not in need of an

antibiotic treatment) could have had a concomitant undetected bacteraemia being the real cause of the fever. This high pre-test probability combined with the danger of bacteraemia supports the IMCI recommendation of treating all severe febrile children with presumptive antibiotics before referring them. Because of the lack of diagnostic tools to prove the viral (non-bacterial) origin of a fever, this recommendation should also be applied upon admission in the hospital, which is not done in many settings in Africa (Reyburn *et al*. 2008) and not explicit in the WHO guidelines for hospital care (WHO 2005a). This would clearly save lives with a limited impact on the development of resistance, as severe children are few.

Pertinence of IMCI according to our findings in non-severely ill children (Table 16)
In non-severely ill children, our findings are quite different since most of the children have a viral disease and the aim is to rationalize antibiotic prescription. Indeed, the leading cause of fever was ARI (50%), which is associated with a virus in the vast majority of the cases (Chapter 9.4). Most of the 20% of children with an unknown aetiology were cured at day 7 without having received an antibiotic, which speaks also for a viral aetiology (13% of these children had indeed influenza and 42% another respiratory virus by PCR).

Starting with the first IMCI diseases for which antibiotic are prescribed, pneumonia, we found that not more than 30% of children with ARI (representing 15% of all children) need antibiotics based on: i) all clinical pneumonia or ii) all ARI without virus documentation. This is probably a conservative estimate as only 5% of all ARI were end-point pneumonia as defined by WHO (Cherian *et al*. 2005). X-ray lacks, however, sensitivity due to a delay in the anatomical consolidation process (Coote & McKenzie 2000). It is also known that most of pneumonia in pre-school children, at least in developed countries, are of viral aetiology (Brodzinski & Ruddy 2009b; Cevey-Macherel *et al*. 2009). The difficulty is to know how to identify children with definite pneumonia. The cut-off point used by IMCI is fast breathing because the latter has been shown as the best clinical predictor for pneumonia (Palafox *et al*. 2000). The problem is that this sign is not specific enough. One possibility would be to raise the respiratory rate cut-off. Using our data, raising it by 10 breath/minute for each age category (very fast breathing: ≥50 for children 2-12 months and ≥60 for children ≥12 months) would have a LR(+) of 6.1 and a LR(-) of 0.69. This would imply that we detect only 35% of documented pneumonia, which is not enough, except if, similarly to 'abnormal abdominal palpation' for typhoid, these children correspond precisely to those at risk of dying of pneumonia [the LR(+) of very fast breathing for severe ARI was 4.4]. This problem is far from being solved, even in Northern countries (Dirlewanger *et al*. 2002), and research is still needed. The aim would be to identify with a simple test children with ARI at risk for a complicated course or those with a bacterial aetiology (co-infection of virus and bacteria is often found; Cevey-Macherel *et al*. 2009) rather those with end-point pneumonia on chest X-ray (that are often of viral origin).

Moving to the next disease for which antibiotics are proposed in IMCI, diarrhoea, we found a virus in as many as 31% of children with febrile gastroenteritis using rapid tests that targeted only 2 viruses

(rotavirus and adenovirus). *Shigella* was present in only 11% of them (1% all children). Similar rates were found in 3 studies from Dar es Salaam and Ifakara including both febrile and non-febrile children (Moyo *et al*. 2007; Sam *et al*. 1992; Vargas *et al*. 2004). These data show that fever is clearly not a good criteria to give antibiotics. The WHO recommendation is to treat with antibiotics only diarrhoea due to *Shigella*. This is the reason why IMCI chose 'blood in stool' as criterion. In our study, 'blood in stool' was mentioned by caretakers in only 2 of the 11 children with *Shigella* and in one of the 90 children without *Shigella*. In practice, this clinical predictor is still the only test available and should be kept in the IMCI decision chart as long as no point-of-care laboratory test is developed.

The last condition for which IMCI proposes an antibiotic treatment is 'ear problem'. In the Fever study, we performed an otoscopy in all children and found that the IMCI criteria of 'ear pain or ear discharge for <14 days' had a LR(+) of 107 and a LR(-) of 0.56 to diagnose acute *otitis media*. However, the real issue here is that numerous studies have shown that the vast majority of uncomplicated acute otitis media are self-limiting, and like all other URTI, do not need to be treated with antibiotics (American Academy of Pediatrics 2004;Morris & Leach 2009). It would thus be appropriate to remove the criteria of 'ear pain' and keep only 'ear discharge for <14 days' (which can reflect an advanced stage of acute *otitis media*) for treating the child with antibiotics, and reinforce the general advice of 'return to health facility in 2 to 3 days (rather than 5 days as presently advised in IMCI) in case of persisting fever'.

For bacterial diseases not included in the IMCI decision chart, urinary tract infections were found in 5.4% and typhoid in 3.3% of the sampled children. Occult bacteraemia was found in only 1.8% of the children living in Dar es Salaam. The crucial question is: at which threshold of probability should a bacterial disease be treated with antibiotics, taking into account the dangerousness of this particular disease. We observed that 6 among the 7 children with untreated occult bacteraemia recovered spontaneously. As we treated immediately children with typhoid (based on rapid test result) and urinary tract infection (based in dipstick result), we don't know the proportion that would have been cured without treatment. What we can say is that ideally, we would have liked to treat all these children with antibiotics in the first place, because they are few (10%). It is clear that this does still not ensure that children at risk of complications or death would be targeted. As no good clinical predictor can be drawn (from our Fever study and from the studies looking specifically at these three diseases), the only way to identify these children is to have an easy and reliable laboratory test. These tests should have much better performance than those commonly used in health facilities in Africa (Widal for typhoid and microscopy for urinary tract infection), and should rule out a diagnosis at a threshold probability of around 10%. For occult bacteraemia, only an invasive and insensitive test exists nowadays (blood culture). So we have no mean to detect this rare condition (Brent *et al.* 2006).

For urinary tract infection, dipsticks should be introduced and replace the direct examination by microscopy (when done). Urine dipsticks are cheap and have a much better specificity than routine microscopy (64% were reported as positive). Using dipsticks would mean treating with an antibiotic 15% of all children, which is still too much (6% had really this infection) but much better than the present situation. In Northern countries, urinary tract infection is looked for in febrile children aged less than 2 years, because symptoms and signs are unspecific in this age group. This is the reason why WHO had proposed, in its attempt to integrate urine analysis in IMCI (WHO 2005c), to test only children < 2 years. Nevertheless, in our study we found that the typical symptoms/signs of urinary tract infection were neither found in the older age group. On the other hand we found that this infection was much rarer in children above 2 years (2.7%) than in younger children (8.1%), hence it would still be reasonable to restrict urine analysis to children less than 24 months. Using urine dipsticks would also have the advantage to treat with antibiotics only 10% rather than 15% of all children.

Typhoid is extremely rare in children younger than 12 months (0.4% in our study). For older children, the Widal test could be replaced by the new generation of Rapid Diagnostic Tests for typhoid (*ty*RDT), provided the price comes down. *ty*RDT are more and more used in Asia although there is still doubt on its performance in outpatients (Naheed *et al*. 2008). However, studies using PCR as gold-standard (rather than blood culture) have shown excellent sensitivity and specificity (Prakash *et al*. 2007). The performance of these new tests is anyway better than the Widal test, especially the one used routinely in health facilities in Africa. When *ty*RDT are not available, the clinical predictor ‘abnormal abdominal palpation’, that had in our study a LR(+) of 7.0 and a LR(-) of 0.83, could be used to decide on antibiotic prescription. In other terms, this predictor would help us to identify 20% of all children with typhoid at the cost of treating 3% of all children with antibiotics unnecessarily. 20% is too low, except if these children correspond precisely to the sub-sample of patients that are at risk for bad outcome, which could be the case knowing the pathophysiology of typhoid (gastrointestinal tract suffering).

Table 16: Proposed changes to the IMCI decision chart based on our findings. *ty*RDT = Rapid Diagnostic Test for typhoid

Branch (main symptom)	***Present recommendation***	***Change proposed***
Cough or difficult breathing	Definition of fast breathing: 2 - <12 months: (50 /min 12 months - 5 years: (40 /min	Definition of fast breathing: 2 - <12 months: (60 /min 12 months – 5 years: (50 /min
Fever	An antimalarial is prescribed in all cases (in highly endemic areas)	Perform a malaria test: If the result is positive, give an antimalarial If the result is negative, do not give an antimalarial
	Typhoid is not considered	*If tyRDT is available:* If the child is (12 months: Perform a tyRDT: If the result is positive, give an antibiotic If the result is negative, do not give an antibiotic *If tyRDT is NOT available:* If the child is (12 months: Palpate the abdomen: If abnormal abdominal palpation, give an antibiotic If normal abdominal palpation, do not give an antibiotic
	Urinary tract infection is not considered	If the child is <24 months: Perform a dipstick on clean urine: If leucocytes or nitrites are present, give an antibiotic If leucocytes and nitrites are absent, do not give an antibiotic
Ear problem	Reported discharge for <14 days is not enough to prescribe antibiotics; pus must be seen draining from the ear	Reported discharge for <14 days is a criteria sufficient to prescribe antibiotics
	Presence of ear pain is a criteria sufficient to prescribe an antibiotic	An antibiotic should be prescribed only when pus is seen or discharge reported for <14 days

Discussion

Our analysis done in the light of the findings of the 'Fever study' confirmed the appropriateness and robustness of the IMCI algorithm that can only be marginally improved using new clinical predictors. We are awaiting for new reliable point-of-care laboratory tests, allowing the identification of the micro-organism causing the illness, preferably for bacterial infections, or even better, the detection of biomarkers of inflammation predictive for the severity or the outcome of the illness (in the same way that procalcitonine is used in intensive care unit). In the meantime, the few changes we propose would save a substantial amount of antimalarials and antibiotics without putting the child at risk for adverse outcome. Targeted treatment of children at the first consultation implies, however, that a clear advice is given to the caretaker about when to return for follow up.

The changes we propose are mainly based on the only available study that has looked at aetiologies of fevers in a comprehensive way. The Fever study was conducted in a particular setting and findings

could be quite different in other places, even in the same country. However, it included children living in a rural and an urban setting and both places had moderate proportions of fever associated with P. falciparum parasitemia (10%), which is the situation that prevails or will prevail in the near future in many settings in Africa. More studies aimed at establishing the aetiologies are needed, and the recommendations of IMCI should continue to be updated accordingly. The safety of this new versions of IMCI need to be assessed carefully, as it was done for the recommendation of withholding antimalarials in children when the mRDT is negative (Chapter 5). This is planned in the frame of the follow-up project (PeDiAtric).

11. General discussion and conclusion

The aim of this thesis was to assess several aspects pertaining to the feasibility of implementing Rapid Diagnostic Tests for malaria (*m*RDT) in near-to-programme conditions in the Tanzanian public health sector. We drew on previous evidence of the high diagnostic performance of *m*RDT (Marx *et al*. 2005; Ochola *et al*. 2006) and on the experience of their reliability and feasibility for the clinical management of non-immune travellers, a population at special risk of complications if not diagnosed in time. Clearly, point-of-care tests could contribute to a dramatic improvement of the management of fevers in Africa and to a considerable saving in terms of antimalarial prescriptions.

The first step of this project was to assess the reliability of *m*RDT when used by health workers (laboratory technicians as well as clinicians) in the real conditions of daily management of patients. For this purpose, we set up a quality assurance system both at central and peripheral level. This system did not detect major problem and showed that the final result of mRDT testing by health workers was reliable.

The next step was to better estimate the pre-test probability of malaria in populations targeted by *m*RDT (febrile patients of all age groups attending a health facility of any type). For this purpose we undertook a systematic review of the studies giving the proportion of patients with associated *P. falciparum* parasitemia (PFPf) in Sub-Saharan Africa (Chapter 4). We found that the median PFPf was 35%, and that it had decreased by half when comparing the period before with the period after year 2000 (44% versus 22%). This relatively low pre-test probability represents another reason to implement *m*RDT in Africa. In Dar es Salaam, because of the very low PFPf (5% during the dry season, Wang *et al*. 2006a), it was even more urgent to start using a reliable malaria test. Microscopy was available in almost all public health facilities in Dar es Salaam, but the quality was extremely low, with an overall sensitivity of 71.4% and specificity of 47.3% for the 12 health facilities we had selected for IMALDIA (Kahama-Maro *et al*, in preparation).

On the request of several Tanzanian stake-holders, in particular clinicians routinely working with patients, we added a component to IMALDIA that was not planned initially, i.e. to assess the safety of withholding antimalarials in children under five years with a negative malaria test (Chapter 5). We did not observe any complication or death due to a missed diagnosis of malaria in our cohort of 1000 children, of which 60% were negative by *m*RDT. We concluded that the strategy of withholding antimalarials in negative children is safe and does not expose the child to an increased risk of bad outcome.

The results of the systematic review coupled with the findings of the safety study led us to question the appropriateness of the WHO recommendation of treating all fevers with antimalarials in children less than five years living in highly endemic areas (Chapter 6; English *et al*. 2009). WHO has now changed its policy, which means that the findings of IMALDIA were considered fully relevant to the up-coming situation of African countries, including Tanzania.

The core of this thesis, and the main objective of the IMALDIA project, was to investigate the feasibility and value of implementing malaria Rapid Diagnostic Tests in the management of fever episodes in an urban malaria setting (Chapter 7). Using 3 different designs, we found a 75% reduction in antimalarial consumption. This massive reduction was due to the higher accuracy of routine *m*RDT compared to routine microscopy (that led to a dramatic reduction in the number of positive patients) and to the confidence of health workers in *m*RDT results (the proportion of negative patients treated with antimalarials dropped from 53% to 7%). The impact was maintained up to the end of the observation period of the project (18 months). Unfortunately, *m*RDT implementation increased the prescription of antibiotics by 50% and did not have a major impact on the quality of the medical consultation (Chapter 10.1).

We took the opportunity of our near-to-program implementation of *m*RDT to perform a cost-saving analysis in a real situation and in a setting representative of many moderate endemic places in Africa (Chapter 8). The conclusion was that costs can be saved on drugs, from both the provider and from the client's perspective. For this reason, the overall expenditure for the patient was lower in health facilities using *m*RDT (by 0.31 USD per patient). However, the overall expenditure for the health system was higher (by 1.31 USD per patient) when using *m*RDT instead of routine microscopy, mainly because of the relatively high price of the device.

The aim of the last study (Chapter 9) was to explore the other causes of fever (beside malaria), in order to generate evidence for a revision of the existing clinical decision-charts for the management of patients, in particular the Integrated Management of Childhood Illness (IMCI). Based on these findings, we could propose a limited series of modifications but concluded that new point-of-care laboratory tests for the main infectious diseases are urgently needed (Chapter 10.2).

11.1 Feasibility of implementing *m*RDT in near-to-programme conditions

During the 18 months of pilot implementation of *m*RDT in 9 health facilities in Dar es Salaam, we achieved a dramatic reduction (of 3/4) of antimalarials consumption. This success was probably due to the way the project was deployed in the field, allowing ultimately clinicians and laboratory technicians to be convinced about the reliability and usefulness of *m*RDT. Moreover, the design used in the project was fully appropriate to detect an effect of such an intervention relying on a behavioural change of clinicians and requiring a health system environment conducive to this change.

The way IMALDIA project was deployed in the field

Trust from clinicians in the test result was gained through a series of crucial steps in the development and implementation of the project:

1) The Tanzanian medical authorities were involved in the project from the start (one of the principal investigators was the City Medical Officer of Dar es Salaam).

2) The principal investigators of IMALDIA and the team working in the field had no doubt on the performance of *m*RDT, once the different steps of the quality assurance system were in place. They therefore did not try to compare results given by *m*RDT with the one given by a blood slide examination, which would have only brought confusion in the mind of end-users.

3) A sensitization meeting was organized at the very start to involve the clinicians in charge of these health facilities, a focal person for each facility, members of the MOH and the person in charge of laboratories in DSM.

4) Five one-day training sessions were organized centrally, in which the vast majority of the health personnel dealing with the patients in the intervention facilities participated. The training was done by the field investigators themselves, with the contribution of the Professor heading the department of parasitology at the University hospital of Dar es Salaam and who was also one of the precursors of mRDT evaluation (Premji *et al*. 1994). An evidence-based approach using predictors, pre-test probabilities of diseases and likelihood ratios of tests leading to clear clinical decision-charts was used. These sessions were highly appreciated by health workers who acknowledged the quality of teaching that was tailored for their daily practice (Figure 24).

5) An organizational strategy for the storage, performance, recording and supervision of *m*RDT adapted to each situation was developed with the focal person and the different persons in charge in the facility, just before receiving the first consignment of tests.

6) Supervision on site took place with decreasing frequency (1, 2, 5, 10 and 15 months after initiation) using pre-defined parameters to be recorded for evaluating the adequacy of *m*RDT use.

In summary, the key of the success of IMALDIA was the involvement of high level health authorities at the start, and of local authorities all along the study, which gave high legitimacy and credibility to the project. The other key was to give clinicians a full understanding of the reasons for the change. The third key element for the success of IMALDIA was to provide clinicians with training material, in particular a clinical decision chart, free from ambiguous messages and inconsistent recommendations.

Figure 24: Group work during a training session

Appropriateness of the study design to detect an effect of mRDT implementation

The pre-requisite for a behavioural change when introducing a new diagnostic tool is an in-depth change of health care provider's disease representation, diagnosis conceptions and treatment habits. To measure the effect of the introduction of this new intervention, the following designs are appropriate, i) a before-and-after study or ii) a cluster randomized study. The minimum level of randomization unit should be the health facility. For a larger study, for example in the frame of *m*RDT implementation at national scale, the unit should even be the district or the region (see Chapter 11.9). In several previous studies, clinicians were asked to apply the standard strategy (presumptive antimalarial treatment) for patient A, the new procedure (*m*RDT) for patient B and to come back to the old strategy for patient C (because of individual randomization). Such a procedure is unlikely to achieve significant improvement in clinicians' behavior. Such procedures and design are unlikely to show success because no radical change is actually implemented and confusion is nearly ensured.

It is interesting to notice that, among the 6 papers published in the area of *m*RDT implementation since the start of IMALDIA, the 3 studies that had a design based on randomization by patient did not show any impact of *m*RDT implementation on antimalarial prescription, while the 3 studies using HF as the level of application of the strategy were successful (see Table 17).

Having a randomized control group might not even be of prime necessity to measure the operational success (not the efficacy or the effectiveness) of a new tool (Victora *et al*. 2004). This objective may be better served by a before-and-after design that avoids the problems of high heterogeneity between health facilities and contamination of the control group by the intervention group. In IMALDIA we did both a cluster randomized and a before-and-after analysis and clearly the latter gave more robust results (closer to the ones found by the longitudinal study based on another source of data).

Table 17: Published studies on *m*RDT implementation, stratified by level of allocation of the intervention (individual versus health facility). RCT = Randomized Controlled Trial.

Reference	Country	Study design	Comparison	Outcome measured	Result
Intervention allocated at the patient level					
Reyburn *et al*. 2007	Tanzania	RCT with 8 months follow up after training	Microscopy *versus* *m*RDT	Proportion of negative patients treated with antimalarials	51% *vs* 54%
Bisoffi *et al*. 2009	Burkina Faso	RCT with repeated cross-sectional surveys after training or refresher course	Presumptive diagnosis *versus* *m*RDT	Proportion of patients treated with antimalarials*	92% *vs* 93% (rainy season) 80% *vs* 84% (dry season)
Ansah *et al*. 2010	Ghana	RCT with 17 months follow-up after training	1. Presumptive diagnosis *versus* *m*RDT 2. Microscopy *versus* *m*RDT	Proportion of patients treated with antimalarials*	93% *vs* 70% 64% *vs* 62%
Intervention allocated at health facility level					
Hamer *et al*. 2007	Zambia	Cross-sectional survey performed one year after *m*RDT implementation at national scale	Microscopy *versus* *m*RDT	Proportion of negative patients treated with antimalarials	58% *vs* 36%
Williams *et al*. 2008	Tanzania	Surveys at baseline and 2 months after training	Before *versus* after *m*RDT implementation	'Overdiagnosis'[#]	55% *vs* 16%
Msellem *et al*. 2009	Zanzibar	Cross-over study (alternate weeks) during 4 months	Presumptive diagnosis *versus* *m*RDT	Proportion of patients treated with antimalarials*	85% *vs* 36%
D'Acremont *submitted* in 2010	Tanzania	RCT with repeated cross-sectional surveys at baseline and 18 months after implementation	1. Before *versus* after *m*RDT implementation 2. Microscopy *versus* *m*RDT	Proportion of patients treated with antimalarials	75% vs 20% 60% vs 22%
D'Acremont *submitted* in 2010	Tanzania	RCT with routine statistics collected over 15 months before and 18 months after implementation	1. Before *versus* after *m*RDT implementation 2. Microscopy *versus* *m*RDT	Reduction in antimalarials consumption	68% 70% vs 32%
Hopkins *in preparation*	Ouganda	RCT with repeated cross-sectional surveys	1. Before *versus* after *m*RDT implementation 2. Presumptive diagnosis *versus* *m*RDT	Proportion of patients treated with antimalarials	77% vs 22% 65% vs 22%

* As a change in the proportion of negative patients treated with antimalarials could not be assessed because the comparative group had no test, we recalculated the overall proportion of patients treated using numbers provided in the paper.

[#] Defined as proportion of negative patients among those with a clinical diagnosis of malaria given by clinicians

11.2 Applicability of the findings of IMALDIA to the deployment of *m*RDT at scale

In order to be as close as possible to programmatic conditions, we did not include strategies or interventions that were unrealistic in the frame of a deployment of *m*RDT at scale: 1) the training sessions were short, only one day; 2) no financial incentives were given to health workers at any level; 3) the frequency and time spent on supervision after *m*RDT initiation was close to what is usually planned (but often not done) by district health teams for this type of activity; 4) for health facilities who did not perform well at the start, we limited our additional meetings with the staff to a maximum of two sessions per health facility.

In summary, our project used feasible tools and strategies for implementation of *m*RDT but applied them in an optimal way. It is clear that in a deployment of *m*RDT at large scale, it is difficult to be optimal at all levels and all the time, and the final result will be highly dependent on the setting, in particular the strength of the health system.

With regard to the applicability of our result to other settings, we performed the same type of study, although without a control group, in a rural setting in Tanzania (Kilombero/Ulanga districts). The adherence of clinicians to the recommendation of not treating negative patients was even higher in that remote setting compared to Dar es Salaam (only 1% of negative patients only received an antimalarial drug). Interestingly, the impact on the overall consumption of antimalarials was less (a 2-fold decrease) due to the much higher proportion of fever cases associated with parasitaemia (39% instead of 8% in Dar es Salaam). A similar study was conducted in Uganda (although without longitudinal data from health statistics) and the preliminary results showed an impact of the same magnitude as ours (RR 0.29 for the before-and-after analysis and RR 0.34 for the cluster-randomized analysis) (Hopkins *et al*. 2008). A cross-sectional survey one year after *m*RDT deployment at scale in Zambia clearly showed problems (a decrease from 58% to only 36% in the proportion of negative patients treated with antimalarials) (Hamer *et al*. 2007). This was the very first experience in Africa (2005) and the training on *m*RDT (integrated in the training for the use of ACT as first line treatment) was very short. It shows that the proper use of *m*RDT cannot be taken for granted and that sustained efforts are needed to make it work on the middle- and long-term.

11.3 Undesirable side-effect of *m*RDT implementation on antibiotic prescription

Because of the lack of guidelines for the management of non-malaria fevers, implementation of *m*RDT runs the risk to increase drastically antibiotic consumption. In IMALDIA, the overall proportion of patients treated with antibiotics reached 72% after *m*RDT implementation. The increase was mainly due to the increased number of malaria-negative patients that were more often treated with antibiotics than positive patients. During our training, we mentioned that the Integrated Management of Childhood Illness (IMCI) algorithm should be used to guide the management of *m*RDT negative

patients, at least for children under five years. Unfortunately, few clinicians had been trained for IMCI (which was deployed in rural Tanzania but not much in Dar es Salaam). Our results highlight the imperative necessity of integrating *m*RDT training in a broader training on management of fevers.

Interestingly, the longitudinal study based on routine statistics did not show any change in the total number of antibiotic tablets consumed by health facilities. Before *m*RDT use, the consumption of antibiotics was already very high (compared to what is expected when IMCI is applied), with about 40% of all patients exiting health facilities receiving an antibiotic. It means that the increase observed in the before-and-after study (including only patients with acute medical problems, and not with surgical, gynecological, obstetrical or chronic problems) was probably diluted in the overall very large consumption of antibiotics by the health facilities. The other hypothesis could be that clinicians prescribed more antibiotics that were not available in the health facility but only in private pharmacies. The overall consumption of antibiotics in control health facilities also increased between 2006 and 2008, which shows that other factors than *m*RDT contributed to this problem. Broader strategies aimed at rational use of antibiotics to reduce the spread of resistance, such as those deployed presently in industrialized countries (Sabuncu *et al*. 2009), are thus urgently needed in Africa.

11.4 Impact of *m*RDT on the selection of patients for malaria testing

Another important aspect of *m*RDT implementation is the selection of patients by clinicians for malaria testing. Potentially, over-testing would lead to replacing drug wastage by test wastage. In the studies published up to date this aspect was not explored, as only patients with history of fever or 'clinical malaria' were included. We deliberately included all patients presenting with a medical condition to explore clinicians' behavior towards malaria test request. A study in Kenya in the microscopy era showed that clinicians test many patients without any history of fever and treat them most of the time (Zurovac *et al*. 2006b). Therefore, during the training we emphasized the necessity of testing only patients complaining of fever. Unfortunately, we did not manage to have an impact on this outcome: about half of non-febrile patients were tested before as well as after *m*RDT implementation. During the feed-back meeting organized after the end of the study, clinicians stated that the pressure of patients for testing was high (much higher than for getting an antimalarial) in particular when coming for a check-up. Their observation that non-febrile patients are sometimes positive (due to incidental parasitemia) did not help clinicians to understand the complexity of malaria infection versus disease, and why non-febrile patients should not be tested.

In the frame of a national scaling up, it is imperative that the National Malaria Control Program first decides on the target population for malaria testing based on the malaria transmission situation and possibly the number of *m*RDT available in the country. Clear guidelines needs then to be given to clinicians, avoiding criteria such as 'clinically suspected malaria based on history and examination'. In IMALDIA we used '*history of fever or temperature > 37.5°C*', a criterion that is widely accepted for

countries of high transmission. However, in the context of decreasing transmission, a choice need to be done between i) restricting malaria testing to a subgroup of patients with a high pre-test probability in order to save tests and ii) widening malaria testing with the aim of detecting all infections in order to reduce malaria transmission. Whatever decision is taken, simple - and if possible evidence-based - criteria need to be chosen and included in the decision chart for clinicians.

11.5 Improvement of the management of malaria and non-malaria fevers

One of the biggest challenges for a clinician working in Africa is when a febrile patient does not have malaria. The feeling of security about having made a diagnosis, and thus knowing what treatment to prescribe, disappears. The alternative diagnoses that clinicians have been taught during their pre-graduate training all need confirmation by a laboratory test (typhoid fever, urinary tract infection etc.) or an X-ray (pneumonia), which are usually unavailable. For a long time malaria has been treated presumptively. Initially this recommendation was for children under five years living in highly endemic areas but this recommendation was extended to older children and adults, to low endemic areas and to setting where laboratory diagnosis was actually available. During the baseline survey of IMALDIA (at the time of microscopy), we asked clinicians about the pre-test and post-test probability of malaria they estimated in the patient they were assessing: the median pre-test probability was 60% (the real one being 8%) and the median post-test probabilities were 85% and 50% when the blood slide was positive or negative, respectively. These probabilities were not influenced by the fact that the patient had a history of fever or not, or was aged less than five years. Clearly, their mental picture of malaria risk was inadequate.

The real incentive for clinicians to adhere to the malaria test will only come when they will get a tool to identify other diseases, based on the existing etiologies of fever. What is needed is a decision chart including a few affordable laboratory tests (see Chapter 10.2). The next step would be to find an incentive to adhere to this decision chart, as it is well known from experiences in Northern countries that the simple provision of practice guidelines is not enough (Cabana *et al*. 1999). This is also one of the obstacles highlighted by the evaluation of the impact of IMCI in the South (Bryce *et al*. 2005). In the North, several initiatives have emerged using computer-based guidelines (Shiffman *et al*. 1999), web-based interactive decision charts (Ambresin *et al*. 2007) or computerized recommendations integrated in the clinician work flow (Damiani *et al*. 2010). In the South, a computerized version of the IMCI teaching module has been developed and recently tested (http://www.icatt-training.org) and different guidelines for the use on mobile phones have been developed and pilot tested (Mitchell *et al*. 2009; Marc Mitchell, *personal communication*). In the continuation of the IMALDIA project, a new research project was designed, in collaboration with D-Tree (http://www.d-tree.org). Its aim is to improve the quality of health care by making standardized diagnostic and treatments easily accessible to providers using electronic decision support systems, with a special emphasis on the rational use of antibiotics and antimalarials (PeDiAtric project).

Another lesson learned from our experience and discussions with health workers is the imperative necessity to harmonize existing guidelines for the management of patients and update them accordingly. As these different guidelines are usually provided in the frame of vertical initiatives, it is crucial that at the top of the health system, stake-holders of the different programs communicate and developed standardized guidelines that are well grounded in the field experience by health workers.

11.6 Translation of research findings into policy and action

The relationship between the City council of Dar es Salaam and the Swiss Tropical and Public Health Institute (Swiss TPH) started in 1990 through the Dar es Salaam Urban health Project (Wyss *et al*. 2000), which aimed at strengthening healthcare and public health infrastructure through a decentralized system (Mtasiwa *et al*. 2003). In this context, a community-based mosquito surveillance program started in 2002 in the frame of the already existing Urban Malaria Control Program (UMCP). This strengthened the relationship between the City Medical Office of Health and the National Malaria Control Program - NMCP (Mtasiwa *et al*. 2004) and brought a favourable environment for operational research in the city. Between 2002 and 2003, a rapid urban malaria appraisal was carried out by a team from the Swiss TPH in 4 African big cities, including Dar es Salaam, where several indicators for the epidemiology of malaria were collected in different areas of the city (Wang *et al*. 2005a). The prevalence of malaria was found to be lower than expected, even in the peripheral areas (from 0.8% in the centre to 3.7% in the surrounding rural areas in school children). At health facility level, the findings were even more impressive: while the vast majority of febrile patients were treated with antimalarials, only 5.2% were in fact positive for malaria. This meant that, at the scale of the city, a considerable number of people were treated unnecessarily with antimalarials drugs. As a result, the City Medical Officer of Health and researchers from the Swiss TPH decided to act on these striking results and designed the IMALDIA project presented in this thesis. Recently, a new operational research project called PeDiAtric was set up on the basis of the findings of IMALDIA and in the same spirit.

During the IMALDIA project, we worked intensively at developing further the good relationship and confidence between the City council and NMCP. With other stakeholders, we managed to collaborate actively in the writing of the ‘National Guidelines for the use of malaria Rapid Diagnostic Tests in Tanzania’, which proposed the introduction of universal malaria testing.

Furthermore, the findings of the systematic review on the proportion of fevers associated with *Plasmodium falciparum* in Africa (Chapter 4), as well as the debate on presumptive malaria treatment in febrile children (Chapter 6), were used by WHO to support their decision to change the policy towards universal diagnosis of malaria. Therefore this work had clearly also an international dimension.

11.7 Implications of *m*RDT deployment for measuring the burden of malaria

Assessing the burden of malaria is an essential exercise, not only for the purpose of having accurate statistics but mainly because it has direct implications for the selection and planning of interventions at national or international level. For example, procurement and even manufacturing of ACTs or *m*RDTs cannot be planned correctly without reliable data on the incidence of malaria. Realistic national figures are needed but, with the decentralization of the health system, having good local data is also important. Indeed, with the decreasing transmission of malaria in Africa, the geographical heterogeneity of the prevalence is increasing (Jorgensen *et al*. 2010). *m*RDT have the potential to bring a great improvement in the reliability of surveillance data. If the *m*RDT results are properly collected in the health facilities and properly transmitted (for example directly through internet or a mobile phone) to the central level, the number of malaria cases managed by the health system can be determined precisely. With the progressive deployment of *m*RDT, the pictures of malaria prevalence will change drastically. One consequence is that there is an apparent decrease in malaria transmission, which in fact is simply due to the introduction of accurate diagnosis. In the coming years, it will be thus essential to know the timing of *m*RDT introduction in each place to accurately interpret the local and national trends of malaria indicators.

In conclusion, malaria control will never be achieved without proper documentation of all malaria cases (Perkins & Bell 2008). With the new worldwide momentum of malaria eradication, resources are being allocated to the documentation and elimination of the reservoir of asymptomatic people, while patients from high-risk communities attending the dispensary do not even have access to proper diagnosis.

11.8 Further research on the impact of *m*RDT implementation

One of the next key steps in the research agenda is to assess use of *m*RDT in the private sector as well as in the frame of the new WHO initiative of integrated management of fever in the community. Their potential in such situations can be very large but it requires careful evaluation.

In addition, it would be desirable to find an appropriate methodology to assess the health impact of *m*RDT use at district or regional level. *m*RDT might have a direct impact on the case fatality rate in admitted patients (Makani *et al*. 2003; Reyburn *et al*. 2004), and by extension in outpatients, if the quality of the management of non-malaria patients is really improved through better diagnostic procedures and treatment. However, measuring the benefit of *m*RDT on mortality will probably not be easy at population level, firstly because this happens in the context of numerous other malaria interventions aimed at decreasing overall mortality. Secondly, the use of *m*RDT for case management might anyway not have much of a direct health impact in settings where the previous habit was to treat presumptively all febrile patients.

In this context, we are probably left with being able to only measure process indicators, such as the proportion of admitted patients with a diagnosis of malaria or the proportion of deaths attributed to malaria, parameters that should both decrease drastically with proper documented diagnosis. Similarly, the proportion of patients diagnosed with malaria at primary level should decrease almost everywhere. Ideally the proportion of febrile patients treated with antimalarials would be a good indicator but this information is rarely available from the routine statistics. The amounts of first-line antimalarial drugs ordered by health facilities to the district should also be reduced.

In conclusion, *m*RDT is a tool aimed at improving the ability of clinician to make the right diagnosis and hence give the appropriate treatment. In a context where the tendency was to treat everybody with an antimalarial and an antibiotic, the short- or middle-term target cannot be better than non-inferiority, at least in terms of mortality. On the other hand, assessing improvement in process indicators after *m*RDT implementation, such as the reduction in antimalarials consumption, is a realistic goal. On the long-term, *m*RDT should lead to health benefits due to the better clinical management and the slowing down of parasite resistance to antimalarials.

11.9 Conclusion

The IMALDIA project provided a deep insight into many aspects of the implementation of *m*RDT in near-to-programme conditions in Tanzania. Our findings show that the introduction of *m*RDT is safe, feasible and useful for the routine management of fever cases in all age groups and at all levels of the health system. It is clearly feasible at large scale, provided the deployment is: i) carefully planned, ii) starts by a quality training that provides clear guidelines, iii) accompanied by regular supervision on site, iv) a few process indicators are monitored, and iv) includes a quality assurance system. The implementation requires flexibility on the part of the health care provider and a strong commitment of all persons involved. We demonstrated that acceptability of the test by patients and caretakers was good. Patients were rather satisfied to be tested and trusted the result.

As malaria diagnosis is only one aspect of the whole management of patients presenting with fever, improving its quality and utilization will not solve all obstacles for making a proper differential diagnosis and prescribing the appropriate treatment. To really improve the quality of care of these patients, it is essential to first develop new guidelines or improve the existing algorithms for clinicians. These decision charts designed for both children and adults should be based on the new evidence available and could include novel point-of-care tests for the key diseases, once these become available. Ideally, biological markers of severity should also be included. These new tools should then be made available to clinicians using new information and communication technologies to improve adherence to the guidelines. Targeting malaria diagnosis was the first step; it is now time to move to the improvement of the quality of the management of childhood and adulthood illnesses using an integrated approach.

12. Recommendations

12.1 Type of *m*RDT that should be used for deployment at scale in Tanzania

- Only brands performing well in the WHO/FIND product test should be used, taking into account the price of the device and the production capacity of the manufacturer
- Different brands of tests should be used to familiarize users with different technologies, to maintain competition between manufacturers and to avoid sudden stock outs due to limited production of one manufacturer

12.2 Target audience, content and planning of the training for *m*RDT use by health workers

- All laboratory personnel and clinicians should be trained for *m*RDT appropriate use; if possible, also nurses and pharmacists.
- Data on the prevalence of malaria in the region where health workers are located should be provided during the training in order to give them a realistic notion of risk.
- Guidelines on the use of *m*RDT in a form of a decision chart should be given and explained to clinicians during the training. It should include only one predictor (fever) or a combination of predictors (in very low endemic areas) for the selection of patients for testing and a clear statement on the action to take upon result of the test. Any ambiguous message, non evidence-based affirmation and contradictive statement should be avoided during the training.
- Practical case studies corresponding to the clinical situations most often seen by clinicians should be proposed and worked out by the clinicians themselves.
- If possible, a training module on the diagnosis and management of non-malaria fevers (for example IMCI) should be added to the session on malaria diagnosis. If this is not possible, a few hours should at least be spent on the differential diagnosis of fever episodes, the approximate prevalence of the most frequent diseases found in the region and the reliability of the laboratory tests used routinely in the place.

12.3 Quality assurance for *m*RDT in the field

- Each new consignment entering the country or the project should be lot-tested in a WHO reference laboratory
- Accurate performance of the device using prepared *Plasmodium* positive (with a known density) and negative blood samples should be assessed on a regular base in all storage places. As soon as the positive control wells (developed presently by WHO/FIND) will be available, the latter should replace these prepared blood samples.

- The ability of all health workers performing *m*RDT should be assessed on a regular basis, by observing them closely while performing a test on a patient.
- Quality control of the end product is not sufficient; all steps of quality assurance mentioned above should be performed.
- Using sub-optimal reference microscopy for quality control should be avoided by all means. When high quality microscopy is not available, no comparison of test results should be made.

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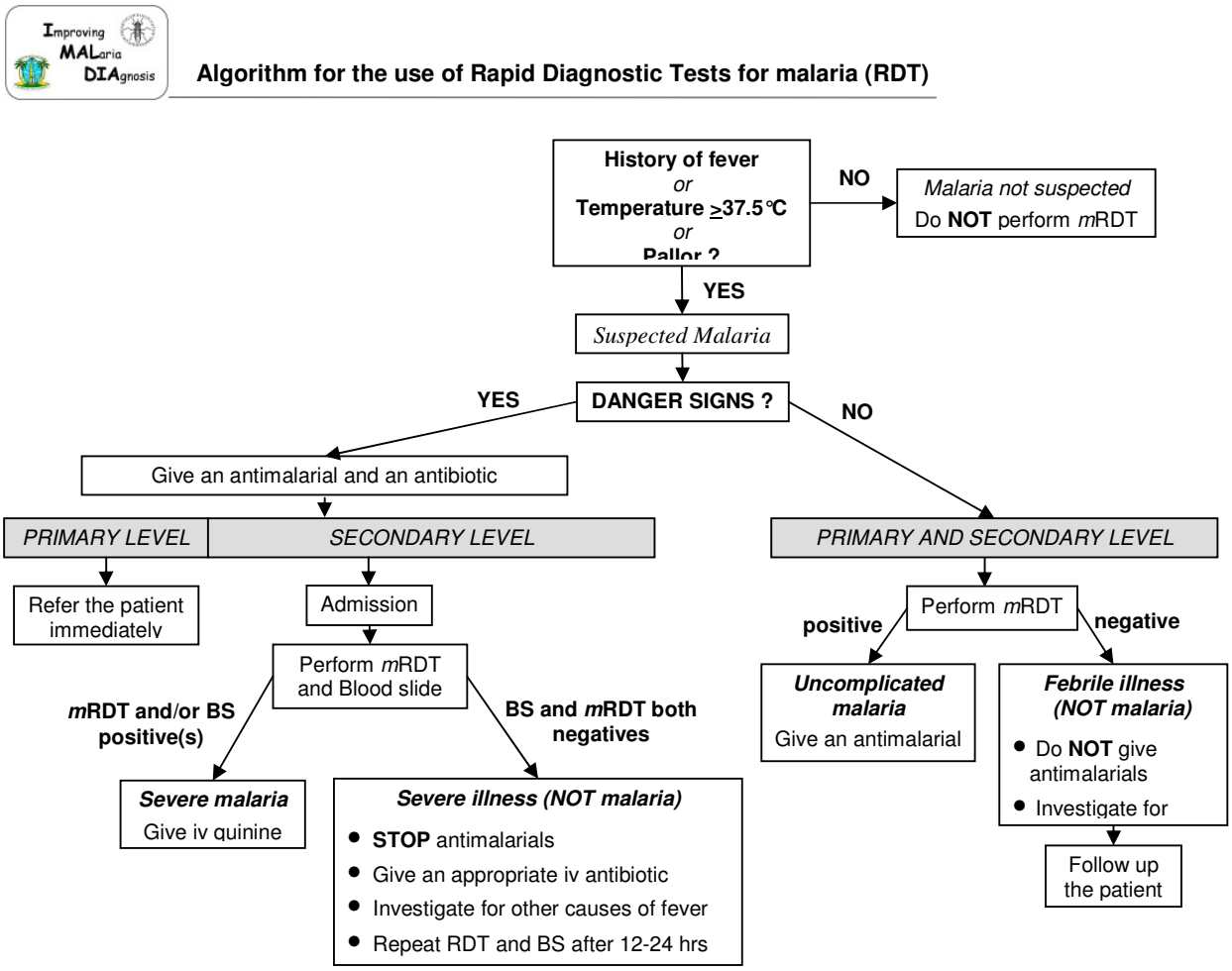
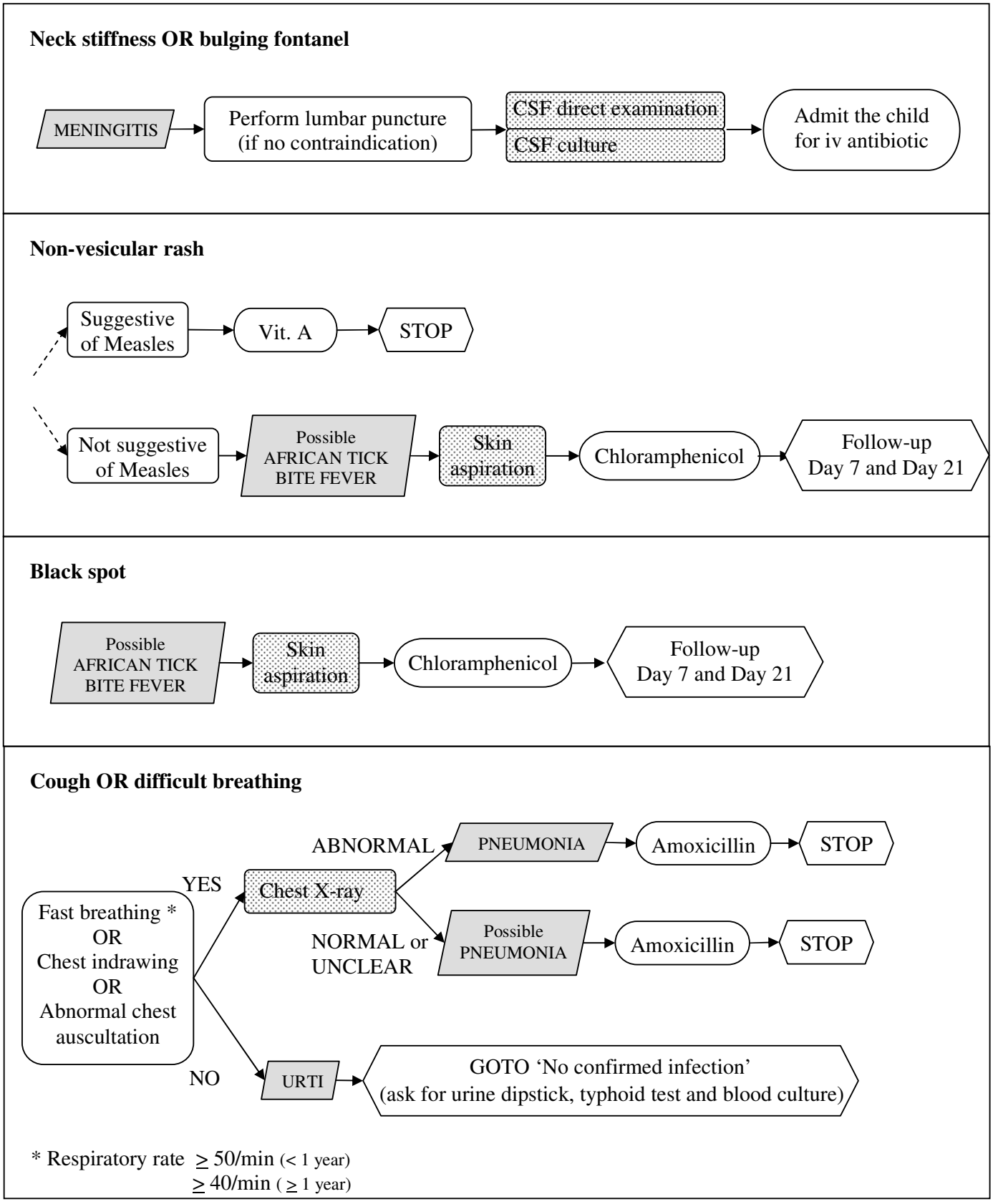
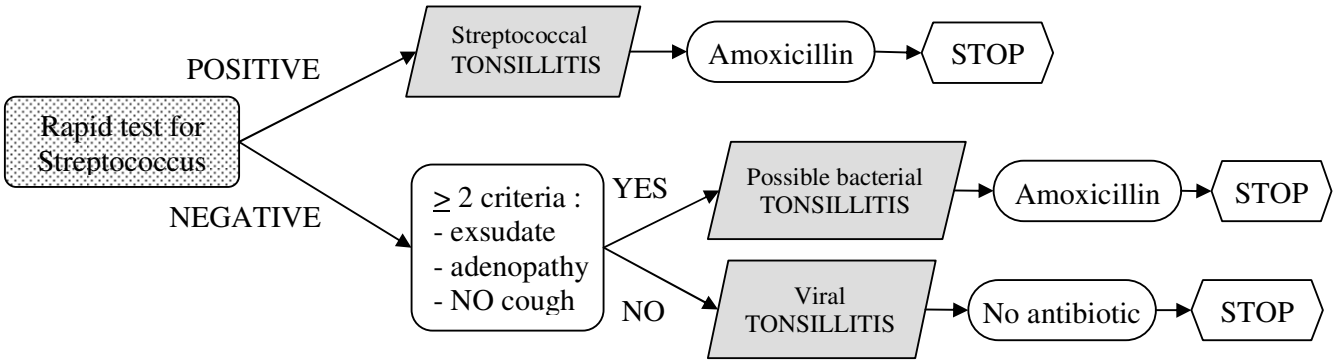
Annex 1: Algorithm for the use of *m*RDT used in IMALDIA project



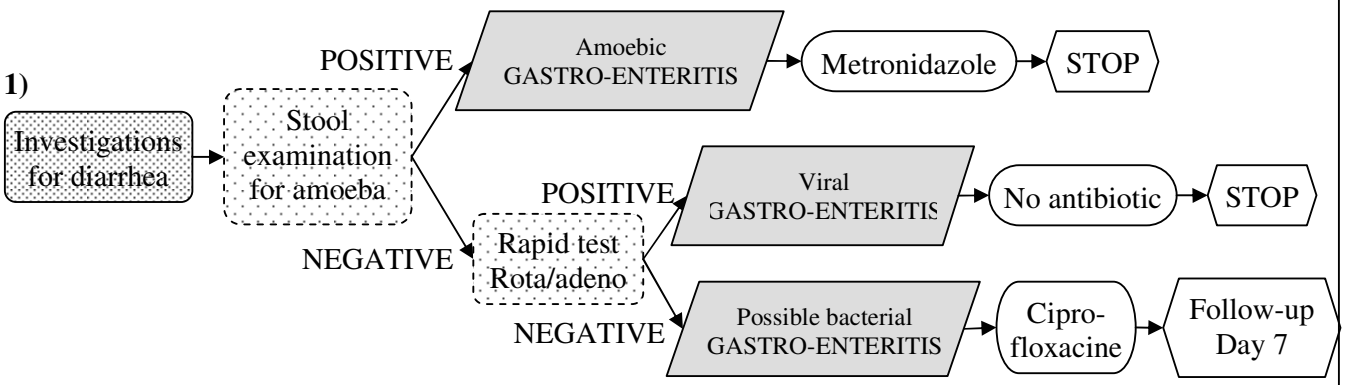
Annex 2: Algorithm for the research clinician undertaking the 'Fever study'

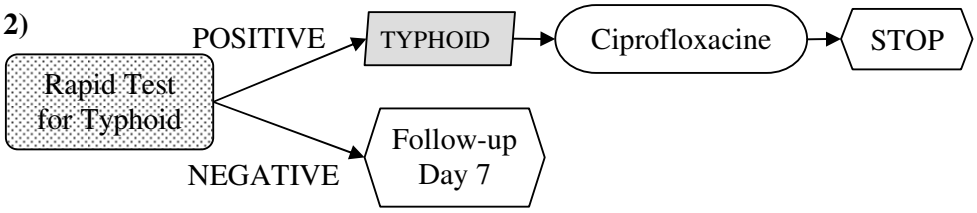


{Pharyngeal redness and enlarged tonsils} OR {tonsil exsudate}



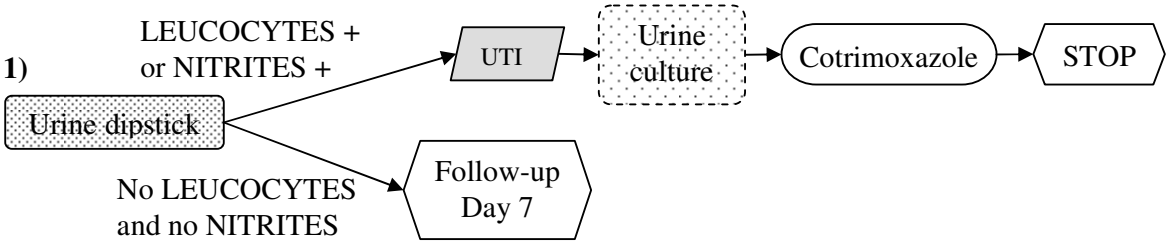
Diarrhea (≥ 3 stools /day)

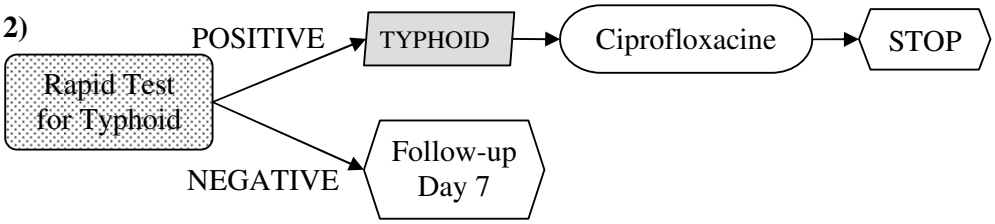




3) Blood culture

No confirmed infection (either clinically or by a laboratory test)





3) Blood culture

Annex 3: Criteria for the computer based diagnosis and its level of probability for the 'Fever study'

Illness	Minimum Criteria to consider the diagnosis	Criteria for a diagnosis of low probability	Criteria for a diagnosis of intermediate probability	Criteria for a diagnosis of high probability	Exceptions
Malaria					
malaria	all children			RDTmalaria positive OR blood slide positive	
Upper Respiratory Tract Infections					
rhinitis	runny nose for ≤ 7 days and no other ARI			runny nose without cough	
Streptococcal tonsillitis	(pharyngeal redness AND enlarged tonsils) OR (tonsil exsudate)			RDT strepto A positive	
Non-streptococcal tonsillitis	(pharyngeal redness AND enlarged tonsils) OR (tonsil exsudate)			RDT strepto A negative	
Pharyngitis	no other ARI outside rhinitis			red pharynx	
Acute otitis media	all children			ear discharge <14 days OR bulging tympanum OR very red tympanum	
Mastoiditis	all children			swelling behind ear	
Sinusitis	runny nose		painful sinus percussion		
Tracheobronchitis	cough AND no fast breathing AND normal chest auscultation	documented typhoid without runny nose	malaria without runny nose OR documented typhoid with runny nose	no malaria without runny nose AND no documented typhoid	If tonsillitis or acute otitis media or mastoiditis → no additional diagnosis
Bronchiolitis					
Bronchiolitis	cough			X-ray= "Bronchitis"	
Bronchiolitis OR tracheobronchitis with asthma	cough AND (ronchi at chest auscultation OR wheezing)			X-ray normal	
Pneumonia					
Non-documented pneumonia	cough AND (fast breathing OR abnormal chest auscultation)			X-ray normal, non interpretable or non available	Ronchi at chest ausc OR wheezing OR chest Xray="B" → bronchiolitis
Documented pneumonia	cough AND (fast breathing OR abnormal chest auscultation)			X-ray="Primary end-point pneumonia"	
Gastroenteritis					
Amoebic gastro-enteritis	diarrhea (≥ 3 stools/day)			stool direct examination positive for amoeba	
Bacterial gastro-enteritis	diarrhea (≥ 3 stools/day)			stool culture positive for salmonella or shigella	
Viral gastro-enteritis	diarrhea (≥ 3 stools/day)			RDT rota-adeno positive	
Unknown gastro-enteritis	diarrhea (≥ 3 stools/day)			stool direct examination negative for amoeba AND stool culture negative for salmonella or shigella AND RDT rota-adeno negative	
Urinary tract infection					
Urinary tract infection	leucocytes or nitrites in urine by dipstick	Urine culture negative (OR E.coli $<10^4$)	No urine culture available OR Urine culture with mixed growth	urine culture positive (E.coli $\geq 10^4$, other than mixed growth)	

Typhoid				
Typhoid	all children	abnormal abdominal palpation AND RDT typhoid negative AND no *Salmonella typhi* in blood or stool AND no urinary tract infection AND no malaria AND no gastroenteritis		RDT typhoid positive OR *Salmonella typhi* in blood or stool
Other				
Sepsis	blood culture positive for a non-contaminant bacteria			no other diagnosis OR other diagnosis unlikely to be due to the bacteria
Meningitis	all children			neck stiffness OR bulging fontanel
Measles	generalized rash		typical rash OR Koplick spots	serology/PCR positive
Mumps	all children			enlarged parotid(s)
Chickenpox	all children			typical vesicular eruption
Fifth disease (Parvovirus B19)	generalized rash		slapped cheek erythema	PCR positive
Rickettsiose	black spot OR purpuric generalized rash		black spot	PCR on skin positive
Relapsing fever	all children			Giemsa thick blood film positive
Skin infection	all children			furonculosis OR pustules OR cellulitis OR skin abscess
Osteomyelitis	all children			elicited pain of a limb OR refusal to move/use a limb OR redness, pain and swelling of a limb
Dental abscess	all children			pain and swelling around tooth
Unknown				
Unknown	all children			No diagnosis of high probability

RDT= Rapid Diagnostic Test; PCR= Polymerase Chain Reaction

Annex 4: Curriculum vitae

Valérie D'ACREMONT

Valerie.Dacremont@unibas.ch

Born 19.12.1971, married, 3 children
Swiss and French nationalities

TRAINING

Academic titles

1995	University of Lausanne, Switzerland	Diploma in Medicine
2003	University of Lausanne, Switzerland	Doctorate in Medicine
2006	University of Basel, Switzerland	Master in International Health
Foreseen	*University of Basel, Switzerland*	*PhD in Epidemiology*

Professional titles

1998	Royal college of Physicians	Diploma of Tropical Medicine and Hygiene
2003	Swiss Tropical Institute	Diploma of Health Care and Management in Tropical countries
2006	Swiss Medical Association (FMH)	Specialist in infectious diseases
2009	Swiss Medical Association (FMH)	Specialist in tropical medicine

PROFESSIONAL EXPERIENCE

Clinical experience

Post-graduate (Senior house officer)

01/1996 - 09/1997	Internal Medicine, surgery, intensive care	Hospital of St Loup, Switzerland
05/1998 - 09/2001	Internal Medicine, Travel Medicine, Epidemiology	Medical Outpatient Clinic (PMU), University of Lausanne, Switzerland
10/2001 - 09/2003	Infectious Diseases, HIV clinic, Hospital Infection Control	University Hospital of Lausanne (CHUV), Switzerland
04/2005 - 03/2006	Infectious Diseases, Hospital consultations	University Hospital of Lausanne (CHUV), Switzerland

Post-graduate (Registrar)

10/2003 - 09/2005	Travel clinic, Internal / Tropical Medicine Health care system for Asylum seekers (FARMED), Vulnerable Population Unit	Medical Outpatient Clinic (PMU), University of Lausanne, Switzerland

Research experience

Research physician

1997 - 2002	Travel Medicine and Vaccinology, with special focus on i) evidence-based travel medicine to investigate clinical and laboratory predictors of malaria, ii) the development and validation of evidence based recommendations for the management of fever in returning travelers and migrants, iii) the conduct of phase I-III clinical trials of new vaccines	Medical Outpatient Clinic, (PMU), University of Lausanne Switzerland
2003	Development of a tool to teach and promote intra-hospital guidelines for the appropriate antibiotic use.	Department of Infectious Diseases, University Hospital of Lausanne, Switzerland

Present activity

Research physician

Since March 2006	Responsible in the field of a 3-years North-South Swiss National Science Foundation project: ' improving malaria diagnosis in health facilities in Dar es Salaam, Tanzania'. Responsible of the 'Study to investigate the causes of fever in children living in urban Dar es Salaam and rural Ifakara, Tanzania'.	Department of Public health and Epidemiology, Swiss Tropical Institute, Basel, Switzerland
	Responsible for the diagnostic component of the ACCESS program in Ifakara, Kilombero district,	Ifakara Health Institute, Tanzania

Consultant in tropical/travel medicine and infectious diseases

Since Jan 2010	Co-management of the travel clinic and responsible for the management of communicable diseases in the community (outpatients and vulnerable populations) in Lausanne	Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Switzerland

PUBLICATIONS

Scientific papers and letters in peer-reviewed journals

1. **D'Acremont V**, Landry P, Darioli R, Stuerchler D, Pécoud A, Genton B. Treatment of imported malaria in an ambulatory setting: prospective study. *British Medical Journal* 2002; 324: 875-877.

2. **D'Acremont V**, Landry P, Müller I, Pécoud A, Genton B. Clinical and laboratory predictors of imported malaria : an aid to the medical decision making for returning travelers with fever. *Am J Trop Med Hyg* 2002; 66:481-6.

3. Genton B, **D'Acremont V**. Rapid diagnostic tests for malaria in returning travellers (electronic letter). *British Medical Journal* 2000, www.bmj.com/cgi/eletters/321/7259/484#EL2

4. **D'Acremont V**, Ambresin AE, Burnand B, Genton B. Practice Guidelines for fever in returning travelers and migrants. *Journal of Travel Medicine* 2003; 10 Supplement 2: S25-S52.

5. Canova L, Birchmeier M, **D'Acremont V**, Favrat B, Abetel G, Karly M, Landry P, Mancini M, Verdon F, Pécoud A, Genton B. Prevalence rate and reasons for refusals of influenza vaccine in elderly. *Swiss Medical Weekly* 2003; 133: 598-602.

6. Staehelin C, Rickenbach M, Egger M, Ledergerber B, Hirschel B, **D'Acremont V**, Battegay M, Wagels T,Bernasconi E, Kopp C, Egger M, Furrer H and the Swiss HIV Cohort Study. Migrants from Sub-Saharan Africa in the Swiss HIV Cohort Study: Importance, Characteristics, Access to Antiretroviral Therapy, Disease Progression and Survival. *AIDS* 2003; 17(15) :2237-44.

7. Genton B, **D'Acremont V**. Intranasal versus injectable influenza vaccine (letter). *Clinical Infectious Disease Journal* 2004; 39: 754.

8. **D'Acremont V**, Herzog C, Genton B. Immunogenicity and safety of a virosomal hepatitis A vaccine (Epaxal®) in the elderly. *Journal of Travel Medicine* 2006; 13(2): 78-83.

Scientific papers and letters in peer-reviewed journals (continuation)

9. **D'Acremont V**, Lengeler C, Genton B. Stop ambiguous messages on malaria diagnosis. *British Medical Journal* 2007; 334: 489

10. Ambresin AE, **D'Acremont V**, Mueller Y, Martin O, Burnand B, Genton B. www.fevertravel.ch: an online study prototype to evaluate the safety and feasibility of computerized guidelines for fever in returning travelers and migrants. *Comput Methods Programs Biomed.* 2007; 85(1): 19-31.

11. Genton B, **D'Acremont V**. Evidence of efficacy is not enough to develop recommendations: antibiotics for treatment of traveler's diarrhea. *Clinical Infectious Diseases* 2007; 44: 1520.

12. Newman-Klee C, **D'Acremont V**, Newman CJ, Gehri M, Genton B. Incidence and types of illness when traveling to the tropics: a prospective controlled study of children and their parents. *Am J Trop Med Hyg* 2007 ;77(4) :764-9.

13. Senn N, **D'Acremont V**, Landry P, Genton B. Malaria chemoprophylaxis: what do the travelers choose, and how does pretravel consultation influence their final decision. *Am J Trop Med Hyg* 2007; 77(6):1010-4.

14. **D'Acremont V**, Tremblay S, Genton B. Impact of vaccines given during pregnancy on the offspring of women consulting a travel clinic: a longitudinal study. *J Travel Med* 2008 Mar-Apr;15(2):77-81.

15. Genton B, **D'Acremont V**, Rare L, Baea K, Reeder JC, Alpers MP, Müller I. Plasmodium vivax and mixed infections are associated with severe malaria in children. *PLoS Medicine* 2008 17; 5(6): e127.

16. Boillat N, Genton B, **D'Acremont V**, Raoult D, Greub G. Fatal case of Israeli spotted fever after Mediterranean cruise. *Emerging Infectious Diseases 2008 Dec; 14(12): 1944-46.*

17. **D'Acremont V**, Lengeler C, Mshinda H, Mtasiwa D, Tanner M, Genton B. Time to move from presumptive malaria treatment to laboratory-confirmed diagnosis and treatment in African children with fever. *PLoS Medicine* 2009; 6(1): e252.