

Appendix 2

Consultation on the economics and financing of universal access to parasitological confirmation of malaria

Pre-read

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D R A F T

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The objective of the consultation is to examine and discuss the following questions:

- (a) What is the economics of expanded (including universal) access to the parasitological confirmation of malaria?*
- (b) What are the current costs of RDT use and their probable future evolution (considering the marginal cost of production, packaging and distribution, and the cost of use in terms of provider skills required and costs of alternative actions if the RDT is negative for malaria)?*
- (c) What are the most viable options for financing expanded (including universal) access to the parasitological confirmation of malaria?*

*It will address the economics and financing of expanded (including universal) access from multiple perspectives, country and institutional arrangements. Discussions will cover both *P. falciparum* and *P. vivax* malaria.*

Overview

Fever is an extremely common presenting complaint in patients in many settings and malaria probably the single most important cause of fever in many malaria endemic settings. It has therefore been appropriate to treat fevers presumptively as malaria, given the availability of an inexpensive, safe and effective anti-malarial treatment, the risks of inadequately treating malaria and the difficulty of confirming a parasitological diagnosis. Several developments in recent years have required a re-think of presumptive malaria treatment strategies.

Resistance to the most affordable anti-malarial drugs (chloroquine and sulphadoxine-pyrimethamine) has spread, necessitating their replacement by the highly efficacious but more expensive artemisinin combination treatments (ACTs). A decrease in malaria transmission and burden of disease has become evident in some settings following major investments in malaria control – primarily the deployment of insecticide treated mosquito nets (ITNs) and ACTs. In this new context, presumptive malaria treatment will lead to increasing wastage of expensive drugs and inadequate identification and treatment of non-malaria febrile illnesses. A large proportion – in many places, the majority - of anti-malarial treatments are taken by people who do not have malaria. Such unnecessary use of ACTs will reduce the potential cost-effectiveness, and therefore sustainability, of ACT-based strategies, including the affordable medicines facility for malaria (AMFm).

The development of Rapid Diagnostic Tests (RDTs) for malaria affords an unprecedented opportunity to improve both the management of patients with fever and the cost effectiveness of malaria treatment policies. In 2006, World Health Organisation's (WHO) Global Malaria Program (GMP) published treatment guidelines recommending pre-treatment parasitological confirmation of malaria in all patients except children under 5 years old living in settings with high, stable transmission, who were to be treated presumptively. March 2010 saw revised treatment guidelines published recommending pre-treatment parasitological confirmation of malaria, in all age groups, wherever possible. This recommendation comes just as the AMFm gets underway, reducing the cost of ACTs and creating an important increase in access to ACTs, but also risking an increase in over-treatment as a result of the improved access. The time is thus right to continue previous discussions and consider the economics and potential financing mechanisms for scaled-up parasitological diagnosis (Whitty, et al in preparation).

This pre-read, and the AMFm-GMP consultation as a whole, does not revisit the recommendation for pre-treatment parasitological confirmation of malaria, nor the technical issues specific to the tests themselves (e.g. performance limits), or the details of cost-effectiveness analyses of different approaches to malaria diagnosis. Instead, this document provides an overview of the current status of malaria diagnostics and draws attention to the considerable challenge of improving prescribers' compliance with negative test results. We review experience with parasitological diagnosis in Africa, which comes mainly from public health facilities, and the experience of malaria diagnostics so far in the private sector, mainly in Asia. This is important as most malaria treatments are sourced from the private sectors and hence parasitological diagnostic capacity must be strengthened there. We consider the challenges moving forward and the major economic considerations, before presenting a draft framework to assess alternative expansion pathways for the scaling up of universal access to parasitological confirmation of malaria.

INTRODUCTION

The expected benefits of parasitological diagnosis

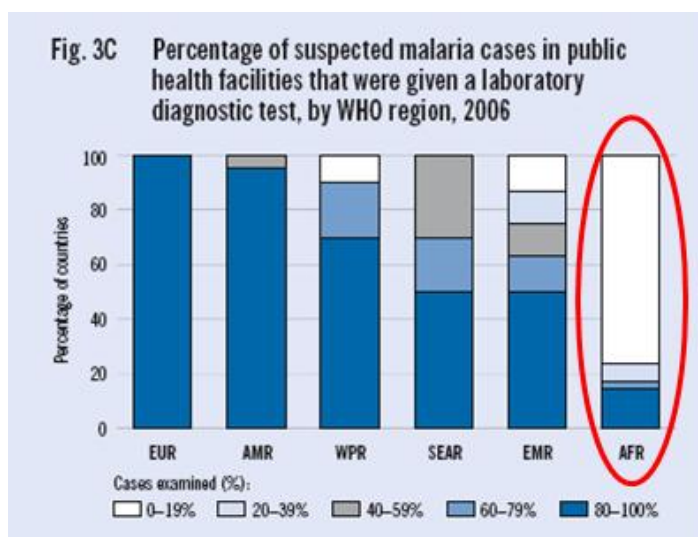
Expanded use of pre-treatment parasitological confirmation of malaria is expected to yield a number of benefits at various levels. Patients will avoid the unnecessary expense and the small risk of adverse effects of unneeded ACT treatments. They should be more likely to have potentially serious non-malarial illnesses identified and treated, and malaria treatment failures more easily recognised and investigated. Prescribers should have increased confidence in their malaria diagnoses and a clear indication of the need to look for non-malaria causes of fever, improving their management of patients with other febrile illnesses. Health systems will have better data to determine the burden of malaria disease and the impact of control programmes, feeding in to better forecasting of drug needs, improved transparency of commodity management and helping to avoid stock-outs in health facilities. At national and global levels, the improved targeting of ACTs should improve the cost effectiveness and therefore sustainability of ACT policies, including the AMFm. Improved appreciation of the true burden of malaria in different countries should facilitate forecasting of global ACT needs and guide the extent of cultivation of *Artemisia annua*, the raw material source for artemisinin. Finally, improved targeting of ACTs should also reduce the rate of development and spread of drug resistance to partner drugs with long half-lives in moderate to high transmission settings, where the longer half-life partner drug in ACTs is at risk of exposure to incoming infections once the artemisinin component has cleared. Many of these benefits will increase as malaria control improves, and be heightened if parasitological diagnosis can be extended through community based initiatives and through the private sector where, in many settings, the majority of anti-malarial treatments are currently provided. In 2006, for example, it is estimated that approximately 70% of all anti-malarial treatments were supplied through the private sector, the unlicensed, unregulated private sector playing the dominant role¹.

While in many countries a large proportion of malaria cases are confirmed by either microscopy or RDTs, on a global scale a small proportion of treated cases are properly diagnosed (see figure – from World malaria report, 2008). Especially in SSA countries there is a long way to move from where we are today to universal pre-treatment confirmation of malaria. The objectives for the consultation deal with the economics and financing of getting from here to there. In order to realise the potential benefits of scaled-up parasitological diagnostics, a number of challenges will need to be overcome.

The tests and systems to support their appropriate use will need to be financed and established; prescribers' and patients' behaviour change will need to be incentivised, a particular challenge for providers in the private sector who stand to lose ACT sales where a negative test result is obtained. Many of the issues will be different in the public sector versus the regulated and unregulated private sectors and at the community level.

THE CURRENT SITUATION

Inappropriate malaria diagnosis: over-diagnosis and missed cases



¹ Biosynthetic artemisinin roll out strategy, BCG/Institute for One World Health, WHO, Dalberg

There is no published estimate of the proportion of outpatient consultations in Africa that result in a malaria diagnosis but review of routine statistics suggests a typical figure of between 25% and 50% of all outpatient diagnoses. One study has collected estimates of overdiagnosis from a number of studies and this suggests that between 28% and 78% (mean 61%) of malaria diagnoses globally are in patients who do not have plasmodium parasitaemia (Amexo et al., 2004). Over the last 18 years studies from individual sites in Africa have found that between 20 % and 98% of malaria diagnoses are made in patients who are blood slide- or RDT-negative for malaria parasites (Reyburn et al., 2006, Mwanziva et al., 2008).

Presumptive treatment has, by definition, 100% sensitivity in malaria diagnosis but there is evidence that it is not systematically practiced; 3 different studies have documented that between 16% and 32% of children under the age of 5 years who qualified for presumptive treatment or who were actually found by a research slide to be parasitaemic, left a health facility with no antimalarial treatment (Font et al., 2001, Zurovac et al., 2007, Nankabirwa et al., 2009).

There are few studies of malaria diagnosis in the private sector or in local drug outlets but the evidence that exists suggests that 'missed malaria' may be more prevalent in drug outlets than health facilities; Kachur et al found that only 17% of treatments for febrile patients presenting to drug outlets in Tanzania were for malaria while 42% of such patients were actually parasitaemic (Kachur et al., 2006).

These figures give some idea of the huge scale of the problem of matching available resources for diagnosis and treatment to all and only those who have malaria. Despite the need to use routinely collected data, with its inevitable inaccuracies, there is a need to estimate the numbers of missed and over-diagnosed cases of malaria in different age groups, and at different transmission intensities, in order to guide the deployment of finite resources.

Quality of routine slide reading

Given the public health importance of blood slide microscopy and the fact that it is, by far, the most common laboratory investigation in Africa, it is remarkable that so little is known about the accuracy of routine blood slide results. Ideally such information would be available through national or regional quality-assurance schemes but, although such schemes are commonly part of MOH policy, there are no documented examples of any such schemes operating over a period of time in Africa.

The evidence of slide quality thus has to be gleaned from observational studies of malaria case management as there are no studies whose primary objective was to assess the accuracy of routine blood slide results. These estimates vary widely but rarely reach the 90% sensitivity and specificity recommended by WHO. The best results are from Zambia where sensitivity and specificity were estimated at 88% and 92% respectively in primary care facilities where laboratory staff had recently been trained (Barat et al., 1999), and from a teaching hospital in Malawi where school-leavers, following basic training, were able to produce results that were <2% discordant with experienced microscopist (Jonkman et al., 1995). Unfortunately in studies of malaria case management there are many more examples of much lower levels of sensitivity/specificity of routine slide results when compared to expert

slide reading. These include 72% / 56% (Zurovac et al., 2007), 79% / 59% (Reyburn H, 2004), 71% / 93% (Reyburn et al., 2006) and 59% / 53% (Nankabirwa et al., 2009).

The reasons for such inaccurate slide results in Africa (said to be much worse than in Asia) are not known but are likely to include poor microscopes and stains (Mundy et al., 2000), high workload, lack of motivation, lack of training or supervision etc. The resources needed to resolve these problems and to establish sustainable and effective quality assurance in slide reading are not known, but this is a neglected area that demands urgent attention if parasitological diagnosis of malaria is to become the norm in Africa.

In summary, the performance of microscopy in most facilities where services are available falls far short of the sensitivities and specificities (both over 70%) used in cost effectiveness analyses to date. There is no suggestion that the general situation is improving and it is unclear how best to remedy this. A combination of increased demand for quality assured services from the patient's perspective, and leaving the onus for demonstrating quality services with the provider, may help to change the situation. In the mean time, prescribers are aware of the lack of QA and often ignore slide results, with high rates of over-treatment of patients whose malaria slides are said to be negative. The net effect is that routine microscopy is rarely available in public health facilities, and where it is, compliance with negative results is very poor.

Prescriber adherence to the results of microscopy and RDTs

Awareness of the problems of inappropriate malaria diagnosis has been increasing over the last 20 years. From 1995, the Zambian MOH increased the availability of microscopy in primary care facilities; in 6 of these Barat et al found that, in spite of the free availability of blood slide microscopy provided by the Ministry of Health, 54% of malaria diagnoses were made presumptively (i.e. without recourse to slide testing) and of patients who were slide tested, 35% were treated for malaria in spite of a negative slide result (Barat et al., 1999).

Similar problems with prescribing inconsistently with parasitological tests have persisted. Almost a decade later a study in northern Tanzania found that a high proportion of patients who were eligible for a parasitological test for malaria (a fever in the current illness with no obvious alternative cause) were actually tested, no doubt boosted by the project's research assistants undertaking the tests when requested. However over 50% of patients who were test-negative were treated with an antimalarial anyway, and this proportion was the same whether the patient was tested by microscopy or RDT (Reyburn et al., 2006).

In both of these studies test-negative antimalarial treatment was more common in children compared to adults, but the differences were minor relative to the strong age-dependency of malaria. There were no other obvious patterns that could explain prescribing of antimalarials in test negative patients. However, test negative children were more likely to be treated with an antibiotic, particularly if an antimalarial had not been prescribed, and this supports statements that overdiagnosis of malaria leads to the neglect of non-malarial illness.

A number of studies have now reported on the effect of introducing RDTs into routine practice following training packages of varying intensity. The two outcomes of greatest interest are the proportion of eligible patients who are RDT tested and the proportion of test-negatives who are treated with antimalarials (nearly all studies have found that test-positives are almost invariably treated with an antimalarial so this is not considered as an outcome of

interest). Of these two key parameters, estimates vary widely and the reasons for this variation are not at all clear, but may partly be explained by the amount of training, supervision or other incentive, the prevailing malaria transmission intensity and the level of staff qualifications.

At one end of the performance spectrum, a study from Zanzibar demonstrated very high levels of use of RDTs and adherence of prescribing to RDT results. However this study included significant training inputs, regular supervision and salary supplements for prescribing staff. A large study from the mainland of Tanzania has also demonstrated similarly good results but again, training and supervision were quite extensive (D'Acremont et al., 2008). However, intense training is not always successful; Bisoffi, Sirima et al provided two rounds of training and regular supervision of prescribing staff in an area of intense seasonal transmission of malaria in Burkina Faso with almost no impact on the strong tendency to prescribe antimalarials for RDT-negative patients (Bisoffi et al., 2009). Clearly there is a need to identify truly effective training packages that are sustainable over large areas.

Evidence from some studies could suggest that the proportion of suspected malaria patients who are RDT tested is related to the proportion of test-negative patients treated with an antimalarial; in outpatient treatment in Tanzania, where over 90% of suspected cases were RDT-tested almost half of the test-negative patients were treated with an antimalarial (Reyburn et al., 2006), while in Southern Tanzania only 21% of patients treated for malaria had been RDT tested but less than 2% of RDT-negative patients received antimalarial treatment (McMorrow et al., 2008). Findings from a study in Zambia were intermediate between these extremes (Hamer et al., 2007) and initial reports from Senegal and Sao Tomé and Príncipe suggest that increasing coverage and large scale use of RDTs have reduced significantly ACT consumption (A Bosman, *pers. comm.*).

Realistic evidence of the effect of RDTs on antimalarial prescribing has been provided by a study of malaria case management in primary care facilities in Zambia following widespread introduction of RDTs with basic training in their use. A cluster randomized survey found that 28% of antimalarial treatments were provided presumptively (i.e. without recourse to RDT testing) and 36% of patients with a negative RDT result were treated with an antimalarial. As in studies cited above, there was relatively little variation in these parameters either by age or transmission intensity, and this finding is consistent with studies of malaria case management with facilities for blood slide microscopy (Nankabirwa et al., 2009).

Studies by Skarbinski and Ansah (Ansah et al., 2010, Skarbinski et al., 2009) both demonstrate that introduction of RDTs into primary care facilities that already have capacity for malaria microscopy has very little impact on overall use of antimalarial drugs but that blood slides are generally replaced by RDT. In addition, Ansah found that in facilities without prior microscopy, antimalarial drug use was reduced by approximately 30% by RDT testing, in spite of almost 50% of test-negative patients being treated with antimalarials. By contrast, Skarbinski et al in the Kenyan study observed a 60% reduction of antimalarials but it was attributable to the baseline training and supervision in the trial rather than the use of RDT or blood slide testing.

The suggestion that prescribers who have grown used to ignoring microscopy results are more likely to ignore the results of RDTs is worrying, and underlines the importance of introducing RDTs carefully. Compliance with RDT results needs to be maximized from the outset in order to build confidence in results and to avoid the spectre of widespread distrust

of RDT results. Further development of RDT QA capacity and careful operational research surrounding the introduction and use of RDTs is required to realise their potential.

In conclusion, there is wide variation in the use and prescriber adherence to parasitological test results in primary care facilities in Africa. While some of this variation may be attributed to the level of training and supervision that is provided, much of it remains unexplained. The level and type of training needed to achieve high levels of test use and prescribing adherence is not known, but are likely to require significant resources.

The influence of qualifications on RDT use and adherence

Higher-trained staff may be less adherent to guidelines than lower trained staff (Rowe et al., 2000) possibly reflecting greater confidence and independence of opinion. A related question is whether a similar difference might exist between primary care prescribers and village health assistants. In this case similar differences in confidence in independent opinions may operate and, in addition, village health workers have not been trained in a culture where every non-specific febrile illness might be labelled as malaria. In support of this, a number of anecdotal reports and at least two studies in press show very high levels of RDT use and prescribing adherence to results in village health workers (Hamer et al, and Premji et al both in press).

In conclusion, there is wide variation in the use of and prescriber adherence to parasitological test results in primary care facilities in Africa. While some of this variation may be attributed to the level of training and supervision that is provided much of this variation remains unexplained. The level and type of training needed to achieve high levels of test use and prescribing adherence is not known; what seems clear is that it will require significant resources and that as levels of test use increase there may be a fall off in prescriber adherence to results. The availability of RDTs affords an opportunity to increase access to diagnostic services but there's a need to maximize prescribers' compliance with test results. How best to achieve this, and how to ensure the receptivity of patients to a negative test result, will be determined by an understanding of why negative test results are often ignored.

Understanding the challenge of negative test results.

For many years prescribers have not had access to diagnostic tests and it has not only been accepted but also recommended for patients with fever to be treated with an antimalarial. Prescribers and patients alike have grown used to this scenario (Chandler et al., 2008). The introduction of diagnostic capacity introduces a conundrum; what to do with those patients who have a negative malaria test result? Some such patients will have self-limiting, non-serious illnesses, while others will have potentially serious pathology which requires appropriate treatment. Tests that reliably distinguish potentially severe disease from non-severe non-malaria disease do not currently exist. The easy and widely accepted thing to do is to prescribe an anti-malarial and it will be necessary to change this in order to maximize the utility of RDTs.

Patients need to know that ACTs are only useful for malaria and that this can be diagnosed using an RDT. The terms for fever and malaria are often synonymous in African societies in which such a large burden of febrile illness has been due to malaria. There is a need to

disentangle the concepts of malaria and fever in the minds of providers and patients alike. Secondly, it is important to have clear agreement on the most appropriate steps to take in someone who has a negative RDT. Who should receive an antibiotic, and which antibiotic should they receive? Who should determine this? If patients present to the unregulated private sector and have a negative RDT, should they then be referred for assessment and management? These questions need to be considered in the context of considerable uncertainties over the epidemiology and aetiology of non-malaria febrile illnesses, and the likelihood that these vary from place to place, and addressed in national treatment guidelines which include specific guidelines for the private sectors.

Generic guidelines have been developed to facilitate the Integrated Management of Childhood Illness (IMCI) and cover three different levels: 1) community care, 2) peripheral health facility and 3) district hospital². In malaria endemic areas, at community level and at health care facility level, children with severe febrile illness are referred without the need for parasitological confirmation of diagnosis. In peripheral health facilities, children with severe febrile illness receive pre-referral parenteral treatment with both anti-malarials and antibiotics. If the febrile child does not present with danger signs, a malaria test is performed and, if the results are negative, the patient is assessed for other possible bacterial causes of fever, to decide on the need for antibiotics (e.g. pneumonia, urinary tract infection, typhoid, cellulitis and osteomyelitis).

Working with the Private Sector

The private sector includes a wide-range of different types of providers, from private hospitals, clinics and licensed pharmacies to unlicensed drug shops, general stalls and itinerant sellers. It is essential to specifically consider these settings for the introduction of RDTs as the majority of malaria treatments are sourced there, and the behaviour and expectations of providers and patients are different to those in the public sector. These differences may make it more difficult to engage in the private sector, especially for reasons surrounding the profit motive. There are also concerns that a focus on the private sector could divert people from investing in the public sector and, as a result, limit access to those who need ACTs. However, failure to engage effectively with the private-for-profit (including informal) sectors will result in much of sub-Saharan Africa having no chance of universal access to parasitological confirmation of malaria for a long time to come.

The optimal timing of involvement of the private sector merits consideration - at the same time or after roll out of subsidised ACTs? Before or after roll out of diagnostics in the public sector? It will be important to consider the implications, and potential for double standards, if RDTs are not firmly established in the formal health care system (both public and private) and the rest of the private sectors at the same time. It probably makes sense to prioritise diagnostics in places where ACTs are most overused – where ACTs are available and, perhaps, where there are low, or declining, levels of malaria. It's important to ensure a regular supply of ACTs and RDTs can be maintained, and that the necessary mechanisms are available to maximise the likelihood of provider co-operation and compliance with test results.

It may be necessary to review the regulatory framework to ensure there is clarity over whether only regulated or licensed providers should be considered a legitimate outlet for

² See <http://whqlibdoc.who.int/publications/2005/9241546700.pdf>

ACTs and for diagnostic testing. Would it be useful and feasible to require the use of an RDT before selling an ACT treatment course in regulated and/or unregulated outlets? What approach should be deployed if a private clinic or laboratory is already using microscopy?

In terms of financing, is there a need and possibility to subsidise RDTs for sale in the private sector? If so how, by how much? What should be the target retail price of ACTs in relation to RDTs in order to incentivise appropriate use of both?

It is likely to be very difficult to forecast the quantities of ACTs and RDTs needed for the private sector, although early experience with AMFm should help inform this challenge.

Experience in the private sector to date

There is currently little information available on the private sector's engagement in malaria treatment activities in south east Asia and south America, where parasitological diagnosis has been standard practice for about a decade, and almost none in Africa.

The earliest experience came from a small-scale and time-limited evaluation of Amazonian barmen who were trained to perform malaria diagnostic tests (Pang and Piovesan-Alves, 2001, Cunha et al., 2001). Microscopy-based diagnosis has been deployed in public health facilities in many countries in Asia for years. In some places this has extended to diagnosis and treatment in the community through mobile clinics and village volunteers (e.g. mobile clinics in Thailand (Ettling et al., 1991), Brazil (Cunha et al., 2001)). The introduction of RDTs may not therefore be such a big leap, and relatively readily taken up where the limiting step has been the logistic difficulties of using microscopy, e.g. by peripheral health facilities and communities. RDTs have been taken up avidly at community level in Cambodia (Yeung et al., 2008b) and Laos (Mayxay et al., 2004). The longest experience of RDT use in the private sector comes from Cambodia, where RDTs have been deployed since 1999.

Experience in Cambodia

Cambodia has a population of 13.4 million people (National Institute of Statistics, 2008) of whom about 2 million live or work in forested areas and are therefore considered at-risk of malaria. Around 60,000 cases/year of malaria are treated in the public health facilities of which around two-thirds are biologically confirmed (Cambodian National Malaria Programme, personal communication). However around 70-80% of patients with malaria symptoms seek treatment in the private sector rather than in the public sector (MSH-RPM, 2003, Yeung et al., 2008b) and are therefore not recorded in official statistics. As in many other malaria-endemic countries the private sector is diverse and includes providers such as doctors, nurses and pharmacists working out of private health facilities, laboratories and pharmacies as well as "unregulated" providers including unlicensed drug shops, general goods shops and itinerant sellers. Traditionally the private sector has been poorly regulated with widespread use of fake drugs, inappropriate treatments and presumptive treatment.

In 1999-2000, in response to rising drug resistance of *P. falciparum* to the first line treatment in Western Cambodia, there was a switch to a combination of artesunate and mefloquine tablets, accompanied by improved diagnosis through the introduction of RDTs and improvement of microscopy in public health facilities.

Involving the private sector

Recognising the importance of the private sector, when the change in antimalarial drug policy was launched the private sector was also targeted. The social marketing of subsidised RDTs (Malacheck) and ACTs (Malarine – a blister-packaged artesunate and mefloquine) was initiated and piloted by the EC-malaria control project in partnership with the Cambodian national malaria control programme (CNM). This was officially launched nationwide in 2002 and handed over to PSI in 2003, when the EC-malaria programme closed.

Many of the early concerns of the programme during the preparatory phase are shared with other current programmes (CNM, personal communication). They include:

- The level of subsidy for RDTs and ACTs
- Whether or not to fix/recommend the retail prices
- Sustainability of a subsidy programme
- Acceptability and cost-effectiveness of RDTs by providers and consumers
- Ability of providers to properly use the tests
- Ability of providers to manage stocks
- The effectiveness of promotional campaigns in convincing consumers to invest in the test
- Whether or not providers signing-up to the programme would stick to agreed terms including collection of data.

Currently there are pilot projects to promote interaction between the public and private sector in order to improve case management and surveillance in the private sector. There has also been a recent crackdown on “illegal” pharmacies.

Prices

The recommended prices of RDTs have fallen since the start of the project. The current recommended price for retail outlets to buy from wholesalers, distributors or sales agents is \$0.50 for a 10-pack dispenser (\$0.05 per test). For ACTs the prices are \$5.00 for a 12-pack dispenser (\$0.42 per pack), \$3.20 for adolescent (\$0.27 per pack) and \$2.20 for children (\$0.18 per pack) (Allen, 2010). The 2007 PSI MAP study found that, in practice, there are large variations in prices retailers pay for the product (Population Services International, 2007). Outlets paid an average price of \$0.75 (range \$0.50- \$2.00) per dose of adult Malarine and \$0.69 (range \$0.50 -\$2.00) per dose of child Malarine, 36% and 25% higher respectively than the recommended price. Malacheck was purchased for an average of \$0.29 (range \$0.19- \$1.25) per test.

In September 2004, after PSI conducted a willingness-to-pay study, the printed recommended retail price (RRP) for Malarine was reduced from 7500 riel (\$1.88) for the adult dose and 4500 riel (\$1.13) for the adolescent dose to 2500 riel (\$0.63) and 1700 riel respectively, and 1200 riel for a new child dose. The RRP for Malacheck is 1000 riel (\$0.25).

In turn, retailers often sold the products to consumers above the RRP, charging an average price of \$1.07 (range \$0.63-\$3.75) and \$0.95 (range \$0.63-\$2.50) for the adult and child doses of Malarine respectively. Malacheck was sold at a mean price of \$0.37 (\$0.25-\$1.25).

Of note, the current expected trade margins according to the recommended prices were therefore 50% on the adult Malarine and 400% on the RDTs (Allen, 2010).

Uptake

In 2002 before the nationwide roll-out, only 18% of interactions between patients with malaria symptoms and private providers resulted in a biological diagnosis (Yeung et al., 2008a)]. In more recent surveys this proportion has increased to as much as 68% (Population Services International, 2006, Allen, 2010).

Malacheck market penetration was on average 42% among private outlets (Population Services International, 2007). Most pharmacies, cabinets and drug stores, but fewer mobile providers from medium and low risk areas, sold the product.

Volume of sales

Following the handover the of the project to PSI, the number of RDTs distributed has gradually increased from around 100,000/ year to 370,420 in 2009 (Allen, 2010). Over the same period sales of ACTs have increased from around 30,242 in 2003 to 281, 116 in 2009. However stock-outs of both commodities occurred making it difficult to draw conclusions regarding relative demand.

Challenges

- Difficulty in market penetration – not reaching the villages
- Stock-outs
- Low uptake of RDTs (being addressed by intense BCC campaign (TV, radio, mobile video unit, posters etc plus increasing the number of medical detailers for face-to-face support)
- Until recently the subsidised RDT was PF specific and did not pick up PV (now being changed to a combination test)
- Lack of data – surveillance data, RDT use in practice, quality of testing, interpretation of results and action after, price paid, acceptability etc

Experience in Africa

The authors are aware of only two studies of RDT subsidies in Africa. One is underway in Uganda and another has been recently completed in Kenya. The latter, a randomized trial of RDTs sold through drug shops in Western Kenya, will be presented during the consultation. RDT subsidies did not induce diagnosis-seeking at drug shops, but appeared to be well accepted and used by clients. However, over half of those with negative RDTs went on to purchase an ACT, suggesting that although RDTs improved targeting, some patients were not easily dissuaded from purchasing an anti-malarial by a negative RDT result.

A note on *P vivax*

The burden of disease due to *P vivax* has been under-appreciated for many years. Although usually present only at low levels of endemicity, it is present in some of the most populous regions of the world. Recent evidence suggests that *P vivax* is not always benign and can cause severe disease and death. Despite these observations, *P. vivax* is not a major killer, and not an important public health problem in Africa where the lack of Duffy antigens in many ethnic groups helps to limit its transmission. Where *vivax* does exist there is a need for specific diagnostics. RDTs capable of detecting *vivax* are currently less sensitive and more expensive than *P falciparum* only tests. The treatment of *vivax* is also more complex, requiring primaquine for radical cure of the dormant liver stage, and yet the safety profile of this drug requires testing for G6PD deficiency, as people with this enzyme deficiency can have serious haemolytic reactions to the drug.

Given the focus of the AMFm on Africa, the fact that *P vivax* is only present at low frequencies in most of Africa, the additional complexities *P vivax* presents for diagnosis and treatment and the already complex situation in considering the roll out of parasitological *P falciparum* diagnosis, *P vivax* is not considered further in this paper.

THE VISION

A situation in which all patients have a sensitive and specific parasitological test performed safely to inform the use of ACTs, whether they present to regulated or unregulated private sector, a community health worker or public sector health facilities.

Challenges in moving forward

A 2008 AMFm consultation considered the pros and cons of targeting and identified three areas of technical concern surrounding the introduction of RDTs (Whitty et al, in prep). The first related to the quality assurance and field durability of RDTs, and the risk that unacceptably high frequencies of false negative results could actually reduce appropriate malaria treatment. Progress on this front has been made with the advent of co-ordinated lot quality testing and WHO/FIND/CDC product testing of malaria RDTs [WHO/FIND 2nd edition](World Health Organization, 2009). The second issue regards the safety of relatively inexperienced personnel drawing blood and the risk of exposure to blood-borne infection, especially with hepatitis B and HIV. The third area relates to the need for adequate incentivisation of shop keepers to perform RDTs and adhere to their results. These last two concerns in particular demand further operational research. The earlier consultation also recognized the challenge of compliance to test results, and evidence generated in the last two years underlines further the importance of paying attention to this.

A framework is needed to inform decisions about the situations in which RDTs should be deployed. This will draw on understanding, from operational experience, of how to assure observation of adequate safety procedures and compliance with test results. Additional factors to consider include the following:

Considerations at the central level

- How should scale-up of parasitological diagnosis be prioritised in different geographic areas and the different ACT-providing sectors (public, regulated private, unregulated private, community)?

- How many tests will be needed? This will be based on estimates of the numbers of patients presenting with fever in different settings.
- What are the net costs of parasitological diagnosis? This will be a function of ACT savings, dependent on the proportion of fevers due to malaria and the provider's likely compliance with test results, and costs of an RDT-based strategy (including an increased need for treatment of other febrile illnesses and for referral).
- How can a reliable supply of RDTs be assured? This is especially important in the light of the ACT stock-outs recently documented in the public sector (Barbour et al., 2009).

Considerations at the point of care.

- How can those who need treatment other than with ACTs be identified reliably? Health workers at different levels can be trained, for example through the Integrated Management of Childhood Illness (IMCI), to identify clinical signs and symptoms suggestive of serious disease, and to give appropriate antibiotics (or to refer) as necessary. Other available point of care diagnostics (e.g. lactate, pulse oximetry etc) may have a role to play in identifying patients at risk in some settings. There may also be a role for new point of care diagnostics to help identify patients likely to benefit from antibiotic treatment or referral.

The revised IMCI algorithm for the management of febrile children now includes the use of malaria diagnostics, though testing is not required in severe febrile illness (where the patient is unable to drink or breastfeed, vomits everything, has had convulsions, is lethargic or unconscious, or has stiff neck), when all such children are given anti-malarial and antibiotic treatment. The management of febrile adolescents and adults, in the context of the IMAAI (Integrated management of adolescents and adult illness) includes malaria diagnostics in the most recent guidelines, although the guidelines for peripheral health facilities (developed in 2004) recommend malaria diagnostics only in specific situations.

At shopkeeper and community levels it will be necessary to assure that robust strategies are implemented to facilitate identification of patients who would benefit from referral.

- How should RDT negative patients be assessed and managed in health facilities? What are the risks, benefits and costs of antibiotic treatment for all RDT negative patients? If it is possible to identify those who are at low risk of severe disease, what is required to make reassurance and symptomatic relief (e.g. with paracetamol) acceptable to prescribers and patients?

How should RDT negative patients be assessed and managed in the private sectors and at the community level? Again, what are the risks, benefits, costs and acceptability of antibiotic treatment for all RDT negative patients? Is there a role for point of care diagnostics which help to identify patients likely to benefit from referral or antibiotic treatment?

If it is possible to identify those who are at low risk of treatment-requiring disease, what is required to make reassurance and symptomatic relief (e.g. with paracetamol) acceptable to prescribers and patients?

Patients with fever are commonly treated presumptively with anti-malarials. Many do not stand to benefit as they don't have malaria. Patients and prescribers alike have grown used to this situation and are frequently unaware that the real cause of their illness is not being treated. Over the years, the same mistake has been repeated with increasing confidence as many illnesses are self-limiting and patients' recovery is incorrectly attributed to the malaria treatment. The introduction of RDTs is the first step in remedying this accepted, but unacceptable, situation. Scale-up of parasitological malaria diagnosis should draw attention to the inadequacy of the status quo and the existing need to strengthen diagnostic, referral and treatment services. The recommendation for pre-treatment malaria diagnosis puts the challenges of adequately recognising and treating severe illness into sharp focus. However these challenges are not new. The scale-up of parasitological malaria diagnosis should be seen as the next step in improving the management of febrile illness and a general public health good.

Costing parasitological diagnosis

Economic issues include allocation of resources (dollars and systemic capacity) to RDT acquisition and use in the context of the closely related decisions on treatment for malaria and on treatment for other febrile illnesses. Various cost effectiveness analyses (Lubell et al., 2007, Lubell et al., 2008b, Lubell et al., 2008a) have discussed the relative merits of microscopy or RDTs over each other or over presumptive treatment; we do not review these here. One of the more comprehensive assessments (Shillcutt et al., 2008) suggested that RDTs would be cost-effective, compared with presumptive treatment, at parasite prevalences up to 62%. The anticipated higher accuracy of RDTs over microscopy in field conditions resulted in a higher cost-effectiveness of RDTs over microscopy across all levels of parasite prevalence. Importantly, in addition to savings on anti-malarial drug costs, the cost-effectiveness of RDTs was largely attributable to improved treatment and health outcomes for non-malarial fevers. Critically, the models assumed that prescribers were compliant with the test results. The authors conclusion that RDTs are potentially cost-effective in most of sub-Saharan Africa requires appropriate management of malaria and non-malarial febrile illnesses to realise the potential of the tests.

To truly understand the costs of a comprehensive RDT-based diagnostics programme it will be necessary to understand better the components of an optimal programme, including the best approach to supporting behaviour change. Scaling up access to RDTs will cost considerably more than the commodities themselves. The financial and opportunity costs of information, education and communication (IEC) activities may be substantial as available evidence suggests that significant behaviour change in response to RDT test results is needed and cannot be assumed (see above). Costs associated with the training of front line health workers, shop keepers and/or community health workers, establishment and maintenance of quality assurance programmes, transport and storage, safe disposal and supervision of the diagnostic services will also need to be considered. Costs will be different in the public, regulated and unregulated private sectors, not least due to the extent of any subsidy for RDTs, and need to be considered separately. There will also be new costs associated with the optimal management of non-malaria fever patients and agreement on how these should be covered. RDTs used in the community or in the private sector are likely

to incur costs related to referral. The costs of possible additional diagnostic testing and antibiotic or other treatment also need to be considered.

Cost savings are expected to result from avoidance of unnecessary anti-malarial doses, improved case management of non-malaria fever, which should prevent progression to serious non-malarial disease, its referral and management. An indirect benefit may be increased confidence in health workers and ACTs, and the cost savings arising from a reduced rate of spread of anti-malarial drug resistance.

Costs will also arise from the collection and management of additional RDT-related data for health information systems, which should ideally be expanded to capture data from the private sectors. This should yield useful dividends through an enhanced ability to target resources and improve transparency of commodity management.

Costs will need to be broken down at different levels, including international finance institutions (WB, GFATM, bilaterals), national (MoF), health facility or private outlet, and community (travel for care-seeking, time to care for the sick).

It is clear that compliance with test results must be included as a critical component to understand cost effectiveness. So far, this has only been evaluated and included in a model of diagnosis for the public sector (Lubell et al., 2008b); this needs to be extended by development of scalable models for individuals purchasing RDTs from small shops and pharmacies. These should help understand how economic and other incentives can be used to encourage patients to seek parasitological confirmation before treatment, and how to encourage prescribers, particularly in the private sector, to correctly use diagnostic tests and comply with their results.

Consideration of the design of a financing and delivery system for malaria diagnostics may also need to address the diagnosis and appropriate management of non-malarial fevers, significantly enlarging the scope of this discussion. However work is ongoing on combination suppositories that have both an antibiotic and an anti-malarial components, although this is primarily intended to facilitate the management of children with severe disease in the periphery.

Strategies for moving forward

The WHO recommendation on diagnosis points explicitly to the exception arising when parasitological diagnosis is not accessible, meaning not available within 2 hours of the patient presenting. In these cases treatment solely based on clinical suspicion – or presumptive diagnosis - should be considered. This is where we are in most African settings today. In the long run it is reasonable to expect that this limitation will be rare. In the short and medium term, however, access constraints are likely to remain significant, particularly in remote areas with poor public health services, which are also likely to bear the brunt of malaria disease and death. Resource allocation decisions need to reflect this constraint, and economic analysis of the 'expansion paths' – ways of moving from where we are today to where we want to be - needs to be undertaken for very disadvantaged regions as well as for (relatively) privileged ones.

Decisions on use of RDTs by patients and providers (in both the public and private sectors) will depend on an understanding of the aetiology of febrile illness and the role of RDTs and

ACTs, the prices they face for RDTs, ACTs and other malaria treatments, and likely on the costs of treatment of other febrile illnesses. The financial architecture of the system will affect these prices; if prices for ACTs are kept low and RDTs remain unsubsidized, incentives for RDT use will be attenuated. If the prices for antibiotics to treat febrile illness are high, then - even if RDTs are cheap or free - patients may be more likely to want an ACT even if the RDT is negative for malaria. Hence use of RDTs, and acting appropriately on the results, depends on the price and availability of the RDT, the community's perceptions of the appropriate management of fever, the price and availability of treatments appropriate to positive and negative RDT results and consumers' and providers' perceptions of the reputation and their confidence in malaria diagnostics and treatment. Previous experience, training and education, in addition to commodity availability and prices, influence the behaviour of consumers and health providers.

The optimal strategy for moving forward will depend on an understanding of many of the challenges in moving forward (see above). In addition, there may be an economic rationale to prioritise one expansion path over another, and for having parallel expansion paths in different sectors (public health facilities, community care, regulated and unregulated private sectors) in the same geographic area at any one time. It may be appropriate to start where the largest gains stand to be made, although a keen eye on feasibility and compliance is required in order to predict this with confidence.

Top level factors to consider include:

- the extent of overtreatment, itself dependent on availability and affordability of anti-malarial drugs (with over-treatment increasing with increasing accessibility) and the prevalence of infection in a setting (low prevalence likely to be associated with over-treatment)
- the likely compliance with test results (partly dependent on prior exposure to diagnostic test results).

Seasonality of transmission should also be considered as, in intensely seasonal transmission settings, the rate of over-treatment may be reduced within the months of transmission. The influence of *P. vivax* on disease burden and perceptions of RDT and treatment efficacy should also be taken into consideration.

An understanding of the age pattern of over-treatment may lead some to consider age-targeting of pre-treatment diagnostics. If over-treatment is more common in adults than in children, greater gains might, in theory, be made by targeting the adults. However, this recommendation has caused some confusion, implying that it is acceptable to presumptively treat children and may lead to difficulties in the later deployment of and compliance with parasitological testing for children.

A framework for thinking about expansion pathways

Budgets constrain both which health interventions can be chosen and how extensively they can be applied. The range of choice expands with the budget. As additional resources become available, health systems may expand coverage of old interventions, add new interventions to existing ones or replace existing ones entirely. For example, with modest incremental resources a country's EPI program might expand coverage of existing interventions but with more substantial new resources it might either add Hib and HepB or

replace DPT with a pentavalent vaccine. For each level of incremental budget there is a combination of intervention types and levels that will maximize the expected gain in health. The *expansion path* shows how that combination evolves with increasing resource availability. The task of standard cost-effectiveness analysis is to identify the expansion path and assess how it varies in response to epidemiology, prices, intervention effectiveness, and systemic constraints.

The following draft framework for identifying the expansion path for diagnosing and treating febrile illness in malarious areas is based on a set of tables to identify the 'interventions' (diagnosis/treatment combinations) that might be selected at different points on the expansion path. For example, with a very limited budget in highly malarious areas health gains might be maximized by presumptive treatment of fever with ACTs. With a more substantial budget the system might expand to less malarious areas using RDTs prior to treatment. These would be stops along the expansion path.

Assumptions

1. Febrile illness is assumed to result from malaria, from other febrile illnesses (OFI) that are non-treatable, from OFIs that are treatable and from co-infection with some of the preceding.
2. OFIs that are treatable can be identified by prescribers trained in IMCI.
3. Individuals infected by malaria (parasitemic) may not be sick from malaria, i.e. the cause of fever in a parasitemic person may not be malaria. The probability that a febrile, parasitemic person is in fact sick from malaria goes up as the parasite prevalence (and thus immunity) in the population goes down.
4. Current diagnostic methods are unable to distinguish between individuals with symptomatic malaria and those with fever and parasitemia but who are unwell for reasons other than the malaria parasites. However, it is probably always worth treating a malaria infection, as even those currently asymptomatic are likely to become symptomatic and may progress rapidly into life-threatening disease.
5. Patients with parasitaemia but acutely sick for another reason will test positive with an RDT, but anti-malarial drugs will not facilitate their recovery. Those with self-limiting illnesses may incorrectly attribute their cure to malaria treatment. Those with progressive bacterial illnesses, who need antibiotics, may deteriorate after a positive RDT and treatment with anti-malarial drugs alone. This may undermine confidence in RDTs and anti-malarial drugs and is why those with asymptomatic malaria and other infections are included in the scenarios.
6. RDTs for malaria are tuned to high sensitivity, i.e. they provide information on whether a person is parasitemic but not on whether the cause of a febrile, parasitemic person's illness is malaria.
7. The base case, or status quo, is malaria treatment for all fevers.

Scenarios

Table 1 has 5 panels, each of which shows an intervention option (diagnosis/treatment combination) and its consequences in different alternative infection states of the patient. Other options are possible. These scenarios are presented for illustrative purposes and the authors recognise the importance of a comprehensive assessment of patients to identify and manage non-malaria causes of fever where ever possible. The panels are:

- A. No test. Presumptive treatment with ACT. The terms 'false positive' and 'false negative' highlight diagnosis/treatment mismatches.
- B. Old IMCI (i.e. no RDT): Presumptive treatment with ACT & AB if signs of severe disease.
- C. New IMCI: RDT with ACT if positive, antibiotic (AB) if signs of severe disease. This is the gold standard if RDTs are perfect tests for malaria and IMCI correctly identifies treatable OFI. This could be applicable beyond public health facilities once a suitable point of care test for treatable OFI becomes available.
- D. Use a malaria RDT and treat with ACT if positive; no treatment if RDT is negative. Referral would be required if signs of severe disease.
- E. Use malaria RDT and treat with ACT if positive; treat with AB if RDT is negative.

The expansion path will depend on: costs of testing (and whether the cost is less than the value of the information provided); dollar costs of treatment with ACTs and ABs; resistance costs of treatment; malaria prevalence (and hence the value of information from testing); and the ratio of treatable to non-treatable OFIs. Table 2 shows illustrative probabilities for different states in more and less malarious areas.

Systemic capacity provides an additional and important dimension of cost. At the periphery (where a large fraction of deaths occur) the system might be an uneducated mother and a local shop that sells a few drugs. This 'system' at the periphery may simply lack capacity to use and interpret RDTs and hence the 'cost' of using RDTs may be substantial travel time (and related mortality probability) and the time and transport costs for the mother of going to a more central health facility. The cost in systems capacity of using RDTs at a well-functioning clinic may be very low indeed. Hence choice of techniques in these environments may differ. For example, the expansion path in a highly malarious peripheral area might be from presumptive treatment (scenario A) at health facilities and shops, to IMCI incorporating RDTs at health facilities (scenario C) in advance of implementing scenario C in shops.

Table 1: Selection of Treatment for Fever

Panel A. Presumptive Treatment with ACTs

Malaria Status		Other Febrile Illness (OFI) Status		
		OFI-free	OFI-nontreatable	OFI-treatable
MF	Parasite Free	XXX	ACT <i>(False positive for malaria)</i>	ACT <i>(False negative for treatable OFI False positive for malaria)</i>
MP	Parasitaemic, not sick from malaria	XXX	(ACT)	(ACT) <i>(false negative for treatable OFI)</i>
MS	Sick from malaria	ACT	ACT	ACT <i>(false negative for treatable OFI)</i>

Notes:

1. All patients sick with malaria are assumed febrile.
2. XXX indicates a test outcome is not possible (since RDT is assumed perfect for parasitaemia and all patients sick from malaria are febrile).
3. Boldface indicates appropriate prescriber's response for underlying condition(s). It is considered appropriate to eliminate malaria parasites even if they are not causing symptoms.
4. Neither ACT nor AB will cure symptoms due to non-treatable OFI. Parentheses around boldface indicate that underlying illness is unlikely to be cured by the treatment.

Table 1: Selection of Treatment for Fever

Panel B. 'Old IMCI': Presumptive Treatment with ACTs and antibiotics if signs of severe disease

Malaria Status		Other Febrile Illness (OFI) Status		
		OFI-free	OFI-nontreatable	OFI-treatable
MF	Parasite Free	XXX	ACT <i>(false positive for malaria)</i>	ACT & AB <i>(false positive for malaria)</i>
MP	Parasitaemic, not sick from malaria	XXX	(ACT)	(ACT) & AB
MS	Sick from malaria	ACT	ACT	ACT & AB

Notes (both panels):

1. All patients sick with malaria are assumed febrile.
2. XXX indicates a test outcome is not possible (since RDT is assumed perfect for parasitaemia and all patients sick from malaria are febrile).
3. Boldface indicates appropriate prescriber's response for underlying condition(s). It is considered appropriate to eliminate malaria parasites even if they are not causing symptoms.
4. Neither ACT nor AB will cure symptoms due to non-treatable OFI. Parentheses around boldface indicate that underlying illness is unlikely to be cured by the treatment.
5. OFIs that are treatable can be identified by prescribers trained in IMCI.

Panel C. 'New IMCI': RDT with ACTs if positive, antibiotics if signs of severe disease

Malaria Status		Other Febrile Illness (OFI) Status		
		OFI-free	OFI-nontreatable	OFI-treatable
MF	Parasite Free	XXX	No treatment	AB
MP	Parasitaemic, not sick from malaria	XXX	(ACT)	(ACT) & AB
MS	Sick from malaria	ACT	ACT	ACT & AB

Table 1: Selection of Treatment for Fever

Panel D. RDT with ACTs if positive, no treatment if RDT negative

Malaria Status		Other Febrile Illness (OFI) Status		
		OFI-free	OFI-nontreatable	OFI-treatable
MF	Parasite Free	XXX	No treatment	No treatment <i>(false negative for treatable OFI)</i>
MP	Parasitaemic, not sick from malaria	XXX	(ACT)	(ACT) <i>(false negative for treatable OFI)</i>
MS	Sick from malaria	ACT	ACT	ACT <i>(false negative for treatable OFI)</i>

Notes (both panels):

1. All patients sick with malaria are assumed febrile.
2. XXX indicates a test outcome is not possible (since RDT is assumed perfect for parasitaemia and all patients sick from malaria are febrile).
3. Boldface indicates appropriate prescriber's response for underlying condition(s). It is considered appropriate to eliminate malaria parasites even if they are not causing symptoms.
4. Neither ACT nor AB will cure symptoms due to non-treatable OFI. Parentheses around boldface indicate that underlying illness is unlikely to be cured by the treatment.

Panel E. RDT with ACT if Positive, AB if Negative

Malaria Status		Other Febrile Illness (OFI) Status		
		OFI-free	OFI-nontreatable	OFI-treatable
MF	Parasite Free	XXX	AB <i>(false positive for treatable OFI)</i>	AB
MP	Parasitaemic, not sick from malaria	XXX	(ACT)	(ACT) <i>(false negative for treatable OFI)</i>
MS	Sick from malaria	ACT	ACT	ACT <i>(false negative for treatable OFI)</i>

Table 2: Prior Probabilities for Malaria and Other Febrile Illnesses**Panel A: High-malaria Zone (parasitaemia = 20%)**

Malaria Status (probability)	OFI Status (conditional on malaria status)		
	OFI-free	OFI-nontreatable	OFI-treatable
MF (0.8)	0	0.8	0.2
MP (0.1)	0	0.7	0.3
MS (0.1)	0.7	0.1	0.2

Panel B: Low-malaria Zone (parasitaemia = 2%)

Malaria Status (probability)	OFI Status (conditional on malaria status)		
	OFI-free	OFI-nontreatable	OFI-treatable
MF (0.98)	0	0.85	0.15
MP (0.005)	0	0.7	0.3
MS (0.015)	0.85	0.05	0.1

Notes:

1. Malaria status probability is conditional on patient's being febrile. OFI status probability is conditional on patient's being febrile and the indicated malaria status.
2. Probabilities in this table are guesses!!

A look at some numbers

Amidst the diverse sets of costs and potential benefits of expanded access to parasitological testing, decisions about the optimal way forward may be facilitated by review of estimates of the numbers of fever episodes, and therefore RDTs needed, and the proportion of these that are likely to be parasite positive. These numbers are not readily available.

The Malaria Atlas Project (<http://www.map.ox.ac.uk>) has estimated the number of paediatric fevers in Africa and the proportion of these which are likely to be associated with *P. falciparum* infection (Gething P et al, in prep). The results suggest that there are 656 million febrile episodes in children under 5 years every year, and that 182 million of these present to health facilities. Of these, 78 million (43%) are likely to be parasitaemic. Hence, if 182 million RDTs were available, and if compliance with test results was perfect, a maximum saving of 104 million treatment courses of ACTs could be possible. These figures compare with an annual RDT procurement figure of ~60 million in 2007, rising to 80-85 million in 2009, and do not take into account the diagnostic needs of people aged over five years. Nevertheless, these limited estimates imply a need to double RDT procurement in order to service the needs of young child presenting to health facilities.

MAP found significant between and within country differences in the predicted incidence of fevers infected with *P. falciparum*, implying a potential to prioritise some areas for the introduction of malaria diagnostics as the cost-effectiveness of diagnostics is known to vary according to intensity of transmission (Lubell et al., 2007). This logic also suggests that prioritisation of settings for the introduction of parasitological testing would be facilitated by monitoring the number of fevers suspected as malaria, the number which test positive in different settings (public versus private versus community) and the various prescribers' compliance to test results (Lubell et al., 2008b).

Critical Gaps

This paper has summarised multiple issues that need to be addressed in order to roll out capacity for the parasitological confirmation of malaria. By the end of the consultation the critical gaps in the knowledge of the economics and financing of parasitological confirmation of malaria should have been identified and prioritised. These may include the following:

- Health information
 - How many febrile presentations are RDT positive?
 - What are the causes of non-malaria fever? What proportion are bacterial/require an antibiotic?
 - What is the extent of test-negative treatment? What treatment combinations are given to those without malaria now?
- What are the components of, and costs of implementing, an optimal RDT programme in different settings (public, regulated private, unregulated private, community)?
 - What messaging is required to maximise compliance of prescribers?
 - What messaging is required to maximise acceptance of patients?

- How can appropriate use of RDTs be incentivised in public health facilities?
- How can appropriate use of RDTs be incentivised in private drug outlets?
- What is the impact of large-scale introduction of ACT and RDTs on treatment seeking behaviour and drug consumption in public versus private sectors.
- To what extent does the introduction of Hib/pneumococcal vaccines affect the recommendations surrounding management of RDT negative fever cases? What is the effect of these vaccines on the epidemiology of non-malaria fevers?

Known relevant ongoing research

To help get a better idea of likely timings for information to become available it may be useful to develop an inventory of currently ongoing relevant research activity. The following is no doubt an incomplete list:

- Studies on non-malaria causes of fever.
 - Tanzania - V D'Acremont, B Nadjm
 - Ghana - S Owusu
 - Mekong (Cambodia, Laos – P Newton)
- Clinton Foundation. Trials of RDT subsidy in private sector (Uganda & Kenya).
- ACT Consortium: operational experience on use of RDTs in public, private (regulated) and community settings. Adherence to RDT results. Unit costs of various health services (OPD visit, malaria microscopy test), prices of drugs and RDTs, Patient adherence to treatment protocol etc.
Documenting Cambodian experience of subsidized RDTs in private sector
- STI model: case management module - describes treatment-seeking, case management practices and adherence to anti-malarials in various settings. Can explore many current policy questions - e.g. impact of wider diagnostic testing on health outcomes and drug resistance, cost-effectiveness of expanding alternative ACT delivery approaches, etc.
- AMFm operational research
- TDRs community based interventions

Timeframe for moving forward

It takes time to move from policy recommendation to implementation at scale. The decision to scale up parasitological diagnosis of malaria dates back several years already. A realistic prediction of timescales is difficult but may be informed by an understanding of the time between policy decisions, roll out and scale up of ACTs and the AMFm. As with ACTs, regulatory actions may be required for the use of RDTs in some countries, to allow their wider use by CHWs and by accredited private sector outlets. As with ACTs, there is a need to increase coverage of RDTs in the public sector and to make RDTs available in the private

sector, moving them beyond the private sector clinics in urban areas where they are most likely found at present.

It may be useful to consider the prospects of parasitological confirmation in phases: What can be expected in the next

- 1-2 years?
 - Program implementation and operations research by multiple parties, informing scalable approaches to the financing and expanded use of diagnostics
 - Development of an RDT financing architecture
 - Expansion from the status quo and learning from operational experience and research
- 5 years?
 - Development of robust and scalable approaches to the management of RDT- negative febrile illness in the private sector
 - Safer, less-invasive tests (for example on urine or saliva)
 - Lower RDT prices
 - Understanding incentives in community, private and public sector
- Over 5 years?
 - Availability of OFI tests?
 - Integration of simplified RDTs and OFI tests into algorithms for the management of illness.

It is important to consider the levels, trajectories and interactions among the factors that will form the context for the scale-up of parasitological diagnosis.

1. Increased availability of, experience with and publicity surrounding treatment options for RDT negative cases, leading to increased provider and patient confidence in and compliance with RDT results.
2. Technological progress, creating continued improvements in RDTs.
3. Funding: there is likely to be continued growth in domestic and external public sector funding for malaria control.
4. Recent favorable trends in malaria incidence and mortality are likely to continue.
5. Operational and health system constraints to expanding use of RDTs will become less important as time goes by.

These trends all point in the same direction: RDT use can be expected to become more desirable and more feasible with time. It should be possible to build on the lessons from scale-up of ACTs and other interventions to make parasitological confirmation of malaria the new norm in Africa.

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