BMJ 2016;352:i107 doi: 10.1136/bmj.i107 (Published 4 February 2016)

ANALYSIS

Achieving universal testing for malaria

Rapid diagnostic tests have the potential to reduce the overtreatment of malaria by 95%, but time and extensive logistical, behavioural, and technical interventions may be required to achieve this, argue **Eleanor Ochodo and colleagues**

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Medical care of populations often treads a fine line between the differing harms of underdiagnosis and overdiagnosis. Underdiagnosis may mean that a disease is advanced by the time it is detected, increasing the risk of death, whereas overdiagnosis leads to healthy people being labelled as sick and treated with drugs that will be of no benefit and may even cause harm.[1] How much underdiagnosis or overdiagnosis can be regarded as "reasonable" is a value judgement and may vary between different stakeholders: consumers, clinicians, or policy makers. It will also vary between diseases and populations and be related to the severity of the illness, the benefits and harms of the treatment, the cost of the treatment, the availability of reliable tests, and the public health effects of the approach taken.

Malaria is an interesting case study because the perceived benefits of overdiagnosis (few missed cases), and the potential harms of underdiagnosis (unpredictable progression to severe malaria and death) led to the promotion of substantial overdiagnosis and overtreatment for many years.[2-4] Up until about 15 years ago, policy makers, including the World Health Organization, promoted a strategy known as "presumptive treatment of malaria" in areas where diagnostic testing (by light microscopy) was unavailable. This strategy recommended that all patients with fever were treated with antimalarials, regardless of the presence or absence of signs of other illnesses, and accepted the substantial overuse of chloroquine because it was cheap and well tolerated.[2 3]

However, the balance has now swung the other way, with policy makers and clinicians increasingly concerned about the clinical, financial, and public health harms associated with overtreatment. The currently recommended firstline antimalarial drugs (artemisinin based combination therapies) are not cheap and malaria prevalence is falling in many countries, raising the relative importance of diagnosing and treating other causes of fever.[4-6] Consequently, the development of rapid diagnostic tests (RDTs) that can be used in basic healthcare services in remote settings led the WHO to recommend a switch to universal parasitological testing before treatment in 2010.[5] Despite the subsequent rapid scale-up of rapid tests, overtreatment remains a problem. We examine the drivers and examine the potential strategies to overcome these.

Why might overtreatment still occur?

The figure⇓ outlines three scenarios that can result in overtreatment of malaria, the different drivers, and possible solutions.

Scenario 1: test not done; fever treated presumptively

The latest WHO data show that the reported rate of diagnostic testing in the African region increased from 41% in 2010 to 65% in 2014.[6] This is impressive progress in the public sector but does not measure the scale of the problem in the private and retail sectors. In Uganda, around two thirds of people seek malaria treatment from retail drug stores, where testing is rarely done,[7] and this situation seems to be replicated in other African countries.[4] In Kenya, over-the-counter malaria medicines were shown to be the most popular first response to fever in children and adults with acute illnesses.[8]

Another reason for not testing is shortage of rapid tests. Cross-sectional studies in Tanzania,[9] Mozambique,[10] and Democratic Republic of Congo[11] estimated that 50%, 59%, and 62%, respectively, of the facilities surveyed did not have RDTs in stock. Even when RDTs are available, they may not be universally used. In one study from Tanzania staff reported reverting to presumptive treatment when patient workload was high or during staff shortages.[9]

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Scenario 2: test result is false positive

A small number of false positive results are inevitable with any diagnostic test, but the high specificity of available RDTs means this number is likely to be negligible in comparison with the "false positives" of presumptive diagnosis.

Table 1⇓ presents the test outcomes for a hypothetical cohort of 100 patients with fever tested with the most commonly used RDTs in settings with different prevalences of malaria. The sensitivity and specificity estimates are derived from meta-analytical summaries of 71 studies included in the Cochrane review of RDT accuracy.[12]

In all four settings RDTs have the potential to reduce unnecessary prescriptions by around 95% compared with presumptive treatment. In absolute terms this means preventing between 19 and 90 unnecessary prescriptions per 100 people tested. The largest number of false positive results would occur in the settings of lowest prevalence but remain very small.

Scenario 3: test result is negative but antimalarial drugs are still prescribed

Increased use of RDTs will be a waste of resources unless health workers use the result to guide prescribing. In a Cochrane review of studies that randomly assigned health workers to using RDT based algorithms or clinical diagnosis, compliance with the RDT result was highly variable across studies. In the most extreme example health workers prescribed antimalarial drugs to 81% of people with negative results.[13] In trials in which health workers adhered to the test result antimalarial prescriptions were reduced by up to three quarters. These are early trials and we would expect adherence to improve during programmatic use.

Several qualitative studies have explored the reasons for health workers ignoring the test result.[14-17] Commonly cited reasons are a lack of trust in the accuracy of tests; fear of the consequences of missing a true malaria case; confusion about the change from previous recommendations; pressure to prescribe from patients; and uncertainty about how to manage the other causes of fever. Studies among patients also report a lack of trust in the test's accuracy, enhanced by conflicting advice from different health facilities and feeling better after taking antimalarial drugs even when the test result is negative.

What are the risks associated with RDTs?

Previous training and guidance to health workers emphasised the danger of missing a case of malaria and sending a child home without treatment.[2] This ingrained belief is likely to take time to change, and health workers will require evidence based reassurance that this new policy is safe.

How common are false negative results?

The hypothetical cohorts in table 1⇓ indicate that the balance of benefit and harms with RDTs is most favourable in areas with low malarial endemicity. In settings with a pretest probability of 5% (5% of fevers are due to malaria), using RDTs could prevent 90 unnecessary antimalarial prescriptions per 100 people tested, with less than one true malaria case being missed.

As the pretest probability gets higher, up to 60%, the balance is closer: with 38 unnecessary prescriptions prevented at the cost of missing three true malaria cases: and in truly epidemic conditions with a pretest probability of 80% there is an argument that reverting to presumptive diagnosis would be the safest and certainly most cost effective thing to do.

While this may be reassuring for those in low endemic settings, concerns have been raised that clinical malaria can occur at parasite counts below those detectable by standard RDTs and the risk of progression to severe malaria may be higher because of lower immunity.[18] These potential risks need quantifying.

What is the risk of severe malaria developing in people sent home without treatment?

In the Cochrane review by Odaga et al, five trials randomised health workers to using RDT diagnosis or clinical diagnosis (presumptive treatment). Despite large reductions in the use of antimalarials when health workers adhered to the RDT result, there were no clinically important differences in the number of people remaining unwell four to seven days later.[13]

We also found a longitudinal study from Tanzania[19] that followed up children with negative results for two weeks after being discharged without antimalarials. Of 1000 children with fever who had RDTs, 603 (60%) tested negative, and it is worth noting the average sensitivity of RDTs would predict around 20 missed cases in this setting. Over the course of the study 587 (97.3%) got better without antimalarials, three (0.5%) had subsequent positive test results at re-attendance and were treated, two (0.3%) died (of sepsis and pneumonia with repeated negative RDT results), and 12 (2%) were lost to follow-up.

This study was done in programmatic conditions close to routine practice and may offer some reassurance that if patients with persisting symptoms are able to return to the health post they will, and without serious consequences. Similar studies and local audits may help to reassure health workers further.

What strategies might be used to reduce overtreatment?

Clearly, countries need a range of strategies across all levels of the health system to fully implement universal testing. Table 2⇓ presents some of the approaches currently being evaluated.

Improved management could help stop RDTs becoming out of stock, and mobile phone technology has been touted as a potential solution. A mobile phone short messaging service (SMS) and web based system was evaluated in rural districts in Tanzania[20] and Kenya.[21] Mobile phones have also been evaluated as a means to improve quality assurance of RDTs[11] and to enable easy access to guidelines and clinical decision aids.[37 39]

A subsidy on artemisinin based combination therapy had some success in increasing its availability in the private sector, and some have advocated for a similar approach to promote the use of RDTs by private drug sellers.[22 40] However, others argue that the economics and effects of a subsidy are far from straightforward.[41]

The effectiveness of training or education required to change the behaviour of both health workers and patients has also been under evaluation. Simple, short training for health workers on using RDTs was evaluated in Cameroon,[31] and more complex training interventions including both the community and patients have been evaluated in three arm cluster randomised trials in Tanzania[32] and Nigeria.[36]

Changing behaviour is rarely easy, and as well as generating their own evidence, malaria experts should draw on the lessons from similar efforts to reduce antibiotic prescribing in other illnesses.[28-30]

In conclusion, universal testing for malaria is a major policy shift that will take time and extensive resources to fully

implement across sub-Saharan Africa. Success will require different interventions across public, private, and retail sectors.

Contributors and sources: EO has a five year research experience in evidence based healthcare with special focus on diagnostic tests. PG and DS have a longstanding experience in evidence synthesis for global health; they coordinate the Cochrane infectious disease group in Liverpool School of Tropical Medicine and lead a network of over 300 people in synthesising evidence to inform health decisions in low and middle income countries. PG is also a member of the WHO malaria technical guidelines group on malaria treatment. EO conceived this article after discussions at a symposium on overdiagnosis. Evidence from systematic reviews, primary studies and technical reports was used to prepare this article. EO had the original idea, wrote the first draft, provided examples, and coordinated the paper; PG provided examples and contributed to the manuscript; DS guided structure and content of the paper, provided examples, and contributed to the manuscript. All authors have agreed with submission and seen the final manuscript. EO is the guarantor of the article.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Accepted: 11 December 2015

Cite this as: *BMJ* 2016;352:i107

Key messages

- Universal testing for malaria will take time and extensive resources to fully implement across sub-Saharan Africa
- Interventions are required to overcome logistical health system constraints and change the beliefs and behaviour of health workers and patients
- Further developments to improve the accuracy of tests are also important

Tables

Table 1| Outcomes of rapid diagnostic testing in hypothetical cohorts of 100 people presenting with fever in settings with different malaria prevalences*

Pretest probability of positive result (%)	No of cases/100 people (95% CI)			
	Non-malarial cause of fever		Malaria is true cause of fever	
	False positives†	True negatives‡	True positives§	False negatives¶
5	5 (3 to 6)	90 (89 to 92)	5 (5 to 5)	0 (0 to 0)
30	4 (3 to 5)	66 (65 to 67)	29 (28 to 29)	2 (1 to 2)
60	2 (2 to 3)	38 (37 to 38)	57 (56 to 58)	3 (2 to 4)
80	1 (1 to 1)	19 (19 to 19)	76 (75 to 77)	5 (3 to 5)

*Type 1 HRP-2 rapid diagnostic test (RDT) with average sensitivity of 94.8% (95% CI 93.1 to 96.1) and specificity 95.2% (95% CI 93.2 to 96.7).[12]

†Number of unnecessary prescriptions that would still occur when using RDTs (the true cause of fever may also go untreated).

‡Number of unnecessary antimalarial prescriptions that could be avoided if RDTs are used instead of presumptive treatment.

§Number of people correctly diagnosed with malaria by the RDT.

¶Number of people with malaria who would be sent home without antimalarials because of a negative RDT result.

Table 2| Potential strategies to curb overtreatment of fever as malaria

Problem	Established approaches	Experimental approaches
Scenario 1: test not done, fever treated presumptively		
RDT shortages	-	Using technology such as short text messaging (SMS), internet, and electronic mapping to track stock of RDTs [20 21]
Limited RDT availability in private drug retail sector	-	Provision of free or subsidised RDTs through the private sector[22 23]
Staff shortages and high patient load in health centres	Use of community health workers to diagnose and treat uncomplicated malaria[24 25]	-
Scenario 2: test positive but the result is a false positive		
Low specificity of tests	Regular quality testing of RDTs from manufacturers by WHO[26]	Enabling external QA of reading and interpretation of RDTs by sending test photographs via SMS[11]
		Urine or fluorescent RDTs[27]
Scenario 3: test negative; but antimalarial drugs are still prescribed		
Uncertainty about RDT accuracy and perceived risk of mortality in people with false negatives results	Interactive educational meetings[28] Multifaceted interventions including health workers, patients and the public [28 29 30]	Evidence based training on the accuracy of RDTs and safety of not treating when results are negative[31 32]
	Accessible formats for guidelines, e.g. summaries[33]	Electronic or mobile friendly guidelines[34]
Uncertainty about how to manage fever when test is negative	Integrated case management of malarial and non-malarial causes of fever[24 25]	Improving referral paths for patients with negative results[35]
Expectation that patients will seek treatment elsewhere	Mass media interventions[38]	Incorporating patient communication skills in training packages of health workers[32 36]
		Use of clinic posters, decision aids and patient pamphlets and community awareness programmes[32 36]
		SMS reminders reiterating the treatment advice based on RDT result[37]

Figure

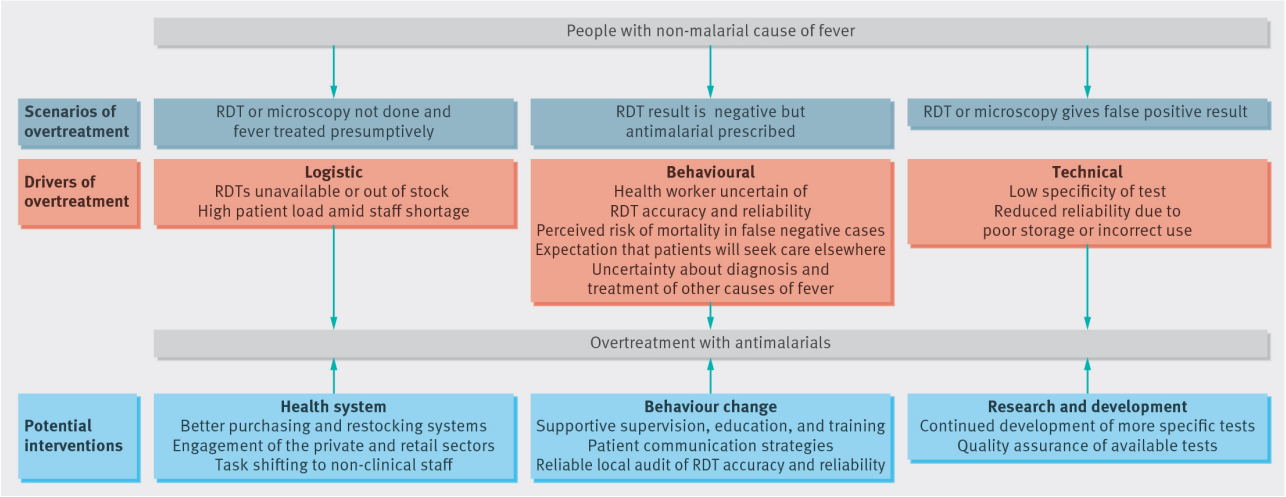

Fig 1 Logic framework of scenarios and drivers of overtreatment despite rapid diagnostic tests (RDTs) with potential interventions