Rapid diagnostic tests compared with malaria microscopy for guiding outpatient treatment of febrile illness in Tanzania: randomised trial

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EDITORIAL by Talisuna and Meya

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ABSTRACT

Objective To compare rapid diagnostic tests (RDTs) for malaria with routine microscopy in guiding treatment decisions for febrile patients.

Design Randomised trial.

Setting Outpatient departments in northeast Tanzania at varying levels of malaria transmission.

Participants 2416 patients for whom a malaria test was requested.

Intervention Staff received training on rapid diagnostic tests; patients sent for malaria tests were randomised to rapid diagnostic test or routine microscopy.

Main outcome measure Proportion of patients with a negative test prescribed an antimalarial drug.

Results Of 7589 outpatient consultations, 2425 (32%) had a malaria test requested. Of 1204 patients randomised to microscopy, 1030 (86%) tested negative for malaria; 523 (51%) of these were treated with an antimalarial drug. Of 1193 patients randomised to rapid diagnostic test, 1005 (84%) tested negative; 540 (54%) of these were treated for malaria (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Children aged under 5 with negative rapid diagnostic tests were more likely to be prescribed an antimalarial drug than were those with negative slides (P=0.003). Patients with a negative test by any method were more likely to be prescribed an antibiotic (odds ratio 6.42, 4.72 to 8.75; P<0.001). More than 90% of prescriptions for antimalarial drugs in low-moderate transmission settings were for patients for whom a test requested by a clinician was negative for malaria.

Conclusions Although many cases of malaria are missed outside the formal sector, within it malaria is massively over-diagnosed. This threatens the sustainability of deployment of artemisinin combination treatment, and treatable bacterial diseases are likely to be missed. Use of rapid diagnostic tests, with basic training for clinical staff, did not in itself lead to any reduction in over-treatment for malaria. Interventions to improve clinicians' management of febrile illness are essential but will not be easy.

Trial registration Clinical trials NCT00146796.

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INTRODUCTION

Presumptive antimalarial treatment for fever with no obvious alternative cause is widely practised in Africa, and studies suggest that this leads to significant overuse of antimalarial drugs.[1-5] This over-diagnosis of malaria in the formal healthcare sector coexists with under-diagnosis of malaria in the community, with the result that antimalarials are often given to people who do not need them and not given to children who do.

The introduction of new antimalarial drugs, particularly artemisinin combination treatments, in Africa is resulting in a large increase in drug costs that currently depends on subsidy.[6] This may become unsustainable if most antimalarial drugs are given to patients who do not have malaria. Treatable, and potentially fatal, bacterial diseases are common and may be misdiagnosed as malaria. Improving the diagnosis of acute febrile illness so that antimalarial drugs are targeted to patients who need them and alternative diagnoses sought in others is therefore a public health priority in Africa.

Rapid diagnostic tests have considerable potential as a tool to improve the diagnosis of malaria.[7 8] Although microscopy remains the gold standard for diagnosis of malaria, its accuracy under operational conditions in Africa is often relatively low and results often do not guide decisions about treatment.[9] Results of rapid diagnostic tests are rapidly available and less liable to the risk of being falsely negative due to parasite sequestration. Initial data indicate that the cost effectiveness of rapid diagnostic tests is reasonable and their use could result in significant savings.[10] However, no studies have examined whether their use leads to improved prescribing practice compared with current diagnostic methods. We compared rapid diagnostic tests with routine microscopy in guiding treatment decisions for febrile patients in Tanzania.

METHODS

We did the study in three public hospitals in northeast Tanzania, in areas in which transmission of *Plasmodium falciparum* is very low, low-moderate, and high (<1, 1-10, and >100 infected bites/person/year). We phased the study to include the peak malaria transmission season at each site. Clinical staff received training in use of rapid diagnostic tests.[11 12] Before the trial, we did a baseline observational study to determine the pattern of

Table 1 | Patients with negative test result treated with any antimalarial drug by malaria test method and age group, stratified by transmission intensity of *Plasmodium falciparum*

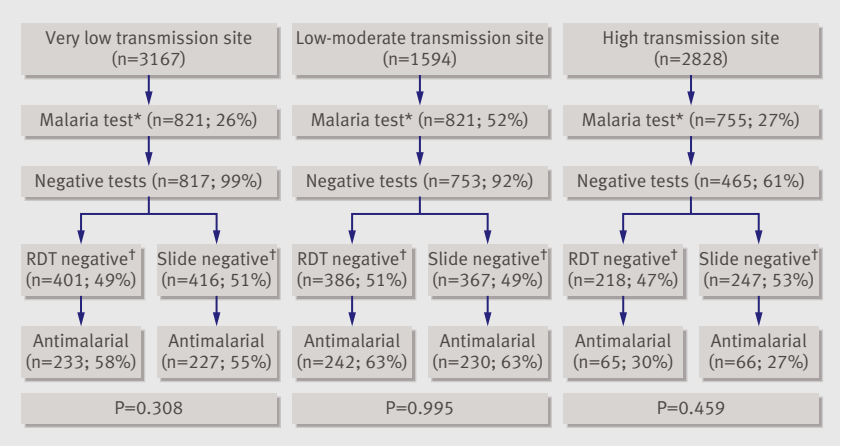
	Slide negative		Rapid diagnostic test negative		
Age group (years)	No	No (%) given antimalarial	No	No (%) given antimalarial	P value*
Low transmission					
<5	185	116 (63)	172	129 (75)	0.013
5-15	38	17 (45)	35	18 (51)	0.568
>15	193	94 (49)	194	86 (44)	0.388
Total	416	227 (55)	401	233 (58)	0.308
Low-moderate transmission					
<5	141	88 (62)	171	110 (64)	0.727
5-15	55	39 (71)	59	44 (75)	0.660
>15	171	103 (60)	156	88 (56)	0.484
Total	367	230 (63)	386	242 (63)	0.995
High transmission					
<5	88	20 (23)	78	32 (41)	0.012
5-15	29	14 (48)	25	9 (36)	0.364
>15	130	32 (25)	115	24 (21)	0.486
Total	247	66 (27)	218	65 (30)	0.459
All sites					
<5	414	224 (54)	421	271 (64)	0.003
5-15	122	70 (57)	119	71 (60)	0.719
>15	494	229 (46)	465	198 (43)	0.240
Total	1030	523 (51)	1005	540 (54)	0.182

*Statistical significance of associations in each stratum assessed with fully interacted logistic regression model that included interactions between treatment and indicator variables for each stratum as covariates.

routine diagnosis of malaria. The entry criterion for the main trial was a clinician's decision to request a malaria test in a patient of any age. We excluded patients for whom the clinician specified microscopy or who were admitted as inpatients for severe disease. A standardised history was taken, followed by randomisation to rapid diagnostic test or blood slide.

Laboratory staff in the clinic did the rapid diagnostic tests, and we used results interpreted by clinicians in the primary analysis. Patients randomised to microscopy were tested according to routine hospital practice. We took a reference slide for later double reading from all participants, and clinic staff reviewed patients with their results before taking final treatment decisions.

The primary outcome of the study was the proportion of patients for whom clinicians requested a malaria test, received a negative result, and prescrib ed an antimalarial drug anyway. We calculated unadjusted odds ratios and then adjusted them in a logistic regression model with potential confounding factors of age, hospital site, a history of fever, a history of cough, and clustering in study sites. Secondary outcomes were the proportion of febrile patients given an antibiotic by test outcome and the proportions of patients for whom antimalarial drugs were correctly prescribed, defined as antimalarial drugs given to patients with malaria parasites seen and not given to those with no parasites seen on the research slide.



Clinic attendances, malaria test results, and antimalarial treatment prescribed at each of the study sites. *Data are shown for cases with complete data; 3, 3, and 13 cases had incomplete data in the low, low-moderate, and high transmission sites. †Positive test results at low, low-moderate, and high transmission hospitals were: rapid diagnostic test 3, 15, and 168; blood slide 1, 53, and 168. All but five patients with positive tests results were treated with an antimalarial drug; reason for omission of treatment in these five not known

RESULTS

The intervention ran from January to August 2005. Of 7589 consultations, 63 patients (0.8%) were treated presumptively for malaria and 2425 (32.0%) were sent for a malaria test, of whom 2416 (99.6%) consented to participate and were randomised to rapid diagnostic test or blood slide. Data were incomplete in 19 (0.8%) patients, and results are shown for the remaining 2397 cases. Characteristics of patients in each arm were similar (see bmj.com).

In all, 523/1030 (50.8%) patients with a negative hospital slide and 540/1005 (53.7%) patients with a negative rapid diagnostic test were prescribed an antimalarial drug (odds ratio 1.13, 95% confidence interval 0.95 to 1.34; P=0.18). Rapid diagnostic tests showed no advantage in any of the transmissions settings (figure); the odds ratio was 1.16 (0.88 to 1.52) at the low transmission site, 1.00 (0.76 to 1.35) at low-moderate transmission, and 1.17 (0.78 to 1.75) at high transmission. Children aged under 5 were more likely to be treated with an antimalarial drug if they tested negative by rapid diagnostic test than if they tested negative by routine slide (table 1).

We used a logistic model to explore associations between presenting features and prescription of an antimalarial drug for a patient with a negative test result. Adults and patients with a history of fever in the previous 48 hours were more likely to be prescribed an antimalarial drug despite a negative test; we found no significant association with the type of test used (see bmj.com).

Antibiotics were prescribed to 51/362 (14.1%) patients who tested positive for malaria and to 1044/2035 (51.3%) with a negative test (odds ratio 6.42, 4.72 to 8.75; P<0.001); the difference was especially marked in children aged under 5 (16.8, 11.3 to 25.1; P<0.001) (table 2). Prescription of an antibiotic was not influenced by test method: 525/1030 (51.0%) slide negative patients and 519/1005 (51.6%) rapid diagnostic test negative patients were prescribed an antibiotic (P=0.76), and 308/414 (74.4%) slide negative and 310/421 (73.6%) rapid diagnostic test negative children aged under 5 were prescribed an antibiotic (P=0.80).

When we used double read research slide results

Table 2 | Prescription of any antibiotic for patients with positive or negative malaria tests by age group

	Positive test		Negative test			
			Antimalarial drug		No antimalarial drug	
Age group (years)	No	No (%) given antibiotic	No	No (%) given antibiotic	No	No (%) given antibiotic
<5	228	33 (14)	495	365 (74)	340	253 (74)
5-15	50	7 (14)	141	49 (35)	100	55 (55)
>15	84	11 (13)	427	143 (33)	532	179 (34)
Total	362	51 (14)	1063	557 (52)	972	487 (50)

as a gold standard, 269/1420 (18.9%) patients prescribed an antimalarial drug had *P falciparum* parasitaemia, and in the low and low-moderate transmission sites this proportion fell to 20/1004 (2.0%). If we define a correct prescription of an antimalarial drug as one that is prescribed when parasites are present on research slides and not prescribed when they are not, 616/1193 (51.6%) of patients randomised to the rapid diagnostic test and 606/1204 (50.3%) randomised to a slide test had a correct prescription of an antimalarial drug (odds ratio 1.05, 0.90 to 1.12; P=0.524). When compared with the double read research slide, hospital laboratory slide results were less sensitive than rapid diagnostic tests (71.3% v 95.4%). However, in spite of this, a few cases of malaria with high parasitaemia were read as negative by rapid diagnostic test (table 3).

DISCUSSION

Malaria is the single most common diagnosis in most hospitals in Africa and consumes a considerable proportion of available resources. During an era of cheap and virtually limitless antimalarial drugs, the policy for treating malaria has assumed that it is safer to treat several cases of non-malarial febrile illness with an antimalarial drug than to miss one true case. Our study shows that this policy is associated with high levels of overuse of antimalarial drugs, especially in low-moderate transmission intensity settings, which are common in many parts of Africa.[13] Clinicians frequently requested tests, but they paid limited attention to negative results, although these did have a greater impact on prescription of antibiotics than of antimalarials.

Table 3 | Sensitivity, specificity, and predictive values of rapid diagnostic test or routine blood slide as judged against research slide results

	Research slide*					
	Positive	Negative	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Negative predictive value (%)	Positive predictive value (%)
Rapid diagnostic test†						
Positive	146	42	95.4 (94.2 to 96.6)	95.9 (94.8 to 97.0)	99.3	77.7
Negative	7‡	985				
Hospital slide						
Positive	97	77	71.3 (68.8 to 73.9)	92.8 (91.3 to 94.3)	96.2	55.8
Negative	39§	991				

*Slide results are positive or negative for any *Plasmodium falciparum* asexual parasites; in addition, two slides were positive for *P malariae* asexual parasites.
†Positive by either laboratory technician or prescribing health worker.
‡Parasite densities/µl were <1000, 0; 1000-4999, 2; 5000-100 000, 2; >100 000, 3.
§Parasite densities/µl were <1000, 15; 1000-4999, 11; 5000-100 000, 8; >100 000, 5.

Impact of over-diagnosis on cost effectiveness

Over-diagnosis of malaria on this scale threatens the sustainability of deployment of artemisinin combination treatment. These drugs are cost effective if used for malaria in areas where other drugs have failed, but this depends on the drug being used for children with true malaria, and cost effectiveness rapidly falls away at high levels of misdiagnosis.[14] Rapid diagnostic tests, although more expensive than microscopy, are still potentially cost effective, but only if clinicians using the test act on the result.[15]

Improving diagnosis of febrile illness is essential, both to target antimalarials and because a large proportion of treatable, and potentially fatal, bacterial diseases are probably being missed.[16] Such an improvement depends on improvements in diagnostic facilities so that clinicians can rely on diagnostic tests, and rapid diagnostic tests are potentially very important for this.[17] Improvement in diagnostic technology needs to be matched, however, by changes in longstanding diagnostic behaviour by clinicians. Deploying rapid diagnostic tests to promote the sustainability of artemisinin combination treatment in Africa may fail unless ways can be found to bring about a major change in current prescribing behaviour.

Potential limitations of rapid diagnostic tests and this study

Current rapid diagnostic tests have limitations, shown in this study by a few tests from patients with high parasite counts being read as negative. Possible technical problems include deletion of HRP-2 genes in certain parasites,[18] "flooding" of the antigen capture sites, and defects in the device membrane (Anthony Moody, personal communication, 2006). This supports the concern that in areas of very high malaria transmission, withholding antimalarial drugs from children under 5 with febrile illness is potentially hazardous even in the face of negative test results. However, it will never be cost effective to order a test knowing that a negative result will be ignored. In other epidemiological settings and age groups, the negative predictive value of test results will be very high and the risks of withholding antimalarial drugs from patients with negative tests will be minimal.

Three reasons exist why this trial might not reflect reality in the rest of Africa. Firstly, prescribers might have altered their normal practice as a result of the study; however, if anything, this is more likely to have encouraged them to follow national policy and take test results into account. Secondly, the levels of over-diagnosis were atypical, but all the available evidence indicates that the findings of over-diagnosis are typical of hospitals throughout the continent.[1-5] Thirdly, the training provided in the trial was considerably more intensive and tailored to individual settings than would be possible in a national roll out, making it unlikely that inadequate training is the main reason for these results. The study reflects behaviour in a hospital setting, and should be interpreted in the context that a substantial proportion of febrile illness is treated outside hospital and malaria is often not treated at all in the community.

Can behaviour be changed?

This trial shows that providing quick and reliable diagnostic tools with basic training may, in itself, have little impact on overuse of antimalarial drugs. Understanding the reasons for, and then changing, the habit of overprescribing antimalarial drugs will need to be a priority if the potential benefits of artemisinin combination treatment and rapid diagnostic tests for malaria are to be realised.

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Competing interests: None declared.

Ethical approval: Ethics committees of the National Institute for Medical Research, Tanzania, and the London School of Hygiene and Tropical Medicine.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Cases of malaria in the community are often missed, but at the same time over-diagnosis of malaria is widespread in Africa

Rapid diagnostic tests are sensitive and specific for falciparum malaria, and could be cost effective if their use guided practice

WHAT THIS STUDY ADDS

In areas of low or moderate malaria transmission, malaria is massively over-diagnosed in hospital outpatients and microscopy results are often ignored.

Deploying rapid diagnostic tests for malaria, with standard training, made no difference to the over-diagnosis of malaria in febrile patients

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CORRECTIONS AND CLARIFICATIONS

Case management for elderly people in the community

Owing to a mistake during editing, the Castlefields project was misrepresented in this editorial by David A Black (*BMJ* 2007;334:3-4, 6 Jan, doi: 10.1136/bmj.39027.550324.47). The text stated that the Castlefields project was an Evercare project, with the implication also that it was run by UnitedHealth Group. Neither is true. The penultimate sentence of the second paragraph should therefore read "Supporting this information were data from a similar project in Castlefields in the UK that had not been subjected to peer review."

Osteoporosis and its management

An error in the labelling of a figure persisted to publication in this Clinical Review by Kenneth E S Poole and Juliet E Compston (*BMJ* 2006;333:1251-6, 16 Dec, doi: 10.1136/bmj.39050.597350.47). The key on figure 2 is incorrect: the solid red line should refer to vertebral fractures and the dotted dark blue line to hip fractures.

This Week

Several errors appeared on the This Week page of the 6 January 2007 issue of the printed journal. In the third item in The Week in Quotes, we referred to self management in men with "uncomplicated lower urinary tract infection" whereas the study described related to uncomplicated lower urinary tract symptoms. In the fourth item of The Week in Numbers, we said that routine check-ups after surgery take place after six months, whereas they take place after six weeks. Neither of the related articles contained these errors. Also, in the Picture of the Week, we misspelt fundraising and wrongly inserted an "r" into "bought." We have already published the first two of these corrections on bmj.com.