The impact of response to the results of diagnostic tests for malaria: cost-benefit analysis

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ABSTRACT

Objective Rapid diagnostic tests for malaria seem cost effective in standard analyses, but these do not take account of clinicians' response to test results. This study tested the impact of clinicians' response to rapid diagnostic test or microscopy results on the costs and benefits of testing at different levels of malaria transmission and in different age groups.

Design Cost-benefit analysis using a decision tree model and clinical data on the effectiveness of diagnostic tests for malaria, their costs, and clinicians' response to test results.

Setting Tanzania.

Methods Data were obtained from a clinical trial of 2425 patients carried out in three settings of varying transmission.

Results At moderate and low levels of malaria transmission, rapid diagnostic tests were more cost beneficial than microscopy, and both more so than presumptive treatment, but only where response was consistent with test results. At the levels of prescription of antimalarial drugs to patients with negative tests that have been found in observational studies and trials, neither test methodis likely to be cost beneficial, incurring costs 10-250% higher, depending on transmission rate, than would have been the case with fully consistent responses to all test results. Microscopy becomes more cost beneficial than rapid diagnostic tests when its sensitivity under operational conditions approaches that of rapid diagnostic tests.

Conclusions Improving diagnostic methods, including rapid diagnostic tests, can reduce costs and enhance the benefits of effective antimalarial drugs, but only if the consistency of response to test results is also improved. Investing in methods to improve rational response to tests is essential. Economic evaluations of diagnostic tests should take into account whether clinicians' response is consistent with test results.

INTRODUCTION

Improved targeting of antimalarial drugs in Africa is a priority as new artemisinin combination therapies, which cost more than previous and now generally ineffective antimalarials, come into use. The widespread practice of treating any non-specific febrile illness as malaria threatens the sustainability of artemisinin combination therapy.[1-4]

Malaria treatment guidelines now recommend that treatment for non-severe malaria should, at least for older children and non-pregnant adults, be restricted to people with positive results on a parasitological test for malaria. In many settings this is difficult to achieve with blood slide testing, which is of variable accuracy and available only in larger health facilities. Rapid diagnostic tests for malaria potentially reduce these problems.[5 6] Studies that have explored the economic consequences of using rapid diagnostic tests alongside artemisinin combination therapies have shown these tests are potentially cost effective, but these studies assume that prescribers respond to negative test results by not prescribing an artemisinin combination therapy.[5 7-9]

The assumption in these models—that prescribers will respond in a way that is fully consistent with test results—is unsafe, and does not conform with observed practice.[2] In Tanzania, a recent randomised trial of rapid diagnostic tests compared with blood slide testing found that in low transmission areas, over 90% of all antimalarials prescribed were given to patients with a negative test result, irrespective of the test method used.[3]

This paper examines the relation between the level of clinicians' response consistent with results of parasitological tests, and the total costs resulting from the use of rapid diagnostic tests and microscopy.

METHODS

We obtained data from a randomised controlled trial carried out in three hospitals in northeast Tanzania.[3] The relevant data for this analysis are prevalence of parasitaemia among febrile patients, clinicians' response to test results, the accuracy (sensitivity and specificity) of the tests, and the cost of diagnosis and treatment. Prevalence is defined as the proportion of febrile patients presenting with parasitaemia, and varies with the rates of transmission of malaria.[10] Consistent response rate is defined as the percentage of negative test results for which clinicians do not prescribe antimalarials. Virtually 100% of patients with positive tests were prescribed an antimalarial, and this was assumed in the model.

We calculated the costs for the management of a simulated population of 1000 patients, including costs of microscopy or rapid diagnostic tests, antimalarials, antibiotics, care for patients with severe illness, and a cost representing the value of life years lost owing to incorrect diagnosis. The analysis uses a cost-benefit framework, taking a societal perspective accounting for both provider costs and the monetary value of years of life lost.

We chose a decision tree as the best model to synthesise the data, represent alternative options, and indicate the most efficient outcomes (see figure 1 on

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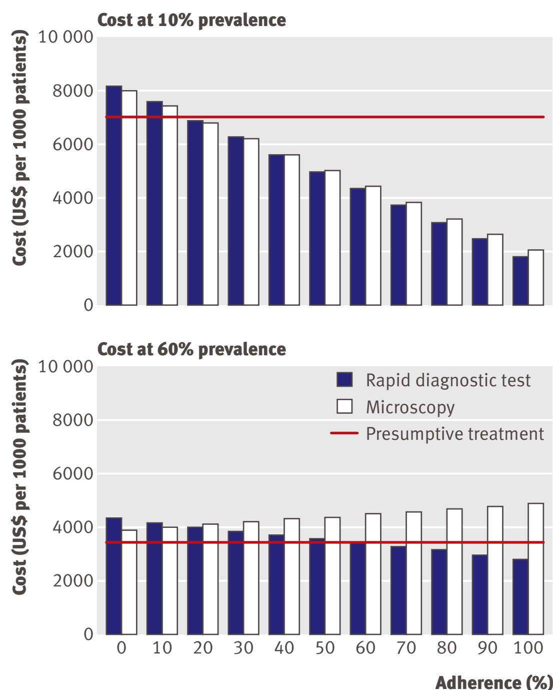

Fig 1 Total costs for rapid diagnostic tests and microscopy, using $150 per year of life lost and the profile of a 15 year old patient

bmj.com). The table shows the variables used in the model.

On the death of a patient the number of years of life lost depends on age and was related to relevant life expectancy tables[11] and discounted at 3%.[12] For the primary analysis, a year of life lost was assigned a cost of $150, reflecting the WHO benchmark for an "attractive" intervention in terms of cost effectiveness.[13] (For a full description of methods see bmj.com.)

Variables in assessing response to malarial testing

Measure	Estimate used	Source	Comment
Costs*			
Rapid diagnostic test	$0.80	Primary data[5]	
Microscopy	$0.28	Lubell et al[5]	Low cost is partly result of short reading time
ACT	$2.40 adult dose	WHO[24]	Quantities adjusted for younger age groups
Antibiotics	$0.30	Primary data[5]	Test negatives adhered to assumed to receive drug of this cost
False negative result	Varies by age, prevalence with respect to probability of untreated malaria becoming severe, and case fatality rates (see below); value of year of life lost=$150	WHO[24]	Value of year of life lost based on WHO benchmark for "attractive" interventions
False positive result	Determined by proportion of non-malarial febrile illnesses that are bacterial, the probability they become severe, and case fatality rates (see below); combined with value for years of life lost		
Accuracies			
Rapid diagnostic test:			
Sensitivity	93%	Primary data	
Specificity	96%	Primary data	
Microscopy:			
Sensitivity	73%	Primary data	
Specificity	93%	Primary data	Â

*Costs were collected in Tanzanian shillings of 2005 and converted to US dollars ($1=1167 Tzs for 2005)

RESULTS

In a low transmission setting (prevalence of malaria 10% in those with febrile illness) and for a 15 year old, using either test incurred higher costs than presumptive treatment when consistent response rate was below 20%, and testing became increasingly attractive as response consistency improved (fig 1).

In a high transmission setting (prevalence of 60%) and for a 15 year old, both tests incurred higher costs than a strategy of presumptive treatment if consistent response rate was below approximately 65% (fig 1).

Figure 2 compares each of the tests directly with presumptive treatment across all levels of prevalence and consistent response rates, showing the proportional change in cost of rapid diagnostic tests and microscopy relative to presumptive treatment. In low prevalence settings, use of either test with consistent response to results led to cost savings of between 50% and 100% as compared with presumptive treatment. As prevalence increases to the medium-high range, however, consistent response rate must increase more than proportionately if use of the tests is to remain attractive. At very high levels of prevalence, both tests appeared more costly, irrespective of response by clinicians, primarily because of imperfect test sensitivities, and presumptive treatment remained the more efficient option.

We also explored the most attractive strategy at all prevalences and levels of consistent response rate, using profiles for patients aged 3, 7, and 25 years (see fig 4 on bmj.com). This indicated that using either parasitological test for younger patients was unattractive in settings of high transmission, even if response to tests was fully consistent.

Sensitivity analysis

Results were most sensitive to the cost assigned to a year of life lost. Higher values for this variable led to scenarios that were more costly and effective being considered more attractive. Figure 3 shows the circumstances under which each of the strategies is most attractive, stratified by cost per year of life lost averted. At a value of $25 (the value where WHO considers interventions to be "very attractive"), rapid diagnostic tests gained some advantage in the mid-range of prevalence as long as response was consistent with results, and microscopy remained the preferred option for low prevalence areas even at low levels of consistent response rate.

Using $150 per year of life lost, rapid diagnostic tests became the preferred option up to a prevalence of about 70%, when presumptive treatment became the more efficient option. At a value of $680—twice the Tanzanian gross national income per capita for the year 2005,[14] an alternative rule of thumb[15]—rapid

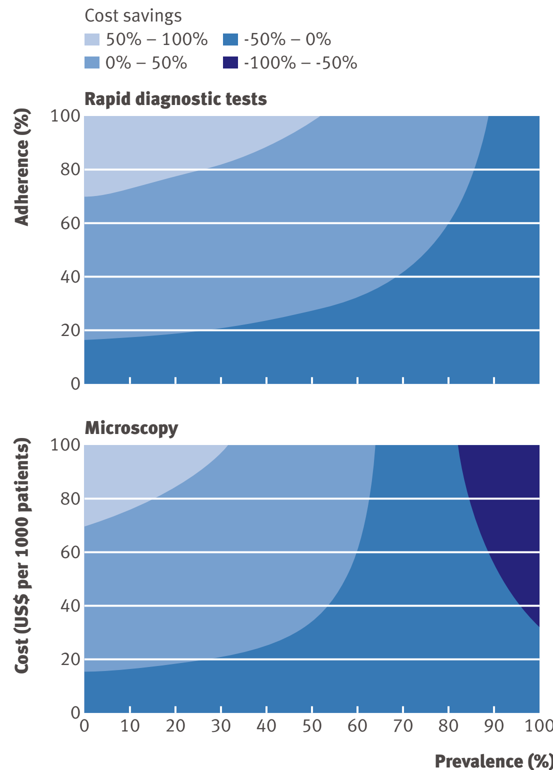

Fig 2 Cost difference of rapid diagnostic tests and microscopy with presumptive treatment as a baseline

diagnostic tests dominated across all but the lowest levels of consistent response rate and highest levels of prevalence.

Lastly, we ran the model using a value for microscopy sensitivity (95%—WHO's minimum requirement for a malaria diagnostic test) higher than that seen in the trial. At this level, microscopy was the preferred option for most levels of consistent response rate and when prevalence was up to 90% (see figure 6 on bmj.com) .

DISCUSSION

This study shows that clinicians' response to test results has a major impact on the total cost of both microscopy and rapid diagnostic tests, and that this varies with level of transmission of malaria. Previous economic analyses of malaria diagnostic tests for febrile patients have ranged from those based on simple formulas (comparing the cost of treatment to the cost of the test plus the cost of treatment across differing levels of prevalence) to more advanced analyses seeking to incorporate test accuracy and the cost of false results.[8 16-19] A recent study evaluating the effectiveness of introducing new diagnostic tests for malaria included several novel elements, such as the infrastructure required for the tests and subsequent accessibility, and an estimate of "harm of treatment" associated with antimalarials.[8] The cost implications of inconsistent response to test results have, however, largely been ignored, despite the overwhelming evidence that this is a problem throughout Africa. This is likely to be relevant to economic evaluations of all diagnostic tests, not just those for malaria.

Limitations

The study assumed that only febrile patients were tested, although in reality almost 20% of antimalarials prescribed were given to patients who did not have a history of fever, of whom only 1.7% were parasitaemic. This runs counter to guidelines such as those of WHO and the Tanzanian Ministry of Health and will increase the waste of resources.[20 21] In addition, the study evaluated the impact of testing on prescribing antimalarials only, although tests may influence clinicians' behaviour in prescribing additional drugs, especially antibiotics.

Three further potential limitations of the methods should be highlighted. Some of the data within the model had to be estimated from indirect sources because locally relevant data are not available. These points are highlighted as "expert opinion" in the tables.

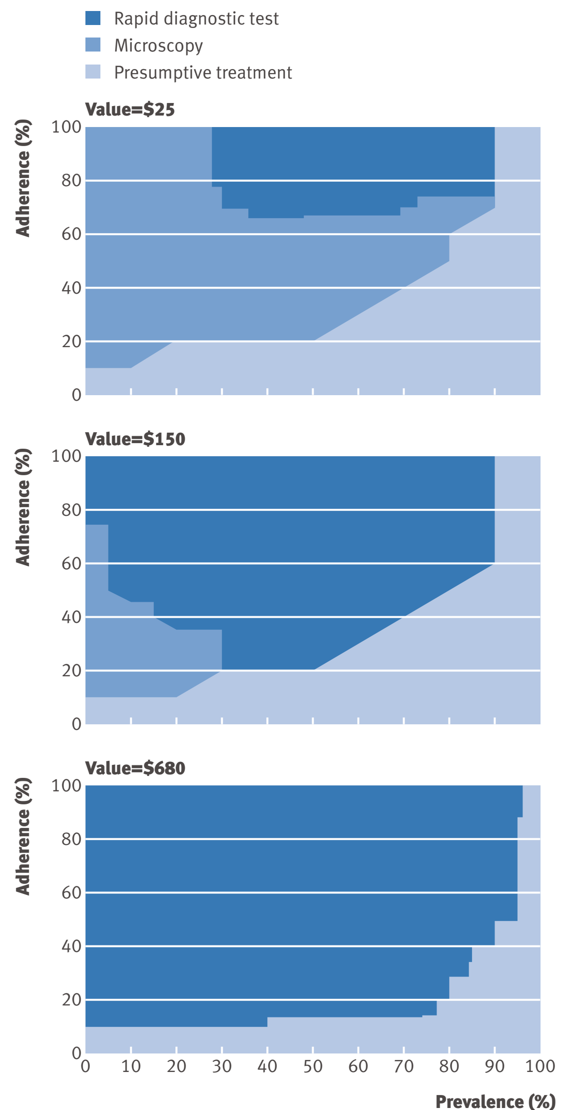

Fig 3 Most efficient strategy by response to test results and prevalence of malaria with respect to value of years of life lost

WHAT IS ALREADY KNOWN ON THIS TOPIC

Introducing new antimalarials requires reconsidering presumptive treatment policies

Use of rapid diagnostic tests before prescription of artemisinin combination treatments can be a cost effective measure in the management of febrile disease

Clinicians often respond to negative results of tests for malaria by ignoring them

WHAT THIS STUDY ADDS

At some of the currently observed levels of response to test results, the use of diagnostic tests will not be cost beneficial

Response to negative test results should be monitored and where necessary consistency should be enhanced before rapid diagnostic tests are widely disseminated

Response to test results should be taken into account in economic evaluations of diagnostic methods

Secondly, the model does not differentiate between patients with mild symptoms but varying levels of parasitaemia, largely because the evidence that level of parasitaemiainfluences outcome is mixed. Thirdly, the methods of estimating rate of transmission from hospital data are inevitably not precise. Characterising transmission is prone to difficulties. In this study we used prevalence of parasitaemia among febrile patients, although this method is subject to several limitations. Data for case fatality rates for untreated malaria cannot be measured precisely, and the interaction between case fatality rates and rates of transmission and age adds an additional level of uncertainty.

Policy implications

This study has confirmed findings that show the potential cost savings from use of a diagnostic test before prescribing antimalarial treatment, if test results are used to guide the prescribing. However diagnostic tests rapidly become less attractive when prescribers even partially ignore negative results. Therefore, the response to test results must be taken into account in designing public health programmes, as investing in rapid diagnostic tests without changing prescribing behaviour is unlikely to be cost beneficial.

Investment in improving the quality of field microscopy is also a priority. In this analysis, because of the low levels of sensitivity of microscopy seen in practice, its use currently results in high total costs in most circumstances. Where microscopy is used for routine diagnosis, measures to ensure higher accuracy as well as response consistent with test results are necessary to maximise cost effectiveness. Changing prescribers' behaviour will have costs, but these can be offset by the savings gained with better response to test results.

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