WHO REPORT
Cost-Effectiveness of Malaria Diagnosis in Sub-Saharan Africa: The Role of Rapid Diagnostic Tests in Rural Settings with High Plasmodium falciparum transmission

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Chantal Morel, Samuel Shillcutt, Catherine Goodman, and Paul Coleman constructed the model with input from several experts. Samuel Shillcutt and Chantal Morel wrote the paper with input from Catherine Goodman, Paul Coleman and Anne Mills.

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ABSTRACT

Early diagnosis and appropriate case management are essential to addressing the malaria burden, and have been advocated consistently by the World Health Organization. Current outpatient diagnostic practice in sub-Saharan Africa (SSA) is based largely on presumptive treatment (PT) of fever with antimalarial therapies. This strategy leads to significant overdiagnosis of malaria due to the overlap of symptoms between malaria and non-malarial febrile illnesses (NMFIs). As a result, antimalarials are overprescribed, and NMFIs are underdiagnosed and inappropriately treated. In addition, many countries in SSA have recently changed first-line malaria treatment to artemisinin-based combination therapies (ACTs), which will raise treatment costs by an order of magnitude. Lateral-flow rapid diagnostic tests (RDTs) and microscopy both provide alternatives to clinical diagnosis and a means to improve treatment and ensure appropriate use of these expensive drugs. Relative to microscopy, RDTs are argued to be easier to use at peripheral health facilities, and therefore may facilitate the expansion of higher quality diagnostic coverage.

This study used decision tree analysis to estimate the cost-effectiveness of three diagnostic strategies relative to each other – RDT, PT and field-standard microscopy – for use in rural areas of SSA with predominant \( P. falciparum \) transmission. In the reference case it is assumed that all patients diagnosed with malaria receive ACT, and all those diagnosed malaria-negative receive antibiotics. Results are calculated in terms of the incremental cost per disability adjusted life year (DALY) averted for each 2-way comparison, and the monetary net benefit based on policy makers’ assumed valuation of a healthy year of life (\( \lambda \)). Highlighting gaps in the current evidence base, results are tested
across different epidemiological settings and according to variations in key parameters using Monte-Carlo simulations and other sensitivity analysis techniques. Attitudes towards risk and $\lambda$ are likely to vary for different decision makers, and uncertainty in these factors is considered.

Results should be regarded as relevant specifically for rural areas where symptom-based diagnosis has been used in the past and resources are limited, rather than in a context of large clinics and facilities where good malaria microscopy and technical expertise are well established. RDTs are cost-effective relative to PT when less than 81% of febrile patients are parasitaemic, and decision makers value healthy life years at $150$/DALY and are willing to accept a 50% chance that their decision is correct. If decision makers wish to be 95% certain that they are correct in their policy decision, RDTs would be considered cost-effective compared to PT when less than 62% of febrile patients are parasitaemic. RDTs are also robustly cost-effective relative to microscopy given these conditions. Cost-effectiveness is most sensitive to malaria prevalence, the cost of the diagnostic test, the cost of ACT, adherence to antibiotics, and factors which influence the severity of NMFIs. Adherence to ACT and the proportion of patients with negative diagnoses that receive antibiotic treatment have moderate impacts on results. Cost-effectiveness is robust to the proportion of patients aged five years or older and second-line treatment costs. Decision makers’ valuation of a DALY averted is relevant when it is at low levels. Variations in the acceptable level of risk (probability of decision not being correct) can be expected to reverse the diagnostic policy decision in a wide range of conditions.
Modelling has allowed for results to be calculated beyond the scope of available evidence, but is subject to several structural uncertainties in treatment seeking behaviour and clinical practice in the field. Moreover, data are still very limited for some parameters, especially those related to the probabilities of severe disease and death. Further work in this area could (1) assess the cost-effectiveness of RDTs in informal outlets (2) assess the cost-effectiveness of microscopy used for multiple diseases (3) compare diagnostic tests to alternative clinical algorithms (4) incorporate provider non-adherence to diagnostic results and quality assurance interventions (5) consider a wider range of HIV prevalence scenarios (6) evaluate diagnosis in low-transmission settings (7) incorporate the potential impact on drug resistance and other changes through time.

In conclusion, the analysis to date provides a strong indication that RDTs are likely to be an important tool in the campaign to roll back malaria in areas of rural Africa with high *P. falciparum* transmission.
# LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACT</td>
<td>Artemisinin-based Combination Therapy</td>
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<td>CQ</td>
<td>Chloroquine</td>
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<td>DALY</td>
<td>Disability Adjusted Life Year</td>
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<tr>
<td>DCP2</td>
<td>Disease Control Priorities Project (Second Edition)</td>
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<td>GBD</td>
<td>Global Burden of Disease</td>
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<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HRP-2</td>
<td>Histidine-Rich Protein 2</td>
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<tr>
<td>ICER</td>
<td>Incremental Cost-Effectiveness Ratio</td>
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<td>IMCI</td>
<td>Integrated Management of Childhood Illness</td>
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<td>MCS</td>
<td>Monte-Carlo Simulation</td>
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<td>INB</td>
<td>Incremental Net Benefit</td>
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<td>$\lambda$</td>
<td>Ceiling Ratio / Valuation of a Healthy Life Year</td>
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<td>NMFI</td>
<td>Non-Malarial Febrile Illness</td>
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<td>$P. falciparum$</td>
<td><em>Plasmodium falciparum</em></td>
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<td>$P. vivax$</td>
<td><em>Plasmodium vivax</em></td>
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<tr>
<td>pLDH</td>
<td>Parasite Lactate Dehydrogenase</td>
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<td>PPV</td>
<td>Positive Predictive Value</td>
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<td>PT</td>
<td>Presumptive Treatment</td>
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<td>RDT</td>
<td>Rapid Diagnostic Tests</td>
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<td>SP</td>
<td>Sulfadoxine-Pyrimethamine</td>
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<td>SSA</td>
<td>Sub-Saharan Africa</td>
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<td>WHO/TDR</td>
<td>World Health Organization - Special Programme for Research and Training in Tropical Diseases</td>
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<td>YLD</td>
<td>Years Lost to Disability</td>
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ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

Introduction 8
The burden of malaria 8
The need to focus on diagnosis and treatment 8
Overdiagnosis of malaria 9
Underdiagnosis of other febrile illnesses 10
Revising first-line antimalarial treatment 11
Diagnostic tools: microscopy and rapid diagnostic tests 13
Gaps in knowledge & Study aims 15

Methods 17
Modelling approach 17
Model structure and data sources 17
Description of interventions and comparators 19
General model assumptions 20
Description of probabilities 21
Costing methods and assumptions 22
Health outcomes 24
Calculation of results under uncertainty  25
Parameter distributions  26
Calculation of cost-effectiveness and net benefit  27
Valuation of health improvements  29
Generation of curves and surface plots  30

Results  32
Costs and health outcomes of each diagnostic strategy  32
Incremental cost-effectiveness  33
Sensitivity analysis on the ceiling ratio  34
Sensitivity analysis on parameters on model parameters  36

Discussion  38
Overview of results  38
Example of a full interpretation of results  40
Comparison to previous studies  42
Limitations to the model  44
Changing policy and policy maker attitudes toward risk  51
Further work  52

Conclusions  54
Works Cited  55

Tables  65

Figures  73

Annexes  112

End Notes  171
INTRODUCTION

The burden of malaria

Despite the suppression and elimination of malaria from much of the world in the 20th century, malaria continues to be one of the most devastating infectious diseases worldwide (Alilio, Bygbjerg et al. 2004; Hay, Guerra et al. 2004; Teklehaimanot, Singer et al. 2005). Over 1 million deaths per year, or 3,000-6,000 deaths per day can be attributed to the disease (Amexo, Tolhurst et al. 2004), many of which are young children and pregnant women in sub-Saharan Africa (SSA) where 90% of malaria deaths occur (WHO 2003a). The effects of malaria are not only felt through individual illness and death, but also in the ability of societies to develop economically (Chima, Goodman et al. 2003; Mills and Shillcutt 2004). One study found that economic growth rates in endemic countries are 1-3% lower than in countries with no malaria (Sachs 2002). Currently the poorest 20% of the world’s population bears 58% of the malaria burden of morbidity and mortality, and receives the worst standard of care. (Breman 2004).

The need to focus on diagnosis and treatment

From vector control to potential vaccines currently being tested, efforts to combat malaria can take various forms. However, it has become widely recognized that early diagnosis and effective case management are keys to addressing the immediate burden of malaria (WHO 1993; Nabarro and Tayler 1998; WHO 2003b; Keiser, Utzinger et al. 2004). The clinical symptoms of malaria include fever, chills, perspiration, stiff neck, runny nose, anorexia, headaches, vomiting, malaise, and general danger signs (WHO 1999; WHO 2000). In much of SSA the decision to treat a patient with an antimalarial is
often made solely on the basis of fever, especially for outpatient care (ODempsey, McArdle et al. 1993; Chandramohan, Jaffar et al. 2002; Reyburn, Ruanda et al. 2006; Zurovac, Midia et al. 2006). The main argument in favour of such presumptive treatment (PT) for malaria is that false negative diagnoses (i.e. failing to identify malaria in a patient) have potentially severe consequences both in terms of health effects and treatment costs. Patients with a false negative diagnosis receive the incorrect treatment and are often sent home – leaving them vulnerable to severe malaria and potential death. Under perfect conditions, PT rules out this outcome (Perkins, Zucker et al. 1997).

**Overdiagnosis of malaria**

The overlap of symptoms between malarial and non-malarial febrile illnesses (NMFIs) results in significant overdiagnosis of malaria with PT (false positive diagnoses) (Greenwood 1997). In SSA, between 20% and 40% of outpatients are diagnosed with ‘fever’ (Chima, Goodman et al. 2003); however, clinical algorithm diagnoses are unreliable in their ability to identify disease (Bojang, Obaro et al. 2000; Chandramohan, Jaffar et al. 2002, Mwangi, Mohammed et al. 2005). In coastal Tanzania, over half of febrile children were diagnosed with malaria according to symptoms of fever, vomiting, and diarrhoea, but only 13-52% of them had parasites confirmed by microscopy (Rooth and Bjorkman 1992). Suspected malaria accounts for 0.5% to 50% of inpatient admissions in different areas of SSA (Chima, Goodman et al. 2003), but evidence from Tanzania suggests that *P. falciparum* malaria may be the cause of as little as 21.6%-61% of positive diagnoses – a figure that falls with age and intensity of transmission (Reyburn, Mbatia et al. 2004; Reyburn, Ruanda et al. 2006; Zurovac, Midia et al. 2006). A review
of estimates from across Africa indicates that approximately 61% of clinically diagnosed cases of malaria are in fact caused by other pathogens (Amexo, Tolhurst et al. 2004). Further, studies from East Africa have found that 48%-79.3% of outpatients with negative blood slides were treated with antimalarials (Reyburn, Ruanda et al. 2006; Zurovac, Midia et al. 2006).

**Underdiagnosis of other febrile illnesses**

It has been argued that this approach to malaria diagnosis needs re-evaluation (Font, Alonso Gonzalez et al. 2001). Overdiagnosis of malaria through PT often results in the underdiagnosis and inappropriate treatment of NMFI, a point which is only recently beginning to receive attention in debates on malaria diagnosis (WHO 2000; WHO 2003b; Amexo, Tolhurst et al. 2004). While a high proportion of NMFI are likely to be self-limiting, such as influenza and other viral diseases; a significant minority will have bacterial aetiology, such as pneumonia, acute respiratory infection, or bacterial meningitis (Sauté Aponte et al., 2003; Berkley, Lowe et al. 2005; WHO 2006a; Brent, Ahmed et al. 2006). Many of these bacterial diseases are major killers of African children. Official estimates from 2002 indicate that 16% of child deaths in Africa were caused by acute respiratory infections and 14% by diarrhoeal diseases (WHO 2002a).

NMFI are frequently overlooked by clinical diagnosis because their symptoms are very similar to malaria. A large part of this literature documents difficulties in diagnosing the cause of fevers among inpatients. In Malawi, 95% of children brought to a hospital and fitting a clinical case definition of pneumonia also met the clinical case definition of malaria (Redd, Bloland et al. 1992). In Tanzania, microscopic evaluation of
patients admitted to hospital and treated for severe malaria revealed that 53.9% did not have malaria parasites (Reyburn, Mbatia et al. 2004). Another study found that splenomegaly – often perceived as a tell-tale sign of malaria – was associated more with non-typhi salmonellae bacteraemia than with malaria (Peters, Zijlstra et al. 2004).

Similar problems are described at the outpatient level. Among children brought to an outpatient clinic in western Kenya, half should have been classified as both pneumonia and malaria cases according to the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) algorithm (Perkins, Zucker et al. 1997). In Uganda, 30% of children brought to peripheral health centres had symptoms that could be diagnosed equally as either of these diseases (Kallander, Nsungwa-Sabiiti et al. 2004).

Misdiagnosis of NMFIs may be highly dangerous, and these illnesses can be even more life-threatening than malaria in some cases. Peters and colleagues calculated a case-fatality rate of 19% for bacteraemia, and Berkley and colleagues found that 26% of all in-hospital child deaths were due to community-acquired bacteraemia (Peters, Zijlstra et al. 2004; Berkley, Lowe et al. 2005a). In Tanzania, 12% of inpatients died who were slide negative for malaria and with severe fever, compared to 7% of slide positive patients (Reyburn, Mbatia et al. 2004). Not only does inappropriate diagnosis of NMFIs have a negative health impact in terms of mortality and morbidity, but also treating misdiagnosed patients whose illness becomes severe is financially costly, adding to the burden on already strained health services.

**Revising first-line antimalarial treatment**

With current first-line malaria drugs failing, the introduction of expensive new
antimalarials represents a major policy change for countries in SSA. For several decades, chloroquine (CQ) was an effective antimalarial treatment available at a relatively low cost. Today, CQ remains the cheapest and most widely available antimalarial drug, but due to parasite resistance it has lost much of its clinical effectiveness throughout Africa (WHO 2003a).\(^1\) In some parts of Africa CQ has been replaced by a similarly-priced antimalarial, sulfadoxine-pyrimethamine (SP). However, resistance to SP is escalating rapidly in eastern and southern Africa and threatens to spread further (WHO 2003a). In addition, other monotherapies such as amodioquine have been shown to fail in clinical practice (Mutabingwa, Anthony et al. 2005), and a recent review of current malaria treatment practices found a low level of adherence to national guidelines, with incorrect antimalarials prescribed in incorrect amounts (Zurovac and Rowe 2006). The consequences of this trend are grave as increasing resistance has been positively associated with malaria related mortality (Zucker, Lackritz et al. 1996; Trape 2001).

Artemisinin-based combination therapies (ACTs) are increasingly used as a replacement to failing first-line antimalarials (RBM 2004; Morel, Lauer et al. 2005). ACTs have been shown to be highly efficacious, and coadministration of artemisinin with a second malaria drug is argued to reduce the likelihood of resistance developing to both drugs (White 1999; White, Nosten et al. 1999; Bloland, Ettling et al. 2000; Amexo, Tolhurst et al. 2004). However, ACTs cost an order of magnitude more than CQ or SP, and introducing them effectively in SSA poses an enormous challenge to public health systems (Bloland, Kachur et al. 2003; WHO 2003c; Arrow, Panosian et al. 2004; WHO 2004a). In addition, many patients may be unable to afford ACTs where user fees apply (Whitty, Allan et al. 2004; Malenga, Palmer et al. 2005; Wiseman, Onwujekwe et al.
2005), and this problem is compounded by supply bottlenecks, continued use of monotherapies, and complications involving the private sector (WHO 2004b; Malenga, Palmer et al. 2005). To cope with the impending expense of widespread use of ACTs, and to prevent these expensive drugs from being wasted on inappropriate treatments, a means to allocate them efficiently is needed, leading to increased interest in the use of tools for parasitic diagnosis (Brinkmann and Brinkmann 1991; Amexo, Tollhurst et al. 2004; Barnish, Bates et al. 2004; Zurovac, Midia et al. 2006).  

**Diagnostic tools: microscopy and rapid diagnostic tests**

The choice of diagnostic technique can have a major impact on how and when patients are prescribed these new drugs. Laboratory-based microscopy is considered the “gold standard” for malaria diagnosis, and involves taking a blood sample, preparing a stained smear, and examining it for parasites (WHO 2000). The advantage of microscopy is that it can achieve high sensitivity at low cost if done correctly under quality-controlled conditions with high diagnostic throughput. However, it is labour intensive, and the time lag between blood collection and patient consultation often prevents results from being taken into account in the diagnosis (WHO 2003b). Especially in rural areas that cannot support their own diagnostic laboratories or attract qualified technicians, there is a lack of capacity for microscopic diagnosis (WHO/TDR 2004; Bell 2004). Even in areas that can maintain laboratories, standards in most African health centres are sub-optimal. Sensitivity is notoriously low due to the lack of high quality equipment, the use of low quality stains and other reagents, and lack of supervision and trained staff (Mundy, Ngwira et al. 2000). For example, in East Africa re-evaluations of Giemsa-stained slides
revealed that standard reading had a sensitivity of 50%-75% and specificity of 59%-96% (Reyburn, Mbatia et al. 2004; Reyburn, Ruanda et al. 2006; Zurovac Midia et al. 2006). Specificity may be reduced due to residues remaining on improperly washed slides (Bell 2005).

Recently developed rapid diagnostic tests (RDTs) have been recognized by the WHO as a potential solution to improve parasitic diagnosis and expand its use (WHO/TDR 2004; Bell 2004). According to WHO standards, these tests should be at least as accurate as microscopy performed by a standard lab technician under normal field conditions (WHO 2000). To perform an RDT, health workers collect blood with microcapillary tubes, mix it with lysing solution and antibody markers, add the mixture to the indicator material, and wash the material with buffer to remove haemoglobin. If malaria antibodies are present in the blood, they will attach to the antibodies in the solution, which will affix to the indicator material indicating a positive result. Some RDTs detect parasite lactate dehydrogenase (pLDH), an enzyme produced by plasmodium asexual blood stages and gametocytes that may be specific to \textit{P. falciparum} or to other human malaria parasites, and can distinguish between species. Other RDTs detect histidine-rich protein-2 (HRP-2), a protein produced by asexual blood stages and immature gametocytes of \textit{P. falciparum}, and are species-specific. HRP-2 tests may also include pan-specific pLDH or aldolase, another plasmodium enzyme, to allow the test to detect other species of plasmodia that infect humans. The costs of \textit{P. falciparum}-only HRP-2 tests vary between $0.60 and $1.00 (WHO 2004a), with tests detecting pLDH being about 40% more expensive. As \textit{P. falciparum} is the predominant form of malaria in SSA, it is unnecessary to distinguish between species in many settings and HRP-2 tests
may suffice. However, the persistence of HRP-2 in patients for sometimes several weeks after parasitaemia has resolved may lead to false positive diagnoses (Moody 2002; Bell, Wilson et al. 2005), and this should be considered when introducing HRP-2 RDTs and developing algorithms for their use (WHO 2000).

RDTs have advantages over PT in their diagnostic precision and potential to help reduce drug costs due to overprescription. RDTs have advantages over microscopy for use in poorly-resourced areas, particularly when diagnostic throughput is low (Goodman 1999; Bell 2004). RDTs can be used at the periphery of health services where lab equipment, electricity, and personnel with minimal training may be absent (Srinvasan, Moody et al. 2000). They have lower capital and maintenance costs, and require less training than microscopy. Van der Meer from Medecins Sans Frontieres estimates that one half-day is needed to train a health worker to use an RDT properly whereas training of a microscopist may require several days (Van der Meer 2003). However, the unit cost of each microscopic diagnosis may be reduced as the patient throughput of a health facility increases (Goodman 1999), and the additional information on parasite biomass is sometimes useful in diagnosis (WHO 2006b). Further, supplies for microscopy do not need sophisticated transport mechanisms, while RDTs require cool-chain conditions to prevent them from spoiling during shipping (WHO 2004c).

Gaps in knowledge & Study Aims

WHO currently makes the tentative recommendation that parasite-based diagnosis should be used for all suspected cases of malaria, with the possible exception of children in high transmission areas and certain other specific situations (WHO 2005a, WHO 2006b), and
that diagnosis should be readily accessible in all areas (WHO 2005b). However, systematic evidence to inform diagnostic decisions is lacking. For febrile patients that present to health facilities in SSA, this study aims to:

1. Use cost-effectiveness analysis to estimate which of the three alternatives for malaria diagnosis (PT, RDT, field microscopy) should be used in differing malaria endemicities as ACTs are introduced.

2. Test how these findings change according to variations in key parameters where information is lacking or is subject to change; for example, according to various valuations of a healthy year of life ($\lambda$), and various acceptable levels of risk.
METHODS

Modelling approach

This study uses a modelling approach which draws on a standardized methodology to compare alternate intervention strategies, and determine key issues and gaps in knowledge when characteristics of the decision have not been observed directly (Drummond 1987; McKenzie and Samba 2004; Briggs, Sculpher et al. 2006). Through this approach, evidence from published sources and expert opinion has been synthesized to predict costs and outcomes according to malaria prevalence. Concerns have been raised about the degree of analyst discretion that the modelling approach sometimes requires in economic evaluation (Buxton 1997). However, modelling also provides advantages over empirical studies, which often are limited to measuring sensitivity and specificity of the diagnostic test, require large sample sizes, and are unable to predict health outcomes for untreated patients for ethical reasons. Models do not have these restrictions, and can test the decision all the way through to health outcomes and costs to the health system as a whole – including the costs of further treatment due to misdiagnosis. It is possible to define parameters according to operational rather than trial conditions using models, and where gaps in data exist, parameter estimates can be varied in sensitivity analyses. Our theoretical results therefore provide an initial framework for informing estimates of the cost-effectiveness of alternative strategies for malaria diagnosis, and highlight important areas for further empirical work.

Model structure and data sources

A decision tree representing ambulatory outpatients presenting to health centres with
fever was developed to compare three strategies for distinguishing malaria from other febrile illnesses in rural areas of Africa with predominant *P. falciparum* transmission.

1. Rapid Diagnostic Tests (RDTs)
2. Presumptive Treatment with Antimalarial Medicines (PT)
3. Field-Standard Microscopy

The decision tree in Figure 1 follows an individual patient from diagnosis and treatment to disease outcomes according to the sensitivity and specificity of each strategy and level of malaria prevalence. The incremental costs and health outcomes of each comparison are calculated according to this structure, according to all possible levels of prevalence of parasitaemia among febrile outpatients presenting at facilities. Instead of describing all possible parameters affecting the choice of diagnostic strategy, the model aimed to capture the influence of key variables on cost-effectiveness, and the relationships between them.

Parameter estimates were abstracted from a variety of sources representing several low-income countries in SSA, or based on expert opinion where empirical estimates were unavailable. Parameter estimates for initial diagnosis and treatment were extracted from recently published data. Parameters describing treatment seeking patterns, costs for programme implementation and secondary treatment, and estimates for the duration of disease, were based mainly on those used in previous models (Goodman, Coleman et al. 2000) (Coleman, Morel et al. 2004). Probabilities describing disease progression and mortality without appropriate treatment are very difficult to test in
medical research, and were defined in consultation with Prof. Christopher Whitty, Dr. Hugh Reyburn, Dr. Jay Berkley, and Prof. Brian Greenwood. All parameter values and their sources are presented in Tables 1-3. In most cases, probability distributions were used to represent parameter uncertainty around best estimates; this methodology is described below in the section entitled ‘Calculation of results under uncertainty’.

**Description of interventions and comparators**

This analysis made cost-effectiveness comparisons between three different diagnostic strategies followed by treatment corresponding with diagnostic outcomes. Recognizing that health providers frequently prescribe antimalarial drugs even when tests are negative (Barat, Chipipa et al. 1999; Reyburn, Mbatia et al. 2004; Reyburn, Ruanda et al. 2006), simplifying assumptions were made that health care workers followed the indications given by the diagnostic tests, and that patients diagnosed positive for malaria received artemisinin-based combination therapy (ACT). Based on guidance from WHO/TDR, it was assumed that all patients with a negative diagnosis received an antibiotic such as amoxicillin. However, as prescribing practices for NMFI diagnoses are likely to vary widely across Africa, the proportion receiving antibiotics was varied in one of the sensitivity analyses (Figure 11).

It was assumed that PT had no diagnostic cost, perfect sensitivity, and zero specificity (C1, P6, P9). A scenario of RDT diagnosis was based on tests detecting HRP-2 in patient blood samples, as 90% of malaria in SSA is *P. falciparum*. In this analysis, the best (most likely) estimate for RDT sensitivity was assumed to be 96% (P5), and the best estimate for specificity to be 95% (P8). While some datasets have shown lower
sensitivities and specificities for HRP-2 RDTs, recent evidence has shown inaccuracies in ‘gold-standard’ microscopy used as the relative value to define RDT specificity, suggesting higher estimates than previous studies suggest (Bell, Wilson et al. 2005).

A scenario of microscopic diagnosis was based on standard practice used in general laboratories of district hospitals and rural health centres in SSA. Both sensitivity and specificity are likely to be lower than those of RDTs in these conditions (Barat, Chipipa et al. 1999; Reyburn, Mbatia et al. 2004). Microscopists in non-specialized laboratories can only be expected to detect parasite densities over 100 parasites per microlitre of blood, and sensitivity is further reduced when slide staining is delayed (Bell 2002). In addition, false parasite sequestration, defective microscopes, and low quality laboratory consumables may lower sensitivity (Mundy, Ngwira et al. 2000). Specificity may be reduced if slides are not washed properly before reusing them, which happens frequently (Bell 2005). Best estimates for field microscopy sensitivity and specificity were assumed to be 82% and 85% respectively (P7, P10). These values are in keeping with published evidence of microscopy in the type of situations where parasite-based diagnosis is likely to be under consideration to replace presumptive diagnosis (Barat, Chipipa et al. 1999; Reyburn, Mbatia et al. 2004; Reyburn, Ruanda et al. 2006).

**General model assumptions**

Assumptions about characteristics of NMFI and treatment seeking behaviour, are outlined in Table 1. Between 50% and 70% of patients were assumed to be aged five years or older, with an average age of 27 years (P2). The average age of patients under five was assumed to be 2 years. The proportion of fever caused by malaria was assumed
to be equal for both adults and children at each point along the x-axis of model output figures. No co-infection between malaria and bacterial infections was assumed.

HIV can be expected to affect results by exacerbating the likelihood and severity of bacterial infection, particularly in adults where HIV prevalence is high (Gordon, Hastings et al. 2002; Gordon, Chaponda et al. 2002; Berkley, Lowe et al. 2005). HIV prevalence varies considerably across the continent; however, the majority of African adults and children in malaria-endemic areas live in areas of moderate to low HIV prevalence. To avoid a very complex decision tree structure, it was assumed that HIV prevalence was relatively low (approximately 10% of over 5s), which is typical outside southern Africa, and therefore had a limited effect on disease progression.7

**Description of probabilities**

The probability of individual patient outcomes occurring was calculated according to the structure of the decision trees outlined in Figures 1a through 1d. From a modelling perspective, the most important differences between diagnostic strategies lie in the initial costs of the tests and their accuracy. After being given a diagnosis, patients are assumed to face the same probabilities, health outcomes, and costs subsequent to first-line treatment regardless of the diagnostic alternative used (Tables 1, 2&3). For every patient diagnosed and treated for febrile illness, there was a probability of cure or treatment failure. Treatment may not have been effective if the patient did not adhere to the full drug regimen, received an inappropriate drug, did not receive treatment, or if the appropriately-taken drug was not efficacious. Values for the efficacy of ACT and amoxicillin were based on 28 day failure rates, with higher values used for ACT
(P13,P16) (IASG 2004). It was assumed that antibiotics were not efficacious for malaria or viral illness, and that antimalarials did not cure NMFI (P13-P18).

Consequences of treatment failure were assumed to be a function of age and type of febrile infection, and to lead either to severe or uncomplicated disease. A disease was defined as ‘severe’ if it warranted inpatient admission. Patients may then have sought no formal care, outpatient care for uncomplicated illness, or inpatient care for severe disease (P19-22). Outpatient care was provided by either a hospital or health centre, resulting in different facility costs. Patients that developed severe disease may have died, fully recovered, or survived with neurological sequelae (P23-P36). It was assumed that all patients with uncomplicated disease recovered fully from their fever. If a patient required secondary treatment from an inpatient or outpatient facility, he was assumed to adhere fully to the treatment schedule.

**Costing methods and assumptions**

Costs were calculated using the ingredients approach through building up total estimates based on the quantity and value of each resource used (Tables 1-3) (Phillips, Mills et al. 1993). These figures were converted to US dollars using market exchange rates, and then inflated to 2002 using US inflation figures. Calculations included health facility costs for both providers and patients. The costs of initial patient consultation through each diagnostic strategy included the cost of the diagnostic test (including materials, staff time, training and quality control) and first-line drug costs. All other costs of first-line treatment were excluded as they were assumed to be the same for each diagnostic strategy considered. Next, variable costs to providers and patients of any
second-line treatment required were included (e.g. drugs, reagents, food). Fixed costs of second-line treatment (e.g. buildings, equipment, supervision and most staff costs) were not considered as they would be equal for each diagnostic strategy (Goodman, Coleman et al. 2000).

The costs of RDTs were based on HRP-2 antigen detection, such as Paracheck® or ICT® diagnostic tests, which cost between $0.60 to $1.00 (C2) (WHO 2004a). The cost of field-standard microscopy depends on the frequency of diagnoses per facility. This analysis considers facilities that make from 1,200 to above 6,800 diagnoses per year, implying a range of costs between $1.27 and $0.32, with a best estimate of 2,000 diagnoses per year (C3) (Figure 2) (Goodman 1999; Goodman, Coleman et al. 2000). This costing assumes that the microscope is used for malaria diagnosis only; however, costs may reduce if the microscope is also used for diagnosis of other diseases.

Costs of an adult dose of ACTs were chosen from the current wholesale price for artemether-lumefantrine (Coartem®) ($2.40), and the price predicted by the Institute of Medicine for market conditions when several ACTs become readily available ($1.00) (C4) (Arrow, Panosian et al. 2004). Costs for an antibiotic regimen were based on the supplier costs for amoxicillin published on the International Drug Price Indicator Guide website for 2005, with a median estimate of $0.71 per adult dose (C5) (MSH 2005). Amoxicillin is a commonly-used antibiotic in SSA; for example, being available at 88% of centres surveyed in Ghana (Bosu and Mabey 1998). For both ACTs and antibiotics, child dosage was taken to cost half the adult dosage (C10) (BNF 2005).

Second-line drug treatment costs for severe malaria consisted of oral and intravenous quinine (C6-C8), with 10 mg/kg of oral quinine prescribed every 8 hours for
7 days. During the same period, 20 mg/kg of intravenous quinine would be prescribed initially, followed by 10 mg/kg every 8 hours (Goodman, Coleman et al. 2000). It was assumed that unresolved uncomplicated malaria was treated by a second-line drug of the same price and efficacy as the first-line antimalarial. Secondary treatment for severe bacterial infection was assumed to be an alternative antibiotic costing twice as much as the one used for an uncomplicated bacterial infection (C9). Costs associated with the management of neurological sequelae were excluded.

**Health outcomes**

Health outcomes encompassed days of sickness, deaths, and years lived with neurological sequelae. These outcomes were measured in terms of Disability-Adjusted Life Years (DALYs) averted, calculated according to standard methods outlined in the Global Burden of Disease (GBD) calculations associated with the recent Disease Control Priorities Project (DCP2), using a discount rate of 3% without age weighting (Fox-Rushby and Hanson 2001; Fox-Rushby 2002; Lopez and Mathers 2006).

For uncomplicated clinical malaria episodes and untreated neurological sequelae, disability weights were based on those estimated by GBD study experts (E3-E6). The causes of NMFI will vary from region to region, and were assumed to be the same as those for malaria for simplicity. In addition, it was assumed that the durations of NMFI and malarial illnesses were equivalent, stratified by severity and appropriateness of case management. Adverse drug reactions were not included in health outcomes. The assumptions made about duration and disability weights for morbidity are outlined in Table 3, and only have a marginal impact on cost-effectiveness results as the vast
majority of the malaria disease burden is made up of mortality. In their calculations of the burden of disease, Murray and Lopez (1996) found that morbidity from episodes and anaemia makes up only 1.5% of the DALYs due to malaria in SSA.\textsuperscript{11}

The relative probability between diseases that patients become severe was a crucial factor affecting results. Values that would produce relatively restrictive estimates of the health benefits of RDTs, but were still within a reasonable range, were selected for the reference case. Because DALY weights and lengths of illness estimates were the same for malaria and bacterial illness, estimates of the relative burden of these diseases were dependant upon model probabilities. Based on consultations with experts, bacterial illness was assumed to be more likely to become severe compared to malaria (P23-P26). However, only 5% to 15% of NMFIs were assumed to have bacterial aetiology, with the rest being self-limiting viral infections. DALYs incurred by each malarial and bacterial case were equal (E1-E19); and viral infections only incurred DALYs associated with uncomplicated illness, which are negligible. Measles was excluded from the 90% of fevers caused by viruses, assuming that its characteristic rash would prevent misdiagnosis as malaria. Therefore, in reference case calculations, the expected severity of NMFI overall was found to be lower than the severity of malaria.

**Calculation of results under uncertainty**

Four types of uncertainty exist in economic models: parameter uncertainty, uncertainty over generalizability of results to different populations or contexts, uncertainty over whether parameter values can be extrapolated into the future, and uncertainty in analytic methods (Briggs, Sculpher et al. 1994). Probabilistic sensitivity
analysis provides a robust method for quantifying the uncertainty resulting from the first three of these categories (Doubliet, Begg et al. 1985; Critchfield and Willard 1986; Critchfield, Willard et al. 1986; Briggs 2000; Briggs, Sculpher et al. 2006). Parameter uncertainty may be defined as variability in sample data if the parameter was evaluated in a trial, or may result from compiling estimates from different studies or experts in a modelling approach. Through our modelling approach, which defines ranges for parameters based on evidence consolidated from a wide variety of settings across SSA, results have been made as generalizable as possible across settings in this region (Tables 1-3). We have also addressed uncertainty in analytic methods to some degree, as discussed in the section ‘Generation of curves and surface plots’.

**Parameter distributions**

For most model parameters, triangular distributions were fitted to low, high, and best (most likely) estimates. However, triangular distributions do not sufficiently account for the probability density around best estimates, and suggest that values near the tails of distributions are more probable than they actually are. Therefore, the triangular distributions served as templates to fit parametric distributions that more accurately distribute probability density around the specified ranges. Parameters representing probabilities within the decision tree were represented by beta distributions bounded by zero and one, which redistribute probability away from the tails of the distribution towards the best estimate. For parameters representing costs, the small chance that complicated patients or adverse economic conditions would lead to dramatically high costs was modelled using lognormal distributions. No best estimate could be
determined for several parameters, such as projected prices, and a uniform distribution was used to represent this uncertainty. Where no uncertainty existed around a parameter estimate, uncertainty was impossible to quantify, or methods were required to be consistent with GBD protocols, point estimates were used.

**Calculation of cost-effectiveness and net benefit**

Monte-Carlo simulations (MCS) were performed to generate probabilistic results using the Palisade® @Risk add-in tool to Microsoft Excel®. In MCS, values for each parameter in the model (probability, cost, and benefit parameters listed in Tables 1-3) are drawn at random from their distribution of uncertainty, which are then used in the formulae that define the decision tree. These formulae calculate the costs and health outcomes associated with each strategy from weighted averages in a process known as ‘rolling back’ the tree. This simulation was iterated 10,000 times to generate results for costs and benefits in order to ‘bootstrap’ the mean values and confidence intervals around them. No correlations were assumed between input parameters unless they were explicitly linked in the model (Tables 1-3).

Cost and health outcome results were generated stochastically through MCS to form Incremental Cost-Effectiveness Ratios (ICERs). Outcomes for each of the three strategies for diagnosing malaria were combined according to the three possible comparisons, and ICERs were calculated using the following equation.

$$\text{ICER} = \frac{C_{\text{Int}} - C_{\text{Comp}}}{E_{\text{Comp}} - E_{\text{Int}}}.$$  

$C = \text{Cost}$; $E = \text{Effect (DALYs incurred)}$, $\text{Int} = \text{Intervention}$, $\text{Comp} = \text{Comparator}$
The difference in the costs of each strategy is the incremental cost, and the difference in DALYs incurred for each strategy is the incremental DALYS averted. When the value of the ICER is less than the ceiling ratio ($\lambda$), which is the decision maker’s valuation of each healthy year of life, the intervention is cost-effective relative to the comparator. Very attractive interventions, which are less costly than the comparator and have better health outcomes (fewer DALYs incurred), are termed “dominant”. Interventions that are more costly and less effective than the comparator (more DALYs incurred) are termed “dominated”.

ICERs can be plotted on a cost-effectiveness plane (See Annexes 1-3), which is a useful method to represent net gains or losses according to both costs and DALYs averted for a particular comparison of interventions (Briggs and Fenn 1998). However, difficulties associated with calculating ratios through stochastic sampling (due to the possibility of generating zero values in the denominator) and discontinuity around the zero of both the x- and y-axes can make results difficult to interpret in some instances (Claxton and Posnett 1996; Briggs 2001). In these cases, it is impossible to measure the best estimate for the cost-effectiveness result, or the confidence intervals around it. The net-benefit statistic provides a solution to these problems by incorporating $\lambda$ to convert the ICER to a linear function that uses a single metric (Sinnett and Mullahy 1998; Briggs 2001). Incremental net benefit (INB) is given as:

$$INB = R_c(E) - C$$
Given the results generated, the net-benefit approach was particularly relevant in this cost-effectiveness analysis of malaria diagnostics. Annex 1 shows that stochastic results span the axes of the cost-effectiveness plane, and are thus subject to discontinuities when measured in two dimensions. Figure 6 (a,c,e) provided later in the results section shows these results after their linear transformation, and clearly indicates where the intervention is cost-effective according to the best estimate for results, and their 90% (two-tailed) and 95% (one-tailed) confidence intervals.

Valuation of health improvements

$150/DALY averted was assumed as the standard estimate for $\lambda$ in the reference case condition, as suggested by the Ad Hoc Committee on Health Research Priorities (WHO 1996). However, $\lambda$ may vary according to the decision-making body that is prioritizing interventions, with several existing methodological approaches to its definition. For example, a multiple of per capita Gross National Income is being used by several current large-scale prioritization initiatives, such as the Commission for Macroeconomics and Health, WHO Choosing Interventions that are Cost-Effective, and some sections of the 2006 Disease Control Priorities Project (CMH 2001; WHO-CHOICE 2006; Jamison, Breman et al. 2006). Further uncertainty stems from influences on policy approval other than cost-effectiveness, such as local epidemiology, synergy with other interventions, burden of disease, and available budget (Musgrove 2000). Even within a single decision-making body, fixed $\lambda$ thresholds may not apply to every intervention considered due to these influences (Cowley, Bobadilla et al. 1995; Devlin and Parkin 2004; Shillcutt, Parkin et al. 2005). To account for uncertainty in $\lambda$, the
probabilities that interventions were cost-effective were plotted across two axes allowing both malaria prevalence and $\lambda$ to vary (Figure 5).

**Generation of curves and surface plots**

In testing if cost-effectiveness results are robust, it is important to consider gaps in the evidence base on parameters and parameter values that are subject to change under different scenarios. This uncertainty was represented using curves and surface plots showing the probabilities that strategies are cost-effective according to a number of conditions. All results, including the reference case, were generated at eleven levels of malaria prevalence in the model population ranging from 0% to 100% to account for all possible epidemiological conditions in SSA.

Nine further sensitivity analyses were performed for model parameters of specific interest to the diagnostic comparisons evaluated (Table 4). These sensitivity analyses were performed using a series of MCSs to generate probabilistic results, while varying one parameter of interest and malaria prevalence as in a two-way sensitivity analysis (Critchfield and Willard 1986; Drummond 1987). Parameters of specific interest included three initial costs and six sets of probability parameters. These parameters were chosen because they were likely to be important to decision makers, because we had prior belief that they would impact results strongly, or because they represented obvious gaps in the evidence base. Initial costs included the cost of diagnosis and the cost of first-line treatment, and were tested across a range from $0-$4, extending beyond all documented costs for these parameters. Adherence to ACT was tested as it affects the probability that malaria cases become severe. Population structure (the proportion of patients five years
or older), was expected to affect the outcomes of both patients with malaria and patients with NMFI. The remaining probability parameters in Table 4 all affect the overall severity of NMFI, which is particularly uncertain due to the limited evidence available and heterogeneity across settings. One of these parameters reflects the assumed protocol adopted for NMFI management – that 100% of patients with a negative malaria diagnosis receive an antibiotic. This percentage was tested between 100%-0%, assuming that where only a proportion of NMFI diagnoses were prescribed antibiotics, this proportion was randomly selected reflecting the lack of data on the accuracy of clinical diagnosis in distinguishing bacterial from viral NMFI.

Because many of the parameters in this model are based on expert opinion rather than empirical studies, more attention should be paid to trends in threshold cost-effectiveness values rather than to point estimates. Net-benefit curves, cost-effectiveness probability curves, and cost-effectiveness probability planes are presented in Figures 4-15. Annexes 1-3 provide an interpretation of reference case results according to cost-effectiveness planes, and Annexes 4-13 show component costs and DALYs incurred under each individual diagnostic strategy according to sensitivity analyses.
RESULTS

All possible combinations of three diagnostic strategies for malaria diagnosis in rural areas of SSA were compared, including PT, RDT, and field-standard microscopy diagnosis. The policy change from PT to RDT diagnosis is the first comparison discussed in each section.

Costs and health outcomes of each diagnostic strategy

The incremental DALYs per patient incurred with each diagnostic strategy relative to PT are shown in Figure 3a – DALYs incurred by PT are standardized to the x-axis. Fewer DALYs are incurred with RDT diagnosis compared to microscopy as RDTs have both better sensitivity and specificity (P5-P10). Both diagnostic strategies have better sensitivities compared to their specificities; however, despite this fact, more DALYs are incurred at high malaria prevalence. This result highlights the fact that malaria not treated appropriately is more severe relative to inappropriately treated NMFI based on the model assumptions – emphasizing the importance of disease severity parameterization in calculating DALYs incurred.

The incremental cost per patient according to diagnostic strategy relative to PT is shown in Figure 3b. The incremental cost of PT is again standardized to the x-axis, but in reality increases with malaria prevalence. This trend exists because malaria that leads to treatment failure has higher secondary drug costs than NMFI that is inappropriately treated (C5-C9). Overall costs increase even more sharply for RDTs and microscopy compared to PT. At low levels of malaria prevalence there is massive over-diagnosis of malaria with PT, and using parasitic diagnosis results in large cost savings through
avoided ACT prescriptions. At high malaria prevalence PT is cost-saving because the costs of diagnosis are avoided, and few antimalarials are wasted. The initial unit cost of RDTs is higher than the initial cost of microscopy (C2-C3), reflecting assumptions on the throughput of microscopy tests per year, and explaining why RDTs are more costly across all prevalence levels.

**Incremental cost-effectiveness**

The incremental cost-effectiveness of comparisons between each of the three diagnostic strategies is given in Figure 4. The curves in this figure can be interpreted from a Bayesian perspective as the probability that strategies are cost-effective, dominant, or dominated by their comparator (Briggs 2001). These probabilities can be interpreted as the level of risk associated with choosing one intervention over another. The level of risk that decision makers are willing to take will depend on their prior opinions, political factors, and the cost of collecting further information. Results are presented in terms of 50% risk and 95% risk as reference points, acknowledging that these thresholds tend to the extremes of risk acceptability and aversion.

Figure 4a shows that RDTs are cost-effective compared with PT with 50% certainty when less than 81% of febrile patients have malaria parasites. This result is also shown in Figure 4b where the curve showing the probability RDTs are cost-effective crosses 50% on the y-axis. If a decision maker wishes to be 95% certain that RDTs are cost-effective, the cost-effectiveness threshold drops to below 62% prevalence. It is 95% certain that RDTs are not cost-effective above 90%. RDTs are likely to be dominant with
50% certainty below 58% malaria prevalence, and dominated above 87% malaria prevalence (Figure 4b).

Microscopy is likely to be cost-effective relative to PT with 50% certainty when less than 67% of febrile patients have malaria parasites (Figure 4 c&d). This threshold drops to below 41% malaria prevalence when 95% certainty is required. Microscopy is not cost-effective with 95% certainty above 83% malaria prevalence, is dominant relative to PT below 62% prevalence, and is dominated above 85%.

RDTs are more than 85% likely to be cost-effective relative to microscopy across all levels of prevalence, and are more than 15% likely to be dominant (Figure 4 e & f). As above, this result assumes a high throughput of fever diagnosis.

**Sensitivity analysis on the ceiling ratio**

The probability that each strategy is cost-effective relative to each alternative strategy was tested according to variations in a decision maker’s valuation of a healthy year of life (\(\lambda\)) (Figure 5). In an approach similar to cost-effectiveness acceptability curves (Briggs 2001), variations in \(\lambda\) were plotted along one axis, while changes in malaria prevalence were plotted along a second axis, with the probability that the intervention is cost-effective represented by plane contours. Areas of the plane were shaded according to the probability that interventions were cost-effective using a value of \(\lambda\) equal to $150/DALY averted. Black areas represent conditions of over 99% certainty, dark grey areas represent conditions of over 95% certainty, and light grey areas represent areas where neither alternative is cost-effective with 95% certainty. Conditions of indifference are represented with a black line through the middle of the light grey area.
Further explanation of these results is explored in Annexes 1-3 with standard cost-effectiveness planes.

The cost-effectiveness of RDT and microscopy diagnosis relative to PT is affected by $\lambda$ across malaria prevalence (Figures 5 a & b). Where malaria is the cause of illness in a small fraction of febrile patients, it is more than 50% certain that RDTs are cost-effective at any value of $\lambda$, more than 95% certain above $50$/DALY averted, and more than 99% certain above $150$/DALY (Figure 5a). By contrast, at high malaria prevalence such as 65%, confidence that RDTs are cost-effective does not rise above 95% at any level of $\lambda$. This reflects the increased probability that PT will be dominant at high prevalence, leading to the vertical contours of the surface plots in Figures 5 a & b.

In the decision to change diagnostic strategy from PT to microscopy, 71-72% malaria prevalence is an important threshold as microscopy becomes less effective and more expensive above this level. At high malaria prevalence, microscopy is more costly due to its combined expenditure on diagnosis and first-line drugs, and also less effective due to its lower sensitivity. However, a small probability exists that microscopy will remain less expensive than PT (Annex 2). This condition makes microscopy an inferior good compared to PT and reverses the diagonal trend of contours at low levels of $\lambda$.

The comparison between RDTs and microscopy in Figure 5c should be highlighted. If a decision maker values healthy life years at above $50$/DALY averted, it is more than 50% likely that RDTs are more cost-effective than microscopy at all levels of malaria prevalence.
**Sensitivity analysis on model parameters**

The robustness of cost-effectiveness results was tested according to the nine sets of parameters outlined in Table 4. These parameters were categorized into three groups – parameters to which the model was sensitive, parameters with a moderate impact on cost-effectiveness, and parameters to which the model was robust.\(^\text{19}\)

Overall, the cost-effectiveness of RDTs compared with PT was most sensitive to cost of the initial diagnostic test, cost of an adult dose of ACT, and parameters that impact disease outcomes for NMFI (Figures 6, 8, 10 & 13). This comparison was moderately sensitive to the probability that a patient adheres to ACT (Figure 9), the probability that a patient diagnosed negative for malaria receives an antibiotic (Figure 11), and the severity of bacterial illness (Figure 12). In Figure 9, even when 100% of patients adhere to ACT, the imperfect efficacy of ACT (P13) prevents PT from becoming strongly cost-effective unless malaria prevalence is very high. In Figure 11, RDTs remain cost-effective below 50% prevalence even when no patients testing negative for malaria receive an antibiotic – RDTs are slightly less effective but much cheaper under these conditions (Annex 9).\(^\text{20}\)

Cost-effectiveness of RDTs versus PT is robust to the proportion of patients aged five years or older (population structure) (Figure 14). It should be noted that malaria prevalence was assumed to be constant across age groups in this analysis, which has reduced the impact of this parameter. In addition, the exclusion of second-line treatment costs from the model had no effect on reference case cost-effectiveness results (Figure 15). These parameters affect each diagnostic strategy relatively equally, and have little impact on incremental calculations.
The pattern of sensitivity analysis results was very similar for the cost-effectiveness of microscopy versus PT, with the exceptions that adherence to ACT was more important at high prevalence, the proportion of the population aged five years or older had a slightly larger impact, and thresholds generally shifted towards lower malaria prevalence (Figures 6-14b).

According to a 50% level of certainty, the cost-effectiveness of RDTs versus microscopy was highly sensitive to the cost of RDT (Figure 6c). The decision was also sensitive to adherence to ACT at high levels of prevalence (Figure 9c). It was slightly sensitive to adherence to antibiotics, the probability NMFI receives an antibiotic, and the probability NMFI is bacterial at low levels of prevalence (Figures 10c, 11c, 13c). If a 95% level of certainty is necessary, this decision becomes more complex.

Results from these sensitivity analyses are provided in greater detail in Annexes 4-13, and customized results specific to local settings can be generated online through an interactive version of this model (www.wpro.who.int/sites/rdt).
DISCUSSION

Overview of results

This study demonstrates that if both antimalarial and antibiotic treatments are taken into account, parasite-based diagnosis is cost-effective compared to PT up to high levels of *P. falciparum* malaria prevalence among febrile outpatients presenting to rural health facilities. Decision makers can be at least 50% confident that RDTs are cost-effective compared to PT below 81% malaria prevalence, and 95% confident below 62% prevalence. In practice the proportion of febrile patients who present with malaria seldom exceeds 60%, with most proportions being lower (Brinkmann and Brinkmann 1991), so this analysis suggests that RDTs are cost-effective for most malaria-affected areas in SSA. Our findings support WHO recommendations that parasite-based diagnosis should be widely practised except in some specific situations (WHO 2006b)

The better health outcomes with parasite-based diagnosis relative to PT do not reflect improved treatment of true malaria cases, as their sensitivities are lower than that of PT. In fact, the only impact of diagnostic tools on malaria cases is to increase slightly the proportion of patients falsely diagnosed malaria negative, which increases costs and DALYs incurred – especially at high prevalence. Rather, the health benefits from diagnosis derive from improved treatment of bacterial NMFIIs, which are assumed to be inappropriately treated with ACT under PT as it is currently practiced. The health benefits to better treatment of bacterial illness should be substantial, with pneumonia alone contributing over 20% to total under-5 mortality in SSA (WHO 2002a; Black, Morris et al. 2003). From a cost perspective, many unnecessary and expensive ACT treatments could be avoided using RDTs, and a substantial number of patients with NMFI
would receive appropriate treatment and be less likely to incur second-line treatment costs. At a combined cost of $1.41 for an RDT and antibiotic for an adult, the initial costs of negative diagnoses are less than the average cost of ACT ($1.70). Similar arguments apply to the comparison of microscopy to PT.

When comparing the two diagnostic tools, RDTs and field-standard microscopy, this analysis suggests very strongly that RDTs are the preferable diagnostic tool. RDT costs are always higher than microscopy at case volumes assumed, but the better accuracy of RDTs means that fewer DALYs are incurred for both malaria and NMFI patients (Figure 3a). Given current levels of RDT and microscopy costs and accuracies, RDTs are always likely to be cost-effective, even with zero-cost microscopy or RDTs costing up to $2 apiece (Figures 6c, 7c). In large facilities, microscopy may offer benefits ignored here of providing parasite counts and diagnosing other diseases.\(^{22}\) The costs of improving standards in microscopy to levels similar to RDTs in Africa are currently unknown, but would probably be significant.

If policy makers are comfortable with 50% certainty, RDTs in rural facilities are robustly cost-effective compared with PT and microscopy under most common prevalence scenarios except malaria prevalence among febrile patients is relatively high, the cost of RDTs is high, adherence to antibiotics is low, patients are unlikely to receive an antibiotic, a very low proportion of NMFI are bacterial, or the valuation of health gain is very low. If 95% certainty is required, the results are more sensitive to malaria prevalence, valuation of health gain, cost of diagnostic tool, cost of ACT, adherence to first-line therapy, proportion of NMFI receiving antibiotics, severity of NMFI, proportion of NMFI that are bacterial, and the proportion of patients aged five years or older.
Similar sensitivity analyses could be used to evaluate the cost-effectiveness of targeting improved diagnosis to certain groups, depending on season, geographic location, and age group. For example, in countries such as Mali, RDTs are likely to be cost-effective with increasing certainty as one moves from the rainforests in the south with high malaria prevalence northward toward the Sahara desert (EANMAT 2006).

**Example of a full interpretation of results of RDT versus PT at 40% malaria prevalence**

A review of 426 studies revealed that, on average, malaria is responsible for causing 40% of illnesses in febrile patients reporting to health clinics in SSA (Brinkmann and Brinkmann 1991). In this section, 40% malaria prevalence is used to illustrate how the model results might be interpreted in a given setting to decide whether to replace PT by RDT. This comparison has been selected as the most widely policy-relevant decision affecting SSA at present.

Reference case results indicate that the decision to introduce RDTs can be made regardless of $\lambda$ if a level of 50% risk is considered acceptable (Figure 5a). If policy makers require a level of 95% certainty in their decisions, they should value each life year at least at $75/DALY averted before introducing RDTs (Figure 5a). This threshold falls well within published values for $\lambda$ – $150/DALY advocated as ‘attractive’ by the WHO in 1996 (WHO 1996) and some multiple of Gross National Income advocated by other recent initiatives (CMH 2001; WHO-CHOICE 2006; Jamison, Breman et al. 2006).

The cost of RDT tests has a limited impact on the policy decision. If an RDT costs below $4, it is preferable to PT with 50% certainty, and is cost-effective with 95%
certainty below $2.30 per test (Figure 6a). These figures are well above our reference case cost assumption of $0.80 (C2), and the WHO reports that at least eight HRP-2 tests costing less than $1.70 are currently available (WHO 2004a).

Likewise, the cost of an adult dose of ACT has little effect on the decision to introduce RDTs over PT. RDTs are cost-effective with a high degree of certainty at any ACT cost above $0.20 (Figure 8a), well below current costs reported for ACTs ($1-$2.40) (Arrow, Panosian et al. 2004).\textsuperscript{23}

Antibiotic adherence is a stronger driver of cost-effectiveness results than ACT adherence. The decision to replace PT with RDTs can be made independently of how well patients adhere to ACT regimens,\textsuperscript{24} but becomes less than 95\% certain if less than 40\% of patients adhere to antibiotics (Figure 9a,10a). There is a scarcity of research on levels of antibiotic adherence; however, the determinants of community antibiotic use have been reviewed by Radyowijati and Haak (2003).\textsuperscript{25}

The probability that a patient diagnosed with NMFI receives an antibiotic must be below 23\% to reverse the decision to introduce RDTs at 95\% certainty (Figure 11a). The slight benefit of using RDTs when no patients with NMFI diagnoses receive antibiotics stems from savings derived from rationing expensive ACTs, which illustrates the importance of this factor.

The probability that bacterial illness becomes severe has very little effect on the decision to replace PT with RDTs based on the range of parameters chosen (Figure 12a). Only if the decision maker is not willing to take a 5\% risk are RDTs not cost-effective below moderately high prevalence (Figure 12). Given that these probabilities were parameterized according to the widest ranges deemed realistic, this result is robust.
The probability that NMFI is bacterial has a very strong impact on the cost-effectiveness of RDTs up to very high levels of malaria prevalence. If the percentage of NMFIIs that are bacterial is less than 20%, it is less than 95% certain that RDTs should replace PT (Figure 13a). More research is needed to estimate parameters associated with the characteristics of NMFI cases presenting to clinics in SSA.

The proportion of patients aged five years or older does not affect the decision to replace PT with RDTs (Figure 14a). However, this result is due in part to the assumption that a constant proportion of febrile cases are caused by malaria across age groups. This assumption is unlikely to hold in endemic areas where fevers in children are more likely to be malarial than fevers in adults.

Cost savings from reduced second-line treatment have little influence on cost-effectiveness in the reference case. Although second-line costs for malaria are higher than those for NMFI (C6-C8 compared to C9), and differences in diagnostic accuracy give secondary costs disproportionate effects between strategies, cost-effectiveness results from this sensitivity analysis remain either dominant or dominated – the same as under reference case conditions (Annex 13). Only if a very high proportion of NMFI is not self limiting (bacterial), are incremental costs affected by changes in secondary costs (Annex 11).

**Comparison to previous studies**

The general argument for the cost-effectiveness of improved malaria diagnosis in low- and middle-income countries is supported by other studies in the literature. A cost-minimization analysis in Brazil evaluated RDTs in the context of a community-based
malaria management programme. In this strategy, bar owners were trained to perform ParaSight® RDTs and provide antimalarials to symptomatic individuals testing positive (Pang 2001). The RDT programme reduced hospital admissions by 53% while doubling the number of patients seen for malaria, resulting in a cost-saving of $60,900 compared to the old programme. A cost-effectiveness analysis comparing two RDTs to microscopy at the Thai-Burmese border found both pLDH and HRP-2 RDTs to be cost-effective (Bualombai, Prajakwong et al. 2003).

To evaluate microscopy against clinical diagnosis, Jonkman et al. conducted a cost-minimization analysis in an urban hospital in Malawi where SP was the first-line malaria treatment (Jonkman, Chibwe et al. 1995). Microscopic diagnosis reduced the number of overall malaria diagnoses by identifying patients with NMFI, and reduced the amount of SP prescribed from 39.9% of total febrile patients to 6.6%. This change resulted in a cost saving of $13,490 per year when drug costs were subtracted from the cost of microscopy. However, this estimate may overstate the cost savings from microscopy as the cost of the microscope, training, supervision, and overheads were not included, and a relatively low value for salary time was used for the cost per slide.

Only one evaluation has examined the cost of malaria diagnosis from a SSA-wide perspective (Goodman 1999). This analysis included the costs of diagnosis and first-line drugs only, and did not consider health outcomes. RDTs and microscopy were compared in low and high transmission settings. Both diagnostic tests were assumed to have a sensitivity of 90% and a specificity of 95%, giving positive predictive values (PPVs) of 15% in low transmission areas, and 50% in high transmission areas. Relative to PT, RDTs were found to be cost-saving when antimalarials cost $2.33 or above in high-
transmission settings, and $1.50 or above in low-transmission settings. Microscopy was cost-saving compared to PT in high-transmission settings if antimalarials cost above $0.76 per treatment, and was cost-saving in low-transmission settings if antimalarials cost above $0.64 per treatment.$^{26}$

Most recently, evidence from Senegal showed that prescribing artesunate-amodiaquine according to microscopy results was 53% cheaper than clinical diagnosis and treatment with chloroquine or intramuscular quinine (Agnamey, Brasseur, et al. 2005). In Ethiopia, RDTs were shown to have the potential to be cost-saving compared to PT in an epidemic setting using ACT, while improving health outcomes for patients with NMFI (Rolland, Checchi et al. 2006). Sensitivity analysis from this study confirmed that cost-effectiveness is reduced with increases in malaria prevalence among patients.

**Limitations to the model**

This model is limited in its application by structural restrictions, uncertainties about parameterization, and limitations to the scope of effectiveness and cost estimates.

*Structural restrictions*

Models inevitably serve as simplified approximations of the true nature and complexity of provider and patient behaviour. The decision tree in this study represents a linear, sequential pattern of treatment seeking and subsequent health outcomes through two rounds of treatment, which is a crude representation of actual practice. Patients have been shown to have complex patterns of treatment-seeking behaviour, using formal and informal providers simultaneously (Kachur, Adeniyi et al. 1998; McCombie 2002). Many
patients with uncomplicated malaria are initially treated at home, while more severe patients – particularly those with convulsions – are taken to a health practitioner (de Savigny, Mayombana et al. 2004). In further work, complexities in tree structure could be better represented with a Markov model, which cycles patients fluidly between care options and health states (Sonnenberg and Beck 1993).

Moreover, the current model structure and treatment-seeking parameters are based on behaviour patterns which existed when chloroquine (CQ) was the first-line therapy (Goodman, Coleman et al. 2001). Changing treatment policy may influence patient behaviour in terms of the proportion of people who seek care and the types of facilities used. For example, use of facilities may increase if ACTs are seen as affordable as and more effective than older drugs such as CQ and SP, but facility use may decline if patients lose confidence when a familiar drug is replaced (Kachur, Adeniyi et al. 1998). Similarly, the availability of a diagnostic test for malaria may provide an incentive for patients to seek diagnosis and treatment at earlier stages of illness, lowering the probability they become severe (P23-P26). ACT has now been introduced as the first-line drug in a large number of countries in SSA (WHO 2004b), and treatment seeking trends are being observed (de Savigny, Mayombana et al. 2004).

From a clinical perspective, this model assumed good clinical practice, a clear hierarchy of first- and second-line drug therapies, and that second-line treatment would be available when needed. However, evidence shows that second-line drugs are often not available at peripheral facilities (Barat, Himonga et al. 1998). In addition, diagnostic tests are often ordered for non-febrile patients, which leads to inefficiencies not considered by this model (Zurovac, Midia et al. 2006). Empirical evidence indicates that clinicians often
prescribe antimalarials (without antibiotics) to patients receiving negative test results –
despite high negative predictive values (Barat, Chipipa et al. 1999; Reyburn, Mbatia et al.
2004; Reyburn, Ruanda et al. 2006; Zurovac, Larson et al. 2006). Moreover, many
physicians do not adhere to guidelines about which specific antimalarial to prescribe even
when the drug is available, which may compromise efficacy (Zurovac, Ndhlovu et al.
2003; Zurovac, Rowe et al. 2004). The cost-effectiveness of diagnostics will be will not
be fully realized unless clinical practice improves.

Particularly in areas of high transmission where immunity is widespread, positive
tests for malaria may not indicate the true cause of febrile illnesses (WHO 2006b).
Malaria parasitemia may be incidental to bacterial co-infections, and prescription of
antibiotics may be appropriate where clinical suspicion is high to avoid delay in
appropriate treatment. This possibility will vary widely between different
epidemiological settings, and should be taken into account when developing management
algorithms incorporating parasite-based diagnosis. This model does not seek to address
this.

Parameter uncertainty

Many of the model parameters were based on expert opinion or limited evidence
and more data could improve the model’s accuracy in a number of areas. Of particular
importance are:

(a) The sensitivity and specificity of RDTs and microscopy under different operational
settings.

(b) Patient adherence to treatment schedules, which affects progression to adverse events
for both malaria and non-malarial febrile illness (NMFI).
(c) Treatment seeking behaviour for initial treatment and following treatment failure.
(d) The composition of NMFIs.
(e) HIV and malnutrition prevalence.
(f) First-line antibiotic prescribing practices.

The accuracy of RDTs is strongly dependent on the skill of the health worker, and several steps in the chain from manufacturing, to distribution, to testing (WHO 2003b, WHO 2006b). While it was assumed in this model that RDTs are correctly prepared and interpreted, and stable at clinic level, this may not always be the case (Funk, Schlagenhauf et al. 1999; Trachsler Schlagenhauf et al. 1999; Jelinek, Grobusch et al. 2000; Tarrow, Knebel et al. 2000). Thus far no study in SSA has been large enough to estimate the true performance of RDTs in the field; however, at least one such study is underway (Mbakilwa, Reyburn et al. 2005). For the full utility of RDTs to be realized, they must perform reliably and accurately under field conditions, and decision makers must have methods to determine the quality of different products (Bell, Wongsrichanalai et al. 2006). An online review of available RDTs has been developed for this purpose (http://www.wpro.who.int/sites/rdt).

The sensitivity values for microscopy are low, but in keeping with published evidence of field microscopy in the type of situations where parasite-based diagnosis is likely to be under consideration to replace presumptive diagnosis (Reyburn, Mbatia et al. 2004; Barat, Himonga et al. 1998). Microscopy sensitivity in hospitals and well-established laboratories, where microscopy is well-supported, is likely to be significantly higher. Diagnosis at this level of health facility is not modelled here. Both RDT-based
and microscopy-based diagnostic accuracies are in part dependent on the quality assurance programmes in place to maintain them.

Progression to adverse events for both malaria and NMFI is strongly dependent on patient adherence to treatment schedules, and few studies have been done in this area. Adherence to ACT is relevant to the decision to introduce diagnostics at high malaria prevalence – particularly for microscopy. Levels of adherence to antibiotics are relatively unknown, but are very important to the decision to introduce RDTs at low malaria prevalence. Strategies such as blister packaging have been shown to improve adherence; however, dissemination of correct clinical practices to junior health workers is a challenge that should be addressed (Kachur, Khatib et al. 2004). More data would also be beneficial on treatment seeking behaviour, particularly following treatment failure. As a simplifying assumption, probabilities that severe and uncomplicated patients return for treatment were set as equal (P21, P22), but these figures are only approximations.

The composition of NMFIIs is likely to have a strong influence on cost-effectiveness and will differ between regions. However, data on alternative treatable diagnoses are surprisingly scarce and model parameter values relied largely on expert opinion to extrapolate from the limited data available. If health outcomes for appropriately treated NMFI patients improve, or the severity of untreated NMFI worsens, parasitic diagnosis will become more favourable relative to PT.

HIV will also have a strong impact on health outcomes by suppressing the patient’s immune system and leaving them vulnerable to severe effects from other diseases. We implicitly assumed low HIV prevalence (10% in adults), which is typical outside of Southern Africa. In areas where HIV is more widespread, case fatality rates
would be expected to rise, especially for adults with NMFI. This scenario would show an increase the cost-effectiveness of diagnostic tools relative to the reference case. Evidence on the impact of HIV on NMFI severity is only beginning to be generated (Gordon, Hastings et al. 2002; Gordon, Chaponda et al. 2002; Berkley, Lowe et al. 2005), and more research is needed. Similarly, the prevalence of malnutrition may influence parameters relating to severe disease and death, leading to invasive bacterial infections such as pneumonia and \textit{E. coli} (Berkley, Maitland et al. 2005).

The appropriate protocol for treating patients testing negative for malaria is unclear, and little evidence is available on antibiotic prescribing (Radyowijati and Haak 2003). Figure 11 shows that the cost-effectiveness of parasitic diagnosis decreases geometrically as smaller proportions of patients receiving a negative malaria diagnosis receive antibiotics. This result can be explained by our assumption that antibiotics are prescribed at random to patients with a diagnosis negative for malaria. However, in reality clinicians may target antibiotics to NMFIIs thought more likely to be bacterial, which would make RDTs relatively more cost-effective. On the other hand, our model assumes that no patients with a positive malaria diagnosis are prescribed antibiotics under PT, RDTs or microscopy. This is unlikely to be the case, especially in countries such as Tanzania where IMCI-style treatment protocols are in use (de Savigny, Mayombana et al. 2004). Such prescribing patterns would reduce the incremental effectiveness and costs of RDT relative to PT, leaving the impact on cost-effectiveness uncertain.

\textit{Scope of effectiveness and cost estimates}

Incremental costs, not total costs, were estimated in this analysis. In other words,
costs that affect diagnostic strategies equally were excluded as they do not affect the cost-effectiveness of the decision. The scope of effectiveness estimates in this model is subject to the usual limitations in cost-effectiveness analysis; other economic outcomes such as impact on income, productivity, education, and the effects that these have on households and firms are omitted (Chima, Goodman et al. 2003).

In addition, changes in parameter values through time have not been considered. RDTs promise to lower the amount of ACT projected to be prescribed in SSA, which may reduce drug pressure and thereby slow the development of antimalarial resistance. However, improved specificity of malaria diagnosis could increase substantially the number of patients receiving antibiotics. If all patients diagnosed negative for malaria receive antibiotics, the probability increases that antibiotic resistance will develop more rapidly. As with malaria, a trade-off exists between achieving a high sensitivity of bacterial infection diagnosis through overprescription, and the potential development of drug resistance.

RDTs can be expected to have further benefits beyond the scope of the model in their impact on malaria transmission and incidence. Particularly in areas of epidemic malaria, RDTs would be useful to monitor early signs of outbreaks, and allow the health sector to target resources for prevention and treatment (Verle, Binh et al. 1996). The benefits from preventing outbreaks are substantial, ranging from prevented mortality to financial savings to already-strained health systems (Mills and Shillcutt 2004).

Logistical considerations relating to a change in policy are also not considered in the analysis. Supply chains are often unreliable in SSA, and doubts may exist about whether diagnostic and drug supplies can be maintained to support a new policy.
Confidence that regulatory bodies can maintain adequate standards in diagnostic training and quality control may also affect the decision. Quality assurance costs have not been considered in this study, and will vary widely dependent on the existing health service structure, and geography. Quality assurance of RDTs should include lot testing after procurement, monitoring in the field, and regular supervision of technicians; microscopy requires cross-checking a proportion of all slides and regular retraining / assessment (WHO 2003b). Bates and colleagues (2004) have shown that relatively simple quality control measures can improve laboratory standards, particularly if tests actually influence diagnostic practice.

Finally, no attention is paid to how benefits and costs are distributed, and what considerations should be paid towards ensuring equity. Research has highlighted the disproportionate burden of malaria on the poor and vulnerable, the greater access to effective treatment of less poor groups, and the importance of targeting interventions toward population groups with the greatest need (Schellenberg, Victora et al. 2003; Barat, Palmer et al. 2004).

**Changing policy and policy maker attitudes to risk**

The bootstrapped confidence limits in the cost-effectiveness acceptability curves and planes in this analysis should be interpreted as the level of risk that a decision maker is willing to accept – i.e. the probability that the strategy implemented is the cost-effective option. Changing diagnostic strategies for malaria is a politically sensitive decision. Decision makers are likely to be relatively averse to taking risks, and may be reluctant to change policy away from the status quo (Goodman, Coleman et al. 2001). It
is therefore helpful to present cost-effectiveness results based on 95% or 99% certainty. However, a strict level of acceptable risk such as 95% confidence can lead to policy inertia, meaning that policies that are likely to be cost-effective will be rejected. It has been argued that the costs imposed by a high level of risk aversion, or the health benefits forgone, outstrip those imposed by infrequently making inefficient decisions. According to this logic, a level of risk closer to 50% should be deemed acceptable (Claxton 1999).

Analytically, the optimal level of risk that a decision-maker should be willing-to-accept before postponing the decision to collect further data can be estimated using expected value of information analysis (Claxton 1999; Fenwick, Claxton et al. 2000). Ultimately, the level of risk that decision makers find acceptable will depend on their ability to view this decision in the wider context of other, similarly-crucial decisions on their agenda.

**Further work**

Arising from the above analysis, the model could be further developed to include:

1. Evaluation of alternative protocols for fever management, such as the Integrated Management of Childhood Illness (IMCI).
2. Evaluation of microscopy in more comprehensive laboratories, to consider use for other illnesses.
3. Consideration of the impact of provider non-adherence to treatment protocols, particularly prescription of antimalarials to patients diagnosed malaria-negative. More work is also needed to investigate the cost-effectiveness of quality assurance strategies to improve provider adherence.
4. Evaluation of RDTs use by community workers or retailers such as drug shops (Arrow, Panosian et al. 2004), and the treatment of malaria and other febrile illnesses at this level (Kallander, Nsungwa-Sabiiti et al. 2004). In areas where parasitic diagnosis of fever is impossible, the use of cotrimoxazole may be evaluated, since it has both antimalarial and antibiotic properties (Bloland, Redd et al. 1991).

5. Consideration of growth in resistance to both ACTs and antibiotics to assess the long-term impact of diagnostic strategies. It may be possible to use existing models of antimalarial drug resistance (Yeung, Pongtavornpinyo et al. 2004), or to apply general patterns of the growth of resistance (Coleman, Morel et al. 2004), to generate a more robust estimate of the cost-effectiveness of diagnosis according to the time frame expected to be used by decision makers.33

6. Further model development to include both high and low HIV prevalence scenarios, and to consider the impact of malnutrition.

7. Division of population into age groups <5 years old, and ≥ 5 years old to account for different levels of malaria prevalence in these patient groups, and modelling of changes in prevalence through time.

8. Adaptation to low-transmission areas, such as Asia and Latin America, considering the use of combination-antigen rapid diagnostic tests that can detect both *P. falciparum* and *P. vivax*, followed by different treatment regimens for each type of infection.
CONCLUSIONS

This study demonstrates that rapid diagnostic tests for malaria are likely to be highly cost-effective compared to microscopy and presumptive treatment across most of Africa in an era of more expensive antimalarials. This is due as much to improved targeting of antibiotics to those who do not have parasites, as to better targeting of antimalarials. Results are relatively robust to extensive sensitivity analysis; however, depend on ensuring accuracy of RDTs in the field, and use of the tests to guide treatment decisions. Further model development could increase the realism of the analysis, and more customised results can be generated online. Efforts to evaluate operational RDT use and test interventions to improve clinician adherence to treatment protocols should be a priority.
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implications of adult malaria diagnosis using microscopy in Kenya." Tropical
Medicine and International Health 11: 1185-94


<table>
<thead>
<tr>
<th>Probability input variable</th>
<th>Type of probability distribution</th>
<th>Best estimate</th>
<th>Low estimate</th>
<th>High estimate</th>
<th>$\alpha$</th>
<th>$\beta$</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1 Prevalence</td>
<td>Point estimates</td>
<td>0%</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td>Estimates</td>
</tr>
<tr>
<td>P2 Proportion of population (age ≥5)</td>
<td>Uniform</td>
<td>50%</td>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td>Estimates</td>
</tr>
<tr>
<td>P3 Proportion of NMFI cases that are bacterial</td>
<td>Beta</td>
<td>10%</td>
<td>5%</td>
<td>15%</td>
<td>19.068</td>
<td>167.885</td>
<td>Whitty, Reyburn, Berkley personal communication</td>
</tr>
<tr>
<td>P4 Probability that a NMFI case receives an antibiotic</td>
<td>Point estimate</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P5 RDT sensitivity</td>
<td>Beta</td>
<td>96%</td>
<td>84%</td>
<td>100%</td>
<td>39.289</td>
<td>2.961</td>
<td>Beadle, Long et al. 1994; Premji, Minjas et al. 1994; Bojang 1999; Craig, Bredenkamp et al. 2002; Bell, Wilson et al. 2005</td>
</tr>
<tr>
<td>P6 Presumptive treatment sensitivity</td>
<td>Point estimate</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estimate</td>
</tr>
<tr>
<td>P7 Microscopy sensitivity (field standard laboratory conditions)</td>
<td>Beta</td>
<td>82%</td>
<td>75%</td>
<td>88%</td>
<td>153.303</td>
<td>34.640</td>
<td>Barat, Chipipa et al. 1999; Reyburn, Mbatia et al. 2004; Zurovac, Midia et al. 2006</td>
</tr>
<tr>
<td>P8 RDT specificity</td>
<td>Beta</td>
<td>95%</td>
<td>90%</td>
<td>100%</td>
<td>91.295</td>
<td>5.275</td>
<td>Bojang 1999; WHO, 2000; Bell, Wilson et al. 2005; Craig, Bredenkamp et al., 2002</td>
</tr>
</tbody>
</table>
Presumptive treatment specificity

Microscopy specificity (field standard laboratory conditions)

Microscopy specificity (field standard laboratory conditions)

Beta 85% 59% 91% 24.598 6.575 Barat, Chipipa et al., 1999; Reyburn, Mbatia et al., 2004; Zurovac, Midia et al., 2006

Adherence and Efficacy

Probability of Adherence - ACT**

Beta 80% 40% 91% 10.929 4.427 Depoortere, Guithman et al., 2004; Depoortere, Salvador et al., 2004; Kachur, Adeniyi et al., 2004; Fogg, Bajunirwe et al., 2004

Probability of Adherence - amoxicillin

Assumed equal to malaria

ACT efficacy (for malaria)

Beta 85% 78% 95% 74.101 12.712 Lefevre, Looareesuwan et al., 2001; Sirima, Tiono et al., 2003 IASG, 2004;

Amoxicillin efficacy (for malaria)

Point estimate 0%

ACT efficacy (for bacterial infection)

Point estimate 0%

Amoxicillin efficacy (for bacterial infection)

Bet 75% 60% 90% 32.530 11.167 Whitty and Greenwood personal communication

ACT efficacy (for viral infection)

Point estimate 0%

Amoxicillin efficacy (for viral infection)

Point estimate 0%

Treatment seeking patterns

Outpatient visit takes place at a health centre

Beta 1-P20

Outpatient visit takes place at a hospital

Beta 32% Aikins, 1995

Patient with severe illness goes to hospital for inpatient care after treatment failure

Beta 48% 19% 88% 5.630 5.471 McCombie, 1996

Patient with uncomplicated illness returns to clinic for outpatient care after treatment failure

Beta P21
Disease Progression***
Illness becomes severe with first-line treatment failure (TF), non-adherence (NA), not reatment (NT), or treated with an incorrect drug ID.

| P2 | Malaria not effectively treated leads to severe disease (age ≥5) | Beta | 1% | 0.01% | 5% | 2.583 | 118.540 | Whitty and Greenwood personal communication |
| 3 | Malaria not effectively treated leads to severe disease (age <5) | Beta | 7.5% | 5% | 10% | 111.226 | 1202.63 | Whitty and Greenwood personal communication |
| 4 | Bacterial illness not effectively treated leads to severe disease (age ≥5) | Beta | 15% | 10% | 25% | 20.593 | 104.104 | Whitty, Reyburn, Berkley personal communication |
| 5 | Bacterial illness not effectively treated leads to severe disease (age <5) | Beta | 30% | 20% | 40% | 33.218 | 76.884 | Whitty, Reyburn, Berkley personal communication |
| 6 | Viral illness not effectively treated leads to severe disease (age ≥5) | Point estimate | 0% | | | | | Whitty and Greenwood personal communication |
| 7 | Viral illness not effectively treated leads to severe disease (age <5) | Point estimate | 0% | | | | | Whitty and Greenwood personal communication |

Neurological Sequelae (Probabilities for both inpatients and severe cases that receive no treatment)

Malaria

| P2 | Severe malaria leads to neurological sequelae (age ≥5) | Beta | 1.5% | 1% | 2% | 47.551 | 3095.92 | Whitty and Greenwood personal communication |
| 9 | Severe malaria leads to neurological sequelae (age <5) | Beta | 3.5% | 2% | 5% | 29.670 | 813.477 | Whitty and Greenwood personal communication |

Bacterial

| P3 | Severe bacterial infection leads to neurological sequelae (age ≥5) | Beta | 3.8% | 1% | 7% | 8.696 | 202.934 | Whitty and Greenwood personal communication |
| 1 | Severe bacterial infection leads to neurological sequelae (age <5) | Beta | 2% | 1.6% | 2.4% | 128.777 | 6288.11 | Whitty and Greenwood personal communication |

Inpatient mortality after first-line treatment failure

| P3 | Inpatient with severe malaria attending an Inpatient facility dies (all ages) | Beta | 10% | 5% | 15% | 19.068 | 167.885 | Whitty, Reyburn, Berkley personal communication |
| 3 | Inpatient with severe bacterial illness attending an Inpatient facility dies (all ages) | Beta | 15% | 10% | 20% | 41.345 | 232.695 | Whitty, Reyburn, Berkley personal communication |
Mortality after no formal secondary care

<table>
<thead>
<tr>
<th>P3</th>
<th>Patient with severe malaria that does not return for formal care will die (all ages)</th>
<th>Beta</th>
<th>25%</th>
<th>15%</th>
<th>40%</th>
<th>17.182</th>
<th>47.417</th>
<th>Whitty, Reyburn, Berkley personal communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td></td>
<td>Beta</td>
<td>P35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Patient with severe bacterial illness that does not return for formal care will die (all ages)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*α and β are moments which describe the beta distribution

**assumed to be a middle estimate between regimen that is co-administered and one that is co-formulated

*** assumed that 10% of patients over 5 are HIV positive
Table 2. Definitions of cost parameters

<table>
<thead>
<tr>
<th>Cost input variable</th>
<th>Type of probability distribution</th>
<th>Best estimate</th>
<th>Low estimate</th>
<th>High estimate</th>
<th>Mean</th>
<th>SD</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnostic costs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C1 Presumptive treatment</td>
<td>Point estimate</td>
<td>$0.00</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Estimate</td>
</tr>
<tr>
<td>C2 RDTs</td>
<td>Uniform</td>
<td>$0.60</td>
<td>$1.00</td>
<td></td>
<td></td>
<td></td>
<td>WHO, 2004b; Bell, 2004</td>
</tr>
<tr>
<td>C3 Microscopy</td>
<td>Lognormal</td>
<td>$0.53</td>
<td>$0.32</td>
<td>$1.27</td>
<td>0.676</td>
<td>1.380</td>
<td>Goodman, 1999; Goodman, Coleman et al., 2000</td>
</tr>
<tr>
<td><strong>Drug costs (Adult Doses)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C4 ACT</td>
<td>Uniform</td>
<td>$1.00</td>
<td>$2.40</td>
<td></td>
<td></td>
<td></td>
<td>Arrow, Panosian et al., 2004</td>
</tr>
<tr>
<td>C5 Antibiotic (Amoxicillin)</td>
<td>Lognormal</td>
<td>$0.71</td>
<td>$0.61</td>
<td>$0.93</td>
<td>0.742</td>
<td>1.100</td>
<td>MSH, 2005; BNF, 2005</td>
</tr>
<tr>
<td>C6 Oral Quinine (10 mg/kg every 8 hours for 7 days)</td>
<td>Lognormal</td>
<td>$3.12</td>
<td>$2.75</td>
<td>$3.67</td>
<td>3.168</td>
<td>1.066</td>
<td>MSH, 1996; WHO, 1995</td>
</tr>
<tr>
<td>C7 Intravenous Quinine (initial dose - 20 mg/kg over 4 hours)</td>
<td>Lognormal</td>
<td>$0.55</td>
<td>$0.45</td>
<td>$0.67</td>
<td>0.556</td>
<td>1.090</td>
<td>MSH, 1996; WHO, 1995</td>
</tr>
<tr>
<td>C8 Intravenous Quinine (per day after - 10 mg/kg every 8 hours)</td>
<td>Lognormal</td>
<td>$0.82</td>
<td>$0.68</td>
<td>$1.01</td>
<td>0.834</td>
<td>1.091</td>
<td>MSH, 1996; WHO, 1995</td>
</tr>
<tr>
<td>C9 Drugs for severe bacterial infection</td>
<td>Point estimate</td>
<td>2*C5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BNF, 2005</td>
</tr>
<tr>
<td><strong>Cost weightings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C10 Child drug dosage as a percentage of adult drug dose</td>
<td>Point estimate</td>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Goodman, Coleman et al., 2000; BNF, 2005</td>
</tr>
<tr>
<td>C11 Cost of transport/logistics, insurance and wastage as a % of drug price</td>
<td>Point estimate</td>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Goodman, Coleman et al., 2000</td>
</tr>
<tr>
<td>C12 RDT training, additional staff time, and quality control as a % of cost</td>
<td>Point estimate</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Goodman, Coleman et al., 2000</td>
</tr>
<tr>
<td><strong>Outpatient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C13 Patient cost: Cost of attending an outpatient facility (excl. fees)</td>
<td>Lognormal</td>
<td>$0.74</td>
<td>$0.18</td>
<td>$1.68</td>
<td>0.871</td>
<td>1.505</td>
<td>Sauerborn, Shepard et al., 1991; Louis, Trebuq et al., 1992; Litvack, Bodart et al., 1993</td>
</tr>
<tr>
<td>C14 Proportion of outpatient facility costs that are fixed</td>
<td>Uniform</td>
<td>$0.74</td>
<td>$0.18</td>
<td>$1.68</td>
<td>0.871</td>
<td>1.505</td>
<td>Asenso-Okyere, Dzator et al., 1997; Gilson, 1992</td>
</tr>
</tbody>
</table>
Proportion of outpatient costs that are drugs: Point estimate 37% (Etting and McFarland, 1992). Provider cost: Health center outpatient facility costs per visit: Lognormal ($0.72, $0.34, $1.35, 0.798, 1.335; Mills, 1991; Etting and McFarland, 1992; Gilson, 1992; Hanson and Nkunzimana, 1992; Gilson, 1992; Barnum and Kutzin, 1993; Kirigia, Snow et al., 1998). Provider cost: Hospital outpatient facility costs per visit: Lognormal ($3.90, $0.91, $6.08, 3.832, 1.376; Gilson, 1992; Barnum and Kutzin, 1993; Kirigia, Snow et al., 1998).

Inpatient

Patient cost: Cost of attending inpatient facility (excl. fees): Lognormal ($3.84, $1.11, $9.37, 4.724, 1.514; Sauerborn, Shepard et al., 1991; Louis, Trebucq et al., 1992; Litvack and Bodart, 1993; CNLP, 1994; Asenso-Okyere and Dzator, 1997).

Proportion of inpatient costs that are drugs: Point estimate 17% (Gilson, 1992; Gilson, 1992; Kirigia, Snow et al., 1998). Proportion of inpatient facility costs that are fixed: Uniform (50%, 75%; Barnum and Kutzin, 1993; Nelson, Weikert et al., 1995; Kirigia, Snow et al., 1998). Provider cost: Cost of inpatient facility per day: Lognormal ($14.15, $4.57, $24.48, 14.750, 1.368; Brewster et al., 1989; Nelson, Weikert et al., 1995; Faye, N’Dir et al., 1996; Nelson, Weikert et al., 1995; Faye, N’Dir et al., 1996).

Average length of stay as an inpatient when die (all illnesses): Point estimate 2 (Brewster et al., 1989; Nelson, Weikert et al., 1995; Faye, N’Dir et al., 1996; Nelson, Weikert et al., 1995; Faye, N’Dir et al., 1996). Average length of stay as an inpatient when have severe malaria and recover: Point estimate 4.50 (Faye, N’Dir et al., 1996). Average length of stay as an inpatient when have severe bacterial infection and recover: Point estimate C23.
Table 3. Definitions of effectiveness parameters

<table>
<thead>
<tr>
<th>Effectiveness input variable</th>
<th>Type of probability distribution</th>
<th>Best estimate</th>
<th>Low estimate</th>
<th>High estimate</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability weights (viral illness can only be uncomplicated followed by cure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E1 Severe illness (age ≥5)</td>
<td>Point estimate</td>
<td>0.25</td>
<td>Estimate</td>
<td>Estimate</td>
<td></td>
</tr>
<tr>
<td>E2 Severe illness (age &lt;5)</td>
<td>Point estimate</td>
<td>0.25</td>
<td>Estimate</td>
<td>Estimate</td>
<td></td>
</tr>
<tr>
<td>E3 Neurological sequelae (age ≥5)</td>
<td>Point estimate</td>
<td>0.473</td>
<td>GBD based on malaria neurological sequelae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E4 Neurological sequelae (age &lt;5)</td>
<td>Point estimate</td>
<td>0.473</td>
<td>GBD based on malaria neurological sequelae</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E5 Uncomplicated illness (age ≥5)</td>
<td>Point estimate</td>
<td>0.172</td>
<td>GBD based on malaria episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E6 Uncomplicated illness (age &lt;5)</td>
<td>Point estimate</td>
<td>0.211</td>
<td>GBD based on malaria episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disability adjusted years of life lost (DYLL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E7 Death at Age 27</td>
<td>Point estimate</td>
<td>24.83</td>
<td>Calculated using standard DALY methodology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E8 Death at Age 2</td>
<td>Point estimate</td>
<td>27.47</td>
<td>Calculated using standard DALY methodology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durations of illness (viral illness can only be uncomplicated followed by cure)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E9 Between first and second visits (days)</td>
<td>Point estimate</td>
<td>4</td>
<td>Estimate</td>
<td>Estimate</td>
<td></td>
</tr>
<tr>
<td>E10 Neurological sequelae (years)</td>
<td>Point estimate</td>
<td>21.81</td>
<td>GBD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E11 Uncomplicated illness cured after first-line treatment (days)</td>
<td>Point estimate</td>
<td>2</td>
<td>Estimate</td>
<td>Estimate</td>
<td></td>
</tr>
<tr>
<td>E12 Uncomplicated illness post-treatment failure (days)</td>
<td>Uniform</td>
<td>14 21</td>
<td>Estimate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E13 Uncomplicated illness untreated (days)</td>
<td>Uniform</td>
<td>E20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E14 Inpatient stay when has severe illness (recover)</td>
<td>Point estimate</td>
<td>C23</td>
<td></td>
<td></td>
<td>Brewster, Kwiatkowski et al., 1990</td>
</tr>
<tr>
<td>E15 Inpatient stay when recovers with NS (days)</td>
<td>Point estimate</td>
<td>10</td>
<td></td>
<td></td>
<td>Goodman, Coleman et al., 2000</td>
</tr>
<tr>
<td>E16 Inpatient stay when has severe illness (days) (dies)</td>
<td>Point estimate</td>
<td>2</td>
<td></td>
<td>Estimate</td>
<td>Estimate</td>
</tr>
<tr>
<td>E17 Illness severe no second visit (recovers)</td>
<td>Point estimate</td>
<td>2*E20</td>
<td></td>
<td>Estimate</td>
<td>Estimate</td>
</tr>
<tr>
<td>E18 Illness severe no second visit (recovers with NS)</td>
<td>Point estimate</td>
<td>2*E20</td>
<td></td>
<td>Estimate</td>
<td>Estimate</td>
</tr>
<tr>
<td>E19 Malaria severe no second visit (days) (dies)</td>
<td>Point estimate</td>
<td>2</td>
<td></td>
<td>Estimate</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Parameters tested in sensitivity analyses (SA) on the cost-effectiveness probability plane

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low SA limit*</th>
<th>High SA limit*</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2 Cost of RDT</td>
<td>$0</td>
<td>$4</td>
</tr>
<tr>
<td>C3 Cost of Microscopy</td>
<td>$0</td>
<td>$4</td>
</tr>
<tr>
<td>C4 Cost of ACT</td>
<td>$0</td>
<td>$4</td>
</tr>
<tr>
<td>P11 Adherence to ACT</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>P12 Adherence to antibiotic</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>P4** Probability that a patient with NMFI receives an antibiotic</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>P25 / P26*** Probability that a patient with bacterial infection becomes severe</td>
<td>Low severity</td>
<td>High severity</td>
</tr>
<tr>
<td>P3 Probability that NMFI is caused by a bacterial infection</td>
<td>0%</td>
<td>100%</td>
</tr>
<tr>
<td>P2 Proportion of presenting population 5 years old or over</td>
<td>0%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Note low and high sensitivity analysis (SA) limits do not always correspond with the low and high estimates used to define the distributions used in the reference case analysis (Tables 1-3).

** When P4 is less than 100%, it is assumed that antibiotics are randomly allocated to patients with NMFI.

***The sensitivity analysis on the probability that a bacterial infection would become severe (P25 and P26) ranged between the low and high estimates used to define the distribution in Table 1.
Figure 1. Cost-effectiveness decision trees. The trees in the following figures may be linked to form the full tree used in the analysis. Patients are distributed to final health states according to the probabilities indicated at each chance node (○) until reaching terminal nodes (►).

a) The root tree maps diagnosis and subsequent events according to malaria and non-malarial febrile illness (NMFI). This tree applies to each of the diagnostic strategies considered in this analysis, and the three components can be connected at a decision node that would lie to the left of this sub-tree.

b) Malaria disease outcome tree after treatment failure (TF), non-adherence (NA), no first-line treatment (NT), or incorrect drug (ID) given to the patient after diagnosis. This tree emanates from chance nodes 2, 3, 4, & 5 (○) on right hand side of the root tree.
c) Bacterial disease outcome tree after treatment failure (TF), non-adherence (NA), no first-line treatment (NT), or incorrect drug (ID) given to the patient after diagnosis. This tree emanates from chance nodes 7, 8, 10 & 12 (o) on right hand side of the root tree.

![Bacterial Illness Disease Progression Diagram]

<table>
<thead>
<tr>
<th>Severe Disease</th>
<th>Residual Probability</th>
<th>Fully Recovers</th>
</tr>
</thead>
<tbody>
<tr>
<td>P25 &amp; P26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated Disease</td>
<td>1-P25 &amp; 1-P26</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>P22</td>
<td>Full Recovers</td>
<td></td>
</tr>
<tr>
<td>Health Centre Outpatient</td>
<td>P19</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Outpatient</td>
<td>P20</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Care</td>
<td>P22</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Formal Care</td>
<td>1-P22</td>
<td>Fully Recovers</td>
</tr>
</tbody>
</table>

Viral Illness Disease Progression

<table>
<thead>
<tr>
<th>Severe Disease</th>
<th>Residual Probability</th>
<th>Fully Recovers</th>
</tr>
</thead>
<tbody>
<tr>
<td>P25 &amp; P26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uncomplicated Disease</td>
<td>1-P25 &amp; 1-P26</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>P22</td>
<td>Full Recovers</td>
<td></td>
</tr>
<tr>
<td>Health Centre Outpatient</td>
<td>P19</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital Outpatient</td>
<td>P20</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient Care</td>
<td>P22</td>
<td>Fully Recovers</td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Formal Care</td>
<td>1-P22</td>
<td>Fully Recovers</td>
</tr>
</tbody>
</table>

d) Disease outcome tree for all patients with viral illness. This tree emanates from chance nodes 9, 11 & 13 (o) on right hand side of the root tree.

![Viral Illness Disease Progression Diagram]
Figure 2. The cost of microscopy is very closely linked to the number of febrile patients diagnosed at a health facility per year because fixed costs – such as the microscope, staff training, and laboratory supervision – remain the same regardless of laboratory throughput. Fixed costs are distributed more widely across diagnoses as throughput increases, thus reducing the cost of each individual diagnosis (Goodman 1999). This costing includes the microscope itself, laboratory supplies, laboratory staff time and training, supervision and laboratory overheads; and assumes that the microscope is used for malaria diagnosis only. Costs to facility may reduce if the microscope is also used for diagnosis of other diseases.
**Figure 3.** Relative to PT (standardized to the x-axis), the incremental DALYs incurred (a), and costs (b) according to each diagnostic strategy. DALYs incurred are affected by the accuracy of diagnosis and relative probability that diseases become severe. Costs are affected by the cost and accuracy of diagnosis, and relative probability that secondary treatment costs will be incurred.

a) Incremental DALYs incurred

![Graph showing incremental DALYs incurred by diagnostic strategies.](image)

b) Incremental costs

![Graph showing incremental costs by diagnostic strategies.](image)
Figure 4. The expected values for the net benefit of each cost-effectiveness comparison across the possible range of malaria prevalence are shown in figures (a,c,e), using a ceiling ratio of $150/DALY averted. Each result is associated with a level of uncertainty represented by 90% confidence intervals. The probabilities that the intervention in each comparison are cost-effective, dominant, and dominated are shown in figures (b,d,f).

a) Incremental net benefit of RDTs compared to PT

b) Probability RDTs are cost-effective, dominant, or dominated relative to PT
Malaria Prevalence Among Febrile Outpatients

- Probability RDTs are Cost-Effective
- Probability RDTs are Cost-Saving (Dominant)
- Probability RDTs Incur Costs at Lower Benefit (Dominated)
c) Incremental net benefit of Field Microscopy compared to PT

![Graph showing incremental net benefit of Field Microscopy compared to PT](image1)

- $20
- $15
- $10
- $5
- $0
- $5
- $10
- $15
- $20

Malaria Prevalence Among Febrile Outpatients

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Malaria Prevalence Among Febrile Outpatients

Probability Field Microscopy is cost-effective, dominant, or dominated relative to PT

![Graph showing probability Field Microscopy is cost-effective, dominant, or dominated relative to PT](image2)

- Probability Microscopy is Cost-Effective
- Probability Microscopy is Cost-Saving (Dominant)
- Probability Microscopy Incurs Costs at Lower Benefit (Dominated)
e) Incremental net benefit of RDTs compared to Field Microscopy

f) Probability RDTs are cost-effective, dominant, or dominated relative to Field Microscopy
Figure 5. Sensitivity analysis: Ceiling ratio
The sensitivity of cost-effectiveness to variations in the ceiling ratio ($\lambda$) was plotted according to disease prevalence for each of the three comparisons. Areas shaded black represent conditions where one strategy is cost-effective relative to the comparator with 99% certainty. Areas shaded dark grey represent 95% confidence intervals. Light grey areas represent conditions of uncertainty, where it is not 95% certain which strategy is cost-effective. The black line through the light grey region represents conditions of indifference, where it is equally likely that each strategy will be cost-effective. Cost-effectiveness was sensitive to changes in $\lambda$, particularly below $150$/DALY.

a) RDT compared to PT
b) Field Microscopy compared to PT

- Microscopy is cost effective relative to PT when:
  - Malaria Prevalence Among Febrile Outpatients > 99%
  - Ceiling Ratio > 95%
  - Ceiling Ratio < 95%

- PT is cost effective relative to microscopy when:
  - Malaria Prevalence Among Febrile Outpatients < 50%
  - Ceiling Ratio 50%
c) RDT compared to Field Microscopy

![Graph showing cost-effectiveness of RDT vs Microscopy]

RDT is cost-effective relative to Microscopy when:
- Malaria prevalence is > 99%
- Ceiling ratio is > 95%
- Ceiling ratio is < 95%
- Ceiling ratio is 50%
Figure 6. Sensitivity analysis: Cost of RDTs
This parameter has a strong impact on the comparison between RDTs and PT, but as expected does not affect the comparison between microscopy and PT. The decision to comparison between microscopy and RDTs is not significantly affected.

a) RDT compared to PT. RDTs become less cost-effective as their cost increases. RDTs are expected to cost $0.80 in reference case conditions, and the line of 50% certainty corresponds with reference case results at 81% malaria prevalence.
b) **Field Microscopy compared to PT.** As expected, the cost of RDTs has no influence on the decision to change policy from PT to microscopy, and contours are vertical. Slight aberrations to the verticality of contours are artefacts from simulations. Reference case results that microscopy is cost-effective with 50% certainty below 67% malaria prevalence are confirmed.
c) RDT compared to Field Microscopy. When RDTs cost less than $1.90, they are cost-effective relative to microscopy with more than 50% certainty at all levels of malaria prevalence.
Figure 7. Sensitivity analysis: Cost of Field Microscopy
This parameter has a strong impact on the decision to change policy to microscopy diagnosis from PT, but does not affect the decision to change to RDT from microscopy diagnosis as expected.

a) RDT compared to PT. As expected, the cost of microscopy has no influence on the decision to change policy from PT to RDTs, and contours are vertical. Slight aberrations to the verticality of contours are artefacts from simulations. Reference case results that RDTs are cost-effective with 50% certainty below 81% malaria prevalence are confirmed.
b) **Field Microscopy compared to PT.** Microscopy becomes less cost-effective as its cost increases. Microscopy is expected to cost $0.65 in reference case simulations, and the line of 50% certainty corresponds with reference case results at 67% malaria prevalence.
c) RDT compared to Field Microscopy. Even if microscopy was provided at zero cost, RDTs are cost-effective relative to microscopy with more than 50% certainty across all levels of malaria prevalence.
Figure 8. Sensitivity analysis: Cost of an adult dose of ACT
This parameter has a strong impact on the decision to change policy to RDT or microscopy diagnosis from PT, but does not affect the decision to change to RDT from microscopy diagnosis as expected.

a) RDT compared to PT. RDTs become more cost-effective as the cost of an adult dose of ACT increases. This trend is not uniform because the incremental difference in proportion of patients who receive ACTs between diagnostic strategies becomes smaller with increasing malaria prevalence. At low malaria prevalence, everyone receives ACT under PT, but the specificity of RDTs screens out 95% of patients with NMFI, who go on to receive antibiotics. At high prevalence, almost every patient receives ACT with both PT and RDT diagnosis. Therefore, raising the cost of ACT affects both sides of the decision tree equally at high prevalence, and the cost-effectiveness outcome is not strongly affected. ACTs are expected to cost $1.70 in reference case simulations, and the line of 50% certainty corresponds with reference case results at 81% malaria prevalence.
b) **Field Microscopy compared to PT.** This comparison is very similar in trend to RDT compared to PT. The confidence intervals are shifted to the left along the malaria prevalence axis because microscopy has lower sensitivity and specificity than RDTs.
c) RDT compared to field Microscopy. RDTs are more than 50% cost-effective relative to microscopy across all levels of malaria prevalence. About the same amount of ACT is prescribed in each strategy, thus, the cost of ACT has little effect on baseline results. This figure confirms the spread of uncertainty around extreme levels of prevalence.
**Figure 9. Sensitivity analysis: Adherence to ACT**

This parameter has a moderate impact on the decision to change policy to RDT or microscopy diagnosis from PT, and has a slight impact on the decision to change to RDT from microscopy diagnosis.

a) **RDT compared to PT.** RDTs become less cost-effective as adherence to ACT increases. The main impact of better adherence to ACTs is that treatment failures due to non-adherence to ACTs are avoided, particularly relevant in areas of high malaria prevalence. All strategies become less costly as secondary treatment costs are avoided, and more effective as unnecessary mortality is avoided. These factors impact PT more strongly than RDT diagnosis because PT has higher sensitivity (Annex 7). The trend in cost-effectiveness is not uniform (i.e. contours become more vertical at higher malaria prevalence) because there is a greater difference in the proportion of patients that receive ACT as their first line drug at low malaria prevalence than at high prevalence. An average of 71% of patients adhere to ACT in reference case simulations, and the line of 50% certainty corresponds with reference case results at 81% malaria prevalence.
b) Field Microscopy compared to PT. The cost-effectiveness thresholds are lower for microscopy than RDTs because microscopy has lower sensitivity and is relatively less effective. Effectiveness is calculated as the product of sensitivity, adherence, and efficacy. For microscopy, this calculation is $(82\% \times 85\% \times 71\% = 50\%)$. For RDTs, this calculation is $(93\% \times 85\% \times 71\% = 57\%)$.
c) RDT compared to Field Microscopy. RDTs are more sensitive than microscopy, so are cost-effective when adherence to ACT is high. At high malaria prevalence, when few patients adhere to ACT, effectiveness between RDTs and microscopy are equal, and the lower costs of microscopy determine its cost-effectiveness (Annex 7, a1,b1). At 0% prevalence, no patient has malaria, so adherence to ACT does not affect the decision, and it does not matter which diagnostic tool is used.
Figure 10. Sensitivity analysis: Adherence to antibiotics
This parameter has a strong impact on the decision to change policy to RDT or microscopy diagnosis from PT, and has a slight impact on the decision to change to RDT from microscopy diagnosis.

a) RDT compared to PT. RDTs become more cost-effective as adherence to antibiotics increases. The main impact of better adherence is that first-line therapy for patients diagnosed with NMFI is less likely to fail, particularly relevant in areas of low malaria prevalence. This change has very little impact on costs, highlighting the fact that second-line treatment of bacterial infection is much less costly than that for malaria (C6-C9). Fewer DALYs are incurred at low malaria prevalence as adherence improves. The trend in cost-effectiveness is not uniform (i.e. contours become more vertical at higher malaria prevalence) because there is a greater difference in the proportion of patients that receive antibiotics as their first line drug at low malaria prevalence than at high prevalence. An average of 71% of patients adhere to antibiotics in reference case simulations, and the line of 50% certainty corresponds with reference case results at 81% malaria prevalence.

1 Compare to Figure 12
b) **Field Microscopy compared to PT.** The cost-effectiveness thresholds are lower for microscopy than RDTs because microscopy has lower specificity and is relatively less effective.
c) RDT compared to field Microscopy. RDTs are more specific than microscopy, so are cost-effective when adherence to antibiotics is high. At low malaria prevalence, when few patients adhere to antibiotics, effectiveness between RDTs and microscopy are equal, and the lower costs of microscopy determine its cost-effectiveness (Annex 8, a1,b1). At 100% prevalence, no patient has NMFI, so adherence to antibiotics does not affect the decision to adopt RDTs with their higher sensitivity for malaria.
Figure 11. Sensitivity analysis: Probability that a patient diagnosed negative for malaria receives an antibiotic
This parameter has a moderate impact on the decision to change policy to RDT and microscopy diagnosis from PT, but has very little effect on the decision to choose RDTs over microscopy. When 100% of negative diagnoses receive antibiotics, results are the same as in the base case.

a) RDT compared to PT. The cost-effectiveness of RDTs increases as more patients receive antibiotics, and NMFI outcomes therefore become less severe. DALYs follow a similar pattern as when adjustments are made to adherence to antibiotics (Figure 10, Annex 8); however, more DALYs are incurred when patients do not receive antibiotics at all. Costs of RDTs increase as antibiotic prescriptions increase – no antibiotics are prescribed under PT, so its costs remain the same. Absence of first line costs accounts for the high cost-effectiveness of RDTs at low prevalence and low antibiotic prescription.
b) Field Microscopy compared to PT. Results for the change from microscopy to PT follow a similar trend as in (a), but are less cost-effective since microscopy has a lower specificity relative to RDTs.
c) **RDT compared to Field Microscopy.** Since RDTs have better specificity relative to microscopy, RDTs are cost-effective with over 50% certainty in all conditions except when all patients have NMFI, and none of these patients receive antibiotics. However, in these circumstances, no malaria diagnostic test at all is recommended.
Figure 12. Sensitivity analysis: Severity of Bacterial Illness
This parameter has a moderate impact on the cost-effectiveness of RDTs and microscopy compared to PT, but has very little effect on the decision to choose RDTs over microscopy. As NMFI becomes more severe, it is more cost-effective to distinguish between these diseases and malaria. The impact of this parameter on cost-effectiveness is somewhat muted as 90% of NMFI is assumed to be self-limiting. Parameter values used in this sensitivity analysis are given in the following table.

<table>
<thead>
<tr>
<th>Patient Age</th>
<th>Probability that bacterial illness becomes severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>P25 5 or over</td>
<td>Low: 10.00%  Moderate: 17.50%  High: 25.00%</td>
</tr>
<tr>
<td>P26 Under 5</td>
<td>Low: 20.00%  Moderate: 30.00%  High: 40.00%</td>
</tr>
</tbody>
</table>

a) RDT compared to PT. RDTs are more cost-effective as bacterial illness becomes more severe. Second-line treatment costs and DALYs incurred increase relatively more for PT as NMFI always goes without appropriate first-line treatment. The effects of variation in these parameters are stronger in areas where NMFI is more prevalent than malaria.
b) Field Microscopy compared to PT. Results for the change from microscopy to PT follow a similar trend as in (a), but are less cost-effective since microscopy has a lower specificity relative to RDTs.
c) **RDT compared to Field Microscopy.** RDTs are cost-effective relative to microscopy with over 50% certainty regardless of the severity of NMFI in the range considered.

![Graph showing the cost-effectiveness of RDTs compared to field microscopy. The x-axis represents malaria prevalence among febrile outpatients, ranging from 0% to 100%. The y-axis represents the probability that NMFI becomes severe, ranging from Low Severity to High Severity. The graph indicates that RDTs are cost-effective relative to field microscopy starting from a probability of NMFI becoming severe above 50%. The cost-effectiveness threshold is marked with different shading levels.](image-url)
Figure 13. Sensitivity analysis: Probability Non-Malarial Febrile Illness is Bacterial
This parameter has a strong impact on the cost-effectiveness of RDT or microscopy compared to PT, but does not affect the cost-effectiveness of RDTs compared to microscopy. As NMFI becomes more severe, it is more cost-effective to distinguish between these diseases and malaria. At very high malaria prevalence, the probability that NMFI is bacterial is irrelevant, thus leading to the vertical contours. Effects may be exaggerated as very high proportions of bacterial illness are considered.

a) RDT compared to PT. RDTs are more cost-effective as a greater proportion of NMFI is bacterial, with the potential to become severe. Second-line treatment costs and DALYs incurred increase relatively more for PT as NMFI always goes without appropriate first-line treatment. At all levels of malaria prevalence commonly found in SSA, RDTs are cost-effective when more than 20% of NMFI is bacterial. Below 34% malaria prevalence, RDTs are always cost-effective.
b) Field Microscopy compared to PT. Results for the cost-effectiveness of microscopy compared to PT follow a similar trend as in (a), but shift to lower levels of prevalence since microscopy has a lower specificity relative to RDTs.
c) **RDT compared to Field Microscopy.** RDTs are cost-effective relative to microscopy nearly independently of the proportion of NMFI that is bacterial. Only when all disease is NMFI and self limiting is the less expensive test recommended. However, malaria diagnosis is not logical under these circumstances at all.
Figure 14. Sensitivity analysis: Proportion of patients 5 years old or older
This parameter has little impact on the decision to change policy to RDT diagnosis, and only slight impact on the decision to change to microscopy diagnosis.

a) RDT compared to PT. Increases in cost and DALYs with increases in the proportion of patients five years old or older are very slight, and have little impact on the decision to change policy from PT to RDTs. The cost of PT increases slightly more at low malaria prevalence, leading to the spreading of the 99% confidence contour (Annex 12). When 60% of the population is 5 years old or older, the line of 50% certainty corresponds with reference case results at 81% malaria prevalence.
b) Field Microscopy compared to PT. The main driver of the decision to change from PT to microscopy is the fact that older patients are less likely to become severe than younger patients with incorrect diagnosis or treatment failure. This factor is more important for microscopy than for RDTs, since microscopy has lower sensitivity and specificity. As the proportion of patients becoming severe decreases, the lower sensitivity of microscopy has less of an impact on results, and microscopy becomes more cost-effective. When 60% of the population is 5 years old or older, the line of 50% certainty corresponds with reference case results at 67% malaria prevalence.
c) **RDT compared to Field Microscopy.** With 0% of patients 5 years old or older, RDTs are more costly than microscopy at high malaria prevalence but also more effective (Annex 12). At low malaria prevalence, these differences are much smaller leading to increased uncertainty. When 50% of patients are 5 years old or older, the difference between DALYs incurred by RDTs and microscopy levels off across prevalence, and results become more uncertain across this population structure.

![Graph showing RDT cost-effectiveness relative to Field Microscopy](image-url)

- **100%** Cost-Effective
- **> 95%** Cost-Effective
- **< 95%** Cost-Effective
- **50%** Cost-Effective

**Malaria Prevalence Among Febrile Outpatients**

**Population Over Five Years Old**
**Figure 15. Sensitivity analysis: Secondary costs excluded**

Results for the decision between RDTs and PT are shown in the following figure to illustrate the impact of secondary costs in the model. Curves were chosen over planes as the tested parameter is not varied over a range, and this figure should be compared to Figure 4. There was no perceptible change in results from the reference case. These results are interpreted in terms of trends in model costs in Annex 13.

RDT compared to PT.
Annex 1. Cost-effectiveness planes: RDT compared to PT

The figures in Annexes 1-3 are incremental cost-effectiveness planes comparing RDTs to PT using reference case assumptions. Incremental DALYs averted are plotted on the x-axis, with incremental costs plotted on the y-axis.

The ceiling ratio affects results only in the northeast and southwest quadrants. In the northeast quadrant, policy makers must make the decision whether to pay more for an intervention that has greater health returns to the investment compared to the comparator strategy. In this case, increases in the decision-maker’s valuation of health willingness to pay improve the chances that the intervention will be approved. In the southwest quadrant, the intervention being evaluated is both less effective and less expensive than the comparator strategy, thus becoming an inferior good. Under these conditions, decision makers will be less likely to decide to save money by accepting a less expensive, less effective intervention as they are willing to pay more for it as they place a higher value on life. If results lie in either the northwest or southeast quadrants, the ceiling ratio becomes irrelevant. Results in the northwest quadrant represent interventions that are more expensive and less effective (dominated interventions), and will always be inadvisable. Results in the southeast quadrant represent interventions that are more effective and less expensive (dominant interventions) and will always be recommended.

The following series of planes represent the decision to change from presumptive treatment to RDTs. At low levels of prevalence, results are clustered around the positive x-axis, so low levels of the ceiling ratio affect only the probability that RDTs will be accepted (a,b,c). As malaria prevalence increases, RDTs become more expensive relative to PT, and eventually exceed the cost of PT (d) (Figure 3b). In addition, more DALYs are incurred with RDTs compared to PT above 82% (Figure 3a). Above this threshold, RDTs become effectively dominated by PT and the decision to reject them is relatively unaffected by changes in the ceiling ratio (e & f).

The spread of results along the y-axis is more pronounced at low malaria prevalence. In these conditions, a large difference exists between PT and RDTs in the proportion of people who require treatment of severe illness. The tails to the lognormal distributions that describe severe treatment costs, such as C18 and C21, extend to very high levels, making it possible for a few patients to incur extremely high total costs. In this case, misdiagnosis of NMFI is more frequent with PT than RDTs at low malaria prevalence. At high malaria prevalence, there are few misdiagnoses on each side of the decision tree, and few extreme values for incremental cost.

The uncertainty along the x-axis is due to uncertainty in the distributions representing probability parameters in the model (beta and uniform) and uniform distributions defining duration of uncomplicated illness (E20, E21). Because these distributions are much more constrained than lognormal, the possibility for extreme outliers does not exist, thus making results along this axis more clustered.
a) 10% Prevalence

RDT compared to PT
10% Prevalence

b) 30% Prevalence

RDT compared to PT
30% Prevalence
c) 50% Prevalence

RDT compared to PT
50% Prevalence

d) 70% Prevalence

RDT compared to PT
70% Prevalence
e) 90% Prevalence

RDT compared to PT
90% Prevalence

f) 100% Prevalence

RDT compared to PT
100% Prevalence
Annex 2. Cost-effectiveness planes: Field Microscopy compared to PT
The following cost-effectiveness planes compare microscopy to PT. Much of the explanation about the trend of cost-effectiveness across malaria prevalence, and the spread of results, is identical to Annex 1. However, the comparison between microscopy and PT is unique in that at high levels of prevalence, microscopy becomes less effective but less costly at low levels of the ceiling ratio. This result indicates that microscopy is an inferior good relative to PT under these specific conditions, with results in the southwest quadrant.

a) 10% Prevalence

Microscopy compared to PT
10% Prevalence
b) 30% Prevalence

Microscopy compared to PT
30% Prevalence

Microscopy compared to PT
50% Prevalence

c) 50% Prevalence
d) 70% Prevalence

Microscopy compared to PT
70% Prevalence

Microscopy compared to PT
90% Prevalence

e) 90% Prevalence
f) 100% Prevalence

Microscopy compared to PT
100% Prevalence

NW

SW

NE

SE
Annex 3. Cost-effectiveness planes: RDT compared to Field Microscopy
The cost-effectiveness planes in this annex compare RDT diagnosis to microscopy. The uncertainty around effectiveness results grows slightly wider in both directions as malaria prevalence increases. This finding stems from the greater probability that patients with malaria become severe and die compared to NMFI (Figure 3), despite the fact that the difference between RDT and microscopy sensitivities is greater than the difference between their specificities (Figure 5). This also confirms the explanation of results in Figure 6 that disease severity has a stronger impact on model results than diagnostic accuracy.

a) 10% Prevalence

RDT compared to Microscopy
10% Prevalence
b) 30% Prevalence

RDT compared to Microscopy
30% Prevalence

RDT compared to Microscopy
50% Prevalence

c) 50% Prevalence
d) 70% Prevalence

**RDT compared to Microscopy**

*70% Prevalence*

![Graph showing the comparison between RDT and Microscopy for 70% prevalence.](image)

e) 90% Prevalence

**RDT compared to Microscopy**

*90% Prevalence*

![Graph showing the comparison between RDT and Microscopy for 90% prevalence.](image)
f) 100% Prevalence

RDT compared to Microscopy
100% Prevalence
Annex 4. Sensitivity analysis: cost of RDT
The model costs of each alternative strategy are presented in this annex according to malaria prevalence for five different RDT costs. Only values for the model cost of RDT are affected. There is no change in any of the trends in costs.

a) Costs according to diagnostic method

a1) $0 RDT Diagnosis

![Diagram showing model costs of diagnostic strategy for $0 RDT Diagnosis]

a2) $1 RDT Diagnosis

![Diagram showing model costs of diagnostic strategy for $1 RDT Diagnosis]
a3) $2 RDT Diagnosis

![Graph showing costs for different prevalence levels.](image)

a4) $3 RDT Diagnosis

![Graph showing costs for different prevalence levels.](image)
a5) $4 RDT Diagnosis

Model Costs of Diagnostics Strategy

Malaria Prevalence Among Febrile Outpatients

- PT Costs
- RDT Costs
- Field Microscopy Costs
Annex 5. Sensitivity analysis: Cost of Microscopy

The model costs of each alternative strategy are presented in this annex according to malaria prevalence for five different microscopy costs. Only values for the model cost of microscopy are affected. There is no change in any of the trends in costs.

a) Costs according to diagnosis

a1) $0 Microscopy Diagnosis

![Graph showing model costs of diagnostic strategy for $0 microscopy diagnosis]

b) $1 Microscopy Diagnosis

![Graph showing model costs of diagnostic strategy for $1 microscopy diagnosis]
a3) $2 Microscopy Diagnosis

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs

RDT Costs

Field Microscopy Costs

a4) $3 Microscopy Diagnosis

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs

RDT Costs

Field Microscopy Costs
a5) $4 Microscopy Diagnosis
The model costs of each alternative strategy are presented in this annex according to malaria prevalence for five different ACT costs. Only values for the model cost of an adult dose of ACT are affected. There is no change in any of the trends in cost.

a) Costs according to diagnostic method. The cost of PT increases dramatically across malaria prevalence with the rising costs of ACT. The increase is of slightly greater magnitude at high malaria prevalence because ACT is used for second-line malaria treatment for uncomplicated patients. The costs of RDT and microscopy also increase dramatically with increasing costs of ACT at high malaria prevalence, and are not strongly affected at low malaria prevalence because few ACTs are prescribed.

a1) $0 ACT
a2) $1 ACT

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

- PT Costs
- RDT Costs
- Field Microscopy Costs

a3) $2 ACT

Malaria Prevalence Among Febrile Outpatients
a4) $3 ACT

Model Costs of Diagnostic Strategy

Malaria Prevalence Among Febrile Outpatients

PT Costs
RDT Costs
Field Microscopy Costs

a5) $4 ACT

Model Costs of Diagnostic Strategy

Malaria Prevalence Among Febrile Outpatients

PT Costs
RDT Costs
Field Microscopy Costs
Annex 7. Sensitivity analysis: adherence to ACT
The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence at five different levels of adherence to ACTs. The main impact of better adherence to ACTs is that treatment failures due to non-adherence to ACTs are avoided at high malaria prevalence. All strategies become less costly as secondary treatment costs are avoided, and more effective as unnecessary mortality is avoided.

a) Costs according to diagnostic method. For all diagnostic strategies, costs do not change at 0% malaria prevalence as ACT adherence changes. Since no patients have malaria, it does not matter if they adhere to ACT. Costs go down as ACT adherence improves at high malaria prevalence due to lower secondary treatment costs. Notice that this decline is not dramatic, and is larger for strategies that have better sensitivities. For PT at 100% ACT adherence and high malaria prevalence, treatment failures due to ACT non-adherence and inefficacy are less costly than those due to incorrect diagnosis of NMFI at 0% malaria prevalence. In comparing the two diseases under these conditions, malaria is less likely to become severe and require second-line treatment than NMFI, despite 90% of NMFI cases being self-limiting.

a1) 0% ACT Adherence
a2) 25% ACT Adherence

![Graph showing model costs of diagnostic strategy for Malaria Prevalence Among Febrile Outpatients.

Malaria Prevalence Among Febrile Outpatients

- PT Costs
- RDT Costs
- Field Microscopy Costs

a3) 50% ACT Adherence

![Graph showing model costs of diagnostic strategy for Malaria Prevalence Among Febrile Outpatients.

Malaria Prevalence Among Febrile Outpatients

- PT Costs
- RDT Costs
- Field Microscopy Costs
a4) 75% ACT Adherence

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a5) 100% ACT Adherence

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs
b) DALYs according to diagnostic method. At high malaria prevalence, DALYs incurred decrease as adherence to ACT improves. This decrease is in proportion to the sensitivity of the strategy. When adherence is a perfect 100% (b5), the effect of drug inefficacy and misdiagnosis can be seen, particularly for PT. Treatment failure due to inefficacy accounts for the DALYs incurred by PT with 100% adherence to ACT at 100% malaria prevalence. This level of efficacy may be explained by drug resistant parasites or other factors.

b1) 0% ACT Adherence
b2) 25% ACT Adherence

Malaria Prevalence Among Febrile Outpatients

DALYs Incurred by Diagnostic Strategy

b3) 50% ACT Adherence

Malaria Prevalence Among Febrile Outpatients
b4) 75% ACT Adherence

Malaria Prevalence Among Febrile Outpatients

b5) 100% ACT Adherence

Malaria Prevalence Among Febrile Outpatients
Annex 8. Sensitivity analysis: Adherence to antibiotics

The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence, for differing levels of adherence to antibiotics. The main impact of better adherence to antibiotics is that treatment failures and unnecessary mortality are avoided at low malaria prevalence. Costs are relatively unaffected, highlighting the low cost of second-line treatment for NMFI.

a) Costs according to diagnostic method. The cost of PT is unaffected as no first-line amoxicillin is prescribed. The costs of RDT and Microscopy drop very slightly as adherence improves, particularly at low prevalence. This result is due to fewer second-line treatments. The drop is small because second-line treatment costs for NMFI are low relative to malaria, and do not strongly affect the model results.

a1) 0% Antibiotic Adherence
a2) 25% Antibiotic Adherence

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

- PT Costs
- RDT Costs
- Field Microscopy Costs

a3) 50% Antibiotic Adherence

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

- PT Costs
- RDT Costs
- Field Microscopy Costs
a4) 75% Antibiotic Adherence

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a5) 100% Antibiotic Adherence

Malaria Prevalence Among Febrile Outpatients
b) DALYs according to diagnostic method. There is no change in the effectiveness of PT since no first line antibiotic is prescribed. The effectiveness of RDT and microscopy improves at low malaria prevalence because effectiveness = specificity * efficacy * adherence. The strongest effect is on RDTs since its specificity is the highest of the three strategies.

b1) 0% Antibiotic Adherence

b2) 25% Antibiotic Adherence
b3) 50% Antibiotic Adherence

![Graph showing DALYs incurred by diagnostic strategy at 50% adherence]

b4) 75% Antibiotic Adherence

![Graph showing DALYs incurred by diagnostic strategy at 75% adherence]
b5) 100% Antibiotic Adherence
Annex 9. Sensitivity analysis: probability that a patient diagnosed negative for malaria receives an antibiotic

The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence, for differing probabilities that a patient diagnosed negative for malaria receives an antibiotic. The main impact of prescribing antibiotics to patients diagnosed negative for malaria is that patients with NMFI receive appropriate treatment. Prescribing antibiotics to NMFI patients incurs costs, but is much more effective than not prescribing them. Reference case results can be seen in a5 and b5, when 100% of negative diagnoses receive an antibiotic.

a) Costs according to diagnostic method. For PT, costs incurred do not change across all levels of antibiotic coverage because all patients receive ACTs instead. At low malaria prevalence, costs increase for RDTs and microscopy as prescription of antibiotics increases. RDTs have the highest specificity, so as more antibiotics are prescribed, the cost of this strategy increases the most. Costs are unaffected at high malaria prevalence because a smaller proportion of patients are diagnosed malaria negative.

a1) 0% patients diagnosed with NMFI receive antibiotic
a2) 25% patients diagnosed with NMFI receive antibiotic

![Graph showing Model Costs of Diagnostic Strategy](image)

Malaria Prevalence Among Febrile Outpatients

a3) 50% patients diagnosed with NMFI receive antibiotic
a4) 75% patients diagnosed with NMFI receive antibiotic

![Graph showing model costs of diagnostic strategy vs. malaria prevalence among febrile outpatients.]

a5) 100% patients diagnosed with NMFI receive antibiotic

![Graph showing model costs of diagnostic strategy vs. malaria prevalence among febrile outpatients.]
b) **DALYs according to diagnostic method.** DALYs incurred at high malaria prevalence do not change with antibiotic prescription since a smaller proportion of these patients are diagnosed malaria negative. Fewer DALYs are incurred by RDT diagnosis than by microscopy because RDTs have better specificity.

b1) 0% patients diagnosed with NMFI receive antibiotic

![Graph showing DALYs incurred by diagnostic strategy](image)

b2) 25% patients diagnosed with NMFI receive antibiotic

![Graph showing DALYs incurred by diagnostic strategy](image)
b3) 50% patients diagnosed with NMFI receive antibiotic

b4) 75% patients diagnosed with NMFI receive antibiotic
b5) 100% patients diagnosed with NMFI receive antibiotic
Annex 10. Sensitivity analysis: severity of bacterial illness
The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence and five different levels of severity for bacterial illness (see Figure 12 for severity definitions). The main impact of the severity of bacterial illness is on the cost of secondary treatment and on DALYs incurred by tests with lower specificity. These effects have the most impact at low malaria prevalence. Effects are muted as severity was varied over a relatively small range.

a) Costs according to diagnostic method. Only a very slight increase in cost for all strategies occurs at low malaria prevalence due to increased second-line treatment costs. This increase has no effect on cost-effectiveness.

a1) Bacterial illness at low severity
a2) Bacterial illness at moderately low severity

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a3) Bacterial illness at moderate severity

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs
a4) Bacterial illness at moderately high severity

a5) Bacterial illness at high severity
b) **DALYs according to diagnostic method.** More DALYs are incurred at low malaria prevalence as bacterial illness becomes more severe. PT is affected the most due to its low specificity. As malaria prevalence increases, the severity of bacterial illness loses impact on results.

b1) Bacterial illness at low severity

![Graph showing DALYs incurred by diagnostic strategy for bacterial illness at low severity.]

b2) Bacterial illness at moderately low severity

![Graph showing DALYs incurred by diagnostic strategy for bacterial illness at moderately low severity.]

b3) Bacterial illness at moderate severity

b4) Bacterial illness at moderately high severity
b5) Bacterial illness at high severity
Annex 11. Sensitivity analysis: probability that non-malarial febrile illness is bacterial
The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence for five different probabilities that NMFI is bacterial. The main impact of the probability that NMFI is bacterial is on the cost of secondary treatment and on DALYs incurred by tests with lower specificity. Effects may be exaggerated as very high proportions of bacterial illness are considered.

a) Costs. A dramatic increase in the frequency of second-line treatment costs causes a large increase in the overall costs of PT at low malaria prevalence as fewer patients are self limiting (moving from a1-a5). This increase is larger for microscopy than RDTs because of the lower specificity of microscopy.

a1) 0% Bacterial illness

![Graph showing model costs of diagnostic strategy against malaria prevalence among febrile outpatients. The graph compares PT costs, RDT costs, and field microscopy costs across different malaria prevalence levels (0% to 100%).]
a2) 25% Bacterial illness

a3) 50% Bacterial illness
a4) 75% Bacterial illness

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a5) 100% Bacterial illness

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs
b) **DALYs.** DALYs incurred at low prevalence increase sharply as more NMFI is bacterial (so a smaller proportion of NMFI cases are self limiting). DALYs incurred increase inversely with specificity of tests. As malaria prevalence increases, the proportion of NMFI that is bacterial loses impact on results.

b1) 0% Bacterial illness

![Graph showing DALYs incurred by diagnostic strategy for 0% bacterial illness.]

b2) 25% Bacterial illness

![Graph showing DALYs incurred by diagnostic strategy for 25% bacterial illness.]

---
b3) 50% Bacterial illness

Malaria Prevalence Among Febrile Outpatients

DALYs Incurred by Diagnostic Strategy

PT DALYs Incurred
RDT DALYs Incurred
Field Microscopy DALYs Incurred

b4) 75% Bacterial illness

Malaria Prevalence Among Febrile Outpatients

DALYs Incurred by Diagnostic Strategy

PT DALYs Incurred
RDT DALYs Incurred
Field Microscopy DALYs Incurred
b5) 100% Bacterial illness
Annex 12. Sensitivity analysis: proportion of patients over 5 years old

The costs and effects of each alternative strategy are presented in this annex according to malaria prevalence with five different proportions of patients over 5 years old. Mortality is set equal across age groups, and the main impact on results is in the probability that illness becomes severe. Increasing the proportion of patients over five increases costs and decreases DALYs incurred across all levels of malaria prevalence for all strategies, but only by very small amounts (less than 0.2 for each).

a) Costs according to diagnostic method. Costs increase only slightly with greater proportions of patients over 5 years old.

a1) 0% of patients over 5 years old
a2) 25% of patients over 5 years old

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a3) 50% of patients over 5 years old

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs
a4) 75% of patients over 5 years old

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs

a5) 100% of patients over 5 years old

Malaria Prevalence Among Febrile Outpatients

Model Costs of Diagnostic Strategy

PT Costs
RDT Costs
Field Microscopy Costs
b) **DALYs according to diagnostic method.** Fewer DALYs are incurred as the proportion of patients over 5 years old declines. Younger patients with malaria are more likely to become severe than older patients by an order of magnitude, and younger patients with NMFI are roughly twice as likely to become severe as older patients. This effect is counteracted by the higher probability that older patients with NMFI develop neurological sequelae.

b1) 0% of patients over 5 years old
b2) 25% of patients over 5 years old

b3) 50% of patients over 5 years old
b4) 75% of patients over 5 years old

b5) 100% of patients over 5 years old
Compared to the reference case (b), removing secondary costs (a) lowers the cost of each strategy in two dimensions – treatment failure and inappropriate diagnosis. At 0% malaria prevalence, the cost of PT falls due to the removal of secondary costs from inappropriate diagnosis. At 100% malaria prevalence, the cost of PT falls due to the removal of secondary costs from treatment failure. Costs fall more at 100% malaria prevalence than at 0% malaria prevalence because the secondary costs of malaria are higher than the secondary costs of NMFI (C6-C8 compared to C9). With no secondary costs, the cost of PT becomes flat across prevalence.

Note that the biggest change caused by eliminating secondary costs can be seen in the comparison between microscopy and PT. This result is due to the fact that the biggest incremental change in cost is between microscopy and PT (the threshold at which microscopy becomes more expensive than PT shifts 11% to the right). At 100% malaria prevalence, the cost of microscopy falls more than for RDTs because RDTs have better sensitivity (P5 compared to P7). This comparison is more noticeable at high prevalence because severe malaria is more costly.

As expected, DALYs are not affected by eliminating secondary costs, and are not shown in a figure.

a) Model costs excluding secondary costs
b) Reference case results (with PT not standardized to the x-axis)
End Notes

1 See the East African Network for Monitoring Antimalarial Treatment website for latest information on parasite resistance to malaria drugs in Africa (EANMAT, 2006).

2 More accurate diagnosis has other public health benefits. With overdiagnosis, fevers that are unresponsive to antimalarials may be included in estimates of drug resistance but actually be caused by a different disease. Conversely, patients that recover after taking antimalarials but have self-limiting fevers may skew perceptions of drug efficacy. Finally, overdiagnosis of malaria affects burden of disease calculations important to disease monitoring and policy making (WHO 2006b).

3 Printed sources included published academic articles and reports, price catalogues, and online resources.

4 For example, among outpatients with negative slide results in Tanzania, 30% were not treated with an antibiotic (Reyburn, Ruanda et al. 2006).

5 The accuracy of parasitic diagnosis is correlated with parasite density. Moody (2002) uses 100 parasites per millilitre as the standard threshold with which to evaluate RDTs.

6 Microscopy sensitivity in hospitals and well-established laboratories, where microscopy is well-supported, is likely to be significantly higher. Diagnosis at this level of health facility is not modelled here.

7 We assumed that approximately 10% of patients over 5 years old were seropositive for HIV when defining model parameters describing disease progression.

8 Note that our definition of ‘severe’ differs from the much narrower criteria for severe malaria specified by WHO.

9 The actual cost of ACTs to African clinics will be contingent upon a variety of factors, including success in obtaining a global subsidy for these drugs early in the supply chain, lower-cost ACT products achieving WHO pre-qualified status, and the maintenance of an adequate harvest of Artemisia annua (Arrow, Panosian et al. 2004; Senior 2005).

10 Since viral illness was assumed to be self-limiting, there was a 0% probability that it would become severe, and only values for uncomplicated disease are relevant.

11 Chronic anaemia from malaria could also be included in YLD calculations, but would be relatively insignificant compared with mortality and neurological sequelae. In addition, it is not clear how treatment of episodes will affect prevalence of chronic anaemia.

12 Testing of a previous version of this model showed that differences are statistically significant between modelled results using triangular distributions as opposed to parametric distributions (Shillcutt unpublished).

13 Lognormal distributions account for the small probability of high costs by having a positive skew. (http://davidmlane.com/hyperstat/A11284.html).

14 See section ‘calculation of cost and net-benefit’ in the methods for definitions of dominant and dominated.

15 The tradeoffs between accepting risk and investing in research to collect further information to inform the decision can be formally evaluated using Expected Value of Information analysis (such as EVPI), which is a current area of methodological development (Fenwick, Claxton et al. 2000).
Examples of populations of febrile patients where malaria prevalence is low exist in regions of Mali just below the Sahara, or adult inpatients in Dar es Salaam Tanzania (Archibald, den Dulk et al. 1998; EANMAT 2006).

Examples of populations of febrile patients where malaria is endemic include areas of Kenya and Tanzania (EANMAT 2006).

An inferior good is less costly than its comparator, but also confers less benefit. For example, SP is substantially cheaper than ACT as a malaria treatment, but is less likely to clear malaria parasites from the patient because of resistance in many areas, so can be classified as an inferior good.

The variation in results inherently reflects the parameter range considered in the sensitivity analysis. For example, future studies may suggest different ranges for the probability that bacterial illness becomes severe (Figure 12), or the proportions of NMFI that are bacterial in origin (Figure 13).

The rationale behind the cost-effectiveness of RDTs at 0% malaria prevalence and 0% antibiotic prescription is as follows: RDTs represent a first-line diagnostic cost, but no first-line treatment costs are incurred. In comparison, no first-line diagnostic cost is incurred by PT, but all patients receive ACT, which is not the appropriate treatment. Since no NMFI patients receive the correct drug in either strategy, health outcomes are the same (Annex 9, b1). However, the initial cost of giving all patients ACT is higher than testing all patients with RDTs, so the cost of the PT strategy is higher (C4 compared to C2). Therefore, RDTs are the cost-effective strategy.

One million deaths from malaria per year translates to 44.7 million DALYs preventable through effective case management, and preventing two million deaths from pneumonia each year would lead to approximately twice this amount (Sazawal and Black 2003; Keiser, Utzinger et al. 2004).

This model assumes that microscopes are used to diagnose malaria only. In some settings, microscopes may be used to detect gastrointestinal parasites, tuberculosis, trypanosomiasis and other pathogens (WHO 2005c), reducing the fixed microscopy costs attributed to malaria diagnosis. Such use may increase the relative value of maintaining a microscope and microscopist in a clinic relative to the value of using RDTs or PT. This additional value of microscopy will vary between clinics and aetiological situations.

Coincidentally, the contour for cost-effectiveness with 95% certainty corresponds to decision-making thresholds used by Medcins Sans Frontiers which consider cost-recovery. In Sierra Leone, an RDT strategy costs the same as clinical diagnosis below 40-50% malaria prevalence among febrile patients. When ACTs cost $2, this threshold rises to 70% (WHO 2006b).

Preliminary data on ACT adherence is mixed. Early evidence showed that 25% of patients discontinued artemisinin when symptoms cleared (Shwe, Lwin et al. 2004). A Zambian study found that 39.4% of patients were probably adherent (Depoortere, Guthmann et al. 2004), and more recent evidence from Tanzania found that 75% of patients completely adhered 48 hours after delivery through existing health systems (Kachur, Khatib et al. 2004). There is some evidence that patients that do not fully adhere with artemisinic regimen still clear all parasites from their system by the fifth day of treatment (Fungladda, Honrado et al. 1998). The main impact of ACT adherence on our results is in the comparison between microscopy and the other two strategies at high prevalence.

Determinants of community antibiotic use reviewed by Radyowijati and Haak (2003) include: use of untrained sources of advice and/or antibiotics, folk beliefs and traditions on antibiotic use, economic considerations, gender preferences, and lack of appropriate knowledge.
Goodman (1999) used 34% malaria prevalence as a high estimate, and 10% malaria prevalence as a low estimate, and did not consider health outcomes so these results are most closely comparable to results in Annex 6 (a1-a5). Goodman’s results differ from this analysis by not considering second-line treatment costs and probabilities; however, Annex 13 shows that these parameters do not have a strong impact on incremental costs at these levels of prevalence. The results presented here show that RDTs and microscopy are cheaper than PT when ACTs cost between $1 and $2. Considering that the current study used a lower cost for RDTs ($0.80 compared to $1.22), and a higher cost for microscopy (mean $0.45 compared to $0.40) our results are very similar to those in Goodman (1999), and where they differ, do so in the expected directions.

In fatal cases of malaria reviewed in Tanzania, 20% were initially treated at home where underdosing of medicine is common. 9.4% of fatal malaria cases were initially treated by a traditional practitioner, while 11.9% of fatal patients did not receive care (de Savigny, Mayombana et al. 2004).

At six health centres in Zambia, 35% of patients with a negative diagnosis according to microscopy were prescribed antimalarials (Barat, Chipipa et al. 1999). At ten hospitals in Tanzania, 39.9% of patients with a negative hospital slide were not treated with antibiotics (Reyburn, Mbatia et al. 2004).

Evidence from small studies is encouraging, finding that health workers perform RDTs with high accuracy in a variety of settings (Premji, Minjas et al 1994; Kilian, Kabagambe, et al. 1999).

Adherence to antibiotics should be investigated across all levels of malaria prevalence, particularly at low levels (Figure 10), and adherence to ACTs should be investigated at high malaria prevalence (Figure 9). Adherence to antibiotics has a strong impact on incremental benefits at low prevalence because first-line antibiotic prescription varies the most widely across diagnostic strategies (Annex 8). Adherence to ACT affects cost-effectiveness at high prevalence due to its effect on both cost and benefits (Annex 7).

Determinants of prescriber and dispenser behaviour reviewed by Radyowijati and Haak (2003) include: lack of appropriate knowledge, lack of trust in or delayed lab results, inappropriate peer norms, unstable or inadequate drug supply, economic incentives, fear of clinical failure/desire to stay on the safe side, desire to meet patient demand, folk beliefs and traditions on antibiotic use, marketing influences, lack of regulation and enforcement, and unclear role as health providers.

Data are not available to inform assumptions about clinician antibiotic prescribing practices, so we assumed they would be given at random to generate conservative estimates of RDT cost-effectiveness.

If antimalarial resistance increases, PT will become even less attractive relative to diagnostic tools – particularly at low malaria prevalence, because the benefits of identifying more true positives with PT are diminished when no effective remedy is available. Conversely, if antibiotic resistance increases, PT will become more preferable relative to diagnostic tools.