Reducing the burden of childhood malaria in Africa: the role of improved diagnostics

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PREFACE

In sub-Saharan Africa, malaria accounts for >1 million deaths annually in children aged <5 years. To combat this rapidly progressing disease, antimalarial drugs are often administered presumptively to children with fever, resulting in massive overtreatment, accelerating the evolution of antimalarial drug resistance and complicating the diagnosis of other acute febrile illnesses. Newer and more effective treatments are now available, but cost limits their use. As antimalarial drug costs increase, diagnostic methods are becoming a crucial component of malaria control and prevention. This paper examines the potential impact of more accessible malaria diagnostic tests on children in sub-Saharan Africa.

INTRODUCTION

Every year, 300–500 million clinical episodes of malaria occur, resulting in ~2 million deaths[1]. A vast majority of these take place in sub-Saharan Africa, and many involve children aged <5 years, among whom estimates of malaria-related mortality range from 541,494 to 1,295,806 deaths each year[2–4]. In the absence of treatment with effective drugs, children can progress to severe malaria in a matter of hours. This condition can present with coma, severe anaemia, acidosis or hypoglycaemia, and mortality rates can reach 30% even among those hospitalized[5,6].

At present, most malaria illnesses in sub-Saharan Africa are diagnosed on clinical grounds alone, without recourse to diagnostic tools. Clinical algorithms, such as the World Health Organization (WHO) Integrated Management of Childhood Illnesses (IMCI) algorithm, are commonly used to diagnose children presenting with fever, but are relatively non-specific[6–9]. Differential diagnosis is difficult because the symptoms of uncomplicated malaria — headache, fatigue, muscle and joint aches, fever, chills and malaise — are common to many other disease syndromes, including influenza, early dengue fever, viral encephalitis, febrile gastroenteritis, early lobar pneumonia, septicaemias, rickettsial infections, leptospirosis and numerous non-infectious conditions[6]. Non-specific symptoms further complicate the diagnosis of even severe malaria and many children are admitted to a hospital with a diagnosis of severe malaria when their symptoms are actually due to other undiagnosed causes[10].

Currently, antimalarial drugs are often administered presumptively to febrile children (that is, children with fever). This practice of overtreatment accelerates the evolution of antimalarial drug resistance and has contributed to the slow progress of malaria control efforts over the past few decades[11,12]. Newer and more effective treatments have become available, but cost is a limiting factor in their distribution. As antimalarial drug costs are increasing, diagnostic methods are becoming a crucial component of malaria control and prevention[13].

Following clinical diagnosis, blood-slide microscopy is the primary diagnostic tool now utilized in resource-limited settings. Expert microscopy is highly sensitive and specific, and allows differentiation of the four malaria parasite species capable of infecting humans: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale* and *Plasmodium malariae*[14]. However, consistent and dependable microscopy requires trained technicians, electricity, well-maintained microscopes and time (~1 h to produce results)[11,14–16]. Referral of patients and transport of blood slides are so time-consuming that they rarely happen. Under field conditions, test performance varies widely[17–19]. Moreover, when microscopy is used, clinicians often mistrust the results and continue to treat those who test negative[17–19]. For these reasons, the use of microscopic diagnosis of malaria is problematic and possibly not appropriate for resource-limited settings, especially in Africa.

Although methods other than microscopy exist for diagnosing malaria, they are not widely used in resource-limited settings. Polymerase chain reaction (PCR) and malaria rapid-diagnostic tests (RDTs) are two such diagnostic tools. PCR is highly sensitive and can differentiate malaria species[14]. However, the cost, time, training and laboratory

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infrastructure requirements make this an unrealistic tool for widespread use in resource-limited settings[14]. Many RDTs are currently available and are being increasingly used in the field. Current RDTs identify *P. falciparum*-specific histidine-rich protein II (HRP2), parasite-specific lactate dehydrogenase (pLDH) or pan-specific aldolase. Barriers to their use include manufacturing quality control, variable field performance, degradation at high storage temperatures and cost[6,13,20]. RDTs that detect HRP2 antigens pose further problems as the antigens can remain in the blood for up to 3 weeks following successful treatment, confounding diagnosis when patients present with multiple fevers in a short time frame[14,20,21]. However, RDTs can be performed close to the home in settings with no infrastructure, and, as the costs of these diagnostics are decreasing, they are becoming more attractive.

Although microscopy, PCR and RDTs can identify parasites in the blood (parasitaemia), they cannot distinguish symptomatic individuals with malaria infection from those with malaria illness. Specifically, they cannot determine whether the parasitaemia is incidental to or the cause of the presenting symptoms. In high-transmission areas, malarial immunity is acquired with increasing age and exposure. As a result, older children and adults suffer fewer and milder clinical attacks. Malaria deaths in these groups are therefore rare[6]. Although partial immunity protects some individuals against the severe manifestations of the disease, it can also complicate the identification of those who truly require treatment[22]. In a non-immune individual, the presence of parasites along with a febrile illness will strongly correlate with disease, and parasitaemia is a useful surrogate for illness for this population. In populations with acquired immunity, there is currently no way to determine which symptomatic parasitaemic individuals have a malaria illness.

In this paper, which reports on an analysis carried out by the malaria working group within the Bill & Melinda Gates Foundation Global Health Diagnostics Forum, we examine the potential health gains associated with improved malaria diagnostics. Our study focused on children aged <5 years with uncomplicated *P. falciparum* malaria in sub-Saharan Africa. We focus on *P. falciparum* because infections with the other species are much less common in this region, and are far less likely to result in severe and complicated disease or death[7].

We considered other scenarios, including identifying patients at risk of progressing to severe malaria, detecting placental parasitaemia in symptomatic and asymptomatic pregnant women, and diagnosing true malaria illness in parasitaemic partially immune populations. However, we decided to focus on children in sub-Saharan Africa largely because of the substantial malaria-related mortality among this population. In this high-risk group, the relationship between malaria parasitaemia and malaria illness is more straightforward than in populations with some degree of acquired immunity, and the presence of peripheral parasitaemia in symptomatic individuals is a useful indicator of malaria illness requiring treatment. Further details of the selection of the diagnostic-intervention node modelled can be found elsewhere[23].

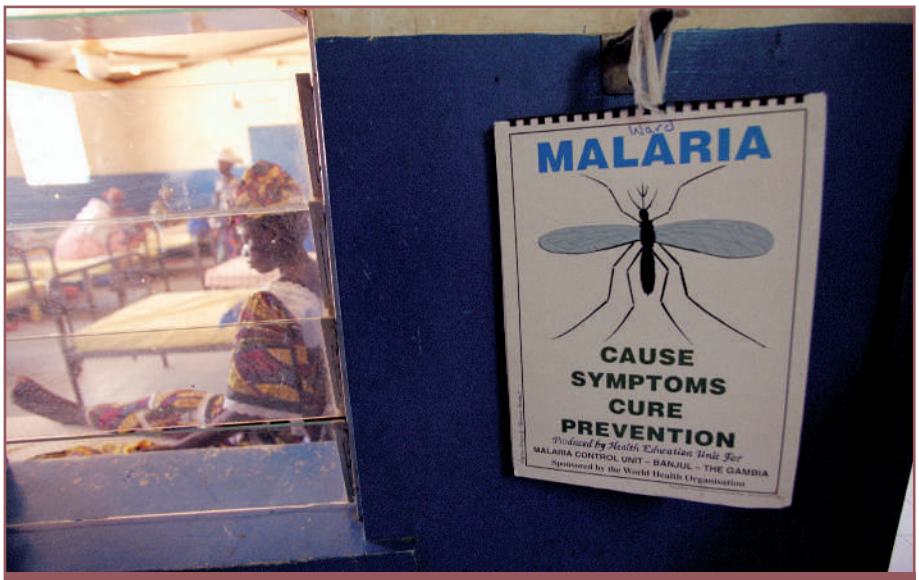
Recently released WHO guidelines recommended providing antimalarial treatment to all febrile children in high-transmission settings[6]. This policy eliminates the need for any diagnostic testing. However, the analyses presented in this paper are based on the assumption that overtreatment of malaria is harmful because it can delay diagnosis of other febrile illnesses, contribute to the development of drug resistance and result in the waste of scarce resources[15,24]. Our study compared the harm resulting from overtreatment with the benefits of using diagnostics in this population.

METHODS

Analytic overview

We developed a decision-tree model for introducing a new diagnostic to detect *P. falciparum* malaria in febrile children aged <5 years. The model was used to calculate the benefits of an improved diagnostic test relative to the status quo in terms of reductions in mortality and overtreatment. The model also identified which characteristics of a theoretical new diagnostic test produced the greatest improvements in health outcomes.

The scenario discussed in this paper assessed the impact of improved malaria diagnostics when a new test was introduced in conjunction with, and as a prerequisite to, improved antimalarial treatment. Consistent with the WHO antimalarial treatment recommendations, our analysis assumed that diagnosis was followed by treatment with an artemisinin combination therapy (ACT)[6]. To determine the benefit of a new diagnostic test above and beyond that of clinical diagnosis, we modelled the impact of a new diagnostic that replaced clinical diagnosis. This was distinct from current field practice, in which a



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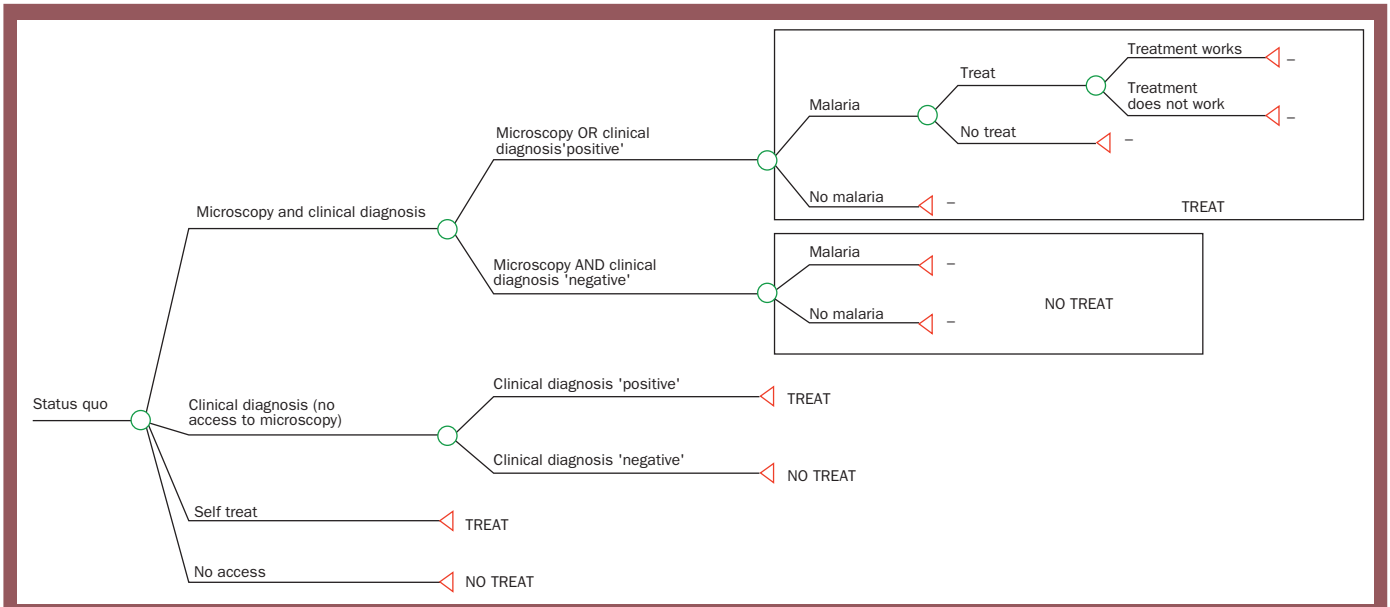

Figure 1 | The status quo of the malaria decision tree

negative microscopy result is sometimes ignored and patients are treated for malaria based on clinical judgement[17,19]. In analyses presented elsewhere, we relaxed the assumptions on access to effective treatment following diagnosis and on provider adherence to the new diagnostic test results[23].

We assumed that in the status quo, those individuals who currently received microscopy and/or clinical diagnosis were also treated with an ACT. All children with access to the new diagnostic were assumed to receive an ACT following a positive test result. We assumed that those who self-treated received less-effective therapy. Several factors contributed to the diminished effectiveness of self-treatment, including poor drug quality, inappropriate dosing, poor compliance and drug resistance[25–27].

The primary health outcome in our model was adjusted lives saved: this composite measure incorporated both immediate lives saved due to

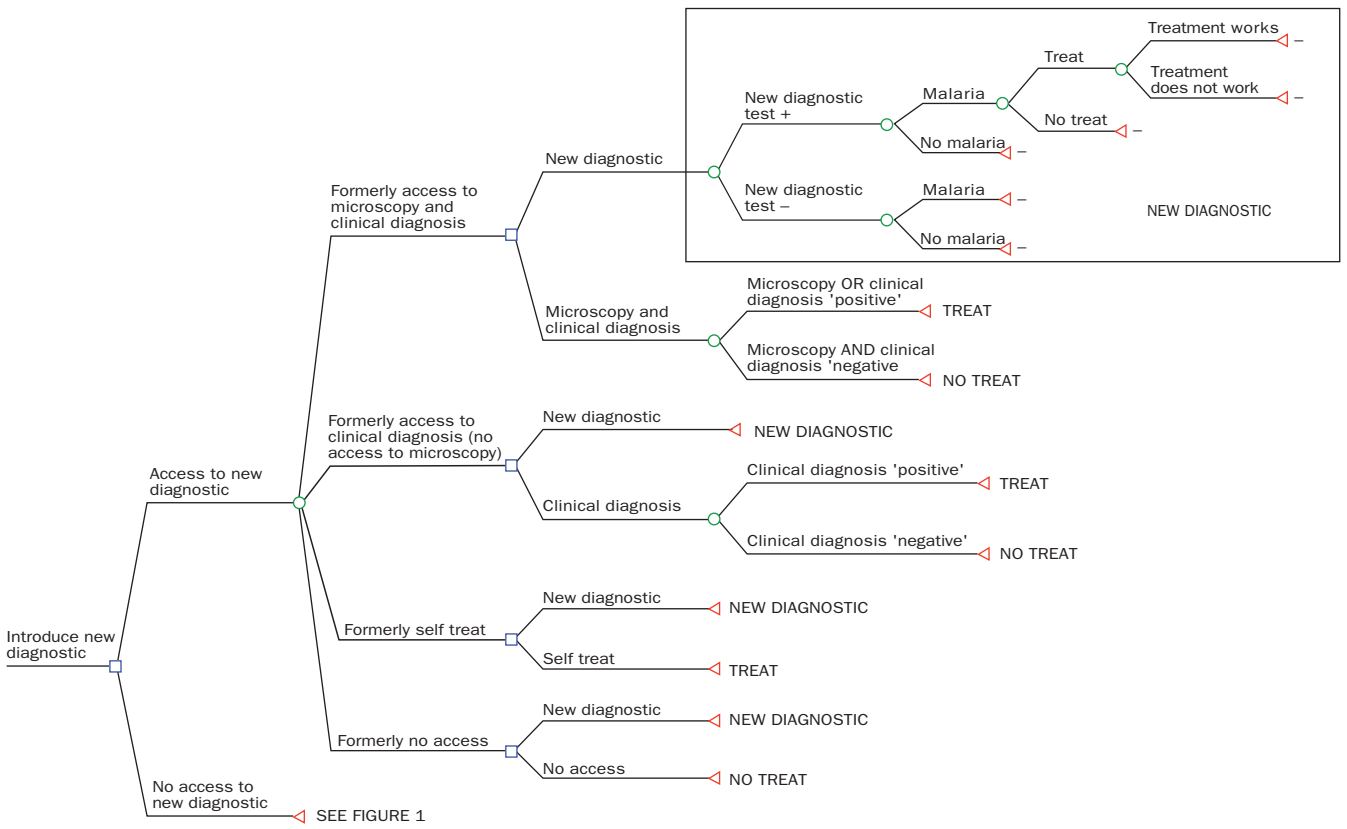

Figure 2 | Decision tree for the introduction of a hypothetical new malaria diagnostic

wider access to diagnostics and improvements in sensitivity, and lives saved indirectly due to reductions in overtreatment and delayed resistance development. Because immediate lives saved was a key component of adjusted lives saved we also reported malaria-related deaths averted. We tracked unnecessary treatments averted, to provide an indication of the lives saved indirectly through reductions in overtreatment. The model did not explicitly track cost savings or deaths averted due to non-malaria illness.

Modelling malaria diagnosis and management

Figure 1 depicts our generalized characterization of current malaria diagnostic practice for symptomatic children in sub-Saharan Africa, or the status quo. Although a single episode of malaria could be associated with several contacts with the health-care infrastructure, for the purposes of constructing this model we used the highest level of care reached for each febrile episode[28,29]. Furthermore, the model assumed that all malaria episodes occurred with fever, and so represented a subset of the annual fever episodes experienced by each child. The model also assumed that all febrile children entering the decision tree had equivalent symptoms, and so did not distinguish cases by severity.

In our model, we first divided febrile children into four categories according to the action taken by the caregiver. The top branch, which was referred to as microscopy and clinical diagnosis, showed children with access to several diagnostic options. We assumed that microscopy was used only when children could wait for the results, and so there was no loss to follow-up. Although the IMCI guidelines promote adherence to test results, evidence indicates that when the symptoms indicate malaria, the providers continue to treat for malaria, even in the presence of a negative test result[17,19]. Children in this category were therefore considered to test positive if this was indicated by either metric (that is, microscopy or clinical diagnosis). The second branch from the top, which was referred to as clinical diagnosis, showed children who were taken to a trained health-care provider, such as a nurse, clinical officer or other medical worker. We assumed that the trained providers knew how to detect malaria using a clinical algorithm, such as the IMCI guidelines. The third branch, which was referred to as self-treatment, applied to children who received treatment procured by a caregiver from a local shop or pharmacy[30]. Our model assumed that children who were self-treated would receive less-effective therapy from these sources than from trained health-care providers. The bottom branch, which was referred to as no access, showed children who did not obtain any malaria diagnosis or treatment, possibly as a result of a lack of transportation or finances. This category also included children taken to traditional healers who did not make use of recognized antimalarials.

Using this model, we simulated the impact of introducing a new diagnostic test that some proportion of febrile children would have access to. Figure 2 depicts the introduction of a hypothetical new diagnostic. This type of test is characterized by its sensitivity, specificity and the percentage of the population with

Table 1 | Parameter base case values and ranges for sub-Saharan Africa*

Parameter	High transmission/medium access		Low transmission/low access		References
	Base case	Range	Base case	Range	
Epidemiology and prevalence					
Children aged <5 years living in the scenario of interest†	44,044,040		14,819,170		32,36 and expert opinion
Annual childhood fever incidence	9	6–10	9	6–10	4
Annual childhood malaria incidence	1.4	1–2	0.18	0–0.5	4
Test characteristics‡					
Sensitivity of microscopy (%)	70	50–90	70	50–90	10,17,19
Specificity of microscopy (%)	65	50–90	65	50–90	10,17,19
Sensitivity of clinical diagnosis (%)	90	80–100	73	65–90	7–9
Specificity of clinical diagnosis (%)	30	20–40	71	60–80	7–9
Health-care access					
Percentage of fever cases who receive microscopy	20	15–25	5	0–10	28 and expert opinion
Percentage of fever cases who receive clinical diagnosis	50	45–55	45	40–50	28 and expert opinion
Percentage of fever cases who self-treat	20	15–25	35	30–40	28,30 and expert opinion
Treatment effectiveness§					
Effectiveness of first-line treatment (%)	85	80–95	85	80–95	41,42
Effectiveness of treatment purchased at pharmacy (%)	50	25–70	50	25–70	26,43
Health outcomes					
Case fatality of untreated malaria (%)	3	1.5–4	3	1.5–4	33‖
Case fatality of those who fail treatment (%)	1	0.5–2	1	0.5–2	Expert opinion
Harm of treatment (lives)¶	0.005	0.0015–0.01	0.0012	0.0005–0.005	31

*Base case values and ranges are listed for two of the six regions; the regions not listed are high transmission/high access, high transmission/low access, low transmission/ high access and low transmission/medium access. For the full parameters, see ref. 23. †Classification of sub-Saharan African countries into those with high, medium and low access to malaria diagnostics was undertaken by the malaria and diarrhoeal disease working groups of the Bill & Melinda Gates Foundation Global Health Diagnostics Forum. Estimates of the number of children aged 0–4 years living in each country were taken as the 2005 medium variant from the 2004 Revision of the United Nations World Population Database (http://esa.un.org/unpp/index.asp?panel=2). ‡Reported test characteristics of microscopy and clinical diagnosis varied greatly. We considered reported performance characteristics from field studies, and then estimated the base points that best reflected combined field experience and operation outside of study conditions. §Treatment effectiveness refers to the combination of drug efficacy, patient compliance and appropriate prescription. ‖Additional academic and field experts were surveyed for estimates of the case fatality rate of untreated uncomplicated malaria. ¶Harm of treatment incorporates factors such as increases in antimalarial drug resistance, opportunity cost of scarce resources and misdiagnosis of alternative underlying cause of symptoms.

access to it. Access to a given diagnostic depends on the infrastructural and user requirements of the test. We assumed that individuals with the best access in the status quo would be the first to access the new diagnostic. In each setting, the new test would be utilized only if it improved health outcomes compared with the status quo.

Model parameters

Table 1 presents the estimates, ranges and sources of the key parameters. There was considerable uncertainty, as well as national or regional variation, surrounding many of the parameters used in the model. For some, there were simply no data available; in these situations, we sought the expert opinions of forum members and, in certain cases, outside academics and/or practitioners in the field.

Estimates of the proportion of patients with access to various levels of health infrastructure (moderate, minimal or no infrastructure) in sub-Saharan Africa were taken from Girosi and colleagues[31]. Moderate infrastructure implied consistent access to running water, electricity, minimal laboratory equipment and a trained provider (such as a nurse or laboratory technician). Minimal infrastructure implied unreliable access to water and electricity, a physical location with no laboratory equipment and a minimally trained provider (such as a pharmcist or village health worker). No infrastructure applied to settings with no reliable water or electricity, and assumed the provider performing the test had no specific training; hence, it essentially described a diagnostic that could be used in the home.

Based on consultations with experts from the malaria and diarrhoeal disease working groups within the Bill & Melinda Gates Foundation Global Health Diagnostics Forum, we classified sub-Saharan African countries as having high, medium or low access to status quo malaria diagnosis. High-access countries were those in which ~85% of children were estimated to have access to a trained provider or microscopy, in contrast to 70% in medium-access countries and 50% in low-access countries. To further refine the model, we used existing estimates of the percentage of the population in each country living in areas of high, low and no malaria transmission[32]. Areas with no malaria transmission were defined by zero prevalence and, thus, not considered in the model. We therefore established six categories combining access and transmission. The estimated numbers of children in each category are presented in Table 2.

Using information from the literature, together with expert opinion, we estimated a case-fatality rate for treatment failures that was in the range of 0.5 to 2%, whereas that for untreated malaria was in the range of 1.5 to 4%[6,33]. Expert views on these parameters varied widely. To determine a base point for the case fatality of untreated malaria, we assumed that the majority of malaria-related mortality derived from progression to severe malaria, and that severe malaria was always fatal if left untreated[33].

We adjusted mortality outcomes to account for the potential harm of treatment, including allergic reactions, development of drug resistance, inappropriate use of scarce resources and the potential delayed diagnosis of other underlying causes of current symptoms. Specifically, for each child treated with an antimalarial, a fraction of a life was assumed to be lost at some point in the future. Limits on the harm of treatment parameter followed the method presented by Girosi and colleagues, and were based on the observation that, although imperfect, the current practice of using clinical diagnosis (without microscopy) to direct treatment decisions was deemed superior to treating everyone and to treating no one[23,31]. From these limits, we estimated a base point of 0.005 for high-transmission settings. This meant that for every 200 antimalarial treatments given, one life was lost in the future.

Sensitivity analyses

Owing to the large uncertainty in many of our base parameter estimates, we conducted a series of one-way and two-way sensitivity analyses. A multi-way probabilistic uncertainty analysis (a Monte-Carlo simulation) was used to estimate the probable range of expected outcomes for each hypothetical new diagnostic examined[34]. For each iteration of the Monte-Carlo simulation, the input parameters were independently drawn from a triangle distribution over the ranges specified in Table 1. The standard deviations of the distribution of outcomes were derived from 1,000 iterations of the Monte-Carlo simulation and were used to measure outcome uncertainty.

RESULTS

Before estimating the impact of hypothetical new diagnostics, we calibrated the model against accepted estimates of the number of malaria-related deaths in children aged <5 years in sub-Saharan Africa. Current estimates gave a combined range of 541,494 to 1,295,806 [3,4,35]. Using the parameters outlined in Table 1, our model predicted 965,578 annual childhood deaths caused by malaria in sub-Saharan Africa. To better represent current treatment practices, we relaxed assumptions on the effectiveness of first-line treatment to 60% and of pharmacy treatment to 30%; in this situation, the model predicted 1,182,970 deaths. The calibration process was also used to exclude exceptionally large estimates of the untreated case-fatality rate. For instance, holding all else constant, an untreated case-fatality rate of 10% would lead to estimates of >3 million childhood malaria deaths annually in sub-Saharan Africa — a clear overestimate.

Table 3 outlines the impact of a policy linking treatment with ACT to a diagnostic test that identifies malaria infection. Each row in Table 3 corresponds to a potential new diagnostic defined by infrastructure requirements (moderate, minimal or no infrastructure), sensitivity and specificity. The infrastructure requirements of a new diagnostic will determine the percentage of children with access to it[31]. We tracked the impact of a new diagnostic using three metrics: adjusted lives saved, malaria-related deaths averted and unnecessary treatments averted. A negative value for the number of malaria-related deaths averted was interpreted as an increase in short-term malaria-related deaths.

Test 20 in Table 3 shows the benefit of a hypothetical 100% sensitive, 100% specific and universally available test. This 'perfect' test would result in 2,784,919 adjusted lives saved, and therefore represented the maximum health gains possible through improved diagnosis. Relative to the status quo, such a test would avert 642,088 malaria-related deaths, 66% of the predicted annual lives lost to malaria in this population, and 528,941,121 unnecessary treatments. Although a perfect test is an unreasonable goal, it provides a benchmark against which to assess trade-offs in terms of decreases in test sensitivity or specificity, or increases in infrastructure requirements.

Table 2 | Sub-Saharan children aged <5 years divided by transmission intensity and access*

	High access (% of total)	Medium access (% of total)	Low access (% of total)
High transmission	10,551,560 (10)	44,044,040 (40)	28,620,160 (26)
Low transmission	6,632,280 (6)	5,551,290 (5)	14,819,170 (13)

*Population of children aged 0–4 years in sub-Saharan Africa living in areas of malaria transmission according to status quo access to malaria diagnostics and malaria transmission intensity. Children living in areas of no malaria transmission were excluded from this calculation.

Tests requiring minimal or no infrastructure produce largest gains

The results indicated that tests requiring moderate infrastructure would have only limited impact, and that increased access would be needed to achieve a significant benefit. For example, a 100% sensitive and 100% specific test requiring moderate infrastructure (Table 3, test 2) would realize only 26% of the potential number of adjusted lives saved. In comparison, an 80% sensitive and 80% specific test requiring only minimal infrastructure (Table 3, test 3) would realize 40% of the potential number of adjusted lives saved, and a 95% sensitive and 95% specific test requiring minimal infrastructure (Table 3, test 9) would achieve 65% of the maximum benefit. Larger gains were possible with a test requiring no infrastructure. At this level, a new diagnostic that was only 90% sensitive and 80% specific (Table 3, test 13) would realize 67% of the maximum benefit.

Sensitivity requirements

Having established the need for a test requiring minimal or no infrastructure, we considered the required sensitivity. The metric of malaria-related deaths averted was used to establish thresholds for sensitivity requirements. As shown by tests 3–6 and 12 in Table 3, some new tests produced an overall benefit in terms of adjusted lives saved (which included malaria-related deaths averted and those averted in the long term through reductions in overtreatment), but resulted in a negative number of malaria-related deaths averted (that is, an increase in the number of immediate malaria-related deaths). Because it was unreasonable to expect clinicians to adopt a diagnostic that produced an increase in malaria-related deaths, a minimal infrastructure test required a sensitivity that was high enough to ensure that a positive number was reported for the malaria-related deaths (Table 3, tests 7–11). To achieve a positive benefit, a minimal infrastructure test required a sensitivity of ≥92% (data shown elsewhere)[23]. Because a test with no infrastructure requirements extended access to those children who currently receive no care, the sensitivity threshold (that is, the point at which positive benefits begin) dropped to 81% (data shown elsewhere)[23].

Once these sensitivity thresholds were established, we then determined minimum sensitivity requirements. To account for uncertainties

Table 3 | Attributable benefits of a new diagnostic that would replace clinical judgment

Test	Sensitivity (%)*	Specificity (%)*	Adjusted lives saved SD†	Malaria-related deaths averted SD‡	Unnecessary treatments averted SD§	Total possible adjusted lives saved (%)‖
Moderate infrastructure¶						
1	95	95	635,993 (177,657)	15,396 (16,680)	141,845,100 (13,780,159)	23
2	100	100	720,178 (164,731)	61,453 (19,528)	153,500,465 (9,157,093)	26
Minimal infrastructure¶						
3	80	80	1,125,343 (398,332)	–260,221 (71,761)	302,893,523 (23,761,961)	40
4	90	80	1,329,135 (454,830)	–14,694 (38,983)	302,893,523 (26,929,491)	48
5	90	90	1,574,136 (199,153)	–14,694 (44,426)	365,028,106 (30,421,389)	57
6	90	95	1,696,636 (267,343)	–14,694 (39,784)	396,095,397 (30,041,704)	61
7	95	80	1,431,031 (402,001)	108,070 (61,464)	302,893,523 (32,129,807)	51
8	95	90	1,676,032 (480,430)	108,070 (48,312)	365,028,106 (31,842,147)	60
9#	95	95	1,798,532 (557,684)	108,070 (54,660)	396,095,397 (19,853,132)	65
10	98	95	1,859,670 (393,620)	181,728 (45,921)	396,095,397 (39,734,068)	67
11	100	100	2,022,928 (288,721)	230,833 (53,055)	427,162,689 (29,167,835)	73
No infrastructure¶						
12	80	80	1,599,205 (429,882)	–6,596 (70,174)	364,781,060 (26,578,084)	57
13	90	80	1,868,415 (343,583)	317,746 (83,601)	364,781,060 (17,713,071)	67
14	90	90	2,192,062 (521,002)	317,746 (96,233)	446,861,090 (35,354,040)	79
15	90	95	2,353,885 (333,462)	317,746 (67,914)	487,901,105 (29,070,712)	85
16	95	80	2,003,021 (493,457)	479,917 (100,575)	364,781,060 (15,211,801)	72
17	95	90	2,326,667 (421,037)	479,917 (106,694)	446,861,090 (30,136,053)	84
18	95	95	2,488,490 (627,778)	479,917 (97,482)	487,901,105 (36,711,469)	89
19	98	95	2,569,253 (584,295)	577,220 (58,806)	487,901,105 (41,085,524)	92
20	100	100	2,784,919 (432,004)	642,088 (96,921)	528,941,121 (18,279,201)	100

The standard deviations for each health outcome are shown in parenthesis. *In the status quo, microscopy sensitivity and specificity are combined with clinical diagnosis; here we assume that the new diagnostic replaces clinical diagnosis. †Lives saved are adjusted to account for the harm associated with treatment and the lives saved through reduction of overtreatment. Therefore, an adjusted life saved is a composite measure reflecting the lives saved through improvements in sensitivity and the lives saved through improvements in specificity. ‡This refers to the number of deaths averted from 1 year of full implementation of the proposed diagnostic and treatment policy. §This refers to unnecessary treatments averted from 1 year of full implementation of the proposed diagnostic and treatment policy, and includes treatments received following microscopy and clinical diagnosis, and those purchased from the pharmacy for self-treatment. ‖The adjusted lives saved by the perfect test (test 20) indicates the maximum reach of a diagnostic in this scenario. This column is the proportion of that maximum addressed by the diagnostic in the given row. ¶A test requiring moderate infrastructure can be performed in a setting where electricity and water are available, and a laboratory is at least minimally equipped (for example, in African hospitals). Staff requirements include nurses, some physicians and a technician with minimal training. A test can be performed in a setting with minimal infrastructure if it does not require water or electricity, and can be administered at a clinic by an individual with minimal training. A test that can be performed in a setting with no infrastructure can be carried out in a home or village with no electricity or water, and by untrained staff or in-home caretakers. See ref. 31 for more detailed information on calculating the percentage of people with access to a new diagnostic requiring moderate, minimal or no infrastructure. #Test 9 refers to the potential reach of existing HRP2-based rapid diagnostic tests to detect clinically relevant parasitaemia (≥500 parasites per μl; see refs. 21,38,39).

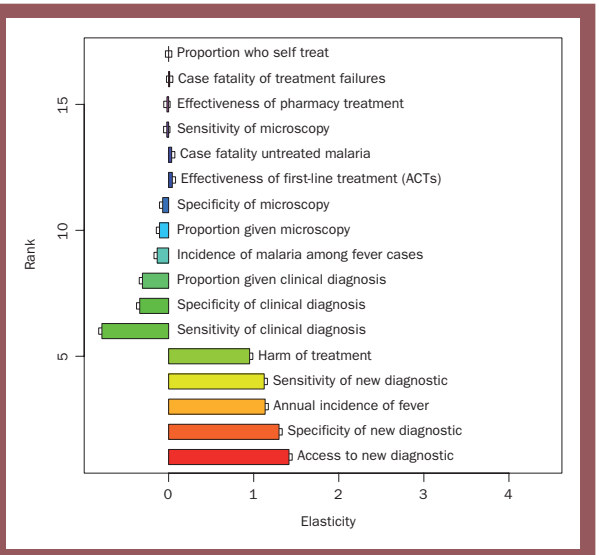

Figure 3 | Elasticities associated with each model input parameter. The base case is a scenario in which the new diagnostic is 95% sensitive, 95% specific and requires only minimal infrastructure (Table 3, test 9). The diagram shows the percentage change in adjusted lives saved for a 1% increase in the given parameter, holding all else constant. For example, a 1% increase in the harm of treatment results in a 1% increase in the total lives saved by a new diagnostic. The parameters are ranked according to their elasticity. The most sensitive parameter is access to the new diagnostic, with an elasticity of ~1.4. This means that a 10% increase in the access to the new diagnostic leads to a 14% increase in total lives saved. ACT, artemisinin combination therapy.

in some of the input parameters and to ensure that a new diagnostic had a significant impact in terms of reducing the number of malaria-related deaths, a test requiring minimal infrastructure needed a sensitivity of ≥95%. A test requiring no infrastructure could achieve an even greater benefit in terms of malaria-related deaths averted with a sensitivity of ≥90%.

Specificity requirements

Because specificity was ≥30% for all status quo diagnostic practices in high-transmission settings, there was a relatively low threshold for test specificity. After meeting sensitivity requirements (95% for minimal infrastructure and 90% for no infrastructure), even a diagnostic that was 50% specific and required minimal infrastructure would avert 139,194,918 unnecessary treatments annually or 155,572,225 if the test required no infrastructure (data shown elsewhere)[23].

Owing to the rampant overtreatment associated with malaria, once the required sensitivity levels had been achieved, greater relative benefits were gained by improving test specificity rather than trying to increase sensitivity further. For example, a 90% sensitive and 90% specific test requiring no infrastructure (Table 3, test 14) resulted in 2,192,062 adjusted lives saved. By increasing test specificity to 95% (Table 3, test 15), 2,353,885 adjusted lives were saved, whereas a similar increase in sensitivity (Table 3, test 17) resulted in 2,326,667 adjusted lives being saved — a difference of 27,218 adjusted lives. By reducing overtreatment, lives were saved indirectly by delaying the development of resistance, conserving health resources and improving the differential diagnosis of alternative causes of fever.

It was therefore our opinion that a minimum infrastructure test should have ≥95% sensitivity and 90–95% specificity. We noted that current malaria diagnostic technology supported this high specificity threshold[21]. Tests 8 and 9 in Table 3 illustrate the health impacts of these diagnostics and should be achievable in the near term.

Because the largest gains derived from tests requiring no infrastructure, it was also our view that long-term improvements in malaria diagnostics must strive to reach individuals who currently have no access to care. A 90% sensitive test and 90% specific test requiring no infrastructure could achieve significant benefits. Test 14 in Table 3 illustrates the health impacts of these requirements.

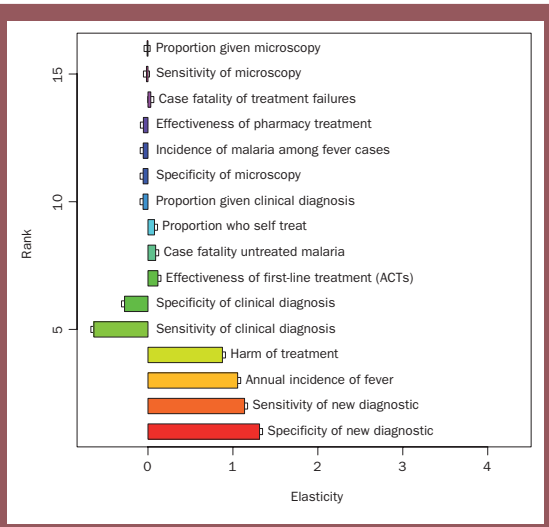

Figure 4 | Elasticities associated with each model input parameter. The base case is a scenario in which the new diagnostic is 90% sensitive and 90% specific, and requires no infrastructure (Table 3, test 14). The diagram reports the percentage change in adjusted lives saved for a 1% increase in the given parameter, holding all else constant. For example, a 1% increase in the annual incidence of fever results in a 1% increase in the total lives saved by a new diagnostic. The parameters are ranked according to their elasticity. The most sensitive parameter is the specificity of the new diagnostic, with an elasticity of ~1.3. This means that a 10% increase in the specificity of the new diagnostic leads to a 13% increase in total lives saved. ACT, artemisinin combination therapy.

Sensitivity analyses highlight trade-offs in test performance

In order to gain a better understanding of how the parameters of the model influenced the recommendations, we carried out a series of one-way and two-way sensitivity analyses. Figures 3 and 4 outline the percentage change in adjusted lives saved for a percentage change in each input parameter (that is, the elasticity of each input parameter) for tests 9 and 14 in Table 3, respectively. Despite the large elasticity of both annual fever incidence and the harm of treatment, the recommendations were found to be robust against large changes in both parameters (data reported elsewhere)[23]. Figures 5 and 6 present two-way sensitivity analyses. Figure 5 highlights the trade-off between the sensitivity and specificity of a new diagnostic, and reinforces the preference for improvements in specificity once minimum sensitivity requirements are met. Figure 6 displays the trade-off between improvements in test specificity and increased access to a new diagnostic.

Table 3 also reports the standard deviations for each health outcome derived from the Monte-Carlo simulation. These standard deviations were large, confirming that the minimum thresholds developed from the reported point estimates should be interpreted cautiously.

DISCUSSION

Many factors contribute to the large number of annual malaria deaths, including behaviour, economics, environment and the extent of drug resistance. Diagnostic tests cannot address all of these issues. However, our model suggests that the introduction of widely available and improved diagnostics, coupled with effective treatment, would result in ~1,800,000

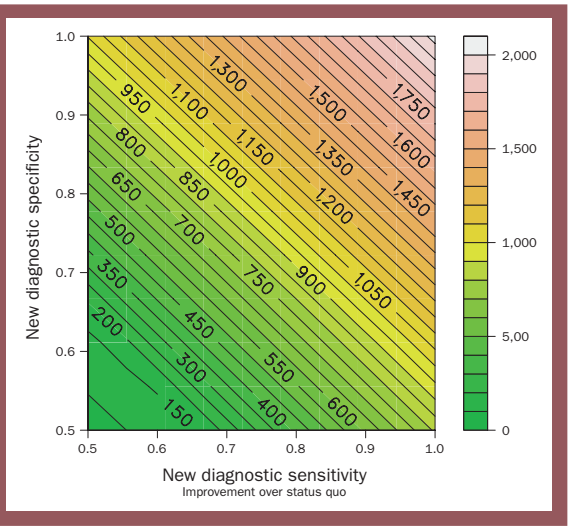

Figure 5 | Trade-off between sensitivity and specificity for a new diagnostic requiring minimal infrastructure. For example, a test that is 70% sensitive and 70% specific will save ~650,000 adjusted lives. An increase to 80% sensitivity and 70% specificity will result in 875,000 adjusted lives saved. The slopes of the isocurves indicate that, for equivalent increases in sensitivity and specificity, improvements in the latter lead to greater gains in adjusted lives saved.

adjusted lives saved. This effect would occur both directly through improved case detection and indirectly through conservation of resources, slowed development of drug resistance and improved differential diagnosis of febrile children. A more specific malaria diagnostic would better identify those children without malaria who need more careful examination to determine an alternate diagnosis. A test with 95% sensitivity and 90–95% specificity that required minimal infrastructure would result in >100,000 immediate malaria-related deaths averted and >365 million unnecessary treatments averted among children aged <5 years in sub-Saharan Africa. A test with 90% sensitivity and 90% specificity that required no infrastructure would result in >300,000 malaria-related deaths averted and >446 million unnecessary treatments averted. These large numbers of unnecessary treatments averted are owing to the now widespread overtreatment of malaria. A significant portion of non-malaria febrile episodes are now mistakenly treated as malaria.

For a new diagnostic to achieve the benefits shown here, the test results must be adhered to. A significant portion of the value of a new diagnostic results from the reduction in unnecessary malaria treatments, and a test cannot significantly reduce overtreatment if providers ignore negative results and continue to treat patients. The results of this analysis show that significant benefits are possible through applying a new malaria diagnostic to treat only those who need it. We note further that the recent WHO recommendation that ACT be adopted as a first-line treatment for malaria in endemic countries would greatly increase the cost associated with treating malaria. If the current practice of excessive overtreatment carries over to the disposition of ACT, health facilities will quickly deplete their stocks of antimalarials and face shortages. The cost of unnecessary treatment borne by the public health-care system and the individual might be substantial with newer and more-expensive treatments. On average, for most countries in sub-Saharan Africa, health-care budgets amount to less than US$20 per person per year, and a single course of ACT for a child costs between US$0.9 and US$1.4[36,37]. Therefore, even if costs fell to US$0.5, a new test requiring minimal infrastructure with 95% sensitivity and 95% specificity would save nearly US$200 million in unnecessary treatments averted in children alone.

This modelling exercise generated a number of insights that will be useful for diagnostic development. Our analysis showed that, to reach high-risk patients in sub-Saharan Africa who currently self-treat or have no access to care, a new diagnostic test should require at most minimal infrastructure. Moreover, a test requiring minimal infrastructure should not rely on electricity or water, but should produce results in <5 min, rely on finger-prick blood, urine or saliva, and be entirely self-contained and simple to use for health-care workers with minimal training. To push diagnostics to the periphery where there is little or no infrastructure, and to access those who currently receive no care, a new diagnostic would have to be suitable for use in the community or home without reliance on electricity or running water, should utilize urine, saliva or finger-prick blood, and be simple enough so that no training would be required. To persuade clinicians to use a new diagnostic, the test must avert malaria-related deaths. A test requiring minimal infrastructure must be ≥95% sensitive and ≥95% specific. A test requiring no infrastructure should maintain ≥90% sensitivity and ≥90% specificity. These key points are summarized in Box 1.

While a no-infrastructure test of the sort described here has yet to be developed, we believe that rapid malarial diagnostics requiring minimal infrastructure with 95% sensitivity and 95% specificity for clinically relevant *P. falciparum* parasitaemia (≥500 parasites per μl) are within reach given the current commercially available HRP2-based tests[21,38,39]. HRP2 is a viable and highly specific biomarker when used for children aged <5 years. The current analysis showed that deployment of such tests to guide treatment decisions for febrile children aged <5 years would drastically reduce overtreatment, and improve the differential diagnosis of alternative underlying causes of fever. A remaining problem is the persistence of HRP2 for several days following treatment, which makes it difficult to differentiate re-infection in areas of high transmission[14,20,21]. Parasite-specific pLDH and pan-specific adolase are also used in current RDTs.

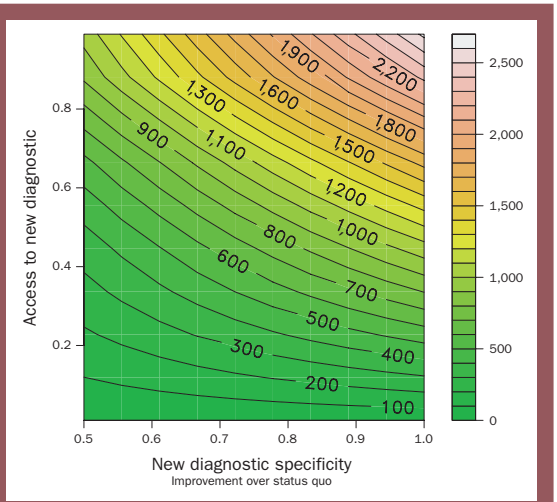

Figure 6 | Trade-off between improvements in diagnostic specificity and broader access to a diagnostic. The omitted parameter is diagnostic sensitivity, which is set to 95%. One way to improve access to a diagnostic is to reduce the infrastructure and user requirements. For example, a diagnostic requiring minimal infrastructure will reach ~75% of the population[31]. A diagnostic that is 70% specific will save 1,000,000 adjusted lives. Improving the diagnostic specificity to 90% will save ~550,000 additional adjusted lives. The graph shows that improvements in access to a diagnostic are more important than improvements in specificity, particularly when the initial access is low. Specificity gains in importance when access to the diagnostic is high. This is seen as the steeper slopes of the isocurves as access reaches >90%.

Although pLDH is more useful for monitoring response to treatment, HRP2 outperforms both pLDH and adolase in the case detection of *P. falciparum* malaria[20,21].

Because all current malaria biomarkers correlate with malaria parasitaemia, they are less effective for adults and older children in areas of high transmission. Therefore, diagnostics using currently available biomarkers will not be effective in determining which semi-immune individuals are symptomatic as a result of being parasitaemic. The variable interpretation of test results for different patient sub populations might complicate introduction of current generation RDTs.

Based on our findings, we have formulated short-term and long-term strategies for advancing diagnostics for malaria in sub-Saharan Africa. In the short term, technology development should focus on stabilizing performance and manufacturing quality assurance of the current HRP2-based rapid tests. The feasibility of this strategy is supported by recent work by Bell and colleagues[13]. Over the long term, efforts should focus on pushing these tests to the periphery by reducing infrastructure requirements, and on investigating new biomarkers for malaria illness to ensure that diagnostics do not have variable interpretations for different patient populations.

There are many practical, technical and behavioural obstacles to achieving a massive scale-up of any new malaria diagnostic, whether in the short or long term. Clinical diagnosis has been the primary means of diagnosing malaria for >100 years and many health workers are resistant to relying on any other method. In addition, moving from clinical diagnosis to reliance on confirmed parasitaemia before treatment for children aged <5 years will require a quantum leap for many health-care workers and caretakers, and will therefore necessitate significant and sustained investments in training and capacity building.

Good logistical supply chains are crucial for converting and maintaining new malaria case-management practices. Significant stock ruptures, which are common in many parts of Africa, can quickly break down confidence in, and the use of, new diagnostics and ACTs. New diagnostics must be designed to cope with the common delays in the supply chain, both in terms of shelf life (≥2 years is needed) and storage conditions in developing countries. Heat stability has been a consistent obstacle for current malaria RDTs. Some manufacturers have addressed this problem by improving heat stability from 30 °C to ≥40 °C[13]. Ideally, heat stability should be improved so that new diagnostics can be used in countries where ambient temperatures of 45 °C are not uncommon.

The design of a diagnostic must also take into account the ease of training and use by health workers with the lowest skill levels, or, for tests requiring no infrastructure, primary caretakers and pharmacy workers. New diagnostics must be robust, simple to use and easy to interpret for those with minimal or no literacy skills. It will be crucial to ensure that health-care and pharmacy workers are trained to educate patients about the benefits of the new tools, and to understand the advantages that new diagnostics can bring in identifying non-malaria cases.

Training in differential diagnosis is a key aspect of strengthening the adoption of a new malaria diagnostic. Targeted education at local and national levels can help to reinforce these messages. It is crucial to ensure the availability of other basic therapies (such as antibiotics) for treating common illnesses that might mimic malaria. Failure to offer an alternative diagnosis and treatment for non-malaria cases will often result in a decision by the care-seeker to buy a less effective (and often inappropriate) treatment at the local pharmacy.

Box 1 | Key messages

- A new diagnostic that reaches individuals who self-treat or have no access to care would save lives and drastically reduce overtreatment. A 95% sensitive and 95% specific diagnostic requiring minimal infrastructure would avert >100,000 malaria-related deaths and ~400 million unnecessary treatments, whereas a 90% sensitive and 90% specific diagnostic requiring no infrastructure would avert >300,000 malaria-related deaths and ~450 million unnecessary treatments.
- Tests should require no electricity or water, produce results in <5 min, rely on finger-prick blood, urine or saliva, and be entirely self-contained and simple to use and interpret, whether by health-care workers with minimal training or for community or home use without training.
- For a new diagnostic to achieve the benefits shown here, providers must adhere to test results, and diagnosis must be followed by prompt and effective treatment.
- The required performance of a minimal-infrastructure test could be attained with existing HRP2-based malaria rapid diagnostic tests. To attain the maximum benefits possible, investment in further test development, training and capacity building will be necessary to push the tests to the periphery.
- Over the long term, a new biomarker will be needed to distinguish malaria illness from malaria parasitaemia in partially-immune patient populations.

Even with good supply chains and adequate training, implementation problems will remain for HRP2-based tests. The association of malaria illness and parasitaemia is stronger for children aged <5 years in high-transmission settings, making current generation RDTs more useful diagnostic alternatives in this population. This poses a challenge for the introduction and adoption of diagnostics that rely on currently available biomarkers in high-transmission settings, because of the need to educate providers and caretakers about the variable interpretation of test results when applied to young children compared with semi-immune older children and adults[40]. There is a clear need to identify new parasite or host biomarkers that would only be present during parasite-induced malaria illness. Such tests could further focus treatment on those who need it most.

There are some limitations to this study. The analyses were based on a simplified characterization of malarial diagnosis and treatment for children in sub-Saharan Africa, and did not capture the dynamic processes of malaria infection, care-seeking behaviour and possible relapse or re-infection. The decision tree modelled a single episode of fever, and did not capture the long-term effects of repeated infections or asymptomatic parasitaemia. Reliable data are currently scarce; therefore, as future field studies are conducted, we will be able to update our input parameters and ranges. Moreover, because we modelled at an aggregate level, we did not capture local changes in treatment policies.

Our model assumed that all individuals with geographic access to the new diagnostic test would benefit from it, ignoring economic and behavioural barriers to care. We did not explicitly consider the cost of treatment or diagnostic testing. From past research, we know that cost can be a crucial barrier to accessing appropriate care[37]. If a new diagnostic test increases cost to the patient and, thus, diminishes access to effective treatment, its widespread deployment might reduce access to care and increase mortality. Other potential barriers that might affect access to care include the time and transportation needed to access diagnostic methods. We also assumed that treatment would be available to all those who tested positive. If this assumption is not met, the actual gains will be less than those modelled here.

Finally, we did not explicitly consider alternative causes of mortality. A potential benefit of more specific malaria diagnosis would be the identification of patients with non-malarial causes of their symptoms. Cross-disease modelling efforts could better illuminate these potential synergies and enumerate the reductions in alternative-cause mortality derived from improved malaria diagnosis.

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