WORKING
PAPER

A Technical Supplement: Reducing the Burden of Childhood Malaria in Africa

The Role of Improved Diagnostics

MARIA E. RAFAEL

WR-419-HLTH

December 2006

This is supporting material to Rafael ME, Taylor TE, Magill A, et al. Reducing the burden of childhood malaria in Africa: the role of improved diagnostics. Nature S1 39-48 (2006)

HEALTH

PREFACE

This working paper contains technical material supporting the article by Rafael et. al. "Reducing the burden of childhood malaria in Africa: the role of improved diagnostics" Nature S1; 39-48 (2006). It is intended to be read in conjunction with that article. This supplement includes additional material referred to in the published article as well as supplementary analyses and tables that were not included in the published paper. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding *Nature* paper, was reviewed by two outside experts and was revised in response to their comments. This work was funded by the Bill & Melinda Gates Foundation to support the Global Health Diagnostics Forum.

ACKNOWLEDGEMENTS

We would like to thank Nick White and Patrick Duffy for helpful comments on an earlier draft.

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A. OVERVIEW

An essential component of evaluating and improving global health is access to appropriate diagnostic tools. Diagnostics are critical for identifying the presence of disease at both the individual and population levels, correctly assessing the nature of disease and designating an appropriate course of treatment, monitoring the effects of interventions (whether preventive or therapeutic), and determining drug resistance and/or recurrence of existing diseases. But despite the key role of diagnostics, they have received less attention on the part of researchers and policy makers than do novel therapeutics or preventive strategies.

This technical supplement, in conjunction with the paper by Rafael et al. "Reducing the burden of childhood malaria in Africa: the role of improved diagnostics" appearing with Nature's December 7th, 2006 issue explores the impact of improved malaria diagnostics.

The malaria working group of the Global Health Diagnostics Forum—Terrie Taylor, Richard Allan and Alan Magill—outlined key intervention points where new malaria diagnostic could significantly effect health outcomes. From these intervention points the working group distilled the top three diagnostic priorities for malaria: a community-based test for malaria illness in symptomatic children, a facility-based test for malaria illness in symptomatic children, and diagnosis of malaria illness in pregnancy. Each of these tests was discussed in the context of divorcing parasite detection from the determination of malaria illness. All of the intervention points considered by the Forum members are discussed in the next section of this supplement. We incorporated the first two modeling priorities into a single model which is presented in Rafael et al.[1] We developed a decision tree model that depicts the current and potential new diagnostic tests given to symptomatic children in sub-Saharan Africa. Parameter and structural uncertainty surrounding malaria in pregnancy prevented detailed analysis of the latter intervention point.

B. METHODS

B.1. OTHER DIAGNOSTIC INTERVENTIONS NODES CONSIDERED

The malaria working group for the Diagnostic Forum identified several areas for which a new diagnostic may significantly effect health outcomes. The paper by Rafael et al. discusses the benefits associated with improved diagnosis of febrile children under the age of 5 in sub-Saharan Africa.[1] Below we present several alternative testing scenarios considered by the malaria working group of the Bill & Melinda Gates Foundation Diagnostics Forum.

Diagnosis of pregnant women

Following children, the working identified the second target population for improved diagnostics as pregnant women. Currently, we do not have a clear understanding of the relationship between parasitemia, malaria illness, and maternal and child health outcomes relating to malaria in pregnancy. The malaria working group identified the need to identify women whose pregnancy would be adversely affected by malaria in medium to high transmission settings and to identify all women infected in low transmission settings. For all transmission intensities, current diagnostic methods do not perform well for identifying malaria infection in pregnancy.

Malaria in pregnancy effect the health of both the mother and child through maternal mortality, maternal anemia, birth weight, spontaneous abortion and stillbirth rates.[2] The primary outcome of interest is low birth weight, for all transmission intensities. From cross sectional studies we know that detectable malaria at birth is associated with a 55-310 gram reduction in birth weight.[3] Low birth weight is defined at less than 2,500 grams at birth. Stekedee et al. estimated that each year malaria in pregnancy leads to 75,000 to 200,000 infant deaths in malaria endemic areas.[4,5] In areas of low transmission, where women have limited immunity, malaria in pregnancy has a greater impact on maternal mortality, spontaneous abortion and stillbirth but there is limited data to assess this impact in detail.[2] Current screening programs suggest that a failure to promptly

diagnose malaria in pregnancy in low transmission areas can lead to significant maternal mortality (François Nosten, personal communication).

Screening asymptomatic pregnant women in high transmission settings

Screening asymptomatic women is of primary importance. In high transmission settings, many women remain asymptomatic throughout pregnancy despite peripheral parasitemia and potentially higher rates of placental parasitemia.[2] Microscopy is useful for detecting peripheral parasitemia but is inadequate for detecting parasites sequestered in the placenta during pregnancy.[6,7] The correlation between peripheral and placental parasitemia is still poorly understood. The consequences of placental malaria are significant on the unborn child and are a major treatable cause of low birth weight.[4,5] Much of the data on placental parasitemia derives from cross-sectional studies of women at delivery. There is a need for detailed longitudinal data on pregnant women in endemic settings. This is what is necessary to establish a clear understanding of the course of malaria in pregnancy and the direct impact on pregnancy outcomes.

Screening asymptomatic women will look very different operationally in high and low transmission settings. We note that there is no definitive evidence that pregnant women in endemic settings remain asymptomatic for the duration of their pregnancy. From studies of the effectiveness of intermittent presumptive therapy (IPT) we know that, in the cross section, there are parasitemic asymptomatic pregnant women. However, we do not observe whether these women expressed symptoms at some point before or after the cross section (Feiko ter Kuile, personal communication). In considering modeling improved diagnostics for screening pregnant women in high transmission settings, we assumed that the majority of women would remain asymptomatic,

Most importantly, in high transmission settings the recommended treatment is IPT.[8] This is, in effect, a policy of treating everyone. In such a setting, the role of a new diagnostic is unclear. Is it to limit treatment to a select group who test positive on the chosen diagnostic? Given current treatment recommendations and standards there is no clear role for improved diagnostics in this setting. A diagnostic is important to the extent that

it influences treatment decisions. If mass treatment is the recommend course then information from a diagnostic may not be used in determining treatment. As sulfadoxine-pyrimethamine (SP) loses efficacy for IPT it will become important to identify those women truly requiring treatment. This would require new diagnostics and new biomarkers.

There is potentially a role for an improved diagnostic to detect malaria and/or placental parasitemia in asymptomatic pregnant women in the future. If, due to increasing resistance to SP and lack of a safe replacement drug, IPT is no longer effective and feasible, then there will be a need to target potentially dangerous treatments to those pregnant women who truly need them (Patrick Duffy, personal communication).

Screening asymptomatic pregnant women in low transmission settings

In low transmission settings women are asymptomatic for a far shorter window of time, a matter of days (François Nosten, personal communication). This leaves a very narrow window for screening. While weekly screening programs are important, they are not amenable to static aggregate models. It may also be the case that it is more important to detect very low levels of parasitemia for this population. Overall, it is unclear what proportion of the total burden of malaria in pregnancy occurs in low transmission settings. Low transmission settings may be a second order concern. Estimates of the total burden of malaria in pregnancy are weighted heavily toward sub-Saharan Africa. There is less understanding of the total burden of malaria in pregnancy outside of Africa and in relation to non-*P. falciparum* malaria.

Testing symptomatic pregnant women in low transmission settings

The malaria working group also discussed the potential for testing symptomatic women in low transmission settings. However, once a woman expresses symptoms, it may be too late to prevent malaria-associated adverse birth outcomes through effective treatment (François Nosten, personal communication). Treatment will prevent further progression of the disease and harm to the mother, but the impact on the fetus is unclear (François Nosten, personal communication). In this setting, in order to assess the impact of

improved malaria diagnostics, we need more information on outcomes for those treated once they express symptoms. Without data on outcomes we cannot assess the attributable benefit of a new diagnostic.

Detecting placental parasitemia for research purposes

Finally, improved diagnostics for malaria in pregnancy would be beneficial for research purposes. A diagnostic able to detect placental parasitemia during the course of pregnancy would be useful in tracking the course and intensity of malaria during pregnancy. It would also aid in assessing the effectiveness of particular treatments in clearing sequestered parasites. While this is important for research purposes and advancing knowledge in the field, for this project we are primarily concerned with diagnostics that directly effect individual health outcomes. We do not focus on public health interventions and research oriented diagnostic tools.

Further diagnostics considered for diagnosis in adult and child populations

The group also discussed diagnosis in adult populations. In medium to high transmission settings, very few adults will develop symptoms. In these transmission settings, the majority will remain asymptomatic and will not get sick. These patients are primarily important from a public health perspective as they perpetuate transmission. If symptoms do develop, the disease can progress quickly. In low transmission settings adult populations have little to no immunity and mortality rates will increase. In low transmission settings it is important to identify all patients ill with malaria and the correlation between parasitemia and malaria illness remains reasonably high, although not ideal. Once we move to diagnosis in patients outside of sub-Saharan Africa, new diagnostics will need to identify several species of malaria, *P. falciparum* and *P. vivax* at the minimum. Treatment and outcomes may vary between species.

Diagnosis of adults in medium to high transmission settings

Diagnosis of malaria in adult populations will vary with the level of acquired immunity in the target population. For adult populations in endemic settings, mortality is not the primary concern; reductions in transmission, over-treatment and the waste of scarce

resources are of primary concern. Adults acquire immunity to malaria illness following repeated exposure to infected bites. This means many adults are parasitemic but likely not ill with malaria and do not require treatment. For this population it is not clear what the true prevalence of malaria illness should be. Malaria illness is ill defined for those with acquired immunity.

Diagnosis of adults in low transmission settings

Diagnosis in non-immune adult populations will mimic diagnosis in children under the age of 5. A test developed to target children under the age of 5 should transfer easily into use in adult populations from low transmission settings. However, there are fewer malaria-related deaths in areas of low transmission and so this population contributes minimally to global malaria mortality. There is potentially a larger impact of improved diagnostics for non-immune adults during malaria epidemics. It is also important to note that, while we characterize immunity as dichotomous, it is in fact continuous and the connection between various levels of immunity and malaria illness is still poorly developed in the literature.

A test for severity

A test for severity was discussed in conjunction with diagnostics for children under the age of 5. A severity test would identify those individuals with uncomplicated malaria most at risk of progressing to severe malaria. This diagnostic would be most useful in non-immune populations—younger children in medium to high transmission settings and all patients in low transmission settings. Currently, there are no biomarkers for severe malaria. Even when patients exhibit symptoms of severe or cerebral malaria there is evidence that current diagnostic methods remain relatively non-specific, complicating the differential diagnosis of ill patients.[9] Such a severity test could potentially require high levels of infrastructure as it is more likely to be carried out at a health facility or hospital where patients can be quickly linked to appropriate treatment. If a severity test were used outside of sub-Saharan Africa it would also need to detect alternate malaria species—*P. vivax* in particular.

Gametocyte screening

Reducing transmission was not seen as a primary target. There was some discussion of screening for gametocytes in asymptomatic populations. Gametocytes are what drive transmission and may be present without a patient expressing symptoms. Some antimalarials, particularly artemisinin derivatives, are effective at killing gametocytes. However, currently, there is no policy of screening for gametocytes. This scenario was not seen as a priority. Due to concerns surrounding resistance development, it is unlikely that effective antimalarials would be given to asymptomatic patients purely to control transmission.

Resistance testing

Resistance testing was discussed, but not seen as a priority. Surveillance data can capture regional resistance patterns. Even with detailed resistance profiles for individual patients it is unclear how this would directly impact treatment decisions. It is unlikely that there would be stocks of numerous antimalarials to choose from for subsequent treatment. For many areas of concern, there are two antimalarials used for the national treatment policy, a first- and second-line drug. Further drug selection may be available through the local pharmacy, but these will be of variable quality. Furthermore, even at low to moderate levels of *in vitro* resistance, antimalarials may maintain therapeutic efficacy.

B.2 SELECTION OF THE FINAL INTERVENTION POINT TO MODEL

Our modeling efforts focused on mortality as a primary outcome. For this reason, we focused on *P. falciparum* malaria and children under the age of 5 in sub-Saharan Africa. Other species of malaria—*P. vivax*, *P. ovale*, and *P. malariae*—carry a far lower mortality risk. *P. falciparum* malaria is most prevalent in sub-Saharan Africa. Children are a modeling priority because they represent the population most dramatically effected by malaria in terms of mortality. Adults do die from malaria, but in far fewer numbers. In much of sub-Saharan Africa, symptomatic and fatal malaria is limited to non-immunes. In high transmission areas, children are the largest non-immune population. In these areas the majority of symptomatic cases will occur in early childhood before immunity develops.

While malaria in pregnancy contributes significantly to the global burden of malaria, there are significant barriers to developing a model to assess the attributable benefit of a new diagnostic. For the population with the largest burden of malaria in pregnancy in terms of low birth weight—asymptomatic pregnant women in high transmission settings—the recommended standard of care is to presumptively treat everyone through IPT programs. In the face of IPT, the role of a new diagnostic is ill defined and somewhat controversial. If further studies determine SP is no longer effective for IPT, then there will be a clear need for improved diagnostics in this population to better target potentially harmful treatment to those who truly need it. In low transmission settings there are reasons to target both symptomatic and asymptomatic pregnant women. In both cases, we lack sufficient understanding of the progression of malaria in pregnancy to estimate outcomes associated with treated and untreated malaria in pregnancy. Furthermore, we will need to understand the connection between maternal and fetal outcomes, expression of symptoms and how those relationships vary with transmission intensity. This will be important in determining where to target diagnosis: among asymptomatic women or to those expressing symptoms. There is initial evidence that in low transmission settings we may require near weekly screening to diagnose women before they develop symptoms (François Nosten, personal communication). For all of these reasons we chose to focus our modeling efforts on diagnosis in children under the age of 5.

As more data become available on the outcomes associated with treated and untreated malaria in pregnancy, the impact on outcomes of developing symptoms, the efficacy of IPT in continuing to prevent malaria in pregnancy and the feasibility of new drugs to be used in pregnancy, this modeling will become crucial for assessing the impact of improved malaria diagnostics in pregnancy. Presently, the paucity of data relating to health outcomes of alternative testing and treatment strategies is a barrier to producing reliable model output that can inform policy and funding decisions.

The paper by Rafael et al. offers details on modeling improved malaria diagnosis for febrile children under the age of 5 in sub-Saharan Africa.[1] The following sections of this technical supplement outline several methodological points pertaining to this model, input parameters and supplementary analyses of the impact of a new diagnostic for childhood malaria.

B.3. INPUT PARAMETERS

In the paper "Reducing the burden of childhood malaria in Africa: the role of improved diagnostics" by Rafael et al. we present select input parameters for high transmission/medium access regions and low transmission/low access regions. **Table B.1** is the full input parameter table.

Table B.1: Parameter Base Case Values and Ranges for sub-Saharan Africa

Parameter#	High Transmission High Access		High Transmission Medium Access		High Transmission Low Access		Low Transmission High Access		Low Transmission Medium Access		Low Transmission Low Access		Reference*
	Base Case	Range	Base Case	Range	Base Case	Range	Base Case	Range	Base Case	Range	Base Case	Range	
Epidemiology & Prevalence													
Children <5 living in the scenario of interest†	10,551,560		44,044,040		28,620,160		6,632,280		5,551,290		14,819,170		*Calculation* with data from [10], *expert opinion* and UN POPIN database
Annual childhood fever incidence	9												[11]
Annual childhood malaria incidence	1.4	1--2	1.4	1--2	1.4	1—2	0.18	0 – 0.5	0.18	0 – 0.5	0.18	0 – 0.5	[11]
Test Characteristics ‡													
Sensitivity of microscopy	70%	50% - 90%											[9,12,13]
Specificity of microscopy	65%	50% - 90%											[9,12,13]
Percent of microscopy test negatives treated	43%	N/A	43%	N/A	43%	N/A	18%	N/A	18%	N/A	18%	N/A	*Calculation*
Sensitivity of clinical diagnosis	90%	80%-100%	90%	80%-100%	90%	80%-100%	73%	65% - 90%	73%	65% - 90%	73%	65% - 90%	[14-16]
Specificity of clinical diagnosis	30%	20% - 40%	30%	20% - 40%	30%	20% - 40%	71%	60% - 80%	71%	60% - 80%	71%	60% - 80%	[14-16]
Healthcare Access													
Percent of fever cases who receive microscopy	25%	10% - 30%	20%	15% - 25%	5%	0% - 10%	25%	10% - 30%	20%	15% - 25%	5%	0% - 10%	[17] and *expert opinion*

Percent of fever cases who receive clinical diagnosis	60%	55% - 65%	50%	45% - 55%	45%	40% - 50%	60%	55% - 65%	50%	45% - 55%	45%	40% - 50%	[17] and *expert opinion*
Percent of fever cases who self-treat	10%	5% - 15%	20%	15% - 25%	35%	30% - 40%	10%	5% - 15%	20%	15% - 25%	35%	30% - 40%	[17,18] and *expert opinion*
Percent of population with access to moderate infrastructure	28.4%	21%-30%											[19]
Percent of population with access to minimal infrastructure	75.7%	60%-80%											[19]
Treatment Effectiveness§													
Effectiveness of first-line treatment	85%	80% - 95%											[20,21]
Effectiveness of treatment purchased at pharmacy	50%	25% - 70%											[22,23]
Health Outcomes													
Case fatality of untreated malaria	3%	1.5% - 4%											[24,25] and *expert opinion*‖
Case fatality of those who fail treatment	1%	0.5% - 2%											*expert opinion*
Harm of treatment (*lives*) ¶	0.005	0.0015 - 0.01	0.005	0.0015 - 0.01	0.005	0.0015 - 0.01	0.0012	0.0005 – 0.005	0.0012	0.0005 – 0.005	0.0012	0.0005 – 0.005	*Calculation*

Parameters that do not change across transmission intensity or status quo access to the new diagnostic are only listed in the first column

* Unless otherwise noted, *expert opinion* refers to the malarial working group of the Bill and Melinda Gates Diagnostics Forum: Alan Magill, Terrie Taylor and Richard Allan.

† Classification of sub-Saharan African countries into those with high, medium and low access to malaria diagnostics was undertaken by the malaria and diarrheal disease working groups of the Bill & Melinda Gates Foundation Global Health Diagnostics Forum. Estimates of the number of children age 0-4 living in each country are taken as the 2005 medium variant from UN's World Population Prospectus: The 2004 Revision Population Database found at http://esa.un.org/unpp/index.asp?panel=2

‡ Reported test characteristics of microscopy and clinical diagnosis varied greatly. Malaria working group members considered reported performance characteristics from field studies and then estimated base points to best reflect 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.

Several parameters require additional explanation not provided for in Rafael et al.[1]

Annual Fever Incidence: To estimate the total number of febrile episodes entering the tree and the prevalence of malaria in this population we rely on estimates from Snow et al.: 9 annual fever episodes for children under the age of 5 in Sub-Saharan Africa.[11] We validate this number by matching it to the population weighted average of annualized childhood fever episodes calculated from the Demographic Health Survey (DHS) data for sub-Saharan Africa (found at http://www.measuredhs.com/aboutsurveys/dhs/start.cfm)

Status Quo Access to Malaria Diagnostics: Estimates of current access to microscopy, clinical diagnosis and self-treatment rely heavily on expert opinion. While there is data on the percent of children treated with a first-line antimalarial through DHS, this information does not directly translate to access to trained clinical diagnosis or microscopy. We relied on the malaria and diarrheal disease working groups of the Bill & Melinda Gates Foundation Diagnostics Forum to classify countries into high, medium and low status quo access to malaria diagnostics. **Table B.2** presents these classifications.

Table B.2: sub-Saharan Africa Countries by Access*

High access	Medium Access	Low Access
Angola	Benin	Botswana
Burundi	Burkina Faso	Ghana
Central African Republic	Cameroon	Kenya
Chad	Cote 'dIviore	Lethoso
Congo	Eritrea	Rwanda
Dem. Rep. of Congo	Gambia	South Africa
Equatorial Guinea	Madagascar	Tanzania
Ethiopia	Malawi	Zambia
Gabon	Mali	
Guinea	Namibia	
Guinea-Bissau	Nigeria	
Liberia	Senegal	
Mauritania	Togo	
Mozambique	Uganda	
Niger	Zimbabwe	
Sierra Leone		
Somalia		
Sudan		
Swaziland		

* In instances where there was a discrepancy between experts we assigned the country to the higher access category.

Children living in areas of high and low malaria transmission: To estimate the number of children under the age of 5 living in areas of high and low malaria transmission for each sub-Saharan African country we use the following data from Korenromp et al and the UN population database 2005 medium variant population estimates found at http://esa.un.org/unpp/index.asp?panel=2 . **Table B.3** presents this data.

Table B.3: Population at Risk of Malaria by Transmission Intensity

	Population at risk for malaria by transmission intensity*			Population under age 5†
Country	**Low/ unstable**	**High**	**Total at risk**	
Angola	53	46	99	2,974,000
Benin	0	100	100	1,441,000
Botswana	13	0	13	218,000
Burkina Faso	0	100	100	2,459,000
Burundi	64	21	85	1,326,000
Cameroon	24	74	98	2,453,000
Central African Republic	0	100	100	640,000
Chad	14	86	100	1,867,000
Congo	0	100	100	750,000
Cote 'dIviore	0	100	100	2,773,000
Dem. Rep of the Congo	10	85	95	11,209,000
Equatorial Guinea	2	97	99	88,000
Eritrea	83	16	99	759,000
Ethiopia	50	14	64	13,063,000
Gabon	0	96	96	193,000
Gambia	0	100	100	231,000
Ghana	2	98	100	3,102,000
Guinea	1	99	100	1,590,000
Guinea-Bissau	0	100	100	310,000
Kenya	57	21	78	5,732,000
Lethoso			0	231,000
Liberia	0	100	100	631,000
Madagascar	36	60	96	3,106,000
Malawi	22	77	99	2,340,000
Mali	10	90	100	2,602,000
Mauritania	59	41	100	526,000
Mozambique	4	96	100	3,291,000
Namibia	8	0	8	268,000
Niger	11	89	100	2,851,000
Nigeria	1	99	100	22,257,000
Rwanda	60	7	67	1,500,000
Senegal	3	97	100	1,845,000
Sierra Leone	0	100	100	958,000
Somalia	96	3	99	1,482,000
South Africa	15	0	15	5,223,000
Sudan	42	56	98	5,216,000
Swaziland	69	0	69	136,000
Tanzania	21	75	96	6,045,000
Togo	0	100	100	1,014,000
Uganda	20	73	93	5,970,000
Zambia	16	83	99	2,011,000
Zimbabwe	54	0	54	1,752,000

* Estimates of the percent of the population living at risk of malaria by high, low and no malaria transmission are taken from Korenromp. "Malaria Incidence at Country Level for the year 2004-- proposed estimates and draft report" WHO/RBM Draft report.

† 2005 population estimates of children under the age of 5 are taken from http://esa.un.org/unpp/index.asp?panel=2

Performance Characteristics of Microscopy: Malaria working group members thought microscopy was extremely variable in it field performance. This is the reason for the large uncertainty range surrounding microscopy sensitivity and specificity. The base values for microscopy sensitivity and specificity were based on the field experience of malaria work group members and were chosen so that, when combined with clinical diagnosis in endemic settings, the percent of patients testing negative with microscopy but subsequently treated approximated rates observed in the literature. Barat et al. observed that 39% of all febrile patients testing negative with microscopy were subsequently treated for malaria.[12] When we combine the base estimates of microscopy sensitivity and specificity—70% and 65%, respectively—with the base case estimates of clinical diagnosis sensitivity and specificity in high transmission settings—90% and 30%, respectively—we calculate that 43% of microscopy test negatives will be treated for malaria.

The Percent of Microscopy Test Negative Patients Treated: This parameter was calculated based on the assumption that a patient was treated when testing positive by either microscopy or clinical diagnosis. We also assumed the two tests were independent. Thus, the formula for calculating the percent of microscopy test negative patients subsequently treated is:

$$= (1 - sens_{Microscopy}) * sens_{Clin\ Dx} * p + spec_{Microscopy} * (1 - spec_{Clin\ Dx}) * (1 - p)$$

The Excel workbook titled "`Combing Tests Worksheet.xls`" shows the combined sensitivity and specificity for two tests. This same process is used to compute the percent of test negatives that are subsequently treated when the new diagnostic is combined with clinical diagnosis in the supplementary analyses presented in section D.

B.4. MODELING HEALTH OUTCOMES

For each access category, the set of sensitivities and specificities listed in the parameter table uniquely divide the children into the following four classes (which we refer to as "test outcome classes")

- **True positives**: these are febrile children with malaria who test positive for malaria and are treated with an antimalarial or who belong to the category of children who self-treat.
- **False Positive**: these are children who do *not* have malaria but are treated with antimalarials based on incorrect microscopy, incorrect clinical diagnosis or because they belong to the category of children who self-treat.
- **False Negatives**: these are children who have malaria but are not treated with antimalarials based on incorrect microscopy, incorrect clinical diagnosis or because they belong the category of children who receive no care.
- **True Negatives**: these are children who do not have malaria and are not treated with an antimalarial. They correctly test negative for malaria with microscopy and/or clinical diagnosis or they belong to the category of children who receive no care.

The generic path probabilities for the four groupings listed above are described in Girosi et al.[26] By multiplying these path probabilities by the total number of cases entering our model—the population times the incidence of fever—we obtain the number of children falling in each of the test outcome classes. We denote these numbers by N_{tp}, N_{fp}, N_{fn}, and N_{tn}. Note that, for each access category, N_{tp}, N_{fp}, N_{fn}, and N_{tn} will vary with disease prevalence and the particular test sensitivity and specificity of the status quo diagnostic. As the status quo test sensitivity increases, N_{tp} will increase and N_{fn} will decreases. Similarly, as the status quo test specificity increases, N_{tn} will increase and N_{fp} will decrease.

To evaluate the impact of a diagnostic, we define health outcomes corresponding to each test outcome class. This implies defining four quantities, that we denote by *TP*, *FP*, *FN* and *TN*, which quantify the "amount of health" assigned to a child in a given test outcome class. Once this is done, the total population health outcome is computed as follows:

$$H=N_{tp}TP+N_{fp}FP+N_{fn}FN+N_{tn}TN$$

We considered several choices for measuring health outcomes: deaths averted, changes in DALYs, reductions in unnecessary treatment and cost. We selected malaria-related deaths averted and reductions in unnecessary treatments. DALYs do not sufficiently measure the disease burden for malaria and can be difficult to interpret. Some of the long-term sequelae of malaria, such as cognitive impairment, are not formally included in DALY calculations. Because malaria-related morbidities are not well captured by DALYs, DALY calculations, in the end, differ little from estimates of total life years lost due to malaria-related mortality. While important, costs are secondary to the purposes of this work. Because we are assessing the impact of potential new diagnostics which may have no current counterpart in use, we focus here on outlining the attributable benefit of a new diagnostics rather than assessing cost-effectiveness ratios. Reductions in over-treatment were thought to be important, particularly in areas of lower prevalence. Malaria symptoms are rather non-specific and in areas sensitized to malaria, it is often the most common supposed cause of fever. However, over-treatment of malaria postpones treating other potential true causes of presenting symptoms; it complicates the differential diagnosis of ill children. Over-treatment potentially leads to increases in non-malaria-related mortality.

To calculate the incremental lives saved through the introduction of a new diagnostic for malaria (compared to the status quo) we calculate the total lives lost for both the status quo and the world with the new diagnostic and then compute the difference between lives lost with the new diagnostic and lives lost with the status quo. The incremental health benefit is then expressed as total lives *saved*. Details of calculating total lives saved are given below.

B.5. COUNTING MALARIA-RELATED DEATHS

The first outcome to consider is whether or not a child dies from malaria. We call this outcome the "direct lives lost". For this outcome we assign a value of 1 to instances in which the child dies of malaria and a value of 0 when the child survives, or when the child does not have malaria to begin with. The health outcome corresponding to a given

test outcome class—true positive, true negative, false positive and false negative—is then the average of these values, weighted by the treatment effectiveness and appropriate case fatality. For example, a child who is in the "True Positive" class following clinical diagnosis receives treatment with effectiveness $eff_{First\ Line}$, the effectiveness of first-line antimalarial treatment. Those failing treatment will die with probability $m_{tp.txfail}$, where $m_{tp.txfail}$ is the malaria-related case fatality for those failing treatment. Therefore we set

$$TP_{ClinDx} = 1 \times (1 - eff_{First\ Line}) \times m_{tp.txfail} + 0 \times (1 - eff_{First\ Line}) \times (1 - m_{tp.txfail}) + 0 \times eff_{First\ Line} = (1 - eff_{First\ Line}) \times m_{tp.txfail}$$

This calculation is the same for each access to care category. The only difference between each access category is the parameter used for treatment effectiveness. For example, children who receive medication purchased at the pharmacy will receive less effective treatment. We set $FN=m_{fn}$, where m_{fn} is the case fatality of untreated malaria. There is no treatment effectiveness parameter in the calculation of FN because those who test negative do not receive treatment. Since children in the "false positive" and "true negative" classes do not have malaria, they will never die of malaria in our model. This, we set $FP=TN=0$. Therefore, for each access category, the total number of direct lives lost (i.e. malaria-related deaths) in the status quo is given by:

$$Direct\ Lives\ Lost_{Access\ Category} = N_{tp} \cdot (1 - eff_{Treatment}) \cdot m_{tp.txfail} + N_{fn} \cdot m_{fn}$$

Recall, N_{tp} and N_{fn} will depend on the underlying disease prevalence and test sensitivity. Counting malaria-related deaths only places no value on test specificity. For this reason we also consider the harm associated with treatment.

B.6. Counting Indirect Deaths due to Harm of Treatment

Whenever a child is treated, either appropriately or inappropriately, some harm to society follows. Each time we treat a child with an antimalarial, we contribute to resistance development. Recent setbacks in controlling malaria have been linked to the development of resistance, particularly to chloroquine.[25,27] When resistance to existing antimalarials increases, at some point in the future, individuals infected with a resistant strain may not respond to treatment, leading to adverse health outcomes or even death. In

addition, once resistance develops, new antimalarials are needed, leading to additional costs and consuming resources. Beyond resistance development, there is an opportunity cost to the money spent on unnecessary treatment. Each time we treat a patient with an antimalarial, we utilize scarce resources that may have been otherwise used to treat patients in need. Lastly, overtreatment of malaria can delay diagnosis of the true underlying cause of presenting symptoms and increase alternative-cause mortality.

We quantify the harm of treatment with a single number, *C*, which represents the fraction of a life lost, at some point in the future, as a result of treating one child. We refer to the total number of lives lost due to harm of treatment as "indirect lives lost". The total number of indirect lives lost is computed as follows:

$$Indirect\ Lives\ Lost = C(N_{tp} + N_{fp})$$

The general method developed to compute a range for C is outlined in Girosi et al.[26] The idea behind that method is that if a test is currently used then using that test must be better than treating everybody and better than treating no one. This is enough information to estimate approximately how much weight the medical community assigns to specificity relative to sensitivity. We use the sensitivity and specificity clinical diagnosis to compute bounds on C as this is the most widely accepted form of malaria diagnosis. The bound on *C* has the following form:

$$\frac{p \cdot (1 - sens) \cdot (FN - TP)}{p \cdot (1 - sens) + (1 - p) \cdot spec} \leq C \leq \frac{p \cdot sens \cdot (FN - TP)}{p \cdot sens + (1 - p) \cdot (1 - spec)}$$

$$\Rightarrow \frac{p \cdot (1 - sens) \cdot (m_{fn} - (1 - eff_{First\ Line}) \cdot m_{tptxfail})}{p \cdot (1 - sens) + (1 - p) \cdot spec} \leq C \leq \frac{p \cdot sens \cdot (m_{fn} - (1 - eff_{First\ Line}) \cdot m_{tptxfail})}{p \cdot sens + (1 - p) \cdot (1 - spec)}$$

where p is the prevalence of malaria among those who access a trained provider, *sens* and *spec* are the sensitivity and specificity of clinical diagnosis, and $eff_{First\ Line}$, $m_{tp.txfail}$ and m_{fn} are as described above. The bounds above are most informative when the test characteristics are poor.

The method presented in Girosi et al. does not prescribe the selection of a particular value for C in the given range.[26] Through consultation with the malaria working group of the Diagnostic Forum, we turn this range into a point estimate for the harm of treatment. Because the sensitivity and specificity of clinical diagnosis and the prevalence of malaria vary by transmission setting, we get two values for C, one for high transmission settings and one for low transmission settings. For the base parameters outlined in the parameter table, and assuming ACTs are universally available following clinical diagnosis, we estimate C to be 0.0012 and 0.005 in low and high transmission settings, respectively. These base points were selected to be 90% of the maximum of the estimated range for C. Note that as treatment effectiveness varies, so too will C. As the effectiveness of treatment increases, we expect the value of C to increase as well.

To interpret C, recall that each time we treat one child we lose a fraction *C* of a life at some point in the future. This means that each time we treat $1/C$ children we lose one life. Therefore, using our estimate of *C*, we lose one (indirect) life for every 200 children we treat for malaria in high transmission settings and one (indirect) life for every 833 children we treat for malaria in low transmission settings.

B.7. ADJUSTED LIVES LOST

Adjusted lives lost is the sum of the direct and indirect lives lost. This composite measure incorporates the relative weight of test sensitivity and specificity through the inclusion of the harm of treatment, C, and subsequent indirect lives lost. This is the criterion that we use to compare any new diagnostic with the status quo. Adjusted lives lost is computed as follows:

$$\begin{aligned} &\textit{Adjusted Lives Lost} \\ &= \textit{Direct Lives Lost} + \textit{Indirect Lives Lost} \\ &= N_{tp}TP + N_{fn}FN + C(N_{tp} + N_{fp}) \\ &= N_{tp}(TP + C) + N_{fn}FN + N_{fp}C \\ &= N_{tp}((1 - eff_{Treatment}) \cdot m_{tp.txfail} + C) + N_{fn}m_{fn} + N_{fp}C \end{aligned}$$

B.8. Modeling the Introduction of a New Diagnostic

Once the status quo is modeled, we simulated the introduction of a new diagnostic with certain test characteristics. First, we developed a "hierarchical access model" for the introduction of the new test. This model assumes that access levels can be rank-ordered, from best to worst, and that the new diagnostic is available first to individuals with the best access to care, and then to individuals with progressively worse access to care. For malaria, this means that the first to receive a new diagnostic will be those who currently receive microscopy. The next population to access a new diagnostic will be those who currently receive clinical diagnosis and so on. Further details on the hierarchical access model can be found in Girosi et al.[26]

Consider children living in countries with high access to status quo malaria diagnostics Based on expert opinion we estimate that 25% of this population has access to microscopy with clinical diagnosis and 60% of the population has access to clinical diagnosis alone. If we postulate that a new diagnostic will reach 50 percent of the population then, through the hierarchical model, the new diagnostic will be available to all children who currently access microscopy with clinical diagnosis and a fraction of those who currently receive clinical diagnosis alone. Specifically, 42 percent of those who currently access clinical diagnosis alone will now also have access to the new diagnostic.

Once the populations who have access to a new diagnostic are identified using the hierarchical access model, it is easy to quantify the health benefits resulting from such an innovation. For each of the populations that now have access to the new diagnostic, we assume that the new diagnostic is adopted only if produces better health outcomes than the status quo. Specifically, we adopt a new diagnostic when it results in few adjusted lives lost than the status quo test.

B.9. Estimating Adjusted Lives *Saved* by a New Diagnostic

The benefit of a new diagnostic is computed as the difference between the health outcome in the world with the new diagnostic and the health outcome in the status quo.

Since health outcome is expressed in terms of adjusted lives, the health gain of a new diagnostic over the status quo is expressed in terms of adjusted lives saved, where adjusted lives saved is the combination of direct and indirect lives saved. The model only selects a new diagnostic for use when it results in fewer adjusted lives lost (or a positive number of adjusted lives *saved*).

More formally, for each access category the adjusted lives saved by the new diagnostic is expressed as follows:

$$\begin{aligned}
&\Delta Adjusted\ Lives\ Saved_{Access\ Category_i} \\
&= Adjusted\ Lives\ Lost\ in\ Status\ Quo_{Access\ Category_i} \\
&- Adjusted\ Lives\ Lost\ with\ New\ Diagnostic_{Access\ Category_i} \\
&= N_{tp}^{SQ}(TP+C) + N_{fn}^{SQ}FN + N_{fp}^{SQ}C - \left(N_{tp}^{NewDx}(TP+C) + N_{fn}^{NewDx}FN + N_{fp}^{NewDx}C\right) \\
&= \Delta N_{tp}(TP+C) + \Delta N_{fn}FN + \Delta N_{fp}C \\
&= \Delta N_{tp}((1-eff_{Treatment})\cdot m_{tp.txfail} + C) + \Delta N_{fn}m_{fn} + \Delta N_{fp}C
\end{aligned}$$

where Δ refers to difference between quantities in the status quo and quantities in the world with the new diagnostic. In our model, for any given access level, the new diagnostic can improve over the status quo through increases in sensitivity or specificity. Improvement in sensitivity will increase the number of true positives and decrease the number of false negatives making $\Delta N_{tp} < 0$ and $\Delta N_{fn} > 0$. Improvement in specificity will decrease the number of false positives making $\Delta N_{fp} > 0$. The total number of adjusted lives saved is the sum of adjusted lives saved in each of the four access categories.

C. Model Calibration and Predictive Validity

We calibrated the predicted number of deaths in the status quo model against accepted estimates of malaria-related mortality among children under the age of 5 in sub-Saharan Africa. The number of malaria deaths in children under the age of 5 was obtained from the status quo model by first computing the number of treated and untreated malaria cases in each access category—microscopy and clinical diagnosis, clinical diagnosis alone, self-treatment and no care—and then multiplying by the appropriate case fatalities. This predicted number of deaths in the status quo must match the total number of observed malaria deaths in children under the age of 5 in Africa. A direct estimate of the number of deaths due to malaria is not available from WHO data. Many deaths occur at home and do not enter country level death statistics.[28] Instead, we validated our predicted number of malaria deaths in the status quo against estimates by the Child Health Epidemiology Reference Group (CHERG) and Snow et al. (2003). CHERG estimated that between 891,445 and 1,295,806 children under the age of 5 died due to malaria in Africa in the year 2000.[29,30] Snow et al. estimated this range to be 541,494 to 1,069,153 childhood deaths.[11].

Using the base case parameter estimates in **Table B.1** we predict 913,203 deaths due to malaria in children under the age of 5. In order to make our model match accepted estimates of the number of deaths due to malaria, we reduced, for all countries, the percent of the population receiving no care. We also reduced our initial estimates of treated and untreated case fatality rates. Note that the population estimates used were for the year 2005, but parameters collected from the literature more closely reflected the year 2000.

Table C.1: Predicted Status Quo Deaths by Sub-population with ACTs as First-Line Treatment (%)

	High Access	Medium Access	Low Access	Total
High Transmission	88,448 (10%)	443,235 (49%)	329,473 (36%)	861,156 (94%)
Low Transmission	11,932 (1%)	10,583 (1%)	29,532 (3%)	52,047 (6%)
Total	100,380 (11%)	453,818 (50%)	359,006 (39%)	913,203

To better represent current treatment standards, we also considered the predicted number of status quo deaths when ACTs are not available in all countries for first-line treatment following microscopy or clinical diagnosis. **Table C.2** presents the predicted number of status quo deaths when we assume less effective first-line and pharmacy bought antimalarials. For these results we assumed the effectiveness of first-line therapy following microscopy or clinical diagnosis was 60% and the effectiveness of medications purchased from the pharmacy was 30%.

Table C.2: Predicted Status Quo Deaths by Sub-population with Current (less effective) First-Line Treatment (%)

	High Access	Medium Access	Low Access	Total
High Transmission	117,901 (10%)	558,532 (49%)	399,639 (35%)	1,076,072 (95%)
Low Transmission	14,004 (1%)	12,246 (1%)	33,781 (3%)	60,031 (5%)
Total	131,905 (12%)	570,778 (50%)	433,421 (38%)	1,136,102

In order to provide the reader with a sense of how the different model parameters effect the predicted number of status quo childhood deaths, we have implemented the calibration procedure in Excel. In the interactive Excel spreadsheet "`All Africa Validation.xls`" users can vary the input parameters used in the model at will to

see how these changes affect the calibration process. We found this to be an excellent tool to interact with field experts and to gain, at the same time, insight into the sensitivity of the model to changes in various parameters.

D. SUPPLEMENTARY ANALYSES

D.1. SENSITIVITY AND SPECIFICITY THRESHOLDS

Because it is not reasonable to expect clinicians and field workers to adopt a test that results in *more* malaria-related deaths in the near term, we used malaria-related mortality to establish minimum thresholds for test sensitivity. In the above discussion of health outcomes, we refer to malaria-related mortality as direct lives lost. Having already established the need for a test that can be used in settings with minimal or no infrastructure, we did not consider sensitivity thresholds for a test requiring moderate infrastructure.

We looked for the break points in malaria-related deaths averted where the value changed from negative (implying an increase in malaria-related mortality) to positive (indicating a decrease in immediate malaria-related mortality). We made very minimal assumptions on test specificity and considered specificities of 25%, 30% and 50%. **Table D.1** reports these results. The grayed tests are those that result in an *increase* in near-term malaria-related mortality and, as such, are infeasible.

Table D.1.: Establishing Minimum Sensitivity Thresholds

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths Averted‡ ***(SD)***
Minimal Infrastructure §				
1	91%	25%	117,650 *(37,193)*	-16,361 *(43,124)*
2	91%	30%	172,649 *(71,902)*	-1,308 *(38,067)*
3	91%	50%	630,916 *(163,095)*	-1,461 *(43,216)*
4	92%	25%	124,853 *(57,563)*	-7,659 *(47,257)*
5	92%	30%	192,264 *(51,006)*	22,446 *(53,075)*
6	92%	50%	650,693 *(184,561)*	22,463 *(48,259)*
7	93%	25%	132,056 *(55,438)*	1,042 *(25,035)*
8	93%	30%	211,879 *(55,711)*	46,201 *(38,968)*
9	93%	50%	670,470 *(192,746)*	46,387 *(55,797)*

Table D.1. Continued

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths Averted‡ ***(SD)***
No Infrastructure §				
10	80%	25%	160,515	-59,794
			(48,098)	*(154,492)*
11	80%	30%	199,326	-59,794
			(39,571)	*(159,646)*
12	80%	50%	657,026	-21,558
			(199,303)	*(111,887)*
13	81%	25%	166,948	-52,048
			(58,533)	*(90,717)*
14	81%	30%	206,181	226,211
			(62,119)	*(171,404)*
15	81%	50%	683,007	9,894
			(240,222)	*(130,004)*
16	82%	25%	173,382	-44,302
			(37,090)	*(112,373)*
17	82%	30%	215,447	237,393
			(53,971)	*(128,792)*
18	82%	50%	708,988	41,347
			(229,649)	*(114,267)*
19	83%	25%	245,077	308,991
			(39,294)	*(124,747)*
20	83%	30%	336,015	324,424
			(64,173)	*(72,387)*
21	83%	50%	944,016	324,271
			(203,463)	*(154,655)*

* While 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 in overtreatment. Therefore, an adjusted life saved is a composite measure reflecting lives saved through improvements in sensitivity and 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.

§ See Olmsted et al. for more detailed information on calculating the percent of children with access to a new diagnostic requiring moderate, minimal or no infrastructure.[19]

SD, standard deviations

Because a new diagnostic is chosen over the status quo diagnostic when it produces a greater number of adjusted lives saved, the decision to adopt a new diagnostic will always be a function of both the sensitivity and specificity of the new diagnostic. For this reason, the minimum sensitivity threshold required to ensure an overall positive number reported under malaria-related mortality averted will increase as specificity decreases. We can see this looking at tests 15 and 16. Test 15 averts malaria-related mortality with

81% sensitivity. However, test 16 does not avert malaria-related mortality with 82% sensitivity. This is because, for test 16, the test specificity is not high enough to select the test in status quo scenarios in which the test sensitivity may produce better outcomes in terms of malaria-related mortality averted. The harm associated with an increase in overtreatment due to a 25% specific test is enough to outweigh the benefit of an 82% sensitive test.

To establish minimum sensitivity requirements we chose 30% as the lowest acceptable specificity. This was in order to mimic the status quo specificity of clinical diagnosis in high transmission settings. If specificity drops below 30%, we see that the sensitivity thresholds for new diagnostics requiring minimal and no infrastructure rise to 93% and 83%, respectively.

Once minimum sensitivity thresholds were established, the malaria working group considered these minimum requirements, uncertainty in the model outputs as reflected in the reported standard deviations and the current performance of existing rapid malaria diagnostics to establish minimum sensitivity requirements for diagnostic development.[31-33] These were ≥95% sensitivity for tests requiring minimal infrastructure and ≥90% sensitivity for tests requiring no infrastructure.

With these base sensitivity requirements set, we then examined the effect of increases in specificity. **Table D.2** outlines these results and was used in conjunction with considerations of the performance of existing rapid malaria diagnostics to establish minimum specificity requirements of ≥95% for a test requiring minimal infrastructure and 90-95% for a test requiring no infrastructure.

Table D.2.: Establishing Specificity Thresholds Given Minimum Sensitivity Requirements

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths ‡ ***(SD)***	Unnecessary Treatments Averted § *(SD)*
Minimal Infrastructure ||					
1	95%	40%	479,643	93,710	89,661,779
			(113,409)	*(36,372)*	*(15,323,713)*
2	95%	50%	710,024	94,235	139,194,919
			(163,661)	*(46,704)*	*(15,557,598)*
3	95%	60%	942,050	94,235	190,517,528
			(225,938)	*(63,284)*	*(22,164,947)*
4	95%	70%	1,186,031	108,070	240,758,939
			(194,402)	*(65,611)*	*(14,342,863)*
5	95%	80%	1,431,031	108,070	302,893,523
			(425,651)	*(51,085)*	*(18,218,270)*
6	95%	85%	1,553,532	108,070	333,960,814
			(398,956)	*(55,566)*	*(33,676,813)*
7	95%	90%	1,676,032	108,070	365,028,106
			(352,041)	*(52,584)*	*(19,884,777)*
8	95%	95%	1,798,532	108,070	396,095,397
			(266,148)	*(38,722)*	*(25,571,972)*
9	95%	100%	1,921,032	108,070	427,162,689
			(527,928)	*(52,209)*	*(24,636,673)*

Table D.2. Continued

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(sd)***	Malaria-related Deaths Averted‡ ***(sd)***	Unnecessary Treatments Averted § ***(sd)***
No Infrastructure ‖					
10	90%	40%	613,435	292,971	89,242,774
			(70,359)	*(68,648)*	*(10,419,089)*
11	90%	50%	917,873	292,649	155,572,225
			(92,251)	*(104,915)*	*(18,317,390)*
12	90%	60%	1,225,336	306,572	213,052,628
			(238,237)	*(97,369)*	*(26,041,077)*
13	90%	70%	1,544,769	317,746	282,701,029
			(172,785)	*(90,496)*	*(21,006,135)*
14	90%	80%	1,868,415	317,746	364,781,060
			(319,759)	*(95,426)*	*(20,735,807)*
15	90%	85%	2,030,239	317,746	405,821,075
			(423,639)	*(113,258)*	*(14,829,073)*
16	90%	90%	2,192,062	317,746	446,861,090
			(467,983)	*(97,156)*	*(27,808,497)*
17	90%	95%	2,353,885	317,746	487,901,105
			(499,929)	*(101,480)*	*(31,400,267)*
18	90%	100%	2,515,709	317,746	528,941,121
			(422,426)	*(115,239)*	*(27,800,631)*

* While 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 in overtreatment. Therefore, an adjusted life saved is a composite measure reflecting lives saved through improvements in sensitivity and 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 now received following microscopy, clinical diagnosis, and those purchased from the pharmacy for self-treatment.

‖ See Olmsted et al. for more detailed information on calculating the percent of children with access to a new diagnostic requiring moderate, minimal or no infrastructure.[19]

SD, standard deviations

D.2. BENEFITS OF RECOMMENDED DIAGNOSTICS BY INITIAL ACCESS TO MALARIA DIAGNOSTICS AND TRANSMISSION INTENSITY

Table 3 in Rafael et al. presents aggregate results for sub-Saharan Africa. **Tables D.3** and **D.4** present the region specific breakdown for the recommended diagnostic tests (Tests 9 and 14 in Table 3 in Rafael et al).[1]

Table D.3: Regional Breakdowns for Test 9 -- 95% sensitive, 95% specific and requiring minimal infrastructure (*SD)*

	Status Quo Access to Malaria Diagnostics		
	High	Medium	Low
High Transmission			
Adjusted Lives Saved	208,411	866,512	619,517
	(47,166)	*(545,799)*	*(103,546)*
Malaria-related mortality averted	8,310	41,363	42,530
	(11,276)	*(35,129)*	*(40,198)*
Unnecessary treatments averted	40,311,875	166,077,243	115,718,429
	(2,206,428)	*(13,469,126)*	*(12,086,987)*
Low Transmission			
Adjusted Lives Saved	18,897	18,767	66,427
	(5,442)	*(4,380)*	*(10,988)*
Malaria-related mortality averted	3,652	3,339	8,876
	(2,404)	*(1,075)*	*(1,933)*
Unnecessary treatments averted	12,832,725	12,967,381	48,187,744
	(1,991,369)	*(2,161,997)*	*(7,288,766)*

SD Standard deviation

Table D.4: Regional Breakdowns for Test 14 -- 90% sensitive, 90% specific and requiring no infrastructure (*SD*)

	Status Quo Access to Malaria Diagnostics		
	High	Medium	Low
High Transmission			
Adjusted Lives Saved	252,502	1,073,360	739,287
	(140,839)	*(369,838)*	*(338,070)*
Malaria-related mortality averted	12,160	132,494	147,525
	(19,169)	*(43,527)*	*(82,546)*
Unnecessary treatments averted	48,319,028	191,404,688	121,933,459
	(4,790,850)	*(32,301,204)*	*(12,678,545)*
Low Transmission			
Adjusted Lives Saved	23,748	24,888	78,277
	(5,979)	*(5,014)*	*(21,789)*
Malaria-related mortality averted	4,425	4,876	16,265
	(1,066)	*(2,119)*	*(13,395)*
Unnecessary treatments averted	16,244,539	16,823,966	52,135,409
	(3,737,557)	*(2,381,371)*	*(1,789,519)*

SD Standard deviation

D.3. PRIMARY RESULTS FOR A DECREASE IN FEVER INCIDENCE

For the results presented in Table 3 of Rafael et al. we assume an annual fever incidence of 9.[1,11] However, early comments on this work suggested that this was a high estimate. Further, country and regional variation surrounding annual fever incidence is high and can relate to seasonal weather changes that influence transmission of malaria and many other febrile illness. To ensure that the recommendations outlined in Rafael et al. were robust to changes in annual fever incidence, we recalculated outcomes assuming an annual fever incidence of 6. **Table D.5** presents these results. Here we see that, although outcomes change, particularly estimates of unnecessary treatments averted, the qualitative message of the results remains the same and supports the recommendations presented in Rafael et al.[1]

Table D.5: Primary Outcomes when Annual Fever Incidence Drops from 9 to 6

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths ‡ ***(SD)***	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved ‖
Moderate Infrastructure ¶						
1	95%	95%	391,716 *(144,705)*	15,396 *(16,269)*	87,098,046 *(10,452,985)*	21%
2	100%	100%	457,973 *(135,102)*	61,453 *(33,124)*	94,329,616 *(11,510,307)*	24%
Minimal Infrastructure ¶						
3	80%	80%	602,773 *(211,302)*	-260,221 *(72,104)*	185,954,650 *(25,268,283)*	32%
4	90%	80%	806,565 *(199,789)*	-14,694 *(41,477)*	185,954,650 *(18,202,485)*	42%
5	90%	90%	955,987 *(216,048)*	-14,694 *(38,445)*	224,506,047 *(28,136,753)*	50%
6	90%	95%	1,030,698 *(333,291)*	-14,694 *(43,930)*	243,781,746 *(20,827,192)*	54%
7	95%	80%	908,461 *(129,540)*	108,070 *(57,789)*	185,954,650 *(16,066,864)*	48%
8	95%	90%	1,057,883 *(296,656)*	108,070 *(34,898)*	224,506,047 *(30,163,672)*	55%
9#	95%	95%	1,132,594 *(321,692)*	108,070 *(65,666)*	243,781,746 *(32,979,530)*	59%
10	98%	95%	1,193,732 *(170,783)*	181,728 *(44,156)*	243,781,746 *(29,377,560)*	62%
11	100%	100%	1,309,201 *(204,035)*	230,833 *(63,394)*	263,057,444 *(35,561,876)*	69%

Table D.5.. Continued

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† *(SD)*	Malaria-related Deaths Averted‡ *(SD)*	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved ‖
No Infrastructure ¶						
12	80%	80%	976,890 *(269,704)*	-6,596 *(117,613)*	224,194,207 *(54,030,271)*	51%
13	90%	80%	1,246,101 *(178,425)*	317,746 *(100,412)*	224,194,207 *(25,640,764)*	65%
14	90%	90%	1,443,488 *(329,188)*	317,746 *(138,594)*	275,120,755 *(33,255,760)*	76%
15	90%	95%	1,542,181 *(217,678)*	317,746 *(77,003)*	300,584,030 *(24,181,944)*	81%
16	95%	80%	1,380,706 *(223,680)*	479,917 *(103,088)*	224,194,207 *(14,182,881)*	72%
17	95%	90%	1,578,093 *(374,882)*	479,917 *(119,900)*	275,120,755 *(34,134,886)*	83%
18	95%	95%	1,676,786 *(306,003)*	479,917 *(44,975)*	300,584,030 *(27,369,486)*	88%
19	98%	95%	1,757,550 *(211,855)*	577,220 *(95,703)*	300,584,030 *(25,446,346)*	92%
20	100%	100%	1,910,085 *(244,434)*	642,088 *(86,597)*	326,047,304 *(30,152,110)*	100%

* While 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 in overtreatment. Therefore, an adjusted life saved is a composite measure reflecting lives saved through improvements in sensitivity and 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 now received following microscopy, clinical diagnosis, and those purchased from the pharmacy for self-treatment.

‖ The adjusted lives saved by the perfect test (test 20) denote 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.

¶ See Olmsted et al for more detailed information on calculating the percent of children with access to a new diagnostic requiring moderate, minimal or no infrastructure.[19]

\# Test 9 refers to the potential reach of existing HRP2-based RDTs to detect clinically relevant parasitemia (≥500 parasites per μl).[31-33]

SD, standard deviations

D.4. Removing Assumptions on Treatment Effectiveness and Provider Adherence to New Diagnostic Test Results

Two critical assumptions underlie the results presented Table 3 of Rafael et al.: the coupling of a new diagnostic with effective treatment, specifically ACTs, and provider adherence to test results. When either of these assumptions is neglected, the projected benefit of a new malaria diagnostic will be less than those presented in Rafael et al.[1]

We first consider the effect of coupling a new diagnostic with less effective treatment. While many African countries are changing their first-line treatment to artesunate combination therapies (ACTs), it will still be several years before ACTs are used throughout the continent. Even for those countries that have recently changed national treatment policy, there have been significant delays in fully deploying ACTs. In **Table D.6** we present results from an analysis that assumes less effective drugs are available following diagnosis and through the pharmacy. Specifically, first-line treatment is assumed to be 60% effective and medications purchased at the pharmacy are assumed to be 30% effective. In the status quo, a positive test result by microscopy or clinical diagnosis is followed by treatment with a first-line antimalarial. Self-treatment is purchased at the pharmacy. Here we assume the new diagnostic does not improve access to treatment for those currently receiving microscopy, clinical diagnosis or self-treating. Thus, those who formerly received microscopy or clinical diagnosis continue to receive treatment with a first-line antimalarial following a positive test result with the new diagnostic. Those who formerly self-treated will continue to access only pharmacy grade medications following a positive test result with the new diagnostic. Those who formerly received no care now are assumed to access pharmacy grade medications following a positive test result with the new diagnostic.

Table D.6: Attributable Benefit of a New Diagnostic that Replaces Clinical Judgment and is Coupled with Less Effective Treatment (no ACTs available)

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths ‡ ***(SD)***	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved ‖ *(SD)*
Moderate Infrastructure ¶						
1	95%	95%	89,157	56,527	12,082,724	14%
			(13,838)	*(17,222)*	*(2,485,394)*	
2	100%	100%	108,669	61,453	16,908,489	17%
			(30,921)	*(19,485)*	*(3,399,498)*	
Minimal Infrastructure ¶						
3	80%	80%	1,113,026	-272,538	302,893,523	43%
			(298,710)	*(58,183)*	*(26,746,323)*	
4	90%	80%	1,291,214	-52,615	302,893,523	50%
			(238,040)	*(40,998)*	*(20,372,103)*	
5	90%	90%	1,536,215	-52,615	365,028,106	59%
			(439,954)	*(71,957)*	*(28,679,342)*	
6	90%	95%	1,658,715	-52,615	396,095,397	64%
			(423,935)	*(59,967)*	*(42,103,592)*	
7	95%	80%	1,380,309	57,347	302,893,523	53%
			(323,830)	*(34,089)*	*(30,817,632)*	
8	95%	90%	1,625,309	57,347	365,028,106	62%
			(498,270)	*(40,893)*	*(33,303,036)*	
9#	95%	95%	1,747,809	57,347	396,095,397	67%
			(398,188)	*(70,644)*	*(30,722,687)*	
10	98%	95%	1,801,266	123,324	396,095,397	69%
			(496,946)	*(56,165)*	*(25,980,553)*	
11	100%	100%	1,959,404	167,309	427,162,689	75%
			(430,860)	*(57,363)*	*(23,657,912)*	

Table D.6.. Continued

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† *(SD)*	Malaria-related Deaths Averted‡ *(SD)*	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved || *(SD)*
No Infrastructure ¶						
12	80%	80%	1,499,077 *(380,429)*	-106,723 *(100,475)*	364,781,060 *(28,313,151)*	58%
13	90%	80%	1,727,904 *(373,562)*	177,235 *(87,051)*	364,781,060 *(28,849,696)*	66%
14	90%	90%	2,051,551 *(481,764)*	177,235 *(60,612)*	446,861,090 *(26,968,535)*	79%
15	90%	95%	2,213,374 *(518,681)*	177,235 *(70,523)*	487,901,105 *(33,197,398)*	85%
16	95%	80%	1,842,317 *(306,041)*	319,214 *(110,565)*	364,781,060 *(33,059,497)*	71%
17	95%	90%	2,165,964 *(627,507)*	319,214 *(75,201)*	446,861,090 *(31,933,058)*	83%
18	95%	95%	2,327,787 *(388,689)*	319,214 *(120,511)*	487,901,105 *(46,290,666)*	89%
19	98%	95%	2,396,435 *(746,712)*	404,401 *(89,958)*	487,901,105 *(20,727,069)*	92%
20	100%	100%	2,604,024 *(596,767)*	461,193 *(67,595)*	528,941,121 *(19,678,055)*	100%

* While 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 in overtreatment. Therefore, an adjusted life saved is a composite measure reflecting lives saved through improvements in sensitivity and 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 now received following microscopy, clinical diagnosis, and those purchased from the pharmacy for self-treatment.

|| The adjusted lives saved by the perfect test (test 20) denote 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.

¶ See Olmsted et al. for more detailed information on calculating the percent of children with access to a new diagnostic requiring moderate, minimal or no infrastructure.[19]

\# Test 9 refers to the potential reach of existing HRP2-based RDTs to detect clinically relevant parasitemia (≥500 parasites per μl).[31-33]

SD, Standard Deviation

Even more detrimental to realizing the potential impact of improved malaria diagnostic is the practice of clinicians, healthcare workers and caretakers of continuing to treat those who test negative. A significant portion of the overall benefit of a new diagnostic is the ability to reduce now widespread overtreatment. However, this benefit is minimal when we consider the introduction of a new diagnostic coupled with clinical judgment. In **Table D.7** we present a scenario in which a patient is treated with effective first-line medications (ACTs) following microscopy, clinical diagnosis and the new diagnostic.

However, in this scenario, a patient is considered to "test positive" with the new diagnostic if he or she tests positive on the actual test *or* is considered to have malaria through the application of a clinical algorithm. We assume those administering the new diagnostic are also trained in clinical diagnosis. This will introduce additional training burdens when pushing new diagnostic to the periphery.

Table D.7: Attributable Benefit of a New Diagnostic Coupled with Clinical Judgment and ACTs

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† ***(SD)***	Malaria-related Deaths ‡ ***(SD)***	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved ‖ *(SD)*
Moderate Infrastructure ¶						
1	95%	95%	89,157	56,527	12,082,724	14%
			(13,838)	*(17,222)*	*(2,485,394)*	
2	100%	100%	108,669	61,453	16,908,489	17%
			(30,921)	*(19,485)*	*(3,399,498)*	
Minimal Infrastructure ¶						
3	80%	80%	190,328	164,727	26,978,566	30%
			(44,217)	*(62,434)*	*(7,929,282)*	
4	90%	80%	210,717	189,290	26,978,566	33%
			(47,886)	*(78,063)*	*(10,218,568)*	
5	90%	90%	288,935	204,572	37,351,651	46%
			(59,320)	*(60,495)*	*(6,722,725)*	
6	90%	95%	329,936	204,572	50,214,695	52%
			(50,976)	*(36,399)*	*(9,652,891)*	
7	95%	80%	220,912	201,572	26,978,566	35%
			(81,464)	*(79,623)*	*(9,080,728)*	
8	95%	90%	299,943	217,702	37,351,651	47%
			(72,621)	*(73,429)*	*(8,289,514)*	
9#	95%	95%	340,944	217,702	50,214,695	54%
			(88,953)	*(58,517)*	*(8,467,107)*	
10	98%	95%	347,549	225,581	50,214,695	55%
			(54,484)	*(46,074)*	*(9,136,224)*	
11	100%	100%	392,954	230,833	63,077,739	62%
			(63,559)	*(53,013)*	*(7,004,024)*	

Table D.7. Continued

Test	Sensitivity*	Specificity*	Adjusted Lives Saved† *(SD)*	Malaria-related Deaths Averted‡ *(SD)*	Unnecessary Treatments Averted § *(SD)*	Percent of Total Possible Adjusted Lives Saved || *(SD)*
No Infrastructure ¶						
12	80%	80%	362,554	558,507	-3,936,965	57%
			(47,828)	*(155,749)*	*(23,858,177)*	
13	90%	80%	389,937	591,423	-3,936,965	62%
			(44,552)	*(186,650)*	*(27,523,500)*	
14	90%	90%	494,306	607,396	13,999,196	78%
			(81,420)	*(165,367)*	*(21,963,997)*	
15	90%	95%	548,469	607,396	30,991,328	87%
			(80,556)	*(173,889)*	*(20,178,541)*	
16	95%	80%	403,629	607,882	-3,936,965	64%
			(48,881)	*(151,725)*	*(21,091,693)*	
17	95%	90%	508,848	624,742	13,999,196	81%
			(92,751)	*(194,477)*	*(21,574,808)*	
18	95%	95%	563,011	624,742	30,991,328	89%
			(109,547)	*(128,011)*	*(17,199,695)*	
19	98%	95%	571,736	635,150	30,991,328	91%
			(50,506)	*(116,243)*	*(18,270,037)*	
20	100%	100%	631,716	642,088	47,983,460	100%
			(69,106)	*(165,866)*	*(19,390,316)*	

* These values represent the underlying sensitivity and specificity of the new diagnostic. However, since we assume that the new diagnostic is combined with clinical diagnosis and a patient will be treated if he or she tests positive by either metric, the overall realized sensitivity of the new diagnostic when implemented this way will be higher than that listed here and the specificity will be significantly lower.

† Lives saved are adjusted to account for the harm associated with treatment and the lives saved through reduction in overtreatment. Therefore, an adjusted life saved is a composite measure reflecting lives saved through improvements in sensitivity and 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 now received following microscopy, clinical diagnosis, and those purchased from the pharmacy for self-treatment.

|| The adjusted lives saved by the perfect test (test 20) denote 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.

¶ See Olmsted et al . for more detailed information on calculating the percent of children with access to a new diagnostic requiring moderate, minimal or no infrastructure.[19]

Test 9 refers to the potential reach of existing HRP2-based RDTs to detect clinically relevant parasitemia (≥500 parasites per µl).[31-33]

SD, Standard Deviation

The Excel worksheet titled "`Combining tests worksheet.xls`" provides an interactive tool for assessing the impact of combining a diagnostic with clinical diagnosis. **Figures D.1** and **D.2** detail the impact on field sensitivity and specificity when we consider a patient to "test positive" when he or she is positive by either the new diagnostic or clinical diagnosis. A patient is considered to "test negative" when he or she

is negative by both metrics. The combined sensitivity will be higher than both the sensitivity of the new diagnostic and the sensitivity of clinical diagnosis. However, this improved sensitivity comes with a cost. The combined specificity will be lower than both the specificity of the new diagnostic and the specificity of clinical diagnosis. A test implemented in this fashion will not reduce overtreatment and, further, there will be no payoff to efforts to improve test specificity.

Figure D.1: Combined Sensitivity of Clinical Diagnosis and a New Diagnostic in High Transmission Settings

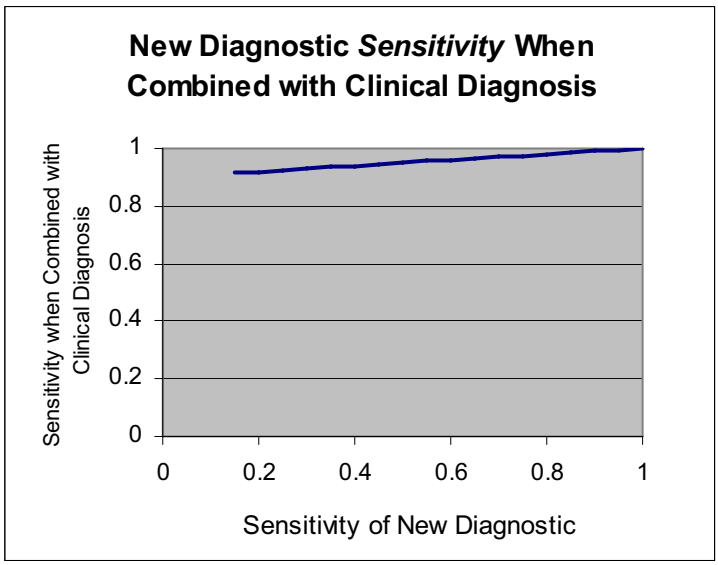
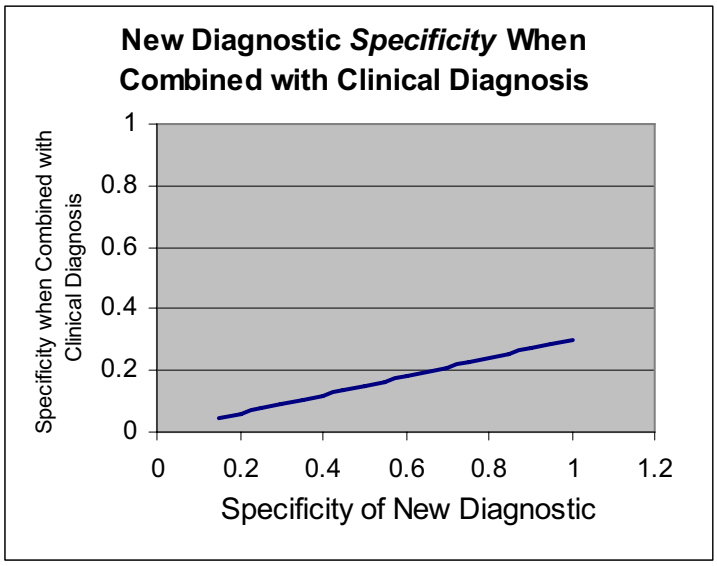


Figure D.2: Combined Specificity of Clinical Diagnosis and a New Diagnostic in High Transmission Settings



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