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Simulations Show Diagnostic Testing For Malaria In Young African Children Can Be Cost-Saving Or Cost-Effective

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Abstract

Malaria imposes a substantial global disease burden. It disproportionately affects sub-Saharan Africans, particularly young children. In an effort to improve disease management, the World Health Organization (WHO) recommended in 2010 that countries test children younger than age five who present with suspected malaria fever to confirm the diagnosis instead of treating them presumptively with antimalarial drugs. Costs and concerns about the overall health impact of such diagnostic testing for malaria in children remain barriers to full implementation. Using data from national Malaria Indicator Surveys, we estimated two-stage microsimulation models for Angola, Tanzania, and Uganda to assess the policy's cost-effectiveness. We found that diagnostic testing for malaria in children younger than five is cost-saving in Angola. In Tanzania and Uganda the cost per life-year gained is $5.54 and $94.28, respectively. The costs projected for Tanzania and Uganda are less than the WHO standard of $150 per life-year gained. Our results were robust under varying assumptions about cost, prevalence of malaria, and behavior, and they strongly suggest the pursuit of policies that facilitate full implementation of testing for malaria in children younger than five.

Malaria is an acute parasitic illness associated with nonspecific symptoms such as fever, body aches, and vomiting, which commonly manifest themselves seven to ten days after infection. An estimated 198 million cases of malaria occurred worldwide in 2013.[1] Severe cases can lead to permanent disability, including neurological and respiratory impairments, or death.

Sub-Saharan Africa bears a disproportionate share of the disease burden: 90 percent of malaria deaths worldwide occur in the region.[2] Malaria also accounts for 14 percent of the region's deaths in childhood (before the age of five). Because of the high mortality risk,

until recently children have been treated immediately for malaria when they have a fever and seek care, regardless of the likelihood that they have a fever from another cause.[3]

Combating malaria consumed nearly $2.3 billion in health care resources globally in 2013[4]—far short of the $5.1 billion believed to be needed to achieve global malaria control and elimination goals.[1] The United States has played an important role in this fight. In 2005 the administration of President George W. Bush launched the US President's Malaria Initiative to rationalize malaria prevention and control efforts, including coordinating funding and programs nationally and internationally. The initiative initially targeted fifteen countries—later expanded to nineteen—for intensive intervention, with a goal of reducing mortality by 50 percent.[5]

In 2009 the administration of President Barack Obama, building on the President's Malaria Initiative, introduced the Global Health Initiative. The expanded program promised to spend $63 billion from 2010 to 2016 on research about and prevention and treatment efforts for malaria and other infectious diseases, such as HIV.[5] Through education, prevention, and improved medication funded by these efforts, malaria mortality rates in Africa have fallen by 58 percent since 2000.[6]

Given the disease's nonspecific symptoms, true cases of malaria can be hard to diagnose. Historically, countries where malaria is endemic have treated people who present with a suspected case of the disease with relatively cheap antimalarial drugs, an approach known as presumptive treatment. Critics have argued that this strategy results in unnecessary drug usage, increased morbidity and mortality from inappropriate treatment of nonmalaria fevers, and increased health care costs.[7,8] It also fuels the serious recurring problem of drug resistance.

For decades, chloroquine and sulfa-based drugs were first-line treatments for malaria. However, by the mid-1980s parasite resistance had undermined their effectiveness.[9] Current guidelines now call for the use of artemisinin-based combination therapy. This is relatively simple to administer and has fewer side effects but is much more expensive than conventional monotherapies.[10] Maintaining the effectiveness of artemisinin-based combination therapy is critical because no alternatives are readily available to treat malaria.

Diagnostic testing prior to treatment is one way to mitigate the spread of drug resistance, since testing limits unnecessary medication use. Malaria rapid diagnostic test (mRDT) kits are now available. They provide immediate, highly accurate results and have far fewer infrastructure requirements than microscopy, the default screening tool.[11]

In 2006 the World Health Organization (WHO) recommended diagnostic testing prior to treatment for fever patients over the age of five, and in 2010 it boldly expanded the age range to include young children, in spite of their high malaria mortality rates, and moved to universal testing.[3] Since then, all countries where malaria is endemic have adopted the policy. However, sub-Saharan countries in particular have struggled with implementing it, as shown by the fact that fewer than 50 percent of suspected cases are tested in many countries.[1] Numerous barriers exist to the full implementation of diagnostic testing for malaria.

Parts of the health systems in sub-Saharan African countries, particularly in rural areas, still lack the infrastructure to supply and perform the tests.[12] Clinicians have also been slow to take up testing, and even when the tests are available and performed, clinicians have been reluctant to forgo prescribing drug treatment even when the test results are negative. Their reluctance reflects both concerns that malaria cases will be missed because the test is not perfect and the fact that presumptive treatment has been the standard of care for decades.[13]

Cost-effectiveness analyses have yet to provide consistent guidance to policy makers regarding universal screening in sub-Saharan Africa. Testing all children would clearly increase costs. Health benefits would mostly accrue to children with nonmalaria fevers, who are more likely to be diagnosed correctly at first presentation as having a fever from another source. Savings from the reduced use of artemisinin-based combination therapy for this group and their lower health care costs might offset the expense of mRDT. However, cost-effectiveness projections have produced mixed results.

The literature has two general branches, both of which employ decision-analytic models. The first branch follows the model of Samuel Shillcutt and coauthors[14] and examines the cost-effectiveness of mRDT versus microscopy, presumptive treatment, or both, where effects are defined as deaths averted. The results are inconclusive, since the preference for mRDT depends on the prevalence of malaria,[15] drug costs,[16] test sensitivity, clinicians' adherence to test results, and the cost-effectiveness standard applied.[17] Importantly, when prevalence is high and drug costs are very low, presumptive treatment has been shown to be the preferred strategy.[15]

The other branch of studies uses a different outcome and has found testing with mRDT to be cost-effective or cost-saving when effectiveness is measured as true cases accurately identified.[18,19] However, the use of this effect measure precludes comparisons with other health interventions that compete for scarce resources.

Methodological limitations further impede the ability of existing analyses to inform policy. Models estimate cost and effects based on a single episode of fever instead of the actual pattern observed, in which children in countries where malaria is endemic average six fever episodes annually.[20] Scaling up results to create annual estimates from the decision-analytic models based on a single fever also lead to substantial overestimates of deaths averted.[16] These models also omit inpatient treatment costs and fail to address the cost and health changes for nonmalaria fever cases,[19] the group primarily affected by the policy.

Our analysis contributes substantially to the literature. We modeled complete treatment pathways for malaria and nonmalaria fevers; allowed for recurrent fever; and included aspects of caregiver and clinician behavior, test properties, varying prevalence rates, and drug costs. We estimated cost-effectiveness from the perspective of the health care system for an annual cohort of children younger than age five in 2010, the base year. We focused on Angola, Tanzania, and Uganda because these countries constitute the first intervention cohort of the President's Malaria Initiative, and we used national data from each country's latest Malaria Indicator Surveys.[21–23]

Study Data And Methods

DECISION-ANALYTIC APPROACH

Consistent with the literature, we used a decision-analytic model to estimate the annual total costs and deaths averted by diagnostic testing, compared to those averted by presumptive treatment for young children in all three countries who present with fever. The model outlines possible treatment sequences and, based on the probability of each event's occurring, produces estimates of the costs and outcomes for the alternative strategies.

Specifically, we constructed a Markov model using the TreeAge Pro software suite, version 2009. We used the Markov form to capture the recurring nature of fevers. Given the important role of probabilities, we used two-stage microsimulation to address uncertainty. For a complete description and a diagram of the model, see online Appendix 1.[24] Below we summarize the model's key features, with a focus on the diagnostic testing arm.

MODEL DESCRIPTION

We began with a hypothetical cohort of 1,000 children. Based on the prevalence of malaria, a child starts in either a fever or a no-fever state. Transmission rates and treatment paths determine how children cycle for 365 days through exposure periods and move between three states: fever, no fever, and death (upon which they exit the cohort). Children average six exposure periods a year, in accordance with observed fever patterns.

During an exposure period, if a fever occurs, some caregivers seek care for their children. These children receive the mRDT, producing a negative or positive result. Some clinicians treat children in accordance with the test results; others do not. The key outcome to avoid is a clinician prescribing artemisinin-based combination therapy when the test result is negative and the child does not have malaria.

Children appropriately treated recover immediately. Others, depending on the treatment given and their disease status, may experience some improvement and then relapse. These "treatment failures" receive care a second time, at a hospital or a health facility. Those with uncomplicated cases ultimately recover. A portion of those with severe cases die—an event to be minimized.

Alternatively, some caregivers do not seek care for a given episode of fever. In this case, children whose disease remains uncomplicated survive. But some of those whose cases become severe die. This group incurs no formal treatment costs.

At the end of the exposure period, during which children can have fever or not, all children either survived or died and exited the cohort. Based on the likelihood of transmission, survivors begin the exposure cycle again, with an average of six cycles per year. Deaths and treatment costs are counted for each cycle and summed for the year.

ADDRESSING MODEL UNCERTAINTY

The model is a pathway of probabilistic events. As noted above, we used two-stage microsimulation to address uncertainty. A key input driving the results is the number of

possible episodes of fevers, malaria or nonmalaria, per child, since each fever involves a likelihood of incurring costs and death.

In the first-stage simulation we defined a variable for exposure period and varied the period length randomly from fourteen to thirty days.[25,26] A separate variable defined fever duration, should a fever occur, based on case severity—whose value also varied randomly. We ran 1,000 iterations at base case values and generated a cohort of 1,000 individual profiles of fever, no-fever, or death episodes for one year, which we used in the second-stage simulation.

Model uncertainty also came from the probability and cost inputs, which we addressed through probabilistic sensitivity analysis—the second stage. First, we used one-way sensitivity analysis to identify the inputs that generated 99 percent of the uncertainty in the results. We then assumed that each of these inputs represented a distribution rather than a single base value with a range.[19]

Next, using the cohort generated from the first stage, which generated unique fever profiles for each child, we ran a second-stage simulation with input values randomly selected from their distributions. Based on 10,000 iterations, we estimated mean and standard error values for costs and deaths associated with mRDT and presumptive treatment.

COUNTRY-SPECIFIC DATA SOURCES

Angola, Tanzania, and Uganda served as the three case-study countries. All three have well established national malaria control programs, and the three collectively have received, through the President's Malaria Initiative and the Global Health Initiative, $490 million in subsidies for drug purchases and infrastructure development since 2005.[27] Descriptive data for each country and base values for model inputs are available in the Appendix.[24] Angola is the wealthiest of the three countries, with a per person gross national product per year of $5,485—roughly ten times that of Tanzania and Uganda. Tanzania had the lowest malaria prevalence, at 6 percent.

Our primary data sources for the model inputs were each country's most recent Malaria Indicator Survey, from 2012 in Angola, 2013 in Tanzania, and 2010 in Uganda. The survey samples households from the national census using a two-stage cluster design, oversampling rural areas. Questionnaires ask about care seeking in relation to fevers, specifically about fevers in the previous two weeks. The surveys have been repeated multiple times in each country.

The national malaria control programs, sponsored by the President's Malaria Initiative, and each country's ministry of health also supplied data. Additional information was drawn from WHO cost databases, World Bank databases on malaria case fatality rates, and published studies. In rare instances, we relied on expert opinion. A complete list of values and data sources for probabilities and cost inputs are included in the Appendix.[24] Critical values are described briefly below.

EPIDEMIOLOGICAL INPUTS

Based on data from the Malaria Indicator Surveys, we calculated the fever transmission rates, which were contingent on the exposure period and prevalence of malaria in the relevant country. Case fatality rates are critical values in the analyses, and estimates of these rates in the literature vary widely. For example, case fatality rates for severe untreated malaria vary by a factor of ten in published studies.[15,19] Few estimates of the rates exist for the subgroup of suspected nonmalaria fevers.

The WHO publishes inpatient case fatality rates for malaria.[1] We assumed that values for nonmalaria fevers were 20 percent higher than those for malaria, which is consistent with the lower bound in the available evidence. For untreated cases of malaria and nonmalaria fevers, we assumed that the case fatality rates were 33 percent higher than those for each type of fever when treated. All case fatality rates were tested in the sensitivity analyses. We also compared the number of deaths predicted by the model and the number of observed deaths reported by the WHO as a calibration check on the model results.[19]

BEHAVIORAL INPUTS

We obtained data about clinicians' compliance with mRDT results from two cross-sectional surveys in Angola and Tanzania and a quasi-experimental study in Uganda.[28–30] The Malaria Indicator Surveys provided data about care-seeking behavior for children. The probability of hospital admission was based on data from the Ugandan survey.

COST INPUTS

We used a gross-costing approach to calculate diagnostic, outpatient, drug, and inpatient costs from the perspective of the health care system. All costs were converted to 2010 US dollars. The national malaria control programs provided data on mRDT costs—including the costs of testing supplies, storage, and drugs—and costs for other antimalarial drugs.

We obtained data on the cost per outpatient visit and hospital bed day costs for each country from the WHO-CHOICE unit cost estimates[31] and inpatient costs from each ministry of health. We did not include estimates of indirect costs because these did not vary by treatment path.

In Angola the government-run drug delivery system is unreliable because of war and theft of supplies. A parallel distribution system, run by nongovernmental organizations, supplies drugs and mRDT to health facilities. As a result, Angola's drug costs are twelve times higher than those in Tanzania and Uganda.

LIMITATIONS

Several limitations should be noted. Our results reflected certain assumptions. We assumed that fevers could occur in consecutive cycles and that having a fever did not affect the likelihood of having a future fever. Also, we did not allow for coinfection or cotreatment. These are important areas for future research and should be incorporated into more advanced models.

We estimated our case fatality rates for nonmalaria fevers as a multiple of case fatality rates for malaria. Similarly, we estimated the case fatality rates for fever cases for which caregivers did not seek treatment as multiples of the case fatality rates for fevers for which treatment was sought. Estimates for untreated cases affected the overall death count but did not vary by treatment pathway. If the nonmalaria case fatality rates were lower than those for malaria, our results overestimated the benefits of testing.

We did not include patient compliance with treatment in the model because data have shown that compliance with medication averaged 90 percent for children with uncomplicated cases of fever, and in severe cases compliance is likely to be higher.[32] We assumed that patients could have up to two health care visits per fever episode. If visit numbers were greater and compliance was lower, overall costs for both strategies could have been underestimated.

Study Results

Exhibit 1 shows the results of the two-stage simulation models with base-case input values. The model estimates deaths averted through screening. We translated these values into life-years gained by multiplying deaths averted by the discounted average life expectancy for children.[33] In Angola mRDT was the dominant strategy because it was cost-saving; the costs per life-year gained through screening were $5.54 for Tanzania and $94.28 for Uganda. These values were cost-effective since they fell well below the WHO standard of cost-effectiveness, which is $150 per life-year gained.

In the second stage of estimation, key model inputs were defined as distributions, and 10,000 simulations were run. Model input values varied in each iteration based on the draw from the distribution. Based on these results, we identified the likelihood that the result—cost-saving or cost-effective—generated by the base-case estimates would occur. Understanding the uncertainty around the estimates is critical for policy makers who are likely to make decisions based on the results.

Cost-effectiveness analyses can produce one of four possible results that are routinely summarized in the cost-effectiveness plane.[34] Two of the results in this case are optimal outcomes: Either diagnostic testing is cost-saving or it involves a reasonable payment for a health gain relative to presumptive treatment.

For Angola the likelihood that diagnostic testing will produce net savings and a health gain is 76 percent, while the likelihood of producing a health gain at a net cost is 4 percent (Exhibit 2). In Tanzania, the likelihood that diagnostic testing will produce net savings and a health gain is 22 percent, while the likelihood of producing a health gain at a net cost is 67 percent (Exhibit 3). In Uganda, the likelihood that diagnostic testing will produce net savings and a health gain is 0 percent, while the likelihood of producing a health gain at a net cost is 64 percent (Exhibit 4). The results for Uganda reflect the country’s relatively high prevalence of malaria and low rates of clinician compliance with negative diagnostic test results.

Using population data, we calculated the annual costs and health benefits of a national policy for diagnostic testing. Angola would save $18.4 million and prevent over 25,000

deaths. Tanzania would need to spend $7.2 million to prevent over 46,500 deaths. The costs for Uganda were the highest, at $33.0 million to avert 12,963 deaths. When one considers that in 2010 donors contributed $45.7 million, $59.9 million, and $60.6 million for malaria control in Angola, Tanzania, and Uganda respectively.[1] it seems reasonable to suggest there is room within existing budgets to fund diagnostic testing efforts.

Discussion

This study comprehensively explored the cost-effectiveness of adopting mRDT for children. We improved on the analytic methods of previous studies, used household data, and accounted for the effect on those with nonmalaria fevers. Incorporating extensive sensitivity analyses, our results suggest that diagnostic testing should be adopted in Angola and Tanzania and strongly considered in Uganda. Our costs per life-year gained fell well below the WHO standard value. They also did not exceed the value of each country's per capita gross national product, another cost-effectiveness guideline.[19]

This analysis compared universal screening to no screening. Some screening is currently taking place, which indicates that infrastructure exists to support it. This means that our results likely provide cost estimates of the implementation of universal screening that are on the high side instead of the low side.

However, offsetting these potentially high estimates is the fact that countries will need to make additional infrastructure investments to support universal diagnostic testing. These include expanding and shoring up distribution networks, particularly in relation to rural areas; improving existing storage facilities to minimize waste; and providing new ones in areas that lack facilities. Improved logistical management is also required to ensure that a reliable supply of testing kits is available throughout the year.

Training health care workers is essential. Clinicians' adherence to test results is critical for the tests to add value. Evidence shows that provider education and training can change practice patterns.[29] One way to promote use and compliance is to provide financial rewards linked to testing. Tying drug subsidies to testing is also worthy of consideration. Educating caregivers about the value of testing, as opposed to immediate treatment, may also encourage the use of testing.

Of the three countries considered here, Angola's infrastructure is likely to be the weakest. There is a 76 percent likelihood that screening is predominantly cost-saving in this country. Therefore, funds no longer needed for nonmalaria cases, which would be treated appropriately in the future, could be redirected to support network development. The same is true of Tanzania, to a lesser degree

The model here can be readily applied to other countries. Probability values and costs can be changed to be country specific, and treatment patterns can be modified as needed to reflect differences in treatment patterns.

International support for malaria programs is substantial. The majority of funds are folded into national malaria control programs and managed by the countries themselves. Unless

international donations increase, generating funds for increased screening is likely to require reallocations within fixed malaria budgets or redistribution of funds from other country initiatives to combat malaria.

Conclusion

Prioritizing spending on health programs is a serious challenge for countries. Exploring the cost-effectiveness of specific interventions can inform these discussions. Screening is cost-effective and buys life-years at a bargain price. Shifting resources to support full implementation of the WHO's policy of universal testing should be seriously considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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NOTES

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34. The four results in this case are as follows: mRDT costs more but averts more deaths than for PT does (mRDT may be cost-effective); mRDT costs less and averts more deaths than PT does (mRDT is the dominant strategy); mRDT costs more and averts fewer deaths than PT does (PT is dominant); and mRDT costs less but averts fewer deaths than PT does (mRDT is not effective).

EXHIBIT 1

Estimated Costs And Deaths Averted Using The Malaria Rapid Diagnostic Test (mRDT) Instead Of Presumptive Treatment (PT), By Country

Country	Cost per child ($)	Incremental cost ($)	Deaths averted	Incremental deaths averted	Cost per death averted ($)	Cost per life-year gained ($)
ANGOLA						
mRDT	68.70	−5.02	0.033	0.003	Cost-saving	Cost-saving
PT	73.72	__[a]	0.030	__[a]	__[a]	__[a]
TANZANIA						
mRDT	12.74	0.93	0.008	0.006	155	5.54
PT	11.81	__[a]	0.014	__[a]	__[a]	__[a]
UGANDA						
mRDT	21.36	5.28	0.014	0.002	2,640	94.28
PT	16.08	__[a]	0.016	__[a]	__[a]	__[a]

SOURCE Authors' analysis.

NOTES "Incremental" is the difference between using mRDT and PT. "Deaths averted" are those prevented by each strategy. All costs were converted to 2010 US dollars. Cost-effectiveness is assessed according to the World Health Organization's standard of $150 per life-year gained. Standard errors for the values are provided in the Appendix (see Note 24 in text).

[a]Not applicable.

EXHIBIT 2

Likelihood That Use Of The Malaria Rapid Diagnostic Test (mRDT) Instead Of Presumptive Treatment (PT) In Angola Will Produce Health Gains Or Losses And Net Savings Or Costs

	Health loss	Health gain
Net cost	3%	4%
Net savings	17%	76%

SOURCE Authors' analysis.

NOTES Health loss is when fewer mRDT deaths than PT deaths are averted. Health gain is when more mRDT deaths than PT deaths are averted. Net cost is when mRDT cost is greater than PT cost. Net savings is when mRDT cost is less than PT cost.

EXHIBIT 3

Likelihood That Use Of The Malaria Rapid Diagnostic Test (mRDT) Instead Of Presumptive Treatment (PT) In Tanzania Will Produce Health Gains Or Losses And Net Savings Or Costs

	Health loss	Health gain
Net cost	10%	67%
Net savings	1%	22%

SOURCE Authors' analysis.

NOTES Health loss is when fewer mRDT deaths than PT deaths are averted. Health gain is when more mRDT deaths than PT deaths are averted. Net cost is when mRDT cost is greater than PT cost. Net savings is when mRDT cost is less than PT cost.

EXHIBIT 4

Likelihood That Use Of The Malaria Rapid Diagnostic Test (mRDT) Instead Of Presumptive Treatment (PT) In Uganda Will Produce Health Gains Or Losses And Net Savings Or Costs

	Health loss	Health gain
Net cost	36%	64%
Net savings	0%	0%

SOURCE Authors' analysis.

NOTES Health loss is when fewer mRDT deaths than PT deaths are averted. Health gain is when more mRDT deaths than PT deaths are averted. Net cost is when mRDT cost is greater than PT cost. Net savings is when mRDT cost is less than PT cost.