Phillips V, Njau J, Li S, Kachur P. Simulations show diagnostic testing for malaria in young African children can be cost-saving or cost-effective. Health Aff (Millwood). 2015;34(7).

Appendix

1. Detailed Model Description

Model Overview

We constructed a decision-analytic model with a Markov specification, using TreeAge Pro suite 2009 (TreeAge Software, Inc, Williamstown, Massachusetts) decision tree software, designed to capture the recurring nature of suspected malaria fevers. Total costs and deaths averted, based on the course of disease and treatment over the year, are aggregated. We use two-stage micro-simulation to address model uncertainty. For illustration, we describe the mRDT arm in Figure 1 below. The PT arm has a parallel structure with testing omitted.

We begin with a hypothetical cohort of 1000 children, and based on prevalence, children begin in either a fever or no-fever state. Transmission rates and treatment paths determine how children cycle for 365 days between three states: fever, no fever and death, upon which they exit the cohort. The initial node “M” represents the Markov cycling specification. Note, events along the pathways, such as care-seeking, are driven by probabilities and referred to as chance nodes, represented by circles in the Figure 1.

When a fever occurs, a proportion of caregivers will seek care for children; others will not. If care is sought, children will receive the mRDT, producing a positive or negative result. If

the test is positive, a portion of clinicians will act on the positive result and prescribe artemisinin-based combination therapy (ACT); the remainder will ignore the result and prescribe antibiotics. If the test is negative, a portion of clinicians will act on the negative result and prescribe antibiotics; the remainder will ignore the result and prescribe ACT.

Based on test sensitivity and specificity, only some tests results will be accurate. These factors and clinician response produce eight patient groups, only a subset of which have been correctly diagnosed and are receiving the appropriate treatment. They are shown in boxed branch of Figure 1. For example, the lower branch shows the path where treatment has been sought, the mRDT is negative, the clinician prescribes an ACT and non-malaria fever is present. This is a very poor outcome as the child receives inappropriate treatment, unnecessary drug use occurs, and testing resources are wasted.

AS shown in the box in Figure 1, the model has eight test/adherence pathways for children receiving formal care: 1) mRDT is positive, the clinician adheres to the test result, child has malaria, and the clinician prescribes ACT; 2) mRDT is positive, the clinician adheres to the test result, child has non-malaria fever, and the clinician prescribes ACT; 3) mRDT is positive, the clinician does not adhere to the test result, child has malaria, and the clinician prescribes antibiotics; 4) mRDT is positive, the clinician does not adhere to the test result, child has non-malaria fever, and the clinician antibiotics.

Given that the mRDT can also be negative, four additional pathways exist: 5) mRDT is negative, the clinician adheres to the test result, child has non-malaria fever, and the clinician prescribes antibiotics; 6) mRDT is negative, the clinician adheres to the test result, child has malaria, and the clinician prescribes anitbiotics; 7) mRDT is negative, the clinician does adhere to the test result, child has non-malaria fever, and the clinician prescribes ACT; 8) mRDT is

negative, the clinician does not adhere to the test result, child has malaria, and the clinician prescribes ACT.

AS shown in the second slide in Figure 1, the top branch traces the treatment pathway for the patient subset who test positive, are true cases and are given ACT. For this group a portion will recover immediately and survive. They will then face a second exposure period and "jump" to the beginning of the model, the initial Markov node.

Others will experience some benefit, then relapse. These "treatment failures" will seek care a second time, some at a hospital or others at a health facility, depending on local infrastructure. At the hospital those with uncomplicated malaria will be referred to outpatient care for treatment and will fully recover. Those with severe malaria will either be admitted or not, depending on factors, such as bed availability, and then will either survive or die, depending on admission status.

Those who present at a health care facility with uncomplicated illness, will receive outpatient care and survive. Those with severe malaria will be referred to a hospital, with a portion receiving a pre-referral test. They will follow the hospital pathway described above and will subsequently survive or die, depending on admission status.

Alternatively, caregivers may not seek care for a given fever episode. For some of these children, their disease may remain uncomplicated, whereby they survive. For the remainder, their disease progresses and they will either die or survive. This group incurs no formal treatment costs.

At the end of the fever episode, all children will have either died and exited the cohort or survived. Based on the likelihood of transmission, survivors will return to the Markov node

and face another exposure period of fever/no fever. The pathway described above for the group with a positive mRDT, who have malaria and who are given ACT is repeated for the other seven groups. The PT arm follows a similar structure with no testing.

Model Uncertainty

The model is a pathway of probabilistic events and we use two stage microsimulation to address inherent uncertainty. A key input driving annual cost and deaths averted is the number of possible fevers per child as each fever involves a likelihood of incurring costs and death. To address this issue, we specify two variables in the model. One is the length of the exposure period during which a child can have a fever or not or die, and the other is fever duration, should a fever occur. They are drawn from independent distributions. They are equal at their maximums as the duration of a fever cannot exceed the exposure period. Estimates of maximum fever duration range from 14 days to 30 days. The average number of annual fevers per child in sub-Saharan Africa is six.

In the first order simulation, at the beginning of exposure period, the model draws a random number from 14 to 30 days to determine the exposure period length. Then, should a fever occur, fever duration is randomly assigned. For example, an uncomplicated fever with successful treatment lasts two days on average, while an uncomplicated case, requiring a second treatment, lasts nine days on average. If no fever occurs, then a child faces the risk of infection at the beginning of the next exposure period.

Based on 1000 iterations at base case values, we generate a cohort of 1000 individual profiles of fever/no-fever/death episodes for one year which is used in the second estimation stage.

Model uncertainty also comes from the probability and cost input which we address through probabilistic sensitivity analysis. First we identify the inputs generating 99% of the uncertainty in the model through one-way sensitivity analysis. For this variable group we assume that each represents a value drawn from a triangular distribution, an unrestrictive form which maximizes the impact of uncertainty. Using the cohort generated from stage one, we run a second-stage simulation where input values are randomly selected from their distributions for each run of 10,000 iterations. This second stage provides estimates of mean and standard error values for costs and deaths associated with mRDT and PT.

Figure 1: mRDT Branch of the Micro-simulation Model

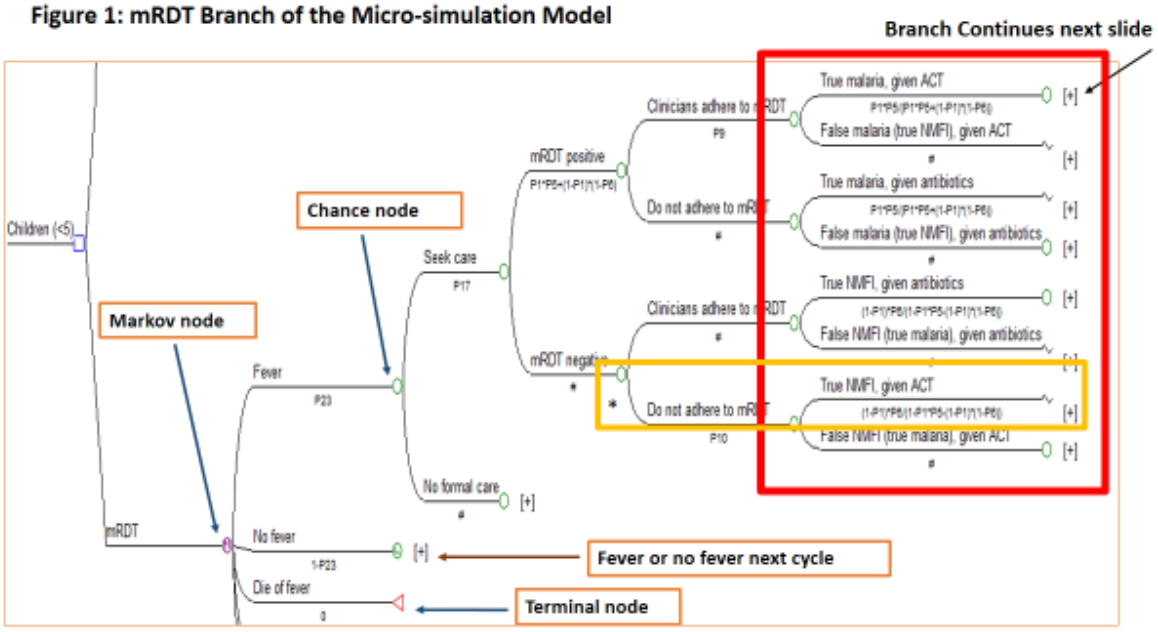

Figure 1: continued

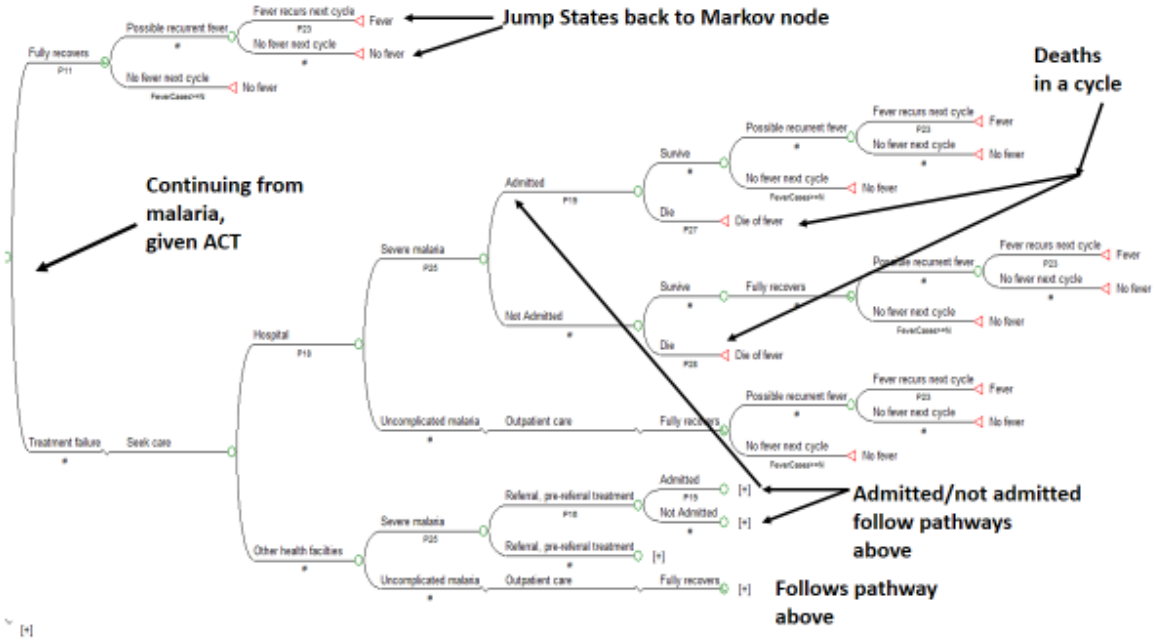

Table 1: Population, Income, and Base Values of Primary Model Inputs by Country

Country	Angola	Tanzania	Uganda
Population[1]	19.5 million	45 million	34 million
GNP per capita[1]	$5485	$591	$547
Epidemiologic probabilities			
Prevalence of Malaria in children age < 5[2]	9.6%	4.9%	55.5%
Inpatient case fatality rate severe malaria[1]	0.045	0.031	0.028
Inpatient case fatality rate for severe non-malaria fever illness[3]	0.054	0.037	0.035
Case fatality rate for severe, untreated malaria[3]	0.060	0.041	0.037
Case fatality rate for severe, untreated non-malaria fever illness[3]	0.072	0.049	0.047
Behavioral probabilities			
% Caregivers seek care for suspected fever[2]	.30	.68	.60
Physician adherence to test[4]	.40	.82	.51
Costs[5] ($)			
mRDT test, distribution & storage	30.25	1.20	1.10
ACT	12.00	1.10	1.25
Inpatient treatment cost for malaria	10.00	1.50	2.00
Cost per bed day	43.17	3.43	3.39

Sources: [1]World Malaria Report, 2013 [2]Malaria Indicator Survey by Country [3]Adjusted case fatality rates from the World Malaria Report, 2013 [4]References in text [5]WHO-Choice_cost_estimates

Table 2: Base Case Model Results by Country

Country & Strategy	Costs per Child ($)	Incr. Costs ($)	Deaths Averted per Child	Incr. Deaths Averted	Cost per Death Averted ($)	Cost per Life-Year Gained ($)
Angola						
mRDT	68.70 (20.89)	-5.02	0.033 (0.020)	0.003	Cost-saving	Cost-saving
PT	73.72 (22.22)		0.030 (0.020)			
Tanzania						
mRDT	12.74 (3.91)	0.93	0.008 (0.006)	0.006	155	5.54
PT	11.81 (3.47)		0.014 (0.010)			
Uganda						
mRDT	21.36 (5.01)	5.28	0.014 (0.010)	0.002	2640	94.28
PT	16.08 (3.84)		0.016 (0.011)			

Note: Incr = Incremental.

Table 3: List of variables, values, and sources for Model by Phillips et al. (2015)

	Variable	Distribution	Base Case	Lower Limit	Upper Limit	Sources	Year
	Epidemiology						
P1	Malaria prevalence among children under 5					P1=(P2+P6-1)/(P5+P6-1)	
	Angola		0.096	*0.010*	*0.182*		
	Tanzania		0.049	*0.010*	*0.088*		
	Uganda		0.555	*0.355*	*0.755*		
P2	Children (< 5) with Positive mRDT results						
	Angola		0.135	0.017	0.247	AMIS, 2011, P51, Table 5.7	2011
	Tanzania		0.092	0.000	0.318	TMIS, 2011, P177, Table 11.5	2011
	Uganda		0.549	0.074	0.801	UMIS, 2009, P81, Table 6.3	2009
	Diagnose						
P3	Presumptive treatment (PT) sensitivity		1.000			Uzochukwu BSC et al., 2009; Shillcutt et al, 2008	
P4	Presumptive treatment (PT) specificity		0.000				
P5	mRDT sensitivity		0.950	0.935	0.962	Abba K et al, 2011	2011
P6	mRDT specificity		0.952	0.934	0.994	Abba K et al, 2011	2011
	Clinician adherence to diagnoses or test results						
P7	Children (<5) diagnosed with malaria under PT strategy receive antimalarial		1.000			Assumed	
P8	Children (<5) diagnosed with NMFI under PT strategy receive antimalarials		0.000			Assumed	
P9	Children (< 5) with positive mRDT results receive antimalarials						
	Angola		0.941	0.882	1.000	Rowe A.K. et al., 2009	2007
	Tanzania		1.000			Mubi M. et al., 2013	2010-2011
	Uganda		0.990			Kyabayinze et al., 2010	2007

P10	Children (< 5) with negative mRDT results receive antimalarials					
	Angola	0.600	*0.400*	*0.800*	Rowe A.K. et al., 2009	2007
	Tanzania	0.125	*0.000*	*0.325*	Mubi M. et al., 2013	2010-2011
	Uganda	0.490	*0.290*	*0.690*	Kyabayinze et al., 2010	2007
	Drug efficacy and adherence					
P11	Efficacy of ACT	0.966	0.860	0.993	Thwing J. et al., 2011	
P13	Efficacy of antibiotics	0.750	0.600	0.900	Shillcutt et al, 2008	
P15	Efficacy of pre-referral treatment (rectal artesunate)	0.490	0.193	0.678	Tozan Y. et al., 2010	
P16	Severe malaria children are referred with pre-referral treatment					
	Angola	0.100	0.000	0.200	PMI MOP 2011, 12, 13	
	Tanzania	0.750	*0.550*	*0.950*	PMI MOP 2011, 12, 13	
	Uganda	0.600	*0.400*	*0.800*	PMI MOP 2011, 12, 13	
	Treatment seeking patterns					
P17	Patients (under 5 years old) seek care					
	Angola	0.298	*0.098*	*0.498*	Angola MIS data, Table 4.7 DHS report 2011	2011
	Tanzania	0.680	*0.480*	*0.880*	Tanzania MIS data, Table 11.1 DHS report	2006/7 & 2012
	Uganda	0.594	*0.394*	*0.794*	Uganda MIS data, Table 4.1, DHS report	2009
P18	Among those seeking care, the probability that patients go to hospitals	0.367	0.094	0.774	UMIS	
P19	Severe malaria children (<5) get inpatient care					
	Angola	0.122	0.001	0.244	Recommendation: increase the all age rate from WHO by 20% for base rate; use adult value as lower & Brent (2006) as higher bounds.	
	Tanzania	0.147	0.001	0.294		
	Uganda	0.133	0.001	0.264		
P20	Severe NMFI children (<5) get inpatient care	P20=P19				
	Disease progression					
P23	Transition to fever in cycle length t	ProbToProb(P31;t/14)				

P24	For patients who did not seek care at first, their disease progress to severe conditions. The probability of care-seeking at that time.	0.000			Structural assumption
P25	Malaria not effectively treated lead to severe conditions (Age < 5)	0.050	0.001	0.099	Lubell
P26	NMFI not effectively treated lead to severe conditions (Age < 5)	P26 = RR1 * P25			
P27	CFR for severe malaria children, inpatient care				
	Angola	0.045	0.001	0.089	Use multiplier 1.20 of adult value; adults seek hosp care, so not so different.
	Tanzania	0.031	0.001	0.061	
	Uganda	0.028	0.001	0.055	
P28	CFR for severe malaria children, without formal care	P28 = RR2 * P27			
P29	CFR for severe NMFI children, inpatient care	P29 = RR1 *P27			
P30	CFR for severe NMFI children, without formal care	P30 = RR2* P29			
P31	Transition to fever in two weeks				
	Angola	0.341	0.250	0.457	MIS, 2011
	Tanzania	0.204	0.071	0.338	MIS, 2011
	Uganda	0.447	0.223	0.661	MIS, 2009
T	cycle length (days)	30	14	30	
RR1	Relative risk (general) comparing NMFI to malaria	1.2	1.05	1.35	Assumed NMFI values 20% higher than those for malaria;
RR2	Relative risk of CFR comparing no formal care with inpatient care	1.33	1.28	1.38	

Assumed informal care values 33% higher than those for malaria and NMFI respectively

COST DETAILS

	Variable	Base Case	Lower Limit	Upper Limit	Cost Adjustments	Source
	Test Cost					
C1	mRDT Costs					
	Angola	3.25	2.00	4.50		Angola NMCP
	Tanzania	1.20	0.45	1.50		Tanzania NMCP
	Uganda	1.10	0.60	1.50		Uganda NMCP
	Outpatient Cost					
C2	ACT cost					
	Angola	12.00	9.00	15.00		Angola's MoH/NMCP
	Tanzania	1.10	0.80	1.25		Tanzania's MoH/NMCP
	Uganda	1.25	0.95	1.50		Uganda's MoH/NMCP
C3	Cost of other antimalarials					
	Angola	6.5	3	10		Angola's MoH/NMCP
	Tanzania	1	0.5	1.5		Tanzania's MoH/NMCP
	Uganda	1.35	0.7	2		Uganda's MoH/NMCP
C4	Cost of antibiotics					
	Angola	6.75	5.00	8.50		Angola's MoH/NMCP
	Tanzania	1.35	0.75	2.00		Tanzania's MoH/NMCP
	Uganda	1.50	0.80	2.20		Uganda's MoH/NMCP
C21	Cost per outpatient visit				Calculated the weighted average from the urban and rural population size. Then conduct adjustment (see C21 tab)	WHO-CHOICEunit_cost_estimates >> 2. User Defined Parameters >> 2008 >> Public. Used the cost for health facilities with no beds.
	Angola	6.24	4.99	7.10		
	Tanzania	0.50	0.45	0.64		
	Uganda	0.47	0.45	0.64		
	Inpatient Cost					
C5	Pre-referral treatment cost (rectal artesunate)	0.41	0.33	0.50	Adjusted for discount at 3% rate in the original paper.	Tozan Y. et al., 2010

C9	Inpatient treatment cost for malaria					
	Angola	10	*7*	*13*		Angola's MoH/NMCP
	Tanzania	1.5	*1.05*	*1.95*		Tanzania's MoH/NMCP
	Uganda	2	*1.4*	*2.6*		Uganda's MoH/NMCP
C15	Inpatient treatment cost for NMFI					
	Angola	8.5	*5.95*	*11.1*		Angola's MoH/NMCP
	Tanzania	2	*1.4*	*2.6*		Tanzania's MoH/NMCP
	Uganda	2.2	*1.54*	*2.86*		Uganda's MoH/NMCP
C18	Hospital bed day cost for severe malaria	C20*t4_Malaria				
C19	Hospital bed day cost for severe NMFI	C20*t4_NMFI				
C20	Cost per bed day				First adjusted for inflation from 2008 to 2010 in LCU. Then adjust for exchange rate to 2010 USD. See spreadsheet C20 for details.	WHO-CHOICEunit_cost_estimates >> 2. User Defined Parameters >> 2008 >> Public. The secondary-level hospital is used as base case. The other two are used as ranges.
	Angola	43.17	41.38	55.82		
	Tanzania	3.43	3.28	4.43		
	Uganda	3.39	3.25	4.38		

Note: All costs in this table now are in 2010 USD