Chapter 15

Cost-Effectiveness of Strategies for the Diagnosis and Treatment of Febrile Illness in Children

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INTRODUCTION

Fever is a common presenting complaint of ill children all over the world. Until recently in Sub-Saharan Africa, fever was synonymous with a presumed diagnosis of malaria. However, malaria is not the only common cause of fever or serious febrile illness (FI) in Sub-Saharan Africa, and the widespread success of malaria control has reduced the region's share of the FI burden. In 2008, 16 percent of the 4.2 million deaths of children in this region were attributed to malaria, 18 percent to pneumonia, and 19 percent to diarrhea (Black and others 2010).

Historically, the response to fever in children in Sub-Saharan Africa was presumptive antimalarial treatment. Cheap, safe, and efficacious antimalarial medications were widely available, and the only method of diagnosis—microscopy—was scarce. The historically inexpensive medicines—chloroquine (CQ) and sulfadoxine/pyrimethamine (SP)—succumbed to the development of drug-resistant malaria parasites; since 2000, these drugs have been replaced as first-line treatment by the more expensive but highly efficacious artemisinin-based combination therapies (ACTs). Rapid diagnostic tests (RDTs) that do not require laboratory facilities or technical training have become available. In light of these two developments, in 2006 the World Health Organization (WHO) recommended that parasitological confirmation precede malaria treatment except in children in high-transmission settings (WHO 2006), and in 2010 the WHO made the recommendation universal, even for highly exposed children (WHO 2010). Most Sub-Saharan African countries have officially adopted this policy, although few have been able to implement it fully.

The major advantages claimed for pretreatment confirmation of malaria are the following:

- Prevention of unnecessary ACT use, which can save money and reduce drug pressure that could lead to resistance
- More appropriate treatment of nonmalaria fevers
- Improved surveillance and better data for planning.

The appropriateness of the WHO test-and-treat policy is clear in low-endemicity settings; it is not so clear in many high-transmission settings, where all of the supposed advantages have been challenged (D'Acremont and others 2009; English and others 2009; Graz and others 2011).

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Many economic evaluations have compared malaria RDTs to presumptive treatment and microscopy, using cost-effectiveness methods and measuring the following:

- Cost per correctly diagnosed malaria case (Bualombai and others 2003; Chanda, Castillo-Riquelme, and Masiye 2009; de Oliveira, de Castro Gomes, and Toscano 2010; Fernando and others 2004; Rolland and others 2006)
- Cost per correctly diagnosed and treated malaria case (Batwala and others 2011; Chanda and others 2011; Lubell and others 2007; Ly and others 2010; Rosas Aguirre, Llanos Zavalaga, and Trelles de Belaunde 2009; Willcox and others 2009; Zikusooka, McIntyre, and Barnes 2008)
- Cost per disability-adjusted life year (DALY) averted (Shillcutt and others 2008).

Others have used cost-benefit analysis (Bisoffi and others 2011; Lubell, Hopkins, and others 2008; Lubell, Reyburn, and others 2008).

Most evaluations have found that an RDT test-and-treat approach performs better than a microscopy test-and-treat approach or presumptive treatment below a certain level of malaria endemicity (Batwala and others 2011; Bisoffi and others 2011; Bualombai and others 2003; Chanda, Castillo-Riquelme, and Masiye 2009; Hansen and others 2015; Ly and others 2010; Mosha and others 2010; Msellem and others 2009; Rolland and others 2006; Rosas Aguirre, Llanos Zavalaga, and Trelles de Belaunde 2009; Shillcutt and others 2008; Uzochukwu and others 2009; Zikusooka, McIntyre, and Barnes 2008; Zurovac and others 2008). Microscopy performed better than RDT in Brazil (de Oliveira, de Castro Gomes, and Toscano 2010), Sri Lanka for *Plasmodium vivax* (Fernando and others 2004), and one high-transmission setting (Willcox and others 2009) and about equivalent to RDT in Ghana (Ansah and others 2013).

The most influential factors affecting the results are malaria transmission intensity (Lubell, Hopkins, and others 2008; Zurovac and others 2008), cost and accuracy of the RDTs (Lubell, Hopkins, and others 2008), age (Zikusooka, McIntyre, and Barnes 2008), season (Bisoffi and others 2011), and response to negative test results (Bisoffi and others 2011; Lubell, Reyburn, and others 2008).

The analysis in this chapter assesses the potential cost-effectiveness of RDTs and their role in treatment strategies for overall FI management in children under age five years, taking into account transmission intensity, treatment setting, and relative availability of antibiotic treatment (or no drug treatment) for nonmalaria FI. It also examines the impact of the availability of different levels of diagnosis on optimal FI management strategy.

METHODOLOGY

Analytic Overview

The reference case for this decision-analytic policy model of FI management is a child under age five years presenting at a point of care (including pharmacies and drug sellers) with fever or history of fever. The model covers a one-month time horizon given the short duration of acute febrile illnesses such as malaria and respiratory tract infections. This chapter presents results for a run of the model using parameters specific to Tanzania, which represent the best estimates from publicly available sources, including the published scientific literature and various reports. The model itself can be adapted to different regions, countries, or settings if local data are available. A key characteristic of the analysis is the planned flexibility of the ranges used for sensitivity analyses, which are varied to reflect current and potential future policy goals or field realities.

The analysis assumes that children with fever may have malaria; treatable nonmalaria febrile illness (T-NMFI), which is illness that responds to appropriate antibiotic treatment; or nontreatable nonmalaria febrile illness (NT-NMFI), which is viral illness. It also assumes that severity assessments are possible at all points of care (which is a simplifying assumption that is not uniformly true) and that, although children may have malaria parasites, the index illness may be caused by something else. (Even in cases of nonclinical malaria infection, it is assumed that eliminating malaria parasites with an antimalarial drug is beneficial.)

The model assesses the costs, effectiveness, and cost-effectiveness of using malaria RDTs and treating children with acute FI with antimalarial drugs, antibiotics, both, or neither. Model parameters include the following: rural versus urban location, type of facility, malaria transmission intensity, etiology of FI, access to diagnostic technology (RDTs and microscopy), antimalarial medications and antibiotics, diagnostic test performance in the field, adherence to negative malaria test results by clinicians or other prescribers, adverse drug events, mortality, and costs (in 2013 U.S. dollars). The analytic framework also allows for the assessment of sequential treatment for FI: children who initially present with mild illness may return with severe illness.

In the base case, malaria diagnosis is by RDTs if available, by microscopy if RDTs are not available, and by no testing if both are unavailable. The base case assumes malaria treatment by ACTs if available, by another

antimalarial medicine if ACT is not available, and by a broad-spectrum antibiotic for strategies that include an antibiotic. Differential access to diagnostic tests and drugs is explicitly built into the model, and the base case allows some patients to go without diagnosis or treatment. Variations in the impact of universal access to ACTs and antibiotics are examined using scenario and sensitivity analyses. The main sensitivity analyses assume universal access to ACTs to mirror the likely near-future state of affairs, but this access depends critically on price.

Key scenario and sensitivity analyses are used to answer policy questions that include the impact on optimal FI management strategy of increasing access to diagnostic tests, antimalarial medicines, and antibiotics and whether increasing access to these commodities would have the greatest impact in low- or high-transmission settings, public or private settings, and urban or rural areas. The analytic framework also allows an assessment to be made of the impact of prescriber adherence to negative tests on the optimal strategy. The model calculates the expected probability of survival and costs for different FI management strategies and estimates the optimal strategy from the standpoint of survival, cost, and cost-effectiveness.

Included are the costs of diagnostic technology (RDTs and microscopy), antimalarial medicines, and broad-spectrum antibiotics; the added cost of assessing severity and administering RDTs; the cost of treating mild and severe disease; and the cost of managing adverse events. Direct nonmedical costs incurred by patients and indirect costs due to lost productivity of parents are not included. Health system costs, cost of health worker training, cost of creating demand with behavior change communication, cost of future ACT and antibiotic resistance, and cost of potential RDT use in the private and informal sectors (such as sharps disposal) are not included. This approach constitutes a modified societal perspective for the analysis (Garrison and others 2010).

Comparators: Potential Strategies for Febrile Illness Management

Seven strategies are compared (table 15.1): three presumptive strategies (P-1, P-2, and P-3) and four diagnosis-based strategies (RDT-1, RDT-2, RDT-3, and RDT-4). The strategies were constructed to encompass the following:

- Historical policy options
- Possible policy options given actual conditions in the field
- Pragmatic policy options given system capacity and health workforce issues

Table 15.1 Modeled Febrile Illness Management Strategies

Comparator	RDT administered	Antimalarial given	Antibiotic given
P-1	To none	All	None
P-2	To none	All	If severe illness
P-3	To none	All	All
RDT-1	To all	If RDT positive	None
RDT-2	To all	If RDT positive	If severe illness and malaria, no antibiotic; if severe illness and no malaria, treat with antibiotic
RDT-3	To all	If RDT positive	If no malaria, treat with antibiotic
RDT-4	To all	If RDT positive	If severe illness, treat with antibiotic

Note: P = presumptive treatment; RDT = rapid diagnostic test.

- Potential future options, given improving access to malaria diagnostic technology, ACTs, new bacterial illness diagnostics, and antibiotics.

Some of the strategies are unlikely to be implemented in the real world but have value as historical comparisons or for assessment of the potential impact of poor implementation. In all cases, the diagnostic technology is presumed to be RDT if available, and if RDTs are not available, microscopy if available. The antimalarial is presumed to be an ACT if available, and if an ACT is not available, an alternative antimalarial.

The strategies are as follows:

- *P-1, presumptive treatment with antimalarials only for all children.* Presumptive treatment of FI because malaria was the historical management option in the vast majority of low-income, resource-constrained settings with high malaria endemicity in the pre-RDT era. It remains the default where RDTs are not available and malaria is still common. Under P-1, a child presenting with fever or a history of fever is treated with an ACT if available, another antimalarial if an ACT is not available, and no treatment if ACTs or other antimalarials are not available. P-1 is the base comparator.

- *P-2, presumptive treatment with antimalarials for all children and presumptive treatment with broad-spectrum antibiotics for children with severe illness.* P-2 is modeled around the original version of Integrated Management of Childhood Illness (IMCI), introduced by the WHO in 1997 in response to increasing under-five mortality in low-income countries (WHO 1999). The original version recommended that all children with fever or a history of fever receive a first-line antimalarial drug and be evaluated for signs of other potential causes of fever, such as rapid breathing for pneumonia, followed by appropriate treatment. It did not explicitly recommend parasitological confirmation of malaria.
- *P-3, presumptive treatment with both antimalarials and antibiotics for all children.* P-3 is included as a fallback position in recognition of the difficulty of clinically assessing children for pneumonia and other serious causes of fever. Such assessment is usually not carried out by caregivers making treatment decisions, even in primary care facilities that are understaffed or staffed by poorly trained health care workers.
- *RDT-1, treatment with antimalarials for children who test positive for malaria and no treatment for children who test negative.* RDT-1 is included in the model to demonstrate the potential consequences of untreated T-NMFI. Children with fever are tested for malaria using RDT or microscopy, and those testing positive are treated with an available antimalarial. No antibiotics are prescribed regardless of test result or disease severity.
- *RDT-2, treatment with antimalarials for children who test positive for malaria and presumptive treatment with antibiotics for children with severe illness who test negative.* RDT-2 mirrors the second iteration of IMCI, which recommended that the assessment of children with fever include diagnostic testing for malaria. In the modeling framework, children with fever or a history of fever are tested for malaria using RDT or microscopy and those testing positive are treated with an available antimalarial. Children testing negative are assessed for signs of disease severity (such as fast breathing, dehydration), and those showing signs of severe disease are treated with a broad-spectrum antibiotic in addition to the antimalarial medicine.
- *RDT-3, treatment with antimalarials for children who test positive for malaria and presumptive treatment with broad-spectrum antibiotics for all children who test negative.* RDT-3 is included in the model to demonstrate the potential consequences of presumptive treatment of all NMFI with antibiotics. In the model, children with fever are tested for malaria using RDT or microscopy, and those testing positive are treated with an available antimalarial. All children testing negative for malaria are treated with a broad-spectrum antibiotic.
- *RDT-4, treatment with antimalarials for children who test positive for malaria and presumptive treatment with broad-spectrum antibiotics for all children with severe disease.* Under RDT-4, children with fever are tested for malaria using RDT or microscopy, and those testing positive are treated with an available antimalarial. All children showing signs of severe disease are treated with a broad-spectrum antibiotic in addition to the antimalarial medicine.

Decision-Analytic Model

The model consists of (1) a "front-end" decision tree that classifies presenting children by their setting of treatment, point of care, diagnostic result, and treatment received, and (2) a "back-end" Markov model that estimates the impact of illness severity, progression, and mortality on costs and outcomes.

The front end of the model is divided into four parts, as shown in figure 15.1: panel a shows FI management strategies, treatment setting, and disease etiology; panel b shows malaria diagnostic test availability and test results (true positive, false negative, false positive, true negative); panel c shows availability and prescription of ACT and antibiotics; and panel d shows availability and prescription of antimalarials (CQ and SP) and antibiotics.

In figure 15.1, panel a, children with FI may present and be treated in rural or urban settings and at one of five points of care: at home by a community health worker, at a general retail outlet, at a drug shop such as duka la dawa baridis in Tanzania or a pharmacy, at a private health facility, or at a public health facility (including nongovernmental organization and faith-based facilities). Children may live and present for treatment in high-transmission-intensity areas (1 or more malaria cases per 1,000 population) or low-transmission-intensity areas (0.051 cases per 1,000 population). Depending on the setting, children may or may not have parasites in their blood. Those who are parasitemic may have clinical malaria or asymptomatic parasitemia, in which case their illness is caused by T-NMFI, usually bacterial infection, or NT-NMFI, usually viral infection. Those who are not parasitemic will similarly have T-NMFI or NT-NMFI. In this analysis, the combined diagnosis of malaria and T-NMFI is modeled, but not the other combined diagnoses such as T-NMFI plus NT-NMFI or malaria plus NT-NMFI.

Figure 15.1 Decision-Analytic Model

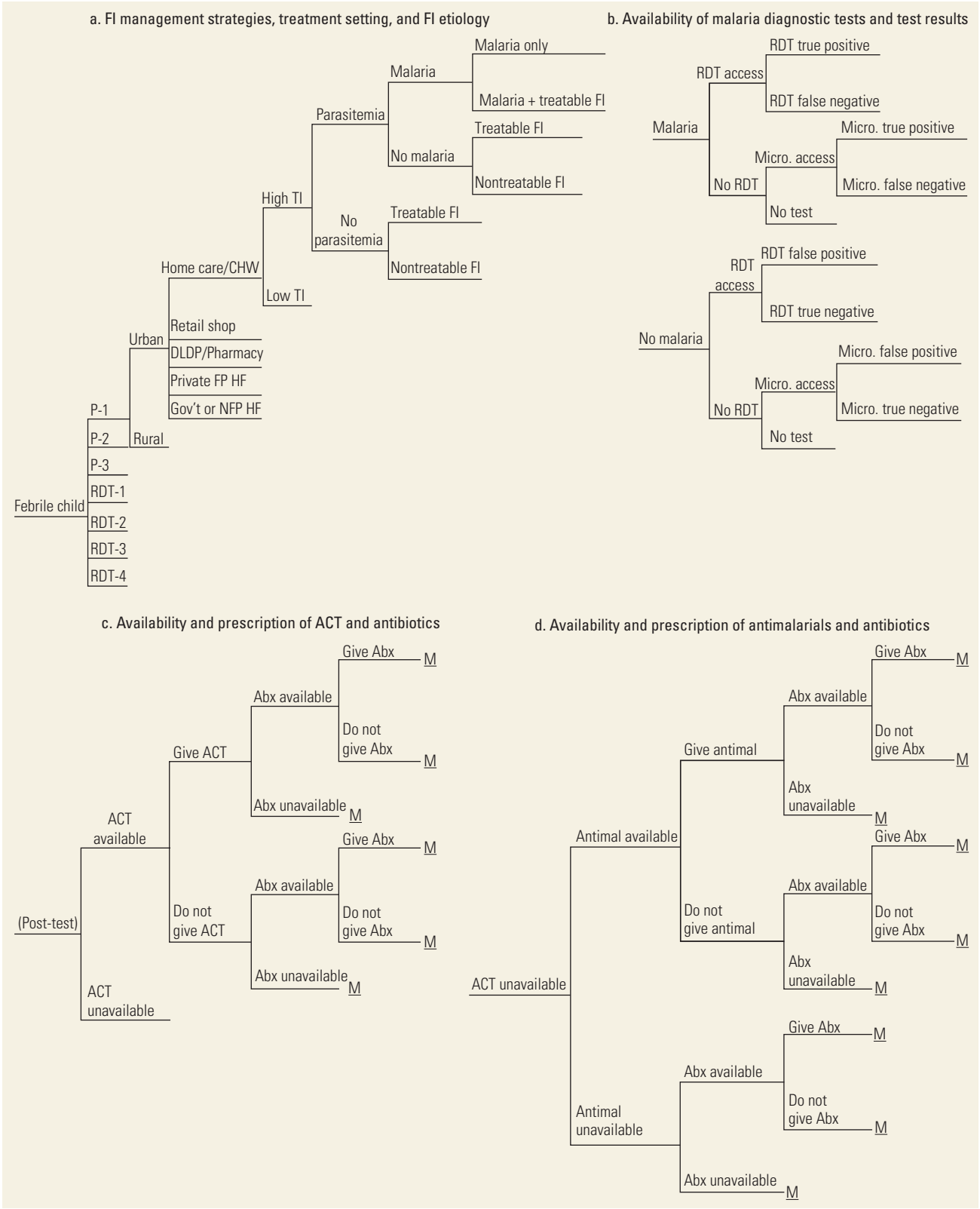

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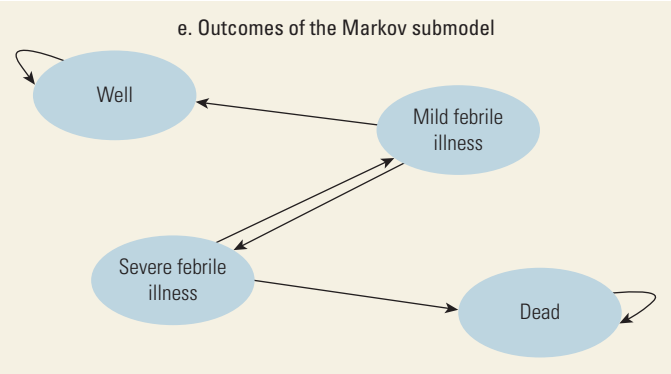
Figure 15.1 Decision-Analytic Model (continued)



Note: Abx = antibiotics; ACT = artemisinin-based combination therapy; Antimal = antimalarial; CHW = community health worker; DLDB = duka la dawa baridi; FI = febrile illness; FP = for profit; Gov't = government; HF = health facility; M = transition to Markov Model; Micro. = microscopy; NFP = not for profit; RDT = rapid diagnostic test; TI = transmission intensity.

In figure 15.1, panel b, children with malaria (malaria only and malaria plus T-NMFI) as well as children without malaria are subjected to diagnostic testing depending on access to testing technology. At the point of care, malaria RDTs may or may not be available. If available, the model assumes that they are the first choice, but if unavailable, the provider uses microscopy, if available. If microscopy is also unavailable, children are assumed to be treated with an antimalarial. Depending on the performance (sensitivity and specificity) of the malaria test used (RDT or microscopy), patients with malaria are divided into two treatment pools: true positive and false negative. Those without malaria are divided into false positive and true negative pools.

In figure 15.1, panels c and d, following the test and depending on the treatment pool, patients are treated with ACTs, antimalarial medicines, or antibiotics depending on their availability and in line with one of the seven FI management strategies in the model. At the point of care it is assumed that if ACTs are available, they are given, but if ACTS are not available, other antimalarials are given. The model also explicitly considers the provider's decision to give antimalarial medicines and antibiotics in the face of positive or negative malaria test results. In the base case, when no medicines are available, children go untreated. Adverse drug events also occur in the model, depending on the drug given, with consequences for cost but not for mortality.

The Markov model (figure 15.1, panel e) divides acute FI into four health states: well, mild illness, severe illness, and dead. All children start in the mild or severe FI health state. During every cycle, assumed to be one week, children in the mild state may progress to severe and children in the severe state may improve and join the mild state. Children in the mild state may also move to the well state, and children in the severe state face a mortality risk. The model does not allow mortality other than from the severe state nor complete wellness without moving through the mild state. Both the well and the dead states are absorbing states. The rates of mortality and progression depend on the medicine received and the true diagnosis as defined earlier in the model. Where diagnostic testing results in false negatives or false positives, the model directs patients into incorrect treatment algorithms, which are included in the model. Given that only two transitions are allowed from both the mild and severe states, the rates of transition from mild illness to well and from severe illness to mild are modeled as complements of progression and mortality, respectively.

Tanzania Parameters

Setting of Febrile Illness Management

Tanzania is 26 percent urban and 74 percent rural (Tanzania NBS 2011); 24 percent of children with fever in urban areas and 39 percent in rural areas did not seek fever treatment from health care providers in 2010 (Tanzania NBS and Macro International 2011), an estimate used to represent children under home care, assuming that their point of care is through a pharmacy or drug shop or a community health worker. Information from Kenya is used in the absence of information from Tanzania to estimate the distribution of point of care by different urban facilities (Molyneux and others 1999). For rural areas, a study from Kilosa, Tanzania (Simba and others 2010), is used. An estimated 73 percent of Tanzania's population live in high-transmission-intensity areas, and 27 percent live in low-transmission-intensity areas (WHO 2012b). The model distribution by setting is presented in table 15.2.

Table 15.2 Modeled Distribution of Children with Febrile Illness in Tanzania, by Management Setting, 2013, Based on Best Estimates

Setting	Base case	Reference
Residence		Tanzania NBS 2011
Urban	0.742	
Rural	0.258	
Point of care		
Urban		Molyneaux and others 1999; Tanzania NBS and Macro International 2011
Home care	0.242	
General shop	0.087	
Pharmacy or drug shop	0.270	
Private health facility	0.298	
Government health facility	0.103	
Rural		Simba and others 2010; Tanzania NBS and Macro International 2011
Home care	0.391	
General shop	0.294	
Pharmacy or drug shop	0.092	
Private health facility	0.166	
Government health facility	0.057	
Transmission intensity		WHO 2012b
High	0.730	
Low	0.270	

Table 15.3 Estimated Average Probability of Malaria Parasitemia and Febrile Illness Etiology in Children in Tanzania, 2013

Indicator	Base case	Reference
Parasitemia		
High transmission	0.423	Patrick Kachur and others 2006
Low transmission	0.013	Zanzibar Malaria Control Program and Karolinska Institute 2012
Malaria		
High transmission		Gosoniu and others 2012
Clinical	0.870	
Asymptomatic	0.130	
Low transmission		Assumption
Clinical	0.999	
Asymptomatic	0.001	
NMFI		D'Acremont 2011
Treatable	0.182	
Nontreatable	0.714	
Malaria and treatable NMFI	0.343	D'Acremont 2011

Note: NMFI = nonmalaria febrile illness.

Parasitemia and Etiology of Febrile Illness

In low-transmission areas (Pemba and Zanzibar), the parasite prevalence among children presenting with fever is 0.13 percent (Zanzibar Malaria Control Program and Karolinska Institute 2012), and all patients with parasitemia are expected to have clinical malaria. In high-transmission areas, the parasite prevalence among children with fever is approximately 42 percent (Patrick Kachur and others 2006), and 13 percent of patients with parasitemia are assumed to be asymptomatic (Gosoniu and others 2012).

Table 15.3 presents the parasitemia and etiology of malaria in Tanzania, assuming that 81 percent of acute respiratory infections and 75 percent of other infections of unknown etiology are due to viruses. A treatable co-infection occurs in 34 percent of patients with malaria (D'Acremont 2011).

Availability and Performance of Diagnostic Tests

Table 15.4 differentiates the availability of diagnostic tests between urban and rural settings, assuming at baseline that diagnosis by microscopy is not available in home care, general shops, and duka la dawa baridis. The sensitivity of microscopy in Tanzania is assumed to be 71.4 percent, and specificity is assumed to be 47.3 percent. The sensitivity of RDTs is 97.0 percent, and specificity is 96.8 percent (Kahama-Maro and others 2011).

Availability of Medicines for Febrile Management

In the absence of data from Tanzania, ACT access information from Uganda is used (ACTwatch Group, PACE, and IE Team 2012), combined with published estimates for segments of the population in Tanzania (Simba and others 2010). As an example, in rural areas, access to ACTs is 71 percent in government facilities and 11 percent in private facilities in rural areas (table 15.5).

Prescribing Practices and Prescriber Adherence to Negative Test Results

Based on a randomized trial in Tanzania comparing RDTs with routine microscopy (Reyburn and others 2007), results in table 15.6 assume that all patients who test positive or are not tested receive antimalarials (Lubell, Reyburn, and others 2008).

Table 15.4 Availability and Performance of Rapid Diagnostic Tests and Microscopy in Tanzania, 2013

Indicator	Base case	Reference
RDTs		
Availability		
Urban		
Home care	0.000	Assumption
General shop	0.001	Assumption
Pharmacy or drug shop	0.056	Albertini and others 2012; CPM 2008
Private health facility	0.835	Assumption
Government health facility	0.635	Masanja and others 2012; assumption
Rural		
Home care	0.000	Assumption
General shop	0.000	Assumption
Pharmacy or drug shop	0.000	Assumption
Private health facility	0.635	Assumption
Government health facility	0.435	Masanja and others 2012
Performance		Kahama-Maro and others 2011
Sensitivity	0.970	
Specificity	0.968	
Microscopy		
Availability		
Urban		
Home care	0.000	Assumption
General shop	0.000	Assumption
Pharmacy or drug shop	0.000	Assumption
Private health facility	1.000	Assumption
Government health facility	0.366	Masanja and others 2012; Tanzania NBS and Macro International 2007; assumption
Rural		
Home care	0.000	Assumption
General shop	0.000	Assumption
Pharmacy or drug shop	0.000	Assumption
Private health facility	0.800	Assumption
Government health facility	0.190	Masanja and others 2012
Performance		Kahama-Maro and others 2011; Masanja and others 2012
Sensitivity	0.714	
Specificity	0.473	

Note: RDTs = rapid diagnostic tests.

Table 15.5 Availability of Antimalarial Medicines and Antibiotics in Tanzania, 2013

Indicator	Base case	Reference
ACTs		
Urban		
Home care	0.999	ACTwatch Group, PACE, and IE Team 2012
General shop	0.560	ACTwatch Group, PACE, and IE Team 2012
Pharmacy or drug shop	0.968	ACTwatch Group, PACE, and IE Team 2012
Private health facility	0.791	ACTwatch Group, PACE, and IE Team 2012
Government health facility	0.780	Chimnani and others 2010
Rural		
Home care	0.550	ACTwatch Group, PACE, and IE Team 2012
General shop	0.747	ACTwatch Group, PACE, and IE Team 2012
Pharmacy or drug shop	0.736	Yadav and others 2012
Private health facility	0.110	Simba and others 2010
Government health facility	0.710	Chimnani and others 2010
Other antimalarial drugs		
Urban		
Home care	0.080	ACTwatch Group, PACE, and IE Team 2012
General shop	0.001	ACTwatch Group, PACE, and IE Team 2012
Pharmacy or drug shop	0.995	ACTwatch Group, PACE, and IE Team 2012
Private health facility	0.960	ACTwatch Group, PACE, and IE Team 2012
Government health facility	0.760	Chimnani and others 2010
Rural		
Home care	0.111	ACTwatch Group, PACE, and IE Team 2012
General shop	0.004	ACTwatch Group, PACE, and IE Team 2012
Pharmacy or drug shop	0.999	ACTwatch Group, PACE, and IE Team 2012
Private health facility	0.943	ACTwatch Group, PACE, and IE Team 2012
Government health facility	0.670	Chimnani and others 2010
Antibiotics		
Urban		
Home care	0.000	Assumption
General shop	0.200	Assumption
Pharmacy or drug shop	1.000	Assumption
Private health facility	1.000	Assumption
Government health facility	0.770	Chimnani and others 2010
Rural		
Home care	0.000	Assumption
General shop	0.500	Assumption
Pharmacy or drug shop	1.000	Assumption
Private health facility	1.000	Assumption
Government health facility	0.790	Chimnani and others 2010

Note: ACTs = artemisinin-based combination therapies.

Table 15.6 Average Probability of Prescription of Different Medicines in Tanzania, by Malaria Diagnostic Test Result, 2013

Indicator	Base case	Reference
Antimalarial prescribed		
RDT positive	1.000	Assumption
RDT negative		Reyburn and others 2007
Low transmission	0.697	
High transmission	0.410	
Microscopy positive	1.000	Assumption
Microscopy negative		Reyburn and others 2007
Low transmission	0.626	
High transmission	0.230	
No test	1.000	Assumption
Antibiotic prescribed		
Malaria test positive	0.140	Reyburn and others 2007
Malaria test negative	0.740	Reyburn and others 2007
No test	0.740	Assumption

Note: RDT = rapid diagnostic test.

Table 15.7 Starting Distributions among Markov States in Tanzania, by Diagnosis, 2013

Indicator	Base case	Reference
Well	0.00	
Mild febrile illness		
Malaria		Lubell, Staedke, and others 2011
Low transmission intensity	0.70	
High transmission intensity	0.87	
Treatable febrile illness	0.70	Lubell, Staedke, and others 2011
Nontreatable febrile illness	0.90	Assumption
Severe febrile illness		
Malaria		Lubell, Staedke, and others 2011
Low transmission intensity	0.30	
High transmission intensity	0.13	
Treatable febrile illness	0.30	Lubell, Staedke, and others 2011
Nontreatable febrile illness	0.10	Assumption
Dead	0.00	

Markov Model Parameters

The starting distributions of patients in Markov states, which depend on etiology and, for malaria, on transmission intensity, are summarized in table 15.7. For malaria and treatable nonmalaria FIs, data from a Delphi survey are used (Lubell, Staedke, and others 2011). For nontreatable nonmalaria FI, a 9:1 ratio of mild to severe disease at baseline is assumed.

Adverse Events

For children receiving ACTs and artesunate-mefloquine, 11.3 percent and 63.0 percent, respectively, experience any adverse event (Mueller and others 2006); these figures are used here as the probability of adverse events for other antimalarials; 16 percent experience any adverse event due to amoxicillin (Garbutt and others 2012).

Costs of Diagnosis and Treatment

The costs of RDTs, microscopy, ACTs, other antimalarial medicines, and antibiotics are from ACTwatch (in the absence of data for Tanzania, data from Uganda are used) and from Health Action's *International Medicines Price Workbook* for Tanzania (WHO 2012a). Personnel costs for performing RDTs and for severity assessment are from Uganda. The personnel cost of treating mild disease is estimated for Tanzania to be US$2.66, based on the cost of a single outpatient visit inflated to 2013 costs (WHO 2011a), and the cost of treating severe disease is estimated to be US$61.07, based on a cost-effectiveness analysis of intravenous artesunate for severe malaria (Lubell, Riewpaiboon, and others 2011). Treating drug-related adverse events is assumed to be equal to the cost of treating mild illness (table 15.8).

Analyses

The base case and the following scenarios were analyzed: (1) universal access to RDTs; (2) universal access to ACTs; (3) universal access to antibiotics; (4) universal access to RDTs and ACTs; (5) universal access to RDTs and antibiotics; (6) universal access to ACTs and antibiotics; and (7) universal access to RDTs, ACTs, and antibiotics. Probabilities were varied by +/− 20 percent, and costs were halved and doubled for sensitivity analyses. TreeAge Pro 2013 was used for the analyses.

RESULTS

In both low- and high-transmission settings and overall, presumptive treatment with ACTs and antibiotics (P-3) leads to the fewest deaths (393 per 10,000 children), and treating only RDT-positive children with an antimalarial alone (RDT-1) leads to the most deaths (484 per 10,000)

Table 15.8 Costs of Diagnosis and Treatment of Febrile Illness in Tanzania

Indicator	Base case (US$)	Reference
RDTs		
Urban		ACTwatch Group, PACE, and IE Team 2012
CHW and home care	1.96	
Public (including PNFP HF)	1.96	
Private FP HF	1.17	
Drug seller (pharmacy or drug shop)	0.98	
General shop or vendor	0.98	
Rural		ACTwatch Group, PACE, and IE Team 2012
CHW and home care	0.78	
Public (including PNFP HF)	0.78	
Private FP HF	1.17	
Drug seller (pharmacy or drug shop)	0.90	
General shop or vendor	0.90	
Microscopy		
Urban		
CHW and home care	—	
Public (including PNFP HF)	0.78	ACTwatch Group, PACE, and IE Team 2012
Private FP HF	0.78	ACTwatch Group, PACE, and IE Team 2012
Drug seller (pharmacy or drug shop)	0.93	ACTwatch Group, PACE, and IE Team 2012
General shop or vendor	—	
Rural		
CHW and home care	—	
Public (including PNFP HF)	0.39	ACTwatch Group, PACE, and IE Team 2012
Private FP HF	0.78	ACTwatch Group, PACE, and IE Team 2012
Drug seller (pharmacy or drug shop)	0.59	ACTwatch Group, PACE, and IE Team 2012
General shop or vendor	—	
ACTs		
Urban		
CHW and home care	0.20	WHO 2011a
Public (including PNFP HF)	4.01	ACTwatch Group, PACE, and IE Team 2012
Private FP HF	9.70	ACTwatch Group, PACE, and IE Team 2012
Drug seller (pharmacy or drug shop)	9.70	ACTwatch Group, PACE, and IE Team 2012
General shop or vendor	9.70	ACTwatch Group, PACE, and IE Team 2012
Rural		
CHW and home care	0.20	WHO 2011a
Public (including PNFP HF)	4.11	ACTwatch Group, PACE, and IE Team 2012

table continues next page

Table 15.8 Costs of Diagnosis and Treatment of Febrile Illness in Tanzania (continued)

Indicator	Base case (US$)	Reference
Private FP HF	9.76	ACTwatch Group, PACE, and IE Team 2012
Drug seller (pharmacy or drug shop)	9.76	ACTwatch Group, PACE, and IE Team 2012
General shop or vendor	9.76	ACTwatch Group, PACE, and IE Team 2012
Non-ACT antimalarials		
Urban		ACTwatch Group, PACE, and IE Team 2012
CHW and home care	0.35	
Public (including PNFP HF)	4.11	
Private FP HF	4.93	
Drug seller (pharmacy or drug shop)	4.93	
General shop and vendor	4.93	
Rural		ACTwatch Group, PACE, and IE Team 2012
CHW and home care	0.35	
Public (including PNFP HF)	2.46	
Private FP HF	4.93	
Drug seller (pharmacy or drug shop)	4.93	
General shop or vendor	4.93	
Antibiotics		
Urban		WHO 2011a
CHW and home care	0.81	
Public (including PNFP HF)	0.78	
Private FP HF	1.86	
Drug seller (pharmacy or drug shop)	1.86	
General shop or vendor	1.86	
Rural		WHO 2011a
CHW and home care	0.81	
Public (including PNFP HF)	0.78	
Private FP HF	1.86	
Drug seller (pharmacy or drug shop)	1.86	
General shop or vendor	1.86	
RDT personnel	0.20	Babigumira and others 2009
Severity assessment	0.30	Babigumira and others 2009
Treatment		
Mild disease	2.66	WHO 2011a
Severe disease	61.07	Lubell, Riewpaiboon, and others 2011
Adverse event	2.66	WHO 2011a

Note: — = not available; ACT = artemisinin-based combination therapy; CHW = community health worker; FP = for profit; HF = health facility; PNFP = private not for profit; RDT = rapid diagnostic test.

(tables 15.9–15.11). In the base case, P-3 is also the least costly strategy (US$251,000 per 10,000 children), but the costs of the strategies vary by less than US$10,000 per 10,000 children in all cases except one (RDT-4—treating RDT-positive children with an antimalarial and all children with severe disease with an antibiotic).

Presumptive treatment with ACTs and antibiotics is the optimal strategy and is highly cost-effective in Tanzania. The ranking of the strategies varies somewhat with endemicity levels, but the leading strategy does not change.

The results are robust to univariate sensitivity analyses. The cost estimates are most sensitive to the

Table 15.9 Survival, Mortality, Costs, and Cost-Effectiveness per 10,000 Children Presenting with Fever in Tanzania

Policy	Survivors	Deaths	Additional lives saved	Cost in 2013 US$	Incremental cost in 2013 US$	Cost-effectiveness
RDT-1	9,516	484	n.a.	258,100	n.a.	Lower than P-1, P-3, RDT-2, and RDT-3
RDT-4	9,562	438	46	263,400	5,300	Lower than P-1, P-2, P-3, RDT-2, and RDT-3
RDT-3	9,563	437	1	255,400	–8,000	Lower than P-1 and P-3
RDT-2	9,563	437	0	256,000	600	Lower than P-1 and P-3
P-1	9,566	434	3	253,500	–2,500	Lower than P-3
P-2	9,606	394	40	258,400	4,900	Lower than P-3
P-3	9,607	393	1	251,000	–7,400	Dominant

Note: n.a. = not applicable.

Table 15.10 Survival, Mortality, Costs, and Cost-Effectiveness per 10,000 Children Presenting with Fever in High-Transmission Areas of Tanzania

Policy	Survivors	Deaths	Additional lives saved	Cost in 2013 US$	Incremental cost in 2013 US$	Cost-effectiveness
RDT-1	9,534	466	n.a.	260,200	n.a.	Lower than P-1, P-3, RDT-2, and RDT-3
RDT-4	9,572	428	38	265,300	5,100	Lower than P-1, P-2, P-3, RDT-2, and RDT-3
RDT-3	9,573	427	1	257,900	–7,400	Lower than P-1 and P-3
RDT-2	9,573	427	0	258,500	600	Lower than P-1 and P-3
P-1	9,587	413	14	255,100	–3,400	Lower than P-3
P-2	9,621	379	34	259,800	4,700	Lower than P-3
P-3	9,622	378	1	252,800	–7,000	Dominant

Note: n.a. = not applicable.

Table 15.11 Survival, Mortality, Costs, and Cost-Effectiveness per 10,000 Children Presenting with Fever in Low-Transmission Areas in Tanzania

Policy	Survivors	Deaths	Additional lives saved	Cost in 2013 US$	Incremental cost in 2013 US$	Cost-effectiveness
RDT-1	9,469	531	n.a.	252,400	n.a.	Lower than P-1, P-3, and RDT-3
P-1	9,508	492	39	249,300	–3,100	Lower than P-3 and RDT-3
RDT-4	9,536	464	28	258,300	9,000	Lower than P-2, P-3, RDT-2, and RDT-3
RDT-3	9,538	462	2	248,700	–9,600	Lower than P-2 and P-3
RDT-2	9,538	462	0	249,500	800	Lower than P-3
P-2	9,566	434	28	254,700	5,200	Lower than P-3
P-3	9,568	432	2	246,100	–8,600	Dominant

Note: n.a. = not applicable.

starting proportion of patients in the severe Markov health state for children with T-NMFI, and mortality is most sensitive to the probability of progression from mild to severe illness for children with T-NMFI.

CONCLUSIONS

Presumptive treatment of all children under age five years with fever, or only those who are severely ill, with both ACTs and a broad-spectrum antibiotic can minimize mortality and is projected to be highly cost-effective by global standards. This result is based on conditions in Tanzania, but it is generalizable to many Sub-Saharan African countries with similar malaria endemicity and health service delivery.

The WHO recommendation of definitive malaria diagnosis before treatment is the clinical practice ideal; physicians aim to make definitive diagnoses before prescribing treatment of any kind. It is a useful goal and should be adopted in clinical settings where a test—microscopy or an RDT—can be conducted reliably. Unfortunately, the places where malaria transmission is highest also tend to be the places where the capacity for testing and reliability are most limited. Drugs are often purchased directly from pharmacies or drug shops or from poorly staffed and provisioned health facilities, both public and private. In these cases, presumptive treatment with antimalarial medicines and antibiotics for all children is the only strategy that prevents the most deaths; it is also optimal from the standpoint of survival and cost-effectiveness. The same conclusion was reached in an independent analysis using a net health benefit approach for six Sub-Saharan African countries (Basu, Modred, and Bendavid 2014).

Price is a major driver of the results of these analyses. If prevailing ACT subsidies were lost and the prices of ACTs were to rise, presumptive treatment would become less attractive from a cost standpoint, but it would not alter the effectiveness side of the equation. Even at a low cost, some individuals are unable to afford ACTs. RDTs have other costs that might further reduce their cost-effectiveness, including the costs of scaling up their use, distribution and storage, sharps disposal, treatment of potential blood-borne infections from needle stick injuries, and behavior change to encourage adherence to test results.

Cost and cost-effectiveness from a model such as this one are but one input into the development of a global treatment policy. This analysis does not monetize certain important externalities, such as the cost of accelerating the development of antibiotic resistance or antimalarial resistance (although the latter may be small). Also important, but impossible to estimate the cost of, is the need to maintain different policies in different areas, even within the same country. Defining the criteria for delineating the areas where each policy would be appropriate is a hurdle that would be created by having two policies. Even more difficult may be deciding when and how to move from a presumptive to a test-and-treat policy as malaria control continues to lower endemicity levels.

Until primary health care is more widely available, a large proportion of fevers in high-transmission rural areas will be managed in the informal sector, where the analysis suggests that it is more cost-effective to focus on treatment than on diagnostics. In low-transmission-intensity areas and in clinical settings with well-trained practitioners, diagnostics are valuable for targeting treatment. Until the burden of malaria declines more broadly, countries might consider a mixture of strategies tailored to local conditions.

NOTE

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US$1,045 or less
- Middle-income countries (MICs) are subdivided:
  (a) lower-middle-income = US$1,046 to US$4,125
  (b) upper-middle-income (UMICs) = US$4,126 to US$12,745
- High-income countries (HICs) = US$12,746 or more.

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