CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

Economics and Financing of Febrile Illness RDTs

Report of Consultation 1

20 October 2011, Seattle

SUMMARY

Not all fevers are malaria, even in countries where malaria is endemic, even in children. This is not new information, but the recently commercialized rapid diagnostic tests (RDTs) for malaria make it ever clearer that in some places a large and—if progress toward malaria elimination continues—declining proportion of fevers are *not* caused by malaria and must be caused by something else. Like malaria, bacterial pneumonia, the other major treatable killer of children, must be treated promptly to avert death or long-term sequelae. Unfortunately, no RDTs exist for bacterial pneumonia or other common causes of fever.

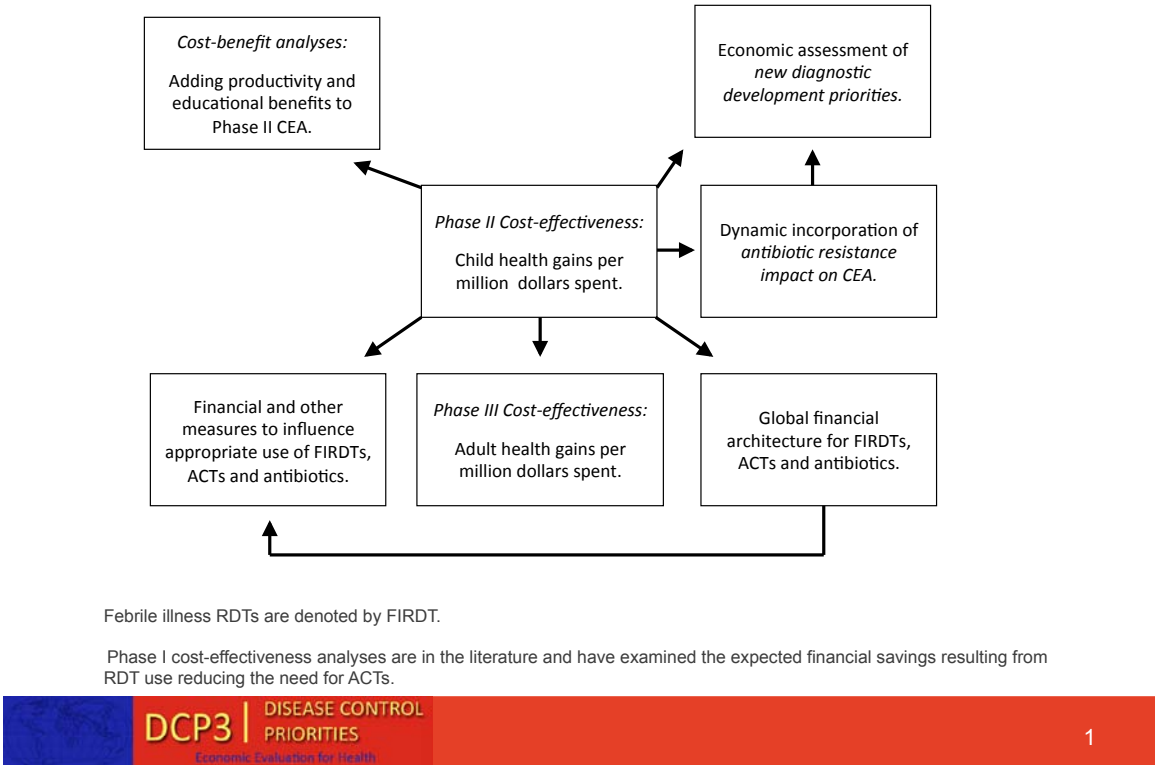
Guidance from the World Health Organization (WHO) as of 2010 is that all suspected malaria cases should be confirmed by RDT or microscopy before patients are treated, but people suffering from fever in malaria-endemic countries commonly go to clinics with minimal laboratory facilities, to more remote outposts of the healthcare system, or to pharmacies or small shops to buy remedies directly. While the WHO advice is still being operationalized, it also raises the issue of how to treat people who do not have malaria, tailored to the types of places people go when they (or others for whom they are caring) have a febrile illness.

RDTs for malaria use a drop of blood and no special equipment but do require minimal training to ensure appropriate use and correct interpretation of results. Thus far, RDTs have not been used in small shops, and their use in Africa has been limited mainly to formal healthcare settings, with some in the hands of trained community health workers.

The problem is obvious, but the solution is not. Even in clinical settings, it is very difficult to diagnose fevers by symptoms alone (though it is possible to reliably identify children with severe pneumonia by, for example, using the Integrated Management of Childhood Illness algorithm). RDTs to guide treatment decisions beyond malaria may come into production within five years, and almost certainly, before ten years. Guidance for the present, when only RDTs for malaria are available, is needed as is a plan for integrating new febrile illness RDTs as they become available.

The aim of the first phase of this project is to define pathways toward universal use of malaria RDTs for children under five with suspected malaria. For most countries in Africa, this means starting from a very low rate of RDT deployment. Factors that will be considered in differentiating approaches are levels of endemicity, formal vs. informal settings of care, and the availability of some treatment (or treatment guidance) for nonmalaria fevers. Financial architecture for malaria RDTs and future febrile illness RDTs is being explored on a parallel track. The project is described schematically below.

1616 P Street NW, Suite 600
Washington, DC 20036
p 202 939 3300 | f 202 939 3460
WWW.CDDEP.ORG



On 20 October 2011, the first consultation brought together major stakeholders and experts on febrile illness and RDTs. The consultation included evaluation of malaria RDTs, which already exist, and RDTs being developed for other conditions. It also provided a starting point for broadening the discussion, from diagnosing and treating children with suspected malaria or suspected pneumonia to viewing "febrile illness" as category that includes these and other causes. The work on cost-effectiveness will begin with malaria RDT use and expand to febrile illness RDTs.

MEETING PROCEEDINGS

The presentations summarized here are not exhaustive but represent a one-day agenda touching on major aspects of febrile illness diagnosis and treatment.

Causes of Febrile Illness

(Based on a presentation by Valerie d'Acremont from WHO)

Malaria is not the only cause of febrile illness where malaria is endemic. This had always been known—both children and adults suffer from other febrile illnesses all over the world. But the known mortality risk of severe malaria, a lack of ready diagnostic tools for differential diagnosis, and an assumption that malaria was responsible for a large share of febrile illness for which treatment was sought supported the practice of presumptive malaria treatment for decades. It is known now—largely because of the studies made possible by RDTs—that malaria is actually much less prevalent than assumed. This situation is likely at least partly a result of effective control measures that are now widespread (mainly insecticide-treated nets). If the trend holds, malaria will become even less

prevalent in the future. The WHO recommendation for universal parasitologic diagnosis for malaria before treatment adds impetus to abandoning presumptive treatment in favor of "diagnosis-directed" treatment.

Little information has been generated to describe the nonmalaria fevers that are common in developing countries. In the work described here, 1,000 children under 10 years old who came to clinics in Tanzania with fever (but were not among those sick enough to be admitted as inpatients) were studied. Half were in urban Dar es Salaam and half in rural Ifakara. The study is remarkable in that it included full clinical and laboratory assessments (based on defined algorithms) to investigate all causes of fever. With a presumptive malaria paradigm, all of these children probably would have received an antimalarial drug. The results: fewer than 10 percent had malaria, half had an acute respiratory infection, and about a quarter of those had pneumonia. A multitude of viruses, rickettsia, and bacteria caused enteric, urinary tract, and systemic infections in many children. For relatively few was more than one infection found.

About one-quarter of the 1,000 children had a disease for which antibiotic treatment would have been appropriate. Identifying the 10 percent with malaria is now feasible, but identifying the 25 percent is not easy. Current clinical criteria of the Integrated Management of Childhood Illness (IMCI) would, in fact, have identified about a quarter of the children as needing antibiotic treatment, but this included only about half of those identified by the more detailed study. The rest would have been treated needlessly, while an equal number who could have benefited from an antibiotic would not have been treated. The degree of consensus and overlap for children with severe (or life-threatening) disease is not known.

How representative is this study? There is little with which to compare the full analysis, so it is impossible to say. Other studies using RDTs for malaria have been reported, however, with a wide range of malaria-positive cases, including much higher proportions than seen here. For example, in a population under study by Jessica Cohen, 90 percent of febrile children were malaria positive. Epidemics are not infrequent and would affect the distribution of causes. We also note that patients were accepted for this study over the course of eight months—not a full annual cycle.

RDTs for Malaria

(Based on a presentation by David Bell from FIND)

FIND and WHO have completed three rounds of tests on malaria RDTs for both falciparum and vivax malaria, with a fourth annual round ongoing. In 2008–09, 41 products were tested; in 2009–10, 29; in 2010–11, 50; and thus far in the fourth round, 46. In addition, FIND and WHO have developed standards for RDTs. Most products did reasonably well when the detection limit was high (2,000 parasites/uL blood), and about half did poorly when the detection limit was low (200 parasites/uL blood). Based on 23 products tested in successive rounds, the predictiveness of the tests has improved, possibly in response to standard setting. An encouraging sign is that tests that fared better in testing have captured a larger portion of market share than those that tested worse. About 20 companies have not submitted their products for testing.

A projected 1 billion tests will be produced in 2011 by 17 manufacturers, which represent only a portion of the total number of manufacturers; thus, this figure is an underestimate of global production. In 2007, only about 25 million tests were produced.

RDTs are pivotal in the move from presumptive to parasite-based diagnosis. The most striking example is in Senegal, where the use of antimalarial treatment has tracked parasite confirmation, based on RDTs or microscopy, since 2007.

As a check on the appropriateness of withholding antimalarial treatment for people who test RDT-negative, researchers followed untreated and treated children to look for the development of malaria and a mortality excess.

The number of cases developing malaria among untreated children is small, and no excess of malaria-related mortality has been detected. There are few studies and they are small, but the outcomes are consistent.

Development of RDTs for Nonmalaria Febrile Illnesses

(Based on a presentation by Deborah Burgess, Bill & Melinda Gates Foundation)

Ruling out malaria is a good first step, but a confident diagnosis or treatment recommendation is also needed. An RDT using, at least initially, a drop of blood, is the goal. In addition to the realities of healthcare in the low-income countries where the childhood pneumonia burden is greatest, three other facts support the importance of an RDT:

- The affected tissue, lower lungs, is not accessible to sampling.
- Blood culture, the gold-standard diagnostic method for invasive pneumonia, has low sensitivity (10 to 12 percent).
- Carriage—the presence of nonpathogenic commensal organisms—makes sampling other sites (e.g., nose or skin) uninformative.

More than one strategy could be used in the end, depending in large part on the setting and on the capabilities of the healthcare worker evaluating the cases. Clinically, the aim is to identify pneumonia based on physical markers that can be detected and in some cases quantified (e.g., breath rate counters). Using biomarkers, researchers are looking either for chemicals in the blood that identify specific organisms or for indicators of "severity" associated with infections caused by various organisms.

Clinical Diagnosis

Clinical diagnosis in this discussion means diagnosis after physical examination only, without laboratory testing. It is what could be done through an IMCI-like algorithm. It assumes that the patient is being examined either in a facility by a trained healthcare worker or in a home by a trained community health worker. RDTs for malaria have already been incorporated into IMCI, and RDTs developed for nonmalaria febrile illness can be, as well.

Biomarkers

Research is under way on both host response and pathogen-specific biomarkers. Host response biomarkers are chemicals produced in response to infection or inflammation, which may vary qualitatively or quantitatively depending on the pathogen but are not diagnostic of a specific pathogen. Pathogen-specific biomarkers can arise from either the pathogen itself or the host response but are diagnostic of a particular pathogen (e.g., malaria).

The three main aims of biomarker research relevant to malaria-endemic countries are (1) differentiating malaria from pneumonia; (2) differentiating viral from bacterial pneumonia; and (3) identifying patients whose pneumonia is severe or becoming severe. The current generation of research focuses on chemicals that can be detected in a finger-stick sample of whole blood. Sampling from tissues or fluids that do not require invasive procedures (e.g., urine or saliva) is of great interest, but tests based on them are a generation away.

Most biomarker research has taken place in developed countries, without malaria, and in those countries chemicals such as procalcitonin and C-reactive protein have distinguished reasonably well between viral and bacterial illnesses. But the levels of these factors are also affected by malaria, making them less useful (or not useful at all) where malaria is present. One or more biomarkers are still likely to distinguish malaria from bacterial from viral fever, but field studies must include populations at risk of malaria.

The Gates Foundation is supporting research on various biomarkers, including exploratory work to examine the array of chemicals released in response to febrile illness (proteome scan); pro-adrenomedullin, natriuretic peptides,

endothelin-1 precursor peptides, copeptin, and cortisol as predictors of disease progression; and angiopoietin 1 (ANG1), angiopoietin 2 (ANG2), and the ratio of ANG1 to ANG2 as markers of severity. Researchers are also looking at the predictive value of combinations of biomarkers.

It will be at least several years before studies have characterized the relationship between biomarkers and disease to the point that clinically useful RDTs can be developed.

Influencing Behavior of Providers and Patients: The Microfinance Environment

(based on a presentation by Jessica Cohen from Harvard University)

RDTs have value only to the extent they are used and their results affect treatment choices. One aspect that can be manipulated is the price to consumers of RDTs. The price relative to artemisinin combination therapies (ACTs) is clearly important but by no means the only factor affecting the choice of whether to use an RDT. In a trial in western Kenya in which patients could obtain RDTs at low prices or for free from drug shops, the rate of diagnosis (with either microscopy or RDTs) doubled, from 22 percent to 44 percent. The price of ACTs, which also varied, was not influential on decisions to use an RDT, even when ACT prices were relatively high. Nearly everyone with a positive RDT also purchased an ACT, but so did 60 percent of those whose RDTs were negative for malaria. Continuing work in western Kenya and in Uganda are following up this initial study and should contribute to developing strategies for increasing the use of RDT results.

Providers are the key to RDT availability, especially in drug shops and other private sector outlets, and their motivations and financial incentives to supply RDTs, ACTs, and other medicines must be considered as well. Ongoing field trials in Uganda confirm that shopkeepers can be influenced, by education and by subsidies, to increase the use of RDTs to determine whether a person has malaria. The details of how best to effect change are still to come, but some preliminary findings include the following:

- RDTs are converging in price to around $1 (with a $.50 wholesale price to shops, meaning a 100 percent markup).
- Rural shops are more likely to sell or promote RDTs than urban ones (because of the proximity of urban shops to health centers).
- RDTs are more often purchased for children than adults.
- Shops are creative in promoting RDTs, with some "bundling" the price for the RDT and treatment.
- RDTs maintain quality (based on lot testing after time in field).
- Most shopkeepers are easily trained and follow the testing protocol.

Behavior regarding RDTs is expected to change over time as the tests become routine and people learn to trust the results, and as malaria incidence continues to decline over time. RDT use can also be encouraged by changing the microeconomic and information environment.

Work to Date on Cost-Effectiveness of RDTs

(based on a presentation by Shunmay Yeung from the London School of Hygiene and Tropical Medicine)

Early cost-effectiveness analyses (CEAs) focused on the benefits that would accrue from using RDTs to identify and treat only those who had malaria versus presumptive treatment for all. Money would be saved by not using ACTs for people without malaria, and chances that a resistant parasite would emerge would be reduced.

The results of RDTs were not always heeded in clinical decisionmaking, however. It is intuitive that the benefits of RDTs accrue only when results affect the treatment decision, particularly in *not* treating with an antimalarial if the RDT is negative. This relationship was quantified to show that in areas of lower malaria prevalence, RDTs still

saved money even with somewhat lower adherence, but the benefits shrink as prevalence increases. In holoendemic areas, the use of RDTs may be a waste of resources.

Since the early studies and the acceptance of the need for diagnosis, the question has shifted from whether to use RDTs or presumptive treatment to how to maximize the cost-effectiveness of fever diagnosis and treatment. The technical characteristics of the tests limit the results that can be achieved, but behavioral change is the key to reaching that limit. The Malaria Consortium has studies under way testing different interventions to increase uptake and adherence to RDT results, in Ghana, Afghanistan, Tanzania, Cameroon, Uganda, and Nigeria.

Cost is a major factor affecting the use of RDTs in both the public and the private sector, but sensitivity to cost differs depending on who is paying for the tests. The willingness to pay for RDTs out of pocket when treatment will also be purchased out of pocket has been studied in a few places, and this, too, has been incorporated into CEAs.

The next generation of CEAs from this group of researchers will consider antibiotic resistance on the cost side of the analyses. A major problem is a lack of diagnostic tools for nonmalaria febrile illnesses.

Cost-Effectiveness Analysis for the Current Project

(based on a presentation by Joseph Babigumira from the University of Washington)

The CEA for the current project builds on conceptual work presented at last year's Global Fund/WHO consultation on the economics and financing of RDTs (see here). It incorporates the goal of reaching universal parasitological diagnosis for malaria for children under five years of age, examining the cost-effectiveness of trajectories to full coverage by emphasizing three areas:

- expansion in low vs. high transmission areas;
- expansion in public vs. private (regulated or unregulated) facilities vs. expansion through community health workers; and
- expansion assuming availability vs. no availability of treatment for nonmalaria febrile illness.

The project will also look at the effect of subsidizing RDTs, ACTs, and/or antibiotics.

Five options for managing febrile illness will be considered:

- presumptive treatment with antimalarial (ACTs or chloroquine or sulfadoxine-pyrimethamine);
- previous IMCI: no fever diagnosis/add antibiotic if severe illness;
- new IMCI: parasitological testing and antibiotic for negative patients with severe illness;
- parasitological testing and no treatment for negative patients; and
- parasitological testing and antibiotics for negative patients.

The analysis will use a disease-based decision-analytic modeling framework. It begins with a hypothetical child who has an acute febrile illness and follows the child's progress over the time horizon of acute illness (a maximum of 21 days).

- Specifics of the CEA project include the following:
- Life expectancy for survivors is added so that life-years and disability-adjusted life-years (DALYs) can be calculated.
- Analyses are conducted from both the societal perspective (all costs) and governmental perspective (direct medical costs incurred by ministries of health).
- Data are obtained from published and unpublished sources.
- The main outcomes of the analysis are cost per life-year gained and cost per DALY averted.

- The baseline analyses to answer the research questions are one- and two-way sensitivity analyses, as well as threshold analyses to examine the effect (on incremental cost effectiveness ratios [ICERs]) of changing important parameters over their policy-relevant ranges.

One of the first challenges will be deciding which estimates to use in base case analyses and a rationale for choices made. Gaps and large uncertainties in data are additional challenges. A major gap in knowledge is the proportion of patients who could benefit from an antibiotic, which is largely unknown and variable by place. D'Acremont's study from Tanzania, described above, begins to provide this information, but few if any other such efforts are likely to be completed soon. Some other studies, now under way, should contribute, including studies of nonmalaria fevers in several African and Asian countries, and studies of RDT subsidies in Africa.