CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy
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Economics and Financing of Febrile Illness RDTs

Report of Consultation 2

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SUMMARY

Rapid diagnostic tests for malaria (mRDTs) have become widely available in the last decade. Before that, the only practicable routine technology for malaria diagnosis was microscopy—much the same as was used by Charles Laveran in 1880, on the occasion of the first time a malaria parasite was seen in a patient's blood sample. Microscopy for malaria diagnosis never became widespread in Africa. On the treatment side, since the mid-20th century, when chloroquine became commonly available, presumptive treatment was the norm, eventually sanctioned by the World Health Organization (WHO). Everyone treated for fever was treated as though they had malaria.

Going forward, malaria control logically becomes febrile illness control. In 2010, WHO changed its recommendation to say that no one should be treated for malaria unless they are positively diagnosed. Because of mRDTs, it is clear that fewer people than previously thought have a fever caused by malaria, and a lot of people have fevers caused by something else. The distribution of causes of fever beyond malaria has been well defined in only a few populations, however.

mRDTs are being effectively used in many different settings, in both the public sector (including community health workers) and the private sector (e.g., as part of social franchising programs). With proper training and incentives, mRDTs can also be used in informal drug shops. More economic and operational research is needed to determine 1) to what degree these different (CHW, drug shop, etc.) models can be relied on for mRDT and ACT scale-up in different contexts, and 2) how best to subsidize or otherwise make provisions for mRDTs.

These facts are recognized widely. The challenge is how best to treat people whose fevers are due to something besides malaria, particularly before the necessary tools are in place. There is no rapid diagnostic test suitable for widespread use for differential diagnosis once malaria is ruled out. Malaria-endemic countries, particularly in Africa, have generally poor health infrastructures and traditionally, a large proportion of febrile patients (or their caregivers) have used the private sector to purchase the drugs they think they need.

Currently, only a fraction of febrile patients in Africa are tested for malaria, even though testing everyone is the recommendation. Testing adds a cost and is available mainly through the (often inadequate) public sector. Testing requires:

- Financing: mRDTs cost about $1 apiece wholesale
- Behavior change: providers and patients

Behavior change is coming slowly after a century during which malaria was assumed to be highly prevalent. A complete transition is likely to take at least several more years and must follow improvements in healthcare, particularly the widespread availability of primary care, which today is absent for many of the poorest people, especially in rural areas, where malaria is likely to be more prevalent than it is in cities. This is because change involves adding a service rather than simply replacing an old medication with a new one. A negative mRDT—meaning something else that may or may not need treatment—denotes a clinical situation that is more appropriately handled by trained healthcare providers (possibly pharmacists) than by untrained drug sellers.

In Southeast Asia, the situation is different. mRDTs have been used widely in Cambodia, in particular, since 2000, including in private sector pharmacies. Lessons for Africa have not yet been drawn from this experience, however.

No one who spoke at the consultation suggested that a coordinated global strategy was being developed to provide diagnostics to the large proportion of people still purchasing malaria treatment through the private sector based on self-diagnosis or to develop guidance for managing patients who do not have malaria and are not in a formal health facility.

Affordable Medicines Facility for malaria—AMFm

AMFm was conceived as a means to get high quality ACTs to people who were buying antimalarial drugs themselves and to discourage the use of artemisinin monotherapies, through the existing market mechanisms that carry half of all antimalarials sold. In the early 2000s, when the idea for AMFm was developed, presumptive treatment was still the recommended norm and the big push against malaria (especially with insecticide-treated nets) was just starting. The idea of a global subsidy combined with the private sector's existing network was new and required a great deal of upfront work for acceptance and financing. mRDTs were not part of the management regimen in Africa and were not part of AMFm.

The debate about whether and how to continue AMFm after the pilot phase is completed at the end of 2012 is about 1) whether it has met its original goals, 2) the strength of objections to those goals and to the way AMFm operates, and 3) whether in the next phase it should take in mRDTs in addition to ACTs. This reignites controversies that arose during debates about AMFm initially, namely the role of private-sector drug shops in Africa and the range of outlets beyond formal healthcare facilities.

MEETING PROCEEDINGS

The presentations and discussions summarized below represent the main points from a two-day event (held in Washington, D.C., on February 23–24, 2012) that covered major aspects of the economics and financing of febrile illness within the framework of increasing availability of rapid diagnostic tests for malaria (mRDTs). Presentations shared both public and private sector experiences; discussion focused on the latter. Appendix 1 is the agenda for the meeting. The PowerPoint presentations from the meeting are linked throughout this report.

Session 1. Background

The second consultation continues a process that began in mid-2010, when the World Health Organization (WHO) and the Global Fund to Fight AIDS, Tuberculosis and Malaria ("the Global Fund") held a meeting to discuss the economics and financing of mRDTs, now that the availability of these rapid tests allows a diagnosis of "not malaria" and WHO has recommended that malaria treatment be offered only after a parasitologic diagnosis. The main purpose of that meeting was to discuss the best ways to use public funds to obtain higher mRDT coverage and to explore the continued role of the Global Fund in financing antimalarials within the new context. Discussants identified a need for impact evaluation and operational research on the microfinancial architecture[1] that might work in different settings to increase mRDT uptake and compliance with mRDT results—that is, to ensure that artemisinin-based combination therapy (ACT; the current first-line recommended treatment for uncomplicated falciparum malaria) is given only when mRDT results are positive. Behavioral concerns, increases in antibiotic use (both appropriate and inappropriate) as a result of negative mRDT tests, and resistance to both antibiotics and antimalarials were also discussed, as was the need for "next-generation" cost-effectiveness analysis.

In October 2011, the University of Washington and the Center for Disease Dynamics, Economics & Policy (CDDEP) cohosted a small one-day consultation titled "Expanding the Use of RDTs for Febrile Illness: Developing the Agenda for Economic and Financial Analysis." This consultation, on the cost-effectiveness and evaluation of mRDTs and RDTs currently under development for febrile illness other than malaria, broadened the discussion further. In many settings it appears that a slow shift is occurring: from diagnosing and treating children with "suspected malaria" or "suspected pneumonia" toward viewing "febrile illness" as a category that includes these and other causes of fever.

During the February 23–24, 2012, consultation participants shared past and ongoing experience with large-scale interventions to expand mRDT use, in both the public and private sectors and in urban and rural settings. Discussants also explored options for testing assumptions about the benefits of mRDTs in different transmission and health care settings, and alternative pathways to achieving those benefits

[1] By "microfinancial architecture," we mean malaria diagnostic and drug financing and delivery mechanisms in both the public and the private (formal and informal) sectors.

with the aim of establishing priority actions. The potential for mRDT and ACT (price primarily) bundling was also discussed

Session 2. RDT expansion: cost-effectiveness of different pathways

Rapid diagnostic tests: beyond cost-effectiveness analyses of mRDTs

Based on a presentation by Shunmay Yeung from the London School of Hygiene and Tropical Medicine—see here.

As mRDTs are increasingly introduced and scaled up, the research agenda is moving beyond mRDT cost, accuracy, and cost-effectiveness analysis to incorporation of resistance and to situating mRDTs within the larger context of nonmalarial RDTs for febrile illness. Findings from Tanzania and Senegal suggest that mRDT roll-out can result in cost-savings from an increase in appropriate ACT prescribing and an overall drop in first-line antimalarial consumption.[2] The questions now are whether and how to account for costs and consequences of antimicrobial resistance. To date, antimalarial and antibiotic resistance have largely been treated as externalities and not included in economic evaluations of diagnostics. As long as diagnostics cost at least as much as treatment, they will appear far less cost-effective than they should. Incentives for mRDT uptake and use may thus be insufficient.

Initial efforts are studying the effect of mRDTs on antimalarial resistance (but are not yet incorporating antibiotic resistance). The first step in estimating the cost of antimalarial resistance is to consider the historical association between drug consumption and resistance. Preliminary work by Lubell highlights the historical consumption and resistance link for chloroquine (CQ), sulphadoxine-pyrimethamine (SP), and amodiaquine (AQ) and shows that when antimalarial resistance is included in the cost-effectiveness analysis, mRDTs become cost-effective faster than if resistance is omitted. Additional research is looking at the effect of diagnostics on the transmission of drug resistance.

The question of what to do with mRDT-negative patients remains. In the absence of parasitological diagnosis, many of these individuals would have been (inappropriately) treated with an antimalarial. Given that RDTs for febrile illness other than malaria do not yet exist, it is impossible to know how many patients will have self-limiting infections that do not require antibiotics and how many will have bacterial infections that may become severe and require antibiotic treatment.

Not prescribing or dispensing an antimalarial requires a considerable behavioral shift for providers, and not expecting one requires a similar adjustment for patients and their caregivers. In many settings, the majority of patients who have an mRDT test will test negative, raising the question of what treatment – if any – they should receive. Health workers need evidence-based guidelines to inform their decisions about which mRDT negative patients should get an antibiotic, which should get an antipyretic and which should receive nothing at all. Recent aetiology of fever studies, which have been

[2] D'Acremont V, J. Kahama-Maro, N. Swai, D. Mtasiwa, B. Genton and C Lengeler. Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study. Malar J. 2011 Apr. 29;10:107 and Thiam S, M. Thior, B. Faye, M. Ndiop, M.L. Diouf, et al. 2011. Major reduction in anti-malarial drug consumption in Senegal after nation-wide introduction of malaria rapid diagnostic tests. PLoS ONE 6(4): e18419. doi:10.1371/journal.pone.0018419.

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carried out or are currently under way in Laos, Tanzania, Zanzibar, Thailand, Cambodia, and Afghanistan, will help inform development of algorithms to guide decision making for malaria-negative patients.

Ongoing cost-effectiveness research is also beginning to tackle the use of mRDTs in conjunction with RDTs that are currently under development for other febrile illnesses. Specifically this research looks at what the cost-effectiveness of adding a non-malaria RDT when mRDTs are already being used. This field is moving very quickly. Some disease-specific RDTs beyond malaria already exist, and a multiplex RDT would be ideal. RDTs for nonmalarial febrile illness may not identify the pathogen, but could instead identify marker of disease severity. Such a tool will inform decisions of when *not* to treat with an antibiotic, which has important implications for antibiotic use and resistance. The ultimate goal is development of a country-level decision tool for program managers to help them decide which tests to use in which settings.

Ongoing mRDT implementation evaluation efforts include identifying determinants of uptake and adherence to test results and determining the costs and consequences of rolling out RDTs in different contexts (e.g., epidemiology, access, quality of existing health services, health-seeking behavior). Different supportive interventions are also being evaluated for their effect on adherence. Operational research composed of complex evaluations of interventions to introduce and increase uptake and adherence to RDTs in high- and low-transmission settings in both the public and private sectors is being undertaken by the ACT consortium and others. These evaluation efforts, alongside programmatic experiences (such as in Cambodia and Senegal), should inform where and how to roll out mRDTs within a given country.

For the past decade, subsidized, socially marketed ACTs and RDTs have been available in Cambodia's private sector and have been freely available in the public sector through the country's 800-plus village malaria workers. In the private sector, patients pay about the same price for a test as for an ACT. Even though the program was never set up for a proper evaluation, several surveys over the years showed fluctuations in RDT and ACT availability and pricing, initial slow uptake of both ACTs and RDTs (the latter was slower than the former), and persistent availability of artemisinin-based monotherapies until 2009.

Recent ACT Watch data reveal that most patients (70% to 80%) access care through the private sector, where fewer than half of providers recommended an RDT. However, focus group discussions found that providers could be grouped into two types: those who simply sell drugs, and better trained providers who see a role for themselves in diagnosis and treatment. The latter were more likely to offer an RDT and were more reluctant to offer an ACT without a test. The resulting recommendation was to differentiate between providers: providing training and support, including supervision and feedback, to the diagnosing providers who stock mRDTs while simply providing the drug sellers with training to refer patients with suspected but unconfirmed malaria.

Interviews with providers found that two-thirds of the time, providers diagnose mRDT-negative fevers as typhoid, which implies prescription of high-cost antibiotics. The most commonly prescribed

medications overall were antipyretics and antiflu medicines (45% of cases) and antibiotics (39% of cases). Colorful packets of "drug cocktails," mixes often containing antibiotics, are the most popular prescribed drugs. Providers with microscopy experience are more likely to doubt the mRDT result, voicing concern about low-density infections and not being able to see parasites. Future research directions in Cambodia include exploring different approaches to incentivize uptake of RDTs and appropriate treatment. Options include a fixed, bundled price for the RDT and either an antimalarial or another appropriate treatment, bundling of RDTs and ACT, heavy discounting of ACTs if the provider buys RDTs in bulk, algorithms for mRDT use, and nonfinancial incentives. The village malaria workers' role may also be expanded to include dispensing of antibiotics and oral rehydration salts, and future research will look at whether these health workers improve equity of access to appropriate management of fever.

Potential cost-effectiveness of increased access to malaria RDTs for management of acute febrile illness in children under five in mainland Tanzania

Based on a presentation by Joseph Babigumira from the University of Washington.

Our ongoing modeling effort explores whether expansion to universal access of rapid diagnostic tests in children is a good use of scarce resources, now that widespread use of high-quality mRDTs is possible. The model compares the cost-effectiveness of subsidizing antibiotics, mRDTs, and ACTs, plus the following alternative febrile illness treatment management strategies:

- presumptive treatment with an antimalarial;
- "old" integrated management of childhood illness (IMCI), with no fever diagnosis, and antibiotics given if the illness is severe;
- and three variations on "new" IMCI that include parasitological testing: (a) an antibiotic is given to negative patients with severe illness, (b) no treatment is given to negative patients, and (c) antibiotics are given to all negative patients.

The cost-effectiveness of those implementation trajectories to full coverage of mRDTs is explored in both low- and high-transmission areas. The model includes branches for different scenarios, such as public or private, urban or rural, diagnosis availability or no availability, mild or severe disease, and positive or negative mRDT result.

Preliminary findings from the model:

- Both old and new IMCI are more cost-effective than presumptive treatment
- Old IMCI would be the most cost-effective option (given the data used) in both low- and high-transmission settings.
- New IMCI would be the most cost-effective option as access to antibiotics and ACTs increases.
- The best gain per dollar (highest cost-effectiveness) for mRDT introduction is in low-transmission areas.
- Subsidizing antibiotics is potentially more cost-effective than subsidizing ACTs, which in turn is potentially more cost-effective than subsidizing RDTs.

- Subsidizing both antibiotics and ACTs is potentially more cost-effective than subsidizing both antibiotics and RDTs, which is potentially more cost-effective than subsidizing both ACTs and RDTs.
- If antibiotic resistance is added to the cost-effectiveness equation, the entire model will change.

Ours is a preliminary model, and results presented are based on an incomplete literature review. Findings will be strengthened by further work. Specifically, the researchers intend to address the following:

- More solid data are needed; the current input data is based on only a few studies.
- The model does not present treatment-seeking behavior accurately, and some double-counting of patients is occurring.
- Adherence to test results is not differentiated by different areas (urban-rural, type of provider).
- Program costs are not included: health system and institutional capacity constraints are likely higher for diagnostic strategies and may favor presumptive treatment and old IMCI.
- The model does not include antimalarial or antibacterial resistance, nor does it address adverse events. It would be useful if the model could also look at cross-resistance between antimalarials and antibiotics.
- It may be useful to expand the model to include a new fever profile (integrated community case management, iCCM), to include a guideline and a variable on clinicians' adherence to that guideline, to address nonfinancial incentives, and to be more explicit about changes in behavior.
- One additional idea would be to model structure, varying access to medicines and diagnostics and adherence to test results by rural-urban setting and by treatment provider.
- Finally, the model does not have an explicit sequence for illness severity.

Session 3. Models of ACT and malaria RDT availability, subsidies, and antibiotic use and resistance

Malaria: treatment, testing and resistance. Will a global subsidy of malaria drugs and diagnostics delay the emergence of resistance and save lives?

Based on a presentation by Geoffrey Johnston, of Columbia University—see here.

Current first-line treatments for malaria are artemisinin-based combination therapies (ACTs) which pair an artemisinin with a longer-lasting partner drug, such as mefloquine, lumefantrine, amodiaquine, or piperaquine. Resistance to antimalarials results from accumulation of mutations. The number of mutations depends upon the mechanism of drug action: in the case of chloroquine (CQ), the parasite evolved a mutated form of a drug transporter (pfcrt) to transport the drug outside the parasite digestive vacuole. In CQ resistance no fewer than four pfcrt mutations have ever been found (and up to eight have been found in a highly resistant isolate).[3] Similarly, resistance to sulphadoxine-pyrimethamine (SP) is characterized by four mutations in each of the folate metabolism pathway

[3] Chen et al. (AAC 2003) and Lakshmanan et al. (EMBO 2005).

proteins dhfr and dhps, and a quintuple mutant (triple dhfr and double dhps) has been associated with in vivo resistance.[4] However, only one single mutation in cytochrome b is associated with resistance to atovaquone.[5] Although various levels of resistance to ACT partner drugs have also been documented in the field, the number of mutations necessary for artemisinin resistance is currently unknown and likely to be large, given the biological potency of the drug.

Until recently, there was no documented evidence of artemisinin resistance even though the drug has been used for decades in Southeast Asia. In 2009 Dondorp et al.[6] found that parasites from western Cambodia exhibited a delayed clearance phenotype, meaning that after treatment with an ACT, these parasites took longer to clear from the body than those in other regions. In addition, an association was found between increased clearance times and a small increase in treatment failure rates (defined as parasite recrudescence during a 42-day follow-up period).[7] Although this delayed clearance can be defined as "early-stage resistance," no genotype has been associated with this resistance (efforts are underway to sequence field isolates), and to date, high-level artemisinin resistance therefore does not exist. Nonetheless, as the parasite mutates, the effects on treatment outcomes and transmission will become more pronounced. It is therefore important to determine likely waiting times to development of more serious forms of artemisinin and partner drug resistance and quantify the effect of treatment and diagnostics on estimated waiting times.

The probability of multisite artemisinin resistance evolution is impossibly low in the absence of drug pressure; drug selection is required to promote mutation emergence and spread. Given the probabilities involved, mutation is likely to be sequential, as occurred with both CQ and SP: the first stage will be selection of parasites with genetic mutations conferring artemisinin resistance, with selection being driven by the long half-life of the partner drug used alongside artemisinin. This effect is called the pharmacodynamics shadow of the partner drug.[8] The second stage involves selection of parasites within a host during an infection, as parasites emerging during this unprotected shadow encounter drug selection for resistance. During the third stage, clinical treatment failure becomes prevalent as parasites develop sufficient resistance mutations to survive therapeutic doses of the drug combination.[9]

Ongoing modeling efforts look at the within-host time course of infections in individuals with no immunity to infection and use these results to predict waiting times to resistance emergence and spread within a population. The baseline scenario simulates the onset of resistance over time in Cambodia, where treatment-seeking behavior has been well characterized.[10] The baseline assumption is that no mRDTs are being used; the adjusted scenario assumes that half of individuals take mRDTs and that all

[4] Gatton and Cheng (J Antimcrob Chemother. 2006).
[5] Fivelman et al. (Malaria J. 2002).
[6] Dondorp et al. (NEJM 2009).
[7] Carrara et al. (PLoS One 2009); O'Brien et al. (Curr Op Inf Dis 2011).
[8] The PK/PD shadow may exert a large selective pressure for the appearance and emergence of resistance, independent of random mutations and treatment failures. The longer the window, the higher the selective pressure and the faster resistance emerges.
[9] Gatton et al. (AAC 2004).
[10] Incardona et al. (Malaria J. 2007).

individuals comply with the test results. Comparing these two scenarios allows for prediction of how waiting times to resistance would change with mRDT uptake and appropriate use.

The following drug pressure and selection parameters were used:

- There is no overtreatment effect for the artemisinin component of an ACT, given its short half-life in the body.
- There is selective pressure for partner resistance in treatment of nonmalarious individuals (and successfully treated individuals), via an increased frequency of rarely occurring mutations.
- Treatment failures caused by treatment delays and poor treatment compliance are inevitable, exert a selective pressure for resistance, and are likely to increase.
- mRDTs may increase the waiting time to emergence of partner drug resistance by decreasing inappropriate ACT treatment. The effect of mRDTs on community treatment-seeking behavior and treatment failure is unclear.

Preliminary modeling findings[11] reveal that mRDTs may increase the waiting time[12] to the emergence of resistance by reducing overtreatment, that mRDT effectiveness depends on the levels of overtreatment in a given areas and the extent to which RDTs can decrease the overusage, and that in areas where malaria causes a small fraction of febrile events, mRDTs may significantly delay resistance in the partner drug. Saving the partner in turn saves the combination therapy for longer.

Balancing antibiotic access and overtreatment for pneumonia in PneuMOD, a pneumococcal disease simulator

Based on a presentation by Itamar Megiddo from CDDEP; see here.

In contrast to the malaria parasite, *Streptococcus pneumoniae* is usually a commensal bacterium. Asymptomatic, at times multistrain carriage is common, and the colonized population can represent an enormous bacteria reservoir (examples include 97% of under-one-year-olds in Gambia[13] and 70% of six-month-olds in South India[14]). However, pneumococcus, which can lead to invasive pneumococcal disease (manifested as pneumonia,[15] meningitis, and/or sepsis) and upper respiratory tract infections, is a leading cause of under-five morbidity and mortality. There are 92 known pneumococcus serotypes, and their distribution is geographically and temporally diverse. Strain diversity is constantly evolving via horizontal gene transfers, recombination, and mutation. Resistance arises from gene transfer and can become prevalent within a population through drug use and resulting selection pressure. There is

[11] Results to date are shared for schematic purposes only; the model needs further tuning before its results can be given with any measure of confidence.

[12] Preliminary results estimate this delay at about a third of a year (however, see footnote above).

[13] Hill, P.C., et al. Nasopharyngeal carriage of Streptococcus pneumoniae in Gambian villagers. *Clinical Infectious Diseases* 43: 673-9 (2006).

[14] Coles, C.L., et al. Nasopharyngeal carriage of resistant pneumococci in young South Indian infants. *Epidemiology and Infection* 129: 491 (2003).

[15] Important gaps remain, however. For example, although severe pneumonia is most often caused by *S. pneumonia*, *H. influenza,* RSV, and other respiratory viruses, studies have shown that the aetiology of severe pneumonia can remain unknown in as many as ~25% of severe cases. Scott, J.A.G., Brooks, W.A., Peirris, J.S.M., Holtzman, D. & Mulholland, E.K. *Journal of Clinical Investigation* 118: 1291-1300 (2008).

evidence that resistance may be higher in urban than in rural areas.[16] The seven-valent conjugate vaccine, introduced in the United States in 2000, has proven very effective; however there is evidence that in some cases, its introduction has resulted in emergence of highly resistant strains.[17]

It is important to recall that antibiotic access, not overuse, may remain the core problem in some settings; indeed, there is evidence of a relationship between population density and antibiotic resistance.[18] Antibiotic shortages and stock-outs may promote misuse (and subsequent subtherapeutic-level dosing, increasing selection pressure for resistance emergence) via substitution with expired or degraded antibiotics or patient underdosing.

Our modeling effort[19] seeks to inform decisions on balancing access and use. It uses the example of a simulation based on serotype 14, which represents 13% of invasive pneumococcal disease in Africa, and penicillin treatment in a population of 100,000 individuals.[20] It considers four baseline scenarios that vary by antibiotic consumption level. The model finds that if mRDT introduction increases empirical treatment with antibiotics when an mRDT result is negative (as recent literature suggests[21]), a subsequent increase in antibiotic resistance will occur. Additionally, the model finds a trade-off between antibiotic use and resistance (between treating more people and more treatment failing). When consumption is very low, increasing use is likely to reduce disease incidence. However, when consumption is not low, increased use may have a big enough effect on resistance to outweigh the benefits of more treatment. When a population switches to a drug to which pneumococcal strains are less resistant, antibiotic resistance falls considerably. However, this trade-off is a bit of a moot point, since resistance to this new antibiotic will eventually rise again (especially if the antibiotic is heavily used). Additionally, if there were a rapid diagnostic test specific to pneumonia, resistance would decrease (through improved drug targeting and appropriate use). Unfortunately, that technology does not currently exist.

Mortality varies with the four antibiotic consumption scenarios. In the low antibiotic consumption scenario the drop in mortality is most significant as the model moves through the consecutive phases of (1) baseline, (2) introduction of mRDT leading to an empirical increase in mRDT-negative cases by 30% (likely reflecting some improvement in appropriate treatment and some overtreatment of viral cases), (3) subsequent introduction of improved pneumococcal diagnostics (likely to result in improved targeting of antibiotics, with an increase in appropriate treatment, a decrease in inappropriate treatment and a resulting decrease in resistance), and (4) a switch of 60% of patients to a drug to which the strain is less resistant (and even better specificity of the drug-bug combination means less resistance, better targeting, and less death). One important message is that treatment with antibiotics may select for

[16] Bruinsma, N. Influence of population density on antibiotic resistance. *Journal of Antimicrobial Chemotherapy* 51: 385-390 (2003).
[17] Dagan, R. Impact of pneumococcal conjugate vaccine on infections caused by antibiotic-resistant Streptococcus pneumoniae. *Clinical microbiology and infections* 15 Suppl 3: 16-20 (2009).
[18] Bruinsma et al. (2003).
[19] Caveats of this model include limited data, limited runs of the model and use of only one serotype in this example, and the sole focus on pneumococcus, which represents a large portion of non-malaria related febrile illness but by no means all.
[20] This is just one example of numbers used to run the model. It can be run incorporating multiple serotypes and different the population sizes.
[21] D'Acremont, V. Oct. 20, 2011. Expanding the use of RDTs for febrile illness: developing the agenda for economic and financial analysis. Ansah, E.K. et al. *BMJ* 340 (2010). Msellem, M.I. et al. *PLoS Medicine* 6 (2009)

resistance among many bacteria that an individual carries (not just the one targeted for treatment), which is considerably different from resistance emergence in malaria parasites. Another message is that one size clearly does not fit all.

Policy messages from models

Based on a presentation by David Smith, of CDDEP; see here.

Models are quantitative reasoning tools that can be helpful in predicting, synthesizing, quantifying effects and uncertainty, evaluating costs and benefits, and ultimately providing input to help decisionmaking. However, the policy options chosen via modeling processes can be only as robust as the models' underlying assumptions. There is a cost-effectiveness breakpoint for mRDT introduction, and modeling can help determine where this point lies in different settings and contexts.

Modeling also can address the complex nature of the biological details that matter when considering mRDT introduction and scale-up—details such as transmission reservoir, immunity, acute versus chronic infections, microbial ecology and competition, mutation rates and mechanisms, and the drug action/pharmacokinetics-pharmacodynamics interaction.

The malaria modeling session (presentation by Geoff Johnston, above) highlighted the importance of the unprotected pharmacokinetics shadow of the partner drug; its effect on resistance critically depends on timing of infection. Treating someone who does not have malaria does not otherwise select for resistance. The benefits of ACT universal access would be fourfold: (1) saving lives; (2) displacing artemisinin monotherapy (which would delay emergence of high-level resistance); (3) reducing incentives to make counterfeit drugs; and (4) stabilizing and encouraging market entry to reduce global ACT stock-outs. Possible policy options to counter ACT resistance include widespread or targeted introduction of mRDTs to reduce overall ACT use and selection of resistance during the unprotected shadow of the partner drug. Multiple first-line therapies would also likely reduce selection for resistance.[22].

Possible costs of an mRDT policy include the costs of the test itself, avoidance or delay in treatment seeking for the true cause of fever, and increased antibiotic use and selection for resistance across all commensal bacteria. Benefits include saved ACT costs when mRDT-negative tests lead to appropriate treatment, reduced selection for malaria resistance, and less empiric antimalarial therapy and reduced burden of bacterial infections.[23]

Preliminary conclusions from the models:

- ACT access is the most important variable for both delayed resistance and lives saved.

[22] See Boni, M.F., D.L. Smith, and R. Laxminarayan, Benefits of using multiple first-line therapies against malaria, PNAS, 105(37).

[23] Reducing malaria may reduce the incidence of bacterial infections (FRCP, D. J. A. G. S., MD, J. A. B., MMed, I. M., PhD, L. O., MSc, S. U., MSc, A. M., MSc, C. N., et al. (2011). Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study. *Lancet* 378(9799), 1316–1323.

- Multiple first-line therapies are an alternative to mRDTs for delaying the emergence of antimalarial resistance, but mRDTs are likely to be cost-effective in some low-endemicity settings.
- Empiric therapy with antibiotics will probably save lives but may increase antibiotic resistance. However, empiric therapy may nonetheless be society's best solution until bacterial RDTs exist.

Discussions about the modeling sessions highlighted the following:

- CHAI is also beginning to work in the area of balancing access and overtreatment.
- A "quick win" might be to focus initially on targeting mRDTs at urban areas (through both public and private sectors) and then explore different models for rural areas.
- Could positive mRDTs help researchers more rapidly identify resistant strains of malaria? If there is treatment failure in an mRDT-positive individual, does this represent a chance to identify the mutation before it has a chance to spread further? Or is this only possible via microscopy?
- Resistance emergence tends to be in low-transmission areas. This may have to do with multiplicity of infection: although the resistant parasites may emerge more rapidly, they may also die out more quickly. Additionally immunity as well as overall population parasite loads are higher in high-transmission contexts.
- Asymptomatic infections will not be detected by mRDTs.

Session 4. Microfinancing of ACTs and RDTs

ACT and RDT funding: Current and projected levels

Based on a brief presentation (oral, no slides) by Sonali Korde, of the President's Malaria Initiative (PMI).

Given the current global economic difficulties, it is somewhat tricky to predict future funding levels for malaria. There are serious concerns about future funding levels, in particular as of 2014. The President's Malaria Initiative (PMI) has been very fortunate to experience steadily increasing budgets since its inception in 2006. In fiscal year 2012 (October 1, 2011–September 30, 2012), PMI was appropriated US$650 million. PMI is working in 17 focus countries (all in Africa), the Mekong focus region, and three non-focus countries. The FY13 budget request is a lower amount, US$620 million.

During 2009, PMI financed procurement of 21.5 million ACTs; this grew to 40 million in 2010 and 42 million in 2011. The jump in ACTs procured from 2009 to 2010 may largely reflect PMI expansion into additional countries (including such populous nations as the Democratic Republic of Congo and Nigeria) and increased funding. PMI supported procurement of 5.3 million RDTs in 2009, 13.7 million in 2010, and 20.3 million in 2011. The total global number of RDTs procured in 2010 was reported by partners to be ~88 million; therefore, PMI procured roughly one-quarter of the global amount. The Roll Back Malaria partnership estimates that 100 million RDTs were procured during 2011.

PMI's RDT and ACT funding amounts per country are bottom-up, driven by country-level malaria plans. Some are consumption based, some are based on epidemiological profiles, some are a

combination of both; however, PMI is actively working with countries to try to move more toward epidemiology-based forecasts for both drugs and diagnostics commodities. At times, PMI steps in to conduct emergency procurements to cover stock-outs. PMI encourages country-level joint quantification of ACTs and RDTs and is supporting Roll Back Malaria partners in the development of a manual to guide this process.

Round-table discussion: RDT and ACT microfinancing

Ramanan Laxminarayan opened this discussion with a short presentation offering three "straw man" scenarios, summarized in Table 1. The status quo (particularly in Africa) is captured in the first line: "Financing only for ACTs," limited in the private sector to countries in the AMFm pilot. Virtually all other malaria-endemic countries have some public sector financing for ACTs, but anyone buying ACTs from private outlets pays market-determined prices, which are quite high relative to chloroquine and sulphadoxine-pyrimethamine. mRDTs are in limited use in the public sector and in some private hospitals and other facilities in Africa. In Southeast Asia (Thailand, Cambodia), mRDTs are well established beyond healthcare facilities, largely because social marketing programs have made them very inexpensive and widely available in the private sector. The ensuing discussion revolved around how to introduce mRDTs widely in Africa in the private sector. ACTs are still not affordable in non-AMFm countries except in the public sector, but how to extend appropriate access was not considered in any detail. References to the situation in Asia served largely as comparators.

Table 1. Possible financing alternatives

	Public Sector	Informal Private Sector
Financing only for ACTs	Still the case in in many countries where microscopy is poor and RDTs are missing	AMFm
Alternative 1: Separate financing and delivery for ACTs and RDTs	Rapid scaleup of both ACTs and RDTs in many countries, but RDTs lag ACTs	Pilot projects involving social marketing. Challenge of tying purchase decisions of ACTs to RDT outcome
Alternative 2: Integrated financing/delivery for ACTs and RDTs but not for NMFI treatment	Both RDTs and ACTs to be provided free of cost	Needs piloting but challenge of inappropriate treatment for NMFIs
Alternative 3: Integrated financing/delivery for ACTs, RDTs and NMFI treatments	Ideal if RDTs for NMFIs were	Possibly ideal but potentially complex

The discussion that ensued was wide-ranging and generally related to aspects of the question, though not all directly about financing. The main ideas discussed are summarized here.

A major question is about the potential for use of mRDTs outside of formal facilities, including some programs already in place in communities. Even though most of them are in the public sector, they involve community health workers (CHWs) and provide an idea of what might be done through the private sector to expand access to mRDTs and ACTs. Specifics include the following:

- The Global Fund supports CHW training. CHWs could be trained broadly to use mRDTs and to treat both those testing positive (with ACTs) and testing negative, using a standard algorithm.
- Integrated community case management (iCCM) for children is at national scale in Ethiopia, Zambia, and Rwanda and near-scale in other countries with PMI, UNICEF, and Global Fund support. iCCM has been used primarily in the public sector, but training has been given in informal shops on a small scale. Shops in which training has taken place could be options for mRDT use.
- In Nigeria, mRDTs use by patented licensed medicines vendors is being explored.
- Madagascar and Rwanda provide ACTs through social marketing, and it may be possible to add mRDTs.
- In Uganda, PSI is working with socially franchised clinics, which (alongside pharmacies) provide diagnosis. Village health workers provide referrals (to clinics). Initially, to introduce the product to clients, RDTs were distributed free of charge. Providers are slowly introducing fees. There is a suggested retail price, but it is not yet met by most clients. VHWs do not receive financial incentives but do receive recognition.

A few other programs that train people who work in accredited drug-dispensing outlets (ADDOs in Tanzania, a similar program in Uganda, and one just starting in Liberia) do not now link to CHWs but have potential to include RDTs among their services. Everyone seems to agree that RDTs should not be available at all shops that have sold antimalarials, especially in the pre-ACT era, and that some training should accompany stocking of RDTs, but how far down the retail chain they should be available is still a matter for research and debate. Also to be addressed are how use outside formal facilities might be monitored and regulated (which will likely vary by country and other characteristics).

Another question is whether to introduce mRDTs without regard to endemicity levels or instead target (say) low-endemicity areas where malaria is likely to be responsible for a smaller proportion of fevers. An algorithm could be devised to maximize cost-effectiveness, but this has not yet been done, at least not formally.

The move to diagnosis before treatment for malaria comes on the heels of 50 years of "treat for malaria first, ask questions later—or not at all." Presumptive treatment was recommended and had long ago become the norm. A change to "diagnose, then treat" will require informing the general public as well as the health professions. This change has already occurred in the public sector in some places in Africa where RDTs have been introduced, such as Zanzibar and Senegal. Ultimately, we want patients and caregivers to seek (and even demand) diagnosis first and ask for treatment appropriate to the results.

It is likely that some form of bundling of ACTs and mRDTs will be at least part of a solution to encouraging the use of mRDTs in ways that will not be cost-prohibitive for patients. Because taking an antimalarial drug has very little risk, a person could logically take one for a fever, rather than be diagnosed first. If the cost of diagnosis is less, the same, or not much more treatment, people are more likely to want a diagnosis than if the cost is much more. The other factor, of course, is the possible benefit of finding that something other than malaria is causing illness, and treatment for that illness is available. Bundling, in this case, may be physical or it may be the price that is bundled. Physical bundling is problematic because the need is not 1:1 (RDT:ACT) or any specific ratio. A 1:1 bundle apparently does exist for the tourist market but would not be appropriate for local use in malaria-endemic countries.

Experience with mRDT implementation and scale-up in different settings should continue to be systematically documented to inform decisions about implementation and research. At the same time, field trials of different types are needed to test the different approaches to bundling and other strategies. Field trials may explore when the public sector can fill needs and when the private sector is needed to bridge coverage gaps. Lessons might be learned from the introduction of HIV testing.

The theoretical rationale behind tying an ACT subsidy to mRDT utilization was discussed. Four key principles would guide design of an incentive mechanism that could function in private retail markets, as follows:

- mRDT use should be preferred to no-mRDT use by both retailer and consumer.
- Retailers should be indifferent to the choice of treatment following mRDT use.
- Consumers should prefer the most appropriate drug indicated by mRDT result.
- From the point of view of those who finance any given subsidy, resources may be better utilized if mRDTs are provided alongside ACT financing relative to no-mRDT provision.

Briefly, these rules call for a two-step subsidy, wherein subsidies for ACTs are tied to mRDT results. ACTs would cost more than mRDTs. Consumers would be encouraged to purchase an mRDT, and if results are positive, they would receive a fully subsidized ACT, possibly via a rebate mechanism. If the result is negative, the consumer will have forgone the cost of the mRDT; however, that is a smaller amount than what would have been spent on an ACT without prior mRDT purchase. Additionally, the consumer has learned that the febrile episode is not malaria. Under this scenario the consumer's incentive is to purchase the mRDT first, rather than the ACT.

From the retailer's perspective, this two-step sale scenario is also advantageous as long as the mRDT profit margin is at least equal to the ACT profit margin. Subsidy financiers should also be supportive of testing this scenario, since limited funding will be better targeted.

Although this sequence of incentives is theoretically attractive, field-testing is needed to determine whether it will survive the realities of private retail markets in sub-Saharan Africa.
One possible experiment to test mRDT/ACT private sector bundling is laid out in Box 1.

Box 1. A two-step sale: RDT financing and delivery in the private sector

Assume an AMFm ACT retail price of $1. RDTs are sold for $0.50. Consumers are encouraged to purchase the RDT before purchasing an ACT. If they have a positive RDT test, then they are given a rebate to cover the cost of the ACT, such that the ACT is free. Rebates are delivered through a mobile phone network.

Consumer's perspective
Default: purchase ACT for $1.
Alternative: purchase an RDT for 50 cents.
Positive test result: $1 rebate to the individual for ACT; i.e. the treatment is free. Total expense: 50 cents for RDT.
Negative test result: individual can buy ACT for $1 but has information that it is of no use. Total expense: 50 cents for RDT.

Because the customer pays 50 cents either way, she should be indifferent between the two results of the RDT. But without the RDT, she spends $1 with no certainty of an ineffective treatment. The lower the RDT cost and the higher the price of ACTs, the greater the incentive to purchase ACTs only after buying an RDT.

Retailer's perspective
Assume the retailer's profit on the ACT sale is 30 cents. As long as the profit margin on the RDT is at least 30 cents, the retailer is always better off with the two-step sale. Without RDTs, he would make 30 cents on every transaction. If he sells RDTs, he makes at least that much but potentially as much as 60 cents.

Financier's perspective
AMFm pays $1 copay with certainty without RDTs. With the financing plan, AMFm pays RDT subsidy of 40 cents (to get price to 10 cents) + $1 for patients who actually have malaria. Assume half of patients test positive.

$1.4p+0.4(1-p)<1$ or $p<0.6$

If the probability of malaria is less than 60%, the RDT financing mechanism saves money relative to status quo. This could, of course, vary by age group.

The experiments that end up being designed would benefit further from inclusion of antibiotics, especially because recent studies show that non-severe febrile illness episodes often do not require antibiotics. Field experiments would need to consider how to counter possible gaming, whereby informal private providers would opt to lie and state that negative mRDTs are positive to gain the double RDT-ACT subsidy. Effective monitoring mechanisms would certainly need to be in place. Testing would also have to consider nonfinancial determinants; for example, caregivers may prefer to purchase an ACT outright and not wait for an mRDT result if they are convinced from prior experience that their child has malaria.

Session 5. Malaria RDT introduction and scale-up

Expanding access to both RDTs and ACTs: Implications for sustainability

Based on a presentation by Logan Brenzel, independent consultant—see here.

The Affordable Medicines Facility–malaria (AMFm) is an innovative financing mechanism for ACTs, with a pilot phase in eight countries: Cambodia, Ghana, Kenya, Madagascar, Niger, Nigeria, Uganda, and Tanzania-Zanzibar. The pilot began in 2010 and will end at the end of 2012, with the aim of rapidly increasing ACT availability and driving out artemisinin (and other) monotherapies. The AMFm Secretariat is housed in the Global Fund. ACT prices for countries are kept low through a donor copayment fund of $216 million. An additional $127 million funds supportive interventions.

A recent modeling exercise,[24] conducted by Brenzel and Young (2011), assessed the financial sustainability of the AMFm over 2013–2017 and the ability of pilot countries to fund both subsidized ACTs and supporting interventions. Governments were assumed to be the sole payor, and a secondary analysis of the costs of RDT use was incorporated into the model. The model also varied the subsidy rate currently financed by the copayment fund.

The model projected 1.7 billion fevers per year in these pilot countries, of which 78% would affect adults. The model estimated 1.5 billion ACT treatments for 2013–2017 (one-third in the public sector, 48% for those five years and older). Total costs, including RDTs, ACTs, and supportive interventions, were estimated at US$490 million.

Using these parameters, the major findings were as follows:

- Assuming a benchmark of 3% of government health expenditures, ACTs provided to the pilot countries under the same subsidy rate and price levels as the current AMFm would be sustainable for all countries.
- Because the AMFm does not currently subsidize the costs of mRDTs, the primary analysis did not include RDTs. However, when mRDTs are added in to the model, preliminary findings show that the additional costs would be 29% of the total (US$142 million). Additionally, three of the eight pilot countries would need to allocate more than 5% of their governments' health budgets, which means that additional external financing would be required for ACT, RDT, and supportive intervention costs in these countries.
- The costs for ACTs, RDTs, and supportive intervention far exceed the countries' current malaria budgets. More work is needed to understand the total resources flowing to malaria programs and to explore the budget lines for malaria drugs, tests, and nets.

Public and private sector experience in countries with PMI programs

Based on a presentation by Larry Barat, of the President's Malaria Initiative—see here.

The U.S. President's Malaria Initiative (PMI) program has provided support for diagnostic testing for malaria since its inception in 2006. Diagnostic testing has received a greater focus since WHO guidance was revised in 2010 to recommend universal diagnostic testing rather than presumptive

[24] A stochastic Markov-type model was developed. Limitations of the exercise are related to data quality and availability: when country-specific data were unavailable, averages of parameters were used, and demand was based on fevers in previous two weeks reported, which may overestimate (or underestimate) true demand. The effect of bednets on demand and the costs of treating nonmalarial fevers were outside the original scope of work of this exercise.

treatment. PMI investments traditionally have been almost entirely focused on the following public sector activities:

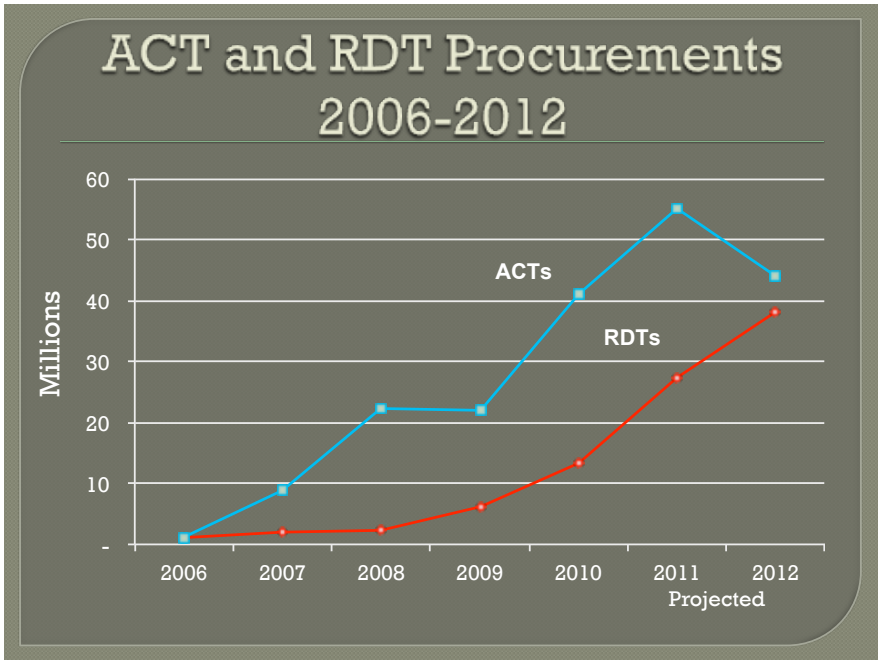
- establishing country systems for quality-assured diagnostic testing for malaria;
- strengthening existing clinical laboratories;
- introducing mRDTs at community and facility levels; and
- changing provider practices.

PMI has supported malaria and laboratory policy development, updating and production of guidelines, training curricula, standard operating procedures and job aids, training and supervision of laboratory and clinical staff, procurement of supplies (mRDTs, microscopes, reagents), strengthening of supply chain management, quality assurance systems for microscopy or mRDTs, monitoring and evaluation, operations research, and communications and behavior change.

PMI promotes scale-up of diagnostic testing in all 19 African countries and the Mekong region where it works. Full- or near-scale quality assurance systems for malaria exist in Benin, Ghana, Mali, and Zanzibar, and significant progress has been achieved in Ethiopia, Liberia, Malawi, Uganda, and Zambia. mRDTs are increasingly being deployed at the community level: this is ongoing in Ethiopia, Liberia, Madagascar, Rwanda, and Senegal and planned for Malawi, Mali, and Zambia. Eleven PMI countries are currently implementing integrated community case management (iCCM).

Figure 1 highlights trends in PMI funding of mRDTs and ACTs from 2006 to 2012. As countries procure increasing amounts of mRDTs, ACTs procurements are slowly decreasing; the considerable drop in ACT use in Senegal, Zambia, and Ethiopia may reflect increased (and appropriate) use of mRDTs. The ACT procurement drop in Ethiopia is also thought to be due to better forecasting.

Figure 1. PMI procurements, 2006–2012



In 2010 PMI trained 17,335 health workers in malaria diagnosis and 36,458 in malaria case management. It also provided financial support for the WHO-FIND RDT lot-testing program and is supporting development and pilot testing of a joint RDT-ACT quantification manual by Management Sciences for Health. Major remaining challenges to PMI RDT operations are changing provider practices (especially at the facility level) and remedying supply chain stock-outs.

RDT scale-up: Experience from Senegal

Based on a presentation by P.M. Thior, malaria expert, Senegal—see here.

Malaria is endemic in Senegal, home to 11 million people, including 2,090,000 children under age five. Despite introduction of long-lasting insecticide-treated nets, ACTs, and community-based interventions, from 2001 to 2006 (prior to mRDT introduction and scale-up) 33-39% of diagnosed fevers in under-five-year-olds and about 33% for the entire population, were caused by malaria.

In 2006, with the aim of rapidly reducing mortality and morbidity, Senegal began to implement the RAMP strategy, consisting of scale-up of WHO-recommended interventions alongside a three-pronged emphasis on quality-assured malaria diagnostics (RDT introduction, microscopy strengthening, and prompt and effective case management using ACTs). Following a successful feasibility study that confirmed the acceptability of RDT use among public health providers, Senegal introduced an RDT pilot in 10 health centers, with Global Fund support. Tools such as training handbooks and implementation manuals were developed and used during health worker cascade training, beginning with the regional and district-level management teams and working down to training of district-level providers. Initial resistance by providers to withholding antimalarials for a negative mRDT was overcome through training and supervision.[25] Patients' views also changed over time: because of targeted information campaigns and provider education, patients increasingly accepted that an RDT was required and the results should be positive before an antimalarial would be prescribed.

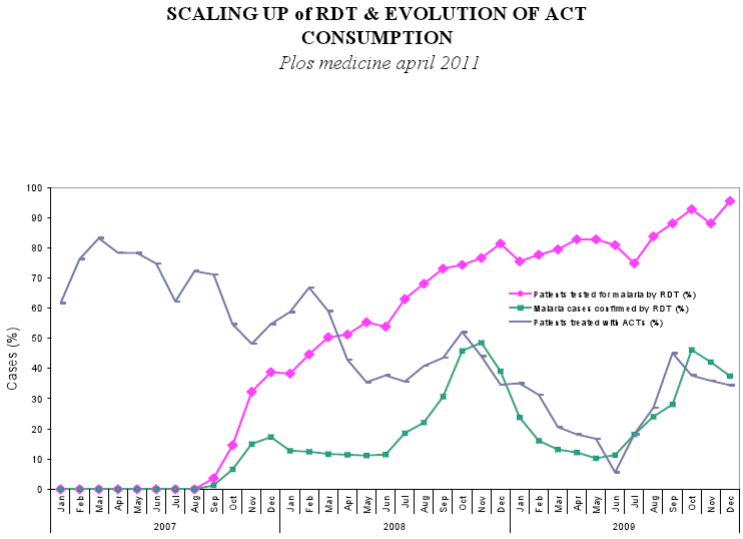
During 2007, 2,607 additional providers were trained, and RDTs were scaled up in health centers and health posts in 65 districts. During 2008, 761 hospital and military sector providers were trained. During 2009 RDTs were introduced in 94% of health huts (the most basic health level), and 3,716 community health workers were trained to use RDTs. Additionally, home-based case management was implemented during 2008–2009. From 2008 to the end of 2010, malaria was not the registered cause for a single death. Of a total of 7,198 fever consultations, 6,707 used an RDT. The RDT was negative in 4,377 cases (~65%), positive in 2,300 cases (~34.3%), and invalid in 43 cases (~0.01%).

Data from 2007–2009, displayed in Figure 2, show how ACT consumption has declined with RDT scale-up in Senegal. In the words of the executive director of the Roll Back Malaria partnership, Senegal's experience demonstrates that "when partners work together, and when strategies to fight against malaria (such as long-lasting insecticide-treated nets, ACTs, indoor residual spraying, RDTs) are

[25] Interestingly, part of the reason that it took time for providers to trust the RDTs was the timing of their introduction—in October, the dry season. The mRDT results were always negative, and providers did not trust their accuracy. Once the rainy season began and mRDT results started to turn positive, providers' confidence in the tests increased.

used in a comprehensive manner and scaled up, an extraordinary success can be achieved."[26] The private sector is not involved in RDT distribution in Senegal; however, NGOs have been engaged in supervision and collection of data.

Figure 2. Scaling-up of RDTs and evolution of ACT consumption



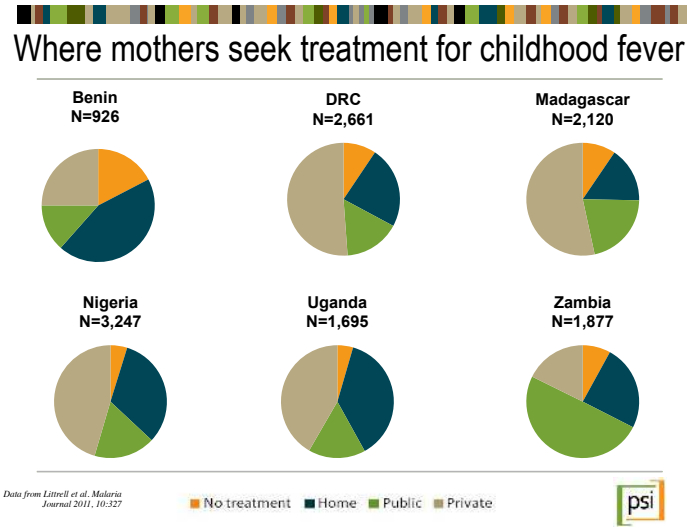
Engaging the private sector in mRDT delivery scale-up

Based on a presentation by Stephanie Dolan, of Population Services International—see here.

Population Services International (PSI) has considerable experience in engaging the private sector in mRDT use. Engaging the private sector is a pragmatic approach, given the WHO recommendation for universal parasitological diagnosis, the risk of overtreatment in the absence of diagnosis, and the concrete reality that in many settings (see Figure 3), a significant proportion of the population seeks care and treatment from the formal and informal private sectors, where mRDTs, when available, are often prohibitively expensive.

Figure 3. Fever treatment-seeking behavior in a sample of African countries

[26] Professor Awa-Marie Coll-Seck, February 8, 2008.



Examples of PSI programs that engage the private sector operate in the following countries:

- Uganda, where socially franchised clinics and pharmacies provide diagnosis, and village health workers provide referrals to clinics. Initially, to introduce the product to clients, RDTs were distributed free of charge. Providers are slowly introducing fees. There is a suggested retail price, but it is not yet met by most clients. Village health workers do not receive financial incentives but do receive recognition.
- Madagascar, where socially franchised clinics provide diagnosis and treatment. Diagnosis by community health workers (CHWs) is being scaled up: some CHWs have been trained and are already providing diagnosis, while others are waiting for RDTs to arrive). CHWs are considered part of the private sector but belong to the community and thus cannot be franchised. However, the Ministry of Health is working to incorporate them into the health system.
- Myanmar, where socially franchised CHWs provide diagnosis and treatment, and an incentive scheme has been employed in the past to encourage adherence to RDT results. Currently, this scheme is being revised, but previously it was awarded based on a point system with the health impact of each commodity considered. RDTs and malaria treatment received equal points. Based on the number of points a worker achieved each month, he received additional compensation. A ratio of confirmed malaria to RDT tests was set. If the confirmed rate was below the threshold over a period of three months in one calendar year, the worker was given malaria refresher training.
- Cambodia, where RDTs and ACTs are distributed through 350 pharmacy providers nationwide on a monthly basis. The program is supported by medical detailers and a behavior change communication (BCC) campaign.

Preliminary results from Uganda reveal that once informed about mRDTs and their usefulness, patients desired testing. PSI programs contemplate four angles when considering scale-up: (1) the product should be easy to use and quality assured; (2) the product should be conveniently located for the client, and the provider should be able to appropriately administer the service; (3) the product

should be affordable and the profit margin reasonable; and (4) the product should be recognized and demanded by the client. Challenges include lax regulatory environments, consumers' failure to demand tests, providers' lack of incentives to stock mRDTs and, when they do provide them, to respond appropriately to negative test results.

PSI seeks to increase mRDT access, increase mRDT demand, improve case management, and strengthen the regulatory and policy environments through the following activities:

- *increasing access:* strengthening procurement standards, developing and implementing training materials and job aids, conducting trade promotions, strengthening quality control (via lot-testing), and fostering consumer recognition of quality-assured mRDTs;
- *increasing demand:* conducting consumer and provider research, developing marketing plans and pricing strategies, considering alternative packaging options, and orienting BCC (mass media, interpersonal communication, point-of-sale materials) message from presumptive treatment of fever to need for testing;
- *improving case management:* developing and adapting algorithms for the private sector, training providers, strengthening standards of care, and increasing supervision and medical detailing; and
- *strengthening the regulatory and policy environments for mRDT introduction and scale-up:* carrying out a systematic review of existing regulations, regularly interacting with stakeholders, and presenting lessons learned and project experience.

Engaging private sector drug sellers in RDT and ACT provision: Challenges and opportunities

Based on a presentation by Edmund Rutta, of Management Sciences for Health—see here.

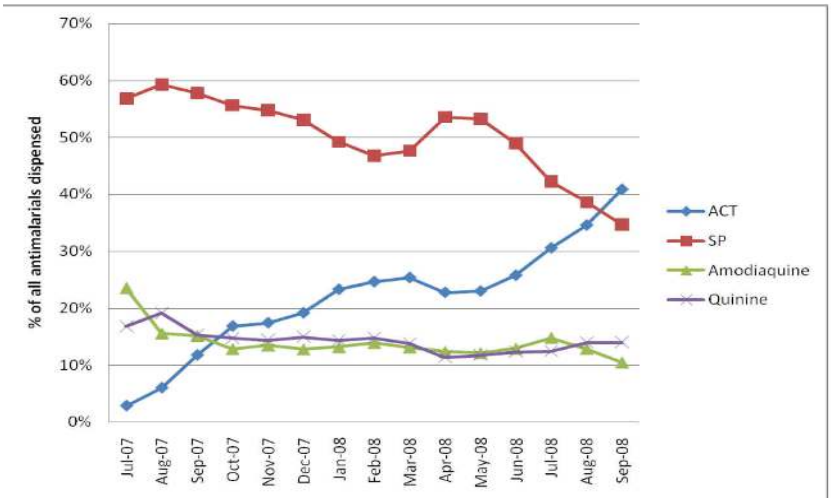
Most fevers continue to be treated in the household setting with drugs purchased by patients or their caregivers from private drug sellers. A handful of countries have embarked upon innovative ways of engaging drug sellers and improving the quality of services to ensure appropriate treatment. These programs seek to build private sector capacity, enhance product availability and quality, ensure pharmaceutical services quality, and increase patients' and consumers' awareness. The best-known example is the Tanzanian accredited drug-dispensing outlet (ADDO) program, which has included ACT delivery since 2007. Similar experiences are under way in Uganda (2008–2010) and Zambia (2008–2011) and just beginning in Liberia.[27] In these models, accreditation serves as a mechanism for increasing private sector access while ensuring quality of services and products. As countries expand access to effective antimalarial medicines, particularly in rural areas, ADDO-type models can provide a mechanism to increase drug and diagnostic access in the private sector while ensuring quality of services and products to safeguard the public's health.

The U.S. President's Malaria Initiative (PMI) supported delivery of subsidized ACTs through 700 ADDOs in two regions in Tanzania. This was before AMFm implementation, and hence the experience helped inform AMFm in Tanzania. ACT availability increased to 40% of antimalarials

[27] Zambia's experience is limited to a pilot in four districts; Uganda is scaling up after piloting in one district, and Liberia is going nationwide, leading with implementation in one county while mobilizing resources to cover the entire country.

dispensed. Within the first year of ACT delivery via ADDOs, sulphadoxine-pyrimethamine (SP, which is no longer recommended) showed a continuous decline, indicating some level of "crowding out" of medicines not recommended for treatment of malaria in the private sector (see Figure 4).

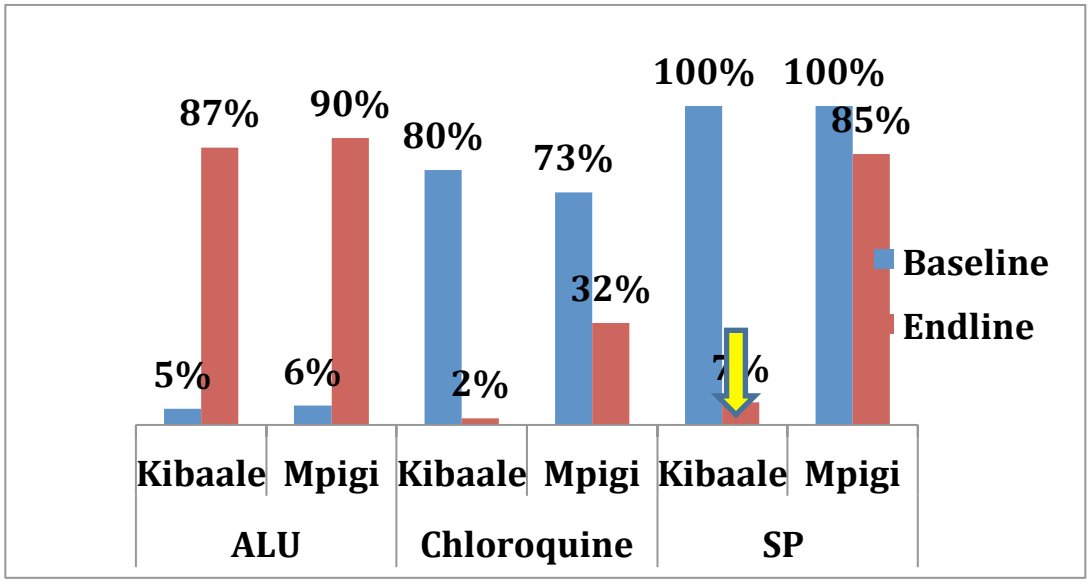
Figure 4. Trend of antimalarials dispensed in ADDOs, 2007–2008



As of July 2011, 49% (3,484 of 7,122) of drug shops in Tanzania were accredited in 14 of 21 regions and 7,226 dispensers had been trained.

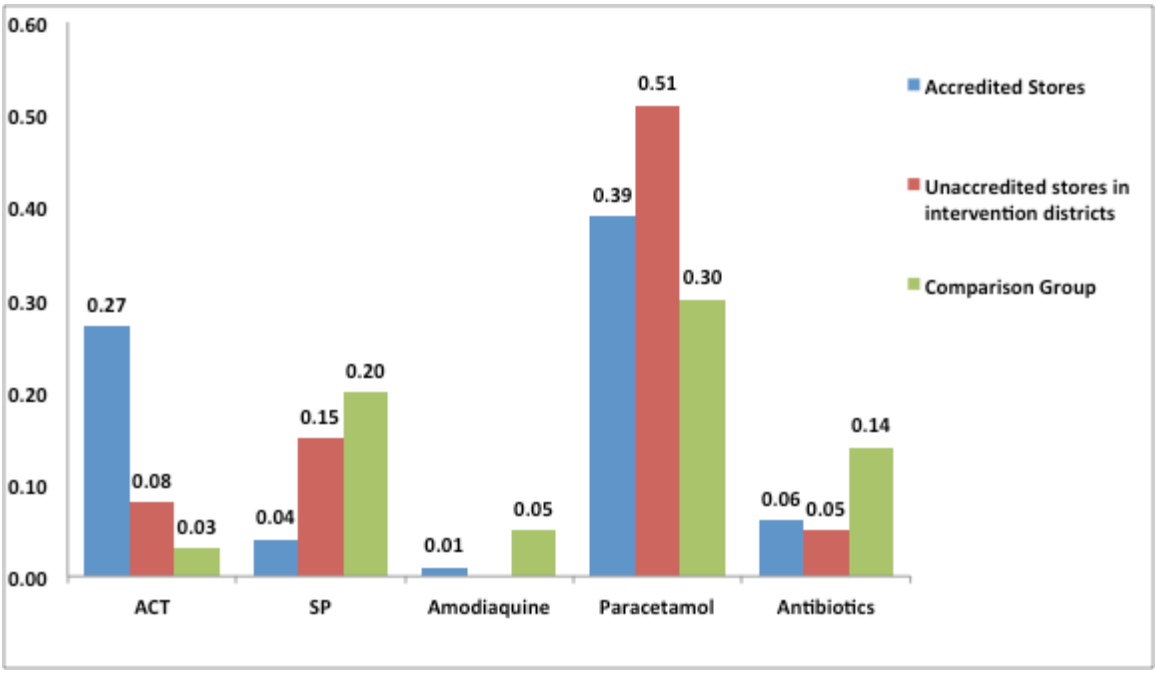
A pilot in Uganda provides further evidence of how interventions to engage and accredit private sector drug sellers can improve the quality of their services; it also shows how careful regulation can improve the availability of effective antimalarials (in this case artemether-lumefantrine) and significantly decrease the availability of less effective drugs (chloroquine and SP) no longer recommended as first-line therapy (see Figure 5 below). The pilot revealed a 31% difference in the percentage of appropriate malaria treatment encounters in the Kibaale district, where the accredited dispenser program was implemented, compared with Mpigi, where other interventions (but no accreditation of informal providers) were being conducted.

Figure 5. Availability of antimalarials in Uganda



One additional initiative, in Zambia, found a significant shift in antimalarial dispensing toward ACTs in accredited stores versus unaccredited stores and comparison districts (Figure 6). Exit interviews found that no mRDT-negative patients received ACTs; however, mystery shopper experiments found instead that 18% of mRDT-negative patients still left with ACTs, which suggests that providers may not trust the test quality, may respond to a patient's desire to purchase an ACT, and/or have a financial incentive that outweighs the costs of potentially having their accreditation revoked.

Figure 6. Evidence of shifting drug use patterns in Zambia



Evidence suggests an improvement in adherence to treatment standards and an increase in caregivers of under-fives seeking treatment at ADDOs following accreditation. Additionally, because of the improved availability of ACTs at private sector drug outlets, drugstores appear to be serving as backups for public clinics that experience stock-outs.

Interventions that have improved access to ACTs and mRDTs have been wide in scope, addressing the overall operations of private drug sellers and using innovative measures to target the regulatory system, policy change, business incentives, capacity building, product quality monitoring, and consumer awareness and education.

Primary challenges to engaging the private sector in delivery of mRDT and ACT remain:

- Regulations in many countries do not allow diagnostic services in pharmaceutical outlets. Regulatory framework amendments, which can entail a lengthy process, are therefore needed to allow for mRDT stocking and use.
- Keeping up-to-date records of day-to-day RDT and ACT transactions can be challenging.
- Intense follow-up and monitoring is required to ensure that drug sellers adapt to and apply new standards without feeling that their entrepreneurship is compromised.
- Even at subsidized prices, maintaining a sufficient ACT and RDT inventory is difficult. Owners tend to have limited or no access to microloans, and their incentives and purchasing power are weak.
- Public facilities are reluctant to accept an mRDT-negative result for a patient tested and referred by a private drug seller.

School-based screening and treatment for malaria in Kenya

Based on a presentation given by Donald Bundy/World Bank and co-prepared by Simon Brooker[28]*—see here.*

The consequences of malaria for the health and education of schoolchildren are well known: malaria causes anemia, which in turn can result in cognitive impairment, reduced attention during lessons, and school absenteeism, all of which lead to poorer educational achievement. Given that school-aged children are reservoirs of malaria transmission and that children can be a mechanism for accessing households, schools are increasingly being considered a possible platform for malaria diagnosis and treatment management.

A recent cluster-randomized trial in Kenya looked at the health and educational outcomes of school-based intermittent preventive treatment. Thirty schools were randomized according to educational strata, the children ranged from 4 to 16 years old, and sulphadoxine-pyrimethamine alongside amodiaquine was administered once a term. Findings highlighted a 90% reduction in the prevalence of malaria parasitemia and a 55% reduction in the prevalence of anemia but no significant improvements in classroom attention or any improvement in examination scores. The lack of educational effect likely reflects poor teaching and suggests that dual interventions targeting improvements in both health and education might be more fruitful.

[28] The work described in this presentation is by Simon Brooker and his team, of KEMRI.

To test this hypothesis in the Kenyan context, a two-pronged health and literacy intervention (the HALI project), a randomized impact evaluation of malaria prevention and literacy instruction in 101 schools on the Kenyan coast, was carried out in 2009–2012 with the specific objectives of assessing the following:

- the effect of malaria prevention on improving anemia;
- the effect of malaria prevention on classroom attention, school attendance, and educational attainment;
- the effect of an enhanced literary program on improving early-grade reading; and
- whether health and education interventions work synergistically.

This project was carried out within the policy context of the Kenyan Malaria Free Schools Initiative, which emphasizes mainstreaming malaria control in the school curriculum, indoor residual spraying of schools, scaling up mosquito net coverage in malaria-endemic and epidemic-prone areas, and testing and treating all children with parasitemia according to the national guidelines.

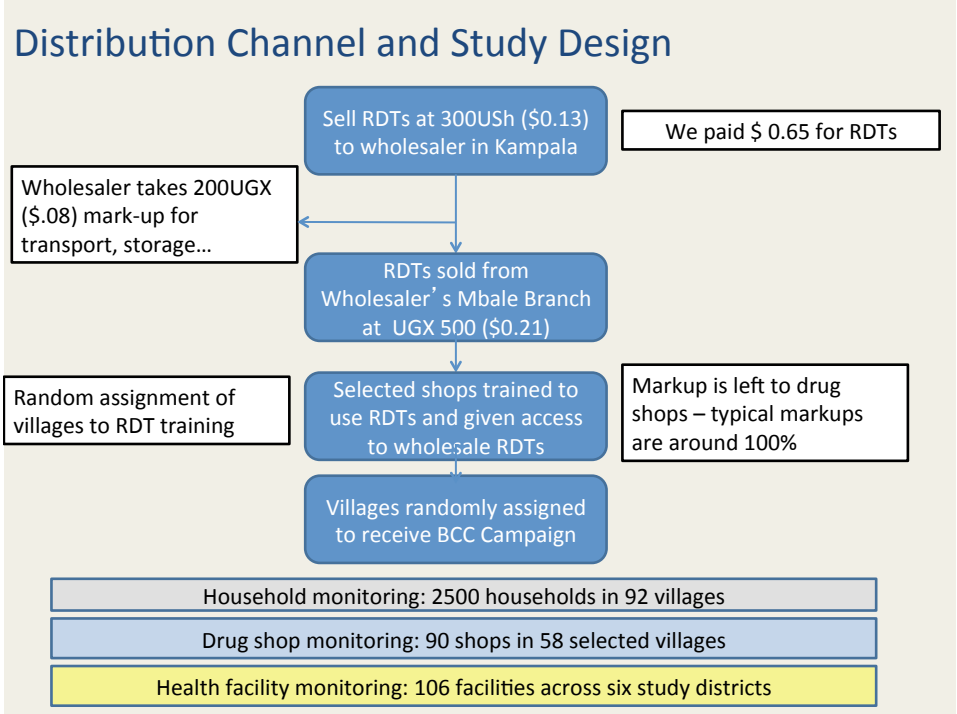
Intermittent screening and treatment (IST) was carried out by mobile health teams who screened children once a term using the Paracheck RDT. Infected children, whether symptomatic or asymptomatic, were treated with ACTs. School-based malaria control through IST was well accepted by the community. There was less understanding, however, of the consequences of asymptomatic parasitemia; improved community awareness is required to ensure full adherence to treatment among seemingly healthy children. Health workers are well positioned to deliver IST because of professional experience and expertise, but understaffing in many facilities often makes them unavailable. Most participants were opposed to having teachers take finger-prick samples but recognized the necessity of involving them.

RDTs in the retail Sector: Some lessons from operational research

Based on a presentation by Jessica Cohen, of the Harvard School of Public Health—see here.

Ongoing research by Cohen, Dickens, and Fink looks at the feasibility and effect of introducing subsidized mRDTs into the retail sector in Uganda. In our experiment, selected registered and licensed shops are trained to use subsidized mRDTs, and villages randomly receive behavior change communication training. The specific mRDT distribution channel and study design are summarized in Figure 7.

Figure 7. Distribution channel and study design



Many shops are not licensed or registered with the Ugandan National Authorities and hence were not eligible for training conducted through the Ministry of Health. Turnover of shop attendants necessitated occasional training workshops for new staff. There was initial uncertainty about baseline training and education of attendants; however, nearly all the participants passed the training and continue to perform well; a monitor, who makes monthly but unannounced visits to observe mRDT administration and address any questions shop staff might have, provides some quality control. In addition, mRDT quality is being tested regularly: a sample of four mRDTs from each shop is collected quarterly for lot-testing.

Initial results from the Uganda experience suggest that overall, shops perform the tests very well; the important period for monitoring is during the first two to three months, since prompt feedback improves shopkeepers' behavior. Self-selection seems to be occurring to some degree: some shops choose not to sell mRDTs but in others it is a routine part of febrile illness management. Ongoing research will look at specific determinants and shop characteristics that predict uptake.

Each shop receives a free initial mRDT box of 40 tests. A total of 396 boxes total were purchased after the initial boxes, but the number of boxes purchased subsequently by each shop was highly variable. Preliminary results show about 90% adherence to mRDT results; shops tend to recommend alternatives, such as cold medicines, antipyretics and, in some cases, antibiotics, when mRDT results are negative. Demand is both patient-driven and supplier-led: sometimes the shop recommends the test, in other cases the patient requests it. Some shops have developed a reputation for testing, and there is evidence that customers seek out these shops. Test quality was excellent: 100% of RDT samples passed lot-testing.

The median mRDT price is a 100% markup, but shops with more competition are likely to charge less. Shops appear to charge different prices to different customers, based on individuals' appearance of ability to pay. There is some evidence of innovation: in two cases shops bundled the price of mRDTs and ACTs, and some shops sometimes offered the mRDT on credit.

Community focus group discussions conducted as part of the ongoing Ugandan experiment revealed that most participants knew how malaria was transmitted and that it could be detected in blood. Most participants had some preconditions for valuing diagnosis: they were aware that other common illnesses present like malaria, or they disliked or were worried about taking antimalarials unnecessarily. Although some people mentioned that diagnosis could help catch serious illnesses sooner and save money, these were not central themes. Participants had experience with cases in which antimalarials were not prescribed after negative test results. They identified the biggest hurdle to diagnosis as the inconvenience of the public sector. We saw generally no awareness of what mRDTs were or how they worked, and willingness to pay for them was limited (but not zero). As a result of these focus group findings, BCC campaigns are now seeking to familiarize individuals with mRDTs, create awareness about their convenient availability at shops, and emphasize the benefits (money, time) of avoiding improper treatment.

Another recent operational research project (by Cohen, Dupas, and Schaner[29]) looked specifically at demand responses to ACT and mRDT subsidies in the retail sector in Kenya. In this study, a total of 2,700 rural poor households in a malaria endemic region were given voucher cards to purchase subsidized ACTs at one of four drug shops. Trained project team members were posted at each shop to sell ACTs and administer mRDTs. Some households were also given a voucher card allowing them to buy subsidized mRDTs at the local shop. There were therefore three study arms: the control (no subsidy for ACT or mRDT), households that received only the ACT subsidy, and households that received both an ACT and an mRDT subsidy.

The four-month study found that the mRDT subsidy significantly increased test taking. Although the ACT subsidy appears to have drawn individuals into the shops, the mRDT subsidy did not, highlighting the need for targeted BCC. Willingness to pay for mRDTs was very high when their price was relatively low, but we saw little difference in mRDT uptake by ACT price. Almost all individuals under 17 tested positive for malaria, and there was very high adherence to test results for all age groups. mRDTs were requested and purchased more often when the person with febrile illness was a child. Finally, the study found that RDT-negative individuals bought more antibiotics.

A third recent operational research study (by Cohen, ongoing) evaluated the effect of packaging and messaging to increase ACT adherence in the Ugandan retail sector. Conducted before the AMFm pilot, this study subsidized ACTs and sold them with different packaging and messages to encourage adherence to treatment. On top of this, mRDTs were randomly offered to patients when they arrived at shops to purchase ACTs. About 96 hours after ACT purchase, a random subsample of households

[29] Cohen, J., P. Dupas, and S. Schaner, Draft, Price subsidies, diagnostic tests, and targeting of malaria treatment: evidence from a randomized controlled trial. March 15, 2012.

was visited to check blister packs and measure adherence. Results from this study are still being evaluated, but preliminary results show that confirmation of a diagnosis of malaria had no effect on adherence to ACTs (defined as completion of the entire treatment course).

Designing and managing randomized control trials for policy evaluation

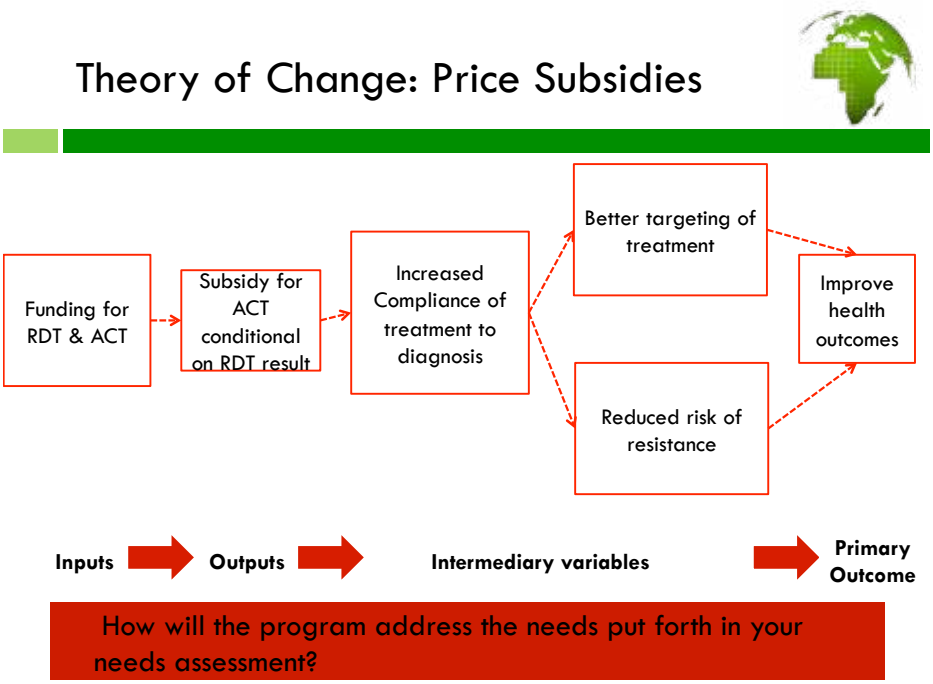
Based on a presentation by Niall Keleher, of Innovations for Poverty Action—see here.

Innovations for Poverty Action (IPA), a nonprofit dedicated to discovering what works to help the world's poor, designs and evaluates programs in real-world contexts and provides hands-on assistance to bring successful programs to scale. In 2010, IPA had 230 projects completed or under way in more than 40 countries. IPA has 14 permanent offices around the world and in many settings works alongside MIT-based JPAL. IPA has specific expertise in designing randomized control trials (RCTs). Example projects include improving immunization coverage in India, use of menstrual cups in Nepal to improve school attendance, small cash incentives for individuals to collect HIV test results, and the association between condom uptake and learning HIV status. IPA-led research on mRDTs would likely address the following questions:

- *Information:* what measures would ensure that mRDT-negative results are adhered to? What training is most effective?
- *mRDT delivery:* which approaches are most effective in private settings, and which in public facilities? How and where can community health workers be involved?
- *Incentives:* on both supply and demand side, what would best promote mRDT uptake and adherence?
- *Additional mechanisms:* in addition to incentives, what other measures, such as supervision and technical solutions, are most effective at ensuring appropriate ACT use?

An example of a study that IPA could run in the context of RDTs and ACTs is suggested in Figure 9.

Figure 9. Studying the effect of RDT and ACT price subsidies



Session 6. Moving forward

The closing session highlighted several priority areas for further research and discussion.

- Even though today's debate is not whether to scale-up mRDTs but rather how, more quantitative evidence on the added value of mRDTs would be useful. The task now is where to prioritize efforts, since scale-up will not happen overnight.
- Many questions remain about RDT and ACT subsidies and should be further tested. In some settings, if people trust the test result, an RDT subsidy may be sufficient to motivate appropriate ACT use; in others both an RDT and an ACT subsidy may be required. There may not be a price structure that works across the board. Willingness to pay for both RDTs and ACTs is likely context-specific. Differences may be rural-urban, depend on malaria endemicity, involve community health workers (CHWs), etc. Whereas the principle in the private sector may be to make ACTs cheaper conditional on a positive RDT result, the public sector principle might be to make the ACT free if the RDT is done. Training can be important to improve adherence to mRDT results; how can it be effectively used? Evidence shows that, over time, adherence to test results improves.
- What do we do for individuals with negative mRDTs while the global health community waits for severity fever tests and algorithms?
- How does antibiotic prescribing change when RDTs are rolled out in different settings? What is happening to mRDT-negative patients in both public and private sectors? Scale-up of mRDTs may well result in increases in antibiotic prescribing, some appropriate and some not.
- What low-hanging fruit and quick-win options might there be for RDT scale-up? Urban areas? The regulated private sector?

- How much can we rely on CHW models for RDT and ACT scale-up? To what degree are CHWs already covering malaria, pneumonia, and other febrile illnesses?
- How much can we rely on shop models for scale-up?
- When patients tested in the informal private sector are referred to a public clinic for treatment, public clinics commonly repeat the test (using another RDT or microscopy), which wastes resources. Is there a way of instituting passive oversight to monitor the private sector? Are there any current existing examples of this?
- Any shift from vertical program thinking to a more comprehensive, integrated febrile illness policy or strategy needs to be carefully thought through. The approach must draw on existing circumstances (the WHO goal and Roll Back Malaria targets for achieving universal access) and include identified value propositions for all organizations involved. For the malaria community, merging malaria into febrile illness would likely mean an opportunity to keep malaria among the top global health priorities. This is especially true in countries where malaria is close to elimination. By innovatively merging febrile illnesses, there may be less chance that malaria significantly drops as a concern (with corresponding funding decreases).

Specific actions considered by the group include the following:

- Elaborate a policy analysis looking at possible future scenarios for AMFm. An AMFm slowdown might well cause ACT prices to rise, which could in turn make it more feasible to subsidize only those ACTs that are dispensed for mRDT-positive patients.
- Develop a paper on the pros and cons of shifting thinking from vertical programs toward febrile illness and what this shift means for how we manage malaria, in terms of both treatment and prevention.
- Elaborate an evidence-informed discussion paper on the most cost-effective options for immediate mRDT scale-up.
- Value-added of mRDT scale-up needs to be better quantified, in terms of costs saved through reductions in ACT use, postponement of artemisinin resistance, and to the degree possible, health outcomes. Limited evidence exists that RDTs can decrease time to diagnosis of nonmalaria causes of fever and hence improve health outcomes. There is also limited evidence that diagnosing common causes of fever (such as malaria) very early results in much smaller outbreaks of pathogens than more severe febrile illness.
- Stimulate more fever aetiology research on a geographical approach to the local febrile illness disease burden. Develop a protocol for rapid appraisal of fever aetiology.
- Elaborate the four, five, or six most typical febrile illness scenarios, environments, and typologies (in terms of malaria prevalence, public versus private involvement, urban-rural setting, season, age, etc.) and then identify which interventions, such as private sector rebates or training and scale-up of CHWs, have the most potential in these settings.
- Conduct a febrile illness health system mapping exercise– of providers, both public and private. How do providers define themselves, as dispensing commodities or providing a service (or both)? What motivates their behavior in diagnosing and treating febrile illness? What training in fever management do they receive?

- Synthesize the literature on CHW models for RDT and ACT scale-up and CHW roles in febrile illness beyond malaria. Specifically, include schemes supported by the Global Fund and the President's Malaria Initiative.