



2012

MALARIA

Diagnostics Market Landscape

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List of Abbreviations

| | | | |
|-------------|--|--------------|--|
| ACT | artemisinin combination therapy | PCR | polymerase chain reaction |
| ALMA | African Leaders Malaria Alliance | pLDH | parasite lactate dehydrogenase |
| AMFm | Affordable Medicines Facility - malaria | PMI | President's Malaria Initiative |
| BMGF | Bill and Melinda Gates Foundation | POC | point of care |
| CDC | Centers for Disease Control and Prevention (USA) | PQR | Price and Quality Reporting (Database) |
| DFID | Department for International Development (UK) | PSCM | Partnership for Supply Chain Management |
| FDA | Food and Drug Administration (USA) | QC | Quality Control |
| FIND | Foundation for Innovative New Diagnostics | RBM | Roll Back Malaria Partnership |
| FISH | fluorescent in situ hybridization | RDT | rapid diagnostic test |
| GMAP | Global Malaria Action Plan | TDR | WHO Special Program for Research and Training in Tropical Diseases |
| GMP | Global Malaria Program | USAID | United States Agency for International Development |
| HIV | human immunodeficiency virus | VPP | voluntary pooled procurement |
| HRP | histidine-rich protein | WHO | World Health Organization |
| HWG | Harmonization Working Group | ZAAI | Zambia Access to ACTs Pilot Initiative |
| LAMP | loop-mediated isothermal amplification | | |
| LLIN | long-lasting insecticidal nets | | |
| LOI | Letter(s) of Intent | | |
| MOT | magneto-optical technology | | |
| MPAC | Malaria Policy Advisory Committee | | |
| NBI | National Bioproducts Institute | | |
| NGO | non-governmental organization | | |
| NIH | National Institutes of Health (USA) | | |
| NMCP | national malaria control program | | |
| PATH | Program for Appropriate Technology in Health | | |

MALARIA DIAGNOSTICS MARKET LANDSCAPE

Executive Summary

This Landscape Report reflects an initiative within UNITAID to describe and monitor the malaria diagnostics landscape, including disease trends, technologies, and market characteristics. This report focuses on the market for malaria diagnostic tests, and on rapid diagnostics tests (RDTs) in particular. Since markets are dynamic, this Landscape Report will be published annually. A complementary report, the UNITAID Malaria Diagnostics Technology Landscape, focusing on existing malaria diagnostic technologies and the product development pipeline, was published in December 2011.¹

This Landscape Report was developed to inform UNITAID's activities and strategies, including decision-making and assessment by the UNITAID Executive Board and Proposal Review Committee. It is also designed to serve other stakeholders interested in understanding the market for malaria RDTs.

Studying the malaria diagnostics market is a timely exercise. The use of diagnostics for malaria is rapidly expanding due to recent changes in treatment guidelines that have spurred public sector scale up of malaria RDTs. The private sector market, to date undeveloped but potentially quite large, also requires exploration. As donors and programs increase their investments in malaria diagnostics, it becomes increasingly important to understand and monitor the market.

Information in this report was collected in a variety of ways, including desk research and literature reviews, where applicable, and through expert interviews. Although the information available on the malaria RDT market is increasing, very little aggregate data is available. As a result, the discussion in this report is based largely on limited data sets supplemented by key informant interviews. The paucity of data is especially evident in the private sector.

Public Health Problem and Commodity Access Issues

3.3 billion people live at risk of malaria across 106 malaria-endemic countries. Although the risk is widespread, cases and deaths are concentrated in Africa. In 2010, over 80% of 216 million estimated cases and over 90% of 655,000 estimated deaths occurred in Africa. While the last decade has seen dramatic reductions in the burden of malaria, largely attributable to substantially increased funding for malaria control since 2000, these gains are fragile and incidence can be expected to rebound quickly if investment is not sustained.

Prompt diagnosis and effective treatment are the cornerstones of malaria case management; patients recover rapidly if diagnosed and treated early. However, if treatment is ineffective or delayed, malaria may rapidly progress to severe disease. In the past, malaria was commonly treated presumptively (i.e., based on symptoms alone). However, this led to massive overtreatment, because malaria symptoms (e.g., fever, headache, and fatigue) are non-specific. A diagnostic test is the only way to confirm that a patient is infected with malaria. In

¹ 2011 Malaria Diagnostics Technology Landscape. Geneva, UNITAID, 2011. Available at: <http://www.unitaid.eu/en/marketdynamics/malaria-diagnostics-landscape>

light of the declining burden of malaria, diagnosis of malaria using a test is increasingly critical as a growing proportion of fevers will not be caused by malaria.

There are several trends in malaria management that influence the market for diagnostic tests, these include:

- **Universal access to diagnosis and scale up of RDTs.** In response to the changing epidemiology of malaria, the World Health Organization (WHO) updated its guidelines for the treatment of malaria in 2010 to recommend testing all suspected cases of malaria before treatment.² Global partners have subsequently set ambitious targets for universal access to diagnosis in the public sector, private sector, and community. Many countries, particularly those in Africa, are currently scaling up malaria RDTs in order to increase access to diagnosis.
- **Improving acceptance of diagnostics and febrile illness management.** Experience to date suggests that many providers do not use a diagnostic test for malaria when it is available and that even when they do they may still prescribe an antimalarial if the patient tests negative for malaria. Reasons for the lack of acceptance are an area of ongoing research and best practices for accelerating uptake and acceptance of tests are urgently needed. It is likely that difficulty in managing non-malaria fever contributes to poor acceptance of malaria diagnostic tests.
- **Constrained donor funding.** Current funding commitments for global health are unclear, threatening global access targets and creating market uncertainty. The Global Fund, the largest financer of the current diagnostic test scale up, is currently undergoing a major strategic reform and is facing fundraising challenges.
- **Initiatives to improve malaria surveillance, expand access to testing through the community and private sectors, and to manage the on-going threat of drug resistance** are also important trends affecting malaria diagnosis.

Although significant public sector scale up of diagnosis has occurred in the last few years, there is still significant ground to cover in order to meet global targets of universal access to testing in the public sector, private sector, and community by 2015. Globally, the percentage of public sector cases that are confirmed with a test has risen from 67% in 2005 to 76% in 2010; however, Africa lags behind with only 45% of cases in the public sector tested. These figures do not reflect overall testing rates, as a large proportions of people—in some countries the majority—turn to the private sector for fever care. Testing is significantly lower or non-existent in the private sector.

Increasing access to malaria diagnostic tests has far-reaching public health implications. With regard to antimalarial drugs, testing allows for improved targeting of medicines to patients who have malaria, thereby reducing wastage and exposure of patients to drugs they do not need. The success of these efforts has been observed in Senegal, a country that scaled up RDTs nationally and has since seen a substantial reduction in artemisinin combination therapy (ACT) usage. However, antimalarial consumption greatly exceeds diagnostic testing in the vast majority of countries, indicating that there is still significant work to be done to scale up diagnostics and reduce overtreatment.

In addition to reducing overtreatment, testing for malaria enables better quality of care. In the case of a positive test result, providers and patients may have more confidence in the malaria diagnosis. In the case of a negative result, alternative causes of fever can be diagnosed and treated without delay.

In addition to the general need to increase access to malaria diagnostic tests, there are several population groups that do not have adequate access to diagnosis due to the lack of appropriate technologies, including pregnant women, populations living in low transmission/elimination settings, and populations in *P. vivax*-endemic areas.

Malaria Diagnostics Technology Landscape

Currently, two technologies are used for routine malaria diagnosis: microscopy and malaria RDTs. Microscopy has been the standard for malaria diagnosis since it was first introduced 100 years ago. In expert hands and ideal

² Guidelines for the treatment of malaria, second edition. Geneva, World Health Organization, 2010. (http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf, Accessed September 2012).

settings it performs well. However, a general lack of sustained investment in microscopy services means that the quality of results varies greatly; under typical field conditions the performance of microscopy is compromised.

Malaria RDTs are point of care, disposable tests that detect antigens produced by the malaria parasite. They are simple to perform and require no laboratory infrastructure. While the quality of products on the market varies, recent evaluations have shown that there are many commercially available RDTs that perform as well as, if not better than, operational microscopy. RDTs may detect one or multiple species of malaria (the latter being “combination tests”). Most suppliers offer several different types of RDTs, and products from a single manufacturer tend to resemble each other. Among different manufacturers, however, there are differences in the format of the RDT, labeling, components included in the test kit, and in the test procedures. One major drawback of malaria RDTs is the lack of methods and technologies for checking the quality of tests.

The malaria diagnostic pipeline includes a number of different technical approaches to detecting malaria. The pipeline includes improvements to existing technologies (e.g., higher performing RDTs, urine based RDTs, and simplified versions of complex reference tests), as well as platforms that take advantage of novel approaches to malaria diagnosis (e.g., spectroscopy and hemozoin detection). While some of the technologies are intended for routine diagnosis, others are designed to be field-applicable reference methods.

Given the acute nature of malaria disease, malaria tests should be both accurate and rapid to be useful in routine malaria diagnosis. Other priorities for malaria diagnostic test R&D include affordability and the ability to widely deploy the test (i.e., tests must be portable, able to withstand high heat and humidity, and simple to perform).

Malaria Diagnostics Market Landscape

The malaria RDT market has expanded rapidly in the past few years, from 45 million tests sold in 2008 to an estimated 120 million sold in 2011. Demand for malaria diagnostics is driven largely by the scale up of malaria diagnostic testing in the public sector, with Africa being the largest market for malaria RDTs. Assuming funding availability, demand growth will continue for the near future as countries scale up diagnosis and place increasingly larger orders for RDTs.

Funding for malaria diagnostics has been provided primarily by the Global Fund and the President’s Malaria Initiative (PMI), and the market’s growth in recent years has been enabled by the relative ease with which funding has been made available. The funding uncertainty associated with the Global Fund, the largest donor for malaria diagnostic testing, comes at a crucial time for the diagnostic test market, as many countries are in the process of dramatically scaling up malaria testing. However, little formal analysis of the effect that funding reductions could have on the market has been undertaken to date.

In the public sector, the main drivers of product selection are price, products’ ability to meet minimum performance thresholds, ease of use, and lead-time. Competitive procurement practices, often promoted by donors, may lead to frequent switching of RDTs, although this is often in contrast with the programmatic desire to stay with the same RDT due to the costs and effort associated with switching RDTs (e.g., retraining of health care workers and publication of new job aids).

Although there is increasing interest at the policymaker level in leveraging private sector channels in order to expand access to diagnosis, there is a relative dearth of information on private sector markets for malaria diagnostics. The optimal model for expanding testing through private sector channels is not clear. There are several operational research projects underway to better understand this market and the potential for an RDT subsidy to increase access to testing and appropriate treatment of fever. For the most part, results have not been published, but the projects are demonstrating the operational feasibility of performing RDTs in the private sector and also highlighting the complexity of this market.

The first commercial malaria RDT was marketed in the mid-1990’s, and now over 40 suppliers offer over 200 products. Although many companies market malaria RDTs, the public sector is increasingly consolidating around a handful of companies. Among the market leaders in 2011 were AccessBio (USA), ITC (South Africa), Orchid Biomedical (India), Premier Medical Corporation (USA), and Standard Diagnostics/Alere (Korea). With one exception, companies supplying this market are small diagnostics companies.

The malaria RDT market attracts many players due to several factors: it is a high growth market, it is relatively easy to develop a product and bring it to market, there is little intellectual property enforcement, and regulatory requirements are low in comparison to other diagnostic tests. However, recent trends contribute to declining attractiveness of this market, including declining prices, short lead times, limited ability to forecast demand for specific products, and the barrier to entry created by new quality initiatives.

With respect to prices, malaria RDTs are relatively inexpensive diagnostic tests, and prices have been declining. In 2010 the weighted average public sector price for *P. falciparum* RDTs was \$.51 and for combination tests it was \$.69. However, it is difficult to establish a reference price for malaria RDTs, as wide variation in pricing has been noted recently, with several tenders being awarded at prices under \$.30 per test. Downward pressure on RDT prices is expected to continue in the coming years, as manufacturers continue to bid strategically in attempts to penetrate new markets, and as malaria program budgets face funding constraints.

Another factor influencing this market is the growing order sizes and the short lead times associated with many orders. While leading manufacturers have generally been responsive and no interruptions in supply have been noted, there are costs associated with these practices as well as potential for the quality of tests to be compromised. These practices also prevent smaller suppliers from competing in the public sector market.

With respect to quality, although the malaria RDT market developed in the absence of any regulatory oversight or quality standards, there are some quality initiatives for malaria RDTs today. Currently the most influential is the WHO Product Testing program, which directly compares the performance of RDTs submitted by manufacturers. Today, nearly all public sector procurement takes the WHO testing results into account and market share data, though limited, indicate share has been shifting significantly in recent years, in particular towards products that performed well in the WHO Product Testing program.

In summary, decreasing prices for RDTs, short lead times associated with many orders, and potential for frequent switching between products (which limits manufacturers' ability to plan production and manage inventory) are creating a market where competition is based on economies of scale and thin margins. There is concern that low prices observed recently for RDTs may not be sustainable, and that the current nature of competition may lead to deterioration in the quality of products and/or the withdrawal of some companies from the market. The incentive to reduce costs at the manufacturing level is particularly concerning in a market that has limited post-market surveillance and whose track record for quality control is unproven.

Market Shortcomings and Their Reasons

The table below summarizes the market shortcomings in the malaria diagnostics market and reasons for these shortcomings.

| Market Shortcoming | Description of Market Shortcoming | Reasons for Market Shortcoming |
|--------------------|---|--|
| Quality | Practical methods and technologies to enable quality control (QC) testing of RDTs are either non-existent or inadequate where they do exist | <ul style="list-style-type: none"> • Low prioritization of QC by RDT buyers and policy makers. • Little incentive for private sector investment in QC technologies. • Current programs for malaria RDT QC are expensive and complex, due primarily to reliance on human-derived specimens, coupled with a multiple challenges delaying development of suitable replacements for human derived specimens (i.e., recombinant antigens). |
| | Information on the quality of malaria RDTs is limited | <ul style="list-style-type: none"> • Low prioritization of QC by RDT buyers and policy makers. • No formal regulatory or post-market surveillance processes in resource-limited countries that consume RDTs. Absence of incentive to undergo alternative stringent regulatory process (e.g., US FDA). • Little downstream quality control of tests due to the lack of suitable technologies for QC (as above). • At the manufacturing level, little is known about the quality management systems for malaria RDTs, however there is reason for concern. In theory, there is little incentive to invest in robust quality management systems at manufacturing level. |

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| Delivery | Insufficient uptake and concern about potential slowing of scale up in public sector | <ul style="list-style-type: none"> • Implementation weaknesses, including weak supply chain management, inadequate training of health care workers, and lack of supervision and quality control. • Insufficient investment in behavior change communication to increase demand for testing and to improve acceptance of RDTs. • Potential for global funding cuts that limit diagnostic test budgets and further scale up of diagnostics. |
| | There is little demand for RDTs in the private sector | <ul style="list-style-type: none"> • Lack of awareness among customers and retailers of RDTs and benefits of diagnosis. • High prices of RDTs. • Limited incentives for private sector suppliers to sell RDTs. • Customers may have limited incentives to purchase RDTs. • Local regulations may prohibit RDTs being performed in private sector. |
| | Limited knowledge of malaria diagnostics markets | <ul style="list-style-type: none"> • Lack of investment in surveillance systems. Need to adapt case reporting systems to reflect change in malaria treatment guidelines (i.e., capture data on diagnostic testing and subsequent treatment.) • Few systems for aggregating information on RDT purchasing; weakness in reporting where it is available. • Large number of products (>200) on the market from many companies makes monitoring supply side difficult. • Little dialogue between suppliers, policy makers, and purchasers. • Complexity of understanding the private sector markets for malaria commodities, limited research undertaken to date. |
| | Inadequate malaria surveillance | <ul style="list-style-type: none"> • No clear guidance until recent WHO surveillance guidelines released (April 2012). • Lack of diagnostic tests led to low quality case reporting data. • Low priority among policy makers, donors, and programs. • Need for coordination across different departments in the public health system. • Weak implementation systems. • Little use of digital/IT solutions. |
| Delivery (ctd.) | Uncertainty about consistent, uninterrupted supply of quality RDTs in light of rapid increases in demand and current market conditions. | <ul style="list-style-type: none"> • Demand increases, in particular increasingly large orders with short lead times. • Frequent switching of RDTs, leading to insufficient predictability of demand for individual products at the manufacturing level. • Uncertainty around supplier capacity, especially with regard to (i) scale up of manufacturing quality systems and (ii) the effects cost reduction measures taken in response to price competition have on quality. • Little incentive to maintain quality due to market conditions (described above) and limited post-market surveillance and downstream monitoring of RDT quality. |
| Availability | No tests for pregnant women, low transmission/elimination settings, and <i>P. vivax</i> | <ul style="list-style-type: none"> • Limited philanthropic and private funding for malaria diagnostics R&D. • Lack of target product profiles, limited work to better define the needs or market for such products. • Malaria diagnostics are complex and costly to develop, in particular to evaluate performance. • Uncertainty and risk at the investment level caused by lack of clarity around regulatory pathway and quality standards for malaria diagnostics, as well as the adoption process for global health products. |
| Acceptability/Adaptability | Low acceptance of RDTs by health workers and patients | <ul style="list-style-type: none"> • Low awareness of declines in malaria prevalence and the benefits of diagnosis. • Difficulty in changing long-standing clinical practices around fever and malaria. • Mistrust of RDTs. • Lack of alternative diagnosis for non-malaria fever due to limited training lack of best practices. • Low availability of commodities for non-malaria fever. |

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|----------------------|---|---|
| | RDTs could be more consumer friendly to reduce training needs and ease difficulty in switching from one RDT to another. RDT kits may not be well adapted for retail channel sales. RDT heat stability is a concern. | <ul style="list-style-type: none"> • Specifications for improving ease of use and interchangeability have not been developed/ communicated. No dialogue between buyers and policy makers and suppliers. • Optimal specifications for test kits sold through retail channels have not been developed. • Little formal research into whether RDT heat stability is an issue. |
| Affordability | RDT prices in the private sector are likely to be unaffordable | <ul style="list-style-type: none"> • Add on costs (mark-ups, taxes, transport etc.) throughout the distribution chain • Patients who test positive or negative must also be able to afford the appropriate treatment (ACT or alternative). |

Potential Market Interventions and Opportunities

Examples of potential market interventions to improve access to malaria diagnostics are provided below. This list is illustrative and not comprehensive.

Examples of potential opportunities and interventions include:

- With regard to quality, **interventions would aim to increase the availability of information on the quality of malaria diagnostics (including development of technologies to simplify QC testing), reinforce competition around quality, ensure consistency during manufacturer scale up, and assure the integrity of tests in the field.** Specifically, there is a need to develop quality control technologies for use at all levels of the supply chain from manufacturer to point of service. While the Foundation for Innovative New Diagnostics (FIND) has been leading efforts to develop QC technologies, no products are available yet. A second quality initiative would involve supporting the WHO Product and Lot Testing program and their transition to a less costly and more sustainable business model. A project recently funded by the Bill and Melinda Gates Foundation (BMGF) and UNITAID aims to address these issues in large part by developing an alternative to the costly human derived specimens currently used. Lastly, work to develop stronger incentives for upstream quality are needed; this might include site visits, stepped-up lot testing, or changes to the WHO Product Testing program.
- **Interventions to stabilize prices of RDTs and improve predictability of demand** would encourage buyers to focus on quality and product characteristics, as opposed to price alone, and would contribute to ensuring the long-term health of the malaria RDT market.
- **Funding for RDTs and interventions to support implementation** (e.g., health worker training, supervision) may be needed, especially in light of the potential reductions in Global Fund resources for malaria diagnostic test scale up. Likewise, technical assistance and programmatic support for implementation challenges are needed.
- **Initiatives to increase demand for testing and to change the approach to fever management** are needed in order to ensure that RDTs are having their intended effect on health outcomes.
- **An intervention to develop the private sector market for malaria RDTs could expand access to testing and improve targeting of ACTs in the private sector.** Given the current uncertainty about how best to structure a program in this area, interventions should be structured with frequent evaluations and flexibility to incorporate new learning. One such project has recently been approved for funding by UNITAID.
- **Investment in new product development** is needed, in particular in products that meet the needs of currently underserved populations, including pregnant women, populations living in low transmission settings, and populations affected by *P. vivax*.
- **Development of mechanisms to strengthen market knowledge**, including strengthening the data on the availability of testing and use of results, improving the completeness of data on RDT procurement, and efforts to collect and synthesize information on the private sector markets.

Conclusions

In contrast to the past few decades, today's malaria diagnostics market landscape is very dynamic. While there has been significant progress in terms of policy and the scale up of diagnosis, this report illustrates several gaps and opportunities to accelerate access to testing in meaningful ways. Quality is a major issue in the RDT market, which developed in the absence of standards and regulation. In light of today's intense competition on price and volatility, quality is a challenge that should be addressed urgently and holistically, both to improve upstream incentives for quality and downstream implementation of quality assurance.

Given the relative lack of information on the private sector, interventions in this area need to be planned with care and flexibility as there is still much to learn about the private sector. Furthermore, private sector interventions may not be the most effective option for increasing access to testing in every setting. For example, in countries with strong public health systems, expanding the reach of the public sector and its use of diagnostics may be a more effective means of increasing testing rates than developing private sector markets.

In the coming years, funding is likely to be a major challenge for malaria programs; the continued scale up of diagnosis in the public sector and beyond is contingent on adequate resources. As the scale up of diagnosis allows for better quality data upon which to base decisions about resource allocation, it would make sense to invest in initiatives that focus on improving case reporting and surveillance. Lastly, the scale up of diagnosis presents an important and unique opportunity to learn about and improve the body of knowledge on the malaria diagnostics market.

Introduction

The *Malaria Diagnostics Market Landscape* has been prepared as part of a broad and on-going effort to understand the market landscape for malaria. At the 30-31 March 2011 UNITAID Board retreat, the Secretariat presented a framework for strategic prioritization of UNITAID investments to maximize UNITAID's public health and market impact. The Board approved the framework, which included among other things preparation of landscape analyses to map current and future trends in disease burden, product development and market evolution for preventatives, diagnostics and medicines used in HIV, tuberculosis and malaria.

The Landscape Reports inform UNITAID's activities, such as calls for Letters of Intent (LOI's) and screening of LOIs and proposals by the Secretariat. They are expected to be critical inputs to the UNITAID strategy, identification of priority niche investments by the Advisory Group on Funding Priorities, and proposal review by the UNITAID proposal review committee. They are also expected to be useful to the broader global health community, and as such are made available on the UNITAID website.

Since markets are dynamic, this Landscape Report will be published annually and will be followed by a semi-annual update. UNITAID's Malaria Diagnostics Technology Landscape³, which focuses on existing technologies and the product development pipeline, complements this report and was recently published.

The paper is structured as follows:

- The Public Health Problem and Commodity Access Issues section provides an overview of malaria disease and case management, the role of diagnostic tests in malaria, as well as disease and programmatic trends in malaria management. This section also summarizes access issues and concerns for malaria diagnostics in resource-limited settings.
- The Malaria Diagnostics Technology Landscape section provides a summary of the malaria diagnostics technology landscape, with particular emphasis on RDTs.
- The Malaria Diagnostics Market Landscape describes the market landscape, including an overview of supply and demand as well as a discussion on competition and the future outlook for the market. The public sector market is considered first, followed by the private sector. As with the section above there is particular emphasis on RDTs.
- The Market Shortcomings section identifies market shortcomings using UNITAID's framework for market analysis and provides possible reasons for why these shortcomings exist.
- The Potential Market Interventions and Opportunities section provides an initial view on potential market opportunities for increasing access to malaria diagnostics.
- The final section provides a conclusion and describes some of the limitations of the paper.
- The appendix, Global Health Donor Landscape, describes the major donors involved in the malaria diagnostics market and their roles.

³ 2011 Malaria Diagnostics Technology Landscape. Geneva, UNITAID, 2011. Available at: <http://www.unitaid.eu/en/marketdynamics/malaria-diagnostics-landscape>

Methodology

The Malaria Diagnostics Market Landscape is compiled by Jennifer Daily with support from UNITAID. This report is based upon:

- Desk review of literature and published and unpublished reports
- Review of existing market data and reports
- Identification of existing sources of aggregate data on the market, and analysis of data when it was available
- Key informant and expert interviews, including representatives from industry, programs, donors, and academia.

Research for this report was conducted from February-April 2012, and information is up to date as of April 2012.

Data Limitations

Although the information available on malaria diagnostic test markets is increasing, there is currently limited reliable aggregate data. In preparing this report, several potential sources of market data were identified and investigated, including malaria RDT manufacturer reporting on RDTs sold, donor funding for and reporting of RDT procurement, and procurement data from countries. Overall, work to aggregate and analyze data from any of these sources has been relatively limited, especially when compared to pharmaceutical markets. In 2011, FIND and WHO both surveyed manufacturers of RDTs in order to estimate the total market size and to get a better appreciation for the impact of the WHO's malaria RDT quality programs on the market. At present, summary information is available from these surveys (2011 World Malaria Report). Other information on RDT markets comes from donor reporting of RDT procurement from major donors including PMI and the Global Fund. In 2009, the Global Fund began requiring that malaria RDTs be included in its Price and Quality Reporting (PQR) database.⁴ For a number of reasons, the current PQR dataset for malaria RDTs is partial, although in future years completeness is expected to improve.

On the demand side, while several groups have attempted to compile data on RDT procurement from countries, this has proven to be challenging. The African Leaders Malaria Alliance (ALMA) and the Roll Back Malaria Partnership (RBM) Harmonization Working Group (HWG) maintain estimates of RDT needs and financing in the African public sector based on analysis of needs and gaps performed by countries. In light of the potential effect that RDT stock outs could have on ACT consumption, in the coming year WHO and partners are planning to expand their monitoring of ACT stock levels at the national level to include RDTs. No forecasts of global RDT demand exist at the moment.

As a result of these limitations, the discussion of the current state of the market for malaria diagnostics in this report is based largely on limited data, supplemented by conversations with various stakeholders, including leading RDT manufacturers. Due to the limited data sets available, validation and triangulation is impossible. The paucity of data is especially evident in the private sector.

⁴ The Price Quality Reporting (PQR) System is a web-based system for tracking the purchases of key pharmaceutical and health products using Global Fund resources. The PQR in its current form was established in early 2009 and transactional data is entered by Global Fund Principal Recipients upon receipt of goods. Local Fund Agents are responsible for verifying the data. The database is publicly available and updated regularly. <http://www.theglobalfund.org/en/procurement/pqr>. The completeness of the dataset for malaria diagnostics has not been assessed formally.

Public Health Problem and Commodity Access Issues

In 2010, 3.3 billion people were at risk of contracting malaria across 106 malaria-endemic countries, with South East Asia, Africa, and the Western Pacific regions having the greatest number of people at risk. Although the risk is widespread, the number of cases and deaths are concentrated in Africa, where the majority of cases are caused by *P. falciparum*, the deadliest species of malaria. In 2010, over 80% of 216 million estimated cases and over 90% of 655,000 estimated deaths occurred in Africa.⁵

Although *P. falciparum* causes the majority of deaths from malaria and receives significant attention, *P. vivax* represents a considerable burden as it is the most widely distributed malaria species. An estimated 2.85 billion people live at risk of *P. vivax* infection, the majority in the tropical belt of Asia.⁶

Malaria disproportionately affects certain vulnerable populations, including young children, pregnant women, and the poor living in remote areas. African children account for the vast majority of deaths from malaria. Malaria in pregnancy has adverse consequences for the mother and the fetus, and may be responsible for as many as 10,000 maternal deaths and 75,000-200,000 infant deaths every year.⁷ Although malaria is preventable and treatable, rural poor populations tend to have limited access to insecticidal nets and appropriate diagnosis and treatment, and as a result they often suffer the most.

Globally, the last decade has seen a dramatic reduction in the burden of malaria, with many countries reducing their burden by more than 50%. This is largely attributable to substantially increased global funding for malaria control since 2000, which has enabled scale up of preventative measures such as long-lasting insecticidal nets (LLINs) and treatment with effective antimalarial medicines (artemisinin-based combination therapy, or ACT). With the recent progress in control, elimination of malaria—defined as the interruption of local transmission—is increasingly possible in areas where transmission has been reduced. Despite this progress, malaria incidence has recently rebounded in several African countries, illustrating the fragility of gains and the need for sustained investment.

Disease and Case Management

Prompt diagnosis and effective treatment are the cornerstones of malaria case management; if diagnosed and treated at an early stage, patients recover rapidly. However, if ineffective treatment is given or treatment is delayed, particularly in *P. falciparum* malaria, individuals may rapidly progress to severe malaria, which requires hospitalization and may be fatal if left untreated. The symptoms of *P. vivax* are similar to those of other malaras, however, *P. vivax* can relapse months and years after treatment because it remains dormant in the liver for extended periods.

The nature and degree of illness from malaria will vary by an individual's background level of immunity, which is determined by the extent of malaria transmission where they live. People living in stable or high transmission areas are infected frequently, however they generally develop some immunity (i.e., they may have parasites circulating in their blood but they will not have symptoms of malaria) by late childhood. Regions of stable and high transmission are largely found in Sub Saharan Africa. In areas of unstable transmission (Asia and Latin America, and increasingly parts of Africa), populations are less likely to develop immunity and people of all ages are at risk of suffering from severe disease if not promptly treated. Epidemics are also a major risk in these areas. While the correlation between illness, immunity and parasite density (the number of parasites in a drop of blood) is not perfect, in general people with low immunity (young children and people living in areas of unstable transmission) will become sick at low parasite densities. Adults living in higher transmission settings will have developed immunity and, while they may have many parasites circulating in their blood, they may not have symptoms of malaria (i.e., asymptomatic infections).

The symptoms of malaria (fever, headache, and fatigue) are non-specific and mimic those of other illnesses, making the diagnosis on the basis of clinical signs and symptoms difficult. Although diagnostic tests are recommended to confirm malaria before treatment, malaria diagnostic tests are not readily available in many

5 World Malaria Report 2011. Geneva, World Health Organization, 2011. Note that accurate estimates of malaria incidence are difficult to make and that these figures have a wide uncertainty interval.

6 Guerra CA et al. The international limits and population at risk of Plasmodium vivax transmission in 2009. *PLoS Neglected Tropical Diseases*, 3 August 2010, 4(8):e774.

7 Kattenberg et al. Systematic review and meta-analysis: rapid diagnostic tests versus placental histology, microscopy, and PCR for malaria in pregnant women. *Malaria Journal*, 2011 Oct 28;10:321.

places where patients seek care. As a result, in malaria-endemic regions, malaria has historically been clinically suspected on the basis of fever (i.e., clinical diagnosis or presumptive treatment) and has been massively over-treated, resulting in overuse and misuse of antimalarial medicines for non-malaria illness.

As the burden of malaria declines, relying on clinical diagnosis is no longer appropriate and diagnostic tests become increasingly critical as many of the fevers are no longer caused by malaria. In response to the changing epidemiology of malaria, the WHO updated its policy on malaria diagnosis in early 2010, recommending that all cases of suspected malaria be confirmed with a diagnostic test before treatment.

Although the most common use of malaria tests is for patient care, the role of diagnostics in surveillance depends on the local epidemiology, as well as available systems and technologies. In most control settings, surveillance focuses on the clinical burden of malaria—the number of sick people and deaths. This is accomplished by health facility case reporting, and by periodic surveys to determine prevalence using diagnostic tests. Often, reporting by health facilities has been based on *suspected cases* (i.e., cases not confirmed with a diagnostic test), leading to poor estimations of disease burden. The current scale up of malaria diagnostic tests presents an opportunity to increase the accuracy of data as only *confirmed cases* of malaria are reported.

In general, as the prevalence of malaria declines and programs shift from control to elimination strategies, additional surveillance activities aimed at identifying all infections and halting onward transmission of malaria will begin. These may include closer monitoring of health facility case reporting to identify potential outbreaks, identification of foci of transmission (i.e., areas with higher transmission in need of targeted interventions), and screening populations for asymptomatic infections (i.e., detecting infection regardless of whether the individual has symptoms), because even asymptomatic infection can cause onward transmission.

Trends in Malaria Management

There are several trends in malaria management, both clinical and programmatic, that influence the market for diagnostic tests. These include:

Universal Access to Diagnosis and Scale up of Malaria RDTs

The downward trend in malaria cases seen over the past decade means that a large proportion of fevers, previously attributed to malaria, are not actually caused by malaria. At the same time, the availability of malaria RDTs, which are portable and simple to use, makes widespread access to malaria testing possible for the first time. This has in turn led to a renewed focus on malaria diagnostic testing, an area that has generally lagged behind treatment and prevention efforts. Following the 2010 WHO guidelines recommending that all suspected cases of malaria be diagnosed before treatment, RBM set specific targets in June 2011 for universal access to malaria diagnosis in the public and private sectors, including case management on the community level.⁸

The scale up of diagnosis is underway, driven in large part by increasing use of malaria RDTs. Most malaria-endemic countries have adopted RDTs and incorporated them, albeit at varying rates, into the public health system.

Improving Acceptance of Diagnostics and Febrile Illness Management

Although the scale up of malaria diagnosis should reduce ACT treatment needs, these benefits will not be realized until established clinical practices around fever management are changed. In truth, the policy of universal diagnosis represents a major paradigm shift for health workers who have for years been instructed to assume that most fevers were caused by malaria and to treat presumptively. Experience to date with the scale up of diagnosis suggests that many providers do not use a diagnostic test when it is available and that, even when they do, they may still prescribe an anti-malarial when the test indicates that the patient does not have malaria.

⁸ The RBM targets are: 1) Achieve universal access to case management in the public sector. By 2013, 100% of suspected cases receive a malaria diagnostic test and 100% of confirmed cases receive treatment with appropriate antimalarial drugs. 2) Achieve universal access to case management, or appropriate referral, in the private sector: By end of 2015, 100% of suspected cases receive a malaria diagnostic test and 100% of confirmed cases receive treatment with appropriate and effective antimalarial drugs. 3) Achieve universal access to community case management (CCM) of malaria: By end 2015, in countries where CCM of malaria is an appropriate strategy, 100% of fever (suspected) cases receive a malaria diagnostic test and 100% of confirmed uncomplicated cases receive treatment with appropriate and effective antimalarial drugs, and 100% of suspected and confirmed severe cases receive appropriate referral. 4) Accelerate the development of surveillance systems: By end of 2015, all districts are capable of reporting monthly numbers of suspected malaria cases, number of cases from all public health facilities, or a consistent sample of them. (Source: *Refined/Updated GMAP Objectives, Targets, Milestones and Priorities beyond 2011*. Geneva, Roll Back Malaria, 2011. Available at: <http://www.rbm.who.int/gmap/gmap2011update.pdf>)

As such, there is still significant work to be done to understand behavior with respect to malaria diagnosis and to document best practices for improving test acceptance.

It is likely that difficulty in managing non-malaria fever contributes to the poor acceptance of malaria diagnostic tests. The declining burden of malaria in many areas means that the vast majority of patients who are tested for malaria will not have malaria. For health workers, a negative malaria test result means that an alternative diagnosis should be sought, which can be challenging given that many health workers are unaccustomed to performing differential diagnosis of fever. There are few diagnostic tests to assist with non-malaria fever diagnosis, and patient expectations may influence treatment decisions.

The impact of RDT use on antibiotic use is also a concern. Antibiotic prescribing has risen in many settings when RDTs are rolled out, suggesting misuse of antibiotics. Overuse of antibiotics has several negative consequences, including wasted resources, increased potential for development of resistance, increased chances of adverse events, and reduced confidence in health services when a patient's illness does not resolve after taking the antibiotic.

At the policy level, therefore, there is an increasing understanding that febrile illness needs to be addressed holistically and in tandem with the scale up of malaria diagnostic tests in order to take full advantage of the scale up of malaria diagnostics and to ensure rational use of both antimalarials and antibiotics.

Improving Malaria Surveillance

Currently there is wide variation in the estimated burden of malaria and it is difficult to accurately detect changes in malaria epidemiology at both the global and local levels. As noted previously, there is an opportunity to vastly improve the quality of data on malaria through expanded use of diagnostic testing. In April 2012, the WHO issued new guidance on malaria surveillance and launched the “3T: Test. Treat. Track.” initiative, emphasizing the need to test every suspected case, to treat every confirmed case, and to report every case. In the coming years as the new WHO surveillance guidelines are implemented and data quality improves, more efficient utilization of malaria resources should be possible as intervention monitoring is strengthened and resources targeted to areas in greatest need.

In lower-transmission settings, surveillance activities are already expanding the role of malaria diagnostic tests and creating a need for new, more sensitive diagnostic tests that can detect asymptomatic infections.

Community and Private Sector Use of RDTs

Because so many people seek care outside of the public sector, universal access to diagnosis will not be achieved unless testing is expanded to the community level and to the private sector. At the community level, models exist for effective community case management using RDTs, and some countries have implemented these at national scale. In other countries, community programs are developing. In the coming years, it is likely that these programs will be expanded to reach more people.

The use of the private sector as a means to increase access to effective antimalarial treatment is being piloted on a large scale through the Affordable Medicines Facility—Malaria (AMFm), an ACT subsidy program hosted by the Global Fund and active in eight countries.⁹ Likewise, there is also increasing discussion about use of private sector channels to increase access to diagnostic testing. A handful of operational research projects on incorporating RDTs into the private sector are underway and UNITAID has recently committed up to \$34 million to a project to create a private sector market for malaria RDTs in five malaria-endemic countries.

Threat of Drug Resistance

A major threat to sustaining the gains in malaria control is the emergence of malaria parasites that are resistant to medicines commonly used to treat malaria. Increasing access to diagnostics and targeting ACTs to confirmed cases limits opportunities for development of resistance to both artemisinins and the longer acting partner drugs, which are increasingly a concern.

⁹ AMFm is a global health financing mechanism aimed at increasing access to effective malaria treatments by reducing the retail price of ACTs, increasing ACT availability and use, and crowding out ineffective treatments that contribute to drug resistance. The program operates by 1) negotiating price reductions with manufacturers of ACTs and 2) subsidizing, through a co-payment at the manufacturing level, the cost of ACTs to buyers (public and private sector). The reduced prices paid by ACT buyers in turn allows for: free/reduced cost ACTs in the public sector and ACT pricing that is comparable to prices of less effective drugs in the private sector.

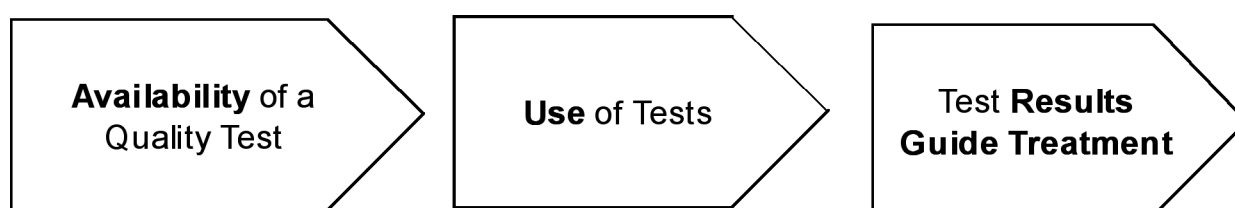
Commodity Access Issues

Although progress has been made in scaling up diagnosis, especially in the public sector, there are significant gaps in access to malaria diagnostic testing.

Access to Malaria Diagnosis Continuum

In considering data on access to testing across the various sectors and geographies, it is important to point out that access to testing encompasses more than availability of a test (Figure 1). In addition to having a high quality test at the point of service, (i) the test must be used and (ii) test results must guide treatment. As noted previously, evidence from RDT scale up to date suggests that even when tests are available, uptake and use of results may be problematic.

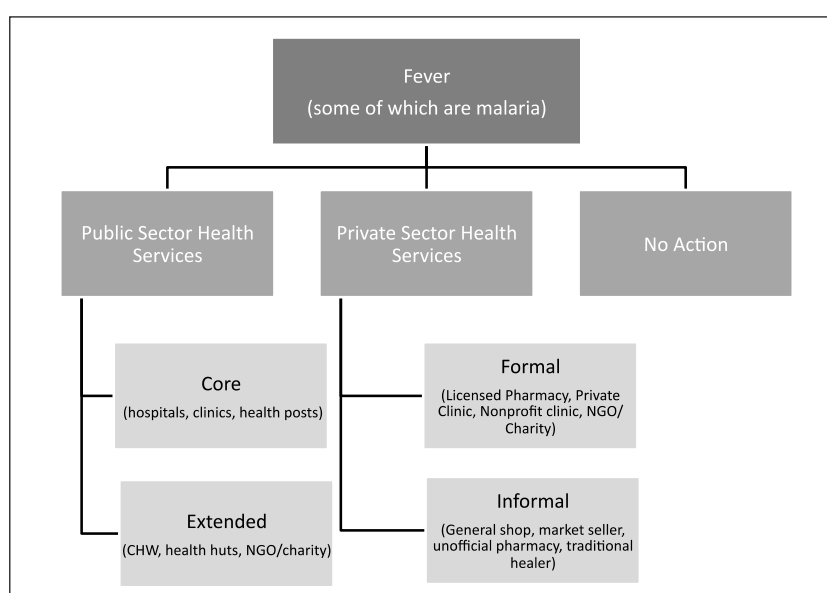
Figure 1: Access to Malaria Diagnosis Continuum



Care Pathways for Fever

Understanding how people seek care for fever is essential for appreciating the gaps in access to malaria testing. Globally, there is tremendous variety in how individuals respond to episodes of fever and symptoms of malaria. As shown in Figure 2, individuals who seek some form of care when they experience symptoms of malaria may do so through public health services or the private sector. The private sector pathway is highly varied in terms of the products, services and skills available, and includes informal channels such as market stalls, kiosks, and traditional healers. In addition, there are individuals who take no action when they experience malaria-like symptoms.

Figure 2: Care Pathways for Fever



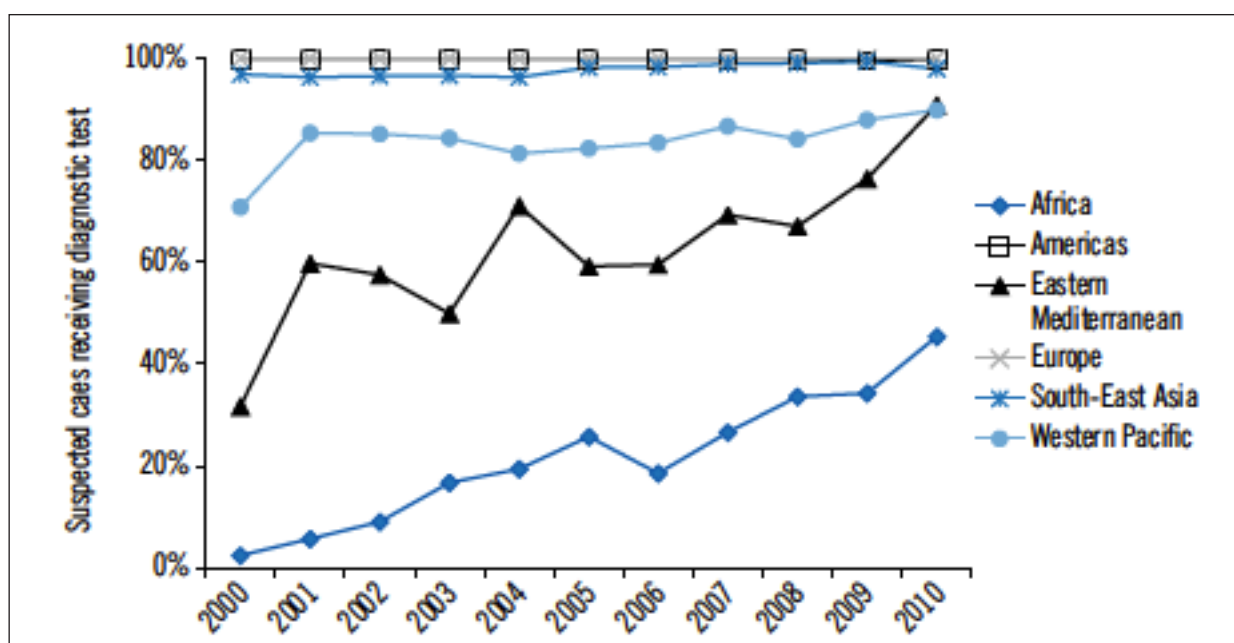
Source: Adapted from *Malaria No More*

The 2008 World Malaria Report estimated that 40% of malaria patients globally seek treatment in the private sector. However, this figure does not reflect the complexity of treatment-seeking behavior, or its variance from one setting to another. Research suggests that the actual proportion of patients seeking care in the private sector varies tremendously by country, as do the types of facilities and providers that are available.¹⁰

Uptake of Diagnostic Tests

WHO data collected from national malaria control programs (NMCPs) shows a steadily increasing number of suspected malaria cases *in the public sector* receive a parasitological test (Figure 3). Globally the percentage of cases reported by the public sector that received a test has increased from 67% in 2005 to 76% in 2010, with Africa lagging significantly behind other regions, where only 45% of public sector cases were tested in 2010.

Figure 3: Proportion of Suspected Malaria Cases Attending Public Health Facilities that Receive a Diagnostic Test



Source: World Malaria Report 2011

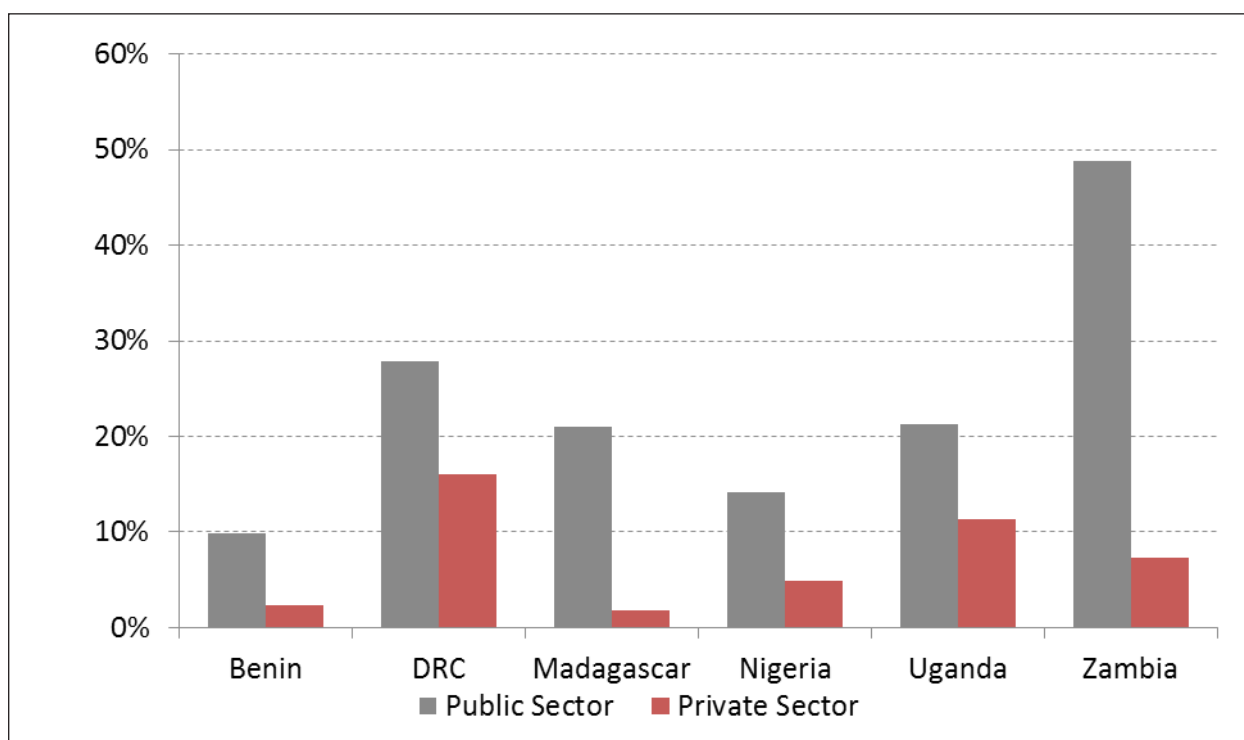
ACT Watch¹¹ data (Figure 4) collected through nationally representative household surveys in six African countries (2008-2010) show low rates of testing in both the public and private sectors.

Both the 2011 World Malaria Report and ACT Watch suggest that private sector testing is minimal and that community level testing still represents a very small proportion of total testing, although community case management is a recommended strategy for effectively increasing access to malaria diagnosis and treatment.

¹⁰ World Malaria Report 2011. Geneva, World Health Organization, 2011.

¹¹ ACT Watch is a five year research project launched in 2008 to monitor anti-malarial supply and demand in seven malaria-endemic countries in Africa and Asia. The project combines supply chain mapping, surveys of households and surveys of outlets.

Figure 4: Percentage of Children Under Five with Fever in Past Two Weeks that Received a Blood Test for Malaria



Source: ACTWatch

Appropriate Management of Fever

In order for RDTs to have an impact on health outcomes, test results must influence patient management and treatment. To date, data on the impact that RDTs are having on malaria and fever management more broadly is limited. While there have been several small studies, there is less evidence for larger-scale efforts. This is in part due to inadequate systems for capturing data on management of patients, and also due to difficulties in measuring the public health impact of improved management of fever. The most frequently cited evidence of the impact of RDTs comes from Senegal, a country that scaled RDTs nationally, primarily through a community health worker program, and as a result has seen improvements in targeting treatment to those who need it, and a resulting substantial reduction in ACT usage.¹² In other countries the results of RDT scale up on ACT consumption are not yet available and/or have been more mixed.

One means of assessing diagnostics scale up is to compare the quantities of ACTs consumed to tests performed. In the African Region the number of ACTs distributed by NMCPs was more than twice the number of tests (RDTs + microscopy) carried out in 2010, suggesting that many patients receive ACTs without diagnostic testing.¹³ Similarly, in 2008, the Global Malaria Action Plan (GMAP)¹⁴ analyzed the optimal ratio of spending on diagnosis to treatment, and suggested that diagnosis spending should be twice that of treatment (Figure 5, far right column). However, as Figure 5 shows, many countries significantly under invest in diagnosis compared to treatment, suggesting that there is room for improving diagnostic test use and acceptance.¹⁵

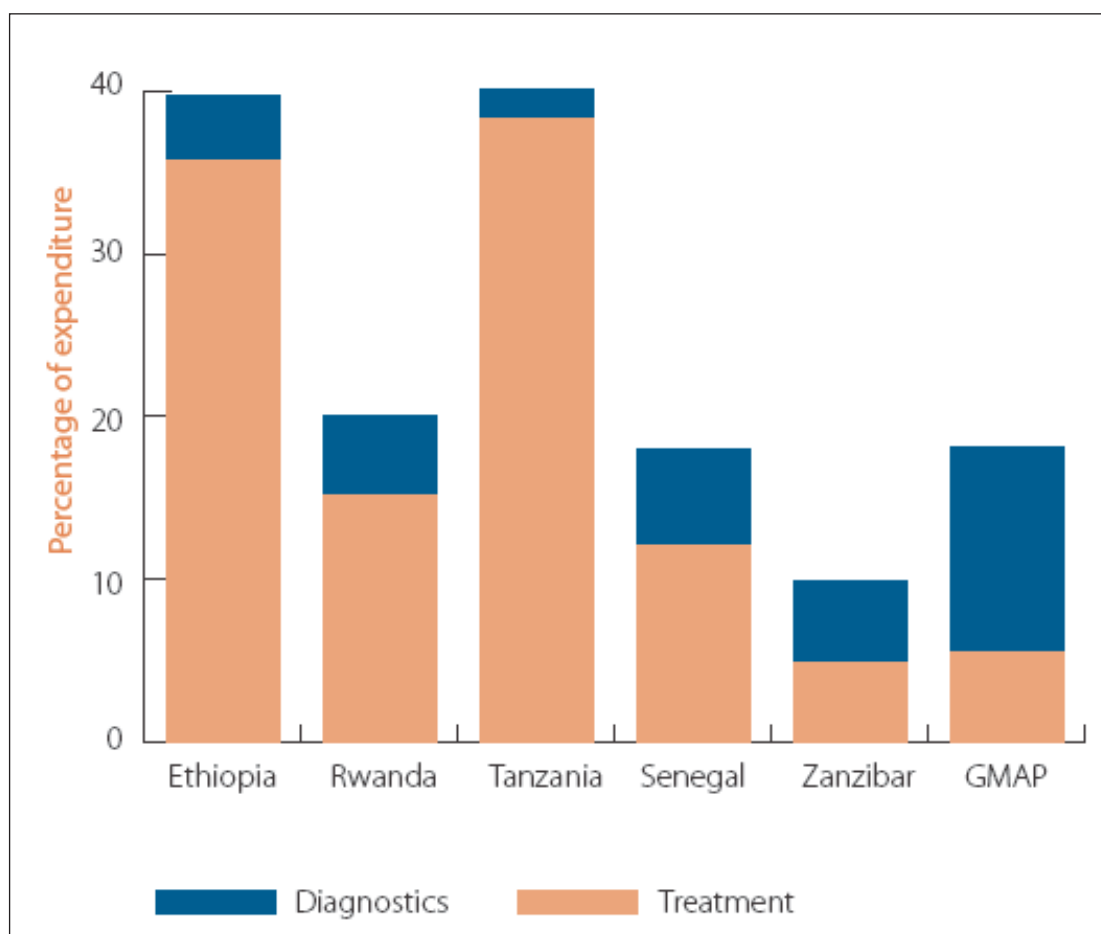
¹² Thiam, S et al. Major Reduction in Anti-Malarial Drug Consumption in Senegal after Nation-Wide Introduction of Malaria Rapid Diagnostic Tests. *PLoS One*, 6(4):e18419

¹³ *World Malaria Report 2011*. Geneva, World Health Organization, 2011

¹⁴ *Global Malaria Action Plan*, Roll Back Malaria Partnership, 2008. The GMAP is a framework for coordinated action on malaria control, which included projections of resource needs for malaria. The GMAP analysis projected that universal access to diagnosis and decreases in the burden of malaria would result in case management spending that was dominated by diagnosis rather than treatment.

¹⁵ *Sustaining the Gains in Global Malaria Control*, October 2011, ALMA, E2PI Evidence to Policy Initiative/Global Health Group, Clinton Health Access Initiative, Republic of Rwanda Ministry of Health

Figure 5: Proportion of Total Malaria Expenditures Spent over 2008-2010 on Diagnostics/ Treatment Compared with Suggested Proportions Projected by GMAP.



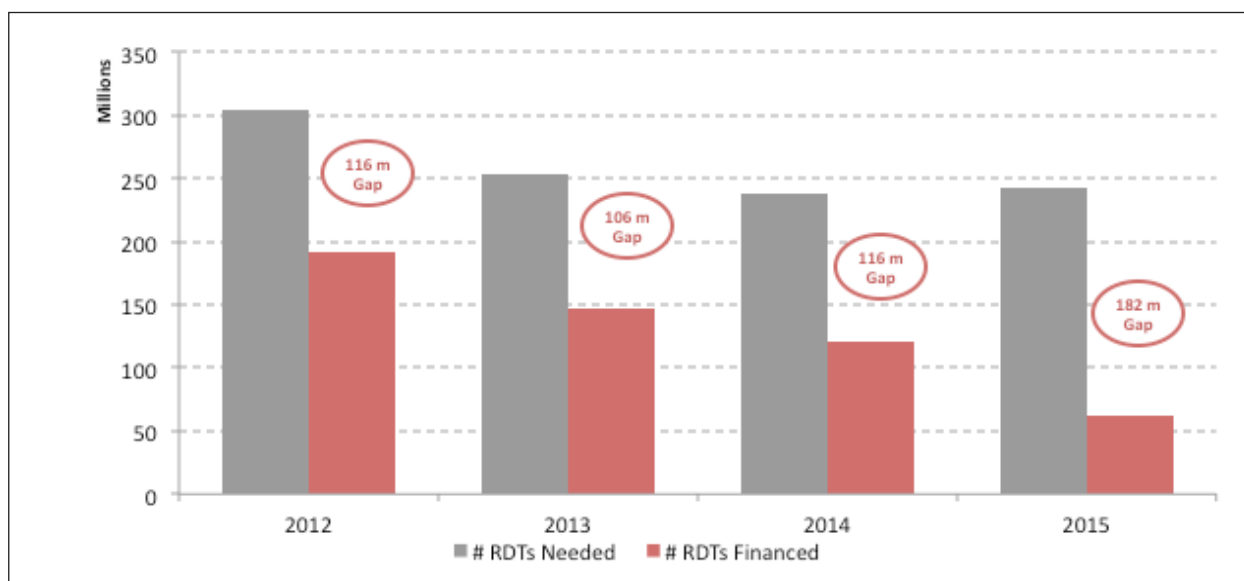
Source: *Maintaining the Gains in Global Malaria Control*

Estimating the Gap in Achieving Universal Access to Testing

Little in-depth analysis has been conducted to estimate the global gap in access to malaria testing. However, the African Leaders Malaria Alliance (ALMA) and the RBM HWG are tracking malaria commodity needs and resource gaps in African countries. Figure 6 projects the number of RDTs needed to achieve and sustain universal diagnosis coverage in the public sector and the current gap in terms of RDTs financed.¹⁶ As Figure 6 shows, approximately 250 million RDTs are needed annually in the African public sector,¹⁷ and approximately half of those are currently funded. Although the gap in 2012-2014 remains fairly constant at approximately 110 million RDTs per year, it is projected to jump substantially in 2015 to 182 million RDTs.

¹⁶ This analysis is based on triangulation of Global Fund, PMI and World Bank data as well as RBM Roadmaps and country level gap analysis where available. The data is a work in progress that is continually updated as new information becomes available.

¹⁷ In 2012 the number of RDTs needed and the amount financed is larger than future years, this is due primarily to disbursement bottlenecks during 2011 that delayed procurement of RDTs. The funding for these RDTs is expected to become available in 2012 allowing for the purchase of these RDTs in 2012. This phenomenon is likely to repeat itself, however, as disbursement delays in other countries are likely to occur in 2012 pushing some of the planned RDT purchasing into the subsequent year.

Figure 6: African Public Sector - Number of RDTs Needed vs. RDTs Financed

Source: ALMA/HWG Data as of 18 March 2012

Unmet Needs: Diagnosis of Special Population Groups

In addition to the general need to increase access to malaria diagnostic tests, there are several population groups that do not have adequate access to malaria diagnosis due to the lack of appropriate technologies. These include:

- Pregnant women, for whom commonly used diagnostic tests (RDTs and microscopy) are largely inadequate for detection of placental malaria. Annually, approximately 125 million pregnancies occur in areas affected by *P. falciparum* or *P. vivax*.¹⁸
- Populations in low transmission/elimination settings, who require more sensitive tests to measure low-level transmission and tests that detect asymptomatic malaria infections. Currently, 36 countries are in the process of moving from controlled, low-endemic malaria to elimination.¹⁹
- Populations in *P. vivax* endemic areas. An estimated 2.85 billion people live at risk of *P. vivax*.²⁰ Without special treatment, *P. vivax* can relapse because it remains dormant in the liver for extended periods of time²¹. Currently, there are no diagnostic tests capable of detecting the dormant liver stage infection that causes relapse. Additionally, there is limited access to tests capable of screening individuals for a common genetic deficiency (Glucose-6-phosphate dehydrogenase “G6PD” deficiency) that causes adverse reactions to primaquine, the drug used to treat the liver stage disease.

Implications of Low Access to Testing

As described above, while progress has been made in increasing access to testing, especially in the African public sector, there is still a long way to go to meet the targets set by RBM. One major implication of low access to testing is overtreatment. Without diagnosis, malaria is massively over treated, resulting in wasted global health resources in both the public sector and in the ACT subsidy program. In the private sector, patients may expend limited personal finances on antimalarial drugs that they do not actually need. Dramatic reductions in antimalarial drug use are possible through scale up of diagnosis, and modeling has shown that RDTs are increasingly cost-effective as transmission rates decline. At the global level the economic effects of overuse are magnified as ACT budgets continue to increase.

18 Delicour S. et al. Quantifying the number of pregnancies at risk of malaria in 2007: a demographic study. *PLoS Med* 2010, 7:e1000221.

19 The Global Health Group and Malaria Atlas Project (2011). *Atlas of Malaria Eliminating Countries*, 2011. San Francisco.

20 Guerra, CA et al. The international limits and population at risk of *Plasmodium vivax* transmission in 2009. *PLoS Neglected Tropical Diseases*, 3 August 2010, 4(8):e774.

21 A typical treatment of *P. vivax* malaria might include an ACT to treat the primary infection plus a 14 day course of primaquine, the drug used to treat the liver stage.

There are several additional benefits to scaling up routine malaria diagnostic testing:

- Testing improves the quality of care for patients with malaria due to increased confidence in the diagnosis. In addition, testing and targeted treatment builds confidence in the effectiveness of ACTs—when they are used only to treat confirmed malaria—and in health services more generally.
- Testing has potential to improve the management of non-malaria fevers by allowing malaria to be ruled out and encouraging appropriate and earlier treatment for the true cause of their fever.
- While antimalarials are considered safe drugs, they are not without potential side effects. Reducing over treatment reduces the risk of unnecessary side effects and possible drug interactions.
- More rational use of antimalarial medicines reduces the selection pressure for drug resistant parasites. In the case of ACTs, the partner drugs with long half-lives are a primary concern.

Another impact of low access to testing is the lack of reliable data on malaria cases seeking care at health facilities and on the effectiveness of interventions. While current facility-based case reporting systems provide “indicative” information on malaria case loads, their accuracy could be improved tremendously through the diagnostic test scale up. Reliable data allows for improved quantification of malaria commodities that may translate into better use of funds and a reduction in stock outs. Given the current emphasis on value for money in malaria, reliable data on which to base decisions about resource allocation is increasingly important.

In addition to routine malaria diagnosis, the lack of suitable diagnostic technologies for detecting malaria in pregnancy, detecting asymptomatic infections, and for *P. vivax*, means that there is room for improvement in individual care and/or overall public health through the development of new technologies that address the needs of these populations groups.

Malaria Diagnostics Technology Landscape

Overview

This section describes the technologies for malaria diagnosis that are current available and that are in the development pipeline. This section draws heavily information provided in UNITAID's 2011 Malaria Diagnostics Technology Landscape.²² Because much of the activity in the malaria diagnostics market today centers on RDTs, this section provides more detail on RDTs than on other technologies.

Two diagnostic tests are routinely used for diagnosing malaria: microscopy and malaria RDTs. Globally, microscopy is estimated to be more widespread than malaria RDTs, although RDT use is growing rapidly and is driving the current expansion in diagnosis. In addition, several specialized laboratory-based tests (polymerase chain reaction [PCR], Loop-mediated isothermal amplification [LAMP], and serology) are occasionally used, generally to investigate clinically complex cases, as a reference method for other tests, or for surveillance and research purposes.

Malaria Rapid Diagnostic Tests (RDTs)

Malaria RDTs are lateral flow tests that employ antibodies to detect antigens produced by the malaria parasite. RDTs may detect one or multiple species of malaria. The most commonly used RDT detects the HRP-II antigen produced only by *P. falciparum* malaria. Other antigens detected by RDTs include parasite lactate dehydrogenase (pLDH) and aldolase antigens. pLDH antigens may be specific to one species (e.g., there is a pLDH only produced by *P. vivax*) or they may be produced by all species of malaria. Using different combinations of target antigen a variety of permutations of malaria RDTs are available, including:

- *P. falciparum* only tests.
- Pan-malaria tests that give a positive result for any species of malaria without differentiating between species.
- Combination tests that distinguish between species²³.

RDTs are available in dipstick, card and cassette formats. The cassette format, in which a test strip is encased in plastic housing, is easiest to use and the most common. RDTs are simple to perform, and although each RDT has specific instructions as to the volume of blood and buffer required, and may differ in time to result and the format of the results read out, the process is generally similar. The first step involves lancing a patient's finger and transferring a drop of blood to the test. After adding buffer and waiting 15-25 minutes, the results appear as a visual line. Depending on the number of species detected, RDTs will have two or more lines in the results window (i.e., a control line and one or more test lines).

RDT Performance

Evaluating the performance of a malaria RDT is a technically challenging, complex, and costly process. Prior to 2009, hundreds of studies (manufacturer and independent) on RDTs had been conducted; however, poor study design and inadequate results reporting made it difficult to evaluate and compare RDT performance.

In 2009, WHO completed its first round of product testing for malaria RDTs.²⁴ This evaluation, a landmark for malaria RDTs, directly compared the performance of dozens of malaria RDTs and concluded that there were many commercially available RDTs that performed as well as, if not better than, operational microscopy. The product testing program and its impact on the RDT market is discussed further in the Market Landscape Section of this report.

22 2011 *Malaria Diagnostics Technology Landscape*. Geneva, UNITAID, 2011. Available at: <http://www.unitaid.eu/en/marketdynamics/malaria-diagnostics-landscape>

23 A variety of types of combination tests are available, for example *P. falciparum*-pan malaria tests (to diagnose a malaria infection and to indicate whether it is caused by *P. falciparum*), *P. falciparum*-*P. vivax* (to differentiate between *P. falciparum* and *P. vivax* infections), or *P. falciparum* - *P. vivax/ovale/malariae* tests (to differentiate between *P. falciparum* infections and infections caused by one of the other species).

24 The WHO Product Testing Program is co-sponsored by the Foundation for Innovative New Diagnostics (FIND), the WHO Special Program for Research and Training in Tropical Diseases (TDR) and the WHO Global Malaria Program (GMP). Testing is performed at the US Centers for Disease Control and Prevention (CDC). Reports from the WHO Product Testing of malaria RDTs include:

- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 1 (2008). Geneva, World Health Organization, 2009. Available at: <http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt-performance>.
- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 2 (2009). Geneva, World Health Organization, 2010. Available at: http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt_round2.
- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 3 (2010-11). Geneva, World Health Organization, 2011. Available at: http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt_round3.

In July 2011, a Cochrane Review²⁵ was conducted to assess the accuracy of RDTs for detecting *P. falciparum* malaria in people presenting to health facilities with symptoms of uncomplicated malaria. The authors analyzed results from 74 trials conducted in Africa, Asia, and South America and concluded that several commercially available RDTs demonstrated acceptable performance (> 90% sensitivity and 90% specificity) across a variety of transmission settings. Although the review found some differences between HRP-II-based RDTs and pLDH-based tests, the differences were slight and the review did not identify any differences between commercial brands of RDTs.

Advantages and Disadvantages of RDTs

Malaria RDTs have several advantages that contribute to their growing use. Operationally, RDTs are simple to use and can be used by low skilled health workers with limited training. They are highly portable and disposable, requiring no laboratory infrastructure, electricity, or instruments. Lastly, malaria RDTs are relatively inexpensive, with the most basic *P. falciparum* tests averaging \$0.51 and tests that detect more than one species averaging \$0.69.²⁶

Malaria RDTs also have several limitations, some more significant than others. These include:

- **Quality Control.** For most diagnostic tests there are technologies and well-established methods for controlling the quality of tests at the central level (i.e., evaluation of tests prior to purchase), when they are delivered to the country, at intermediate points in the distribution chain, and at the point of service. These quality control technologies and methods have been developed by international bodies, public health laboratories, and/or are commercially available. For RDTs, however, practical methods and technologies to enable quality control testing are inadequate. There are no practical means of confirming the performance of an RDT in the field and, while programs exist at the international level to evaluate tests prior to purchase and delivery to country (i.e., the WHO Product Testing Program for malaria RDTs and WHO Lot Testing Program²⁷), these programs rely on limited donor-funding and will be undergoing a transition to a more sustainable business model that is not without risks.
- **Issues with the HRP-II Antigen.** Although they are the most widely used type of RDT, HRP-II-based RDTs have two main shortcomings: (i) they may not distinguish between an active and previous malaria infection, and (ii) variation in the expression of HRP-II by the malaria parasite, particularly in South America, can lead to false negatives.
- **Heat Stability.** There has been little formal evaluation of RDT heat stability and actual conditions of use (i.e., temperature and humidity). In general, RDTs are at risk of deterioration and reduced sensitivity when they are exposed to heat and humidity for prolonged periods. Malaria RDTs are generally labeled to be stable at 4° to 30°-37° C for 18-24 months. Conditions in some malaria-endemic settings will at times exceed these manufacturer recommendations; however, the effect on RDT performance has not been extensively analyzed.
- **Limit of Detection.** While the sensitivity of high-performing RDTs is thought to be acceptable for diagnosis of malaria in people with symptoms, it may not be adequate for reliable detection of low-density infections in asymptomatic individuals.
- **Speciation.** Although RDTs are proven effective for detecting *P. falciparum* malaria and differentiating it from other forms of malaria, there is significantly less data on their ability to distinguish between the other species (i.e., *P. vivax*, *P. ovale*, and *P. malariae*) of malaria.
- **Quantification.** RDTs are not able to quantify parasite density, which is useful in assessing the severity of illness and for monitoring a patient's response to treatment.

25 Abba K, et al. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database Systematic Reviews*, 6 July 2011;(7):CD008122. The Cochrane Collaboration is a non-profit organization that prepares systematic reviews of evidence about health-care interventions to inform policy and practice.

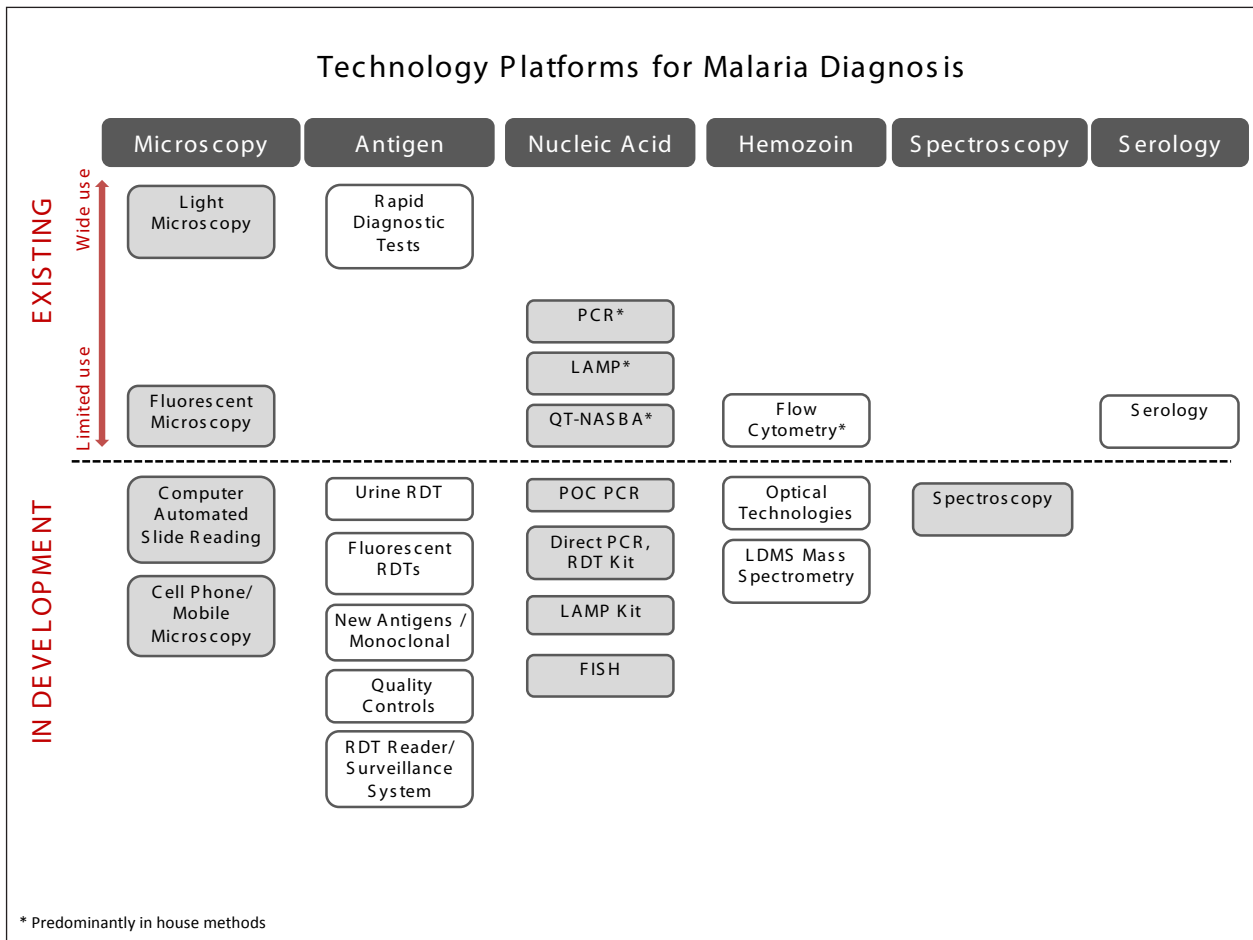
26 Weighted average prices for 2010 reported in World Malaria Report 2011. Pricing in current market is highly variable, see discussion in Market Landscape Section of this report for more information on current RDT prices.

27 The WHO and partners operate a lot testing program for malaria RDTs that is designed to detect major flaws in RDT performance. Lot testing involves taking a sampling of RDTs from each lot (or batch) of RDTs and sending them to one of two international reference laboratories for quality control testing. The testing is designed to detect major flaws in RDT performance and to supplement batch release testing at the manufacturing level and in-country quality control testing.

Malaria Diagnostic Pipeline Technologies

There are a number of technologies for malaria diagnosis in the development pipeline that employ a variety of technology platforms and approaches to diagnosing malaria. Figure 7 summarizes the different approaches to malaria diagnosis, the majority of which aim to improve ease-of-use and/or sensitivity, especially at low parasite densities. The pipeline includes improvements to existing technologies as well as several novel technologies that use approaches not previously widely used for malaria diagnosis (i.e., hemozoin detection and spectroscopic approaches).

Figure 7: Technology Platforms for Malaria Diagnosis



Research and Development Priorities

To be useful in routine practice, any malaria test should be both accurate and rapid, due to the acute and life-threatening nature of malaria disease. Other priorities for malaria diagnostic research and development are affordability and test formats that are widely deployable. With respect to affordability, low cost is critical given the high volume of fevers that should be tested globally each year and the incomes of populations most affected by malaria. With respect to ease of deployment, malaria tests should be portable, robust enough to withstand extreme heat and humidity, and require minimal or no operator training or input to process the test. Existing technologies rely on blood samples; a non-invasive test would improve ease of use and safety, and would likely be game changing. In addition, technologies that improve upon the existing limits of detection and ability to differentiate between species are also important, especially in lower transmission areas. Technologies that effectively address (i) the needs of malaria in pregnancy and (ii) the unique characteristics of *P. vivax* are also priorities.

Technology Developers and Product Offering

Malaria diagnostic technologies are being developed by a variety of developers, including academic institutions, research and development companies, start-up companies, product development partnerships, and existing malaria RDT manufacturers. Technologies actively being commercialized are listed in Table 1, with additional details available in UNITAID’s 2011 Malaria Diagnostics Technology Landscape.²⁸

The products in the development pipeline can be broadly grouped into two categories:

- Technologies that are largely reference-oriented; i.e., that due to cost or complexity are unlikely to be used for large-scale clinical screening, but may take the place of traditional PCR methods or expert microscopy.
- Those that have broader clinical and or screening application.

Ultimately, the ability of these technologies to compete with RDTs on cost, ease-of-use, and additional value will be critical to their uptake in the market. As most of these tests are in the early stages of development, their performance remains to be seen, although most are expected to have a limit of detection that is superior to that of existing technologies. The prospect of reagentless diagnosis at low cost is promising, as is a non-invasive test, which would overcome blood safety challenges and improve ease of use. Lastly, although many of the technologies require use of a device, many developers are considering built in connectivity, data management, and global positioning systems that would enable improved malaria surveillance.

Table 1: Malaria Diagnostics Pipeline

| Name | Developer | Description | Earliest Availability |
|---|--|--|-----------------------|
| Urine Malaria Test | Fyodor | Dipstick test to detect fever due to malaria in urine. | 2013 |
| Fluorescent RDTs | AccessBio | RDT using fluorescent dye and an RDT reader to improve the sensitivity of RDTs at low parasite densities. | 2013 |
| New monoclonal antibodies | FIND and partners; various RDT manufacturers and other organizations . | Various groups working to develop monoclonal antibodies / improve existing antibodies with respect to sensitivity, specificity, and stability. | unknown |
| Positive Control Wells for RDTs | FIND and partners | Positive control wells are small plastic containers coated with recombinant parasite antigen (i.e., a genetically engineered parasite antigen) that when reconstituted with water and applied to an RDT produces a positive reaction on the RDT. Positive control wells are intended to be used by test operators to check that RDTs perform to an acceptable level. Other quality control panels based on the same technology are also under development. | unknown |
| RDT Reader and Cloud Information Services | Fio Corporation | RDT reader and cloud information services to improve malaria RDT quality assurance and malaria surveillance. | 2012 |
| MicroPCR | Tulip Group & Bigtec Labs | POC PCR instrument | 2012 |
| PanNAT Malaria Assay | Micronics | POC PCR instrument | 2014 |
| NALFIA (Nucleic Acid Lateral Flow Immunoassay) | MALACTRES Consortium | PCR test kit containing primers, reagents and lateral flow device for running test. Test is based on direct PCR method, using a traditional PCR thermocycler, followed by detection using the NALFIA, a disposable lateral flow device. | 2012 |

²⁸ 2011 Malaria Diagnostics Technology Landscape. Geneva, UNITAID, 2011. Available at: <http://www.unitaid.eu/en/marketdynamics/malaria-diagnostics-landscape>

| | | | |
|---|----------------------------|---|-----------|
| LAMP Malaria Diagnostic Kit | FIND, Eiken Chemicals, HTD | Commercial Loop-mediated isothermal amplification (LAMP) test kit containing primers and reagents needed to run assay using bench top laboratory equipment. | 2012 |
| Malaria FISH Assay | ID-Fish Technology | Fluorescent in Situ Hybridization (FISH) test kit that contains probes and reagents for detecting malaria in blood samples using a fluorescent microscope. | 2012 |
| DFxP (Dark-Field Cross Polarization) | Intellectual Ventures Lab | POC device that detects hemozoin, a byproduct of the malaria parasite's metabolism. | 2013/2014 |
| Magneto-optical Technology (MOT) | University of Exeter | POC device that detects hemozoin, a byproduct of the malaria parasite's metabolism. | 2013/2014 |
| SpectraWave and SpectraNet | Claro Scientific | Reagentless POC device using optical profiling technology to diagnose malaria and perform complete blood counts | 2014/2015 |
| Spectraphone | Quantaspec | Molecular detection system using a handheld device to detect malaria in blood slides. | 2014 |

Source: UNITAID 2011 Malaria Diagnostics Technology Landscape.

Malaria Diagnostics Market Landscape

Given the need for rapid, point-of-care diagnostics and the corresponding scale up of malaria RDTs, this market landscape report focuses on the market for RDTs in particular. This section focuses initially on the public/non-governmental organization (NGO) sector market, and is followed by a brief discussion of the private sector market.

Overview: Public Sector Malaria RDT Market

As described in the Methodology Section of this report, there is limited reliable aggregate data on the malaria diagnostics test market, although there is increasing information available. As a result, the following discussion of the current state of the market for malaria diagnostics is based largely on limited data, supplemented by conversations with various stakeholders, including leading RDT manufacturers.

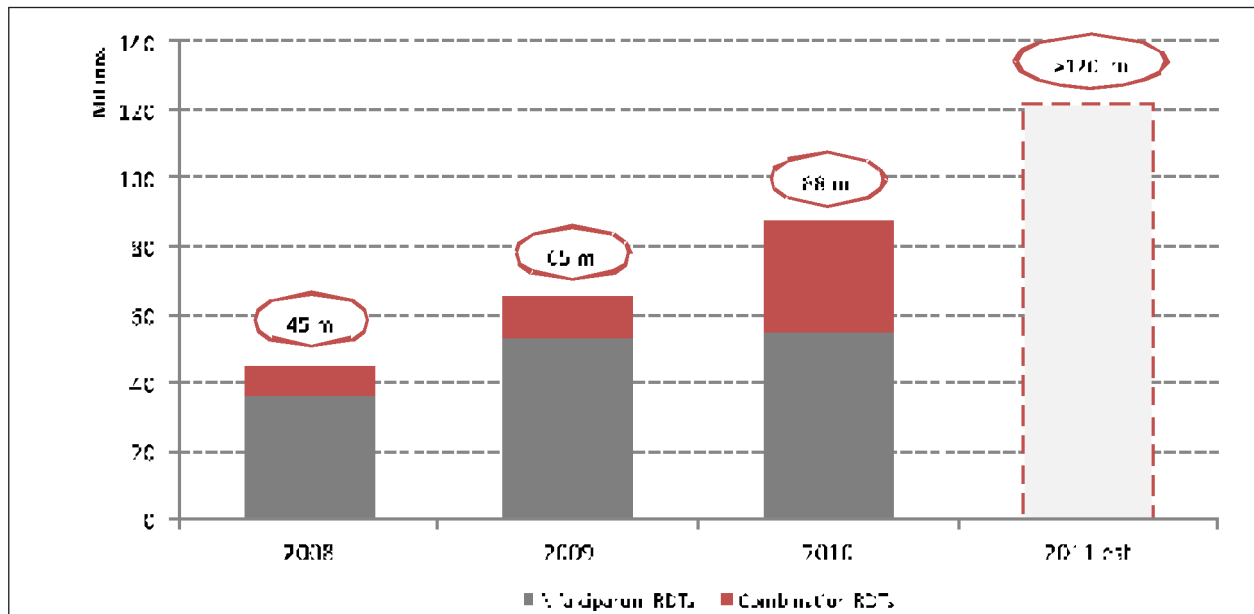
Market Development and Current Size

The first commercial malaria RDT, ParaSight F, was made in 1994 by Becton Dickinson and fewer than 10 million tests are estimated to have been sold in the 1990's.²⁹ In the early 2000's RDT use grew in response to the introduction of ACTs, which were significantly more expensive than previous antimalarial drugs. Early adopters of RDTs included international NGOs and lower-prevalence countries, largely in Asia and Southern Africa, where RDTs were adopted by national programs in the early to mid-2000's. However, many of these countries have well-developed microscopy networks and they tend to buy smaller volumes, i.e., < 500,000 RDTs per year.

Widespread adoption and use of RDTs was the exception rather than the norm in Africa in until very recently. By recommending universal diagnosis, the 2010 WHO Malaria Treatment Guidelines created a large push for malaria RDT adoption and scale up. Meanwhile, the 2009 WHO Product Testing program results contributed to increasing acceptance of RDTs at the policy level. In addition, major advocacy bodies such as RBM and donors like PMI have been increasingly focused on diagnosis.

As a result, an increasing number of countries have adopted a policy of providing diagnostic testing to all age groups (85% of countries in 2010, up from 74% in 2009). These changes in policy are reflected by rapid growth in the malaria RDT market in recent years. Figure 8 shows data for 2008-2010 compiled by the WHO through a survey of manufacturers participating in the Product Testing Program. Based on discussions with a handful of suppliers conducted for this report, **the 2011 market is estimated to total well over 120 million RDTs.**

29 Frost & Reich, Chapter 5: Malaria Rapid Diagnostic Tests: Access to Diagnostics. In: *Access: How do Good Health Technologies Get to Poor People in Poor Countries?*, Cambridge: Harvard University Press, 2008. Burgess D, Assuring the Quality of Malaria Rapid Diagnostic Tests: Presentation at the FIND WHO Advisory Forum for Malaria Diagnostics, 4 November 2007.

Figure 8: Malaria RDT Market (based on supplier reported volumes of RDTs sold)

Source: 2011 World Malaria Report for 2008-2010, based on responses from 31 of the manufacturers participating in the WHO Product Testing Program. Estimate for 2011 based on author's discussions with suppliers.

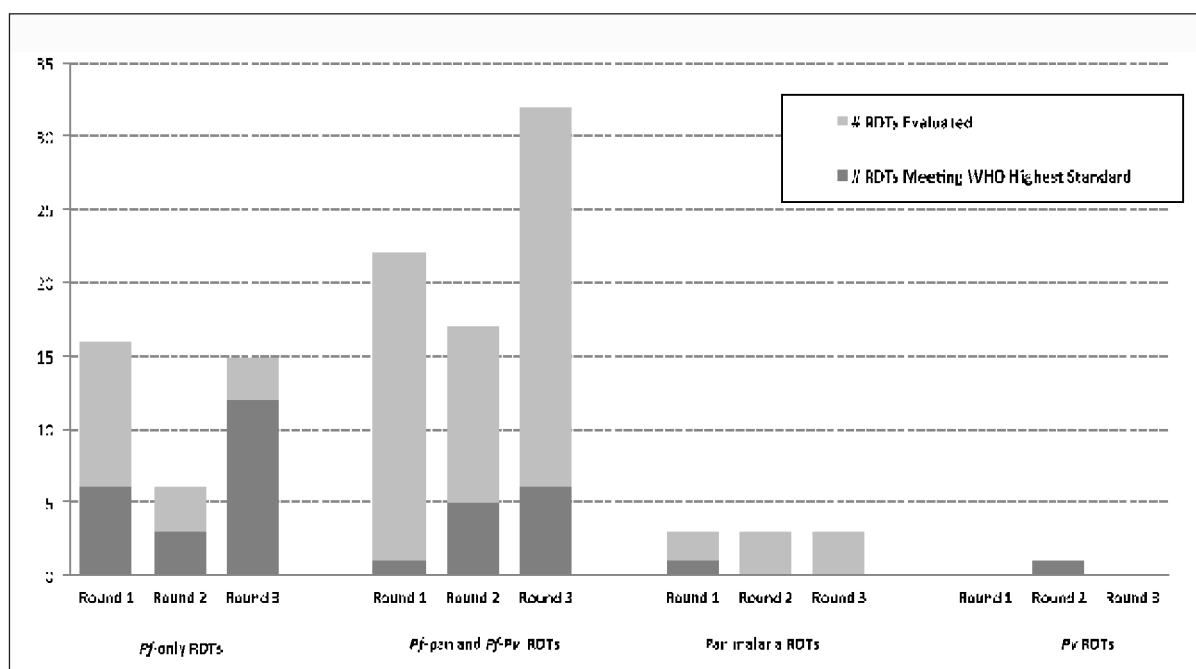
Range of Product Types

In the late 1990's only three tests were commercially available; by 2008, over 40 products were available, and two of the original three ceased to be marketed.³⁰ **Today, with over 200 products on the market, the malaria RDT market is challenging to monitor.** Repackaging and reselling of malaria RDTs and/or their key components is also quite common. Most malaria RDT manufacturers have a variety of tests in their portfolio, although certain versions are not sold in significant volumes. By far the most commonly used RDT is the *P. falciparum*-only detecting test. As Figure 8 shows, these tests previously comprised approximately 80% of the market; however, **since 2010 the use of combination tests has grown.**

The WHO Product Testing Program is the entry point to the public sector market (the largest segment of the malaria RDT market). Of the tests evaluated in the first three rounds of Product Testing, approximately 30% were *P. falciparum*-only detecting HRP-II tests from 22 different companies. As shown in Figure 9, a relatively high proportion of the *P. falciparum*-only tests have demonstrated performance that meets WHO's standards for RDT procurement.

Although more than two thirds of the tests submitted to the program detect multiple species of malaria, the proportion of these that have met WHO's procurement recommendations is significantly lower (< 20%; Figure 9). As a result, while there are many product options for buyers of *P. falciparum*-only tests, fewer high-performing multispecies tests are available.

30 Frost & Reich, Chapter 5: Malaria Rapid Diagnostic Tests: Access to Diagnostics. In: *Access: How do Good Health Technologies Get to Poor People in Poor Countries?*, Cambridge: Harvard University Press, 2008.

Figure 9: WHO Product Testing - Number of RDTs Evaluated and Proportion Meeting WHO's Recommended Performance Criteria³¹

Source: Author's analysis, based on published WHO Product Testing results

Among the RDTs on the market, there is variation in labeling, procedures (e.g., time to result, drops of buffer), and the format of results readout. While individual RDT products from a single manufacturer tend to resemble each other, there are differences among manufacturers in the format of the RDT, the readout, labeling, components included in test kits, and test procedures. These differences present a challenge to malaria programs when orienting health workers to RDTs and switching from one RDT to another, especially in the early years of the RDT introduction when health workers are still familiarizing themselves with the technology more generally. As a result, there is a movement among RBM partners to standardize RDTs, with an emphasis on consistency in labeling, instructions/job aids, blood transfer devices, and possibly the number of drops of buffer required.

Prices

Analysis conducted for the World Malaria Report found that in 2010 the weighted average price for *P. falciparum*-specific RDTs was \$.51 (range \$.42-.88) and \$.69 for multispecies tests (\$.58-1.05) and that the weighted average prices for both types of tests fell by 11%-15% annually from 2008-2010.³² In 2011, the prices appear to have continued to decline; however, recently there has been wide variation in pricing, making it difficult to cite a reference price for malaria RDTs. For example, while the prices cited above are common, several recent tenders for *P. falciparum* tests have been awarded at below \$.30.

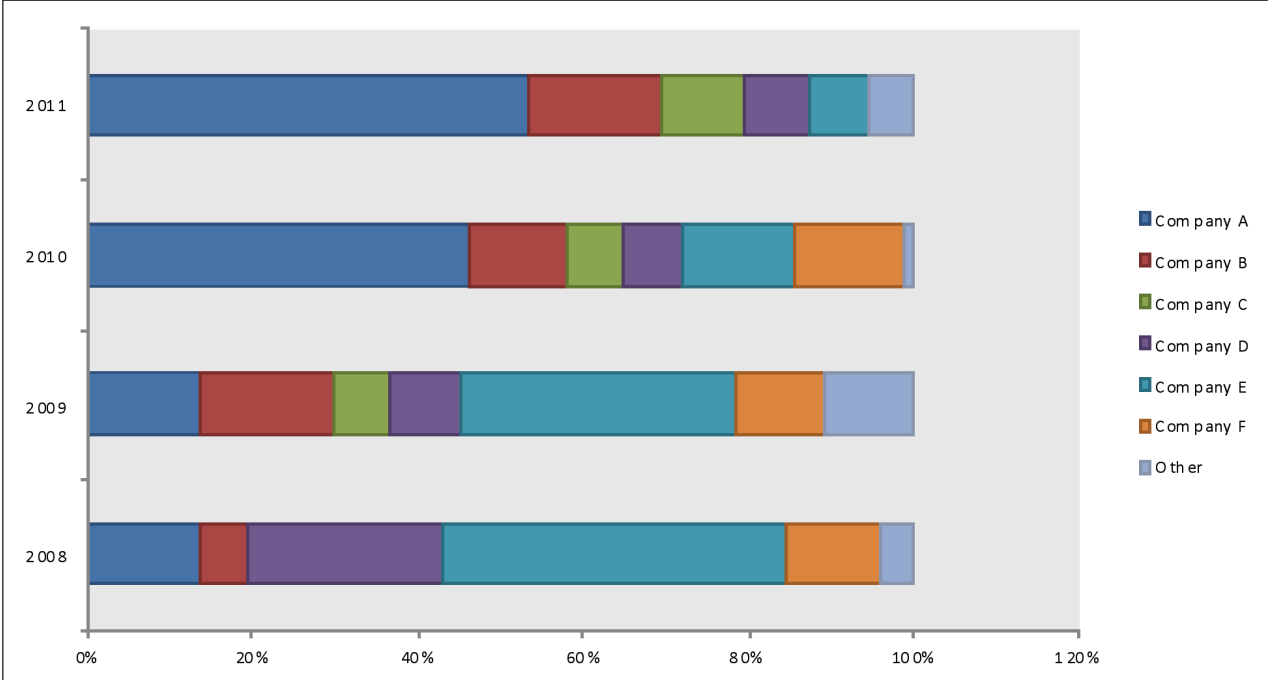
Market Share

Although there are a large number of companies involved in the market, in recent years the public sector market appears to be dominated by a handful of companies, including AccessBio (USA), ITC (South Africa), Orchid Biomedical (India), Premier Medical Cooperation (USA), Span Diagnostics (India), and Standard Diagnostics/Alere (Korea). Although data on this market is largely incomplete, analysis of PMI and Global Fund PQR data representing approximately 50% of the global market (Figure 10) suggests that market share has fluctuated significantly in the past few years.

³¹ Prior to April 2012, the WHO had different recommendations for *P. falciparum* tests, depending on transmission intensities. This chart shows RDTs meeting the highest standard, i.e., a panel detection score of $\geq 75\%$ at 200 parasites/ μl , a false positive rate of $< 10\%$ and an invalid rate of $< 5\%$. The recommendation for *P. vivax* detection is the same as for *P. falciparum* tests.

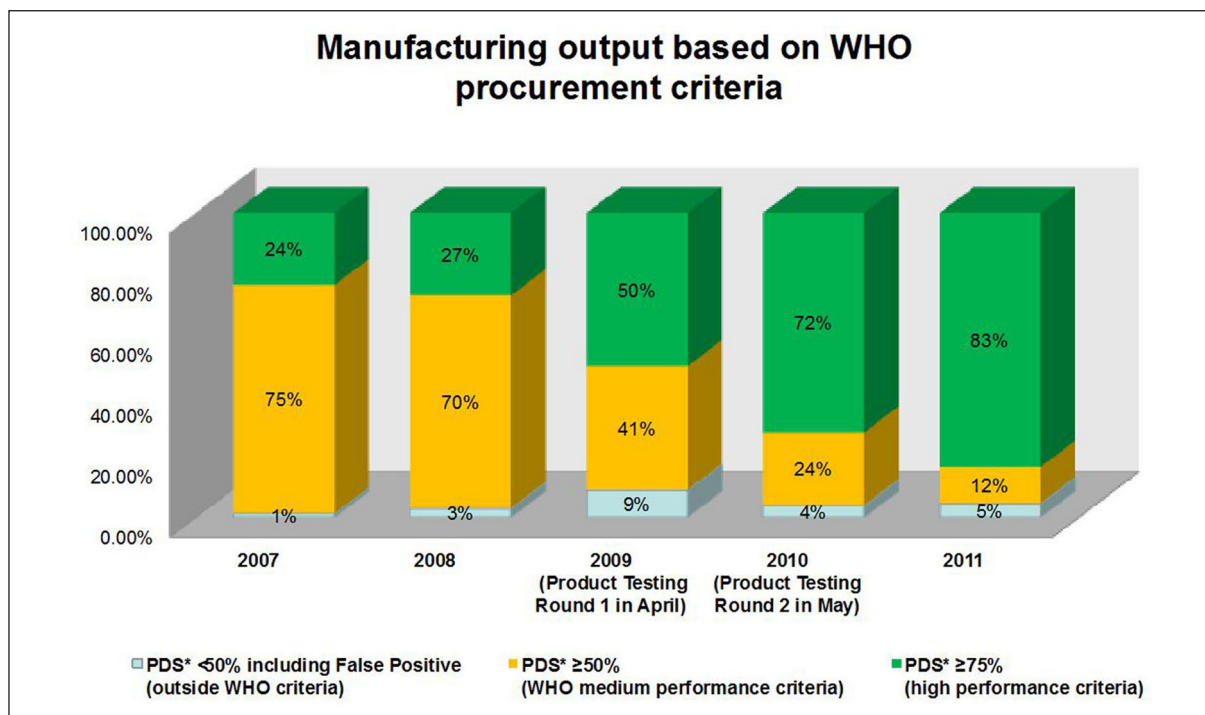
³² World Malaria Report 2011. Geneva, World Health Organization, 2011.

Figure 10: Malaria RDT Market Share, based on data from two largest donors (note that PMI dataset is complete while Global Fund data, as reported in PQR database, is incomplete)



Source: Author, based on PQR and PMI data

The market is also shifting at the product level. In 2011, FIND surveyed seventeen leading RDT manufacturers and found that **the market is shifting to better performing products** (Figure 11).

Figure 11: RDT Volumes Sold by Panel Detection Score

Source: Data provided to FIND by 17 manufacturers participating in the WHO malaria RDT Product Testing Program

Quality Standards

There are currently several quality initiatives for malaria RDTs, among them the WHO's Product Testing Program and WHO procurement recommendations that have recently impacted the market. It should be noted, however, that **these are recent developments in a market that developed largely in the absence of regulatory oversight or quality standards**. In practice, many resource-limited countries do not require regulatory approvals or cannot enforce regulatory standards for diagnostics like malaria RDTs.

When the malaria RDT market developed in the early 2000's, many RDT suppliers did not pursue any regulatory processes.³³ Due to issues around product performance and quality in the field, in the early 2000's a global initiative emerged, coordinated by the WHO, to establish quality standards for RDTs. This work was slow to take effect, though—in large part due to limited funding. Meanwhile, the market for RDTs continued to grow, but with mixed results for RDTs reported from the field. Finally, the WHO Product Testing program was launched in the late 2000's and the lot testing program was expanded. After publication of the first round of Product Testing results in 2009, the WHO Global Malaria Program (GMP) played a role in shaping policy around quality. More recently, the WHO Prequalification Program for Diagnostics has begun work on malaria RDTs. Despite the progress these initiatives have made, there are challenges associated with imposing quality standards in an already developed market.

The following is a discussion of the major quality initiatives, including WHO Product Testing, WHO GMP RDT Procurement Guidance, WHO Prequalification Program for Diagnostics, and lot testing.

WHO Product Testing

The WHO Product Testing Program for malaria RDTs is a laboratory evaluation program that directly compares the performance of RDTs to each other using a standardized panel of specimens and procedures. The results are published in a report format and are available through an on-line tool that enables users to easily identify RDTs

³³ To date, only one malaria RDT has FDA approval: this test was developed by a small biotechnology company in the USA, Binax (now part of Alere), in partnership with the US Military, which required an FDA approved test. This test is primarily marketed to the US/EU markets.

meeting specific criteria.³⁴ The WHO Product Testing program is co-sponsored by the Foundation for Innovative New Diagnostics (FIND), the WHO Special Program for Research and Training in Tropical Diseases (TDR), and the WHO GMP. Testing is performed at the US Centers for Disease Control and Prevention (CDC) in Atlanta.

The first round of test results was published in 2009, and subsequently two additional rounds have been completed. The Product Testing Program has been more popular than initially expected, in part due to manufacturers' desire to have multiple products in their portfolio evaluated. As a result, limits had to be placed on the number of products submitted per manufacturer to each round of testing. In total, 120 tests have been through the Product Testing Program, including 24 resubmissions (See Figure 9). A fourth round evaluating 43 RDTs is currently underway with results expected in late 2012.

The Product Testing Program got off the ground primarily through funding from BMFG, with additional funding from other donors. In its current form, the testing program is complex and has been relatively costly to establish and maintain. This is primarily due to technical challenges of evaluating malaria diagnostics and the need to develop a new specimen bank of human derived malaria samples to support the testing. Going forward, this program and the Lot Testing Program (see below) will be restructured to reduce costs and to transition to a predominantly self-funded business model. This will be accomplished in large part by replacing the human derived specimen bank with lower-cost recombinant antigen panels (i.e., manufactured antigen panels) and by charging a user fee for product testing. This transition is expected to take several years and in the meantime WHO Product Testing will operate as it currently does. The transition will be supported by a nearly \$10 million grant from UNICEF as well as by the BMGF funding for panel R&D and continued operations of the testing program.

The impact of the WHO Product Testing Program on the malaria RDT market has been significant. When the first round of tests were released, the results contributed to broader acceptance of malaria RDTs by convincingly demonstrating that there are many *P. falciparum* RDTs that perform as well as microscopy in field conditions.³⁵ Currently, while there are still a number of products on the market that may be substandard quality, there are several that are performing well in terms of their ability to detect malaria and their limited false positive and invalid rates. There is also ample evidence that the Product Testing Program has impacted demand in the public sector markets. Currently nearly all procurement is based on the Product Testing results.

Product Testing results indicate that the performance of RDTs has improved over the course of the program, suggesting that the program has created an incentive for product improvement among RDT manufacturers. An increasing proportion of RDTs in the later rounds of testing have met the minimum WHO-recommended procurement criteria (See Figure 9). In addition, many tests have been resubmitted to the program (one in Round 2 and 23 in Round 3) and have shown improvement. The testing program has, however, documented variation between lots of the same test, underscoring the importance of quality control/quality assurance measures.

One adverse effect of the program relates to its timeline: from expression of interest to publication of results the program can take > 18 months. For companies, the long delay pushes out the launch date and potential revenues associated with new products, thereby reducing potential return on investment and creating a disincentive for product development and improvement.

WHO Global Malaria Program (GMP) RDT Procurement Guidance

The GMP, in consultation with experts, develops recommendations for malaria diagnostic test product selection that form the basis for WHO RDT procurement and are shared through an information note on the WHO GMP website for use by countries and other organizations.³⁶ The first WHO product selection criteria were published in 2010 after the first round of Product Testing, and **since the publication of the Product Testing**

³⁴ Reports from the WHO Product Testing of malaria RDTs include:

- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 1 (2008). Geneva, World Health Organization, 2009. Available at: <http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt-performance>.
- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 2 (2009). Geneva, World Health Organization, 2010. Available at: http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt_round2.
- Malaria Rapid Diagnostic Test Performance: Results of WHO product testing of malaria RDTs: Round 3 (2010-11). Geneva, World Health Organization, 2011. Available at: http://apps.who.int/tdr/svc/publications/tdr-research-publications/rdt_round3.
- FIND Interactive Guide for Product Testing:
http://www.finddiagnostics.org/programs/malaria-afs/malaria/rdt_quality_control/product_testing/malaria-rdt-product-testing/index.jsp

³⁵ Note that expert microscopy can be more sensitive than RDTs, but in most countries there are only a handful of microscopists achieving true "expert" status. The performance of microscopy in the field varies greatly and is often poor.

³⁶ WHO. 12 April 2012. Information Note on Recommended Selection Criteria for Procurement of Malaria Rapid Diagnostic Tests (RDTs). Accessed 3 May 2012. Available at: http://www.who.int/malaria/diagnosis_treatment/diagnosis/en/index.html

results and guidance from GMP, market share has gradually been shifting to the RDTs with better results in the Product Testing Program. One analysis showed that 83% of RDTs procured in 2011 had panel detection scores greater than 75%, compared with only 24% of RDTs procured in 2007 before the Product Testing Program began (see Figure 11).

The current WHO guidance on RDTs was revised in April 2012 following a meeting of the Malaria Policy Advisory Committee (MPAC), which recommended raising the standards for *P. falciparum* RDTs. Previously there had been two performance thresholds, one for high transmission settings and one for low and moderate transmission settings. The new guidance recommends that the more demanding of the two standards apply to all transmission levels. The change reduces the number of recommended *P. falciparum* tests from 24 to 21.

To ease interpretation of the Product Testing results and to improve malaria RDT procurement more generally, the WHO GMP has published guidelines, including the information note which is a brief memo with product selection criteria recommendations, and a comprehensive manual on RDT procurement published in 2011.³⁷

WHO Prequalification Program for Diagnostics (PQ)

In general, the WHO Prequalification Program for Diagnostics reviews and recommends diagnostic devices, for a number of diseases including malaria, of sufficient quality for UN procurement. However, in practice, prequalification status is used more broadly, with many national programs and donors looking to WHO prequalification due to the absence of meaningful regulatory processes at the country level for diagnostic tests.

The PQ process includes dossier review, product testing in a qualified laboratory (for malaria RDTs PQ relies on the WHO Product Testing Program) and manufacturing facility quality inspections (i.e., good manufacturing practice inspections). As of March 2012, WHO PQ had approved two malaria RDTs and an additional 14 from six companies were undergoing the review process. In its current form, PQ has been operational for two years, and application processing has taken longer than desired. This is due to a number of factors, including PQ's workload, as it is currently working through a backlog of applications across several diseases. Also contributing to the lengthy timeline are challenges related to the inexperience of malaria RDT manufacturers with regulatory processes, including assembly of dossiers, and deficiencies noted during good manufacturing practice inspections that require re-inspection (as opposed to the more expeditious submission of written plans of action, which are commonly used when non-conformities are minor). In addition, confusion about the role of the PQ program and the WHO Product Testing Program has caused delays in submission of applications to PQ. Over time, the timing and process is expected to improve, both due to efficiencies at the WHO and increased manufacturer experience.

WHO PQ status is not yet a requirement for UN procurement of RDTs, or of any major donor or RDT purchaser, in part due to the limited number of malaria RDTs that have been prequalified. Since the timing of prequalification of additional malaria RDTs is uncertain, it is unlikely that the PQ status will become a procurement requirement in the near term.

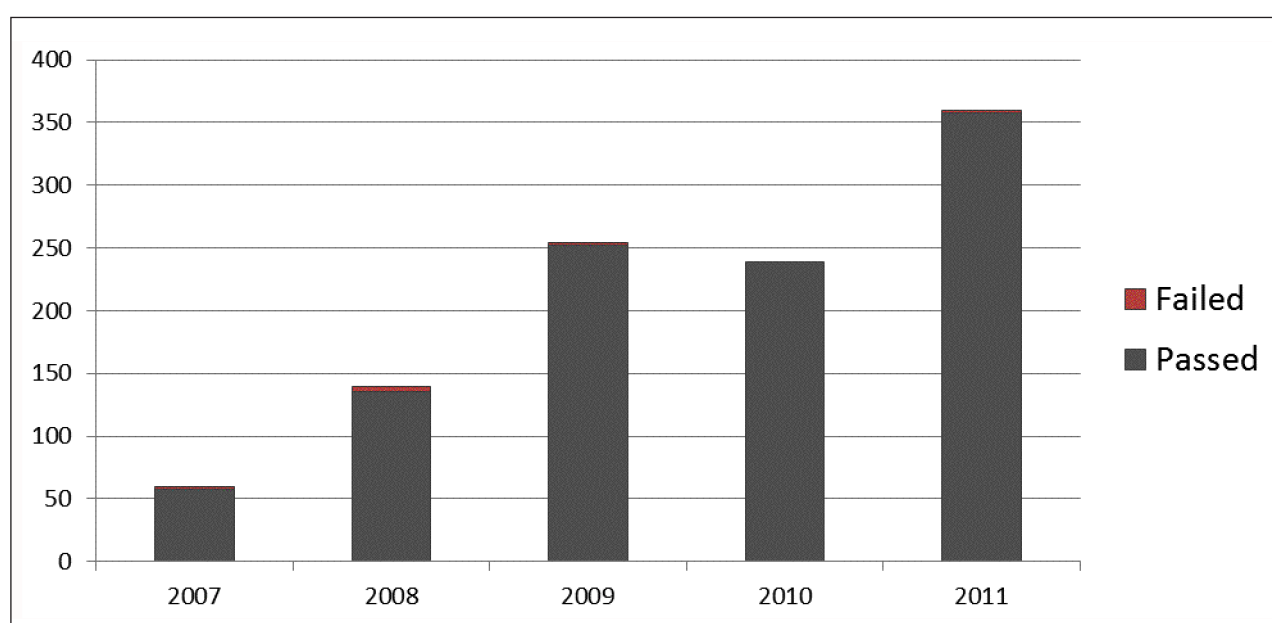
Current uncertainty around the timelines for the PQ process and timing of PQ status becoming a quality standard in the market has an unfavorable effect on private sector malaria RDT-related investments. First, because of the long timelines associated with the PQ process, the launch date for a new product and associated revenues may be delayed, thereby reducing potential return on investment and making an investment in malaria R&D less attractive than other R&D opportunities within a company. Similarly, the long timelines for the PQ process and uncertainty around when PQ status will become a requirement are disincentives for manufacturers considering investment in new manufacturing facilities (often done in an effort to reduce costs and meet increasing demand). From a manufacturers perspective, the risk of long delay between completion of construction on a new facility and obtaining pre-qualification status for that facility (thereby allowing the facility to produce RDTs for sale into the major markets) must be mitigated in order to warrant investment in a new manufacturing facility.

³⁷ Universal Access to Malaria Diagnostic Testing Manual. Malaria RDT Procurement Manual. Accessed 31 March 2012. Available at: http://www.who.int/malaria/diagnosis_treatment/diagnosis/en/index.html

Lot Testing

As with any diagnostic test, independent quality control testing of malaria RDTs purchased from manufacturers is recommended. Currently, the only practical mechanism for doing so is through a lot testing program operated by FIND and partners. The program allows buyers of RDTs to test individual lots of RDTs before using them. It involves taking a sample of RDTs from each lot (i.e., batch) of RDTs procured and sending them to one of two international reference laboratories for quality control testing. The testing involves an initial test of the RDTs as well as testing at later intervals to assess the stability of the test over its shelf life. The testing is designed to detect major flaws in RDT performance and to supplement batch release testing at the manufacturing level and in-country quality control testing. Although the WHO Lot Testing Program is based on some of the same protocols and specimen panels as the Product Testing Program, the extent of testing is very limited (both the number of RDTs and the number of samples in the panel) and therefore it is not as rigorous as the WHO Product Testing Program.

Figure 12: Lot Testing - Number of Lots Tested and Results



As shown in Figure 12, to date, over 1,000 lots have been tested (or are in process of testing, as the whole process takes 2 years) and demand has been growing steadily since the program began. Approximately three quarters of the lots tested have been *P. falciparum*-only detecting RDTs.

Although the program has been free to end users, and demand has grown significantly, uptake is modest: in 2011 FIND estimates that 30-50% of lots from the public sector market were tested. Overall, passing rates are extremely high, with 99% of lots passing, and the majority of failures occurring in the combination tests. It should be noted that the high passing rates may not be a reflection of the quality of RDTs used globally, as the vast majority of RDTs submitted for evaluation are from agencies with strict procurement criteria.

As with the Product Testing Program, this program was funded centrally through donors and going forward, the program will undergo a transition to reduce costs and reliance on donor funding and decentralize lot testing to the country level. This will be accomplished through the development of recombinant antigen panels that are cheaper and easier to mass-produce than human derived specimen panels. Once the panels have been developed and validated, it is expected that they will be sold to reference laboratories that will then perform lot testing for RDTs procured by local programs and institutions. In addition, the panels will be marketed to manufacturers for use as a reference standard in product development and quality control. This transition is expected to take several years, in the meantime Lot Testing will continue at the current laboratories.

Public Sector Malaria RDT Demand

Public Sector RDT Demand Growth

Demand for malaria diagnostics is driven largely by ministry of health procurement. Geographically, **Africa is the largest market for RDTs**, followed by South East Asia. National Malaria Program reporting to the WHO shows that most of the RDTs delivered in 2010 were used in Africa (65%) followed by SE Asia (30%) and the Eastern Mediterranean region (5%).³⁸ Conversations with suppliers also suggest that Africa is the largest and fastest growing segment of the market for RDTs.

The recent growth in this market is driven primarily by public sector scale up. The WHO 2010 recommendation of universal access to diagnosis has had a significant impact in terms of driving adoption of RDTs. Although several countries have reached national scale with malaria RDTs, many others are still in the process of scaling up and therefore demand for RDTs is increasing every year as they move from pilot phase to national scale. The World Malaria Report attributes much of the increase in testing rates in Africa to increased use of RDTs, which accounted for nearly one third of confirmed cases in 2010.³⁹ Annual demand for RDTs has grown tremendously among African countries over the past several years, with orders of over 5 million RDTs per year becoming increasingly common.

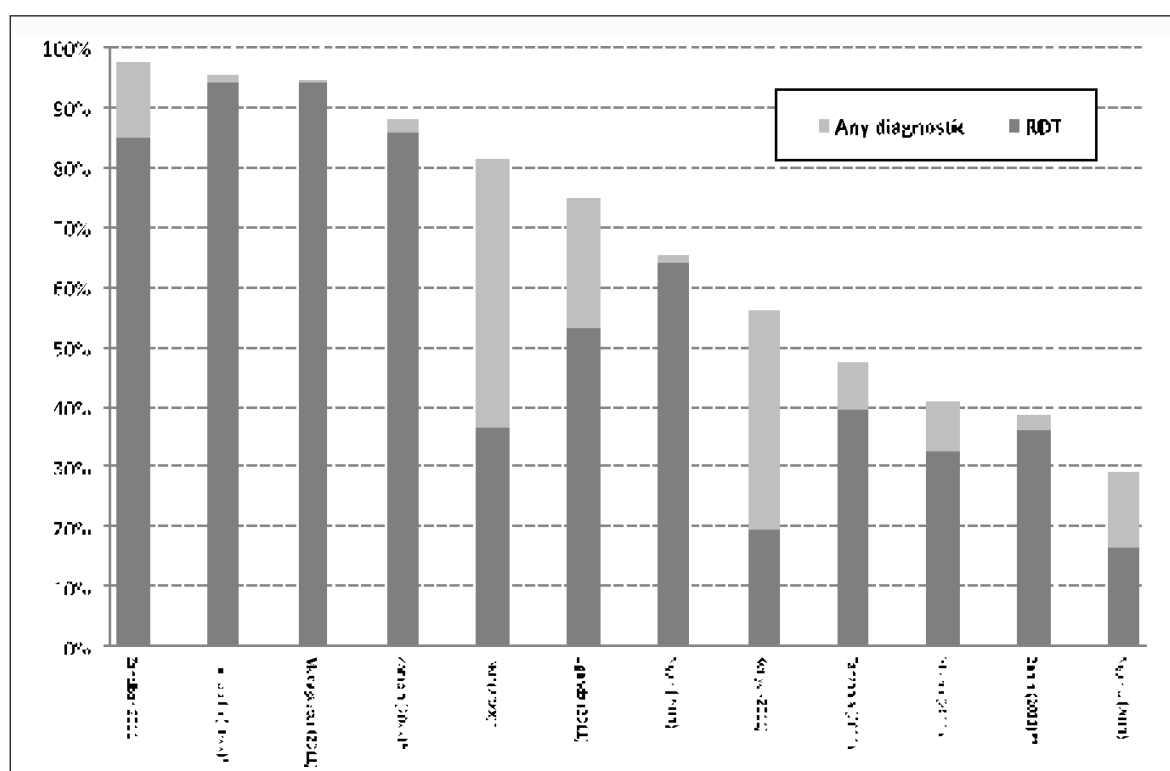
Diagnostic Test Availability in Public Health Facilities

The availability of diagnostic tests in the public sector has been assessed through outlet surveys conducted in several countries. Figure 13 shows the availability of any malaria diagnostic (either microscopy or RDT) and of RDTs in public health facilities sampled. Public sector availability varies greatly; it is high in Zambia, Cambodia, Madagascar and Zambia as compared to Nigeria, Benin and Ghana.

³⁸ World Malaria Report 2011. Geneva, World Health Organization, 2011.

³⁹ World Malaria Report 2011. Geneva, World Health Organization, 2011.

Figure 13: Public Sector Availability of Malaria Diagnostic Testing: % of Facilities with any Diagnostic Test / RDTs



* Designates public and non-profit sector facilities combined.

Source: ACT Watch Outlet Surveys except where denoted with ** indicating data from the Independent Evaluation of the Affordable Medicines Facility—malaria (AMFm) Phase I, Preliminary Report of July 18, 2012. Available at: <http://www.theglobalfund.org/en/amfm/independentevaluation>

Product Selection and Procurement

Public sector malaria RDT procurement is typically conducted through a tender process that is run by the country or outsourced to agents. Orders are generally placed once a year with staggered delivery. The procurement process can be lengthy and irregular, contributing to risk and instability in the market. Among procurements outsourced to agents, the Global Fund Voluntary Pooled Procurement (VPP) mechanism is most influential, with expected procurement of > 45 million RDTs in 2012.

Factors driving product selection include meeting product specifications (namely performance in the WHO Product Testing Program and factors related to ease-of-use), **price**, and **lead time**. It should be noted that, although meeting a minimum RDT performance threshold is a criteria for product selection, the RDTs with the highest performance in the Product Testing Program are not able to obtain a price premium in this market.

Product selection challenges include navigating the huge range of RDTs on the market and assessing the technical performance of RDTs. Understanding the range of products can be quite confusing; however, the process of identifying RDTs that meet a program's needs has been eased by the WHO product selection guidelines, WHO malaria RDT procurement manual, and FIND's on-line tool for identifying products meeting certain specifications. Local studies to evaluate sensitivity and specificity of RDTs are not recommended by the WHO as the primary basis of product selection due to the technical challenges of designing and implementing robust studies. However, the number of countries that are conducting local studies is increasing and adding complexity to the procurement process.

Donor Funding for Malaria RDTs

Funding for diagnostic test procurement is provided primarily by the Global Fund and PMI, and to a lesser extent by other donors and governments themselves. **The market's growth over the past several years has been enabled by the relative ease in which funding has been available** for malaria control, including for diagnostic test scale up. Although donor funding for malaria has grown substantially throughout the past decade, it is thought to have peaked at \$2 billion in 2011. Resources are expected to plateau or decline in the coming years due to the impact of the on-going global economic crisis on development assistance.

In light of the current funding situation, **reductions in resources for global health may constrain the future pace of RDT demand growth**. In particular, the Global Fund, the largest malaria donor and main financier of diagnostic test scale up, is currently undergoing a major strategic reform and is facing significant fundraising challenges. As a result, the extent of Global Fund resources that will be available for malaria over the coming years is uncertain.

Although ambitious global targets have been set and many countries are in the process of dramatically scaling up diagnostics, **little formal analysis of the effect that the funding predicament could have on the market has been undertaken to date**. In the near term, the changes may have little impact, as many programs have large unspent grant disbursements that should continue to fund diagnostic scale-up activities. However, countries facing major funding gaps in their overall malaria control programs will need to prioritize between different programs, potentially disrupting diagnostic testing levels and programmatic support for diagnosis. Uncertain funding for the scale-up of diagnosis may also negatively impact the RDT market at large.

At the country level, national programs are concerned about protecting gains achieved in malaria control and the ability to scale up further. However, it is difficult for countries to take action with little specific information available on future funding levels. It is likely that the coming years will see national programs focused on diversifying their funding base, identifying efficiencies in programs, prioritizing higher impact initiatives, and exploring opportunities for reprogramming.

With respect to procurement and quality standards, donors generally support country decision-making around RDTs. Donor policies are typically in line with WHO GMP recommendations for RDTs and with international standards around competitive bidding. Detailed information on individual donors, including funding levels for malaria diagnostics, types of support, and future plans, is available in the Appendix: Global Health Donor Landscape.

Expanding RDT Use to the Community

In the future, additional demand for RDTs may also stem from expanded use of diagnostics in the community and private sectors. Decentralization of RDTs through home-based management or community case management of malaria is likely to follow the public facility-based scale up of RDTs in many countries. Currently, models for community use of RDTs exist and have been successfully piloted in a number of countries. Forty-eight countries reported use of RDTs at the community level in 2010, up from 38 in 2009.⁴⁰ However, many of these programs are currently very small, and limited in geographic reach. National scale up will depend in part on funding availability and, when it occurs, will likely manifest as incremental to existing public sector demand.

Public Sector Malaria RDT Supply⁴¹

Malaria RDT Supplier Characteristics

Companies supplying malaria RDTs are diverse and vary in terms of size, years of operation, range of diagnostics business lines, degree of vertical integration, and geographic location. Of the handful of companies that dominate the public sector market, there is only one major multinational company, Alere, that controls several RDT brands, the largest being Standard Diagnostics (SD Bioline). Other suppliers to the public sector tend to be small diagnostics companies, some focused almost exclusively on the global malaria RDT market, while others also have modestly sized lateral flow test businesses and/or reagent businesses. Many companies that manu-

⁴⁰ *World Malaria Report 2011*. Geneva, World Health Organization, 2011.

⁴¹ Unless otherwise noted, this discussion focuses on the largest market for RDTs, the public health sector. To date, 44 companies have participated in the WHO malaria RDT Product Testing Program (which is now required to access this market). There are also RDT suppliers that do not participate in the Product Testing Program and are predominantly selling in smaller volumes outside of the donor funded public sector.

facture and market their own product also perform manufacturing of complete unlabeled RDTs or components of RDTs for other suppliers.

As described above, the public sector market is consolidating around a handful of suppliers. Although there are 18 different companies on the list of WHO-recommended RDTs, many are not very active in the public sector market. While some of these companies are focused on market niches and smaller market segments (for example, the Indian private sector or the international traveler market), others are new players that have not penetrated the public sector. In addition, several companies are active in other rapid test markets and it is likely that they have developed malaria RDT products to round out their portfolio of products but are not actively producing and marketing these tests.

Market Attractiveness and Innovation

The malaria RDT market appears to be attractive based on a number of key characteristics:

- It is a high growth market;
- It is relatively easy to develop and bring product to market, due in large part to the wide availability of the key active ingredient—monoclonal antibody—and simplicity of RDT production more generally;
- There is little intellectual property enforcement;
- Regulatory requirements are lower than for other diagnostic tests; and
- There are few large multinational companies in the market.

However, **recent trends, especially the erosion in prices, have reduced margins and contribute to the declining attractiveness of the RDT market.**

For new entrants, barriers to entry are emerging. For one, products must be evaluated by the WHO Product Testing Program in order to access the largest market segment, the public sector market. A second emerging barrier to entry is having adequate manufacturing capacity and access to working capital in order to successfully respond to tenders, which can require millions of RDTs to be delivered within 4-8 weeks of signing a contract.

Another measure of market attractiveness is innovation. In general, the incentives for ground-breaking innovation in the RDT market are limited. The current downward trend in pricing for malaria RDTs generally contrasts with the business principles of introducing a new product, as the malaria RDT market is unlikely to pay a premium for new products, and companies are therefore unlikely to recapture their R&D investment through price premiums.

Despite these market conditions, there are new companies interested in this market and existing suppliers frequently improve products. Much of the innovation, however, appears to be reactive, including redesign of existing RDTs that performed poorly in the Product Testing Program, efforts to reduce costs, and exploration of alternative sources of monoclonal antibody due to recent changes in the structure of this market.

Manufacturing Process and Inputs

For malaria RDTs, the major components of test kits include nitrocellulose and other membranes for the test strips, monoclonal antibodies and reagents (for preparation of blocking solutions, buffer, gold conjugate), plastic cassettes, foil pouches, alcohol swabs, desiccants, lancets, blood transfer devices, buffer bottles, packaging boxes with labels, and product inserts. The majority of these components are commodities, sourced from Asia and costing ½-3 cents each, with the plastic cassette and foil pouch generally costing the most. With the exception of nitrocellulose, other membranes, and monoclonal antibodies, there are several suppliers of components. Manufacturers purchasing high volumes of these commodities (e.g., companies that have large lateral flow tests businesses for malaria and other diseases that can use the same components for several products) should be able to negotiate favorable prices and terms. Quality nitrocellulose and membranes are available from a limited number of suppliers; RDT manufacturers typically work with one primary supplier.

Malaria RDT technology is based on monoclonal antibodies that have been manufactured to bind to specific antigens. These are available from a limited number of commercial sources and are produced in-house by few RDT manufacturers. Estimates of the per-test cost of monoclonal antibody vary, as manufacturers use different quantities and combinations of monoclonal depending on the product. Assuming a commercial source of anti-

body is used, the antibody cost for RDTs ranges from 2-9 cents per test, with the multi-line combination tests and smaller production runs having a higher cost per test.

National Bioproducts Institute (NBI), a not-for-profit organization based in Kwa Zulu Natal, South Africa, is a leading global source of monoclonal antibodies HRP-II and aldolase and has been supplying RDT manufacturers since 1998. NBI markets seven different antibodies, three HRP-II and four aldolase; however, one HRP-II antibody comprises the vast majority of its sales (~75%). NBI sells to approximately 25 customers, of which 14 have been consistently procuring over the past few years. Order sizes vary significantly, as RDT manufacturers keep limited quantities of monoclonal antibody in inventory and place orders for antibodies when awarded a contract. Pricing is volume dependent, with larger orders receiving a discount.

NBI developed the clones for producing malaria monoclonal antibodies in the late 1990's and produces ascites in a modern mouse colony that is then further processed into monoclonal antibodies. The start-up time for producing monoclonal antibodies is approximately 4-5 months. Due to the lack of predictability in demand and the RDT manufacturers' expectations for delivery of antibodies (2-4 weeks), NBI has increased its stock of intermediate raw material equivalent to 12 months based on current supply levels. Once an order is received, the intermediate raw material undergoes a purification step and quality control testing before release and shipping, allowing NBI to deliver within 3-4 weeks.

As a not-for-profit company, NBI aims to make its products available at prices affordable to resource-poor countries affected by malaria. Therefore, pricing of monoclonal antibodies aims to cover direct costs and make a contribution to overheads and to a modest operating surplus required to fund ongoing operations and capitalization projects at NBI. NBI's sales of malaria monoclonal antibodies steadily increased following a decline in 2008, and leveled off in 2011.

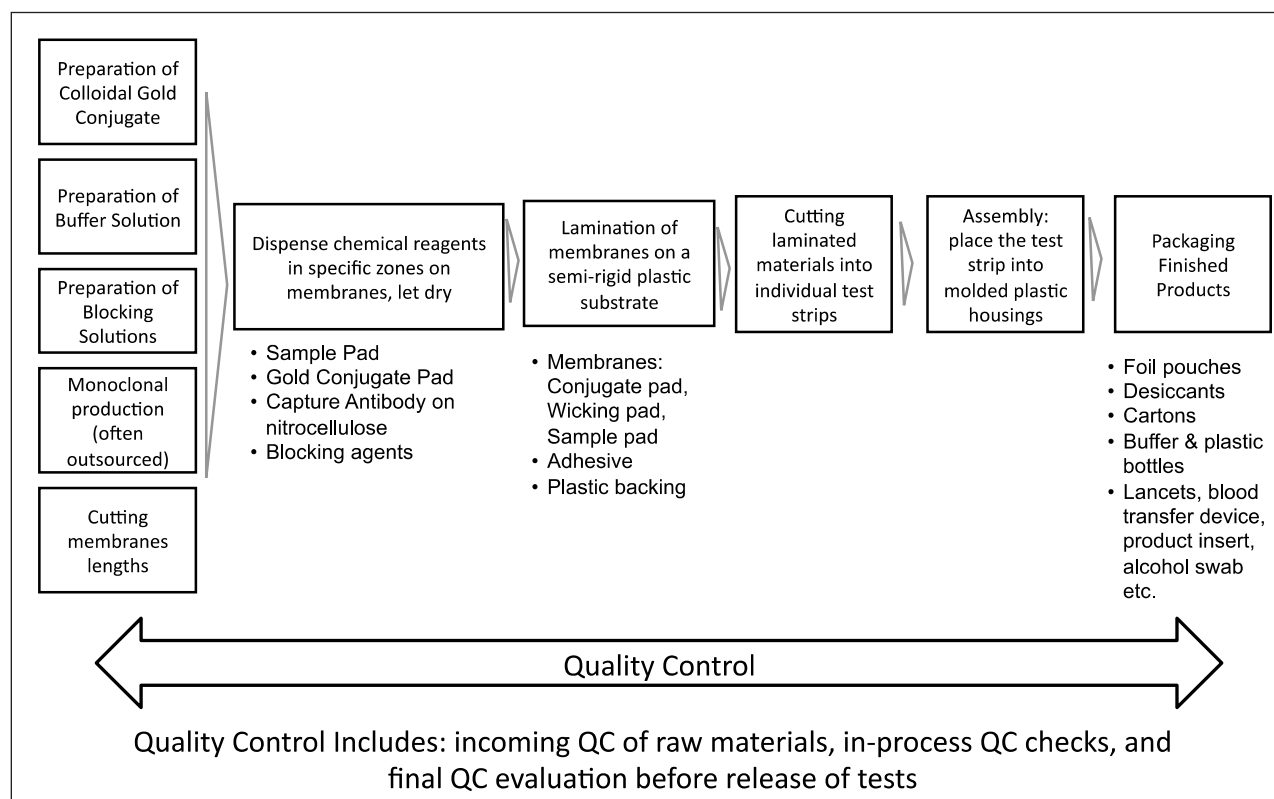
AccessBio (New Jersey, USA), a leading manufacturer of malaria RDTs, became the primary commercial source of pLDH monoclonal antibodies in late 2011 when it acquired the clones for the pLDH monoclonal antibody business from Flow Inc., an American research and development company that initially developed and marketed the pLDH monoclonal antibodies. AccessBio outsources manufacturing of the antibodies to two American companies specializing in monoclonal production, and sells through two primary distributors, Vista Diagnostics (Seattle, WA, USA) and Arista Biologicals (Allentown, PA, USA).

Although twenty different monoclonal antibodies are available, in 2010 over 90% of pLDH antibody sales were for five antibodies: two pan-malaria antibodies, two *P. vivax*-specific antibodies, and one *P. falciparum*-specific antibody.⁴² As is the case with NBI, order sizes vary tremendously and pricing is volume dependent. The lead-time for producing pLDH monoclonal antibody is approximately three months. If AccessBio or its distributors has an antibody in inventory, an order can be filled within a week, otherwise it can take three months to fill an order. The price of commonly used pLDH monoclonal antibodies is somewhat lower than that of HRP-II from NBI; however, approximately one and a half to two times as much pLDH is used on a typical two-line pan malaria RDT as compared to a two-line HRP-II detecting RDT. Sales of pLDH have been generally increasing over the years.

The major steps in malaria RDT manufacturing are outlined in Figure 14. In addition to the components described above, a major cost of RDT manufacturing is labor. **Demand growth coupled with rising labor costs in most markets has led to increasing automation in malaria RDT manufacturing.** If designed correctly, automation can drive down costs and improve quality. The degree of automation among RDT manufacturers varies, with the majority of production being a mix of automation and manual work. Larger manufacturers operating in high labor cost environments tend to have higher degrees of automation. In general, in malaria RDT manufacturing several pieces of equipment (typically costing \$50-300,000, although fully automated customized equipment can cost >\$1 million) may be used for key steps (dispensing reagent onto membranes, laminating), with technicians still monitoring the process and feeding the equipment. Steps like final packaging of goods into cartons is rarely automated. The decision to automate is influenced by access to equipment suppliers and maintenance, as well as external factors such as local government incentives for employment.

⁴² AccessBio began marketing the pLDH monoclonal antibodies in mid-2011, therefore it has limited experience with the business to date. The information here draws primarily from Flow's historical experience.

Figure 14: RDT Manufacturing - Major Steps and Inputs



Source: Author

Shipping and Distribution

Other costs relate to shipping and distribution. Short delivery timeframes and requirements for cool chain result in shipping by air, which is relatively expensive. Air shipping adds 10-18% to the RDT price, while shipping by boat adds 2-3% but takes an additional 6-8 weeks, thereby reducing the remaining shelf life of RDTs when they arrive in country.

Most companies have local distributors who represent them in country and can provide product support. Some distributors will stock small quantities of RDTs for sale to local NGOs and the private sector. Functions performed by a distributor may include (i) gathering information related to local tenders and responding to them, (ii) ensuring the RDT is registered locally with relevant agencies and bodies, (iii) orienting the ministries of health on the product, (iv) assisting with receipt of shipments, local transport, and customs clearance, and (v) providing training and technical support/troubleshooting. The downward pressure on prices in the tender market has put pressure on distributor margins and often limits the role of local distributors. In addition, international procurement mechanisms (e.g., VPP, PMI, UNICEF/WHO) that purchase directly from manufacturers further limit the role of distributors in this market.

Cost Reduction

Due to the erosion of margins, RDT manufacturers are pursuing several cost reduction strategies, including increasing automation to reduce labor costs as discussed above. Relocating manufacturing is another option that companies are exploring. This often involves shifting some of the more manual steps of RDT manufacturing (cutting, final assembly, and packaging) to new facilities located in lower-cost labor environments and/or closer to the customer to reduce transportation and handling costs. Backwards integration into monoclonal supply is another strategy that several companies have implemented to reduce costs and better control raw material supply. Lastly, reconfiguring of tests and kits is another cost reduction strategy that suppliers may explore. This could involve using less material in each test, reducing the materials required for packaging, or changing ac-

cessories included in the kit. As with any diagnostic test, however, changes must be validated internally and regulatory agencies/quality programs notified appropriately. Major product changes may require resubmission to the WHO Product Testing Program or review by the WHO Prequalification program. New manufacturing facilities would also require re-inspection by WHO Prequalification. As mentioned previously, the timelines associated with these quality programs may negatively affect the decision to invest in these areas.

Public Sector Summary: Malaria RDT Market Outlook

Pricing

Conversations with manufacturers and procurement agents suggest that **increasingly low prices (e.g., < \$.30/test for *P. falciparum* RDTs) represent strategic attempts by manufacturers to penetrate new markets, and that these prices are not sustainable in the long term.** At the same time, **continued downward pressure on prices in the coming years** is expected as funding becomes more scarce and malaria programs aim to maximize the number of RDTs purchased with limited budgets.

Another trend affecting the market is the relatively **frequent tendering and pressures to switch RDTs in order to comply with procurement standards around competition, creating a highly volatile market**, especially in comparison to other rapid tests, like those for HIV, where local algorithms have had the effect of stabilizing the market. The instability in the malaria RDT market contributes to price variation and limits companies' ability to forecast and plan production. Recently, donors have responded to this challenge by relaxing the requirements around competition.

Manufacturing Capacity and Lead Times

As mentioned, delivery schedules are often a factor in RDT product selection. Because funding disbursements are often released on short notice and malaria programs are often at risk of missing grant targets, **programs frequently request expedited delivery of RDTs.** It is common for the first delivery of RDTs to occur 4-8 weeks after the contract is awarded, although shorter and longer timeframes are also possible.

Manufacturing capacity has not yet led to supply interruptions of malaria RDTs and buyers report that the major RDT suppliers are generally responsive to relatively demanding delivery timeframes. **However, the volatility in the market and urgency associated with many tenders are major challenges for RDT manufacturers.** Manufacturers do not generally keep large stock of finished goods in inventory due to the risk of product expiry and the typical requirement that products have 80% of their shelf-life remaining upon delivery to country. As a result, RDTs often are manufactured to order, requiring a careful balancing of demand and inventory (raw materials, intermediate product, and finished goods) in order to meet delivery timelines. Because lead times of several weeks are common for many raw materials and components, manufactures may keep a stock of these goods or place orders for these in advance of having a signed contract—however, there is a working capital cost associated with doing so. To rapidly manufacture large quantities of RDTs, manufacturers often add additional production shifts. However, this also requires stepped-up quality control to ensure that workers are adequately trained and supervised.

It is not possible for some manufacturers to meet aggressive delivery deadlines for large orders. Because countries may switch from one brand of RDT to another from year to year, manufacturers have limited ability to prepare forecasts for inventory and production management purposes. In addition, irregularities in procurement practices have financial implications for manufactures because their working capital is at risk.

Future

Overall, **pressure on pricing and volatility in the malaria RDT market is creating a market where competition is based on economies of scale and thin margins.** There is significant concern that the recent low prices will not be sustainable in the long term, and that **the current nature of competition may lead to deterioration in quality of the product and/or withdrawal of some suppliers from the market.** The incentive to reduce

costs at the manufacturing level is particularly concerning in a market that has limited post-market surveillance and whose track record for quality control at the manufacturing level is unproven.

Private Sector Market for Malaria RDTs

There is increasing interest among policy makers and advocates in leveraging private sector channels as a potential means of increasing access to malaria diagnosis and of better targeting ACTs. However, **there is a relative dearth of information on existing private sector markets.** In addition, **development of the private sector market for RDTs raises several policy and implementation questions that have not yet been addressed.**

Several research projects are underway to better understand this potential market; however, it is difficult to generalize from the study findings, given the complexity and size of the private sector. As such, the discussion below is based in large part on anecdotal information gathered from conversations with manufacturers (primarily those who supply the public sector) and experts and investigators working in this area. The discussion also includes a very limited set of data from ACT Watch supply chain and outlet surveys⁴³ and one published informal survey of private sector outlets conducted in 2009 by FIND.⁴⁴

Availability of Diagnostic Tests in the Private Sector and Market Size

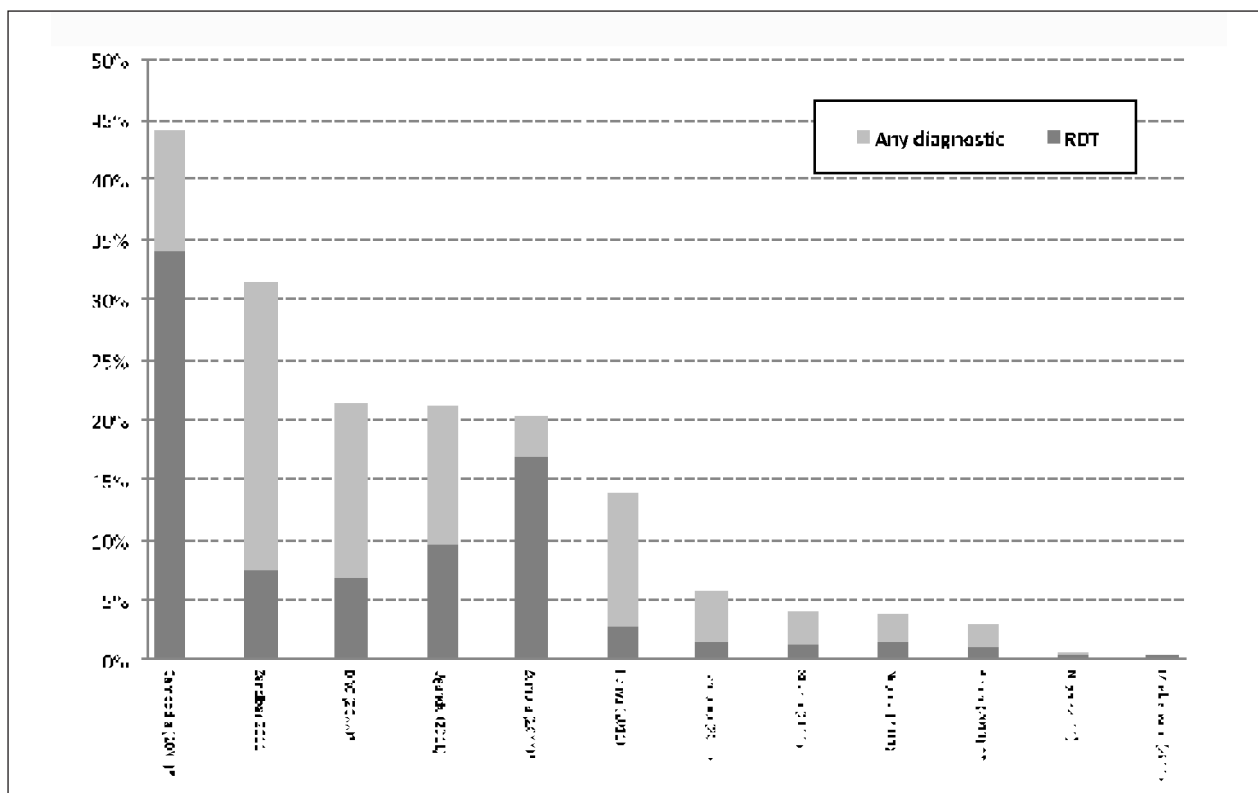
There are several possible channels for malaria diagnostic testing in the private sector, including private health facilities (hospitals and clinics), stand-alone private laboratories, registered pharmacies, drug shops, general stores, itinerant vendors, and other less formal outlets.

As shown in Figure 15, ACT Watch data from several countries indicate that the availability of diagnosis in private sector retail outlets selling antimalarial medicines is small or minimal in many highly endemic countries. Likewise, a survey conducted by FIND found limited availability of RDTs in the private sector—11% of outlets visited had RDTs, most of these being private clinics with qualified providers. Cambodia, where test availability is relatively high, has had a private sector subsidy for RDTs and ACTs in place for ten years that has increased availability of RDTs in the private sector.

⁴³ Available at: <http://www.actwatch.info/results>

⁴⁴ Albertini et al. Preliminary enquiry into the availability, price and quality of malaria rapid diagnostic tests in the private health sector of six malaria-endemic countries. *Trop Med & Intl Health*. Feb 2012; 17(2):147-152. This paper discusses a survey of 324 formal sector outlets that was conducted across 6 countries.

Figure 15: Private Sector Availability of Malaria Diagnostic Testing—Percent of Outlets Selling Antimalarial Medicines with Diagnostic Testing Services



Source: ACT Watch Outlet Surveys except where denoted with ** indicating data from the Independent Evaluation of the Affordable Medicines Facility—malaria (AMFm) Phase I, Preliminary Report of July 18, 2012. Available at: <http://www.theglobalfund.org/en/amfm/independentevaluation>

ACT Watch studies also suggest considerable variation in RDT availability among private sector outlets, with higher availability in more formal outlets (e.g., health facilities and pharmacies) and minimal availability in less formal outlets. In Uganda, for example, ACT Watch found 54% of health facilities and pharmacies surveyed had diagnostic services, compared with 7% of drug stores, and 0% of general retailers and itinerant vendors.

It should be noted that in many countries, private diagnostic laboratories exist and would likely provide malaria diagnostic services; however, this segment of the market has not been studied.

Conversations with leading malaria RDT suppliers suggest that **the private sector malaria RDT market is not very large—10-15% of the total market globally—and is not growing as rapidly as the public sector market.**⁴⁵

Products Offered

There is minimal data available on products offered in the private sector. The FIND survey reported that a variety of RDT brands were available, and that only in one country was there an overlap between the brand of RDT chosen by the NMCP and the brand available in the private sector. This survey also found that nine of 14 RDTs collected from the sites passed quality control testing. The quality of tests in the private sector needs additional exploration.

In some countries, suppliers report that malaria antibody tests are popular, especially in the private sector. Because they serve as a marker of exposure and not of current infection, antibody tests are not recommended for malaria case management.

⁴⁵ Of note: it is very likely that suppliers who are less active in the public sector are supplying the private sector, so this estimate may be somewhat biased.

Private Sector Supply Chain

At the RDT manufacturing level, the leading public sector suppliers do not report selling many RDTs to the private sector (5-15% of overall volumes). There is little consensus among these RDT manufacturers about the potential of this market, while some are pursuing it, others do not see it as worthwhile. It is also likely that several RDT manufacturers who are not very active in the public sector play a more active role in the private sector markets.

At the country level, ACT Watch looked at availability of RDTs at the wholesale and retail levels (see Table 2 and Figure 16). In general, the number of wholesalers that RDTs pass through before reaching a retail outlet varies; it may be as few as two or as many as four or five. The surveys show low availability of tests in the private sector supply chain, limited turnover of RDTs at the wholesale level, and wide variation in the prices wholesalers pay and charge for RDTs. Markups tend to be in the 30-60% range, but the purchase price paid by wholesalers varies, as do the retail prices for RDTs, which range from \$.20 to several dollars per test.

Private sector distribution of RDTs in Cambodia has been dominated by a social marketing program to sell subsidized RDTs and ACTs to wholesalers and retailers in the private sector.⁴⁶ The program also includes behavior change communication and training of private health care providers. RDTs in this program are branded as Mal-check and sold at \$.05 to wholesalers, with a recommended selling price of \$.24.

Table 2: ACT Watch Findings on Malaria RDTs Distribution Chain⁴⁷

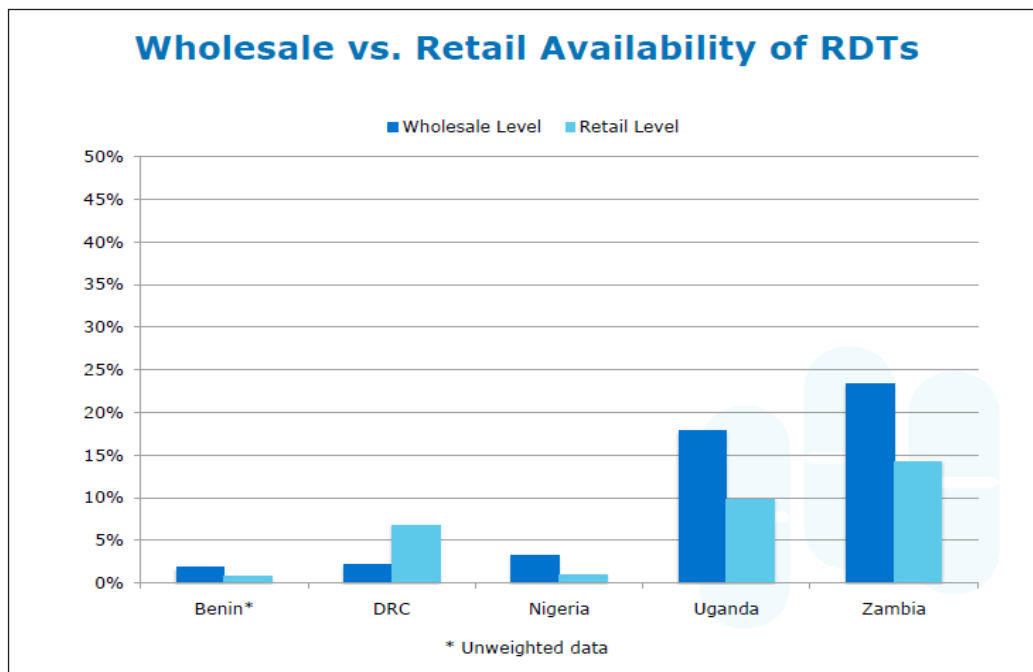
| | Cambodia | Nigeria | Zambia |
|--|---|--|--|
| Availability | 86% of wholesalers stocked RDTs. 89% of all RDTs stocked were Mal-check, the socially marketed brand | 4% of wholesalers stocked RDTs | 23% of wholesalers stocked RDTs at time of survey; 40% reported having stocked them in past 3 months. |
| Volumes Sold (in the past week) | Wholesalers reported relatively low volumes of RDTs sold in the past week, possibly due to timing of survey which was at the end of the malaria season. | Of the very few wholesalers who stocked RDTs, the median number of tests sold was 315 among wholesalers who supplied wholesalers and 25 among wholesalers supplying retailers. | Among the few wholesalers who stocked RDTs low volumes were sold, however, there was wide variation due to higher volumes among wholesalers selling to wholesalers (median 250 RDTs in past week.) |
| Purchase Price (median) | \$.05 wholesalers supplying wholesalers \$.19 wholesalers supplying retailers | \$.71 | \$3.06 wholesalers supplying wholesalers \$5.19 wholesalers supplying retailers |
| Percent Mark ups | 33%, with mark ups for wholesalers selling to retailers being lower (33%) than the mark up on sales between wholesalers (62.5%) | 40% | 51.7% (n=1) wholesalers supplying wholesalers 47.5% wholesalers supplying retailers |
| Absolute Mark ups | \$.05 | \$.32 | \$2.38 |
| Retail Prices of RDTs | \$0.35 median price for RDTs \$0.71 for microscopic testing in the private sector. ⁴⁸ | >\$3.00 ⁴⁹ | Not available |

46 ACT Watch Supply Chain Survey Cambodia, available at <http://www.actwatch.info/results/> (accessed 11 April 2012)

47 All data comes from ACT Watch Supply Chain Surveys, available at <http://www.actwatch.info/results/> (accessed 1 April 2012) unless otherwise noted.

48 Littrell, M. Case management of malaria fever in Cambodia: results from national anti-malarial outlet and household surveys. *Malaria Journal* 2011, 10:328

49 ACT Watch, iHEA supply chain presentation, 2011 _Study Design: Supply Chain Survey. The potential of the private sector to promote the integration of rapid diagnostic tests for malaria into developing country health systems: a multi-country study. Available at <http://www.actwatch.info/results/> (accessed 18 April 2012)

Figure 16: ACT Watch - Wholesale vs. Retail Availability of RDTs

Source: ACT Watch, iHEA supply chain presentation, 2011. Study Design: Supply Chain Survey. The potential of the private sector to promote the integration of RDTs for malaria into developing country health systems: a multi-country study.

Manufacturing and Costs

From a cost of goods perspective, RDTs for the private sector are likely to be slightly more expensive than for public sector procurement. Private sector volumes are often lower than the public sector and require individual packaging of tests or smaller package sizes. Costs associated with these include individual small box printing (which can be more expensive than larger boxes), increased labor costs associated with more packaging requirements, and the cost of individual buffer tubes and inserts in local languages.

Private Sector Demand for RDTs

Relatively little is known about consumer demand for malaria diagnostics, although a handful of researchers are currently studying, or have recently published on, factors affecting consumer demand, such as awareness, preferences, and willingness to pay.

Geographically, RDT suppliers report that the private sector is larger in some, but not all, Asian countries (e.g., India, Thailand, and Vietnam) than in African countries. Currently, private laboratories and clinics comprise the majority of private sector sales as opposed to retail drug outlets/shops. Malaria RDT suppliers also report that private sector laboratory customers (i) generally prefer combination tests, (ii) tend to be quality conscious (although the standard used is not necessarily in-line with the WHO recommendations), (iii) may require more technical support, and (iv) tend to focus more on test presentation than buyers in the public sector.

Prices

Data on prices of RDTs in the private sector is scarce, and limited to a very small survey by FIND and limited ACT Watch data. For example, the FIND survey obtained prices on 24 different RDTs, which ranged from \$1.00 to \$16.81, with a mean price of \$7.51. These prices included the cost of the test and, where applicable, performance of the test. The ACT Watch and Independent Evaluation data set is considerably larger than FIND's (n > 600), with median prices for an RDT ranging from \$0.58 to \$3.22 across 10 African countries.⁵⁰ In general, due to cur-

⁵⁰ ACT Watch Outlet Surveys and the Independent Evaluation of the Affordable Medicines Facility – malaria (AMFm) Phase I, Preliminary Report of July 18, 2012. Available at: <http://www.theglobalfund.org/en/amfm/independentevaluation>

rent manufacturer selling prices for RDTs and the supply chain markups described above, retail prices for RDTs are likely to be unaffordable for most of the population given the average income in areas affected by malaria.

Malaria RDT suppliers also report that manufacturer selling prices are frequently higher in the private sector than in tender markets, and that the price paid by consumers is likely several times the price of the RDT sold by the manufacturers due to sales and distribution markups.

Operational Research: RDT Subsidies

There are several ongoing operational research projects on malaria RDTs in private sector. Results are largely unpublished, but many investigators plan to publish before discussions around the AMFm continuation in late 2012. A brief summary of several of the more publicized projects is provided below, including some of the early findings.

As described above, Cambodia has over ten years of experience with socially marketed RDTs and ACTs in the private sector, and is the only country with a national program of this type. There has been little formal, comprehensive evaluation of this program. A case study reviewing various household and provider surveys on the project was published in 2011⁵¹ and found that it took many years to increase product awareness among consumers and retailers. In addition, improvements in product availability and uptake were slow to emerge, especially in remote areas and among the informal providers who are a popular source of treatment in Cambodia. The program highlights the need for robust monitoring and evaluation programs, well designed communications strategies, and reliable availability of products. Other challenges relate to increasing uptake of RDTs and the difficulty in creating incentives and appropriate messaging to encourage adherence to case management guidelines. In particular, the complexity of the three-part message—(i) test before treatment, (ii) take the recommended drug if positive, and (iii) do not to take an antimalarial if negative—has been a challenge.

In 2009 a small pilot in western Kenya⁵² tested the impact of subsidizing ACTs and RDTs in rural drug shops. The study involved randomly assigning households to one of three groups: (i) a control group that received no subsidy for ACT or RDT, (ii) an ACT subsidy group, in which households received vouchers for reduced-price ACTs, and (iii) an ACT and RDT subsidy group, in which households received vouchers for reduced-price ACTs and RDTs (either free or \$.20/test). Trained study staff were posted at the drug shops to monitor the program. The study found that:

- People were very willing to use RDTs. The RDT subsidy (whether free or \$.20) increased the testing rates for malaria, from 22% in the comparison group to 43% in the subsidy group.
- Adherence to test results was an issue: while nearly all RDT-positive individuals purchased an ACT, half of RDT-negative individuals also bought an ACT.
- Over-treatment was an issue for adults in particular. Among adults, ACT use increased; however, only 25% of adults who took a subsidized ACT were positive for malaria.

Another study being conducted in several districts of Eastern Uganda,⁵³ is looking at the conditions required for sustainable distribution of RDTs in drug shops. The study provides RDTs to wholesalers who offer them to a randomly selected group of drug shops at subsidized prices. The study has been monitoring whether the shops stock, sell, and promote RDTs, the prices offered, the storage conditions for RDTs, and quality of testing performed by shopkeepers. Preliminary results support the operational feasibility of the private sector supply chain distributing RDTs and of training shopkeepers to store and perform RDTs acceptably. It also shows some desire among shopkeepers to stock RDTs and sell them at affordable prices. The study will also measure the impact of a communications campaign on RDT use and adherence to test results.

The Zambia Access to ACTs Pilot Initiative (ZAAI)⁵⁴ is an ACT and RDT subsidy program implemented in 2010 in four districts and three control districts of Zambia. This program involved accrediting informal drug shops, training on protocols for ACT dispensing (shops could not sell ACTs without confirmed malaria diagnosis), and a communications campaign aimed at increasing community awareness of testing and treating with an ACT.

51 This section draws on: Yeung et al. Socially Marketed rapid diagnostic tests and ACT in the private sector: ten years of experience in Cambodia, *Malaria Journal*. 2011, 10:243

52 This section draws on: J-pal Policy Briefcase (Jan 2012), A Balancing Act: Subsidizing Drugs and Diagnostics for Malaria.

53 This section draws on: Cohen et al. Evaluating the feasibility of introducing malaria diagnosis in the retail sector: Evidence from Eastern Uganda. Preliminary Findings from Baseline Household Surveys. January 2012.

54 This section draws on: Preliminary results from the Zambia Access to ACTs Pilot Initiative (ZAAI), presentation made in at Innovations In Health Care Financing And Service Delivery: Making Malaria Treatment Available meeting, World Bank, Washington D.C., 8-9 December 2011.

Both ACTs and RDTs were sold at no cost to wholesalers who then supplied the accredited shops. A recommended selling price was provided by the investigators.

While ZAAI results are not yet published, conversations with the investigators about preliminary results indicate that RDT uptake was strong, and the majority of patients were tested. In addition, adherence to the testing protocol was relatively high: the vast majority of those who tested negative did not receive an ACT and most of the ACTs sold went to patients who had been tested. Challenges related to this program included the need to regulate drug shops. ACTs are prescription-only in Zambia and therefore only available legally at registered pharmacies that are mainly located in urban centers. This project, working with the Zambian government, had to develop an accreditation program for the informal drug shops.

Other studies are also looking at RDT use and subsidies in the private sector, including several qualitative studies and pilots of RDTs in the private sector that are being conducted in connection with the AMFm grants.

Private Sector Market Summary

There is growing interest in the potential for the private sector to increase access to malaria diagnosis and to reduce over-use of ACTs. However, the optimal model(s) for expanding access to diagnosis through the private sector is not currently clear and many unanswered questions remain.

Studies like those described above are increasing confidence in both the suitability of private sector supply chains for distribution of RDTs and the ability of retail shopkeepers to stock and perform RDTs at affordable prices. With respect to the quality of the RDTs in these subsidized programs, two of the projects included collecting a sample of RDTs from shops for quality control testing; all of the RDTs passed the testing, suggesting that their performance had not been significantly impaired by transportation and storage conditions. The studies have also established that there is some demand for and willingness to pay for RDTs among retail outlet customers.

Although the studies have shed light on some areas of RDT use in the private sector, several unanswered questions remain. Acceptance of RDTs and management of non-malaria fever in the private sector are challenges. As in the public sector, there are cases in the private sector where negative RDT results guide treatment decisions and cases where they do not. In addition, the pilots highlight the complexity of segmenting the retail market and understanding the motivations of retailers. While profit maximization may be the primary motivation of some businesses, others cite “service delivery” and building “community trust” as motivations.

Additional research is needed to determine the appropriate subsidy level for RDTs and for treatment. Setting the appropriate subsidy must take into account both supply- and demand-side incentives. Retailers must have an incentive to stock and sell RDTs at affordable prices. With respect to customers, treatment seeking behavior and willingness to pay for an RDT may differ and change depending on people’s perceptions of how likely it is that they have malaria and their trust in the RDTs themselves.

Related to demand for diagnosis is the need for communication campaigns to increase awareness of RDTs and the value of diagnosis; however, the most effective messages and strategies for delivering a relatively complex message have yet to be worked out.

In order to scale a program, operational challenges also must be addressed, including ensuring providers can perform the tests and are familiar with the protocols (in light of high staff turnover experienced at many retail outlets). The design of systems for monitoring quality of testing and treatment and waste management logistics are also key. The cost and human resources requirements of wide geographic scale up must also be analyzed and considered.

In many countries, regulations may limit the ability of certain private outlets to sell diagnostic tests or may require that individuals performing tests have specific qualifications. Regulation of the private sector is a sensitive issue in many countries and the desire to make RDTs available in the private sector may be in conflict with efforts to regulate the informal private sector, including both drug shops and private laboratories.

Lastly, because of differences in the prevalence of malaria, the composition of the private sector, and the relative strength of the public sector, it is likely that private sector approaches to increasing diagnosis and improving ACT targeting will be more effective in some countries than in others. Analysis of the best approach for increasing access to testing, including evaluations of cost-effectiveness, are currently being conducted.

Malaria Diagnostics Market Shortcomings and Their Reasons

The key market shortcomings described below relate to assuring the quality of RDTs, especially given the current market conditions, and expanding delivery to the private sector. There are also additional issues around availability, acceptability/adaptability, and affordability.

Quality

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| Market Shortcoming | Quality: practical methods and technologies to enable quality control testing are nonexistent and inadequate where they exist. |
| Description | <p>For most diagnostic tests there are technologies and well-established methods for checking the quality of the tests along the value chain from manufacturer to point of service. These technologies and methods have been developed by international bodies, public health laboratories, and/or are commercially available. Practical methods and technologies to enable quality control testing of malaria RDTs, however, are nonexistent and inadequate where they exist. Specifically,</p> <ul style="list-style-type: none"> • There is no practical tool for confirming the performance of an RDT in the field. FIND and partners have been leading an effort to develop positive control wells for RDTs, although there is no product yet. Recently BMGF announced additional support to FIND to develop manufacturing capacity and to implement demonstration projects for the positive control wells. • While programs exist at the international level to evaluate tests prior to purchase (i.e., WHO Product Testing) and to evaluate RDTs as they are delivered to countries (i.e., WHO Lot Testing), these programs are expensive and would benefit from technological advances that would allow reduced reliance on the human-derived specimen bank and allow for simplification of the testing procedures. • Recently, BMGF and UNITAID committed over \$10 million to FIND/WHO to restructure the existing WHO product and lot testing programs to reduce costs and reliance on donor funding. The transition will involve the development of quality control testing that is based on recombinant antigen panels and a move to a user-fee model of testing. The program is not without risks, however, including technical risk around development of recombinant panels and implementation risk. The transition is expected to take several years. In the near term, both product and lot testing are expected to continue to operate as they do now. |
| Reasons | <ul style="list-style-type: none"> • Insufficient awareness/prioritization of diagnostic test quality control among RDT buyers and policymakers. Lack of well-articulated demand for quality control technologies or product specifications. • Little incentive for private sector investment in quality controls due to: (i) the lack of definition around the market (no product specifications; demand and willingness to pay have not been articulated), and (ii) the overall nature of malaria RDT market (low margin business with little incentive to invest in R&D). • Current malaria RDT quality control programs are expensive due to technical challenges associated with reliance on human-derived and cultured quality control specimens. These include: (i) the characterization of samples required for quality control purposes is technically challenging and available only in well-equipped malaria laboratories, (ii) regulatory requirements make international shipment of samples difficult, (iii) shipping blood under controlled conditions is expensive and may affect the integrity of specimen, and (iv) the relative lack of stability of the antigens detected by malaria RDTs (as compared to the antibodies detected by other common tests used for global health, HIV and hepatitis tests for example). • In theory it is possible to manufacture antigens (i.e., recombinant antigens) that are cheaper and more easily produced than human-derived specimens used for RDT quality control purposes. Reasons for the lack of recombinant-based technologies include: (i) technical complexity related to the production of recombinant antigen-based quality controls, in particular the stability of recombinant antigens is a challenge, and (ii) among the companies with technical capacity and experience required to develop a recombinant quality control, there is likely little awareness of the need for these tools (moreover, given the current market dynamics, there is little financial incentive to undertake R&D necessary to develop and commercialize recombinant quality controls and FIND and partners have been active in this space for several years). |

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| Market Shortcoming | Quality: Information on the quality of malaria RDTs is limited. |
| Description | <p>There is little insight into upstream quality (i.e., quality systems at the manufacturing level) and limited post market surveillance/downstream monitoring of quality. The only source of reliable information on RDT product performance, the WHO Product Testing Program, is undergoing restructuring, and this program primarily addresses only one aspect of quality, i.e., performance of the product. The WHO Diagnostics Prequalification Program, designed to address quality at multiple levels, has proven to be a lengthy process, with only two malaria RDTs approved since 2010. Although there are 14 RDTs at various stages of the prequalification process at the time of this report, the timing of approvals is unpredictable. Uncertainty and risk in the market are caused in part by uncertainty associated with these programs' status and timelines and limited coordination and transparency around the roles of various quality programs.</p> <p>Although there is some debate around the existing quality programs (largely related to technical issues related to protocols and procedures), players on both the supply and demand side of the market agree that there is a need for some form of quality standards and evaluation in the malaria RDT market. An absence of quality programs in this market will likely precipitate the exit of suppliers from the market, especially those whose products are among the higher-performing products.</p> <p>The lack of information on quality is particularly alarming considering current market conditions, characterized by intense competition around price, short delivery times, and larger orders that can exacerbate quality problems.</p> |
| Reasons | <p>On the demand side, reasons for limited information on quality include:</p> <ul style="list-style-type: none"> • Insufficient awareness and/or prioritization of quality standards for diagnostic tests among malaria RDT customers and policy makers. • Countries with markets for malaria RDTs are generally resource poor and do not have formal regulatory processes or post-market surveillance programs for diagnostics. In countries that do have effective diagnostic test regulation, the market for malaria diagnostics is minimal (e.g., limited to travelers or military), therefore manufacturers have no incentive to engage in a costly and time consuming regulatory process that would holistically address quality.⁵⁵ • Little downstream quality control of tests due to lack of methods/technologies to implement (as above). <p>On the supply side, little is known about RDT quality and manufacturer quality systems; however, reasons for concern include:</p> <ul style="list-style-type: none"> • At the manufacturing level, there is little incentive to invest in robust quality systems. The reasons for this include a market that attracts new entrants (due to the high growth potential, limited regulation, little intellectual property enforcement, ease of access to key active ingredients, and ease of rapid test production more generally), but that is ultimately a low-margin business with increasingly intense competition around price. In addition, there is little business justification for investing in in robust quality management systems because customers have little ability to differentiate between good and poor quality manufacturing. • Further challenges around quality at the manufacturing level include many of the same challenges faced by international bodies attempting to evaluate RDTs. These include the technical complexity of evaluating malaria RDTs, difficulty in accessing quality control standards, and relative inexperience in quality management among some malaria RDT manufacturers (due to the small size of companies, limited local government requirements for diagnostics manufacturing). |

⁵⁵ Although some malaria RDTs have a CE mark, due to the risk classification system used by the EU system, the CE Mark requirements for malaria diagnostic tests are largely an administrative exercise and are not very stringent and do not include a full quality evaluation.

Delivery

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| Market Shortcoming | Delivery: Insufficient uptake of diagnostics and concern about potential slowing of scale up in the public sector. |
| Description | <p>After a slow start, adoption of RDTs has been more rapid in recent years. However, given the targets for universal access, there is still significant ground to cover to improve delivery of RDTs in the public sector.</p> <p>There is also increasing concern about sustaining progress and the pace of diagnosis scale up in the coming years due to funding challenges. Although RDTs are relatively inexpensive and prices are declining, the scale required to achieve universal access means that diagnostics budgets will need to increase significantly. For example, currently an estimated 500 million additional tests would need to be financed over the 2012-2015 period for Africa to achieve universal access to diagnosis in the public sector.⁵⁶ Because many of the governments in malaria-affected regions have limited resources, they rely on donor funding to support scale up of diagnostic testing. Funding shortfalls may ultimately limit budgets for RDTs or for programmatic interventions (training, communications, supervision) that are critical for ensuring appropriate use of RDTs.</p> |
| Reasons | <p>Reasons for current delivery issues include supply chain deficiencies like delays in accessing donor funds, cumbersome product selection processes, weak quantification methods, weak in-country distribution systems. Other factors contributing to slow uptake include limitations in training of health workers (in particular the content of training), inadequate quality assurance and supervision, and insufficient investment in communications/behavior change campaigns to increase demand for testing and transform the approach to fever management (the latter is discussed further under acceptability, below).</p> <p>Reasons for the potential risk to diagnosis scale up in the future stem primarily from reliance on a limited number of donors whose funding for malaria may be limited in the coming years. While RDT costs are offset by reductions in ACT budgets, it takes time to see the results. The total cost to the health care system is also affected by other factors including the human resources and overhead costs associated with RDTs.</p> |
| Market Shortcoming | Delivery: there is little demand for diagnostics in the private sector. |
| Description | <p>In practice, a large proportion of people bypass the public health sector for treatment of malaria, with their first response to perceived malaria episodes being self-diagnosis and purchase of an anti-malarial drug at a private shop. There is little demand for RDTs in the private sector, which given its reach and distribution capacity may be a missed opportunity to increase access to testing.</p> <p>UNITAID has recently funded an RDT scale-up project to begin to generate substantial demand for RDTs, and through operational research, better understand how RDTs can be scaled up in the private sector. However, it is likely to be several years before RDTs would be available in the private sector on a widespread basis.</p> |
| Reasons | <p>The reasons for this market shortcoming are an area of on-going research; however, potential factors contributing to lack of development of the private sector market include:</p> <ul style="list-style-type: none"> • Lack of awareness among customers and retailers of RDTs and of the benefits of diagnosis. • Affordability of tests (discussed below). • Limited or misaligned business incentives for players in the private sector market at all levels (importers, wholesalers, retailers etc.) to sell RDTs given the lack of demand from customers, the potential profit margin compared to that of drugs, and the availability of free/cheap diagnosis in the public sector. • At the customer level, incentives to test before treating may also be limited or misaligned. Customers with limited financial resources may opt to purchase only an antimalarial rather than an RDT and an antimalarial (if positive). Ideally the cost to consumers for “fever” diagnosis and treatment would be the same regardless of the result of the RDT (e.g., RDT-positive + ACT cost = RDT-negative + alternative treatment cost). • Local regulations governing where a diagnostic test can be performed and who is authorized to perform them currently prevent diagnosis in many private sector channels. |

⁵⁶ ALMA/RBM HWG estimate, data as of 18 March 2012.

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| Market Shortcoming | <p>Delivery: Insufficient information on malaria diagnostics markets to serve as an evidence base for market monitoring and to inform future decisions.</p> |
| Description | <p>Market monitoring based on evidence and data is needed to ensure continued health of the malaria RDT market, guide decision-making, and inform future interventions. Currently there is limited information on malaria diagnostics, especially in comparison to medicines markets. Major gaps include:</p> <ul style="list-style-type: none"> • Monitoring access to testing. At the highest level, improving the accuracy of malaria and fever incidence estimates would provide a better sense of the global need for malaria diagnostics and allow better tracking of progress toward meeting the need. Systems for monitoring changes in test availability, uptake, and the appropriate use of results are also needed. This information will allow for better tracking of progress towards universal access goals and more accurate ACT forecasts that take into account the effect of RDTs on ACT consumption. • Monitoring supply and demand dynamics. Healthy markets for global health products are characterized by affordable prices and adequate incentives for suppliers to produce quality products at these prices. Monitoring key market indicators and trends (e.g., market size, type and quality of products on the market, prices, market share, customer ordering, number of manufacturers, and cost and supply of inputs) helps identify potential market failures. Currently, the information used to monitor the malaria RDT market is based on limited, largely un-validated data. Additional data would increase confidence in these estimates by allowing for triangulation and would allow for a more complete understanding of the market. • Understanding private sector markets for diagnostics. Despite the tremendous interest in developing the private sector markets for malaria diagnostics, discussions on this topic have been impeded by a lack of market intelligence and evidence upon which to make decisions. Major information gaps include too little understanding of the channels for diagnostics distribution (including the role of private labs and retail outlets in various countries), too little understanding of the economic and behavioral incentives related to stocking and selling RDTs, limited understanding of consumer demand for RDTs and price elasticity, and insufficient knowledge of the regulatory and policy environment around diagnostics in each country. |
| Reasons | <ul style="list-style-type: none"> • The poor quality of data on access to testing stems largely from the lack of investment in malaria surveillance, resulting in relatively imprecise estimates of malaria incidence. Additionally, routine diagnostic testing for fever is new to many health systems, and appropriate reporting mechanisms that capture information on testing and subsequent treatment may not be in place yet. • Reasons for the lack of information on supply and demand dynamics include difficulty in accessing and aggregating information on procurement and demand from the individual RDT purchasers. Presently, donor reporting on funding for diagnostics and procurement of RDTs is the only source of data and these data sets are often incomplete. From a supply perspective, there is less coordination globally of the diagnostics community compared to medicines. For example, the lack of regulation for diagnostics means there is often no record of what is “on the market” in a particular country. In the case of malaria RDTs the sheer number of products available makes it difficult to identify those companies that are actually active in the market. • Interest in private sector markets has only emerged recently with the calls for universal access to testing and the AMFm. The complexity of the private sector and lack of precedent for diagnostic testing at the retail level pose new challenges for researchers working in this area. |

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| Market Shortcoming | Delivery: Inadequate malaria surveillance |
| Description | Malaria surveillance, in particular case reporting by facilities, is inadequate, both in terms of completeness and the reliability of data. Current scale up in diagnostics creates unprecedented opportunity to improve the quality of data and to use this information to more effectively manage programs. Improving case reporting requires programmatic changes to improve relevance and accuracy of data collected at the facility level. In addition, to streamline the aggregation, analysis and use of data for decision-making, technology solutions are required. |
| Reasons | <ul style="list-style-type: none"> • No clear guidance/standards for malaria surveillance until recently-released WHO Disease Surveillance for Malaria Control & Elimination (April 2012). • Lack of diagnostic tests led to low-quality case reporting data. • Surveillance has been a low priority for policy makers, donors, and countries. • Weakness in country-level implementation of surveillance systems. • Little use of digital and IT solutions for processing. |

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| Market Shortcoming | Delivery: uncertainty about consistent uninterrupted supply of quality RDTs in light of rapid increases in demand and current market conditions. |
| Description | While suppliers have generally been responsive to demand and there have been no RDT shortages noted to date, there is concern about availability of quality-assured RDTs going forward given current market conditions. |
| Reasons | <p>Reasons for concern about continued supply of quality RDTs include:</p> <ul style="list-style-type: none"> • Dramatic increases in RDT demand, increasingly larger order sizes. • Short lead times for many orders, caused by a combination of delays in accessing funding disbursements and poor planning at country level. • Insufficient predictability of demand for individual products at the manufacturing level due to volatility in the market. • Uncertainty around supplier capacity, especially with regard to scaling up manufacturing quality systems and the effect on product quality of cost reduction initiatives taken in response to erosion of margins and intense competition on price. Limited post-market surveillance and downstream monitoring of RDT quality creates little incentive for quality assurance at the manufacturing level. |

Availability

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| Market Shortcoming | Availability: No tests for pregnant women, low transmission and elimination settings, or <i>P. vivax</i> (liver stage and G6PD). |
| Description | Existing diagnostic tests are not suitable for special populations and circumstances, including screening pregnant women, people living in elimination/low transmission settings, and populations affected by <i>P. vivax</i> . |
| Reasons | <ul style="list-style-type: none"> • Limited private and philanthropic funding for malaria diagnostics. A recent report estimated that malaria diagnostic R&D received \$23 million during the 2004-2009 period, representing just 1% of the global R&D spend for malaria. Although diagnostics are less costly to develop than drugs and vaccines, the report concludes that diagnostics are massively underfunded and calls for an immediate quadrupling of funding to \$50 million/year.⁵⁷ Developers of malaria diagnostics report challenges attracting private sector investment in this area, and predominantly rely on a limited number of philanthropic and public sector funding sources (for example, BMGF, NIH, US Department of Defense, and the EU). While these forms of funding are generally available for early stage work, as developers move to commercialize a product, funding becomes scarce. Private funding sources, e.g., venture capital or multinational diagnostics companies, may not view malaria diagnostic technologies as profitable enough to warrant investment. Development of new diagnostic products requires extensive expenditures that may not be justified by returns on investment. The lack of familiarity with the new technology adoption process in global health and unclear regulatory pathways for these products also contribute to hesitation at the private investor level. Ultimately, limited R&D funding results in delays in the development of some technologies and means that some will never come to market. • There has been little work to better define the market for several of these unmet needs: there is no consensus around target product profiles, and limited market research to better understand desired characteristics, required specifications, demand, and market size. • Another challenge related to bringing a malaria diagnostic test to market is the complexity and cost associated with evaluating a malaria test. Access to samples and clinical study design are major challenges, as is the geographic heterogeneity of malaria. Clinical trials for malaria diagnostic tests can be costly and difficult, as ideally multiple studies would be conducted in a variety of malaria-endemic areas. In these studies, hundreds of samples need to be evaluated against a reference standard. The current “gold standard” for malaria is microscopy, but PCR is often more sensitive and specific; therefore, many studies will use both. The facility conducting the study must have malaria microscopy expertise as well as PCR capacity covering the length of the study. • The lack of clarity around the regulatory pathway and quality standards for malaria diagnostics also poses a challenge, potentially delaying the introduction of new products or hindering their uptake. The multiplicity of global organizations with different standards for product evaluation and quality assurance poses a daunting challenge for product developers. Meeting the needs of different organizations can be a very expensive and logistically challenging. • Lastly, many malaria technology developers are smaller companies or academic organizations that lack the infrastructure and capacity required to commercialize a product. Establishing partnerships with companies with the necessary global sales, regulatory, distribution, and manufacturing capacity adds to the length of time required to bring a product to market. |

⁵⁷ Staying the Course? Malaria Research and Development in a Time of Economic Uncertainty. Seattle: Path; 2011.

Acceptability/Adaptability

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| Market Shortcoming | Acceptability/Adaptability: Low acceptance of RDTs by health workers and patients. |
| Description | Even when they are available, RDTs may not be used and negative results are often ignored. In many settings there appears to be low acceptance of RDTs by health workers and patients. |
| Reasons | <p>Reasons for low uptake and low acceptance of results include:</p> <ul style="list-style-type: none"> • Lack of awareness among health workers and patients of the decreasing incidence of malaria, of RDTs, and of the value of testing. • Difficulty changing long-standing clinical practice. • Mistrust of RDTs, in some cases attributable to providers' past experience with poor/variable quality malaria diagnostics (both microscopy and RDTs). • Lack of alternative diagnosis of fever due to limited training and lack of guidance/best practices on non-malaria fever management. • Low availability of appropriate treatment for non-malarial fever. |

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| Market Shortcoming | Adaptability: RDT kits could be more consumer-friendly and optimized for private sector retail sales; heat stability is an ongoing concern. |
| Description | <p>RDTs are not ideally adapted for resource-limited settings, there are three main areas of concern:</p> <ul style="list-style-type: none"> • Improvements to labeling, job aids, and blood transfer devices could improve adaptability (i) by making RDTs more consumer friendly and thereby reducing training needs, and (ii) by easing difficulties related to switching from one RDT to another. • The optimal specifications for test kits sold through retail channels requires attention. Research conducted with malaria RDT manufactures, local suppliers, and consumers is needed to ensure that the product offering is well adapted to retail settings, including optimal branding and messaging, packaging of kits, product inserts, blood transfer devices, buffer dispensers, etc. • The need for improved heat stability is another concern. Current implementation guidelines suggest that RDTs are vulnerable to heat and recommend maintenance of a cool chain during distribution and storage, which is not practical in most malaria-endemic settings. The extent of RDT deterioration due to routine field conditions has not been well documented, resulting in continued recommendations for cool chain, and limited insight into whether or not there is really a need for technological improvements to RDTs. |
| Reasons | <ul style="list-style-type: none"> • Lack of dialogue. The desired specifications for improving ease of use and interchangeability have not been clearly articulated or communicated to manufacturers, nor has the supply-side impact of such changes been assessed. • While discussions on developing an optimal test kit for private retail channels are recent, there may be little incentive for manufacturers to take this work on themselves. Low margins and a competitive business environment create limited incentive for manufactures to invest in market research or product changes. • Lack of formal research into whether or not RDT heat stability is an issue. • There has been relatively little research on improved heat stability at the monoclonal antibody level. |

Affordability

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| Market Shortcoming | Affordability: RDT prices in the private sector are likely to present affordability issues. |
| Description | There is very little representative data on private sector prices for patients paying out of pocket, but given average incomes in malaria-endemic areas and preliminary willingness to pay studies, there is reason to believe that the cost of an RDT alone will be unaffordable to many. Furthermore, the RDT is usually paired with some form of treatment or follow up care and these costs must be considered. |
| Reasons | Reasons for RDT affordability in the private sector include: <ul style="list-style-type: none">• Add-on costs throughout the private sector distribution chain (e.g., mark-ups, taxes, transport, carrying costs, etc.).• The realization that patients who test positive/negative must also be able to afford the medicines required to treat their illness. |

Potential Market Interventions and Opportunities

There are a number of potential interventions and opportunities that could improve access to malaria testing and contribute to better quality fever management in resource-poor settings. These include initiatives focused on:

- Assuring the quality of malaria diagnostic tests;
- Increasing market stability by reducing price volatility and focusing competition on quality;
- Improving delivery and availability of RDTs in the public and private sectors;
- Supporting development of new technologies targeting populations for which current technologies are inadequate;
- Improving the acceptance of RDTs among health workers and patients, and their adaptability; and
- Increasing market knowledge.

The interventions listed in the following subsections are illustrative and not exhaustive.

Assuring the Quality of Diagnostic Tests

Interventions focused on quality would aim to increase the available information on the quality of malaria diagnostics, reinforce competition around quality, ensure consistency during manufacturer scale up, and assure the integrity of tests in the field. An optimal program would include improved coordination at the policy level, and improved communication around the expectations for quality and the status of various quality monitoring programs. A comprehensive program would also encompass guidance and quality assurance activities for new malaria diagnostic technologies when they come to market.

Specific opportunities to improve quality include:

Development of quality control standards for RDTs for use at the manufacturing level (for batch release and R&D purposes), at reference laboratories (in-country and regional), and at the point of use (positive control wells). As an ever-increasing number of patients are tested using RDTs, and the supply chain lengthens and becomes less controlled, such as in the case of community or private sector use of RDTs, the importance of checking the tests becomes more acute. Intervention in this area involves (i) investment in R&D for development of appropriate quality control technologies, (ii) development of sustainable business models, including marketing and distribution strategies, and (iii) building consensus on quality controls among policy makers, donors, RDT customers, and suppliers, including the specifications for controls. While some work has been done in this area, led by FIND, no products are available yet. The future of these initiatives is not clear, due not only to technical risks associated with product development, but also due to business-related challenges including funding the development and commercialization of these quality control products. Implementation risks associated with restructuring of the Product Testing and Lot Testing program are also a concern.

Support for the Product Testing Program. When the first round of results was released in 2009, the Product Testing Program highlighted the market's inability to identify high performing tests. Since then, the program has had a significant impact on the market for malaria RDTs and all major RDT buyers rely on the program. As noted in this report, there are several improvements to RDTs that may come to market soon and will need to be evaluated. As such, it is critical that the program continue to exist.

Intervention in this area would involve addressing some of the shortcomings of the existing program, including its relative cost and complexity, reliance on donors, and the turnaround time. Development of a more efficient and cost-effective method for evaluating RDTs would be beneficial, but requires significant R&D investment to develop and validate recombinant antigen-based quality control panels to reduce reliance on the human-derived specimen bank. A lower cost program that relies primarily on user fees to cover its expenditures would be more sustainable. Other changes in policies and procedures could improve incentives for upstream quality control and the program's turnaround time. BMGF and UNITAID have recently announced funding for further development of recombinant panels and a subsequent restructuring of the product and lot testing programs to be more financially sustainable.

Development of Stronger Incentives for Upstream Quality. Although the WHO Diagnostics Prequalification Program is a first step to address upstream quality, in light of progress to date, there is a need to address the immediate concern about current market dynamics and their potential effect on the quality of RDTs. Although various scenarios are imaginable there are two specific activities that might serve this purpose. The first is the expansion of lot testing (or a similar program) together with the development of strategies to increase its uptake (e.g., orientation of RDT buyers to the value of lot testing, mechanisms for random selection of lots at the manufacturing level and in the field for testing). Second, the Product Testing Program also could be strengthened to improve upstream quality by (i) requiring periodic resubmission in order to remain on the WHO's procurement list and (ii) through random selection of RDT lots submitted to testing (to prevent manufacturers from submitting specially prepared batches of RDTs to the program).

Increasing Stability in the Market

Mechanisms to reduce volatility in the market would refocus the current competition on price towards a healthier balance of competition on price, quality, and product specifications. For example, mechanisms like longer-term supply agreements—covering pricing and including some form of quality monitoring—might reduce volatility and benefit customers, as more predictable pricing would be possible for high-quality products that meet their needs. More predictability around funding disbursements and improvements in procurement planning would reduce pressure on lead times. In addition, stabilization of prices would improve the attractiveness of the market from suppliers' perspective and encourage suppliers of high-quality RDTs to remain in the market.

Public and Private Sector Delivery

Several demand-side interventions focused on improving delivery of malaria diagnostics would increase access to testing and the quality of febrile illness management.

In the public sector, facilitating rapid scale up of RDTs might include the following interventions:

Funding for RDTs and supporting interventions. RBM estimated that in the African public sector alone, 45 million RDTs were needed but not funded in 2011.⁵⁸ In 2012 this gap grew to 116 million RDTs.⁵⁹ In light of the potential decreases in donor funding, funding for RDTs as well as programmatic support for diagnosis may be needed. Hypothetically, decreases in donor funding for malaria will force national programs to reduce budgets and reprogram funds; it is possible that limited resources would be spent on commodities, while programmatic activities would be cut. In the case of diagnosis, many countries are in the midst of scale up and paradigm change around fever. Reductions in programmatic support like training and supervision, which are critical to uptake and appropriate use of tests, may jeopardize the long-term impact of the tests.

Technical assistance and programmatic support. Many countries have set ambitious targets for diagnostic test scale up but may need technical assistance and/or additional funding for programmatic activities to help overcome implementation challenges and to accelerate access to testing. Although the challenges at the country level are diverse, common areas requiring support include:

- Supply chain management to ensure the availability of products at the point of service.
- Development of training, supervision, and quality assurance programs. The RDT rollout has highlighted the need for refresher courses on differential diagnosis and management of fever. However, training programs are costly and take health workers away from their posts. As such, it is important that content be high quality and that the format be practical. With respect to supervision and quality assurance, sustainable models are needed, with particular attention to the period immediately following the RDT introduction.
- Effective management of grants requires technical assistance that reduces bottlenecks in accessing donor funds and improves compliance with financial management requirements.

Deploying RDTs without **addressing behavior change** limits the impact of diagnosis and wastes public health resources. Therefore, **initiatives to increase demand for testing and to change the approach to fever management are needed.** Provider behavior change is an area of ongoing research, and experts suggest that (i) adherence seems to improve with time, (ii) lower-skilled workers following algorithms tend to use tests and adhere

⁵⁸ Renshaw M, Roll Back Malaria Procurement and Supply Management Working Group and Medicines for Malaria Venture, 2009.

⁵⁹ ALMA/RBM HWG estimate, data as of 18 March 2012.

to results more frequently than more highly-trained providers, and that (iii) health workers in settings that have had access to diagnostics in the past (i.e., microscopy) are less likely to accept RDTs. In the near term, there is a need for more research on models for behavior change and a need to document best practices. Longer-term work in this area would include the development of strategies for non-malaria fever management and implementation of these initiatives at the national level. Funding for broader fever management programs, including commodities to improve differential diagnosis and appropriate fever management (e.g., oral rehydration salts, antibiotics, etc.), is needed.

The quality of **malaria case reporting is weak**, thereby limiting the ability of program managers not only to quantify RDT and drug needs, but also to efficiently deploy malaria program resources overall. **RDT scale up presents an unprecedented opportunity to increase the overall effectiveness of malaria programs through better quality data that can be used to monitor the effectiveness of interventions.** In light of the new WHO guidelines on surveillance, an initiative to further understand the barriers to improving case reporting and to accelerate development of improved systems is needed. An exploration of the technologies available to streamline data collection, reporting and analysis would also be a useful starting point for a program designed to catalyze investments in this area. In light of the current focus on value for money in malaria, investment in improved data on which resource allocation decisions can be made could ultimately lead to longer-term efficiencies. Related to the need for improved data on malaria is the need to better understand and monitor the effect of RDTs on ACTs in order to inform global forecasting efforts for these commodities.

An intervention **to develop the private sector market for RDTs** could expand access to testing and improve targeting of ACTs in the private sector. An intervention in this area would likely begin with additional research and might lead to national-scale programs in select countries. A program structured with periodic evaluations and flexibility to incorporate learning would be ideal. Currently, a handful of operational research programs are underway and providing some insight into potential methods of increasing access to testing in the private sector. However, there are a number of unanswered questions about how an initiative would be optimally structured. In addition, the operational research projects are revealing the complexity and heterogeneity of the private sector, both between countries and within countries, suggesting that a one-size-fits-all approach would not be effective.

UNITAID recently funded one project to develop the private sector market in five malaria-endemic countries.

Availability and Adaptability of Technologies

Potential interventions to improve availability of tests for pregnant women, low transmission settings, and populations affected by *P. vivax* would include initiatives to build consensus around product specifications and desired characteristics, conduct preliminary market research on demand, and develop guidance and consensus around the quality and regulatory requirements for new products coming to market. In addition, funding for malaria diagnostic test R&D is insufficient and initiatives to fund developers of pipeline technologies could accelerate the commercialization of products.

With respect to adaptability of current RDTs, three areas of work are needed. First is dialogue among stakeholders and suppliers about possible improvements and desired characteristics for RDTs. With respect to discussions on standardization, further consensus building on items to be standardized and analysis of the feasibility is needed. Second, market research is required to identify the optimal specifications for test kits marketed in private retail channels. Lastly, formal research into heat stability of existing RDTs is also required in order to decide whether there is a case for additional intervention in this area.

Market Knowledge

Currently there is limited reliable data on the market for malaria RDTs. This lack of data means that decisions regarding malaria RDTs, both at the policy and company level, are often made based on the opinions of few people. Improving market knowledge will help to develop an evidence base for market monitoring and targeted future interventions. This knowledge is important for several reasons, including ensuring the long-term supply of affordable, high-quality malaria diagnostics, especially in light of the market's rapid growth and evolution. Market knowledge is also needed to inform decisions about future policies and programs, in order to assess their potential impact on the market and to prevent adverse consequences. Finally, as donors and programs

increase their investment in malaria diagnostics, especially in a time of declining resources for global health, it is important to have information on the effectiveness of interventions in order to maximize the investment in diagnostics.

Among the potential interventions to improve market knowledge are systems that would improve the accuracy of access to testing data. At the highest level this involves strengthening surveillance systems. As diagnostic testing is scaled up, systems for monitoring changes in test availability, uptake, and the appropriate use of results are needed. This data should be analyzed to refine the current estimates of the gap in access to testing, the financing needs for diagnostics, and the effect that RDTs have on ACT consumption.

Efforts to improve the quality and availability of data on malaria diagnostic procurement (e.g., strengthening reporting in the Global Fund PQR and similar databases) would contribute to improved ability to monitor supply and demand trends in the market. Since the challenges related to monitoring market dynamics for malaria diagnostics are shared with other diagnostics for global health, initiatives to strengthen data gathering and research to improve market knowledge for all diagnostic categories might be considered. Finally, a forum for dialogue between suppliers (RDT manufacturers and monoclonal suppliers), RDT customers, and policy makers would be beneficial, as there is currently limited interaction and communication among these groups. Engaging suppliers more formally and systematically in collecting data on the market might also be possible.

Market and operational research is needed in many areas to inform investment in the private sector, including analysis of private sector distribution channels (including regulation and policy), understanding retailer and customer incentives, and development of appropriate products and communications strategies.

Conclusions

In contrast to the past few decades, today's malaria diagnostics market landscape is very dynamic. While there has been significant progress in terms of policy and the scale up of diagnosis, this report illustrates several gaps and opportunities to accelerate access to testing in meaningful ways. Quality is a major issue in the RDT market, which developed in the absence of standards and regulation. In light of today's intense competition on price and volatility, quality is a challenge that should be addressed urgently and holistically, both to improve upstream incentives for quality and downstream implementation of quality assurance.

Given the relative lack of information on the private sector, interventions in this area need to be planned with care and flexibility as there is still much to learn about the private sector. Furthermore, private sector interventions may not be the most effective option for increasing access to testing in every setting. For example, in countries with strong public health systems, expanding the reach of the public sector and its use of diagnostics may be a more effective means of increasing testing rates than developing private sector markets.

In the coming years, funding is likely to be a major challenge for malaria programs; the continued scale up of diagnosis in the public sector and beyond is contingent on adequate resources. As the scale up of diagnosis allows for better quality data upon which to base resource allocation decisions, it would make sense to invest in initiatives that focus on improving case reporting and surveillance. Lastly, the scale up of diagnosis presents an important and unique opportunity to learn about and improve the body of knowledge on the malaria diagnostics market.

APPENDIX 1: Glossary of Terms and Acronyms

| | |
|----------------------------|--|
| CE / CE marking | A mark placed on products in the European Economic Area that indicates the product conforms with requirements of EU directives. CE stands for Conformité Européenne (European Conformity). |
| G6PD | Glucose-6-phosphate dehydrogenase. Glucose-6-phosphate dehydrogenase (G6PD) is an enzyme in the human body that is essential for basic cellular functions. |
| Hemozoin | A malaria parasite produces hemozoin crystals as a byproduct of its metabolism of hemoglobin: After infecting a person, the parasites enter red blood cells and feed on hemoglobin, an iron-bearing molecule that plays a key role in supply of oxygen throughout the body. The parasite is unable to use the iron-containing part of hemoglobin, and sequesters it in the form of tiny crystals called hemozoin. The presence of hemozoin in a patient is a strong indication of malaria infection. |
| MAB | Monoclonal antibody. An antibody produced from a single clone of cells. It has a uniform structure and specificity. |
| Malaria control | Reducing the malaria disease burden to a level at which it is no longer a public health problem ⁶⁰ . |
| Malaria elimination | The interruption of local mosquito-borne malaria transmission; reduction to zero of the incidence of infection caused by human malaria parasites in a defined geographical area as a result of deliberate efforts. Continued measures to prevent reestablishment of transmission are required. ⁶¹ |
| Parasite density | Parasite density refers to the volume of parasites in a given quantity of blood, usually expressed as the number of parasites per microliter of blood (e.g., 5,000 parasites/ μ l) or as the percentage of red blood cells infected with parasites (e.g., 1% parasitemia). The density depends on a number of factors, including the species of parasite, genetic and immunological factors of the patient, the duration of the malaria infection, and the effectiveness of any treatments already taken. Parasite densities vary tremendously, and densities at all levels may lead to clinical illness (depending on the individual), and may contribute to transmission of malaria. |
| PCR | Polymerase chain reaction. A laboratory method developed in the mid-1980's that allows for a particular segment of nucleic acid to be copied limitlessly. This copying (or amplification) makes it easier to detect minute quantities of nucleic acid in a sample. |
| Thermal cycler | Laboratory instrument used to achieve the rapid changes of temperature required for PCR. The thermal cycler contains a thermal block with holes for tubes containing the samples. The thermal cycler is programmable to precisely control temperature increase/decrease steps, the length of time that a reaction is held at a particular temperature, and the number of cycles that are completed. |

⁶⁰ World Malaria Report 2011. Geneva, World Health Organization, 2011.

⁶¹ World Malaria Report 2011. Geneva, World Health Organization, 2011.

APPENDIX 2: Global Health Donor Landscape

The Global Fund and the US President's Malaria Initiative (PMI) have been the primary funders of malaria diagnostic test procurement and as such their policies have significant influence on demand for RDTs. Other important funders of the malaria RDT market include the Bill and Melinda Gates Foundation (BMFG), the World Bank, and the UK Department for International Development (DFID). These donors intervene at various points on the diagnostics value chain, ranging from funding R&D to supporting RDT procurement. This section provides background on donor priorities and strategies, as well as details on procurement policies for malaria diagnostics (where relevant).

Global Fund

The Global Fund remains the single largest international funder of malaria control and malaria diagnostic testing, having provided approximately 65% of all international disbursements for malaria RDTs in 2011.⁶² As of 2010, the cumulative Global Fund budgets and expenditures for the malaria diagnosis service delivery area were \$133 million and \$83 million, respectively. In 2010 alone, \$74 million was budgeted and \$46 million expended on malaria diagnosis.⁶³

The Global Fund is currently undergoing major strategic reform as well as fundraising challenges.⁶⁴ Due to this uncertainty, in late 2011, the Global Fund announced the postponement of the eleventh round of funding until mid-2013 or early 2014, when a more strategic approach to grant making will begin. As an interim measure, it established a Transitional Funding Mechanism to which eligible countries can apply in 2012 to prevent interruption of essential services before the new round of funding is available. The Global Fund also announced changes to the process for grant renewals.

Current Role in Malaria RDT Market

Procurement: The Global Fund is a funding instrument, founded on principles of country ownership. As such it does not direct the activities that it funds, so long as the proposed plans are consistent with international standards, such as guidance from the WHO, and so long as products are procured competitively in a fair and transparent manner and in accordance with Global Fund Quality Assurance Policy for diagnostic products to achieve the lowest possible price.⁶⁵

Global Fund recipients, largely Ministries of Health, are responsible for the procurement of diagnostic tests. They can either purchase directly or outsource this function to procurement agents. Many countries use a tender process to purchase directly from the manufacturer; major procurement agents active in Global Fund malaria RDT tenders include UNICEF and the Partnership for Supply Chain Management (PSCM). The latter is operating as procurement agent for the Global Fund's Voluntary Pooled Procurement (VPP) mechanism.

The VPP mechanism procured 13 million RDTs in the 18 months to end 2010; 27 million RDTs in 2011 and expects to procure at least 45 million RDTs in 2012. Because of the increasing volumes procured and the variation in the pricing of RDTs that it has observed, VPP has recently included malaria RDTs as "core products" in its portfolio and will be considering during 2012 strategic approaches to both achieve better value for money and also a more sustainable market.

Quality Standards: Since March 2011, a Quality Assurance Policy for Diagnostics has been in force for Global Fund-financed grants. For malaria RDTs, it was estimated that most grant recipients are already in compliance with the policy, which, regarding the selection of the product, requires that all malaria RDTs purchased be selected following the WHO-recommended selection criteria for RDT procurement. In addition, the Global Fund requires that countries implement other quality testing measures for RDTs, including participation in the WHO Lot Testing Program.

⁶² *Review of HIV/AIDS, Tuberculosis and Malaria Landscape for the Global Fund Strategy 2012-2016*. Geneva, The Global Fund, 2011.

⁶³ *World Malaria Report 2011*. Geneva, World Health Organization, 2011.

⁶⁴ The Global Fund had hoped to have \$12 billion available for the 2011-2013 funding period, but had only been able to secure \$10 billion from donors as of late 2011.

⁶⁵ In certain cases, for products for which local procurement capacity is insufficient, as determined by the Global Fund through the Procurement and Supply Management Assessment, recipients must use established services of agents acceptable to the Global Fund.

Switching Costs: As a general principle, the Global Fund requires competitive procurement for any commodity, including RDTs. Typically, this involves annual bidding in many countries. However, in recognition of the programmatic complexities and cost of switching RDTs on an annual basis, as well as the potential impact over the market and quality of final products due to lack of predictability on orders for manufacturers, the Global Fund allows continuation of procurement of a selected RDT for up to three years (after a competitive selection process) provided there is no evidence of problems with the selected RDT.⁶⁶ The Global Fund also encourages countries to consider the total cost of ownership when comparing bids, which includes the programmatic costs of switching RDTs (retraining, printing and distribution of manuals and job aids).

Future Role in Malaria RDT Market

The Global Fund is currently in a period of transition, with a new strategy for 2012-2016 being planned and implemented, and with funding of new rounds, which are currently projected to be smaller than in recent years, postponed. In the near term, the impact of changes at the Global Fund are difficult to estimate, although it is clear from the policy documents and conversations with managers at the Global Fund that malaria diagnosis scale up is considered part of case management more generally and is therefore a priority. For example, among indicators in the new Global Fund strategy are number of “diagnoses with RDTs” and “courses of ACT administered to *confirmed* malaria cases.” Among the other changes in the Global Fund’s new strategy that could impact the market for diagnostic tests are the following: more predictable funding, rather than the round system, and an initiative to undertake market-shaping efforts to accelerate the introduction of new technologies and to influence the prices/cost of current procurement.

The funding uncertainty associated with the largest donor for malaria diagnostic testing comes at an interesting time for the diagnostic test market, as many countries are in the process of dramatically scaling up malaria diagnostic testing. Little formal analysis of the effect that these changes could have on the market has been undertaken to date. In the next near term, the changes may have little impact, as many existing grantees have large unspent disbursements that should continue to fund diagnostic scale-up activities. However, in countries facing major funding gaps in their overall malaria control programs, prioritization decisions may need to be made between different programs and these could affect diagnostic testing levels and programmatic support for diagnosis. In addition, as existing grant programs come to an end or are up for renewal, the effect of the funding uncertainty on the scale-up of diagnosis and the RDT market more generally may be more pronounced.

President’s Malaria Initiative (PMI)

The US PMI, active in 20 countries (including the Greater Mekong sub-region), has become the second largest international malaria donor, with a budget of \$650 million in 2012.

PMI considers diagnosis an integral part of malaria programs and since its inception in 2006 has been supporting holistic diagnostic efforts in-country through technical assistance as well as procurement of RDTs, microscopes, and related consumables. PMI allocated \$37 million to diagnostic services (i.e., support for both microscopy and RDT) in 2011.⁶⁷ PMI has procured nearly 45 million RDTs since 2006, with procurement increasing steadily every year and reaching over 20 million RDTs in 2011.

PMI’s support varies tremendously by country, and is driven by country needs. Every year, PMI works with countries to develop Malaria Operational Plans that outline the technical assistance and implementation support that PMI will provide as well as the commodities to be procured with PMI funds. To date, PMI’s work in diagnosis encompasses both microscopy and RDTs, and it has invested considerably both in improving quality assurance systems for diagnostics and in training and supervision of health workers. To date, several countries that PMI supports have established national quality programs for diagnosis and several others are nearing national scale. PMI has also been supporting community case management of malaria in over half of the countries where it works, and has seen success in several countries.

In the coming year, PMI will undertake an assessment in three countries to get a better appreciation for the levels of uptake of diagnostic testing and their impact on the care and treatment given to patients. PMI also

⁶⁶ Quick Facts on Procuring Malaria Rapid Diagnostic Tests with Global Fund Grants, December 2011, Geneva, The Global Fund, 2011. Available at: <http://www.theglobalfund.org/en/procurement/>

⁶⁷ World Malaria Report 2011. Geneva, World Health Organization, 2011.

expects to expand community case management and to explore private sector approaches to increasing access to case management, including diagnosis.

PMI performs malaria RDT procurement on behalf of countries, primarily through the USAID DELIVER project. Currently, PMI's criteria for RDT quality are in line with WHO recommendations; in addition, manufacturers must agree to pre-shipment lot testing. PMI maintains a list of pre-selected vendors for RDTs that is established through periodic requests for expressions of interest.⁶⁸ PMI's list of eligible RDTs for procurement includes fewer tests than the WHO recommended list; however, in PMI's experience, the leading malaria RDT manufacturers are well represented and its pre-selection process has not conflicted with a country's product selection⁶⁹. Furthermore, a waiver process exists allowing countries to procure products not included on the PMI list as long as they meet PMI's technical criteria (which are similar to WHO recommendations). In the future, PMI is likely to follow the FIND/WHO Product Testing recommendation for procurement; it does not anticipate any additional quality standards for RDTs in the near term. With appropriate justification, PMI allows countries to specify the RDT to be procured in order to avoid high programmatic costs associated with switching RDTs every year.

World Bank

The World Bank is also a major funder of malaria control activities. Since 2005, its Malaria Booster Program has committed over \$772.8 million to 22 projects in 20 African countries. World Bank funding for malaria is based on demand from countries. Although country demand and new funding for malaria decreased after 2010, it may increase over the next few years in light of the current funding environment in which other financiers face resource flow challenges. The World Bank funding model differs significantly from that of other major malaria funders, as it supports a variety of sectors and generally works directly with the ministries of finance to provide funds that are structured as a mix of grant, credit, or loan, depending on the country. Although funds are provided directly to governments' treasuries to be spent as if they were their own, the World Bank requires a careful project plan, quality checks, and audits.

With respect to malaria, the Booster Program aims to help countries scale up core malaria control interventions while strengthening health systems more broadly, including supply chain, information systems, and human resources. With respect to malaria diagnostics, the World Bank places emphasis on mainstreaming of malaria diagnosis and treatment into routine health care.

Since 2005 World Bank resources have been used to procure > 15 million RDTs for African programs and this number is expected to grow in coming years. Procurement is a country-led process, but must follow World Bank guidelines and is subject to quality reviews. The World Bank recognizes the programmatic cost implications associated with introducing and scaling up RDTs in countries and thus the Bank's technical specialists recommend that countries consider two-year tenders with staggered delivery, taking note of the procurement process and to reduce the risk of RDT expiry in facilities.

Bill and Melinda Gates Foundation (BMGF)

The Bill and Melinda Gates Foundation (BMGF) has been active in supporting various quality initiatives for malaria diagnosis, including the FIND-led work on product testing, lot testing, and development of positive control wells. Funding for this five-year quality initiative ended in 2011 and BMGF is currently exploring potential options for continuing to support the work, in particular the development of positive control wells.

BMGF also plays a key role in funding R&D for new diagnostic technologies, and with respect to malaria its interest is primarily in the unmet needs associated with low-level transmission/ elimination settings. The Foundation will be working with PATH to better define the needs in this area and to develop target product profiles, after which they will assess their next steps in this area. The BMGF's Discovery Diagnostics Group focuses on crosscutting diagnostic platforms, including some for fever management that may incorporate malaria diagnosis. Although BMGF is exploring the potential for expanded use of malaria and fever management diagnostics, in particular deployment in the private sector, it has yet to develop a definitive strategy in this area.

⁶⁸ Preselected RDTs available at: <http://deliver.jsi.com/dhome/procurementnews/currenteois>

⁶⁹ Personal communication with author.

Department for International Development (DFID)

DFID is another major donor to malaria efforts. DFID provides direct bilateral funding to countries for malaria control and is expected to increase its spending from \$66 million in 2009 to \$260 million in 2015 (excluding support to the Global Fund and UNITAID, indirect funding for malaria through other health programs, and spending on malaria diagnostics R&D).

UNITAID

UNITAID is another major donor to malaria efforts. UNITAID projects include support for ACT and LLIN scale up, AMFm, ACT and raw materials forecasting, and work to secure the supply of raw materials for ACTs. In early 2012 UNITAID announced funding for two malaria diagnostics initiatives, including nearly \$10 million to support the WHO Product and Lot Testing programs and over \$30 million to support the development of private sector markets for RDTs in five endemic countries. In addition to funding malaria initiatives, UNITAID aims to monitor the markets for malaria commodities, including medicines, diagnostics, long lasting nets and vaccines. This work involves annual publication of landscape analysis on these markets as well as periodic updates.

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