



2014

Malaria Diagnostics Technology and Market Landscape

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ABBREVIATIONS

ACT	artemisinin-based combination therapy	GPS	global positioning system
AIDS	acquired immunodeficiency syndrome	G6PD	glucose-6-phosphate dehydrogenase
ALMA	African Leaders Malaria Alliance	HIV	human immunodeficiency virus
AMFm	Affordable Medicines Facility-malaria	HWG	Harmonization Working Group
° C	degree Celsius	kg	kilogram
CE Mark	European Conformity (Conformité Européenne)	ISO	International Organization for Standardization
CHAI	Clinton Health Access Initiative	LAMP	loop-mediated isothermal amplification
cm	centimetre	LCD	liquid-crystal display
DFID	United Kingdom Department for International Development	LED	light-emitting diode
DFxP	dark-field cross polarization	LOD	limit of detection
DNA	deoxyribonucleic acid	LLIN	long-lasting insecticide-treated mosquito nets
DRC	Democratic Republic of the Congo	MAb	monoclonal antibody
ELISA	enzyme-linked immunosorbent assay	mL	millilitre
FDA	Food and Drug Administration (United States)	mm	millimetre
FIND	Foundation for Innovative New Diagnostics	MOT	magneto-optical technology
FISH	Fluorescent In Situ Hybridization	NALFIA	nucleic acid lateral flow immunoassay
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria	NBI	National Bioproducts Institute
		NGO	nongovernmental organization
		POC	point of Care
		PCR	polymerase chain reaction

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PCW	positive control well	TPP	target product profile
PMI	United States President's Malaria Initiative	µL	microlitre
PQR	Price and Quality Reporting (Global Fund)	US	United States
PSI	Population Services International	USAID	United States Agency for International Development
p/µL	parasite per microlitre	UV	ultraviolet
QA	quality assurance	V	volt
QC	quality control	VPP	Voluntary Pooled Procurement
QT-NASBA	quantitative nucleic acid sequence-based amplification	WHO	World Health Organization
RDT	rapid diagnostic test	WHO GMP	WHO Global Malaria Programme

EXECUTIVE SUMMARY

Introduction

This report is part of an ongoing initiative within UNITAID to describe and monitor the landscape for malaria commodities. It focuses on technology and market dynamics around malaria diagnostic products. It includes an overview of the current diagnostics technology and market landscape, a high-level perspective on barriers to access, and potential opportunities for market-based interventions to address these barriers. Information in this report was derived through a variety of methods, including desk research, literature reviews, dataset analyses and consultation with experts. Although the information available on the malaria rapid diagnostic test (RDT) market is increasing, very little aggregate data is available. As a result, the discussion in this report is based largely on analysis of limited datasets supplemented by many key informant interviews.

Public health problem

There are 3.1 billion people across 104 endemic countries at risk of malaria, with an estimated 291 million cases and 660 000 malaria deaths in 2010. Although risk is widespread, cases and deaths are concentrated in Africa, where the majority of cases is caused by the *Plasmodium falciparum* species. While the last decade has seen dramatic reductions in the burden of malaria, largely attributable to increased funding and scale-up of malaria control activities since 2000, these gains are fragile and incidence may 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 can rapidly progress to severe disease. In the past, malaria was often treated presumptively (i.e. based on symptoms alone). However, this leads 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 2010, the World Health Organization (WHO) began recommending testing all suspected cases of malaria before treatment. Global partners have subsequently set ambitious targets for universal access to diagnosis in the public sector, private sector and at the community level. Many countries, particularly in Africa, are scaling up malaria RDTs in order to increase access to diagnosis.

There are several trends in malaria management that influence the market for diagnostic tests, among the most important are:

- **Constrained donor funding and slowing of progress:** A levelling off of funding for malaria has led to a slowing of progress compared to the previous decade of gains and poses a threat for programmes that need to maintain gains and further expand activities to reach universal coverage targets. In particular, strategic changes and fundraising challenges at the Global Fund to Fight AIDS, Tuberculosis

and Malaria (Global Fund), the largest financier of the current diagnostic test scale-up, are creating uncertainty.

- Private sector markets: Although a large proportion of the population purchases drugs for malaria in the private sector, testing in this sector is minimal. In the past two years, several projects began that aim to develop models for increasing access to testing in the private sector. Despite progress, several unanswered questions remain, suggesting that this market may take time and effort to develop.
- Implementation challenges: Common implementation challenges include weak supply chains that limit the availability of tests at the point of service, encouraging use of tests by clinicians and patients, and improving fever management practices more broadly. Overcoming these challenges is critical to improving testing rates and assuring that malaria diagnostics have a positive public health impact.
- Weak information systems: In the past year, concerns have grown about the lack of information needed to monitor the impact that diagnostic test scale-up is having on quality of care.
- Elimination: As malaria burdens decrease, elimination of malaria is increasingly possible in many areas. In the past year, discussions have focused on epidemiological changes that occur as transmission declines, namely: (i) transmission becomes more concentrated in particular populations and/or geographies; and (ii) the proportion of asymptomatic individuals rises, and many of these individuals have parasite loads that are undetectable by RDT or microscopy. The first epidemiological shift is prompting operational research on how to best identify and respond to these foci of transmission. The second change is creating a need for diagnostics with an extremely low limit of detection (LOD) to identify asymptomatic individuals.
- *Plasmodium vivax*: An estimated 2.85 billion people live at risk of *P. vivax*, the majority in the tropical belt of Asia. In the past year, interest in this species of malaria has grown. For diagnostics, there is room for improvement in the sensitivity of diagnostics for *P. vivax* as well as a need for a point-of-care (POC) test to rule out G6PD deficiency (glucose-6-phosphate dehydrogenase is an enzyme in the human body that is essential for basic cellular functions), a condition that may cause an adverse reaction to primaquine, one of the medicines used to cure *P. vivax*.

Commodity access

Although meaningful public sector scale-up of diagnosis has occurred in the past 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 at the community level by 2015. Globally the percentage of public sector cases that are confirmed with a test has risen from 67% in 2005 to 77% in 2011. In Africa, the region with the lowest access to testing, increases in diagnostic testing rates in the public sector were minimal: 47% of cases were tested in 2011, a 2% increase over 2010.

These figures, however, do not represent overall testing rates as a large proportion of people, in some countries the majority, turn to the private sector for fever care. Testing rates continue to be very low or non-existent in the private sector.

Increasing access to testing has far reaching public health implications. With respect to antimalarial drugs, overtreatment is common, and testing allows for improving targeting of medicines to patients who have malaria, thereby reducing wastage and exposure of patients to drugs they do not need. Currently, anti-malarial consumption greatly exceeds diagnostic testing, indicating that there is still significant work to be done to scale up diagnosis and to reduce overtreatment. In addition, testing for malaria enables better quality of care. In the case of a positive case result, providers and patients can have more confidence in the diagnosis. In the case of a negative result, alternative causes of fever can be diagnosed and treated without delay.

In addition to the need to scale up testing more generally, there are several populations for which existing tests are insufficient, for example: tests with an improved LOD for elimination settings and for *P. vivax* case management; a POC G6PD test; and a test for pregnant women.

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 and in expert hands and ideal 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 POC, 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, the WHO Product Testing Programme for Malaria RDTs (hereafter the Product Testing Programme) has 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”). For common use scenarios, a variety of high-performing products are available; however, in some categories there are fewer options (e.g. *P. falciparum* pLDH-based tests).

Most suppliers offer several different types of RDTs, and while the products from a single manufacturer tend to resemble each other, between manufacturers there are differences in the format of the RDT, labeling, components included in the test kit and in the test procedures. Given the unprecedented scale of users, it is possible that operator errors occur when switching products and a current Roll Back Malaria Partnership initiative is exploring the potential for harmonizing RDTs.

As in the past, the malaria diagnostic pipeline includes a number of different approaches to detecting malaria. The pipeline includes improvements to existing approaches (e.g. higher-performing RDTs, urine-based RDTs, simplified versions of complex reference tests) as well as platforms that take advantage of novel approaches to malaria diagnosis (e.g. spectroscopy; hemozoin detection). While some of the technologies are intended for routine diagnosis and screening, others are designed to be field applicable reference methods. To be useful in routine malaria diagnosis, malaria tests should be both accurate and rapid, given the acute nature of malaria disease. Other priorities for malaria diagnostic test research and development (R&D) include affordability and the ability to widely deploy the test (i.e. portability; ability to withstand high heat and humidity; simple to perform).

The malaria RDT market landscape

Malaria RDT demand continues to grow rapidly, from 45 million tests sold in 2008 to 205 million in 2012. While RDTs are sold globally, demand growth is driven by increasingly larger orders from the African public sector, where many countries are scaling up RDTs nationally. Despite this growth, the estimated need for testing greatly exceeds the current market size and substantial growth is required to achieve universal access targets. For example, in Africa the need is 1.4 billion tests for 2013 through 2016, yet the funded demand is 498 million. Donors, mainly the Global Fund and the United States President’s Malaria Initiative (PMI), have enabled recent growth in the RDT market and it will be important to monitor how recent changes at the Global Fund impact malaria diagnostics budgets in the coming years.

If the goals for universal access to diagnostic testing are to be met, there is also a need to improve access to testing in the retail private sector. This segment remains small, but it represents a significant potential market for diagnostics in many countries given how many people access treatment for fever through retail channels. However, developing these markets is proving to be a challenge, due to the heterogeneity of markets, lack of evidence and experience, and the usual complexities associated with introduction of a new service in any market. As a result, the retail market segment is likely to take some time to mature, and near-term growth is likely to be incremental.

In the public sector, the main drivers of product selection are price, a products’ ability to meet minimum performance thresholds as demonstrated by the Product Testing Programme, maximum recommended storage temperature, ease of use (including differences from the currently used RDT) and lead time.

With respect to prices, malaria RDTs are relatively inexpensive tests, and intense competition in the past few years has led to pricing declines. For example, in 2010, the weighted average public sector price was US\$.49 for *P. falciparum* RDTs and US\$.68 for combination tests. In 2013, average prices were US\$.32 for *P. falciparum* RDTs and US\$.38 for P.f./Pan tests. Wide variation in pricing is common, with competitive bids usually resulting in lower pricing.

The most commonly used RDT, by volume, continues to be the *P. falciparum*-only test. However, combination test use is common: more countries reported procuring a combination test in 2012 than a *P. falciparum*-only test.

Procurement data analysis suggests that the majority of countries have experience with multiple RDTs: half of countries switched test type between 2010 and 2013 (mostly from a *P. falciparum*-only test to a combination test), and 72% switched brand since 2010, often resulting in lower pricing. While competitive procurement practices may lead to frequent switching of RDTs, 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; publication of new job aids).

With respect to quality, the WHO/Foundation for Innovative New Diagnostics (FIND) Product Testing Programme, which assesses the relative performance of RDTs, remains the most influential quality standard in the market. Beginning in 2013, manufacturers are required to resubmit products every five years to remain on the WHO list of RDTs recommended for procurement. The Product Testing Programme is undergoing several transitions in order to streamline operations and reduce cost. As the changes are expected to take several years and depend on successful development of new technologies (i.e. recombinant antigen testing panels), in the near term the programme should continue normal operations.

Other quality initiatives include the WHO/FIND Lot Testing Programme, which tests about half of the donor-funded RDT lots prior to their distribution to the field. The lack of heat stable, easy-to-use, quality controls (QCs) for checking RDTs in the field remains a gap, as does the lack of insight into manufacturing quality systems. Although the WHO Prequalification Programme for Diagnostics is reviewing malaria RDTs, suppliers are not progressing quickly through this system.

Procurement data analysis suggests that market share has been shifting significantly in the past five years: in 2010 and 2011 shifts towards products with higher performance in the Product Testing Programme occurred. More recently in 2012 and 2013, the market has been consolidating around three suppliers: Access Bio; Alere (Standard Diagnostics); and Premier Medical Corporation. These companies' tests are among the highest-performing products in product testing, however, they are not able to obtain a price premium for higher-performing products, due to procurement practices that generally favour the lowest priced product that meets a minimum performance threshold.

The consolidation of the market is in contrast with the large number of companies with malaria RDTs in their portfolio. The malaria RDT market seems to attract many players due to its rapid growth and the large "need" for tests, the relative ease of developing a product and the low regulatory requirements in comparison to other diagnostic tests. However, recent price declines have made the public sector market unattractive, and at least one formerly dominant supplier has reduced malaria RDT production capacity and exited the public sector market. Other companies appear to be targeting niche market segments, such as the formal private sector. Barriers to entry also have emerged, limiting access to the largest market segment, the public sector. Among the barriers are: (i) participation in the WHO/FIND Product Testing Programme, which can take two years; (ii) working capital and capacity to deliver large public sector orders rapidly; and (iii) WHO prequalification, which is not yet required, but is a lengthy process that may be prioritized in the future. More recently, economies of scale in production, cost advantages (e.g. favourable access to materials such as monoclonal antibodies or MAbs) and local product registration are shaping competition and make it difficult for new entrants to succeed in the market.

While suppliers continue to drive prices lower through competitive bidding, the sustainability of low prices has become an important concern in the past year. Low prices represent strategic attempts by RDT suppliers to capture and penetrate new markets as well as efforts to use inventory and ensure capacity

utilization (e.g. avoid costs associated with shutting down production). However, current pricing appears to be approaching the cost of production for many suppliers, and is creating an unsustainable market and little incentive for investment in quality or in innovation.

Market shortcomings

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

Category	Shortcoming	Primary reasons
Quality	QCs for RDTs do not exist	<ul style="list-style-type: none"> ■ Low awareness and prioritization among stakeholders and buyers, in particular, when the market was first developing. ■ Little incentive for private investment in development of QC technologies. ■ Technical complexity of developing controls.
Quality	RDT manufacturing and field-level quality unknown	<ul style="list-style-type: none"> ■ Limited regulation and oversight in countries that consume or produce RDTs. ■ WHO prequalification process is slow. ■ Limited experience of RDT manufacturers with stringent regulatory requirements. ■ Market cannot differentiate between quality at the manufacturing level; no incentive for suppliers to invest. ■ Low awareness and prioritization among stakeholders and buyers, in particular, when the market was first developing. ■ Practical QC technologies do not exist (as above).
Delivery	Uncertainty about consistent supply of quality RDTs	<ul style="list-style-type: none"> ■ Low prices, approaching cost of production, lead to supplier exit and market consolidation. ■ Market has limited ability to verify product quality and might not detect shortcomings in product quality. ■ Thin margins and market's relative inability to assess/value quality create little incentive for quality at the manufacturing level. ■ Uncertainty around scale-up of manufacturing quality systems commensurate with rapidly scaling up production and short lead times; uncertainty about the effects of cost reduction on quality systems.
Delivery	Insufficient uptake of RDTs compared to need	<ul style="list-style-type: none"> ■ Implementation weaknesses, e.g. weak supply chain management; inadequate health worker training; lack of supervision/QA. ■ Limited demand for RDTs, low awareness and acceptance of tests in some areas. ■ Potential funding reductions for malaria, may limit scale-up. ■ Information gaps, mainly limited monitoring of the testing scale-up and its impact due to weak reporting systems.

Delivery	Limited market for quality RDTs in the private sector	<ul style="list-style-type: none"> ■ Low awareness among consumers and supply chain actors. ■ Low availability in retail outlets due to low awareness and little pull from potential customers. ■ Local regulations may prohibit diagnosis or follow-up treatment. ■ RDT (and subsequent treatment) prices may be unaffordable. ■ Where available, quality of RDTs is unknown. ■ Limited market knowledge upon which to make decisions about developing these markets.
Delivery	Inadequate malaria surveillance	<ul style="list-style-type: none"> ■ Historically, limited use of diagnostics led to poor quality data and, therefore, low prioritization. ■ New guidance released in 2012, implementation is slow. ■ Weak implementation, e.g. need for coordination across different departments of health systems. ■ Limited use of digital/information technology (IT) solutions.
Availability	No tests for elimination settings, to support diagnosis and treatment of <i>P. vivax</i> , and for pregnant women	<ul style="list-style-type: none"> ■ Current market conditions are a disincentive for investment in malaria diagnostic test R&D. ■ Limited work to define the needs or market for new products. ■ Limited philanthropic and private funding for R&D.
Acceptability	Low acceptance of RDTs	<ul style="list-style-type: none"> ■ Lack of alternative diagnosis for non-malaria fever due to lack of training, protocols and tests to assist with differential diagnosis of fever. ■ Low availability of commodities for non-malaria fever. ■ Low awareness of declines in prevalence. ■ Mistrust of RDTs; lack of QC for RDTs.
Adaptability	Poorly adapted RDTs; while today's RDTs are a great improvement over microscopy in terms of adaptability, there is room for improvement	<ul style="list-style-type: none"> ■ Specifications for improvements have not been systematically developed, validated or communicated. ■ Little dialogue between users, policy-makers and manufactures.

Opportunities for market intervention

There are a number of potential market interventions and opportunities to improve access to malaria diagnostics and to contribute to better quality fever management in resource-poor settings. These include market-shaping interventions that are already under way as well as new opportunities.

Among the existing initiatives are a number of projects aimed at developing private sector markets for diagnosis and treatment, work to improve the quality of malaria RDTs through development of recombinant antigens that will be used for product evaluation and for QC testing. A number of market intelligence projects are planned, including monitoring the uptake of diagnostics and medicines in the private sector, global RDT forecasting and analysis of the markets for RDT raw materials. Work to improve user friendliness and harmonization of RDTs is under way, as is work to support development of new diagnostics for elimination settings and radical cure of *P. vivax*.

A selection of potential new opportunities are described below, which include both immediate and longer-term interventions for consideration.

- Perhaps the most urgent need is for demand shaping interventions to ensure the long-term sustainability of the RDT market, given recent pricing declines and consolidation. Reliance on a few donors presents opportunity for coordinated action, and discussions with leading procurers suggests that they are considering revising their approach. Mechanisms to refocus current competition on price towards a healthier balance of competition on price, quality, innovation and other factors should be explored. The expected impact on the market would be to encourage suppliers to remain in the market, to encourage long-term sustainable pricing and to promote investment in quality and innovation.
- A fund to achieve the appropriate RDT and ACT (artemisinin-based combination therapy) ratios would aim to accelerate growth in demand for RDTs, thereby correcting the size of the RDT market relative to ACTs and to generate market information on the appropriate ratio of diagnostics to medicines. It would diversify the concentrated donor landscape and possibly address gaps in coverage as the Global Fund transitions to new models of funding. The additional market intelligence generated through this project would have far reaching impact for both the market (e.g. more reliable commodity forecasts) and public health (e.g. by allowing programmes to monitor the impact of diagnosis scale-up and to tailor to interventions based on need).
- The scale-up of diagnostics in the private sector also represents an opportunity to support greater access to malaria diagnosis. In the near term, work to fill the evidence gaps is needed, through accelerated sharing of information generated by existing projects as well as supporting work to address remaining knowledge gaps. Later, as large-scale retail programmes develop, additional funding will be needed. While it is not clear whether an RDT subsidy will be required, substantial catalytic investments in demand generation activities and supply chain incentives will be required to assure RDT availability. Other components, such as communications campaigns, training and supervision, quality assurance (QA) and monitoring and evaluation will be ongoing and require considerable support.
- With respect to quality, stronger incentives for upstream quality are needed, as are new technologies for conducting QC at the point of service. Interventions might include strengthening programmes such as WHO prequalification or adoption of alternative standards. This could be coupled with technical assistance to RDT manufacturers to ensure that a number of them achieve the quality standards within a reasonable time frame. Support for the scale-up of positive control wells (PCWs), when they are available, would address the currently limited information on RDT quality in the field, address concerns about RDT heat stability and potentially contribute to increased acceptance of RDTs.
- In terms of unmet needs, work is under way to stimulate product development for radical cure of *P. vivax* and for diagnostics to support elimination. As the current efforts are early in the product development pathway, there is scope for intervention along the value chain. The market for *P. vivax* interventions is relatively large, yet complex because a variety of commodities are needed to support radical cure (accurate *P. vivax* diagnosis, POC G6PD screening tests, medicines to treat blood and liver stage infections). The market for elimination is likely more fragmented and still somewhat undefined due to ongoing operational research on active case detection strategies for elimination. In addition to monitoring these landscapes, potential near-term opportunities to engage upstream include: catalysing development of products for improved *P. vivax* diagnosis; facilitating market entry of POC G6PD tests; and supporting operational research around the role of diagnostics in active case detection. As product development progresses, support for product validation (e.g. access to well-characterized samples and clinical trials networks; consensus on validation standards), policy endorsements and quality registrations could decrease timelines. As new diagnostic tests come on the market, there likely will be scope for market creation work, possibly initial co-funding of procurement to achieve optimal pricing and to stimulate scale-up of manufacturing. Going forward, it will be important to monitor the various initiatives and developments in these areas.

- Improving surveillance and fever management are high priorities in the malaria community and there also might be scope for market interventions in terms of increasing use of technologies for streamlining reporting and analysis of surveillance data, and for supporting commodity access for fever management.
- Lastly, there are a number of market intelligence projects that would be meaningful to markets and provide public health value. Among the highest priority are initiatives to monitor diagnostics access and targeting of ACTs, work to develop information on the retail market for RDTs, costs of production analysis to inform negotiations around sustainable RDT pricing and improving the completeness of procurement data. At the country level, systems for monitoring test usage and quality issues and to improve the overall estimates of malaria incidence are needed. Lastly, to stimulate product development for unmet needs, analysis of potential demand is needed.

Conclusion

While there has been significant progress in the scale-up of malaria diagnosis recently and an increase in interventions shaping malaria diagnostics markets, this report highlights several important gaps and opportunities to accelerate access to testing in meaningful ways.

Even as burdens decline, testing needs will remain high until the population at risk is reduced to zero. In the coming years, funding is apt to be a major challenge for malaria programmes; the continued scale-up of diagnosis in the public sector and beyond is contingent on adequate resources. As diagnostic capacity increases, there is a game-changing opportunity to improve the epidemiological picture of malaria and it would make sense to invest in strengthening case reporting and surveillance.

Current RDT market conditions highlight the need to revisit procurement strategies with an eye towards refocusing competition to ensure the longer-term health of the market. Market conditions are also affecting quality and innovation. With respect to quality, current conditions highlight the importance of existing quality initiatives and the relevance of additional upstream and downstream work. In terms of innovation, current market conditions create a disincentive for innovation.

With respect to the pipeline, while there is scope for incremental improvements, malaria RDTs present a compelling value proposition. While new products have come on the market in the past year, they target specialized use scenarios and are not replacing RDTs. At the same time, the declines in *P. falciparum* are highlighting the need for new technologies for specific market segments, such as for elimination settings and for radical cure of *P. vivax*, and work has begun to support development of products in these areas. However, in general, progress of many pipeline technologies has slowed in the past year, in part due to lack of funding and lack of clear pull from the market.

Finally, 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. Operational research, work to define the needs and markets for new technologies, and monitoring and evaluation efforts to better understand the market and the impact of investments are urgently needed.

1. Introduction

The *2013 Malaria diagnostics technology and market landscape* has been prepared as part of a broad and ongoing effort within UNITAID to describe and monitor the disease, technology and market landscapes for commodities used in the prevention, diagnosis and treatment of malaria. This report focuses on malaria diagnostics.

The UNITAID landscape reports provide the intelligence needed to identify, design and support interventions with the most potential to optimize public health and market effects. The first set of landscapes, for HIV/AIDS, tuberculosis (TB) and malaria diagnostics, were developed in 2011 in response to a request from the UNITAID Executive Board. For malaria, comprehensive reviews of both the technology and market landscape for malaria diagnostics have been produced as well as shorter update reports. Content from these reports has been used to provide critical strategic context guiding the UNITAID decision-making process for new projects. For example, in June 2012, the Executive Board approved projects to scale up malaria rapid diagnostic tests (RDTs) in the private sector of five African countries and to conduct quality control (QC) testing of malaria RDTs. Similar complementary landscapes have now been prepared for malaria medicines and vector control commodities. These landscape analyses, as well as those for HIV and TB, were critical inputs for the development of the UNITAID Strategy 2013–2016 (http://www.unitaid.eu/images/strategy/UNITAID-Strategy_2013-2016-Full-English.pdf).

Studying the malaria diagnostics market is a timely exercise. The use of diagnostics for malaria is rapidly expanding due to 2010 changes in treatment guidelines and the ensuing public sector scale-up of malaria RDTs. The private sector market, to date undeveloped but potentially quite large, is also an area of active exploration. Progress in reducing the burden of malaria is creating new technology needs. As donors and programmes increase their investments in malaria diagnostics, it becomes increasingly important to understand and monitor the market. In addition to identifying opportunities for market interventions that could have considerable public health and market impact, this landscape is designed to serve other stakeholders and the broader global health community interested in understanding the malaria diagnostics market. As such, the landscape is published on the UNITAID website.

The *2013 Malaria diagnostics technology and market landscape* is structured as follows:

- Section 3 addresses the public health problem and provides an overview of malaria disease and case management, the role of diagnostic tests in malaria, as well as disease and programmatic trends malaria management.
- Section 4 summarizes commodity access and availability issues (i.e. needs that are not met by currently available technologies) for malaria diagnostics in resource-limited settings.
- Section 5 summarizes the malaria diagnostics technology landscape, including a review of existing technologies, technologies that have recently entered the market and the research and development (R&D) pipeline.

- Section 6 describes the market landscape, including growth, pricing, market share and quality standards as well as an overview of supply and demand. Both the public and private sector markets in malaria endemic countries are considered.
- Section 7 identifies market shortcomings using the UNITAID framework for market analysis and provides possible reasons for why these shortcomings exist.
- Section 8 addresses opportunities for market intervention and provides an initial view of potential market opportunities for increasing access to malaria diagnostics.

The report concludes with some thoughts on future directions and the role of innovation, and includes four annexes with additional information:

- Annex 1: Overview of performance and operational characteristics of malaria diagnostics;
- Annex 2: Technologies that have recently entered the market;
- Annex 3: Malaria technology developers and technologies in the pipeline;
- Annex 4: Global health donor landscape.

2. Methods

The primary objectives of this landscape are:

- to describe the current landscape of available malaria diagnostics as well as those in the R&D pipeline (“technology landscape”);
- to describe key characteristics of the malaria diagnostics market, with a focus on RDTs, as well as trends over time (“market landscape”);
- to identify market shortcomings and resulting opportunities to improve access through market-based approaches.

This landscape was developed and written by Jennifer Daily with support from UNITAID. Research for this report was conducted in July–October 2013, and information is up to date as of October 2013.

Technology landscape methods

While the existing technologies for malaria diagnosis, mainly microscopy, RDTs and polymerase chain reaction (PCR), have been written about extensively,¹ there is significantly less prior work on the malaria diagnostics pipeline.^{2, 3} Unlike the case of medicines, or HIV and TB diagnostics, where technology landscaping exercises have been undertaken, the malaria diagnostic landscape reports by UNITAID represent the first attempts to document and publish the malaria diagnostics pipeline.

Given the need for rapid, near-patient testing in malaria, the research for this report focused on technologies that are amenable to point-of-care (POC) formats and those being developed commercially for widespread use (as opposed to those that require well-equipped laboratories or developed primarily for research purposes).

1 See, for example:

- Erdman LK et al. Molecular approaches for diagnosis of malaria and characterization of genetic markers of drug resistance. In: Persing DH et al., editors. *Molecular microbiology: diagnostic principles and practice*, second edition. Washington (DC): ASM Press; 2011.
- Drakeley C, Cook J. Potential contribution of sero-epidemiological analysis for monitoring malaria control and elimination: historical and current perspectives. In: Rollinson D, Hay S, editors. *Advances in parasitology*, volume 69. Burlington: Academic Press; 2009:299–352.
- Murray CK, Gasser RA, Magill AJ, Miller RS. Update on rapid diagnostic testing for malaria. *Clin Microbiol Rev.* 2008;21:97–110.
- Wilson ML. Malaria rapid diagnostic tests. *Clin Infect Dis.* 2012 June;54(11):1637–41. Epub 1 May 2012.
- Moody A. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev.* 2002 January;15(1):66–78.
- Abba K et al. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database Syst. Rev.* 2011;(7):CD008122.
- Wongsrichanalai C, Barcus MJ, Muth S, Sutamihardja A, Wernsdorfer WH. A review of malaria diagnostic tools: microscopy and rapid diagnostic test (RDT). *Am J Trop Med Hyg.* 2007 December;77(Suppl. 6):119–27.
- Erdman LK, Kain KC. Molecular diagnostic and surveillance tools for global malaria control. *Travel Med Infect Dis.* 2008 January–March;6(1–2):82–99. Epub 19 November 2007.
- Hawkes M, Kain KC. Advances in malaria diagnosis. *Expert Rev Anti Infect Ther.* 2007 June;5(3):485–95.

2 For example, a 2012 publication focuses on one segment of the pipeline—advances in nucleic acid-based testing that have potential POC applications for malaria diagnosis: Cordray MS, Richards-Kortum RR. Emerging nucleic acid-based tests for point-of-care detection of malaria. *Am J Trop Med Hyg.* 2012 August;87(2):223–30.

3 Bio Ventures for Global Health (BVGH) maintains an online database of the pipeline for various health products that reflects UNITAID research on the malaria diagnostics pipeline (<http://www.bvgh.org/Biopharmaceutical-Solutions/Global-Health-Primer/Diseases/cid/ViewDetails/ItemID/7.aspx>. Accessed 20 November 2013).

Information sources used to identify products in the development pipeline include stakeholder interviews, targeted literature and Internet searches, and published and unpublished reports. Unlike medicines, there are few business intelligence databases for diagnostics, and because diagnostics for global health are largely unregulated, trials are not necessarily registered nor do they appear in public databases. Although this exercise aimed to be as complete as possible, the picture is constantly evolving and a totally exhaustive search is not possible, therefore, it is possible that technologies have been unintentionally left out.

Once a technology was identified, semi-structured interviews and correspondence with the technology developers, using a standardized form, provided specific information on each product, including product specifications, information on the developer and stage of development. Most of the detailed interviews occurred during July–October 2013. However, in some instances, the developers were not available to provide information on their work or were not advanced enough in the development process to provide significant detail. In addition, developers of several products included in previous landscapes were not available and, as a result, the most current information has been included (last updated in 2012).

The product descriptions and development timelines rely largely on information and best estimates from the technology developers. Because these products are in the development phase, the ultimate performance and operational characteristics could change by the time the product is launched. Similarly, projections of market launch will shift as time goes by, as will price estimates.

Market landscape methods

Currently, comprehensive data and business intelligence resources on diagnostic tests for global health do not exist. Therefore, the market landscape methodology used a diverse set of information sources: (i) review of literature, published and unpublished reports; (ii) analysis of aggregate data (when available); and (iii) discussions with experts, including representatives from industry, policy-makers, donors, implementers and academia.

Desk review methods

Although the malaria RDT market is growing rapidly, to date little has been published on its characteristics. While there are many publications on local markets, (e.g. example results of private sector RDT pilots or acceptance of RDTs in a particular country), there is significantly less work on global trends. Recent work considers the availability of RDTs in the public and private sector, adoption of RDTs and RDT pricing and procurement analysis.

Market data analysis

In preparing this report, several potential sources of market data were identified and investigated, however, overall work to aggregate data from any of these sources has been relatively limited. As such, three datasets were analysed: RDT procurement data; access and availability data from ACTwatch; and Roll Back Malaria Partnership/African Leaders Malaria Alliance (ALMA) data on testing needs and funding in Africa.

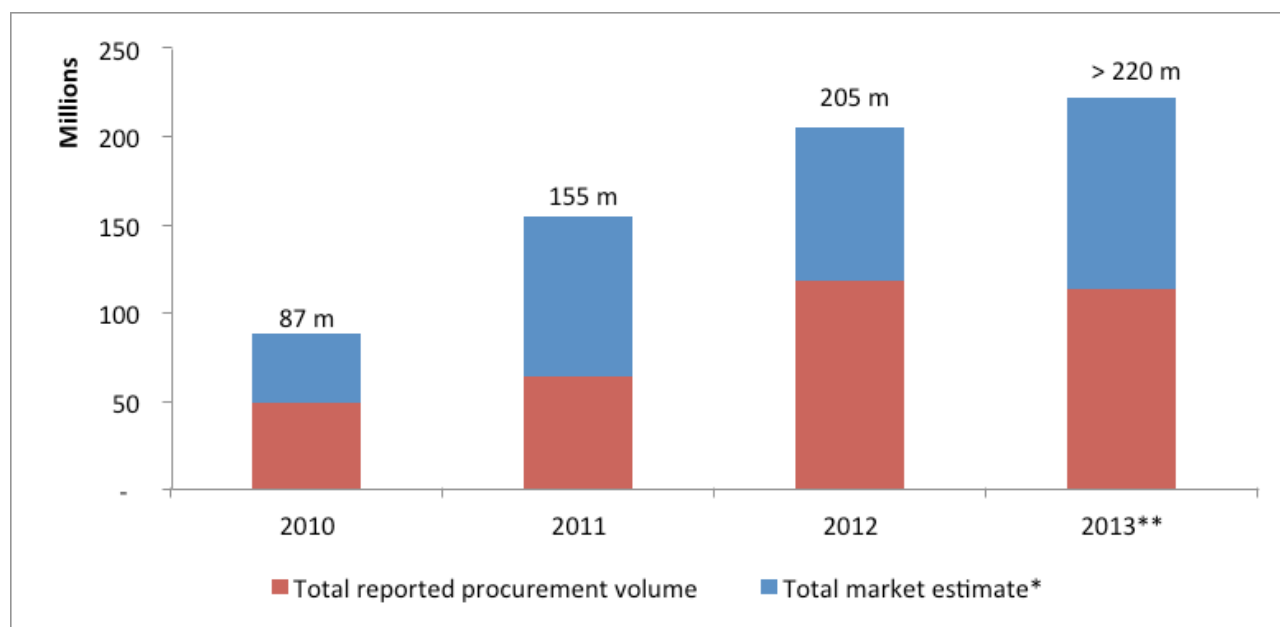
Procurement data analysis

In order to understand the market size and key trends, the Clinton Health Access Initiative (CHAI), with input from the author of this report, analysed procurement data. This involved compiling and analysing procurement data from the two largest donors for malaria diagnostics, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and the United States President's Malaria Initiative (PMI), for the period 2007–2013. John Snow International provided procurement data on behalf of PMI, which was combined with data from the Global Fund Voluntary Pooled Procurement (VPP) and data publicly posted on the Global Fund Price and Quality Reporting (PQR) system.⁴ In total, 656 transactions, representing

⁴ In 2009, the Global Fund began requiring that malaria RDTs be included in its PQR database. The PQR system is a web-based system for tracking the purchases of health products using Global Fund resources. The PQR in its current form was established in early 2009 and transactional data are entered by Global Fund Principal Recipients upon receipt of goods. The database is publicly available and updated regularly. The dataset for malaria diagnostics is partial although, in future, completeness should improve. Note that in the procurement data analysis, VPP data replaced those PQR entries that specified VPP as the procurement method.

> 388 million RDTs, from 2007 to 2013 were analysed. After cleaning the data, analysis included market growth, types of RDTs procured, procurement methods, the pricing trends and market share by company. The results were reviewed by PMI and the Global Fund and validated informally through interviews with leading malaria RDT manufacturers (described below). The dataset represents 41–58% of the global RDT market in 2010–2013 (Figure 1).

Figure 1. Reported procurement volumes for RDTs compared to global RDT market size



Note:

* Blue and red bars together represent total RDT market size; 2010–2012 totals are based on WHO surveys of manufacturers participating in the Product Testing Programme from the World malaria report (for the respective years).

** 2013 represents partial year of data (9 months for PMI and PQR, 11 months for VPP); the 2013 total market size estimated based on total sales of major manufactures for 10 months, extrapolated for 12 months and assuming these represent 75% of market, based on historical data.

Source: CHAI/author procurement data analysis.

The procurement data analysis exercise highlights many challenges that limit our understanding of the market for malaria RDTs. With respect to data sources, the analysis relied on Global Fund and PMI data, as other donors/institutional buyers (e.g. World Bank; the United Nations Children’s Fund; World Health Organization [WHO] Bulk Procurement; Médecins sans Frontières) do not have centralized databases or do not make information easily available. Although a significant volume of data was available, it represents only half of the total market, and within each dataset detail was often lacking. For example, Global Fund PQR data are incomplete, total volume of entries reported for VPP is 30% less than the volumes provided by the VPP procurement agent for 2009–2012. Additionally, mistakes in data entry or missing data are common (e.g. 5% of transactions do not include quantity, manufacturer or product detail). PMI does not maintain a publicly accessible database, and when it makes data available no specific price reference points are provided; rather, average prices are provided, limiting the ability to analyse pricing in detail. Lastly, there is little standardization around how information is reported, between systems and within systems, making it challenging at times to know precisely which RDT brand and type were purchased and what is included in the stated prices.

ACTwatch

ACTwatch is a multicountry research project that began in 2008 to monitor antimalarial and RDT supply and demand. It began with seven malaria endemic countries: Benin, Cambodia, the Democratic Republic of the Congo (DRC), Madagascar, Nigeria, Uganda and Zambia. In most countries, ACTwatch has conduct-

ed three rounds of outlet surveys, two rounds of household surveys and a supply chain mapping exercise. Results of ACTwatch studies are available on line (<http://www.actwatch.info>).

The most recent data from ACTwatch on diagnostic test availability, products and testing rates have been included in this report, however, since few surveys were conducted in 2012 much of the data are from 2011 surveys and unchanged since the last edition of the landscape. Phase two of ACTwatch, comprising outlet surveys and exit interviews, began in 2013 with the original countries as well as Kenya, Myanmar and Tanzania.

Roll Back Malaria Partnership/ALMA

On the demand side, while several groups have attempted to compile data on RDT procurement from countries, this has proven to be challenging. ALMA and the Roll Back Malaria Partnership Harmonization Working Group (HWG) maintain estimates of RDT needs and financing in the African countries based on analysis of needs and gaps performed by countries. These estimates have been included in this report.

Key informant interviews

Stakeholders

To gain a better appreciation for market trends, interviews with policy-makers, product quality evaluators, researchers, donors, procurement agents and implementers were needed. For the *2013 Malaria diagnostics technology and market landscape*, 25 stakeholders were interviewed. To the extent relevant to the interviewee, the following topics were covered: (i) trends in malaria policy and management; (ii) funding climate; (iii) RDT procurement trends; (iv) private sector markets; (v) RDT market shortcomings; (vi) implementation challenges; (vii) products (e.g. product selection; how well adapted); (viii) role of their organization; and (ix) expectations for market evolution in the next five years. Additional stakeholder interviews took place in early 2013 as part of an opportunity scoping exercise aimed at identifying opportunities for market intervention.

Industry

To provide more detail on the structure of the industry, nine semi-structured interviews with representatives from eight RDT suppliers (including all suppliers with > 5% market share in the Global Fund and PMI databases described above) were conducted. The supplier interviews covered the following topics: (i) sales volumes and trends; (ii) new product development activities; (iii) concerns and challenges, including external factors such as competition and internal factors such as operations; and (iv) private sector markets for RDTs. Additionally, interviews with the two leading manufacturers of monoclonal antibodies (MAbs), the key raw material for malaria RDTs, were conducted.

Data limitations

Due to the lack of data on diagnostics, this report relies on partial datasets supplemented by extensive qualitative research. As a result, it is difficult to be precise about many of the findings, and additional data would lend more confidence to the results. For example, although procurement data were analysed, the dataset is incomplete, representing approximately half of the market. In order to validate the findings, we relied on supplier self-reporting of RDT volumes, which introduces potential bias. The paucity of data is especially noticeable in the private sector. It is also important to note that this work focused largely on the global health market for RDTs, and only the primary suppliers to this market segment were contacted.

3. Public health problem

Species of malaria

Malaria is a preventable and highly treatable parasitic disease. It is transmitted when a female Anopheles mosquito infected with the *Plasmodium* bites a person. There are five parasite species that cause disease in humans with variable prevalence based on geographic area. They are: *Plasmodium falciparum*; *Plasmodium vivax*; *Plasmodium ovale*; *Plasmodium malariae*; and *Plasmodium knowlesi*. Although *P. vivax* is the most widely distributed malaria species, *P. falciparum* receives the most attention as it is the most deadly. While *P. ovale* and *P. malariae* are thought to be much less prevalent than *P. vivax* and *P. falciparum*, the true burdens of these diseases are not well documented because current diagnostic methods do not document them reliably. *P. knowlesi* is a species that primarily causes malaria among monkeys, however, in recent years human cases have occurred in South-East Asia.

Disease burden and distribution⁵

At a global level, 3.1 billion people across 104 endemic countries were at risk of malaria, with the South-East Asia, African and Western Pacific WHO regions having the greatest number of people at risk (Figure 2). Although the risk is widespread, the number of cases and deaths are concentrated in Africa, where the majority of cases is caused by *P. falciparum*. Of the estimated 219 million malaria cases in 2010 (a range of 154–289 million), approximately 80% was in Africa and of the estimated 660 000 malaria deaths in 2010 (a range of 490 000–836 000), 91% was in Africa.⁶

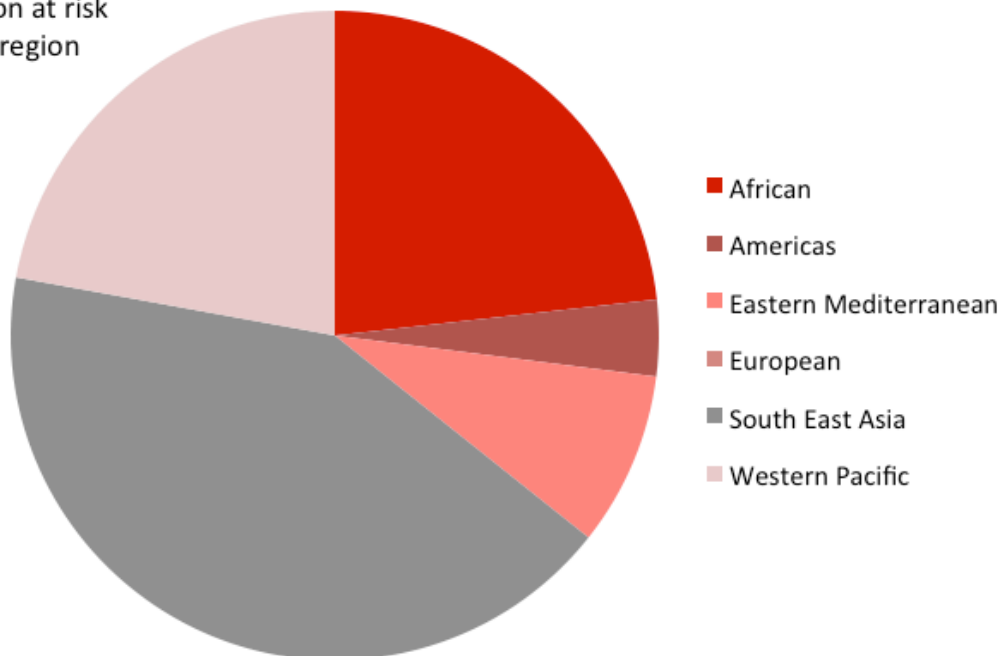
From a market perspective, the number of suspected fevers needing testing drives diagnostics demand. Suspected fevers is both a function of the population at risk (i.e. all fevers in populations at risk should be tested, even though the majority will not be caused by malaria) as well as the malaria burden (i.e. a high burden of malaria will contribute to a higher number of fevers).

⁵ Unless otherwise noted, statistics are drawn from the 2012 *World malaria report*.

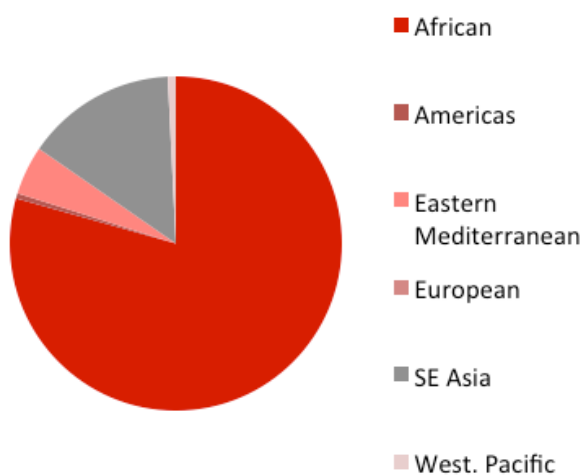
⁶ Note there are wide uncertainty intervals associated with these estimates and varying approaches to estimating the burden of malaria. Note there are wide uncertainty intervals associated with these estimates and varying approaches to estimating the burden of malaria.

Figure 2. Malaria population at risk, cases (estimated), 2010, and malaria deaths (estimated) by WHO region, 2010

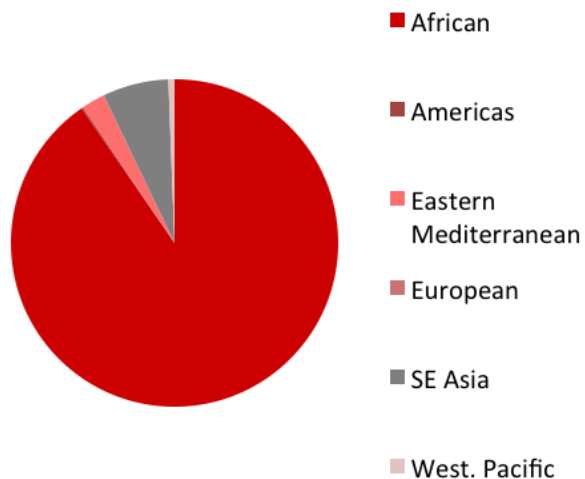
Population at risk
by WHO region



Malaria cases



Malaria deaths



Source: 2012 World malaria report. Geneva: WHO; 2012.

High-burden countries and vulnerable populations

At the country level, there is substantial variability in malaria disease burden. Although 99 countries have ongoing malaria transmission, the burden is highly concentrated. For example, within Africa, 10 countries account for more than 70% of African malaria cases (56% of cases globally) and an estimated 430 000 malaria deaths each year (Figure 3). Globally, DRC India, and Nigeria comprise an estimated 40% of malaria cases.

Figure 3. The 10 countries representing >70% of Africa's malaria burden



Source: WHO Malaria Situation Room website. (http://www.who.int/malaria/areas/malaria_situation_room/en/)

Malaria disproportionately affects certain vulnerable populations, including young children, pregnant women and the poor living in remote areas.⁷ Children aged under 5 years account for 86% of deaths from malaria.⁸ 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.⁹ 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.

Recent progress and changes in epidemiology as transmission declines and approaches malaria elimination

Globally, the last decade has seen a dramatic reduction in the burden of malaria, with many countries reducing their burden by more than 50%. Additionally, malaria mortality rates have fallen by more than 25% globally since 2000, and by 33% in the WHO African Region.¹⁰ 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 insecticide-treated mosquito nets (LLINs) and of effective antimalarial treatments (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 to very low levels. While the goal of malaria control is to reduce cases and deaths from malaria, the goal in elimination is to interrupt the chain of local malaria transmission. The Global Health Group at the University of California San Fran-

7 2012 World malaria report. Geneva; WHO; 2012.

8 2012 World malaria report. Geneva; WHO; 2012.

9 Kattenberg et al. Systematic review and meta-analysis: rapid diagnostic tests versus placental histology, microscopy, and PCR for malaria in pregnant women. *Malar J.* 2011 October;28(10):321.

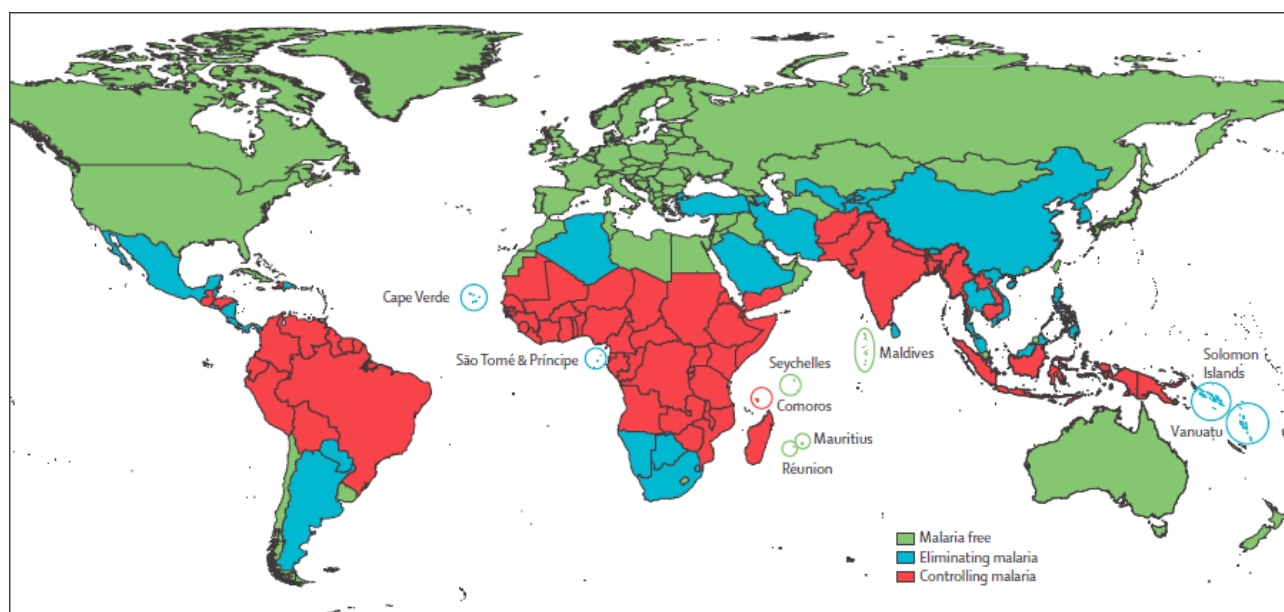
10 WHO Malaria fact sheet No. 94, reviewed March 2013 (<http://www.who.int/mediacentre/factsheets/fs094/en/>, accessed 28 September 2013).

cisco, reports that 34 countries are moving from controlled low-endemic malaria to elimination and that these countries have reduced the number of malaria cases by 85% from 2000 to 2010 (Figure 4).¹¹

As transmission declines to very low levels, epidemiological shifts in malaria occur and parasites become increasingly clustered in small geographical areas (“hotspots”) and among certain populations (“hot-pops”). Instead of a concentration of malaria cases in young children and pregnant women, as transmission declines the proportion of malaria cases in older children and men rises. This is generally attributed to the overall decline in cases and to occupational or behavioural factors (e.g. men who work and sleep in forests) that put men at higher risk for malaria than the general population. Additionally, an increasing number of cases are “imported” as opposed to transmitted locally (e.g. truck drivers travelling to higher transmission areas may contract malaria and become a source of further transmission when they return home). Malaria also tends to become increasingly concentrated in harder to reach populations, such as migrant workers or remote communities that might have lower access to health services and preventive measures.

Another common trend in eliminating countries is the increasing proportion of cases due to *P. vivax*, in large part because *P. falciparum* responds more quickly to control measures than does *P. vivax*. Of the 34 malaria eliminating countries, currently 26 have a malaria burden solely or mainly due to *P. vivax*.¹²

Figure 4. Categorization of countries as malaria-free, eliminating malaria or controlling malaria, 2012



Source: Cotter C et al. The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet. 2013 September;382(9895):900–11.

Global targets

In 2005, the World Health Assembly and Roll Back Malaria Partnership set a goal to reduce the number of malaria cases and deaths by 75% by 2015, compared to levels in 2000.¹³ WHO estimates that only 50 of 99 countries with ongoing malaria transmission are on target to meet malaria case incidence of 75% by 2015.¹⁴ With respect to diagnostics, the Roll Back Malaria Partnership in June 2011 set specific targets for universal access to malaria diagnosis in the public and private sectors, as well as in the community by

¹¹ Cotter C et al. The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet. 2013 September;382(9895):900–11.

¹² Cotter C, et al. The changing epidemiology of malaria elimination: new strategies for new challenges. Lancet. 2013 September;382(9895):900–11.

¹³ Resolution WHA58.2. Malaria control. Geneva: WHO; 2005 (WHA58/2005/REC/1; http://apps.who.int/gb/ebwha/pdf_files/WHA58-REC1/english/A58_2005_REC1-en.pdf, accessed 28 September 2013).

¹⁴ 2012 World malaria report. Geneva: WHO; 2012.

2015.¹⁵ Currently, an estimated 77% of suspected cases in the public sector are tested. Testing rates in the private sector and community are not well documented, but are significantly lower or minimal depending on the setting.

Role of malaria diagnostics: case management and surveillance

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 malarias, however, *P. vivax* and *P. ovale* can relapse weeks and months after treatment because of a dormant liver form (hypnozoites, absent in other species) that can persist in the liver for extended periods.

Malaria illness

The nature and degree of illness from malaria depend in part on the individual's background level of immunity, which is determined primarily by the extent of malaria transmission where they live. Although people living in stable or high transmission areas are infected frequently, they generally develop some immunity (i.e. they may be infected and have parasites circulating in their blood, but they will not have severe symptoms of malaria) by late childhood. Regions of stable and high transmission are largely found in sub-Saharan Africa. In areas of unstable and low 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 density¹⁶ (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 ill at low parasite densities. Adults living in higher transmission settings will have developed immunity and, while they may have parasites circulating in their blood, they may not have symptoms of malaria (i.e. asymptomatic infections).

Importantly for elimination settings, even asymptomatic infections can cause onward transmission of malaria. Ideally, many of these asymptomatic infections as possible would be identified and treated to reduce transmission; however, since such individuals might not feel ill, they will not present at health facilities and must be sought out proactively in the community. Additionally, these infected individuals often have very low-density parasitaemia that is below the detection limit of RDTs and microscopy, ("sub-patent infection"), presenting further challenges for their identification. The proportion of asymptomatic and/or subpatent infections in a community as well as their contribution to onward transmission (i.e. what level of parasitaemia is sufficient to cause transmission; for how long do individuals carry parasites) is an area of active research that has implications for diagnostics, in particular, the optimal limit of detection (LOD) of a test (i.e. the ability of the test to detect very low levels of parasites circulating in the blood).

¹⁵ The Roll Back Malaria Partnership targets are: (i) achieve universal access to case management in the public sector: by 2013, 100% of suspected cases receives a malaria diagnostic test and 100% of confirmed cases receives treatment with appropriate antimalarial drugs; (ii) achieve universal access to case management, or appropriate referral, in the private sector: by end of 2015, 100% of suspected cases receives a malaria diagnostic test and 100% of confirmed cases receives treatment with appropriate and effective antimalarial drugs; (iii) achieve universal access to community case management of malaria: by end of 2015, in countries where community case management of malaria is an appropriate strategy, 100% of fever (suspected) cases receives a malaria diagnostic test and 100% of confirmed uncomplicated cases receives treatment with appropriate and effective antimalarial drugs, and 100% of suspected and confirmed severe cases receives appropriate referral; and (iv) 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 Partnership; 2011 (<http://www.rollbackmalaria.org/gmap/gmap2011update.pdf>, accessed 28 September 2013).

¹⁶ Parasite density refers to the volume of parasites in a given quantity of blood, usually expressed as the number of parasites per microlitre of blood (e.g. 5000 parasites/ μ l) or as the percentage of red blood cells infected with parasites (e.g. 1% parasitaemia). 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 could lead to clinical illness (depending on the individual) and could contribute to transmission of malaria.

WHO policy: malaria case management

The symptoms of malaria (fever, headache, fatigue) are non-specific and mimic those of other illnesses, making the diagnosis on the basis of clinical signs and symptoms difficult. Historically, due to the high burden of disease, its potential severity and the low availability of diagnostic tests, malaria was often clinically suspected on the basis of fever and treated (i.e. “clinical diagnosis” or “presumptive treatment”). As the burden of disease declines, this results in massive overtreatment of malaria and misuse of antimalarial medicines for non-malaria illness.

In response to the declines in malaria, in early 2010, WHO updated its policy on malaria diagnosis, recommending that all cases of suspected malaria be confirmed with a diagnostic test before treatment. For *P. falciparum* malaria, the WHO recommended treatment is an ACT. For *P. vivax*, two medicines are needed: a drug (chloroquine or an ACT) to treat the blood stage infection and a drug (primaquine) to treat the liver stage infection that causes relapse.

There have been no recent changes in the WHO malaria diagnostic policy, and implementation of the 2010 WHO policy recommendation for parasitological diagnosis for all suspected cases is under way. In addition, in 2012, WHO launched a Test, Treat, Track (3T) Campaign, further underscoring the importance of scaling up malaria diagnostics and ensuring that the data generated through testing are systematically captured by surveillance systems.

Diagnostics for routine case management

To be useful in clinical management, any malaria test should be both accurate and rapid, due to the acute and potentially life-threatening nature of malaria disease. Given the high volumes of fevers that should be tested globally each year, and the incomes of populations affected by malaria, low cost is critical. Malaria tests should be portable, robust enough to withstand extreme heat and humidity and require minimal/no operator training or input to process the test.

Role of malaria diagnostics in surveillance

Although the most common use of malaria tests is for case management, the role of diagnostics in surveillance depends on the local epidemiology as well as available systems and technologies. In general, as transmission of malaria declines and programmes shift from control to elimination strategies, surveillance activities that involve diagnostic tests increase.

Surveillance in control settings

In most control settings, surveillance focuses on the clinical burden of malaria (i.e. the number of ill people and deaths as opposed to people who are infected with malaria). This is accomplished primarily by reporting of malaria cases by health facilities, and by periodic prevalence surveys using diagnostic tests. Historically, reporting by health facilities has been based on a combination of both *suspected cases* (i.e. cases not confirmed with a diagnostic test) and *confirmed cases*, providing limited insight into the actual disease burden and programme effectiveness. With the adoption of universal diagnosis policies, diagnostic capacity is increasing and linking results with reporting systems represents an opportunity to gain an increasingly accurate picture of malaria incidence that may be used to monitor progress and to target interventions.

Surveillance activities for malaria elimination settings

As malaria prevalence declines, additional surveillance activities begin, aimed at developing a finer-grain picture of transmission and at monitoring the effectiveness of interventions. Surveillance activities in elimination settings are characterized by: (i) a shift in focus to individuals as opposed to aggregate population-level data; (ii) efforts to strengthen passive case detection (i.e. accurately identify and report all cases in health facilities); and (iii) an emphasis on identifying all infections, including asymptomatic and/or subpatent infections,¹⁷ because these may contribute to onward transmission of malaria.

Therefore, in addition to the systems used in control settings, surveillance activities involving diagnostics in very low-transmission and elimination settings also include:

Passive case detection¹⁸

- Efforts to ensure that as many cases of malaria as possible are detected accurately and reported through passive case detection systems. This includes increasing access to health facilities, ensuring that providers test all suspected cases, provide appropriate treatment and patient education and report all cases immediately. Efforts must extend to private sector facilities as well as public health facilities.¹⁹
- Efforts to improve the speed, accuracy and monitoring of health facility case reporting data so that programmes can rapidly respond to outbreaks and identify potential foci of transmission.

Active case detection²⁰

There are several forms of active case detection:

- Reactive case detection is common in low-transmission settings. Health workers perform follow-up visits in the community for cases that present to clinics (“index case”). During these community visits individuals who reside or work in proximity to the confirmed case are tested to see if they have been infected with malaria and appropriately treated. In some programmes, only febrile individuals are tested, in others, all individuals are tested, irrespective of symptoms. Often other members of the household and neighbours may harbour malaria parasites, but may not be symptomatic. Additional vector control or educational measures are frequently taken during these visits.
- Proactive case detection includes screening and treatment of high-risk populations, for example, individuals travelling from higher transmission areas, people living in particular areas of ongoing transmission and populations such as migrant or forest workers who visit areas where transmission occurs. These programmes might include fever screening followed by testing or testing and treatment alone. Proactive case detection is often called focal screen and treat (FSAT) or mass screen and treat (MSAT).

Surveys

- As transmission declines, nationally representative prevalence surveys become impractical as very few positive cases are found despite large sample sizes. Smaller scale population surveys are used to identify high-risk groups/foci of transmission that need intervention. In some instances, once a focus of transmission is identified mass drug administration also could be used (without diagnostics).

Quality Assurance (QA)

- From a diagnostics perspective, all of these activities rely on the ability to accurately detect infections. Elimination programmes must implement more intensive QA/QC activities for diagnostics, for

17 Asymptomatic or subclinical infections are infections in individuals who have no symptoms associated with malaria. Subpatent infections refer to infections with parasite densities that are below LOD of routinely used diagnostic tests such as microscopy or RDTs. Subpatent infections (e.g. microscopy negative/PCR positive) are common in low-transmission settings and their contribution to transmission might be significant and is an area of ongoing research.

18 Passive case detection refers to the detection of malaria cases through health facilities, i.e. in individuals who are ill and seek care at health facilities.

19 Currently, WHO recommends that microscopy be used as the primary means of diagnosis and/or that when an RDT is used to guide initial patient management that microscopy is performed to confirm the result. Sources: Malaria elimination: a field manual for low and moderate endemic countries. Geneva: WHO; 2007; Disease surveillance for malaria elimination operational manual. Geneva: WHO; 2012.

20 Active case detection strategies focus in, particular, on identifying and treating all infections, including those that do not present at health facilities as early as possible in order to reduce chances of onward transmission.

example, the national reference laboratory might routinely confirm all positive cases and a proportion of negatives using expert microscopy or molecular tests.

Origin analysis

- An area of ongoing research is the use of genetic analysis of confirmed cases to determine the origin of the infection (i.e. to differentiate between locally transmitted and imported cases). The source of infection guides the appropriate response and also helps gain an appreciation of whether local transmission is ongoing, or whether most malaria is imported.

The specific set of activities that countries take to identify infections and measure transmission in elimination settings is varied and is an area of ongoing research. For example, while reactive case detection is the most commonly implemented form of active surveillance, a recent review illustrated that there is little consistency in the implementation across countries.²¹ Currently, there is little guidance on when or whether these activities should be implemented (e.g. at what level of transmission, systems and capacity prerequisites). Likewise, the effectiveness of active case detection activities and optimal strategies for their implementation are an area of active research.

These surveillance activities as well as the changes in epidemiology that occur when transmission declines have important implications for diagnostic tests. These are discussed along with other unmet needs in this report (Section 4).

Trends in malaria policies and practices

Notable trends and priorities in malaria that influence diagnostic markets include:

Constrained donor funding and slowing of progress. Perhaps the most important concern in malaria management is the levelling off of funding that has led to a slowing progress, compared to the previous decade of gains, and puts recent gains at risk. A recent review identified a weakening of malaria programmes following funding disruption as the single greatest cause of malaria resurgence.²² Generally, since the global financial crisis, international donor funding has become less certain. In particular, the uncertainty associated with the largest international funder of malaria programmes, the Global Fund, continues due to fundraising challenges and strategic reform, including its New Funding Model. Although the New Funding Model has been launched, funding levels for malaria programmes and the allocation of funds between prevention and case management remain uncertain. To date, conversations with experts suggest that there have been no major interruptions or slow downs in malaria diagnosis scale-up due to funding shortages. The continued progress may be attributed to declines in RDT prices that have stretched diagnostics budgets. However, future funding may limit the pace of diagnosis scale-up, in particular, in the private sector.

One consequence of the constrained funding environment is a greater focus on value for money and investing strategically. For example, there is a growing recognition that a handful of high-burden countries contribute disproportionately to the burden of malaria and that global targets for reducing malaria will not be met without increasing focus on these countries. The Malaria Situation Room²³ has been established to support the 10 highest-burden African countries and will synthesize data on funding, commodities, intervention coverage and impact, with an aim of identifying and resolving bottlenecks. Reforms at the Global Fund also reflect a desire to invest more strategically, including a reorganization of staff to better support the high-burden countries, and for more involvement in grant development so as to improve alignment of Global Fund-supported programmes with best practice.

Scale-up of diagnostics and implementation challenges. In Africa, where testing rates are low, programmes continue to prioritize diagnosis scale-up, largely through RDTs. While some countries have achieved national scale-up in the public sector, many of the higher-burden countries are still in the pro-

21 Smith Gueye C et al. Active case detection for malaria elimination: a survey among Asia Pacific countries. *Malar J.* 2013 October 9;12:358.

22 Cohen JM et al. Malaria resurgence: a systematic review and assessment of its causes. *Malar J.* 2012 April;11:122.

23 The Malaria Situation Room is a collaboration between WHO, the Roll Back Malaria Partnership, the United Nations Special Envoy, the International Federation of Red Cross and Red Crescent Societies (IFRC) and ALMA.

cess of scaling up. There are several challenges emerging from the diagnostic scale-up related to ensuring availability of tests at the point of service, encouraging use of tests, monitoring clinical practice and improving febrile illness management. There is increasing focus on improving diagnostic services for fever (as opposed to simply supplying a new commodity), which is inherently complex and requires behaviour change on the part of providers and patients who have for years equated fever with malaria.

Where diagnostics have been scaled up, common challenges include policy and supply chain weaknesses limiting test availability at the point of service and poor adherence to diagnostic test results. For example, conversations with experts suggest that confusion about the policy (e.g. who should be tested; whether to use RDTs or microscopy) leads to frequent stockouts of both RDTs and microscopy supplies. While adherence to diagnostic test results remains an issue²⁴ and undermines the benefits of testing, an unpublished review²⁵ suggested that over time acceptance of RDT results has been increasing (assuming commodity availability).

Related to the difficulties in improving use of RDTs is the inability of programmes to monitor case management practices effectively due to weaknesses in reporting. Currently, the necessary data are often captured at the health facility level in patient registers, however, the systems for reporting data impede monitoring.²⁶ Until reporting systems can be improved, periodic health facility surveys are suggested as a means of monitoring progress in case management practices. WHO and its partners are developing standardized survey methodologies and tools.

Related to monitoring clinical practice is the need to strengthen febrile illness management. Given today's epidemiology, a large population will test negative. However, many providers are unaccustomed to performing differential diagnosis of fever, and the health systems where they work might not be supportive of an alternative diagnosis. Therefore, there is a growing focus on strengthening the management of febrile illness more holistically. At the global level, WHO has been reviewing guidance and strategies for improving management of febrile illness, hosting an informal consultation on fever management in early 2013. Operationally, there is scope for operations research to improve algorithms and guidance on fever management. Programmatically, there is significant work to be done to improve the management of non-malaria fever, including strengthening supply chains, improving coordination of various groups working in this area, increasing funding, improving monitoring of programmatic indicators and strengthening the workforce.²⁷ Practically, WHO is leading Race Access Expansion (RaCE) 2015, a five-country implementation programme for integrated community case management of childhood illnesses.²⁸

With respect to markets, the scale-up of diagnosis has created demand for RDTs and will have implications for ACT usage, which should decline. Eventually, work on non-malaria fever will likely impact the markets for existing health products (e.g. antibiotics; zinc; oral rehydration salts) and may eventually create demand for new products that would help with fever management.

The weaknesses of malaria surveillance systems more broadly are a growing concern, as highlighted in the *2012 World malaria report* and the WHO Test, Treat, Track Campaign in 2012. Currently, the global picture of malaria is incredibly imprecise. WHO reports that existing surveillance systems capture only

24 In some countries, adherence hovers around 60–70% (Ghana), while in others it is higher ~80% (Malawi). Source: Barat L. Update from diagnosis workstream. Presentation at the meeting of the Roll Back Malaria Partnership Case Management Working Group, Veyrier du Lac, France, 5–7 March 2013.

25 Bosman, A. Redressing the market imbalance between diagnostic testing and treatment of malaria. Presentation at the Multilateral Initiative on Malaria (MIM) conference, Durban, South Africa 6–11 October 2013.

26 For example, test results are often reported through the laboratory information systems, while treatment statistics are reported through national health information systems. As a result, it is not possible to know whether all patients with positive test results received an ACT, or whether some of the ACTs were provided to patients who were not tested or who tested negative.

27 Gill C et al. Bottlenecks, barriers and solutions: results from multicountry consultations focused on reduction of childhood pneumonia and diarrhoea deaths. *Lancet*. 2013;381:1487–98. Doi:10.1016/S0140-6736(13)60314-1.

28 Globally, malaria, diarrhoea and pneumonia are the leading causes of death in the postneonatal period. RaCE 2015 was launched by WHO GMP in 2012. Objectives include: (i) catalysing the scale-up of community case management thereby increasing coverage of access to diagnostic treatment and referral services for the major causes of childhood mortality; (ii) generating evidence to inform WHO policy recommendations and programmatic guidance on integrated community case management; and (iii) stimulating review of policy (in particular, diagnostic and antibiotic use at the periphery) and regulatory environment for disease management in countries, including adaptation of supply management and surveillance systems. RaCE will be implemented by selected NGOs (e.g. Save the Children, International Rescue Committee, World Vision), with the ministries of health in a leadership position during 2013–2017 in DRC, Malawi, Mozambique, Niger, and Nigeria (two states). RaCE is funded by the Canadian International Development Agency (CIDA) (\$ 74.5 million Canadian dollars). Source: WHO GMP (http://www.finddiagnostics.org/resource-centre/reports_brochures/malaria-diagnostic-test-report.html).

10% of cases. Moreover, 41 countries, representing 85% of the malaria burden, do not have adequate systems in place to generate data that are useful for monitoring trends, identifying geographic differences and decision-making.²⁹ In short, progress towards meeting malaria targets is not possible to ascertain in many countries due to the lack of data. Prior to the diagnosis scale-up, data on “suspected malaria cases” were not very valuable. However, now increased diagnostic capacity represents a game-changing opportunity to improve the picture of malaria and to make data-driven decisions at both the local and global levels about resource allocations. From a market perspective, weak surveillance results in poor appreciation of malaria incidence and commodity markets (e.g. appreciating the demand for tests and the impact that scale-up of RDTs may have on ACT demand).

Development of the private sector markets for RDTs. Several recent studies have highlighted the need to target ACTs to those who test positive, especially in the private sector. For example, a study in Tanzania found that of people who visited drugs stores with fever, 81% who purchased an ACT was not infected with malaria. Of those who were infected, 31% purchased an ACT.³⁰ A recent modelling exercise estimated that 655 million antimalarial treatments are sold annually in the African private sector, one third of which are taken by individuals with malaria.³¹ These studies have further highlighted the need to improve access to diagnosis in the private sector, and suggest that annual testing needs are in the hundreds of millions.

In 2012 and 2013, activities aimed at developing the private sector markets for diagnostics intensified. Many projects, ranging from operational research to large-scale implementation pilots, have begun to improve the knowledge base and to increase access to diagnosis in the private sector. Despite the progress, several unanswered questions remain, in particular, management of RDT-negative patients and financial incentives for consumers and supply chain actors that encourage testing and appropriate fever management. At the local level, regulatory barriers to case management in the private sector must be addressed. Funding to support private sector programmes as well as their long-term sustainability are also important concerns that have yet to be adequately addressed.

Of note, in late 2012, the Global Fund decided not to continue its large ACT subsidy, Affordable Medicines Facility-malaria (AMFm), as a stand-alone programme, but rather to integrate it into the regular grant making activities.³² The programme did not include RDTs or activities around targeting ACTs to confirmed cases, and the Global Fund Board has encouraged incorporating diagnostic testing into private sector programmes going forward. The Roll Back Malaria Partnership, through the AMFm Task Force and Case Management Working Group, is leading efforts to better appreciate the existing evidence base and remaining knowledge gaps related to development of private sector markets and improved case management, with an aim to developing strategic and programmatic guidance as soon as possible. In addition, the AMFm Task Force is exploring the need for and feasibility of additional financial support for private sector programmes.

29 2012 World malaria report. Geneva: WHO; 2012.

30 Goodman C et al. Evaluating interventions to improve ACT access and targeting—results from the IMPACT2 project 2013 (<http://www.actconsortium.org/pages/project-4.html>, accessed 6 October 2013).

31 Cohen J et al. Public health: optimizing investments in malaria treatment and diagnosis. *Science*. 2012 November;338(6107):612–4.

32 AMFm was a global health financing mechanism hosted by the Global Fund and aimed at increasing access to effective malaria treatments by reducing the retail price of ACTs, increasing ACT availability and use and crowding out of ineffective treatments that contribute to drug resistance. The programme involved subsidizing the cost of ACTs, was implemented at national scale for two years in eight countries, and was supported by a pool of funds that was separate from other Global Fund programmes. In late 2012, the Global Fund Board decided to integrate AMFm activities into its routine grant-making processes, i.e. there would no longer be a special pool of funds for subsidizing private sector case management; going forward, countries could elect to include a private sector subsidy programme in their malaria grants.

P. vivax. An estimated 2.85 billion people live at risk of *P. vivax* infection, the majority in the tropical belt of Asia.³³ For many countries outside of Africa, including the majority of elimination countries, *P. vivax* is the primary concern of malaria programmes. In addition, there have been increasing reports on severe disease from *P. vivax* in the literature.³⁴ As a result, at the global policy level, there is renewed interest in the species; for example, WHO has begun developing a strategy for *P. vivax* control and elimination.

With respect to diagnostics, there is room for improvement in the sensitivity of RDTs for *P. vivax* as well as a need for POC tests to rule out G6PD deficiency (glucose-6-phosphate dehydrogenase is an enzyme in the human body that is essential for basic cellular functions), a common genetic disorder that may cause a severe reaction to primaquine, the medicine used to prevent *P. vivax* relapse. Much of the current R&D activity in this area relates to G6PD testing. Several research groups are evaluating new tests for G6PD, including a large project led by PATH to support the development of POC G6PD tests. WHO has recently proposed a formal review of G6PD testing in 2014 to support improved access to primaquine for radical cure of *P. vivax*.³⁵

Elimination. With the progress in malaria control over the past 10 years, malaria elimination—defined as the interruption of local transmission—is increasingly possible in areas where transmission has been reduced. Currently, 34 countries are actively pursuing elimination.³⁶ Globally, recent work in this area includes publication of *Case studies on malaria elimination* by the Global Health Group and WHO, increasing funding for elimination operational research and product development by the Bill and Melinda Gates Foundation, growing focus on elimination in the literature, and the increasing presence of regional groups focused on elimination (e.g. the Asia Pacific Malaria Elimination Network, the Elimination Eight).

With respect to diagnostics, there is an emerging view that more sensitive tests are needed for elimination settings. In 2012, PATH launched the DIAMETER initiative to support the development of diagnostics for malaria elimination, initially through development of use scenarios and target product profiles (TPPs) for elimination diagnostics. In addition, WHO convened a meeting in late 2013 to review diagnostics for low-transmission and elimination settings.

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

34 Price RN et al. *Vivax malaria: neglected and not benign*. *Am J Trop Med Hyg*. 2007 December;77(Suppl. 6):79–87. Antinori S et al. Severe *Plasmodium vivax* malaria: fact or fiction? *Clin Infect Dis*. 2012 December;55(11):1581–3.

35 Proposal for an Evidence Review Group (ERG) on G6PD testing to support increased access to primaquine for radical cure of *Plasmodium vivax* and for malaria chemoprophylaxis. WHO Malaria Advisory Policy Committee meetings (<http://www.who.int/malaria/mpac/sep2013/en/index.html>, accessed 30 September 2013).

36 The Malaria Elimination Group at the University of California San Francisco defines eliminating countries as those that have adopted or are seriously considering adopting strategies for elimination and maintains a list of these countries on its website (<http://www.malariaeliminationgroup.org/resources/elimination-countries>). Note that this list is broader than the WHO programme phase classifications of elimination and pre-elimination countries.

4. Commodity access

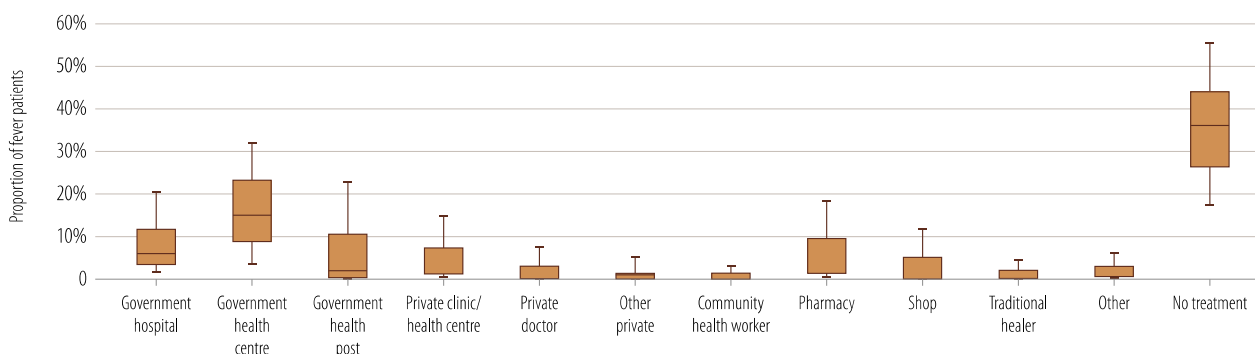
This section presents available data on access to testing. First, the most common use of malaria diagnostics is considered: testing for case management. Second, unmet diagnostic needs are described.

Access to malaria diagnostics (clinical use)

In considering data on access to malaria testing, it is useful to understand the context in which testing takes place, including the care pathways for fever (Figure 5) and the continuum of care (Figure 6).

Although malaria-like fevers occur frequently, the ways in which individuals respond to episodes of fever and symptoms of malaria vary tremendously. Individuals who seek some form of care when they experience symptoms could do so through public health services and/or the private sector, which is highly varied in terms of products, services and skills, and includes informal channels such as market stalls, kiosks and traditional healers. In addition, there are many individuals who take no action when they experience malaria-like symptoms. Figure 5 illustrates the variety in treatment-seeking behaviour for fever, including a high proportion of people who seek no treatment.

Figure 5. Treatment source used for fever cases



Note:

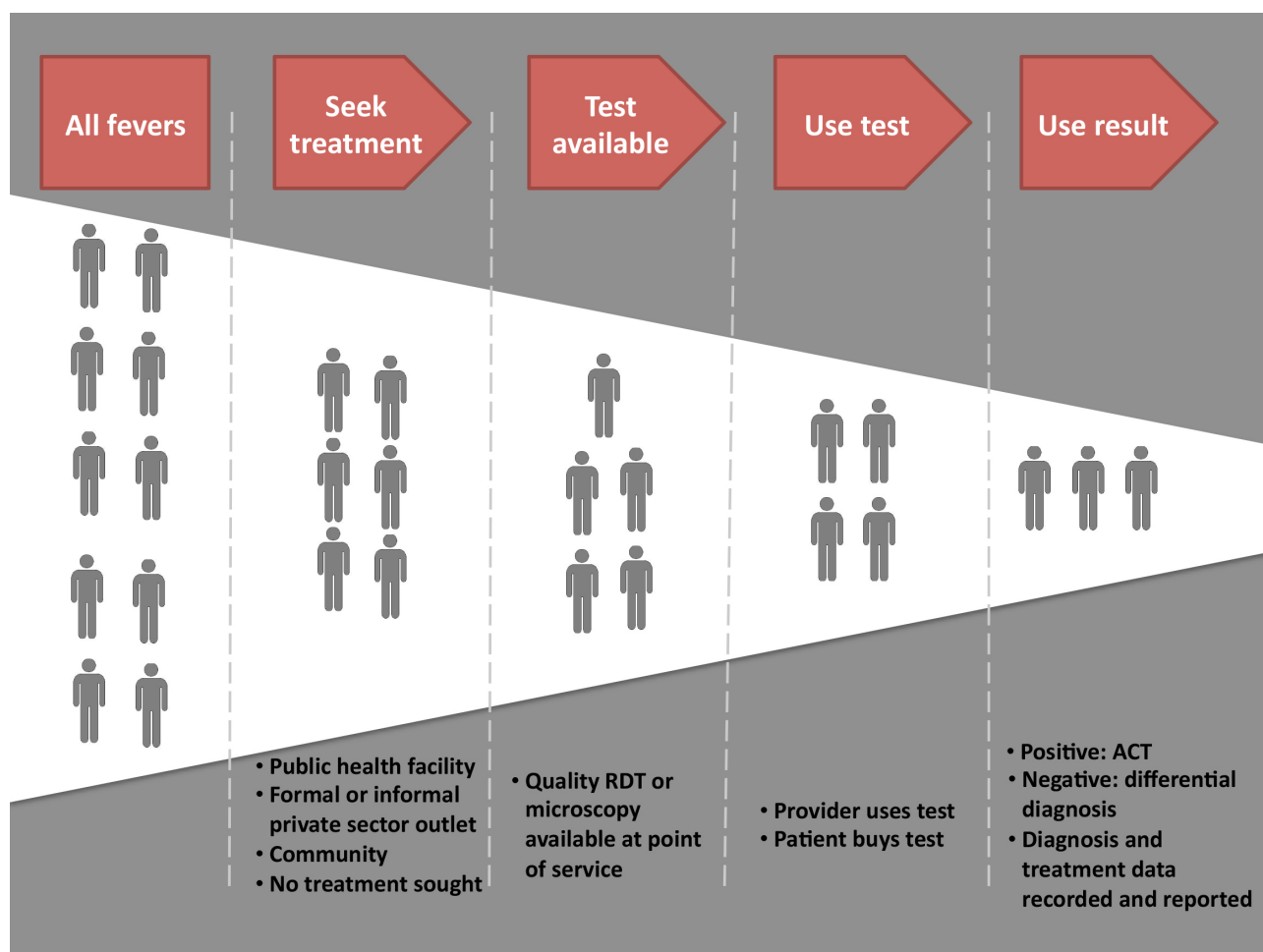
The top and bottom lines are the 90th and 10th percentile; the box represents the limits of the 25th and 75th percentile; the horizontal lines through the box is the median value.

Source: 2012 World malaria report. Geneva: WHO; 2012 (from Household Surveys since 2000).

Access to malaria testing also depends on the availability of a quality test at the point of service, which is generally higher in public health facilities and the formal private sector. The provider must choose to use a test and perform it accurately. If applicable, the patient must be willing to pay for it. Next, the individual should be managed according to the results. For positive cases, this means receiving a quality-assured

treatment (an ACT) and for negative cases, a differential diagnosis of the fever is warranted. Lastly, data on the fever (suspected malaria case), testing results and treatment must be recorded and reported. Evidence from the RDT scale-up to date suggests that even when tests are available, uptake, use of results and case reporting may be problematic.

Figure 6. Malaria diagnosis continuum

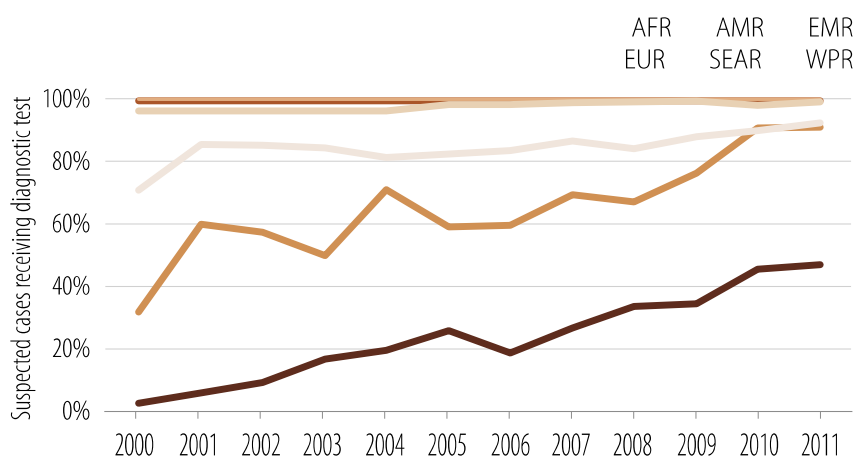


Source: Author analysis.

Uptake of diagnostic tests

Public sector testing rates. A slow, but steadily increasing number of suspected malaria cases in the public sector receive a parasitological test (Figure 7). Globally, 77% of suspected cases in the public sector was tested in 2011, representing an increase of 1% over 2010, and of 11% since 2005. In Africa, the region with the lowest access to testing, increases in diagnostic testing rates in the public sector were slight: 47% of cases was tested in 2011, a 2% increase over 2010.

Figure 7. Proportion of suspected malaria cases attending public health facilities that receive a diagnostic test



Source: NMCP reports

Note:

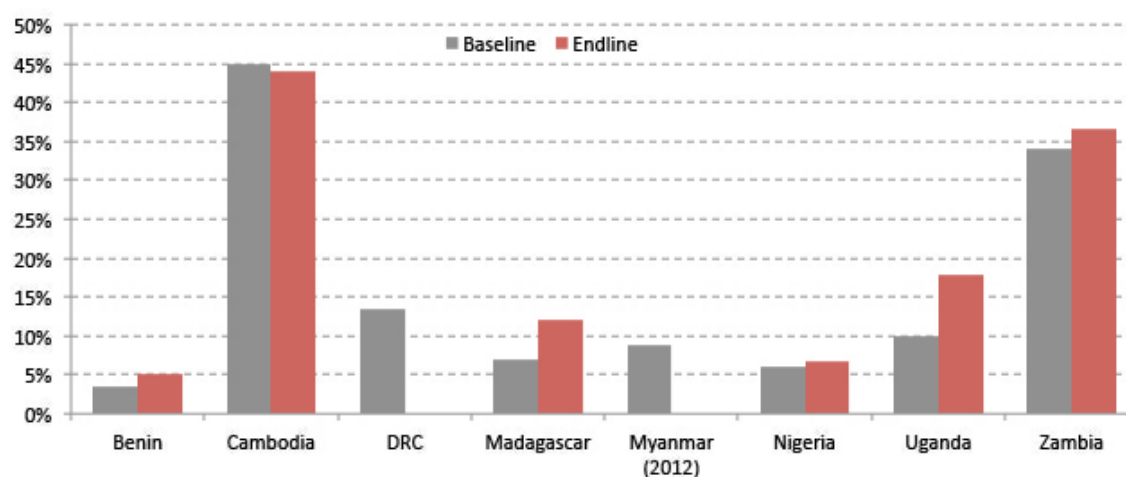
AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asia Region; WPR: Western Pacific.

Source: 2012 World malaria report. Geneva: WHO; 2012 (based on national malaria control programme reporting).

Overall testing rates (public, community and private sectors). Because many people with fever seek care outside of the public sector, universal access to diagnosis will not be achieved unless testing is expanded to the community level and private sector. Household surveys can be used to estimate diagnostic testing rates across all sectors. For example, ACTwatch Household Surveys on the percentage of febrile children who received a diagnostic test in 2009 (baseline) and 2011–2012 (endline) show modest growth in diagnostic testing (Figure 8). However, even at endline, testing remained low, ranging from 5% in Benin to a high of 36.5% in Zambia, and 45% in Cambodia, where a private sector RDT programme has been in place for over 10 years.³⁷

37 ACTwatch Group, ABMS/Benin, ASF/DRC, PSI/Madagascar, SFH/Nigeria, PACE/Uganda and SFH/Zambia. ACTwatch baseline and endline Household Survey results 2009–2012: Benin, Democratic Republic of Congo, Madagascar, Nigeria, Uganda, Zambia. Washington (DC); PSI; 2013 (www.actwatch.info).

Figure 8. Percentage of children aged under 5 years with fever in past two weeks who received a blood test for malaria, 2009 and 2011–2012



Note:

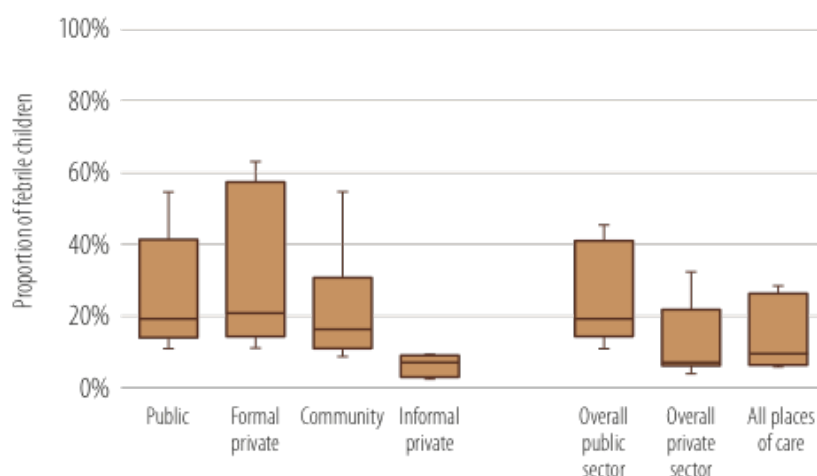
Baseline data for Myanmar are for 2012, the first year of the ACTWatch project in Myanmar.

Source: Author analysis of ACTwatch Household Survey results 2009–2012.

Information on testing uptake in the private sector is generally limited, but suggests that in most African countries the role of the private sector in providing diagnosis is limited. For example, the *2012 World malaria report* includes a summary of data comparing testing in the private sector and the public sector from nine household surveys conducted in Africa during 2010 and 2011 (Figure 9). The data suggest that public sector and formal private sector health facility testing rates are similar, but that community and informal private sector testing rates are lower. Likewise, while community level diagnosis is a WHO priority, the number of countries that reported community RDT use has not increased in the past year and, overall, patients tested with RDTs in the community represent a small fraction of patients who received a test.³⁸

³⁸ 2012 World malaria report. Geneva: WHO; 2012.

Figure 9. Proportion of febrile children who had a blood test, by place of care in nine African countries, 2010–2011



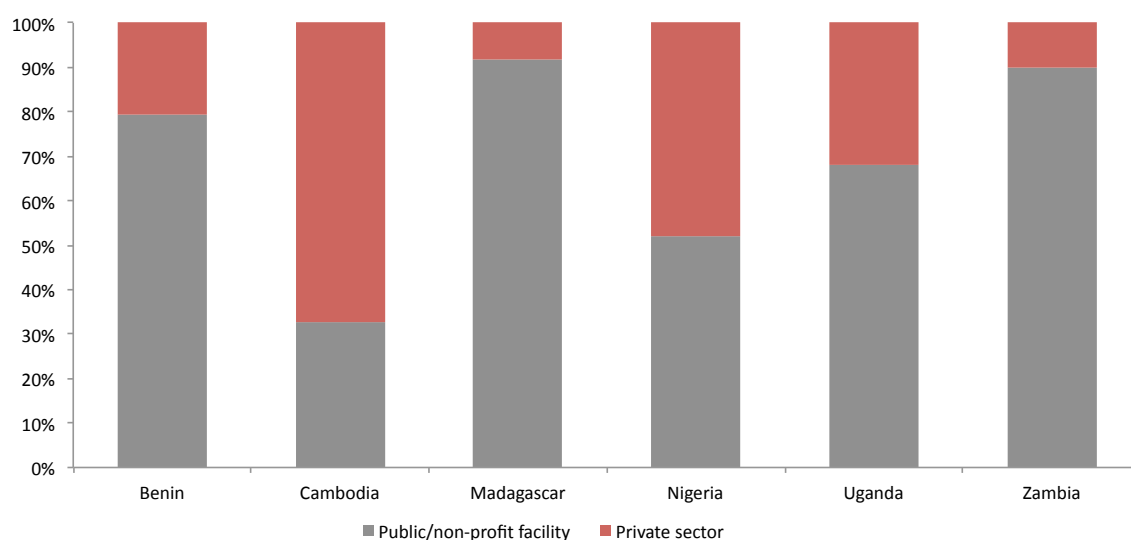
Note:

The top and bottom lines are the 90th and 10th percentile; the box represents the limits of the 25th and 75th percentile; the horizontal lines through the box is the median value.

Source: 2012 World malaria report, Household Surveys 2010–2011 from nine African countries (Burkina Faso, Burundi, Liberia, Madagascar, Nigeria, Rwanda, Senegal, Uganda, Zimbabwe).

Data on the source of testing from ACTwatch Household Surveys also suggest that the public sector is the main source of diagnosis in Africa (Figure 10). Only in Cambodia, where there has been a private sector RDT programme in place for 10+ years, does the private sector play a greater role than the public sector as a source of diagnosis.

Figure 10. Source of diagnostic test for febrile children who had a blood test, 2011–2012



Source: Author analysis of ACTwatch Endline Household Survey results 2011–2012.

Use of test results: appropriate management of fever

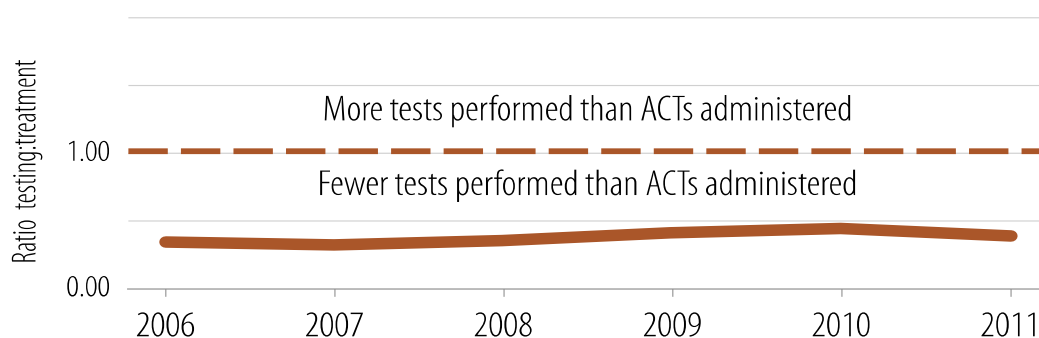
In order for diagnostics to impact health outcomes, test results must influence patient management and treatment. To date, the systems to monitor patient-level care have been lacking and it is difficult to assess the impact that the diagnostic test scale-up is having on care for febrile illness. There are several considerations, including how many suspected cases are tested, what proportion of confirmed cases receive the recommended ACTs and the management of individuals who test negative for malaria.

A recent analysis combined household and facility surveys from Zambia and illustrates the various steps where breakdowns in case management of malaria-infected individuals occur. Only 55% of children with malaria-like fever sought treatment from an appropriate provider and, when they did, diagnostic testing was performed only in 70% of cases. While ACTs were prescribed to the majority of children testing positive, over a quarter of caregivers did not understand the regimen. Overall, this study estimated that only 25% of malaria-infected children is effectively managed. Additionally, this study found that 30% of the febrile children who did not seek care from an appropriate provider had malaria infections, contributing to ongoing illness and transmission.³⁹

This example from Zambia provides insight into appropriate management of individuals infected with malaria, however, it does not shed light on the management of non-malaria fever or on ACT targeting. One simplistic approach to assessing the impact of diagnostics on case management is to compare the quantities of ACTs consumed to the number of malaria tests (microscopy and RDT) performed. This approach has limitations, because not all ACTs are taken by individuals who test positive, and not all individuals who test positive receive an ACT. However, in the absence of better information, these proxies are often used.

The ratio of diagnostics to ACTs in most African countries continues to be the inverse of what it should be: the total number of tests in the public sector was less than half the number of ACTs distributed (Figure 11). Considering case positivity rates, WHO suggests that this ratio should be more than two times as many tests as ACTs.⁴⁰

Figure 11. Ratio of RDT and microscopy performed to ACTs distributed, WHO African Region, 2006–2011



Source: NMCP reports

Source: 2012 World malaria report. Geneva: WHO; 2012.

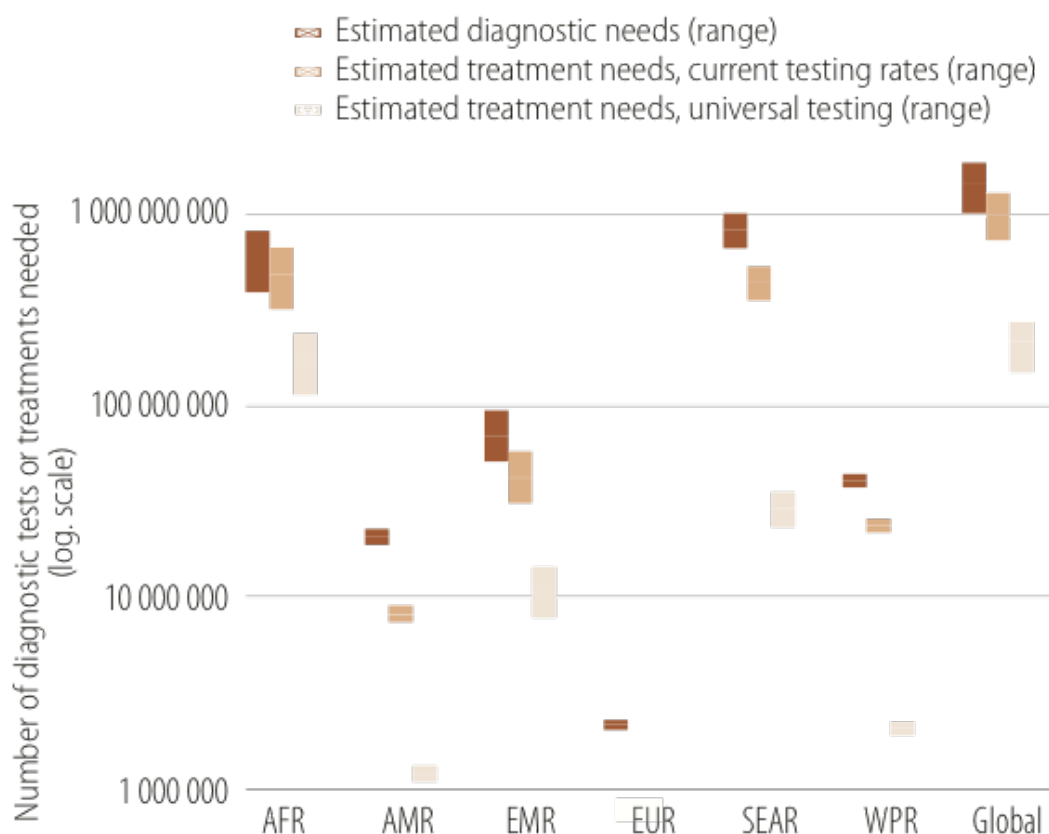
39 Littrell M et al. Documenting malaria case management coverage in Zambia: a systems effectiveness approach. *Malar J.* 2013 October;12:371.

40 2012 World malaria report. Geneva: WHO; 2012.

Gap in access to universal testing

Refined analysis of the global gap in access to malaria testing is lacking. In the *2012 World malaria report*, WHO estimated the “need” for diagnostic testing (i.e. the number of suspected cases that need to be tested to achieve universal access to testing) to be well over 1 billion tests globally, with the African Region and the South-East Asia Region representing the greatest need (Figure 12).⁴¹ Although there are wide uncertainties associated with these estimates, comparing this to the number of diagnostic tests reported (~170 million microscopy slides examined in 2011 and 155 million RDTs sold in 2011 per the *World malaria report*), it is clear that there is significant scale-up required to achieve universal diagnosis and subsequent reductions in overtreatment.

Figure 12. Estimated malaria diagnostic and treatment needs, by WHO region, 2010



Notes:

Vertical axis is logarithmic scale, each unit increase on the axis represents a tenfold increase in the number of diagnostic tests or treatments needed.

Estimated treatment needs for current and universal testing rates not shown for the European Region as it is below 1 million.

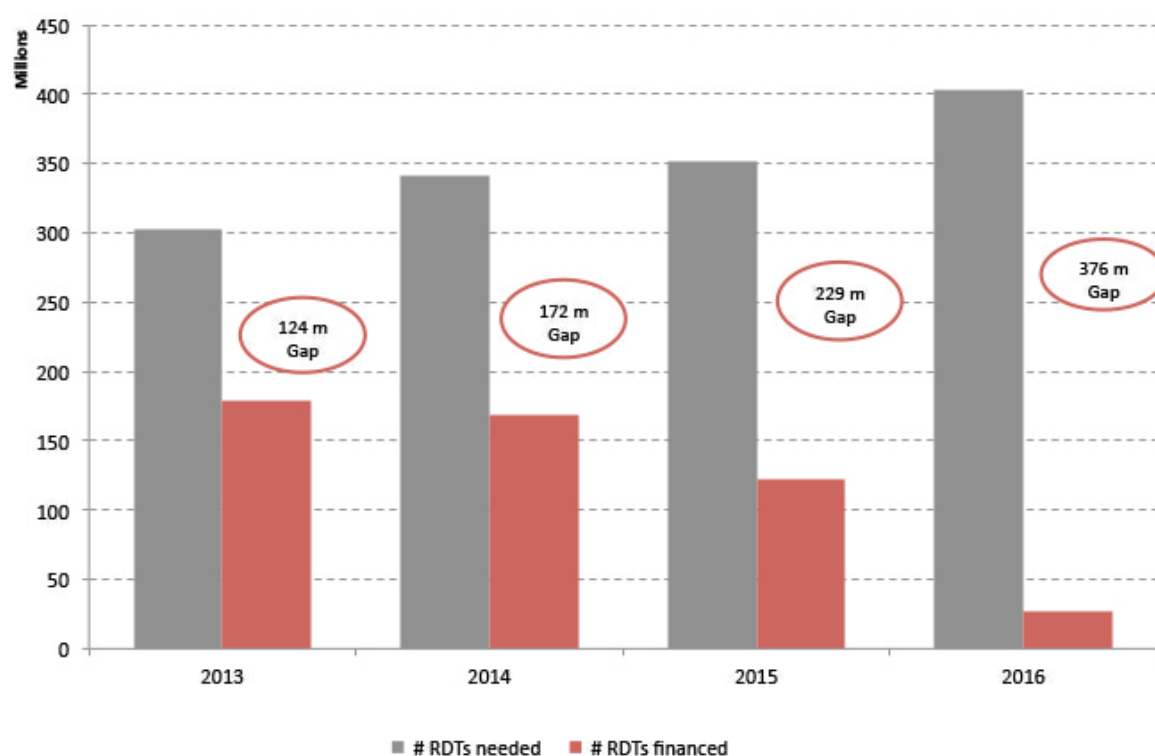
AFR: African Region; AMR: Region of the Americas; EMR: Eastern Mediterranean Region; EUR: European Region; SEAR: South-East Asia Region; WPR: Western Pacific Region.

Source: 2012 World malaria report. Geneva: WHO; 2012.

⁴¹ Other researchers, estimating total malaria-like fevers that would need testing, have made similar estimates: for example, in 2007, one group estimated 1.064 billion malaria-like fevers in Africa and 399 million in Asia and the Americas. This analysis was limited to 80 countries where *P. falciparum* dominates. Source: Kiszewski A et al. Estimated global resources needed to attain international malaria control goals. *Bull World Health Organ.* 2007 August;85(8):623–30.) Another group estimated that there were 656 million malaria-like fevers in African children aged 0–4 years in 2007. Source: Gething PW et al. Estimating the number of paediatric fevers associated with malaria infection presenting to Africa’s public health sector in 2007. *PLOS Med.* 2010 July;7(7).

With respect to commodity gaps, the Roll Back Malaria Partnership HWG has analysed commodity needs and financing for 42 African countries through 2016.⁴² Their analysis shows declining ACT needs and considerable growth in RDT needs, from 303 million RDTs in 2013 to 403 million in 2016, reflecting increasing scale-up in the public sector and community level and, in 16 countries, expansion of RDTs to the private sector. The HWG then compared the projected need to RDTs financed (Figure 13). Despite the intent to scale-up RDTs, sizable and growing gaps in financing exist: only 36% of the projected RDT need from 2013–2016 is currently financed. Since plans for private sector testing are very modest, the gaps will impact the public sector. The HWG estimates that full replenishment of the Global Fund would cover only 60% of the gap. Without financing for RDTs, declines in ACTs cannot be realized.

Figure 13. Projected RDT needs versus RDTs financed for African countries, 2013–2016



Source: Author analysis of the Roll Back Malaria Partnership HWG data on commodity needs, prepared for Global Fund Replenishment Meetings

Implications of low access to testing

While progress has been made in expanding access to diagnostic testing in the past few years, there is still significant work to be done to achieve universal coverage. One of the major implications of low access to diagnostic testing is overtreatment with ACTs, resulting in wasted health resources. Additional benefits of scaling up diagnostic testing include improving the quality of care for febrile patients with and without malaria reducing the potential risk of unnecessary side-effects from antimalarials and reducing the selection pressure for drug resistant parasites. Lastly, now that diagnosis is possible on a widespread basis through the use of malaria RDTs, linking diagnosis results with surveillance systems represents a game-changing opportunity to gain a realistic picture of the malaria burden and to begin to make data-driven decisions at both the local and global levels about resource allocations.

⁴² This analysis, conducted in preparation for the Global Fund Replenishment Meetings, involved each country projecting RDT and ACT needs for the public sector, community level and private sector, taking into consideration their existing microscopy services, absorptive capacity and strategies for scaling up case management.

Unmet needs in malaria diagnosis

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

Elimination and low-level transmission

Currently, 34 countries are in the process of moving from controlled low-endemic malaria to elimination,⁴³ and the epidemiological changes and active case detection activities are creating new demands for diagnostic tests. There is an emerging consensus that malaria-eliminating programmes require more sensitive tests to measure low-level transmission and to detect asymptomatic malaria infections.

In general, given differing country contexts and approaches, there are many different types of improved diagnostics that would be optimal, potentially contributing to a very fragmented market for new diagnostics to support elimination. Although there are many instances where a new diagnostic would be “nice to have”, Figure 14 describes some of the emerging highest priorities for diagnostics to support elimination. Generally speaking, there is more consensus about needs in passive case detection than in other areas, in part due to ongoing work to refine approaches for active case detection and laboratory-based analytics.

With respect to passive case detection, existing tools used at health facilities for diagnosis (RDT and microscopy) are likely adequate for detection of clinical cases of *P. falciparum*.⁴⁴ However, for *P. vivax*, tests with a low LOD are necessary as are POC G6PD tests in order to administer drugs required to prevent relapse and to reduce transmission. A strong quality programme is imperative to ensure accuracy of testing, and practical solutions are currently lacking. An optimal QA/QC programme would involve programmatic work as well as new technologies to enable large-scale QC of RDTs. Features that would be nice to have include high specificity as each positive case will trigger relatively expensive follow-up in the community. Another desirable feature is the ability to capture data and transmit these in real time as notification and reporting become critical to elimination programmes success.

From a diagnostics standpoint, active case detection is demanding as it is done in the community, often in challenging, remote settings. Ideally, results are available immediately so that the patient can be treated and additional responses initiated. Moreover, recent evidence⁴⁵ suggests that active case detection would optimally identify all infections, a large proportion of which is not symptomatic and might have low parasite densities (i.e. below LOD of microscopy and RDTs). Therefore, sensitivity and a very low LOD are high priorities. If large populations need to be screened, a high-throughput test with very low LOD would be beneficial.

There is considerably less certainty about the need for new commercial tests to support other elimination activities such as surveys, QA/QC and origin analysis. In general, prevalence surveys become less informative as transmission declines. Additionally, since most prevalence survey-related diagnostic activity takes place at a central reference laboratory, standardization on protocols and possibly commercial reagent kits would be important, but the need for new platforms and systems is less compelling. Similarly, there is a need for standardization of the use of molecular methods when they are employed as a confirmatory or QA/QC tests. Lastly, there is ongoing research to develop and standardize approaches, such as serology or genetics analysis, to monitor low levels of transmission and to ultimately confirm that malaria has been eliminated.

As this discussion illustrates, the area of diagnostics for elimination is evolving, with researchers and programmes aiming to identify the optimal set of approaches and to answer a number of questions around the optimal diagnostics. PATH is currently leading an effort through its DIAMETER project to better define the priorities for diagnostics for elimination. This work involves country-level interviews to understand vari-

43 Cotter C et al. The changing epidemiology of malaria elimination: new strategies for new challenges. *Lancet*. 2013 September;382(9895):900–11.

44 It is possible that some countries may require POC G6PD testing for single-dose primaquine use; see discussion under *P. vivax* and G6PD testing below.

45 It is known that subpatent, asymptomatic cases play a role in maintaining malaria transmission in low prevalence areas. The degree to which they contribute to onward transmission is an area of ongoing research and, as a result, the optimal sensitivity of a diagnostic test for these settings has yet to be determined. Source: Okell LC et al. Factors determining the occurrence of submicroscopic malaria infections and their relevance for control. *Nat Commun*. 2012;3:1237.

ous use case scenarios for diagnostics and the associated constraints, technology landscaping to appreciate the pipeline, market research and the development of TPPs, which are expected in 2014.⁴⁶ Future work may involve supporting selected products as they move through the development pipeline.

Figure 14. Emerging priorities for new diagnostics to support elimination

	Passive case detection	Active case detection
Objective and description	<p>Detect as many cases as possible in people attending clinics with fever/history of fever – most common use of malaria diagnostics</p> <p>Locations: health facilities, clinics, Community Health Worker programmes, private sector, etc.</p>	<p>Detect clusters of infection, including asymptomatic, low-density infections</p> <p>Performed in the field, at the community/household level</p> <p>Optimally, treatment is immediate and other response measures are taken (e.g. education; vector control)</p> <p>Many forms of active case detection:</p> <ul style="list-style-type: none"> ■ reactive: positive case in health facility triggers screening of household and neighbours ■ proactive: periodic screening and treating of high-risk groups (communities with ongoing transmission, border screening, migrants) ■ surveys to identify high-risk communities and populations
Time to result	Immediate	<p>Ideally, immediate to reduce loss to follow-up and cost of community visits</p> <p>Currently, turnaround times can be one day</p>
Diagnostic technology used today/future needs	<p><i>Existing</i></p> <ul style="list-style-type: none"> ■ microscopy and RDT <p><i>Needs</i></p> <ul style="list-style-type: none"> ■ scalable QA/QC systems ■ improvements needed in Pv LOD. ■ POC G6PD ■ technologies to enable accurate and complete reporting in real time 	<p><i>Existing</i></p> <ul style="list-style-type: none"> ■ RDT and microscopy ■ molecular: dried blood spot for testing at laboratory using PCR, LAMP ■ serology for surveys to identify foci of infection <p><i>Needs</i></p> <ul style="list-style-type: none"> ■ new technology desirable: highly sensitive, speciation, portable, little operator input, rapid results ■ high-throughput, high-sensitivity test useful for surveys
Degree of consensus	<p><i>High</i></p> <ul style="list-style-type: none"> ■ for Pf, microscopy and RDT are practical and sufficient for clinical cases ■ for Pv, more sensitive test desirable, POC G6PD required 	<p><i>Medium</i></p> <ul style="list-style-type: none"> ■ emerging consensus: more sensitive POC test is needed to detect asymptomatic/subpatent infections; optimal level of detection of diagnostic test is unclear ■ although programmes are implementing many forms of active case detection, optimal approach/strategy is TBD, and effectiveness has not been evaluated

Priorities

For Pf existing tools likely sufficient; for Pv improvement in sensitivity needed + POC G6PD test. Both supplemented by QA/QC and real time reporting.

New POC diagnostic beneficial: must be field deployable, highly sensitive and provide immediate result.

Source: Author analysis.

⁴⁶ This information will be verified in the next edition of the Landscape.

***P. vivax* diagnosis**

An estimated 2.5 billion people live at risk of *P. vivax* and it infects between 130 and 435 million people per year.⁴⁷ With respect to diagnostics, there are two emerging priorities. First, improvements in LOD of existing diagnostics are needed to ensure that *P. vivax* is accurately detected. A second need is for POC tests capable of screening individuals for a common genetic deficiency—G6PD deficiency—that causes adverse reactions to primaquine, the drug used to treat the liver stage disease.

With respect to improved *P. vivax* detection, the biology of *P. vivax* results in relatively low parasite density infections in blood, which makes detection more challenging than *P. falciparum*. In general, microscopy is more widely used than RDTs to confirm suspected malaria in *P. vivax* endemic areas. Microscopy quality is often variable, with speciation often being particularly weak. While malaria RDTs are available for *P. vivax* infections, evidence of performance in low-density infections is limited compared to *P. falciparum*-detecting RDTs.⁴⁸ However, in general, evidence on RDTs indicates that their sensitivities decline with parasitaemia and, as a result, they are less likely as a category to perform well at very low densities. Thus, there is a growing call for improved diagnostics for *P. vivax*.

The need for a POC G6PD test relates primarily to treatment:⁴⁹ without special treatment, *P. vivax* can relapse because it remains dormant in the liver for extended periods of time.⁵⁰ Currently, the recommended treatment of *P. vivax* includes a drug (chloroquine or ACT) to treat the primary infection plus a 14-day course of primaquine, the drug used to treat the liver stage. However, the use of primaquine is limited, due to:

- Need for a POC G6PD test: primaquine can cause mild to severe adverse reactions (hemolysis) in people with G6PD deficiency, an enzymatic deficiency affecting 2–15% (and up to 40%) of the population in malaria endemic countries. Although WHO recommends G6PD testing before primaquine administration in regions where G6PD deficiency prevalence is relatively high, practical means of testing at POC do not exist. Therefore, providers frequently forgo primaquine completely, putting the patient at risk of relapse, or prescribe it without knowing G6PD status, putting the patient at risk of adverse reaction.
- Poorly adapted drug: compliance with primaquine is also low, mainly because it is a 14-day regimen. A new shorter course drug, tafenoquine, is in development, targeting 2017 for United States Food and Drug Administration (FDA) submission, and may greatly improve patient adherence. However, tafenoquine also causes hemolysis in patients with G6PD deficiency, thus will not be administered without a G6PD test.

The implications of low access to G6PD testing and to primaquine are twofold: at the individual level, relapse of illness is possible; and, at the population level, the infectious reservoir of disease remains and contributes to onward transmission of *P. vivax*. Since *P. vivax* does not respond well to traditional control measures, it will be difficult to eliminate without treating the liver stage. Consequently, the need for a POC G6PD test is among the highest priorities for *P. vivax* control and elimination.

Current availability of POC G6PD tests, while not the primary focus of this report, is relatively limited. The CareStart G6PD RDT by Access Bio resembles an RDT in terms of format and process. This product has undergone several clinical evaluations recently, the results of which are expected in early 2014. A second POC test, the Binax Now G6PD test is on the market, however, its format, processing steps, temperature requirements and cost prohibit wide-scale deployment. Both of these POC tests provide a qualitative result.

47 Battle KE et al. The global public health significance of *Plasmodium vivax*. *Adv Parasitol.* 2012;80:1–111. Douglas NM et al. Chemotherapeutic strategies for reducing transmission of *Plasmodium vivax* malaria. *Adv Parasitol.* 2012;80:271–300.

48 For example, the Pv panels in the Product Testing Programme are not as extensive as the Pf panels.

49 A second need for G6PD testing (though not necessarily POC) relates to the WHO recent recommendation to provide low-dose primaquine, in addition to an ACT, to all Pf cases as a means of blocking transmission in elimination and artemisinin resistance contexts. Evidence regarding the safety of this strategy is limited, and as such the policy has not been widely adopted. As a first step in considering implementation of low dose primaquine, many countries are undertaking surveys to appreciate the prevalence and types of G6PD deficiency among their populations. These surveys require G6PD diagnostics—either POC or laboratory based—depending on the approach.

50 Currently, there are no diagnostic tests capable of detecting the dormant liver stage infection that causes relapse.

With respect to POC G6PD test development, several unknown questions remain requiring clinical and operational research. Of greatest relevance is the lack of data on what constitutes “normal G6PD activity” and the threshold level of G6PD deficiency that induces severe reactions when taking primaquine, or in the future tafenoquine.⁵¹ Given the changes in standards of care and tolerance to risk since the launch of primaquine in the 1950s, the launch of tafenoquine will likely require a quantitative POC G6PD test that detects deficiency and measures enzyme activity. With respect to the pipeline, experts suggest that some promising technologies for quantitative G6PD screening at POC are in development.

PATH has been working to support G6PD test development through market landscaping activities, evaluations of existing tests, development of a specimen repository and development of TPPs. The PATH G6PD Initiative now aims to support and manage the development, clinical evaluation and registration of G6PD tests that inform radical cure treatment decisions. This will be achieved through global and local community engagement, clinical studies, regulatory pathway mapping, market research and direct investment in diagnostics product development. The product development work will focus on tests to support radical cure of *P. vivax* (through treatment with drugs such as primaquine and tafenoquine) and PATH aims to have at least two products enter the clinical evaluation stage. The multiyear project is funded by the Bill and Melinda Gates Foundation and the United Kingdom Department for International Development (DFID).

In light of the growing interest in this area, WHO, which has not recently reviewed diagnostics for G6PD deficiency or provided guidance on testing, expects to hold a meeting in 2014 to review evidence on POC G6PD deficiency tests and their use to guide safe administration of primaquine. Based on the outcome of this review, additional WHO guidance in this area may become available.

Placental malaria

Annually, approximately 125 million pregnancies occur in areas affected by *P. falciparum* or *P. vivax*.⁵² Commonly used diagnostic tests (RDTs and microscopy) are largely inadequate for detection of placental malaria.

The biology of a *P. falciparum* malaria infection in a pregnant woman differs from that of a non-pregnant individual in ways that are dangerous to the mother and the fetus and that make diagnosis of malaria during pregnancy challenging. In all malaria infections, the *Plasmodium* parasites infect the body’s red blood cells. During pregnancy, the *P. falciparum*-infected cells sequester in the placenta,⁵³ (i.e. the infected cells become attached to the placenta rather than circulating in the peripheral blood). Dangers to the mother and fetus, such as maternal anaemia and low birth weight, occur when malaria parasites infect the placenta. The sequestration also has the effect of reducing the number of infected cells circulating in the peripheral blood that can be detected by traditional malaria diagnostic methods. One study showed 5.6% of woman had malaria in the peripheral blood, while 60.5% had infection in the placenta.⁵⁴

Further complicating the detection of malaria in pregnancy is the effect that the infection has on a pregnant woman: many pregnant women who are infected with malaria do not have classical symptoms of malaria. The effect that malaria infection has on pregnant women is governed by a number of factors, not all of which are completely understood. In general, a women’s immunity may be compromised during pregnancy, thereby increasing her risk of developing severe complications from malaria. However, a pregnant women’s acquired immunity to malaria also depends on transmission intensity (as in the case of any adult) as well as the number of times she has been exposed to malaria during previous pregnancies. Typically, in endemic settings, pregnant women are more susceptible to symptoms of malaria in their first pregnancy and less susceptible to malaria symptoms in future pregnancies. Pregnancy associated

51 Domingo GJ et al. G6PD testing in support of treatment and elimination of malaria: recommendations for evaluation of G6PD tests. *Malar J.* 2013 November;12:391.

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

53 Others species of malaria do not appear to sequester to any significant degree in the placenta or other tissue.

54 Anchang-Kimbi JK et al. Diagnostic comparison of malaria infection in peripheral blood, placental blood and placental biopsies in Cameroonian parturient women. *Malar J.* 2009 June;8:126.

immunity does not appear to eliminate the infection, but does seem to maintain it at a low-parasite level; however, the level of parasitaemia that is actually harmful to the mother and fetus is not clear.

Intermittent preventive treatment of malaria in pregnancy, recommended by WHO, is the most common strategy used to reduce the risk of malaria in pregnant women and fetuses in areas of stable malaria transmission. This involves administration of several doses of an antimalarial drug (usually sulfadoxine-pyrimethamine or SP) to all women attending routine antenatal clinics, regardless of whether they have any symptoms of malaria. Intermittent preventive treatment is designed to clear any infection present and to act as a prophylaxis to prevent infection in the future. However, due to drug resistance, new strategies for managing malaria in pregnant women are being explored. Among the alternatives are strategies for use of more effective medicines and intermittent screening and treatment. The later involves screening all pregnant women for malaria on a regular basis and treating only those who have parasites (known as intermittent screening and treatment or IST). The question then becomes: What is the best diagnostic test for screening? Although research in this area is somewhat limited, today's technologies routinely used for case management (microscopy and RDTs) are probably not sensitive enough to detect all cases of placental malaria. Research for this report did not identify any focused efforts to develop diagnostics for pregnancy, however, experts suggested that more sensitive diagnostics, for example, those developed for elimination settings, might have applications in pregnant women.

5. MALARIA DIAGNOSTICS TECHNOLOGY LANDSCAPE

This section describes the various approaches to diagnosing malaria and commonly used technologies for malaria diagnosis, technologies that have recently entered the market and those that are in the development pipeline. Because much of the activity in the malaria diagnostics market today centres on RDTs, this section provides more detail on RDTs than on other technologies.

Approaches to diagnosis and existing malaria diagnostic technologies

There are several approaches to malaria diagnosis (Table 1) based on detection of different biomarkers and technology platforms. Existing malaria diagnostics include: commonly used RDTs (i.e. antigen detection) and microscopy, and the more specialized nucleic acid detection methods (e.g. PCR and loop-mediated isothermal amplification/LAMP). Approaches that are largely still under development include hemozoin detection, spectrographic methods and serology. This section provides an overview of each approach and description of existing technologies where relevant.

Table 1. Summary of approaches to malaria diagnosis

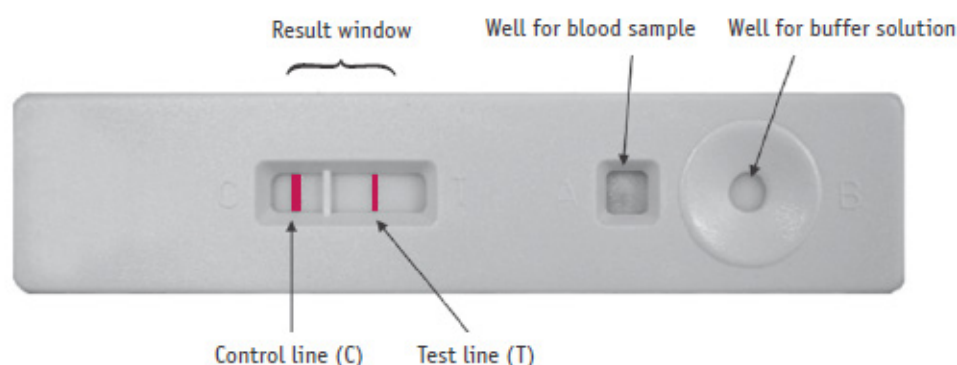
Approach	Description	Stage of development/use
Antigen	Disposable lateral flow tests that detect antigens produced by malaria parasite.	Rapidly growing market; 155 million in 2011 and growing. Incremental R&D.
Microscopy	Direct visualization of parasite using microscope (platform technology) and stained slides.	Mature market, many sources; ~170 million/year. Incremental R&D, largely focused on automating slide preparation and reading.
Nucleic acid (PCR, LAMP)	Detection of parasite DNA. Laboratory, instruments (platform technology) and trained technicians required.	Minimal, research and reference use only. Laboratory-based method, little standardization of methods, very limited availability of commercial test kits. R&D of POC devices and test kits.
Hemozoin	Detection of by-product of parasite. POC device for malaria.	R&D of POC devices under way.
Spectroscopic	Detects optical signature of molecules associated with parasite. Platform device.	R&D of POC devices under way.
Serology	Detection of antibodies to malaria parasites, signifies exposure as opposed to active infection. Laboratory, instruments and trained technicians required.	Minimal use (blood bank screening in developed countries elimination setting surveillance). Methods for surveillance largely under development.

Antigen-detecting malaria 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 pLDH and aldolase antigens; pLDH antigens may be specific to one species (e.g. there is a pLDH produced only by *P. vivax*) or they may be produced by all species of malaria. Using different combinations of target antigen, a variety of types of malaria RDTs are available, including:

- *P. falciparum*-only tests, which only detect *P. falciparum* malaria;
- pan-malaria tests, which give a positive result for any species of malaria without differentiating between species;
- combination tests, 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).

RDTs are available in dipstick, card and cassette formats, although the cassette format (Figure 15), 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, the time to result and the format of the results readout, 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, and RDTs will have two or more lines in the results window (i.e. a control line and one or more test lines).

Figure 15. Schematic representation of a malaria RDT cassette

Source: Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva: WHO; 2011.

Malaria RDT performance

Evaluating the performance of malaria RDTs 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 appreciate and compare RDT performance.

In 2009, WHO completed the first round of product testing for malaria RDTs.⁵⁵ 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 WHO Product Testing Programme for Malaria RDTs (hereafter the Product Testing Programme) and its impact on the RDT market is discussed further in the market landscape part of this report (Section 6).

In July 2011, a Cochrane Review⁵⁶ 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 analysed results from 74 trials conducted in Africa, Asia and South America and concluded there are several commercially available RDTs that demonstrated acceptable performance (>90% sensitivity and 90% specificity) across a variety of transmission settings. Although the review found some differences in 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 limitations 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 portable and disposable tests, requiring no laboratory infrastructure, electricity or instruments. Lastly, malaria RDTs are inexpensive. Despite the compelling list of advantages, compared to other methods malaria RDTs also have several limitations, some more significant than others. These include:

QC. For most diagnostic tests there are technologies and well-established methods for checking the quality of tests at the central level (i.e. evaluation of tests prior to purchase) when they are delivered to the

55 The WHO Product Testing Programme is co-sponsored by FIND, the WHO Special Programme for Research and Training in Tropical Diseases and the WHO GMP. Testing is performed at the United States Centers for Disease Control and Prevention in Atlanta. Reports are available online and include (http://www.finddiagnostics.org/resource-centre/reports_brochures/malaria-diagnostic-test-report.html):

- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 1 (2008). Geneva: WHO; 2009.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 2 (2009). Geneva: WHO; 2010.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 3 (2010–11). Geneva: WHO; 2011.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 4 (2012). Geneva: WHO; 2012.

56 Abba K et al. Rapid diagnostic tests for diagnosing uncomplicated *P. falciparum* malaria in endemic countries. *Cochrane Database Syst. Rev.* 2011 July;(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.

country, at intermediate points in the distribution chain and at the point of service. These QC technologies and methods have been developed by international bodies, public health laboratories and/or are commercially available. With respect to malaria RDTs, practical methods and technologies to enable QC testing are inadequate. There are no practical means of confirming the performance of an RDT in the field, and while lot testing⁵⁷ at the international level is available to evaluate tests prior to delivery to countries, its utilization could be improved.

Variation of HRP-II antigen. Although they are the most widely used type of RDTs, HRP-II-based RDTs have limitations in some geographic regions related to variation in the expression of HRP-II by the malaria parasite. Globally, variation in HRP-II expression is quite common, and in a few instances complete deletion of the gene responsible for HRP-II may lead to false-negative RDTs. To date, this has been well documented in the Amazon region of South America, and in these areas HRP-II-based tests are not recommended. More recently, several reports of potential HRP-II deletion in areas outside of Latin America have been made,⁵⁸ and there is room for additional research on the extent of deletions and their cause.⁵⁹

LOD. While the sensitivity of today's 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 have proven to be fairly adept at detecting *P. falciparum* malaria and differentiating it from other forms of malaria, there are significantly fewer data on their ability to detect and distinguish between the other species (i.e. *P. vivax*, *P. ovale* and *P. malariae*) of malaria.

Differentiating between current and past infections (i.e. persistent antigenaemia). Although they are the most widely used, HRP-II-based RDTs may not distinguish between an active and a previous effectively treated malaria infection because the HRP-II antigens can persist in the blood stream for several weeks after successful malaria treatment, resulting in a positive RDT even though the individual does not have an active infection. In practice, this issue complicates the diagnosis of fever and is covered in training of providers on interpretation of RDTs. In addition, it means that HRP-II RDTs are not effective for monitoring the response to treatment. Unlike HRP-II, it appears that pLDH and aldolase antigens are more closely correlated with active infection, though these antigens can persist for a few days after elimination of viable parasites from the blood.

Heat stability. 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 labelled as stable at 4–30 °C⁶⁰ for 18–24 months. Conditions in some malaria endemic settings will at times exceed these manufacturer recommendations. The extent to which these conditions affect RDTs is not known, as there is no external QC for RDTs and there has been minimal formal evaluation of RDT heat stability and actual conditions of use.⁶¹ Despite these concerns, anecdotal evidence and the results of product testing and lot testing suggest that many of the higher-performing RDTs are quite stable.⁶²

Quantification. RDTs are not able to quantify parasite density, which would be useful in assessing the severity of illness and for monitoring a patient's response to treatment.

57 WHO, FIND and partners operate a lot testing programme 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 QC 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 QC testing.

58 See, for example:

- Wurtz N et al. Pfhpr2 and pfhrp3 polymorphisms in Plasmodium falciparum isolates from Dakar, Senegal: impact on rapid malaria diagnostic tests. *Malar J.* 2013 January;12:34.
- Kumar N et al. Genetic deletion of HRP2 and HRP3 in Indian Plasmodium falciparum population and false-negative malaria rapid diagnostic test. *Acta Trop.* 2013 January;125(1):119–21.
- Koita OA et al. False-negative rapid diagnostic tests for malaria and deletion of the histidine-rich repeat region of the hrp2 gene. *Am J Trop Med Hyg.* 2012 February;86(2):194–8.

59 Akinyi S et al. Multiple genetic origins of histidine-rich protein 2 gene deletion in Plasmodium falciparum parasites from Peru. *Sci Rep.* 2013 September;3:2797.

60 Some RDTs are labelled as stable up to 40 °C, however, the majority are labelled as stable up to 30 °C. Source: Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in endemic settings. *Clin Microbiol Infect.* 2013 May;19(5):399–407.

61 Albertini A et al. Malaria rapid diagnostic test transport and storage conditions in Burkina Faso, Senegal, Ethiopia and the Philippines. *Malar J.* 2012 December 6;11:406.

62 Product testing programmes include a limited assessment of heat stability; lot testing programmes test RDTs periodically over their shelf life to ensure that they are meeting minimal performance standards.

Microscopy

Microscopic examination of slides for presence of malaria parasites has been the standard for malaria diagnosis since it was first introduced nearly 100 years ago. In settings where the most basic laboratory is available, examination of dye-stained blood smears for malaria parasites using a light microscope is common.

The process is relatively simple. It involves collecting a drop of blood on a glass slide, staining the slide, allowing it to dry and examining the slide using a standard laboratory microscope. Both a thin smear and a thick smear may be prepared. In the thin smear, a very small quantity of blood is spread on a slide such that the cells do not overlap; the slide is fixed and stained so the cells are intact. In the thick smear, a larger drop of blood is spread on a slide such that cells are layered on top of each other concentrating the cells in a relatively small area, and then stained. Because the thick film contains more cells, it is examined first to search for malaria parasites. The thin film is used to get a closer look at the parasites themselves; that is, to look at their shape to determine the species of malaria present. A skilled microscopist can identify the species of malaria, ascertain the developmental stage of the parasites (certain forms of the parasite suggest early stage infection or severe infection) and count the number of parasites in a given quantity of blood (higher numbers of parasites are associated with severity; after treatment with an effective antimalarial drug, the parasite density should rapidly decrease).

Microscopic diagnosis, in ideal settings, is highly sensitive and specific. In expert hands, microscopy is considered the “gold standard” against which other malaria diagnostics are evaluated. In ideal conditions, an expert microscopist can detect parasites at densities fewer than 10 µl of blood. However, under typical field conditions, the performance of microscopy is compromised due to: (i) poor quality microscopes, stains and slides; (ii) insufficient training and supervision; (iii) interruptions in electricity; (iv) insufficient time to stain and examine slides; and (v) an absence of QA systems. Staining and interpretation are labour intensive (30 minutes per slide) and require considerable expertise, particularly for species identification and in cases of low parasite density.

Microscopy involves an upfront purchase of microscopes (good quality microscopes from leading suppliers cost US\$ 1000–1500), ongoing training (a refresher training course every three years for all microscopists), supervision and QA, and purchase of relatively inexpensive consumables and reagents.⁶³ From a laboratory systems perspective, microscopy is advantageous because it has applications for other diseases and it is widely available; nearly every laboratory has a microscope and all laboratory technicians receive training in microscopy. Although microscopy QA/QC suffer from lack of investment (QA/QC for microscopy is human-resource intensive and many public laboratory systems are understaffed), there are well-established methods for monitoring the quality of testing.

The microscopy market is mature: although a number of companies manufacturer microscopes, a few global optics companies—Olympus, Zeiss, and Nikon, in particular—are known for the quality of their objective lenses and production systems and dominate the microscope market. For example, a survey of 90 microscopes in one African country found 16 different manufacturers, but two thirds are from three leading manufacturers.⁶⁴

In terms of improvements, a number of significantly less expensive (e.g. < US\$ 500) microscopes are available; however, their quality and durability has not been proven on a widespread basis. Another recent improvement involves the use of light-emitting diode (LED) in order to address the need for an artificial light source for high-quality microscopy. Over the years, other technological efforts (e.g. use of fluorescent dyes to reduce the time required to scan microscopic fields) to improve the performance and operational challenges associated with traditional light microscopy have been developed, however, few of these have gained significant uptake for malaria diagnosis.

⁶³ Supplies needed include: lancets, alcohol swabs, cotton gauze, glass slides, Giemsa stain and other common laboratory chemicals, staining vessels and glassware for measuring liquids, immersion oil, lens cleaners, tally counters and timers.

⁶⁴ Mundy C et al. Evaluation of microscope condition in Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2000 September–October;94(5):583–4.

Nucleic acid detection: PCR & LAMP

Nucleic acid detection refers to the detection of parasite genes (DNA/RNA) in a sample. These relatively new laboratory techniques, developed in the past 25 years, are highly sensitive, capable of detecting nucleic acid in minute quantities (i.e. a single molecule in a specimen) and, as a result, have revolutionized diagnostic medicine in many fields. With respect to malaria, several highly sensitive techniques for detecting the nucleic acid of the malaria parasite have been developed or are in the pipeline. Among these nucleic acid detection systems, PCR is the most commonly used and mature. Given the declines in prevalence and resulting need for more sensitive diagnostics, and the need to confirm RDTs, molecular methods are receiving more attention. However, many factors limit their use including: (i) high cost; (ii) high infrastructure and equipment needs; (iii) lack of standardization; (iv) limited availability of the multiplicity of required laboratory supplies; and (v) limited availability of trained laboratory technicians.

PCR-based tests

PCR tests detect malaria parasites in a blood sample by multiplying the nucleic acid present in the sample. This process, called amplification, is accomplished through the use of special reagents that catalyse gene replication and through precise control of the environment in order to create favourable conditions for the reactions. In one cycle of PCR, it is theoretically possible to double the amount of target gene present; the cycle is typically repeated several times to produce large quantities (i.e. millions of copies) of the target gene. The product of this amplification process is then analysed for the presence of malaria using a variety of detection methods. PCR is able to detect extremely low parasite densities, surpassing microscopic and antigen detection methods in sensitivity and specificity. With regard to LOD, PCR can detect as few as 1–5 p/μL of blood as compared to 50–100 p/μL for microscopy or RDTs.

Currently, PCR requires a very well-equipped laboratory and technicians trained in molecular biology. In addition to the upfront investment in laboratory infrastructure, equipment and training for technicians, PCR is also several times more expensive on a per test basis (US\$ 1.40–5.00)⁶⁵ than microscopy and RDTs. As a result, malaria PCR is used for research, epidemiological surveys and as a reference standard against which other methods are evaluated. Even in facilities with PCR capacity, it is generally not used to diagnose patients as the results are not immediately available to the clinician and it is expensive. Even so, PCR is sometimes used to investigate complex cases; for example, to establish species after diagnosis has been made with microscopy or RDT. In elimination settings, where QC of microscopy and RDTs is paramount, PCR may be used to confirm positives and a proportion of negatives.

In general, there are three main types of malaria PCR: (i) conventional PCR (gene amplified and detected, result is qualitative); (ii) nested PCR (uses two rounds of PCR, one to amplify a pan-malaria gene and a second to speciate); and (iii) real-time PCR (amplification in a closed tube, real-time monitoring of the reaction as it progresses, provides a semi-quantitative result by species). Real-time PCR is probably the most commonly used method today as it requires less handling, is less prone to contamination and, although it is generally more costly on a per test basis, has advantages due to its automation.

Commercial QC kits for PCR are not widely available or used; each laboratory typically develops its own assays and protocols. The lack of standardization requires highly trained operators capable of troubleshooting and developing QA methods. It also makes results from different laboratories difficult to interpret and compare as the protocol followed and QA measures taken frequently differ. WHO is planning a meeting for late 2013 to discuss the role of molecular methods in malaria, in particular, in low-transmission/eliminating countries. Outcomes of this meeting will be considered in the next edition of the UNITAID landscape.

Isothermal nucleic acid-based tests

Isothermal nucleic acid methods amplify DNA/RNA at a stable temperature, obviating the need for PCR thermal cyclers, which are relatively expensive. Isothermal methods that have been used for malaria include LAMP and, to a lesser extent, quantitative nucleic acid sequence-based amplification, or QT-NASBA.

⁶⁵ Cordray MS, Richards-Kortum RR. Emerging nucleic acid-based tests for point-of-care detection of malaria. *Am J Trop Med Hyg.* 2012 August;87(2):223–30.

LAMP is a diagnostic test platform developed 20 years ago by Eiken Chemical LTD, a Japanese company that retains control of the intellectual property rights for LAMP. It is a bench-top platform using isothermal DNA amplification technology, whereby parasite DNA is amplified at a stable temperature and the by-products of amplification are detected using a real-time turbidimeter or visually by fluorescence. Eiken and FIND recently launched a commercial LAMP test kit (see below for technologies that have recently entered the market) and there are several research laboratories developing LAMP assays for malaria.

In general, the LAMP procedure begins with a sample preparation step to extract DNA, followed by amplification and detection of DNA through reactions at a constant temperature using a heating block or water bath. During the process, large quantities of DNA are amplified, enabling simpler end-point detection as compared to PCR methods. In addition, the DNA sequences are amplified in such a way that the products fold into a looped structure causing the reaction mixture to appear turbid. Following amplification, detection is conducted through various methods, including visual (i.e. detection of turbidity), by using a fluorescent dye and ultraviolet (UV) light to enhance visual detection, or through use of an instrument to measure turbidity or fluorescence.

Compared to PCR, LAMP has not been as widely studied, however, recent work suggests that LAMP achieves sensitivity and specificity comparable to PCR and well above RDTs and microscopy. It also has many operational advantages over PCR, including: (i) the possibility of simpler sample preparation; (ii) no need for a thermocycler, which can be expensive; (iii) rapid time to result compared to many PCR methods; (iv) use of a closed system to reduce contamination; (v) lower cost; and (vi) because processing of LAMP is less technically complex than PCR, training and infrastructure requirements are reduced. Despite these advantages, LAMP is a laboratory-based test as it employs several instruments, reagents and consumables, requires stable power and takes several steps that should be completed by dedicated trained laboratory technicians.

QT-NASBA uses RNA rather than DNA for amplification. It employs a series of enzymatic reactions to produce RNA amplification without the need for thermal temperature cycling. It achieves high sensitivity and specificity, with LOD comparable to PCR methods. Although QT-NASBA platforms are used quite frequently for HIV testing, it is only occasionally used in malaria. No commercial kits are available for QT-NASBA. One advantage of QT-NASBA, when compared with malaria PCR and LAMP, is its ability to discriminate between gametocytes and asexual forms of malaria.

Hemozoin detection

Several new platforms based on detection of hemozoin⁶⁶ are in development for malaria diagnosis. Hemozoin was discovered and linked to malaria in the 1800s, however, it has not been used as a primary means of diagnosing malaria. While it is possible to see hemozoin in certain stages of the parasite's lifecycle using microscopy (in this case, it is commonly referred to as malaria pigment), it is not always detectable by traditional microscopy. None of the existing POC diagnostics employ hemozoin detection, although there are several devices in development.

Spectroscopy

Spectroscopy involves the absorption of particular wavelengths of electromagnetic radiation (e.g. light) by molecules in a sample. The way different molecules interact with particular wavelengths of electromagnetic radiation is unique and provides information about characteristic features of the molecules. This information is used to classify and characterize the sample.

There are many spectroscopic techniques, differing in the regions of the electromagnetic spectrum analysed (e.g. UV light; visible light; infrared radiation; microwave). In general, spectroscopic instruments contain a stable source of radiant energy, which passes through a wavelength selector and filter in order to isolate the desired portion of the spectrum and to focus it on the sample. A photodetector then measures

⁶⁶ A malaria parasite produces hemozoin crystals as a byproduct of its metabolism of haemoglobin: after infecting a person, the parasites enter red blood cells and feed on haemoglobin, 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 haemoglobin 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.

the light that has passed through the sample, and the data are subsequently compared to that of a reference spectrum in order to classify the sample and provide a result.

There are no platforms that currently use spectroscopic approaches; there are two devices in development.

Serology

Malaria serology⁶⁷ refers to the use of antigens to detect malaria antibodies, which are a marker of exposure to malaria.⁶⁸ Although initially developed as a diagnostic test, serologic tests are not used for diagnosing malaria for two reasons: (i) it is not possible to distinguish between current and past infections, and antibodies to malaria parasites are not present during the acute phase of an infection; and (ii) they appear several days later. Serologic tests for malaria are, however, used to detect exposure to malaria, because antibodies to malaria parasites remain in the body long after an infection has been cleared.

The detection of exposure to malaria has several applications, including screening blood at blood banks (primarily done in developed countries using commercially available ELISA kits). With elimination on the global agenda, programmes are looking for effective means of monitoring transmission as malaria prevalence drops and the use of serology is being explored. In low-transmission settings, a population may be screened for exposure to malaria, which serves as a proxy for transmission. The relative exposure level to malaria can be compared across different geographies, age groups or periods of time, and may be used to monitor and evaluate programmatic interventions (e.g. a drop in antibody levels would indicate successful interventions, a lack of antibodies in children aged under 5 years compared to older children would indicate a drop in transmission five years ago) to identify foci of transmission or to confirm elimination of malaria from an area.

Serological tests have many advantages for population screening: they are species specific, detect antibodies at very low concentrations, are relatively inexpensive and are amenable to a high-throughput format.

Technologies that have recently entered the market

Several of the technologies in the development pipeline were launched in 2012 or early 2013 (Table 2). Two developers have launched products aimed at simplifying molecular methods: Eiken Chemical LTD/FIND have launched a commercial LAMP kit and the Tulip Group and Bigtec Labs have launched a POC PCR platform. In addition, two companies, Fio Corporation and Holomic LLC, have launched products aimed at improving RDT QA and surveillance through use of readers and cloud information services.

These technologies are described below and a more detailed profile of operational characteristics, including pricing, is available in Annex 2.

67 This section draws from two sources: Parasitological confirmation of malaria diagnosis. WHO technical consultation on 6–8 October 2009. Geneva: WHO; 2009 (<http://www.who.int/malaria/publications/atoz/9789241599412/en/index.html>); and Drakeley C, Cook J. Potential contribution of sero-epidemiological analysis for monitoring malaria control and elimination: historical and current perspectives. In: Rollinson D, Hay S, editors. *Advances in parasitology*, volume 69. Burlington: Academic Press; 2009:299–352.

68 The human body produces antibodies in response to an infection and these antibodies provide some protection from disease. Each time a person is infected, antibodies are boosted and, over time, the antibodies are lost; the kinetics of this immune response depend primarily on age and transmission intensity. A person who has not been infected by malaria will not have malaria antibodies.

Table 2. Summary of malaria diagnostic technologies that have recently entered the market

Product	Developer	Description	Launch date
LAMP Malaria Diagnostic Kit	Eiken Chemical LTD and FIND	Commercial LAMP test kit containing primers and reagents needed to run assay using bench-top laboratory equipment.	2012
MicroPCR	Tulip Group and Bigtec Labs	POC real-time quantitative PCR instrument.	2013
Fio-net	Fio Corporation	Universal RDT reader and cloud information services to improve malaria RDT QA and malaria surveillance.	2012
Holomic Rapid Diagnostic Reader	Holomic LLC	Universal RDT reader attachment for smart phones and software to read RDTs and transmit results to a secure cloud information service.	2013

Nucleic acid detection: PCR and LAMP

LAMP Malaria Diagnostic Kit (Eiken Chemical LTD, FIND)

Eiken Chemical LTD and FIND launched a reaction kit for LAMP in July 2012. The product comprises reaction tubes containing dried-down primers and reagents for amplifying parasite DNA, along with positive and negative controls. Although various LAMP methods for malaria have been published, this is the first commercially available kit. The LAMP Malaria Diagnostic Kit received the CE Mark (indicating a product in the European Economic Area that conforms with requirements of European Union directives) and two clinical evaluations have been completed.⁶⁹

After publication of trial results in April 2013, there has been growing interest from researchers and programmes in the use of LAMP as a reference method for surveillance and for research purposes. Currently, several operational studies are under way to look at potential applications for the LAMP malaria kit, including its suitability for detection of asymptomatic infections in elimination settings.

FIND and partners are undertaking further R&D of the LAMP assay including: (i) development of a *P. vivax* reaction tube (prototypes to be ready end of 2014); (ii) simplification of the DNA extraction process from dried blood spots (prototypes ready end of 2015); (iii) development of a high-throughput system that would allow for hundreds of samples to be processed in one day; and (iv) automating the readout of the test results (expected to be in field evaluation early 2016). For additional information, see Annex II.

Truelab™ micro PCR platform (Molbio Diagnostics: Tulip Group/Bigtec Labs Joint Venture)

In 2013, Molbio Diagnostics launched the Truelab™ system, a POC PCR platform and malaria assay. The system comprises an analyser, (Truelab™ Uno - real-time micro PCR analyser), a sample preparation device and kit (Trueprep™ MAG) and a chip-based test for *P. falciparum* (Truenat™ Malaria Pf). The system is a platform with multiple applications: the first assay launched was a TB diagnostic, followed by malaria; and other applications, including HIV and dengue are in process.

The first malaria assay, a *P. falciparum* test, was launched in May 2013, and a *P. falciparum/vivax* test is expected before the end of 2013.⁷⁰ Currently, several evaluations of the platform are under way, including one by India's National Institute of Malaria Research and several for TB. Additional planned R&D includes further simplification and automation of the sample preparation step (near term) and a fully integrated system (long term). For additional information, see Annex 2.

⁶⁹ See two publications: Hopkins H et al. Highly sensitive detection of malaria parasitemia in a malaria-endemic setting: performance of a new loop-mediated isothermal amplification kit in a remote clinic in Uganda. *J Infect Dis.* 2013 August;208(4):645–52; and Polley SD et al. Clinical evaluation of a loop-mediated amplification kit for diagnosis of imported malaria. *J Infect Dis.* 2013 August;208(4):637–44.

⁷⁰ This information will be verified in the next edition of the Landscape.

RDT readers

Fio-net (Fio Corporation)

Fio-net, launched by Fio Corporation in 2012, is an infectious disease management solution used to remotely monitor the quality of RDT-based diagnosis and adherence to clinical protocols and to automate data reporting. Fio-net comprises: the Deki Reader, a universal reader of commercially available RDTs, equipped with software to guide clinical workflow and capture patient and health worker data; airFio, a secure cloud database that aggregates data transmitted by Deki Readers over a mobile phone network; and Spiri, a management web portal for accessing reports and analysis tools.

In early 2012, Fio Corporation completed trials in Colombia and Tanzania, which demonstrated > 98% concordance between the Deki Reader's interpretation of RDTs and that of expert RDT technicians. To date, Fio-net has been deployed in 13 countries for a range of usages, including health system strengthening in public health facilities and expanded service offerings at privately owned dispensaries and clinics. Among the intended uses that have been demonstrated are reduced RDT error rates, remote monitoring of health workers (e.g. test processing; clinical practice) and RDT stockouts.

Fio Corporation is ISO 13485 certified and the Deki Reader is CE marked for use with malaria and dengue RDTs; additional disease applications, including HIV and syphilis, are planned for release in 2014. For additional information, see Annex 2.

Holomic Rapid Diagnostic Reader (Holomic LLC)

Holomic LLC, a company founded in 2011 to commercialize technologies from the Ozcan Laboratory at the University of California Los Angeles, has several technologies in the pipeline with potential malaria applications, including a recently launched cellphone-based Holomic Rapid Diagnostic Reader (HRDR-200). The HRDR platform comprises a lightweight opto-mechanical smartphone attachment and a customized software application to digitally read and quantitatively analyse RDTs. The system is integrated with a secure cloud-based system and aims to enable more reliable rapid diagnostic testing, instant access to electronic health records and real-time, wide-area diagnostic data collection.

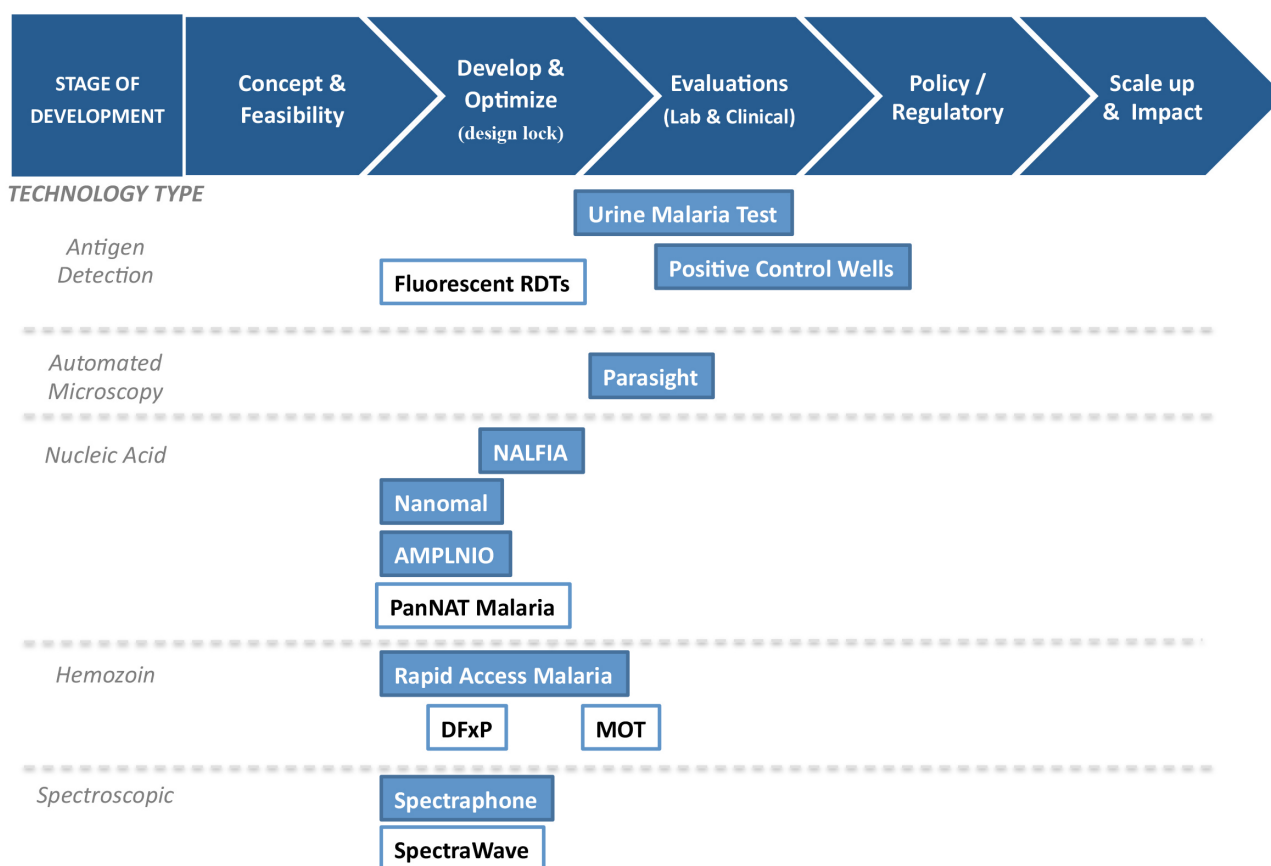
Originally launched in June 2012, a second generation Holomic Reader, the HRDR-200, was launched in July 2013. A fluorescent version is under development. Holomic LLC has conducted several evaluations with a variety of RDTs, including malaria RDTs. The company is currently marketing the product to RDT manufacturers and distributors, and the reader is currently being used by RDT vendors for clinical laboratory evaluation and potential OEM sales with their rapid tests. In the longer term, Holomic LLC plans to sell readers directly to RDT buyers.

For additional information, see Annex 2.

Technologies under development

The technology pipeline for malaria diagnostics is described in Figure 16 and Table 3. For technologies that are sufficiently far along in their development, a more detailed technology profile has been developed and is available in Annex 3.

Figure 16. Malaria diagnostics technology pipeline overview



Solid background indicates current information; white background indicates project on hold or no current information available.

Source: Author analysis

Table 3. Summary of technologies in the development pipeline profiled in Annex 3

Category	Name	Developer	Description	Earliest availability
Microscopy	Parasight	Sight Diagnostics LTD	Automated microscopy platform using novel staining technique and state-of-the-art machine vision technology to interpret images.	2014
Antigen	Urine malaria test	Fyodor Biotechnologies	Dipstick test to detect fever due to malaria in urine.	2014
Antigen	Fluorescent RDTs	Access Bio	RDT using fluorescent dye and an RDT reader to improve the sensitivity of RDTs at low parasite densities.	Pre-clinical complete, on hold
Nucleic acid	PanNAT™ malaria assay	Micronics	POC PCR instrument with malaria assay.	Timeline TBD
Nucleic acid	NALFIA	DIAGMAL Consortium	PCR test kit containing primers, reagents and lateral flow device for running the test. Test is based on direct PCR method, using a traditional PCR thermocycler, followed by detection using the NALFIA, a disposable lateral flow device.	2017
Hemozoin	DFxP	Intellectual Ventures	POC device that detects hemozoin.	No update available
Hemozoin	MOT	University of Exeter	POC device that detects hemozoin.	No update available
Hemozoin	Rapid Assessment of Malaria	Disease Diagnostics Group LLC (spin-out of Case Western University)	POC device that detects hemozoin.	2015
Spectroscopic	SpectraWave and SpectraNet	Claro Scientific	Reagent-less POC device using optical profiling technology to diagnose malaria and perform complete blood counts.	TBD funding dependent
Spectroscopic	Spectraphone	QuantaSpec	Molecular detection system using a handheld device to detect malaria in blood slides.	2015, contingent on funding

Automated microscopy/optical methods

Globally, there are multiple efforts under way to improve microscopy, not only for malaria but also for other health applications. Current efforts to improve malaria microscopy focus on reducing the size and cost of microscopes and on automation to improve efficiency and objectiveness. Broadly speaking, areas that are being explored can be grouped into a few categories: automated smear preparation and staining; computer assisted slide reading; and cellphone-/mobile-based microscopy.

Automated smear preparation and staining. Since many errors in microscopy stem from poor quality smear making and staining, technology developers are working to automate this process so as to standardize the quality of the smears and staining and to reduce operator input.

Computer-assisted slide reading. The goal of using computers to automate the reading of malaria smears is to provide an objective and reliable result and to improve efficiency. Reducing or eliminating human involvement in interpretation of slides reduces variability and subjectivity. In addition, limiting the amount of human intervention required to process slides improves efficiency and reduces labour requirements.

Various groups are working to develop these systems and several have been reported in the literature. Typically, thin smears are made and stained as they would be for traditional microscopy. The slides are then put under a microscope, illuminated and focused, and a digital image is taken. Image processing software and computer algorithms are used to interpret the images, including detecting the presence of parasites, determining the species present, lifecycle stage and quantifying the parasite density.

Cellphone-based microscopy. Closely related to the automated interpretation of microscopy images is the miniaturization and incorporation of microscopes into cellphones. Some of these technologies are based on miniature lenses, while others take advantage of lens-free approaches. For example, a group at the University of California Berkeley has developed the CellScope, a microscope attachment for a cellphone, and has published a journal article on its ability to capture images of malaria-infected red blood cells from smears.⁷¹ Holomic LLC is developing the LUCAS, a lens-free, lightweight microscope. LUCAS employs digital holography and has a large field of view, which enables faster scanning of smears for parasites.

While some of these technologies rely on transfer of images to a remote location for interpretation by a trained technician, others use computer software in the cellphone to automate the interpretation of images.

Although several groups are working in this area, research for this report identified only one company, Sight Diagnostics LDT (Isreal), in the later stages of development. Their Parasight device combines a novel automated staining and smear-making process with machine vision techniques for interpretation of the slide. A custom-designed cartridge is used to create and stain a standardized thin blood smear. The cartridge is loaded into the device that scans and analyses it, using state-of-the-art machine vision techniques, and provides a quantitative result for *P. falciparum* and *P. vivax*. The first generation device, a bench-top instrument capable of batch processing, is expected to launch in India in 2014. A second generation device will be portable. Additional disease applications are expected. (See Annex 3 for more detail.)

Antigen-detecting RDTs

Several efforts are under way to improve upon existing RDT technologies, which involve: (i) the use of urine as a sample rather than blood; (ii) efforts to enhance the signal and sensitivity of RDTs by use of fluorescent dyes and a handheld reader; (iii) the development of new MAbs for use on RDTs; (iv) the development of QCs for RDTs; and (v) the use of RDT readers to strengthen QA and surveillance. The discussion below provides examples of efforts to improve RDT technology; given the large number of companies and organizations involved in malaria RDTs, there are likely additional efforts under way.

Urine malaria test

Fyodor Biotechnologies (Maryland, US) is developing a urine-based malaria rapid test for the diagnosis of malaria in individuals with fever. The test uses immunochromatographic technology to detect malaria proteins or fragments shed in the urine of persons with fever. The first generation product, which detects *P. falciparum*, is undergoing clinical validations in Nigeria and is expected to be launched in 2014. (See Annex 3 for more detail.)

Fluorescent RDTs

In response to the need for improved sensitivity and LOD in malaria RDTs, companies are developing RDTs that generate a fluorescent signal. The technology is similar to traditional RDTs, except that MAbs (HRP-II

⁷¹ Breslauer DN et al. Mobile phone-based clinical microscopy for global health applications. PLOS One. 2009 July;4(7):e6320.

or pLDH) are coated onto tiny particles that contain a fluorescent reagent (e.g. europium) instead of being attached to colloidal gold. In order to read the results, the fluorescent signal must be viewed using UV light, typically by inserting the RDT into a device that provides a digital readout. Access Bio is among the companies with a fluorescent RDT in development. (See Annex 3 for more detail.)

New target antigens and MAbs for diagnosis of malaria

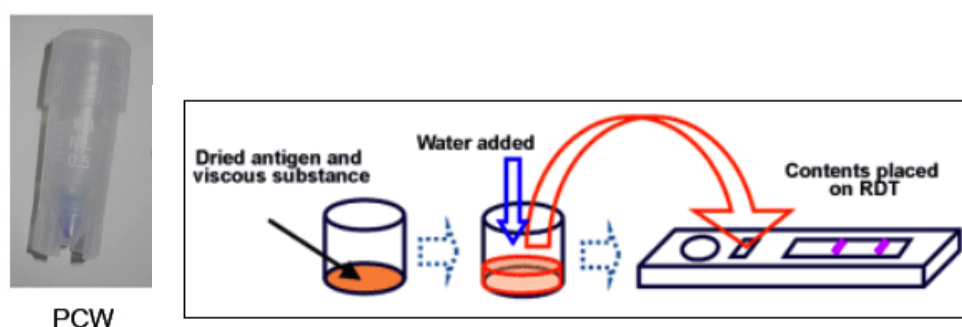
A limited number of efforts are under way to develop new antigens and MAbs to address some of the shortcomings of RDTs, such as improving the heat stability of tests by improving the binding agents, identification of antigens that are highly conserved and consistently expressed, identification of antigens that can be used to monitor response to treatment (e.g. antigens that are highly expressed and rapidly cleared from the body immediately after an infection is cleared) and identification of less expensive antibodies.⁷² The groups working to develop new antibodies include the National Bioproducts Institute and Vista Diagnostics International. Some malaria RDT manufacturers are also exploring this area.

QCs for RDTs. FIND and partners are developing positive control wells (PCWs), which are QCs intended for use at POC to check that RDTs are working acceptably. PCWs are small plastic wells coated with a small amount of recombinant parasite antigen (i.e. a genetically engineered parasite antigen) stable at ambient temperature. When reconstituted with water and applied to an RDT, the recombinant antigen solution produces a positive reaction on the RDT (Figure 17).

PCWs are in the final stages of field trials to evaluate use, utility and acceptability in routine health-care settings. Results of these trials are expected early 2014, and the WHO Malaria Advisory Policy Committee is expected to review the evidence and make a recommendation on PCW use mid-2014.

Marketing plans (including whether the PCWs will be co-packaged with RDTs or distributed separately), pricing and the product launch date have not yet been finalized. Going forward, specifications will be available for PCW manufacturing—under the WHO Global Malaria Programme (GMP) conditions—by interested third parties.

Figure 17. PCW, photo and illustration of use



Sources: WHO GMP (photo) and FIND (illustration).

QCs for RDTs also have been developed by several malaria RDT manufacturers (e.g. Orchid Biomedical Systems; CTK Biotech; Standard Diagnostics in development), however, these controls have yet to be widely evaluated and their use is not widespread.

72 Kattenberg JH et al. New developments in malaria diagnostics: monoclonal antibodies against Plasmodium dihydrofolate reductase-thymidylate synthase, heme detoxification protein and glutamate rich protein. MAbs. 2012 January–February;4(1):120–6. Griffiths K et al. Shark variable new antigen receptor (Vnar) single domain antibody fragments: stability and diagnostic applications. Antibodies. 2013;2(1):66–81. Lee N et al. Identification of optimal epitopes for Plasmodium falciparum rapid diagnostic tests that target histidine-rich proteins 2 and 3. J Clin Microbiol. 2012 April;50(4):1397–405.

RDT readers. In response to the need for improved infectious disease data and improved RDT QA, companies are developing systems that read RDT results and wirelessly transmit data to a secure cloud server. Two recently launched products are described above and it is likely that other companies are also developing systems to enhance RDTs.

Nucleic acid detection (PCR, LAMP, FISH)

Several initiatives to reduce the cost and complexity of nucleic acid-based technology are under way, including the development of fully integrated POC instruments as well as initiatives focusing on one or more aspects of nucleic acid testing.⁷³ Among the latter are efforts to simplify sample preparation (e.g. purification of DNA away from other sample components; or to develop direct blood assays requiring no extraction) to develop lower cost or instrument-free amplification, to develop quality assured, commercially available test kits and to develop detection systems that are quick and appropriate for resource-constrained settings. Although there are several POC PCR platforms currently on the market and in the pipeline, most do not currently include malaria assays. The discussion below focuses on PCR, LAMP and FISH, respectively.

PCR. The PCR pipeline includes efforts to develop fully integrated POC PCR platforms with malaria specific assays, including:

- The Tulip Group and Bigtec Labs (India) launched the TrueLab™ micro PCR platform and a *P. falciparum* assay in 2013. Ongoing R&D includes development of additional species detection assays and a fully integrated system. (See Section 5: Technologies that have recently entered the market and Annex 2.)
- Micronics, a Sony Group Company (Washington, US) is developing the PanNAT™ system, a fully automated PCR system with primers, molecular beacon fluorescent probes and other reagents contained within a microfluidics cartridge. The malaria test has been developed in the laboratory and while further development is planned, no timelines have been established for product launch. (See Annex 3 for more detail.)
- The Nanomal Consortium, led by St. Georges University and QuantuMDx Group (United Kingdom),⁷⁴ is a European Union-funded project to develop a POC handheld device to both diagnose malaria and to detect drug resistance. The device will analyse a fingerstick blood sample, collected on a disposable cartridge, using a low-cost PCR and sequencing platform developed by QuantuMDx. A working prototype of the device has been developed and is being optimized. Malaria is expected to be one of the first assays commercialized, with an initial field trial planned for 2014.
- Amplino (the Netherlands) has an early stage effort to develop a low-cost quantitative PCR instrument and malaria assay. The technology is currently in prototype form and has been designed with simplicity and low cost in mind (targeting US\$ 250 for the device and < US\$ 2 for each test).

In addition to development of fully integrated systems, technology developers are working to improve certain aspects of PCR such that it is more field ready. One commercial effort to reduce sample preparation and simplify detection is the nucleic acid lateral flow immunoassay (NALFIA) technology, which is being developed by the DIAGMAL Consortium⁷⁵ with European Union funding. Simplifications to traditional PCR methods include: (i) the assay is a direct PCR, meaning it uses whole blood and does not require any sample preparation; (ii) after performing traditional PCR amplification, detection of DNA is done using the NALFIA, a disposable lateral flow test device; and (iii) a commercial kit will contain all of the necessary primers, reagents and the NALFIA required to run the test. The product has been demonstrated in proof of concept studies and is undergoing further evaluation and optimization, with an launch in 2017. (See Annex 3 for more detail.)

⁷³ Cordray MS, Richards-Kortum RR. Emerging nucleic acid-based tests for point-of-care detection of malaria. *Am J Trop Med Hyg.* 2012 August;87(2):223–30.

⁷⁴ Other consortium members are the Karolinska Institute, Stockholm, and Tübingen University, Germany.

⁷⁵ The translation of direct-on-blood PCR-NALFIA system into an innovative near POC diagnostic for malaria (DIAGMAL Consortium) project is coordinated by the Royal Tropical Institute in Amsterdam, with Foresite Diagnostics (United Kingdom); Q-Bioanalytic (Germany) and the Global Innovation Network (Finland).

Isothermal nucleic acid-based tests. Several groups are working to improve the adaptability of LAMP technology for resource-poor settings so as to provide performance similar to PCR, but with significantly decreased infrastructure, training and processing requirements. As noted, FIND and Eiken Chemical LTD have recently launched a commercial LAMP kit, and FIND and partners continue to do additional development work on this platform. Others groups are also reportedly working on simplifications and high-throughput versions of LAMP.

Fluorescent In Situ Hybridization (FISH). ID-FISH Technology Inc (California) is developing a malaria assay based on FISH technology. FISH technology takes advantage of fluorescent probes that bind with parasite RNA causing malaria-infected cells to fluoresce when viewed under a fluorescent microscope. The test is most suitable for fairly well-equipped laboratories as it requires trained technicians to perform multiple steps using bench-top laboratory equipment. No recent information was available on this product since the publication of the UNITAID *Malaria diagnostics technology landscape—semi-annual update* in 2012; see the UNITAID *Malaria diagnostics technology landscape* (2011) and the 2012 semi-annual update documents for additional information.

Hemozoin detection

Among the more novel approaches to malaria diagnosis are devices based on the detection of hemozoin. The technologies under development take advantage of unique properties of hemozoin, including its optical properties (hemozoin crystals scatter and depolarize light in a unique way and differently than a red blood cell) and magnetic properties (it is slightly magnetic due to its derivation from iron-containing haemoglobin).

The hemozoin-based technologies are designed to be handheld devices that use fingerprick blood samples collected into a disposable sample chambers and inserted into a device. There are no reagents and results are available in less than five minutes. One possible advantage of hemozoin-based technologies is the potential to develop a non-invasive test, whereby hemozoin measurements would be taken directly through the skin, obviating the need for a blood sample.

The pipeline for malaria diagnostics based on hemozoin detection includes:

- The University of Exeter (United Kingdom) is leading development of a magneto-optical technology (MOT) portable device that detects hemozoin. MOT involves applying a magnetic field to the sample, causing alignment of any hemozoin crystals present. Polarized lasers then compare the transmittance of light before and after the application of the field; a change in transmittance, measured by a photo-detector, indicates the presence of hemozoin. A prototype has undergone laboratory studies and preliminary field studies. The first generation device uses a fingerprick blood sample; an early prototype of a second generation technology that takes measurements through the fingernail has been developed. (See Annex 3 for more detail.)
- Disease Diagnostic Group LLC (Ohio) is an early stage start-up company developing a rapid assessment of malaria (RAM) device. This technology applies a magnetic field to the sample, aligning hemozoin crystals and measuring light transmittance. Field studies of a prototype device have recently commenced, with an expected launch date in 2015. (See Annex 3 for more detail.)
- Intellectual Ventures Laboratory (Seattle, Washington, US) is developing a dark-field cross polarization (DFxP), an automated handheld device based on optical technologies to detect hemozoin. After loading a fingerprick blood sample into a disposable sample chamber in the device, it screens many fields of view using a dark-field illuminator and cross polarizers to capture the scattered and depolarized light from hemozoin. An image processing software identifies and quantifies the hemozoin present in the sample. The device is in prototype stage. (See Annex 3 for more detail.)

Spectroscopy

The research for this report identified two spectroscopic approaches in the development pipeline. Both of these technologies use blood samples, provide results within a few minutes and aim to be reagent-less. One of the technologies also will provide a blood count, combining diagnosis of anaemia as well as malaria.

- QuantaSpec (Vermont) is developing the Spectraphone, a POC system with multiple applications, including malaria. The system comprises a spectral imaging platform and a software system that recognizes the unique infrared signature of molecules present in the target pathogen. A prototype has been developed and further work to miniaturize and improve the spectral range of the device is under way. Despite progress on the platform, the malaria assay development has slowed; a malaria assay may be available in 2015, depending on funding. (See Annex 3 for more detail.)
- Claro Scientific (Florida) is developing SpectraWave and SpectraNet, reagent-less POC diagnostics systems based on optical profiling technology. The systems have broad applications; a malaria diagnostic and complete blood count analysis are among many assays being developed. The Claro Scientific system combines two technologies: (i) the SpectraWave instrument for sample preparation, multidimensional spectral analysis and transmittance of sample data; and (ii) SpectraNet a computer software and database system that analyses, interprets and stores the sample profile and delivers results. An early prototype has been developed. (See Annex 3 for more detail.)

Serology

Several academic and research groups are working to develop serologic methods for use in low-transmission settings. A number of challenges currently limit use of this method, including:

- **Identifying the optimal set of antigens.** Each individual's immune response to malaria differs as do the parasites and antigens present during an infection. The optimal set of antigens needs additional R&D; a combination ELISA would minimize workload and optimize output.
- **Little standardization in the assay.** Most of the laboratories conducting serological tests for survey purposes are research laboratories using in-house protocols and favoured antigens. The lack of a standardized protocol and/or inexpensive commercial kits limits uptake.
- **Lack of availability of mass-produced antigens.** The growing demand for serological surveys requires large quantities of standardized recombinant antigen as well as appropriate positive and negative assay controls. Currently, research laboratories produce antigens.
- **Standardization of results interpretation.** The interpretation of results requires modelling work to define standard cutoffs for positive and negative reactivity levels and to generate a simple readout usable by malaria programmes.

Among the groups working in this area are the London School of Hygiene & Tropical Medicine and the University of California San Francisco.

R&D priorities and the potential role of new technologies

Depending on their performance, several of the technologies in the pipeline might meet unmet needs in terms of product availability (e.g. diagnostics for elimination settings; *P. vivax*; pregnant women). There are several other areas where new technology would be beneficial, but the needs are not as acute, for example, diagnostics that address some of the operational challenges associated with microscopy, which is commonly used in hospitals and/or as a QC method.

Generally, advantageous features for pipeline technologies include:

- Improvements to LOD are a focus of many technology developers. LOD is an emerging priority for elimination settings and in the future as more countries reduce transmission it is likely to become a point of differentiation for diagnostics. Tests that are field deployable and can rapidly identify asymptomatic infections are a priority. There are several pipeline technologies spanning various approaches that might be able to address these needs, depending on their performance.
- Existing technologies rely on blood samples; a completely non-invasive format would improve acceptance, simplify operations and reduce safety issues. Currently, a urine-based RDT is undergoing clinical trials and a hemozoin detection device that detects malaria through the fingernail is in early prototype stage.
- The prospect of reagent-less diagnosis at low cost is promising as it reduces operator input and eliminates any special handling requirements for supply chain and storage.
- As the malaria community increases its focus on *P. vivax* generally, and in the future as G6PD tests come on the market and primaquine uptake is improved, there is likely to be increasing focus on the ability to diagnose *P. vivax*, including addressing current constraints in the accuracy and LOD of microscopy and RDTs.

Other factors that may influence technology adoption are tradeoffs between disposable formats, such as RDTs, and devices that might limit access, but would include the ability to capture and transmit data. The latter may be attractive programmes strengthening their surveillance and monitoring and evaluation activities. Additionally, the quality of testing is an increasing concern in the malaria community, and there is a need for practical QC procedures, both for RDTs and for new diagnostics that come on the market.

New technology development: market challenges

In addition to the technical challenges associated with developing a new malaria diagnostic, there are several market-related challenges that technology developers face. Among the major challenges are:

- Balancing cost and features/performance: malaria RDTs are inexpensive and represent a compelling value proposition that has widespread utility. There are shortcomings, for example, in the invasiveness of the test, or LOD, but the investment required to overcome these may not be achieved at a price that the larger market can afford.
- Funding R&D: there is limited private sector investment and philanthropic funding sources for malaria diagnostics. A recent report estimated that diagnostic R&D received US\$ 23 million during the 2004–2009 period, representing 1% of the global R&D spending for malaria. Although diagnostics are less costly to develop than drugs and vaccines, the report concluded that diagnostics are massively underfunded and called for an immediate quadrupling of funding to US\$ 50 million/year.⁷⁶ 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, the Bill and Melinda Gates Foundation, the United States National Institutes of Health, the United States Department of Defence, DFID and European Union funding). Private funding sources (e.g. venture capital; 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,

⁷⁶ Staying the course? Malaria research and development in a time of economic uncertainty. Seattle: PATH; 2011.

especially in light of current market conditions. The lack of familiarity with the new technology adoption process in global health and unclear regulatory pathways for these products also impede commercial investment. Ultimately, the limited R&D funding results in delays in the development of some technologies and means that some will never come on the market.

- Lack of TPPs and market intelligence: the optimal product characteristics and the potential market for several of the unmet needs have not been clearly defined, leading to low awareness among potential technology developers of needs and poor ability to develop a business case for investment. For example, there are no TPPs and only limited market research to better understand desired characteristics, required specifications and demand for new tests. Of note, PATH has been actively addressing this issue for both G6PD testing and elimination diagnostics.
- Complexity of evaluating malaria tests: access to samples and clinical study design have been major challenges for developers as is addressing 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, especially for novel biomarkers and platforms. 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. Thus, the facility conducting the study must have malaria microscopy expertise as well as PCR capacity for the length of the study. Currently, a few donor-funded programmes provide access to samples for R&D purposes (e.g. the PATH G6PD programme has put together a specimen bank that is used for development stage product evaluation and the malaria RDT lot testing programme has been available to developers of antigen-detecting RDTs; the Product Testing Programme makes panels available to participants).
- Market access: the lack of clarity around product validation, regulatory and policy endorsements requirements for malaria diagnostics also poses a challenge, potentially delaying the introduction of new products or hindering their uptake. Globally, the multiplicity of organizations that might have different standards for product evaluation poses a daunting challenge: meeting the needs of different country programmes, donors and policy organizations can be relatively expensive and logistically challenging.
- Manufacturing and commercialization capacity: many of the technology developers involved in malaria are smaller companies or academic organizations that lack the infrastructure and capacity required to commercialize a product. Establishing partnerships with companies having requisite global sales, regulatory, distribution and manufacturing capacity adds to the length of time required to bring a product to market.

Technology pipeline summary

Several new technologies have come on the market recently, including nucleic acid detection tests and RDT readers. The molecular platforms address specialized needs, rather than replace RDTs or microscopy for routine clinical diagnosis, given their cost and operating requirements. The recently launched RDT readers may enhance the value of RDTs, although the trade-off between enhanced quality and reporting must be balanced with the cost and potential limitations in accessibility due to the introduction of a device.

The pipeline products can be broadly grouped into two categories: (i) those that are largely reference technologies that, due to cost or complexity are unlikely to be used for clinical case management on a large scale, could be used as a reference method or for surveillance; and (ii) technologies that have a broader screening application (both passive and active case detection). Some of these may represent improvements to existing technologies (e.g. urine as a sample; new monoclonals), while others are novel platforms (e.g. hemozoin detection; spectroscopic approaches). Ultimately, the ability of new technologies to compete with RDTs in terms of cost, ease of use and enhanced diagnostic performance will be critical to their uptake in the market. Many of the products aim to have a better LOD than RDTs and microscopy and, therefore, may be relevant to screening in low-transmission contexts.

At this point, it is difficult to say what role pipeline products might play or what impact they might have on the market as in most cases performance data are preliminary and have not been widely validated in the field. Assuming a POC format that is impervious to environmental conditions can be achieved, performance in terms of LOD and speciation will likely be key determinants in how the market receives them. Another critical factor is cost and, as with any technology under development, target pricing is only finalized at the end of the development process. The majority of the products in the pipeline are device based, which may ultimately limit access as compared to an RDT; however, devices offer value in terms of built-in connectivity, data management and GPS that could improve malaria surveillance, which is increasingly prioritized by programmes. While the timing indicated by developers suggests some products may be coming on the market soon, timelines are often optimistic and the path to market is not always straightforward and, therefore, it could be some time before these new products penetrate the market meaningfully.

6. MALARIA RDT MARKET LANDSCAPE

Given the need for rapid, POC diagnostics and the corresponding scale-up of malaria RDTs, this market landscape report focuses on the market for RDTs in particular.

Growth and evolution of the malaria RDT market

In 1994, Becton Dickinson made the first commercial malaria RDT, ParaSight F. Fewer than 10 million tests are estimated to have been sold in the 1990s.⁷⁷ In the early 2000s, 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 nongovernmental organizations (NGOs) and lower prevalence countries, largely in Asia and Southern Africa, where RDTs were adopted by national programmes in the early to mid-2000s. 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 until recently. By recommending universal diagnosis, the *2010 WHO guidelines for the treatment of malaria* drove malaria RDT adoption and scale-up. Meanwhile, the 2009 Product Testing Programme results contributed to increasing acceptance of RDTs at the policy-maker level. In addition, major advocacy bodies such as the Roll Back Malaria Partnership and donors such as 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 (88% of endemic countries in 2011, up from 85% in 2010, and 74% in 2009).⁷⁸ These changes in policy are reflected in the rapid growth in the malaria RDT market in recent years. The latest published data on the market size are from the *2012 World malaria report*, which estimated 155 million RDTs in 2011, an increase of 67 million RDTs over 2010 (Figure 18).⁷⁹ In 2012, test volumes are anticipated to be 205 million.⁸⁰ Despite growth in testing, the need for testing is several times current demand.

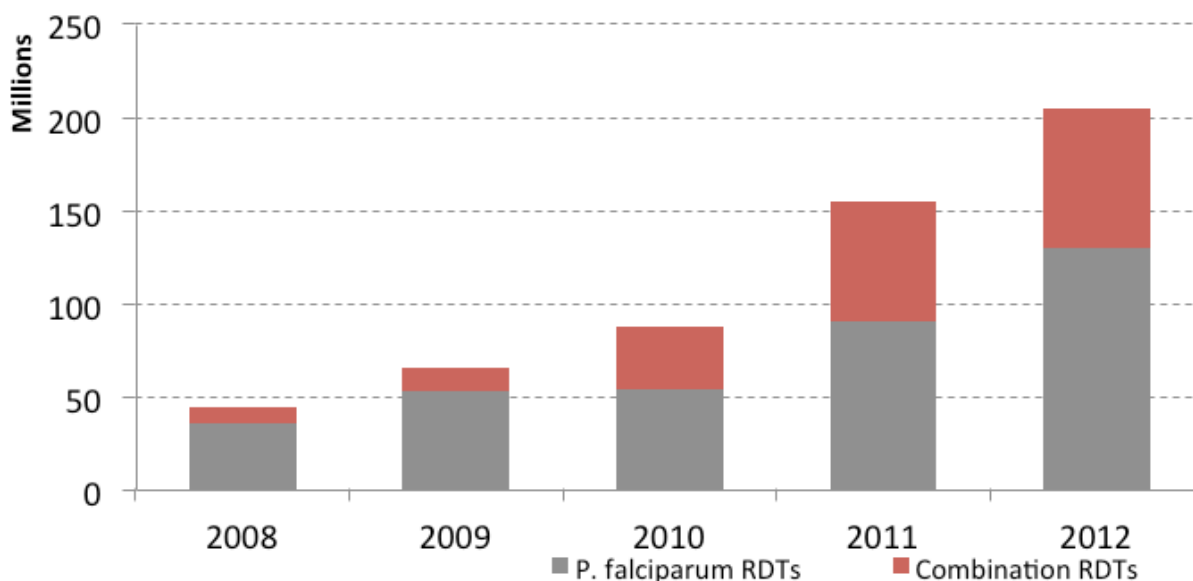
77 Frost L, Reich M. Malaria rapid diagnostic tests: access to diagnostics (chapter 5). Access: How do good health technologies get to poor people in poor countries? Cambridge: Harvard University Press; 2008. Burgess D. Assuring the quality of malaria rapid diagnostic tests. Presentation at the FIND WHO Advisory Forum for Malaria Diagnostics, Philadelphia, PA USA, 4 November 2007.

78 2012, 2011, 2010 World malaria reports. Geneva: WHO; 2012, 2011, 2010.

79n 2012 World malaria report. Geneva: WHO; 2012.

80 2013 World malaria report. Geneva: WHO; (forthcoming).

Figure 18. Malaria RDT market size



Source: 2012 World malaria report. Geneva: WHO; 2012 (based on responses from manufacturers participating in the WHO Malaria Product Testing Programme for Malaria RDTs; 31 suppliers in 2008–2010, 24 suppliers in 2011–2012).

Range of product types

In the late 1990s, only 3 tests were commercially available; by 2008, over 40 products were available, and 2 of the original 3 ceased to be marketed.⁸¹ In 2013, 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, are 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. In 2008–2009, these tests comprised approximately 80% of the market, however, in 2010 and 2011 the use of combination tests grew (Figure 19). In 2012 and 2013, procurement data analysis suggests that the proportion of *P. falciparum*-only-detecting tests increased.

Selection of high-performing products

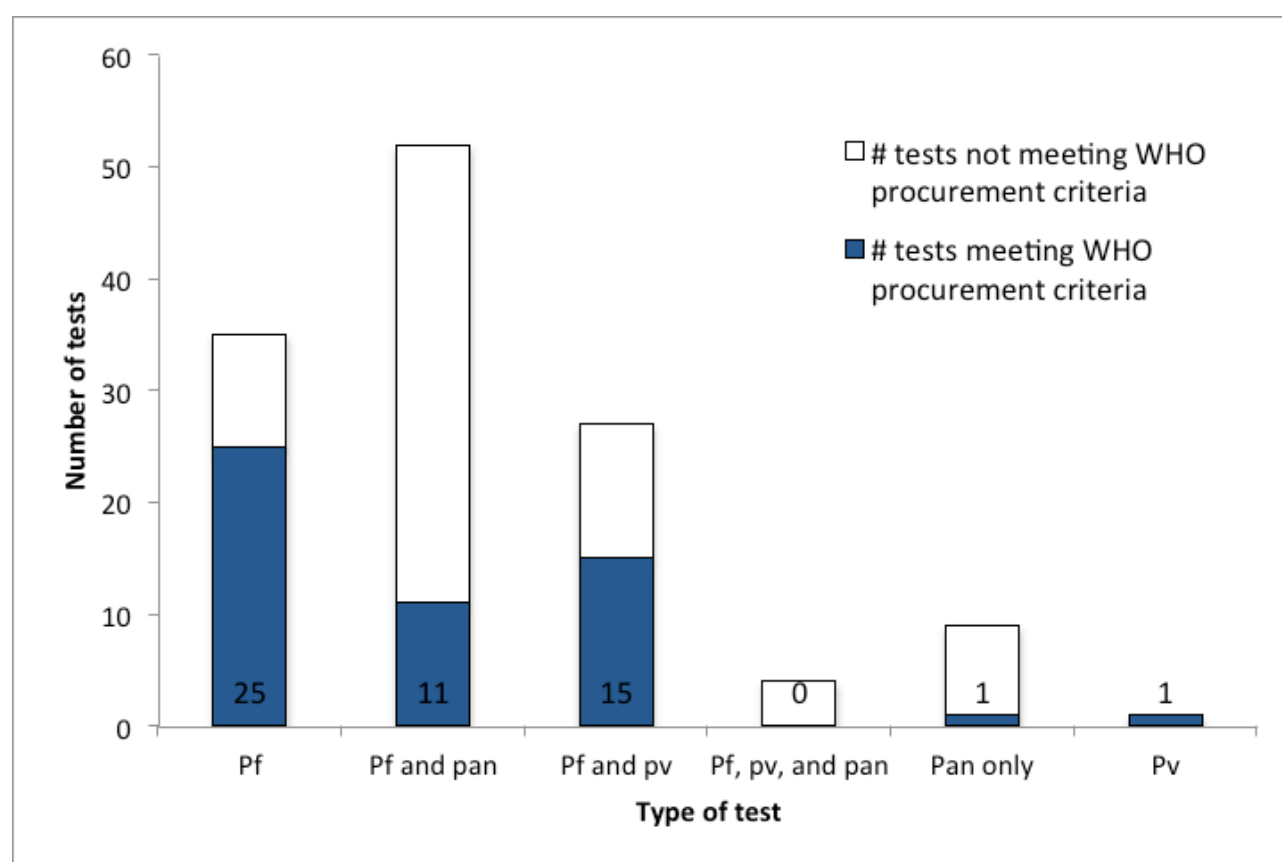
For the sake of this analysis, it is useful to look at the Product Testing Programme, which is the entry point to the public sector market (the largest segment of the malaria RDT market) to get a better appreciation for the range of products available. Overall, 128 unique products have been through product testing; of these, 53 (41%) from 26 manufacturers have met the WHO recommendations for procurement. Notable trends in the availability of RDTs include:

- Overall, performance of RDTs has been strongest in the Pf-only category: over 70% of those tested meets WHO criteria, currently 25 *P.f.* tests from 21 different manufacturers meet WHO recommendations for procurement. As a category, Pf + pan tests have fared poorly; while 52 tests have undergone evaluation, only 11 meet WHO criteria, for an overall “pass rate” of 21% (Figure 19).
- Since early 2012, 17 tests were added to the list of products meeting WHO procurement recommendations. The largest increase was in the “Pf and Pv” category, which increased from 4 tests to 15.

⁸¹ Frost L, Reich M. Malaria rapid diagnostic tests: access to diagnostics (chapter 5). Access: How do good health technologies get to poor people in poor countries? Cambridge: Harvard University Press; 2008.

- Roughly half of the 53 tests meeting WHO recommendations for procurement is *Pf*-only tests and half is combination tests, which is in line with reported sales volumes. However, there is also a range of antigens that may be employed to target a particular species (e.g. *Pf* tests may target HRP-II, pLDH, or both) and within the combination test category, there are a range of different types of tests (e.g. *Pf-pan*; *Pf-pv*; *Pf-Pvom*; *pan*). Therefore, customers looking to address particular epidemiological needs or uses may not have as much selection as this list suggests. For example, there is only one high-performing pLDH-based *P. falciparum* test and one pan-only test.
- The vast majority (45 of 53) of products meeting WHO recommendations is the cassette format, the remainder is either in card or dipstick format.

Figure 19. WHO Product Testing Programme (Rounds 1–4): number of RDTs tested and meeting WHO recommended performance criteria by type of RDT⁸²



Source: Author analysis, based on published WHO product testing results.

⁸² Prior to April 2012, WHO had different recommendations for *P. falciparum* tests, depending on transmission intensities. Figure 19 shows RDTs meeting the highest standard, i.e. a panel detection score of $\geq 75\%$ at 200p/ μ l, 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.

User friendliness and adaptability of RDTs

In general, RDTs are simple to perform, and low-skilled health workers and retail shopkeepers have been able to perform them accurately and safely with training and supervision. However, end-user error in performing and interpreting RDTs is commonly reported anecdotally and in the literature. Some common challenges involve switching between RDT products, errors associated with the presentation or components of the tests, and abnormalities in the test strip arising from manufacturing.

- Switching between individual RDTs could cause problems, even though, in general, the process for performing an RDT is similar across brands: a drop of blood is transferred to the test, after adding buffer and waiting 15–25 minutes results appear as a visible line. However, among different manufacturers there are differences in the format of the RDT, labelling, components included in the test kit and in the test procedures. These differences can present a challenge for test operators who often need to be familiar with more than one product type, for example, when multiple products are deployed in a country or when a programme wishes to change products. A brief review has shown 80% harmonization in main parameters (e.g. cassette format; position and labelling of the test and control lines; reading time⁸³) and in-depth analysis of the degree to which RDTs are harmonized is under way (see the Roll Back Malaria Partnership/Institute for Tropical Medicine project below).
- Shortcomings in packaging, labelling and in instructions for use as well as shortcomings in the contents of the kits (e.g. desiccants without humidity indicators; pipette transfer devices with no volume mark; insufficient/evaporated buffer) are well documented and can lead to errors by end-users.⁸⁴
- Deficiencies in manufacturing of the tests also may contribute to end-user challenges. Common anomalies are documented by the WHO Lot Testing Programme; for example, red backgrounds, incomplete clearing of blood or failure to flow.⁸⁵ These types of issues present challenges for users in interpreting test results and may reflect problems with manufacturing QC.

At present, it is unclear how frequently these errors occur as there are no feedback systems in place for collecting data on RDT QA in a widespread manner. When errors are noted, the root cause is often difficult to trace. This makes it difficult to formulate an appropriate response. In general, many of these potential end-user errors can be addressed through training, use of job aides and supervision. While training programmes aim to address these challenges, task shifting in public health facilities and high turnover rates among shopkeepers frequently mean that those who attend training are not ultimately the test operators. Given the decentralized nature of testing and the need to train and supervise thousands of operators, there is also scope for improving RDTs to make them more user friendly and to reduce the programmatic burden of deploying them widely.

The Roll Back Malaria Partnership Procurement and Supply Management Working Group is supporting work by the Institute of Tropical Medicine in Belgium to further analyse the degree of similarity between RDTs and to assess potential options for harmonizing RDTs so as to make them more interchangeable. The group has analysed 57 different RDTs from 22 manufacturers for similarities and differences. It also has reviewed the tests for compliance with common diagnostic standards, and conducted interviews and literature reviews to identify common problems with RDT use. Based on this, it has made suggestions for further harmonization of RDTs as well as for improving quality and user friendliness. Work is still under way, however, early feedback suggests that there may be scope in the near term for some improvements to RDTs, for example, improvement to and/or further alignment on instructions, labelling of the kit, components, test lines, sample and buffer wells. A consultation is scheduled for late 2013 to review the ITM findings and recommendations for harmonization, and update on this initiative will be included in future editions of this landscape.

83 Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO GMP; 2013.

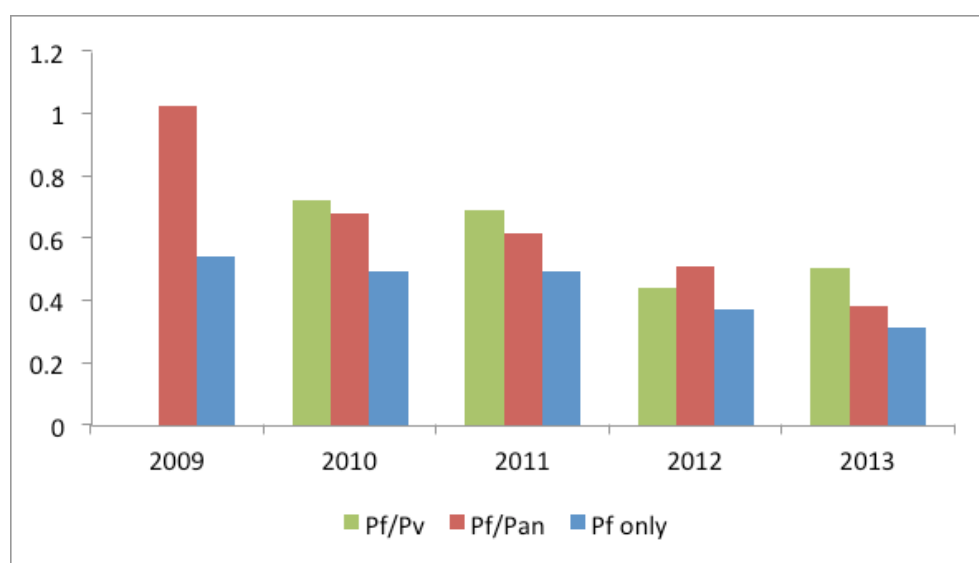
84 Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in endemic settings. *Clin Microbiol Infect*. 2013 May;19(5):399–407.

85 For a full list of the abnormalities that lot testing may note, see the WHO Lot Testing Programme website (http://www.finddiagnostics.org/export/sites/default/programs/malaria-afs/malaria/rdt_quality_control/lot_testing/malaria_rdt_guide_for_observations_30jul13.pdf, accessed 10 October 2013).

Prices

Downward pressure on RDT pricing continues and average prices have been decreasing by 14–17% each year over the last four years. Average prices for *Pf* RDTs were US\$.37 and US\$.32 in 2012 and 2013, respectively. For *Pf/pan* tests weighted average prices were US\$.51 and US\$.38 in 2012 and 2013, respectively (Figure 20). Conversations with suppliers and procurement groups support these findings, suggesting that in larger competitive tenders *P. falciparum*-only RDT pricing is in the mid-twenties. However, there is continued wide variation in pricing for the same product, with competitive bids often resulting in lower prices.⁸⁶

Figure 20. Weighted average test prices (US\$) by year for *Pf*-only and combination RDTs



Source: CHAI/author procurement data analysis 2009–2013, represents 78% of total procurement data received. Filtered by INCO term to include only EXW and only entries that include test type. Weighted average prices calculated for all data based on total cost and total volumes, except for PMI that provided average prices by year and test type.

At the country level, procurement data analysis suggests declining prices with a corresponding trend of increasing procurement volumes by each country. However, countries do experience increases in prices when they switch from a *Pf*-only RDT to a combination test.

There has been no new formal analysis of RDT prices in the private sector. Data on RDT prices in the private sector are scarce, and limited to a very small survey by FIND in 2009⁸⁷ and ACTwatch 2011 outlet survey data. For example, the FIND survey obtained prices on 24 different RDTs, which ranged from US\$ 1.00 to 16.81, with a mean of US\$ 7.51.⁸⁸ The ACTwatch and Independent Evaluation dataset is considerably larger than that of FIND, yet still limited ($n > 600$), with median prices for an RDT ranging from US\$ 0.58 to US\$ 3.22 across 10 African countries.⁸⁹

There are also limited data on the retail supply chain for RDTs in the private sector. ACTwatch Supply Chain Surveys (the majority conducted in 2009) show low availability of tests in the private sector supply chain, limited turnover of RDTs at the wholesaler level and wide variation in the prices wholesalers pay for RDTs and the prices they charge. Markups tend to be in the 25–50% range, and 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 five. In

⁸⁶ Procurement data analysis, personal communication with VPP and John Snow International (procurement agent for PMI), May 2013. Price analysis of malaria rapid diagnostic test kits. DELIVER Project Task Order 7. Washington (DC): USAID; December 2012.

⁸⁷ 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*. 2012 February; 17(2):147–52. This paper discusses a survey of 324 formal sector outlets that was conducted across six countries.

⁸⁸ These prices included the cost of the test and performing the test where that was applicable.

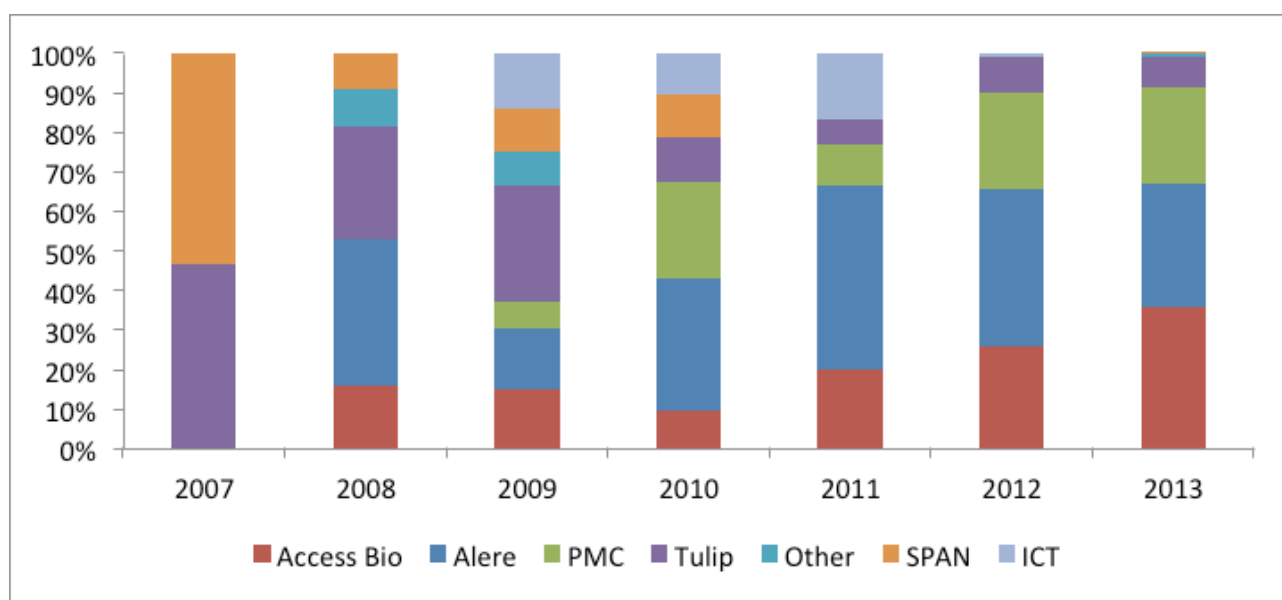
⁸⁹ ACTwatch Outlet Surveys and the Independent Evaluation of the Affordable Medicines Facility-malaria (AMFm) Phase I, Preliminary Report, 18 July 2012 (<http://www.theglobalfund.org/en/amfm/independentevaluation/>).

2013, WHO surveyed five diagnostics wholesalers in African countries, which showed wholesalers paying US\$.28–.50 for Pf-only RDTs and US\$.30–.65 for combination tests. For higher volume orders, prices were generally less expensive. The average markup prior to in-country distribution was between 20% and 40%, with some wholesalers adding additional storage and distribution costs.⁹⁰

Market share

Although there are a large number of companies involved in the market, analysis of procurement data (representing approximately half of the global market) shows increasing consolidation of the market around three suppliers in 2012–2013 (Figure 21). Many suppliers suggest that recent price declines have made the public sector tender market less attractive. At least one formerly dominant supplier has reduced malaria RDT production capacity and exited the donor-funded market, focusing instead on sales to the formal private sector (e.g. private hospitals; laboratories; clinics; NGOs).

Figure 21. Malaria RDT market share, based on procurement data analysis



PMC = Premier Medical Corporation

Source: CHAI/author procurement data analysis.

The market is also shifting at the product level. In 2011, FIND surveyed 17 leading RDT manufacturers and found that the market was shifting to better-performing products.⁹¹ Conversations with experts and analysis of procurement data indicate that this trend has continued.

Quality standards for malaria RDTs

There are currently several quality initiatives for malaria RDTs, among them the Product Testing Programme and WHO procurement recommendations that recently have impacted the market. It is notable, 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 such as malaria RDTs. Thus, when the malaria RDT market developed in the early 2000s, many RDT suppliers did not pursue any regulatory processes.⁹² Due to issues around product performance and quality in the field, in the early 2000s a global ini-

⁹⁰ Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO/GMP; 2013.

⁹¹ Analysis by FIND based on 2011 survey of 17 leading RDT manufacturers.

⁹² To date, only one malaria RDT has FDA approval: this test was developed by a small biotechnology company in the United States, Binax (now part of Alere), in partnership with the United States military. This test is primarily marketed to the returning travellers/military markets.

tiative emerged, coordinated by WHO, to establish quality standards for RDTs. This work was slow to take foot, meanwhile the market continued to grow, but with continued reporting of mixed results for RDTs in the field. Finally, in the late 2000s the Product Testing Programme was launched and the WHO Lot Testing Programme expanded. After publication of the first round of product testing results in 2009, the WHO GMP played a role in shaping policy around quality and more recently the WHO Prequalification Programme for Diagnostics has begun work on malaria RDTs. Despite the progress that these initiatives have made, there are challenges associated with imposing quality standards in an already developed market.

The following is a discussion of the various quality initiatives.

WHO product testing for malaria RDTs

The Product Testing Programme is a laboratory evaluation programme that directly compares the performance of RDTs to each other using a standardized panel of specimens and procedures.⁹³ The programme is only available for blood-based RDTs targeting antigens produced by the malaria parasite. The results are published in a report format⁹⁴ and are available through an online tool that enables users to filter through large amounts of data to identify RDTs meeting specific criteria.⁹⁵

Four rounds of testing have been completed representing 128 individual products; the fifth round evaluating 44 RDTs from 34 manufacturers is currently under way (Table 4). One notable change to the programme in the past year is a new requirement that manufacturers resubmit their tests every five years in order to remain listed in the *WHO Product testing report* and to be eligible for WHO procurement. This means that 22 tests (from 15 companies) originally evaluated in Round 1 and not subsequently re-evaluated must participate in Round 5 to remain on the list. Of those 22, only 10 RDTs from 5 companies, have been submitted.

Demand for product testing

The Product Testing Programme has been more popular than initially envisioned, in part due to resubmissions and the desire of manufacturers to have multiple products in their portfolio evaluated.⁹⁶ As a result of higher than expected demand for testing, limits have been placed on the number of products submitted per manufacturer to each round of testing.

Table 4. Number of products and companies submitting RDTs to product testing by round

Round	# Products submitted	# Companies submitting	# of resubmitted products
R1	41	21	n/a
R2	29	13	1
R3	50	23	23
R4	48	27	13
R5	44	34	>10

Source: Author analysis based on the Round 4 *WHO Product testing report*.

93 This product testing programme is co-sponsored by FIND, the WHO Special Programme for Research and Training in Tropical Diseases and the WHO GMP. Testing is performed at the United States Centers for Disease Control and Prevention, in Atlanta.

94 Reports from WHO product testing of malaria RDTs are available online and include (http://www.finddiagnostics.org/resource-centre/reports_brochures/malaria-diagnostic-test-report.html):

- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 1 (2008). Geneva: WHO; 2009.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 2 (2009). Geneva: WHO; 2010.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 3 (2010–11). Geneva: WHO; 2011.
- Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs: Round 4 (2012). Geneva: WHO; 2012.

95 The FIND interactive guide for product testing (http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/).

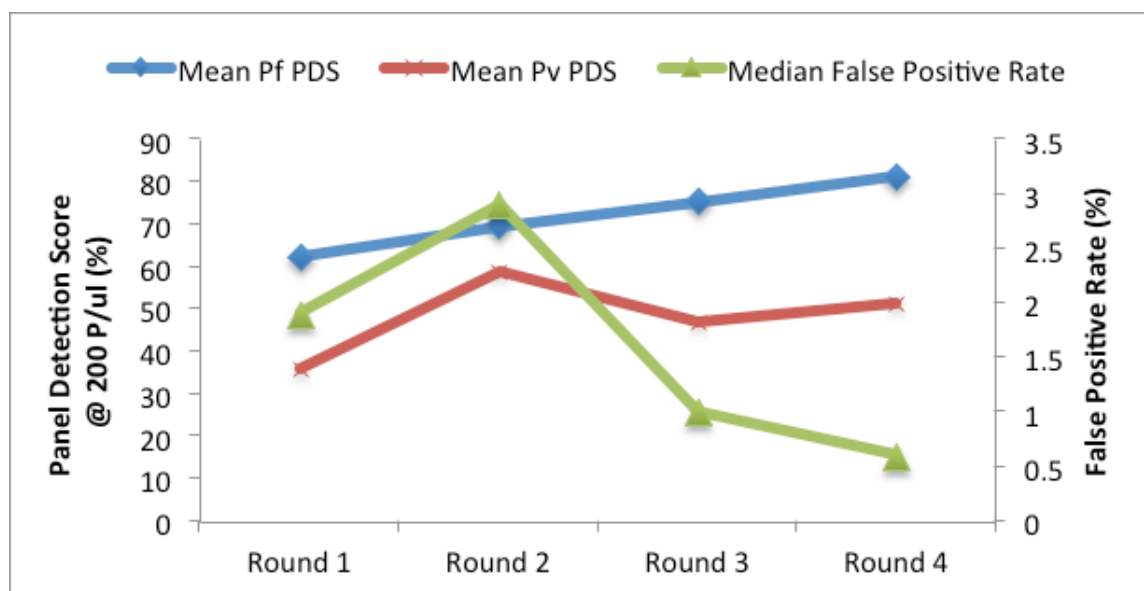
96 For example, in the fifth round of testing alone, 41 manufacturers representing 99 products (57 of them new products), expressed interest in the programme.

Impact on the market

The Product Testing Programme has had a significant impact on the malaria RDT market, on multiple levels. First, when the first round of tests were released, the results contributed to broader acceptance of malaria RDTs because the results convincingly demonstrated that there were many *P. falciparum* RDTs that perform as well as microscopy in field conditions.⁹⁷ Second, the product testing forms the basis of WHO recommendations for RDT procurement as well as donor procurement standards. Today, nearly all donor-funded procurement is based on the product testing results.⁹⁸

In terms of RDT performance as a whole, the performance of RDTs has generally improved since the programme began, suggesting that product testing has created an incentive for product improvement among RDT manufacturers. For example, the majority of resubmitted tests has maintained performance or shown improvement. Additionally, there is an increasing trend in the ability of RDTs submitted to detect low-density malaria infections, as shown in the increasing panel detection scores of *P. falciparum*-detecting RDTs (Figure 22).⁹⁹ Similarly, the number of false-positive tests results has been declining since the second round of testing. As a result of improving performance, an increasing proportion of RDTs in the later rounds of testing have met WHO procurement recommendations.

Figure 22. Performance of RDTs in product testing over time, as shown by mean panel detection scores and median false-positive rates by round



Source: Author analysis based on Round 4 WHO Product testing report.

One unfavourable effect of product testing on the market relates to its timeline: from expression of interest to publication of the results of the programme can take > 18 months. In addition, the programme does not operate continuously, so the wait time for manufacturers for feedback is generally much longer. For companies, the long delay pushes out the launch date and associated revenues for new/improved products and thereby reduces the return on investment.

⁹⁷ Note that expert microscopy can be more sensitive than RDTs, there are a limited number of microscopists achieving true “expert” status. The performance of microscopy in the field varies greatly and is often poor.

⁹⁸ The influence of product testing in the private sector has not been analysed; however, there are likely many tests in the private sector that have not been tested (see discussion of private sector demand below) and, therefore, it can be assumed that the programme has been less influential in the private sector. Discussions with malaria RDT suppliers confirm that private sector standards might not be in line with those of WHO.

⁹⁹ In order to evaluate the ability of a particular test to detect *Plasmodium* antigen, several panels of specimens were assembled for WHO product testing of malaria RDTs. These panels include wild-type panels comprising *P. falciparum* and *P. vivax* samples derived from infected patients and culture panels comprising *P. falciparum* specimens that were grown in the laboratory. The panel detection score is a number between 0 and 100, calculated as the proportion of times a malaria test gives a positive result against samples positive for malaria in a panel at a specific parasite density (e.g. four tests at 200 p/μl). The panel detection score (alternatively called the detection rate) is a combined measure of: (i) the ability of a particular test to detect *Plasmodium* antigen in a specimen; and (ii) the consistency of this result across two or more tests (RDTs from the same lot or from different lots). Note that the panel detection score/detection rate is not the sensitivity or the positivity rate of the test.

Transition of product testing to recombinants and a more sustainable business model

In 2013, FIND and partners began a programme to transition product testing to recombinant-based panels as opposed to the relatively expensive human-derived samples currently used. This transition is supported by a grant from UNITAID as well as by funding for the recombinant panel R&D from the Bill and Melinda Gates Foundation. It is expected that recombinant QC panels also will be available for manufacturer purchase and to country programmes for QC activities (e.g. lot testing at national reference laboratories as opposed to central laboratories).

The recombinant technology has been in development for several years and its equivalency to the current product testing panels is being evaluated (in Round 5 of product testing). FIND reports that this work is progressing as expected, and that additional data on the recombinants will be available in mid-2014. The timeline for the transition to recombinant technology and other changes to the programme has not been established as it depends on ongoing evaluations of the recombinants. However, it is expected to take place over the next three years and will involve significant consultation with stakeholders and manufacturers. An initial round of consultations with RDT manufacturers occurred in late 2013 and early 2014.

This transition is expected to reduce reliance on donor funding by reducing the cost of product testing and introducing a user fee. Additionally, it should improve the turnaround time for product testing and create a common standard in the market for RDT performance evaluation and QC activities.

WHO GMP RDT procurement guidance

The WHO 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. The first WHO product selection criteria were published in 2010 after the first round of product testing, and since then market share has gradually been shifting to the RDTs with better results in the product testing Programme.¹⁰⁰

WHO Prequalification Programme for Diagnostics

In general, the WHO Prequalification Programme for Diagnostics reviews and recommends diagnostic devices of sufficient quality for United Nations procurement. However, in practice, prequalification status is used more broadly, with many national programmes and donors looking to WHO prequalification due to the absence of stringent regulatory processes at the country level for diagnostic tests. The prequalification process includes dossier review, product testing in a qualified laboratory (for malaria RDTs; the Product Testing Programme) and manufacturing facility quality inspections (i.e. good manufacturing practice inspections).

As of September 2013, three malaria RDTs were WHO prequalified, an increase of one test since last year. An additional 15 tests from 7 companies were undergoing the review process.¹⁰¹ Malaria RDT manufacturers are progressing more slowly through the WHO prequalification process than manufacturers of tests for other diseases. While there have been some challenges related to prequalification processes (e.g. confusion about prequalification and product testing and understanding prequalification requirements), RDT suppliers are progressing slowly due to inexperience with stringent regulatory systems and weaknesses in the quality management systems.¹⁰² In general, manufacturers located in countries with more stringent regulations proceed more quickly through prequalification¹⁰³ as do manufacturers of products that are highly regulated.¹⁰⁴ For RDT suppliers, achieving prequalification status has been a challenge, often requir-

¹⁰⁰ An analysis by FIND 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 Programme began. Analysis by FIND based on 2011 survey of 17 leading RDT manufacturers.

¹⁰¹ Status of applications to the WHO Prequalification Programme for Diagnostics (http://www.who.int/diagnostics_laboratory/pq_status/en/index.html), accessed 10 September 2013).

¹⁰² WHO Prequalification Programme for Diagnostics, personal communication, 8 October 2013. Specific challenges include: poor traceability of product/product identification systems; poor design control/failure to lock in a design; poor dossiers; and weakness in quality management systems noted during inspections requiring repeat inspections.

¹⁰³ The two companies with prequalified RDTs are in France and the Republic of Korea.

¹⁰⁴ HIV RDTs are generally subject to more stringent regulation than malaria RDTs and are proceeding through the WHO Prequalification Programme for Diagnostics more rapidly.

ing multiple inspections, follow-up and investment in quality management systems (e.g. including revising protocols; increasing staff; purchase of new instrumentation).

To date, the impact of the WHO Prequalification Programme for Diagnostics on the market has been somewhat mixed. Although donors, policy-makers and manufacturers generally support the concept of stronger upstream quality standards, slow progress is increasingly a concern. WHO prequalification status is not yet a requirement of any major donor or purchaser and since the timing of prequalification of additional malaria RDTs is uncertain, it is not clear when such status might become a priority.

In general, the market does not appear to value, either through price premiums or increased market share, prequalification status. While one of the prequalified malaria RDT suppliers has a large market share, it also offers highly competitive pricing for a high-performing test. Another prequalified supplier does not have significant market share, and is not competitive in the tender market due to higher pricing. In 2012, Notices of Concern issued by the WHO Prequalification Programme for Diagnostics for two manufacturers caused some apprehension in the market and there is at least one example of a country switching products due to these notices.¹⁰⁵ Overall, however, while the notices may have hurt business, both of the affected companies still maintain moderate to large market share. From an industry perspective, the long timelines associated with prequalification as well as the multiple uncertainties create a disincentive for investment in innovation or in capacity.

European Union CE Mark^{106 107}

A number of malaria diagnostic tests, including malaria RDTs, are CE marked. Currently, due to the way that the European Union classifies malaria diagnostic tests, the significance of the CE Mark is limited: it is an administrative procedure that does not include a full quality evaluation. However, the European Union is currently in the midst of a legislative process that would reform its regulation of all in vitro diagnostics, modelled after the Global Harmonization Task Force guidelines.¹⁰⁸ The changes would likely reclassify malaria diagnostics into a higher risk category,¹⁰⁹ and they would be subjected to more rigorous review including quality systems site inspections, design file/dossier review and post market monitoring of product use in the field. In order to maintain the CE Mark, manufacturers will need to comply with the new system. It is expected that the new legislation will be adopted in 2014–2015 and followed by a transition period as it is implemented.

Lot testing for malaria RDTs

As with any diagnostic test, it is recommended to independently check the quality of malaria RDTs purchased from manufactures. Furthermore, the Product Testing Programme consistently reports variations between the two lots of RDTs tested. Currently, the only practical mechanism for checking RDT performance is through the WHO Lot Testing Programme operated by WHO and FIND.¹¹⁰ The testing is designed to detect major flaws in RDT performance and although it is based on some of the same protocols and specimen panels as the Product Testing Programme, the extent of testing is limited (both the number of RDTs and the number of samples in the panel).

¹⁰⁵ Price analysis of malaria rapid diagnostic test kits. DELIVER Project Task Order 7. Washington (DC): USAID; December 2012.

¹⁰⁶ The CE Mark is a mark placed on products in the European Economic area that indicates the product conforms with requirements of European Union directives. CE stands for *Conformité Européenne*.

¹⁰⁷ This section based on European Diagnostic Manufacturers Association, personal communication, August 2013.

¹⁰⁸ The Global Harmonization Task Force is a group of regulatory agencies and industry that came together to standardize medical device regulations, including in vitro diagnostics, around the world. The group developed and disseminated basic guidelines on regulatory practice. While the group has been disbanded, the International Medical Device Regulators Forum has assumed its mission of global harmonization (<http://www.imdrf.org/index.asp>).

¹⁰⁹ It is expected that malaria RDTs would be Class C, with Class D being the highest risk category for HIV tests/blood grouping tests.

¹¹⁰ The programme 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 QC testing, which 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 number of lots tested has increased significantly since the programme began, and currently approximately half of all lots undergo testing.¹¹¹ As the programme is designed to detect major flaws in RDTs, nearly all RDTs tested pass. Recently, the programme began providing commentary on any anomalies noted during testing.¹¹² While these do not constitute failures of the lot to detect malaria, they could present challenges for end-users such as needing to repeat the RDT or difficulty in interpreting results. If they occur frequently, they could suggest deficiencies in manufacturing QC.

As with the Product Testing Programme, lot testing has been funded centrally through donors and, going forward, the programme will undergo a transition to reduce reliance on donor funding and to 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 available to reference laboratories that will then perform lot testing for RDTs procured by local programmes and institutions. FIND expects to begin piloting lot testing at the country level in 2015. In addition, the panels will be marketed to manufacturers for use as a reference standard in product development and QC. This transition is happening in connection with the changes to the Product Testing Programme described above, and is expected to take several years. In the meantime, lot testing will continue at the current laboratories.

Malaria RDT demand

Public sector

Demand growth

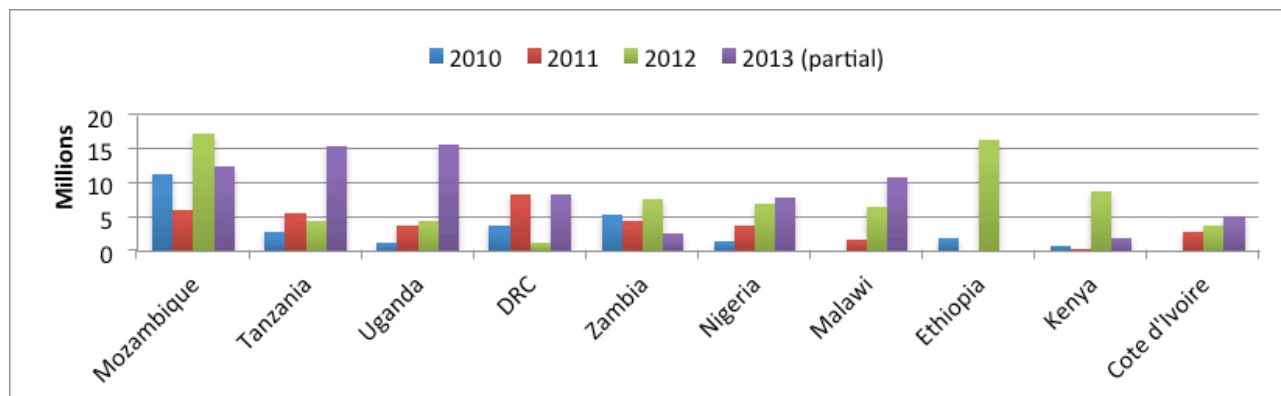
The public sector scale-up of RDTs is driving growth, although it is more advanced in some countries than others. Conversations with manufacturers and reporting by countries indicate that Africa is the largest market for RDTs, followed by South-East Asia. Most of the increase in testing in the African region is attributable to the increase in use of RDTs, which accounted for 40% of cases tested in the region in 2011, compared to one third in 2010.¹¹³ Procurement data confirm these trends. Within the reported data, the 10 highest-volume countries in 2010–2013 were African, and represented 65% of the reported procurement volumes during this period. Review of annual procurement volumes also suggests that much of the growth in the market stems from countries procuring increasingly larger volumes each year, however, given incompleteness of data, it is difficult to generalize (Figure 23).

111 Most recently, in 2012, 567 lots underwent testing, which is an increase of 55% over the previous year. In the first half of 2013, over 500 lots were tested. Estimates of the proportion of lots being tested are difficult to make, although there has been growth in lot testing, many factors influence these estimates (average lot size, market growth) and not enough data are available to fully appreciate the changes. Starting in mid-2013, the lot testing programme is requesting additional detail on lots tested (e.g. lot size and destination country) in order to better appreciate the proportion of the market that is undergoing lot testing.

112 These include items such as an intense red background that can obscure test lines, incomplete clearing of blood, problems with the test line or the flow of the sample and buffer. For a full list of the abnormalities that lot testing may note, see the Lot Testing Programme website (http://www.finddiagnostics.org/export/sites/default/programs/malaria-afs/malaria/rdt_quality_control/lot_testing/malaria_rdt_guide_for_observations_30jul13.pdf, accessed 10 October 2013).

113 2012 World malaria report. Geneva: WHO; 2012. 2011 World malaria report. Geneva: WHO; 2011.

Figure 23. Annual procurement volumes reported for the 10 highest-volume countries (2010–2013)

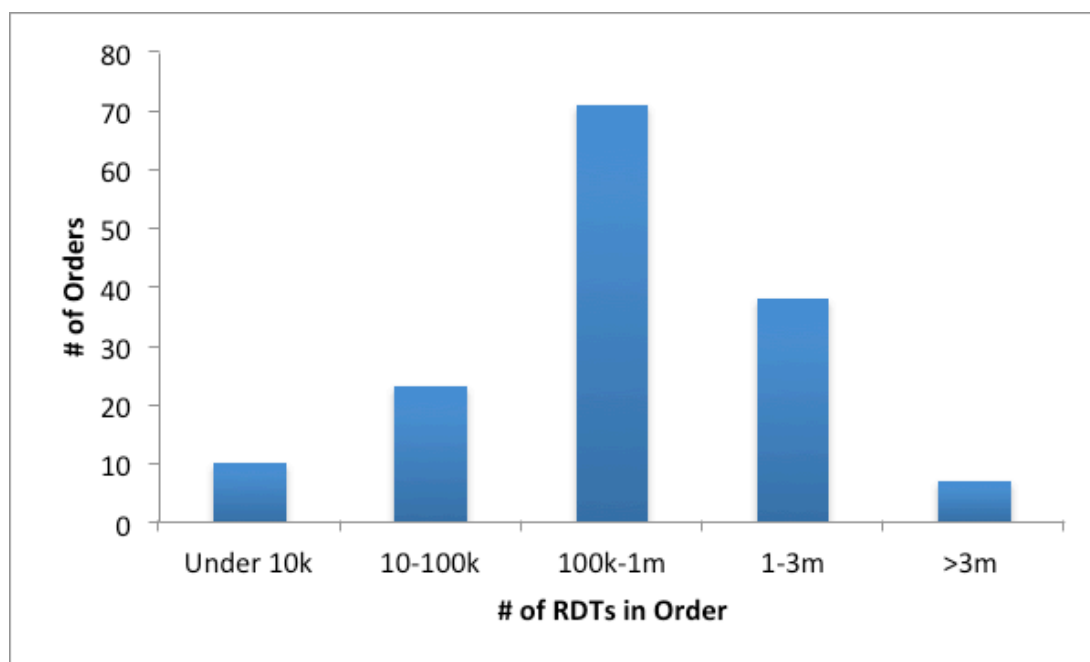


Source: CHAI/author procurement data analysis.

Order sizes

When considering order size procurement data, it is common for a country’s annual volume of RDTs to comprise multiple “orders”,¹¹⁴ with the reasons for this including staggered delivery and delivery to different locations within the country, funding by different donors and use of multiple procurement methods. Analysis shows a tremendous range in reported order sizes, ranging from < 10 000 to several million tests. In 2012, the largest orders delivered were 2–7 million tests, with an average order size of 790 000 (Figure 24).

Figure 24. Size of malaria RDT orders in 2012



k = thousand; m = million

Source: CHAI/author procurement data analysis; 59 countries representing 149 orders in 2012.

¹¹⁴ For example, in the procurement data analysed for this report, 58% of countries reported more than two orders in 2012.

Public sector procurement methods

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 for large orders. The procurement process can be lengthy and irregular, contributing to risk and instability in the market. Procurement data analysis suggests that most countries have used more than one procurement method (e.g. VPP; direct from manufacturer; John Snow International; other procurement agents), but within a given year, most (e.g. 75% in 2012) reported data for only one method.

Procurement data suggest that the top three procurement methods were directly from the manufacturer, through VPP and through PMI. The two largest procurement mechanisms are Global Fund VPP, which procured 41 million RDTs in 2012 and expects to procure > 50 million RDTs in 2013, and PMI, which procured nearly 29 million RDTs in fiscal year 2012.

Public sector product selection

Product selection in the public sector is generally conducted through a formal process involving a committee of local experts and stakeholders established by the national malaria control programme that develops a set of specifications and a short list of RDTs eligible for procurement. Generally, this process occurs every few years, as once an RDT has been selected and rolled out, programmes prefer to continue using it for a couple of years to avoid the programmatic costs of switching RDTs. Although not recommended by the WHO due to their complexity, local performance evaluations are sometimes conducted.

Factors driving product selection in the public sector include meeting product specifications (mainly performance in the Product Testing Programme, storage temperature requirements and factors related to ease of use), price and lead time. Of note, although minimum RDT performance thresholds are criteria for product selection, manufacturers of the highest-scoring RDTs do not obtain a price premium in this market. However, some of the highest-performing products do have larger market share.

Increasingly, products must also be registered with the local regulatory authority in order to participate in tenders. Little is known about the various local registration requirements; suppliers report that this process can take many months and is handled by their local agents or distributors. Distributors suggest that a product dossier and sample test kits are frequently required.¹¹⁵

Other trends in product selection include the following.

Pack size. RDTs are available in individually packaged units as well as bulk packages. Analysis of procurement data suggests that for the public sector, packs of 25–30 are by far the most popular, with individually packaged tests being very uncommon and larger packs (90 RDTs/pack) also not very common.

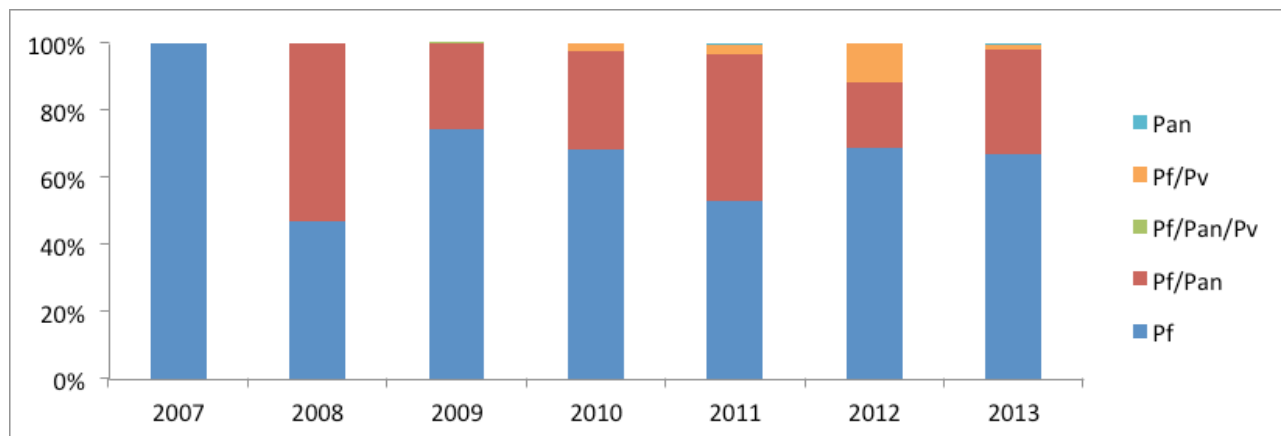
Type of RDTs. *Pf*-only tests continue to be the most procured type of test by volume (Figure 25). However, at the individual country level, more countries reported procuring a combination test in 2012 than a *Pf*-only test, suggesting that the volumes of combination tests are generally smaller than of *Pf*-only tests. For example, of the 59 countries reporting data in 2012, 37 (63%) procured a combination test. Of these 59 countries, 6 procured both a *Pf*-only and a combination test (Figure 26).

Procurement data indicate that half of countries switched types between 2010 and 2013.¹¹⁶ Of these, the majority switched from a *Pf*-only test to a combination test.

¹¹⁵ Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO GMP; 2013.

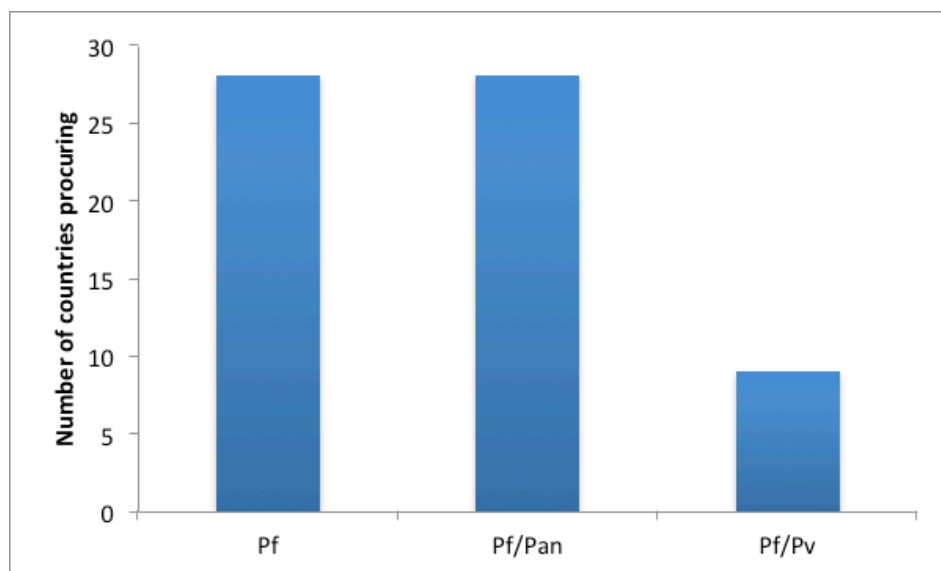
¹¹⁶ Analysis of data from 2010 through 2013, and including only countries with more than one year of data.

Figure 25. Procured test types by year (% of procurement volume)



Source: CHAI/author procurement data analysis.

Figure 26. Number of countries procuring Pf-only and combination tests (Pf/pan and Pf/Pv) in 2012

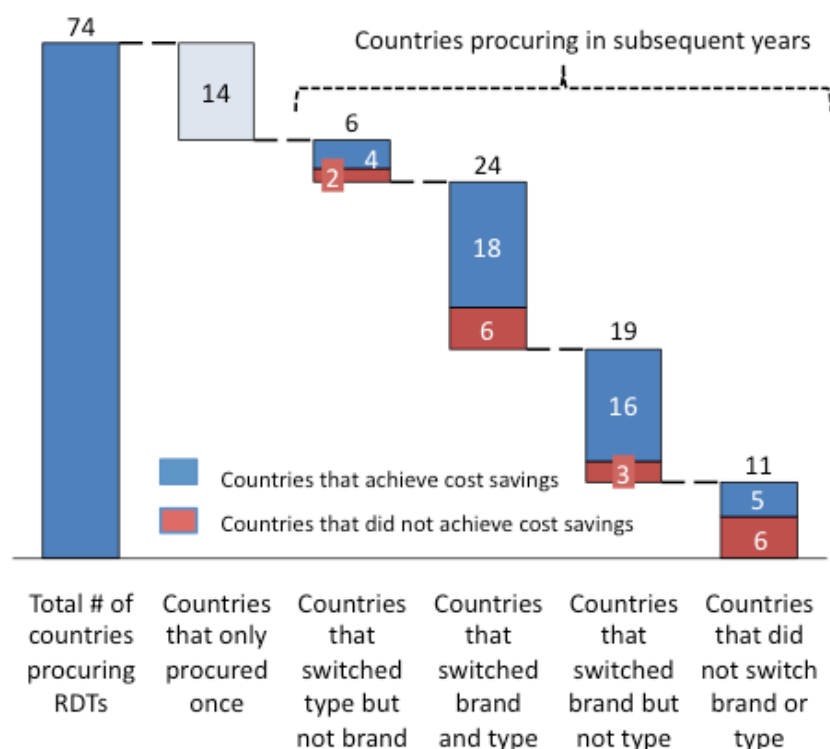


Source: CHAI/author procurement data analysis.

Switching between brand of RDTs. Data also indicate that countries have experience with multiple brands of RDTs; 72% of countries analysed switched brands between 2010 and 2013.

Overall, procurement data analysis suggests that the majority of countries has experience with multiple RDT products, either different brands or types of RDTs. Analysis shows that sole sourcing generally results in higher prices;¹¹⁷ in the majority of cases switching to another brand or type of RDT results in lower prices (Figure 27). However, these savings must be weighed against the programmatic costs of switching products (e.g. training expenses; operator error).

117 Procurement data analysis, personal communication with VPP and John Snow International (procurement agent for PMI), May 2013. Price analysis of malaria rapid diagnostic test kits. DELIVER Project Task Order 7. Washington (DC) USAID; December 2012.

Figure 27. RDT product types and/or brand switching and effect on price, 2010–2013

Source: CHAI/author procurement data analysis. Represents 88% of data. A country “switches type” of RDT when it chooses an RDT that detects different antigens (e.g. switching from a pf-only to a pf-Pan test). A country “switches brand” when it selects an RDT from a different manufacturer. Cost savings defined as a price difference between last and first order during the 2010–2013 time frame.

Donor funding for malaria RDTs

The Global Fund and PMI, and to a lesser extent other donors and governments themselves, fund malaria RDT procurement. Procurement data show that many of the highest-volume countries receive funding to procure RDTs from more than one donor.

The market’s growth in the past few 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 US\$ 2 billion in 2011 and in the coming years resources are expected to plateau or decline due to the ongoing global economic crisis and its potential to reduce development assistance.

With respect to procurement and quality standards, donors generally support country decision-making around RDTs. Donor policies are in line with the WHO GMP recommendations for RDTs and with international standards around competitive bidding. Detailed information on individual donors, including funding and procurement of malaria diagnostics, types of support and future plans, is available in Annex 4.

Private sector demand for RDTs

Overall private sector markets for RDTs are small, but growing, albeit at a significantly slower pace than public sector demand. With respect to market size, conversations with leading malaria RDT suppliers suggest that the private sector market is modest; globally, they estimate it to be 10–15% of the total market. Given the intense price competition in the public sector tender markets, many leading RDT suppliers are shifting focus to private sector markets. Geographically, RDT suppliers report that the private sector is larger in some (but not all) Asian countries (e.g. India; Thailand; Viet Nam) than in African countries.

At the country level, there are often two distinct private sector channels: (i) the formal private sector (i.e. hospitals; larger clinics and private laboratories; local NGOs); and (ii) retail outlets where antimalarial drugs are sold to consumers. Most malaria RDT suppliers have local distributors who serve the formal private sector. These distributors tend to be diagnostics/medical device distributors and they generally do not service the retail outlets where antimalarial drugs are sold to consumers. Currently, the formal private sector comprises the majority of private sector malaria RDT sales, although in many countries the potential size of the retail outlet drug shop (based on size of antimalarial medicines sold in this channel) is several orders of magnitude larger than the formal private sector market. Findings from a review of RDT prices indicated that prices tend to be higher in the private health facilities than in the retail outlets.¹¹⁸

In terms of product selection in the private sector, malaria RDT suppliers also report that formal private sector customers often prefer combination tests, tend to be quality conscious (although the standard used is not necessarily in line with the WHO recommendations), may require more technical support and tend to focus more on test presentation than buyers in the public sector. A survey conducted by FIND in 2009 reported that a variety of different brands of RDTs were available in formal private health facilities; only in one country was there an overlap between the brand of RDT chosen by the national malaria control programme and the test available in the private sector. This survey also found that 9 of 14 RDTs collected from the sites passed QC testing.¹¹⁹

The second private sector channel for RDTs, retail outlets where antimalarial drugs are sold, is currently a very small RDT market segment. These outlets are generally serviced by pharmaceutical supply chains, where awareness of RDTs is low¹²⁰ and that are less likely to stock RDTs and/or where RDT turnover is low. Relatively little is known about RDT product selection and stocking decisions in this channel. However, outlet survey data from ACTwatch indicate that, where available, a variety of RDT brands are found, including many that have not been evaluated by the Product Testing Programme (Table 5).

Leading RDT manufacturers are only beginning to establish distribution to the retail outlets selling RDTs, which is happening largely in connection with pilot projects to develop private sector markets for RDTs. These pilot projects are largely donor funded and as such the procurement criteria and quality standards are in line with public sector standards.

118 Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO GMP; 2013.

119 Albertini A. 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*. 2012 February; 17(2):147–52.

120 ACTwatch Supply chain surveys available at <http://www.actwatch.info>.

Table 5. Identified manufacturers and brands of malaria RDT products audited in the 2011 ACTwatch surveys among public health facilities and all other outlet types, by country

Manufacturer	Brand	Submitted for product testing during RT-3	Benin		Cambodia		Madagascar		Nigeria		Uganda		Zambia	
			PHF	Others	PHF	Others	PHF ^a	Others	PHF	Others	PHF ^b	Others	PHF	Others
Access Bio Inc	CareStart	Yes	X		X	X	X	X	X		X			
Acon Biotech	Unspecified / Plasmostest ^c	Yes		X		X			X	X		X		
Acumen Diagnostics	Diaspot	No							X	X				
Aragen Biotech	Unspecified	No										X		
Astel Diagnostics	Astel Pf Cassette	No									X	X		
Atlas Link Technology	Nova Test	No										X		
Atlas Medical	Rapid Test Strip	No		X										
Bhat Biotech India	MaleriScan	Yes		X								X		
Bioland	NanoSign	Yes											X	
Biosynex	Unspecified	Yes										X		
Bio Vege Med	Unspecified	No		X										
Chian Pharmed Co	Unspecified	No		X										
CTK Biotech	On Site Rapid Test	Yes										X	X	
Cypress Diagnostics	Malaria Quick Test	No					X					X		
Global Device	Unspecified	No							X	X				
Highgate	Whole Blood Cassette	No										X		
Human GMBH	Hexagon Malaria	Yes										X		
ICT Diagnostics	ICT	Yes	X	X									X	X
InTec Products	Advanced Quality	Yes				X								
Inverness Medical	Binax Now Malaria	Yes				X								
Jei Daniel Biotech	Unspecified	No		X										
Lab-care Diagnostics	Accucare One Step	No										X		
Launch Diagnostics	Accusay	No										X		
Medsorce Ozone Biomedicals	Malaria Antibody Test	No		X										
Nano Biotech	Nano Malaria	No										X		
Nantong Egnes Biotech	Unspecified	No										X		
Omega Diagnostics	Micropath	No								X				
Orchid Biomedical Systems	Paracheck	Yes	X	X		X	X		X	X		X	X	
Pistis Diagnostic Ltd	Unspecified	No							X					
Premier Medical Corporation	First Response	Yes							X	X		X	X	
Span Diagnostics	Parahit	Yes										X		
SSA Diagnostics and Biotech Systems	Unspecified	Yes										X		
Standard Diagnostics	SD Bioline	Yes	X	X			X	X	X	X		X	X	
Vision Biotech	Clear View ^d	Yes						X				X	X	
Wondfo Biotech	One Step Whole Blood Test ^e	Yes			X	X				X		X	X	
Unspecified	Life Tech Whole Blood Strip	n/a										X		

PHF: Public health facility; Others: All other outlet types present in the country

^a In Madagascar, CareStart from Access Bio Inc and SD Bioline from Standard Diagnostics were also available from community health workers;

^b In Uganda, SD Bioline from Standard Diagnostics were also available from community health workers;

^c Brand details were recorded as Plasmostest in Benin, but not recorded for RDTs from Acon Biotech in other countries;

^d Brand details were not recorded for 2 Vision Biotech RDTs audited in Madagascar and 1 RDT audited in Zanzibar;

^e Brand details were not recorded for 2 Wondfo Biotech RDTs audited in Ghana; in Cambodia 25 RDTs from Wondfo Biotech were branded as Malacheck, the brand name used by PSI's subsidised RDT program.

Source: Stephen Poyer, ACTwatch

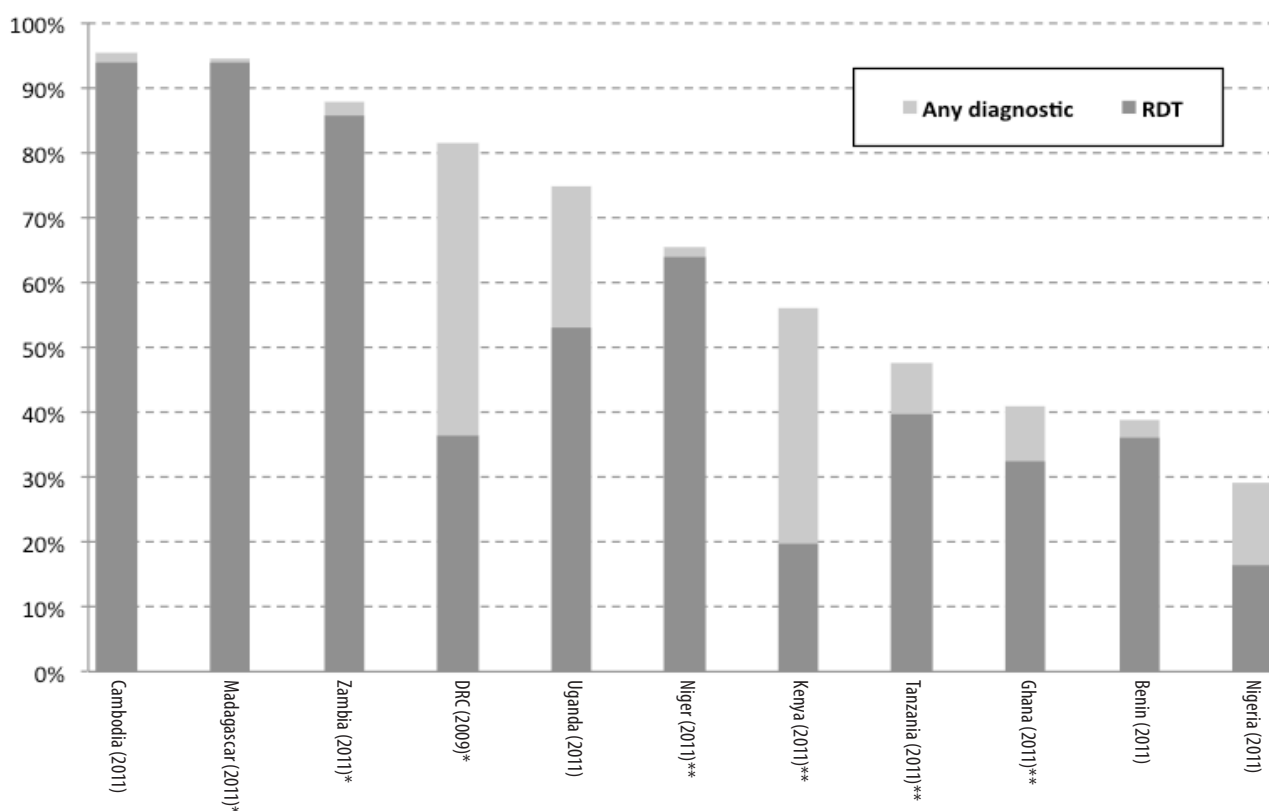
Diagnostic test availability

There has been no new large-scale surveys of public and private facilities to assess test availability since the ACTwatch surveys in 2011, which are included here. Another round of outlet surveys is under way and results should become available in 2014.

Health facilities: public and private not for profit

The availability of diagnostic tests in the public sector has been assessed through outlet surveys conducted in several countries. Figure 28 shows the availability of any malaria diagnostic (either microscopy or RDT) and of RDTs in public health facilities sampled. As can be seen, public sector availability varies greatly: it is high in Cambodia, Madagascar and Zambia as compared to Ghana, Benin and Nigeria. Since these surveys were conducted in 2011, there likely has been significant progress in the scale-up of diagnosis in many countries. However, conversations with experts also suggest that in the public sector stockouts of RDT and microscopy supplies are common and would limit availability of testing services.

Figure 28. Public sector availability of malaria diagnostic testing: percentage of facilities with any diagnostic test/RDTs



* Designates public and non-profit sector facilities combined.

Source: ACTwatch Outlet Surveys except where denoted with ** indicating data from the Independent Evaluation of the AMFm Phase I, Preliminary Report of 18 July 2012 (<http://www.theglobalfund.org/en/amfm/independentevaluation/>).

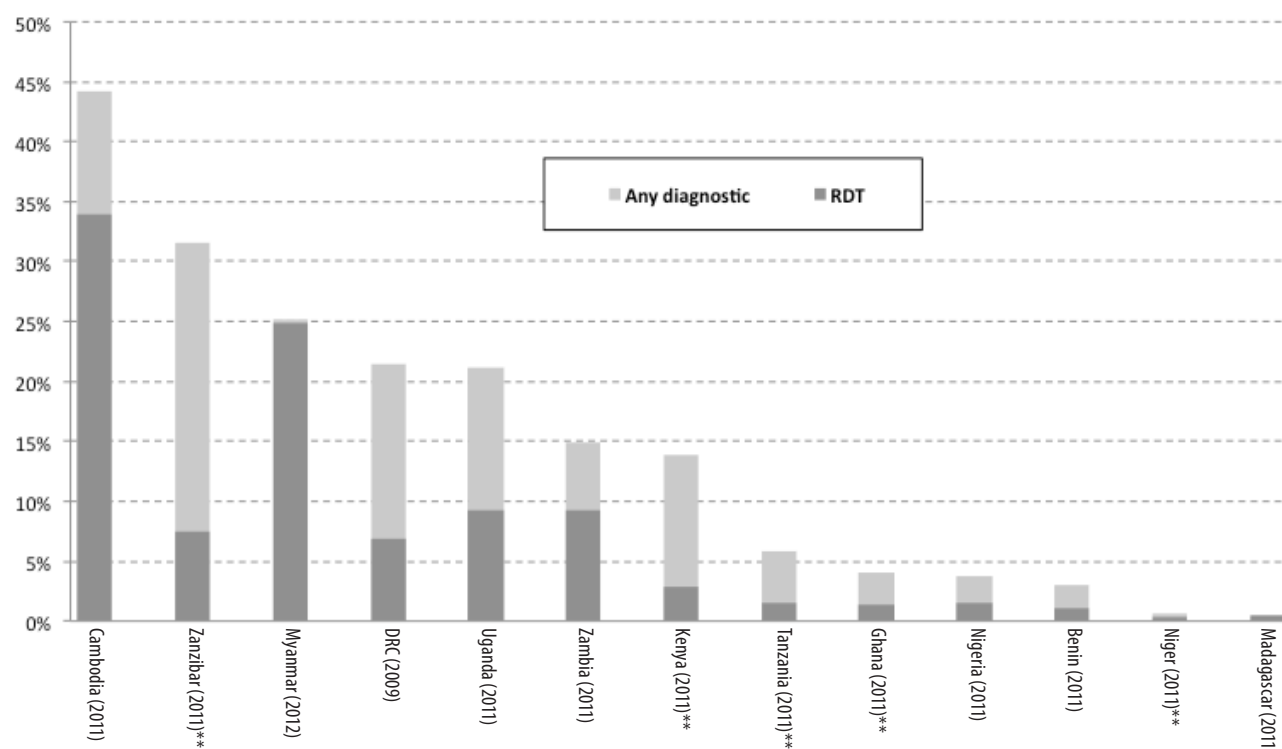
Private sector: retail outlets

As seen in Figure 29, ACTwatch data from several countries indicate that the availability of diagnosis in private sector retail outlets selling antimalarial medicines is small/minimal in many highly endemic countries. Likewise, the survey conducted by FIND found limited availability of RDTs in the private sector: 11% of the outlets visited had RDTs; the vast majority of outlets with RDTs were 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 10 years, which has increased availability of RDTs in the private sector.

ACTwatch studies also suggest considerable variation in availability among private sector outlets, with test availability being highest in more formal outlets, for example, health facilities and pharmacies, and minimal in less formal outlets. In Uganda, for example, ACTwatch found 54% of health facilities and pharmacies surveyed had diagnostic services, compared to 7% of drug stores and 0% of general retailers and itinerant vendors.

It is worth noting that in many countries, private diagnostic laboratories exist and likely would provide malaria diagnostic services, however, this segment of the market has not been studied.

Figure 29. Private sector availability of malaria diagnostic testing of outlets selling antimalarial medicines, percentage that have diagnostic testing services



Source: Author analysis of ACTwatch Outlet Surveys except where denoted with ** indicating data from the Independent Evaluation of the AMFm Phase I, Preliminary Report of 18 July 2012 (<http://www.theglobalfund.org/en/amfm/independentevaluation/>).

Future demand for malaria RDTs

In general, assuming continued donor funding, the public sector scale-up of RDTs should continue as many countries have not yet reached the national scale. Community level use of RDTs is expanding, approximately half of all malaria endemic countries report use of RDTs at the community level,¹²¹ however, many of these programmes are currently very small and limited in geographic reach. National scale-up will depend in part on funding availability and, when it occurs, it will likely manifest as incremental to existing public sector demand. The development of private sector retail channels for RDTs is receiving a lot of attention at the global level; however, in the near term, demand from this sector is likely to be modest due to the many complexities associated with this market. Although no global forecast of malaria RDT demand currently exists, RDT forecasting exercises are planned for 2014–2015.

Future donor funding for malaria RDTs

In light of the current funding situation, reductions in resources for global health could constrain the future pace of RDT demand growth. In particular, the Global Fund, the largest malaria donor is conducting

121 2012 World malaria report. Geneva: WHO; 2012.

a major fundraising initiative and is launching the New Funding Model. As a result, in the coming years, the extent of Global Fund resources for malaria is uncertain.

The timing of the uncertainty in funding associated with the largest donor for malaria comes at an interesting time for the market, as 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. However, in the coming years, depending on Global Fund allocations, countries may face funding gaps in their overall malaria control programmes, and these could affect diagnostic testing levels and programmatic support for diagnosis in the public sector as well as expansion plans for the private sector. In addition, as the New Funding Model is rolled out, countries may encounter temporary gaps in funding that could impact the scale-up of diagnosis in that country and, if gaps are frequent, the RDT market more generally.

At the country level, national programmes are concerned about protecting gains achieved in malaria control and the ability to scale up further. Currently, many countries are developing Concept Notes to support applications to the Global Fund. Although the New Funding Model is a rolling process, many countries would like to apply for funding as soon as possible so as to avoid interruptions between grants and to anticipate delays associated with the new system.

With respect to private sector case management, currently available resources are probably not sufficient to support the activities required to ensure widespread scale-up of case management in the private sector. While the Global Fund Replenishment Targets include funding for case management in the private sector, the estimates used are not very precise and it is likely that the majority of grant funds will be allocated to public sector commodity needs (e.g. LLINs; ACTs; RDTs), leaving limited resources for potential private sector programmes.

Roll Back Malaria Partnership HWG analysis of RDT needs and financing in Africa

An analysis of RDT needs and financing for 42 African countries through 2016 sheds some light on how countries plan to move forward with diagnostic scale-up as well as high-level insight into RDT demand. Figures 30 and 31 compare the total need for RDTs in Africa for 2013–2016 with the number of RDTs financed. The total need is projected to be 1.4 billion and Nigeria, Uganda, DRC, Mozambique, Ethiopia and Tanzania comprise the largest RDT needs (Figure 30). However, there is often a significant difference between RDT needs and actual demand, with funding being a major factor influencing whether or not demand is realized. As such, RDT financing may be more indicative of actual future demand. Figure 31 shows 498 million RDTs financed, and that need does not correlate to financing (e.g. for DRC and Nigeria, two countries with significant RDT needs, less than a quarter of the need is actually financed).

Figure 30. RDTs needed in African countries, % of need from the private sector, 2013–2016

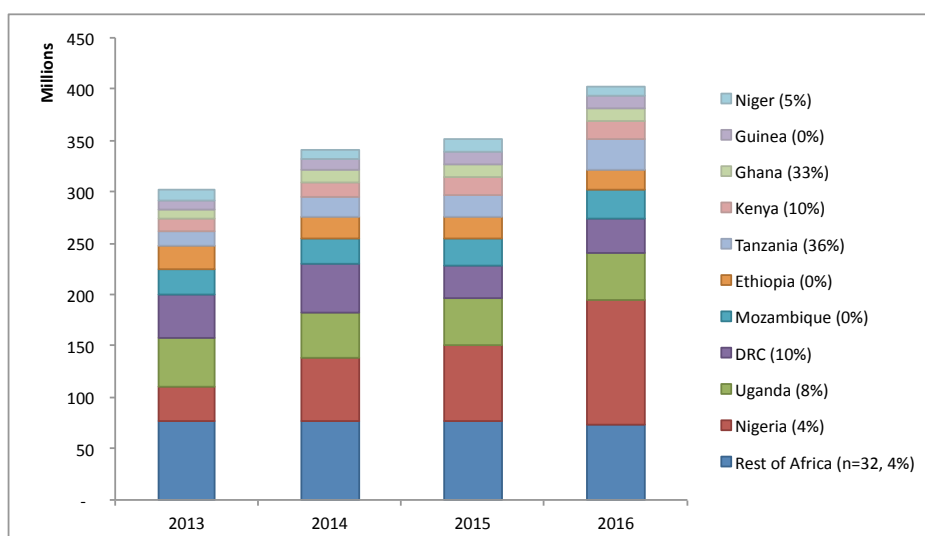
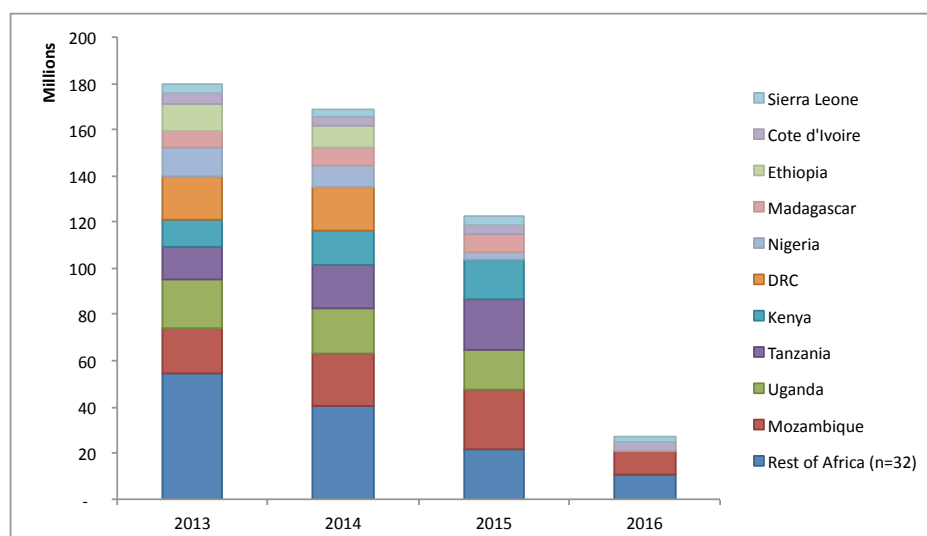
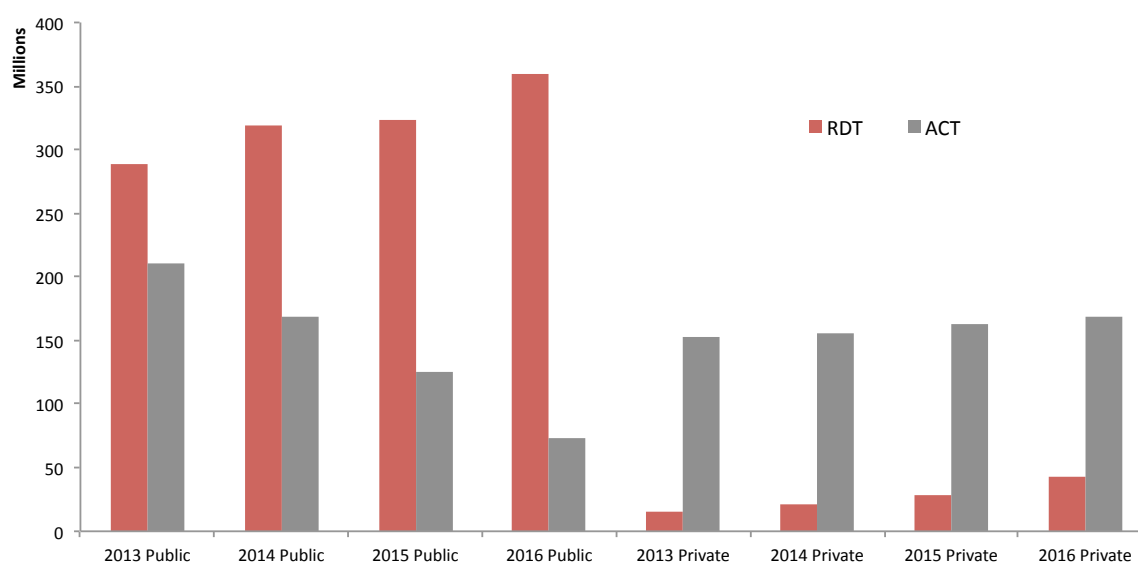


Figure 31. RDTs financed in African countries, 2013–2016

Source: Author analysis of the Roll Back Malaria Partnership HWG data on commodity needs, prepared for Global Fund Replenishment Meetings.

With respect to the private sector, Figure 32 shows how countries are planning to scale up RDTs in the public/community sectors compared to the private sector, and what impact they expect RDTs to have on ACT needs. While public sector RDT needs continue to grow as ACT needs decline, the reverse is true in the private sector, where ACT needs are increasing (albeit very slowly) and remain significantly above RDT needs, suggesting a slow implementation of diagnosis in the private sector.

Figure 32. RDT and ACT needs by sector for 42 African countries, 2013–2016

Source: Author analysis of the Roll Back Malaria Partnership HWG data on commodity needs, prepared for Global Fund Replenishment Meetings.

Private sector market development

If the goals for universal access to diagnostic testing are to be met, there is a need to improve the quality of care of malaria in the retail private sector, which is often the first place where people seek care for fever. Despite the increased focus on development of private sector markets in the past year, and the existing

operational research and pilot projects under way, recommendations and best practice for expanding fever case management, including diagnosis, to the private sector do not exist. The market is proving to be complex, especially when compared to the introduction of ACTs, and many unanswered questions remain, in particular, management of RDT-negative patients and incentives to encourage testing and appropriate fever management. Some of the emerging findings and the major challenges associated with diagnosis scale-up are described below.

Emerging findings

The heterogeneity of the private sector, both between countries and within countries, makes generalizing from any one experience challenging. However, implementers and researchers have noted several common experiences with RDTs in the private sector:¹²²

- There seems to be a general willingness to use RDTs and acceptance of RDTs among both customers and retailers. Notably, some studies have found that private sector providers consider diagnostic capacity to be a service that helps professionalize and legitimize their business, while other retailers view RDTs as another commodity. Among customers seeking care for fever, many are aware that fever might be caused by diseases other than malaria and seem open to testing before treatment.
- Operationally, many studies have demonstrated that it is feasible to safely and accurately diagnose malaria in the private sector using RDTs, even in the less formal drug shops. However, cost-effective means of training retailers (especially in light of high staff turnover) and of providing QA remain a challenge.
- Evidence from AMFm and from limited pilots suggests that private sector supply chains may be more efficient than public sector supply chains at increasing the availability of commodities.
- As in the public sector, operational research suggests that adherence to RDT results varies: 11–49% of individuals with a negative RDT still being prescribed an antimalarial.¹²³

Challenges

Among the common challenges to large-scale implementation of diagnosis in the private sector are the following.

Regulations. Local regulations often govern where testing can be performed and the type of provider who may perform testing. In many countries, current regulations prohibit testing in the retail private sector. In addition to testing regulations, prescribing and selling antimalarial medicines and medicines for non-malaria fever (e.g. antibiotics) are also considerations.

Managing negative results. There is a need to identify methods for improving adherence for test results, including the development of practical strategies for managing RDT-negative individuals in the private sector. In many countries, private providers would be expected to refer to the public sector the severe cases or cases where a diagnosis cannot be established. However, in most instances, referral systems between private and public sector do not exist, and when a referral is made, patients might not be managed appropriately at the receiving facility.

Support and incentives. Appreciating the mix of support and incentives needed to establish testing in the private sector is proving to be a complex matter, in part due to fundamental differences in the nature of diagnostics compared to other commodities. For example, selling RDTs implies providing a diagnostic service, which includes performing the RDT accurately, interpreting the results and treating the patient based on the test results. As a result, introducing diagnosis will require provision of training on how to perform the test and on clinical protocols (e.g. who should be tested and how to manage customers based on results). Compared to ACTs (i.e. a new product in the well-established malaria medicines market), RDTs

¹²² This section draws on expert interviews as well as the Roll Back Malaria Partnership document Diagnostic testing in the retail private sector: lessons learned. Meeting report of the Roll Back Malaria Partnership Case Management Working Group, London, 29–30 April 2013. September 2013. This meeting included a review of the results of more than a dozen small-scale studies and pilots from eight countries in Africa and South-East Asia.

¹²³ Diagnostic testing in the retail private sector: lessons learned. Meeting report of the Roll Back Malaria Partnership Case Management Working Group, London, 29–30 April 2013. September 2013.

are a new product category with no existing demand. Introduction of a new product category is inherently more complex than launching a new product to an already established market and requires a multifaceted set of interventions involving consumers, retailers and other supply chain actors to generate demand and to increase availability of tests. Major evidence and experience gaps include:

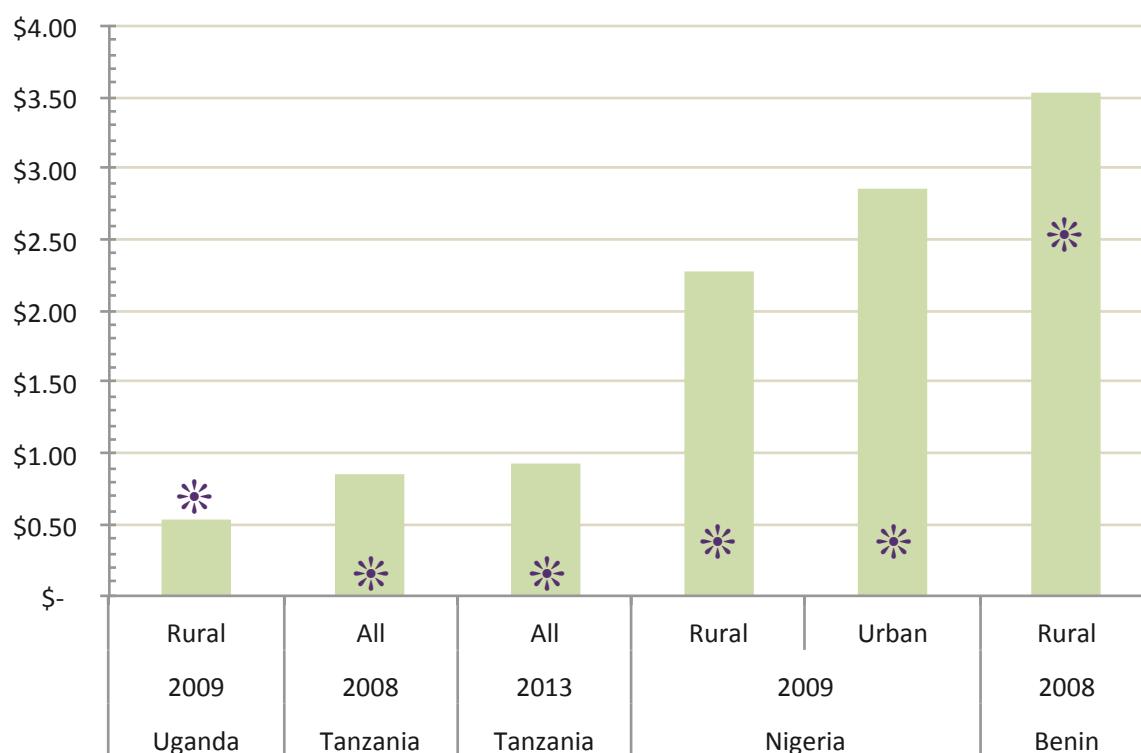
- **Demand generation:** among consumers and retailers, awareness of the value of diagnostic testing and the availability of RDTs is generally low. While there is a general consensus that behaviour change communications and provider training are needed to generate awareness and ultimately demand for diagnosis, experience in this area is limited. Evidence from Cambodia, the only country with a national RDT subsidy programme for the private sector, suggests that the messaging around diagnosis is complex and needs careful consideration.¹²⁴ It is also unclear if demand generation alone will be enough to pull RDTs through the supply chain and to increase retail availability.
- **Pricing:** from a financial perspective, customers must be able to afford testing, along with any treatments. Currently, there is little evidence of customer willingness to pay for testing alone and perhaps, more importantly, for testing combined with treatment. Nor is there much evidence on supply chain markups and resulting retail prices for RDTs. Figure 33 compares existing willingness-to-pay data with prices; note that this analysis is based on very limited data and might not be generalizable. Additional pricing and willingness-to-pay research (based on real world settings as opposed to survey data) would be beneficial. It is also likely that affordability as well as retail prices would vary among countries and even within countries. While a subsidy for RDTs may be needed to make tests affordable to consumers, current evidence is insufficient to make a determination of whether it is needed and, if so, at what level.
- **Supply chain incentives:** in order to increase availability of RDTs at retail outlets, appropriate incentives must be in place for the retail supply chain to distribute and stock RDTs. While different models and incentives for encouraging uptake by the supply chain have been mapped at a theoretical level, few have been evaluated in practice.

Scale and sustainability. A final challenge involves reaching scale and sustainability. Currently, many research and implementation projects are delivering promising results. However, these are often small projects, which are human resource and financially intensive. Scaling to a national level may require significant rationalization and planning. Furthermore, given the immense support required in terms of training, supervision/QA, waste disposal, monitoring and evaluation, and what is likely to be an extensive communications campaign given the paradigm shift that is required, substantial funding is needed. The experience from Cambodia suggests that many of these activities need to be ongoing.¹²⁵ Lastly, if a subsidy is used to support the initial development of the RDT market, the long-term sustainability of the subsidy and the market also must be considered.

124 Yeung S et al Socially marketed rapid diagnostic tests and ACT in the private sector: ten years of experience in Cambodia. *Malar J.* 2011 August;10:243.

125 Yeung S et al Socially marketed rapid diagnostic tests and ACT in the private sector: ten years of experience in Cambodia. *Malar J.* 2011 August;10:243.

Figure 33. RDT willingness to pay and private sector RDT prices (US\$) (prices designated with an *)



Sources: Willingness to pay data and image from the Results for Development Institute, Washington DC; median RDT prices from ACTwatch 2011 Private Sector Outlet Surveys.

Implementation pilots

Over a dozen operational research and pilot projects are exploring the use of RDTs in the private sector and improving case management for fever. These projects are expected to produce evidence in the near term (2014), their findings will be reviewed in the next edition of the Landscape. Among the larger scale projects are:

- Population Services International (PSI) is leading a UNITAID-funded programme to develop private sector markets in Kenya, Madagascar and Tanzania. While the approach will differ in each country, PSI will be supporting direct marketing to consumers and branding of product and/or outlets to drive demand.
- In Nigeria and Uganda, the Malaria Consortium (as part of the PSI UNITAID-funded programme) is contracting directly with malaria RDT manufacturers to provide a number of supplies (e.g. gloves; timers) and to undertake certain aspects of marketing and programmatic support (e.g. product promotion; stock management; training; supervision; waste management services).
- CHAI has launched a national initiative in Kenya and Tanzania to sell low-cost RDTs through the formal private sector (e.g. hospitals; clinics; dispensaries) without a subsidy. This programme includes negotiated pricing with several RDT manufactures, agreements with local distributors that limit margins and demand generation activities. In Tanzania, an additional pilot study in accredited drug dispensing outlets using a subsidy for RDTs also is being conducted.

Conclusion: private sector market development

In recognition of the complexity of introducing diagnostics into the private sector, the current lack of understanding and evidence and the heterogeneity of markets, there is an emerging consensus that scaling up diagnosis will prove more complex than introducing ACTs and that a nuanced approach is needed.

While many countries are considering expansion of diagnosis to the private sector, the best approach and models are unclear given the lack of evidence and experience with this relatively complex market. The lack of clarity contrasts with a sense of urgency related to timelines for the Global Fund New Funding Model and a general desire to continue recent momentum of case management scale-up.

As a result, there is an increasing focus on generating and sharing results from operational research projects and pilots as well as on accelerating the development of best practice recommendations. In connection with this, there is a need to map remaining knowledge gaps to develop a prioritized research agenda for future work.

Malaria RDT supply

Malaria RDT suppliers

Companies supplying malaria RDTs are diverse: varying in terms of size, years of operations, 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, controlling 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 have modest-sized lateral flow test businesses and/or reagent businesses. Many companies that manufacture and market their own products also perform manufacturing of complete unlabelled RDTs or components of RDTs for other suppliers.

As described above, the public sector market is consolidating around a few suppliers. Although there are 26 different companies on the list of WHO recommended RDTs, many companies are not very active in the public sector market. While some of these companies are focused on market niches/smaller market segments (e.g. the Indian private sector; the international travellers markets; businesses with large labour forces affected by malaria), 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.

Barriers to entry and market attractiveness

On the surface, the malaria RDT market appears attractive: (i) volumes are high and growing; (ii) it is relatively easy to develop a product and bring it to market (due to commercial availability of the key active ingredient—MAB—and ease of rapid test production more generally); (iii) there is little intellectual property enforcement; (iv) regulatory requirements are lower than with other diagnostic tests; and (v) 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 Product Testing Programme in order to access the largest market segment, that is, the public sector market. A second emerging barrier to entry is pricing; delivering RDTs at the current low prices requires significant cost advantages and economies of scale. Having adequate manufacturing capacity and access to working capital is also required in order to successfully respond to tenders, which can require millions of RDTs to be delivered within four to eight weeks of signing a contract. Lastly, local registration of products is increasingly a requirement for importation and for participation in tenders, and these processes can take several months to complete.

Another measure of market attractiveness is innovation. In general, the incentives for groundbreaking 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 improved 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 Programme, efforts to reduce costs and exploration of alternative sources of MAb due to recent changes in the structure of this market.

Manufacturing process and inputs

There have been no recent changes to manufacturing processes, which are described in the *2012 Malaria Diagnostics Market Landscape*.

MAbs

Malaria RDT technology is based on MAbs, antibodies that have been manufactured to bind to specific antigens. Currently, MAbs are available from a limited number of commercial sources or are produced in-house by a few RDT manufacturers. The National Bioproducts Institute (NBI, Kwa-Zulu Natal, South Africa) is the major commercial source of HRP-II MAb, and Access Bio is the major source of pLDH antibody. Estimates of the cost of a MAb test vary, as manufacturers use different quantities and combinations of monoclonal depending on the product. Assuming a commercial source of antibody is used, the antibody cost for RDTs ranges from 2 to 9 cents per test, with the multiline combination tests and smaller production runs having a higher cost per test.

NBI, a South African not-for-profit organization, is a leading global source of malaria MAbs to HRP-II and aldolase. NBI has been supplying RDT manufacturers since 1998 and the industry relies heavily on its antibodies. NBI markets seven different antibodies, three HRP-II and four aldolase; however, two HRP-II antibodies comprise the vast majority (approximately two thirds) of its sales. NBI sells to approximately 23 customers (including MAb distributors and researchers, but primarily to RDT manufacturers); 14 of these customers have been consistently procuring over the past few years. Order sizes vary tremendously; there is no standard order size, since RDT manufacturers keep limited quantities of MAb in inventory and place orders for antibodies when awarded a contract. Pricing is volume dependent, with larger orders receiving a significant discount.

NBI developed some of its clones for producing HRP-II malaria MAbs in the late 1990, with aldolase clones being developed more recently. There is an active programme in place to ensure that the quality and yield potential of the clones remain consistent. MAb rich-ascitic fluid is produced in a high-throughput mouse colony for further processing. The start-up production time is approximately four to five months. Due to the lack of predictability in demand and the RDT manufacturers' expectations for quick delivery of antibodies (two to four weeks), NBI strives to maintain stock levels of ascitic fluid at 12 months based on current sales. Once an order is received, the specific ascitic fluid is purified and QC-tested before being released for shipping, allowing NBI to deliver within three to four weeks.

Currently, NBI is finalizing its ISO 13485 accreditation process. They are also working on the development of new malaria MAbs and are expanding their portfolio of activities towards the discovery of MAbs to other neglected diseases. Their intent is to use their expertise and experience to continue to provide highly specific, sensitive and stable antibodies to meet the needs of manufacturers making POC products. NBI intends to collaborate with researchers who identify new biomarkers for which a MAb can be developed.

As a not-for-profit company, NBI aims to make products available to manufacturers at prices that ensure the affordability of POC devices to resource-poor countries affected by malaria and other neglected diseases. Therefore, pricing of MAbs aims to cover direct costs, make a contribution to overhead costs and to a modest operating surplus to fund ongoing operations, research and capital projects at NBI. Its sales of malaria MAbs steadily increased following a decline in 2008. After growth in 2012, they levelled off again in 2013. Sales generally track international tender awards and their associated funding.

Access Bio (New Jersey, United States), a leading manufacturer of malaria RDTs, became the primary commercial source of pLDH MAbs in late 2011 when it acquired the clones for the pLDH MAb business from Flow Inc, which is the American R&D company that initially developed and marketed the pLDH MAbs.

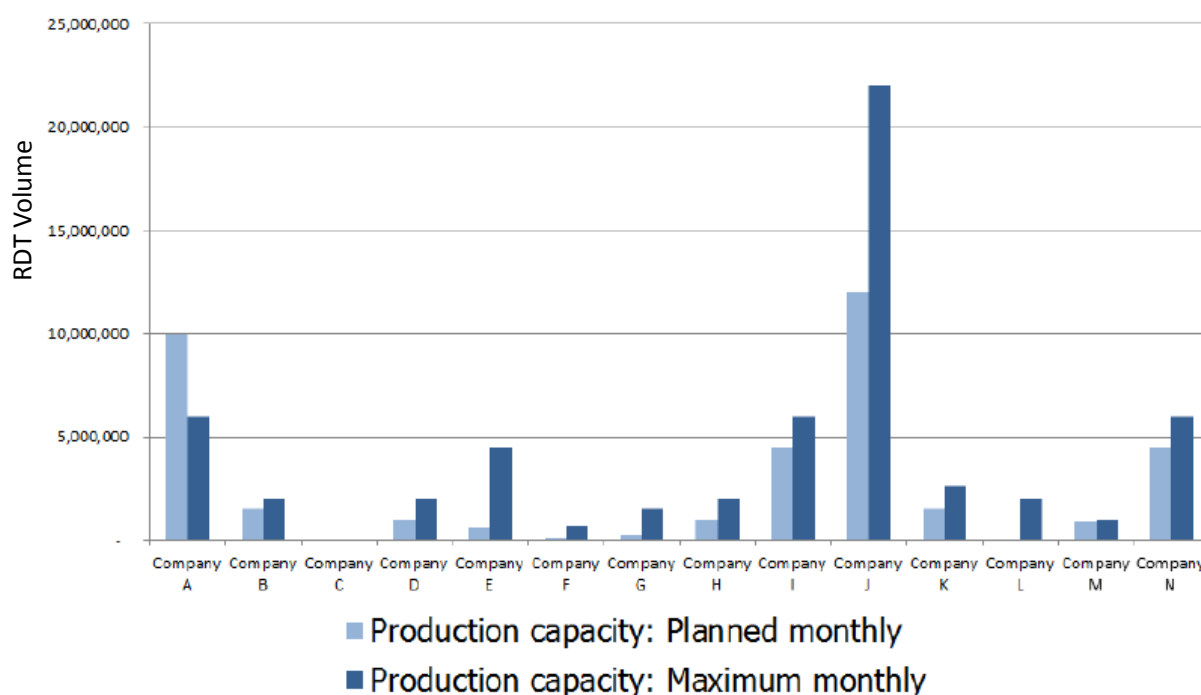
Access Bio outsources manufacturing of the antibodies to two American companies specializing in monoclonal production, and sells through Vista Diagnostics (Seattle, Washington, US).

Although 20 different pLDH MABs are available, over 90% of pLDH antibody sales came from five antibodies: two pan-malaria antibodies; two *P. vivax* specific antibodies; and one *P. falciparum* specific antibody. As with NBI, there is no standard order size, and order sizes vary tremendously. Pricing is volume dependent, with larger orders receiving a discount. The lead time for producing pLDH MAB is approximately three months unless the antibody is in inventory. The wholesale price of commonly used pLDH MABs 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 steady since Access Bio acquired the business.

Manufacturing capacity and lead times

Malaria RDTs are made to order, suppliers generally do not maintain significant inventories of finished goods. Although they are made to order, globally, production capacity is generally not considered to be a limiting factor in this market. In 2013, WHO surveyed 14 manufacturers that represent 80% of the RDT market and found a broad range in planned production capacity (from 15 000 to 12 million RDTs) and in maximum capacity (from 40 000 to 22 million RDTs) (Figure 34).¹²⁶

Figure 34. Planned and maximum monthly production capacity in number of individual RDTs



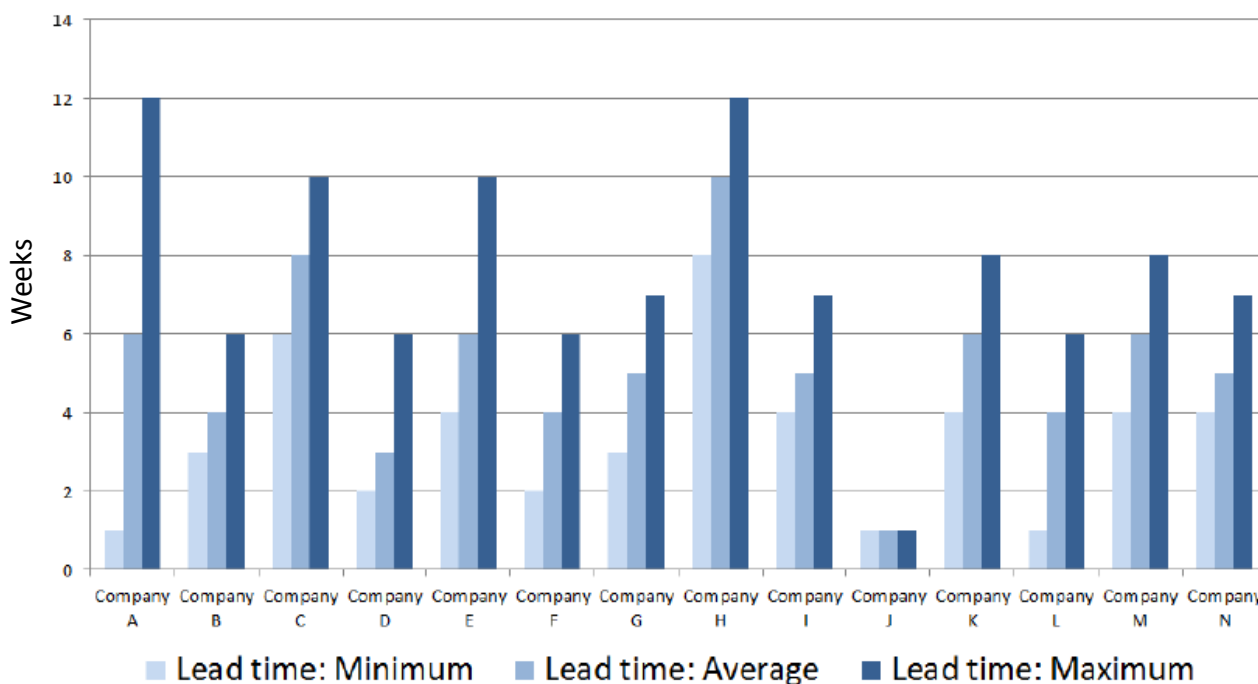
Source: WHO Feasibility Assessment of a global subsidy mechanism for malaria rapid diagnostic tests.

In the WHO survey of manufacturers conducted in 2013, the average lead time was five weeks, however, there were large variations between manufacturers¹²⁷ minimum and maximum lead times (1 week minimum to 12 weeks maximum) (Figure 35). Lead times can be affected by inventory of components and raw materials as well as existing supply commitments. Larger orders typically have longer lead times.

¹²⁶ Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO GMP; 2013.

¹²⁷ Feasibility assessment of a global subsidy mechanism for malaria rapid diagnostic tests at manufacturer level managed by the Global Fund. Geneva: WHO GMP; 2013.

Figure 35. Minimum, average and maximum lead times in weeks



Source: WHO Feasibility Assessment of a global subsidy mechanism for malaria rapid diagnostic tests.

Shipping and distribution and cost reduction

There have been no recent changes to shipping, distribution and cost reduction, which are described in the *2012 Malaria diagnostics market landscape*.

Summary of the malaria RDT market

Despite demand growth, declining prices and margins make the malaria RDT market increasingly unattractive. The market is characterized by competition on price, the ability to deliver rapidly and meeting minimum quality standards. Barriers to entry have emerged, including the need for economies of scale (including production capacity, strong logistics management and access to working capital) and meeting quality standards such as product testing. While demand is likely to continue to increase as malaria control countries continue to scale up diagnostic services in the public sector, other market segments, such as the private sector market, may take time to mature.

These dynamics have important implications for RDT quality and for innovation. With respect to quality, market conditions put RDT quality at risk. The quality of a specific product could suffer due to cost pressures and resulting reductions in manufacturing QA activities. In addition, it is possible for one of the leading suppliers' RDTs not to perform well in future rounds of product testing. The market conditions also limit the business incentives for new product development at a time when improvements to existing RDTs as well as development of new technologies to address unmet needs are needed.

7. MARKET SHORTCOMINGS AND THEIR REASONS

This section describes market shortcomings and their reasons.

Quality

Description of market shortcoming	Reasons for market shortcoming
<p>No practical QC technologies for RDTs. Most diagnostic tests are not marketed without QCs and for most tests there are well-established methods for checking quality along the value chain from manufacturer to point of service. Practical technologies for RDT QC do not exist and are inadequate where they do exist. For example:</p> <ul style="list-style-type: none">■ Heat stable QCs for use at the point of service are not available, controls in development have yet to come on the market and/or be extensively evaluated.■ Product and lot testing programmes for malaria RDT QC are expensive and complex due primarily to reliance on human-derived specimens. Suitable replacements for human-derived specimens (i.e. heat stable recombinant antigens for QC) are in development, but have yet to come on the market.	<ul style="list-style-type: none">■ Little incentive for private sector investment in QC technologies.■ Low awareness and prioritization of QC among buyers, donors and policy-makers, in particular, as the RDT market was first developing.■ Although recombinant antigens are cheaper and more easily produced than human-derived specimens for RDT QC purposes, reasons for the lack of recombinant controls include: (i) technical complexity related to their development and production, in particular, stability of antigens; and (ii) among the companies with technical capacity and experience required to develop controls, there is likely limited awareness and little financial incentive for R&D.

<p>Limited information on the quality of malaria RDTs. The market has little ability to monitor product quality, <i>in particular, manufacturing and field-level quality</i>¹²⁸ (see above for monitoring quality in the field). With respect to manufacturing-level quality, the WHO Prequalification Programme for Diagnostics has proven to be a lengthy process, with three malaria RDTs approved since 2010 and unpredictable timing for future approvals.</p> <p>The absence of quality programmes may precipitate the exit of suppliers from the market, especially those whose products are among the higher-performing products. Quality is also at risk given current market conditions (i.e. intense competition around price, short delivery times and larger orders), which could exacerbate manufacturing quality problems.</p>	<ul style="list-style-type: none"> ■ No formal regulatory and postmarket surveillance processes in countries that consume large volumes of RDTs. No systems for aggregating information on RDT problems. ■ No business incentive for manufacturers to undergo an alternative stringent regulatory process (e.g. FDA). ■ WHO Prequalification Programme for Diagnostics not functioning optimally; slow progress of malaria RDT suppliers. ■ Limited experience of RDT suppliers with robust quality standards, due to lack of regulations in markets where RDTs are produced and sold. ■ Suppliers reluctant to invest in stronger quality management systems due to thin margins and inability of market to recognize and value upstream quality. ■ Market developed in absence of standards; buyers, donors and policy-makers did not initially prioritize QA/QC due to limited experience with diagnostics QA and lack of consensus on standards for QA. ■ Practical QC technologies do not exist (see above) and are challenging to develop, which limits a country's ability to evaluate quality and increases the cost of QC for manufacturers.¹²⁹ ■ Uncertainty around the proportion of lots that undergo lot testing due to the lack of intelligence (e.g. lot size; order sizes/destination).
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¹²⁸ While the product and lot testing programmes have shaped the market significantly, their focus is limited: product testing demonstrates a manufacturers ability to produce two high-performing batches of RDTs, it does not address ability to manufacture quality batches at scale. Lot testing covers approximately half of the market and it aims to identify major deficiencies; standards are not as rigorous as product testing.

¹²⁹ "Cost" includes the upfront cost of developing/accessing controls, which could be more expensive than routine implementation of QC measures during manufacturing.

Delivery

<p>Uncertainty about consistent uninterrupted supply of quality RDTs. Given current conditions, there is a risk that the quality of tests may suffer and/or that high-quality suppliers might exit the market. While suppliers have generally been responsive to demand and there have been no RDT shortages noted to date, relatively little is known about the quality of RDTs on the market (see above). Furthermore, market conditions have resulted in supplier exit and market consolidation, which increases reliance on a handful of suppliers; quality issues at a single manufacturing site (e.g. product recalls; poor performance in product evaluation) could disrupt the market.</p>	<ul style="list-style-type: none"> ■ Current RDT pricing and resulting margins leave little incentive for manufacturers to produce quality RDTs. ■ The market's inability to value quality at the manufacturing level creates little incentive for supplier investment in manufacturing quality systems. Current procurement practices do not take into consideration quality at the manufacturing level. ■ Market has limited ability to verify product quality and might not detect shortcomings in product quality. No systems for aggregating and reporting of issues. ■ Uncertainty around scale-up manufacturing quality systems commensurate with rapidly scaling production, especially in light of large orders, short delivery time frames and the increasingly consolidating market. ■ Uncertainty about the effects of cost reduction measures, taken by suppliers in response to price competition, on product quality.
<p>Compared to the global need for fever testing, insufficient uptake of diagnostics and concern about potential slowing of scale-up. After a slow start, adoption of RDTs has been rapid in recent years and demand is increasing. However, given the targets for universal access, there still is significant ground to cover to improve delivery of RDTs at public health facilities, in the community and in the private sector. There is also increasing concern about sustaining the pace of diagnosis scale-up in the coming years due to funding challenges. Funding shortfalls could ultimately limit RDT commodity purchasing or programmatic interventions that are critical for ensuring appropriate use of RDTs.</p>	<ul style="list-style-type: none"> ■ Implementation weaknesses, including weak supply chain management, inadequate training of health-care workers, lack of supervision and QA. ■ Insufficient investment in behaviour change communications to increase demand for testing and to improve awareness and acceptance of RDTs. ■ Potential reductions in global funding for malaria that might limit diagnostic test budgets and the scale-up of malaria diagnosis. ■ Lack of information for monitoring progress in diagnostic scale-up and impact on fever management impedes taking corrective action (e.g. refresher training or increased supervision to sites and health workers that are not adhering to protocols). Lack of information due to weakness in reporting and surveillance systems. Information gaps include: estimates of the total "need" for diagnostics compared to current access; patient-level data on testing and treatments; and clarity on donor funding levels for RDTs.

<p>Limited market for quality RDTs in the private sector despite this being a significant market for treatment.</p>	<ul style="list-style-type: none"> ■ Lack of awareness among customers of the benefits of diagnosis and of malaria RDTs. ■ Market prices for RDT (and treatment) is likely unaffordable to some consumer segments. Price distortion of ACTs (due to subsidies in some countries) might reduce consumer willingness to pay for RDTs. ■ Low availability of RDTs in retail outlets due to: low awareness among supply chain actors and retailers; little “pull” from customers; and limited incentives for the private sector supply chains and retailers to stock and sell RDTs. ■ Local regulations might prohibit performing RDTs in the private sector as well as prescribing of treatments for malaria and non-malaria fever. ■ When available, the quality of many RDTs sold in the private sector is unknown. ■ Limited market intelligence and knowledge base upon which to make decisions about investing in and developing these markets.
<p>Inadequate malaria surveillance, in particular, case reporting by facilities, both in terms of completeness and reliability of data. Recent increases in diagnostic capacity present an opportunity to improve data quality and to use this information to more effectively manage programmes.</p>	<ul style="list-style-type: none"> ■ Historically, limited use of malaria diagnostic tests led to low-quality case reporting data,¹³⁰ resulting in de-prioritization of surveillance by programmes, donors and policy-makers. ■ No clear guidance until recent (April 2012) WHO surveillance guidelines released. ■ Need for coordination across different departments in the public health system to improve reporting. ■ Weak implementation systems. ■ Recordkeeping and reporting is often paper based, little use of digital/information technology (IT) solutions.

¹³⁰ For example, health facilities might have reported the number of cases of malaria, but it would not be clear if these were “suspected” cases or “confirmed” cases (or a mix of the two). Reporting suspected + confirmed cases would overestimate the malaria burden.

Availability

<p>No tests for low-transmission/elimination settings to support effective diagnosis and treatment of <i>P. vivax</i> and for pregnant women.</p>	<ul style="list-style-type: none"> ■ Current low prices and market conditions for RDTs are disincentive to R&D. New technologies may be more expensive than RDTs, and it is unclear whether the market will value innovation (i.e. willingness to pay for these products may be low given precedent set by RDT prices.) ■ Lack of TPPs and limited work to better define the needs. ■ Lack of information on the potential demand for new products, demand may be fragmented and less readily predictable for some new product markets. ■ Limited philanthropic and private funding for malaria diagnostics R&D. ■ Malaria diagnostics are complex and costly to develop, in particular, to evaluate performance. ■ Lack of clarity around validation, regulatory and policy requirements for malaria diagnostics as well as the adoption process for global health products create uncertainty and risk at the investment level.
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Acceptability/adaptability

<p>Low acceptance of RDTs, even when available RDTs may not be used, and negative results are often ignored.</p>	<ul style="list-style-type: none"> ■ Low awareness of declines in malaria prevalence and of benefits of diagnosis. Limited data on malaria incidence due to historical lack of diagnostic capacity and lack of investment in surveillance/reporting systems. ■ Difficulty in changing longstanding clinical practices around fever and malaria. ■ Lack of alternative diagnosis for non-malaria fever due to lack of training, protocols and tests to assist with differential diagnosis of fever and commodities for non-malaria fever. ■ Mistrust of RDTs; lack of QCs for RDTs.
<p>Poorly adapted RDTs. While today's RDTs are a great improvement over microscopy in terms of adaptability, there is scope for improvement. There are two main concerns to be addressed:</p> <ul style="list-style-type: none"> ■ RDTs could be more consumer friendly to reduce training needs, improve QA and ease difficulty in switching from one RDT to another; ■ RDT kits may not be well adapted for retail channel sales. 	<ul style="list-style-type: none"> ■ Specifications for improving ease of use and interchangeability have not been systematically developed, validated and communicated. ■ Optimal specifications for test kits sold through retail channels have not been studied or developed. ■ Limited dialogue between RDT users, policy-makers and suppliers. ■ No systems for aggregating information on challenges with existing RDTs to build the case for investment in improvements. ■ Current market conditions limit incentives for investing in improved RDTs.

Affordability

<p>RDT prices in the private sector may be unaffordable, however, current data on market prices and willingness to pay are limited.</p>	<ul style="list-style-type: none">■ Add-on costs (e.g. markups; taxes; transport) throughout the distribution chain.■ Patients who test positive or negative also must be able to afford the appropriate treatment (ACT or alternative).■ Lack of information (e.g. willingness to pay for diagnosis and treatment; markups; pricing) to gauge extent of affordability problem.
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8. OPPORTUNITIES FOR MARKET INTERVENTIONS

There are a number of potential market interventions and opportunities to improve access to malaria diagnostics and contribute to better quality fever management in resource-poor settings. These include initiatives focused on assuring the quality of malaria diagnostic tests, supporting delivery and availability of RDTs in the public and private sectors, assisting the development of new technologies targeting populations for which current technologies are suboptimal, improving the acceptance of RDTs and increasing market knowledge.

This section begins with an overview of market-shaping interventions that are under way, and is followed by a more detailed discussion of new opportunities. This section is not specific to the UNITAID mandate and business model, but rather represents a range of market-based interventions that could be undertaken by different global health actors and stakeholders.

Market interventions: work in progress

There has been a significant increase in malaria diagnostics market-shaping work in recent years. A number of projects that address the market shortcomings described above are already under way or are planned for the near future. The progress is notable; however, in many areas, there is scope for additional work or refinement of existing programmes. Table 6 provides an overview of various market initiatives, many of which have been noted previously in this report.

Table 6. Market interventions under way

Description	Market shortcoming addressed	Lead implementer
Development of private sector markets for diagnosis and treatment	Delivery, Affordability	<ul style="list-style-type: none"> ■ PSI ■ Malaria Consortium ■ CHAI ■ Various pilots and operational research efforts (e.g. ACT Consortium; University of California San Francisco/Society for Family Health; PMI)
Transition product and lot testing to more sustainable business model, including development of recombinant QC panels	Quality	<ul style="list-style-type: none"> ■ FIND ■ WHO
Develop QCs for field use (PCWs)	Quality	<ul style="list-style-type: none"> ■ FIND
RDT harmonization: review of RDTs currently on the market, development of optimal specifications and opportunities for standardization	Adaptability	<ul style="list-style-type: none"> ■ Roll Back Malaria Partnership ■ Institute for Tropical Medicine (Belgium)
ACTwatch II: monitor uptake of ACTs and diagnostics	Market Intelligence	PSI
ACT and RDT forecast	Market Intelligence	UNITAID issued requests for proposal, implementer TBD
Development of TPP elimination diagnostics	Availability	PATH
Development of POC G6PD tests	Availability	PATH
Analysis of the market for malaria RDT raw materials (MABs)	Market Intelligence	William Davidson Institute

Market interventions: new opportunities

Several examples of potential new opportunities for market intervention are described below. While some of these interventions could be acted on immediately, others are medium or longer term. Many of these interventions address multiple market shortcomings. This list is illustrative and not exhaustive. While some potential interventions are well developed, others are approaches that could be considered for further exploration and working up.

Shaping demand to ensure long-term sustainability of market (near term) *Market shortcoming addressed: Delivery*

Malaria RDT prices have declined significantly in the past four years, and several key indicators (e.g. consolidation of the market; exit of suppliers) suggest that there is cause for concern about the long-term sustainability of prices and about the overall health of the market (e.g. product quality; diverse supply base). Although current low prices enable greater access to testing, the risk of disrupted supply of quality RDTs is increasing. Furthermore, the thin margins for RDTs limit incentives for investment in innovation, capacity or quality.

Currently, assuming a minimum set of standards are met, procurement decisions often focus on price, and do not take into consideration other important criteria, including quality and incentives for innova-

tion. Mechanisms to refocus the current competition on price towards a healthier balance of competition on price, quality, innovation and other factors should be explored. Reliance on a few donors presents an opportunity for coordinated action. For example, major buyers might develop more holistic criteria for evaluating bids or consider longer-term supply agreements.

The expected effect on the market would be sustainable affordable prices as well as encouraging suppliers of high-quality RDTs to remain in the market. A healthier market also fosters investment and innovation (e.g. incremental improvements to user friendliness/harmonization of RDTs; investment in developing new markets such as the retail private sector; or new technologies such as tests with improved *P. vivax* LOD).

In terms of public health impact, continued access to high-quality diagnostic commodities is critical to achieving diagnostic coverage targets and to improving case management overall (e.g. targeting of ACTs is only possible with quality diagnostics). Conversations with leading procurers of RDTs suggest that they are or will be reconsidering current practices in the near term.

A number of analyses would shed additional light on this issue and inform response:

- Cost of goods analysis would provide insight into the cost of producing an RDT and sustainable prices for good quality, well-adapted products. However, appreciating the cost to produce a quality test, in a market where quality standards are undefined, will be a challenge.
- Analysis of the degree of similarity and differences between RDTs would provide an appreciation of product interchangeability; likewise, analysis of the programmatic costs of switching RDTs would inform the relative tradeoff between price and switching RDTs.
- Analysis of bids received by major procurement agents would provide additional insight into pricing the degree of consolidation/exclusion of suppliers.

Fund to achieve appropriate RDT/ACT ratios (near and medium term) *Market shortcomings addressed: Delivery, Acceptability, Market Intelligence*

A fund for RDTs and ACTs would have two aims: (i) accelerate the growth in demand for RDTs, thereby correcting the size of the RDT market relative to ACTs; and (ii) generate market information on the “appropriate” ratio of diagnostics (RDTs plus microscopy) to ACTs by location and season. As such, a programme would include two components:

- Funding for procurement of commodities to be accessed by national programmes: for every 1 ACT procured, > 1 RDT would be required (as appropriate for setting). Procurement of ACT and RDTs through this fund would incorporate market-shaping activities to ensure sustainable supply of quality RDTs and ACTs at affordable prices (e.g. demand shaping to ensure long-term sustainability as described above). “Light touch” criteria would be in place to access funding, including demonstrated ability to absorb additional ACTs and RDTs and the existence of programmatic components to support case management, in particular, activities aimed at raising awareness, uptake and adherence to RDTs.
- Funding for market intelligence, including data collection activities that would provide insight into the appropriate treatment to diagnostic test ratio (i.e. what is relative “demand” for diagnosis and ACTs in a particular market and how these will change over time) and would monitor progress towards appropriate case management.

This is primarily a market-expanding intervention for diagnostics (and market inefficiency fixing/expanding for medicines). It also would diversify the concentrated donor landscape and potentially address gaps in coverage as the Global Fund transitions to new models of funding. Assuming that a sizable fund is needed, market-shaping activities also would be implemented to improve the long-term sustainability of the RDT market. The health impact is increased access to appropriate case management, which should reduce the burden of malaria and improve the quality of fever management overall. The additional market intelligence generated through this project would have far reaching impact for both the market (e.g. allowing for more reliable commodity quantifications at the national level and global forecasts) and public health (e.g. allowing programmes to tailor interventions to areas based on need and epidemiology).

Support scale-up of diagnosis in the private sector (near and medium term) Market shortcomings addressed: Delivery, Affordability

The private sector represents a potentially large opportunity to expand access to diagnosis, but is proving to be very complex. Both immediate and medium-term interventions are needed:

- In the near term, additional evidence is needed to inform decision-making and to develop recommendations and guidance. Accelerating the sharing of evidence generated by existing projects is a priority. Second, mapping the information that will become available in the coming year against the list of unanswered questions is needed to identify additional needs. These could be addressed through funding pilots that include extensive monitoring and evaluation components to ensure effective implementation, demonstrate impact and document best practices and strategies.
- Later, as country programmes begin to develop plans for national programmes, additional funding likely will be needed. Given current RDT pricing and limited data on willingness to pay, the need for an RDT subsidy is not clear. However, even without a subsidy, introducing a new diagnostic service likely will require substantial catalytic investment in demand generation activities and supply chain incentives to improve RDT availability. Thereafter, ongoing costs include continuing communications campaigns, training, supervision, waste management, QA, reporting and monitoring and evaluation. All of these components must be considered in programme design and budgeting, although who best performs these functions is an area of ongoing research.¹³¹

This is a market expanding intervention, primarily addressing market inefficiencies that currently limit the access to testing and case management in the private sector. The public health impact is increased coverage of quality case management, which has a primary effect of reducing malaria morbidity and mortality.

Strengthening manufacturing quality (medium term) Market shortcoming addressed: Quality

Possible interventions focusing on strengthening upstream incentives for quality include strengthening of a programme such as WHO prequalification and/or adoption of alternative standards (e.g. revised CE Mark requirements) that focus on the manufacturing-level quality systems. This could be coupled with support to RDT manufacturers (e.g. mock inspections; dossier reviews; onsite technical assistance) to ensure that a number of manufacturers achieve the new standards within a reasonable time frame. In the near term, expansion or adaptation of the product and lot testing programmes to create stronger incentives for quality might be considered as a mechanism for further improving incentives for quality of RDTs. In terms of next steps, interventions in this area need careful planning and coordination, including analysis of current timelines for WHO prequalification and consultation with stakeholders.

This intervention has a market fixing focus, and would encourage investment in quality systems at the manufacturing level. In terms of health impact, the initiative would contribute to improving access to high-quality RDTs, which would bolster acceptance of RDTs and ensure that individuals receive accurate diagnoses.

PCW market introduction and scale-up (near/medium term) Market shortcomings addressed: Quality, Availability, Acceptability of RDTs

Currently, there are no practical and scalable methods for performing RDT QC in the field. PCWs are QCs intended for use at the point of service to confirm that RDTs are working acceptably. FIND has been developing PCWs, which currently are undergoing field trials. The WHO Malaria Policy Advisory Committee is expected to review the evidence from these trials in late 2014 and make a policy recommendation. Assuming a positive outcome, when they are commercially available, a project to catalyse the adoption and scale-up of PCWs would involve funding for their procurement coupled with demand side work (e.g. local policy work; development of usage recommendations; end-user training).

¹³¹ For example, one model being tested has RDT manufacturers undertaking many of these functions (e.g. training; reporting; supervision; waste management), the cost of which will be included in the RDT price. Another model being considered involves contracting with first-line buyers to perform functions such as demand generation and promotion. In other models, many of these activities are taken on by a local NGO or social marketing operation.

This intervention would catalyse the development of a new market, accelerating adoption and scale-up of QCs and creating an incentive for manufacturers to produce controls at affordable prices. In addition, scale-up of controls should increase the currently limited information available on RDT quality in the field (e.g. confirming heat stability of RDTs in actual conditions of use), potentially contributing to increased acceptance of RDTs. In terms of health impact, the initiative would contribute to improving access to high-quality RDTs, which would bolster acceptance of RDTs and ensure that individuals receive accurate diagnoses.

Next steps for a PCW project include: (i) monitoring results of field trials and WHO policy development; (ii) development of a business plan and marketing strategy for PCWs; and (iii) review of any other QC products on the market or in the pipeline.

Market intelligence projects (near term) *Market shortcomings addressed: Delivery, Market intelligence*

The lack of market intelligence in malaria diagnostics leads to uncertainty in the commodity markets, constrains the management of programmes and limits effective monitoring and evaluation. There is a range of activities that would be meaningful to markets and provide public health value. Among them are:

- **Diagnostics access and case management:** data gathering efforts to better appreciate the uptake of malaria diagnostics; what the correct ratio of ACTs to diagnostics (RDTs + microscopy) should be; the extent of appropriate targeting of ACTs; and causes of non-malaria fever.
- **Private sector:** there is scope for a range of work to better inform development of private sector markets—e.g. work around economic and other incentives for retailers to stock and appropriately sell RDTs and ACTs; better understanding of consumer demand, including willingness to pay (based on real data, considering diagnosis and treatment costs); and further insight into effective demand generation/communication strategies.
- **Costs of production:** on the supply side, a cost of goods exercise would inform negotiations around sustainable RDT pricing and enable a better appreciation of the costs associated with implementing robust manufacturing quality systems.
- **Monitoring supply and demand:** stronger systems for capturing and aggregating RDT procurement data (e.g. order size; price; supplier; product type and brand; shipping method) are needed to monitor trends in the market. Because there are over 200 products on the market, monitoring the supply side is challenging. In light of the concentration of funders, improved reporting of donor-supported RDT procurement is a more practical approach. However, currently only about half of the market is reported through available systems.
- **Quality:** there are currently no systems for reporting and monitoring problems (e.g. end-user error; device and components problem) with malaria RDTs. While issues are commonly reported in the literature or anecdotally, these are currently not monitored on a systematic level, making it difficult to assess the extent of the problem and to respond.
- **At the country level,** systems for monitoring usage of diagnostics has potential to improve quantifications and reduce stockouts and wastage for malaria commodities more generally.
- **Unmet needs:** preliminary market analysis of the major unmet diagnostics needs is required to stimulate investment in these areas. Currently, PATH is working on POC G6PD and elimination diagnostics. Analysis of the market for improved *P. vivax* diagnostics and pregnant women would help define these markets.
- **Size of the malaria RDT market:** there is intrinsic uncertainty in malaria estimates, including the number of suspected fevers needing testing, tests performed and positivity rates/incidence, due to historical lack of investment in surveillance systems and weak diagnostic capacity. In particular, country reporting systems are inadequate in many of the highest-burden countries. As a result, several gaps exist related to malaria markets—e.g. estimates of the global need for tests (i.e. number of suspected cases); the number of tests performed (there is a sizable gap in reporting of RDTs sold

as reported by manufacturers and RDTs distributed as reported by national programmes); and the number of confirmed positive cases (malaria incidence).

In general, there is a need to develop market intelligence to facilitate sustainable diagnostics markets and to inform efficient market interventions. From an industry perspective, the lack of information increases the risk associated with this market and limits investment. For example, the case for investment in the development of new products and new markets is difficult to make without adequate information on the potential size of new markets. From a demand perspective, the lack of insight into demand leads to potential mismatches in the volumes of products procured compared to the need. In addition, given the increasing heterogeneity of malaria, tailoring interventions to specific areas/populations is increasingly good value for money; however, currently available information is insufficient in many areas to do so.

Surveillance (near term) Market shortcomings addressed: Delivery, Market intelligence

The scale-up of diagnostics represents a potential paradigm shift for malaria surveillance and programme management, however, at present the potential gains in these areas are not being realized. Currently, diagnostic test results are not plugging into data systems and, therefore, data-driven decision-making is not possible in malaria. Improved data on malaria is critical for programmatic decision-making, especially in a context of increasing focus on value for money. In addition, elimination of malaria is only possible when surveillance systems provide real-time feedback on malaria cases. Although improving malaria surveillance would require significant programmatic work, there likely is scope for market intervention to accelerate adoption of technologies to streamline surveillance activities. Investment in this area would start with understanding the barriers, mapping of potential technical solutions and eventual scale-up of technology solutions to streamline data collection, reporting and analysis. From a market perspective, this intervention focuses on expanding the market for a range of technologies that leverage the data generated by diagnostics. The health impact is potentially far reaching, as improved monitoring and evaluation of case management and surveillance activities becomes possible.

Improving fever management (medium/longer term) Market shortcomings addressed: Delivery, Acceptability of RDTs

One of the primary reasons for poor RDT acceptance is difficulty in managing non-malaria fever. Clinical practice is difficult to change, and the 2010 policy of universal diagnosis represents a major paradigm shift for individuals who have for years been treating fevers presumptively as malaria. In addition, declines in malaria incidence and recognition that many fevers are not caused by malaria have catalysed work to improve the management of fever more broadly.

Commodity access is one of several challenges to improving fever management. Significant programmatic work also will be required to improve outcomes (e.g. refining algorithms for fever; improving referral systems; behaviour change communications; health worker training; supply chain strengthening). Despite the need for programmatic work, it is worthwhile to explore potential market interventions aimed at improving fever management practices and acceptance of RDTs. For example, procurement of key commodities (e.g. RDT; ACT; antibiotics; oral rehydration salts; zinc), combined with market-shaping interventions to improve supply, adaptability and quality of these commodities, could be beneficial. In the longer term, work to develop new products for non-malaria fever indications would start with studies to better understand causes of fever and thereby inform demand for new products or new clinical protocols, as appropriate. This would be followed by development of TPPs, investment in R&D and comprehensive scale-up programmes when products come on the market. Although not a primary focus of this report, work to develop POC fever management diagnostics is under way, but in the early stages of development. Approaches included improved tests for common causes of fever, tests that assist in management of patient (i.e. markers of severity or prognosis) and tests to identify bacterial infections.¹³²

132 WHO informal consultation on fever management in peripheral health-care settings: a global review of evidence and practice. Geneva: WHO; 2013.

Radical cure of *P. vivax* (medium/long term) Market shortcomings addressed: Availability of POC G6PD Test, Adaptability of medicine for radical cure

Vivax malaria is undertreated, primarily due to poorly adapted medicines (primaquine) for radical cure of vivax and the lack of POC diagnostic to rule out G6PD deficiency.¹³³ Difficulties in diagnosing *P. vivax* might also be a factor, as RDTs for *P. vivax* may not be sensitive enough to detect all clinical cases and microscopy quality in typical field conditions often is compromised. POC G6PD tests as well as an improved medicine (tafenoquine) are in development.

There is scope for catalysing market demand and uptake of these new products and, depending on the timing, a combination of interventions spanning the value chain, all aimed at improving radical cure of *P. vivax*, might be considered. Near term, upstream interventions focused on diagnostics might include catalysing the development of improved products for *P. vivax* diagnosis and facilitating market entry of new G6PD tests. As medicines and diagnostics development continues, international and in-country work is needed to establish validation standards and then to expedite approvals, policy endorsements and registrations required for widespread adoption. If a G6PD test were available prior to the launch of tafenoquine, interventions aimed at scaling it up and improving access to primaquine would fix current inefficiencies in access to radical cure; although, ultimately, improved drugs would lead to greater health impact. Once new diagnostics and medicines are on the market, a market-creating programme involving co-funding initial scale-up of POC G6PD tests and treatment across selected countries would aim to reduce prices for G6PD testing (and medicines) through economies of scale and ensure sufficient incentive to invest in manufacturing capacity. In some countries, there would be a significant private sector component of this scale-up. All of these market interventions would need to be supported by significant programmatic work, including training, communications and monitoring and evaluation.

Developments in the *P. vivax* landscape affecting investment in this space that should be closely monitored include:

- POC G6PD test pipeline: one POC G6PD RDT (Care Start by Access Bio) is undergoing evaluations. Other tests are reportedly in the development pipeline, though not as advanced.
- PATH's diagnostics group has been supporting G6PD test development through market landscaping activities, evaluations of existing tests, development of a specimen repository and development of TPPs. Going forward, PATH aims to support and manage the development, clinical evaluation and registration of G6PD tests that inform radical cure treatment decisions.
- Tafenoquine is undergoing clinical trials and would launch in 2017. It is expected that tafenoquine would not be marketed without a quantitative POC G6PD test.

The market impact of a radical cure *P. vivax* programme would include catalysing development of new products for *P. vivax* diagnosis and creating markets for new G6PD tests and tafenoquine. Specifically, the market impact includes:

- creating incentives for manufacturers to invest in the development of new products;
- generating demand and facilitating uptake of new products (through support for local evaluations, policy work);
- improving acceptance of new products by ensuring that quality aspects are adequately addressed during development and commercialization;
- supporting creation of sizable, sustainable markets for new products once they are available.

¹³³ Two medicines are needed to cure *P. vivax* (and *P. ovale*): a drug to treat the blood stage infection (e.g. chloroquine or an ACT) and a drug to treat the liver stage infection that causes relapse. Currently, a 14-day course of primaquine is recommended for relapse prevention; however, it is grossly underutilized because (i) it is not safe for people with G6PD deficiency and POC G6PD screening tests are not available; and (ii) compliance is low due to the length of the regimen. Extremely low utilization of primaquine has two consequences: at the individual level, relapse of a potentially severe illness occurs; and, at the community level, onward transmission of *P. vivax* occurs. A new shorter course drug targeting the liver stage, tafenoquine, is currently being developed by Glaxo/Smith/Kline (2017 launch). Although more acceptable to patients than a 14-day drug, tafenoquine also will be contraindicated in patients with G6PD deficiency and require G6PD testing.

The health impact would be considerable, as *P. vivax* is the most widely distributed species of malaria affecting billions of people. There is a paucity of data on coverage of radical cure, however, experts suggest that primaquine is grossly underutilized. Ensuring radical cure would contribute to reduced morbidity, as relapse will be less frequent. It is also a public good in that radical cure reduces the reservoir of *P. vivax* in the community thereby reducing transmission. Improved coverage of radical cure for *P. vivax* might accelerate elimination of malaria in many countries where transmission has been reduced to low levels and *vivax* is the dominant species.

New high-performing malaria diagnostics (long term) Market shortcoming addressed:

Availability

Priority diagnostic needs for elimination settings include very sensitive POC tests for screening asymptomatic infections. Currently, there are technologies in the malaria diagnostic pipeline that may fit the needs for elimination settings. The extent to which these new products will be relevant depends largely on performance data, cost and the degree to which they are POC (i.e. require minimal training; little operator input; durability). At this point, it is too early in the product development phase to make an evaluation.

One impediment to product development has been the absence of well-defined TPPs and preliminary market information required to inform investment decisions. The PATH DIAMETER project is addressing this gap through development of use scenarios, TPPs and market analysis. TPPs are expected to be complete in mid-2014.

Depending on the timing, interventions to support development of new diagnostics for elimination might span the value chain. As it is early in the product development pathway, immediate interventions include funding or incentives to catalyse investment in product development and operational research to generate more evidence about the role of highly sensitive tests in elimination programmes, which would inform both the market size and policy development. Medium-term interventions would include support for product validation (e.g. access to specimens; field trials networks; development of validation standards and requirements) and for regulatory approvals (e.g. mapping regulatory requirements in target markets). The longer-term need for market interventions is difficult to predict, but once a product is available, support for scale-up might include coordinating procurement across what is likely to be a fragmented market. Interventions to improve the affordability of new products also would be needed, for example, initial co-funding to promote manufacturer investment in capacity until the market reaches the scale at which lower pricing is possible or establishment of mechanisms to consolidate demand to obtain optimal pricing and ensure supply.

Developments in the elimination landscape that are important to monitor include:

- progress of the PATH DIAMETER project;
- WHO GMP recommendations for diagnostics in low-transmission and elimination settings, including updates to the elimination guidelines and recommendations about the role of molecular diagnostics in low-transmission settings,¹³⁴
- a number of groups, including the Malaria Eradication Scientific Alliance, the Global Health Group at the University of California San Francisco and the Malaria Control and Elimination Partnership in Africa (a PATH programme), looking at the effectiveness of elimination approaches and tactics; the outcomes of this research are expected in the next two to three years and may affect the size of the market for new diagnostics.

The expected market impact is creation of a market for a new class of diagnostics to support elimination. The public health impact is substantial in that elimination reduces the total population affected by malaria globally, and access to better tests might accelerate progress towards elimination in countries by making surveillance activities more effective in identifying and responding to the populations that continue to transmit malaria.

¹³⁴ WHO GMP, Malaria Policy Advisory Committee (<http://www.who.int/malaria/mpac/sep2013/en/>).

9. CONCLUSION

Future directions in access to testing, malaria RDT market

While there has been significant progress in the scale-up of malaria diagnostics recently, this report highlights several gaps and opportunities to accelerate access to testing in meaningful ways. Even as malaria burdens decline, testing needs will remain high until the population at risk is reduced to zero. Although 325 million tests were reported in 2011, the need for testing to achieve universal access to malaria diagnosis is estimated to be well over a billion tests per year.

In the coming years, it is likely that the malaria diagnostics market will continue to grow, driven by increasing use of RDTs in the public sector as countries, in particular, those in Africa and South-East Asia, aim to confirm all suspected cases. However, the continued scale-up in the public sector is contingent upon adequate resources, and in 2014 and 2015 it will be important to monitor how changes at the Global Fund affect malaria budgets and diagnostic test demand.

Near-term growth from both the retail private sector and the community level use of diagnostics is likely to be incremental. Although many projects aim to define the optimal strategies for developing these markets, many unanswered questions and challenges must be overcome before these markets reach scale. With respect to the private sector, market intelligence as well as sharing of insights learned through pilots and operational research would accelerate progress.

In light of the intense competition on price and market consolidation, risk of market disruption is currently high, and the long-term availability of quality RDTs is a concern. Efforts to monitor the quality of RDTs and to promote a healthier market (i.e. balance affordable prices with the need for quality and innovation) are urgently needed.

The current market conditions highlight the importance of existing work on quality, which has long been a major concern in malaria diagnostics. The WHO Product and Lot Testing Programmes have improved quality in the public sector, however, there is scope for additional work, including commercialization and scale-up of QC technologies such as PCWs, and stronger incentives for upstream QA systems. Extending the influence of this work to the private sector, as it develops, also will become a priority.

In addition to market shortcomings, several evidence gaps (e.g. how to change clinical practices around fever management; strengthen surveillance systems; develop private sector markets; improve effectiveness of active case detection) must be addressed to optimize the public health impact of malaria diagnostics and to ensure continued growth in access to testing. Ultimately, the pace at which these gaps are addressed will affect the health impact of increased diagnostic capacity, the growth of the market for existing diagnostics and the potential market for new diagnostics.

Role of innovation

Malaria RDTs represent a compelling value proposition: they are disposable, easy to perform, sufficient for clinical diagnosis and, perhaps most important, among the least expensive diagnostic tests available. It is not surprising, therefore, that they are driving the current increases in access to testing, although there is scope for incremental improvement (e.g. improving LOD or harmonization of instructions). While several new malaria diagnostic technologies have come on the market recently, none are replacing RDTs. Rather, the new malaria diagnostics are addressing smaller market segments where RDTs and microscopy have not been adequate (i.e. POC PCR and LAMP) or, in the case of RDT readers, enhancing the role of RDTs.

With respect to unmet needs in malaria diagnosis, major gaps include tests for low-transmission/elimination settings, tests relating to effective diagnosis and treatment of *P. vivax*, and tests for screening pregnant women. In addition, there is an urgent need for technologies for malaria RDT QC. Despite these needs for new technologies, the specifications for new products have not been well defined, nor are the potential markets. With the exception of *P. vivax* testing, few of these markets are likely to be as large as the current market for case management, which is fairly well served by RDTs and microscopy.

While there is a range of products in the development pipeline, current malaria RDT market conditions create a strong disincentive for investment in innovation. Although several new additions to the malaria diagnostic pipeline were noted during research for this report, the development of several existing pipeline technologies has slowed. Limited R&D funding as well as lack of clear pull from the market are the primary reasons for the slowing of progress.

Market intelligence needs

There is also an urgent need for additional data on the malaria diagnostics markets and on the effect that increases in diagnostic testing are having. For example, reported procurement data represent only half of the market. While research and limited programme data suggest that RDTs are having a positive health impact, current information systems are unable to demonstrate large-scale impact or to capture the impact on fever care more generally. In addition, inadequacies in information systems make it difficult to monitor interventions and to identify opportunities for improving value for money through targeting of interventions. Information on potential new diagnostics markets is also underdeveloped.

In contrast to previous decades, today's malaria diagnostics market landscape is very dynamic. Going forward, it will be important to continue to monitor the malaria RDT market and to consider interventions that support growth in access to testing and that ensure long-term sustainability of the market. At the same time, new needs for diagnostics are emerging that are driven by differing epidemiological settings and populations, and linkages with other commodities are becoming more important (e.g. the impact of RDTs on ACT markets). As the needs and potential markets for malaria diagnostics change, a more nuanced approach to monitoring the diagnostics markets will be needed.

ANNEX 1: OVERVIEW OF PERFORMANCE AND OPERATIONAL CHARACTERISTICS OF MALARIA DIAGNOSTICS

This section considers the performance and operational characteristics of malaria diagnostic tests that are typically considered when decisions are being made as to the choice of test. Desirable characteristics for diagnostic tests vary depending on the epidemiology and the goals of testing (e.g. patient management; active case detection). It is unlikely that any one test meets the need of every programme.

Performance characteristics

In malaria diagnostic testing, the performance of the test is of utmost importance. In general, malaria tests are designed to distinguish infected from uninfected individuals. The key performance characteristics are sensitivity, specificity and LOD.

Sensitivity refers to the probability (percentage) that patients with an infection will have a positive result using the test under evaluation, as compared to the result of the reference or “gold standard” test.¹³⁵ As the sensitivity of a test increases, the number of false negatives decreases. In malaria, a high sensitivity has always been important as a missed diagnosis may have serious consequences.

Specificity is the probability (percentage) that patients without the infection will have a negative result using the test under evaluation, as compared to the result of the reference or “gold standard” test. As the specificity of a test increases, the number of false-positives decreases. Due to the concerns about overtreatment and a desire to improve the quality of care, the specificity of a diagnostic test is now becoming a priority for many malaria programmes.

Another parameter often used to describe the performance of malaria diagnostic tests is LOD, which refers to the lowest quantity of parasites that can be detected in a sample.

In terms of performance characteristics for malaria patient management, the *WHO Guidelines for the treatment of malaria* recommend that malaria diagnostics have 95% sensitivity at 100 p/μL.¹³⁶ For screening and surveillance in elimination settings, more sensitive tests are desired. One recent expert group suggested a minimum detection threshold of 20 p/μL and a sensitivity of ≥95%¹³⁷ for these settings.

¹³⁵ The reference, or “gold standard”, is the best available approximation of a true result and is used as the reference method for assessing the performance of other test methods. In malaria diagnosis, thick and thin film microscopy performed by accredited expert microscopists has been considered the gold standard and is commonly used as the reference method when evaluating other malaria diagnostic tests. However, PCR is usually more sensitive for detection and species identification. As such, PCR is often included in evaluations as an additional reference method.

¹³⁶ Guidelines for the treatment of malaria, second edition. Geneva: WHO; 2010 (<http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html>).

¹³⁷ malERA Consultative Group on Diagnoses and Diagnostics. A research agenda for malaria eradication: diagnoses and diagnostics. PLOS Medicine. 2011 January; 8(1):e1000396.

Of note, the WHO product testing of malaria RDTs¹³⁸ employs several alternative measures of malaria diagnostic test performance that are commonly used to describe test performance.¹³⁹ These measures include a panel detection score (also referred to as a detection rate) and a false-positive rate. The panel detection score is a number between 0 and 100, calculated as the proportion of times a malaria test gives a positive result against samples positive for malaria in a panel¹⁴⁰ at a specific parasite density (e.g. four tests at 200 p/μL).¹⁴¹ A false-positive rate is the percentage of all tests of a particular product that gave a positive result when it should not have.

Operational characteristics

In addition to performance, the operational characteristics of a malaria diagnostic test have a significant impact on test adoption and use. Table A1.1 presents several of the key operational characteristics for malaria diagnostic tests.

138 Reports from the WHO product testing of malaria RDTs Rounds 1–4 (http://www.who.int/malaria/publications/rapid_diagnostic/en/index.html).

139 Sensitivity and specificity are only established during field trials of a diagnostic test. The metrics used in the WHO product testing of malaria RDTs are for laboratory-based evaluations.

140 In order to evaluate the ability of a particular test to detect *Plasmodium* antigen, several panels of specimens were assembled for the WHO product testing of malaria RDTs. These panels include wild-type panels comprising *P. falciparum* and *P. vivax* samples derived from infected patients and culture panels comprising *P. falciparum* specimens that were grown in the laboratory.

141 The panel detection score/detection rate is a combined measure of: (i) the ability of a particular test to detect *Plasmodium* antigen in a specimen; and (ii) the consistency of this result across two or more tests (RDTs from the same lot or from different lots). Note that the panel detection score/detection rate is not the sensitivity or the positivity rate of the test.

Table A1.1: Operational characteristics of malaria diagnostic tests

Characteristic	Explanation
Type of technology and format	<p>Type of technology: As described in this report, a variety of technologies and scientific approaches (e.g. ranging from magnification and direct visualization of the parasite; measurement of the light patterns produced by by-products of the parasite; detection of parasite nucleic acid) are possible for malaria diagnosis; each method has advantages and disadvantages in terms of performance and operational characteristics.</p> <p>Format: With regard to testing format, malaria diagnostic tests include disposable tests as well as portable, table top, and large laboratory instruments. For patient management and reactive case detection, disposable and portable formats allow tests to be widely deployed and to reach those who need them, particularly those in remote areas without health facilities. For prevalence surveys, where samples may not be processed immediately but collected and processed at a central laboratory, larger instruments may be acceptable.</p> <p>With regard to instruments, some instruments are designed only to diagnose malaria, while others are platforms that can be used to investigate other diseases and conditions. A platform that has multiple applications may be advantageous, depending the relevance of the other applications to the local setting.</p>
Output	In addition to a qualitative result (positive/negative for malaria), malaria diagnostics could provide other information, including species of the parasite, stage of parasite development and quantification of parasite density. The device can also measure additional parameters such as haemoglobin or other causes of fever.
Turnaround time and capacity	<p>The turnaround time (or time to result) and the number of tests that could be processed at a time and in one day varies greatly. Many of the portable and disposable malaria devices process one sample at a time in a matter of minutes. Larger instruments tend to have the ability to process multiple samples, but could take longer.</p> <p>For patient care, results are ideally available within minutes, allowing for treatment of the patient during their visit. Unless patient volumes are high, devices that process one sample at a time are acceptable and likely to be more efficient for malaria case management. Likewise, for active case detection, it is usually desirable to have an immediate result so that treatment can be administered immediately.</p> <p>For some surveillance activities, samples are collected in the field and processed later. The ability, therefore, to process a number of samples at once (high throughput) is beneficial and a fast turnaround time is less important.</p>
Sample requirements and stability	<p>Common samples used for malaria diagnosis include capillary and venous blood. In addition, the use of alternate sample types (urine, saliva) and non-invasive techniques are being explored.</p> <p>The most common sample collection method for malaria testing is fingerprick blood, collected by pricking the finger (or the heel in infants) with a lancet and capturing blood drops on a slide, filter paper, with a small capillary tube/similar device or directly into a cartridge that will then be used to run the test.</p> <p>For malaria patient management, the sample is usually processed immediately because results are needed rapidly. As a result, long-term sample stability is not a critical operational characteristic. However, for surveillance, stability of the sample could be an important criteria when samples are being collected in the community and then transported to a central laboratory for processing.</p>
Environmental requirements for device and reagents	<p>Malaria is common in tropical and subtropical environments, therefore, the stability of the test and the ability of the device to operate in extreme heat and humidity is critical.</p> <p>Long-shelf life at extreme temperatures is also important due to the nature of supply chains, which, especially in the case of remote areas affected by malaria, can be quite long and poorly controlled.</p>

<p>Protocol complexity</p>	<p>Protocol complexity refers to the number of steps required to collect the sample, prepare it for testing, transfer it to the testing platform, initiate and monitor the testing process and interpret the results.</p> <p>In general, the health and laboratory systems of many areas affected by malaria are overburdened and suffer from shortages in trained staff capable of preparing samples, performing complex tests and interpreting results. In addition, testing is increasingly being performed outside of the formal health facilities by shopkeepers and community workers. Therefore, testing processes that involve simple sample collection, limited sample preparation, require minimal supervision during the testing process and are easily interpreted are advantageous.</p>
<p>Cost per test</p>	<p>Tests must be affordable for those at risk of infection. From an individual patient's perspective, malaria affects the poor disproportionately and their ability to pay for a malaria test is limited. From a public health systems perspective, malaria diagnostic test budgets are growing, but are under pressure. Because so many people live in areas affected by malaria and suffer from fever, many millions of tests are needed on an annual basis. Even as malaria prevalence decreases, the overall fever rate is unlikely to decline rapidly, and testing volume will likely remain high.</p>
<p>Cost per instrument</p>	<p>Similar to the per test cost indicated above, a low cost per instrument is important especially considering the need for widespread deployment of malaria diagnostic tests.</p>
<p>Power requirements</p>	<p>In many situations where malaria diagnostic tests are needed, there might not be a constant source of centrally distributed electricity. Even in large cities power cuts are frequent. Therefore, to avoid the use of expensive generators and devices to stabilize the power supply, tests that do not require power are required. For devices needing power, low-power utilization and the ability to use battery or solar power are advantageous.</p>
<p>Training and technical sophistication</p>	<p>Tests vary in their degree of sophistication and recommended level of training required to collect and prepare the sample, perform the test and interpret the result. A variety of test operators representing a range of skill sets are possible—from highly skilled laboratory technicians to lay persons. However, laboratory human resources shortages are common in many areas of the world affected by malaria, and there is increasing interest in the deployment of malaria diagnostic tests within the private sector or in the patients' home; therefore, techniques that can be performed by lay people are needed. The amount of and differing lengths of time required to train an operator are also important criteria for test utilization and the quality of test results.</p> <p>Related to the technical sophistication of a test and required training is support from a vendor. Often, vendors that offer technical support and training programmes to test operators and those with a local presence are preferred.</p>
<p>Durability and maintenance</p>	<p>For testing platforms that include a portable device, robust construction with durable components and few moving parts is important. Furthermore, the vendor's plan to address non-functioning devices (i.e. will devices be serviced on site or will non-functioning devices be exchanged by the vendor) is often considered.</p>

<p>Infrastructure requirements</p>	<p>People seek care for malaria both within the health system and outside of it. The infrastructure and personnel available within different settings have an important impact on which diagnostic tests are available and most appropriate. Within the health system, there are generally four or five levels of laboratory services.¹⁴²</p> <p>Level I: Primary health post and health centres that predominantly serve outpatients. These facilities might not have formal laboratories, per se, and clean water, refrigeration and electricity might or might not be available. Often these facilities do not have a dedicated laboratory technician, and only a limited menu of diagnostic tests are available (rapid tests, simple microscopic examinations, POC glucose/haemoglobin measurements) with diagnostic testing performed by a nurse or an assistant.</p> <p>Level II: These include district/primary hospital laboratories that serve in-patients as well as outpatients. Usually these facilities will have a laboratory staffed by one or more trained laboratory technicians. In addition to tests performed at Level I laboratories, more sophisticated instruments are often available for full blood counts, chemistry panels and HIV monitoring.</p> <p>Level III: This level includes the laboratories at regional and provincial hospitals. These facilities have dedicated laboratory space, automated analysers and a separate microbiology space, and uninterrupted power supply systems. Formally trained technicians and technologists staff these laboratories.</p> <p>Level IV: These include national and multicountry reference laboratories that possess the infrastructure, equipment, information systems and logistical systems of sophisticated reference laboratories. They play a central role in management of the national laboratory system as well as in surveillance, clinical trials and evaluation of new technologies.</p> <p>Although it varies by country, there are two other important settings where malaria diagnostic tests may be performed: in the community and in the private sector. In some areas, village or community health workers perform malaria diagnosis. These health workers are often lay persons who have one or more weeks of training and receive periodic supervision and resupply from a health facility or NGO. Outside the health system, in the private sector, individuals seek care for malaria within a wide variety of settings and infrastructures and from a wide range of personnel, some highly skilled, others with no formal training.</p>
<p>Results display and storage</p>	<p>The results display on malaria diagnostic tests ranges tremendously. At one end of the spectrum is microscopy, which requires a visual scan for parasites across hundreds of microscopic fields. At the other end of the spectrum is a “positive/negative” readout on a device screen.</p> <p>In general, a simple, unambiguous output is preferred in resource-constrained settings. When the readout is visual or requires interpretation by a human reader/evaluator, an element of subjectivity is introduced to the test and, depending on the complexity of the interpretation, may require additional time and operator training. Automation of results interpretation and display reduces the labour requirement of a test as well as the potential variation between operators.</p> <p>In addition to results display, a variety of functions can be incorporated into testing platforms, including results storage, wireless transmission of results and printing capacity.</p>

¹⁴² Drawn from the Consultation on Technical and Operational Recommendations for Clinical Laboratory Testing Harmonization and Standardization, Maputo, Mozambique, 22–24 January 2008. Geneva: WHO; 2008 (http://www.who.int/hiv/amds/amds_cons_tech_oper_lab_test.pdf).

<p>QA/QC</p>	<p>Quality, including regulatory approvals, product evaluations, availability of controls and external QA programmes, is an important factor in adoption of diagnostic tests.</p> <p>With respect regulatory approvals, the regulatory framework in many resource-constrained countries is often ambiguous and poorly enforced. Often, policy-makers in resource-constrained countries will look to approvals from stringent regulatory authorities (e.g. FDA; CE Mark). In malaria, however, the cost of obtaining FDA approval is often prohibitive, particularly if the testing platform is used exclusively for malaria and lacks other disease applications for which there may be a more profitable developed world market. Even when a technology platform receives FDA approval, this approval is usually for an application other than malaria—the malaria assay itself is unlikely to undergo FDA evaluations. Due to the risk classification system used by the European Union system, the CE Mark requirements for malaria diagnostic tests are currently not very stringent and do not include a full quality evaluation.</p> <p>WHO plays an important role in providing guidance on new technologies. For example, the WHO Prequalification Programme for Diagnostics reviews products and identifies those whose quality is deemed sufficient for United Nations procurement tenders. Many national programmes will look to the WHO Prequalification Programme for Diagnostics in the absence of FDA or similar approvals.</p> <p>With regard to performance evaluations, there is one major programme, the Product Testing Programme for Malaria RDTs, for evaluating malaria diagnostics. However, this programme has been designed for antigen-detecting tests and, therefore, cannot be used by the majority of tests in the development pipeline.</p> <p>The compatibility of a test with any existing, external QA programmes and the availability of QCs from commercial sources or public health laboratories are also important considerations.</p> <p>In general, the availability of a standardized test kit from a commercial manufacturer (as opposed to a protocol developed by a laboratory “in-house” for performing a test) reduces the QA/QC burden on poorly staffed laboratories in resource-constrained countries, especially when deploying a test across numerous sites or in settings where testing volumes are high. A test kit from a reputable manufacturer is more likely to have been through a stringent regulatory review and includes a well-validated testing protocol, QCs and technical support.</p>
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ANNEX 2: TECHNOLOGIES THAT HAVE RECENTLY ENTERED THE MARKET

Table A2.1 LAMP Malaria Diagnostic Kit (Eiken Chemical LTD and FIND)

Platform characteristics	
Type of technology	<p>Bench-top platform using isothermal DNA amplification technology, whereby parasite DNA is amplified at a stable temperature and the by-products of amplification detected using a real-time turbidimeter or visually by fluorescence.</p> <p>The product launched comprises reaction tubes containing dried-down primers and reagents for amplifying parasite DNA, along with positive and negative controls. Although various LAMP methods for detecting malaria have been published in the literature, this is the first commercially available malaria kit for LAMP.</p> <p>In addition to reaction tubes, LAMP requires the following:</p> <p>Sample preparation: several DNA extraction methods are possible. Sample processing kits, the PURE Method kit,¹⁴³ are available from Eiken Chemical LTD. FIND has validated an alternative DNA extraction method, a boil and spin method requiring a centrifuge and taking <10 minutes. Standard operating procedures for both methods are available on the FIND website. Alternative conventional DNA extraction methods are also effective.</p> <p>Amplification requires a heating block. These are available from Eiken or conventional incubators (e.g. PCR thermocyclers) can be adapted.</p> <p>Detection: following amplification, detection may be accomplished through visual or automated methods after 40 minutes reaction time. Most commonly, detection is done: (i) through detection of fluorescence under a UV or blue LED light when sufficient by-products of the LAMP reaction has been formed; or (ii) to eliminate the subjectivity involved in visual detection, an incubator that includes that also measures turbidity (turbidimeter, available from Eiken Chemical LTD) can be used.</p>
Output	Qualitative (positive or negative) result for <i>P. falciparum</i> or <i>Plasmodium</i> (i.e. pan-malaria). <i>P. vivax</i> specific test is under development.
Performance	Clinical evaluation of the LAMP Malaria Diagnostic Kit included a study in Uganda (endemic site) ¹⁴⁴ and in the United Kingdom (travellers), with real-time collection and testing of samples from patients who showed symptoms suggestive of malaria. Compared to nested-PCR, sensitivity and specificity of Pan-LAMP were around 97.0% and 99.2%, respectively, and for Pf-LAMP around 93.3% and 85.0%, respectively. ¹⁴⁵

143 After collection of blood from a fingerprick (or filter paper) the process involves transferring the sample into a lysis tube, boiling and attaching the tube to a purification device, squeezing the device to transfer the processed sample to the LAMP reaction tube using a dropper cap that fits onto the purification device. The procedure takes < 10 minutes.

144 For the Uganda site, technicians had no previous molecular training, and were working in simple laboratory spaces with basic equipment.

145 See two publications: Hopkins H et al. Highly sensitive detection of malaria parasitemia in a malaria-endemic setting: performance of a new loop-mediated isothermal amplification kit in a remote clinic in Uganda. *J Infect Dis.* 2013 August;208(4):645–52; and Polley SD et al. Clinical evaluation of a loop-mediated amplification kit for diagnosis of imported malaria. *J Infect Dis.* 2013 August;208(4):637–44.

Turnaround time/capacity	<p>Time to result is <1 hour, including sample preparation: >10 minutes and 30–40 minutes to run the assay.</p> <p>Current platform (8-well format) processes 6 patient samples at a time plus two controls for one set of primers; approximately 24 patients can be tested per day (four runs per day).</p> <p>A high-throughput platform is in development based on a 96-well format.</p>
Sample needed/stability	<p>A sample of 30–60 µL of whole blood collected from a fingerprick or in a heparin tube. Dried blood spots are also possible, with additional elution step required to prepare sample.</p> <p>Samples are stable at room temperature for a few days and longer-term storage is possible using filter paper or refrigeration/freezing.</p>
Environmental requirements	<p>LAMP reaction tubes are stable for 12 months at <30 °C.</p> <p>There are no temperature or humidity requirements for device operations.</p>
Testing protocol	<p>Sample is processed by boil and spin or PURE method:</p> <p>Boil and spin: (i) transfer 60 uL blood to lysis buffer; (ii) incubate at 95 °C for five minutes; (iii) centrifuge; (iv) transfer supernatant to dilution tube; (v) transfer 30 uL to LAMP reaction tube.</p> <p>PURE method: (i) transfer 30 uL blood to lysis tube; (ii) incubate at 70 °C for five minutes; (iii) transfer sample to the PURE Method Eiken tube; (iv) squeeze tube to mix contents; (v) transfer sample to reaction tube using dropper cap.</p> <p>LAMP reaction:</p> <p>(i) insert LAMP reaction tube into heating block or into turbidimeter to 65 °C for 40 minutes; (ii) read result in real time with turbidimeter or at the end of the reaction by fluorescence.¹⁴⁶</p>
Cost/test	<p>Pricing of approximately US\$ 5 per reaction tube (ex-works) (varies with volume, shipping destination, exchange rates).</p> <p>~US\$ 10 for Eiken Pure Method sample preparation kit.</p>
Cost/instrument	<p>A standard heating block can be used. Heating block = ~US\$ 400–10 000, lower prices may be possible with increasing volumes. Real-time turbidimeter = ~US\$ 10 000.</p>
Power requirements	<p>Instruments require electricity; battery operation is possible.</p>
Training/technical sophistication	<p>Four days training for laboratory technicians; primary skills required include sample collection, biosafety and basic microbiology laboratory skills.</p>
Durability/maintenance	<p>Several heating blocks and turbidimeters are available; maintenance and useful life vary by model.</p>
Infrastructure requirements	<p>Laboratory-based technology appropriate for district hospital level and higher. Potential for field-based use in specific circumstances such as surveys, when technician available.</p>
Result display and storage	<p>Results are qualitative and are typically read visually by fluorescence, or read by turbidimeter and archived using specific software.</p>
QA/QC	<p>CE marked.</p> <p>The reagent kit includes positive and negative controls.</p>

146 Complete standard operating procedures for the LAMP assay, PURE, and boil and spin methods (http://www.finddiagnostics.org/programs/malaria-afs/lamp/standard_procedures/index.html, accessed 29 October 2013).

Table A2.2 Truelab™ micro PCR platform (Molbio Diagnostics: Tulip Group/Bigtec Labs Joint Venture)

Platform characteristics	
Type of technology	<p>The microPCR device is a portable (dimensions: 210 mm × 140 mm × 109 mm, weight: 0.9 kg) real-time PCR device that takes microPCR chips (microchips). In the first generation product, sample preparation is done independently using a semi-automatic device and a disposable cassette. The second generation devices will integrate sample preparation into the device.</p> <p>The core technology used in the platform is fluorescent probe-based real-time PCR. Specific genes from <i>P. falciparum</i> are amplified in a duplex reaction format. The reaction is done in a disposable microchip, with integrated thermal cycling capabilities, to enable faster turnaround time. All reagents are preloaded in a stabilized form on the chip, designed to be user friendly and robust. As the microchips are disposable and self-sealing, the reactants do not come in contact with the device, reducing contamination. The device has real-time fluorescence monitoring capability with a touchscreen/ personal digital assistant (PDA) phone interface for user input and data output. The device is powered by a rechargeable lithium ion battery pack.</p>
Output	Currently, an assay for <i>P. falciparum</i> is available; a <i>P. vivax</i> assay is under development. The result is quantitative.
Performance	Performance evaluation studies have shown that the microPCR is superior to current diagnostic methods such as microscopy and RDT. The sensitivity and specificity are estimated to be >99% with a lower LOD of 2 p/μL of blood.
Turnaround time/ capacity	Time to results 45–60 minutes, including sample preparation, with the microPCR run time of 30–45 minutes per sample. As the sample processing is done in parallel to microPCR, about 12 samples could be analysed in an 8-hour shift.
Sample needed/ stability	A sample of 100 μL of human whole blood, either fingerprick or venous blood, ideally processed immediately after collection. If preservation is required, the specimen can be frozen and stored for up to three days.
Environmental requirements	The individually packed, disposable microchips are stable for one year at 2–30 °C. Device operating requirements: temperature of 15–30 °C and relative humidity 10–80%.
Testing protocol	The first generation of the technology includes a sample preparation stage followed by transfer of the purified sample to the microchip for loading into the device. Steps include: (i) fingerprick/venous blood collection; (ii) transfer of blood to the sample processing device; (iii) transfer of purified sample to the microchip; (iv) load microchip into device and run assay; (v) read result.
Cost/test	Initially, US\$ 15 per test, including sample preparation.
Cost/instrument	US\$ 8000 for the analyser, sample preparation device, printer and micropipettes.
Power requirements	Rechargeable lithium ion battery pack.
Training/technical sophistication	A medium skilled operator could perform the test. The training time expected is one to two days.
Durability/ maintenance	The microPCR device is designed with durability in mind; if repairs are needed, the plan is to swap out non-functional devices for new ones.

Infrastructure requirements	<p>Due to the sample processing steps, the first generation technology is most appropriate for a laboratory setting, e.g. from a basic laboratory in a district hospital to higher levels of the system, where a technician is available to perform the necessary steps. However, it would be possible to use the technology outside of a laboratory at a health clinic or in the community due to its portability and battery power. The second generation platform will integrate the sample preparation, rendering the device more robust for use at even lower levels of the health system.</p>
Result display and storage	<p>The test result is displayed on the device screen. The device stores 5000 test results internally. Results also can be transmitted to remote locations, pushed to a central server in encrypted form for future analysis and disease surveillance through global system for mobile communications (GSM) and WiFi networks, and can be printed through WiFi or an optional Bluetooth printer.</p>
QA/QC	<p>Regulatory/pre-market approvals include:</p> <ul style="list-style-type: none"> ■ licensed by the Directorate of Food and Drugs Administration, Goa, India; ■ Molbio Diagnostics is certified under ISO 13485; ■ malaria test conforms to the CE Mark requirements.

Table A2.3 Fio-net (Fio Corporation)

Platform characteristics	
Type of technology	<p>Fio-net is an infectious disease management solution that combines mobile diagnostics with cloud information services. It aims to improve the quality of diagnostic test processing and case management at the point of service and provide health managers with real-time data for infectious disease surveillance, remote QC of diagnostic testing and remote monitoring of adherence to clinical protocols.</p> <p>The Fio-net system comprises:</p> <ul style="list-style-type: none"> ■ Deki Reader: a mobile universal reader of commercially available RDTs that guides clinical workflow and testing protocols, and captures patient and health worker data (23 cm x 13 cm x 10 cm, photo below); ■ airFio, a secure cloud database that aggregates data transmitted by Deki Readers over the mobile phone network; ■ Spiri, a secure web portal where authorized users can review data, access customizable reports, remotely monitor POC activity and communicate directly with workers at POC. <p>Fio-net can optionally be configured to include Deki Phones and Deki Tablets for use in clinical settings for capturing non-RDT-based diagnostic results.</p>
Output	<p>The Deki Reader provides a digital dataset including:</p> <ul style="list-style-type: none"> ■ interpretation of RDT result; ■ high-resolution image of RDT at time of interpretation; ■ date, time and GPS location; ■ health worker ID and facility ID; ■ patient data: patient ID, demographics, health worker entered responses to custom forms (unlimited fields). <p>Spiri provides automatically generated reports via the web portal. Reports are customizable, but can include RDT test accuracy, worker activity, clinical case management and epidemiological tracking.</p> <p>The system also provides two-way communication between managers and the field is for secure dissemination of clinical protocols, data capture forms, alerts, software updates and messages.</p>
Performance	<ul style="list-style-type: none"> ■ Trials in Colombia and Tanzania demonstrated >98% concordance between the Deki Reader's interpretation of RDTs and that of expert RDT technicians. ■ Sensitivity and specificity are functions of the RDT being read.
Turnaround time/ capacity	<ul style="list-style-type: none"> ■ RDT incubation time is subject to RDT manufacturer's recommendations. ■ Deki Readers can simultaneously process and track up to eight RDTs. ■ While data upload speed largely depends on local mobile networks, Fio-net deployments suggest that the vast majority of data is uploaded within minutes, and ~90% of data uploaded within two hours.
Sample needed/ stability	<ul style="list-style-type: none"> ■ Sample type, volume and stability depend on RDT manufacturer's recommendations
Environmental requirements	<ul style="list-style-type: none"> ■ RDT environmental requirements subject to manufacturer's recommendations. ■ Deki Reader: 5–40 °C and relative humidity 80% for temperatures up to 31 °C (decreasing linearly to 50% relative humidity at 40 °C). Altitude up to 2000 metres.

Testing protocol	<ul style="list-style-type: none"> ■ Run daily QC check on Deki Reader. ■ Auto-detect RDT model and match to specific patient. ■ Prepare RDT and start built-in incubation timer on Deki Reader. ■ Insert RDT for interpretation when prompted. Deki Reader interprets the RDT and provides result (positive, negative, invalid) to operator on screen. Inconclusive result returned if there is evidence of misuse. ■ Patient record automatically transmitted to airFio cloud.
Cost/test	<ul style="list-style-type: none"> ■ Fio-net's pricing model is similar to prepaid cellphone plans, with no upfront capital cost and pricing based on the volume of data transmitted. ■ The range in pricing on a per test basis is comparable to the price of an RDT and includes rental of the Deki units, airFio storage and data aggregation, information services through Spiri, and local training, service and support.
Cost/instrument	
Power requirements	<ul style="list-style-type: none"> ■ Internal battery recharged via power outlet or solar panel. ■ Up to four days of operation per charge. ■ Power supply: AC 100–240 V, 50–60 Hertz, 5.0 V/2.0.
Training/technical sophistication	Designed to be performed by low-skilled health workers. Though not required, basic training typically takes one day.
Durability/maintenance	Ruggedized design survived military drop testing and environmental testing. Water and dust resistant per international IP 53 standard.
Infrastructure requirements	Appropriate for use in community and at health facilities of all levels. Designed for use even in minimal infrastructure settings. Requires SIM card and intermittent access to electrical power.
Result display and storage	<ul style="list-style-type: none"> ■ Results displayed on the Deki Reader's screen and in Spiri web portal. ■ Local storage (i.e. on Deki Reader) of 1000+ records. ■ Records are automatically transmitted when in mobile phone network range. ■ Unlimited cloud storage capacity.
QA/QC	Fio-net is ISO 13485 certified and the Deki Reader is CE marked for use with malaria and dengue RDTs.



Table A2.4 Holomic Rapid Diagnostic Reader (HRDR) (Holomic LLC)

Platform characteristics	
Type of technology	<p>The HRDR is a portable, smartphone-based lateral-flow immunoassay reader. The system utilizes a custom-designed opto-mechanical attachment (127 mm x 35 mm x 64 mm) and smartphone application to digitally read and quantitatively analyse RDTs for a variety of diseases and applications (see photo of reader below).</p> <p>The universal reader accommodates the majority of the RDTs in the market; using its smart tray design, RDTs are manually loaded into the reader attachment without any mechanical components. After loading the RDT, using the opto-mechanical hardware attachment the cellphone camera acquires enhanced raw images of the RDTs. The reader application running on the cellphone processes the images and generates a detailed test report that can be locally stored on the cellphone memory or shared with a secure cloud server.</p>
Output	Qualitative and quantitative output, depends on the type of RDT.
Performance	<p>Sensitivity and specificity are functions of the RDTs being read.</p> <p>The reader provides “trans-visual” sensitivity¹⁴⁷ and lower than 1% coefficient of variation. The reader digitally quantifies minor colour variations on RDTs that are not seen by the human eye, therefore, it can improve the accuracy and LOD.</p>
Turnaround Time/capacity	<ul style="list-style-type: none"> ■ The time it takes to run one test is a function of the incubation time for the RDT being read. ■ The reader processes an RDT in 30 seconds. ■ Assuming RDT incubation time of 15 minutes, the reader could run more than 500 samples per day on battery, more than 900 samples per day with charger.
Sample needed/stability	Sample type, volume and stability are functions of the RDT being read.
Environmental requirements	<ul style="list-style-type: none"> ■ RDT environmental requirements subject to manufacturer’s recommendations ■ Device operates within normal cellphone operating conditions. No reagents or storage requirements.
Testing protocol	Steps: (i) prepare RDT; (ii) attach opto-mechanical attachment to cellphone and start the reader application on cellphone; (iii) insert the RDT into the smart tray of the attachment; (iv) enter data and press “run test”; (v) results displayed on cellphone, including diagnosis and image of RDT. Operator can choose to save result, wirelessly transmit to printer or upload test results to a secure cloud server that collects and organizes the uploaded test results and provides a global real-time spatio-temporal disease map.
Cost/test	Cost of cloud storage and data are highly customizable.
Cost/instrument	US\$ 995 for low volumes and US\$ 500 for higher volumes.
Power requirements	Battery powered (rechargeable). Charging requirements: 100–240 V, 50–60 Hertz 0.2 Amp, or computer USB port (5 V 0.8 Amp).
Training/technical sophistication	Designed to be performed by low-skilled health workers, less than half a day of training required.
Durability/maintenance	The device is expected to last at least five years. The device comes with a warranty and an option to purchase additional warranty. Maintenance is offered by Holomic LLC per the warranty plan in place.
Infrastructure requirements	Appropriate for use in the community and at health facilities of all levels.

¹⁴⁷ Trans-visual sensitivity is a term coined to convey that the reader can quantitatively read RDTs that are not visible to the human eye.

Result display and storage	Results are displayed on the user interface of the smartphone application. Results can be stored on the phone, printed via a Bluetooth printer and uploaded to a remote, secure cloud server. Test results may be viewed on cloud and exported from cloud in an Excel or similar format.
QA/QC	Registered as a Class I medical device. Plans for CE marking by end of 2013 ¹⁴⁸ and moving forward with FDA approval for clinical use with rapid tests in the United States. Holomic LLC and its Quality Management System are certified and comply with the ISO 13485:2003 international standard for medical devices.



148 This information will be verified in the next edition of the Landscape.

ANNEX 3: MALARIA TECHNOLOGY DEVELOPERS AND TECHNOLOGIES IN THE PIPELINE

Parasight (Sight Diagnostics LTD)

Sight Diagnostics LTD (Jerusalem, Israel) was founded in 2010 to develop its computer vision platform for blood analysis and parasite detection. Malaria diagnosis is the first application being developed for the platform. Sight Diagnostics LTD's technology uses a novel sample preparation method with custom-designed and low-cost cartridges to create and stain a standardized "thin blood smear". The cartridge is loaded into the device that scans and analyses a large number of fields, taking high-resolution images. Images are processed using state-of-the-art machine vision techniques, similar to those used in the automotive industry. The first generation device will be a bench-top instrument capable of batch processing; a second generation lower-throughput portable device is anticipated. The company has raised private funding to support the work and conducted a clinical trial of the prototype instrument in India, in collaboration with the National Institute of Malaria Research. Sight Diagnostics LTD expects to launch the product in India in 2014. Other disease applications are expected, including Chagas disease and babesiosis.

Table A3.1 Parasight

Platform characteristics	
Type of technology	The first generation technology is a bench-top device (approximately 50 cm x 40 cm x 40 cm) that uses custom-built disposable cartridges (75 mm x 25 mm) to automate and improve on routine microscopy through a unique sample preparation process and machine vision technology. A special disposable cartridge is used to instantly create and stain a uniform "thin smear" from a drop of blood. The smear-making process requires minimal training and uses a novel stain developed for this technology to improve interpretation of the blood images. The device scans the slide, taking high-resolution images that are then interpreted by a machine vision algorithm. A second generation lower-throughput, portable device is anticipated.
Output	Detection of malaria, differentiation between <i>P. falciparum</i> and <i>P. vivax</i> , quantification of parasitaemia.

Performance	<p>Sensitivity of 99.4% and specificity of 98.0%, based on clinical trial of prototype instrument.</p> <p>Sensitivity of P1 device versus PCR calculated for different parasitaemia ranges</p> <table border="1" data-bbox="440 383 1412 692"> <thead> <tr> <th></th> <th>Sensitivity</th> <th></th> <th></th> </tr> <tr> <th>Parasitaemia range (p/uL)</th> <th>%</th> <th>In numbers</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>100–200</td> <td>50%</td> <td>1/2</td> <td>9.5–91%</td> </tr> <tr> <td>200–500</td> <td>100%</td> <td>7/7</td> <td>72–100%</td> </tr> <tr> <td>500–1000</td> <td>100%</td> <td>14/14</td> <td>83–100%</td> </tr> <tr> <td>>1000</td> <td>100%</td> <td>141/141</td> <td>98.1–100%</td> </tr> <tr> <td>Overall</td> <td>99.4%</td> <td>163/164</td> <td>96.6–99.9%</td> </tr> </tbody> </table> <p>Specificity of P1 device versus PCR</p> <table border="1" data-bbox="440 775 1090 909"> <thead> <tr> <th>Specificity</th> <th></th> <th></th> </tr> <tr> <th>%</th> <th>In numbers</th> <th>95% CI</th> </tr> </thead> <tbody> <tr> <td>98%</td> <td>196/200</td> <td>95–99.2%</td> </tr> </tbody> </table>		Sensitivity			Parasitaemia range (p/uL)	%	In numbers	95% CI	100–200	50%	1/2	9.5–91%	200–500	100%	7/7	72–100%	500–1000	100%	14/14	83–100%	>1000	100%	141/141	98.1–100%	Overall	99.4%	163/164	96.6–99.9%	Specificity			%	In numbers	95% CI	98%	196/200	95–99.2%
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Turnaround time/capacity	<p>First generation device is intended for larger case loads and processes batches of 20 samples (smaller batches are allowed). Each sample takes <5 minutes to process, including sample preparation.</p> <p>Second generation device will be smaller and process one sample at a time.</p>																																					
Sample needed/stability	<p>A sample of 5 µL whole blood, taken either from a tube of intravenous blood (up to 48 hours after collection) or a fingerprick.</p> <p>A low-cost fixed-volume pipette is provided with the instrument to facilitate sample handling.</p> <p>After a sample is prepared, it must be scanned by the device within one hour.</p>																																					
Environmental requirements	<p>No special environmental requirement for the device; device is designed to operate in conditions typical to clinics in India and Europe.</p> <p>Reagent shelf life and refrigeration needs are currently TBD.</p>																																					
Testing protocol	<p>Steps: (i) collect 5 µL of blood from fingerprick or tube using supplied fixed-volume pipettor and deposit into a tube prefilled with a proprietary solution; (ii) load 50 µL of sample using a second provided fixed-volume pipettor into disposable cartridge; blood instantaneously fills the cartridge; (iii) insert cartridge into device (no incubation or additional processing); (iv) result is available in less than five minutes per sample; result is displayed on the screen and communicated to the laboratory information system.</p>																																					
Cost/test	<US\$ 3 per test																																					
Cost/instrument	US\$ 5000–8000																																					
Power requirements	The device can operate using wall power or battery, and is designed to tolerate intermittent power.																																					
Training/technical sophistication	The device can be operated by a lay person, less than one half day training.																																					
Durability/maintenance	The device is designed for a lifetime of five to seven years in the field with annual routine service. Major repairs will be conducted by swapping malfunctioning devices to avoid down time.																																					

Infrastructure requirements	First generation device is bench-top technology, targets health facilities with laboratories and larger patient loads.
Result display and storage	Results are displayed on an integrated computer screen as well as communicated through the laboratory information system (LIS). The device can also store results internally.
QA/QC	CE Mark application in process. Positive controls will be available to ensure instrument is properly calibrated and functioning. In addition, internal computer software performs basic checks with each sample processed.
Availability	2014

Urine Malaria Test (Fyodor Biotechnologies)

Fyodor Biotechnologies (Maryland, US) is developing a urine-based test for the diagnosis of malaria in individuals with fever. It's Urine Malaria Test (UMT) is a one-step dipstick assay that uses immunochromatographic technology to detect malaria proteins or fragments shed in the urine of persons with fever. Originally developed at Johns Hopkins University, Fyodor Biotechnologies licensed the urine malaria test technology in 2008. The first generation product, which detects *P. falciparum* malaria, is in clinical validation stage (<http://clinicaltrials.gov/ct2/show/NCT01921413?term=urine+malaria+test&rank=1>), and expected to be launched in 2014. A second generation product for *P. falciparum* and *P. vivax* malaria diagnosis is in pre-clinical development.

Table A3.2 Urine Malaria Test

Platform characteristics	
Type of technology	Disposable one-step urine dipstick based on immunochromatographic detection of malaria parasite proteins in urine.
Output	First generation product is a two-line test that will differentiate "fever due to <i>P. falciparum</i> malaria" from fever due to some other cause. The results are visible: two lines indicated fever due to <i>Pf</i> malaria; one line (the control line) indicates fever due to other causes. Second generation product (due in 2015) will be a three-line test that detects both <i>P. falciparum</i> and <i>P. vivax</i> malaria.
Performance	The test is designed to detect the presence of malaria proteins or fragments present in urine during fever. Interim analysis of ongoing field trials shows that the test achieves >90% sensitivity and 90% specificity for the detection of <i>P. falciparum</i> malaria. The urine test has an LOD of 125 p/μL blood, comparable to current blood-based RDTs.
Turnaround time/ capacity	Test results are available in 20–30 minutes.
Sample needed/ stability	The device requires about drops drops (100–200 μL) of urine. The test is a real-time test and intended to be performed immediately after sample collection.
Environmental requirements	Stability studies of the urine test have not been completed, however, it is being designed with stability in mind and is anticipated to have a 12-month or longer shelf life and recommended storage conditions of 25–30 °C.

Testing protocol	The urine malaria test is a one-step test with no requirement for sample preparation. The testing protocol is: (i) collect urine sample; (ii) open packaging and dip test into sample; (iii) allow test to dry for 20 minutes; (iv) read results.
Cost/test	US\$ 0.75–1.50 per test.
Cost/instrument	No instrument.
Power requirements	None.
Training/technical sophistication	Test is designed for point-of-need use by lay people and procedures are simple: no sample preparation, no blood draws, no buffers are required.
Durability/maintenance	Not applicable; disposable test.
Infrastructure requirements	No infrastructure required; test is designed for point-of-need use at all levels of the health system.
Result display and storage	Results appear as visible lines on the test strip. No results storage.
QA/QC	Clinical validation study under way, conforming to the ICH Harmonised Tripartite Guideline for Good Clinical Practice and 45CFR46 and 21CFR50, the WHO–FIND–CDC Malaria RDT Product Testing Methods Manual (Version 3), and the abbreviated or non-significant risk provision of the Investigational Device Exemptions (IDE) Regulations (21 CFR Part 812.2(b)). Product manufacturing is done under ISO 13485:2003 standards.
Availability	Expected in early 2014. ¹⁴⁹

¹⁴⁹ This information will be verified in the next edition of the Landscape.

Fluorescent Rapid Diagnostic Tests (Access Bio)

Access Bio (New Jersey, US), a leading manufacturer of malaria RDTs, is developing a lateral flow test that generates a fluorescent signal that will improve on LOD of traditional malaria RDTs. The RDTs are similar in terms of processing and format to traditional RDTs, but are read using a specialized UV reader also being developed by Access Bio. The technology has undergone pre-clinical evaluations and further development, including clinical trials, are on hold pending maturation of market for highly sensitive, POC malaria diagnostics. Access Bio also plans to develop fluorescent RDTs to detect HIV antibodies and chlamydia antigens using the same reader.

Table A3.3 Fluorescent Rapid Diagnostic Tests

Platform characteristics	
Type of technology	Disposable RDTs based on time-resolved fluorescence technology to detect of malaria antigens in samples, RDT results are read using a portable RDT reader. Time resolved fluorescence RDTs are similar in terms of components and reactions to traditional malaria RDTs except that MAbs are coated onto tiny particles that contain europium instead of being attached to colloidal gold. The europium particles fluoresce when viewed with UV light. A portable RDT reader equipped with a UV LED reads the results and converts the fluorescent signal to a digital readout for the user. The reader incorporates a time resolving function to improve sensitivity. The approximate dimensions of the RDT reader are 14 cm x 21 cm x 14 cm (see photo below).

Output	Qualitative and quantitative results for <i>P. falciparum</i> , <i>P. vivax</i> and pan-malaria. Several types of RDTs will be available (e.g. two-line; three-line) to detect <i>P. falciparum</i> , <i>P. vivax</i> , pan-malaria and HRP-II deleted <i>P. falciparum</i> .
Performance	Pre-clinical studies suggest that the technology may be >100 times more sensitive than traditional RDTs.
Turnaround time/capacity	Test results are available in 15 minutes.
Sample needed/stability	For a blood sample: 5 µL whole blood from fingerprick or venipuncture. For a urine sample: sample quantity TBD, likely two to three drops.
Environmental requirements	RDTs are expected to have a 24-month shelf life with recommended storage temperature of 4–30 °C.
Testing protocol	Testing protocol: (i) collect blood sample; (ii) transfer 5 µL of blood to RDT; (iii) add two drops of buffer; (iv) wait 15 minutes for reaction to occur; (v) insert test into RDT reader and view results.
Cost/test	Targeting US\$.75–1.00 for a single-line test.
Cost/instrument	Targeting US\$ 500–1000 per instrument.
Power requirements	RDT reader is battery operated with a charger.
Training/technical sophistication	Designed to be performed by low-skilled health workers, less than one half day of training required for new test operator.
Durability/maintenance	RDTs are disposable. RDT reader is expected to last at least three years under normal operations. Non-functioning readers will be swapped out.
Infrastructure requirements	Appropriate for health facilities at all levels.
Result display and storage	Results appear on the RDT reader screen. Capacity for printing, storage of results in the device and wireless transmission of results can be built into the device.
QA/QC	Access Bio plans to submit the product to the WHO Prequalification Programme for Diagnostics.
Availability	Pre-clinical evaluations complete, further development on hold pending maturation of market for highly sensitive POC malaria diagnostics.



PanNAT™ Malaria Assay (Micronics)

Micronics, a Sony Group Company, is developing the PanNAT™ Assay system, a fully automated PCR system with primers, molecular beacon fluorescent probes and all other reagents contained within a microfluidics cartridge. Processing involves collection of a fingerprick blood sample on to a disposable cartridge that is inserted into the device. Among the assays being developed for the system is a malaria test, the PanNAT™ Malaria Assay. It has been developed in the laboratory, but has yet to undergo field trials.

Table A3.4 PanNAT™ Malaria Assay

Platform characteristics	
Type of technology	The PanNAT™ system combines microfluidics and PCR techniques into a portable machine (12 x 12 inches). It uses disposable microfluidics cartridges (4 x 3 inches). All sample preparation, amplification and detection occur in the cartridge once inserted into the PanNAT™ device. In this design, as the sample moves through the cartridge containing reagents, the reactions occur. The process combines silica membrane DNA capture, PCR-based amplification and end-point molecular beacon fluorescence detection. The PanNAT™ device provides for the on cartridge fluid movement, heat cycling, optical detection and result interpretation software.
Output	Qualitative result for <i>Plasmodium</i> genus (i.e. pan-malaria) and <i>P. falciparum</i> malaria.
Performance	Analytical detection of 5–10 p/μL compared to 50–100 p/μL for microscopy or RDTs.
Turnaround time/ capacity	~30 minutes per sample; one sample processed at a time.
Sample needed/ stability	A 50 μL fingerprick whole blood sample.
Environmental requirements	Cartridges will be stable for two years at room temperature.
Testing protocol	Steps: (i) collect fingerprick blood sample; (ii) transfer sample to cartridge using a capillary tube; (iii) insert cartridge into PanNAT™ device to initiate the test; (iv) wait 30 minutes to read results. Note: it may be possible to lance the patient's finger and collect blood sample directly onto the cartridge.
Cost/test	Targeting US\$ 3–4 per test.
Cost/instrument	Targeting <US\$ 1000–4000 per instrument.
Power requirements	Instrument designed to run for eight hours on battery, recharged with AC mains electricity, a car battery or inexpensive solar panel.
Training/technical sophistication	Designed to be performed by low-skilled health workers. Approximately one half day of training would be required to operate the device.
Durability/ maintenance	The device has maintenance-free design. Non-functioning devices will be exchanged by the company.
Infrastructure requirements	Device is designed to be used anywhere, including rural settings and health facilities.
Result display and storage	Results are displayed on an LCD screen. The PanNAT™ device is Wi-Fi enabled and can store up to 350 test results before prompting the user to download or delete the results.
QA/QC	The PanNAT™ platform will have FDA approval; approvals for the malaria assay are TBD. Each assay contains bplexed endogenous internal positive controls within the cartridge.
Availability	TBD. Developer has not established timeline for completing development of the malaria assay.

NALFIA (DIAGMAL Consortium)

DIAGMAL¹⁵⁰ is a consortium developing a molecular test for detection of malaria that is more readily adapted to resource-constrained settings than traditional PCR methods. The DIAGMAL assay includes several simplifications to traditional PCR methods: (i) the assay is a direct PCR, meaning it uses whole blood and does not require any sample preparation; (ii) after performing traditional PCR amplification, detection of DNA is done using a disposable lateral flow test device, the NALFIA; and (iii) a commercial kit will contain all of the necessary primers, reagents and the lateral flow device required to run the test. After successful published proof of concept laboratory evaluations and field evaluations in Burkina Faso and Thailand,¹⁵¹ the assay is now being further studied in Kenya.

In the coming year the developers will be fine-tuning the product, improvements include: optimizing the amplification process, stabilization of the reagents and development of a closed unit for transfer of the amplified products to the NALFIA stick to reduce potential contamination leading to false-positive reactions. After laboratory evaluations, it will undergo additional trials in endemic settings. The developers expect to submit to the WHO Prequalification Programme for Diagnostics.

Table A3.5 NALFIA

Platform characteristics	
Type of technology	Commercial PCR kit containing primers, reagents and the lateral flow device required to run the test. Direct PCR method, no purification of whole blood sample required. Amplification is performed on a traditional PCR thermocycler, followed by detection using a disposable NALFIA. The primers used in PCR process have ligands attached; antibodies on the NALFIA bind to the ligands.
Output	The output is qualitative. A variety of primers that detect <i>Plasmodium</i> genus (i.e. pan-malaria), <i>P. falciparum</i> , and <i>P. vivax</i> malaria are anticipated. An internal amplification control will be included. The NALFIA is a generic strip that can detect up to three different items, depending on the combination of primers used, allowing for customization of the assay and flexibility depending on needs.
Performance	To date, trials have shown sensitivity and specificity that is comparable to traditional PCR-based assays.
Turnaround time/capacity	One hour to process a sample from start to finish; possible to process 96 samples per hour, or around 400 per day.
Sample needed/stability	A 1 µL fingerprick whole blood sample. Samples are stable at room temperature for a few days, longer term storage is possible with refrigeration or freezer storage.
Environmental requirements	The NALFIA are expected to be stable for several years at 30 °C. Storage requirements for reagents and test kits is 4 °C.

150 DIAGMAL Consortium, funded through a European grant: translation of the direct-on-blood PCR-NALFIA system into an innovative near POC diagnostic for malaria is coordinated by the Royal Tropical Institute in Amsterdam, the Netherlands (leading scientific and evaluation work). Partners include: Foresite Diagnostics in the United Kingdom (lead for manufacturing the NALFIA strip); Q-Bioanalytic in Germany (leading work to optimize amplification process, stabilize reagents); and Global Innovation Network in Finland (leading work on development of a closed system for amplification and transfer to the NALFIA).

151 See two sources: Mens PF et al. Direct blood PCR in combination with Nucleic Acid Lateral Flow Assay for the detection of *Plasmodium* species in malaria endemic settings. *J Clin Microbiol.* 2012;50(11):3520–5; and Mens PF et al. Development, validation and evaluation of a rapid PCR-Nucleic Acid Lateral Flow Immuno-Assay for the detection and differentiation of *Plasmodium* species. *Malar J.* 2012;11:279.

Testing protocol	The test involves: (i) collection of a fingerprick blood sample; (ii) transfer into tubes containing primers for PCR; (iii) insertion of the tube into the PCR instrument; (iv) after 40–50 minutes transfer of PCR product to lateral flow test strip using pipette; (v) wait five minutes for reaction and read results.
Cost/test	Final prices have not been determined; target prices for kits is approximately US\$ 2.
Cost/instrument	Several PCR instruments are available and cost varies depending on the instrument selected.
Power requirements	The detection system requires no power; PCR amplification instruments require a stable source of AC mains electricity.
Training/technical sophistication	The test requires several steps, and should be performed by a trained laboratory technician. The primary skills required include pipetting. Approximately one to two days of training would be needed to train operators.
Durability/maintenance	The NALFIA is a disposable device. Several PCR instruments are available; useful life and maintenance requirements vary by model.
Infrastructure requirements	The technology requires a well-equipped laboratory with refrigerator (4 °C) and stable electricity as well as trained technicians. Therefore, it is most suited for regional and reference-level laboratories.
Result display and storage	Results are read visually. Disposable device, no storage capacity (though the used device can be stored for later reference).
QA/QC	WHO prequalification is expected. The kits will be manufactured in conformance with ISO 13485 standards. The NALFIA has a control line that indicates that the amplification was successful and that the lateral flow strip is functioning properly.
Availability	Launch of commercial kit targeted for 2017; although kits will be available for research use only in next one to two years.

Dark-Field Cross Polarization (DFxP) (Intellectual Ventures)

Intellectual Ventures (Seattle, US), a privately held company focused on inventions, was founded in 2000 by former senior executives at Microsoft. Intellectual Ventures is developing a hemozoin detection device, called Dark-Field Cross Polarization (DFxP). The technology combines, optimizes and automates two methods: dark-field and cross polarization microscopy. DFxP has several advantages over either method on its own: in terms of performance, the signal to noise ratio of the combined system is 50. On their own, both dark-field and cross polarization microscopy require a trained user who can identify haemozoin crystals. The DFxP system produces automated images of haemozoin that are significantly easier to interpret using image-processing software.

An external investor-funded “Global Good Fund” supports the work of Intellectual Ventures to develop technologies and products for developing world settings, including several malaria technologies. In 2012, the technology was undergoing field studies and additional design work; an up-to-date timeline for commercialization is not available.

Table A3.6 Dark-Field Cross Polarization

Platform characteristics	
Type of technology	DFxP is an automated microscope-based device that uses a dark-field illuminator and cross polarizers to capture the scattered and depolarized light from hemozoin. ¹⁵² After loading a fingerprick blood sample in a disposable sample chamber into the device, the DFxP microscope screens many different fields of view using a dark-field illuminator and cross polarizers; an image processing software identifies and quantifies hemozoin crystals present in the sample. Final form has not been engineered, however, the developers expect the device to be both compact and portable. The device uses disposable sample collection chambers.
Output	Device provides a quantitative result for hemozoin content, which in preliminary laboratory studies is correlated to parasitaemia. The device does not differentiate between species.
Performance	In preliminary laboratory studies, the detection limit for infected red blood cells is 1–5 parts per million, equivalent to 5–25 p/μL.
Turnaround time/ capacity	<3 minutes. Hundreds of scans per day possible.
Sample needed/ stability	Current prototype uses 20 μL blood from a fingerprick, possible that future versions will require less blood.
Environmental requirements	The device does not use reagents; no need for cold chain. The device components are also expected to be highly stable in hot and humid conditions.
Testing protocol	Steps: (i) collect fingerprick blood sample (<20 μL blood) into disposable sample collection chamber; (ii) insert chamber into device and press start; (iii) wait three minutes to read results.
Cost/test	Competitive with current RDTs.
Cost/instrument	Unknown at this time. Targeted for field availability.
Power requirements	Planned to be battery powered.
Training/technical sophistication	Device is intended to be used by low-skilled health workers, less than one half day training required to operate the device.

152 Hemozoin is a byproduct of the malaria parasite's consumption of haemoglobin and its presence in peripheral blood indicates infection with malaria.

Durability/ maintenance	Device is still in the prototype phase and is being designed for rugged field conditions.
Infrastructure requirements	The device is intended for use out in the community as well as in health facilities at all levels.
Result display and storage	Final form has not yet been designed. Results likely to be displayed on an LCD screen.
QA/QC	Regulatory approvals TBD once commercial partner has been selected. Device QA/QC TBD.
Availability	Not available at this time.

Magneto-optical Technology (MOT) (University of Exeter)

The MOT development is led by the University of Exeter in the United Kingdom.¹⁵³ The MOT test is based on hemozoin detection and is designed to be a portable rugged POC device, suitable for low-skilled health worker use and priced to compete with microscopy and RDTs. The project began in 2005 and was funded first by the European Commission and subsequently by the Bill and Melinda Gates Foundation. A prototype has undergone laboratory studies and a small-scale manufacturing run was completed in 2012 to support preliminary field studies in Sierra Leone and Thailand.

Currently, the intellectual property for MOT is owned by Exeter. Commercialization will occur through licensing of the technology to a commercial partner or by spin-out of a company from the university.

The first generation device uses a fingerprick blood sample, a second generation technology aims to be non-invasive, taking measurements through the fingernail and removing the need for blood samples. An early prototype of the second generation instrument has been evaluated in Kenya; additional engineering design work is under way to miniaturize the device (although in its final form it may be the size of a large shoebox) and to speed up the patient interface and processing time, as the existing device requires the patient to remain still for > 1.5 minutes.

Table A3.7 Magneto-optical Technology

Platform characteristics	
Type of technology	<p>The MOT device is portable (about the size of a credit card machine that can be brought to a table) and uses disposable sample cells.</p> <p>The technology is based on detection of hemozoin¹⁵⁴ and takes advantage of two properties: (i) hemozoin crystals are weakly magnetic because they are derived from haemoglobin and contain iron; and (ii) due to their shape, hemozoin crystals have unique optical properties.</p> <p>The MOT test involves applying a magnetic field to a sample, causing alignment of any hemozoin crystals present.¹⁵⁵ The device then employs polarized lasers to compare the transmittance of light before and after application of the magnetic field to the sample. A photo-detector in the device measures the change in transmittance of light that would indicate the presence of hemozoin and a microprocessor interprets the change in light and provides the result to the test operator.</p>
Output	<p>Readout is a qualitative result for the <i>Plasmodium</i> genus (e.g. pan-malaria), does not differentiate between species.</p> <p>Device also quantifies the hemozoin content, which, based on preliminary laboratory studies is correlated to parasitaemia levels. Future field trials will look at correlation between hemozoin and parasitaemia levels, and the commercialized device may include an optional quantitative readout.</p>
Performance	<p>Targeting >90% sensitivity and specificity at 100 p/μL. Improvements to LOD are theoretically possible; however, cost of final product will increase with use of more sophisticated technologies.</p>
Turnaround time/capacity	<p>One minute per sample; one sample processed at a time.</p>
Sample needed/stability	<p>A sample of 50 μL fingerprick blood. The sample is meant to be processed immediately, under laboratory conditions settling of the blood starts to occur after about 15 minutes.</p>

153 MOT was originally developed in collaboration with several partners, including the University of Coventry (United Kingdom), the University of Uppsala (Sweden), the Royal Tropical Institute (Netherlands) and the companies Philips Research Eindhoven, Metis Instruments, and Euroad.

154 After invasion of malarial parasites into red blood cells the parasites digest haemoglobin. The heme component is toxic to the parasite so it converts it into hemozoin, which are rod-shaped crystals.

155 This phenomenon is called the Cotton-Mouton effect, in the absence of a magnetic field the hemozoin crystals orient randomly.

Environmental requirements	<p>The device uses standard electronic components and is designed to operate in tropical conditions. The device case will be hermetically sealed, with the exception of the sample space.</p> <p>The device uses a disposable sample cell and a lysing agent, neither of which requires cold chain storage.</p>
Testing protocol	<p>Steps: (i) collect fingerprick blood sample (50 µL); (ii) transfer sample to disposable sample cell; (iii) add lysing agent (50 µL); (iv) insert sample cell into device; (v) read result in one minute.</p> <p>Currently, fingerprick blood sample and lysing agent are pipetted into the sample cell, additional work and field studies will aim to simplify this process, perhaps by including lysing agent in disposable sample cell and collecting blood directly into sample cell.</p>
Cost/test	Targeting <US\$ 0.05 for disposable sample cell and lysing agent when mass produced.
Cost/instrument	Targeting <US\$ 500 per device.
Power requirements	The device uses a lithium iron cell battery capable of performing >50 measurements with one charge; likely that commercialized device will perform >100 measurements and will include a solar charger.
Training/technical sophistication	Device intended to be used by low-skilled health workers, major skill required is sample collection and transfer to device. Approximately one half day training required to operate the device.
Durability/maintenance	<p>Device is designed for rugged field conditions; expected to last more than years.</p> <p>A “dummy” sample cell that will be used to calibrate the instrument periodically.</p> <p>Non-functioning devices will be exchanged.</p>
Infrastructure requirements	Device is intended for use in the community as well as at all health facility levels.
Result display and storage	<p>LED readout for results.</p> <p>GPS and mobile communications technology may be built in, enabling remote diagnosis and software updates.</p>
QA/QC	<p>The approach to quality/regulatory approvals is TBD. Blinded field trials are planned in collaboration with well-respected malaria laboratories.</p> <p>Dummy sample cells will be used to calibrate the instrument. In addition, self-checking routines are likely to be included in the operational software of the microprocessor.</p>
Availability	Timeline unavailable at this time.

Rapid Assessment of Malaria (RAM) Device (Disease Diagnostic Group LLC)

Disease Diagnostic Group LLC (DDG) (Ohio, US) is an early stage start-up company that is developing a portable hemozoin detection system called the Rapid Assessment of Malaria (RAM) Device. The device detects hemozoin by applying a magnetic field to the sample, which aligns any hemozoin crystals present and measures light transmittance through the sample. The device is designed to be inexpensive, yet robust, using readily available electro-optical components and injection molding manufacturing. Disease Diagnostic Group LLC has licensed the technology from Case Western Reserve University and has partnered with its School of Medicine on field studies using a miniaturized prototype device in Peru. The project is funded through the Case-Coulter Translational Research Partnership, Ohio Third Frontier, and the National Collegiate Inventors and Investors Alliance.

Table A3.8 Rapid Assessment of Malaria Device

Platform characteristics	
Type of technology	<p>The RAM device is portable (2 x 3 x 4 inches) and uses disposable plastic cuvettes (.5 x .25 x 1.75 inches).</p> <p>The technology is based on detection of hemozoin¹⁵⁶ and takes advantage of two properties: (i) hemozoin crystals are weakly magnetic because they are derived from haemoglobin and contain iron; and (ii) due to their shape, hemozoin crystals have unique optical properties.</p> <p>The RAM device applies and releases a strong magnetic field to a fingerprick blood sample to align any hemozoin present in the sample. A laser in the device illuminates the sample and detectors on either side of the sample measure the relative light transmission. Light passing through a liquid containing hemozoin that has been aligned by a magnetic field is attenuated. The resulting diagnosis is displayed on an LCD screen for the test operator.</p>
Output	Qualitative result for <i>Plasmodium</i> genus (e.g. pan-malaria, does not differentiate between species). The LCD screen readout includes the raw amount of light transmission, the amount of hemozoin present, and estimated parasitaemia.
Performance	The proof of concept laboratory study indicated 97% sensitivity, and 81% specificity as compared to PCR.
Turnaround time/capacity	Less than one minute per sample, one sample processed at a time.
Sample needed/stability	Fingerprick blood sample (50 µL) is collected directly into a plastic cuvette. Samples are stable for more than months.
Environmental requirements	The current device is expected to maintain documented efficacy up to 40 °C. There is no reagent in the cuvette and, therefore, no refrigeration requirement and unlimited shelf life.
Testing protocol	Steps: (i) collect fingerprick blood from patients finger directly into disposable cuvette; (ii) add water (lysing agent), cap and invert cuvette; (iii) insert cuvette into RAM device and press test button; (iv) read result in less than minute.
Cost/test	Targeting US\$.25 for disposable sample collection cuvette.
Cost/instrument	Targeting US\$ 2000 for the RAM device.
Power requirements	Two rechargeable lithium ion batteries. Device is designed to minimize power consumption and also has a universal charging port located on the exterior. One full charge will last up to 40 hours of testing or over 2400 tests.

¹⁵⁶ After malarial parasites enter red blood cells, the parasites digest haemoglobin. The heme component is toxic to the parasite so it converts it into hemozoin which are rod-shaped crystals.

Training/technical sophistication	Device intended to be used by low-skilled health workers with less than one half day training. The LCD display and button form a user interface that serves as a step-by-step guide to usage. In the future, audible instructions will be provided, lowering the technical sophistication further.
Durability/maintenance	Device is expected to last for approximately 200 000 samples and be replaced if a certain test or time threshold is not reached before failure.
Infrastructure requirements	The RAM device is for use in the field/community as well as at all levels of the health system. It was designed for low-resource settings and has no supplementary requirements.
Result display and storage	Results are displayed on an LCD screen and can be downloaded through use of a USB cable to either a smartphone or computer. Units will have Bluetooth capabilities and built-in storage. Future RAM devices will have the capacity to support malaria surveillance activities, for example, to capture additional patient data, communicate with remote databases and to provide GPS location. Access to the software application and database system would be an additional monthly cost to users.
QA/QC	Manufacturer will provide RAM Calibration Q-vets, for administrators to run once daily to confirm device is working properly and has maintained accuracy. An LED on the exterior alerts the user that the internal components are functional and that the device is on. WHO prequalification is planned. Will be manufactured in conformance with ISO 13485:2003 and ISO 9001: 2000 standards.
Availability	Final product available in 2015; beta units available in 2014.

SpectraWave and SpectraNet (Claro Scientific)

Claro Scientific (Florida, US) began operations in 2006 to commercialize SpectraWave and SpectraNet, a reagent-less POC diagnostics system based on optical profiling technology. The system has broad applications, among them malaria diagnosis and complete blood count assays to improve malaria and anaemia care.

The Claro Scientific system comprises (i) the SpectraWave instrument for sample preparation, multidimensional spectral analysis and transmission of the sample data file; and (ii) SpectraNet, a computer software and database system that analyses, interprets and stores the sample data and delivers the results to the test operator. The technology takes advantages of several optical analysis methods to collect up to 1 million quantitative data points about the sample. The software then analyses the sample data profile using an integrated interpretation model, based on studies conducted with the University of South Florida on the physical and chemical changes to red blood cells and parasites that occur during the course of malaria infection. Claro Scientific also has partnered with OneBlood (formerly Florida Blood Services) to develop technologies capable of providing complete blood count analysis. In addition to the malaria and anaemia assays, Claro Scientific is developing technologies for other applications including: diagnosis of hospital acquired bacterial infection; dialysis; urine parameters; and blood culture capability (the latter requires modified instrumentation).

Table A3.9 SpectraWave and SpectraNet

Platform characteristics	
Type of technology	<p>The Claro Scientific integrated diagnostic system combines two technologies: (i) the SpectraWave instrument for whole blood sample preparation, multidimensional spectral analysis and transmission of the sample data file; and (ii) SpectraNet a computer software and database system that analyses, interprets and stores the sample profile and delivers results.</p> <p>SpectraWave is designed to be portable. An early prototype, built from off-the-shelf components, fits in a case (approximately 18 x 10 x 6 inches). The final fully integrated device is intended to be a significantly smaller, handheld device (approximately the size of three cellphones stacked together).</p>
Output	<p>Parameters measured include:</p> <ul style="list-style-type: none"> ■ malaria: detection of malaria; speciation of malaria parasite; identification of the life-cycle stage of the parasite; quantification of infection (% of red blood cells); ■ blood count parameters: haemoglobin; hematocrit; mean corpuscular volume; mean corpuscular haemoglobin concentration; red blood cell count; white blood cell count; differentials; platelet count; ■ monitoring of drug effectiveness (proof of concept).¹⁵⁷
Performance	<p>Malaria LOD is currently ~200 p/μL of blood although Claro Scientific expects to achieve lower LOD through optimization of sample preparation and inclusion of data collected using additional optical methods (angular scattering and fluorescence data).</p> <p>Blood count parameters perform within the acceptable ranges for automated systems currently on the market.</p>
Turnaround time/capacity	<p>Less than 5 minutes per sample. Initial platform will analyse one to five samples at a time. Technology will be scaled into instruments capable of multiple sample analysis in future.</p> <p>Process 96 samples per day (assumes an 8-hour day, including sample preparation).</p>
Sample needed/stability	<p>A 100 μL blood sample from a fingerprick or venous puncture.</p> <p>Sample is directly injected into SpectraWave and diluted in 1 mL saline.</p> <p>A sample from a fingerprick needs to be analysed immediately; venous sample from an EDTA tube must be analysed within 24 hours.</p>
Environmental requirements	<p>The platform does not require any reagents.</p> <p>Components are highly stable and designed to withstand wide variation in temperature and humidity.</p>
Testing protocol	<p>System start up will provide onboard diagnostic checks of both the sample preparation and the spectral acquisition hardware and software. Daily start-up takes less than three minutes to complete.</p> <p>The testing protocol is: (i) collection of fingerprick/venous blood sample; (ii) load sample through the intake port on the system; (iii) press the start button; (iv) read results. All sample preparation and analysis will take place without further operator intervention.</p>
Cost/test	<p>The system has been developed to operate without reagents and consumables to manage the cost per test to below US\$ 0.50.</p>
Cost/instrument	<p>US\$ 10 000–15 000.</p>
Power requirements	<p>Direct source 12 V or rechargeable battery</p>

157 Serebrennikova YM et al. Spectrophotometric detection of susceptibility to antimalarial drugs. *Malar J.* 2013 August;12(1):305.

Training/technical sophistication	All testing can be performed by a lay person, with minimal training less than one half day.
Durability/maintenance	<p>SpectraWave is designed to provide a long service life due to robust components and little to no moving parts. Based on current prototypes and component selection criteria, the system is expected to last more than five years.</p> <p>Claro Scientific will have a combination of a cross-shipping policy for units that are non-functional and onsite training for minor system issues and maintenance. SpectraWave also will have onboard internal system diagnostics that run upon start-up each day. This will identify and resolve any system issues that arise. In addition, these diagnostics will allow remote access to SpectraWave that Claro Scientific and end-users can use to resolve issues quickly.</p>
Infrastructure requirements	The platform has been designed to be robust, fully automated and easy to use and is, therefore, appropriate for use at all levels of the health system.
Result display and storage	<p>Results will be displayed in a format relevant to the test being conducted (e.g. positive or negative for infections; numerical counts for red blood cells).</p> <p>Results will be shown on the SpectraWave screen, have the ability to be printed using an onboard printing system, or transferred electronically to another device (e.g. via USB drive; Internet connection; laboratory information system).</p> <p>Optical profiles can be stored in SpectraNet for patient monitoring, epidemiological analysis and rapid development of new tests.</p>
QA/QC	<p>SpectraWave will have its own onboard QA/QC systems that will ensure proper operation and self-calibration. In addition, these systems will keep an internal log file that will be used to pre-empt, identify and resolve maintenance and system related issues.</p> <p>The following regulatory approvals will be sought:</p> <ul style="list-style-type: none"> ■ malaria/anaemia system (CE Mark); ■ whole blood analysis system (FDA approval and CE Mark); ■ bacterial identification and resistance system (FDA approval and CE Mark).
Availability	Timeline for malaria assay not available, depending on fundraising. System is at laboratory prototype stage. Claro Scientific is currently in the process of raising capital to fully integrate the system into a smaller portable device. Once funding is secured, the prototypes will be available for trials in 6–12 months.

Spectraphone (QuantaSpec)

QuantaSpec (Vermont, US) is an R&D company that creates infrared spectroscopy technologies for detecting pathogens and chemicals with applications for global health, national defence, homeland security and food safety. It is developing a POC molecular detection system for malaria. The system comprises a spectral imaging platform and a software system that recognizes the unique infrared signature of molecules present in the target pathogen.

Through a United States Army Medical Research contract, the technology was initially developed on an expensive laboratory-based infrared spectroscopy system. A field-robust, low-cost, lightweight, hand-held system was demonstrated last year, and in 2013-2014 QuantaSpec expects to further miniaturize and improve the spectral range and resolution of the device.

Despite the progress in development of the hardware, progress on the software required for malaria diagnosis has slowed in the past year due to the lack of funding for malaria specific applications of the technology. As a result, although the device may be launched sooner (for another application), the malaria test will not be available until 2015, depending on funding.

Table A3.10 Spectraphone

Platform characteristics	
Type of technology	Portable device employing infrared spectroscopy to detect malaria and other pathogenic organisms in blood. Sample preparation consists of making a thin smear on a specially coated slide and staining the smear with Giemsa. ¹⁵⁸ The slide is inserted into an instrument that measures the infrared spectrum of the sample on the slide and applies a computer-based algorithm to the data generated by the sample to identify the presence of <i>Plasmodia</i> . Analysis of the data is based on the principle that every molecule has a unique infrared signature, meaning certain wavelengths of light are absorbed or reflected.
Output	Qualitative result for <i>Plasmodium</i> , differentiates between <i>P. falciparum</i> and <i>P. vivax</i> malaria. Future versions of the device will be capable of running multiple assays, including malaria, and possibly drug resistance markers (already demonstrated for chloroquine) and febrile illness testing (several bacterial and fungal species demonstrated).
Performance	To be determined for the SpectraPhone handheld device. In pre-clinical studies of the laboratory-based system, The sensitivity was 98.8% to 100% (95% CI) for differentiating <i>Plasmodia</i> -infected blood from salmonella-infected blood and uninfected blood with a specificity of 95.4–100% (95% CI). The sensitivity and specificity for detecting <i>P. falciparum</i> was 98.4–100% and 97.7–100% (95% CI). The sensitivity and specificity for <i>P. vivax</i> was 95.4–100% and 98.8–100% (95% CI). The sensitivity and specificity for detecting either chloroquine-susceptible strains and chloroquine-resistant strains was 97–100% and 98.7–100% (95% CI). The lower LOD is a single parasite.
Turnaround time/capacity	The goal is one minute per sample. One sample is processed at a time. Hundreds of samples can be processed in one day.

¹⁵⁸ Although the technology has been developed using Giemsa stained slides, the developers would like to create a reagent-less system and to validate the system on unstained and unfixed smears.

Sample needed/ stability	<p>The sample collected is a fingerprick blood sample (~10 µL) collected on a specially coated slide. The process is identical to preparing a slide for routine microscopy: the slide is stained with Giemsa and fixed in methanol.</p> <p>Although extensive studies have not yet been conducted on sample stability, experience suggests that the samples would be stable for several months at room temperature; furthermore, the samples would not be as vulnerable to interference due to the unique spectra of infrared light associated with different organisms (e.g. the spectra of dust differs greatly from that of a parasite).</p>
Environmental requirements	<p>No cold chain requirements for the slides or Giemsa.</p> <p>The device should be used in a non-condensing environment.</p>
Testing protocol	<p>The testing process involves: (i) collection of a fingerprick blood sample on a specially coated slide; (ii) staining and fixation of the slide; (iii) insertion of slide into instrument for analysis; (iv) readout of result.</p>
Cost/test	<p>Estimated to be US\$ 0.12 per diagnosis (when manufactured at scale).</p>
Cost/instrument	<p>Targeting US\$ 1000–2000 per device (when manufactured at scale). QuantaSpec expects to partner with a large manufacturing company to mass produce the device.</p>
Power requirements	<p>The handheld system will be battery powered and rechargeable by solar cell.</p>
Training/technical sophistication	<p>The major skill required to perform the test is collection of blood and preparation of a smear. The test is designed for use by a minimally skilled health worker with limited training less than one half day).</p>
Durability/maintenance	<p>The device is expected to have a 10-year service life, and the manufacturer has a worldwide service network.</p>
Infrastructure requirements	<p>The device is intended to be used in the community and at all levels of the health system. If Giemsa staining is required, it would most likely be used at health facilities where a technician and small laboratory space is available.</p>
Result display and storage	<p>Results are displayed on a video screen. Test results can be stored or reported wirelessly to the national health ministry with time and date stamp, GPS location and test result.</p>
QA/QC	<p>Regulatory strategy and market approval strategy still under development.</p> <p>Internal QCs can be provided by manufacturer.</p> <p>External QC is similar to that for visual microscopy.</p>
Availability	<p>2015, contingent on funding.</p>

ANNEX 4: GLOBAL HEALTH DONOR LANDSCAPE

According to a recent mapping of development assistance for malaria, the top five funders for malaria from 2009 to 2011 were the Global Fund (57%), the United States (26%), the United Kingdom (7%), the World Bank (6%) and Canada (1%), with the majority of assistance going to sub-Saharan Africa (76%).¹⁵⁹ The Global Fund and 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 stakeholders affecting the malaria RDT market include the donors the Bill and Melinda Gates Foundation, the World Bank, DFID and UNITAID. These donors intervene at various points in the diagnostics value chain, ranging from funding R&D to supporting RDT procurement and delivery. 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 for malaria diagnostic testing; it has supported malaria programmes in 97 countries and through the end of 2011 had approved US\$ 6.5 billion and disbursed US\$ 4.4 billion in funding for malaria.¹⁶⁰ Its malaria investments have been growing over the years, and in 2011 it invested US\$ 6 billion in malaria, representing approximately half of global funding for malaria.¹⁶¹ In terms of how these funds are allocated, approximately half of its funding has been spent on prevention (including nets, indoor residual spraying and malaria in pregnancy).¹⁶² Diagnosis, including RDTs, is a growing component of Global Fund funding; one analysis estimated that 5.2% of its malaria programme grants in 2012 were for diagnosis.¹⁶³

Transitions at the Global Fund

Currently, the Global Fund is in a period of transition. Several recent changes and events may affect malaria markets, including fundraising results, implementation of its new strategy (including staffing reorganization and launch of the New Funding Model) and its decision in late 2012 to mainstream AMFm, an ACT subsidy programme.

At the highest level, the majority of the Global Fund income comes from donor governments, which represents more than 90% of the contributions received.¹⁶⁴ The GF estimates it needs US\$ 15 billion to support its work for the 2014–2016 period and it is actively seeking to raise funds with a major Replenishment

159 Kates J et al. Mapping the donor landscape in global health: Malaria. Kaiser Family Foundation: August 2013 (kff.org).

160 Strategic investments for impact: Global Fund results report 2012. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2012.

161 Strategic investments for impact: Global Fund results report 2012. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2012.

162 Strategic investments for impact: Global Fund results report 2012. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2012.

163 Zhao J et al. Adoption of rapid diagnostic tests for the diagnosis of malaria, a preliminary analysis of the Global Fund programme data, 2005–2010. PLOS One. 2012;7(8):e43549.

164 Strategic investments for impact: Global Fund results report 2012. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2012.

Meeting held in late 2013. Given global economic challenges and reforms under way at the Global Fund, it is unclear if the fund will reach its US\$ 15 billion goal.

In November 2011, the Global Fund Board adopted a new strategy for 2012–2016, focused on investing more strategically in high impact and strong value for money. In connection with this, it has reorganized its staff to improve grant management and to focus on high-impact countries.¹⁶⁵ It is also implementing the New Funding Model, which changes the grant application, approvals and grant management processes. The model is designed to help the Global Fund invest more strategically and provides countries with more predictability around funding levels and flexibility in applying for funds. The model was launched in early 2013, and will be implemented in a phased manner until it is fully operational in 2014.

Both the uncertainty associated with Global Fund fundraising efforts and unanswered questions related to the New Funding Model create risk of reductions in malaria diagnostics budgets. First, if the Global Fund is not successful in fundraising, there will be reductions in the total funding allocations to countries going forward. Second, as part of the New Funding Model, the Global Fund will indicate to each country the total amount of money they can expect, called “indicative funding”. The country must then decide how to allocate this funding between HIV, TB and malaria and health systems strengthening efforts. It is unclear how malaria programmes will fare compared to other priorities. Lastly, in countries facing major funding gaps in their overall malaria control programmes, prioritization decisions may need to be made between case management and prevention, and these could affect diagnostic testing levels and programmatic support for diagnosis.

Although the impact of these changes at the Global Fund is difficult to estimate, it is clear from policy documents and conversations with managers that malaria diagnosis scale-up is a high priority, as part of quality case management and in support of the WHO Test, Treat, Track Campaign. Additionally, the new more proactive role that Global Fund staff will play in proposal development is expected to ensure that programmes are both pragmatic and strategic in their approach to diagnosis scale-up.

The Global Fund also decided in November 2012 not to continue its large ACT subsidy, AMFm, as a stand-alone programme, but rather to integrate it into the regular grant-making activities.¹⁶⁶ Going forward, countries can include a co-payment mechanism to improve private sector access to ACTs in their core Global Fund grants. The Global Fund also has suggested that incorporation of diagnostic testing into a private sector subsidy programme be explored.

Malaria RDT procurement activities

Procurement: 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. Increasingly, countries are using the Global Fund pooled procurement mechanism to procure RDTs.

With respect to product selection, as a funding instrument, the Global Fund does not direct the activities that it funds; it only requires that procurement plans be consistent with international standards, such as guidance from WHO, and that products are procured competitively in a fair and transparent manner and in accordance with the Global Fund Quality Assurance Policy for Diagnostic Products to achieve the lowest possible price.¹⁶⁷

Pooled procurement: A VPP mechanism was launched in 2009 in order to improve the efficiency and cost-effectiveness of Global Fund recipient procurement. The VPP mechanism procured approximately

¹⁶⁵ High-impact countries are the 20 countries with the greatest burdens of HIV, TB and malaria and in which the Global Fund has the greatest investments.

¹⁶⁶ AMFm was a global health financing mechanism hosted by the Global Fund and aimed at increasing access to effective malaria treatments by reducing the retail price of ACTs, increasing ACT availability and use, and crowding out of ineffective treatments that contribute to drug resistance. The programme involved subsidizing the cost of ACTs, was implemented at the national scale for two years in eight countries and was supported by a pool of funds that was separate from other Global Fund programmes. In late 2012, the Global Fund Board decided that the AMFm activities would be integrated into its routine grant-making processes, i.e. there would no longer be a special pool of funds for subsidizing private sector case management, going forward countries may elect to include a private sector subsidy programme in their malaria grants.

¹⁶⁷ 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.

13 million RDTs in the 18 months prior to the end of 2010; 27 million RDTs in 2011; and 41 million RDTs in 2012. It expects to procure more than 50 million RDTs in 2013.^{168, 169} The Partnership for Supply Chain Management has been serving as the procurement agent for VPP.

As part of the reforms at the Global Fund, procurement functions are undergoing a strategic reorganization, including changes in the way it works with suppliers. Going forward, the Global Fund procurement team expects to work more directly with suppliers, through framework supply agreements. The role of procurement agents will be reduced; agents will primarily place orders and manage delivery to countries under these framework agreements. Implementation of this new strategy is phased, focusing on one product category at a time, beginning in 2013 with LLINs and ACTs. Malaria RDTs supply negotiations are planned for 2014. The strategy for each product differs, and depends on the market dynamics for that particular product. For example, multiyear supply agreements with underwritten demand based on forecasts might be appropriate for one market, while competitive tenders would be more appropriate for another. However, the process for developing a strategy is similar for all products: it begins with manufacturer meetings and consultations with other major procurers/donors. This is followed by a deep dive to better understand the market, including visits to manufacturers. A procurement strategy for the particular product is then developed and implemented. The aim is to develop supply agreements for pooled procurement that also will be available to grant recipients who are not using the Global Fund procurement mechanism. With respect to malaria RDTs, the Global Fund aims to balance value with sustainability of the market, and is concerned about the current low prices.¹⁷⁰

Quality standards: Since March 2011, a Quality Assurance Policy for Diagnostic Products has been in force for Global Fund-financed grants. For malaria RDTs, most grant recipients were already in compliance with the policy, which, regarding the selection of the product, requires that all malaria RDTs purchased be selected in accordance with the WHO recommended selection criteria for RDT procurement. The Global Fund also maintains a list of eligible RDTs on its website.¹⁷¹ In addition, the Global Fund requires that countries implement other quality testing measures for RDTs, including participation in the WHO Lot Testing Programme. In April 2013 a review of the Global Fund Quality Policy for Diagnostics was conducted, no major changes for malaria RDTs are expected in the revised policy.

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 on 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.¹⁷² 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).

President's Malaria Initiative (PMI)

PMI, active in 19 focus countries, the Greater Mekong subregion and three non-focus countries, has become the second largest international malaria donor, with a budget of US\$ 650 million in 2013.

PMI considers diagnosis an integral part of malaria case management and since its inception in 2006 has been supporting holistic diagnostic efforts in-country through technical assistance and implementation support, as well as procurement of RDTs, microscopes and related consumables. With respect to RDTs,

¹⁶⁸ Global Fund Procurement Team, personal communication, 8 November 2013.

¹⁶⁹ This information will be verified in the next edition of the Landscape.

¹⁷⁰ Global Fund Procurement Team, personal communication, 8 November 2013.

¹⁷¹ Rapid diagnostic test (RDT) kits for malaria, version 8. May 2013 (<http://www.theglobalfund.org/en/procurement/quality/diagnostics/>, accessed 8 August 2013).

¹⁷² Quick facts on procuring malaria rapid diagnostic tests with Global Fund grants, December 2011. Geneva: Global Fund to Fight AIDS, Tuberculosis and Malaria; 2011 (<http://www.theglobalfund.org/en/procurement/>).

PMI has procured 62.5 million RDTs since 2006 through fiscal year 2012, with procurement increasing steadily every year. In fiscal year 2012, nearly 29 million RDTs were procured.¹⁷³

The PMI 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, the PMI work in diagnosis encompasses both microscopy and RDTs, and it has invested considerably in improving QA systems for diagnostics as well as in training and supervision of health workers. For example, in fiscal year 2012 over 28 000 health workers were trained in malaria diagnosis with PMI support. In addition to supporting laboratories, improving clinical management of malaria and fever is a PMI priority. In all countries, PMI is supporting clinical training and supervision of health workers. In countries with community health worker programmes, PMI is supporting integrated community case management using RDTs.

In the coming year, PMI will be continuing its work to scale up diagnosis in the context of comprehensive case management, in both the public sector and the community. In addition, it is supporting pilot programmes to increase the use of RDTs and improve case management in the retail private sector.

PMI provides technical support for case management through a combination of country-specific bilateral projects and through the MalariaCare Project, which is implemented by PATH, with PSI, Medical Care Development International and Save the Children United States as partners. This project, awarded in late 2012, continues the work of the PMI Improving Malaria Diagnosis Project in scaling up diagnostic testing and quality of laboratory services, and has an expanded focus on improving the capacity of health workers to manage malaria and other febrile illnesses appropriately. Through its partners, the MalariaCare Project supports both health facility, community and private sector case management.

With regard to procurement, PMI performs malaria RDT procurement on behalf of countries, primarily through the USAID DELIVER Project. Currently, the PMI criteria for RDT quality are in line with WHO recommendations; in addition, manufacturers must agree to preshipment lot testing. PMI maintains a list of preselected vendors for RDTs that is established through periodic requests for expressions of interest.¹⁷⁴ The PMI 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 preselection process has not conflicted with a country's product selection.¹⁷⁵ Furthermore, if a country were to request a product not included on the PMI list, but meeting PMI's technical criteria (which are similar to WHO recommendations), then a waiver process exists for procurement. In the future, PMI will continue 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.

173 The President's Malaria Initiative Seventh Annual Report to Congress, April 2013.

174 Preselected RDTs (<http://deliver.jsi.com/dhome/procurementnews/currenteois>).

175 PMI, personal communication, 5 August 2013.

World Bank

The World Bank is also a major funder of malaria control activities. Currently, its malaria support is integrated into broader health systems projects, which is a reflection of the World Bank focus on health outcomes rather than on particular diseases. Previously, support for African malaria programmes was provided through the Malaria Booster Program. Since 2005, the World Bank has committed over US\$ 966 million to more than 22 projects across 20 countries in sub-Saharan Africa and India. This reflects a 15-fold increase compared with World Bank spending on malaria control efforts between 2000 and 2005. A number of new projects are currently under development including Ghana, Togo and the Senegal River Basin (Guinea, Mali and Senegal) with Sierra Leone already approved by the Board.

World Bank funding for malaria is based on demand from countries, and its funding model differs significantly from that of other major malaria funders. The World Bank 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 the funds are provided directly to the government's treasury to be spent as if it were their own, the World Bank requires a careful project plan, quality checks and audits.

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

Since 2005, World Bank resources have been used to procure 22.3 million RDTs for African programmes 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 World Bank technical specialists would 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

The Bill and Melinda Gates Foundation plays a key role in malaria funding. Its role spans the value chain and includes investing in R&D, advocacy and support for global policy-making as well as supporting catalytic in-country programmes, in particular, demonstration projects and areas where new learning is needed to inform global policy and future investment.

To guide its work in malaria, the Bill and Melinda Gates Foundation has recently developed a new strategy, Accelerating to Zero, which focuses on malaria eradication. Eradicating malaria has important implications for diagnostics: currently, malaria is both massively overdiagnosed and treated (e.g. presumptive diagnosis; ignoring test results) and underdetected and treated (e.g. subpatent and asymptomatic infections). As such, improving the accuracy of malaria diagnosis is a high priority. In connection with this, the Bill and Melinda Gates Foundation is funding the PATH DIAMETER project, aimed at supporting development of new diagnostics to support malaria elimination. In addition to the need for new highly sensitive diagnostics, other diagnostic priorities include POC G6PD tests and tests for monitoring transmission/enabling the certification of malaria elimination. Regarding the former, the Bill and Melinda Gates Foundation is contributing to the PATH G6PD test initiative.

Department for International Development (DFID)

DFID is another major donor to malaria efforts. The role of DFID in malaria spans the value chain and includes R&D, operational research and support for in-country scale-up. DFID provides both multilateral funding (e.g. support for the Global Fund) and direct bilateral funding to countries (e.g. health systems funding). It also supports NGOs and Product Development Partnerships and the WHO GMP. As an example, several of the programmes that DFID is currently funding include product development partnerships working on RDTs, support to scale up availability and use of RDTs in the public sector, initiatives to expand private sector markets for diagnostics, and ACT and RDT market monitoring initiatives. DFID also plays an important role at the global policy level, in particular, advocating for stronger malaria case and fever case management practices.

In terms of strategy, the work of DFID is guided by a strategic plan that will be in place until 2015: the Malaria Framework for Results, Breaking the Cycle: Saving Lives and Protection the Future. With respect to malaria diagnostics, the DFID focus is on case management, and it considers diagnostics as well as management of non-malaria fever to be an integral part of case management. In addition to strengthening case management practices and ACT targeting, a recent audit of the DFID malaria programme highlighted the need to generate more data on the burden of malaria, the importance of scaling up diagnosis in the private as well as public sector, and improving cost-effectiveness and value for money assessments of malaria interventions and programmes. The United Kingdom aims to dramatically reduce illness and death from malaria in countries most affected and, as such, its funding is focused on high-burden countries.

UNITAID

UNITAID is another major donor to malaria efforts, uniquely focused on market-based approaches to increasing access to health products. UNITAID works globally, through a wide range of actions and implementers, to address market shortcomings. Its recently adopted 2013–2016 Strategy¹⁷⁶ refines its current business model and guides future work. Underpinning its work are market intelligence activities, including monitoring the markets for key products through annual landscaping exercises, and annual market forums to vet and prioritize market interventions.

UNITAID projects have included support for ACT and LLIN scale-ups and to AMFm. In 2012, UNITAID funded two malaria diagnostics initiatives, specifically nearly US\$ 10 million to FIND to support the Product Testing and Lot Testing Programmes and over US\$ 30 million to PSI to support the development of private sector markets for RDTs in five endemic countries. Market intelligence projects include ACT, RDT and artemisinin demand forecasting, support for ACTwatch and work to better understand the supply of raw materials for ACTs and RDTs.

¹⁷⁶ See (<http://www.unitaid.eu/en/strategy>).