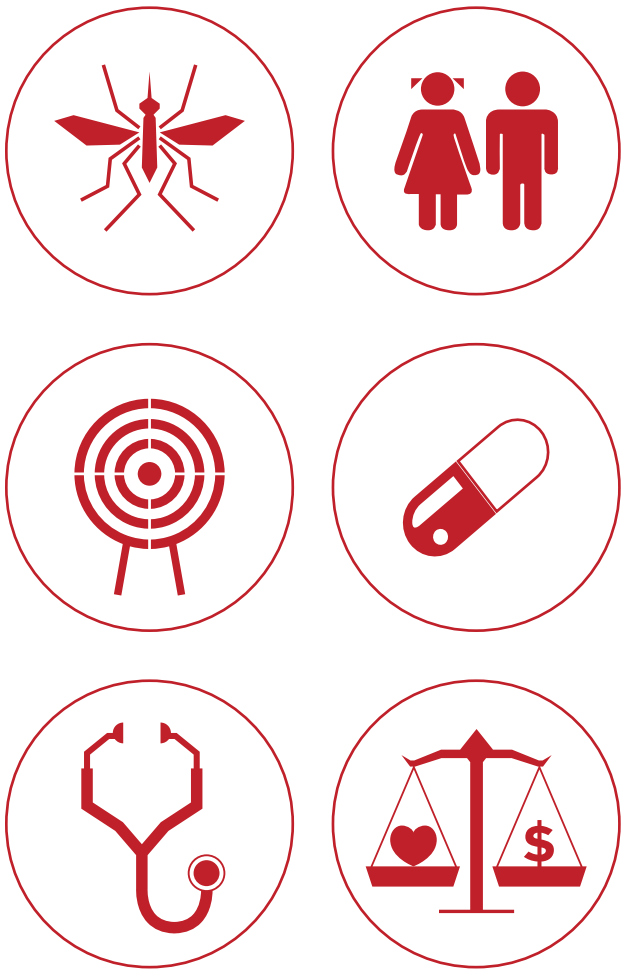
LANDSCAPE

MALARIA DIAGNOSTICS TECHNOLOGY AND MARKET LANDSCAPE

3rd EDITION
APRIL 2016



UNITAID

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Abbreviations

ACT	artemisinin-based combination therapy
ALMA	African Leaders Malaria Alliance
°C	degree Celsius
CE Mark	European Conformity (Conformité Européenne) mark
CHAI	Clinton Health Access Initiative
cm	centimetre
DFID	Department for International Development (United Kingdom)
DNA	deoxyribonucleic acid
ELISA	enzyme linked immunosorbant assay
FIND	Foundation for Innovative New Diagnostics
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Global Malaria Programme
GPS	global positioning system
GTS	Global Technical Strategy for Malaria 2016–2030
G6PD	glucose-6-phosphate dehydrogenase
Hb	haemoglobin
HRP-II	histidine rich protein-II
HWG	Harmonization Working Group (Roll Back Malaria Partnership)
IPTp	intermittent preventive treatment in pregnancy
ISO	International Organization for Standardization
ISTp	intermittent screening and treatment in pregnancy
kg	kilogram
LAMP	loop-mediated isothermal amplification
LED	light-emitting diode

LOD	limit of detection
MAb	monoclonal antibody
mL	millilitre
MPAC	Malaria Policy Advisory Committee
NAAT	nucleic acid amplification test
ng	nanogram
NGO	nongovernmental organization
PCR	polymerase chain reaction
PCW	positive control well
Pf	*Plasmodium falciparum/P. falciparum*
pLDH	parasite lactate dehydrogenase
PMI	United States President's Malaria Initiative
POC	point of care
PPM	Pooled Procurement Mechanism (Global Fund)
PQ	WHO Prequalification of In Vitro Diagnostics Programme
PQR	Price and Quality Reporting (Global Fund)
PSI	Population Services International
Pv	*Plasmodium vivax/P. vivax*
Pvom	*Plasmodium vivax, ovale, malariae*
p/µL	parasites per microlitre
QA	quality assurance
QC	quality control
QMS	quality management systems
R&D	research and development

RBC	red blood cells
RDT	rapid diagnostic test
RNA	ribonucleic acid
TB	tuberculosis
TBD	to be determined
µL	microlitre
UMT	Urine Malaria Test™
UNICEF	United Nations Children's Fund
US	United States
USAID	United States Agency for International Development
USB	universal serial bus
US CDC	United States Centers for Disease Control, Atlanta
US FDA	United States Food and Drug Administration
UV	ultraviolet
VPP	Voluntary Pooled Procurement
WHO	World Health Organization

Executive summary

Introduction and methodology

This report is part of an ongoing initiative within UNITAID to describe and monitor the malaria diagnostics technology and market landscape. It includes a review of the current research and development (R&D) pipeline and the rapid diagnostic test (RDT) market, analysis of the markets overall health and discussion of potential opportunities for market-based interventions to address challenges. Information in this report was derived through a variety of methods, including desk research, procurement dataset analyses and consultation with experts.

Public health problem, commodity access and malaria policy

Globally, since 2000, there has been a 37% decrease in malaria incidence; however, progress is both uneven and fragile. Many countries have reduced transmission to very low levels and over one third of the 96 malaria-endemic countries have committed to elimination in the coming decades. At the same time, declines in incidence and mortality have been slower in the countries that have the highest burden of disease. To address these epidemiological shifts and ensuing challenges, in May 2015, the World Health Assembly adopted a new World Health Organization (WHO) Global Technical Strategy for Malaria 2016–2030 (GTS), a 15-year roadmap for malaria. The GTS sets out targets for control and for elimination. With respect to diagnosis, the GTS emphasizes the need to achieve universal coverage of core interventions, including diagnostic testing, as well as the need for innovative delivery and new diagnostic product development. Additionally,

it stresses the importance of surveillance, and diagnostic testing underpins many surveillance activities.

In 2010, WHO began recommending that all suspected cases of malaria be tested before treatment. Since then progress has been most pronounced in the public sector, especially in Africa where an estimated 65% of cases were tested in 2014, a 24% increase over testing rates in 2010. However, hundreds of millions of fevers remain undiagnosed, and presumptive treatment is still common, particularly in the private sector, as is seeking no form of treatment for fever.

Quality and regulatory programmes

For malaria RDTs, there are several quality programmes in place, including the WHO Product Testing Programme, the WHO-FIND Lot Testing Programme and the WHO Prequalification of In Vitro Diagnostics Programme (PQ). The Product Testing Programme has been most influential, although there are still gaps in the malaria RDT quality continuum (see Section 7 and 8). These programmes are currently only available for blood-based RDTs; the regulatory pathway for new diagnostics is less clear. Other regulatory programmes are challenging from a resource and cost perspective (e.g. United States Food and Drug Administration/US FDA) or are largely administrative procedures that do not include a full quality evaluation (e.g. due to the risk classification system, obtaining a CE Mark does not include full quality evaluation for malaria tests).

Technology landscape

Since the last *Malaria diagnostics technology and market landscape*, three products have come to market: in 2014, Sight Diagnostics Ltd launched Parasight, an enhanced automated microscopy system; in 2015, Fyodor Biotechnologies launched the Urine Malaria Test™ (UMT), and in early 2016 Meridian Biosciences launched the ***illumi****gene*® Malaria diagnostic system. Initial uptake is in the private sector; additional evidence is likely required for public sector adoption, as well as policy and regulatory processes. The adoption of two molecular technologies that launched in 2012–2013

has not been rapid, due in part to limitations in the current platform's capabilities, high prices and the need for additional evidence on performance and field use required to inform decisions about use and policy.

Overall, the pipeline includes a number of technologies, including improvements to existing technologies (e.g. RDTs; nucleic acid tests) and novel platforms (e.g. hemozoin). The degree of progress among pipeline technologies varies. While there has been relatively rapid progress in a few areas (e.g. development of point of care/POC G6DP tests and highly sensitive RDTs; the aforementioned recently launched products) additional work (e.g. evidence; policy endorsements; regulatory approvals) will be needed to support widespread adoption. In contrast, many technologies that have been in the pipeline for several years are not advancing rapidly through the later stages of development (e.g. evaluation; regulatory/policy; introduction stages).

A highly sensitive *Plasmodium falciparum (Pf)*-only RDT is likely to launch in 2017. However, the market for these tests remains ambiguous. While recent research has highlighted the extent of the "asymptomatic reservoir" (people who are infected and do not have symptoms), researchers are working to identify the optimal intervention mix for addressing this reservoir, and the role of new diagnostics needs to be proven out. As a result, it is not clear how highly sensitive RDTs will be positioned in the market.

Work by the Foundation for Innovative New Diagnostics (FIND) and partners to develop field-stable positive controls (i.e. positive control wells/PCWs) has been ongoing; however, technical challenges remain, as do questions around the market and business plan. Meanwhile, a few RDT manufacturers have developed controls, although little information on their specifications or evidence of their performance is available to inform use.

With respect to nucleic acid amplification tests (NAATs) for malaria, progress varies. POC NAAT devices that require minimal operator input are in the pipeline, and would overcome some of the major hurdles in expanding access to NAATs. However, the price point at which this is achievable may be several times that of alternative, less sensitive malaria diagnostics. Because performance improvements are the main advantage of NAATs, evidence of their performance will influence their overall value proposition.

There are several hemozoin-detecting technologies in the pipeline, however, for many it will be some time before device development is complete and evidence of performance becomes available. The latter will be critical, given some debate about the suitability of hemozoin as a biomarker for malaria. Currently, hemozoin devices might play a role in clinical diagnosis, and depending on the ultimate limit of detection (LOD) achieved, as screening diagnostics in elimination settings.

One notable development in the pipeline is several non-invasive technologies. In addition to the UMT, two hemozoin devices in development take measurements directly through the skin. Lastly, researchers have reported on saliva and breath sampling methods; however, translating these novel approaches into diagnostics that can be used in the field and effectively compete with malaria RDTs will take time.

With respect to radical cure,[1] one company has launched two POC G6PD tests, and other products, supported by PATH, are in development (earliest availability 2017–2018). A number of gaps in the evidence base for G6PD deficiency have challenged development of new tests. Additionally, the market for POC G6PD tests has not been comprehensively assessed, and it is not clear how many products the market might support. Initial market research also suggests that introduction will be challenging (e.g. clinician behaviour change; developing national policies for use of G6PD testing and primiquine).

Ultimately, in the largest malaria market segment, the clinical diagnostics market, the ability of new technologies to compete with RDTs in terms of cost, ease of use and diagnostic performance will be critical to their uptake. RDTs have 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 market can bear. Other smaller market segments include diagnostics used in research, by national programmes (e.g. surveys; quality assurance/QA and quality control/QC) and drug resistance monitoring as well as potential market segments emerging as a result of the changing epidemiology of malaria (e.g. improved tests for *Plasmodium vivax/Pv*; tests to support elimination). While highly sensitive *Pf* RDTs and POC G6PD tests are advancing, other areas, such as improved non-*Pf* diagnostics, have not progressed.

Perhaps one of the greatest challenges to the malaria diagnostics pipeline is a disconnect between product development and the market needs. Several recent reports include a multitude of R&D needs for malaria diagnostics, however, these are not well prioritized nor are the optimal product characteristics described. Also, the business opportunity for many new products may not be very compelling, although in most instances it has not been analysed. At the same time, it is not always clear which indication for use/market segment the technologies in the pipeline are targeting. Other challenges that hinder progress of new malaria diagnostics include: funding challenges; the complexity of evaluations; regulatory requirements; and limited commercialization capacity of developers as many are small organizations.

Malaria RDT market

After rapid growth from 2008–2013 (48% annual growth rate) the malaria RDT market size plateaued in 2014 at 314 million RDTs. Despite sizable unserved demand, it is not surprising for growth to slow compared to prior rates for a number of reasons. First, many countries have already achieved reasonably high rates of testing in the public sector and will continue to expand testing, however, increases are likely to be incremental given the challenges of reaching the periphery. That said, there are still a few high-burden countries that need to significantly scale public sector RDT use, and this will drive

[1] Radical cure refers to complete elimination of malaria parasites from the body, inlcuding the dormant liver stage parasites in *P. vivax* and *P. ovale*.

near-term growth. Second, with respect to the private sector, where many patients turn for fever care, several projects are addressing some of the initial barriers to developing these markets (e.g. regulatory and policy changes; behaviour change strategies; training and supervision; QA). However, additional work is likely needed, particularly around affordability and sustainability of models for testing in the retail sector. Without concerted effort, private sector demand growth is likely to be slow. Finally, one third of people with fever do not seek any form of care; raising awareness of the need for diagnosis and directing these populations to providers that test before treating will take time.

Malaria RDT prices have declined, from an average of US$ .52 for a *Pf*-only RDT in 2010 to US$ .27 in 2014, with some tenders achieving prices in the low twenties and high teens. Limited cost analysis suggests that the lower prices (i.e. high teens, low twenties) are indeed below cost for some manufacturers and may not be sustainable. However, there is still considerable variability in pricing, which keeps the averages higher and allows those companies with very low average costs to make modest profits on some orders. Procurement data analysis indicates that the majority of countries have experience with multiple brands and types of RDTs. However, differences in test procedures (e.g. wait times; number of drops of buffer) limit switching between RDTs, despite global-level harmonization efforts that have focused on labelling and instructions for use. This results in a substantial number of orders being sole sourced often at higher prices, and likely increases competitiveness resulting in lower prices in large openly competed tenders.

Overall, competition has improved the affordability of RDTs, although the low prices may put the market's longer-term health at risk. Already the market is highly concentrated, raising concerns about supply security. In 2014, three companies comprised 96.8% of the donor-funded market. Since one of these suppliers has been providing another with semi-finished components, 96.8% of the market is effectively relying on two suppliers, even though there are 29 companies with RDTs meeting WHO recommendations. It is not clear what caused this consolidation, however, the leading suppliers appear to have been highly committed to the malaria business: they have a portfolio of tests types that are among the highest-performing products; they have built out production capacity capable of filling large orders rapidly; and they have focused on cost reduction.

Balancing the supplier base and affordable pricing in the malaria RDT market is challenging. With extreme consolidation comes risks to supply security and of price setting. For example, acquisition of one company by another, fire at a plant, a quality issue or business decision to exit the market at one of these companies could disrupt supply globally. While the chance of these occurring is small, it is possible. Another risk involves price setting: when a market is dominated by two suppliers, power theoretically begins to shift to the suppliers and they can begin to set pricing. While price setting does not appear to be happening in the malaria RDT market, suppliers may be opportunistic (e.g. offering low prices on competitive tenders, but then charging high prices for expedited or sole sourced orders).

Among the barriers to entry in the malaria RDT market, the ability to produce large orders (i.e. millions of tests) rapidly, at low cost, is now critical. While there are few

companies with high-performing RDTs intent on entering the market, many need to invest in production capacity before they will have a meaningful presence in the market, i.e. be capable of competing effectively on price and lead time. Other potential "new entrants" may already have low cost production capabilities, but need to improve the technical performance of their RDTs before they can enter the public sector market.

Practically speaking, given the relative concentration of buyers, interventions at the global procurement level (e.g. global supply agreements with several suppliers, including some of today's smaller producers) are likely the best means of diversifying the public sector supply base. Even at the global procurement level, incentives or slight price increases may be required to attract sufficient suppliers to the market and to encourage investment required for these suppliers to compete meaningfully in the market. It will be important to monitor developments at the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), which has begun to review its RDT procurement strategy.

These market dynamics also have important implications for innovation and RDT quality. Current market conditions limit the business incentives for new product development at a time when there is a lengthy R&D agenda for malaria diagnostics. Today, a substantial proportion of groundbreaking innovation in the RDT market is happening in response to donor initiatives.

Regarding quality, market conditions put RDT quality at risk in that the quality of a specific product could suffer due to cost pressures and or rapid production scale-up. The Product Testing Programme continues to have a substantial effect on the market in terms of informing buyers about the performance of products, and nearly all public sector procurement relies on this programme. Despite the improvements in quality that this programme has driven, quality gaps remain, including limited information on manufacturing-level quality management systems (QMS) and information on the quality of products in the field.

With respect to WHO PQ, as of November 2015, 12 malaria RDTs from four companies were prequalified and there were no additional RDTs in the WHO PQ pipeline. In general, RDT manufacturers have progressed slowly through WHO PQ. Although to be eligible for the Product Testing Programme suppliers must have a valid ISO 13485 certificate (the relevant ISO standard for in vitro diagnostics), WHO-led site inspections demonstrate that manufacturing quality systems vary and understanding and implementation of ISO 13485 is inconsistent. Even so, the leading manufacturers have become prequalified, and more than 90% of the public sector market is prequalified because the suppliers with the largest market share have prequalified their RDTs.

In light of the recent increase in the number of RDTs that are prequalified, as well as market conditions and a few product quality issues, WHO is considering requiring prequalification of malaria RDTs beginning late 2017. A decision is likely in early 2016. While this would allow consumers to differentiate between manufacturers based on their QMS, in addition to their performance in the Product Testing Programme, it also introduces a new barrier to entry, and could increase risk to supply security.

Market shortcomings

Major market shortcomings include the limited uptake of RDTs compared to need, including limited markets in the private sector; challenges related to the quality of RDTs in the field and at the manufacturing level; and the impact of low prices on the market's health, including the concentration of suppliers and risk this creates for market disruption. Inadequate surveillance and the lack of tests to support elimination and case management of *P. vivax* are also shortcomings.

Opportunities for market intervention

There are several opportunities for market intervention that would improve access to quality malaria diagnostics. There is an urgent need for demand-shaping interventions at the procurement level to ensure the long-term sustainability and health of the RDT market. And there is significant scope for expanding the market for RDTs, in particular, delivery strategies that target populations that are currently not seeking care for fever or that are receiving care at outlets that do not provide quality testing before treatment. Given current market conditions, opportunities to further improve quality both at the manufacturing level and in the field are also critical. With respect to the R&D pipeline, work on the regulatory pathway is needed, as well as improved alignment of the market needs and technology developers. Progress in development of POC G6PD tests may also present opportunities to improve access to safe and appropriate management of *P. vivax*. Depending on the results of research on elimination strategies (e.g. testing out different approaches to addressing the asymptomatic reservoir), there may also be scope for supporting introduction of highly sensitive diagnostics in some areas.

There are also several important market intelligence gaps and areas that will be critical to monitor in the coming year. For example, additional data on the use and impact of RDTs are needed as well as improvements in procurement data. With respect to expanding the market for diagnostics, additional market information at the country level is needed to design approaches for meeting unserved demand. Regarding the technology pipeline, market research is needed to better understand the needs and the market opportunity for new diagnostics. Going forward, if the Global Fund alters its procurement strategy, if WHO introduces prequalification as procurement criteria for RDTs or if the new highly sensitive RDTs are launched, then monitoring the impact of these changes on the market will also be important.

1. Introduction

The 2016 *Malaria diagnostics technology and market landscape* is part of a broad and ongoing effort to understand the technology and market landscapes for malaria diagnostics. Previous editions of this landscape report are available at: http://www.unitaid.eu/en/resources/publications/technical-reports.

This landscape report, the third edition, is intended to complement these earlier reports, stimulating discussion and informing potential opportunities for market intervention to improve access to effective malaria diagnostics. To serve this purpose, this report:

- reviews the public health problem of malaria and critical access issues related to malaria diagnostics (Section 3);
- describes current regulatory and quality programmes for malaria diagnostics (Section 4);
- summarizes the malaria diagnostics technology landscape, including a review of existing technologies and the research and development (R&D) agenda, progress in key areas and market challenges related to technology development (Section 5);
- analyses the malaria rapid diagnostic test (RDT) market (Section 6);
- identifies major market shortcomings and resulting opportunities to improve access through market-based approaches (Sections 7 and 8);
- includes several annexes that provide additional detail on items discussed in this report, including profiles of technologies that are sufficiently far along in their development (Annex 4).

A dynamic understanding of existing and forthcoming technologies is key for UNITAID in facilitating access to appropriate malaria diagnostic tools through market-based interventions. As such, this landscape is intended to be a living document, updated as the malaria diagnostics market evolves, to highlight potential opportunities for market-based interventions to improve access to effective malaria diagnostic commodities.

2. Methodology

This landscape was developed by Jennifer Daily with support from UNITAID. Information in this report was collected in a variety of ways, including primary sources (e.g. interviews with technology developers and other experts; procurement data analysis) and extensive review of secondary sources (e.g. literature reviews, published and unpublished reports; World Health Organization (WHO) policies; developer websites). A description of key data sources and methods is provided below. In general, due to limited data on malaria diagnostics,[2] this report relies on partial datasets supplemented by qualitative research. Research for this report was conducted in January–September 2015, and information is up to date as of September 2015, with two exceptions: data on the malaria burden and access to testing reflect the most recent WHO *World malaria report* published in late 2015 and the status of products undergoing the WHO Prequalification of In Vitro Diagnostics Programme (PQ) has been updated as of the end of 2015.

Diagnostics technology landscape methods

While the existing technologies for malaria diagnosis have been written about extensively, the UNITAID landscapes represent the first attempts to document and publish the malaria diagnostics pipeline. Given the need for rapid, near-patient testing in malaria, this report focuses 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).

Information sources used to identify products in the development pipeline include stakeholder interviews, targeted literature and Google searches, CORDIS and European Union Horizons databases, and published and unpublished reports. With the dissemination of the UNITAID landscapes reports since 2012, diagnostics developers also approach the author with product information to be included in the reports. Although this exercise aims to be as complete as

[2] For example, there are no data/business intelligence resources on diagnostic tests for global health, procurement data on malaria RDTs represent only half of the market and information on orders is not complete nor standardized and data on private sector markets are limited to surveys conducted every one to three years in a limited number of countries.

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 provided specific information on each product, including product specifications, information on the developer and stage of development. Most of the detailed interviews occurred during the first half of 2015. 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.

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. Developers have provided most of the performance data in this report based on laboratory validations; there are few independent studies, when these are available they have been specifically referenced. Similarly, projections of market launch will shift as time goes by, as will price estimates.

Market landscape methods

Given the need for rapid, POC diagnostics and the corresponding scale-up of malaria RDTs, the market section of this report focuses on malaria RDTs. Brief comments about other market segments are found in the technology part of Section 5.

Comprehensive data and business intelligence resources on diagnostic tests for global health do not exist. Therefore, the market landscape methodology relies on: (i) desk review of policies, meeting proceedings, and 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.

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 from donors and major procurers; access and availability data from ACT Watch; 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, procurement data from major donors and procurers were analysed. A data set comprising 1297 individual orders totalling 675

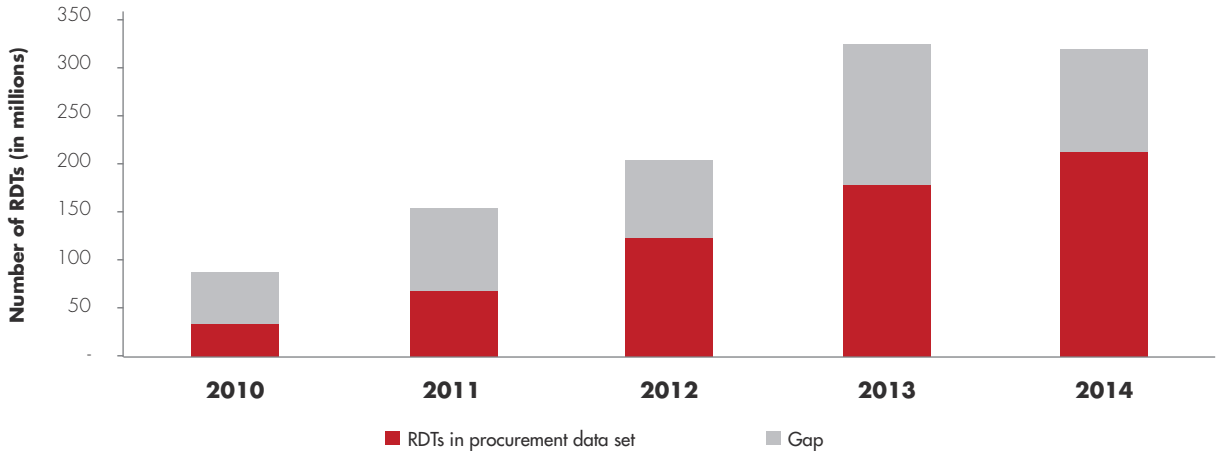
million RDTs in 2007–2014[3] was assembled. This dataset represents 40–67% of the global RDT market in 2010–2014 (Figure 1). Data sources included: the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), the United States President's Malaria Initiative (PMI); WHO; and the United Nations Children's Fund (UNICEF) (Figure 2). Global Fund data included orders from its pooled procurement mechanism (PPM) supplemented by orders publicly posted in the Global Fund Price and Quality Reporting (PQR) system.[4]

Major steps in cleaning the data included removing duplicates and completing product-specific information on each product (e.g. extracting information from free text descriptions in order to assign test type, format, pack size, brand and vendor). After cleaning the data, analysis included market growth, types of RDTs procured, procurement methods, the pricing trends and market share by company. For pricing analysis, shipping terms varied, so pricing analysis generally excluded those orders that were not ex-works.

Results were reviewed during the peer review process for this report and were also reviewed informally during interviews with key stakeholders and leading malaria RDT manufacturers.

FIGURE 1

Number of RDTs in procurement dataset compared to global RDT market size estimates



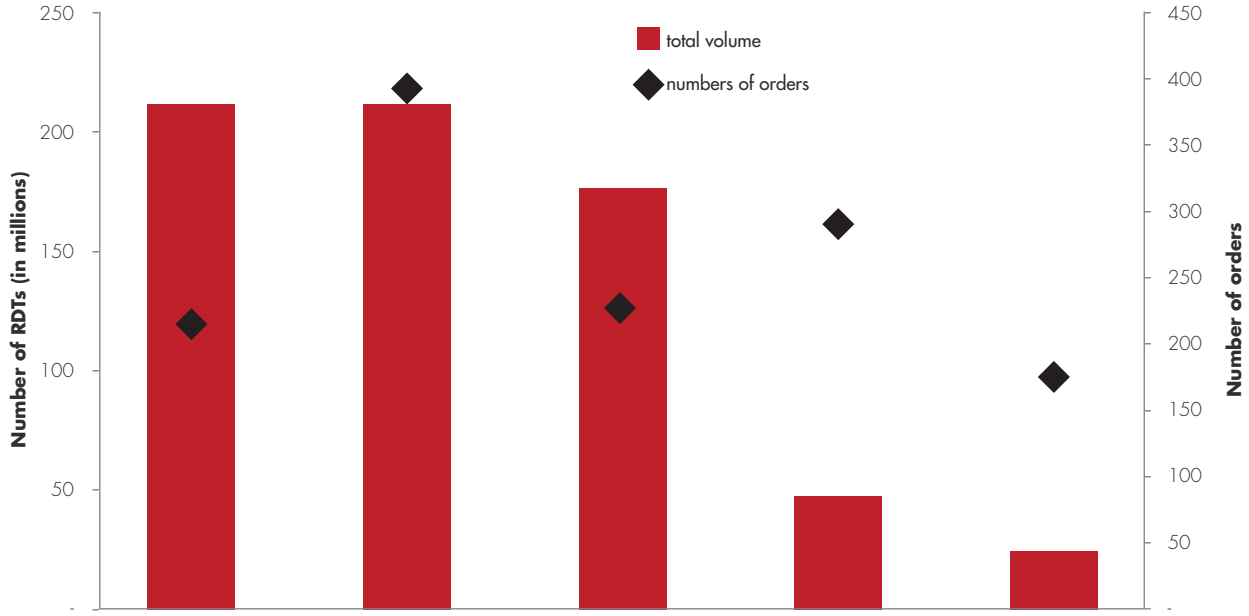
Note: Red and grey bars together represent total RDT market size; 2010–2014 totals are based on WHO surveys of manufacturers participating in the Product Testing Programme from the WHO World malaria report (for the respective years).
Source: Procurement data analysis, WHO World malaria report (for the respective years).

GF, Global Fund

[3] Global Fund PPM, UNICEF and WHO data are complete for the 2014 calendar year. PMI data are as of mid-December 2014 and include RDT procurements that would be delivered in early 2015. PQR data were accessed on 27 February 2015.

[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/PPM data replaced those PQR entries that specified VPP as the procurement method.

FIGURE 2
Source of data in the procurement dataset



Source: 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 four sources, as other donors/institutional buyers do not have centralized databases or are unable to make information readily 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. 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.

ACT Watch

ACT Watch is a multicountry research project that began in 2008 to monitor antimalarial and RDT supply and demand. In most countries, ACT Watch has conducted several rounds of outlet surveys, two rounds of household surveys and a supply chain mapping exercise. Results of ACT Watch studies are available online (http://www.actwatch.info). The most recent data from ACT Watch on diagnostic test availability have been included in this report.

Roll Back Malaria Partnership/ALMA

On the demand side, attempts to collect RDT procurement data directly from countries have 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. Estimates from May 2015 have been included in this report.

Acknowledgements

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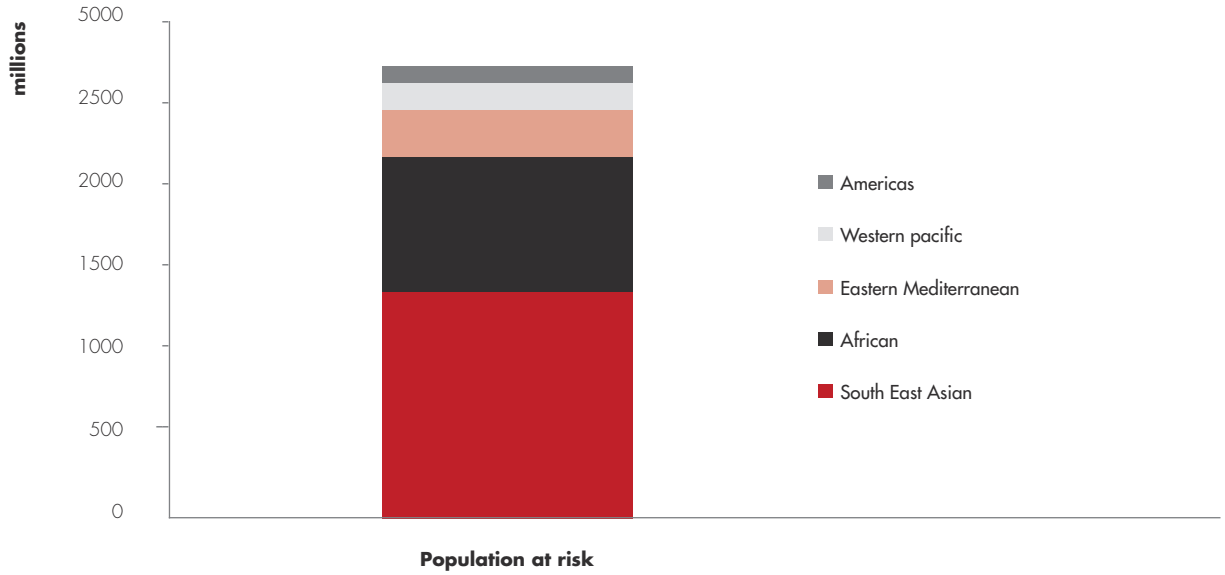
3. Public health problem and commodity access

Over 2.8 billion people across 96 countries were at risk of malaria in 2014 *(1)* (Figure 3) and the number of people living in malaria-affected countries is expected to increase in the next 15 years, given expected population growth in these regions *(2)*. In 2014, there were an estimated 214 million cases of malaria and 438 000 deaths. Although the risk is widespread, the number of cases and deaths is highly concentrated in Africa (88% of cases and 90% of deaths) due to the dominance of the *Plasmodium falciparum (Pf)* species in Africa, which is the most deadly species *(1)*. *Plasmodium vivax (Pv)* is the most widely distributed malaria species, responsible for half of the cases outside of Africa.

FIGURE 3

Population at risk for malaria by WHO region, 2014



Source: World Health Organization 2015 (1).

Role of diagnostics in managing fever/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, there can be many other reasons why a patient might present with fever, and presumptive treatment results in massive overtreatment of malaria and misuse of antimalarial medicines for non-malaria illness. Since 2010, WHO has been recommending testing to confirm any suspected case before treatment.

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. *P. vivax* and *Plasmodium ovale* can relapse weeks and months after treatment unless the dormant liver form (hypnozoites, absent in other species) is also treated.

From a market perspective, the number of suspected fevers drives the potential market size for malaria diagnostic tests. The number of suspected fevers is a function of: (i) the population at risk (i.e. most fevers in populations at risk should be tested, even though a substantial proportion will not be caused by malaria); and (ii) the malaria burden (i.e. a high burden of malaria will contribute to a higher number of fevers in the population overall).

Role of malaria diagnostics in surveillance and programme management

Malaria diagnostic test result data underpins many surveillance activities and is an important analytical tool that supports malaria programme management, for example, providing information on case prevalence to inform targeting of interventions.

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), which is typically passive. This is accomplished primarily by reporting of malaria cases by health facilities and by periodic prevalence surveys. Historically, reporting by health facilities has been based on a combination of both presumptively treated cases (cases not confirmed with a diagnostic test) and confirmed cases, providing limited insight into the actual disease burden. As diagnostic capacity increases and surveillance strengthens there is an opportunity to gain an increasingly accurate picture of malaria incidence that may be used to monitor the effectiveness of interventions, to assess progress and to inform programmatic decision-making.

As malaria prevalence declines, additional surveillance activities begin, aimed at developing a finer-grain picture of transmission. Surveillance activities in elimination settings are characterized by a shift in focus to individuals as opposed to aggregate population-level data and an emphasis on identifying all infections, including asymptomatic and subpatent[5] infections, because these may contribute to onward transmission of malaria. Annex 1 describes many of the surveillance activities that utilize malaria diagnostics; the specific set of activities that programmes take to identify infections and measure transmission is varied, and there is little guidance or best practice available.

Changes in epidemiology

Global disease reductions, although this progress is fragile and uneven. Since 2000, there has been dramatic reduction in the global burden of malaria, with incidence falling by 37% and deaths by 60% between 2000 and 2015 *(1)*. However, gains are uneven and fragile. The highest-burden countries have seen slower decreases in their malaria burden *(1)*. Additionally, modelling suggests that if malaria intervention coverage remains at current levels, incidence could actually increase moderately as a result of a partial loss of malaria immunity among populations that have recently experienced substantial reductions in transmission *(2)*.

P. vivax. It is increasingly recognized that *P. vivax* presents a major challenge for malaria control and elimination *(1)*. Although for many years *P. vivax* was considered to be relatively benign, severe disease and death have been reported from all regions *(3)*. Many of the control measures that work effectively for *P. falciparum* work less well for *P. vivax;* in areas where both species exist, *P. falciparum* incidence usually declines more rapidly than *P. vivax*. As a result, *P. vivax* is the predominant species in countries that are candidates for malaria elimination. The increasing focus on *P. vivax* is creating demand for new diagnostics (discussed in Section 5).

[5] Subpatent refers to infections that are below the detection limit of commonly used diagnostics such as RDTs and microscopy.

Elimination. The progress in some countries in reducing their burdens to very low levels puts malaria elimination in reach. Over one third of countries with ongoing transmission have committed to move from controlled low-endemic malaria to elimination in the coming decades *(4)*. The shifting epidemiology has several implications for diagnostics, including a need for new diagnostics and new approaches to delivering them (discussed in Section 5). Epidemiologically, recent research indicates that as transmission declines, many infections are asymptomatic[6] yet are still transmitting malaria. Ideally, as many of these asymptomatic infections as possible would be identified and treated to interrupt transmission; however, since these individuals do not feel ill, they will not present at health facilities and must be sought out proactively in the community. Moreover, many of these asymptomatic individuals have very low-density parasitaemia, below the limit of detection (LOD) of RDTs and microscopy (referred to as "subpatent" or "submicroscopic" infections), presenting challenges for their identification, and creating a need for new more sensitive diagnostic tests capable of detecting a larger proportion of the asymptomatic reservoir. Finally, in low-transmission settings parasites become increasingly clustered in small areas and specific populations that are often hard to reach and have lower access to health services.

Global targets for malaria

In light of recent progress and the potential for malaria to resurge, in 2015, the Sixty-eighth World Health Assembly adopted in resolution WHA68.2 the WHO Global Technical Strategy for Malaria 2016–2030 (GTS), a new 15-year roadmap for malaria control and elimination *(2)*. The GTS establishes ambitious targets: by 2030, it aims to further reduce malaria incidence and mortality by 90% and to eliminate malaria from 35 countries. With respect to diagnosis, the GTS emphasizes the need to achieve

[6] Note about immunity, asymptomatic malaria infection and transmission: While the correlation between illness, immunity and parasite density is not perfect, in general, people with low immunity (e.g. young children and people living in areas of very low transmission) are likely to become ill at low parasite densities. (Parasite density refers to the volume of parasites in a given quantity of blood, and depends on several factors, including species, genetic and immunological factors of the patient, duration of the malaria infection and the effectiveness of any treatments already taken). Adults living in higher-transmission settings usually have developed immunity and, while they may have parasites circulating in their blood, they may not have symptoms of malaria (i.e. asymptomatic infections). An individual's background level of immunity is determined primarily by the extent of malaria transmission where they live. For example, people living in stable or high-transmission areas are infected frequently and they generally develop some immunity by late childhood.
The association between infection and clinical symptoms in areas of unstable or low transmission (Asia and Latin America, and increasingly parts of Africa) is not completely understood. For many years, it was believed that populations in low-transmission areas were less likely to develop immunity and people of all ages would develop symptoms of malaria, even with low density infections, and seek treatment at a health facility. However, researchers using molecular tests have found that the number of asymptomatic infections outnumbers the symptomatic infections in all transmission areas (5). Little is known about the reservoir in different settings (e.g. size, parasite density and dynamics) and how it contributes to transmission. While experts believe that some proportion of these individuals should be identified and treated in order to interrupt transmission, the best way to do this is not clear and will be informed by additional research on the reservoir's characteristics and infectivity.

universal coverage of core interventions, including diagnostic testing, and highlights the importance of linking test results to surveillance, monitoring and evaluation systems. It also identifies several areas where innovation is necessary, including innovative delivery methods and new diagnostic technologies (discussed in Section 5).

Malaria diagnostics policies

Clear predictable policy and regulatory processes are essential for ensuring safe and effective use of diagnostics and for accelerating adoption and use of new products. As new diagnostics become available, the WHO Global Malaria Programme (GMP) and national programmes play an important role in making policy recommendations about their use that have implications for markets. For example, inclusion of a diagnostic test in WHO guidelines, as well as in national guidelines, often leads to increased public sector procurement, awareness of the test among public sector providers (e.g. through official trainings; job aids) and may increase awareness of the test among private providers. Additionally, most donors only fund products that are consistent with WHO and national guidelines.

WHO GMP policies and guidelines include recommendations about when testing should be performed, minimum performance standards for key diagnostic technologies, preferred operational characteristics and recommended quality assurance (QA) measures. Frequently, WHO also provides implementation guidance. The WHO Malaria Policy Advisory Committee (MPAC) has been in place since 2011 to advise on policy recommendations for malaria. In practice, it meets twice a year, and is supported by several expert committees (e.g. Evidence Review Groups, convened on an ad hoc basis to provide draft recommendations to MPAC on specific issues, and Technical Expert Groups). MPAC priorities and meeting agendas are established with the WHO GMP and with input from malaria-endemic countries.

At the country level, national malaria programmes usually convene an expert committee to update national treatment guidelines every few years, and generally countries, especially those relying on donor funding, align their diagnostic policies with WHO recommendations. Other relevant guidelines include those for integrated management of childhood illnesses and national laboratory policies; ideally (although often not the case) these are aligned with the national malaria control programme policies on malaria diagnosis.

The primary WHO guideline for diagnosis is the 2010 recommendation that that all cases of suspected malaria be confirmed with a parasitological test (microscopy or RDT) before treatment in order to guide rational use of antimalarial medicines *(6)*. In addition, in 2012, WHO launched the T3: Test. Treat. Track initiative, underscoring

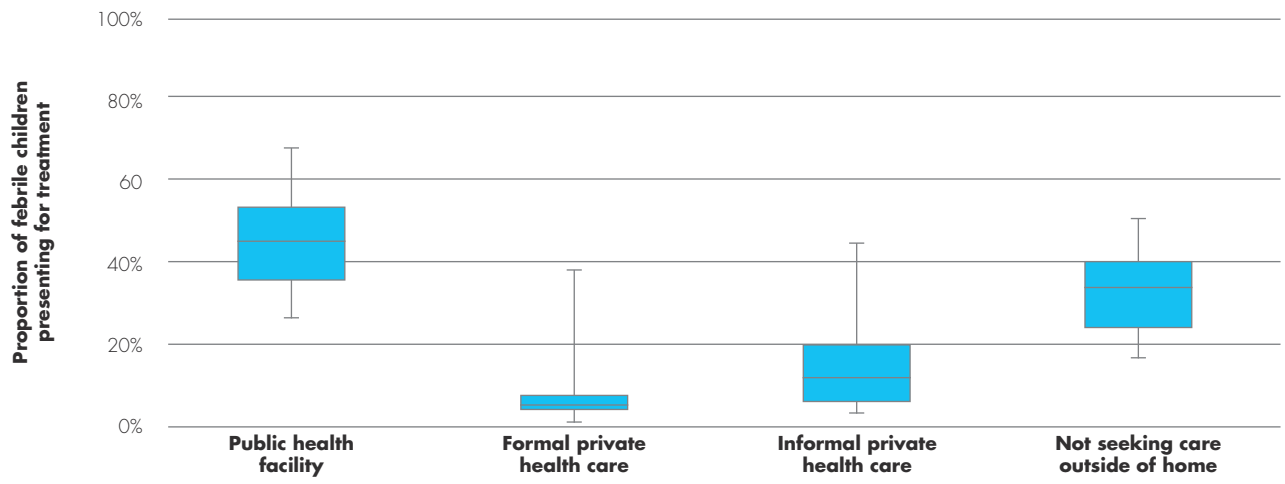
the importance of scaling up malaria diagnosis and ensuring that the data generated through testing are systematically reported. Alignment with WHO testing policy is high among countries, however, universal access to testing will take some time to achieve given the low testing rates, seen particularly in the high-burden countries, as will strengthening surveillance. WHO also plays an important role in malaria RDT procurement by establishing recommendations based on minimum performance criteria and maintaining a list of independent product performance against these criteria. It has also issued guidance on G6PD testing, testing in pregnancy and use of high-sensitivity diagnostic tests in low-prevalence settings. Annex 2 provides an overview of relevant WHO policies relating to malaria diagnosis.

Access to malaria diagnostics for case management

Although malaria-like fevers occur frequently, the ways in which individuals respond vary. 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 (e.g. 35% of febrile children under 5) *(1)* who take no action when they experience malaria-like symptoms (Figure 4).

FIGURE 4

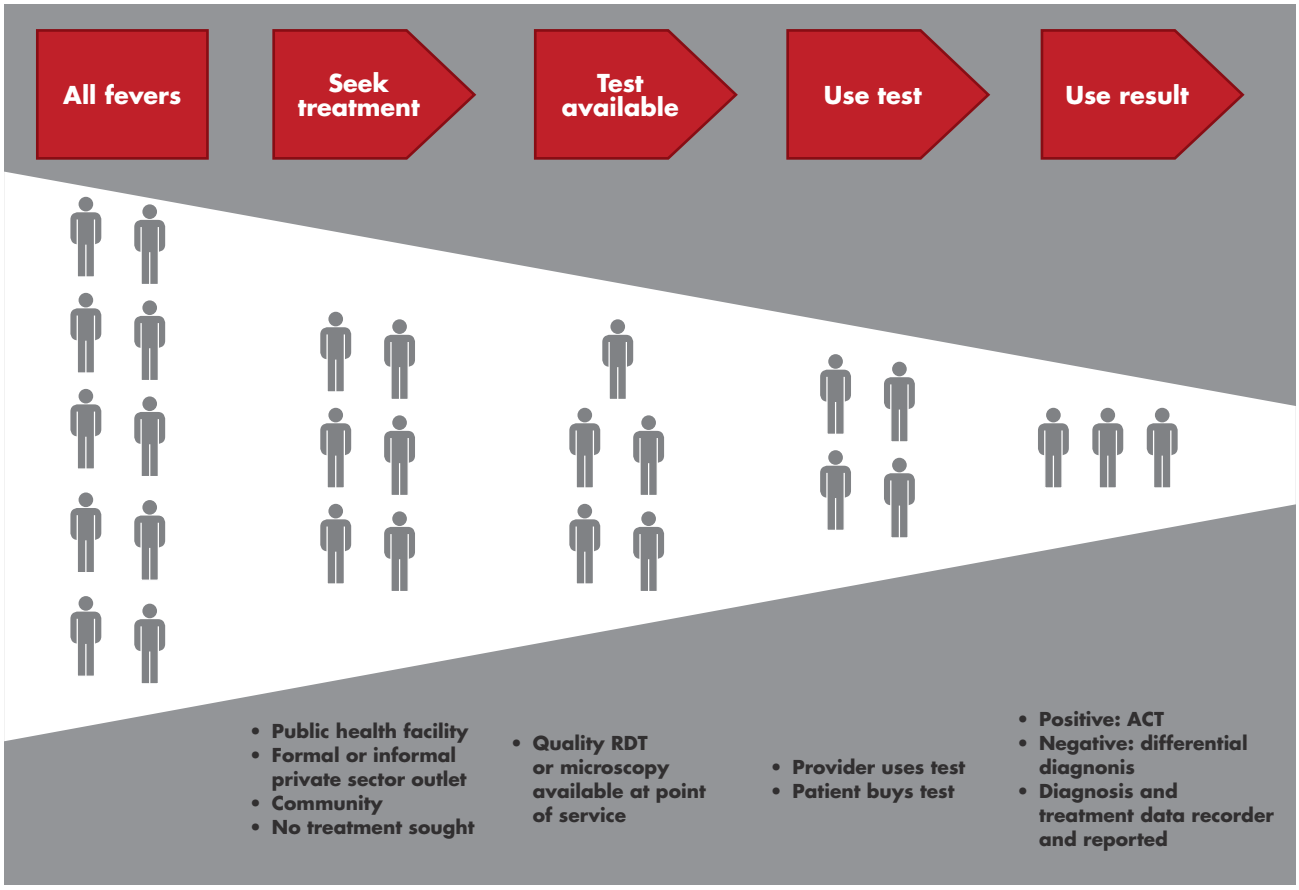
Proportion of febrile children presenting for treatment by health sector, sub-Saharan Africa, 2013–2015



Source: World Health Organization 2015 (1), based on household surveys.

Access to malaria testing also depends on the availability of a quality test at the point of service. 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 – for example, an artemisinin-based combination therapy (ACT) – and for negative cases, an alternative diagnosis or referral. Lastly, data on the fever, testing results and treatment must be recorded and reported (Figure 5). Evidence from the diagnostics scale-up to date suggests that even when tests are available, uptake, use of results and case reporting may be problematic.

FIGURE 5
Malaria diagnosis continuum



Source: Author analysis..

Testing rates

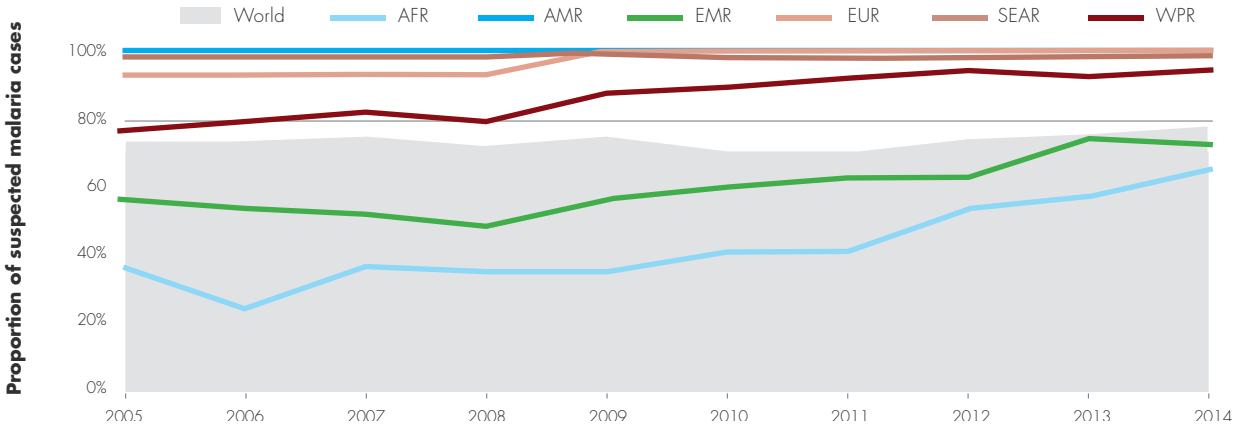
All available data suggest steady progress in increasing access to diagnosis, however, a substantial proportion of suspected malaria cases do not receive a diagnostic test. Presumptive treatment and seeking no form of care are common. Access varies by geography and sector, and is influenced by other factors, for example, living in rural areas and poverty are strong predictors of poor diagnostic test access *(7)*.

Within the public sector, a steadily increasing number of suspected malaria cases receive a parasitological test (Figure 6). In Africa, the region with the lowest access to testing, 65% of cases were tested in 2014, a 24% increase over the rate in 2010 when WHO began recommending that all fevers be tested *(1)*.

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 conducted in Africa from 2013 to 2015 indicate that for children under 5 public sector testing (median 53%) was much higher than formal private sector testing (median 36%) and informal private sector testing (median 6%) (Figure 7).

FIGURE 6

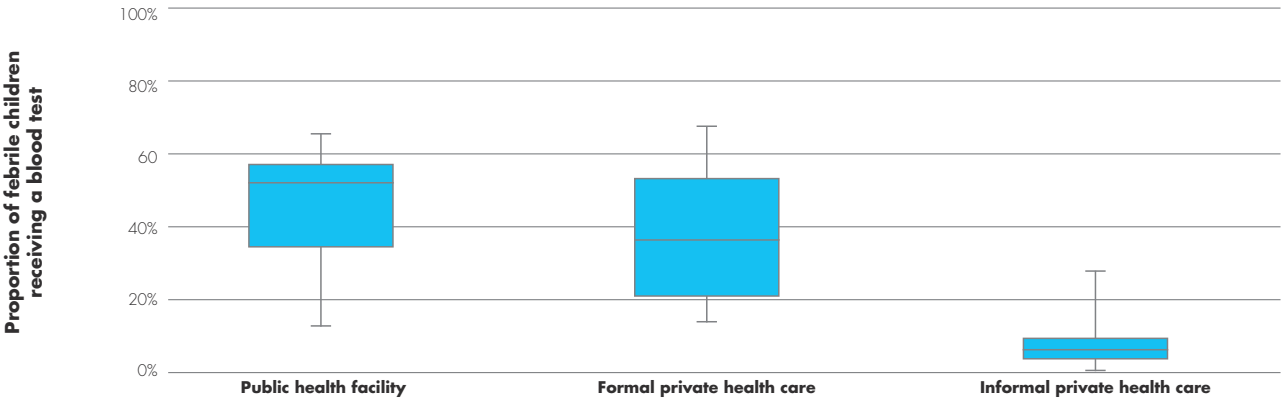
Proportion of suspected malaria cases attending public health facilities receiving a diagnostic test (2005–2014)



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: World Health Organization 2015 *(1)*.

FIGURE 7

Proportion of febrile children who had a blood test, by health sector, sub-Saharan 2013–2015



Source: World Health Organization 2015 *(1)*.

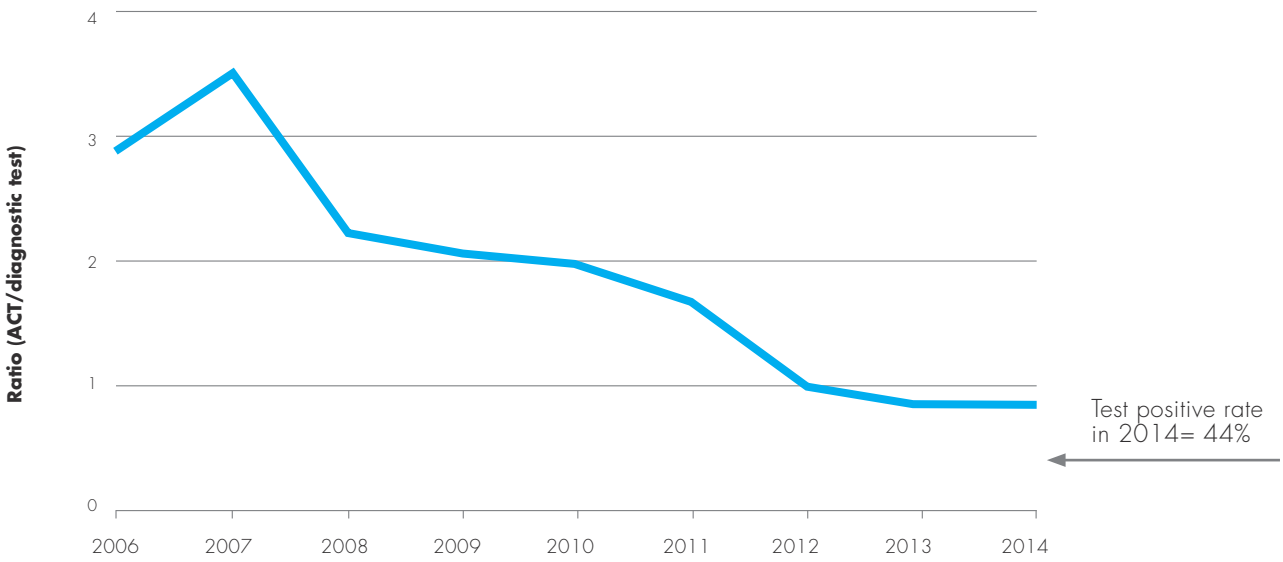
Use of test results: appropriate management of fever

In order for diagnostics to impact health outcomes, test results must influence patient management and treatment. To date, 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.

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.[7] For the first time in 2012, the total number of tests in the African public sector exceeds the number of ACTs distributed (Figure 8), however, considering test positivity rates (<44% across all sub-Saharan African countries), this number of diagnostic tests should exceed ACTs considerably *(1)*.

FIGURE 8

Ratio of ACT treatment courses distributed to malaria diagnostic tests (RDT and microscopy) performed, African Region, 2006–2014



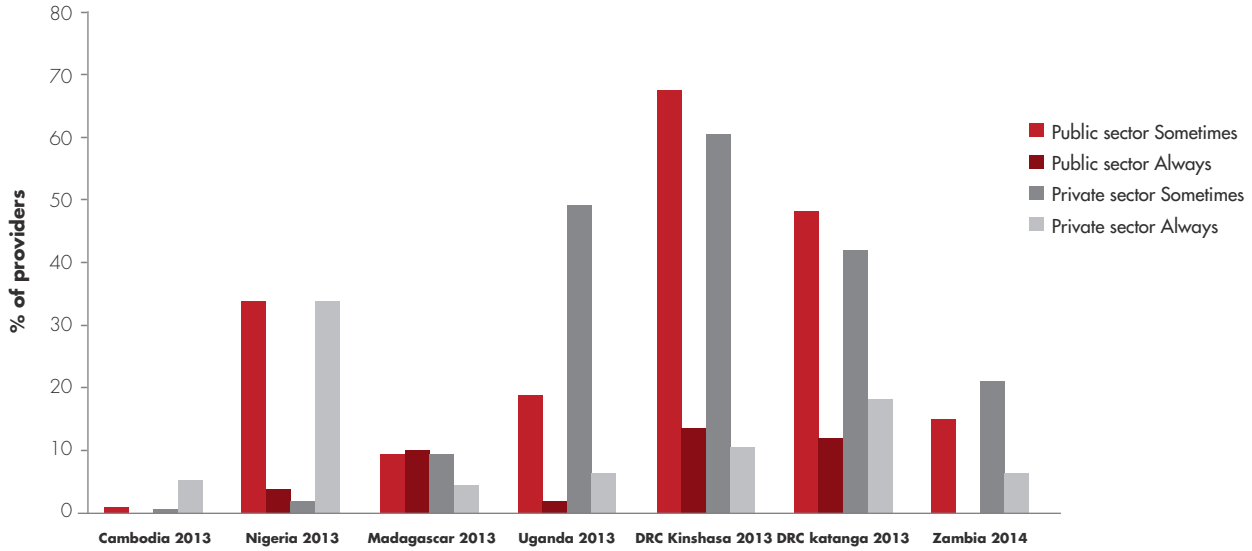
Source: World Health Organization 2015 *(1)*.

ACT Watch surveys indicate varying degrees of adherence to RDT results. In some countries, many public and private sector providers would "sometimes" or "always" recommend an antimalarial even when RDT results are negative (Figure 9).

[7] 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.

FIGURE 9

Percentage of providers reportedly recommending a client with negative RDT take an antimalarial



DRC, Democratic Republic of the Congo
Source: ACT Watch Outlet Surveys.

Implications of low access to testing

While progress has been made in expanding access to diagnostic testing in the past few years, presumptive treatment is still common, as is seeking no form of treatment for fever, and 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 personal and government and donor resources as well as potentially contributing to drug resistance. Additional benefits of scaling up diagnostic testing include improving the quality of care for febrile patients with or 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.

4. Performance, quality and regulatory programmes

This section describes various performance, quality and regulatory initiatives for malaria diagnostics; note that several of them are only relevant to malaria RDTs.

WHO Product Testing Programme (only for malaria RDTs)

In response to issues around product performance and quality in the field, in the early 2000s, a global initiative emerged to establish quality standards for RDTs.[8] This initiative resulted in the launch of the WHO Product Testing Programme, a laboratory evaluation that directly compares the performance of RDTs to each other using a standardized panel of specimens and procedures. The programme is voluntary and is available to ISO 13458 certified companies producing blood-based RDTs targeting parasite antigens. Since 2008, six rounds of testing have been completed representing 247 products, comprising 171 individual products and 52 product resubmissions. The call for expression of interest for the seventh round began in 2015. The results are published in a report format[9] and are available through an online tool that enables users to filter through large amounts of data to identify RDTs meeting specific criteria.[10]

Since the fifth round of testing, manufacturers must resubmit their tests every five years in order to remain listed in the *WHO Product testing report* and to be recommended for WHO procurement. Changes and improvements to RDTs may

[8] The programme was coordinated initially by the WHO Regional Office for the Western Pacific and the WHO Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and subsequently by WHO/GMP and FIND. Testing is performed at the US CDC.

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

[10] The FIND interactive guide for product testing is available online (http://www.finddiagnostics.org/programs/malaria/find_activities/product_testing/malaria-rdt-product-testing/).

also trigger resubmission *(8)*. 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. As a result of higher than expected demand for testing, often limits have been placed on the number of products submitted per manufacturer to each round of testing.

WHO-FIND Lot Testing Programme (only for malaria RDTs)

The Lot Testing Programme operated by WHO and the Foundation for Innovative New Diagnostics (FIND) is designed to detect major flaws in RDT performance. The programme allows buyers of RDTs to test individual lots (i.e. batches) of RDTs before using them. Users send a sample of RDTs from each lot to one of two recognized reference laboratories for quality control (QC) testing, which includes an initial test of the RDT as well as later testing at intervals to assess the stability of the test over its shelf life. 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) and is insufficient to make fine distinctions in RDT performance. The number of lots tested, as well as the average lot size, has increased since the programme began. Cumulative results are published twice annually.[11]

WHO Prequalification of In Vitro Diagnostics Programme (PQ)

The WHO PQ provides independent technical information on the safety, quality and performance of diagnostic in vitro diagnostics for priority diseases that are suitable for use in resource-limiting settings. The first priority of the WHO PQ is to review and recommend diagnostic devices of sufficient quality for UN procurement. However, in practice, prequalification status is used more broadly, with many national programmes and donors looking to the WHO PQ due to the absence of robust regulatory processes at the country level for diagnostic tests.

[11] Cumulative lot testing results are available online (http://www.finddiagnostics.org/about/what_we_do/successes/malaria_rdt_lot_testing_results/index.html).

The WHO PQ process is comprehensive, including dossier review, independent product evaluation in a qualified laboratory (the Product Testing Programme for malaria RDTs) and site inspections to review manufacturing quality management systems (QMS). In order to improve efficiency, in mid-2014, the WHO PQ established limitations for WHO workdays as well as for manufacturer responses. The WHO PQ charges a fee of US$ 12 000; however, in an effort to reduce reliance on donor funding, it is considering increasing the contributions from manufacturers.

With respect to malaria diagnostics, currently blood-based malaria RDTs are within the WHO PQ scope, which is likely to expand to include G6PD testing in the near future. Expansion to other types of tests is possible, depending on priority needs identified by WHO and funding.

Global Fund/UNITAID Expert Review Panel for diagnostics

Although it has not been used for malaria diagnostics before, it would also be possible for the Global Fund/UNITAID Expert Review Panel for diagnostics (ERPd) to determine that a new product is acceptable for procurement by the Global Fund and UNITIAD. The panel is a relatively new mechanism, comprising experts that assesses the potential risks and benefits associated with use of diagnostics that are not prequalified or regulatory authority approved. The panel makes time-limited recommendations for procurement, with the expectation that manufacturers will submit products to the WHO PQ or to a robust regulatory process. The panel schedule is ad hoc and initiated by the Global Fund and UNITAID based on market demand and product availability.

Other regulators

US FDA

The United States Food and Drug Administration (US FDA) regulates in vitro diagnostic assays under the guidelines for medical devices.[12] There is only one

[12] The specific regulations of a medical device are determined by its classification as a Class I, II or III device, where Class I and II devices pose little risk to a patient. Typically, in vitro diagnostic assays are classified as either Class I or II devices and, therefore, are subject to relatively less stringent regulations. Class III devices require a pre-market approval from the US FDA, which is only granted if the pre-market approval application includes sufficient data to demonstrate safety and efficacy of the device. Class I and II devices can be approved through an alternate process (510(k) application in which approval is granted if the new device is determined to be equivalent in safety and efficacy to an existing US FDA-approved device that is intended for the same use.

company, Binax (now owned by Alere), with a US FDA-approved malaria RDT, the Binax Now malaria test that received 510(k) clearance in 2007. The test was developed by Binax in partnership with the Walter Reed Army Institute, which needed a rapid malaria test for use by the US military. Because the test would be sold to the US military, it required US FDA approval. However, finding a diagnostics company that was willing to work with the military to seek US FDA approval was difficult. Many larger diagnostics companies did not view the business as profitable enough to warrant investment in the costly and lengthy US FDA approval process and smaller companies lacked the experience and resources to bring a test through the US FDA process *(9)*. Currently, the Binax Now test is many times more expensive than other non-US FDA-approved RDTs used in the public sector and is marketed in developed countries, primarily to the military, laboratories and international travellers.

European Union CE Mark[13]

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.[14] The changes would likely reclassify malaria diagnostics into a higher-risk category,[15] 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. The new legislation would likely have a 5-year transition period and, therefore, is unlikely to affect the market in the near term.[16]

Local regulators

While each country may have local processes and registrations, in practice, standards are generally limited and are poorly enforced for malaria diagnostics.

[13] 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 Europeénne.

[14] 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).

[15] It is expeted that malaria RDTs would be Class C, with Class D being the highest-risk category for HIV tests/blood grouping tests.

[16] The discussion of the proposed changes to the European Union regulations is based on personal communication with the European Diagnostic Manufacturers Association in August 2013. No update was available for this edition of the landscape.

TABLE 1
Summary of approaches to malaria diagnosis

Approach	Description	Use	Market characteristics
Antigen (mRDT)	Disposable lateral flow tests that detect antigens produced by malaria parasite. Portable and minimal training required.	Clinical diagnosis.	314 million RDTs sold in 2014. Rapidly growing market (38% annual volume growth, 21% annual revenue growth 2008–2014); size and growth attractive to suppliers, although in 2014 demand dipped slightly (see Section 6). Low unit cost. Incremental R&D (e.g. improving existing products to meet minimum standards or reduce costs); ground-breaking innovation is largely donor supported.
Microscopy	Direct visualization of parasite using microscope (platform technology) and stained slides. Requires training, electricity, simple reagents and QA/QC for reliable results.	Clinical diagnosis, monitoring response to treatment, QA/QC, surveillance and research.	197 million slides read (predominantly public sector) and reported to WHO in 2013. Mature, stable market. Multiple suppliers of equipment, regents and consumables. Low unit cost, especially at high volumes. R&D largely focused on developing automated systems, cell phone systems.
Nucleic acid (PCR; LAMP)	Detection of parasite DNA. Complex tests that require highly sophisticated laboratory (less so for LAMP), instruments (platform technology) and trained technicians.	Small niche market. Used for research, surveillance and reference.	Laboratory-based method, little standardization of methods, limited availability of commercial, quality-assured test kits. Cost per test multiple times that of RDT and microscopy. Multiple R&D initiatives. R&D focuses on development of simpler devices (i.e. POC) and methods and of quality-assured-test kits. Some focus on reducing cost per test.
Hemozoin	Detection of hemozoin, a by-product of parasites. POC device for malaria. Possibility of non-invasive sampling.	Pipeline technology. Tests in development target clinical diagnosis and surveillance, possibly detection of asymptomatics.	No tests exist yet; several R&D efforts. R&D focuses on development of low-cost, reagentless, POC devices.
Spectro-scopic	Detects optical signature of molecules associated with parasites. Platform technology.	Pipeline technol-ogy.	No tests exist yet; three R&D efforts. R&D focuses on development of low-cost, reagentless rapid devices.
Serology	Detection of antibodies to malaria parasites, signifies exposure as opposed to active infection. Laboratory, instruments and trained technicians required.	Minimal use, primarily for blood bank screening. Methods for surveillance (for use in elimination settings) largely under development.	Small market for existing commercial ELISA kits used in blood bank screening. R&D to effort to identify optimal methods and standardize for surveillance use in elimination settings.

5. Malaria diagnostics technology landscape

This section describes the various approaches to diagnosing malaria, commonly used technologies and technologies in development. This is followed by a summary of progress in the development pipeline and of the malaria diagnostics R&D agenda. Two high-priority areas, diagnostics for *P. vivax* management and for elimination, are also described in more detail. This section concludes with a discussion of market challenges.

Note that 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. For technologies that are sufficiently far along in their development, a more detailed profile is available in Annex 4.

Overview of approaches to malaria diagnosis

There are several approaches to malaria diagnosis (Table 1) based on detection of different biomarkers and technology platforms.

Antigen-detecting malaria RDTs

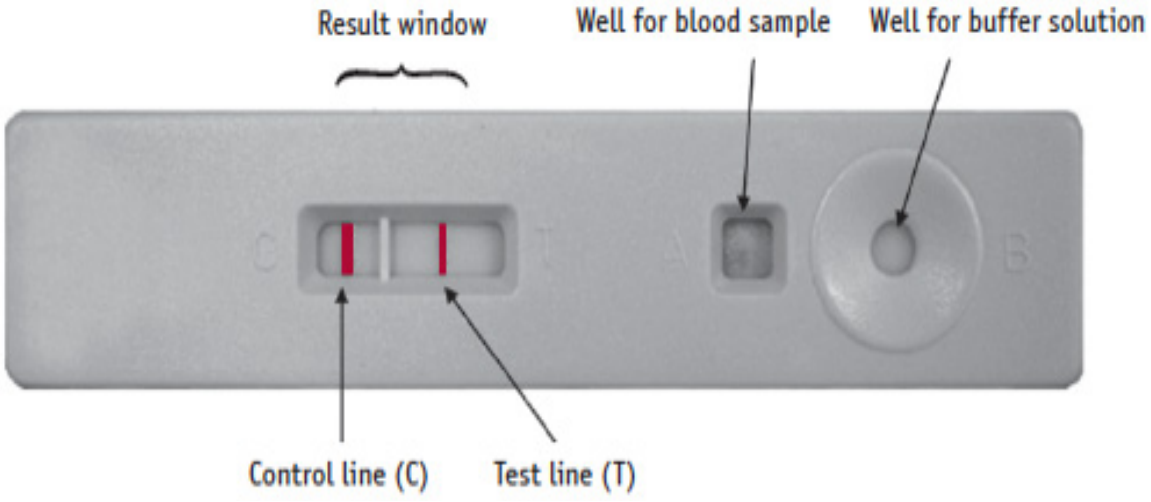
Malaria RDTs are lateral flow tests that employ antibodies to detect antigens produced by the malaria parasite. RDTs may detect one or multiple species of malaria: the most commonly used RDT detects the HRP-II antigen produced only by *P. falciparum* malaria. Other antigens detected by RDTs include pLDH 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 that only detect *P. falciparum* malaria;
- pan-malaria tests that 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 10), 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, RDTs will have two or more lines in the results window (i.e. a control line and one or more test lines).

FIGURE 10

Schematic representation of a malaria RDT cassette



Source: World Health Organization 2011
Good practices for selecting and procuring rapid diagnostic tests for malaria. Geneva: World Health Organization; 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 Round 1 of the Product Testing Programme for malaria RDTs (Section 4). This landmark evaluation concluded that there were many commercially available RDTs that performed as well as, if not better than, operational microscopy. In addition to the Product Testing Programme, two Cochrane reviews have been published on RDTs:

- A 2011 review (74 trials) concluded that there are several commercially available RDTs that demonstrated acceptable performance in detecting *P. falciparum* (>90% sensitivity and 90% specificity) across a variety of transmission settings. The review found that HRP-II-based RDTs tended to be more sensitive than pLDH-based tests, but that pLDH-based tests were more specific, although the differences were slight. The review did not identify any differences between commercial brands of RDTs *(10)*.

- In 2014, a review of RDTs for detecting *P. vivax* (37 trials) found that RDTs detecting *P. vivax* to be more sensitive (95% sensitivity) than tests with a pan line for non-*Pf* malaria[17] (sensitivity range 78–89%). The authors suggest that for clinical practice, tests for non-*Pf* malaria may be useful in areas where the majority of infection is caused by *P. falciparum*, but for *P. vivax*-endemic areas, tests designed to detect *P. vivax* specifically are more relevant and accurate *(11)*.

Advantages and limitations of RDTs

Malaria RDTs have several advantages that contribute to their growing use. Operationally, low-skilled health workers with limited training can use RDTs. They are portable and disposable, 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 testing at various levels, including when they are delivered to the country 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.[18] For malaria RDTs, practical methods and standardized technologies to enable QC testing in the field have not been widely adopted, largely due to limited availability of field-stable control materials. Dried tube specimens were developed in 2012 *(12)*, however, these are relatively complex to develop (e.g. careful characterization and standardization of parasites) and have yet to be extensively validated in the field *(13)*.

Variation and deletion 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 (e.g. variation in the number and arrangement of the genes coding

[17] There are a variety of tests with a pan line for non-Pf malaria. Most commonly, these tests have a test line for Pf and then a pan line. Common combinations include: HRP-II and pan aldolase HRP-II and pan pLDH; Pf-pLDH and pan pLDH.

[18] See: UK NEQUAS (http://www.ukneqas.org.uk/content/Pageserver.asp) and One World Accuracy (http://www.oneworldaccuracy.cdriedom/HealthMetrx/public/prepareProgram s.do?provider=CEQAL).

for HRP-II) is quite common. However, a review of 458 parasite isolates from across the world concluded that the variation did not contribute to reduced sensitivity of RDTs at 200 p/µL *(14)*. However, in a few instances, complete deletion of the gene responsible for producing 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, there have been several reports of potential HRP-II deletion in areas outside of Latin America *(15-18)*. Because of the public health implications (i.e. compromised RDT sensitivity; need to change to a different type of RDT or to microscopy) experts have called for further studies to verify the existence of potential HRP-II deletions and to estimate their prevalence *(18)*. Empirical data gained through widespread use of RDTs suggest that HRP-II deletions are not that common.

Parasite density. While the sensitivity of today's high-performing RDTs allows for accurate diagnosis malaria in people with symptoms, the LOD is not adequate for reliable detection of very low-density infections in asymptomatic individuals *(19, 20)*. High parasite density/high concentrations of antigens may also result in false negatives due to the prozone effect.[19]

Heat stability. In general, RDTs are at risk of deterioration and reduced sensitivity when they are exposed to heat and humidity for prolonged periods. The majority of malaria RDTs are labelled as stable at 4–40 °C for 18–24 months. Data from lot testing show that most RDTs retain performance after prolonged periods (e.g. 18 months) in storage and failures are infrequent and occur primarily after storage and on the *P. vivax* testing lines (see the lot testing discussion in Section 6). Conditions in some malaria-endemic settings will at times exceed the manufacturers' recommendations; the extent to which these conditions affect RDTs is not known, although there have not been any documented instances of test strip failure in the field attributable to heat instability. Recently, problems related to evaporation of buffer in single-use kits caused WHO to issue guidance against procuring single-use RDT kits (see Section 6 and Annex 6).

Detection and differentiation of non-*Pf* malaria. Although RDTs have proven to be fairly adept at detecting *P. falciparum* malaria and differentiating it from other forms of malaria, there may be scope for improving the performance of *P. vivax* detection *(3)*.[20] Additionally, there are minimal data on the ability of RDTs to detect and distinguish between the other species (i.e. *P. ovale, P. malariae, P. knowlesi*) *(21)*.

[19] The prozone effect is a false-negative (or falsely faint results) due to an excess of antigen. In the case of high density parasite infections, high antigen concentrations may block all of the available binding sites of the detection and capture antibodies in the test, preventing the binding of the antigen-antibody complex to the capture antibody. As a result, the test line does not appear.

[20] While improved *P. vivax* diagnostics would be helpful in elimination settings (for detection of the asympomatic reservoir), the need for improved *P. vivax* RDTs for clinical use is unclear. In general, *P. vivax* infections generally have lower parasite densities than P. falciparum infections and this might lead to the conclusion that a more sensitive test is required for *P. vivax* compared to P. falciparum. However, a recent review found few clinical *P. vivax* cases with submircoscopic parasiteaemia, suggesting that microscopy and RDTs are adequate for *P. vivax* case management. [Source: Cheng Q, Cunningham J, Gatton ML. Systematic review of sub-microscopic *P. vivax* infections: prevalence and determining factors. PLoS Neglected Tropical Diseases. 2015;9(1):e3413. doi: 10.1371/journal.pntd.0003413] The 2015 WHO Technical Brief on *P. vivax* recommends current RDTs (those that perform well at 200 p/µL) for detection of acute *P. vivax* infections, but also includes among "needed innovations" development of *P. vivax* tests that have an LOD of 25 p/µL for clinical settings and even lower for detection of asymptomatics in elimination settings.

Differentiating between current and past infections (i.e. persistent antigenaemia). 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 is covered in training of providers on interpretation of RDTs and it means that HRP-II RDTs cannot be used for monitoring the response to treatment. Unlike HRP-II, it appears that pLDH antigens are more closely correlated with active infection, disappearing from the blood from two to three days after effective treatment.

Quantification. RDTs are not able to quantify parasite density, which is useful for monitoring a patient's response to treatment and is at times used, along with clinical symptoms, to assess the severity of illness.

Improving antigen-detecting RDTs

Several efforts are under way to improve upon existing RDT technologies. 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)

Fyodor Biotechnologies (Maryland, US) has developed a urine-based malaria rapid test for the diagnosis of malaria in individuals with fever. The Urine Malaria Test™ (UMT) is a dipstick assay that uses immunochromatographic technology to detect specific *P. falciparum* protein fragments shed in the urine of febrile malaria patients. The test is simple to use: the UMT strip is dipped into a sample cup filled with urine and allowed to stand at room temperature for 20 minutes before the results are read. Compared to a traditional RDT, the UMT has fewer steps (no buffer, no sample transfer device) and avoids the safety risks associated with blood handling, however, limited validations suggest that sensitivity is below that of high-performing malaria RDTs and high-quality microscopy *(22)*. The UMT was launched in 2015, initially in Nigeria. Additional trials and markets are under consideration and a second-generation product for *P. falciparum* and *P. vivax* malaria diagnosis is in pre-clinical development (see Annex 4 for more detail).

QCs for RDTs

QCs for malaria RDTs may become available in the next one to two years:

FIND, MicroCoat Biotechnologie (Germany) and partners are finalizing development of positive control wells (PCWs) 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 distilled water and applied to an RDT, the

recombinant antigen solution produces a positive reaction on the RDT. Results of field trials in the Lao People's Democratic Republic and Uganda are being submitted for publication in 2016. The first product to launch will be an HRP-II and aldolase PCW; piloting will begin in February 2016 in the United Republic of Tanzania and Kenya. The development of a PCW for pLDH-based tests has been technically challenging (due to its relatively complex molecular structure) but is ongoing. While the technical development work has progressed with the support of donor funding, aspects of the business model (e.g. demand; pricing; distribution) and commercialization plans (e.g. regulatory and policy work) are pending.

Malaria RDT manufacturers also have developed QCs for RDTs; however, information on product specifications is limited. Additional studies and evidence are likely required to assess the performance and suitability of these QCs prior to widespread adoption and use.

From a policy and implementation level there are also several questions related to PCWs that will influence the use and ultimately the market for these products. There is no target product profile or minimum product standards for PCWs (e.g. heat stability requirements, the LOD that the PCW should be calibrated to detect). Additionally, from a market perspective different scenarios for use of PCWs are possible, for example, providers could use them at the point of service to check RDTs or supervisors might use them as tools. Training programmes and procedures for reporting PCW results also need to be developed. WHO is likely to convene an Evidence Review Group on field-adapted malaria RDT QC in 2016 concerning these items.

Recombinant panels

FIND and partners are developing recombinant panels for use in RDT QC at national reference laboratories (lot testing) and for purchase by RDT manufacturers and developers (as reference samples). The manufacturer will be MicroCoat Biotechnologie (Germany) and piloting in the current product and lot testing laboratories began in 2015. A final product is expected in 2016. As with the PCWs, work to develop HRP-II and aldolase recombinants is nearly complete; work on pLDH is ongoing (see Section 6 for information on how these developments are likely to be implemented).

Highly sensitive malaria RDTs

The Bill & Melinda Gates Foundation, in connection with several partners, including the PATH DIAMETER project and FIND, is leading an effort to develop highly sensitive malaria RDTs to support active case detection. As of October 2015, one manufacturer has developed a test that it claims has an improved LOD by a factor of 10 with naked eye reading. This highly sensitive RDT is expected to move into field-testing in active case detection programmes in 2016 and to launch in 2017.

The Bill & Melinda Gates Foundation initiative also includes research into the sensitivity of existing RDTs, work to characterize the asymptomatic reservoir and to

assess the impact of new diagnostics on elimination, and development of evaluation standards (e.g. HRP-II standards; a specimen bank of low-density asymptomatic infections to evaluate RDT performance and establishment of comparator assays).

The Global Good Fund at Intellectual Ventures (US) is working with GE Global Research and GE Ventures to develop an advanced lateral flow assay and reader system capable of detecting asymptomatic malaria. The partnership was announced in early 2015 *(23)* and builds on work that General Electric (GE) has done on lateral flow immunoassay technology as well as Global Good's development of a prototype reader that will detect nanoparticles tagged to key biomarkers for malaria. The team will be evaluating all aspects of lateral flow testing, including sample input, the kind of paper used, the signal generation and the reader to develop an improved system. GE suggests that a commercial model of the system could go to market in the next three to four years. While malaria is the first application, the team expects to explore use of the platform for other immunoassay-based diagnostics.

Other improvements

- **Design**. Atomo Diagnostics (Australia) has developed the AtomoRapid™, a lateral flow platform that integrates multiple steps involved in rapid testing into one device. A specially designed cassette contains a contact activated lancet, blood collection and transfer mechanics, and the test strip in one device to enable easier, safer testing. The AtomoRapid™ *Pf*/pan test was released in late 2104, however, it did not meet WHO procurement criteria in Round 6 of the Product Testing Programme. Atomo Diagnostics is also developing a device that integrates the buffer that is expected in 2016. In addition to marketing its own tests, Atomo Diagnostics works with diagnostics manufacturers to adopt their rapid tests to the Atomo platform and is working on additional designs for improved ease of use and functionality. Biosynex (France) and Hema Diagnostic Systems (US) both produce tests that do not require blood transfer devices because the sample collection area of the test is exposed, and blood transfer is done by putting this area of the device in direct contact with a drop of blood on the patient's finger. The Immunoquick Contact Falciparum RDT by Biosnyex and the Rapid 1-2-3® Pf/Pv by Hema Diagnostic Systems have been through the Product Testing Programme and meet WHO recommendations for procurement. Although all of these tests have ease of use advantages, they are typically more expensive than traditional RDTs.

- **Fluorescence**. In response to the need for improved sensitivity and LOD in malaria RDTs, companies are developing RDTs that generate a fluorescent signal and are read using an RDT reader device. The technology is similar to traditional RDTs, except that monoclonal antibodies (MAbs) 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 ultraviolet (UV) light, typically by inserting the RDT into a device that

provides a digital readout. Access Bio Inc. and Vista Diagnostics International are among the companies developing fluorescent RDTs.

- **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 commercially available products with malaria applications (Fio Deki reader and Holomic HDR-200) are profiled in the *2014 Malaria diagnostics technology and market landscape*, and it is likely that other companies are developing systems to enhance RDTs. Holomic has developed a beta version of the RDT reader application using the Google glass platform, whereby an image is transferred to a cloud for reading and interpretation.
- **MAbs**. A few efforts are under way to improve MAbs (for both existing antigens and new target antigens) and to address some of the shortcomings of RDTs (e.g. heat stability, specificity and LOD; reducing cost; identifying antigens that are highly conserved and consistently expressed and antigens that are rapidly cleared from the body immediately after an infection is cleared) *(24-26)*. Among the groups working to develop new antibodies are academic groups, RDT manufacturers and major MAbs suppliers such as Arista Biologicals, National Bioproducts Institute and Vista Diagnostics International.
- Several academic groups have reported (i.e. proof of concept) on improvements to particular aspects (e.g. sampling; labelling; detection; LOD) of malaria antigen detection tests, for example, improving the labelling by substituting the gold dyes commonly used in malaria RDTs with carbon nanofiber forests grown on glass microballoons *(27)*. Significant improvements in RDT sensitivity were also gained through a sample preparation process (using a self-contained extraction device that purifies and concentrates HRP-II) prior to conventional RDT processing *(28)*. Other researchers aiming for non-invasive testing developed a skin patch to detect HRP-II in mice *(29)* and saliva-based tests *(30)*.

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. In ideal settings, microscopy is highly sensitive and specific. 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)

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 (e.g. periodic refresher training courses for all microscopists), supervision and QA, and purchase of relatively inexpensive consumables and reagents.[21] 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 suffers 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 manufacture microscopes, a few global optics companies – Nikon, Olympus and Zeiss, 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 *(31)*.

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.

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.

Parasight (Sight Diagnostics Ltd)

Although several groups are working in this area, only one company, Sight Diagnostics Ltd (Israel), has developed and launched an automated microscopy platform. The technology uses a novel sample preparation method with custom-designed and

[21] 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.

low-cost cartridges to create an enhanced automated microscopist. The cartridge is loaded into the device, which scans and analyses a large number of fields, taking high-resolution images. Images are processed using state-of-the-art machine vision techniques. The first-generation device is a benchtop instrument capable of batch processing. Results of clinical trials in India and South Africa are forthcoming and the device has been placed in several large malaria pathology laboratories for customer validation in Europe, India and South Africa. The company is developing a low-throughput portable device (expected in 2016) and a complete blood count analysis (i.e. five point differential) for the existing platform (see Annex 4 for more detail).

Other efforts to improve and automate microscopy are described below.

Automated smear preparation and staining. Since many errors in microscopy stem from poor quality smears and staining, developers are working to automate this process to reduce operator input and to standardize quality. While automated slide preparation and staining instruments are available, they are not widely used for malaria, and tend to be used in developed country haematology laboratories. These systems are typically high throughput and work with larger quantities of blood collected in tubes which may require a blood draw rather than fingerstick *(32)*.

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. 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, life-cycle stage and quantifying the parasite density.

Various groups have been working on automated microscopy systems *(33-39)*. One active effort is the Autoscope, being developed by the Global Good Fund at Intellectual Ventures (US), which aims to be a low-cost, portable, automated microscope that reads smears. It is being developed with the drug efficacy monitoring and research applications in mind and currently developmental prototypes are in the field for initial testing.

Cell phone-based microscopy. Closely related to the automated interpretation of microscopy images is the miniaturization and incorporation of microscopes into cell phones. Some of these technologies are based on miniature lenses, while others take advantage of lens-free approaches. Recent developments include:

- IanXen (United Kingdom) xRapid technology is an early stage iPhone-based system using optical microscopy and an image analysis system to diagnose and quantify malaria parasitaemia. The system will be available both as an attachment to the eyepiece of a standard microscope and as an independent iPhone-based system (using a specially designed sleeve that attaches to an iPhone). In 2015, prototype testing began in laboratories and in the field.

- Researchers at the Indian Institute of Science are developing a hand-held device that combines microscopy, microfluidics and image processing to diagnose and quantify malaria. The device, currently in the proof-of-concept stage, uses a microfluidic cartridge to process samples, an traditional optical reader and image processing software *(40)*.

Other efforts to develop miniaturized microscopes and cell phone-based microscopy have been described in the past (e.g. CellScope; LUCAS; Lifelens, see previous *Landscapes*), however, these projects do not appear to have advanced to later stages of development for malaria diagnosis.

Nucleic acid detection

Nucleic acid detection refers to the detection of parasite genes (DNA/RNA) in a sample. These 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 *(41)*.

Given the declines in prevalence and the resulting need for more sensitive diagnostics, molecular methods are receiving more attention. In 2014, WHO issued new guidance on molecular diagnostics in low-transmission settings, recommending that once diagnostic scale-up is complete (e.g. RDTs and microscopy), low-transmission areas consider more sensitive diagnostics for epidemiological research and surveys *(42)*. There is a range of nucleic acid amplification tests (NAATs), with different performance characteristics, throughput, cost per test, equipment, infrastructure and training requirements. Due to a lack of evidence, WHO does not provide guidance on optimal platforms for country programmes *(42, 43)* (see Annex 2 for more detail).

Despite the advantages of molecular methods, many factors limit their use including: (i) high cost; (ii) high infrastructure and equipment needs; (iii) lack of standardization of methods and reference assays, and QA/QC programmes; (iv) supply chain challenges, e.g. ensuring availability of a multiplicity of required laboratory supplies; and (v) limited availability of trained laboratory technicians. Among the highest priority challenges is the need for standardization of methods, gold standard comparator assays and centralized QA/QC programmes to ensure quality and comparability of results *(41, 42, 44-46)* The lack of standardization makes results from different laboratories difficult to interpret and compare as the protocol followed, reference standard used and QA measures taken frequently differ.

The pipeline includes several initiatives to reduce the cost and complexity of nucleic acid-based technology, including the development of fully integrated POC instruments as well as initiatives focusing on one or more aspects of nucleic acid testing.(47) 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.

The following discussion focuses on polymerase chain reaction (PCR) and loop-mediated isothermal amplification (LAMP), as PCR is the most widespread NAAT and a substantial amount of work has been done to develop LAMP as a possible alternative to PCR in resource-poor settings. Although there are several POC PCR platforms currently on the market and in the pipeline (e.g. Alere; Cepheid; Phillips), most do not currently include malaria assays.

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, generally surpassing today's microscopic and antigen detection methods in sensitivity and specificity. With regard to LOD, PCR can detect as few as 1 p/μL of blood (using a fingerprick sample) as compared to 50–100 p/μL for microscopy or RDTs. Using higher volumes of blood (e.g. venepuncture rather than fingerprick), researchers have developed ultrasensitive PCR with an LOD of 22 p/mL *(48)*.

Generally, 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 reagents only, also requires significant investment in infrastructure, equipment, materials, etc.) than microscopy and RDTs *(47)*. 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. It is also used for surveillance purposes, and ultrasensitive PCR using high volumes of blood have been used to study the asymptomatic reservoir.

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.

Although a few commercial kits for PCR are available, they are not widely 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.

Active efforts to commercialize PCR-based malaria assays for use in resource-poor settings are described below; those sufficiently far along in the development have also been profiled in Annex 4.

Truelab™ micro PCR platform (Molbio Diagnostics)

In 2013, Molbio Diagnostics (India, a joint venture of the Tulip Group and Bigtec Labs) launched the TrueLab™ micro PCR platform and a *P. falciparum* assay. The Truelab™ 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 tuberculosis (TB) diagnostic, followed by malaria, hepatitis, H1N1 and dengue. Other applications are in process (see Annex 4 for more detail). Although the initial malaria test was launched in 2013, ongoing R&D to improve the system includes:

- A three-wavelength PCR device will soon replace the existing two-wavelength device, allowing for three independent PCR reactions on one chip (i.e. internal control, and two additional channels for testing).
- A *P. falciparum/P. vivax* test has been developed and validated internally, and will be introduced with the three-wavelength PCR device. Evaluations in India are planned.
- A higher-throughput device that runs four chips at a time, the Truelab™ Quattro, is expected in 2016. It will have a throughput of 45 tests in eight hours.
- A disposable, cartridge-based fully automated sample prep system is under validations.
- A fully automated system is in the prototype stage; it is expected to launch in late 2016.

NALFIA DIAGMAL (DIAGMAL Consortium[22])

The DIAGMAL Consortium is a collaborative project (European Union Framework 7 project) aiming to develop a molecular test for detection of malaria that is more readily adapted to resource-constrained settings than traditional PCR methods. The DIAGMAL assay provides several advantages to traditional PCR methods: (i) the assay is a direct PCR, meaning it uses whole blood and does not require any sample preparation; (ii) following PCR amplification, amplicons are transferred through a closed transfer unit to the detection device thereby circumventing risk of contamination (i.e. false positives); (iii) the detection of DNA is carried out using a disposable lateral flow test device (nucleic acid lateral flow immunoassay or NALFIA); and (iv) the kit contains all of the necessary primers and reagents in a stabilized form and the lateral flow device required to run the test. The test format is multiplex, allowing for the simultaneous and specific detection of *P. falciparum* and *P. vivax* as well as general detection of other human *Plasmodium* species. Early development and field evaluations were carried out under the now complete European Union project MALACTRES. After successful published proof–of-concept laboratory evaluations and field evaluations in Burkina Faso and Thailand *(49, 50)* the assay is now being further evaluated in Kenya and Viet Nam. In 2015–2016, the developers will progress the DIAGMAL assay to a market-ready product and subsequently look to perform further evaluations in specific settings (e.g. elimination; malaria in pregnancy). Launch is targeted for 2017 (see Annex 4 for more detail).

Nanomal (St. Georges University/QuantuMDx Group)

The Nanomal consortium, led by QuantuMDx (United Kingdom) and St. Georges University in London[23], is a European Union-funded project to develop a POC PCR system for malaria. The Q-POC™ device, developed by QuantuMdx, is a hand-held PCR and sequencing platform that uses disposable cartridges. The entire process from DNA extraction to detection occurs within the cartridge after insertion into the device, with results available in 20 minutes. A working prototype of the Q-POC™ device has been developed, and is being tested with the malaria assay cartridge. Nanomal is planning clinical trials for the malaria assay in the second half of 2016, and the target launch date is late 2017 (see Annex 4 for more detail).

Accutas (Aquila Diagnostic Systems Inc.)

Accutas is a hydrogel-based POC molecular diagnostic system for malaria, based on a hydrogel matrix that contains all of the reagents for performing DNA amplification by real-time PCR. Reagents are stored within a gel that is desiccated to enable long-term storage at room temperature. The hydrogel is reconstituted with the addition of

[22] The translation of a 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).

[23] Other consortium members: the Karolinska Insititute and Tubingen University.

whole blood, with no DNA extraction step required. Processing involves collection and transfer of a fingerprick blood sample to a disposable tube, and once inserted into the instrument, results are returned within two hours. The Accutas system is designed to be low cost and easy to use. Several field evaluations are planned for 2015–2017. In the coming year, Aquila Diagnostics Systems Inc. will be partnering to manufacture the POC PCR instrument and will be developing assays for other common causes of fever. The company also has a research version of the system that uses disposable microfluidic chips rather than tubes (see Annex 4 for more detail).

Scout (Amplino)

Amplino is a startup developing the Scout, a low-cost PCR platform for malaria, including a POC quantitative PCR instrument and malaria assay. The technology is in an advanced prototype stage and designed with simplicity, ease of usability, robustness and low cost in mind. The company is targeting US$ 250 for the device and <US$ 2 for each test. In 2015, Amplino has been finalizing its business model, fundraising and establishing field trials.

PanNat™ malaria assay (Micronics)

Micronics, a Sony Group Company (US), is developing the PanNAT™ system, a fully automated PCR system. The malaria assay has been developed in the laboratory, but further work is on hold for the near term while the company focuses on other application launches. See the *2014 Malaria diagnostics technology and market landscape* for more information on the technology.

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. Other isothermal methods (e.g. thermophilic helicase-dependent amplification; recombinase polymerase amplification) have been described, but are not fully developed or established for malaria diagnosis *(51, 52)*.

LAMP is a diagnostic test platform developed in 2000 by Eiken Chemical Ltd, a Japanese company that retains control of the intellectual property rights for LAMP. It is a benchtop platform using isothermal DNA amplification technology, whereby parasite DNA is amplified at a stable temperature and the by-products of amplification are detected based on changes in turbidity or emission of a fluorescent signal.

The LAMP procedure usually beings with a sample preparation step to extract DNA, followed by amplification and detection of DNA through reactions at a constant temperature using simple instruments (usually heating blocks or water bath, although thermocyclers and other instruments are possible). 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 structured 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 UV light to enhance visual detection, or through use of an instrument to measure turbidity or fluorescence.

Recent work suggests that LAMP can achieve sensitivity and specificity comparable to PCR and well above RDTs and microscopy. LAMP 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) reduced contamination; (v) lower cost; and (vi) reduced training and infrastructure requirements because processing LAMP is less technically complex than PCR.

Despite these advantages, LAMP is a laboratory-based test as it employs several instruments, reagents and consumables, often requires stable power and takes several steps that should be completed by dedicated trained laboratory technicians. Differentiating between species is also more complex using LAMP compared to a multiplex PCR. Generally, in LAMP it is necessary to carry out several reactions (e.g. first test for presence of *Plasmodium* [i.e. pan-malaria], then test for individual species) in order to identify species, adding cost and complexity. In addition, there is a lack of standardization in methods of sample collection, DNA extraction, amplification and detection. A range of approaches has been described recently, and evidence for most approaches is limited *(46, 53)*. For programmes wanting to adopt LAMP, identifying the optimal setup could be challenging.

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 decreased infrastructure, training and processing requirements.

LoopAmp (FIND and Eiken Chemical Ltd)

The most advanced initiative is a partnership between FIND and Eiken Chemical Ltd (Japan) to develop commercial LAMP kits. In 2012, the partnership launched the first commercial LAMP reaction test kit for malaria, LoopAmp, and several clinical evaluations have been completed (see Annex 4). 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 that is also stable at ambient temperature and does not require refrigeration. Primary advantages include heat stability of the dried-down reagents and QA of a complete kit. Compared to the reagent cost of in-house LAMP assays (US$ 0.28–2.66, reagent cost only) *(53, 54)*, the LoopAmp test is more expensive (~US$ 5.00), however, it is important to recognize that the reagent costs cited above do not take into account costs associated with maintaining a cold chain, a supply chain capable

of sourcing multiple reagents and the need for highly trained technicians capable of putting reaction mixtures together and performing QC.

FIND and partners are undertaking further R&D of the LAMP assay including: (i) development of a *P. vivax* reaction tube; (ii) simplification of the DNA extraction process from dried blood spots (prototypes have been evaluated in Zanzibar, United Republic of Tanzania; data analysis is ongoing); (iii) development of a high-throughput system that would allow for hundreds of samples to be processed in one day (demonstrated in a reference laboratory, results forthcoming); and (iv) automating the readout of the test results (completed for low-throughput LAMP). The development of a high-throughput sample processing kit in particular will enable LAMP to be scaled more easily and used for large-scale population screening efforts for malaria elimination (see Annex 4 for more detail).

LabDisk system (DiscoGnosis Consortium)

The DiscoGnosis Consortium, led by Department of Microsystems Engineering (IMTEK) and its strategic partner Hahn-Schickard in Germany,[24] is developing a POC lab-on-a-disc that tests for several febrile tropical diseases (malaria, dengue, typhoid, pneumonia) at the same time. The LabDisk platform has multiple applications; a European Union Framework 7 grant is supporting proof of principle and initial validations of the febrile tropical disease panel. In this system fingerprick blood is collected and transferred to a disposable disc containing all the reagents to perform the assays. The disc is inserted into the LabDisk Player and results are available within one hour with no further operator input. Malaria is detected using LAMP to amplify parasite DNA of *P. falciparum, P. vivax, P. malariae, P. ovale* and *P. knowlesi* and immunoassay to detect *Pf*-HRP-II and *Pf*-pLDH antigens. Prototypes of the LabDisks and LabDisk Player have been developed as have instruments for disc fabrication. For the malaria assay and tropical disease panel, initial validations are planned for early 2016. Additional funding is currently being sought to support interface with algorithm-based decision management system, larger clinical trials, development of a higher-throughput system and development of an electricity-independent operation of the LabDisk Player (see Annex 4 for more detail).

RealAmp, (US CDC)

The United Stated Centers for Disease Control (US CDC) has been active in developing and improving LAMP assays for malaria parasite detection. For example, RealAmp uses fluorescent dyes for detection. This platform uses a portable tube scanner, combining a heating block and a fluorescent reader, to perform amplification and provide an objective result based on fluorescence. Initially designed with input from CDC researchers, it is available in a 12-tube format from QIAGEN (Netherlands).

[24] Other consortium members include: Rohrer AG (Switzerland); University Hospital Basel (Switzerland); European Foundation for Clinical Nanomedicine (Switzerland); University Medical Center Göttingen (Germany); University of Stirling (United Kingdom); Magnamedics Diagnostics BV (Netherlands); MAST Group Ltd (United Kingdom).

In 2014, results of the first RealAmp field evaluations in India and Thailand were published. This trial utilized a two-tube reaction "kit" that included all reagents necessary for running LAMP at sites in Thailand *(54)*. Further improvements to the LAMP assays for malaria are being pursued with commercial partners to improve on sensitivity, sample preparation and lyophilization of reagents for field use.

Illumi**gene*® ***Malaria (Meridian Bioscience)

In 2010, Meridian Bioscience Inc. (US) launched ***illumi**gene*®, a molecular (NAAT) diagnostic system that is based on Loop-mediated isothermal amplification (LAMP) technology and in January 2016, Meridian received CE Mark for a malaria assay the system. The goal of the ***illumi**gene*® Malaria product is to address current diagnostic challenges such as simplification of sample preparation from blood, reagent stability under ambient conditions, ease of use for the end user and affordable pricing. The system includes a small benchtop instrument, the ***illumi**pro*-10™, that performs incubation and detection by measuring the change in light transmission through the sample. The ***illumi**gene*® Malaria DNA Amplification Assay detects *Plasmodium* parasite at the genus level; the kit contains all reagents and consumables needed to perform the test (sample preparation tubes, assay tubes with dried down (lyophilized) reagents, reagent buffers and external controls). Sample preparation takes less than two minutes of hands-on time and automated results are available in 40 minutes. Meridian Bioscience utilized the technical expertise of the US CDC on this project and clinical trials were conducted at Cheikh Anta Diop University of Dakar, Senegal. (See Annex 4 for more detail).

NINA (PATH and University of Calgary)

PATH and the University of Calgary have developed a non-instrumented nucleic acid amplification (NINA) technology for LAMP for detection of low-density infections that may contribute to transmission. The NINA heater requires no electricity and resembles a small thermos. Inside, an exothermic reaction generates the heat necessary for amplification to take place. The use of an engineered phase change material allows for stable temperature control and reproducibility. In a 2014 trial at the health centre level in Ethiopia using the LoopAmp kit from Eiken Chemical Ltd results were favourable *(55)*. PATH is currently evaluating potential commercialization partnerships for the reusable configuration of the NINA heater and is also collaborating to evaluate 150 prototypes of a disposable configuration of the NINA platform.

From a market perspective, the use scenarios for LAMP are not yet well defined. The relative complexity of LAMP means that it is not likely to be a clinical test for case management in control settings, but more applicable to surveillance efforts, elimination settings, and returning travellers in non-endemic countries *(43)*. Currently, several operational studies are under way to look at potential applications for the LAMP, including its suitability for detection of asymptomatic infections in elimination settings. The commercial LoopAmp kit is the most widely validated, however, it

remains relatively expensive given low demand. While alternative LAMP assays and setups have been published, most need further validation and commercialization in order to move beyond research tools.

At the implementation level, high-throughput systems and systems capable of detection of all species would simplify use of LAMP for surveys. Additionally, standardization and consensus around the optimal sample preparation, assay design, amplification platform, detection systems and reference standard for evaluation would build acceptance of LAMP.

Hemozoin detection

Several new platforms based on detection of hemozoin[25] 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 life-cycle using microscopy (in this case, it is commonly referred to as malaria pigment), it is not always detectable by traditional microscopy.

No existing POC diagnostics are based on hemozoin detection, though there are several devices in development. Although the technologies under development differ in technical approach, they generally take advantage of two unique properties of hemozoin: (i) its optical properties (hemozoin crystals scatter and depolarize light in a unique way and differently than a red blood cell/RBC); and (ii) magnetic properties (it is slightly magnetic due to its derivation from iron-containing haemoglobin).

Most of the hemozoin-based technologies are designed to be hand-held 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. Non-invasive tests, whereby hemozoin measurements would be taken directly through the skin, obviating the need for a blood sample, are also being developed and are described below. It is also possible that hemozoin concentration correlates to parasite density and, therefore, a quantitative result might be used for prognostic purposes, to assess response to treatment, or for drug development.

Disadvantages of using hemozoin as a biomarker include inability to distinguish between species of malaria and difficulties detecting hemozoin during the earliest stage of the parasite life-cycle (i.e. little or no hemozoin is present during the ring

[25] A malaria parasite produces hemozoin crystals as a by-product of its metabolism of haemoglobin: after infecting a person, the parasites enter RBCs 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.

stage of the parasite's life-cycle, approximately 6–12 hours after initial infection; as the parasite matures into trophozoite and schizont stages it becomes more metabolically active and hemozoin becomes abundant and more easily detectable). It is unclear what effect these disadvantages will have on hemozoin-based diagnostic test performance. It may depend on the intended use (e.g. as a replacement for RDTs/microsocpy in clinical diagnosis, or as a highly sensitive test for detecting asymptomatics) and the platform's ability to detect early stage infection. While several developers are pursuing hemozoin-based technologies, at least one has suspended efforts to work with this biomarker *(56)*. This disagreement about hemozoin's suitability as a biomarker and the implications for use scenarios and ultimately market potential warrant further study.

Technologies based on hemozoin include:

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

The Magneto-optical Technology (MOT) development is led by the University of Exeter, United Kingdom.[26] 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 & Melinda Gates Foundation. A prototype has undergone laboratory studies and preliminary field studies in Sierra Leone and Thailand. The first-generation device uses a fingerprick blood sample; a second-generation technology aims to be non-invasive, taking measurements through the fingernail. The developers are currently working to establish a diagnostics company to further develop and commercialize the test (see Annex 4 for more detail).

Rapid Assessment of Malaria (RAM) Device (Disease Diagnostic Group Inc.)

Disease Diagnostic Group Inc. (DDG) (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 moulding manufacturing. A 2015 version of the RAM device is now undergoing trials in Nigeria with the University of Lagos and Malaysia with the National Blood Centre (see Annex 4 for more detail).

Magneto-optical device (MOD) (Meditopian LLC)

Meditopian LLC (US) is in licensing negotiations with Case Western Reserve University for rights to a portable malaria diagnostic device using hemozoin detection (MOD, magneto-optical device) that rapidly (one minute) detects all species of malaria. The technology is achieving detection down to very low levels of parasitemia (< 10 p/μL). Early field trials in Peru have demonstrated

[26] 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.

high sensitivity and specificity (>97%). Pricing is planned to be approximately US$1 per test, which includes the disposable cuvette and a reader (based on volume purchases). The device is currently in trials in Peru and will be in an elimination study in Kenya. Meditopian LLC plans to complete final product development and commercialize the product for global distribution (see Annex 4 for more detail).

Recently, several early stage (i.e. proof-of-concept/laboratory prototype), new technologies based on hemozoin detection have also been reported in the literature, including:

- The Singapore-MIT Alliance for Research and Technology has published about an early stage hemozoin detection system. The team has developed a laboratory prototype of a magnetic resonance relaxometry (MRR)[27] system to detect low-density parasitaemia by measuring how hemozoin crystals interfere with the normal magnetic spins of hydrogen atoms *(57)*.

- A group at Rice University (US) has built a laboratory prototype and demonstrated in human non-invasive transdermal detection of malaria infection in a reagentless 10-second procedure. The test works as follows: a laser pulse passes through the skin to blood vessels, exciting the hemozoin and causing vapor nanobubbles to form around the hemozoin. Then the device measures the acoustic signals of these hemozoin-generated nanobubbles to detect malaria. The team aims to develop a device capable of large-scale screening of asymptomatic infections without blood sampling *(58, 59)*.

- Researchers at Budapest University of Technology and Economics have developed a magneto-optical method for detection of hemozoin. The system is based on a cylindrical arrangement of magnets around the sample. The magnets create a force aligning the hemozoin crystals. When the ring of magnets is rotated the crystals follow the rotation, and a polarized light measures changes in transmission intensity of the sample to detect hemozoin. The system uses a small (fingerstick) quantity of whole blood, which must be lysed. Currently, the team has developed a benchtop prototype that has undergone laboratory evaluations; they expect to test it in the field to further validate the method. Commercialization partners are being considered *(60, 61)*.

As noted in the *2014 Malaria diagnostics technology and market update,* Intellectual Ventures has stopped work on its hemozoin detection platform. The decision was based on evidence that hemozoin is not present in detectable quantities in crystalline form in young ring-stage parasites *(56)* and the inability to speciate.

[27] Magentic resonance relaxometry is similar to commonly used magentic resonance imaging (MRI), however, the device developed is miniturized and less expensive.

Spectroscopy

Spectroscopy involves the absorption of particular wavelengths of electromagnetic radiation (e.g. light) by molecules in a sample. The manner in which different molecules interact with particular wavelengths of electromagnetic radiation is unique and provides molecule-specific 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 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, though research for this report identified a few spectroscopic approaches. Both Spectraphone by QuantaSpec and SpectraWave/SpectraNet by Claro Scientific use blood samples, provide results within a few minutes and aim to be reagentless. The Spectraphone is a POC system with multiple applications. It 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 (see the *2014 Malaria diagnostics technology and market landscape* for more detail). The Claro Scientific reagentless POC system is based on optical profiling technology and 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. A malaria diagnostic and complete blood count analysis are among many assays being developed (see the *2014 Malaria diagnostics technology and market landscape* for more detail). The timelines for these technologies depend on funding, since the last *Landscape* work to develop the platforms has advanced; however, malaria assay development has stalled due to prioritization of other applications. In addition to these commercial efforts, academics at Monash University and the University of Melbourne (Australia) recently reported on an infrared spectroscopy system (using Attenuated Total Reflection-Fourier Transform Infrared Spctroscopy) that detects early stage malaria. The group is developing a portable prototype that it will pilot in Thailand *(62)*.

Serology

Malaria serology refers to the use of antigens to detect malaria antibodies, which are a marker of exposure to malaria.[28] *(63, 64)* 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 (ii) antibodies to malaria parasites are not present during the acute phase of an infection, they appear several days after initial infection. 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 a few applications, including screening blood at blood banks (primarily done in developed countries using commercially available enzyme linked immunosorbant assay/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 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. However, a number of challenges limit their use:

- **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

[28] 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.

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.

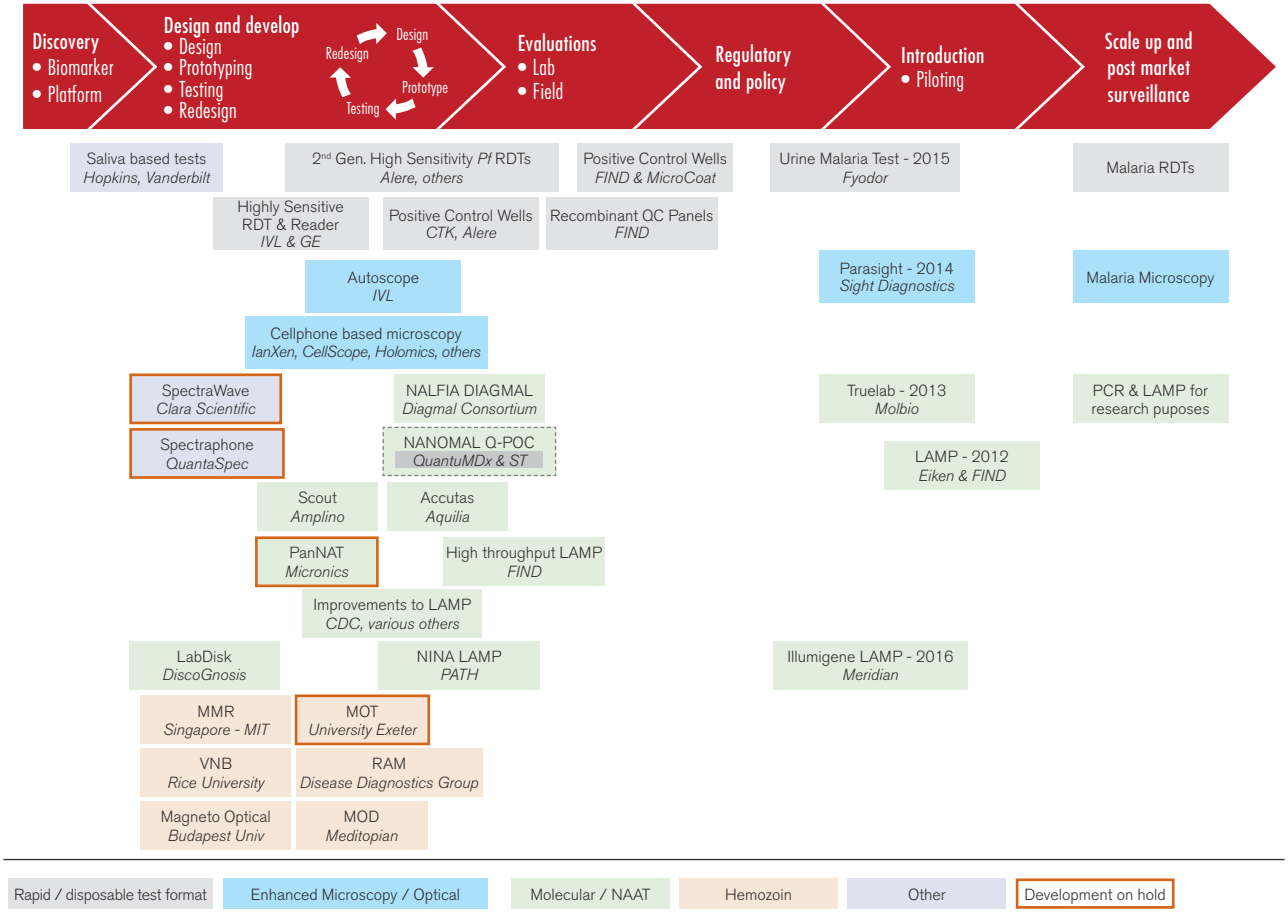
Among the groups working in this area are the London School of Hygiene & Tropical Medicine, the University of California San Francisco, and FIND. At this point the work is still exploratory.

Technology pipeline progress and the malaria R&D agenda

Products in the malaria diagnostics pipeline (Figure 11) include improvements to existing technologies (e.g. infection detection tests; automated microscopy), and others are novel platforms (e.g. hemozoin detection; spectroscopic approaches). The intended use for pipeline technologies varies, some address a specialized need and are reference technologies. Due to their cost and/or complexity they are unlikely to be used for clinical case management on a large scale (e.g. PCR; LAMP). Other technologies have broader screening applications, both for symptomatic patients (e.g. UMT) as well as asymptomatic infections (e.g. highly sensitive RDTs). Some of the technologies may be used in clinical case management as well as in infection detection, although for most it is too early to tell because key characteristics (e.g. performance data and pricing) are not yet available.

FIGURE 11

Malaria diagnostics technology pipeline overview



Source: Author analysis.

Since the *2014 Malaria diagnostics technology and market landscape*, three diagnostics have come to market.

- Sight Diagnostics Ltd launched Parasight in 2014. Parasight is positioned as an alternative to manual microscopy for laboratories that process a high volume of malaria slides. Further evaluation and piloting is under way, and several laboratories in Africa and India have purchased the system. Performance and pricing will be critical to Parasight's uptake.

- Fyodor Biotechnologies launched the UMT in late 2015. The UMT is well positioned for the retail private sector, which is the first stop for many febrile patients and would benefit from a simple test that avoids blood sampling. Additional data on its performance, affordability, usability and acceptance are needed, as these are key factors that will influence its uptake.

- Meridian Bioscience Inc. launched the ***illumi****gene*® Malaria diagnostic system in 2016. The product has the advantage of being a complete quality assured testing

system, however, the product has only just launched. Additional performance data is desired, and regulatory approvals as well as developing world pricing and distribution remain to be seen. Also, species-specific assays may be preferred to the current *Plasmodium* genus assay.

Work to improve malaria RDTs is driven primarily by donors, responding to needs expressed by some programmes and technical experts. Highly sensitive RDTs are being developed with funding from the Bill & Melinda Gates Foundation. This initiative includes several "go/no go" decision points thus future funding for product development is uncertain. However, the technical work has already resulted in more sensitive RDTs that could come to market in the next two years. Perceived demand for these highly sensitive RDTs, as well as R&D capacity, will likely inform decisions by other RDT manufacturers, who are not part of the programme, to develop highly sensitive RDTs.

Work to develop positive controls for malaria RDTs has been ongoing for several years, yet no suitable control for field use has been launched and validated sufficiently to inform adoption. There are several questions around the market (e.g. how controls might be used and packaged; size of demand) and the optimal technical specifications for the controls. As a result, it is difficult for policy-makers and national programmes to assess controls and to plan for adoption. Similarly, it is difficult to make business decisions around manufacturing, marketing and pricing.

With respect to nucleic acid tests, several organizations report progress (e.g. Accutas; Nanomal, Meridian), while progress at others has slowed or even stalled. POC NAAT devices that require minimal operator input are in the pipeline, and these systems would overcome some of the major hurdles limiting use of nucleic acid tests (e.g. training; supply chain; infrastructure; equipment). However, the price point at which this is achievable may be several times that of alternative malaria diagnostics. Actual performance of the pipeline tests in the field also remains to be seen. Because improved performance is the main advantage of nucleic acid technologies, it will influence "willingness to pay" and the overall value proposition of any NAAT.

Although the commercial kit was introduced in 2012, a number of factors contribute to relatively slow LAMP uptake: it is a moderately complex test to implement (requires a laboratory, trained technician, sample prep, and multiple tests for speciation); while the infrastructure and equipment investment is far less than PCR, the cost of the quality assured LAMP assays is high compared to "home brew" PCR and LAMP methods (even though these are not nearly as field deployable as a commercial kit). From a customer perspective, even with the quality-assured LoopAmp kit or ***illumi****gene*® malaria system, the literature includes a myriad of methods for sample preparation, amplification, and detection. For some customers this flexibility may be welcome, but for others, the lack of consensus about which methods are best could slow adoption. Lastly, while LAMP technology is well positioned as an easier to implement, less expensive test for conducting surveillance or QA/QC, a high-throughput platform is needed, but remains under development.

Most of the hemozoin technologies are relatively early stage; prototypes have been

developed and demonstrated on humans in small trials, however, it will be some time before device development is complete and evidence of their performance is available. Given the debate about the suitability of hemozoin as a biomarker, performance data from the field will be key to their acceptance and ultimately their positioning in the market, and extensive evaluations may be needed, depending on the indication for use. Currently, hemozoin devices might play a role in clinical diagnosis and, depending on ultimate LOD achieved, they could be useful screening diagnostics in elimination settings.

Work to develop both spectroscopic approaches and serological assays (to identify pockets of malaria transmission in elimination settings) is ongoing but still early stage. Two of the spectroscopy platform developers have prioritized other applications over malaria due to a lack of funding for the malaria assay.

One noticeable development in the pipeline is several technologies that do not require blood sampling. The first to launch is the UMT, which requires a urine sample. Two hemozoin devices that take measurements directly through the skin without any blood draw are in development. Lastly, researchers have reported on early stage work on saliva *(30)* and breath sampling *(65, 66)*.[29] Translating these novel approaches into diagnostics that can be used in the field and effectively compete with malaria RDTs will take time.

Ultimately, in the clinical diagnostics market (the largest market segment), the ability of new technologies to compete with RDTs in terms of cost, ease of use and diagnostic performance will be critical to their uptake in the market. RDTs have 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 market can bear. In terms of progress, while some technologies have advanced, others have not, in particular to the later stages of development (e.g. evaluations; introduction; scale-up).

In addition to case management, there are several smaller existing market segments, which are largely laboratory based, including reference tests, QA/QC testing, surveys and drug resistance monitoring (Figure 12). At the same time, changes in malaria epidemiology and shifting global priorities are expanding the role of malaria diagnostics and creating new potential market segments. While RDTs and microscopy are adequate for routine case management, there are several areas where existing technology is not adequate; as a result, the malaria diagnostics R&D agenda is lengthy (Figure 13). For example, over 10 unique diagnostics needs were identified by the 2009–2010 MalERA Consultation[30] *(67)* and several of these are reflected in the GTS *(2)* as well as recent reports by the Asia Pacific Malaria Elimination Network and PATH *(68, 69)*.

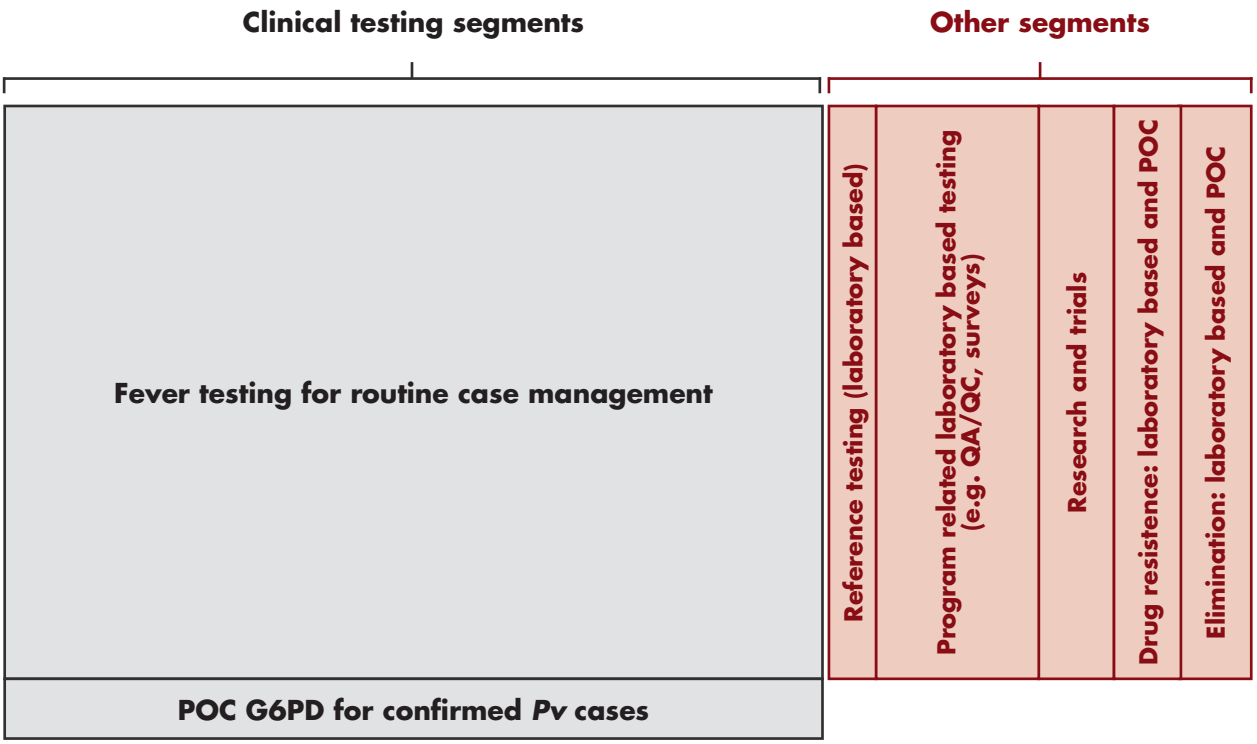
A thorough prioritization of the R&D needs has not been undertaken, and is likely debatable. Additionally, the degree of progress across these areas varies – in some cases new technologies have advanced and in others there has been no progress. For most

[29] Not a focus of this report because they are very early stage.

[30] In 2009–2010, the MalERA process engaged over 250 experts to discuss eradication. Results of this process, published in a 2011 series of papers, outlined the need for new tools (including diagnosics) resources, approaches and training. The MalERA findings are currently being updated.

of the needs, there has been limited market analysis (e.g. review of the landscape and technology pipeline; analysis of the potential market size and the commercial viability of a new product). An update of the MalERA Consultation is occurring in 2015–2016; this may bring welcome focus to the R&D agenda. However, since it focuses on eradication, it will not necessarily take the perspective of high-endemic countries into account.

FIGURE 12
Malaria diagnostics market segments



Note: Segment size is illustrative, not necessarily to scale.
Source: Author analysis.

Detailed analysis of progress for each R&D need is beyond the scope of this report. Several unmet needs (RDTs and QCs for RDTs; non-invasive diagnostics; improved microscopy) are described above, and two of the higher-priority needs, diagnostics for *P. vivax* management and for elimination, are described below. Unmet diagnostics needs that are not explored include: diagnostics to support differential diagnosis of fever; diagnostics for malaria in pregnancy;[31] and diagnostics for drug resistance. Automated readers and technologies that link diagnosis with data systems are also relevant, but beyond the scope of this report.

[31] Although diagnostics for malaria in pregnancy have been considered in previous Landscapes, the WHO recent review of ISTp and recommendation to continue with IPTp suggests that for most settings, new diagnostics for screening pregnant women is not a priority. That said, some of the more sensitive diagnostics being developed may play a role in the future in screening pregnant women, especially in pre-elimination settings: today, it is clear that RDTs and microscopy miss some of the asymptomatic infections during pregnancy; however, the clinical relevance of these infections is not clear.

In 2009–2010, the MalERA Consultation proposed the following R&D agenda for diagnostics to support malaria eradication: (i) improvements in malaria RDTs (greater consistency in *Pf* detection, more sensitive stable tests for non-*Pf* parasites); (ii) RDT QCs for use in the field and at the national level; (iii) non-invasive diagnostics; (iv) improved microscopy staining and interpretation; (v) multiplexing tests for fever diagnosis; (vi) field G6PD detection test; (vii) high-throughput field tools for detection of low-density parasitaemia (for use in survey or active case detection); (viii) minimally invasive rapid detection of low-density infections for screening of migrants/travellers; (ix) high-throughput field molecular detection capable of use at the district level of below; and (x) hypnozoite detection.

In 2015, the WHO Global Technical Strategy for Malaria 2016–2030 (GTS) identified the following new product needs: (i) improved RDTs for non-*Pf* parasites; (ii) hypnozoite diagnostics; (iii) PCWs and decentralized RDT QC; (iv) highly sensitive screening tests for elimination; (v) serological screening tests to monitor transmission; (vi) POC G6PD detection tests to support *P. vivax* case management; (vii) multiplexing to support differential diagnosis of fever; (viii) automated microscopy; (ix) development of non-invasive tests; and (x) test for drug resistance markers. Key operational research and service delivery innovation priorities include: (i) testing the effectiveness of different screening strategies both at higher transmission levels and in elimination settings; (ii) improving the understanding of treatment-seeking behaviours in order to increase demand for testing and case management; (iii) improving public and private provider adherence to guidelines for detecting, treating and recording malaria cases; and (iv) implementation research on effective deployment of existing tools.

Diagnostics to support *P. vivax* management

Approximately 35% of the world's population is at risk of *P. vivax*, and there were an estimated 15.8 million symptomatic cases of *P. vivax* malaria globally in 2013 (uncertainty range 11.9–22.0 million). For several years, the research agenda for *P. vivax* has been neglected, however, with the declines in *P. falciparum*, the relative burden of *P. vivax* is increasing. Additionally, *P. vivax* predominates in the majority of countries that are poised for elimination in the near term. With respect to diagnostics, there are three primary needs described below.

Improved *P. vivax* detection

The biology of *P. vivax* results in relatively low parasite density infections (approximately 10 times lower than *P. falciparum*)*(3)*, 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. However, microscopy quality is often variable, and speciation is challenging. While there are several malaria RDTs capable of detecting acute infections (e.g. panel detection score >90% at 200 p/µL) *(70),* because RDT sensitivity declines with parasitaemia today's RDTs

are less likely to perform well at very low densities (i.e. <200 p/µL). As such, a POC diagnostic for *P. vivax* with an LOD of 25 p/µL is desired *(3)*.

Although prioritized by the MalERA Consultation in 2010 *(67)*, progress has been limited. There has been an increase in the number of RDTs capable of detecting infections at 200 p/µL and at least one R&D effort to develop new monoclonals for pLDH. Although some of the technologies in the pipeline may have greater sensitivity for *P. vivax*, nothing in a POC format appropriate for clinical use has advanced beyond the design and development stage. One challenge for RDT developers is demonstrating performance at the lower LOD: currently, the Product Testing Programme is calibrated to parasite densities of 200 p/µL, and the evidence required by key agencies and potential buyers (e.g. WHO; national malaria programmes) for a test claiming to detect densities below this level is not clear. From a market perspective, a new affordable POC *P. vivax* test could expand access to testing (i.e. capture some potential demand that is currently being treated presumptively) and improve the quality of current screening (i.e. replace current *P. vivax*-detecting RDTs and variable quality microscopy).

POC G6PD tests

Background[32]

The need for a POC G6PD test relates primarily to treatment: without special treatment, *P. vivax* can relapse because it remains dormant in the liver for extended periods of time. Currently, the recommended treatment of *P. vivax* includes a drug to treat the primary infection (chloroquine or ACT) plus a 14-day course of primaquine, the drug used to treat the liver stage (i.e. "radical cure"). However, the use of primaquine is limited due to concerns around adverse reactions (i.e. haemolysis in people with G6PD deficiency) and poorly adapted drugs (i.e. primaquine is a 14-day regimen). A new shorter course drug, tafenoquine, may greatly improve patient adherence (currently in Phase III clinical trials, breakthrough designation by the US FDA). However, tafenoquine also causes haemolysis 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.

[32] A second need for G6PD testing (though not necessarily POC) relates to the WHO 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. WHO does not recommend G6PD testing in this instance. However, as a first step in considering implementation of low-dose primaquine, many countries are undertaking surveys to appreciate the prevalance and types of G6PD deficiency among their populations. These surveys require G6PD diagnostics – usually laboratory based – depending on the approach.

Technology landscape: POC G6PD tests

A number of commercial laboratory tests can diagnose G6PD deficiency, but these are not suited for use in settings where patients exposed to and infected with *P. vivax* live because they require skilled technicians, specialized equipment, cold chain and controlled environmental conditions. As a result, development of a POC G6PD test is among the highest priorities for *P. vivax* control and elimination.

Both quantitative and qualitative formats of POC G6PD tests are possible. Historically, a laboratory-based qualitative test (the Fluorescent Spot Test) has been used to screen for G6PD deficiency prior to administration of primaquine. Qualitative tests for G6PD deficiency can fairly accurately diagnose males and females with severe G6PD deficiency, however, they do not perform as well in females with intermediate G6PD activity levels and who may still be at risk of significant drops in haemoglobin concentration. Quantitative tests for G6PD deficiency can discriminate individuals with intermediate G6PD activity levels. Access to tafenoquine will most likely require access to quantitative G6PD tests. Target product profiles, developed by PATH, are available for both qualitative and quantitative tests to support radical cure treatment regimens.

In general, the POC qualitative tests are easy to perform, requiring no instruments and minimal training (i.e. similar to a malaria RDT). They are also likely to be less expensive than quantitative tests. Disadvantages include the visual readout that is more subjective than that of a quantitative test and the potential for qualitative tests to categorize some females as "normal" although they are actually "intermediate" and at risk of haemolysis due to a genetic phenomenon called lyonization that can cause a proportion of their cells that are deficient to be masked by the normal cells.[33]

POC quantitative tests can be hand-held biosensors that directly measure G6PD activity in blood samples based on the electro-chemical sensors. These systems utilize disposable strips that may be loaded with reagents necessary to perform the test. While these tests are able to effectively classify women, they are more expensive than a traditional RDT format.

Two POC screening tests have recently become commercially available, and there are at least three other POC products in the pipeline (Table 2).

[33] G6PD deficiency is a genetic disorder, and the gene coding for G6PD is found on the X chromosome. Since women have two X chromosomes and men have only one, there are differences in the way the disorder behaves in male and females. The disorder is more common in men because with only one copy of the X chromosome a mutation on the gene for G6PD will cause G6PD deficiency. Women have two X chromosomes, therefore, it is possible for women to have a proportion of RBCs with an X chromosome that is normal and a proportion of RBCs with abnormal X chromosomes (referred to as heterozygous females). Among heterozygous females, the proportion of deficient versus normal RBCs varies, and as a result a heterozygous female's G6PD enzyme levels may be normal (>80% activity), intermediate (30–80% activity) or deficient (<30% activity). A female with intermediate activity is at risk of haemolysis, although a qualitative test with a 30% cutoff (the typical cutoff) would classify her as normal.

TABLE 2
POC G6PD tests pipeline[34]

Type	Test and developer	Stage of development and use	Description (available technologies only)
Qualitative	CareStart™ G6PD RDT Access Bio Inc.	• Launched in 2013. • Several trials have been completed; not all results peer reviewed. • External controls and visual read-out card under development	Resembles an RDT in terms of form and process. Can be stored and performed at relatively high temperature and humidity levels. Uses a colourless dye that changes to purple-coloured in the presence of G6PD-active enzyme (see Annex 4 for more detail).
Quantitative	CareStart™ G6PD Biosensor Access Bio Inc.	• Launched in November 2014. • Field trials under way. • Version that includes Hb available in early 2016.	Hand-held device that utilizes strips to provide a quantitative result for G6PD enzymatic activity. The test measures the electrical changes associated with NADPH/NADP + reactions (see Annex 4 for more detail).
Quantitative	PATH G6PD Initiative	• Laboratory evaluations in early 2016. • Field trials in late 2016. • 2017–2018 launch[a]	G6PD/HbB combo quantitative platform.
Qualitative	PATH G6PD Initiative	• Proof of prototype in 2016. • 2017–2018 launch[a]	RDT format with control line.

One challenge related to developing POC G6PD tests has been the relative lack of evidence about G6PD deficiency and the effects of primaquine treatment on G6PD deficient individuals, e.g. the threshold level of G6PD deficiency that induces severe reactions when taking primaquine *(71)*. Although new evidence is emerging, many questions remain, especially with regard to management of heterozygous females with intermediate G6PD levels, different screening algorithms and case management scenarios, cost-effectiveness *(72)* and understanding the extent to which treatment can be safely administered without G6PD testing *(3)*. A number of programmes are conducting primaquine safety studies that will provide some insights into these questions.

Initiatives to support POC G6PD test development and introduction

Asia Pacific Malaria Elimination Network. APMEN was established in 2009 to support malaria elimination in Asia Pacific and is composed of 18 Asia Pacific countries that are pursuing malaria elimination, as well representatives of academia and key multilateral agencies. The APMEN *Vivax* Working Group supports operational research, including multiple studies focused on G6PD testing *(68)*. Since 2012, APMEN and partners, including PATH, have hosted three workshops on G6PD testing that have covered identification of knowledge gaps, target product profile development, development of evaluation standards and implementing POC G6PD testing *(71-74)*.

[34] The Binax Now G6PD test by Alere/Binax has been on the market for several years, however, its format, processing steps, temperature restrictions and cost (US$ 20) render this test unsuitable for malaria case management in developing countries (72). Although the test is US FDA approved (510k clearance), it has not been tested in field conditions.
[a] Progression to commercialization is contingent on successful prototype development

PATH G6PD initiative. The PATH G6PD test initiative is a multiyear project supporting product development and improved G6PD testing at POC. The initiative is primarily funded by the Bill & Melinda Gates Foundation and the United Kingdom Department for International Development (DFID); PATH is also partnered with GlaxoSmithKline (GSK) and the Medicines for Malaria Venture, which are developing tafenoquine. Initial work focused on landscape analysis to identify and evaluate candidate G6PD deficiency tests. After development of a target product profile for POC G6PD tests and normative guidelines for the evaluation of G6PD tests *(71)*, PATH is now supporting the development, clinical evaluation and registration of POC G6PD tests (Table 2). In addition, PATH has developed a specimen repository with highly characterized blood samples from people with a range of G6PD enzyme activity. This repository is available to any test developer, thereby reducing the cost and accelerating the timeline for new POC G6PD test development *(75)*.

WHO. In light of the growing interest in *P. vivax*, the WHO GMP has held several reviews and developed recommendations about POC G6PD testing (Annex 2). With regard to quality, none of the POC G6PD tests have undergone a stringent regulatory review, however, it is likely that the WHO PQ scope will be expanded in the near future to include G6PD testing.

Market for POC G6PD tests

From a market perspective, although some thought has been given to various implementation scenarios, limited work has been done to estimate demand for POC G6PD tests. The potential market for malaria-related G6PD testing is driven by the number of confirmed *P. vivax* cases, however, other potential uses of a POC G6PD test, for example, newborn screening in high-prevalence countries, will impact the size of the opportunity as will the extent to which POC tests replace existing laboratory G6PD testing. One study commissioned by the Medicines for Malaria Venture in Brazilian, Indian and Indonesian clinical practices found that providers have low awareness of the risk of haemolysis suggesting that incorporating G6PD testing into clinical practice will be challenging due to poor awareness of the need for the test, costs and operational issues *(76)*.

Detection of liver stage (hypnozoite)

Liver stage infections cannot be detected using current diagnostics methods and research is needed to develop tools that can detect hypnozoites in order to better define *P. vivax* prevalence and to assess the efficacy of drugs against liver stage of *P. vivax (3)*. Research for this report did not uncover any work to develop a hypnozoite detection test. At this point, the liver stage is not well understood and no biomarkers have been developed; discovery of a biomarker might stimulate diagnostic test development.

Diagnostics for elimination and low-level transmission

Currently, approximately one third of countries where malaria is endemic are in the process of moving from controlled low-endemic malaria to elimination, and the epidemiological changes as well as surveillance activities (e.g. active case detection) are creating new demands for diagnostic tests. There are many elimination-related interventions that require diagnostics, including passive and active case detection, surveys and QA/QC. The extent to which new tests would accelerate elimination can be debated *(77)*. Although there are many instances where a new diagnostic would be "nice to have", the commercial case may be difficult to make for each of the various "needs".

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 (42)*. However, as discussed previously, more robust QC for RDTs, improvements in sensitivity of non-*Pf* RDTs and POC G6PD tests are needed.

Regarding surveillance, there is interest in more sensitive tests that can identify asymptomatic, subpatent individuals who may contribute significantly to transmission. These new more sensitive tests would likely be used in active case detection. 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 appropriately, depending on the results. Testing may be done on a large scale, in which case high-throughput formats are needed, or at a smaller level (e.g. household level). Test operators may be community health workers or laboratory technicians, depending on the setting.

There are two areas of research that will influence the market for new highly sensitive tests. First, the sensitivity requirements are not well understood,[35] however, the sensitivity (in particular LOD) will influence the optimal technology platform (e.g. molecular; lateral flow) and cost of the test. Second, research on the impact of screening and treatment programmes compared to alternate interventions, in particular mass drug administration,[36] will influence the market size for new highly sensitive diagnostics. Thus far, using malaria RDTs or microscopy, screen and treat strategies have not been successful because a proportion of the infected population that is capable of transmission is not detected. However, it remains to be seen

[35] While research and modelling is beginning to provide information on the asymptomatic reservoir, several questions remain, including what level of parasitaemia leads to transmission and, therefore, needs to be detected by the diagnostics.

[36] Mass drug administration is the treatment of the entire population in a defined area with an antimalarial drug without first testing each individual for infection and regardless of the presence of symptoms. Screening and treatment involves testing each individual in a population for malaria and providing treatment to those with a positive test result. Both methods have advantages and disadvantages, and their impact on interrupting transmission is currently being studied.

what impact screen and treat interventions would have using a more sensitive diagnostic. Therefore, the market for new diagnostics, such as highly sensitive RDTs or POC NAATs, is somewhat undefined. Research to understand some of these key questions is under way and results are expected in the next one to two years.

Other elimination activities that rely on diagnostics include surveys, improving QA/QC, and origin analysis. However, the need for commercial solutions to support these activities is unclear. For example, since most prevalence survey-related diagnostic activity takes place at a central reference laboratory, priorities include simplification and standardization of procedures, cost reduction and QA/QC, as opposed to development of new commercial products. There is also ongoing work to develop and standardize serology and genetics analysis, monitor low levels of transmission, investigate cases and ultimately confirm that malaria has been eliminated, however, since these would take place in central laboratories, it is not clear if commercial solutions are necessary.

As this discussion illustrates, the area of diagnostics for elimination is evolving, with programmes and researchers aiming to identify the optimal intervention mix to support elimination and to answer questions around the ideal set of diagnostics for elimination. From a business perspective, the market opportunity is difficult to define. Furthermore, while the multiplicity of use scenarios and needs may exist, from a market perspective it would make sense to prioritize and focus on technologies that may suit multiple needs so as not to overly fragment the market.

Malaria diagnostics technology development challenges

Technology developers face several common market challenges, which are described below.

Limited awareness of the needs and market opportunity

A common challenge, and perhaps one of the primary reasons for limited pipeline progress, is disconnect between technology development and the actual market need for new diagnostics. Given the potential size of the malaria diagnostics market and relatively low testing rates, it might appear that existing technologies are not adequate to meet what appears to be a significantly underserved demand. However, this is not the case: there is broad consensus that RDTs and microscopy are adequate for clinical diagnosis. Innovation on how best to deliver these existing technologies is urgently needed.

There are, however, segments of the market for which existing technologies are not adequate. For most of the items on the diagnostics R&D agenda, there are some vague ideas around the need, but little consensus and specificity around the optimal product characteristics. In some instances, additional research is needed to inform the target product profile and potential use scenarios for a new test. Furthermore, there has been very little work to define these market segments, and while it is likely that these segments are relatively small and fragmented, leading to poor business case for investment, this has yet to be fleshed out. For example, within nucleic acid testing, multiple market segments are possible:

- There is a market(s) for NAATs used in special situations (e.g. a reference test; test for investigating complex cases; testing in areas with drug resistance) where simple-to-use, less expensive (on a total cost basis), low-throughput NAATs could expand testing, and replace some microscopy.
- Another market segment is surveillance, where a high-throughput format is needed. Whether the test needs to return results rapidly and be performed near the patient depends on the purpose of the survey.
- In the premium private sector and in the developed world (if regulatory approvals are sought) it is conceivable for low-throughput POC NAATs to replace RDTs and microscopy.
- If affordable and easy to use, NAATs could also become more widespread for clinical use in drug-resistant areas where it is important to monitor response to treatment. A POC, low-throughput format would likely be optimal for this indication.

It is not clear how compelling these segments might be from a business perspective, nor which market particular technologies in the pipeline are targeting.

The lack of work to define needs, use scenarios and markets has led to low awareness among potential technology developers of specific needs, limited understanding of the market opportunity and poor ability to develop a targeted value proposition and business case for investment. Frequently, the price the market is willing to bear is not aligned with the proposed technology. Market information is also critical to making tradeoffs during the development process, for example, between pricing and LOD. Because many of the technology developers are small organizations, they have limited wherewithal to conduct detailed market research. In many instances, technology has advanced ahead of the business plan. As a result, while there are some interesting technologies in the pipeline, when it comes to product development and field trials, which require considerable funding and support, products may stall.

Limited funding and pull from the market

Although diagnostics are less costly to develop than vaccines and medicines, funding for R&D and commercialization is a challenge *(78)*. Diagnostics development costs between US$ 2 million for a simple test and up to US$ 50 million for a more

complex tool *(79)*. Developers of malaria diagnostics predominantly rely on a limited number of philanthropic and public sector funding sources to support R&D, for example, the Bill & Melinda Gates Foundation, the United States National Institutes of Health, the United States Department of Defence, DFID and the European Union. Although some malaria diagnostics developers have raised private funding, in general, private funding sources (e.g. venture capital; multinational diagnostics companies) may not view malaria diagnostic technologies as profitable enough to warrant investment: development expenditures may not be justified by returns on investment, especially in light of current RDT market conditions. In addition, most of the priority "needs" for new malaria diagnostics are in segments that are likely to be smaller and more fragmented than the clinical diagnostic market. The lack of familiarity with the global health financing systems, the new technology adoption process in global health and unclear regulatory pathways also impede commercial investment. Ultimately, funding challenges result in delays in the development of some technologies and mean that some will never come on the market. Although there are donor-funded initiatives to develop diagnostics, in general, funding to develop malaria diagnostics is limited and there are variable estimates around what level of funding is needed compared to what is actually available *(78-82)*.

Evaluations

The complexity of evaluating malaria tests can slow progress: access to well-characterized samples, clinical study design and addressing the geographic heterogeneity of malaria have challenged developers. 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, and the optimal reference standard is debatable. Currently, a few donor-funded programmes provide access to samples for R&D purposes and/or evaluation purposes, for example, the PATH G6PD programme, the Product Testing Programme and Lot Testing Programme for RDTs and FIND is developing a specimen bank and standards for highly sensitive RDTs.

Policy and regulatory pathway

Updating policies to include a new malaria test and meeting regulatory requirements also pose a challenge for test developers, potentially delaying the introduction of new products or hindering their uptake. On the policy side, it is likely that a new diagnostic would be reviewed by MPAC (Section 3), however, timelines are difficult to predict. Timelines for developing national guidance for new diagnostics are also unpredictable.

Because regulation is often weak in endemic countries, donors, procurers and some national programmes often look to stringent regulatory bodies or to WHO for recommendations. Obtaining clearance from stringent regulatory bodies (e.g. US FDA) is cost prohibitive for most malaria diagnostic tests that will only be sold in

the developing world. While there is a clear pathway at WHO for antigen-detecting malaria RDTs (i.e. the Product Testing Programme for performance evaluations and the WHO PQ for a full quality review), other malaria diagnostic platforms are not currently within the WHO PQ scope.[37] Even RDTs with improved sensitivity (e.g. RDTs claiming to have an LOD below 200 p/µL) would not be sufficiently challenged by the current Product Testing Programme and would require an alternative independent evaluation.

Globally, the multiplicity of organizations that might have different regulatory requirements and 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, especially for smaller diagnostics companies with limited experience and global reach.

Commercialization capacity

While some of the technology developers are larger companies with manufacturing and commercialization capacity, the fewer regulatory requirements during the diagnostics development process (compared to medicines and vaccines) mean that many of the technology developers involved in malaria are smaller companies or academic organizations that lack the infrastructure and capacity required to fully develop and 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.

In conclusion, recently launched technologies address specialized needs, rather than replace RDTs for routine, POC clinical diagnosis, given their cost and operating requirements. The UMT may expand testing, especially in the private sector, but given its performance, it is less likely to replace RDTs where they are already established. While there has been relatively rapid progress in recently launched technologies (e.g. UMT; Parasight; ***illumi****gene*® Malaria), many technologies are stalled or not advancing quickly to market. Perhaps one of the greatest challenges to the malaria diagnostics pipeline is the disconnect between product development and the market. Additionally, funding challenges, evaluation needs and standards, regulatory and policy paths and commercialization capacity all hinder progress of new technologies.

[37] Note that it is likely that POC G6PD tests will be added to the WHO PQ scope in the near future.

6. Malaria RDT market landscape

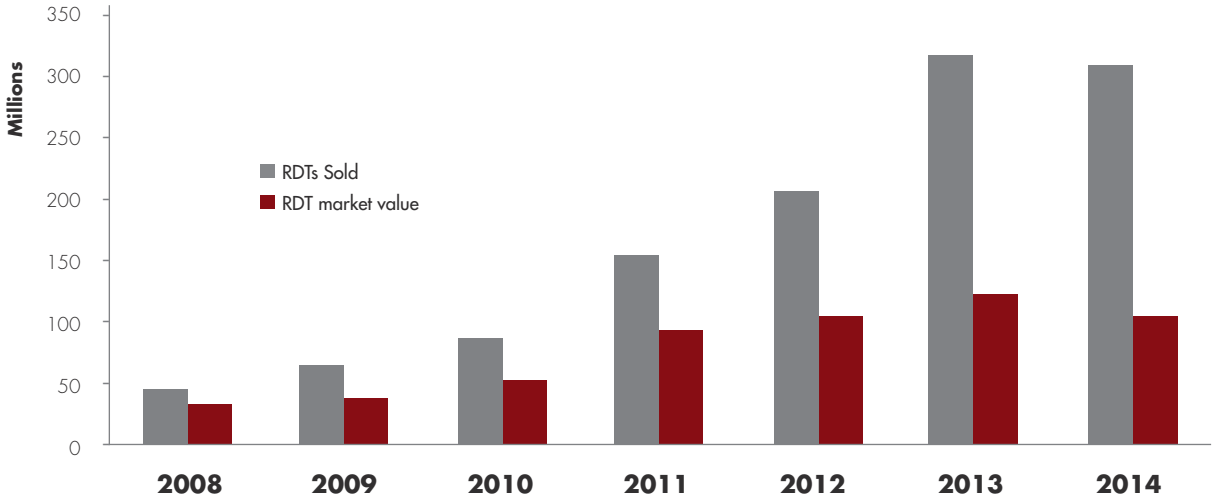
Growth and evolution of the malaria RDT market

In 1994, the first commercial malaria RDT came to market. However, the market for malaria RDTs only began to grow rapidly in 2010, prompted by the WHO recommendation to test all patients with suspected malaria and the results of Round 1 of the Product Testing Programme. Demand for malaria RDTs has grown from 46 million RDTs sold in 2008 to 319 million[38] in 2013 (48% annual growth rate 2008–2013) and dipped slightly to 314 million in 2014 (38% annual growth rate 2008–2014) *(1)*. During the 2008–2014, period the market value grew at a slower rate (21% annual growth rate) due to the decreasing prices of RDTs, from US$ 32 million to US$ 103 million (Figure 14). Malaria diagnosis now depends as much on RDTs as it does on microscopy, and Africa has experienced great increases in testing due to the scale-up of RDTs, which comprise 71% of the diagnoses made in the region in 2014 *(1)*.

[38] Market size figures are based on annual WHO surveys of manufacturers participating in the malaria Product Testing Programme. RDT manufacturers are asked to report how many RDTs were sold each year; however, they may underestimate the true size of the market because some RDT manufacturers do not participate in this programme.

FIGURE 14

Malaria RDT market size and value



Sources: Geneva: World Health Organization; 2015 (1)(based on responses from manufacturers participating in the WHO Product Testing Programme for Malaria RDTs); Author analysis of market value based on average prices calculated from procurement data.

Public and private sector diagnostic test availability

Data on diagnostic test availability are limited to ACT Watch surveys that occur every one to two years in a selection of countries. Data indicate that availability in the public and private not-for-profit health facilities has been increasing (Figures 15 and 16). Countries that were early adopters of malaria RDTs have achieved high coverage (e.g. Cambodia; Zambia), while in others, availability remains low even in the public sector (e.g. Democratic Republic of the Congo; Nigeria).

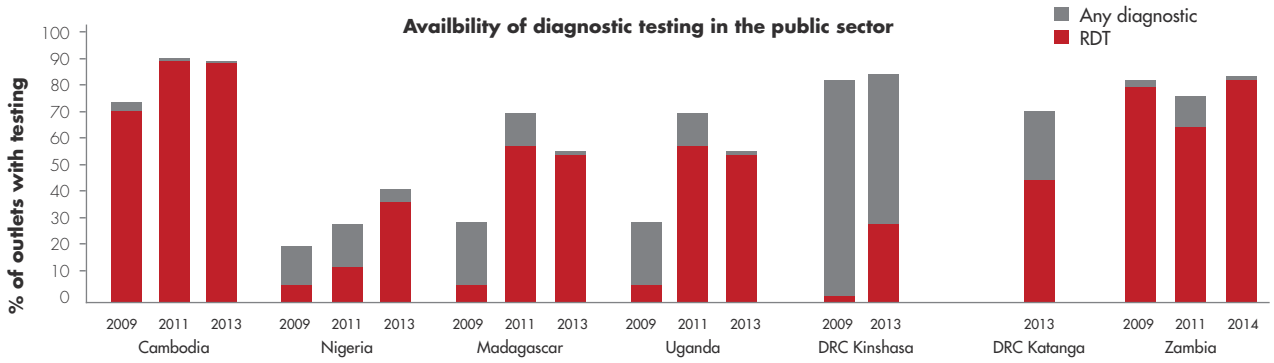
In many countries the private sector plays a bigger role in treating fever than the public sector (Annex 5); however, the availability of diagnosis in private sector retail outlets is generally quite low (Figure 16). Cambodia is a notable exception: private sector test availability is relatively high due to a private sector subsidy for RDTs and ACTs that has been in place for over 10 years.

Within the private sector there is considerable variation in diagnostic test availability by outlet type, with test availability being highest in more formal outlets and minimal in less formal outlets. Notably, outlets selling the highest volumes of antimalarials typically have extremely limited diagnostic test availability (Annex 5).

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

FIGURE 15

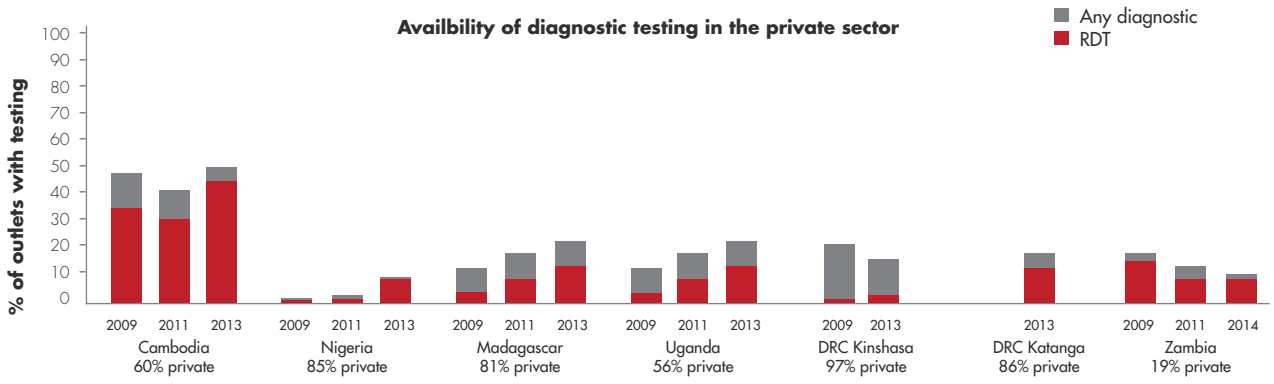
Public sector availability of malaria diagnostic testing: % of facilities with any diagnostic test/RDTs



DRC, Democratic Republic of the Congo
Source: ACT Watch Outlet Surveys.

FIGURE 16

Private sector availability of malaria diagnostic testing: % of outlets selling antimalarial medicines that have any diagnostic/RDT



DRC, Democratic Republic of the Congo
Source: ACT Wtatch Outlet Surveys.

Range of malaria RDT products and suppliers

The large number of products as well as frequent supplier entry and exit make monitoring the malaria RDT market challenging. In the late 1990s, only 3 malaria RDTs were commercially available; by 2008, over 40 products were available, and 2 of the original 3 ceased to be marketed *(9)*. A 2014 review found 55 companies and over 150 products.[39] Despite the large number of suppliers and products, most are not active in the public sector, and many are not active in the market at all. Repackaging and reselling of malaria RDTs and/or their components occur and suppliers often have several malaria RDTs in their portfolio, although certain versions are not sold in significant volumes.

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. As of September 2015 (i.e. Round 5), 147 unique products have been through product testing; of these, 59 (40%) from 29 manufacturers have met the WHO recommendations for procurement *(8)*. Although a large number of products meet WHO recommendations, it is not known how many continue to be produced[40] and even as the pool of existing products and manufacturers changes, demand for product testing remains high as new companies attempt to enter the market.

Overall, for the most commonly used test categories (e.g. *Pf*-only; *Pf*/pan; *Pf/Pv*) the number of tests meeting WHO recommendations is high (Table 3). However, customers looking to address particular epidemiological or clinical needs may not have quite as much selection as this list suggests.[41] The selection of WHO recommended tests changes periodically, primarily as a result of additional RDTs meeting WHO requirements[42] and compulsory resubmissions to the Product Testing Programme, which can decrease the number of recommended tests.

[39] Institute for Tropical Medicine in connection with work commissioned by the Roll Back Malaria Partnership Harmonization Task Force. Unpublished data, 2014.

[40] For example, in the most recent round of the Product Testing Programme (Round 6), there were 19 products up for compulsory resubmissions, and only 2 of these were submitted, suggesting that the remainder are no longer being marketed to the public health market. Although these companies did not resubmit, other new companies continue to enter the market and submit RDTs for evaluation.

[41] Within each category of tests, there is a range of antigens that may be employed to target a particular species. There are use scenarios where a specific combination of target antigens is needed, and the number of RDTs with this specific combination of antigens may be limited. For example, in the Amazon region, pLDH-based tests detecting Pf and Pv are needed and the selection of high-performing pLDH-based P. faldiparum tests is limited.

[42] For example, Round 5 results did not change the number of Pf-only tests recommended by WHO, however, there was a significant increase (seven tests) in the number of recommended Pf/pan tests in this round.

TABLE 3

RDT product selection: number of tests meeting WHO recommendations (after five rounds of the Product Testing Programme)

Type of test		Number meeting WHO recommendations
Pf-only	Pf-only	24
Combination tests	Pf/pan	18
	Pf/Pv or Pf/Pvom	13
	Pan	2
Pv-only	Pv	1

Source: WHO Product Testing Programme results.

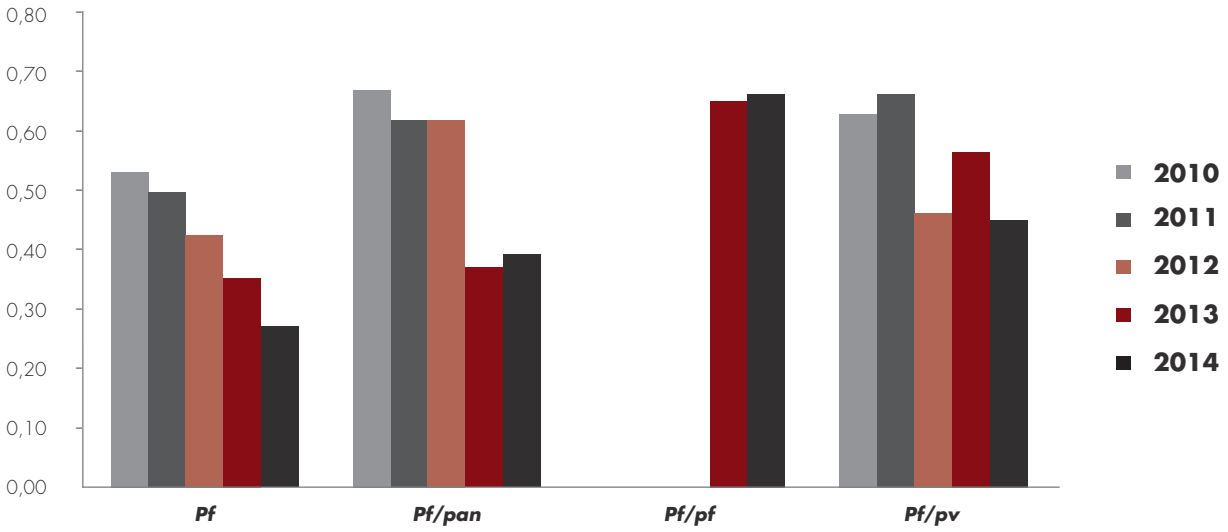
Prices

Public sector prices

Prices have declined rapidly in recent years in the public sector market. From 2010 to 2014, average prices decreased for *Pf*-only and *Pf*/pan tests from US$ 0.52 to US$ 0.27 (-43%) and from US$ 0.67 to US$ 0.38 (-48%), respectively (Figure 17). Conversations with suppliers and procurement groups support these findings, suggesting that in larger competitive tenders *P. falciparum*-only RDT pricing is in the low twenties. Recent procurement data show that prices of *Pf*–only RDTs in some tenders are as low as US$ 0.18 per test *(83)*. However, there is continued wide variation in pricing for the same product (Figure 18), with competitive bids often resulting in lower prices *(84)*.[43]

[43] Global Fund PPM representative, procurement data analysis; personal communication; May 2015.

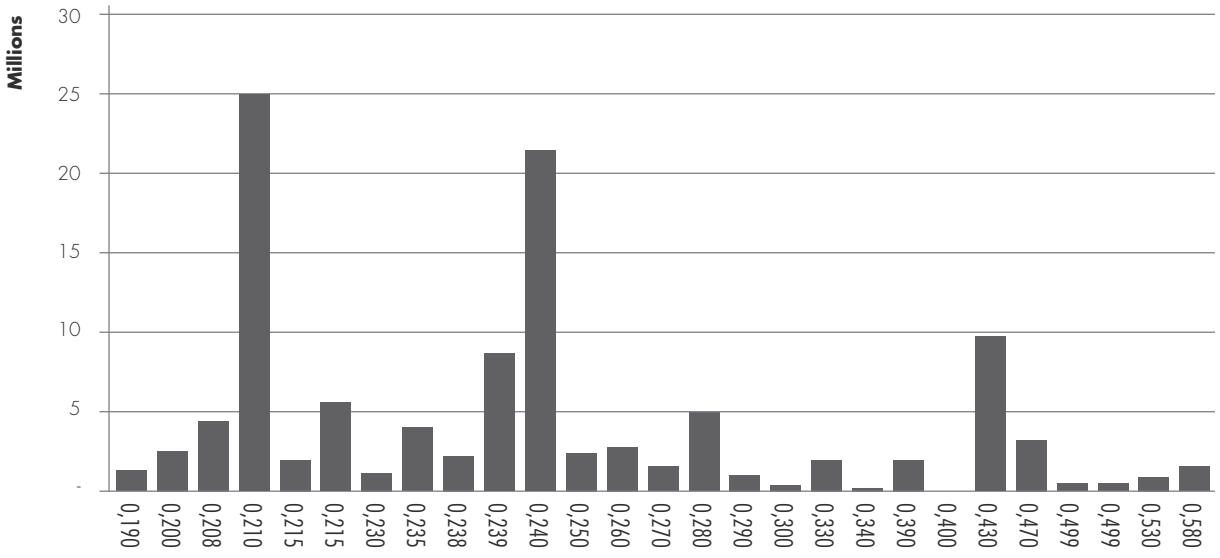
FIGURE 17
Weighted average test prices (US$) by year for RDTs



Notes: Represents 77% of total procurement data received. Filtered by INCOterms to include only ex-works entries and only entries including test type. Data are biased to certain procurement methods because they exclude UNICEF and some of the PQR data. PMI, VPP and WHO prices were given as ex-works. Weighted average prices calculated for all data based on total cost and total volumes.

Source: Procurement data analysis.

FIGURE 18
Volume of Pf-only RDTs at given price (2014)

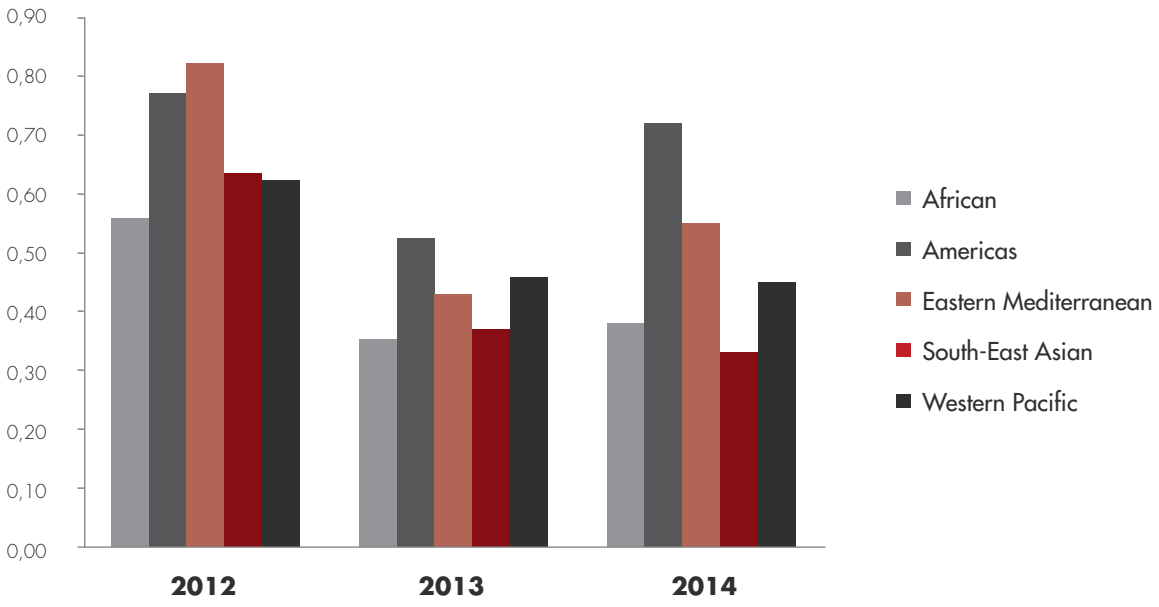


Notes: Represents 77% of total procurement data received. Filtered by INCOterms to include only ex-works entries and only entries including test type. Data are biased to certain procurement methods because they exclude UNICEF and some of the PQR data. PMI, VPP and WHO prices were given as ex-works.

Source: Procurement data analysis.

Regional price trends are difficult to assess due to differences in test type preferences and the limited number of orders in the procurement datasets from regions outside of Africa. However, data do suggest that pricing is lower in Africa and South-East Asia compared to other regions (Figure 19).

FIGURE 19
Weighted average Pf/pan test prices ($US) by region



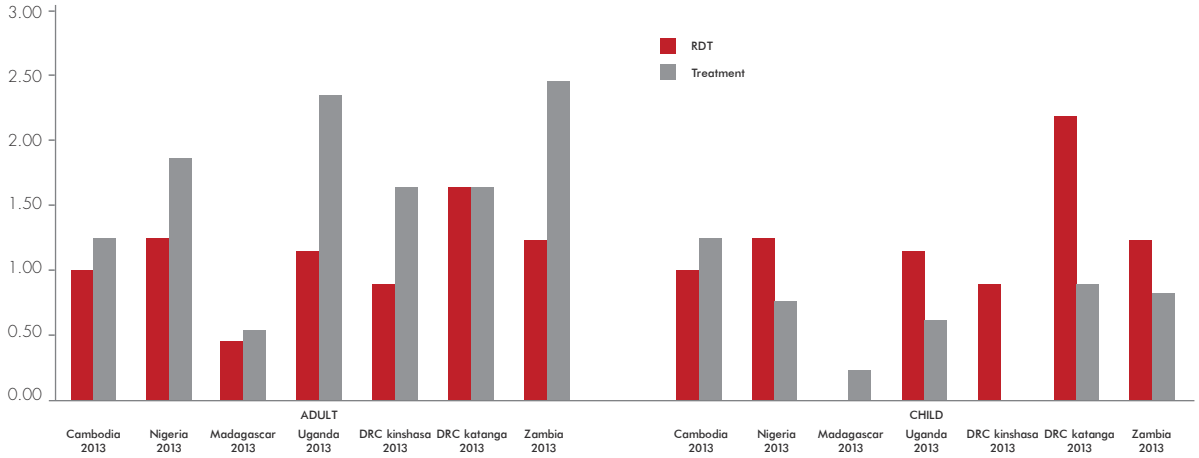
Notes: Represents 77% of total procurement data received. Filtered by INCOterms to include only ex-works entries and only entries including test type. Data are biased to certain procurement methods because they exclude UNICEF and some of the PQR data. PMI, VPP and WHO prices were given as ex-works. Weighted average prices calculated for all data based on total cost and total volumes.
Source: Procurement data analysis.

Private sector prices

There are relatively little data on RDT prices in the private sector due to limited efforts to collect them and the overall low availability of RDTs in most private sector markets. That said, the latest ACT Watch data from 2013 and 2014 surveys show median RDT prices of US$ .50–2.00; however, these figures should be interpreted very cautiously, as there is significant variation in prices within countries, and in all countries except Cambodia and Uganda the sample size is small (i.e. less than100) due to low overall availability of RDTs. For adults, the price of diagnosis is generally below the cost of treatment, although the price of an RDT for children is often higher than a child's treatment (Figure 20). Overall, ACT Watch surveys found RDT prices to be lower than microscopic diagnosis (except in Uganda).

FIGURE 20

Median price for private sector testing and treatment for adults and children (US$)



DRC, Democratic Republic of the Congo

Notes: For many countries, the sample size for RDT prices is quite limited. Testing price is the total cost to consumers including consultation and/or service fees. Adult equivalent treatment dose is the dosage needed to treat a 60 kg adult. Children's treatment is QA artemether-lumefantrine or artesunate-amodiaquine for a 10 kg (2-year-old) child.

Source: ACT Watch Outlet Surveys.

Market share (by volume of RDTs)

Public sector

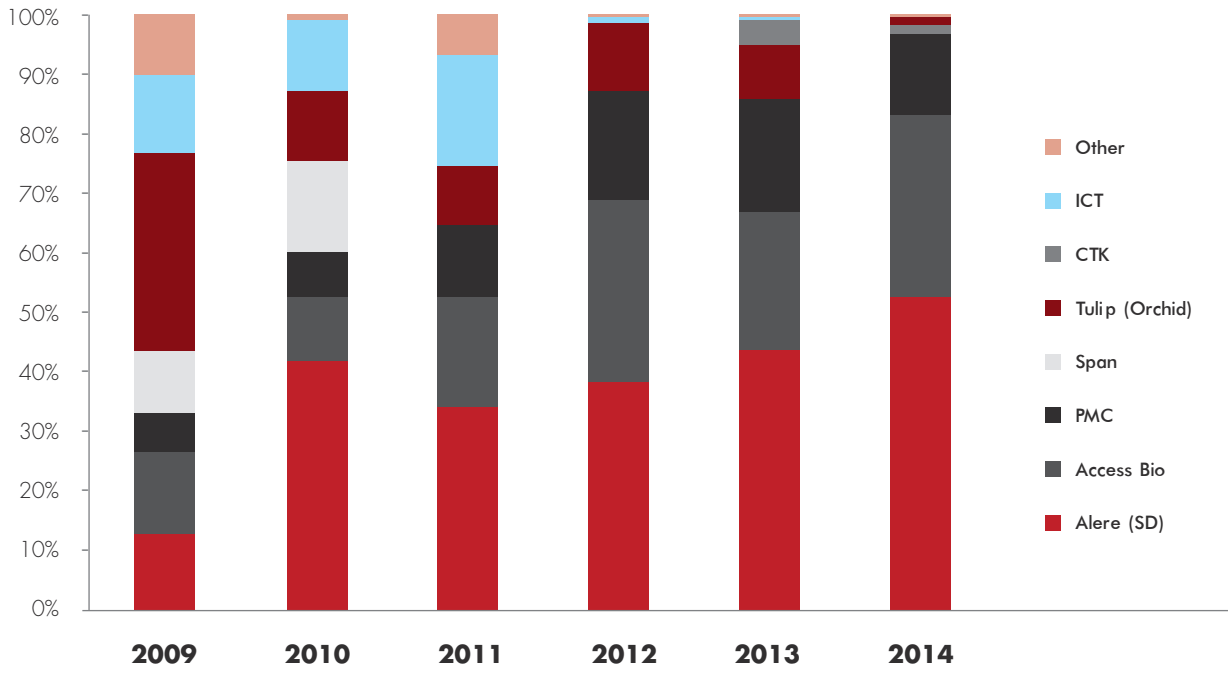
Although there are a large number of companies involved in the market, analysis of procurement data (representing approximately half of the global market) shows increasing consolidation of the market around three suppliers in 2012–2014 (Figure 21): in 2014 these suppliers comprised 96.8% of the market. Since one of these suppliers has been providing another with semi-finished test components, 96.8% of the market is effectively relying on two suppliers. Many suppliers suggest that recent price declines have made the public sector tender market less attractive. Some of the formerly dominant RDT suppliers have disengaged from the global health markets due to low pricing and/or inability to fill large orders rapidly.[44] When two suppliers dominate a market, power theoretically begins to shift to the suppliers and they can begin to

[44] While these companies may have "exited" the public health tender market for the most part, a few procurers report occasional bids, so they are not completely inactive. Review of their annual volumes, however, shows that their volumes have stagnated or declined, and that an increasing proportion of their malaria RDT volumes are sold to the private sector. These companies' RDTs performed less will in the Product Testing Programme than other RDTs that meet WHO criteria and/or have other quality problems that may have impacted their malaria RDT business.

set pricing. While price setting does not appear to be happening in the malaria RDT market, suppliers may be opportunistic (e.g. offering low prices on competitive tenders, but then charging high prices for expedited or sole sourced orders).

The market has also shifted at the product level. After the Product Testing Programme results were first released, there was a shift to better-performing products. More recently, there has been increasing consolidation of the market around a few brands, with Alere/Standard Diagnostics Inc. dominating the *Pf*/pan and *Pf/Pv* test categories and more of a diverse supply base in the *Pf*-only test category.

FIGURE 21
Malaria RDT market share, by volume of RDTs



CTK, CTK Biotech Inc.; ICT, ICT International; PMC, Premier Medical Corporation Ltd; SD, Standard Diagnostics Inc.
Source: Procurement data analysis.

Private sector

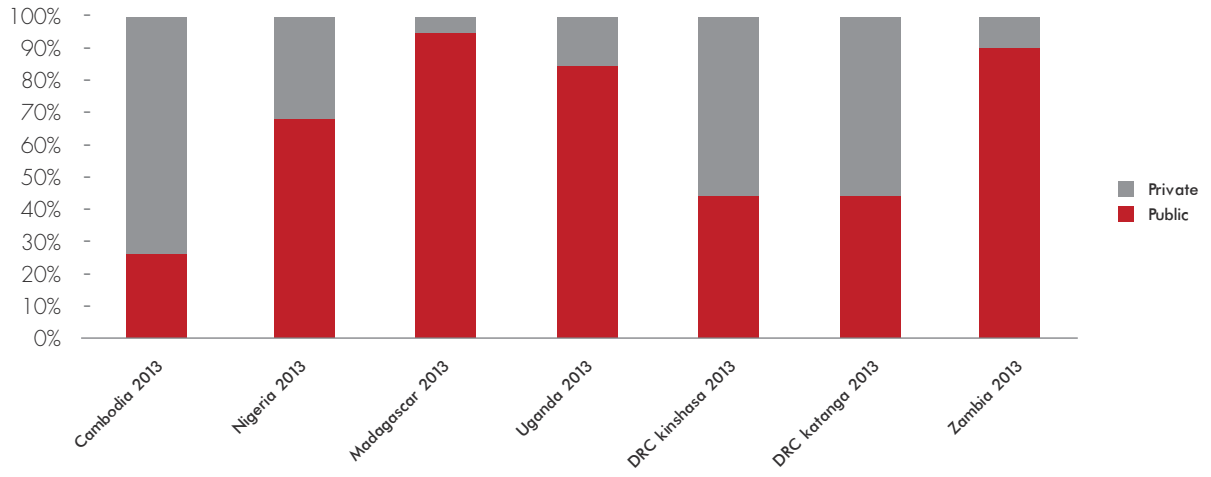
Data on private sector market share are extremely limited although ACT Watch does monitor this market for selected countries through its outlet surveys. Across the ACT Watch countries, the leading public sector malaria RDT suppliers (Access Bio Inc.; Alere/Standard Diagnostics Inc.; Orchid Biomedical Systems; Premier Medical Corporation Ltd) dominate the market (see Annex 6). Analysis of 2013 and 2014 RDT sales volumes from 16 suppliers also supports this finding.

At the country level, the overall volume of RDT testing done by the private sector varies (Figure 22). In most countries, the public sector performs the majority of RDTs. In

Cambodia, however, private sector RDT availability is high, and most of the RDTs performed across the market were in the private sector. In the Democratic Republic of the Congo and Nigeria, RDT availability is relatively low across both public and private sectors, and the private sector performs a substantial proportion of RDTs (56% and 30%, respectively).

FIGURE 22

Proportion of RDTs performed by the public versus private sector



DRC, Democratic Republic of the Congo

Notes: For each RDT found in an outlet, surveyors asked how many tests were performed using that particular product in the past week, which is the numerator; the denominator is the total number of tests performed across the whole market.

Source: ACT Watch Outlet Surveys.

Malaria RDT quality

The impact of various quality and regulatory programmes (Section 4) on the RDT market is described below as well as recent challenges with RDT quality and adaptability.

WHO Product Testing Programme

The WHO Product Testing Programme has had a significant impact on the malaria RDT market, on multiple levels, including the Round 1 contribution 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.[45] Currently, product testing forms the basis of WHO recommendations for RDT procurement and nearly all donor-funded procurement is based on the product testing results. In terms of RDT performance as a whole, the performance of RDTs has generally improved since the programme began, suggesting that product testing

[45] 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.

has created an incentive for product improvement among RDT manufacturers.

In 2013, WHO, FIND and partners began a programme to transition product testing to a more sustainable business model, by introducing fees and sourcing more readily available reference materials to replace the resource-intensive collection, dilution, characterization and cryopreservation of samples from patients infected with malaria parasites. Funding from UNITAID and other donors supports this transition. A user fee ($US 8000) was introduced in Round 6. Despite an initial decline in demand in Round 6, the demand for product testing has returned to past heights in Round 7.

Initially, the Product Testing Programme aimed to replace most of the human-derived specimens with less expensive recombinant antigen-based panels. Recombinant technology has been in development for several years, however, there have been challenges finding recombinants that perform in a highly comparable way to wild type parasites, particularly for pLDH. Therefore, it is likely that in the future, product evaluations will continue to be based on performance against real parasites, but include smaller panels of culture *P. falciparum* isolates and wild-type *P. vivax*.

Although the recombinant panels are unlikely to be used to assess product performance in the Product Testing Programme, they will be used to determine reference data and trends that can guide lot verification (i.e. lot testing) and/or lot release (part of manufacturers' QC processes). More specifically, a benchmark LOD against the recombinant would be set during product testing (i.e. each product would be assessed against a panel of recombinant antigen dilution). Subsequently, this product-specific LOD will be used by lot testers and manufacturers to check for shifts in RDT performance that could represent either improved or diminished performance. The recombinant antigen dilutions used in product testing will also be commercially available to laboratories that carry out lot verification and to RDT manufacturers.

It is not yet clear to what extent these changes will reduce the overall costs of the current Product Testing Programme and Lot Testing Programme, and if they will improve the turnaround time for product testing results (currently 18 months).

WHO-FIND Lot Testing Programme

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 Lot Testing Programme operated by WHO and FIND, which is designed to detect major flaws in RDT performance. The number of lots tested, as well as the average lot size, has increased since the programme began. According to data collected from lot testing requesters, the 927 lots submitted for testing in 2014 represented about half of the malaria RDT market.

Experience with lot testing has generally been positive, nearly all RDTs tested pass, although this "pass rate" may not reflect the quality of RDTs used globally since

products submitted are generally from agencies that are more likely to use lot testing than other buyers.

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 and is happening in connection with the changes to the Product Testing Programme, as described above.

Malaria RDT product challenges: quality and adaptability

Overall, experience to date with malaria RDTs has been positive, although there are no feedback systems in place for collecting data on RDT quality in a widespread manner. This section describes several issues related to individual product quality, adaptability of RDTs and alignment of procurement practices with WHO recommendations. Additional detail on these issues is available in Annex 6.

Delisting of RDTs. Three companies have been affected by non-performance in product testing resubmissions and/or prequalification site inspections; this has resulted in delisting from one or more recommended product lists (e.g. WHO GMP recommended RDTs; WHO PQ; Global Fund list of RDTs). These changes have been recent, and some companies are working to remedy the problems and become reinstated. The impact on the market has been minimal in the case of one company with a small market share, and remains to be seen for others since some of the changes are recent.

Lot testing. Lot testing experience has generally been positive, with nearly all RDTs passing. Generally, the failures that have occurred in lot testing relate to weakness of a pan or *Pv* line against low-density *P. vivax* samples, especially after incubation for several months, suggesting that stability may be a problem for some products. In addition, the lot testing found that the diluent solution included in individually packaged kits had evaporated prior to the shelf life of the product, leading WHO to issue a recommendation not to procure affected products (10 products from leading malaria RDT manufacturers). While individually packaged kits are a small proportion of the market, programmes have procured several million mainly for community and retail private sector use. As of September 2015, the three affected manufacturers are working to remedy the problem.

Adaptability and RDT harmonization. In general, RDTs are simple to perform, however, end-user error in performing and interpreting RDTs is commonly reported anecdotally and in the literature (e.g. switching between RDT products; errors associated with the presentation or components of the tests; abnormalities in the test strip). In 2013, the Roll Back Malaria Partnership commissioned a task force to explore how RDTs could be harmonized to improve user-friendliness, reduce operator error and address training needs associated with switching brands of RDTs. The

resulting Harmonization Task Force has made many recommendations concerning improved device labelling, packaging, accessories and instructions for use *(85)*. This list of recommendations will be incorporated into the Product Testing Programme (Round 7) and the WHO PQ review of dossiers in 2016. While these changes should improve the quality of RDTs and reduce operator error, RDTs will continue to differ in procedures and as such the impact on competition may not be substantial, as changing from one test kit to another will require retraining of all health-care workers in the new test procedures. Complete harmonization of RDTs requires changes to test procedures and is not considered feasible in the near term.

Alignment with WHO recommendations. Quality standards for RDTs in the private sector, and in at least one instance the public sector, are not always aligned with WHO recommendations and could lead to availability and use of RDTs whose quality is not assured. ACT Watch data and anecdotal reports indicate that there are RDTs on the market whose quality is not assured; however, the extent of this issue is difficult to appreciate given a relative lack of data. For example, RDTs that have not been evaluated by the Product Testing Programme are stocked in the private sector as well as the public sector. However, ACT Watch data on usage of these tests (e.g. number of tests provided to patients or sold to customers) indicate that public health facilities generally use RDTs that have been evaluated by product testing. One notable exception is Uganda, where an RDT from Astel comprises 12% of the total market, largely due to its use in public facilities. Similarly, private sector sales of RDTs products from manufacturers that have been evaluated by the Product Testing Programme dominate private sector sales. However, this data should be interpreted cautiously; first, it is limited in terms of number of countries and, second, overall sales of RDTs in the private sector are quite low to begin with. If RDT sales in the private sector increase, it will be important to monitor market share and to take measures that support use of quality-assured RDTs.

WHO PQ

As of the end of 2015, 12 malaria RDTs from four companies (Access Bio Inc.; Alere/Standard Diagnostics Inc.; Arkray Inc./Span Diagnostics Ltd; Premier Medical Corporation Ltd) were WHO prequalified. There are no additional products in the WHO PQ pipeline *(86)*.

In general, malaria RDT manufacturers have progressed slowly through the WHO PQ process due to poor quality dossier submissions and weaknesses identified in site inspections. Although to be eligible for the Product Testing Programme, suppliers must have a valid ISO 13485 certificate, the level of quality at the manufacturing level varies. WHO-led site inspections demonstrate that for many manufactures, a full understanding and implementation of ISO 13485 standards are lacking. Several factors contribute to the challenges, including the fact that most malaria RDT manufacturers are not located in jurisdictions with strict regulatory oversight and, therefore, they have not had much experience with dossiers and stringent QMS

requirements. For many malaria RDT suppliers, achieving prequalification status has been a challenge, often requiring additional studies to support product performance claims, multiple site inspections and investment in QMS (e.g. revising QC protocols; improving supplier control procedures; increasing QA/QC staff; purchase of new instrumentation).[46]

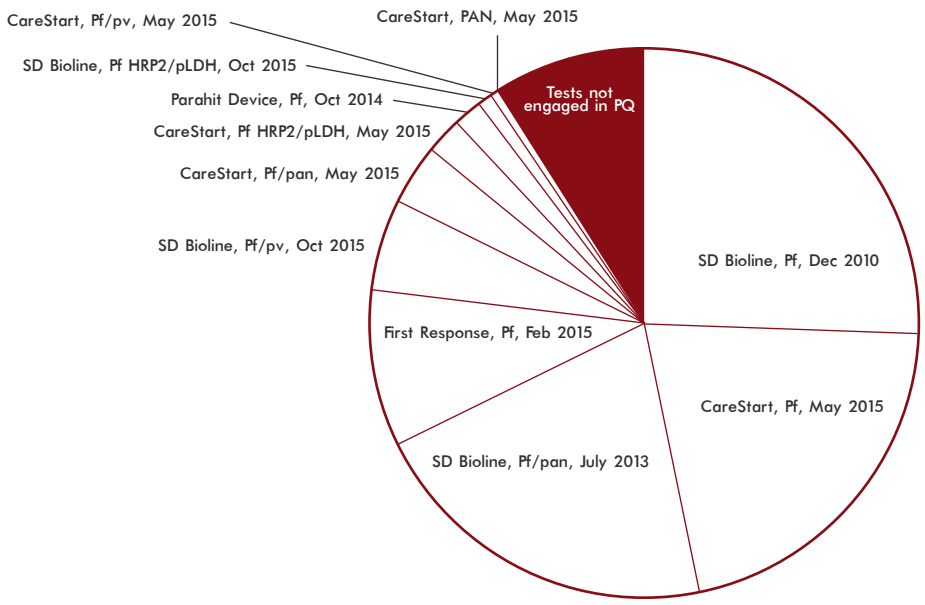
To date, the impact of the WHO PQ on the market has been limited. Although WHO prequalification is not a requirement of any major donor or purchaser, >90% of the public sector market is already prequalified because the suppliers with the largest market share have prequalified their products (Figure 23). From an industry perspective, while several of the leading public sector suppliers are undergoing prequalification, the vast majority of companies making malaria RDTs are not undergoing prequalification. Additionally, the market does not appear to value, either through price premiums or increased market share, prequalification status: while three of the prequalified malaria RDT suppliers have significant market share, they also offer highly competitive pricing for high-performing tests. The fourth prequalified supplier has limited market share.

Given market conditions that put pressure on quality, observed lot-to-lot variation and recent RDT quality issues (described below) and apparent discrepancies in implementation of ISO 13458 among RDT manufacturers, the WHO GMP is currently considering whether only WHO prequalified RDTs should be recommended for procurement. This would create a stronger incentive for RDT suppliers to invest in robust QMS and would further increase the evidence available to consumers on the quality of the products. WHO will likely take a decision on this change in early 2016, after considering among other things the potential market impact. If the policy does change, it would not go into effect immediately, there would be some period of time between the announcement of the requirement and implementation.

[46] WHO prequalification team, personal communication, 22 May 2015; Malaria RDT suppliers, personal communication, March–May 2015.

FIGURE 23

2014 Product market share with brand, test type and prequalification date



Feb, February; Oct, October; PQ: prequalification; Dec, December

Note: Market share data are for 2014 and prequalification status information is as of year-end 2015. Among the "tests not engaged in PQ" are the individually packaged format of tests that are already prequalified.

Source: Procurement data analysis.

Malaria RDT demand

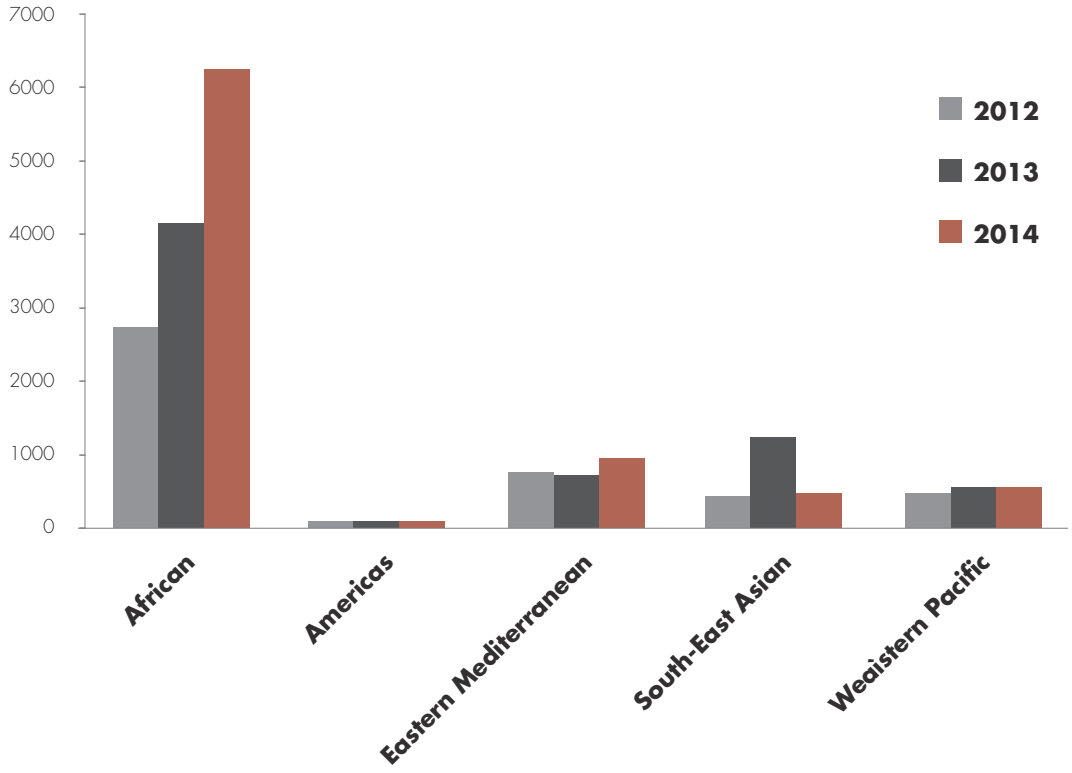
Current public sector demand

Public sector demand growth

The public sector scale-up of diagnostics has driven RDT demand growth, although it is more advanced in some countries than others. Geographically, Africa followed by South-East Asia are the leading RDT markets. Review of annual procurement volumes by country suggests that much of the growth in the market stems from countries procuring increasingly larger volumes each year (Figure 24). Within the reported public sector procurement data, the 15 highest-volume countries in 2010–2014 were African countries and India, and it is not uncommon for these countries to procure more than 10 million tests per year. Together, these countries represented 71% of the procurement data analysed in this report.

FIGURE 24

Average annual procurement volumes per country, by region, 2012–2014



Source: Procurement data analysis.

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. Although not recommended by WHO due to their complexity, local performance evaluations are sometimes conducted. Generally, this process occurs every few years, as once an RDT has been selected and rolled out, programmes prefer to continue using it to avoid the programmatic costs of switching RDTs. While the costs of switching may diminish as countries gain more experience with RDTs, they increase as RDTs become more widespread and decentralized.

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, lead time and local registration. 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.

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 relatively uncommon (7–9 million tests/year reported in the procurement dataset for 2012–2014, approximately 3-8% of total volumes).[47] Until the quality problems with individually packaged kits are resolved, volumes of single kits may decline, although increasingly programmes prefer this packaging for community- and retail-level testing.

Type of RDTs. By volume, *P. falciparum*-only-detecting tests (i.e. HRP-II detecting; two-line tests) are the most commonly procured. In 2008–2009, these tests comprised approximately 80% of the market. Since then, use of combination tests has increased and *P. falciparum*-detecting tests are now approximately 60% of the market (Figure 25). However, at the individual country level, more countries report procuring a combination test than a *Pf*-only test (Figure 26) and the volumes of combination tests procured are generally smaller than of *Pf*-only tests. Of the 62 countries reporting data in 2014, only 14 (23%) exclusively procured *Pf*-only tests. Procurement data indicate that over two thirds of countries switched types between 2010 and 2014.[48] Of these, the majority switched from a *Pf*-only test to a combination test.

Brand of RDTs. Procurement data as well as ACT Watch data indicate that countries have experience with multiple brands of RDTs; 88% of countries analysed switched brands between 2010 and 2014. While countries generally prefer not to split tenders, in one recent case a tender was split between two products due to concerns about the ability of one company to produce a large volume of RDTs.[49]

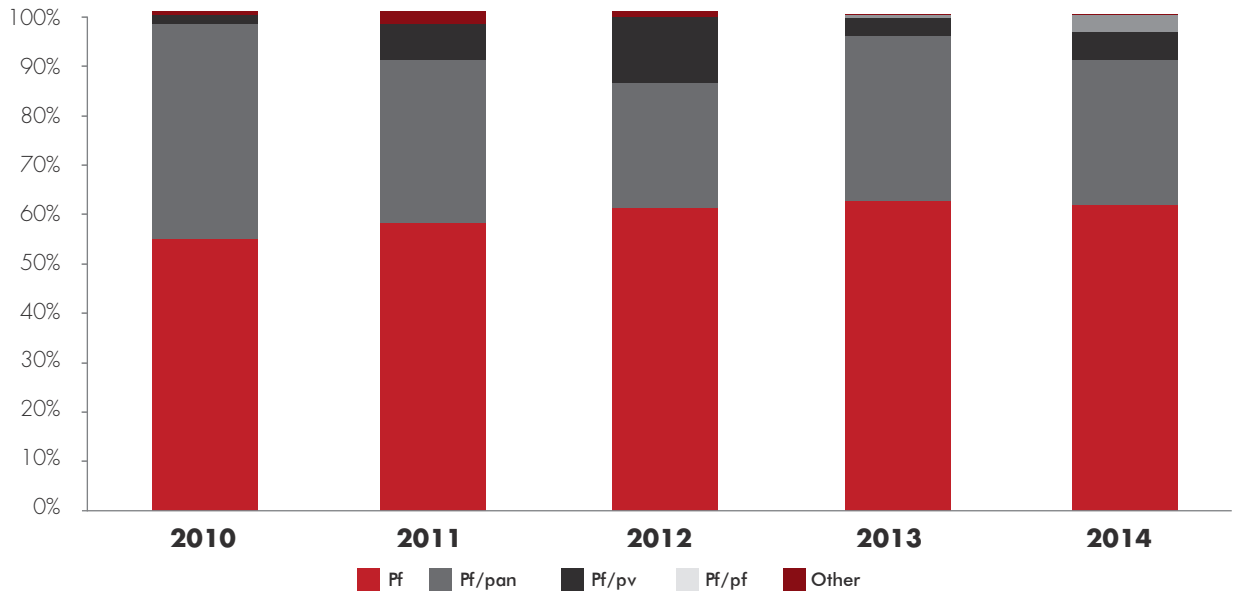
[47] Note that the procurement dataset does not include UNITAID-funded procurement of RDTs for the private sector, which would add a few million individually packaged tests/year.

[48] Analysis of data from 2010 through 2014, and including only countries with more than one year of data.

[49] Global Fund PPM representative, personal communication, 27 August 2015.

FIGURE 25

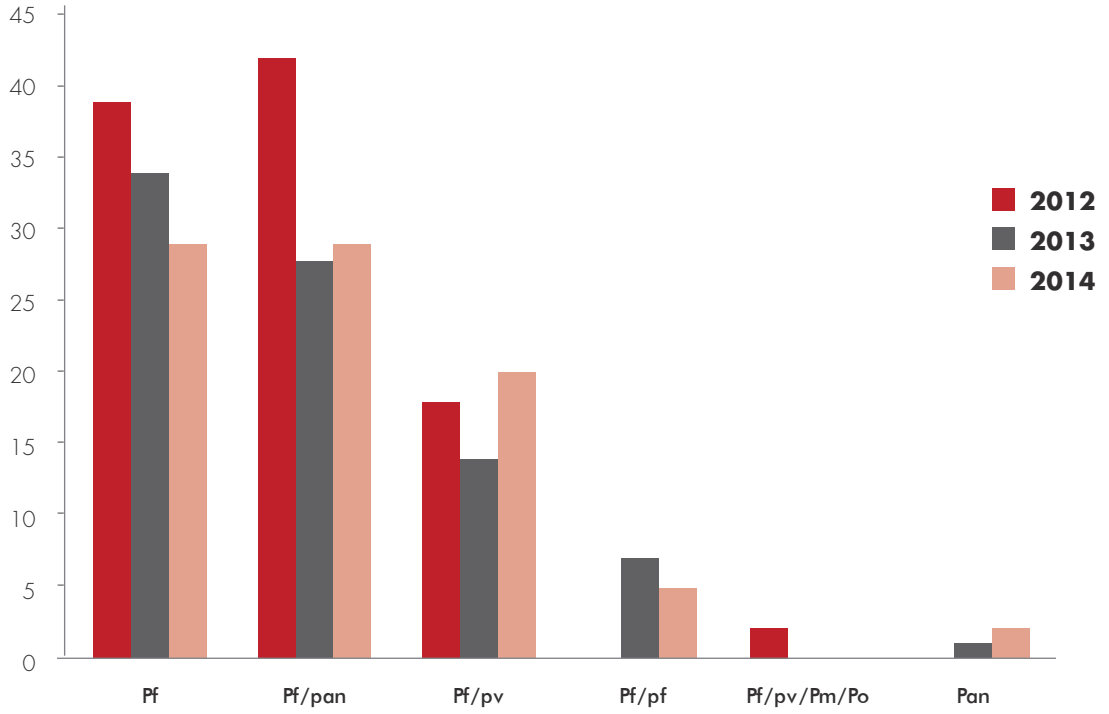
Procured test types by year (% of procurement volume)



Source: Procurement data analysis.

FIGURE 26

Number of countries procuring Pf-only and combination tests, 2012–2014



Pf, P. falciparum; Po, P. ovale; Pm, malaraie; *Pv, P. vivax*

Source: Procurement data analysis.

Donor and public sector procurement practices

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. The Global Fund and PMI are the major donors funding malaria RDTs, and as a result their policies and practices have a major influence on the market.[50] In 2014, the Global Fund funded at least 125 million RDTs[51] and PMI funded 75 million RDTs.[52] Procurement data show that many of the highest-volume countries receive funding to procure RDTs from more than one donor.

In terms of procurement method, there are several channels that national programmes use to procure RDTs with donor funding. Global Fund recipients, largely ministries of health, are responsible for the procurement of diagnostic tests. They can purchase directly through a competitive tender process, outsource this function to procurement agents (e.g. WHO Procurement; UNICEF Procurements; IDA Foundation; Crown Agents) or use the Global Fund Pooled Procurement Mechanism (PPM, formerly Voluntary Pooled Procurement or "VPP"). With PMI funding, all procurement is done through the PMI contracted agent, currently JSI Deliver.

Procurement data analysis suggests that most countries have used more than one procurement method and that the top three procurement methods were through PMI, through PPM/VPP and directly with the manufacturer (Figure 27). Generally, orders are placed once a year with staggered delivery for large orders, however, the procurement process can be lengthy and irregular, contributing to risk and instability in the market.

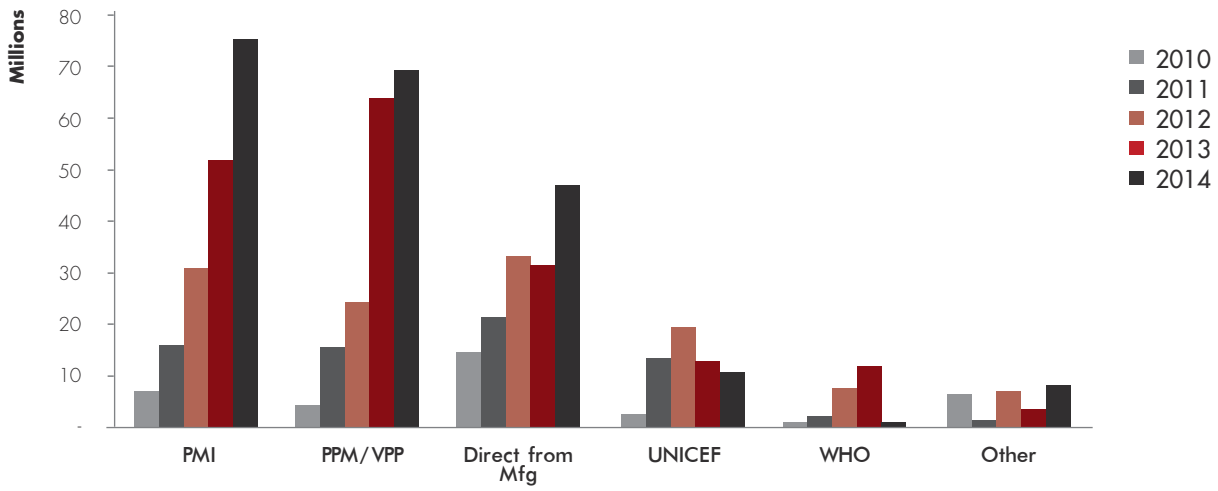
[50] Others funders include DFID, UNITAID, the World Bank, regional development banks, NGOs and national governments. Compared to the Global Fund and PMI, these groups generally fund significantly fewer malaria RDTs, and have limited capacity to document, aggregate and/or or share their procurement activities and data.

[51] It is likely that the Global Fund funded more than 125 million RDTs in 2014 because reporting is not complete. The following were reported: 69 million through PPM/VPP; 47 million procured by countries directly from the manufacturer; 9.5 million procured by countries using the procurement agents IDA Foundation and WHO.

[52] PMI's procurement for 2014 is exceptionally high because it wanted to ensure no disruptions in commodities for country programmes as it transitions procurement to a new system and contract (i.e. the Global Health Supply Chain-Procurement and Supply Management contract).

FIGURE 27

Annual RDT volumes by procurement method, 2010–2014



Mfg; manufacturer
Source: Procurement data analysis.

Additional detail on procurement policies and practices of major procurers are described in Annex 7. One upcoming change that will affect the market is a review and restructuring of malaria RDT procurement by the Global Fund PPM. Since the procurement mechanism at the Global Fund began, malaria RDTs have been procured through individual procurements based on county requests. However, PPM is in the process of reviewing this approach. Based on discussions with the Global Fund and how it has approached other markets, PPM is likely to work more directly with suppliers, through framework supply agreements with several manufacturers. These agreements would extend over a two-year period; in doing so they could shift competition to the global level, rather than the individual country level. The tentative timeline includes issuing a tender in mid-2016 and signing framework agreements later in 2016.

Current private sector demand for RDTs

Little work has been done to understand demand for RDTs in the private sector. Based on conversations with leading malaria RDT suppliers and review of RDT supplier sales volumes, a reasonable market size estimate would be approximately 20% of the total malaria RDT market (~60 million RDTs). Overall, private sector markets for RDTs are smaller and more fragmented than the public sector, but growing, albeit at a significantly slower pace than the public sector. 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.

In many countries there are two distinct private sector channels: (i) the formal private sector (i.e. hospitals; larger clinics and private laboratories; local nongovernmental organizations/NGOs); and (ii) 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 market (based on size of antimalarial medicines sold in this channel) is several orders of magnitude larger than the formal private sector market. However, a major obstacle to testing in the retail private sector are regulations that prohibit where testing can be performed and the professional cadres that can perform testing and subsequently provide treatment. Some countries are altering regulations to expand testing at the retail level, largely in connection with NGO-supported projects.

Most malaria RDT suppliers have local distributors who serve the formal private sector. These distributors do not always serve the retail outlets where antimalarial drugs are sold to consumers; in order to serve these markets, new distribution arrangements may be required (e.g. through establishing relationships with pharmaceutical distributors; subcontracting to distributors with greater geographic coverage).

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.

The second private sector channel for RDTs, retail outlets where antimalarial drugs are sold, is currently a very small RDT market segment. Pharmaceutical supply chains generally service these outlets, and awareness of RDTs is low, as are RDT stocking and sales. Relatively little is known about RDT product selection and stocking decisions in this channel. However, outlet survey data from ACT Watch indicate that, where available, a variety of RDT brands are found, including many that have not been evaluated by the Product Testing Programme (Annex 6). Leading RDT manufacturers are only beginning to establish distribution to the retail outlets selling RDTs, which is happening largely in connection with NGO projects to develop private sector markets for RDTs. These projects are largely donor funded and as such the procurement criteria and quality standards are in line with public sector standards.

Future demand for malaria RDTs

To date, there are no refined estimates of the need for malaria diagnostics (e.g. the total potential market) nor demand forecasts for malaria RDTs. In 2015, UNITAID began funding a consortium (Clinton Health Access Initiative/CHAI, IMS Health and the University of California San Francisco) to forecast RDT and ACT demand, filling an important market intelligence gap. Until this analysis is available, a summary of relevant factors influencing demand includes the following.

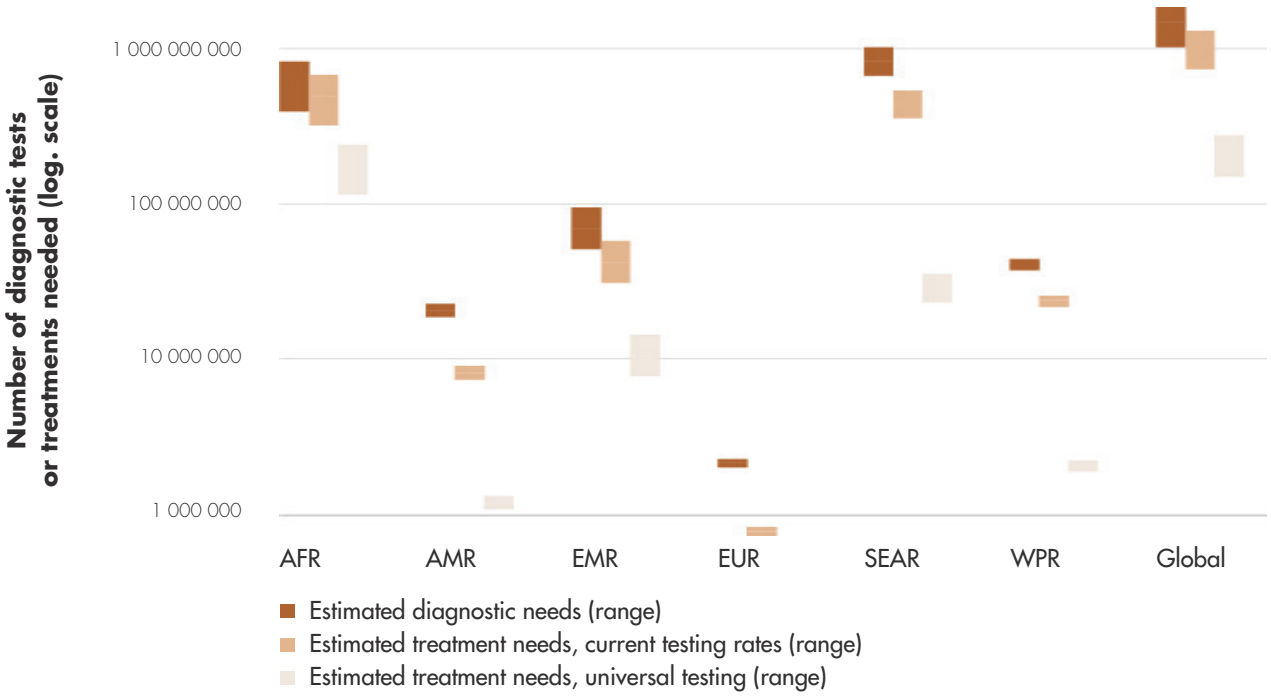
Potential market size

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 (Figure 28).[53] Although there are wide uncertainties associated with these estimates, comparing this to the 516 million diagnostic tests[54] reported to WHO in 2013 implies that there was significant unmet potential demand.

FIGURE 28

Estimated malaria diagnostic and treatment needs, by WHO region, 2010



Estimated treatment needs for current and universal testing rates not shown for European Region, as below 1 000 000

Source: World Malaria Report 2011, NMCP reports

Estimated diagnostic needs = suspected malaria cases, derived from estimated confirmed cases and programme reported test positivity rates; Estimated treatment needs, current testing rates = confirmed + presumed cases, derived from the proportion of febrile persons seeking care by health sector, proportion suspected cases tested by health sector, reported test positivity rates; Estimated treatment needs, universal testing = estimated confirmed cases, 2010. Treatment needs include treatment for all Plasmodium species.

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

Notes: Vertical axis is logarithmic scale, each unit increase on the axis represents a 10-fold 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.

Source: World Health Organization 2012. (87)

[53] 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 the Americas and Asia. 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).]

[54] There were 197 million microscopy slides examined in 2013 and 319 million RDTs sold in 2013 per the 2014 World malaria report.

Factors influencing future demand

RDT demand is likely to continue to grow over time given the large gap in access to testing and the compelling value proposition that RDTs represent in terms of malaria diagnostic technologies (e.g. convenience; price; quality). However, the rate of growth seen between 2008 and 2013 is unlikely to be sustained. Factors influencing demand growth include the following.

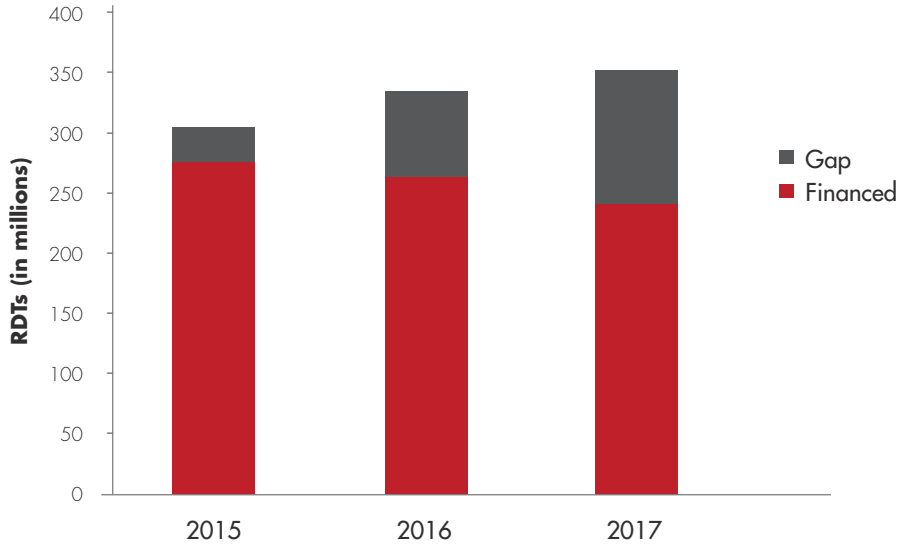
Public sector RDT penetration. Penetration of RDTs in the public sector is fairly high, however, additional RDTs will be needed to reach coverage targets. For example, the Roll Back Malaria Partnership HWG data indicate that the "need" for RDTs in African continues to grow: from 305 million RDTs in 2015 to 354 million in 2017 (8% compound annual growth rate) (Figure 29). Several high-burden countries (e.g. Democratic Republic of the Congo; Mozambique; Nigeria) still need to significantly scale up public sector RDT use, which should result in large increases in their demand. At the same time, the HWG data indicate that many countries' RDT needs are stabilizing. These countries have made significant progress (e.g. >75% cases tested), however, achieving 100% testing in the public sector will require additional scale-up. Given the challenges associated with reaching the periphery, demand growth in countries with relatively high testing rates is likely to be incremental. Community-level use of RDTs is expanding (e.g. integrated Community Case Management "iCCM" programmes); 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, will likely manifest as incremental to existing public sector demand.

Many of the highest-volume malaria RDT countries rely heavily on donor funding for their malaria RDTs. The strategic reform and New Funding Model implementation at the Global Fund caused some concern about malaria programme budgets and diagnostic budgets, however, analysis from the HWG suggests that public sector case management, including malaria RDTs, has been prioritized. Still, it will be important to monitor how the changes in funding for malaria and the allocation of funds by programmes impact diagnostic test budgets and RDT demand *([55])*. HWG data indicate that some countries have sizable gaps between the projected RDT need and RDTs financed. However, the proportion of malaria RDTs that are financed (79%) is higher than in the past (Figure 29), and a handful of countries (Nigeria; Uganda; United Republic of Tanzania) comprise 87% of the overall financing gaps.

[55] For example, the largest Global Fund malaria allocations went to Nigeria (US$ 499 million) and the Democratic Republic of the Congo (US$ 419 million) and both countries received substantial funding increases over previous years. This reflects the Global Fund strategy of focusing on high-burden countries. Other countries were considered "overallocated" and their allocations will be reduced by 25% over previous years (if possible without cutting essential programmes). Angola, Burundi, Eritrea, Ethiopia, Ghana, Kenya, Liberia, Madagascar, Nigeria, Rwanda, Sao Tome and Principe, and Zimbabwe are among the "overallocated" countries. The timing of net campaigns is also a challenge for malaria programmes, as these can increase the total budget by 70% during the years they occur. Eliminated countries reported a 21% decreas in funding (http://www.globalfundadvocatesnetwork.org/wp-content/uploads/2014/12/GF-funding-elimination-Briefing.pdf, accessed 18 September 2015).

FIGURE 29

RDTs needed and financed in African countries, 2015–2017



Source: Author analysis of the Roll Back Malaria Partnership Harmonization Working Group (HWG) data on commodities.

Private sector RDT sales. 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. There are several donor/NGO-supported projects to expand this market[56] and more detailed findings from these pilots should become available in 2016. However, early answers suggest that there has been progress in adapting policies and regulation around testing in the retail private sector, testing demand generation activities targeting provider behaviour and consumer awareness, and developing models for training, supervision and QA/QC. Remaining challenges include affordability, sustainability and referrals. Longer term, as public scale-up is achieved, focus on the private sector is likely to increase and moderate demand may materialize, however, this market is more relevant in some countries than in others.

Elimination. Elimination is unlikely to impact demand for malaria RDTs in the near term as none of the eliminating countries (e.g. 34 countries defined by the University of California San Francisco) are high-volume RDT users *(88)*.

Substitution. It is unlikely that any alternative malaria diagnostic technologies will impact malaria RDT demand in the near term. Microscopy use has been growing, but not dramatically; it is unlikely that increased microscopy testing would negatively affect RDT growth. There are no diagnostics in the pipeline that would come to market and replace RDTs in the near term. However, the Bill & Melinda Gates Foundation funded work to develop a second-generation highly sensitive RDT that may lead to a new category of RDTs launching within the next two years. These

[56] For detailed information on initiatives to develop the private sector, see previous Landscapes.

new “highly sensitive” malaria RDTs are intended to be used to detect asymptomatic infections in very low-transmission settings. Although this initiative is still in early stages, already at least one of the companies involved in this programme has developed an RDT claimed to be 10 times more sensitive than today’s RDTs. Neither the market size (see Section 5) nor positioning of these new RDTs have been finalized. It is possible that these highly sensitive RDTs will be marketed as “replacements” for existing RDTs, using superior performance to gain market share. Alternatively, the improved RDTs may be sold at higher prices in lower volumes.

In summary, it is reasonable to expect continued RDT demand growth in the near term as countries that have yet to reach scale in the public sector continue to expand testing; additional donor funding might enable more aggressive growth in these countries. Once RDT scale-up in the public sector facilities is achieved, the pace of growth is likely to slow, as reaching the unserved demand at the community level and in the private sector is challenging. Demand increases are likely to be more incremental, especially in the absence of focused global initiatives to support expansion of these markets.

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 engage in the public sector market, few are major diagnostics companies;[57] other suppliers 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. Although 29 companies are eligible (i.e. meet the WHO procurement criteria), the public sector market is consolidated around a few suppliers. Limited private sector market data suggest that the same companies dominate private markets, although there is considerably less concentration. Some companies that have not engaged in the public sector are focused on market niches/smaller market segments (e.g. the Indian private sector; international travellers markets; businesses with large labour forces affected by malaria). Some companies also perform manufacturing of complete unlabelled RDTs or components of RDTs for other suppliers.

[57] Alere (US$ 3 billion annual revenue) controls several RDT brands, the largest being Standard Diagnostics (SD Bioline). Arkray Inc. (~US$ 500 million annual revenue), a privately held Japanese diagnostics company, recently acquired Span Diagnostics Ltd (India).

Barriers to entry

On the surface, the malaria RDT market appears attractive: (i) the market size is large 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, several barriers to entry[58] have emerged in the public sector market, including:

- Product testing: Products must perform acceptably in the Product Testing Programme in order to access the largest market segment, that is, the public sector market. Experience from multiple rounds of testing suggests that for many companies it is challenging to develop an RDT that consistently performs well at low parasite densities. While the number of HRP-II-detecting RDTs that perform well in product testing is fairly high, a much lower proportion of multi-species RDTs meet WHO recommendations.

- Need to produce at low cost: Delivering RDTs at the current low public sector prices requires significant cost advantages and economies of scale. It is clear that low-cost production, and resulting prices, have become a challenge for some formerly dominant malaria RDT manufacturers; some have exited the public sector market and are focusing on other products or on the private sector.

- Capacity to fill large orders: Manufacturing capacity and access to working capital are required to successfully fill large orders, which can require millions of RDTs to be delivered within four to eight weeks.

- Switching costs: Countries are reluctant to switch brands of RDTs because the costs are high (e.g. retraining users, developing new guidelines, supply chain issues). This results in sole sourcing of RDTs, usually for a time limited period, and limits the frequency of open competition, i.e. opportunities for new entrants to compete for a country's business.

- Registration: Local registration of products is increasingly a requirement for importation and for participation in tenders, and these processes can take several months to complete. Registering in multiple countries can be challenging for small companies that do not have a global distribution structure in place.

Potential "new entrants" to the public sector market are primarily small rapid test manufacturers based in Asia, although there are a few larger Chinese rapid test manufacturers. While there are a few companies with high-performing products intent on entering the RDT market, many need to invest in production capacity before they will be able to have a real presence in the public sector market, i.e. be capable

[58] Barriers to entry are obstacles that prevent new competitors from easily entering a market. There are many potential sources of barrier to entry, including regulation, licensing requirements, high start-up costs, economies of scale and other cost advantages, intellectual proprety, etc. Barriers to entry can protect incumbant companies and restrict competition.

of competing effectively on price and lead time. Other potential "new entrants" may already have low-cost production capabilities, but they need to improve the technical performance of their tests before they can enter the public sector market.

Innovation

Given the current market conditions, there is a lack of incentive for investment in malaria RDT product development. 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. Although companies are working to develop highly sensitive malaria RDTs for elimination, this innovation is externally funded. Other innovation is largely incremental and reactive (e.g. to improve performance in product testing to reduce costs or to improve control over MAbs).

Manufacturing costs, inputs and processes

Manufacturing costs

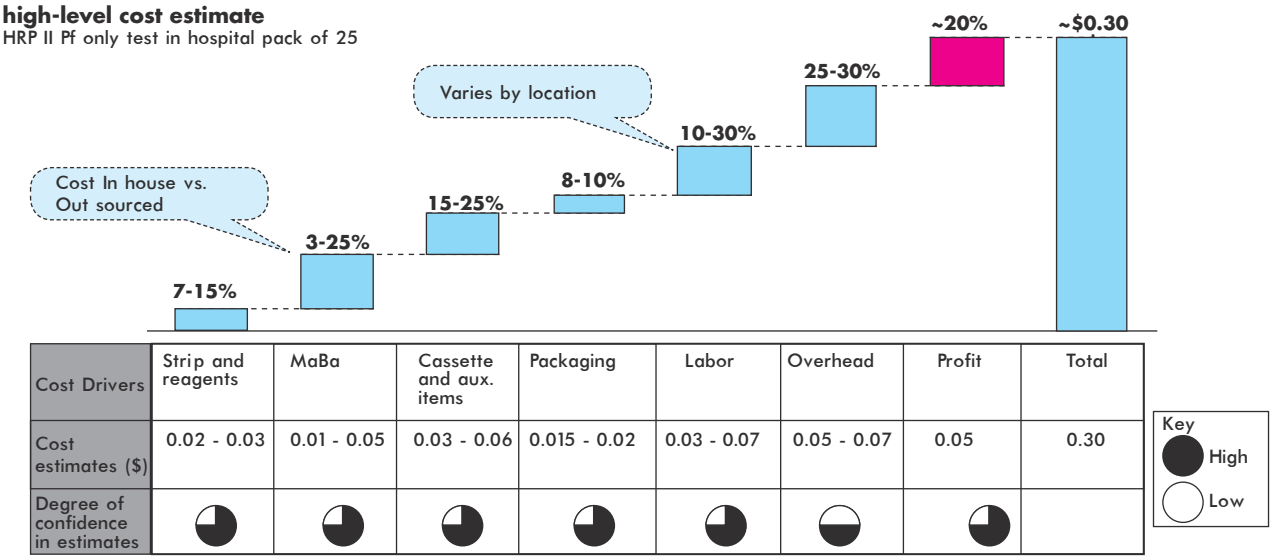
With respect to manufacturing costs, limited data exist. Key inputs to making RDTs include: MAbs; commodities sourced from Asia and costing one half to three cents (pennies) apiece, with the plastic cassette and foil pouch generally costing the most; and nitrocellulose and membranes, available from a limited number of suppliers. In 2014, CHAI conducted a cost analysis based on actual costs from two malaria RDT manufacturers (Figure 30). Key findings are as follows:

- Total costs could range from US$ 0.16–0.23, depending on the level of automation, production volumes and allocation of indirect costs. Profit and overhead increase the total cost by US$ 0.10–0.12.
- The cost of MAbs is highly dependent on whether they are produced in-house or purchased commercially.
- Labour costs also vary greatly depending on location and levels of automation.
- Single kit packaging costs an additional US$ .05–0.10.
- Additional MAbs required for multi-species tests are US$ 0.02–0.05 per test.

While this analysis is informative, it would be stronger if additional manufacturers had participated. In addition, costing analysis at this level of detail (i.e. pennies) is challenging with differing accounting practices influencing costs.

FIGURE 30

Cost estimate for a malaria RDT (Pf-only HRP-II-detecting test, in hospital pack of 25)



Source: 2014 CHAI analysis based on actual costs from two malaria RDT manufactures.

MAb Market

Of malaria RDT components, the most critical raw material are MAbs, antibodies that have been manufactured to bind to specific antigens. These are available from commercial sources or produced in-house. The market for MAbs is relatively opaque because, for commercial reasons, RDT manufacturers do not always disclose the source and type (e.g. epitopes targeted; isotype; subclasses)[59] of MAbs employed in their tests. Anecdotal information, including conversations with malaria RDT manufacturers and leading MAbs suppliers, as well as one published paper, (89) suggest that in the 2000s the MAbs market was quite concentrated around two sources:

- The National Bioproducts Institute (South Africa) was the major source of MAbs binding to HRP-II and aldolase. The Institute developed its MAbs in the 1990s and has been producing and supplying them since 1998, primarily to RDT manufacturers but also to researchers and distributors.
- Flow Inc. (Portland, Oregon, US) developed MAbs binding to pLDH, and initially developed an RDT using these MAbs. In 2011, the company sold its pLDH business to Access Bio Inc., one of the major RDT manufacturers. Access Bio Inc. currently outsources MAbs manufacturing and uses Vista Diagnostics International as a distributor of pLDH MAbs.

[59] These are characteristics used to describe MAbs. An epitope is a very specific molecular shape/pattern of a protein that is recognized by the MAb. Antibodies are categorized into isotypes and subclasses based on their structural and biological functions. Note that this detailed information on the type of MAb may not even be known to the RDT manufacturer, as it is not always available from the suppliers of MAbs.

Currently, more companies produce MAbs in-house and there are several sources of antibodies, although it is not clear how many of these are suppliers producing their own MAbs nor how well these MAbs work in malaria RDTs.[60] Conversations with manufacturers and experts suggest that a handful of antibodies dominate the market due to their performance. Additionally, increasing demand for multi-species RDTs, the sale of the pLDH business to Access Bio Inc. and the pressure to reduce RDT manufacturing costs have caused RDT manufacturers to explore options for controlling their MAbs supply by developing their own clones and producing MAbs (in-house or outsourced to companies specializing in MAbs production). To date, a few of the market leading RDT manufacturers control the supply of MAbs for all/some of the MAbs used in their RDTs. Other RDT and MAbs manufacturers are working to develop alternatives to the leading MAbs that have better performance or are less expensive.

Today, it is not clear how concentrated the MAbs market is, the extent of in-house MAbs production or what share of the market the two formerly dominant MAbs suppliers have. Similarly, the pipeline for new MAbs is not well known.

Manufacturing process

There have been no recent changes to manufacturing processes, which are described in the *2012 Malaria diagnostics market landscape*.

Increasingly, low-cost production is critical to competing effectively in the global tender market. Conversations with manufacturers suggest that cost advantages are due to a variety and often a unique combination of factors, including: use of more efficient production equipment; producing MAbs in-house; production know-how gained over time; commanding better terms from raw materials suppliers; and geographic advantages (e.g. favourable labour rates and policies; government incentives).

The degree of automation among RDT manufacturers varies, larger manufacturers operating in high labour cost environments tend to have higher degrees of automation. The decision to automate is influenced by access to equipment suppliers and maintenance, as well as external factors such as local government incentives for employment. If designed correctly, automation can drive down costs and improve quality.

Production capacity and lead times

Among the dominant suppliers, production capacity is generally not considered to be a limiting factor in this market and procurement agents report that quoted lead times are generally short and met on time. In general, suppliers have "lateral flow" production capacity that can be used to manufacture many different types of RDTs, not just malaria RDTs. For example, of the four suppliers that have prequalified products there is an estimated 785 million with lateral flow capacity, of which 484

[60] William Davidson Institute, Malaria rapid diagnostic test supply-side landscape analysis report, unpublished report, 2015.

million are specifically for malaria RDTs.[61] For some companies, capacity is a limiting factor due to the large order sizes and short lead times.

Capacity, does affect production practices. The public sector market is characterized by large order sizes, short lead times and the "winner takes all" nature of the tender market. Malaria RDTs are made to order and manufacturers only begin producing when an order is in hand. As a result, poor resource utilization (e.g. equipment and labour are sometimes idle) and more expensive raw materials (e.g. spot market buying and expedited shipping for some raw materials) increase the average cost per test *(90)*. Manufactures must also focus significant energies on managing logistics.

Despite low prices, the leading suppliers have expanded and improved their malaria RDT production capacity in the past few years, as the ability to rapidly produce large orders at low cost is an advantage in this market. Conversations with leading suppliers also suggest that pricing strategy is often linked to capacity: a desire to keep production lines operating at full capacity at times results in pricing that is at or below cost due to the assumption that "it is better to have some revenue to cover costs rather than none".

Shipping and distribution

There have been no recent changes to shipping and distribution in the public sector, these are described in the *2012 Malaria diagnostics market landscape*. Limited information on private sector supply chains, based on ACT Watch Supply Chain Surveys (the majority conducted in 2009), is also available in the *2012 Malaria diagnostics market landscape*.

[61] Draft assessment of the market impact of requiring WHO prequalification for malaria RDTs. Unpublished report. Geneva: World Health Organization; January 2016.

7. Market shortcomings

Table 4 summarizes the market shortcomings in the malaria diagnostics market using the UNITAID framework for market analysis and provides the primary reasons for why these shortcomings exist.

TABLE 4
Market shortcomings of the malaria diagnostics market

Category	Shortcoming	Primary reasons
Availability/ Affordability	Concentration of suppliers creates appreciable risk of supply security in the event of unpredictable events (e.g. acquisition; fire at a plant; decision to exit market; failure in product testing); current pricing may not be sustainable in the long term.	• Buy side structure includes competitive tenders that emphasize lowest priced bid, contributing to a "winner takes all" market. • Suppliers may offer pricing that approaches/is below cost due to: (i) desire to fill unused production capacity; (ii) strategic attempts to develop new markets or to win tenders in specific markets; and (iii) internal focus on volume targets, as opposed to the bottom line (profitability). • Low-cost production and capacity to rapidly produce large orders (i.e. more than 10 million RDTs) have become barriers to entry for the public sector market. Low prices, approaching cost of production, have led to supplier exit from the public sector markets. • Potential new entrants with high-performing products likely need to invest in capacity to become competitive on price; other companies with low-cost, large lateral flow production capacity do not have high-performing malaria RDTs.
Affordability	RDTs may be unaffordable in some markets.	• Supply chain markups from the manufacturer to final service delivery point. • Low volumes procured by the private sector means pricing may not be competitive.

Category	Shortcoming	Primary reasons

Quality	Field-level quality of RDTs largely unknown; no low-cost QCs for field use.	• Technical complexity of developing field stable, easy-to-use, controls.
		• Little incentive for private investment in development of RDT QC technologies:
		  o market opportunity is undefined (e.g. use scenarios; size of demand; willingness to pay);
		  o lack of detail on the need, including consensus on optimal specifications and characteristics.
		• Weak regulation of malaria diagnostics in countries that consume RDTs means that there are no regulations that require use of controls.

Quality	Variable/unknown quality at RDT manufacturing level.	• No awareness of differences in manufacturing QMS and their potential impact on product quality among stakeholders and buyers.
		• Weak diagnostics regulations in countries that consume or produce malaria RDTs do not require rigorous review of manufacturing-level quality systems.
		• Limited incentives for suppliers to invest in QMS because: (i) market does not currently differentiate based on QMS; and (ii) market rewards low-cost production, often in contrast to investment in quality.
		• Relatively few malaria RDT suppliers have become WHO prequalified:
		  o limited incentive to undergo the WHO PQ process;
		  o slow progress of RDT suppliers due to limited experience with stringent regulatory requirements;
		  o slow progress of the WHO PQ.

Demand and adoption	Insufficient uptake of RDTs compared to need.	• Limited demand for RDTs; low awareness and acceptance of tests in some areas. • Reliance on donor funding and potential funding reductions may limit scale-up plans and/or actual scale-up in the future.

Category	Shortcoming	Primary reasons
Demand and adoption	Limited market for quality RDTs in the private sector.	• Local regulations may prohibit diagnosis or follow-up treatment. • Low awareness among consumers and supply chain actors resulting in low availability in retail outlets and little pull from consumers. • Limited margin/incentive to stock RDTs for some supply chain actors. • RDT (and subsequent treatment) prices may be unaffordable. • Where RDTs available in the private sector, quality may be unproven. • Limited market knowledge (e.g. information on demand; potential profitability) upon which to make decisions about developing these markets. • Hesitation among some malaria RDT suppliers to invest in developing these markets independently.
Demand and adoption	Low acceptance of RDTs by providers.	• 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 (poor delivery) of commodities for non-malaria fever. • Low awareness of declines in malaria prevalence. • Mistrust of RDTs (concern about heat stability, LOD, possibility of other species when *Pf*-only tests used); lack of QC for RDTs.
Demand and adoption	Low diagnostics use contributes to poorly informed malaria programme delivery (i.e. delivery is not informed by high-quality complete data, reducing efficiency and impact).	• Reductions in malaria are unevenly distributed thus increased importance of a tailored, evidence-based response. • Historically, low-quality case data due to limited use of diagnostics (i.e. reporting of suspected cases instead of actual cases). Poor quality data led to low prioritization. New guidance on surveillance monitoring and evaluation released in 2012 *(91, 92)*, but implementation is slow/weak. • Limited use of digital/information technology (IT) solutions. • Limited experience and capacity to analyse and use data to inform programmes.
Demand and adoption/ Delivery	Insufficient uptake of RDTs compared to need.	• Information gaps limit ability to identify and respond where RDT uptake lags and/or where RDTs are not informing treatment. • Implementation weaknesses, e.g. weak supply chain management; inadequate health-worker training; lack of supervision/QA.

Category	Shortcoming	Primary reasons
Innovation	Lack of tests to support diagnosis and treatment of *P. vivax* (improved LOD of diagnostics, POC G6PD test, test for hypnozoites) for elimination settings.	• Limited work to define the needs or product characteristics for new technologies. • No prioritization of the multiple "needs" for new technology. • Uncertain demand. Limited work to define market opportunity and business case for new products. Incentive to invest may be low; demand for some new products may be low or fragmented. • Current RDT market conditions are a disincentive for investment in malaria diagnostic test R&D. • Limited philanthropic and private funding for R&D. • Unclear regulatory requirements and pathways for new malaria diagnostics.
Innovation	Poorly adapted RDTs; while today's RDTs are a great improvement over microscopy in terms of adaptability, there are limitations (e.g. RDTs are not interchangeable; poor heat stability of single kits; room for improvement in labelling, instructions, components to simplify and improve quality).	• Specifications for improvements to harmonize RDTs have only recently been developed, not yet widely communicated. Harmonization on procedures not feasible in the near term; would require appropriate market incentives and product evaluations. • Lack of quality oversight during product development (e.g. no requirement that heat stability validations be conducted according to international standards).

8. Opportunities for market interventions

This section addresses opportunities for market intervention and provides an initial view of potential market opportunities for increasing access to malaria diagnostics. It 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: works in progress

In recent years, several market-shaping initiatives have been undertaken to improve access to malaria diagnosis. 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 5 provides an overview of various market initiatives, many of which have been noted previously in this report.

TABLE 5
Market interventions under way

Description	Market shortcoming addressed	Lead implementer
Development of private sector markets for diagnosis and treatment	Delivery; Affordability	• PSI, Malaria Consortium • CHAI • Various pilots and operational research efforts (e.g. PMI, ACT Consortium, University of California San Francisco/ Society for Family Health)
Transition of product and lot testing to a more sustainable business model, including development of recombinant QC panels	Quality	• FIND • WHO
Develop QCs for field use (PCWs)	Quality	• FIND
RDT harmonization: review of RDTs currently on the market; development of optimal specifications and opportunities for standardization	Adaptability	• Roll Back Malaria Partnership • Institute of Tropical Medicine (Belgium)
Development of highly sensitive RDTs for elimination settings	Availability	• Bill & Melinda Gates Foundation • PATH • FIND
Development of POC G6PD tests	Availability	• PATH
ACT Watch II: monitor uptake of ACTs and diagnostics	Market intelligence	• PSI
ACT and RDT forecast	Market intelligence	• CHAI • IMS Health • Global Health Group • University of California San Francisco

Market interventions: additional opportunities

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

Global procurement level work to improve market sustainability

Perhaps the most urgent need is for demand-shaping interventions at the procurement level to ensure the long-term health and sustainability of the RDT market, given recent pricing declines and consolidation. Practically speaking, reliance on a few donors presents an opportunity for coordinated action, and interventions at the global procurement level are likely the best means of diversifying the supply base.

Mechanisms to refocus current competition on price towards a healthier balance of competition on price, quality, innovation and other factors such as total cost of ownership should be explored. One of the unique challenges to RDT procurement are the differences between malaria RDTs: while malaria RDTs are more interchangeable than other diagnostics, they are not completely interchangeable. The Roll Back Malaria Partnership Harmonization Task Force work suggests that in the near term it is not feasible to completely align RDTs *(93, 94)* and, therefore, any pooled procurement programmes or long-term agreements must carefully take into consideration demand for specific products.

The expected impact on the market of interventions in this area would be to encourage suppliers to remain/participate in the public sector market, to support long-term sustainable pricing and to promote investment in quality and innovation (e.g. WHO prequalification standards; implementation of RDT Roll Back Malaria Partnership Harmonization Task Force recommendations; development of the retail private sector; development of new technologies such as for *P. vivax* management and elimination settings). Even with the large purchasing power of the institution buyers, incentives or slight price increases may be required to attract sufficient suppliers to the market and to encourage these suppliers to invest such that they can then compete meaningfully in the market.

Currently, the Global Fund PPM is considering new approaches to RDT procurement, including global supply agreements spanning a period of time. Details of the PPM strategy are yet to be worked out, and it will be important to monitor progress over time. If demand shaping at the global procurement level is not possible and/or does not have the desired effect, monitoring of market share and pricing (including bid

analysis and pricing for sole sourced versus openly competed orders) would provide more insight into the risks to supply security and pricing.

Expanding the market for malaria diagnostics

Expanding the market for malaria RDTs is an urgent priority. Although significant progress has been made in the public sector, many countries have a ways to go to achieve the high levels of coverage required to impact ACT overtreatment. Typically, diagnostic scale-up has first occurred in the public sector facilities; however, there are vast numbers of people not attending these facilities. Innovative approaches for expanding the RDT market to these populations need to be developed, tested and scaled up. Reaching this "unserved demand" is not straightforward, as often relatively little is known about these potential markets (e.g. limited quantification of the various potential market segments; understanding of provider behaviour and treatment-seeking behaviour; or analysis of distribution channels).

Programmes seeking to expand the market for malaria RDTs should be grounded in market research to better understand demand, to prioritize different market segments and to identify marketing and distribution strategies for these target populations. Pilots that test strategies for overcoming challenges could then be followed by scale-up. These programmes could target people who presumptively diagnose and treat, as well as those who currently do not seek care for fever. Based on the specific country context, the focus may be on the formal or informal private sector, on strengthening and extending the public sector and/or on community health worker programmes. Regardless of approach, components such as communications campaigns to raise awareness of RDTs, provider training on national guidelines and supervision, QA and monitoring and evaluation will be ongoing and require sustained support. In the retail private sector, mechanisms to ensure affordable RDT prices should be explored because as these markets develop, volumes are likely to be both low and fragmented, resulting in higher-priced RDTs than in the public sector.

Ensuring quality of malaria diagnostics

There are several opportunities to support the quality of malaria diagnostics:

Regulatory pathways. For new products coming to market, regulatory pathways at the global and country levels are not clear. Work in this area would involve formalizing roles and establishing processes at the global level. With respect to performance evaluations, evaluation standards and expectations are needed as new technologies come to market. For example, both highly sensitive RDTs and improved *P. vivax* RDTs would need to be evaluated against samples with very low parasite densities; the Product Testing Programme panels are not calibrated to challenge the sensitivity of these RDTs.

Concurrently, a longer-term programme for strengthening regulatory capacity (including post market surveillance) for malaria RDTs at the country level is needed.

This work could involve multiple diseases and contribute to development of markets for quality diagnostics more broadly. For example, in many countries, local registration requirements are unclear, lengthy and/or poorly enforced. Standardizing registration requirements across several countries could reduce work for regulators and manufacturers, allowing for more rapid product registration. Similarly, regional coordination on QC programmes (e.g. post-market surveillance in regional reference laboratories) could also streamline work and reduce costs *(95)*.

The market impact of improving regulatory processes includes reducing the uncertainty and associated risk to technology developers and accelerating the timeline for new products coming to market. From a demand perspective, clear pathways will help donors and consumers to readily identify recommended, high-quality products.

Strengthening the incentive to invest in quality at the manufacturing level. Given recent quality issues with malaria RDTs,[62] the level of lot-to-lot variation seen in product testing programmes and market factors that put pressure on quality (e.g. cost reduction efforts; rapid production scale-up), it is timely to consider options for implementing a system that provides more insight into quality at the manufacturing level and that creates an incentive for manufactures to invest in QMS.

Work in this area might involve several components including: (i) agreement among relevant stakeholders on a quality standard, such as the WHO PQ, and a timeline for implementation; (ii) development of new policy and new processes for the transition and implementation; (iii) support to the implementing organization (e.g. ensuring adequate capacity at the WHO PQ to handle applications in a timely manner); (iv) communications to RDT manufacturers, procurers and local regulators to ensure awareness of new policies; and (v) potentially, technical support to RDT manufacturers to ensure they move expeditiously through the system.

Expanding the information on the quality of malaria RDT dossiers and manufacturing would allow consumers to identify manufactures with systems capable of maintaining quality throughout the design and production process, thereby reducing the risk of poor quality products in the field. When large procurers align to the new standard, it would also send a signal to the market about the importance of quality, and create an incentive for manufacturers to invest in QMS. Finally, stronger QMS is a safeguard against some of the current market pressures (e.g. rapid scaling production; cost pressures).

One major risk is the potential negative impact on supply security, as higher quality standards create an additional barrier to entry that could prevent suppliers from participating in the public sector market. For example, currently, two manufacturers dominate the public sector market. A fire at a plant, a quality problem in product testing or a business decision to exit the market at one of these companies could disrupt global supply. However, were they to occur today, there are multiple eligible

[62] For example, evaporation of buffer in individually packaged tests; all of one company's products delisted from the Global Fund due to quality issues uncovered during the WHO PQ inspections; and two products delisted by the WHO PQ for poor performance in Round 5.

suppliers that could meet current demand (albeit at higher prices and costs of switching RDTs at the country level). If quality standards at the manufacturing level were higher, it is likely that fewer companies would be eligible to supply RDTs and could step in to meet demand should there be disruption at one of the leading manufacturers. Therefore, work in this area must carefully consider impact on the market, and should be aligned with any work at the global procurement level on market sustainability.[63]

Strengthening field level quality. For malaria RDTs, practical technologies for performing QC in the field as well as systems for systematically reporting problems are needed. Development of field stable QC for malaria RDTs has been a challenge, both from a technical perspective (e.g. no suitable pLDH recombinant has been found yet) and from a business perspective (e.g. limited incentives for investment). A PCW developed by FIND will be piloted in 2016 and it is likely that controls from a few RDT manufacturers will become available in the coming year. Thus far, there is limited information on these products (i.e. specifications) and on their performance. Nor is it clear how they will be used, or how any "RDT failures" would be resolved and reported.

Work in this area would aim to accelerate the introduction and uptake of QC for RDTs and to support systems for monitoring RDT use. Initially, information on existing and pipeline controls needs to be compiled and analysed, and compared to a set of optimal product characteristics. Evidence on performance of these controls is likely lacking, and independent studies to assess controls will likely be needed. In addition, operational research and piloting is needed to develop use scenarios, guidance for use of controls and training materials. For FIND's PCWs, and possibly others, this operational research would inform demand, packaging and distribution strategies. As demand estimates and pricing are not yet available, it is not clear if additional support might be required to ensure affordability or sufficient incentive to manufacture controls. At the country level, post market surveillance systems need to be developed and strengthened; such work would likely apply to malaria RDTs as well as other diagnostics.

The market impact of a programme to improve RDT quality is related to improving the targeting of ACTs through use of high-quality diagnostics. More specifically, this work would address a gap in the quality continuum by improving the information on RDT quality in the field, for example, by allowing supervisors to distinguish between poor quality products and operator error. Controls could also address concerns about the heat stability of RDTs, and potentially contribute to increased RDT acceptance and ultimately improved case management.

Additional opportunities to improve quality and regulation of malaria diagnostics would include development of a programme to standardize and quality assure molecular diagnostics, including standardization of protocols, development of standardized QC procedures and development of an international external QA programme. Since molecular methods are increasingly used in epidemiological

[63] Draft assessment of the market impact of requiring WHO Prequalification for malaria RDTs. Unpublished report. Geneva: World Health Organization; January 2016.

surveys and in research, it is becoming important to standardize their use so that results are reliable and can be compared across laboratories.

Improving the quality of RDTs where they are available, in particular, in the private sector. At the country level, the quality of RDTs in the private sector is not well regulated, and available evidence indicates that where RDTs are available the quality of many products is unknown. Overall, given limited evidence on availability and market share of "non-QA RDTs", it is difficult to appreciate the risk that inferior quality RDTs pose; however, it would be wise to explore this issue and intervene early if necessary, especially in markets where the retail private sector is a large source of antimalarials and there is interest in introducing RDTs. Work in this area could begin with information gathering and might explore options such as: (i) strengthening regulation of diagnostics in countries with large private sector markets; (ii) strategies that "pull" quality products through the private sector, or that shift demand to those outlets that are "quality assured"; (iii) or procurement mechanisms that make the leading quality assured-suppliers the most price competitive in these markets or give some other kind of advantage to these products.

Supporting development of new malaria diagnostics

Epidemiological changes in malaria are creating a need for new diagnostic tools and strategies. One of the major challenges concerning the development pipeline is a multiplicity of "R&D needs", with limited prioritization of needs, articulation of desired product characteristics and analysis of market opportunities. At the same time there is low awareness of the market needs among technology developers. This disconnect is reflected in the variable progress of the malaria diagnostics pipeline overall; while some areas have advanced, in others there has been limited or no progress, especially in the later stages of development (i.e. evaluation, policy/regulatory, introduction and scale-up stages).

Efforts to better align the development pipeline with the needs and the market would improve market efficiency and resource utilization. Work in this area might involve gathering stakeholders to prioritize needs; and for high priority products to articulate desired product characteristics and to do preliminary analysis of the potential market opportunity. In some areas, work at the country/user-level could inform what is really needed and how the new diagnostic might be used (e.g. what problem the new technology is trying to solve). A communications strategy would be needed to ensure that technology developers are well informed of the outcomes of these exercises. At the donor level, early work to understand the market, including regulatory and policy requirements, could inform what kinds of support and incentives might be needed to stimulate private sector investment in these areas.

In 2016, the MalERA Consultation work on the R&D agenda for diagnostics to support elimination will be revisited, which is welcome given the shortcomings described above and the rapid evolution of research on elimination. However, it is not clear if this

process will prioritize among the multiple needs, or provide significantly more detail on product characteristics and market opportunity. Because this forum focuses on elimination, it also lacks perspective of current needs in high-burden countries.

For the POC G6PD test development as well as development of highly sensitive RDTs, donors are funding some market-related work; however, there may be scope for additional work. For example, in G6PD testing operational research is needed to inform implementation strategies; similarly for highly sensitive RDTs research will be required to demonstrate impact in different scenarios and to define the role of highly sensitive diagnostics in elimination.

In addition to monitoring these product development initiatives, there are potential opportunities to engage upstream such as: catalysing development of products for improved diagnosis of non-*Pf* malaria, including development of product evaluation schemes; and supporting research on non-invasive screening methods and on biomarkers for hypnozoites. Downstream, additional work is also needed, for example, to generate evidence about the performance of recently launched products (e.g. UMT; Parasight; PCWs), and to inform how other products, such as these and the commercial LAMP assays, might be used in the field.

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 and to understand the potential markets for new products. Early identification of market challenges and solutions for overcoming these will support rapid uptake and impact of new products.

Surveillance and fever management

Improving surveillance and fever management are high priorities in the malaria community. Several areas of potential work warrant further investigation, including: (i) innovation around approaches focused on the asymptomatic reservoir, including optimal strategies for delivery of diagnostics and treatment; (ii) increasing use of technologies that streamline reporting and analysis of surveillance data; and (iii) supporting commodity access for fever management. Currently, the optimal approach to addressing the asymptomatic reservoir is unknown, and several research projects are under way to answer key questions. The need for additional work in this area should be explored more fully. Similarly, there are many new technologies that assist with reading test results, reporting results and data analysis. While there may be scope for scaling these, they have not been comprehensively evaluated nor has the market for these technologies been analysed. With respect to integrated fever management, further exploration of market issues and opportunities is warranted. In addition to improving coverage of essential commodities (e.g. RDTs; ACTs; amoxicillin; oral rehydration salt; zinc), there may be scope for supporting development and scale-up of technologies that are new or that have not been widely

available in resource-poor settings (e.g. new respiratory rate timers; pulse oximeters for severe pneumonia; diagnostics that assist with differential diagnosis of fever).

Market intelligence

Overall, malaria programmes could be more optimally managed if high quality data were used to drive decisions. From a market perspective, many of the market shortcomings and opportunities for intervention described in this report have components related to the limitations in market intelligence.

With respect to malaria RDTs, there are there are several areas where improved market intelligence would be meaningful. For example, market-tracking systems based on procurement data could be institutionalized to routinely track malaria RDT market indicators. While the availability of malaria RDT data has been increasing (e.g. the procurement analysis in this report included UNICEF and WHO data for the first time) the current dataset is quite incomplete, representing only half of the market. While private sector sales may account for some of this gap, it is difficult to know whether the remainder is due to poor reporting or other causes. Improving the completeness of information for each RDT order in these datasets, including standardized information on product identification, would also strengthen analysis for particular product types (e.g. single-use kits). The sizable gap between RDT sales reported by suppliers and RDT distribution reported by countries is another concern that has yet to be investigated (e.g. RDT suppliers report selling twice as many RDTs as national malaria country programmes report distributing).

Given current RDT market conditions, deeper dives into some aspects of the market would be beneficial. Bid analysis would be helpful in understanding the supply base and the risk to supply security; supplier reported sales information (already collected by WHO) could also be used to monitor the supply base. Greater transparency around pricing and analysis of the impact of sole sourcing could improve current pricing variability. Going forward, if the Global Fund alters its procurement strategy, if WHO introduces prequalification as procurement criteria for RDTs or the new highly sensitive RDTs are launched, then monitoring the impact of these changes on the market will be important. Additionally, forecasts of demand would help align supply and demand and allow RDT manufacturers to make informed decisions about investing in the market.

With respect to expanding the market for diagnostics, there are several areas where additional market information (at the country level) is needed to design approaches for meeting unserved demand (e.g. identifying and segmenting the market that is currently unserved, quantifying these segments, prioritizing them, characterizing consumer behaviour for priority segments, distribution channel analysis, etc.) In the public sector, where RDTs have been rolled out, information on coverage and on targeting of ACTs is needed to reach universal coverage and to improve fever management. For case management, diagnostics reporting provides information

on where cases are highest and ACT need is highest, and this can inform supply chain management. Data on appropriate use of RDTs and ACTs can inform follow-up interventions.

Finally, with respect to the technology pipeline, there are several areas where limited market intelligence leads to inefficiency. As mentioned above, market research is needed to better understand the needs and the market opportunity for new diagnostics. This information could be used to better align technology development with the needs; and would inform donor decisions about external incentives (both the need and type) that could foster private sector investment.

Conclusion

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, variability in epidemiology is leading to new diagnostic needs, 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 comprehensive approach to monitoring the diagnostics markets is needed to ensure long-term health of the market and to improve market efficiency.

Annex 1. Surveillance in low-transmission settings

TABLE A1.1

Surveillance activities in low-transmission and elimination settings

Activity	Description and goals in elimination settings
Passive case detection	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. Elimination programmes aim to detect as many cases of malaria as possible through passive case detection systems. Efforts may involve increasing access to health facilities, ensuring that providers test all suspected cases and provide appropriate treatment. Efforts must extend to private sector facilities as well as public health facilities. Programmes also aim to improve the speed, accuracy and monitoring of case reporting so that programmes can rapidly respond to outbreaks and identify potential foci of transmission.
Reactive active case detection	Active case detection strategies focus on identifying and treating all infections, including identifying individuals who are carrying parasites, but do not seek care and treating those infections as early as possible in order to reduce chances of onward transmission. Reactive case detection is common in low-transmission settings and involves health workers performing follow-up visits in the community for cases that present to clinics ("index cases"). 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 active case detection	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 (using a diagnostic test) mass drug administration also could be used.
Quality assurance (QA) Quality control (QC)	From a diagnostics perspective, passive and active case detection rely on the ability to accurately detect infections. Elimination programmes must implement more intensive QA/QC activities for diagnostics, for example, the national reference laboratory might routinely confirm all positive cases and a proportion of negatives using expert microscopy or molecular tests.
Origin analysis	Origin analysis involves the use of genetic testing 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.

Annex 2. WHO malaria diagnostics policies

WHO malaria case management guidelines

In response to the declines in malaria, in 2010, WHO updated its policy on malaria diagnosis, recommending that all cases of suspected malaria be confirmed with a parasitological test (microscopy or RDT) before treatment in order to guide rational use of antimalarial medicines *(6)*. In addition, in 2012, WHO launched the T3: Test. Treat. Track initiative, underscoring the importance of scaling up malaria diagnostics and ensuring that the data generated through testing are systematically reported. Alignment with WHO policy is high among countries, however, universal access to testing will take some time to achieve given the low testing rates.

Other notable WHO recommendations related to diagnosis in case management include:

- WHO is not prescriptive about whether a country uses RDTs or microscopy, and it recommends that a QA programme support both microscopy and RDTs *(96)*.
- With respect to non-*Pf* species, WHO cautions that RDTs remain relatively insensitive for detection of *P. malariae* and *P. ovale*; microscopy is generally preferred for speciation *(97)*.
- WHO recommends that any work to improve ACT access in the private sector also include RDTs, and holistically approach fever management in children. In light of drug resistance, private sector initiatives should ensure targeting of ACTs, and include strong education, behaviour change, training and communication components. Programmes need to consider long-term sustainability and take country context into account (e.g. strength of the public health systems; availability of community health workers) *(98)*.
- In general, WHO does not see a role for nucleic acid tests in clinical management of malaria or in routine surveillance systems; these techniques are reserved for population surveys and focus investigations in malaria elimination programmes *(97)*.

WHO malaria RDT procurement guidance

The WHO GMP first published product selection criteria for malaria RDTs in 2010 after completing Round 1 of the Product Testing Programme. Since 2012, the WHO malaria RDT procurement criteria have been as follows: (i) for the detection of *P. falciparum*, the panel detection score against all *P. falciparum* samples should be at least 75% at 200 p/µL; (ii) for the detection of *P. vivax*, the panel detection score against all *P. vivax* samples should be at least 75% at 200 p/µL; (iii) the false-positive rate should be less than 10%; and the invalid rate should be less than 5%. WHO is currently considering whether only WHO prequalified RDTs be recommended for procurement; a decision is likely in early 2016.

WHO guidance for relapsing malaria and G6PD testing[64]

In 2015, WHO updated its recommendations for relapsing malaria, recommending that primiquine be given to all confirmed *P. vivax* and *P. ovale* cases in all settings *(97)*. However, implementation of this policy is not straightforward: primaquine is not safe for people with G6PD deficiency, a common enzymatic deficiency affecting 3–35% of the population in malaria-endemic areas. Depending on the level of deficiency and dosage of the drug taken, G6PD deficient patients will experience haemolysis, in some cases fatal, after taking primaquine. Therefore, prior to administering primaquine, WHO recommends providers ascertain the patient's G6PD status *(97)*.

Currently, G6PD testing is not widely available outside of hospitals with sophisticated laboratories. Tests that may be used at the lower levels of the health systems have recently come to market; however, there are some limitations that complicate management of patients. In particular, heterozygous females with intermediate G6PD deficiency may be misclassified by current qualitative tests as having "normal" G6PD activity, although some proportion of them are at risk of haemolysis.[65] As such, WHO recommends treating all "normal" women with primaquine, and counselling them to stop taking the medicine and to seek care if they have any signs of haemolysis *(97)*.

[64] Note about another use of primaquine: in order to further reduce transmission in pre-elimination or elimination programmes, a single dose of primaquine is recommended in addition to ACT for most patients with P. falciparum. In this instance, G6PD testing is not recommended by WHO because the recommended dose is unlikely to cause serious toxicity (97. World Health Organization. Guidelines for the treatment of malaria. Third edition. Geneva: 2015. http://www.who.int/malaria/publications/atoz/9789241549127/en/.

[65] G6PD deficiency is a genetic disorder, and the gene coding for G6PD is found on the X chromosome. Since women have two X chromosomes and men have only one, there are differences in the way the disorder behaves in male and females. The disorder is more common in men because with only one copy of the X chromosome a mutation on the gene for G6PD will cause G6PD deficiency. Women have two X chromosomes, therefore, it is possible for women to have a proportion of RBCs with an X chromosome that is normal and a proportion of RBCs with abnormal X chromosomes (referred to as heterozygous females). Among heterozygous females, the proportion of deficient versus normal RBCs varies, and as a result a heterozygous female's G6PD enzyme levels may be normal (>80% activity), intermediate (30–80% activity) or deficient (<30% activity). A female with intermediate activity is at risk of haemolysis, although a qualitative test (with a 30% cutoff) would classify her as "normal". (Intermediate deficiency versus normal G6PD activity cannot be discerned with a qualitative test.) This creates challenges for diagnosis and categorization of the deficiency in heterozygous females.

Currently, many national policies are not aligned with the WHO recommendations for primaquine and G6PD testing and clinical practice frequently deviates from national policy for a variety of reasons *(99)*. Many national programmes anticipate challenges in implementation of the WHO recommendations and have requested additional guidance from WHO *(100)*.

WHO recommendations for POC G6PD tests

For primaquine, WHO recommends that POC G6PD tests meet the following standards: >95% sensitive for G6PD enzyme activity levels below 30% of normal; >95% negative predictive value when the diagnostic tests yields a non-deficient result (i.e. greater than 30% normal G6PD activity). Tests should be stable at 30–40 °C and the visual readout should clearly distinguish between deficient and normal patients *(101)*. WHO also recommends that small-scale piloting of newly released POC G6PD tests inform broader decisions about expanding use of POC G6PD testing.

WHO policy on malaria in pregnancy

Since 1998, WHO has recommended intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine in areas of high to moderate transmission.[66] In October 2015, an Evidence Review Group confirmed that IPTp with sulfadoxine-pyrimethamine remains highly effective and cost effective and continues to recommend it over alternative strategies such as intermittent screening and treatment in pregnancy (ISTp) *(102)*. ISTp is a strategy whereby RDTs are used to screen pregnant women and treatment is provided to RDT positive women. That said, several programmes are considering ISTp due to very low levels of transmission (i.e. pre-elimination settings), high proportions of *P. vivax* and/or high sulfadoxine-pyrimethamine resistance.

WHO guidance on diagnostics in low-transmission and elimination settings

WHO is currently updating guidance on malaria elimination, which has not been comprehensively reviewed since the publication in 2007 of the Malaria elimination field manual. An Evidence Review Group was established in 2015 to develop a new operational manual for elimination that should be available in late 2016. Currently, guidance on malaria diagnosis and surveillance for elimination settings is contained in several documents *(91, 103)* and two recent Evidence Review Groups have covered topics related to diagnostics in elimination settings *(42, 43, 104)*. Key diagnostics-related policies are highlighted in Table A2.1.

[66] IPTp involves presumptively treating women with sulfadoxine-pyrimethamine several times during antenatal visits.

TABLE A2.1

WHO guidance on diagnostics in low-transmission and elimination settings

General recommendations: subject to change/update in 2016
• Microscopy remains the preferred technology for diagnosing malaria from the start of the pre-elimination programme; when an RDT is used to guide treatment, a slide should also be made and read as soon as possible.
• A working QA system for microscopy is a precondition to proceeding to elimination phase.
• There is no guidance on when to begin active infection detection activities, nor are WHO guidelines prescriptive about how active case detection is undertaken (e.g. the extent of active case detection; type of sampling).
2013 Evidence Review Group: diagnostics in low-transmission settings
• RDTs and microscopy should be used for diagnosing clinical malaria in all transmission settings.
• In low-transmission areas (e.g. parasite prevalence rates <10%), after fully scaling diagnosis and treatment, more sensitive diagnostic methods may be considered for epidemiological research, surveys aimed at identifying submicroscopic infections and identifying foci of infection.
• Standardization of protocols as well as development of quality standards and an international external QA scheme for molecular methods should be prioritized in order to ensure quality and comparability of results by different researchers and national programmes using molecular methods.
• Currently, there is a range of molecular methods available, with different performance characteristics, throughput, cost per test, equipment, infrastructure and training requirements. Current research is insufficient to provide recommendations on which platforms are optimal for country programmes. The Evidence Review Group suggested that programmes considering adopting these more resource-intensive methods select one that is a "significant improvement" over expert microscopy (e.g. methods able to detect 2 p/µL or fewer).
2015 Evidence Review Group: review of mass drug administration and mass/focal screening and treatment
• Mass screening and treatment (MSAT) and focal screening and treatment (FSAT) are not recommended as interventions to interrupt transmission of malaria. • Mass drug administration may be considered in very specific situations detailed in the recommendations.

Sources: (42, 91, 103, 104)

Annex 3. R&D and programmatic stakeholders

R&D stakeholders

Research for this report found the following donors with malaria diagnostics investments: the Bill & Melinda Gates Foundation; the United States National Institutes of Health, the European Union, the United Kingdom Department of International Development (DFID); and the United States Department of Defence. Most of these organization's funding opportunities are broad and not exclusively focused on malaria. National governments and industry also play a role, although it is generally poorly documented *(82)*.

Key stakeholders in R&D for malaria diagnostics include:

The Bill & Melinda Gates Foundation

The Bill & Melinda Gates Foundation's 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, in late 2013, the Bill & Melinda Gates Foundation adopted the Accelerating to Zero strategy that focuses on malaria eradication. The Foundation's main initiatives in diagnostics are leading development of a highly sensitive RDT and supporting development of POC G6PD tests.

Foundation for Innovative New Diagnostics (FIND)

FIND is a product development partnership for diagnostics. FIND's 2015–2020 strategy focuses on complete diagnostic solutions that take into consideration implementation issues such as policy change and QA systems, as well as linkages to treatment and care. FIND is organized around four pillars:

I) Catalysing product development: As of 2015, FIND supports developers of high-priority products and products meeting target product profiles rather than

directly funding manufactures or investing in biomarker discovery research. Support includes technical expertise, access to diagnostics industry experts and access to specimen banks and reference materials.

II) Guiding use and policy: FIND leads and facilitates clinical trials, defining evidence needs for new products and support development of international guidelines.

III) Accelerating access: FIND's work in this area will include facilitating national policy and rollout plans and development of QA programmes.

IV) Advocacy: FIND works to measure and communicate the impact of diagnostics, encourage investment in diagnostics, and to shape the global agenda for diagnostics.

Regarding malaria, FIND continues to work on development of PCWs for RDTs, the RDT WHO Product Testing Programme and the WHO-FIND Lot Testing Programme, ensuring quality of testing in the retail private sector, and LAMP. It is also supporting the Bill & Melinda Gates Foundation initiative to develop highly sensitive RDTs for elimination, primarily through building a specimen repository of blood from asymptomatic patients. Future priorities include supporting the development of: (i) highly sensitive RDTs for elimination of *P. falciparum* malaria; (ii) *P. Vivax* serology biomarkers (as evidence of recent infection to enable surveillance and elimination of reservoirs); (iii) QA support for drug resistance surveillance networks; and (iv) in the longer term, less complex tests for antimalarial drug resistance surveillance. In the future, as biomarkers become identified, FIND expects to support development of POC tests for fever.

PATH

PATH is an international non-profit organization focused on improving global health through innovation, working broadly across vaccines, medicines, diagnostics and devices. In 2014, the PATH Malaria Center of Excellence was launched to align PATH's malaria work across platforms. PATH's diagnostics initiatives include:

- DIAMETER: The Diagnostics for Malaria Elimination Toward Eradication programme is developing diagnostics to support elimination efforts, including highly sensitive rapid tests. The Bill & Melinda Gates Foundation is the primary funder and PATH is acting as the project manager and the implementing partner for various components supporting development of highly sensitive rapid tests.
- The G6PD project aims to accelerate the development and introduction of POC G6PD tests for primaquine and, in the future, for tafenoquine. This work is largely supported by DFID and the Bill & Melinda Gates Foundation.
- MalariaCare: An initiative that works in high-burden countries to expand diagnosis and appropriate care of fever through provision of technical assistance. This is a

United States Agency for International Development (USAID) contract awarded in 2012 to support PMI countries.

- MACEPA: The Malaria Control and Elimination Partnership Africa works with countries to test and plan interventions to eliminate malaria and to build the evidence base for interventions that will lead to elimination.

Programme donors

Funding for malaria programmes in 2013 was US$ 2.7 billion and is expected to rise to US$ 3.2 billion in 2016. The Global Fund has provided the largest share of malaria funding, 40% of the total, with PMI providing 26%, domestic funding 20%, the Government of the United Kingdom 7% and the World Bank 3% *(80)*. The vast majority of the multilateral and bilateral funding for malaria goes to countries with high burden of malaria; in eliminating countries, national governments provide nearly 80% of funds *(105)*.

Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund)

The Global Fund remains the single largest international funder of malaria control. Its 2012–2016 strategy focuses on investing more strategically 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.[67] It has also implemented the New Funding Model, designed to support strategic investments, provide countries with more predictability around funding levels and improve flexibility in applying for funds. The model became fully operational in 2014, and as of the end of 2014, 111 new concept notes had been received (75% approved), of these, 41 are for malaria programmes (approximately 50% of the expected malaria programmes) *(106)*.

The Global Fund's main focus with respect to malaria in high-burden countries is to reduce morbidity and mortality; for diagnostics this means that a rational, pragmatic plan must be in place for scaling up diagnosis of fever in accordance with the WHO 3T: Test. Treat. Track initiative. The Global Fund supports both microscopy and RDTs and related QA activities. Addressing all sectors and channels where the population seeks malaria care is an increasing focus; in the future, this will become more critical as public sector scale-up is achieved. In addition to its focus on high-burden countries, the Global Fund supports low-transmission programmes and expects to play a role in programmes progressing towards elimination as outlined in the WHO GTS.

President's Malaria Initiative (PMI)

PMI, active in 19 focus countries and the Greater Mekong subregion, is the second largest international malaria donor, with a budget of US$ 665 million in 2014.

[67] 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.

PMI considers diagnosis an integral part of malaria case management; since 2006, it has been supporting holistic diagnostic efforts in-country through technical assistance and implementation support, as well as procurement of RDTs, microscopes and related consumables. Every year, PMI works with countries to develop Malaria Operational Plans that outline the support and commodities that PMI will provide.[68] PMI support varies by country and is driven by country needs. 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. It has also worked generally to strengthen supply chains and forecasting to improve availability of commodities at the point of service.

In 2015, PMI launched a new five-year strategy. Targets are largely in line with the GTS and include reducing mortality by one third and morbidity by 40% in PMI countries, and assisting at least five PMI countries to meet the WHO criteria for pre-elimination *(107)*. Highlights from a diagnostics perspective include: (i) supporting and sustaining scale-up of case management; (ii) developing and testing new ways of reaching high-risk and the hard-to-reach populations; (iii) working with countries to develop information and surveillance systems to identify highest-risk populations; and (iv) supporting piloting, adoption and scale-up of new tools (e.g. more sensitive diagnostics) and new approaches to delivery (e.g. community-based delivery, improving fever management in drug shops, piloting targeted interventions for hard to reach populations).

Department for International Development (DFID)

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. 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. 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 engaged in finding new ways to prevent, treat and diagnose HIV/AIDS, TB and malaria more quickly, more cheaply and more effectively. It takes game-changing ideas and turns them into practical solutions by helping to fast-track access and reduce costs of new, more effective medicines, technologies and systems. In 2012, UNITAID funded two malaria diagnostics initiatives: US$ 10 million to FIND to support the WHO Product Testing Programme and WHO-FIND Lot Testing Programme; and over US$ 30 million to Population Services International

[68] Malaria Operational Plans (http://www.pmi.gov/resource-library/mops/fy-2016).

(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 and support for ACT Watch. Past malaria projects have included support for ACT and long-lasting insecticide-treated mosquito net scale-up and to the Affordable Medicines Facility-malaria (AMFm).

World Bank

World Bank 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. 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 its 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.

Roll Back Malaria Partnership

The Roll Back Malaria Partnership is a multilateral organization launched in 1998 by several partners to provide a coordinated global response to malaria and to halve the world's malaria burden by 2010. However, in 2015, its Board closed the Partnership and commenced a restructuring process to improve the Partnership's effectiveness in the post-2015 global malaria response.

Annex 4. Technology developer and product profiles

Urine Malaria Test™ (Fyodor Biotechnologies)

Fyodor Biotechnologies (Maryland, US) has developed a urine-based rapid test for the diagnosis of malaria in individuals with fever. The Urine Malaria Test™ (UMT) is a non-invasive, one-step dipstick assay that uses immunochromatographic technology to detect specific *P. falciparum* protein fragments shed in the urine of febrile malaria patients. It is intended to facilitate the rapid diagnosis of *P. falciparum* malaria, and to support the differential diagnosis of *P. falciparum* infections from other fever-causing conditions. Originally developed at Johns Hopkins University, Fyodor Biotechnologies holds the exclusive global license to the UMT™ technology. The UMT™ has been validated in a multicentre clinical trial,[69] and was launched in 2015. A second-generation product for *P. falciparum* and *P. vivax* malaria diagnosis is in pre-clinical development.

TABLE A4.1
Urine Malaria Test™ (UMT)

Platform characteristics	
Type of technology	Disposable one-step urine dipstick based on immunochromatographic detection of malaria parasite proteins in urine. The indication for use of the UMT is fever suspected of being malaria. The test is designed to detect the presence of malaria proteins or fragments secreted in the urine during fever.
Output	The UMT is a two-line test that differentiates "fever due to *P. falciparum* malaria" from fever due to other cause. The results are easily read: two lines indicate fever due to *P. falciparum* malaria; and one line (the control line) indicates that the test worked and the fever is probably not due to *P. falciparum* malaria.
Performance	Children under 5 years show a sensitivity of 93% and a specificity of 83%. Among all ages, overall UMT sensitivity is 85% and specificity is 84% for the detection of *P. falciparum* malaria. The UMT has an LOD of 1 *nanogram*/mL of the target protein or its fragments in urine.
Turnaround time/capacity	Test results are available within 25 minutes.
Sample needed/stability	The device requires about 10 drops (100–200 µL) of urine. The test is a real-time test and intended to be performed immediately after sample collection.

[69] See: http://clinicaltrials.gov/ct2/show/NCT01921413?term=urine+malaria+test&rank=1

Platform characteristics	
Environmental requirements	Unopened UMT kit has a shelf life of 24 months from date of manufacture. The UMT should be stored in a dry area at 2–30 °C.
Testing protocol	The UMT is a one-step test with no requirement for sample preparation. The testing protocol is: (i) collect patient's urine in a clean dry container; (ii) fill the Sample Cup (provided in the kit) with urine sample, up to the ridge; (iii) remove test strip from packaging pouch; (iv) dip the white end of the strip into the freshly collected urine specimen, with arrows pointing down; (v) allow strip to stand in the sample for 25 minutes; and (vi) read the result.
Cost/test	Not available.
Cost/instrument	No instrument required.
Power requirements	None.
Training/technical sophistication	Test is designed for point-of-need use and procedures are simple: no sample preparation, no blood draws, no buffers are required, and testing procedure is one-step.
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 for at least four hours.
QA/QC	• Clinical trial implemented per 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. • Registered by Nigeria's regulatory agency, the National Agency for Food and Drug Administration and Control (NAFDAC).
Availability	Launched in 2015.

Parasight, Sight Diagnostics Ltd

Sight Diagnostics Ltd (Israel; formerly known as Parasight) was founded in 2011 and has developed a computer vision platform for blood analysis and parasite detection. Malaria diagnosis is the first application being developed for the platform. The technology uses a novel sample preparation method with custom-designed and low-cost cartridges to create an enhanced automated microscopist. 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 is a benchtop instrument capable of batch processing; a low-throughput portable device is expected in 2016. The company has also begun developing a complete blood count analysis (i.e. five point differential) for the existing platform.

The company has raised private funding and conducted clinical trials in India and South Africa (publications forthcoming). The device has been placed in several large malaria pathology laboratories for customer validation in Europe, India and South Africa. Distribution has been established and initial sales have occurred.

TABLE A4.2
Parasight

Platform characteristics	
Type of technology	The first-generation technology is a benchtop 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 in early 2016.
Output	Detection of malaria, differentiation between *P. falciparum* and *P. vivax*, quantification of parasitaemia. Platelet, white blood cells, RBC and haemoglobin readouts have also been added to the commercial version.
Performance	Sensitivity of 98% and specificity of 99%, based on clinical trials.
Turnaround time/ capacity	First-generation device is intended for larger case-loads (e.g. laboratories performing more than 7000 tests/year) and processes batches of 30 samples. (Note that smaller batches are possible. Each disposable cartridge contains five tests; six cartridges can be loaded at a time. As one cartridge is processed, another can be loaded.) Approximately 20 tests can be completed in one hour. Each sample takes less than five minutes to process, including sample preparation. A second portable device will be smaller and process one sample at a time.
Sample needed/ stability	A sample of 5 µL whole blood, taken either from a tube of intravenous blood (up to 48 hours after collection) or a fingerprick. A low-cost fixed-volume pipette is provided with the instrument to facilitate sample handling. After a sample is prepared, it must be scanned by the device within one hour.
Environmental requirements	No special environmental requirement for the device; device is designed to operate in conditions typical to clinics in Africa, Europe and India.
Testing protocol	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.
Cost/test	Available upon request, based on testing volumes, geography, etc.
Cost/instrument	Available upon request, based on testing volumes, geography, etc.
Power requirements	The device can operate using wall power or battery, and is designed to tolerate intermittent power.
Training/technical sophistication	A low-skilled technician could run the test; the system requires pipetting. Expected training time is one half-day.
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	Device is benchtop 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 marked. 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	Launched in 2014. Low-throughput system expected in 2016.

Truelab™ micro PCR platform (Molbio Diagnostics)

In 2013, Molbio Diagnostics (India, a joint venture of the Tulip Group and Bigtec Labs) launched the TrueLab™ micro PCR platform and a *P. falciparum* assay. The Truelab™ 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, hepatitis, H1N1 and dengue. Other applications are in process.

Although the initial malaria test was launched in 2013, ongoing R&D to improve the system includes:

- A three-wavelength PCR device will soon replace the existing two-wavelength device, allowing for three independent PCR reactions on one chip (i.e. internal control, and two additional channels for testing).
- *P. falciparum/P. vivax* test has been developed and validated internally, and will be introduced with the three wavelength PCR device. Evaluations in India are planned.
- A higher-throughput device that runs four chips at a time, the Truelab™ Quattro, will have a throughput of 45 tests in eight hours.
- A disposable, cartridge-based fully automated sample prep system is under validations.
- A fully automated system is in prototype stage and expected to launch in late 2016.

TABLE A4.3

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

Platform characteristics	
Type of technology	The microPCR device is a portable (dimensions: 210 mm x 140 mm x 109 mm; weight: 0.9 kg) real-time PCR device that uses 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. The core technology used in the platform is fluorescent probe-based real-time PCR. Specific genes from *P. falciparum* 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 pre-loaded 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 thus 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.

Platform characteristics	
Output	Currently, an assay for *P. falciparum* is available; a *P. vivax* assay is under development. The result is quantitative.
Performance	The sensitivity and specificity are estimated to be >99% with a lower LOD of 2 p/µL of blood.
Turnaround time/ capacity	Time to result is 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 the 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 15–30 °C; 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; and (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	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. The second-generation platform will integrate the sample preparation, rendering the device more robust for use at even lower levels of the health system.
Result display and storage	The test result is displayed on the device screen. The device stores 5000 test results internally. Results also can be transmitted to remote locations, sent to a central server in encrypted form for future analysis and disease surveillance through a global system for mobile communications (GSM) and WiFi networks, and can be printed through WiFi or an optional Bluetooth printer.
QA/QC	Regulatory/pre-market approvals include: • licensed by the Directorate of Food and Drugs Administration, Goa, India; • Molbio Diagnostics certification under ISO 13485; • malaria test conforms to the CE Mark requirements.
Availability	Launched in 2013, see the Molbio Diagnostics website: http://www.molbiodiagnostics.com

NALFIA DIAGMAL (DIAGMAL Consortium)

DIAGMAL[70] is a nucleic acid lateral flow immunoassay (NALFIA) that is being

[70] The 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).

developed by a consortium under a European Union Framework 7 project. DIAGMAL is a molecular test for detection of malaria that is more readily adapted to resource-constrained settings than traditional PCR methods. The DIAGMAL assay provides several advantages to traditional PCR methods: (i) the assay is a direct PCR, meaning it uses whole blood and does not require any sample preparation; (ii) following PCR amplification, amplicons are transferred through a closed transfer unit to the detection device thereby circumventing risk of contamination ("false positives"); (iii) the detection of DNA is carried out using a disposable lateral flow test device, the NALFIA; and (iv) the kit contains all of the necessary primers and reagents in a stabilized form and the lateral flow device required to run the test. The test format is multiplex, allowing for the simultaneous and specific detection of *P. falciparum* and *P. vivax* as well as general detection of other human *Plasmodium* species. The test also contains an internal amplification control, providing built-in QC. After successful published proof-of-concept laboratory evaluations and field evaluations in Burkina Faso and Thailand *(49, 50)* the assay is now being further evaluated in Kenya and Viet Nam.

In the next 18 months, the developers will progress the DIAGMAL assay to a market-ready product and subsequently look to perform further evaluations in specific settings (e.g. elimination; malaria in pregnancy). The developers expect to submit it to the WHO PQ.

TABLE A4.4
NALFIA

Platform characteristics	
Type of technology	Commercial PCR kit containing stabilized primers, reagents and the lateral flow device required to run the test. Direct PCR method, no purification of whole blood sample or DNA isolation required. Amplification is performed on a traditional PCR thermocycler, followed by detection using a disposable NALFIA. The primers used in the PCR process have ligands attached; antibodies on the NALFIA bind to the ligands.
Output	The output is qualitative. Primers that detect *Plasmodium* genus (i.e. pan-malaria), *P. falciparum* and *P. vivax* malaria are included (target is the 18S rRNA gene). An internal amplification control is included. The NALFIA is a generic strip that can detect up to three different markers, depending on the combination of primers used, allowing for customization of the assay and flexibility depending on needs.
Performance	Detects 1 p/µL.
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 1–5 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 is expected to be stable for up to two years at 30 °C. Storage requirements for reagents and test kits is at ambient temperature.
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 a closed transfer unit; and (v) wait five minutes for reaction and read results.
Cost/test	Final prices have not been determined; target prices for kits is €5.
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. Work to include battery operated or solar powered systems are being considered.
Training/technical sophistication	The test requires several steps, and can be performed by a moderately trained laboratory technician. The primary skill required is 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 an equipped laboratory with stable electricity as well as moderately trained technicians; 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). Possible to take a picture of the NALFIA strip for storage.
QA/QC	• WHO prequalification is expected. • The kit 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 the next 18 months.

Nanomal (St. Georges University/QuantuMDx Group, United Kingdom)

The Nanomal Consortium, led by QuantuMDx and St. Georges University in London,[71] is a European Union-funded project to develop a POC PCR system for malaria. QuantuMDx is a biotechnology company developing the Q-POC™ platform, a low-cost POC molecular platform with multiple applications. The hand-held device, operated by a touchscreen, accepts disposable cartridges that are pre-loaded with reagents and probes required to process the sample. No sample preparation or operator input is required, and results are available in approximately 20 minutes. Depending on the application, additional DNA sequencing technologies for drug resistance testing are also possible. Among the first assays being developed are malaria diagnosis, multidrug resistant-TB (MDR-TB) diagnosis, a genetic test for optimizing warfarin dosing, and tumour profiling. Additional diseases are anticipated in the future.

A working prototype of the Q-POC™ device has been developed and is being tested with the malaria assay cartridge. Nanomal is planning clinical trials for the malaria assay with a target launch date in late 2017. Partnerships for manufacturing and distribution are under consideration.

TABLE A4.5
Nanomal

Platform characteristics	
Type of technology	The hand-held device, operated by a touchscreen, accepts disposable cartridges that are pre-loaded with reagents and probes required to process the sample. The entire process from DNA extraction to detection occurs along one fluidic channel on the cartridge. No sample preparation is required; the cartridge blends the sample using beads to release DNA and a novel filter extracts the DNA. Following extraction, lyophilized reagents are rehydrated by the sample as it moves through the channels, and a proprietary continuous flow thermal cycler amplifies DNA. Detection is done on a nanoarray of wires that have the ability to detect changes in impedance. Electricity is run across the wire and if DNA binds to probes bound to the nanowire, a change in impedance is measured. Depending on the application, additional sequencing technologies for drug resistance testing are also possible. Results are available in 20 minutes.
Output	▪ Qualitative result for five malaria species. ▪ Additional drug susceptibility testing is possible, and depending on use case it may be possible to have an adaptable system, e.g. a positive/negative result for some users; and for advanced/specialized users, additional DNA analysis of markers of drug resistance.
Performance	Performance studies not yet available, anticipated in 2016.
Turnaround time/capacity	20 minutes per sample, one sample processed at a time. One device could process 20–25 samples/day.
Sample needed/stability	Whole blood. Sample volume is TBD, depending on market needs and desired sensitivity and LOD; e.g. a higher volume of blood from a venous draw (which would undergo pre-processing in the cartridge) would be more sensitive than a 15 µL whole blood from a fingerstick.
Environmental requirements	• Designed for use in remote or resource scarce settings. • Reagents are lyophilized and contained within cartridges.
Testing protocol	Steps: (i) collect blood sample; (ii) input the sample into the cartridge; (iii) insert the cartridge into the device and press go; and (iv) result appears onscreen in 15–20 minutes.

[71] Other consortium members: the Karolinska Insititute and Tubingen University.

Platform characteristics	
Cost/test	TBD; targeting below the current cost of POC molecular tests currently on the market.
Cost/instrument	TBD; targeting <£1000.
Power requirements	Battery powered, no need for stable electricity.
Training/technical sophistication	Device intended to be used by low-skilled health workers, major skill required is sample collection. Approximately one half-day of training required to operate the device.
Durability/ maintenance	TBD
Infrastructure requirements	Intended for use in the community as well as at all health facilities.
Result display and storage	• Results are displayed on a touchscreen. • Results can be stored on the device, sent to a printer, transferred to a computer or database in the cloud via USB or WiFi. • Built-in GPS technology and a secure mobile data connection will allow for real-time surveillance.
QA/QC	The malaria assay and device will be CE marked.
Availability	2017

Accutas (Aquila Diagnostic Systems Inc.)

Aquila Diagnostic Systems Inc. is a Canadian company developing the Accutas, a hydrogel-based POC molecular diagnostic system for malaria, as well as other applications (e.g. veterinary POC testing). The core technology and intellectual property are based on a hydrogel matrix that contains all of the reagents for performing DNA amplification by real-time PCR. Reagents are stored within a gel that is desiccated to enable long-term storage at room temperature. The gel is loaded into strips of 8 or 16 tubes to which diluted blood is added directly to rehydrate the reagents with no DNA extraction step required. The strip of tubes, including control reactions, is run on a miniaturized instrument designed for use in the field. Pathogen DNA is amplified using real-time PCR and products are detected using LED-induced fluorescence. Each tube can run a single test on a separate sample or a strip of tubes can be used to test a sample for multiple targets.

The Accutas system is designed to be low cost and easy to use. Processing involves collection and transfer of a fingerprick blood sample to a disposable tube. Once inserted into the instrument, results are returned within two hours. To date, tests have been developed for a qualitative result for *Plasmodium* genus and for *P. falciparum* and *P. vivax*. The hydrogel is stable at room temperature and is reconstituted with the addition of whole blood.

After successful proof-of-concept laboratory evaluations *(108)* and patenting of the hydrogel chip technology, several field evaluations are planned in partnership with Dr. Stephanie Yanow of the University of Alberta for 2015–2017, including: trials in the Solomon Islands with the University of Queensland and the Asia Pacific Malaria Elimination Network; a survey on the Amazon River with the United States Navy Medical Research Unit in Peru; a collaboration with the Ugandan Ministry of

health to conduct a trial in Ugandan hospitals; and several malaria vaccine trials in collaboration with Sanaria and Griffith University in Australia.

In the coming year, Aquila Diagnostics Systems Inc. will be partnering to manufacture the POC PCR instrument and will be developing assays for other common causes of fever. The company also has a research version of the system that uses disposable microfluidic chips rather than tubes.

TABLE A4.6
Accutas

Platform characteristics	
Type of technology	The Accutas system comprises: • Disposable plastic tubes containing desiccated hydrogel reagents for malaria PCR. Tubes are stored at room temperature and are rehydrated by unprocessed blood. No DNA extraction, only sample dilution is needed, and the system works on direct blood PCR. Amplification and detection occur in the tube once inserted into the device. The primers for the malaria test target the 18S rRNA gene of *Plasmodium*. • Low-cost, portable, real-time PCR machine. In addition, conventional PCR tubes and plates filled with the hydrogel master mix are available to be run on conventional laboratory-based PCR instruments.
Output	Qualitative result for *Plasmodium* genus and species specific tests for *P. falciparum* a *P. vivax*. Quantitative result system under development.
Performance	• Initial testing of laboratory prototype systems on patient samples: 96.7–97.4% sensitivity and 93.8–100% specificity compared to conventional real-time PCR *(108)*. • 2 p/µL LOD for *P. falciparum*.
Turnaround time/capacity	• Time to result is one to two hours; targeting one hour. • Current platform (8-well format) processes 6 patient samples at a time plus positive and negative controls; approximately 30 patients can be tested per day (five runs per day) per instrument.
Sample needed/stability	A 25–50 µL fingerprick whole blood sample.
Environmental requirements	Reagents stable at room temperature (30 °C) for six months.
Testing protocol	The test involves: (i) collection of a fingerprick blood sample; (ii) sample dilution; (iii) transfer of sample using capillary tube to PCR tube; (iv) insertion of the tube into the instrument; and (v) wait for results.
Cost/test	Final prices have not been determined; target price per test is US$ 2–4 when produced at scale.
Cost/instrument	Final prices have not been determined; target prices for instrument is US$ *3000*–4000 when produced at scale.
Power requirements	Low power requirements (12 V). The instrument will run on AC mains electricity or batteries.
Training/technical sophistication	Designed to be performed by low-skilled health workers.
Durability/maintenance	Designed with durability and portability in mind and to be used in remote settings.

Infrastructure requirements	Appropriate for health facilities at all levels.
Result display and storage	Onboard touchscreen with data storage, wireless and GPS capabilities.
QA/QC	The approach to quality and regulatory approvals has yet to be determined. Positive and negative controls available from the manufacturer.
Availability	Commercial launch of a system is targeted for 2016 although the expectation is to make hydrogel tubes as well as a complete POC system (instrument and chips) available sooner for research use only.

LoopAmp (FIND and Eiken Chemical Ltd)

In 2012, FIND and Eiken Chemical Ltd launched the first commercial LAMP reaction test kit for malaria, the LoopAmp. 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 in the literature, this is the first commercially available kit that is also stable at ambient temperature and does not require refrigeration. Primary advantages include heat stability of the dried-down reagents and QA of a complete kit.

FIND and partners are undertaking further R&D of the LAMP assay including: (i) development of a *P. vivax* reaction tube; (ii) simplification of the DNA extraction process from dried blood spots (prototypes have been evaluated in Zanzibar, United Republic of Tanzania; data analysis ongoing); (iii) development of a high-throughput system that would allow for hundreds of samples to be processed in one day (demonstrated in a reference laboratory; results forthcoming); and (iv) automating the readout of the test results (completed for low-throughput LAMP). The development of a high-throughput sample processing kit, in particular, will enable LAMP to be scaled more easily and used for large-scale population screening efforts for malaria elimination.

TABLE A4.7
LAMP Malaria Diagnostic Kit (FIND and Eiken Chemical Ltd)

Platform characteristics	
Type of technology	Benchtop 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. 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 field-stable commercially available malaria kit for LAMP. In addition to reaction tubes, LAMP requires the following: • Sample preparation: several DNA extraction methods are possible. Sample processing kits, the PURE Method kit,[1] are available from Eiken Chemical Ltd. FIND has validated an alternative DNA extraction method, a boil and spin method requiring a centrifuge and taking less than 10 minutes. Standard operating procedures for both methods are available on the FIND website. Alternative conventional DNA extraction methods are also effective. • Amplification requires a heating block; available from Eiken Chemical Ltd or conventional incubators (e.g. PCR termocyclers) can be adapted. • 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 included incubator that also measures turbidity (turbidimeter, available from Eiken Chemical Ltd) can be used.
Output	Qualitative (positive or negative) result for *P. falciparum* or *Plasmodium* (i.e. pan-malaria). *P. vivax* specific test is under development.
Performance	Clinical evaluation of the LAMP Malaria Diagnostic Kit included a study in Uganda (endemic site)[2] 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. Subsequent studies in Columbia and Zanzibar, United Republic of Tanzania have confirmed these results and have demonstrated usefulness of LAMP for the detection of asymptomatic infections *(109-112)*.
Turnaround time/ capacity	• Time to result is less than one hour, including sample preparation: approximately 10 minutes and 30–40 minutes to run the assay. • 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). • A high-throughput platform for population screening is in development based on a 96-well format to test more than 350 samples per day (four runs per day).
Sample needed/ stability	• 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. High-throughput format uses dried blood spots. • Samples are stable at room temperature for a few days and longer-term storage is possible using filter paper or refrigeration/freezing.
Environmental requirements	LAMP reaction tubes are stable for 12 months at <30 °C. There are no temperature or humidity requirements for device operations.

Testing protocol	1. Sample is processed by boil and spin or the PURE Method: Boil and spin: (i) transfer 60 µL blood to lysis buffer; (ii) incubate at 95 °C for five minutes; (iii) centrifuge; (iv) transfer supernantant to dilution tube; and (v) transfer 30 µL to LAMP reaction tube. PURE Method: (i) transfer 30 µL blood to lysis tube; (ii) incubate at 70 °C for five minutes; (iii) transfer sample to the PURE Method Eiken Chemical Ltd tube; (iv) squeeze tube to mix contents; and (v) transfer sample to reaction tube using dropper cap. 2. LAMP reaction: (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.[3]
Cost/test	• Pricing of approximately US$ 5 per reaction tube (ex-works, varies with volume, shipping destination and exchange rates). • ~US$ 10 for Eiken Chemical Ltd PURE Method sample preparation kit.
Cost/instrument	A standard heating block can be used. Heating block is ~US$ 400–10 000, lower prices may be possible with increasing volumes. Real-time turbidimeter is ~US$ 10 000.
Power requirements	Instruments require electricity; battery operation is possible.
Training/technical sophistication	Four days training for laboratory technicians; primary skills required include sample collection, bio-safety and basic microbiology laboratory skills.
Durability/ maintenance	Several heating blocks and turbidimeters are available; maintenance and useful life vary by model.
Infrastructure requirements	Laboratory-based technology appropriate for district hospital level and higher. Potential for field-based use in specific circumstances such as surveys, when technician available.
Result display and storage	Results are qualitative and are typically read visually by fluorescence, or read by turbidimeter and archived using specific software.
QA/QC	CE marked. The reagent kit includes positive and negative controls.
Availability	Kits can be ordered directly from Eiken Chemical Ltd by writing to Mrs Noriko Uke at noriko_uke@eiken.co.jp.

illumi*gene*® Malaria (Meridian Bioscience)

Meridian Bioscience was founded in 1977, and is a fully integrated life science company that manufactures, markets and distributes a broad range of innovative diagnostic test kits, purified reagents and biopharmaceutical enabling technologies. The global headquarters is based in Cincinnati, Ohio (US) and houses research and development, marketing, manufacturing, warehousing, and administrative offices. In addition, Meridian employs approximately 580 people worldwide, with 12 worldwide office locations, and sells in over 70 global markets.

In 2010, Meridian launched ***illumi****gene*®, a molecular (NAAT) diagnostic system that is based on Loop-mediated isothermal amplification (LAMP) technology. Since then, Meridian has had 6 ***illumi****gene*® products FDA cleared: *C. difficile*, Group B *Streptococcus*, Group A *Streptococcus*, *Mycoplasma pneumoniae*, *Bordetella pertussis,* and Herpes simplex virus type 1 and type 2, in addition, there are 3 ***illumi****gene*® products CE Marked – Chlamydia, Gonorrhoea, and Malaria.

In January 2016, Meridian received CE Mark for a malaria assay for its *illumi*gene® Molecular diagnostic system. The goal of the ***illumi*gene®** Malaria product is to address current diagnostic challenges such as simplification of sample preparation from blood, reagent stability under ambient conditions, ease of use for the end user and affordable pricing. The system includes a small benchtop instrument, the ***illumi*pro-10™**, that performs incubation and detection by measuring the change in light transmission through the sample. The ***illumi*gene®** Malaria DNA Amplification Assay detects *Plasmodium* parasite at the genus level; the kit contains all reagents and consumables needed to perform the test (sample preparation tubes, assay tubes with dried down (lyophilized) reagents, reagent buffers and external controls). Sample preparation takes less than two minutes of hands-on time and automated results are available in 40 minutes. Meridian Bioscience utilized the technical expertise of the US CDC on this project and clinical trials were conducted at Cheikh Anta Diop University of Dakar, Senegal.

TABLE A4.8
*illumi*gene® Malaria (Meridian Bioscience)

Platform characteristics	
Type of technology	The ***illumi*gene®** malaria system is based on LAMP technology. The system comprises a bench top instrument, the Meridian ***illumi*pro-10™**, and ***illumi*gene®** Malaria assays kits containing reagents and consumables needed to perform the test (sample preparation supplies, two chamber assay tubes containing assay and control reagents, reagent buffers and controls). Detection is performed by measuring the change in transmission of light through the sample tubes as the reaction occurs. The assay targets a 214 base pair sequence of a *Plasmodium* species mitochondrial DNA noncoding region, a region of the *Plasmodium* genome that is conserved across all five species. Two versions of the assay kit, differing in their sample preparation procedures, are available: i) the ***illumi*gene®** Malaria assay has a two minute / three step sample preparation process, while the ii) the ***illumi*gene®** Malaria PLUS assay has a more sophisticated five minute/ five step sample preparation process which improves the sensitivity of the test.
Output	Qualitative result for *Plasmodium sp.*
Performance	Clinical evaluation includes a study conducted in Senegal. Compared to thin and thick film microscopy, performance was as follows: • ***illumi*gene®** Malaria: sensitivity 100%, specificity 89.3% • ***illumi*gene®** Malaria PLUS: sensitivity 100%, specificity 82.7% Limit of Detection (LOD) • ***illumi*gene®** Malaria: o *P. facilparum* – 2 p/µL o *P. vivax* – 0.25 p/µL • ***illumi*gene®** Malaria PLUS: o *P. facilparum* – 0.125 p/µL o *P. vivax* – 0.063 p/µL

Platform characteristics	
Turnaround time/ capacity	• Time to result is approximately one hour: sample preparation is approximately 2-5 minutes followed by 40 minutes to run the assay. • Processes 10 patient samples at a time plus controls for each patient sample. Approximately 80 patients can be tested per day per instrument (eight runs per day).
Sample needed/ stability	• Venous whole blood (50µL needed to run the assay) in EDTA tube. • Samples are stable at room temperature for 7 days, up to 14 days refrigerated (2-8 °C). • Samples may be frozen and thawed 2 times after storage at -20 °C prior to testing
Environmental requirements	Assay kits are stable at room temperature (2-30 °C) for 18 months. If refrigerated, kits should be brought to room temperature before use.
Testing protocol	Sample preparation for ***illumi****gene*® Malaria: (i) add 50 µL of the collected venous whole blood sample (with EDTA) to one tube of Buffer I, and mix by inversion 5 times; (ii) transfer 50 µL of lysate into Sample Preparation Apparatus; (iii) gently squeeze the Sample Preparation Apparatus and collect 5 to 10 drops into a clean tube. Sample preparation for ***illumi****gene*® Malaria PLUS: (i) add 50 µL of the collected venous whole blood sample (with EDTA) to one tube of Buffer I, and mix by inversion 5 times; (ii) transfer 250 µL of the prepared sample to the top of an appropriately labeled and prepared *M-prep* Column. Wait approximately 2 minutes, or until the sample has been absorbed by the column and flow stops.; (iii) add 250 µL of *M-prep* Buffer II to the top of the *M-prep* Column. Wait approximately 2 minutes, or until the red-colored buffer is absorbed by the column and flow stops; (iv) remove the last drop of liquid from the column tip with a clean tube, and discard; (v) place a clean tube under the *M-prep* Column; (vi) add 250 µL of *M-prep* Buffer III to the top of the *M-prep* Column. Wait approximately 2 minutes or until flow stops. Test procedure: (i) transfer 50 *µL* of the sample to both the test and control chambers of the ***illumi****gene*® test device and close the cap; (ii) tap the device on the bench and examine for rehydration and air bubbles; (iii) insert devices into the illumipro-10 and initiate run; (iv) read result.
Cost/test	TBD
Cost/instrument	Instrument is provided at no cost.
Power requirements	Instruments require electricity; battery operation is possible.
Training/technical sophistication	Half-day of training for laboratory technicians; primary skills required include sample collection, pipetting, biosafety and basic microbiology laboratory skills.
Durability/ maintenance	The ***illumi****pro*-10™ comes with a 3 year warranty. If the instrument becomes defective, or stops working, Meridian will replace it with a new instrument at no charge.
Infrastructure requirements	Appropriate for health-facilities with laboratory access.
Result display and storage	Results are displayed as Positive or Negative on the ***illumi****pro*-10™ at the conclusion of the run. Up to 1000 individual test results or 200 batches of results can be stored on the instrument.
QA/QC	CE marked. FDA clearance is currently being evaluated by Meridian. Each device contains an internal control well that controls for amplification inhibition, assay reagents and sample processing effectiveness. External control kit available from Meridian. Calibration of the ***illumi****pro*-10™ is not required. Self-diagnostics are performed at power-on, start of a run, and for test device placement and optics path verification.
Availability	Available; launched in January 2016.

DiscoGnosis project on the LabDisk system (consortium led by the Department of Microsystems Engineering [IMTEK] at Freiburg University, Germany)

DiscoGnosis is a seven member consortium, led by IMTEK (and its strategic partner Hahn-Schickard) in Germany,[72] that is developing a POC lab-on-a-disc that tests for several febrile tropical diseases (malaria, dengue, typhoid and pneumonia) at the same time. The LabDisk platform has multiple applications; and a European Union Framework 7 grant is supporting proof of principle and initial validations of the febrile tropical disease panel.[73]

With this system, IMTEK and partners aim to (i) provide a sample-to-answer result, with no manual steps within one hour; (ii) detect both nucleic acid (DNA/RNA) and proteins (e.g. antigens) in one run; and (iii) test for several diseases in one run in a multiplex way. The goal is to use the LabDisk as a diagnostic tool for management of patients with febrile syndrome and, in the future, also as an epidemic surveillance tool.

In the LabDisk system, fingerprick blood is collected and transferred to a disposable disc containing all of the reagents and buffers required to perform the assay. The disc is inserted into the LabDisk Player and results are available within one hour with no further operator input. The system's core is a microfluidic platform that uses centrifugal forces in combination with valves *(113)* and mixing principles to handle liquids. Both nucleic acid (LAMP isothermal method) and immunoassays are performed in one run. The LabDisk Player detects the analysis outcome via fluorescence or (chem)luminescence and results are displayed on a screen.

The system is designed to be modular in terms of microfluidic components, adaptable to assays, and open to other technology platforms. For example, IMTEK/Hahn-Schickard expects to customize the tests that are available on the disc to meet the needs of a particular geographic region (i.e. depending on local disease prevalence; endemic or epidemic profiles) or type of health facility (e.g. a reference hospital may need a different panel than a health centre) or sample matrix (e.g. swab, sputum, saliva, apart from the currently used blood). It is also testing use of recombinase polymerase amplification (RPA) and other isothermal techniques on the platform.

For the malaria assay and tropical disease panel, initial small-scale validations are planned for 2016 at the Pasteur Institute in Senegal. Through a partnership with Life Assays Diagnostics (Pty) Ltd (South Africa) and funding from the Anglo American Foundation and SHIP/MRC, Hahn-Schickard also plans to develop a combined LabDisk-lateral flow nucleic acid test that differentiates between viral and bacterial pneumonia (3-year project started in 2015). Additional funding is currently being sought to support interface with algorithm-based decision management system,

[72] Other consortium members include: Rohrer AG (Switzerland); University Hospital Basel (Switzerland); European Foundation for Clinical Nanomedicine (Switzerland); University Medical Center Göttingen (Germany); University of Stirling (United Kingdom); Magnamedics Diagnostics BV (Netherlands); MAST Group Ltd (United Kingdom).

[73] See: www.discognosis.eu and https://www.youtube.com/watch?v=UvcZwOXTRuk&feature=youtu.be

larger clinical trials, development of a higher-throughput system and development of an electricity-independent operation of the LabDisk Player.

From a business perspective, Hahn-Schickard is seeking to establish a company that will perform disc manufacturing and assay integration in the LabDisk. Prototypes of the LabDisks and LabDisk Player have been developed as have instruments for disc fabrication. Future work will focus on decreasing the prices of the discs. Partner companies will develop assays and provide reagents. Partners will also handle distribution.

TABLE A4.9
DiscoGnosis on the LabDisk system

Platform characteristics	
Type of technology	LabDisks are disc-shaped plastic disposable chips (similar to a CD) that use microfluidic unit operations to handle the whole blood sample and perform fully automated analysis by microfluidically integrating assay steps that would otherwise need a whole laboratory to be performed – e.g. extraction; purification *(114)*; amplification and detection of DNA/RNA *(115)*; ELISA. The LabDisk Player is a portable device resembling a CD-player, it has a small footprint (26 x 17 x 9 cm), weighing 2 kg and handles the LabDisk via precise protocols (rotation frequencies, acceleration, deceleration profiles). It includes a fan and a heater for isothermal amplification and detection system for fluorescence/(chemi)luminescence readout. After inserting the sample, the systems performs: • Nucleic acid analysis: DNA/RNA is extracted and purified using an on-disc bead-based extraction system. The purified DNA/RNA is distributed to reaction chambers through an interplay of centrifugal forces and thermodynamic valves. Amplification occurs in the chambers using lyophilized reagents that are reconstituted by the purified DNA. Amplification is isothermal (LAMP). • Immunoassay: plasma separation and bead-based ELISA are integrated in the disc (assay, washing steps in microfluidic chambers; detection via fluorescently labelled nanoparticles). • Buffers are stored in aluminium pouches ("stickpacks") and released during centrifugation *(116)*. • Tests are performed in parallel: while sample processing occurs for DNA/RNA analysis, the immunoassays are proceeding; then LAMP takes place. • Detection by fluorescence. Tropical disease panel assays: • Malaria is detected using LAMP to amplify parasite DNA of *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale and P. knowlesi* and immunoassay to detect HRP-II and pLDH antigens. • Dengue fever is detected using RT-LAMP to amplify viral RNA. • Typhoid fever is detected using LAMP to amplify bacterial DNA (S. Typhi/Paratyphi). • Pneumonia is detected using LAMP to amplify bacterial DNA (*Streptococcus pneumoniae*).

Output	Qualitative results for a panel includes: • Malaria: o *P. falciparum* DNA, *P. malariae* DNA (already developed in tube); o *P. vivax* DNA, *P. ovale* DNA (under development); o *P. knowlesi* DNA (primer sets available, pending for validation); o *Pf*-HRP-II antigen; pLDH antigen (assays developed with Flow Cytometry); integration in disc estimated April 2016. • Dengue fever: DENV1-4 RNA (already developed in tube). • Pneumonia: *Streptococcus pneumoniae* DNA (already developed in tube). • Typhoid fever: *Salmonella* Typhi/Paratyphi DNA (already developed in tube and integrated in disc).
Performance	Performance studies not yet available, anticipated in early 2016.
Turnaround time/ capacity	One sample processed at a time, run time is one hour. Eight samples processed per day. Developers expect to increase throughput by nine times (more than 70 samples per 8-hour shift).
Sample needed/ stability	50 µl whole blood for nucleic acid analysis; 100 µl whole blood for immunoassay; fingerprick collection
Environmental requirements	• LabDisk Player operational requirements: temperature range: +10 to +40 °C. Humidity range: 20–90% relative humidity (non-condensing). • Reagents are lyophilized and contained within discs. Discs are stable for 18 months at room temperature.
Testing protocol	Steps: (i) collect blood sample; (ii) input the sample into the disc; (iii) insert the disc into the device and press go; and (iv) result appears onscreen in one hour.
Cost/test	Current estimate of <US$ 10 per disc when produced at scale. Working to further reduce cost through manufacturing and throughput improvements.
Cost/instrument	Targeting less than few thousand US dollars per device.
Power requirements	Development of an electricity-independent operation of the LabDisk Player is planned (battery/solar panel).
Training/technical sophistication	Device intended to be used by low-skilled health workers, major skill required is sample collection and transfer to the disc. Approximately one half-day of training required to operate the device.
Durability/ maintenance	Devices will be swapped out, "emergency" devices will be sent to replace the broken device, the latter is sent to the manufacturer, repaired and sent back to the site.
Infrastructure requirements	Suitable for use at the primary/health post level and higher.
Result display and storage	• Results are displayed on a graphical user interface. • Data storage capacity and transmission of results currently at proof of principle. Further concept including a standalone/laptop-free Player is currently under review. • Plan to develop algorithms that can support patient management based on test results and other information (e.g. clinical symptoms; vitals; history).
QA/QC	• Positive and negative controls included in the disc. • WHO prequalification will be sought. • European Conformity-in vitro diagnostic (CE-IVD)/US FDA clearance will be sought and quality management will be established in all involved components (LabDisk, Player and assay manufacturing facilities) as soon as the related funding is secured (private/public/investor).
Availability	Year of expected launch is 2019–2020 for the entire system; components (such as individual assays) may be available in the market earlier.

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

The Magneto-optical Technology (MOT) development is led by the University of Exeter, United Kingdom.[74] 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. 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.

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 more than a minute and a half.

The developers are currently working to establish a diagnostics company to further develop and commercialize the test.

TABLE A4.10
Magneto-optical Technology

Platform characteristics	
Type of technology	The MOT device is portable (about the size of a credit card machine) and uses disposable sample cells. The technology is based on detection of hemozoin 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. The MOT test involves applying a magnetic field to a sample, causing alignment of any hemozoin crystals present.[4] 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.
Output	Readout is a qualitative result for the *Plasmodium* genus (e.g. pan-malaria), does not differentiate between species. The device also quantifies the hemozoin content, which, based on preliminary laboratory studies, is correlated to parasitaemia levels. Future field trials will look at the correlation between hemozoin and parasitaemia levels, and the commercialized device may include an optional quantitative readout.
Performance	Targeting >90% sensitivity and specificity at 100 p/µL. Improvements to LOD are theoretically possible; cost of final product will increase with use of more sophisticated technologies.
Turnaround time/ capacity	One minute per sample; one sample processed at a time.

[74] 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.

Platform characteristics	
Sample needed/ stability	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.
Environmental requirements	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. The device uses a disposable sample cell and a lysing agent, neither of which requires cold chain storage.
Testing protocol	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; and (v) read result in one minute. 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.
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 more than 50 measurements with one charge; likely that commercialized device will perform more than 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	Device is designed for rugged field conditions; expected to last more than two years. A "dummy" sample cell that will be used to calibrate the instrument periodically. Non-functioning devices will be exchanged.
Infrastructure requirements	Device is intended for use in the community as well as at all health facility levels.
Result display and storage	LED readout for results. GPS and mobile communications technology may be built in, enabling remote diagnosis and software updates.
QA/QC	The approach to quality/regulatory approvals is TBD. Blinded field trials are planned in collaboration with well-respected malaria laboratories. Dummy sample cells will be used to calibrate the instrument. Self-checking routines are likely to be included in the operational software of the microprocessor.
Availability	Timeline unavailable at this time.

Rapid Assessment of Malaria (RAM) Device (Disease Diagnostic Group Inc.)

Disease Diagnostic Group Inc. (DDG) (Boston, US) is an early stage start-up company that is developing the Rapid Assessment of Malaria (RAM) Device, a portable hemozoin detection system. 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 moulding manufacturing. Disease Diagnostic Group Inc has developed its own intellectual property for RAM. A 2015 version of the RAM device is now

undergoing trials in Nigeria with the University of Lagos and Malaysia with the National Blood Centre. The project is funded through awards and grants, as well as commercial partners. The company plans to engage further with clinical and commercial partners in the coming year.

TABLE A4.11
Rapid Assessment of Malaria (RAM) Device

Platform characteristics	
Type of technology	The RAM device is portable (2 x 3 x 4 inches) and uses disposable plastic cuvettes (.5 x .25 x 1.75 inches). The technology is based on detection of hemozoin 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 and crystalline nature, hemozoin crystals have unique optical properties. The RAM device applies and releases a strong magnetic field to a fingerprick blood sample to align any hemozion 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.
Output	Qualitative result for *Plasmodium* 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 studies with the Disease Diagnostic Group R&D and clinical partners indicate 93% sensitivity and a detection limit of less than 1 parasitized cell/µL.
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.
Environmental requirements	The current device is expected to maintain documented efficacy up to 40 °C. There is no reagent in the cuvette thus unlimited shelf life and no refrigeration requirement.
Testing protocol	Steps: (i) collect fingerprick blood from patients finger directly into disposable cuvette; (ii) add water (lysing agent) and cap; (iii) insert cuvette into RAM device and press test button; and (iv) read result in less than one 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 2000 tests.
Training/ technical sophistication	Device intended to be used by low-skilled health workers with less than one half-day of 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 involved in malaria screening and has no supplementary requirements.

Platform characteristics	
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, e.g. 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 cuvettes for administrators to run once daily to confirm device is working properly and has maintained accuracy. An exterior LED 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 for sale to unregulated private customers in 2016; beta units deployed and available in 2015.

Magneto-optical Device (MOD) (Meditopian LLC and Case Western Reserve University)

Meditopian LLC (US) is in licensing negotiations with Case Western Reserve University for rights to a portable malaria diagnostic device using hemozoin detection (MOD, magneto-optical device) that rapidly (one minute) detects all species of malaria. The technology is achieving detection down to very low levels of parasitemia (<10 p/μL). Early field trials in Peru have demonstrated high sensitivity and specificity (>97%). Pricing is planned to be approximately US$1 per test, which includes the disposable cuvette and a reader (based on volume purchases). The device is currently in trials in Peru and will be in an elimination study in Kenya. Meditopian LLC plans to complete final product development and commercialize the product for global distribution

TABLE A4.12
Magneto-optical Device (MOD)

Platform characteristics	
Type of technology	Portable device using magneto-optical detection of hemozoin
Output	Qualitative and quantitative result for *Plasmodium* genus (e.g. pan-malaria, does not currently differentiate between species). The device quantifies hemozoin which has been correlated to parasitemia levels. The output is quantified as parasites/ µL.
Performance	Sensitivity 97%, specificity 100% in a study of 118 Peruvian field samples compared to PCR. LOD is 10 p/ µL though samples as low as 0.8 p/ µL have been detected in laboratory settings. Work is underway to reliably detect less than 5 p/ µL.
Turnaround time/ capacity	Time from blood collection to result is 90 sections/sample, approximately 15 samples per hour or 120 per day. The number of tests per day is only limited by the time needed to gather information and organize subjects before testing.
Sample needed/ stability	Fingerprick blood sample of 25 µL is transferred to a cuvette containing water.
Environmental requirements	The device will operate at any temperature or humidity seen in the field. The disposables have an essentially unlimited shelf life with no special storage requirement.
Testing protocol	Steps: (I) collect fingerprick blood from patients finger; (II) transfer a drop of blood to a custom cuvette; (III) insert cuvette into portable reader; and (IV) read result after 90 seconds.
Cost/test	Tests will be approximately $1 each.
Cost/instrument	The reader will be provided at no additional cost with a volume purchase.
Power requirements	The device currently uses rechargeable batteries which can run for at least 200 tests on a charge.
Training/technical sophistication	Device intended to be used by low-skilled health workers with less than one half-day of training. A pictorial instructional manual demonstrates how to turn on the machine, placing a finger stick of blood into a cuvette then into the machine. Non-subjective results are clearly displayed.
Durability/ maintenance	The device is expected to last for many years in normal use or at least 50,000 tests. Failed units will be replaced through a swap.
Infrastructure requirements	The technology can be used in clinics and hospitals as well as easily transported to the field.
Result display and storage	Results are displayed on the device as a red LED if malaria is detected or a green LED if malaria is not detected. The device will have Bluetooth capability to relay quantified parasites/ µL to a phone or computer. A cloud-based solution will be available to track the information.
QA/QC	The regulatory plan is to initially obtain a CE mark including ISO 13485 certification under a US quality system. FDA clearance will follow. The device will conduct an internal self-check when first activated.
Availability	Units expected to be available in 2018.

CareStart™ G6PD RDT and G6PD Biosensor (Access Bio Inc.)

Access Bio Inc. (United States; Republic of Korea), a leading manufacturer of malaria RDTs, has developed two POC tests for G6PD deficiency: a G6PD RDT and a G6PD Biosensor. The G6PD RDT is a qualitative test, similar in terms of format and processing to malaria RDTs. The test was launched in 2013 and has undergone several clinical evaluations, although not all have been published yet. This test is positioned primarily for the public tender market as a tool to guide primaquine use.

A quantitative G6PD biosensor device was launched in November 2014. It is similar to a hand-held glucose meter and uses a disposable blood sample strip to provide a quantitative result for G6PD activity within a few minutes. The biosensor is positioned as a screening tool for newborns and as a test to guide primaquine use. To date, Access Bio Inc. has fulfilled sample orders from more than 25 countries and is establishing distribution agreements for the biosensor with private sector distributors in Asia and the Middle East.

TABLE A4.13
CareStart™ G6PD RDT

Platform characteristics	
Type of technology	The CareStart™ G6PD test is a disposable lateral flow test, similar in format and processing to a malaria RDT. The technology employs a tetrazolium dye that changes to purple-coloured formazan in the presence of G6PD enzymes.
Output	Qualitative results for G6PD deficiency, based on a threshold of 30% G6PD enzyme activity.
Performance	Over 95% sensitivity for Class 1 and 2 G6PD deficiency defined by WHO. Equivalent performance to the commonly used laboratory-based test (Fluorescent Spot Test).
Turnaround time/ capacity	Test results are available in 10 minutes.
Sample needed/ stability	2 µL whole blood from fingerprick or venepuncture.
Environmental requirements	Test has been designed with stability and environmental conditions in mind: • 12-month shelf life with recommended storage temperature of 4–30 °C; • a range of assay temperatures (18–32 °C) is acceptable.
Testing protocol	Testing protocol: (i) collect blood sample in included capillary tube; (ii) transfer 2 ml blood to sample well of RDT; (iii) add two drops of buffer to assay buffer well; (iv) wait 10 minutes for reaction to occur; and (v) view results.
Cost/test	US$ 1.50 per test.
Cost/instrument	No instrument.
Power requirements	None.
Training/ technical sophistication	Designed to be performed by low-skilled health workers at the POC, less than one half-day of training required for new test operator.
Durability/ maintenance	Not applicable; disposable test.
Infrastructure requirements	No infrastructure required; appropriate for health facilities at all levels.
Result display and storage	Results appear as a visible colour in the test window. The purple colour appears for normal samples and no colour appears in the test window for deficient samples.
QA/QC	CE marked. Developing a set of external QCs (deficient, intermediate, normal) and a visual readout card.
Availability	Currently available; several clinical trials completed, although not all have been published.

TABLE A4.14
CareStart™ G6PD Biosensor

Platform characteristics	
Type of technology	The CareStart™ G6PD biosensor is a hand-held reader that in conjunction with a disposable test strip, provides a quantitative G6PD activity result within four minutes. The biosensor technology directly measures G6PD activity from collected blood based on electro-chemical properties of the sample. As the NAPDH reaction occurs, the device measures the change in electric current and converts this change into voltage that is proportional to enzymatic activity.
Output	The result shows G6PD enzyme activity at 30 °C and expressed as units/decilitre. Addition of Hb is under development.
Performance	The Biosensor is currently undergoing evaluations at several sites; results are expected in 2016.
Turnaround time/ capacity	Test results are available in four minutes.
Sample needed/ stability	5 µL whole blood from fingerprick or venepuncture.
Environmental requirements	Test has been designed with stability and environmental conditions in mind: • disposable test strips have a 2-year shelf life (three months once the package is opened) with recommended storage temperature of 4–40 °C; • device operates at room temperature (up to 40 °C) and has an internal sensor for temperature calibration.
Testing protocol	Testing protocol: (i) turn the device on and insert the test strip; (ii) prick finger using a lancet and bleed 20–30 µL; (iii) touch finger with the collected blood to the end of the test strip, allowing blood to completely fill the window of test strip, device will beep to indicate sufficient blood transfer; and (iv) wait four minutes to view results.
Cost/test	US$ 2.50 per test strip, packs of 25 strips.
Cost/instrument	US$ 500.
Power requirements	Battery operated; rechargeable.
Training/ technical sophistication	Designed to be performed by low-skilled health workers at the POC, less than one half-day of training required for new test operator. Interpretation of test results may require additional training on G6PD threshold activity for different drugs and G6PD variants.
Durability/ maintenance	One year warranty.
Infrastructure requirements	No infrastructure required; appropriate for health facilities at all levels.
Result display and storage	Results appear as a quantitative result on the screen. Internal memory storage of up to 1000 results.
QA/QC	Electronic calibrator for the strips. Developing liquid external controls.
Availability	Currently available; several clinical trials under way.

Annex 5. Contribution of public and private sector outlets to malaria management

TABLE A5.1

Market composition, market share and availability of diagnostic testing

	Market composition: outlets stocking antimalarials	Outlet antimalarial market share[a]	% outlets with malaria blood testing available
Cambodia 2013			
Public health facility	14.8	32.7	94.5
Pharmacy	14.7	20.4	60.1
Itinerant drug vendor	18.7	13.6	45.4
Private for-profit health facility	17.9	12.4	85.3
Community health worker (village malaria worker)	17.3	7.1	96.1
General retailer	7.5	7.1	9.6
Drug store	9.1	6.7	50.9
Private not-for-profit health facility	0.0	0.0	0.0
Nigeria 2013			
Drug store (Proprietary Patent Medicine Vendor)	64.7	69.6	7.1
Public health facility	16.8	13.7	49
General retailer	6.8	7.4	0.0
Pharmacy	1.1	4.7	7.6
Private for-profit health facility	6.0	3.0	62.4
Community health worker	1.7	0.8	8.4
Private not-for-profit health facility	1.6	0.6	49.4
Itinerant drug vendor	1.3	0.2	0.0

	Market composition: outlets stocking antimalarials	Outlet antimalarial market share[a]	% outlets with malaria blood testing available
Madgascar 2013			
Drug store	8.2	34.1	1.1
General retailer	20.9	14.0	0.5
Pharmacy	0.6	13.8	1.0
Private for-profit health facility	5.1	10.6	47.5
Public health facility	10.3	10.5	88.9
Itinerant drug vendor	2.5	8.9	0.0
Community health worker	51.7	7.4	88.8
Private not-for-profit health facility	0.7	0.7	83.6
Uganda 2013			
Public health facility	6.3	36.1	90.3
Drug store	42.8	28.1	12.3
Private for-profit health facility	12.4	16.7	67.6
Pharmacy	1.5	11.4	55.7
Community health worker	35.7	4.0	53.4
Private not-for-profit health facility	1.4	3.7	100
General retailer	0.0	0.0	0.0
Itinerant drug vendor	0.0	0.0	0.0
Democratic Republic of the Congo (Kinshasa) 2013			
Drug store	77.4	89.1	0.3
Private for-profit health facility	16.5	5.7	92.8
Private not-for-profit health facility	3.5	2.2	91.3
Pharmacy	0.5	1.9	20.0
Public health facility	2.0	1.1	90.1
Community health worker	0.0	0.0	0.0
General retailer	0.1	0.0	0.0
Itinerant drug vendor	0.0	0.0	0.0

	Market composition: outlets stocking antimalarials	Outlet antimalarial market share[a]	% outlets with malaria blood testing available
Democratic Republic of the Congo (Katanga) 2013			
Drug store	60.9	67.0	6.2
Private for-profit health facility	17.8	15.8	72.7
Public health facility	10.5	10.4	75.8
Private not-for-profit health facility	6.5	4.2	75.6
General retailer	4.3	2.7	4.3
Community health worker	0.0	0.0	0.0
Pharmacy	0.0	0.0	0.0
Itinerant drug vendor	0.0	0.0	0.0
Zambia 2014			
Public health facility	28.1	73.4	91.3
Drug store	26.1	10.0	10.6
General retailer	27.9	5.4	0.1
Private not-for-profit health facility	2.0	5.3	100.0
Pharmacy	2.7	2.4	50.9
Community health worker	9.3	2.1	83.8
Private for-profit health facility	3.9	1.4	87.5
Itinerant drug vendor	0.0	0.0	0.0

[a] % antimalarials distributed in the week before the survey by outlet type.

Source: ACT Watch Outlet Surveys.

Annex 6. Additional information on quality and adaptability of RDTs

Product delisting

In September 2014, compulsory resubmissions to Round 5 of the Product Testing Programme resulted in two products no longer qualifying for WHO procurement and delisting from the WHO PQ:

1. The Biosynex Immunoquick Malaria *falciparum* product was removed from the WHO list of recommended RDTs as well as the Global Fund list and was delisted by the WHO PQ. As this *Pf*-only product is not price competitive or widely used in the public sector, the effect on the market was minimal.

2. The Premier Medical Corporation Ltd. First Response pLDH/HRP-II combo test was removed from the WHO list of recommended RDTs as well as the Global Fund list. This is a common combination test (14–19% market share of *Pf*/pan tests in 2013 and 2014). Because its performance in the Product Testing Programme fell just shy of the minimum standard, some countries and donors have elected to continue with already planned procurement, while others elected to stop procuring it. The manufacturer has submitted a new version of the product for evaluation in Round 6.

Prequalification has also resulted in changes to the recommended list of malaria RDTs. In 2012, the WHO PQ issued a Notice of Concern for the Tulip Group Inc. (parent company of Orchid Biomedical Systems and Zephyr, maker of the formerly dominant Paracheck RDT) regarding problems identified during initial site inspections for prequalification. Despite additional inspections, in 2015 the WHO PQ closed the Tulip Group's application due to failure to remedy the outstanding issues. Although the Tulip Group's products remain on the WHO list of recommended RDTs, the challenges with prequalification have resulted in delisting from the Global Fund list of eligible RDTs *(117)*.

Lot testing

Experience with lot testing has generally been positive, nearly all RDTs tested pass, although this "pass rate" may not reflect the quality of RDTs used globally since products submitted are

generally from agencies that are more likely to use lot testing than other buyers. Many of the failures that have occurred in lot testing relate to weakness of a pan or *Pv* line against low-density *P. vivax* samples. Challenges noted during lot testing include the following.

Individually packaged RDTs. Individually packaged RDTs, containing single-use buffer vials, are available from a number of RDT manufacturers. While they remain a small proportion of the market, programmes have procured several million mainly for community and retail private sector use. In 2013 and 2014, malaria programmes and the Lot Testing Programme found that the diluent solution included in individually packaged kits had evaporated prior to the shelf life of the product. This problem was noted for 10 products from three market-leading manufactures (Access Bio Inc.; Alere/Standard Diagnostics Inc.; Premier Medical Corporation Ltd). As such, WHO has issued an information notice recommending that no new orders be placed with single-use buffer vials until improved products become available *(118)*. To remedy the problem, the three affected manufacturers have sourced new vial material and are in the process of validation studies (both accelerated and real time), which will be reviewed by the WHO PQ. It is expected that new individually packaged RDTs will be available in 2016.

At the country level, given the decentralized nature of malaria testing, it is difficult to recall RDTs, so manufactures and country programmes are working to ensure that RDTs with evaporated buffer are not used. In many cases the RDTs are used before the shelf life is over and sufficient buffer remains. Going forward, some countries have switched to multipacks, while others prefer individually packaged kits, the procurement of which is evaluated on a case-by-case basis.

Anomalies. Anomalies[75] are encountered across all products at varying frequencies, and while they 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. Since the programme began providing commentary on anomalies noted during testing it has seen improvement.[76]

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.

At present, it is unclear how frequently these errors occur in RDTs used in the field, as

[75] 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).

[76] Nora Champouillon, FIND, personal communication, 19 May 2015.

there are no feedback systems in place for collecting data on RDT quality 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. In 2013, the Roll Back Malaria Partnership commissioned a task force to explore how RDTs could be harmonized to improve user-friendliness, reduce operator error and address training needs associated with switching brands of RDTs. The resulting Harmonization Task Force assessed the level of similarities and differences between malaria RDTs and identified opportunities for improving user-friendliness and harmonization of RDTs. The Harmonization Task Force has made many recommendations concerning improved device labelling, packaging, accessories and instructions for use *(85)*.

WHO expects to publish these recommendations in a guidance note to manufactures that will contain required items (those already required by ISO 13485) and preferred characteristics, with the preferred items aiming to improve user friendliness. This list of recommendations will be incorporated into the Product Testing Programme (Round 7) and the WHO PQ review of dossiers in 2016. While these changes should improve the quality of RDTs and reduce operator error, RDTs will continue to differ in procedures and as such the impact on competition may not be substantial, as changing from one test kit to another will require retraining of all health care workers in the new test procedures. Complete harmonization of RDTs requires changes to test procedures and is not considered feasible in the near term.

Alignment of local procurement standards with WHO recommendations

Quality standards for RDTs in the private sector, and in a few instances the public sector, are not always aligned with WHO recommendations and could lead to availability and use of RDTs whose quality is not assured. ACT Watch data and anecdotal reports indicate that there are RDTs on the market whose performance has not been evaluated by the Product Testing Programme, however, the extent of this issue is difficult to appreciate given a relative lack of data.

While most of the RDTs found on shelves during ACT Watch surveys in Cambodia, the Democratic Republic of the Congo, Madagascar, Nigeria, Uganda and Zambia were made by companies that have had their RDTs evaluated by the Product Testing Programme, RDTs that have not been evaluated are available,[77] in particular in Nigeria (44% of RDTs

[77] ACT Watch surveys included audits of RDTs found on the shelves in public and private sector outlets, as well as estimates of market share for the RDTs found. The surveys captured manufacturer and brand, but detailed information on the product was not captured so it is not possible to determine whether an RDT found during an audit meets WHO recommendations. However, it is possible to know whether the company that produced the audited test has had any RDTs evalauted by the Product Testing Programme.

found on shelves were from companies that have not had their tests evaluated) and Uganda (21% of RDTs) (Table A6.1).

However, even though RDTs of unknown quality are available (i.e. stocked), they are not necessarily provided to patients/customers in high volumes. ACT Watch data on RDT usage[78] indicate that public health facilities generally use tests from manufacturers that have had their RDTs evaluated; one notable exception is Uganda, where an RDT from Astel comprises 12% of the total market, largely due to its use in public facilities. While the ACT Watch surveys also documented sales of RDTs of unknown quality by the private sector in Cambodia and Nigeria, their share of the total market is low (5% and 2%, respectively). In Cambodia the low usage of RDTs with unknown quality is likely due to the private sector social marketing programme that promotes an RDT that meets WHO recommendations, whereas in Nigeria the overall volume of RDTs sold by the private sector is very low.

TABLE A6.1

Availability and market share of RDTs produced by companies that have had their tests evaluated by the WHO Product Testing Programme (public and private sector)

Country and survey year	Number of different RDTs found on shelves during audits	% of RDTs made by companies that have had their RDTs evaluated by WHO Product Testing Programme	Market share
Cambodia 2013	8	88%	95% of market is from companies that have submitted their RDTs to product testing (Access Bio Inc.; Alere/Standard Diagnostics Inc.; Premier Medical Corporation Ltd).
Democratic Republic of the Congo Kinshasa 2013	3	100%	
Democratic Republic of the Congo Katanga 2013	6	100%	
Nigeria 2013	9	56%	98% of market is from companies that have submitted their RDTs to product testing (Access Bio Inc.; Alere/Standard Diagnostics Inc.; Arkray Inc./ Span Diagnostics Ltd; Orchid Biomedical Systems).
Madagascar 2013	5	100%	
Zambia 2014	8	100%	
Uganda 2013	14	79%	87% of the market is from companies that have submitted their RDTs to product testing; 13% of the market is RDTs that have not been submitted, largely attributed to use of Astel RDTs (12% market share) in the public sector.

Source: ACT Watch Outlet Surveys.

[78] Provision to patients or sale to customers.

Annex 7. Procurement processes

Global Fund malaria RDT 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 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, however, its disease advisers provide guidance on product selection. Procurement plans must be consistent with international standards, such as guidance from WHO, and products must be 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.[79] The Global Fund also maintains a list of eligible RDTs on its website, which is mostly aligned with WHO recommendations *(117)*.

In recognition of the programmatic complexities, including impact on qualty of care, and cost of switching RDTs on an annual basis, the Global Fund allows continuation of procurement of a selected RDT for up to three years (after a competitive selection process). In practice, this means that a country can sole source the RDT in years 2 and 3, with review by the Global Fund to ensure that the pricing and terms are reasonable.[80] While it is possible that two thirds of the RDTs procured with Global Fund funding are sole sourced, the actual frequency and impact on pricing has not been analysed systematically, although procurement data do not indicate that suppliers are frequently raising prices in years 2 and 3. Conversations with the Global Fund suggest that sole sourcing is most common in the larger countries where retraining costs would be substantial.

The Global Fund launched a procurement mechanism in 2009 in order to improve the

[79] 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. In addition, the Global Fund requires that countries implement other quality testing measures for RDTs, including participation in the Lot Testing Programme. In April 2013, a review of the Global Fund Quality Policy for Diagnostics was conducted; no major changes for malaria RDTs were noted in the revised policy.

[80] If an unreasonable quote is received, a competitive tender can be initiated.

efficiency and cost-effectiveness of Global Fund recipient procurement. This mechanism, the Pooled Procurement Mechanism (PPM),[81] procured over 60 million RDTs in both 2013 and 2014. The Partnership for Supply Chain Management is currently the procurement agent for PPM. Previously, malaria RDT procurement has not actually been pooled; it has been done through individual procurements based on country requests (some are sole sourced, others are openly competed). However, the Global Fund PPM group is in the process of reviewing its malaria RDT procurement strategy. Based on discussions with the Global Fund and how it has approached other markets, PPM is likely to work more directly with suppliers, through framework supply agreements with several manufacturers. These agreements would extend over a period of time and would shift competition to the global level, rather than the individual country level. The role of procurement agents will be reduced; agents will primarily place orders and manage delivery to countries under these framework agreements.

Although the number of products meeting Global Fund standards is quite high (more than 25 qualified manufacturers, more than 20 *Pf*-only products) procurement data included only five suppliers in 2014, with nearly all volumes going to Access Bio Inc., Alere/Standard Diagnostics Inc., and Premier Medical Corporation Ltd. On average, the Global Fund (PPM and countries procuring directly) achieves the lowest prices of all procurers and PPM leads the market with low prices. This is likely attributed to the large overall volumes, as well as the emphasis it places on competitive tenders.

PMI malaria RDT procurement

PMI performs malaria RDT procurement on behalf of countries, currently through the USAID DELIVER Project. Procurement is done on a one-off basis, based on country requests, and may be sole sourced or competed (open or limited competition). Requests for quotation (including price, lead time and registration status) are sent to eligible suppliers that have been prequalified through an expression of interest process. The PMI criteria for RDT performance are in line with WHO recommendations; in addition, manufacturers must agree to preshipment lot testing, demonstrate an ability to respond to and meet international tenders, as well as demonstrate financial stability. The PMI list of eligible RDTs for procurement includes fewer suppliers and tests than the WHO recommended list; however, in PMI's experience, the leading malaria RDT manufacturers are represented and its preselection process has not conflicted with a country's product selection. PMI currently has six qualified RDT suppliers and 16 products *(119)* and maintains long-term agreements with these suppliers that establish ceiling prices based on historical procurement for malaria RDTs. In practice, suppliers frequently quote below the ceiling prices.[82] PMI procured from three companies in 2014: Access Bio Inc.; Alere/Standard Diagnostics Inc.; Premier Medical Corporation Ltd.

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. In 2015, PMI also issued guidance limiting the use of combination tests in sub-

[81] Formerly Voluntary Pooled Procurement or VPP.

[82] Jennifer Wray, PMI, personal communication, August 2014.

Saharan Africa (except where epidemiologically appropriate). Many countries have been requesting combination tests in the hopes of identifying non-*Pf* species, in particular *P. malariae.* PMI is limiting their use because: (i) there is limited evidence supporting the performance of multi-species RDTs on species other than *P. falciparum* and *P. vivax*; (ii) multi-species tests can be more expensive; and (iii) multi-species tests are more complicated to implement. The impact of this change on the market remains to be seen.

In practice, since 2007, a substantial proportion of PMI's volumes have been sole sourced, and procurement data indicate that prices for sole-sourced RDTs were higher than openly competed procurements.

Going forward, PMI's malaria RDT procurement is expected to transition to a new system. In April 2015, USAID announced the award of a new US$ 10.5 billion 8-year procurement contract, the Global Health Supply Chain contract to a consortium led by Chemonics. The timeline for this transition is currently difficult to predict; after some contractual issues, *(120)* as of December 2015, project implementation has commenced under Chemonics, and will temporarily run in tandem with the JSI Deliver project until the JSI Deliver projects' contract is completed.

UN agency procurement

Several of the UN organizations, mainly UNICEF, WHO, and UNDP, procure RDTs on behalf of programmes and Ministry of Health. The volumes procured by these organizations are significantly less than that of PMI and the Global Fund, and order sizes are typically smaller as well.

The WHO procurement process is described below. The specifics for the other organizations were not investigated in depth, although they are likely similar to that of WHO because the tender that initiates WHO procurement is conducted jointly with other UN agencies, and prices and terms are shared among the various agencies.

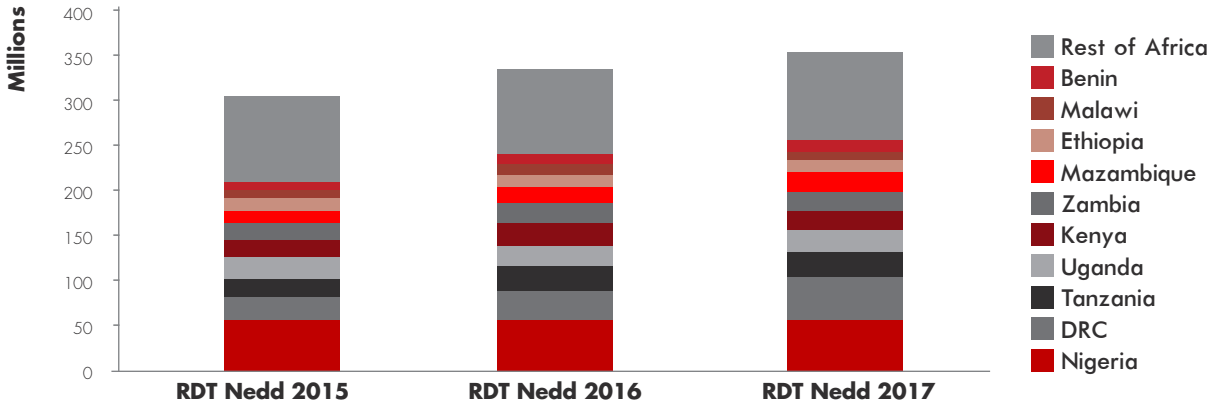
The WHO process begins with an annual tender and all suppliers with products meeting WHO requirements are invited to quote. The quotes form the basis of 1-year supply agreements (extendable to two years) that specify terms, including price, INCOterms (usually delivery to the closest airport) and remaining shelf life. The product specifications and prices are then published in the WHO procurement catalogue that is available to WHO offices. Buyers select from the RDTs in the catalogue, requesting a specific RDT. Infrequently, WHO receives a specific procurement request (e.g. a non-standard packaging of RDTs) requiring an off-catalogue procurement.

In 2015, WHO had supply agreements with 17 manufacturers (over 30 RDTs). The prices ranged from US$ 0.23 for *Pf*-only tests to US$ 0.76 for multi-species tests (single kit pricing is higher).[83] Procurement data indicate that in 2014, WHO procured from Access Bio Inc., Alere/Standard Diagnostics Inc., and Premier Medical Corporation Ltd.

[83] Draft assessment of the market impact of requiring WHO prequalification for malaria RDTs, Unpublished report. Geneva: World Health Organization; January 2016.

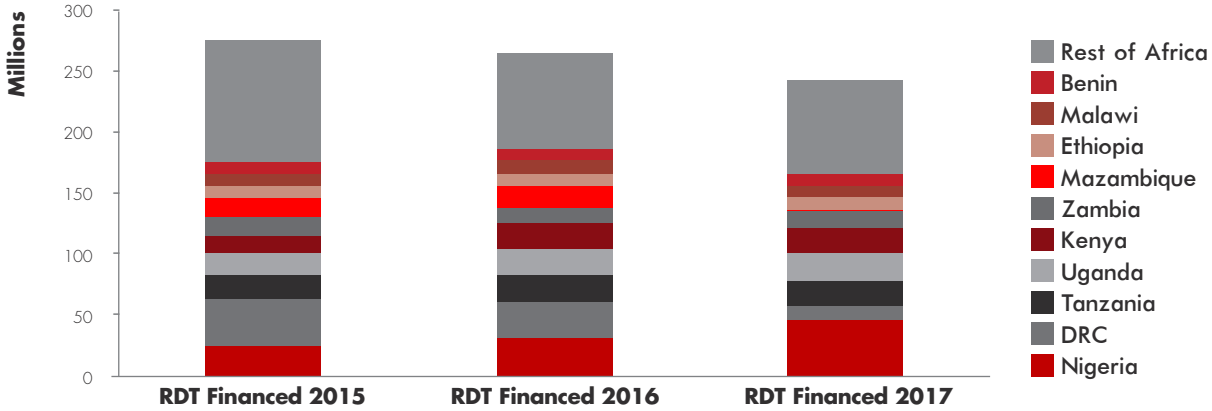
Annex 8. RDT need compared to RDT financing

FIGURE A8.1
RDTs needed in African countries, 2015–2017



DRC, Democratic Republic of the Congo; Tanzania, United Republic of Tanzania
Source: Author analysis of the Roll Back Malaria Partnership Harmonization Working Group (HWG) data on commodities.

FIGURE A8.2
RDTs financed in African countries, 2015–2017



DRC, Democratic Republic of the Congo
Source: Author analysis of the Roll Back Malaria Partnership Harmonization Working Group (HWG) data on commodities

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UNITAID Secretariat

Chemin de Blandonnet 10
– BIBC III – 8th Floor
1214 Vernier Switzerland

T +41 22 791 55 03
F +41 22 791 48 90
unitaid@who.int
www.unitaid.org

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