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# Malaria Diagnostics Landscape Update

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## Abbreviations

| | |
|---|---|
| **ACT** | artemisinin-based combination therapy |
| **ADDO** | accredited drug dispensing outlet |
| **AIDS** | acquired immunodeficiency syndrome |
| **°C** | degree Celsius |
| **CE mark** | European Conformity (Conformité Européenne) |
| **CHAI** | Clinton Health Access Initiative |
| **ELISA** | enzyme linked immunosorbant assay |
| **FIND** | Foundation for Innovative New Diagnostics |
| **Global Fund** | Global Fund to Fight AIDS, Tuberculosis and Malaria |
| **G6PD** | glucose-6-phosphate dehydrogenase |
| **HRP2** | histidine rich protein 2 |
| **HIV** | human immunodeficiency virus |
| **IDT** | infection detection test |
| **LAMP** | loop-mediated isothermal amplification |
| **LFIA** | lateral flow immunoassay |
| **PCW** | positive control well |
| ***Pf*** | *Plasmodium falciparum* |
| **pLDH** | parasite lactate dehydrogenase |
| **PMI** | United States President's Malaria Initiative |
| **POC** | point of care |
| **PQR** | Price and Quality Reporting (Global Fund) |
| **PSI** | Population Services International |
| ***Pv*** | *Plasmodium vivax* |
| **p/µL** | parasites per microlitre |
| **QA** | quality assurance |
| **QC** | quality control |
| **R&D** | research and development |
| **RDT** | rapid diagnostic test |
| **TPP** | target product profile |
| **µL** | microlitre |
| **US** | United States |
| **VPP** | Voluntary Pooled Procurement |
| **WHO** | World Health Organization |

## Executive summary

This report updates and highlights changes in the malaria diagnostics market since the *UNITAID 2014 Malaria diagnostics technology and market landscape*.

There has been only a slight change in the malaria burden estimates since the last landscape. While the past decade has seen tremendous reductions in the global burden of malaria, it is increasingly apparent that decreases have been uneven both between and within countries, underscoring the need to strengthen diagnostics capacity and surveillance systems. In terms of access to testing, 197 million slides were read and 319 rapid diagnostic tests (RDTs) were sold in 2013, and for the first time the number of tests performed in the African public sector exceeded artemisinin-based combination therapies (ACTs) distributed. However, compared to the global testing need, which exceeds 1 billion tests annually, significant scale-up is required to achieve universal access to testing. While access has been increasing in the public sector (from 44% tested in 2010 to 64% in 2012), testing in the community and private sector is minimal.

There are a number of changes in malaria policies and practices that shape the malaria agenda and market for diagnostics. Since the *2014 Landscape*, the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) completed its replenishment and the New Funding Model (NFM) has been implemented. Although the impact on diagnostic budgets remains to be seen, early indications suggest that countries are likely to maintain the scope and scale of their diagnostics activities in the near term. In 2014, the World Health Organization (WHO) issued new guidance on molecular diagnostics, noting that RDTs and microscopy should be used for clinical malaria in all transmission settings, and recommending that, once diagnostic scale-up is complete, low transmission areas consider more sensitive diagnostics for epidemiological research and surveys. Globally, standardization of molecular methods and development of quality assurance (QA) schemes will be critical to ensuring quality and comparability of results.

With respect to the technology pipeline, several developers report progress although it is not clear that the pipeline will address gaps equitably. Notable progress includes development of positive control wells (PCWs) for RDTs (2015 availability), development of highly sensitive RDTs for use in elimination settings (2017 availability) and a WHO review of evidence on the performance of a new point-of-care (POC) G6PD test.

The RDT market continues to grow rapidly, from 45 million RDTs sold in 2008 to 319 million RDTs in 2013. Limited procurement data analysis suggests that prices remain low but variable (approaching the cost of goods sold for some orders) and the market has consolidated around two suppliers.

With respect to quality, the WHO/Foundation for Innovative New Diagnostics (FIND) Product Testing Programme released a fifth round of results: while the number of recommended combination tests has increased, two products are no longer recommended. Only one supplier has WHO prequalified products because no new suppliers have gained prequalification and one of the formerly prequalified products was delisted due to poor performance in the Product Testing Programme. The Roll Back Malaria Partnership Harmonization Task Force, commissioned to explore opportunities to improve interchangeability of RDTs,

has made many recommendations concerning labelling, packaging and instructions; however, complete harmonization of RDTs was not considered feasible in the near term. The implementation timeline for the new recommendations remains to be seen.

There have been few changes to RDT supply since the *2014 Landscape*. Suppliers report that economies of scale, capacity utilization and optimizing use of labour and inventory are key considerations that influence pricing of RDTs. Suppliers are generally not aggressively pursuing private sector markets outside of nongovernmental organization efforts – Population Services International (PSI), the Malaria Consortium, Clinton Health Access Initiative (CHAI) – and have mixed feelings about these programmes.

An analysis of diagnostics markets in elimination settings found that the largest "new" market segment is likely to be for POC tests for screening asymptomatic populations, although this market is likely to be small and fragmented.

Major market shortcomings include: (i) challenges related to the quality of RDTs in the field and at the manufacturing level; (ii) the concentration of suppliers and risk this creates for market disruptions; and (iii) the limited uptake of RDTs compared to need, including limited markets in the private sector. Inadequate surveillance and the lack of tests to support elimination, case management of *Plasmodium vivax* and for pregnant women are also gaps.

There are several opportunities to improve access to malaria diagnostics. Perhaps the most urgent need is for demand-shaping interventions at the procurement level to ensure the long-term sustainability and health of the RDT market. Given current market conditions, opportunities to further improve quality are critical. Recent evidence on performance of the AccessBio POC G6PD test may also present opportunities to improve access to safe and appropriate management of *P. vivax*.

There are also several important market intelligence gaps and areas that will be critical to monitor in the coming year. For example, improved data on the use of RDTs are needed (e.g. RDT suppliers report selling twice as many RDTs as national malaria control programmes (NMCPs) report distributing; procurement data are available for only half of the market). Going forward, it will be important to analyse the effect of the Global Fund's fundraising challenges and the New Funding Model on diagnostic budgets. The Global Fund is also expected to review its RDT procurement strategy in the coming year; as the largest RDT buyer, its changes will no doubt impact the market.

## Introduction and methods

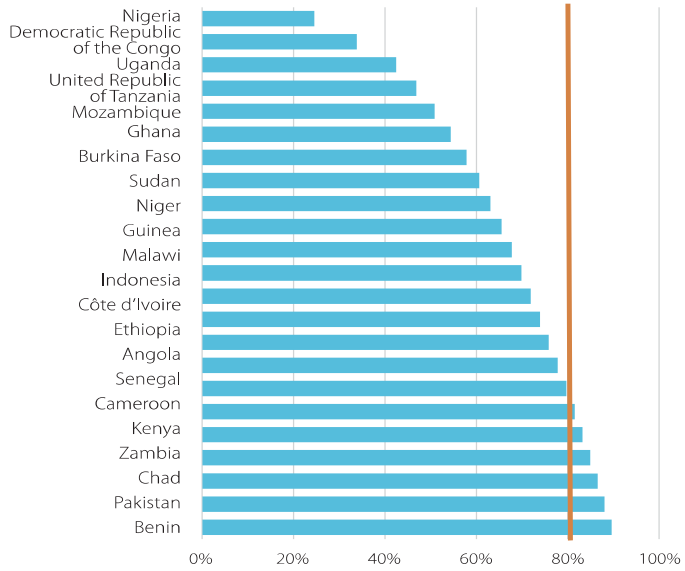
This report updates and highlights changes in the malaria market since the UNITAID *2014 Malaria diagnostics technology and market landscape (2014 Landscape)*.[1] It is based on the review of published reports and meeting presen tations, literature review, interviews with experts and feedback from four leading rapid diagnostic test (RDT) suppliers and from six technology developers. Research for this update was completed in July and August 2014 and information should be considered up to date as of the end of August 2014, with one exception: data on the malaria burden and access to testing reflect the most recent *World malaria report published in late 2014 [1]*. Additional detail on the technology pipeline and market will be available in the next edition of the UNITAID *Malaria diagnostics landscape* (2015).

## Public health problem

Since the *2014 Landscape*, there has been only a slight change in the malaria burden estimates. Approximately 3.2 billion people, across 97 countries, were at risk of malaria in 2013. There were an estimated 198 million cases (range 124–283 million) and 584 000 deaths from malaria (367 000–755 000 range) *[1,2]*. Although the population at risk is spread across the globe, the vast majority of cases and deaths occurs in sub-Saharan Africa (Figures 1 and 2).

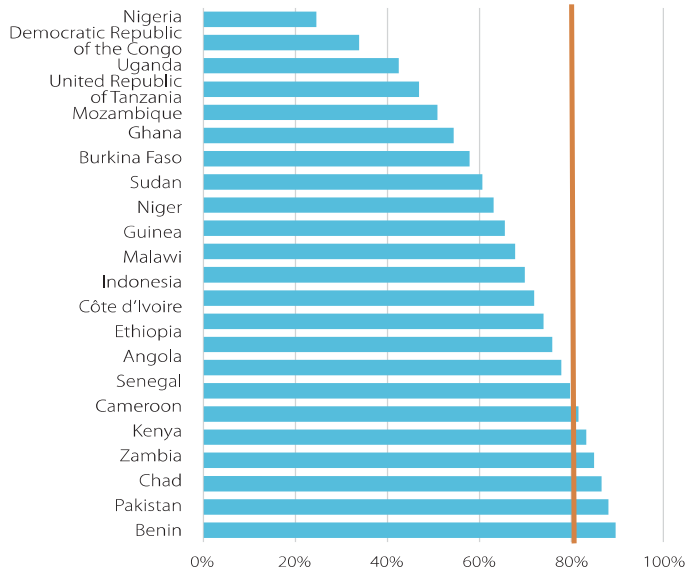
1 Available at: http://www.unitaid.eu/en/resources/publications/technical-reports.

**Figure 1. Cumulative proportion of the global estimated cases accounted for by the countries with the highest number of cases**




*Source:* World malaria report 2014 *[1]*.

**Figure 2. Cumulative proportion of the global estimated deaths accounted for by the countries with the highest number of deaths**




*Source:* World malaria report 2014 *[1]*.

Since 2000, scale-up of malaria control efforts has contributed to tremendous reductions in the burden of malaria globally, and has contributed to increasing heterogeneity of malaria burdens, both between and within countries. Even within African countries, the decreases in morbidity and mortality have been uneven, while a substantial proportion of the population continues to live in high endemic areas; some areas have achieved very low levels of transmission *[3,4]*. For some countries that have reduced transmission to very low levels, malaria elimination, either national or progressive,[2] is now within reach.

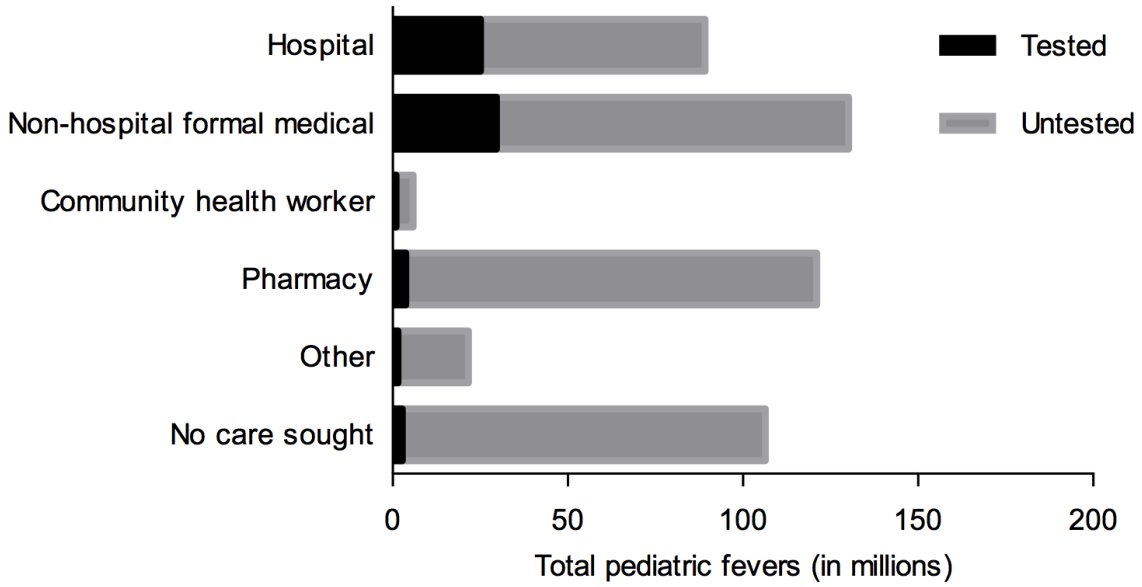
## Access to malaria diagnosis[3]

Since 2010, the World Health Organization (WHO) has recommended that all people with suspected malaria receive a diagnostic test before treatment *[5]* and, in 2011, the Roll Back Malaria Partnership set ambitious targets for universal access to testing in the public sector, private sector and at the community level *[6]*. Broadly speaking, access to testing depends on treatment-seeking behaviour (e.g. whether care is sought at all and, if so, where) as well as on the availability and use of malaria diagnostics.

### Gap in access and testing rates

Globally, estimates of the gap in access to malaria testing (e.g. the estimated need versus current access) are not robust, however, all data suggest there is room for significant improvement, especially in the private sector and at the community level. For example, in 2013, 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 *[2]*. Comparing this to the global volumes of tests reported in 2013 (319 million malaria RDTs sold and 197 million slides read in endemic countries) *[1]*, significant scale-up is needed to achieve universal access to testing. Similarly, a recent review of testing for paediatric fevers in sub-Saharan Africa concluded that only 16.9% of febrile children under five years old was tested in 2010, at the outset of the WHO guideline change. In particular, this review noted minimal levels of testing at the lower levels of the health setting and least formal settings, where paediatric fevers are commonly managed (Figure 3) *[7]*.

**Figure 3. Estimated paediatric fevers attending and tested by source of care in 13 countries in 2010**




*Source:* Johansson et al. *[7]*.

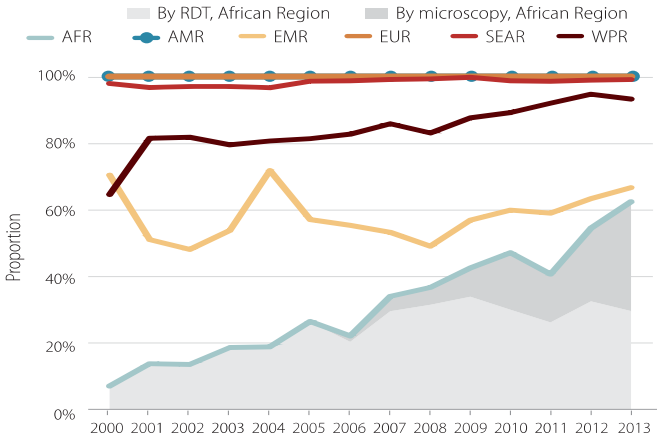
2 Progressive elimination refers to elimination of malaria in selected geographic regions followed by other areas, or elimination of one species followed by other species.

3 This section draws on the *World malaria report 2014* unless otherwise noted.

Since the publication of the *2014 Landscape*, more recent data on testing rates have become available from WHO and the United States President's Malaria Initiative (PMI); the highlights are described below.

**Public sector testing rates**: WHO estimates that global public sector testing rates have grown steadily from 44% in 2010 to 64% in 2012 *[2]*. WHO data indicate that despite progress, the African Region (62% suspected cases tested in 2013, up from 47% in 2010), the South-East Asia Region (56% suspected cases tested in 2012, excluding India where testing rates are high) and the Eastern Mediterranean Region (63% suspected cases tested in 2012) lag behind (Figure 4). Data analysed by PMI for 10 African countries with reliable statistics showed variable rates of increase in public sector testing (Figure 5).

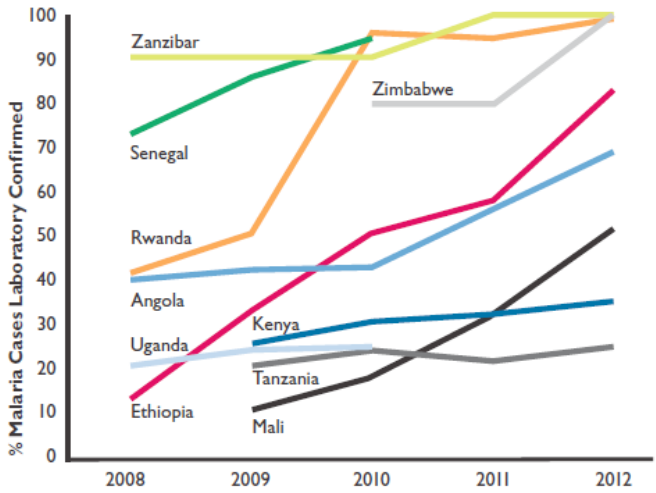
**Figure 4. Proportion of suspected malaria cases attending public health facilities that receive a diagnostic test, 2000–2013**




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:* National malaria programme reporting to WHO. World malaria report 2014 *[1]*.

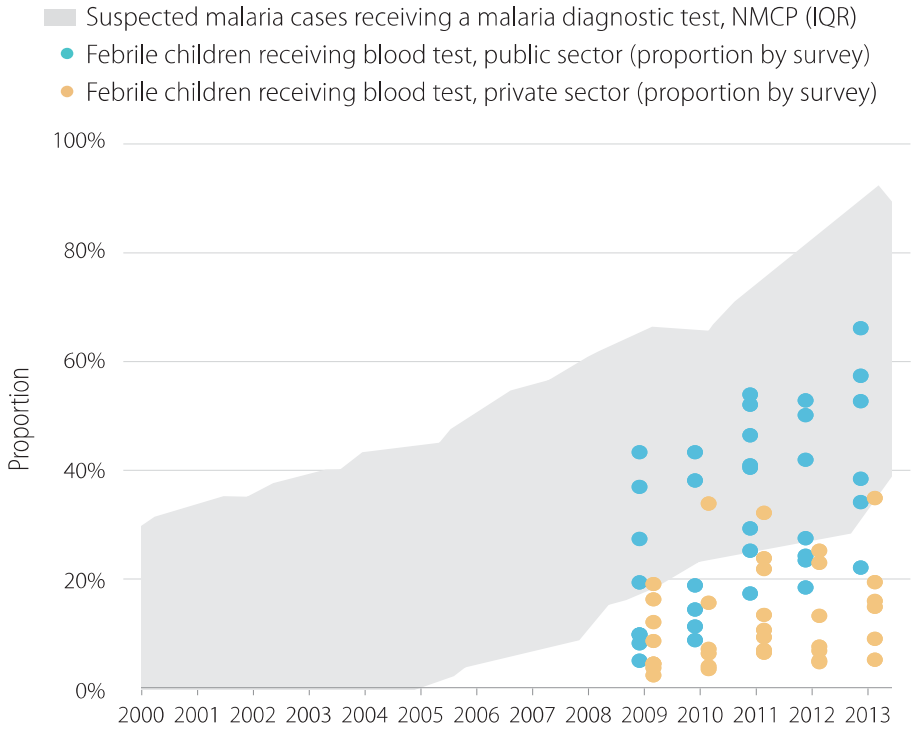
**Figure 5. Proportion of suspected malaria cases confirmed with a laboratory diagnostic test, 10 countries**




*Source:* PMI Annual Report, reproduced with permission. Based on public sector data as reported in the Health Management Information System (HMIS). Includes only countries from which data reliability was high or representative of most if not all facilities.

**Private sector testing rates**: In many countries, the private sector plays an important role in fever care and malaria drug provision, yet information on diagnostic testing in this sector is limited. Among 41 household surveys conducted during 2009–2013, the proportion of children under 5 years old who received a diagnostic test for suspected malaria was lower in the private sector (9% median, interquartile range 6–18%) than in the public sector (31% median, interquartile range 17–43%) (Figure 6) *[1]*.

**Figure 6. Proportion of febrile children who had a blood test, by health sector, in household surveys, and proportion of suspected malaria cases receiving a parasitological test in NMCP reports (sub-Saharan African countries with available survey data 2000–2013)**




IQR, interquartile range
*Source:* World malaria report 2014 *[1]*.

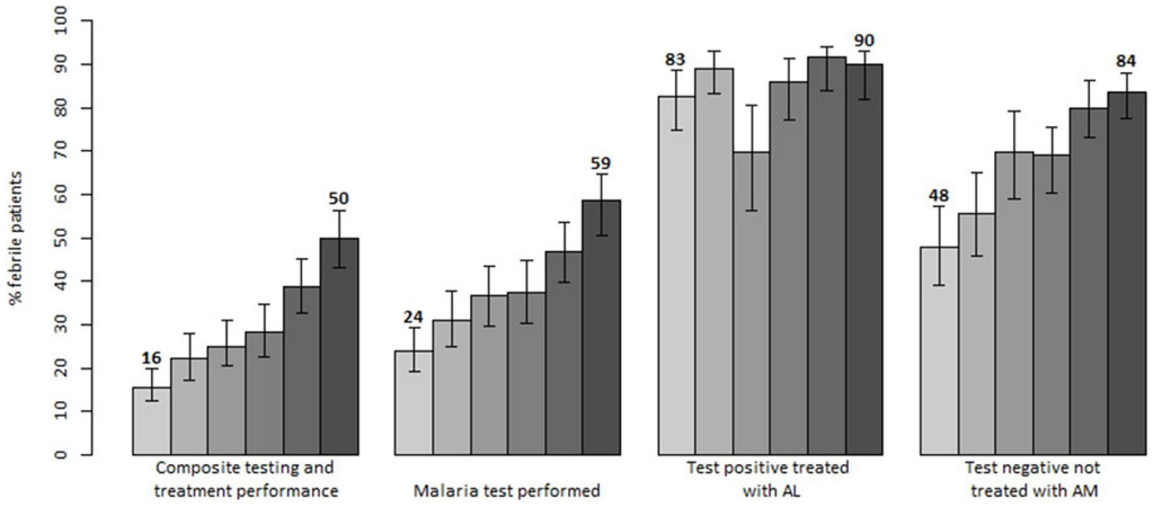
**Community level testing**: 48 of 90 countries reported a policy for RDT use at the community level in 2012; however, country reporting of testing volumes is low: 15 million RDTs were used at this level in 2012, 13 million of these in India *[2]*.

## Impact of diagnostics

The impact of diagnostics on antimalarial overuse and on treatment of fever is difficult to assess globally given the lack of systems for capturing these data. Available evidence suggests that implementation is highly variable, but in many instances there is room for improvement in care-seeking behaviour, availability of diagnostic testing, uptake of tests among providers and patients, and managing fever based on test results. For example:

- A Cochrane review of seven RDT trials found that introducing RDTs reduced antimalarial prescribing by up to three quarters, with similar outcomes for patients as compared to presumptive treatment. However, adherence to test results was highly variable, as were antibiotic prescribing rates after introducing RDTs *[8]*.
- At the national scale, Senegal and Zambia have reported reduced overtreatment of malaria as a result of public sector scale-up of RDTs *[9,10]*. Recent surveys in Kenya also suggest improvement in overtreatment and in testing rates. Between 2010 and 2013, overall use of a first-line antimalarial (artemether-lumefantrine) was nearly halved, and testing and treatment in accordance with guidelines increased from 16% to 50% in Kenya (Figure 7) *[11]*.
- WHO reports that in the African public sector, more tests were performed as artemisinin-based combination therapy (ACT) were distributed in 2013 *[1]*. However, given prevalence rates, the ratio of ACTs to diagnostics should be higher (>2) indicating that there is still a need to scale diagnostic services (Figure 8).
- WHO analysis of household surveys indicates that overall a minority (median 17%, interquartile range 9–27%) of febrile children received a test for malaria *[1]*. Moreover, a high proportion of children without confirmed malaria received ACTs, suggesting that testing is not performed or results not adhered to *[2]*.

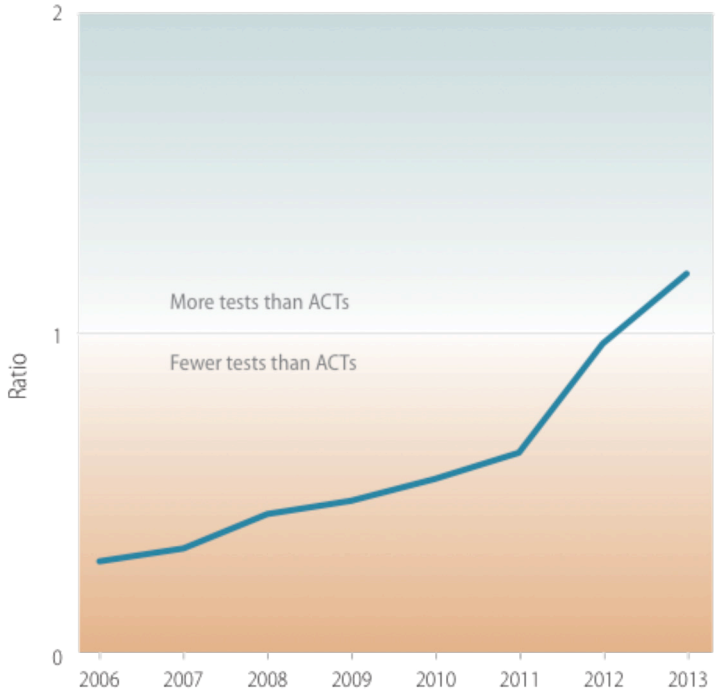
**Figure 7. Trends in key diagnostic and treatment indicators reflecting performance of the new case management policy in Kenya: results of six national surveys between 2010 and 2013 (each bar corresponds to a different survey)**




AL, artemether-lumefantrine; AM, antimalarial

*Source:* Zurovac et al. *[11]*.

**Figure 8. Ratio of malaria diagnostic tests (RDT and microscopy) provided to ACTs distributed by NMCPs, African Region, 2006–2013**



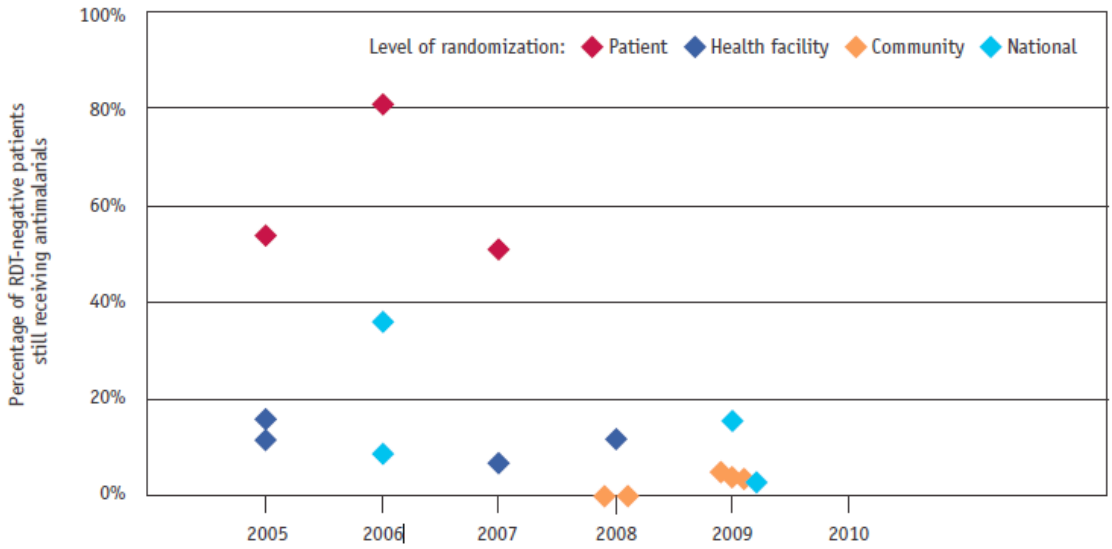

*Source:* National malaria programme reporting to WHO. World malaria report 2014 *[1]*.

## Adherence to test results

A review of evidence on adherence to RDT results found adherence tended to improve with time and was better at lower levels of the health system and for workers with less professional training (Figure 9) *[12]*. A second paper reviewing use of RDTs at the community level found better adherence to test results in Integrated Community Case Management (iCCM) programmes as compared to Community Case Management of malaria (CCMm), likely because alternative diagnosis and medications for other diseases makes it easier for community health workers to adhere to results *[13]*.

Researchers are also working with national programmes to test the impact of enhanced training and other interventions to promote RDT adherence among providers. Thus far, these programmes have demonstrated substantial reductions in overtreatment among malaria-negative patients *[14,15]*.

**Figure 9. Level of adherence of health workers to the results of malaria RDTs by type of study**




*Note:* Study design also influenced adherence to RDT results. For example, when randomization occurred at the patient level (e.g. some patients are tested while others are not), adherence was typically poor, whereas when an entire facility was using RDTs (more reflective of actual implementation) adherence was typically better.

*Source:* WHO informal consultation on fever management in peripheral health-care settings: a global review of evidence and practice *[12]*.

### Unmet diagnostic needs

In addition to the general need to scale malaria diagnostic testing, there are several groups for which current tests are inadequate, for example: (i) tests with improved sensitivity for elimination settings and for *Plasmodium vivax;* (ii) point of care (POC) G6PD deficiency screening tests; and (iii) tests for screening pregnant women. While there has been progress in addressing some of these needs, products for most of these use scenarios are largely still in development.

## Trends in malaria policies and practice

The *2014 Landscape* highlighted several important trends related to: (i) constrained donor funding; (ii) development of private sector markets for RDTs; (iii) implementation challenges affecting use of RDTs and microscopy at the POC; (iv) weaknesses in information systems that limit the ability to monitor the diagnostic scale-up; and (v) the increasing focus on both elimination of malaria and on *P. vivax*. These trends continue to shape the malaria agenda and the market for diagnostics.

Since the *2014 Landscape,* notable trends and developments impacting malaria diagnostics markets include the following.

**Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) replenishment and New Funding Model (NFM)**. In December 2013, donors pledged US$ 12 billion to the Global Fund for 2014–2016. Although this represents a 30% increase over the previous three-year period, it is US$ 3 billion short of the goal. Additionally, a significant proportion of these resources had already been allocated to existing commitments and grants *[16]*.

At the same time, the Global Fund is implementing the NFM, which includes both a new method of allocating funds to programmes as well as new processes for applying for and receiving funds.[4] In March 2014, countries received their allocations *[17]* and are currently in the process of applying for funding. The majority of malaria endemic countries is expected to submit concept notes for review in 2014 or in early 2015 *[18]*.

4 For more information, see the *2014 Landscape*, Annex 4: Global health donor landscape.

Since the development and review of concept notes is still under way, **it is not yet clear how limited funds and the NFM will affect malaria programme budgets**, and diagnostic budgets in particular. Overall, there is a sense that "new" malaria funding is less than expected; however, at the country level, funding when compared to historical levels varies considerably, with some countries faring better than in the past and others facing significant gaps *[18,19]*. For many large programmes, potential funding decreases have shifted the focus from "scaling up" to "sustaining gains", and several countries are facing difficult prioritization decisions, including expansion of diagnosis and treatment to the private sector. Early indications are that countries are likely to maintain the scope and scale of their case management activities in the near term; however, many large programmes are projecting significant funding gaps in 2016 and 2017 *[18]*.

**Increasing recognition of the heterogeneity of malaria burdens**, both between and within countries, is stimulating discussion around developing new strategies that suit the increasingly complex epidemiology within a country as well as strategies for accelerating malaria elimination. Central to these discussions is **the importance of strengthening diagnostics capacity and surveillance systems** so that an accurate picture of the malaria burden can be used to assess the impact of interventions, to stratify countries by epidemiology and to customize responses accordingly *[3,20]*.

**New guidance from WHO on the role of molecular diagnostics in low transmission areas**. In December 2013, a WHO Evidence Review Group reviewed the evidence on diagnostics in low-transmission settings and made several new recommendations, which were approved by the Malaria Policy Advisory Committee in March 2014 *[21,22]*. Among the recommendations are:

- a reaffirmation of the use of RDTs and microscopy for diagnosing clinical malaria in all transmission settings;
- in low-transmission areas, after fully scaling diagnosis and treatment, more sensitive diagnostic methods may be considered for epidemiological research, surveys aimed at identifying submicroscopic infections, and for identifying foci of infection;
- standardization of protocols as well as development of quality standards and an international external quality assurance 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.

Today, 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. That said, the Evidence Research Group suggested that programmes considering adopting these more resource-intensive methods select one that is a "significant improvement" over expert microscopy *[22]*. The meeting also highlighted a number of evidence gaps, related to transmission and acceleration of elimination in low-transmission settings, which are needed to inform further guidance in this area.

In addition to these developments, forthcoming results from several initiatives are expected to further shape the malaria diagnostics market. These are noted below and will be reviewed in future editions of the UNITAID landscape.

- **Development of the retail private sector market for RDTs**: Several large-scale pilots, including the UNITAID-funded Population Services International (PSI) projects in five African countries and the Clinton Health Access Initiative (CHAI) projects in Kenya and the United Republic of Tanzania, are under way. These projects will report mid-term results in 2015. In addition, ACTwatch has been conducting private sector outlet surveys in several countries and is publishing results in late 2014 and early 2015. These and other operational research studies are expected to answer key questions related to private retail markets for RDTs that should inform programme design and potential large-scale investment in this area.

- **Global Fund**: Preliminary analysis of the impact of the Global Fund replenishment and the NFM on diagnostic budgets is expected by early 2015, as the majority of countries will have submitted applications for funding. This analysis will have important implications for future RDT demand, as donor funding has enabled rapid growth in recent years. The Global Fund Sourcing and Supply Management Department is also expected to revise its procurement strategy for malaria RDTs in early 2015. As the largest procurement mechanism for malaria RDTs, the changes may affect the market significantly.
- **POC G6PD testing**: WHO held an Evidence Review Group on G6PD testing in October 2014 and the Malaria Policy Advisory Committee will consider recommendations in March 2015. This meeting will focus on the use of qualitative POC G6PD tests to support primaquine use, in particular evidence related to the CareStart POC G6PD test. New WHO policy around POC G6PD testing would be a key step in developing the POC G6PD testing market and increasing access to radical cure for *P. vivax*.
- **WHO strategy**: WHO is developing several strategic documents, including a Global Technical Strategy for 2015–2030, which will likely be finalized for the World Health Assembly in mid-2015. The draft strategy sets out targets for the next 15 years *[20]*. It emphasizes the need to achieve universal coverage of core interventions such as diagnostic testing and highlights the importance of linking test results to real-time data systems so that decision-making can be aligned with country goals. WHO is also developing a strategy focusing on *P. vivax* that will include a technical brief on *P. vivax* and review of the many evidence gaps for *P. vivax* management. Complementing this are several thematic and country reviews. Altogether, this work is expected to highlight the burden of *P. vivax*, which is increasingly recognized as contributing to severe disease, and to underscore the need for increasing access to radical cure to *P. vivax*.

## Technology landscape updates

This section highlights changes to the malaria diagnostics technology landscape, which is discussed in detail in section five of the *2014 Landscape*.[5] As of August 2014, no new technologies have entered the market. This section is based primarily on information provided by developers of technologies. If technologies that appear in the *2014 Landscape* do not appear in this update, it is either because the developer did not provide an update or indicated that there were none at this time. For more information on each of the technologies below, refer to Annexes 2 and 3 of the *2014 Landscape*.

### Product development partnership updates

**Positive control wells (PCWs)**. The Foundation for Innovative New Diagnostics (FIND) has completed development and field evaluation of prototypes of PCWs, which are plastic tubes containing critical concentrations of dried down recombinant antigens (HRP2, pLDH, aldolase) that are reconstituted with water to allow RDT users to perform quality control of RDTs in the field. Results of field trials in the Lao People's Democratic Republic and Uganda are being submitted for publication before the end of 2014 and it is expected that PCWs will be commercially available, pending the following:

- evaluation of the preliminary PCW manufacturing runs in order to ensure equivalency or better performance to prototypes;
- development of marketing and distribution strategies for the PCWs as well as regulatory plans;
- development of a plan for monitoring use of PCWs in the public and private sectors.

In 2015, WHO is also planning to convene an Evidence Review Group on field-based malaria RDT quality control measures that will include a review of the PCWs developed by FIND and their partners, existing quality control methods used in the field and commercially available positive controls for RDTs. This group will also consider potential use scenarios for widespread quality control implementation.

5 Available at: www.unitaid.eu/en/resources/publications/technical-reports.

**Recombinant panels**. FIND is also developing recombinant panels for use in RDT quality control at national reference laboratories (lot testing) and for purchase by RDT manufacturers and developers (as reference samples). Piloting of these will begin in 2015 in the current lot testing laboratories in Cambodia and the Philippines and a final product is expected in 2016.

**Loop-mediated isothermal amplification (LAMP)**. FIND has completed development of the high-throughput kit for sample processing for LAMP. It is now doing tech transfer to a manufacturer and will start field evaluation (for population screening for detection of asymptomatic infections in at least three countries) in 2015.

**Infection detection test (IDT)**. The PATH DIAMETER (Diagnostics for Malaria Elimination towards Eradication) project has been working to build consensus on the technical specifications for elimination diagnostics, and has recently published an overview of use-scenario specifications *[23]* as well as a draft target product profile (TPP) for an infection detection lateral flow immunoassay (LFIA) (Table 1).[6] The proposed LFIA is a qualitative test for *Plasmodium falciparum* infections, intended for use in active infection detection interventions and for identifying the subclinical transmission reservoir. The form factor of the proposed product will have the look and feel of a traditional malaria RDT, and will detect very low concentrations of HRP2 antigen. This project is moving towards commercialization of a new test, with several work-streams, including discovery of an optimal capture and detection system, optimization on the LFIA platform and driving global consensus towards development of standardized references (HRP2 ELISA reference methods and recombinant proteins) for research and development (R&D) and quality assurance. The timeline is regulatory approval of a new test by 2017.

6 For the most recent and complete version of the TPP, see the PATH DIAMETER project website at: http://sites.path.org/dx/malaria/malaria-elimination/.

**Table 1. Summary TPPs for IDTs**

| Variable | Minimal requirement |
|---|---|
| **1. Design** | |
| 1.1 Format | Lateral-flow immuno-chromatographic strip in cassette format |
| 1.2 Target analyte | *Pf* HRP2 |
| 1.3 Sample type/collection | Peripheral whole blood from finger stick (heel prick for infants) |
| 1.4 Sample volume | 1–50 µl |
| 1.5 Detection | High-contrast, clear results for naked-eye, indoor and outdoor reading; reader compatible |
| **2. Performance** | |
| 2.1 Species differentiation | *Pf* only |
| 2.2 Analytic sensitivity / limit of detection | 100pg PfHRP2/ml in whole blood (recombinant HRP2 will be provided) |
| 2.3 Diagnostic / Clinical sensitivity | 95% on provided HRP2 panels |
| 2.4 Diagnostic / Clinical specificity | 90% on provided HRP2 panels |
| 2.5 Target shelf life / stability | 24 months at temperatures between 2°C and 30°C; stable for 2 weeks at 40°C |
| 2.6 Ease of use | One or fewer timed steps; instructions should include diagram of method and results interpretation |
| 2.7 Ease of results interpretation | Clear positive/negative readout in indoor and outdoor lighting conditions; language-appropriate instructions |
| 2.8 Operating temperature | 20°C to 35°C |
| **3. Regulatory** | |
| 3.1 Product registration path | • Target country regulatory requirements<br>• World Health Organization prequalified |

ml; millilitre
*Note:* This is an executive summary of the TPPs, revision 2.
*Source:* PATH.

## Malaria diagnostics technology developers updates

Disease Diagnostic Group, LLC (DDG), developer of the Rapid Assessment Malaria (RAM) portable haemozoin detection system, completed a field trial using its hand-held alpha prototype in Peru in February 2014. An updated version of the RAM device is now undergoing trials in India with Bosch Healthcare. Since the start of 2014, DDG raised the equivalent of a seed-stage financing round through awards and grants to support the technology's commercialization and is planning to engage further with clinical and commercial partners in the coming year.

Holomic LLC, maker of the Holomic Rapid Diagnostic Reader (HRDR-200) has launched a new version of the HRDR-200 with quick response code (QR code) capture and additional calibration features. It has also recently launched a fluorescent reader, the HRDR-300. This reader is available in both portable smartphone-based or bench-top versions and uses patent pending technology to analyse LFIAs. Both the HRDR-200 and HRDR-300 are currently in the process of CE (European Conformity) marking and United States Food and Drug Administration approval for POC applications. Holomic LLC has also developed a

software programme for test developers and RDT manufacturers. This application provides deeper insight into test data and reader calibration.

Intellectual Ventures has stopped work on the Dark Field Cross Polarization (DFxP) haemozoin detection platform. The decision was based on evidence, consistent with previous experience and confirmed by dark field imaging, that haemozoin is not present in detectable quantities in crystalline form in young ring-stage parasites *[24]*. Young ring-stage parasites are a significant proportion of forms found in peripheral blood during a *P. falciparum* infection, while late-stage parasites are commonly sequestered, reducing the proportion of parasites detectable by this method. Species differentiation is also limited when based on haemozoin. Intellectual Ventures, therefore, concluded that haemozoin would be a poor biomarker for malaria, especially at low parasite densities. Intellectual Ventures is now working to develop an antigen detecting platform for very low antigen concentrations/population screening use scenarios, adaption of nucleic acid amplification test (NAAT)-type platforms for near-patient use in screening, and digital imaging aimed at parasite quantification for research purposes.

Sight Diagnostics Ltd is developing Parasight, a computer vision platform for blood analysis and parasite detection. Malaria diagnosis is the first application, and Sight Diagnostics Ltd continues to advance the Parasight platform and is placing the device in large malaria pathology laboratories for customer validation in India and South Africa. The company has also recently completed a Series B fundraising round of US$ 5 million and has begun work on its next application, a complete blood count analyser.

## POC G6PD screening test updates

With the renewed interest in *P. vivax* and in malaria elimination, development of a POC G6PD deficiency screening test to support use of primaquine and tafenoquine (in development) is a priority. Generally speaking, product development concerns: (i) development of a POC qualitative test for use with primaquine; or (ii) development of a quantitative device that measures enzyme activity for use with tafenoquine.

There are many laboratory-based G6PD tests on the market, however, in addition to simplifying test procedures and instrumentation, developing a POC G6PD test requires overcoming environmental conditions (for both performing the test and for storing reagents) that cannot be maintained at the point of service. Currently, the CareStart G6PD RDT (AccessBio) is receiving significant attention due to its simplicity and stability: the test is similar in form and processing to a malaria RDT and can be stored and performed at relatively high temperature and humidity levels. Although several trials have been completed, not all results have been published. Experts suggest that the CareStart G6PD RDT performance is compatible with the fluorescent spot test, the most widely used qualitative laboratory-based screening test for G6PD deficiency. A WHO Evidence Review Group reviewed G6PD testing, including the CareStart G6PD test in late 2014. More details on this test are provided in Annex 1.

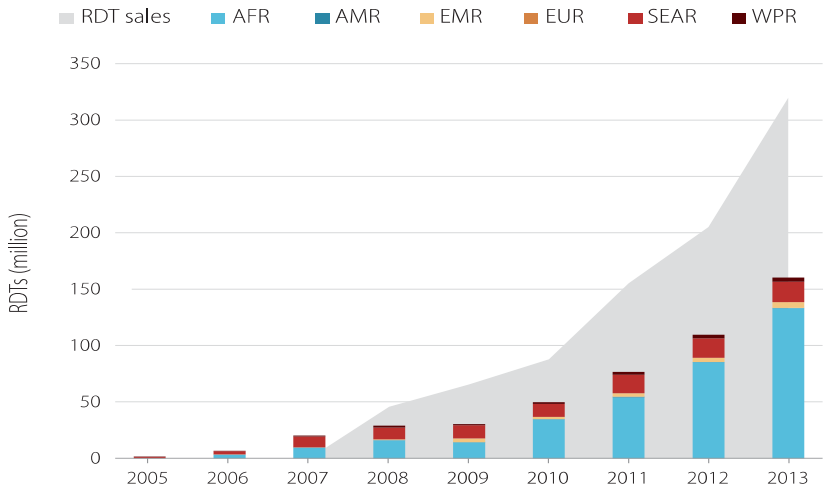
The PATH G6PD initiative has developed a TPP for POC G6PD tests, and is now supporting the development, clinical evaluation and registration of POC G6PD tests (late 2017 product availability), including development of a companion test for tafenoquine.

# Market landscape update

## RDT market size, prices and market share

The malaria RDT market has been growing rapidly, from 45 million tests sold in 2008 to 319 million in 2013 (Figure 10) *[1]*.

**Figure 10. Number of RDT sales to public and private sectors and number of RDTs distributed by NMCPs, by WHO region, 2005–2013**




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:* Manufacturer reporting to WHO. World malaria report 2014 *[1]*.

Although the total volume of tests has increased, the market value has not grown as rapidly due to declining unit prices.

Full analysis of procurement data was not done for this update, but will be repeated for the next edition of the UNITAID landscape. A limited procurement data analysis, supplemented by conversations with major RDT buyers and leading RDT suppliers, suggests little change in the pricing (Table 2) and market share trends identified in the *2014 Landscape*. In particular, low prices have precipitated supplier exit from the market and consolidation. In 2012, three manufactures comprised 90% of the market and, in 2013, four had 98% of the market. However, since one of the three highest-volume manufacturers procures semi-finished product from one of the others, 90% of the public sector supply is actually dependent on two manufacturers.

**Table 2. Weighted average test prices (US$) based on 2013 procurement data analysis**

| Type | 2012 (US$) | 2013 (US$) |
|---|---|---|
| *Pf* only | .37 | .32 |
| *Pf*/pan | .51 | .38 |
| *Pf/pv* | .44 | .50 |

*Source:* 2014 Malaria diagnostics technology and market landscape *[30]*.

Limited procurement data analysis conducted for this update included Global Fund Price and Quality Reporting (PQR) data for 2012, 2013 and half of 2014. The data set was downloaded on 29 July 2014 and included 236 transactions from 61 countries totalling 177 million RDTs. Analysis suggests:

- the market continues to be dominated by three companies: AccessBio; Alere (parent company for Standard Diagnostics/SD); and Premier Medical Corporation;
- *Pf*-only tests continue to be the most procured type of test by volume (although there may be changes of 5–10% year-to-year in the overall proportion of *Pf*-only versus combination tests);
- pricing is difficult to analyse given the limited data set and dominance of Global Fund Voluntary Pooled Procurement (VPP) transactions in some years; however, 2013 and 2014 averages seem similar to or lower than the averages reported in the *2014 Landscape*;
- low prices reported in the PQR are: US$ 0.21 for a *Pf*-only test; US$ 0.30 for a *Pf*/pan test; and US$ 0.36 for a *Pf/Pv* test;
- there continues to be large variance in pricing for similar products and order sizes.

An analysis of PQR data for RDTs, ACTs and long-lasting insecticide-treated mosquito nets (LLINs) was published in late 2013 *[25]*. This analysis included data from 2005–2012 and showed declining prices across all malaria commodities, although declines in RDTs prices were not as large as other commodities. This can be explained in part by the lack of differentiation in the analysis between test types: *Pf*-only RDTs are relatively less expensive than combination tests, however, combination test use likely increased during the period analysed. The analysis also suggests that VPP achieved lower pricing than other procurement methods and showed regional variation in RDT prices, with the cheapest pricing in Africa and Asia and much higher prices in Latin America. Again, analysis of pricing by test type may explain some of these differences.

## Malaria RDT products: quality and selection

Given the large number of malaria RDTs on the market, it is useful to look at the results of the WHO/FIND Product Testing Programme, which is the entry point to the public sector market, to gain a better appreciation for the range of products available and the number of manufacturers supplying the market.

**Selection of high-performing RDTs**. WHO released results of the fifth round of product testing in July 2014. A total of 147 unique products have been through the Product Testing Programme and many of them have been evaluated more than once. As of August 2014, official recommended RDT lists have not been updated. However, based on the authors analysis of the round five report *[26]*, the number of high-performing products meeting WHO recommendations for the most commonly procured tests remains high: there are 25 *Pf*-only tests (no increase) and 18 *Pf*/pan tests (an increase of 7 tests) available. However, for less commonly used test types, such as pLDH-based *P. falciparum* tests and pan-only-specific tests, selection remains limited.

**RDT performance in round five**. Results from round five were similar to those reported in previous rounds, with slight variations. Overall, a high level of performance has been observed for *P. falciparum* detecting tests, and performance of *P. vivax* detection has been improving steadily over the rounds *[26]*.

Recently, the Product Testing Programme began requiring manufacturers to resubmit their tests every five years in order to remain listed in the *WHO Product testing report* and to be eligible for WHO procurement. In this round, 10 products from 6 manufacturers were compulsory resubmissions. The performance of the majority of compulsory resubmitted products was comparable to previous performance, with a couple exceptions. One *Pf*-only product no longer qualifies for WHO procurement, however, this test is not commonly used in the public sector. One more commonly used combination test is now just (<1%) below the threshold; this product (made at a new manufacturing site) has been submitted for evaluation in the sixth round of testing.

**Number of suppliers entering and exiting the market**. The demand for product testing is one gauge of the number of suppliers entering and exiting the RDT market. For example, of the 15 manufacturers due for compulsory resubmission, 9 manufacturers did not participate and their RDTs (12 products total) are no longer listed in the product testing reports, suggesting that these companies have exited the RDT market.

At the same time, demand for product testing remains high as new companies attempt to enter the market. The sixth round of testing began in June 2014 and for the first time included a user fee. While the number of interested manufacturers is somewhat diminished, new companies are still submitting products.

**WHO Diagnostics Prequalification Programme**. As of August 2014, only Alere's SD BIOLINE *Pf*-only and *Pf*/pan tests are prequalified. The other formerly prequalified product was delisted as a result of its performance in the compulsory resubmission to round five of product testing. The WHO Prequalification Programme continues to process applications from five manufacturers (Span Diagnostics; Premier Medical Corporation; Alere; AccessBio; Orchid Biomedical Systems) *[27]*. The RDT suppliers undergoing the process report varying degrees of progress.

**mRDT (malaria rapid diagnostic test) Harmonization Task Force**. 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 Task Force, supported by researchers at the Institute of Tropical Medicine in Belgium, assessed the level of similarities and differences between malaria RDTs and identified opportunities for improving user-friendliness and harmonization of RDTs. The Task Force has made many recommendations concerning improved device labelling, packaging, accessories and instructions for use *[28]*. However, complete harmonization of RDTs requires changes to test procedures and was not considered feasible in the near term. The Task Force has submitted recommendations to the Roll Back Malaria Partnership Board and, pending approvals, next steps include working with donors, regulators, policy-makers, national malaria programmes, and manufacturers on implementation.

## Malaria RDT demand

### Public sector demand for RDTs

The public sector scale-up of RDTs is driving market growth, although it is more advanced in some countries than in others. Since the *2014 Landscape*, there has been little new information on public sector demand for RDTs.

Data reported by countries on RDTs distributed suggest that the vast majority of RDTs is deployed in the African Region (83%) followed by the South-East Asia Region (11%) and the Eastern Mediterranean Region (3%) *[1]*. Even with the rapid expansion of RDTs in the African Region, microscopy is also being scaled up: African countries reported performing 50 million microscopy slides in 2013, up from 33 million in 2010 *[1]*.

Conversations with RDT suppliers suggest that Asian markets might be slightly larger than WHO data suggest and that, in several Asian countries, the formal private sector for testing is quite developed. Overall, however, there is a bias towards microscopy in many Asian countries, resulting in fewer "high-volume" RDT customers compared to Africa. There are many explanations, including well-developed microscopy networks that pre-date RDTs, the need to follow up patients more closely to monitor response to treat-

ment/identify potential drug resistance and overall less confidence in RDTs. Despite this, in some countries, a significant number of people are not being tested, and there is an opportunity to expand the use of RDTs in Asia.

**Donors.** The Global Fund and PMI are the major funders of malaria RDTs and their policies influence the market greatly. Notable recent developments include:

- Changes to the Global Fund allocation and grant-making processes are still being implemented, and the impact on diagnostics budgets is difficult to assess at this time. It is likely that the RDT market's continued growth in 2013 is primarily a result of increasingly larger orders from countries that are continuing to scale public sector diagnosis using previously allocated Global Fund grants.
- The Global Fund Sourcing and Supply Management Department will be reviewing its approach to RDT procurement in early 2015 and it will be important to monitor how any changes affect the market.
- PMI has altered its procurement process by implementing framework agreements with several RDT manufacturers from its pre-selected RDT list. Among other things, these agreements establish ceiling prices for RDTs.

**Procurement methods**. The major public sector RDT procurement methods continue to be direct from manufacturer, through the Global Fund pooled procurement mechanism and through John Snow International (procurement agent for PMI) (Table 3).

**Table 3. Volume of RDTs procured by large procurers (in millions of RDTs)**

| Procurement method | 2012 | 2013 |
|---|---|---|
| Global Fund Pooled Procurement | 41 | 63 |
| PMI (fiscal year) | 29 | 52 |

**Product selection.** Product selection has not been systematically analysed and anecdotal information suggests that:

- Several countries have experienced problems with buffer solutions, and in at least one instance this has prompted a switch to more costly packaging of RDTs with individual buffer vials.
- Many national programmes are interested in multi-species tests, although there is debate about whether local epidemiology justifies these more costly and complex tests. However, other factors such as clinician confidence in test results (e.g. in the case of a negative *Pf*-only test, clinicians may suspect other species and treat for those) may influence these decisions.
- National programmes often feel pressure from donors to select the lowest priced RDT, despite it not being in-line with programme needs. In some instances, different RDTs may be provided to a country by different funding sources *[29]*.
- Countries often limit bidding to RDTs meeting more stringent requirements than the WHO recommendation of a 75% panel detection score. This likely contributes to consolidation of the market around products with the highest panel detection scores.
- Some countries have chosen to conduct RDT performance evaluations locally and compared RDTs to substandard microscopy, resulting in discrediting of high performing RDTs *[29]*.

### Private sector demand for RDTs

As the scale-up of diagnosis in the public sector progresses, many programmes are exploring development of the retail private sector markets for RDTs because the local retail shop is often the first stop for many seeking care for fever. Given the complexity and evidence gaps, developing these markets is proving to be a challenge *[30]*. Currently, at least 20 operational research and pilot projects are exploring the use of RDTs in the private sector. Many of these projects are expected to produce results in 2015.

Among the larger projects is a UNITAID-funded programme to develop private sector markets for RDTs, led by PSI with partners the Malaria Consortium, FIND, Johns Hopkins School of Public Health (JHSPH) and WHO. In Kenya, Madagascar and the United Republic of Tanzania, PSI is supporting direct marketing to customers to drive demand. In Nigeria and Uganda, the Malaria Consortium is contracting directly with malaria RDT manufacturers to provide a number of supplies and services and to undertake certain aspects of marketing and programmatic support. These projects began implementation in 2014 and mid-term surveys are being conducted (starting from October 2014–January 2015).

CHAI-led projects in Kenya and the United Republic of Tanzania began in June 2013 and January 2014, respectively. The CHAI programme aims to sell low-cost RDTs through the formal private sector without a subsidy. It includes negotiated RDT pricing with five malaria RDT manufacturers and agreements with local importers that limit margins. As of September 2014, 2.45 million RDTs have been procured by participating importers and 70% has been sold to nongovernmental organization programmes and on the open market (around 1 million RDTs sold to the open market) *[31]*. In the coming years, CHAI will continue to monitor the impact of the programme through a range of activities, including surveys to assess stocking and availability as well as price.

CHAI has also supported a pilot study in the United Republic of Tanzania on introducing RDTs in accredited drug dispensing outlets (ADDOs). The intervention began in April 2013 with dispenser training and the introduction of RDTs into ADDOs in two rural districts. In one district, dispensers were provided with a recommended selling price (~US$ 0.66 per RDT) and, in the second district, RDTs were subsidized (~US$ 0.30 per RDT). An adjacent third district served as a control. Endline data collection was completed in May 2014 and preliminary findings showed that introducing RDTs in ADDOs and training dispensers to properly perform RDTs resulted in increased diagnostic uptake and adherence to test results thereby increasing the probability of suspected malaria patients receiving effective treatment. At baseline, only 1% of surveyed shops had RDTs available; at endline, RDTs were found in 84% of participating ADDOs. In the intervention districts, two thirds of patients seeking treatment for suspected malaria (*and physically present*) were tested in the ADDOs and overall fever case management improved. At baseline, 38% of suspected malaria patients purchased an ACT. At endline, in intervention shops, 71% of RDT test-positive cases received an ACT, while 15% received another type of antimalarial; and 6% of patients that tested negative for malaria received an antimalarial. Subsidizing RDTs did not have a significant impact on diagnostic use among patients *[31]*.

PMI, PSI, the ACT Consortium and several academic researchers are also supporting programmes and conducting research on RDT introduction in the private sector. The ACT Consortium, CHAI, WHO and PMI are conducting a systematic review of both peer reviewed and grey literature on introducing malaria RDTs in the retail private sector and this review is expected in early 2015.

### Summary demand for RDTs

For now, the outlook for RDTs is relatively positive, with African countries reporting >200 million funded RDTs in both 2014 and 2015 *[18]*). However, it will be important to monitor country progress through the Global Fund NFM and to analyse the impact on programme budgets. It is possible that diminished funding will force countries to prioritize buying LLINs over case management, or ACTs over RDTs.

At the same time, there are significant gaps in knowledge about the use of RDTs. For example, there have been no new data on the availability of diagnostic testing at public and private outlets since the 2011 ACTwatch surveys. These outlet surveys are currently being repeated and should provide insight into stocking

and availability of RDTs in several large markets. In addition, while 319 million RDTs were sold in 2013, largely to the public sector, only 160 million were reported to have been distributed by national malaria control programmes (NMCPs) *[1]*. While some of the gap may be attributed to time lags, monitoring and evaluation of RDT use need improvement.

Assuming continued donor funding for diagnostics, public sector scale-up will be achieved in the coming years, and RDT market growth may slow. Growth through community-level case management and the retail private sector channels will likely be slower than growth to date unless significant efforts and investments are made. Currently, many challenges exist, among them regulatory and policy restrictions on who can draw blood and prescribe treatment as well as where RDTs and/or ACTs can be sold. As a first step to changing regulations, piloting of case management with RDTs by different providers and/or in different settings may be required.

## Malaria RDT supply

There have been no major changes in the supply of malaria RDTs since the publication of the *2014 Landscape*. Although there are 29 companies with one or more products meeting WHO criteria, the vast majority is not active in the public sector market, which has consolidated around three companies, one of which supplies raw materials to another, effectively leaving two manufacturers.

Achieving economies of scale is now a key driver of the malaria RDT business. For leading suppliers, capacity utilization (e.g. maintaining full scale production) and optimizing use of labour and inventory (both raw materials, intermediate and finished product) are key considerations and may influence bidding. For example, companies may elect a price that approaches or is below the cost of production rather than forego all income for a potential order in order to optimize production. In addition, low pricing is offered strategically in attempts to penetrate new markets that are considered growth markets. In other words, a low-priced bid is offered with an expectation that the country will elect to use the same RDT in the future[7] and that volumes will increase as the country scales diagnosis. While the initial year may be less profitable for an RDT manufacturer, as volumes grow profits should improve.

With respect to the retail private sector, the leading RDT suppliers generally have not been aggressively pursuing this market and have mixed feelings about current nongovernmental organization-sponsored programmes to develop it. Additionally, the downward trend in RDT pricing contrasts with the public health priority to invest in development of retail markets. This is primarily due to the need to engage and compensate local distributors to develop and support the retail sector. Given the dominance of international tenders in the malaria RDT market, manufacturers typically do not have a strong in-country presence and knowledge of local supply chains, in particular retail supply chains. As such, an RDT manufacturer would need to rely on local distributors who are familiar with local markets, consumers and supply chains. In light of current RDT pricing, profit margins for potential RDT distributors are limited and malaria RDT manufacturers report that it can be difficult to engage and keep the attention of local distributors on malaria RDTs.

## Elimination diagnostics markets

The size of elimination diagnostics markets is difficult to predict. There has been considerable refinement of the needs for these markets in the past year *[23]* and the active infection detection market[8] appears to be the largest "new" market segment emerging from these discussions. A 2014 PATH report focused on elimination markets, in particular for active IDTs *[32]*, and combined qualitative research with analysis of both published and unpublished data reported by NMCPs to WHO in 2012. Highlights include the following.

7 Countries often prefer to use the same RDT for several years due to the programmatic costs of switching RDTs (e.g. retraining a large number of health workers; dissemination of new job aids on performing the RDT). After an initial competitive bid, the Global Fund allows countries to sole source a product for up to three years. PMI also allows countries to procure the same product without competitive bids.

8 As countries move along the continuum from control to elimination, there is a shift in emphasis from detecting only clinical cases to actively seeking out and treating infections ("active infection detection") in order to reduce the malaria transmission reservoir in the community and thereby drive down transmission. Tactics vary, but usually involve teams of health workers visiting communities and testing individuals who may or may not be symptomatic.

**Existing market size**. The 34 eliminating countries (as defined by the University of California San Francisco Malaria Elimination Group[9]) performed an estimated 20.9 million diagnostics tests in 2012, comprising approximately 5% of the global malaria diagnostics market. The vast majority of the tests was microscopy, although RDT use was on the rise.

**Active infection detection**. Many programmes, both control and elimination phase, have a policy for active case detection, suggesting that there is a continuum from malaria control to elimination, and that some "elimination" tactics, such as reactive case detection, are not exclusive to elimination countries. Analysis of NMCP reporting to WHO suggests that the extent to which countries conduct active infection detection varies considerably although, with some exceptions, there is a general tendency towards an increasing proportion of active testing volumes compared to passive (i.e. testing sick people coming to health facilities) in the countries that are further along in the elimination process. There is also a wide variety in the annual volumes of tests used for active case detection. Volumes in Brazil are exceptional (nearly 1.5 million tests/year), but usually programmes reported significantly smaller volumes. In terms of diagnostic method, nearly all of the tests performed for active case detection in 2012 were by microscopy.

**Evidence gaps**. Malaria elimination is a rapidly evolving area; currently, many evidence gaps regarding optimal strategies for eliminating malaria are being explored. These gaps and the resulting lack of guidance make analysing the potential market for diagnostics to support elimination challenging. Among the key questions that will influence the market are:

- understanding the role of sub-patent, asymptomatic infections and their contribution to ongoing malaria transmission;
- identifying the optimal, most effective strategies for active infection detection;
- appreciating through improved surveillance the number and size of areas that have reached very low levels of transmission and high coverage of control interventions and are, therefore, considering active infection detection or other elimination strategies;
- appreciating the impact of highly targeted interventions (e.g. hotspots) on transmission;
- testing strategies for reducing transmission to very low levels in endemic countries thereby accelerating elimination, including revisiting the role of approaches such as mass screen and treat and mass drug administration for burden reduction.

9 WHO characterizes all countries by programme phase using a combination of epidemiological and operational criteria. In 2013, WHO classified 19 countries as in the elimination or pre-elimination phase with an additional 7 countries in the prevention of reintroduction phase *[2]*. The Malaria Elimination Group has a broader definition of "malaria eliminating countries" that is based on whether a country has adopted a strategy for elimination. At the time of the analysis, this was a set of 34 countries (Malaria Elimination Group website at: www.malariaeliminationgroup.org/resources/elimination-countries, accessed 8 September 2014).

## Market shortcomings

Table 4 summarizes the market shortcomings in the malaria diagnostics market and the primary reasons for these shortcomings.

**Table 4. Market shortcomings of the malaria diagnostics market**

| Category | Shortcoming | Primary reasons |
|---|---|---|
| Quality | QCs for RDTs do not yet exist; field-level quality largely unknown. | ■ Low awareness and prioritization among stakeholders and buyers, in particular, when the market was first developing.<br>■ Little incentive for private investment in development of RDT QC technologies.<br>■ Weak regulation of malaria diagnostics (e.g. regulations might recommend/require use of controls) in countries that consume RDTs. Limited post-market surveillance.<br>■ Technical complexity of developing controls. |
| Quality | Limited knowledge of quality at the RDT manufacturing level. | ■ Weak regulation and oversight in countries that consume or produce RDTs.<br>■ WHO prequalification process is lengthy.<br>■ Limited experience of RDT manufacturers with stringent regulatory requirements.<br>■ Market has limited ability to assess quality systems at the manufacturing level, limiting incentives for suppliers to invest.<br>■ Low awareness and prioritization among stakeholders and buyers, in particular, when the market was first developing. |
| Delivery | Concentration of suppliers creates risk of supply disruption due to supplier exit from the RDT market; production or quality problems at a single manufacturer. | ■ Low prices, approaching cost of production, have led to supplier exit and market consolidation.<br>■ Leading suppliers have sufficient production capacity, however, there is risk to global supply if one supplier has quality or capacity problems.<br>■ Uncertainty around scale-up of manufacturing quality systems commensurate with rapidly scaling production and short lead times.<br>■ Uncertainty about the effects of cost reduction on product quality and market might not detect changes in product quality. |
| Delivery | Insufficient uptake of RDTs compared to need. | ■ Limited demand for RDTs; low awareness and acceptance of tests in some areas.<br>■ Implementation weaknesses, e.g. weak supply chain management; inadequate health-worker training; lack of supervision/QA.<br>■ Potential funding reductions for malaria may limit scale-up in the future.<br>■ Information gaps, mainly limited monitoring of the testing scale-up and its impact, due to weak reporting systems. |
| Delivery | Limited market for quality RDTs in the private sector. | ■ Low awareness among consumers and supply chain actors.<br>■ Low availability in retail outlets due to low awareness and little pull from potential customers.<br>■ Limited margin/incentive to stock RDTs for some supply chain actors.<br>■ Local regulations may prohibit diagnosis or follow-up treatment.<br>■ RDT (and subsequent treatment) prices may be unaffordable.<br>■ Where RDTs available in the private sector, quality may be unproven.<br>■ Limited market knowledge upon which to make decisions about developing these markets. |
| Delivery | Inadequate malaria surveillance. | ■ Historically, limited use of diagnostics led to poor quality surveillance data and, therefore, low prioritization.<br>■ New guidance released in 2012 *[33,34]*, but implementation is slow/weak, e.g. need for coordination across different departments of health systems.<br>■ Limited use of digital/information technology (IT) solutions. |

| | | |
|---|---|---|
| Availability | No tests for elimination settings, to support diagnosis and treatment of *P. vivax*, and for pregnant women. | ■ Limited work to define the needs or market for new products.<br>■ Demand for some new products may be low and fragmented.<br>■ Current RDT market conditions may be a disincentive for investment in malaria diagnostic test R&D.<br>■ Limited philanthropic and private funding for R&D. |
| Acceptability | Low acceptance of RDTs. | ■ Lack of alternative diagnosis for non-malaria fever due to lack of training, protocols and tests to assist with differential diagnosis of fever.<br>■ Low availability of commodities for non-malaria fever.<br>■ Low awareness of declines in malaria prevalence.<br>■ Mistrust of RDTs (concern about heat stability, limit of detection, possibility of other species when *Pf*-only tests used); lack of QC for RDTs. |
| Adaptability | Poorly adapted RDTs; while today's RDTs are a great improvement over microscopy in terms of adaptability, there is room for improvement. | ■ Specifications for improvements have only recently been developed, not yet widely communicated. |

## Opportunities for market interventions

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

### Market interventions: works in progress

There has been a significant increase in malaria diagnostics market-shaping work in recent years. A number of projects that address the market shortcomings described above are already under way or are planned for the near future. The progress is notable; however, in many areas, there is scope for additional work or refinement of existing programmes. Table 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<br>■ CHAI<br>■ Various pilots and operational research efforts (e.g. PMI, ACT Consortium, University of California San Francisco/Society for Family Health) |
| Transition product and lot testing to more sustainable business model, including development of recombinant QC panels | Quality | ■ FIND<br>■ 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<br>■ Institute of Tropical Medicine (Belgium) |
| Development of IDTs for elimination settings | Availability | PATH |
| Development of POC G6PD tests | Availability | PATH |
| Analysis of the market for malaria RDT raw materials (monoclonal antibodies/MAbs) | Market intelligence | William Davidson Institute |
| ACTwatch II: monitor uptake of ACTs and diagnostics | Market intelligence | PSI |
| ACT and RDT forecast | Market intelligence | CHAI, IMS Health, and the Global Health Group, University of California San Francisco |

## Market interventions: new opportunities

Several examples of potential new opportunities for market intervention are described below; noting 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.

- 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. Reliance on a few donors presents an opportunity for coordinated action, and discussions with the Global Fund procurement group indicates that they are considering new approaches to RDT procurement. 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 is the differences between malaria RDTs: while malaria RDTs are more interchangeable than other diagnostics, they are not completely interchangeable. The Harmonization Task Force work suggests that in the near term it is not feasible to completely align RDTs *[18,28]* 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 in the market, to support long-term sustainable pricing and to promote investment in quality and innovation (e.g. investment in meeting WHO prequalification standards; implementation of RDT Harmonization Task Force recommendations; development of the retail private sector; development of new technologies such as for *P. vivax* management and elimination settings).

- A programme (e.g. fund; incentives; funding restrictions) to achieve the appropriate RDT and ACT ratios would aim to accelerate growth in demand for RDTs thereby **correcting the size of the RDT market relative to ACTs and to generate market information on the appropriate ratio of diagnostics to medicines**. The additional market intelligence generated through this project would have far-reaching impact for both the market (e.g. more reliable commodity forecasts) and public health (e.g. by allowing programmes to monitor the impact of diagnosis scale-up and to tailor to interventions based on need).
- The **scale-up of diagnostics in the private sector** also represents an opportunity to support greater access to malaria diagnosis. In the near term, work to fill the evidence gaps is needed, through accelerated sharing of information generated by existing projects as well as supporting work to address remaining knowledge gaps. Regulatory and policy barriers at the country level also need to be addressed, and these may require local pilots to generate evidence. Currently, much of the focus has been on developing African retail markets for RDTs, however, given the important role that the private sector plays in many Asian countries, efforts to develop these markets might also be considered. Later, as large-scale retail programmes develop, additional funding will be needed. While it is not clear whether an RDT subsidy will be required, substantial catalytic investments in demand-generation activities and supply chain incentives will be required to assure RDT availability. Other components, such as communications campaigns, training and supervision, quality assurance (QA), and monitoring and evaluation, will be ongoing and require considerable support.
- With respect to quality, **stronger incentives for upstream quality are needed**, as are new technologies for conducting quality control (QC) at the POC. Upstream interventions might include strengthening programmes such as WHO prequalification or adoption of alternative standards. This could be coupled with technical assistance to RDT manufacturers to ensure that a number of them achieve the quality standards within a reasonable timeframe. With so few prequalified products, no large procuring bodies currently give preference to prequalification status, limiting the incentive for manufacturers to aggressively pursue prequalification. Assuming consensus can be reached on a standard for manufacturing quality systems (e.g. WHO Prequalification Programme) donors and procurement groups could indicate when they might give preference to products meeting this

standard, sending a stronger signal to the market of the relative importance of quality systems. **Support for the use and scale-up of PCWs**, when they are available, would address the currently limited information on RDT quality in the field, address concerns about RDT heat stability and potentially contribute to increased acceptance of RDTs.

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 quality control procedures and development of an international external quality assurance programme. Since molecular methods are increasingly used in epidemiological surveys and in research, it is becoming important to standardize their use so that results are reliable and can be compared across laboratories.

In the longer term, **strengthening regulatory capacity** for malaria RDTs at the country level would support 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 quality control programmes (e.g. post-market surveillance in regional reference laboratories) could also streamline work and reduce costs *[35]*.

- In terms of unmet needs, work is under way to **stimulate product development of diagnostics to support radical cure of *P. vivax* and for diagnostics to support elimination**. As the current efforts are early in the product development pathway, there is scope for intervention along the value chain. The market for *P. vivax* interventions is potentially large, yet complex because a variety of commodities are needed to support radical cure (e.g. accurate *P. vivax* diagnosis; POC G6PD screening tests; medicines to treat blood- and liver-stage infections). The market for elimination is likely more fragmented and still somewhat undefined due to ongoing operational research on active case detection strategies for elimination. In addition to monitoring these landscapes, potential near-term opportunities to engage upstream include: (i) catalysing development of products for improved *P. vivax* diagnosis; (ii) facilitating market entry of POC G6PD tests; and (iii) supporting operational research around the role of diagnostics in active case detection. As product development progresses, support for product validation (e.g. access to well-characterized samples and clinical trials networks; consensus on and development of validation standards), policy endorsements and quality registrations could decrease timelines. As new diagnostic tests come on the market, there likely will be scope for market creation work, possibly initial co-funding of procurement to achieve optimal pricing and to stimulate scale-up of manufacturing. Going forward, it will be important to monitor the various initiatives and developments in these areas.
- Improving **surveillance and fever management** are high priorities in the malaria community and there also might be scope for market interventions in terms of increasing use of technologies for streamlining reporting and analysis of surveillance data, and for supporting commodity access for fever management. 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).
- Lastly, there are a number of **market intelligence projects** that would be meaningful to markets and provide public health value. Among the highest priority are: (i) initiatives to monitor diagnostics access and targeting of ACTs; (ii) work to develop information on the retail market for RDTs; and (iii) improving the completeness of procurement data. At the country level, systems for monitoring test usage and quality issues and to improve the overall estimates of malaria incidence are needed. Finally, to stimulate product development for unmet needs, analysis of potential demand is needed.

## Conclusion

While scale-up of RDTs in the public sector continues, and there has been some notable progress in the development of new technologies and in retail markets for RDTs, several important challenges threaten the long-term health of the malaria diagnostics market.

First, while current RDT prices have enabled expansion of testing, the long-term sustainability of the market is an urgent concern. The market has consolidated around two manufacturers, creating risk to supply security. Conditions also create a disincentive for manufacturers to invest in priority areas such as development of retail private sector markets, meeting the RDT Harmonization Task Force recommendations or investing in WHO prequalification. Additionally, although the market's rapid growth is attractive, these conditions may deter investment in innovation at a time when the next generation of diagnostics for elimination and *P. vivax*, in particular, is needed.

Second, the current market conditions also underscore the importance of monitoring product quality through existing quality initiatives, such as product and lot testing. Similarly, work to fill gaps in the quality control continuum should be prioritized and accelerated where possible, mainly improving incentives for manufacturing quality systems and development of field-level quality control programmes.

A third challenge relates to the urgent need for data to assess the extent to which different market segments have been penetrated (i.e. the need for testing, test availability and use) and what impact RDTs are having on care, including targeting of ACTs. Additionally, the impact of changes at the Global Fund on case management budgets (at the public, private and community levels) should be closely monitored in the near term, and new resources identified to fill gaps so as to maintain the current momentum in public sector scale-up. Given their complexity, demand from the private and community sectors likely will be slower to emerge and more incremental than public sector demand, especially without large, targeted efforts and investments to support development of these markets.

Lastly, with respect to new technology development, while there has been progress in some areas, it is not clear that the current pipeline meets all gaps equally. For example, current efforts focus largely on *P. falciparum*, while improvements to the limit of detection for *P. vivax* tests are needed for case management and elimination. Similarly, it is possible that new more sensitive tests developed for elimination markets may have application in screening pregnant women for malaria, but no concerted efforts exist to develop tests for this use. Market intelligence is also critical to better define the potential markets for new products that will inform the business case for investment in these areas, inform the operational research agendas and identify possible market interventions that would accelerate development and access to new diagnostics.

Preliminary analysis suggests that the markets for new diagnostics are likely to differ from malaria RDT markets in many ways. For example, POC G6PD tests have applications beyond malaria, including newborn screening in some countries. Demand for tests to support elimination is likely to be low and fragmented compared to the RDT market, which may result in higher pricing to cover costs of R&D, manufacturing and distribution. In addition, the number of manufacturers entering these markets may be limited, resulting in limited price competition. Market interventions in these areas may include developing standards to assess quality and performance, similar to what has happened in the malaria RDT market. However, it is also likely that affordability and distribution challenges (i.e. availability of tests in smaller markets) may differ substantially from the malaria RDT market and require different approaches.

# Annex 1

## CareStart G6PD RDT (AccessBio)

AccessBio (New Jersey, United States), a leading manufacturer of malaria RDTs, has developed a G6PD RDT that is intended for use at the POC. The G6PD RDT is similar in terms of processing and format to malaria RDTs. The test is currently on the market and has undergone several clinical evaluations, although not all have been published yet. AccessBio also has developed a quantitative G6PD biosensor device that is expected to be released in the coming year.

### Table A1.1 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. |
| **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:<br>■ 12-month shelf life with recommended storage temperature of 4–30 °C;<br>■ a range of assay temperatures (18–32 °C) is acceptable. |
| **Testing protocol** | Testing protocol: (i) collect blood sample; (ii) transfer 2 µl 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. |
| **Availability** | Currently available; several clinical trials completed, although not all have been published. |

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