

THE STATE OF THE

MALARIA

RDT

MARKET

2018

CONTEXT

Malaria diagnosis is a cornerstone of malaria control and elimination. When rapidly diagnosed and treated appropriately, infected patients recover quickly. Since 2010 the WHO has recommended testing before treatment, (1) and in the past eight years access to diagnostic testing has grown significantly, especially in the public sector. In 2010 the testing rate among suspected malaria cases in the Africa public sector was 36% and by 2017 it was 82%. (2)

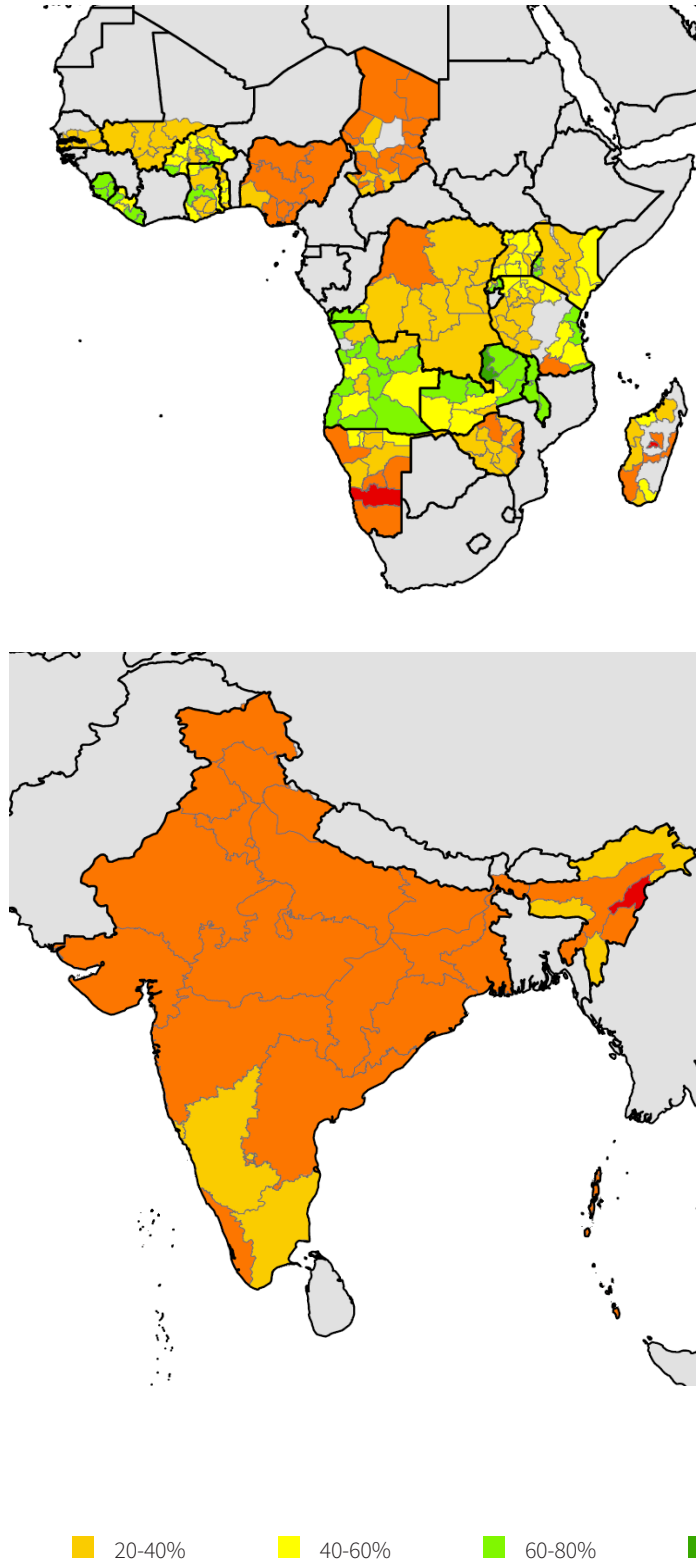
Yet, household surveys still show an estimated 70% of febrile children under five in Africa not being tested (3; 2) (Figure 1), and although testing in public facilities has increased, 40% of febrile children are not brought for any treatment. (2) Among those who do seek care, only 52% are taken to a trained provider¹ where testing is relatively common (61% are tested). Testing rates are very low among other providers, for example 11% of febrile children taken to a pharmacy or the informal private sector are tested. (2)

Closing the gap in testing will not be possible without greater attention to channels outside of the public sector, including the formal private sector, retail settings, and the community level. The relative importance of each of these channels varies from place to place, and hence the strategies for increasing testing rates must be tailored to the local context.

With the current level of investment and coverage of interventions, countries are not on track to reach the WHO Global Technical Strategy targets of reducing incidence and deaths by 40% by 2020. (2) While deaths are declining, incidence has plateaued, and the gains are not sufficient to reach targets. Against this backdrop, quality case management – diagnosis and treatment – is a critical intervention.

1 Such as health workers in public facilities, formal private sector, or community health workers.

FIGURE 1 Proportion of children under 5 who received a diagnostic test among those who had fever and for whom care was sought.



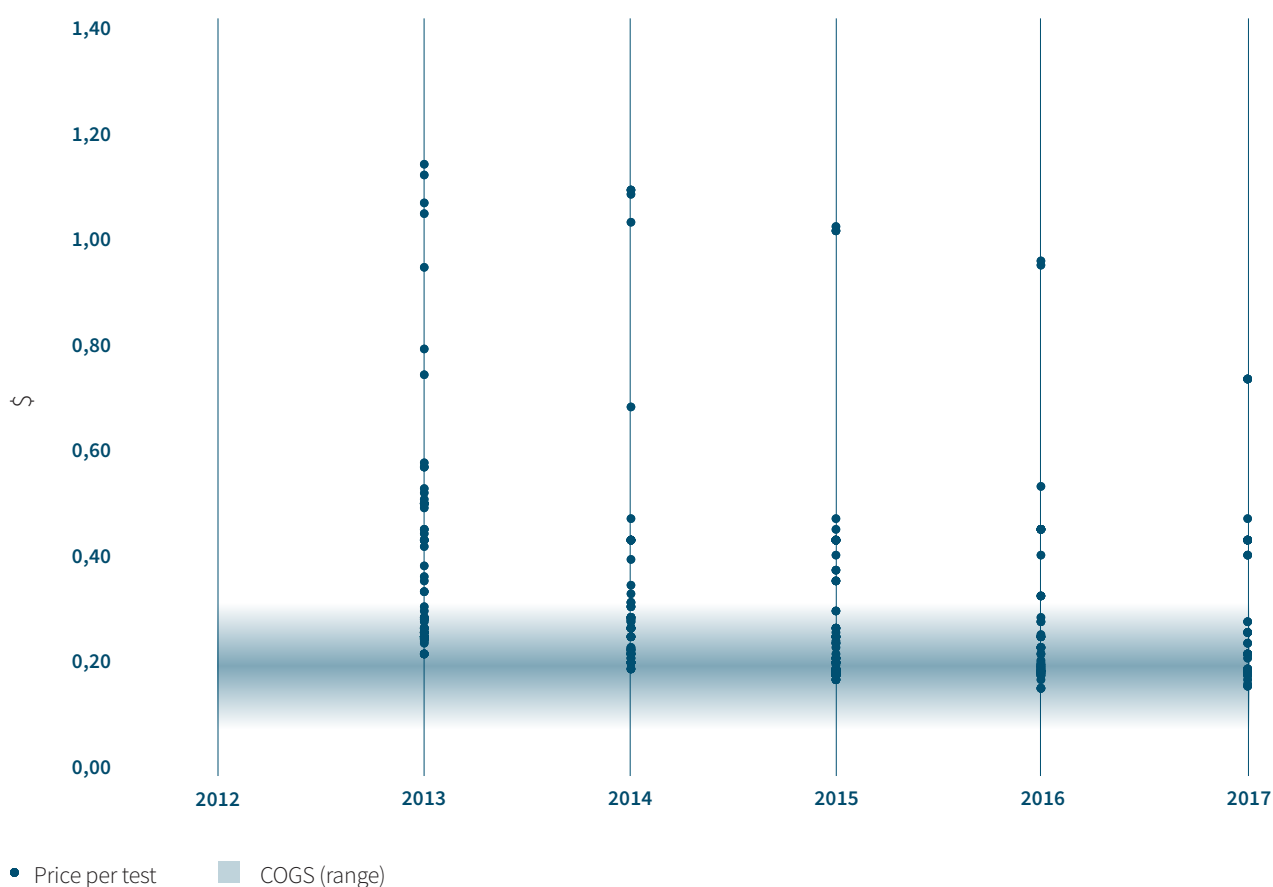
Source: WHO and Fatima Suleman et al. based on household surveys.

MALARIA RDT MARKET: KEY INDICATORS

Malaria RDTs have made a tremendous contribution to the scale up of diagnosis and effective malaria case management, and ensuring RDT quality and delivery has been a major focus of the WHO, donors, and partners.

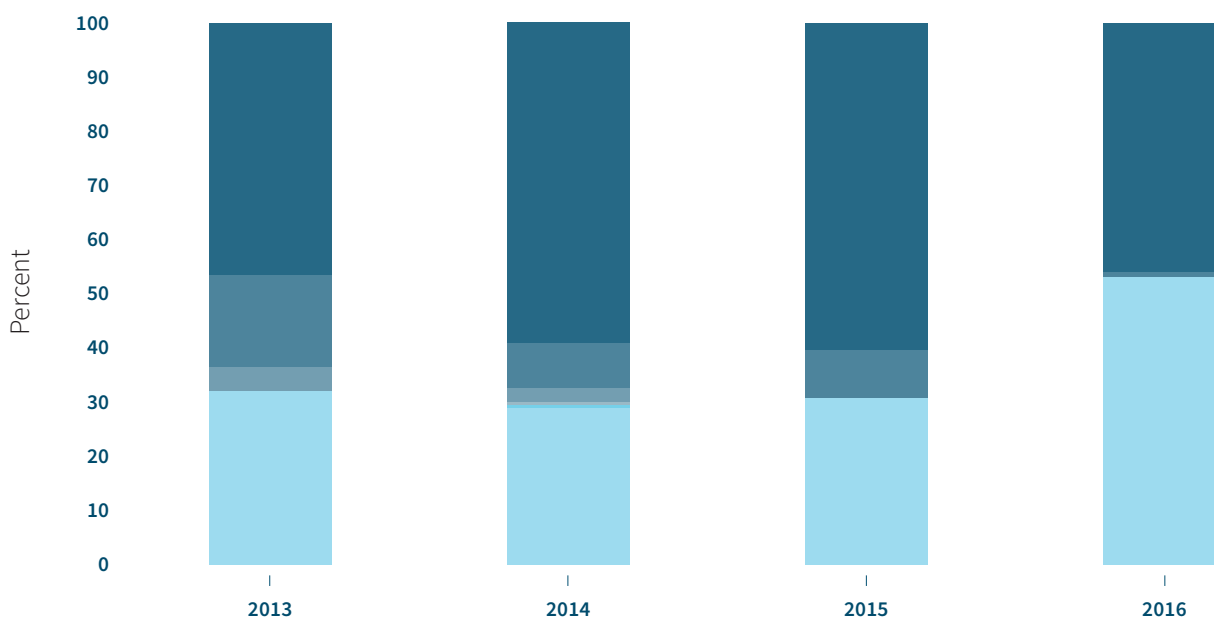
However, several indicators suggest that the long-term health of the market is at risk. Recent public sector procurement data shows that little progress has been made in addressing key market challenges: prices at low, unsustainable levels and market consolidation around two manufacturers, putting supply security at risk (Figures 2 and 3). While these trends are not new (4) (5), their persistence jeopardizes progress made to date in scaling up quality diagnosis and case management. These conditions have resulted in exclusive reliance on a single supplier for a key product, and a general failure of the pipeline to keep pace with emerging demand.

FIGURE 2 Malaria RDT prices have decreased (hospital packs *Pf*-HRP2 RDTs)



Source: analysis of PMI and Global Fund procurement data by Theodoor Visser, CHAI, for the RDT Procurement Task Force. Supplier interviews.

FIGURE 3 Market share by supplier: the market continues to be dominated by 2 suppliers, comprising 85% or more of the RDT volumes since 2013



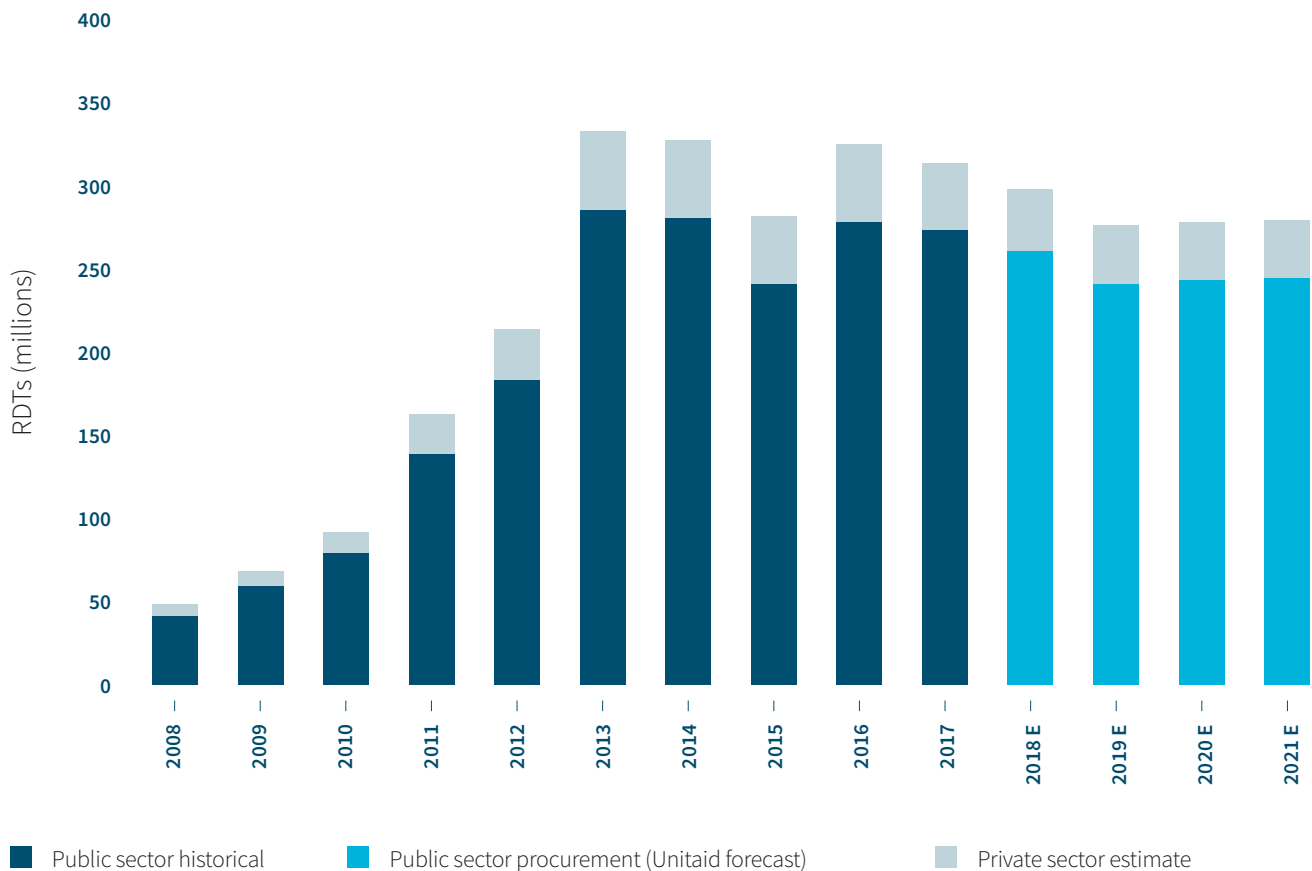
Source: analysis of PMI and Global Fund procurement data by Theodoor Visser, CHAI, for the RDT Procurement Task Force.

DEMAND

RDT market size

After years of growth, malaria RDT volumes have plateaued, and the future market size depends heavily on available funding for public sector malaria programs. The last Unitaïd forecast projected a contraction of the public sector RDT market in proportion to declining resources for malaria programs overall. (6) Indeed, national malaria programs are facing difficult prioritization decisions among core interventions given the smaller funding envelopes. However, experience to date suggests that when budgets are limited, programs do prioritize commodities for public sector case management, including RDTs, but they often do not sufficiently fund programmatic components, such as training and supervision. (7) In light of this relative prioritization of case management, it is reasonable to project global malaria RDT volumes (public and private sectors) in the 300-350 million range for the coming years. (Figure 4).

FIGURE 4 RDT market size and projections for future (by volume)



Source: WHO World malaria reports, estimates of RDTs supplied by manufacturers not reporting to WHO; Unitaid ACT/RDT Forecast.

While new strategies for reaching populations outside the public sector are urgently needed if global targets are to be met, these will be slow to materialize in an environment of declining funds. In the current round of Global Fund grants integrated community case management (“iCCM”) has been prioritized over private sector case management (7). Of 21 high burden countries in Africa, 12 have iCCM programs covering more than half of the districts/regions in the country and 6 have more focal programs. Despite this, household surveys indicate that 3% of febrile children were taken to community health workers, where approximately half are tested. (2) Although iCCM is expanding, given the difficulties in establishing and funding community programs, their growth is slow, and hence they are not expected to contribute significantly to malaria RDT volumes in the near term.

In several higher burden countries, many patients seek care in the retail private sector, a channel that distributes a large proportion of anti-malarial medicines. Outside of pilot programs, testing is seldom conducted in retail outlets. Among projects to develop these markets was a \$30 million Unitaid supported pilot project in Kenya, Nigeria, Madagascar, Tanzania and Uganda that ended in 2016. Overall, these pilots and other studies

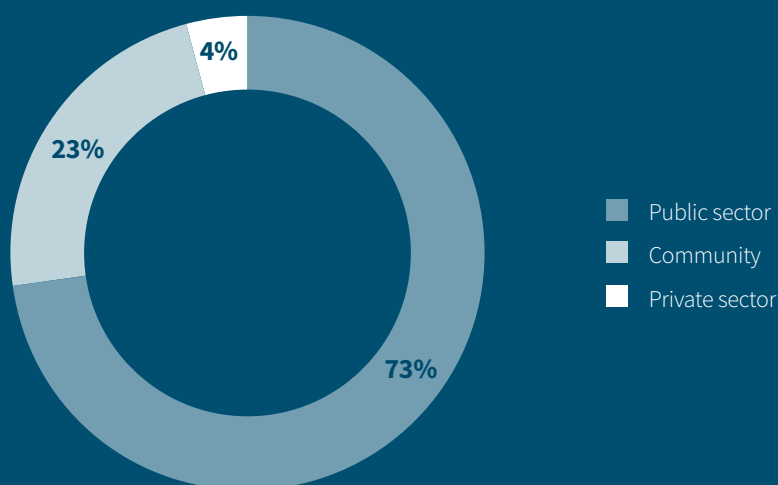
demonstrated that with training and oversight, the quality of testing and fever case management in the private sector is similar to that of the public sector. Additionally, while some markets required subsidy, in others catalytic investments to increase the supply of RDTs in retail outlets and to generate demand resulted in development of private markets not requiring RDT subsidies. The pilots also made progress in generating the evidence required to enact national policies and regulations conducive to malaria testing in retail outlets. However, RDT use in the retail private sector is far from being well-established: additional market development work is needed. For example, depending on the country, needs may include additional evidence to support policy and regulatory change, demand generation, and supply chain priming. Moreover, even when a subsidy is not required to ensure affordability of RDTs to consumers, on-going programmatic oversight from Ministries of Health will always be needed. For example, monitoring and evaluation, provider training, supervision, and quality assurance in retail settings.

BOX I

Public, private and community level use of RDTs

A review of data from 53 Global Fund supported countries (June 2018) indicates that of the RDTs financed in 2018, 4% were intended for the private sector and 23% for community level testing. Despite the relatively low proportion of RDTs intended for private sector and community use, over half of countries have included some funding for RDTs in the private sector and three-fourths include RDTs for community level use in their budgets.

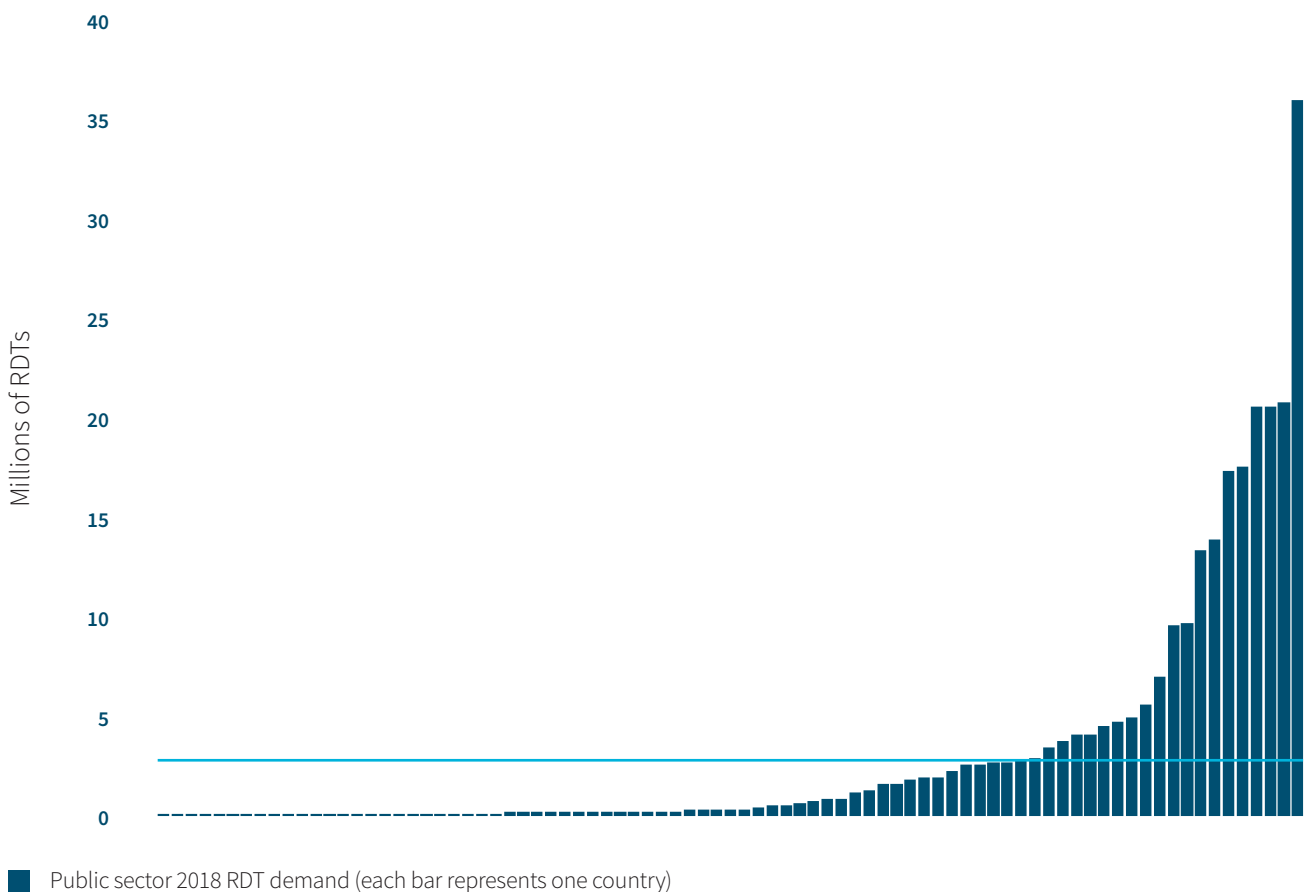
RDTs financed 2018 (53 Global Fund supported countries)



Source: RBM/ALMA compiled data for 53 countries from GF grants and NSPs. June 2018. Data here for 2018, but data are representative of 2019 and 2020.

There is quite a range in the relative proportion of RDT vs microscopy use in countries, and a range in the size of RDT demand across countries. (Figure 5). Sixteen countries comprise 80% of global malaria RDT demand and, with the exception of India, they rely heavily on RDTs for malaria diagnosis. On the other hand, half of malaria endemic countries use fewer than 1 million RDTs a year, either because the population at risk is smaller or because they deploy them sparingly, primarily at the community level. Many of the latter rely heavily on microscopy, due to large installed bases and established networks; a policy of following up patients who receive treatment to ensure parasite loads are declining (which can only be performed by microscopy); or concerns about the performance of RDTs. (8)

FIGURE 5 Estimated public sector 2018 RDT demand for 83 countries compared to mean value (light blue line) of 3.2 million



Source: analysis of RDT demand for the RDT Procurement Task Force.

Shifting demand for test brand and type

Although the malaria RDT market size is relatively constrained by funding, demand for specific tests is shifting due to broader trends and events, including: greater acceptance of RDT interchangeability, increasing focus on both malaria elimination and *Plasmodium vivax* (*Pv*), and the emergence of HRP2 deletions in Africa.

Greater acceptance of RDT interchangeability and competition

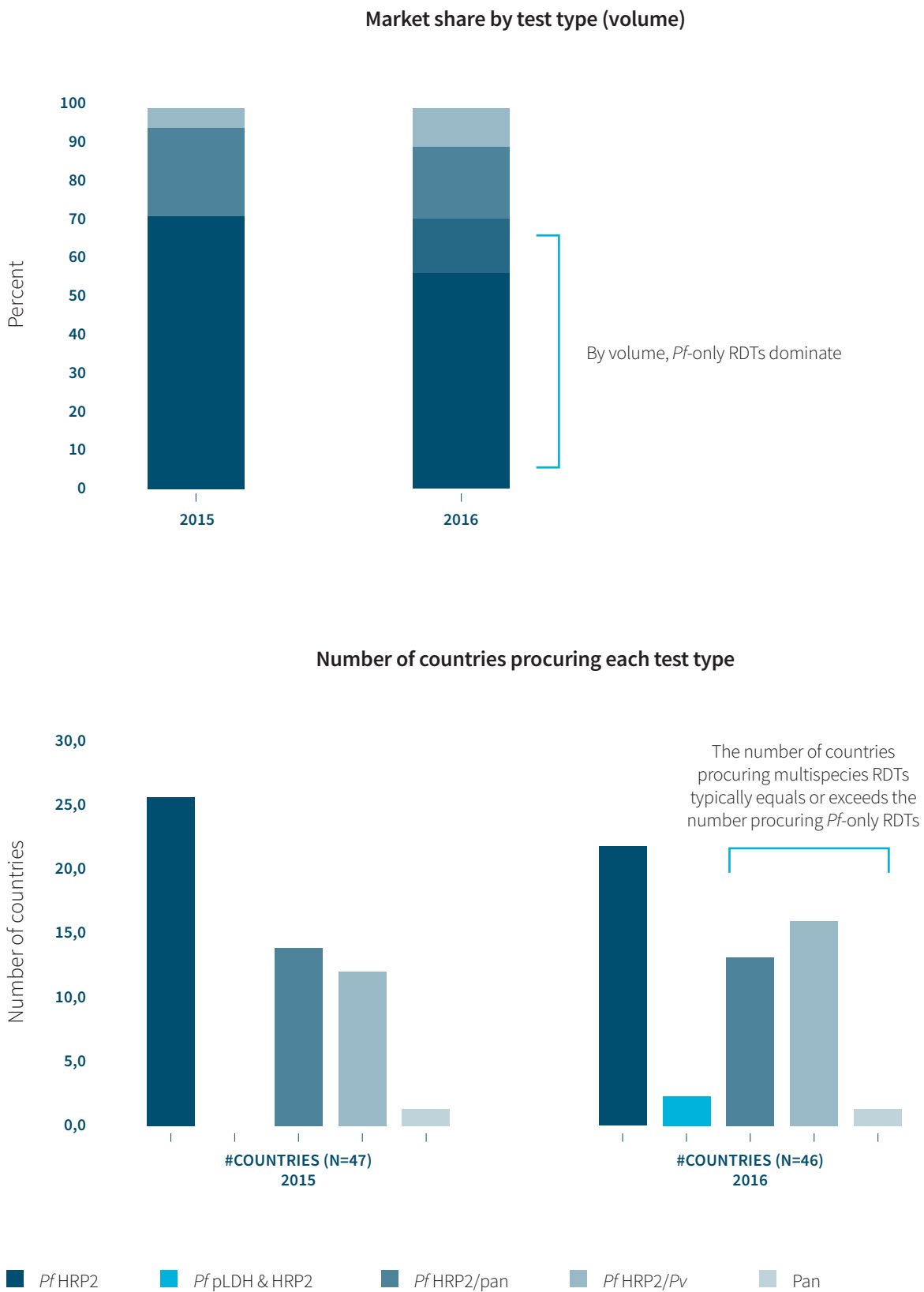
Most health workers now have several years of experience with RDTs, including use of multiple brands and test types. Procurement data and recent surveys indicate that many countries have been using multiple brands concurrently (9) (10), and that for the most part, operators use tests correctly, despite variation in test protocols (e.g. different wait times, drops of buffer) (11). As the interchangeability of RDTs becomes more widely accepted, the expected market implication is increasing competition for RDTs resulting from decreased sole-sourcing - a practice often justified by prior experience with a specific RDT. For example, in March 2018 the US President's Malaria Initiative (PMI) announced that it would severely limit country requests for specific malaria RDTs unless justified epidemiologically. To support this policy change, PMI provides directed technical assistance to countries around development of generic training materials, job aids, and training practicums that include several brands of RDTs. Anecdotally, the Global Fund Pooled Procurement Mechanism (PPM) has found that even when countries request a specific RDT, they may be willing to consider alternatives if substantial cost savings are possible.

Multi-species detection

While *Pf* HRP2 only RDTs dominate the market in terms of test volume, many countries contend with multiple malaria species and therefore over half of countries procure multispecies tests, but typically in lower volumes than *Pf* HRP2-only tests. Of multispecies tests, currently *Pf* HRP2/pan RDTs have a greater market share than *Pf* HRP2/*Pv* RDTs (Figure 6), although the number of countries procuring each is not as disparate.

Predicting which type of multispecies RDT a program will select is difficult: while some prefer a test with a pan line to ensure coverage of *all species*, others select *Pf/Pv* tests in order to identify patients needing primaquine. Going forward, with the increasing emphasis on *P. vivax*, and introduction of tafenoquine, programs are likely to focus on improving the rate of radical cure and as a result will shift from RDTs with a pan line to RDTs with a *Pv* line. This is also creating demand for more sensitive *Pv* RDTs, as *Pv* infections often present with low parasite densities and the limit of detection for *Pv* RDTs is not as good as that of HRP2 RDTs. (12) However, since many of the countries where *Pv* is present have a long history with microscopy and often a preference for it, (8) the overall market effect is likely to be modest.

FIGURE 6 RDT types: market share by volume, number of countries procuring



Source: analysis of PMI and Global Fund procurement data.

Elimination

Efforts to eliminate malaria are creating demand for highly sensitive RDTs to detect subclinical infections; however, in the near term this market will be a niche. Currently, the main potential use scenario for these tests is active case detection (ACD)², and while many countries perform some ACD, the resource intensive nature of ACD usually limits the overall scale of activities. The countries where ACD is relevant generally require multispecies diagnosis, and there are no highly sensitive multispecies RDTs on the market yet (see Innovation section below). Additionally, many of these countries rely heavily on microscopy for malaria diagnosis, even using it for ACD despite the operational challenges. Until multispecies highly sensitive RDTs are available, this preference for microscopy is unlikely to change. (8)

HRP2 deletions

The most commonly used RDTs for diagnosing *P. falciparum* malaria are based on detection of HRP2 (and in some cases the related HRP3 protein³) which is specific to *Pf*. Ten years ago, researchers discovered *Pf* parasites in the Amazon region that lacked the genes that encode the HRP2 and HRP3 proteins. More recently, researchers and programs in other countries have reported parasites with HRP2 and HRP3 deletions.⁴ The frequency and distribution of deletions are not yet fully understood, but, in some countries the incidence threatens the usefulness of HRP2-only RDTs.

The WHO Global Malaria Program (GMP) has responded with specific advice for conducting investigations of suspected deletions and has developed a global response plan. WHO also recommends use of alternative RDTs in countries where prevalence of HRP2 deletions exceeds 5% among symptomatic patients. (13) As a result, demand for RDTs that do not exclusively rely on HRP2 for *Pf* detection is expected to increase in the coming years.

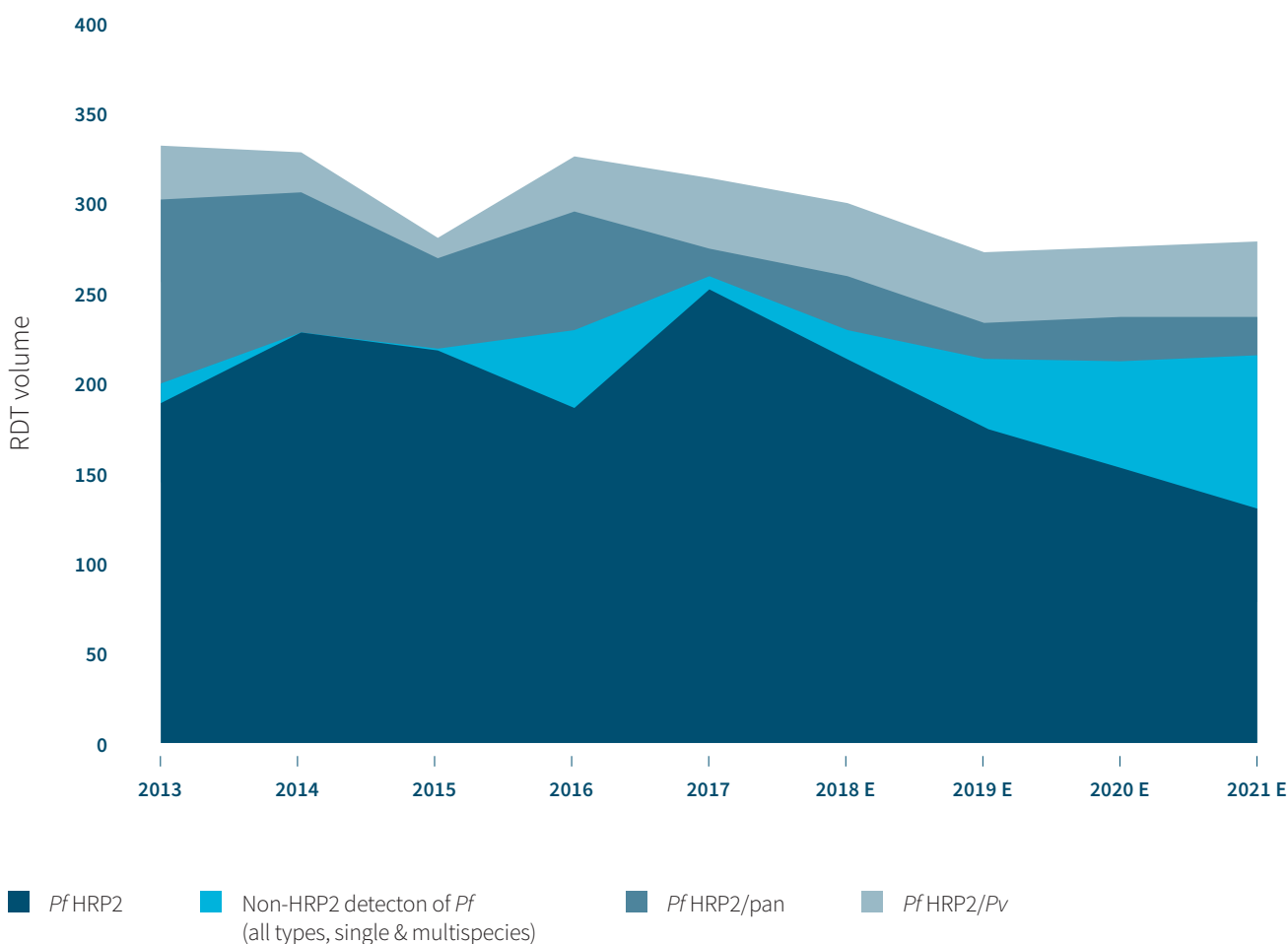
Demand for these *Pf* non-HRP2 RDTs is difficult to forecast because the scope of deletions and the pace at which deletions spread are not known. Moreover, even when the intent to replace an RDT is made, operational factors influence the timing of switching tests. Nonetheless, considering that almost half of current public sector RDTs are used in countries that have reported *Pf* HRP2/3 deletions and this increases to 85% when their neighbours are included, it is plausible that demands for alternative tests could emerge quickly over the next few years. Based on several assumptions, Figure 7 illustrates one scenario of how demand for tests that do not rely exclusively on HRP2 for *Pf* detection may evolve in the next few years. This projection assumes that the overall public sector market size remains relatively flat and that countries with reported deletions as of mid-2018 begin to shift their volumes to new tests at a faster rate than neighbouring countries.

2 Active case detection refers to detection by health workers of malaria cases at the community and household levels. It can consist of screening for fever followed by parasitological test of febrile patients, or as testing of the target population without prior screening for fever. Active case detection is often undertaken in response to a confirmed case (reactive) or in high-risk groups (proactive). Passive case detection refers to detection of malaria cases among sick patients who visit health services for care.

3 In some parasites, only the gene for HRP2 is deleted “single deletion” but HRP3 is still produced. In other cases, both the HRP2 and HRP3 expressing genes are deleted (“dual deletion”). Although the monoclonal antibodies (mABs) used in the RDTs target HRP2, as many mABs cross-react with HRP3, the test may still return a positive result on the HRP2 antigen line even when HRP2 genes have been deleted.

4 For the most up-to-date information see the WHO malaria threats map: <http://apps.who.int/malaria/maps/threats/>

FIGURE 7 Demand for malaria RDTs by product type, including tests that do not rely exclusively on HRP2 for *Pf* detection.



Source: projection of RDT demand for the RDT Procurement Task Force.

Note: Tests for deletions includes any test that does not rely exclusively on HRP2 for *Pf* detection, and could be *Pf*-only tests or multispecies tests.

Demand is indicative of one scenario. It is based on several estimates, some of which have high levels of uncertainty, including: i) estimated annual volumes of RDTs by country; ii) categorization of countries into one of four categories: widespread deletions, reported deletions, neighbors, and low risk;⁵ and iii) assumptions about how quickly the countries will switch RDTs.⁶ There is considerable uncertainty related to assumptions ii and iii, because little is known about the actual spread of deletions which depends on multiple factors, such as pressure from use of HRP2-based RDTs, care seeking rates, adherence to test results; and because operational factors, such as policy updates, registration and procurement of new RDTs, will influence the timing of a switch.

5 Risk categories based on WHO malaria threat map and WHO Response plan to *Pf* HRP2 gene deletions (final draft document reviewed in September 2018).

6 Specifically, the projection assumes that in countries where deletions have been reported, 10%, 20%, 30% and 40% of RDT volumes in 2018, 2019, 2020, and 2021 respectively shift to tests that do not rely exclusively on HRP2 detection for *Pf*. For neighbouring countries there is a one-year lag, i.e. 0%, 10%, 20%, and 30% of RDT volumes in 2018, 2019, 2020, and 2021 respectively shift to tests that do not rely exclusively on HRP2 detection for *Pf*.

Donor funded procurement

Donor funded procurement represents over half of the global RDT market by volume, with the Global Fund's PPM and PMI being the largest institutional buyers.⁷ The Global Fund also funds substantial RDT procurement that does not go through PPM, but is managed by the grantee or its designated procurement agent. In the past, approximately 20% of the market was procured through this route (11).

Until recently, PMI and Global Fund PPM have both used spot procurement methods, in response to country requests, to buy RDTs. While many of these tenders have been competitive, some have been sole sourced, for example, when a national program requests to continue using the same RDT to avoid switching costs (e.g. retraining health workers, new job-aids). Pricing analysis indicates that sole sourcing can result in prices that are up to two times as high as openly competed tenders, and contributes to wide price variation in the market. Suppliers with sizable volumes of sole-sourced RDTs are then in a position to use revenues from sole sourced products to subsidize their bids in openly competed tenders. These dynamics along with the winner-takes-all approach of openly competed tenders, have contributed to prices that are approaching or below cost, especially for small and medium sized manufacturers.

In light of these dynamics and the resulting near exclusive reliance of the public sector on two RDT manufacturers, the Malaria RDT Procurement Task Force is working to align on procurement strategies to improve the health of the RDT market. Considerations include: moving away from spot procurements to long term agreements to help stabilize pricing and provide suppliers with visibility into demand; allocating demand to multiple suppliers, based on factors other than price; and limiting country requests for restricted procurement unless epidemiologically justified. PMI recently launched a new procurement strategy, which has long term agreements, allocates across multiple suppliers using criteria beyond price, and limits sole sourcing of RDTs. UNICEF and the Global Fund PPM are also restructuring procurement of malaria RDTs in light of these principles, which should result in new procurement practices in 2019.

⁷ As an example, recent procurement volumes for the major institutional buyers are as follows: The Global Fund PPM procured 105 million RDTs in 2017 and projects 161 million as for 2018. PMI procured 63 million RDTs in 2017 and 85 million as of June 2018. UNICEF typically procures 10-20 million RDTs annually.

QUALITY

The quality landscape for malaria RDTs is changing, with increasing pre-market controls (e.g. WHO Prequalification) and slow progress on the development of robust downstream quality control products and systems. A persistent challenge for any stakeholder trying to assess RDT quality (i.e. end users, procurers and manufacturers, as well as innovators evaluating a new products), is that malaria QC materials are challenging and expensive to obtain, manipulate, and characterize appropriately.

WHO Prequalification

As of January 2018, the WHO recommended procurement criteria for *Pf* HRP2 only RDTs became WHO prequalification. For the many other types of RDTs, the WHO will gradually implement the prequalification requirement, however, the requirement through the end of 2018 is valid ISO 13485:2003; submission of an application for WHO prequalification; and acceptable performance in the latest round of WHO product testing (14). As of January 2018, the Global Fund restricted all malaria RDT procurement to WHO prequalified RDTs, and some countries began requiring only WHO Prequalified RDTs. PMI expects to align with this policy as well, since the majority of the RDTs it currently procures already meet these standards.

Malaria RDT Product Testing

From 2010-2018 the performance of malaria RDTs in the WHO-FIND's Malaria RDT product testing program has informed the vast majority of public sector procurement, resulted in high performing products gaining market share. The eighth round of Product Testing has recently concluded, and the report detailing results is expected to be published in 2018. In connection to the transition to WHO Prequalification as the recommended procurement criteria for malaria RDTs, all manufacturers participating in round 8 were required to apply to WHO Prequalification. Following round 8, Product Testing (the laboratory evaluation component of WHO Prequalification) will no longer occur in annual rounds, but will be incorporated into the overall PQ process and be initiated site inspections and dossier review. Prequalification will use the same pass/fail criteria as Product Testing to inform decisions on performance, and while composite tables on product performance will no longer be published, details on individual RDT performance will be available in the PQ public reports. Additionally, the laboratory evaluation will no longer include a heat stability assessment and there will no longer be a requirement for manufacturers to resubmit products every five years to Product Testing as Prequalification includes a reportable change process as well as periodic re-inspections of manufacturing sites.

Malaria RDT Lot Testing

Since 2008, FIND and the WHO have coordinated a centralized lot testing program for malaria RDTs that was performed at selected international laboratories. This widely-used program was supported for over ten years by donors, and in an effort to make the program self-sustaining, it attempted to develop and commercialize recombinant antigen panels that could replace the culture and clinical quality control materials that are both expensive to collect and to characterize and not easily reproducible. The vision was that affordable, stable and reproducible recombinant panels would also allow for at least partial decentralization of lot testing to national reference laboratories.

In 2017 and 2018, FIND and Microcoat launched HRP2, *Pv* LDH, and *Pf* LDH recombinant panels; however, in July 2018, the WHO-FIND RDT Evaluation Programme Steering Committee reviewed the technical dossier and concluded that based on the currently available data, (in particular limited evidence on methods of use), they could not recommend decentralized, recombinant-based lot testing. Therefore, the existing WHO-coordinated lot testing activities at the Research Institute for Tropical Medicine in the Philippines, based on cultured and clinical quality control samples, will continue with some modifications until the QC stocks are exhausted over the next 2-3 years.⁸

UNICEF, PMI, and the Global Fund are each exploring options for lot testing going forward. PMI expects to continue pre-shipment lot testing using a risk-based framework. The Global Fund encourages and funds post market surveillance programs for laboratory diagnostics, which includes malaria RDT activities at all levels of the supply chain. Manufacturers also frequently utilize lot testing services, either to align with purchasers' requests or to support their own quality control activities.

Quality controls for malaria RDTs

Field-stable quality controls for use at the site level (i.e. positive control wells) could help detect deficient RDTs and ensure user confidence in RDTs more generally. These controls rely on availability of highly stable recombinant antigens, and when the objective is to detect shortcomings in performance, the control should be calibrated to approach the limit of detection of the RDT.

In January 2017, FIND and Microcoat, a German biotech company, launched HRP2-only positive control wells intended to work with multiple RDTs. However, limited data on performance and methods of use is available to make a recommendation on their use, and as a result uptake has been limited. Through this experience, it also became evident that finding a single concentration of recombinant antigen that works with all brands of RDTs is difficult and therefore, depending on the use scenario, product specific controls may be necessary.

⁸ Requests for testing RDTs pre-shipment and/or post shipment or based on concerns/complaints from the field will be processed. The National Institute for Malaria Research in India and the ANDI Centre for Excellence Malaria Diagnosis Centre, University of Lagos also plan to maintain lot testing services according to WHO-FIND procedures, to meet national needs.

Recombinant and culture standards

Despite the widespread use of malaria RDTs, few common standards have been available for evaluating malaria RDT performance. The Product Testing program had been supplying manufacturers' panels that are similar to those used in testing, however this will end in 2018 as funding expires and Product Testing is integrated into the WHO Prequalification process.

FIND has been leading efforts to fill this gap. In 2017, FIND and the UK National Institute for Biological Standards and Controls (NIBSC) launched a *Pf* recombinant standard which serves as a WHO International Standard for the two *Pf* proteins, HRP2 and *Pf* pLDH.⁹ A *Pv* (pLDH) standard is in development (expected in 2019). FIND and Microcoat have also developed three HRP2 recombinant reference materials (Types A, B and C)¹⁰, and pLDH standards are in development (expected in 2019).

The WHO is in parallel exploring new collaborations to generate a commercially available stock of well-characterized *Pf* cultured QC material as well as exploring opportunities to produce *Pv*-LDH through genetically edited *P. knowlesi* cultured isolates.

S U P P L Y

The malaria RDT supplier landscape continues to evolve, although many of the market fundamentals remain the same: for several years market share has consolidated around two main competitors in spite of the existence of many other malaria RDT manufacturers (4) (11).

Malaria RDT suppliers vary in terms of location, size, degree of vertical integration, manufacturing capacity and the relative contribution of malaria RDTs to their business. Recent events affecting the dominant players include the purchase of Standard Diagnostics/Alere by Abbott in 2017, as well as an \$8 million investment by the Global Health Investment Fund in Access Bio, intended to expand their low-cost production capacity. Meanwhile, other companies develop malaria RDTs and submit products to WHO for evaluation each year, however, none have realized meaningful market share. With the exception of Access Bio, Standard Diagnostics (now a division of Abbott), and a few medium sized manufacturers (e.g. PMC, Orchid) malaria RDTs are not a core business. Lateral flow test manufacturers tend to offer a range of RDTs for many infectious diseases and other conditions. Malaria RDTs are a part of this larger portfolio; often malaria tests are used to engage new customers, once a supplier is 'in the door' the focus shifts to cross-selling other types of RDTs.

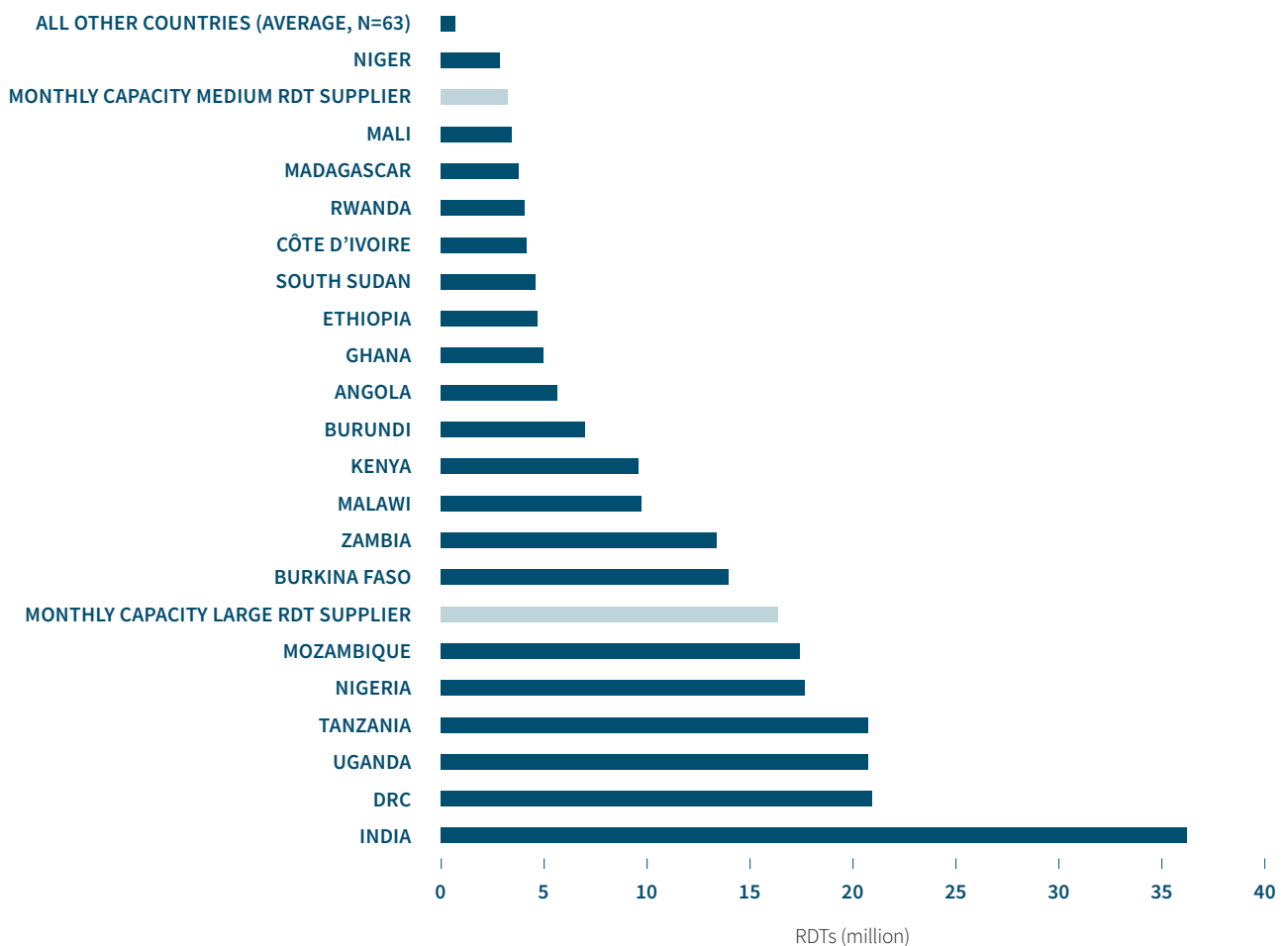
9 See: https://www.nibsc.org/products/brm_product_catalogue/detail_page.aspx?catid=16/376

10 See: <https://www.finddx.org/find-negotiated-product-pricing/#mc-hrp2>

The nature of competition in the malaria RDT market is influenced by several factors, including the public sector procurement structure described previously (i.e. two large procurers using spot procurement), as well as the leading manufacturers' business strategies, and more general barriers to entry.

On the supply side, competitive advantages around high volume production create barriers to entry. Both of the leading malaria RDT suppliers have invested in automated, high volume production lines, used almost exclusively for malaria tests. They have also developed know-how and expertise in malaria RDT production. These investments confer two advantages: these suppliers can take advantage of economies of scale, and offer prices below that of medium and smaller companies where unit costs are higher. Second, their production capacity allows them to rapidly fill enormous orders, which can require millions of RDTs to be delivered within 6-8 weeks. (Figure 8)

FIGURE 8 Typical monthly manufacturing capacity of large and medium sized malaria RDT suppliers (light blue) compared to public sector annual malaria RDT demand from high volume countries (blue).



Source: analysis of RDT demand for the RDT Procurement Task Force, malaria RDT supplier interviews.

This ability to produce at low cost has challenged formerly dominant malaria RDT manufacturers; some have exited the public sector market and are focusing on other products or on the private sector. It also discourages potential new entrants, most of whom cannot offer such low prices. The ability to quickly respond to large orders is also a barrier for most new entrants. Capacity among Indian, other US, European and African RDT manufacturers is typically a fraction of the capacity of the leading two malaria RDT suppliers, and makes it difficult for them to even consider some of the larger tenders. While a few Asian manufacturers have enormous lateral flow test manufacturing capacity, currently product performance and quality systems limitations prevent them from entering the public sector malaria RDT market, and therefore they do not actually produce many malaria RDTs.

In the past couple of years, malaria RDT prices have often approached the cost of goods, even for high volume suppliers. For companies with highly automated production lines and associated high fixed costs (e.g. equipment amortization, labor, space), resource utilization is critical, and is closely linked to pricing strategy. These manufacturers focus on optimizing production line utilization, and at times will bid on tenders at prices that are at or below unit cost, in order to gain volume and keep production running at the most cost-efficient level.

The reliance of the market on two suppliers creates two risks, the first relates to monopoly pricing and the second relates to supply security, i.e. whether there is sufficient supply to meet demand. For both it is important to consider not just overall capacity, but also capacity by product type and a manufacturer's incentive to produce.

Pricing below cost for an extended time puts pressure on product quality as manufacturers attempt to reduce costs. Low prices could also financially jeopardize an incumbent supplier. If one of the larger suppliers exited the market because it was no longer able to compete at current prices, there is a theoretical risk that the remaining supplier would use its monopoly position to raise prices, especially to recoup prior losses. However, this risk is tempered, especially in the large *Pf* HRP2 only market segment, by the presence of other WHO Prequalified suppliers that are presently sitting on the sidelines, but would enter the market again if prices rise. Therefore, in the *Pf*-only market we could expect prices to increase moderately,¹¹ but to be tempered by competition. Overall, if a large incumbent exited, total prequalified capacity would approach total demand (~300 million RDTs/year) in theory. However, pragmatically, disruption is likely as alternate suppliers come on line, each requiring an incentive to produce malaria RDTs.

11 In order for these suppliers to prioritize malaria RDTs over other products, prices may need to increase so that they are comparable to the margins made on RDTs for other markets.

For other product types, the risks around availability and pricing are higher. Although current total annual RDT manufacturing capacity for the five companies with prequalified RDTs exceeds global RDT demand forecasts, when product type is considered, capacity is an issue. As analysis of product availability in the next section illustrates, for some product types, no suitable RDTs exist today, and while for others there may be just one product available, from one of the two incumbent suppliers. If one of the large suppliers were to exit the market, it is likely that some disruption in global supply would occur as market share by product type shifts, and remaining suppliers could command premium pricing until additional products become available.

Other barriers to entry in the malaria RDT market relate to quality. Since 2010, high performance in WHO product testing has been required for participation in the public sector market. More recently, WHO Prequalification is being gradually extended to malaria RDTs. Because of the lack of regulation in markets where RDTs are produced and sold, most malaria RDTs suppliers do not have experience with stringent regulatory processes and the time, culture shift, and investment required to prequalify the first product is generally significant. It is not uncommon for manufacturers to make multiple attempts at WHO PQ before success. The two leading RDT manufacturers began prequalifying their products several years ago, and as a result have the most WHO prequalified products. For new companies, making the business case to invest in prequalification is difficult in light of the low malaria RDT prices.

Another barrier relates to global health experience, including having a large geographic footprint (e.g. registration and distributors serving all major malaria endemic countries) and familiarity with the international tendering practices. For companies without global health experience, it takes time to obtain local registration and to understand the various procurement processes. In some smaller markets, the selection of registered RDTs is limited, or distributor mark ups quite high due to limited competition and costs of servicing small markets.

Going forward, competition is likely to increase as a result of reduced sole sourcing which often only served to solidify incumbent's positions by reducing the frequency of open tenders and by effectively subsidizing some of the lower priced competitive tenders. Additionally, while there appear to be a few companies with high-performing malaria RDTs intent on entering the market, they will first need to become WHO prequalified. Some will also need to expand their production capacity before they would be able to have a real presence in the public sector 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 they need to improve the technical performance of their tests and their quality management systems before they can meaningfully engage in the market.

RANGE OF AVAILABLE PRODUCT TYPES

The limited availability of selected product types has emerged as a critical market gap: while sufficient selection exists for some product types, such as the *Pf* HRP2 only tests, product selection is quite limited or nonexistent for other product categories. Moreover, as suppliers attempt to address the emerging needs by developing new products (i.e. different antigen detection set ups), it is becoming extremely complicated to monitor the new product variants that are on the market, and to understand their potential application, and whether they meet the relevant global quality standard. For several of the new products, there is no consensus yet about the relevant standards for performance evaluation and quality, or the evidence needed to assess impact.

Among the traditional test types (those relying on HRP2 for *Pf* detection) there are an acceptable number of quality products available for each of the three main categories, and in light of the WHO prequalification pipeline there will likely be additional products using HRP2 for *Pf* detection prequalified in 2019.

In contrast, availability of RDTs for countries with HRP2 deletions is poor. Existing RDTs that detect *Pf* LDH have either not demonstrated performance on *Pf* parasites lacking HRP2¹², or have performed poorly on *Pf* panels that do express HRP2. For the first time, the eighth round of Product Testing included a panel of parasites with deletions, and the performance of many RDTs on the HRP2 expressing panel versus the non-expressing panel was inconsistent. Overall the round eight results will not influence product availability significantly for countries with deletions. Considering these developments, the WHO GMP is updating product selection guidance and longer term, plans to assemble a larger panel of samples with deletions to further study the performance of tests designed to detect *Pf* in parasites with HRP2/HRP3 deletions.

Given the dynamic nature of the spread of HRP2 deletions, WHO GMP and WHO Prequalification policy are still evolving. Currently, there are three tests using *Pf*LDH that are WHO-prequalified, however, these are not currently recommended by the WHO GMP for case management in areas with deletions because they do not meet WHO performance criteria.¹³

12 While some were assessed in Round 8, they did not meet WHO performance criteria for case management.

13 Specifically, the *Pf* LDH line does not meet WHO GMP performance criteria when tested on panels of HRP2 expressing parasites. WHO Prequalification is based on the claims made by manufacturers in the RDT's instructions for use (IFU). In the IFU the claim is detection of *Pf* LDH, rather than detection of *Pf* with HRP2 deletions. The WHO is working on information and public reports that reflect these products intended use and limitations.

For the growing number of countries with HRP2 deletions, the current lack product availability could require a compromise on malaria detection and/or implementation of mitigating strategies. For countries where *Pf* dominates, RDTs with one test line detecting both HRP2 and *Pf* LDH are preferred for case management;¹⁴ however, the performance of *Pf* LDH products in Round 8 on deleted panels was inadequate. An alternative therefore is the pan-LDH only test. There is one prequalified pan-RDT that has been evaluated favorably on a panel of parasites with deletions. Additionally, two pan-RDTs were evaluated favorably in Round 8, and these are manufactured by sister companies of the prequalified pan-LDH test. A fourth pan-only test meets WHO performance criteria on traditional panels, but has not been assessed on panels with deletions nor is it in the WHO prequalification pipeline.

For multispecies countries that need a combination test that can detect HRP2 expressing and non-expressing parasites as well as non-falciparum infections, there are no WHO prequalified tests that also meet WHO performance requirements. While there is one prequalified test, it has not performed well on a panel with deletions. There is an additional test that has performed well on traditional and non-HRP2 expression panels, however it is not yet in the prequalification pipeline.

TABLE I Malaria RDTs for case management: product availability by setting and test type as of 31 December 2018

Status (Year-end 2018)					Outlook		
Category	Test type	# Prequalified	# meeting performance criteria**	# meeting criteria for countries with deletions***	# PQ-ed and meeting criteria	Demand	“Pipeline (PQ pipeline, tests meeting performance criteria)”
Conventional mRDTs	<i>Pf</i> HRP2	5*	>25	N/A	5*	Largest market by volume; declining as a result of rising HRP2 deletions	4 products in the PQ pipeline, including one highly sensitive RDT.
	<i>Pf</i> HRP2 / pan	3	>20	N/A	3	2 nd largest market; slight contraction possible as countries shift to <i>Pv</i> and to RDTs that do not rely exclusively on HRP2 for <i>Pf</i> detection.	3 products in the PQ pipeline.
	<i>Pf</i> HRP2 / <i>Pv</i>	4	>20	N/A	3	Many small volume countries.	4 products in the PQ pipeline.

14 The rationale is: *Pf* LDH detects parasites with HRP2 deletions. HRP2 is included because its sensitivity and stability tend to be higher than that of LDH, and is therefore valuable for detecting the (large) proportion of infections that do still express HRP2/3. Note that for surveillance of HRP2/3 deletion purposes, it is useful to have a *Pf* LDH line and a separate HRP2 test line.

Pf dominant countries with deletions	Pf single test line with PfLDH ± HRP2	1	4****	0	0	Long-term increasing demand, as a test with pfLDH and HRP2 on one line may be preferred for Pf countries with deletions as it is similar to the traditional RDTs. Despite demand, no products have met performance criteria on both HRP2 expressing and nonexpressing panels.	"AccessBio has a PQ-ed RDT, however it did not perform adequately in Round 8 against panels with HRP2 deletions. There are no tests in the PQ pipeline. Of tests meeting traditional performance criteria: <ul style="list-style-type: none"> • 2 RDTs (from AccessBio sister companies) did not perform adequately in Round 8 against panels with HRP2 deletions. • SD/Abbott have not assessed their RDT against a panel with HRP2 deletions, nor is this test in the PQ pipeline. The company is also developing a pfLDH/HRP2 test using its highly sensitive platform (late 2019, BMGF support)"
	Pf, two test lines, one with PfLDH the other with HRP2	1	2	0	0	Current primary use is for pfHRP2/3 deletion surveys.	There is one PQ-ed test SD/Abbott and one in the PQ pipeline (AccessBio), however neither has met criteria on panel of parasites with deletions. No other tests submitted to product testing for this category.
	Pan	1	4	3****	1	Near-term increasing demand for Pf-dominant countries with HRP2 deletions if no single line Pf-LDH & HRP2 tests available.	AccessBio test is PQ-ed and met performance criteria on deleted panel. No products in PQ pipeline. <ul style="list-style-type: none"> • Two RDTs from AccessBio sister companies meet all performance criteria, but are not in PQ pipeline. • One product meeting traditional performance criteria has not been evaluated on a panel with deletions, nor is it in the PQ pipeline.
Multispecies countries with deletions	PfLDH ± HRP2 /Pv	1	2	1	0	Small but immediate demand from Southern American countries, potentially higher volumes required from countries that need to identify Pv for radical cure (horn of Africa, India, Myanmar etc.)	SD/Abbott RDT is PQ-ed, but did not meet criteria on parasites with deletions in Round 8. No tests in WHO PQ Pipeline. Of those meeting traditional performance criteria, Biocredit RDT met performance in prior round of testing, has been assessed favorably on parasites with deletions, but needs to undergo PQ.
	PfLDH ± HRP2/pan	0	2	0	0	Conventional Pf/pan test type is largest by volume, so countries with deletions may prefer test with a pan line; however growing desire to have definitive Pv diagnosis for radical cure may temper demand.	Two products from AccessBio in the WHO PQ pipeline. One has not been assessed on a panel with deletions; the second did not meet performance criteria on panel with deletions.

* Five PQ-ed tests, however one is an improved version of a previously prequalified test by the manufacturer.

** Performance criteria in Product Testing, defined as: i) panel detection score, ≥ 75% at 200 parasites/μL; false-positivity rate of < 10%, and invalid rate of < 5%.

*** Includes performance on panel of Pf strains with HRP2/3 deletions.

**** Includes the PQ-ed product, and 2 products from sister companies.

INNOVATION

Despite their value, RDTs under-perform in several key areas related to performance (e.g. *Pf HRP2* deletions, detection of species other than *P. falciparum*, limited sensitivity for elimination settings). However, manufacturers of RDTs are hesitant to commit substantial internal funds to malaria diagnostics R&D, thus innovations have been slow to materialize. The majority of R&D to improve malaria RDTs so that all major epidemiological needs are met results from donor funding, rather than arising organically from a compelling business case within a company. Further exacerbating the market consolidation risks, is the fact that the majority of donor funded projects are with the leading suppliers, due to their expertise in product development and manufacturing. When RDT manufacturers invest on their own, they are more likely to invest in complementary products (e.g. G6PD tests, or Malaira+CRP combo tests) rather than improving the existing generation of malaria RDTs.

Improving malaria RDT performance

There are two donor supported efforts to improve RDT sensitivity, with a particular focus on detecting asymptomatic infections and elimination settings. These highly sensitive RDTs achieve higher sensitivity through a number of mechanisms, including different capture and detection chemistries or blood volumes; and they will likely be priced higher than traditional RDTs (approximately US\$1.00).

The first product, developed with BMGF support, was announced in April 2017 by Standard Diagnostics/Alere (now Abbott). The Alere™ Malaria Ag P.f. is similar to conventional RDTs in terms of format and processing (no reader required), and has a tenfold improvement in the detection of HRP2 compared to conventional malaria RDTs (i.e. LOD of 80 pg/mL vs 800 pg/mL HRP2). (15) This test is in the WHO PQ pipeline and several partners are conducting field studies to assess the performance of the test.

A second product, initially developed by Global Good/Intellectual Ventures, will be manufactured by Access Bio. This highly sensitive HRP2 RDT is expected to come to market in 2019, and will be followed by a highly sensitive LDH test in 2020. Initial lab results suggest that the HRP2 test is 30-fold more sensitive than conventional RDTs. The test does not require a device for reading results; however, prototypes currently use 100 µl of fingerstick blood, requiring a different lancet than conventional RDTs.

In light of these new products, the WHO GMP is considering the role of new highly sensitive tests, primarily through its Evidence Review Group process. The latest meeting recommended and outlined a series of “pragmatic studies” aimed at assessing the impact of highly sensitive tests in order to inform policy recommendations around use of highly

sensitive RDTs. On the table are multiple use cases, across different transmission intensities, for example, screening pregnant women, active case detection, and household surveys. Additionally, the impact of highly sensitive tests in case management needs study, as there is concern about their use in highly endemic settings.

BMGF has also invested in improving the performance of *Pf* LDH and *Pv* LDH detection to support case management. For now, two products are envisioned, and both are expected to have a *Pf* line that includes both HRP2 and *Pf* LDH. The first product, a *Pf* LDH + HRP2 (single line) RDT, is expected in late 2019 followed by a *Pf* LDH + HRP2 (single line) / *Pv* RDT in early 2020. Both are being developed by Standard Diagnostics/Abbott.

Other innovation

Access to well characterized samples is a challenge for innovators, and while donors have supported work in this area discussions with test developers suggest that gaps remain. In 2018, FIND launched a specimen bank for development of improved malaria diagnostics. This initiative includes banking of blood samples from asymptomatic individuals infected with *Pf* and *Pv* across seven countries.¹⁵ Additionally, FIND has collaborated with ZeptoMetrix to develop a standardized *Pf* culture panel, comprising samples in a range of HRP2 concentrations from six cultured strains.¹⁶ FIND also worked with Microcoat to develop commercially available recombinant HRP2 standards for evaluating the analytical performance of new assays (see Quality above). Samples and standards for other species and antigens, as well as for parasites with HRP2 deletions, remain a gap.

In terms of new monoclonal antibody development, NBI is beginning a two-year effort to develop improved pLDH antibodies. Additionally, Vista has been working with mAbDx to produce a number of new hybridomas for both HRP2 and pLDH.

While there are examples of RDT manufacturers innovating incrementally around ease of use, these formats cannot achieve pricing that is competitive with traditional RDT mass market prices, and as a result these have not gotten much traction in malaria. However, in 2017, the US company Fyodor launched its Urine Malaria Test in Nigeria and Liberia, where it is licensed for over the counter use and sold in pharmacies and private hospitals and clinics, at prices ranging from \$1.00-3.00. Donors are also exploring the potential for saliva and urine-based malaria rapid testing.

There are a variety of other efforts to develop malaria tests that are not lateral flow based (11) (4), including non-invasive methods (hemozoin transdermal tests, breath tests) and

15 See: <https://www.finddx.org/specimen-banks/>

16 See: <https://www.finddx.org/find-negotiated-product-pricing/#zmx-hrp2>

automated microscopy platforms. However, many are early stage, and not poised to significantly impact the case management market in the near term. Furthermore, despite its shortcomings, the malaria RDT value-proposition is difficult to surpass. Not only are RDTs minimally invasive, robust, and easy to use, but also fierce competition has made malaria RDTs exceptionally inexpensive. RDT prices have effectively ‘anchored’ thinking around malaria testing; and any new technologies would need to have significant advantages to command higher prices.

CONCLUSION

After years of progress in scaling up malaria diagnosis with RDTs, today, advances are threatened by neglect of key market fundamentals. First, the malaria RDT pipeline has failed to keep pace with emerging needs generated by changing malaria epidemiology. We lack high performing products for some emerging key areas. Second, materials and systems for rapidly evaluating new tests and supporting their introduction are insufficient. Third, with the spread of HRP2 deletions to high volume countries in Africa and South East Asia, the nascent trust that providers and patients have put in malaria RDTs may be eroded. While expanding case management in private sector markets, the community level, or to fevers more broadly are priorities in many countries, it is imperative that development and introduction of new, high performing tests that meet the new epidemiological conditions programs face are prioritized.

These gaps in the pipeline no doubt are a long term consequence of several underlying market challenges. Given the highly centralized nature of malaria RDT procurement, there is an opportunity to influence the long-term health of the market so as to improve supply security, and ultimately, to ensure that innovation keeps pace with needs. However, action has been slow to materialize, and as a result, the risks associated with continued reliance on two suppliers are especially high: downstream quality measures are underdeveloped at a time when highly competitive, low prices could compromise product quality. Moreover, current prices continue to threaten the financial solvency of the malaria RDT business, increasing the risk of supplier exit. Efforts to diversify the market and to address long term health are urgently needed. While PMI has recently taken measures to address these market issues, coordinated efforts would have greater impact.

Methods

Methods for this report included data analysis, interviews and discussion with key stakeholders, and desk review (Figure 9). Additionally, several reviewers provided valuable suggestions including: Jane Cunningham, Xavier Ding, Lisa Hare, Aziz Jafarov, Susan Nazzaro, and Theodoor Visser. The report draws heavily on materials and discussions of the Malaria RDT Procurement Taskforce, in particular a July 2018 workshop where major procurers, donors, and policy makers gathered to analyze the health of the RDT market and to discuss alignment of procurement strategies to address major shortcomings. In preparation for the July 2018 meeting, Theodoor Visser (CHAI) and Jen Daily (Consultant to Unitaid) prepared an analysis of the malaria RDT market, and this report includes or builds this work. This report is up-to-date as of Year end 2018.

FIGURE 9 Methods.



Data analyzed

- Procurement data PQR and PMI (~30-60% total markets)
- WHO GMP survey of suppliers in product testing; HRP2 Deletions MPAC documents; 2015 supplier capacity survey
- CHAI/Unitaid: forecast of ACT/RDT
- PMI MOPs; ALMA/RBM commodity gap analysis; World Malaria Report data
- Product testing results (through R7), R8 suppliers
- PQ pipeline



Stakeholder interviews

- WHO PQ
- WHO GMP
- BMGF - China
- BMGF - R&D
- Global Good - R&D
- PMI PSM team
- Unitaid - supply expert
- CHAI - supply expert

3**Desk review**

- Previous analyses and presentations to RDT
 - Procurement Task Force:
 - WHO PQ & GMP analyses
 - CHAI Procurement analyses
 - PMI market strategy, PJMI supplier & COGS analyses
 - FIND/WHO RDT survey
 - FIND Business Case HS combo RDT, Non-invasive market report
 - Imperial College modeling HRP2 deletions

4**Suppliers: new and old**

- Access Bio
- Standard Diagnostics/Abbott
- Premier Medical Corporation
- Tulip (Orchid, Zephyr)
- SD Biosensor
- National Bioproducts Institute (mabs)
- Meril
- Nectar
- Brief updates: Omega, Humasis, RapiGen, Wondfo, Intec, Orient Gene

ABBREVIATIONS

ACD	active case detection
FIND	Foundation for Innovative New Diagnostics
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
G6PD	glucose-6-phosphate dehydrogenase
HRP2, HRP3	histidine rich protein 2 (and 3)
iCCM	integrated community case management
LDH	Lactate dehydrogenase
mABs	monoclonal antibodies
PCW	positive control well
Pf	<i>Plasmodium Falciparum</i>
pLDH	parasite lactate dehydrogenase
PMI	United States President's Malaria Initiative
PMS	post market surveillance
POC	point of care
PPM	Pooled procurement mechanism (Global Fund)
PQR	Price and Quality Reporting (Global Fund)
Pv	<i>Plasmodium vivax</i>
p/μL	parasites per microlitre
QA	quality assurance
QC	quality control
R&D	research and development
RDT	rapid diagnostic test
μL	microlitre
US	United States
WHO	World Health Organization

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