MALARIA DIAGNOSTICS MARKET AND TECHNOLOGY LANDSCAPE

4TH EDITION

Unitaid
Innovation in Global Health

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EXECUTIVE SUMMARY

Introduction

The Unitaid 2023-2027 Strategy includes quality malaria case management as a programmatic priority. Considering recent shifts in the malaria rapid tests markets and COVID-19 pandemic disruptions, it is both timely and important for Unitaid to update its understanding of the markets for existing and pipeline malaria diagnostics and the work of other stakeholders. This 2022 malaria diagnostics market and technology landscape report, the fourth edition, intends to stimulate discussion in the malaria community and inform potential opportunities to improve access to effective case management, acknowledging the foundational role that malaria diagnostics play in the continuum of care.

Public health challenges and access

Progress in malaria control has stalled and 2020's estimated 241 million malaria cases exceeded global targets by 110 million. While the COVID-19 pandemic disrupted access to case management, malaria programs were not on track to meet goals before the pandemic.

Children comprised most of 2020s 627,000 malaria deaths, yet household surveys indicate that only 27% of febrile children receive a diagnostic test. While testing is available in most public facilities and increasingly in communities, up to 40% of the African population seeks care in retail outlets where testing is not widely available. Additionally, the quality of fever management, including fever caused by other diseases, and case reporting need strengthening.

P. falciparum HRP2/3 gene deletions are spreading in high-burden countries, threatening case management's underpinning diagnostic tool: HRP2 detecting RDTs. When parasites with deletions become dominant, HRP2 detecting RDTs could miss many infected patients, potentially increasing morbidity and mortality and undermining confidence in diagnostic tools. The WHO recommends that countries periodically survey the prevalence of deletions and switch to alternative RDTs if existing tests would miss more than 5% of symptomatic patients. Although scientists expect continued expansion, the drivers and rate of HRP2/3 deletions spread are not well understood.

Malaria RDT market

In 2020, WHO prequalified RDT manufacturers supplied 419 million malaria RDTs; significant growth is not expected in the coming years. In 2019 and 2020, the WHO prequalified nine new malaria RDTs. Currently, there are several prequalified RDTs for each of the conventional case management test types (i.e. HRP2 detecting test for Pf, Pf/pan, and Pf/pv). However, options for areas with Pf HRP2/3 deletions are limited: one company has three RDTs with ERPd status, and two other companies have products in development.

Since 2020, the malaria RDT supplier base has shifted significantly. Previously, intense competition reduced malaria RDT prices, resulting in near-exclusive reliance on two suppliers, even though several met WHO performance and quality recommendations. In 2018 and 2019, large procurers implemented new procurement approaches to diversify the supply base, stabilize prices, and limit country preferences for particular products. These were coming into effect in early 2020 when one of the dominant suppliers had quality

problems that precluded further procurement. At the same time, increased demand for COVID-19 diagnostics encouraged leading suppliers to shift production away from malaria RDTs to higher margin COVID-19 RDTs. Procurers issued additional tenders to avert a potential 100 million malaria test shortfall. The tenders went to seven suppliers, effectively accelerating the diversification of the supply base that was already underway.

After years of trending downwards, malaria RDT prices have risen slightly since 2019, an expected result of supply base diversification, new procurement approaches, and inflation. The malaria Pf HRP2 detecting RDT remains the dominant (70-80% of volumes) product in the donor-funded market.

Procurers' new strategies have changed the nature of competition in RDT markets: RDTs based on HRP2 detection are now commodity products supplied by multiple manufacturers interchangeably. Notably, the new RDTs being developed for settings with HRP2/3 deletions have varying test line configurations and are not necessarily 'interchangeable.' Few countries with HRP2/3 deletions have purchased Pf LDH detecting RDTs, and volumes have been low.

Although their headquarters may be elsewhere, the current WHO-prequalified malaria RDT suppliers are manufacturing in Korea, China, and India. A few suppliers are global diagnostics companies; several are medium-sized manufacturers primarily focused on LMICs. Experience with global health markets, delivering large orders, and robust quality management vary among suppliers.

During the pandemic, the capacity of WHO-prequalified malaria RDT suppliers increased from 800 million to over 2 billion RDTs annually. For some large manufacturers, the incentive to produce malaria RDTs will be influenced by fluctuating demand for COVID-19 RDTs and production-line optimization (e.g. filling excess production capacity with high-volume RDTs such as malaria or shutting down capacity).

Supporting radical cure with G6PD testing

Without POC G6PD testing, people infected with *P vivax* cannot safely receive anti-relapse medicines, presenting an ongoing risk to their health and potential for onward disease transmission. Tafenoquine, an improved anti-relapse medicine, has just come to market, creating momentum for radical cure, including POC G6PD testing. Unlike the malaria RDT market, only people with confirmed Pv need testing; therefore, the POC G6PD market is relatively small, and available products are few and more expensive. One quantitative test, a handheld device, is currently available for donor-funded procurement (ERPd status). Other late-stage products are in development, and one will likely submit to PQ in 2023. Adoption is complex as country approaches to radical cure differ, and G6PD tests generally have limited stability, making reaching the lowest levels of the health system challenging.

Many donors, Unitaid included, support operational research and implementation of radical cure; ensuring no gaps in support for programs will be essential. On the supply side, a proactive approach to managing the pipeline could ensure the introduction of an additional product.

Point-of-care malaria diagnostic technology landscape

A high-level scan of the technology landscape reveals many technical methods for detecting malaria. Yet, in the near- to medium-term malaria, RDTs and microscopy are expected to be the mainstays of case management. Other technologies will likely address specific use cases where they uniquely add value.

Recently launched and late-stage technologies include digital microscopy and POC hemozoin tests. Studies to support their use are ongoing. There are various nucleic acid detecting approaches for malaria, ranging from LAMP combined with simplified processing and read-out systems to CRISPR technologies for ultrasensitive detection. While the pandemic accelerated progress for point-of-care molecular platforms generally, whether malaria assays are developed for these platforms will depend on identifying use cases with attractive market potential. The WHO expects biosensor-based diagnostics to play a major role in LMICs in the medium to long term because they offer low-cost, highly sensitive detection. While there are several examples of biosensors for malaria in the literature, none appear to be at an advanced stage of development.

There is increasing interest in minimally invasive, extremely rapid (i.e. one minute) malaria tests. Various biomarkers and technology platforms are being explored, including lateral flow tests detecting gametocyte biomarkers in saliva, transcutaneous hemozoin detection, and volatiles. Most efforts are early stage.

Market shortcomings and challenges

Innovation and availability

Incentives to drive malaria RDT innovation are limited because of small profit margins and uncertain demand for improved products. Recent malaria RDT advances are primarily donor-funded, and progress is slow. Notably, prequalified tests for settings with HRP2/3 deletions are urgently needed. Manufacturers lack reliable information on how quickly deletions will spread, which countries will likely require new tests, and how procurers will approach these tests (e.g. pricing, sourcing based on product differentiation).

Developers have recently launched several malaria diagnostic innovations, including highly sensitive RDTs, digital microscopes, and POC hemozoin devices. However, their introduction is not progressing rapidly. There are varying levels of evidence for these products and different degrees of consensus around the need and use cases for some products. For case management, malaria RDTs represent a compelling value proposition: to compete with RDTs, new technologies need precise cost, speed, ease of use, or performance advantages. Traditional microscopy, despite shortcomings, is also well entrenched. Policy, regulatory, and procurement structures are not always conducive to new products addressing niche market segments or lacking consensus on need and impact. Against this backdrop, developers must identify where new products can add value and develop compelling evidence of impact, often an expensive and time-consuming activity.

Quality

The donor-funded market primarily relies on WHO Prequalification to assure quality. In-market quality control is variable and primarily comprises centralized lot testing, which will end in the coming years. Little is known about the private and domestic malaria RDT

market segments, but anecdotal evidence suggests that quality is inconsistent, despite sizable volumes in some domestic procurement. Drivers of limited quality include low buyer awareness of the benefits of solid quality systems, higher costs and, therefore, prices for quality assured RDTs compared to non-quality assured tests, and weak national regulatory systems.

Affordability

Although malaria RDT prices have increased slightly since 2019, HRP2 detecting tests remain affordable. Pricing of new tests for settings with deletions (Pf LDH detecting RDTs) has yet to be firmly established as volumes procured to date have been very small. However, anticipated higher prices could limit coverage. The market for these new tests is small and fragmented; low volumes and limited competition may preclude price decreases in the near term.

Adoption

Adoption of Pf LDH tests has been slower than expected as countries undertake surveys to assess the prevalence of deletions and the need to switch. While studies are underway in many countries, challenges include the complexity and timelines of the studies, affordability, and limited availability of alternative RDTs for settings with deletions.

Reaching those not seeking care for fever and those who access the informal private sector is a perennial challenge. They are not monolithic groups, and various approaches may be needed to reach them. Pilots have demonstrated that testing in retail outlets is possible, yet market development is time-consuming and resource-intensive. Pricing in retail outlets may be too high for consumers, deterring uptake. At the same time, low demand and limited margins for retailers and supply chain actors may discourage continuous stocking and distribution.

Supply

While the malaria RDT supply base has diversified, its strength is tenuous. Large suppliers may prioritize more profitable product lines or recalibrate their manufacturing capacity, and smaller suppliers are yet to demonstrate their ability to deliver quality RDTs at scale reliably.

Opportunities for intervention

There is a range of opportunities to support the malaria RDT market, and several of them require collective action to promote sustainable access. Others aim to expand quality case management or support innovation.

Creating conditions for sustainable access

It is a priority to understand HRP2/3 gene deletions situation (e.g. the number of countries affected, studies underway, and timelines) and country readiness for alternative tests. Concerning the former, the WHO is constructing a dashboard, but it requires urgency and support. Closely monitoring affordability and volumes of new tests as the market develops is vital, as is monitoring the advancement of pipeline products to ensure sufficient product offering, healthy competition, and supply security. Procurers also need to define and signal how they will approach new RDTs.

Proactive monitoring of the malaria RDT supply base is warranted, including new entrant quality and reliability, as well as incentives to produce malaria RDTs in the context of COVID-19 RDT demand and production capacity changes.

Forums for multistakeholder dialogue around R&D priorities would support more efficient investment in product development and commercialization of new technologies. Dialogue would also improve understanding of the evidence needed to support the adoption of novel products - including the various quality and policy review requirements at the global and local levels.

Catalyzing new approaches to quality case management

To address significant gaps in access to quality case management, formative research to understand barriers and develop human-centered design delivery models is needed. In countries where the retail sector plays a significant role in fever care seeking, approaches grounded in understanding the heterogeneous retail segments and their business models are needed. It is also worthwhile to consider how digital innovations could support improved case management in various settings.

In markets that are not donor-funded, an initiative targeting both supply and demand sides of the market could improve the quality of malaria RDTs and other RDTs. Funding and technical assistance could be provided to companies to support their quality management systems, aiming for WHO prequalification. This could be coupled with advocacy and technical support to local regulators and procurement bodies to increase awareness of the benefits and value of selecting quality-assured products.

Optimizing the development and adoption of new technologies

Additional work is needed to identify high-impact use cases and develop supporting evidence for recently launched products, including digital technologies and RDTs with improved sensitivity.

Market interventions to support innovation include direct funding for development. When technologies utilize novel biomarkers or technology platforms, trial costs and timelines are likely to be high and long. Simultaneous investments in developing mechanisms for evaluating and reviewing any novel test "category" are also needed to accelerate quality and policy endorsement of newly developed products.

As the malaria RDT lot testing program is ending, it is worthwhile to revisit quality control materials. Given slim margins and limited financial incentives, an intervention to support quality control material development (either by a third party or by the test manufacturer) for malaria and other RDTs might be beneficial.

ABBREVIATIONS AND ACRONYMS

ACT	artemisinin-based combination therapy
BMGF	Bill and Melinda Gates Foundation
CE Mark	European Conformity (Conformité Européenne) mark
CHAI	Clinton Health Access Initiative
CHW	Community Health Worker
COVID-19	coronavirus disease 2019
ERPd	Expert Review Panel for diagnostics (Global Fund, Unitaid)
EUL	Emergency Use Listing (WHO Prequalification)
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	Global Malaria Programme
G6PD	glucose-6-phosphate dehydrogenase
HBHI	High Burden High Impact
HRP	histidine rich protein
IV	International Units
LAMP	loop-mediated isothermal amplification
mAb	monoclonal antibody
mL	millilitre
NIH	United States National Institute of Health
PAVE	Partnership for Vivax Elimination
PCR	polymerase chain reaction
PDP	Product Development Partnership
Pf	*Plasmodium falciparum/P. falciparum*
pLDH	parasite lactate dehydrogenase
PMI	United States President's Malaria Initiative
POC	point of care
PPE	personal protective equipment
PPM	Pooled Procurement Mechanism (the Global Fund)
PQ	WHO Prequalification of In Vitro Diagnostics Programme
PQR	Price and Quality Reporting (the Global Fund)
Pv	*Plasmodium vivax/P. vivax*
p/µL	parasites per microlitre
QMS	quality management systems
R&D	research and development
RBM	Roll Back Malaria Partnership
RDT	rapid diagnostic test
TPP	Target Product Profile
TSS	Technical Specification Series (WHO Prequalification)
µL	microlitre
UNICEF	United Nations Children's Emergency Fund
US	United States
US CDC	United States Centers for Disease Control
US FDA	United States Food and Drug Administration
WHO	World Health Organization

I. INTRODUCTION

Unitaid's mission is to expand the reach of the best health products for those who need them most, designing and investing in innovative approaches to make quality health products available and affordable in low- and middle-income countries (LMICs). Unitaid accelerates the introduction and adoption of key health products, using market-shaping approaches to enable suitable, affordable, quality supply. The Unitaid Strategy for 2023-2027 prioritizes quality case management, including diagnostics that underpin case management and, when combined with accurate test reporting, inform programmatic decisions on resource allocation. Considering recent shifts in the malaria rapid tests markets and COVID-19 pandemic disruptions, it is both timely and important for Unitaid to update its understanding of the markets for existing malaria tests, the diagnostic technologies in development, and the work of other stakeholders. This 2022 malaria diagnostics market and technology landscape report, the fourth edition, intends to stimulate discussion and inform potential opportunities to improve access to effective malaria case management, acknowledging the foundational role that diagnostics play.

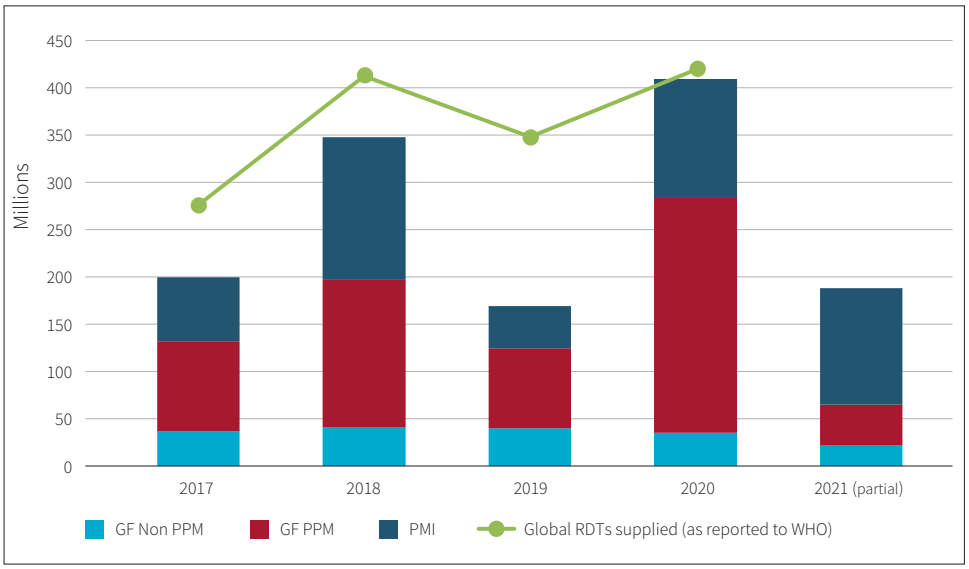
METHODS

This market and technology landscape report was prepared by reviewing information in the public domain, including policymaker and partner reports, peer-reviewed publications, and institutional and corporate websites. This desk review was supplemented by discussions with partners and experts and semi-structured telephone interviews with malaria rapid diagnostic tests (RDT) manufacturers.

Procurement data analysis

Procurement data analysis sheds light on how the pandemic, supply base, and procurement changes have affected the malaria RDT market. For this report, procurement data from the President's Malaria Initiative (PMI) and the Global Fund's Price and Quality Reporting (PQR) system were analyzed. In total, the data set contains 1014 individual orders totaling 1.3 billion RDTs over the 2017-2021 period. While data incompleteness can be a challenge in any year, the pandemic appears to have delayed some reporting for 2019 in particular (Figure 1).

FIGURE 1. Data sources for procurement data analysis



Note: GF PPM = Global Fund Pooled Procurement Mechanism, GF Non PPM = direct procurement by countries, reported to the Global Fund's Price and Quality Reporting system.

Technology landscape

An abundance of technical methods for malaria detection is possible, and while many are reported in the literature, it is beyond the scope of this report to cover them exhaustively. As such this report focuses on the major approaches to diagnosing malaria, with a few illustrative examples of a particular type of technology or approach. The focus is deliberately on rapid approaches that do not require extensive laboratory infrastructure, cold chain, or trained staff. Active product development efforts were identified by scanning funding agency websites for projects, searching industry news sites, and through discussions with stakeholders. This was supplemented by targeted literature searches, focusing on review articles and a selection of recent publications. This report relied on desk research; technology developers were not engaged directly. Thus, the information is only as current and reliable as sources permitted.

The landscape suggests opportunities for interventions that may improve malaria diagnosis and case management. These suggestions are not exhaustive and are intended for consideration; they do not necessarily reflect a scope of work to be supported by Unitaid.

2. PUBLIC HEALTH CHALLENGE AND ACCESS TO MALARIA DIAGNOSIS

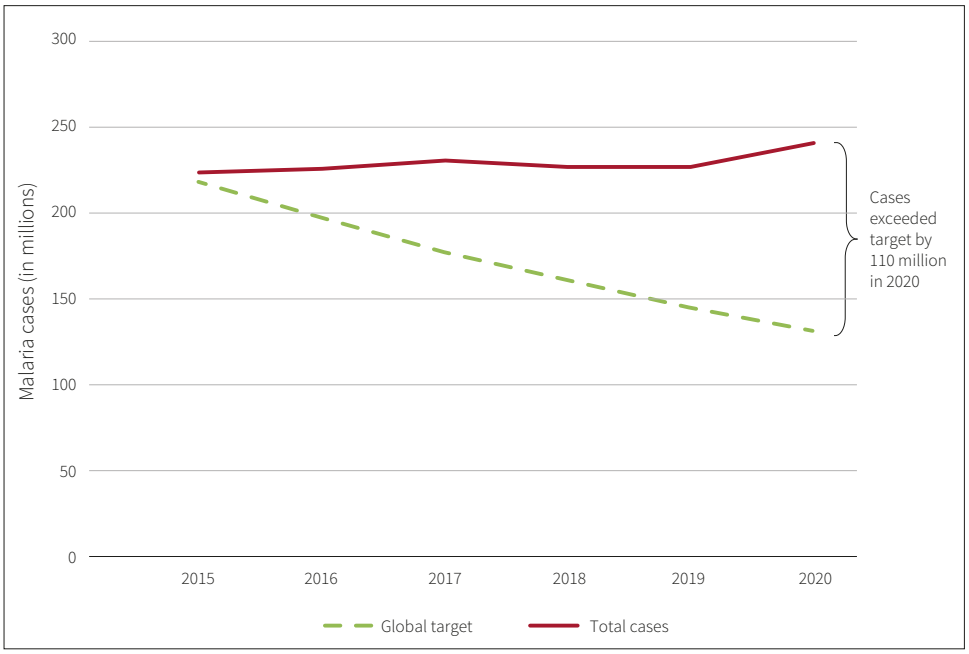
MALARIA BURDEN AND GLOBAL TARGETS

Globally, 4 billion people live in malaria risk areas across 85 malaria endemic countries. In 2020, there were 241 million malaria cases, an increase of 14 million from 2019, with most of the increase occurring in Africa. An estimated 627,000 people died from malaria in 2020, an increase of 69,000 from 2019. Overall, cases remain concentrated in Africa (95% of cases), and deaths affect children (77% of deaths are in children under five). (1)

During the first year of the COVID-19 pandemic, modest interruptions in prevention and case management activities led to increased malaria cases and deaths. However, the collaborative effort of the WHO, National Malaria Programs, and partners prevented a potential worst-case scenario, the doubling of malaria deaths.(2) While malaria prevention and case management services have largely resumed, the impact of ongoing waves of COVID-19; challenges with the supply of essential malaria commodities; and uncertainty about funding for malaria given competing resource needs contribute to ongoing uncertainty about how the pandemic will ultimately impact malaria.(3)

Although during 2000-2015, malaria case incidence reduced dramatically, since 2015 progress has stagnated. At the same time, populations living in malaria-risk areas have increased, and funding has plateaued, effectively reducing the funding available per population at risk. As a result, the world is not on track to achieve global malaria targets for 2016-2030 (Figure 2).(4)

FIGURE 2. Global malaria cases vs. targets



Source: adapted from RBM Partnership

At the country level, progress varies. Before the pandemic, approximately one-third of endemic countries were progressing towards global targets, including many low-incidence countries included in the WHO "Elimination 2025 Initiative," a cohort of 25 countries with the potential to eliminate malaria by 2025. In contrast, progress plateaued in approximately one-third of countries, and in the remaining third, malaria incidence increased. In 2018, the WHO and partners launched the High Burden High Impact (HBHI) response to reinvigorate progress. The initiative focuses on the eleven countries comprising 70% of the global malaria burden and supports them in achieving global malaria targets. Among the HBHI elements are galvanizing political will and using data to inform tailored subnational responses. One early finding is that 43% of HBHI country populations live in urban areas, prompting an upcoming WHO review on urban malaria.

P. falciparum histidine-rich protein 2/3 deletions

P. falciparum histidine-rich protein 2 and 3 (HRP2/3) gene deletions threaten the underpinning diagnostic tool for global malaria testing and in turn, case management progress. The vast majority of RDTs diagnosing *P. falciparum* (Pf) malaria are based on detection of HRP2, a protein that is specific to Pf, and a closely related protein, HRP3. A decade ago, researchers discovered Pf parasites in the Amazon region that lacked the genes for encoding the HRP2 and HPR3 proteins.[1] In the past five years, Asian, Middle Eastern, and African countries have reported parasites with HRP2 and HRP3 deletions.[2] Scientists do not understand the cause of deletions. While selection pressure from use of HRP2 RDTs is a potential contributing cause, the Amazon area, where scientists first noted deletions, did not use RDTs widely. Nevertheless, experts anticipate continued geographical expansion and increasing prevalence of HRP2/3 deletions. Parasites with deletions can become dominant in a region, in some places, they are the majority.(1) In these instances, HRP2-detecting RDTs could miss many infected patients, potentially increasing morbidity and mortality and undermining confidence in these critical tools.

The WHO Global Malaria Program (GMP) published a global response plan in 2019 (5), is tracking published reports of HRP2/3 deletions through the Malaria Threat Maps, and has developed survey protocol templates for countries to assess the prevalence of deletions causing false-negative HRP-2 RDTs.(6) If these surveys find that Pf HRP2/3 deletions are leading to >5% false negative HRP2-RDTs in symptomatic patients, the WHO recommends switching to an alternate RDT that uses lactate dehydrogenase (LDH) specific for *P. falciparum* to detect Pf, although quality-assured options are limited. (5)

1 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, many mAbs cross-react with HRP3, so an RDT could still return a positive result on the HPR2 antigen line even when HRP2 genes have been deleted.

2 For the most up-to-date information see the WHO Malaria Threats Map: http://apps.who.int/malaria/maps/threats/

WHO GUIDANCE

The WHO has recommended testing, using quality assured microscopy or RDTs, and treatment based on the results for over a decade. Broadly speaking, the guidance has not changed.

The WHO GMP responded swiftly to the pandemic and in April 2020, published guidance to jointly address malaria and COVID-19.(7) The WHO stressed the potentially devastating effects of the pandemic on malaria morbidity and mortality. Recognizing that malaria illness shares many signs and symptoms with COVID-19, the guidelines emphasized the importance of early care-seeking for febrile illness and continued malaria case management, including testing for malaria and COVID-19. To minimize the risk of COVID-19 transmission, WHO recommends full personal protective equipment (PPE) for health workers conducting malaria RDTs. If PPE or RDTs are not available, the WHO recommends presumptive malaria treatment as a temporary measure, prioritizing based on available ACT and RDT stocks. In exceptional situations (i.e. major increases in malaria cases and death), countries may consider mass drug administration or presumptive treatment.

The WHO has also expanded its guidance on case management of relapsing malaria. (8) (9) The malaria species *P. vivax* and *P. ovale* form hypnozoites, a dormant parasite stage that hides in the liver undetected by diagnostic tests. These hypnozoites can cause relapse after the cure of the acute blood-stage infection. To prevent relapse, additional treatment is needed to clear the hypnozoites from the liver. Two treatments are available: a 14-day course of primaquine[3] or a single-dose treatment, tafenoquine. Both primaquine and tafenoquine can cause hemolytic anemia in patients with intermediate G6PD activity or low G6PD activity (deficient) patients. WHO guidance recommends that the G6PD status of an individual be known before administering primaquine. Tafenoquine's drug labeling requires a >70% of normal G6PD activity threshold, which can currently only be determined through quantitative G6PD testing. WHO expects to develop guidelines on the use of point of care G6PD tests and tafenoquine in 2022-2023.

Gaps in the normative guidance relate primarily to improving case management for fever beyond malaria. Malaria's most common symptom, i.e. fever, is also very non-specific and is associated with many common diseases. As malaria prevalence decreases in many geographies, it becomes increasingly important for health care workers to consider other potential causes of fever in patients. For example, because individuals in endemic areas build immunity to malaria, it is possible for a patient to be co-infected with malaria and another disease, and the malaria infection may not be causing their illness. Managing patients who do not have malaria has become an acute challenge, leading to overuse of antibiotics. While some guidelines for young children are available, they may not reflect current epidemiology and guidance is lacking for older children and adults. The lack of diagnostics for "non-malaria fevers" challenges policymakers, as a febrile illness is difficult to diagnose clinically.

Malaria programs increasingly rely on the data generated through malaria testing to manage their response. While testing has always been paramount to elimination efforts, countries with higher burdens are increasingly interested in using diagnostic test data to stratify and target interventions geographically. For example, by 2018, 50 countries were using District Health Information Software 2 (DHIS2), which has helped subnational malaria strategy tailoring, especially in HBHI countries. (10)

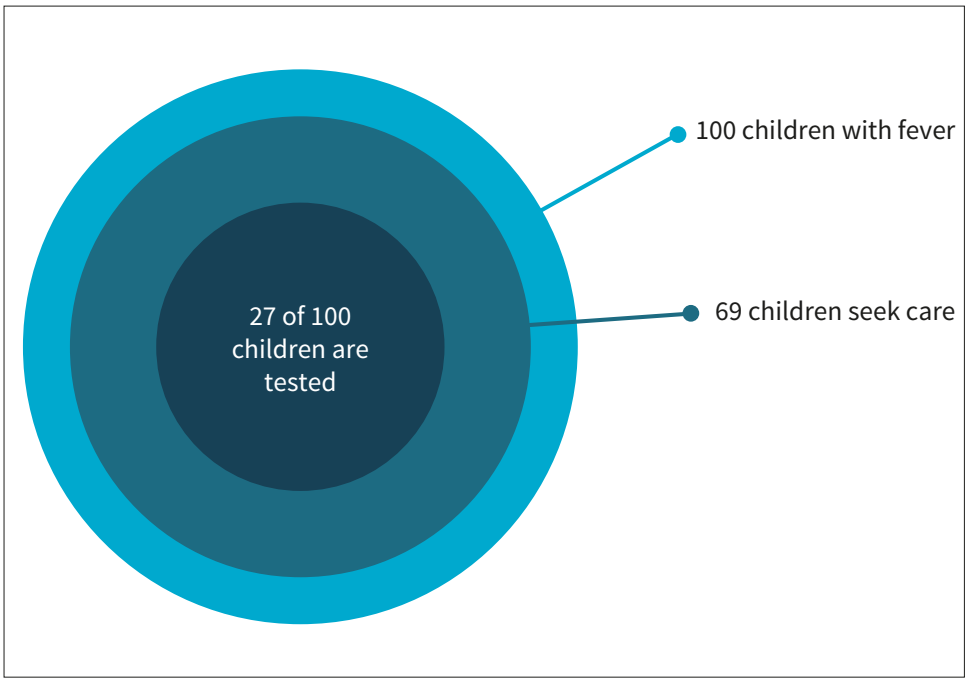
3 In some countries a 7-day course is used.

ACCESS TO TESTING

Household surveys are used to estimate fever prevalence, treatment-seeking rates, and appropriate case management. Comparing surveys conducted 10-15 years ago to those undertaken since 2015 shows that testing among children seeking care increased from 21% to 39% overall, while fever prevalence rates and care-seeking rates improved modestly. (1) These surveys suggest that care-seeking has shifted modestly from private to the public sector. The increase in the testing rate is likely a result of scaling up malaria RDTs in the African public sector.

Despite the progress, most children under five are not tested. Approximately two-thirds of children seek care for fever, and only 39% receive a malaria test. Overall, approximately 27 of 100 febrile children are tested. (1) (Figure 3) At the same time, surveys show that many children receive ACTs without testing. Equity analysis indicates that poorer households had higher fever prevalence in most countries, while wealthier families had higher treatment-seeking behaviors. (10) With a few exceptions, the percentage of children receiving a test is generally high in the public sector, slightly lower in the private professionally staffed clinics and hospitals, and minimal in pharmacies, drug shops, and other less formal outlets where many seek care.

FIGURE 3. Illustrative proportion of children under five with fever seeking care and tested



Source: adapted from World malaria report 2021. Based on 20 countries with baseline and follow up household surveys. In these surveys, about 20% of children had a fever in the period preceding the survey, 69% of them seek care, and, of those, a median of 39% are tested. Note that ranges vary significantly between countries, with only 9% of children tested in some countries versus 49% in others.

Impact of the Covid-19 pandemic on malaria testing

In early 2020, outpatient visits across most countries declined because of lockdowns and restrictions on movement, messaging that encouraged febrile individuals to isolate, and fear of acquiring COVID-19 infection at health facilities. Additionally, many health systems lacked the necessary personal protective equipment and other measures to assess patients safely. Malaria programs also universally reported delays in receiving case management and prevention commodities. As a result, malaria testing rates declined, especially in the early months of 2020.

However, messaging in malaria-endemic countries soon changed to encourage prompt-care seeking for fever. Additionally, health facilities secured protective equipment and adopted fever protocols incorporating malaria and COVID-19. Programs implemented supply chain measures to mitigate disruption, including distributing products within countries, and for 2021, revised quantifications, increased buffer stocks, and accelerated order placement. In many countries, health facility attendance and malaria testing had improved by late 2020. However, malaria care remains impacted by COVID-19 and occasionally by stockouts of PPE, RDTs, and/or ACTs.

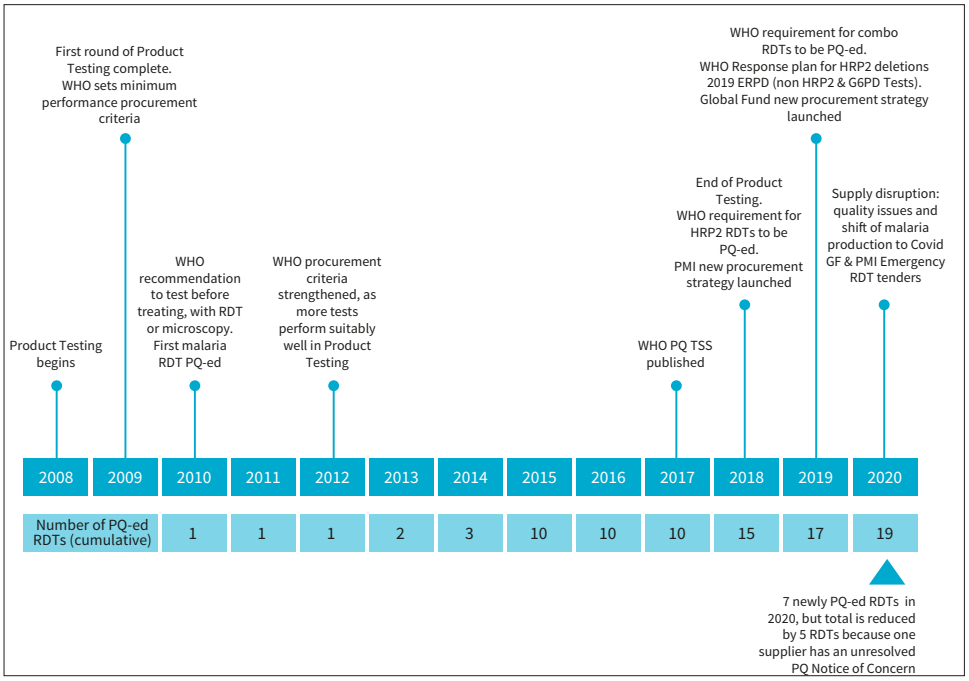
It is challenging to generalize further as the experiences of each country and even within countries differ. For example, reporting by selected sample of health facilities in 23 countries to the Global Fund revealed a 22% overall testing decline in Q2 2020, however individual country declines ranged from 4% to 78%. By Q1 2021, testing overall was down 4.6%, but still seven countries had reductions of more than 30% in malaria testing. While most did not, a few countries experienced increased consumption of malaria RDTs in 2020, attributed to increased fever care-seeking at the community level. For some programs relying on domestic malaria funding, future budgets are uncertain, as countries shift funds to COVID-19. Several elimination programs reported fewer imported cases, and some experienced increased local transmission and reduced active case finding activities. In summary, the pandemic is disrupting public sector testing to varying degrees, and there remain substantial gaps in testing access, especially where care-seeking in the private sector is high. Moreover, while the normative guidance suggests that malaria diagnostics should always be in the COVID-19 pathway (and vice versa), there is no data on whether this policy is implemented.

The implications of limited access to malaria testing include delayed or misdiagnosis, over-treatment and wastage of medicines. When malaria diagnosis is not available, presumptive malaria treatment is common, and other causes of febrile illness, many clinically indistinguishable from malaria, are neglected. Neglect for other diseases also occurs when health workers seeing malaria patients do not sufficiently consider co-infection and other causes of fever alongside malaria. The pandemic has spotlighted the importance of diagnostic testing and would be timely to revisit fever management practices more broadly to ensure quality care for malaria, COVID-19, and other febrile illnesses. (1) (3) (11)

3. MALARIA RDT MARKET

WHO QUALITY CRITERIA AND PROGRAMS

FIGURE 4. Evolution of quality monitoring for malaria RDTs and number of WHO prequalified RDTs by year



* Note: one company has five WHO prequalified malaria RDTs, however, it is not active in the malaria RDT market. It has an unresolved Notice of Concern from WHO PQ, which prevents selling into the donor-funded malaria RDT market. Moreover, in 2022, it confirmed that while it may consider malaria RDTs again in the future, its near-term focus was COVID-19 RDTs.

Source: Author analysis of WHO IVD Prequalification website, timeline adaptation from Cunningham et al (12).

Since malaria RDTs launched into an unregulated market in the 1990s, product quality standards have progressively strengthened, resulting in increased acceptance and uptake of malaria RDTs (Figure 4). (12) In 2008, the WHO and partners created an international RDT quality control program for malaria RDTs, comprising: i) Product Testing, a centralized performance evaluation, and ii) Lot Testing, a post-procurement quality verification program. From 2010 to 2018 the performance of malaria RDTs in the Product Testing program informed most public sector procurement, resulting in an increasing market share for high-performing products. (12) Product Testing as a stand-alone activity ended in 2018 and was subsumed under the WHO Prequalification process, representing the laboratory evaluation component. WHO subsequently began a phased policy for recommending prequalification for malaria RDTs according to RDT type (Table 1). The policies of major donors funding malaria RDT procurement are mostly aligned with the WHO treatment guidance and product selection recommendations.

TABLE 1. WHO recommended criteria for selecting and procuring RDTs (13)

Test type	WHO Recommendation
Pf only HRP2 detecting RDTs	WHO PQ, January 2018
Pf/pan and Pf/pv detecting HRP2	WHO PQ, January 2019
Pf LDH detecting RDTs for deletions	• ISO 13485:2003 • Submission to WHO PQ • Meeting WHO performance criteria on HRP2 expressing and non-expressing panels calibrated to 200p/µL (based on WHO laboratory assessment performed at the US Centre for Disease Control (CDC)).
Pf LDH combo RDTs detecting RDTs for deletions	• ISO 13485:2003 • Submission to WHO PQ • Meeting WHO performance criteria on HRP2 expressing and non-expressing panels calibrated to 200p/µL (based on WHO laboratory assessment performed at the US CDC).

WHO Prequalification

The WHO PQ process comprises three components:

Review of the product dossier

Evidence and studies supporting the product's performance claims are an essential component of the dossier review. In 2017 the WHO published malaria RDT Technical Specification Series (TSS) outlining the minimum verification and validation expectations, especially for studies establishing the analytical performance of the test (i.e. features of the test that should be validated in the lab) and the clinical performance (i.e. studies of test performance in the hands of intended users on patient samples). (14)

WHO PQ is planning to update the malaria RDT TSS in anticipation of changing epidemiology and new products and to reflect advances in evaluation processes for antigen detecting tests. In particular, the updated TSS will specify the studies needed to support claims about RDT performance in parasites with HRP2/3 deletions (PQ also verifies this through the performance evaluation, described below). The TSS is also likely to require assessment and reporting on the RDT's analytic sensitivity in terms of the lowest antigen concentration detected. This represents a shift, as historically, manufacturers and evaluators express the performance of malaria RDTs in terms of parasite concentration, i.e. "parasites per microliter," which is a metric used in malaria microscopy. However, malaria RDTs do not measure parasite concentration; they detect antigens. The parasite concentration may not correlate well with antigen concentration, especially for HRP2, so, using this metric introduces complexity and imprecision that must be taken into account. Historically, data on antigen concentrations in malaria-infected patients was limited. However, increasing published data on antigen concentration, parasites per microliter, and pyrogenic threshold for malaria (i.e. level of infection that leads to a fever, or "clinical disease") makes it feasible to begin appreciating antigen concentration and how it correlates to symptomatic and asymptomatic malaria illness. As with any TSS update, manufacturers who have already prequalified their product will have three years to comply with new requirements.

Performance evaluation

WHO PQ conducts laboratory performance evaluations for all products. When product testing results are available PQ uses them. Otherwise, PQ commissions evaluations at US CDC labs using a panel and protocols similar to Product Testing.

A noteworthy addition to the evaluation, is the incorporation of WHO International Pf and Pv antigen Standards for malaria RDTs. CDC will evaluate malaria RDTs using the newly available WHO International Standards (Box 1), and PQ will report the lowest concentration of antigen detected (expressed in International Units).

Manufacturing site assessment

WHO PQ includes manufacturing site inspections to assess compliance with the requirements of ISO13485 and the relevant TSS. The inspections are generally performed on-site; exceptionally, WHO conducts them remotely.

In 2016, when the WHO announced that prequalification would soon be a requirement for malaria RDTs, submissions to PQ increased. Since the number of malaria applicants has dropped to ~5 per year. Currently, 19 tests from seven suppliers are prequalified, and eight tests from four suppliers[4] are in the PQ pipeline.

Overall, malaria RDT dossier processing timelines have been longer than usual, and during the pandemic travel restrictions precluded some site inspections. Since 2020, rapid antigen and point-of-care COVID-19 tests have been the WHO's highest priority, and as of Q1 2022, applications for other tests remain medium priority. (15) In addition to many COVID-19 Emergency Use Listing (EUL) applications, the volume of change notifications requiring WHO PQ review increased during the pandemic, as manufacturers sought to expand their production capacity or to increase their raw materials suppliers (i.e. qualify additional "back up" raw materials suppliers). Despite the challenges, WHO has prequalified 21 tests since the start of the pandemic, including seven malaria RDTs.

BOX 1. WHO INTERNATIONAL REFERENCE STANDARDS FOR PF AND PV RDTS

WHO International reference standards are well-characterized malaria samples prepared from culture or from human blood that test evaluators and developers can use to assess malaria RDT performance objectively. FIND and the National Institute for Biological Standards and (NIBSC) collaborated to develop malaria RDT antigen standards. The WHO Expert Committee on Biological Standardization (ECBS) approved the Pf HRP2/LDH and Pv LDH standards in 2017 and 2020 respectively.

Because the standards are often derived from human samples, their quantity is finite, and the intention is for manufacturers, test developers, evaluating labs to use them to assess new RDTs or to calibrate other quality controls material. Unlike other samples, these international reference standards are not assigned parasite or antigen concentrations, i.e. they do not have "parasites per µL" or "picogram of antigen per mL". Instead, they use a generic unitage, "International Units (IU)," that serves as the comparator. In practice, evaluators serially dilute the standard, assess the lowest concentration that the RDT detects, and report in International Units. The use of and reporting against one widely accepted standard can be one means of comparing test performance.

4 Note this does not include products from one company with five WHO prequalified malaria RDTs and one pipeline product because the company is not active in the malaria RDT market.

Expert Review Panel for diagnostics

For critical diagnostics that are applying to WHO PQ or another stringent regulatory assessment, the Global Fund/Unitaid Expert Review Panel for diagnostics (ERPd) provides an interim solution allowing procurement by the Global Fund and Unitaid. The panel considers the potential risks and benefits of diagnostics. It makes time-limited procurement recommendations, with the expectation that manufacturers will then submit products to the WHO PQ or to a stringent regulatory process. Opportunities for evaluation are initiated by the Global Fund after partner consultation; the schedule for diagnostic products tends to be ad hoc. In 2019, the Global Fund ran the ERPd process for Pf LDH and POC G6PD tests. The panel granted ERPd status to Rapigen's three BIOCREDIT malaria RDTs and SD Biosensor's G6PD system (both of these described in more detail below).

Quality control

Post-purchase quality control for malaria RDTs remains a challenge. Historically, mRDT post-purchase quality control relied heavily on donor-funded lot testing at centers collaborating with the WHO. Despite the impact on the market, the collection, preparation, and characterization of clinical samples for lot testing (and product testing) are difficult and expensive. Several years ago there was a global effort to transition to recombinant panels, which can be manufactured synthetically; however, these were not suitably equivalent to clinical samples and work was discontinued. (16)

Currently, WHO offers centralized lot testing using cultured and clinical samples for free until the sample stocks are depleted, likely 2023.[5] In the future, WHO's international reference standards (above) are expected to support the calibration of lot testing panels in a more decentralized manner. Demand for lot testing has decreased from 700-800 lots per year to 450-500 lots per year in 2020/21. Larger lot sizes partly explain the decrease, additionally, the Global Fund lessened lot testing requirements as WHO PQ was implemented for malaria RDTs. PMI has scaled back volumes by implementing a risk-based lot testing strategy, however, with many new suppliers, PMI's testing volumes remain moderately high.

Additional QC measures included a multi-year Bill and Melinda Gates Foundation (BMGF)- and Unitaid-supported effort led by FIND to develop universal quality controls (i.e. positive control wells that could be used for any brand of malaria RDT). Technically, it was impossible to make a single universal control material because of differences in RDT manufacturer's monoclonal antibodies (mAbs), which detect a variety of antigen epitopes. The WHO has proposed manufacturers develop control materials for individual RDTs, and developed protocols for quality control development. (17) It remains to be seen if manufacturers accept and use this guidance.

5 Currently, WHO supports free lot testing at Research Institute for Tropical Medicine in the Philippines. Additionally, two laboratories that have previously collaborated with WHO on lot testing may offer service: National Institute of Malaria Research (NIMR), New Delhi, India and the ANDI Centre of Excellence for Malaria Diagnosis, University of Lagos, Nigeria

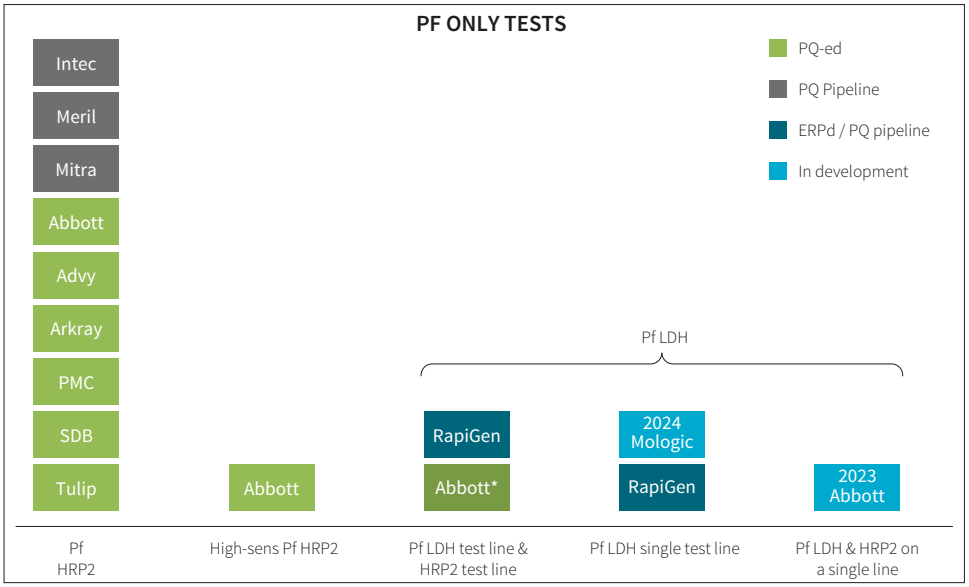
PRODUCT OFFERING

In 2019 and 2020, the WHO prequalified nine new malaria RDTs, bringing the total to 19 prequalified tests.[6] This includes at least five prequalified RDTs for each of the "conventional" case management test types, i.e. Pf-only, Pf/pan, and Pf/pv - where Pf detection is by HRP2. (Figure 5)

For areas with Pf HRP2/3 delations, there are limited quality-assured RDTs. A few products, with notably different test line configurations (Figure 5), have launched or are in development. In lab testing, the sensitivity of these new Pf LDH tests exceeds that of the earlier, or "conventional" pf LDH tests. Rapigen has three RDTs based on more sensitive Pf LDH with ERPd status in the PQ pipeline, and Abbott and Mologic are also developing RDTs that include more sensitive Pf LDH (see the Innovation section below for details on the products). Although programs may also consider pan LDH RDTs for areas with HRP2/3 deletions, no products currently meet the donor-funded market requirements[7] and pan tests do not differentiate between Pf and Pv.

Additionally, there are three prequalified Abbott tests that have more nuanced use cases, including a highly-sensitive RDT and two RDTs that include HRP2 and Pf LDH. Although the latter two tests are prequalified, neither test's pf LDH line met the WHO threshold for panel detection in Product Testing and the WHO does not recommend them for case management in areas with deletions.[8]

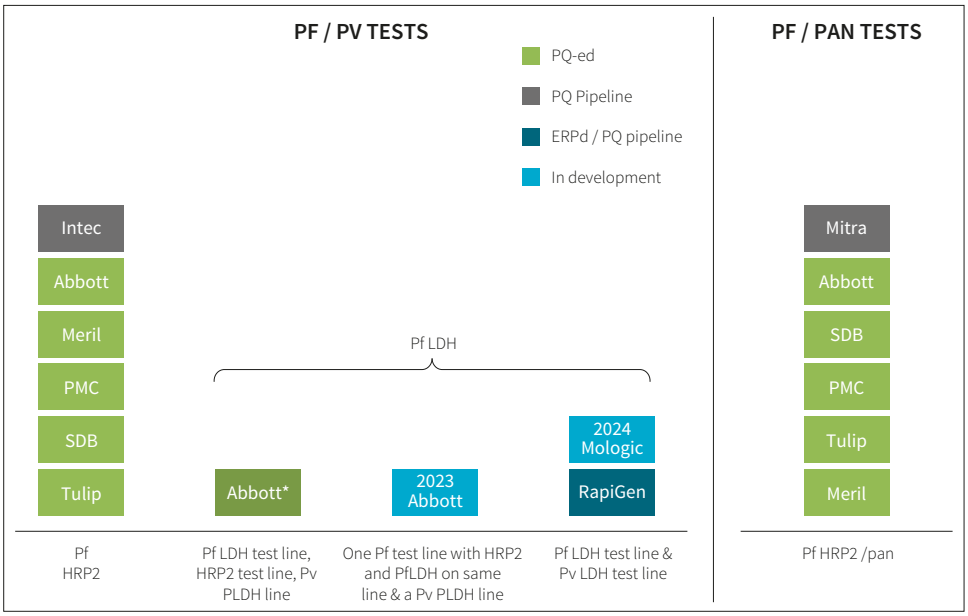
FIGURE 5. Donor-funded market malaria RDT product offering, according to test type and development status, by manufacturer



6 The total was 24 PQ-ed RDTs; however, one supplier with five PQ-ed RDTs has not been active in the market since early 2020, effectively reducing the total.

7 AccessBio's CareStart Pan test remains prequalified, however, it has an outstanding Notice of Concern from WHO PQ and has decided to focus on other products, effectively exiting the malaria RDT market since 2020.

8 Tests are prequalified based on having sufficient evidence to back up the manufacturer's claims, and these tests claim an "ability to detect Pf LDH." Because they do not make any specific claims about detection of Pf in parasites with HRP2/3 deletions, WHO Prequalification did not specifically assess this. WHO GMP does not recommend their use for clinical management in areas with deletions because pf LDH test lines' panel detection score was below the minimum criteria. One of the WHO PQ public reports specifically includes this limitation, while the other test's public report was issued several years ago, before widespread use for case management in settings with deletions was a major concern.



*The Product testing results for the pfLDH component of these tests do not meet WHO GMP minimum criteria, therefore they are not recommended for clinical management in populations where HRP2/3 deletions are present.

Abbreviations: SDB = SD Biosensor, PMC = Premier Medical Corporation

MARKET SEGMENTS, SIZE AND FORECASTS

As context for appreciating the malaria RDT market size and forecasts, it is helpful to segment the malaria RDT market by the funding stream/payor (Figure 6). Reliable information on the international donor-funded market, the dominant market segment, is comparatively more available than the domestically funded RDTs segment, while information on the privately funded RDT market segments is anecdotal at best.

FIGURE 6. Global malaria RDT market segments by funding stream/channel, illustrative market size estimates

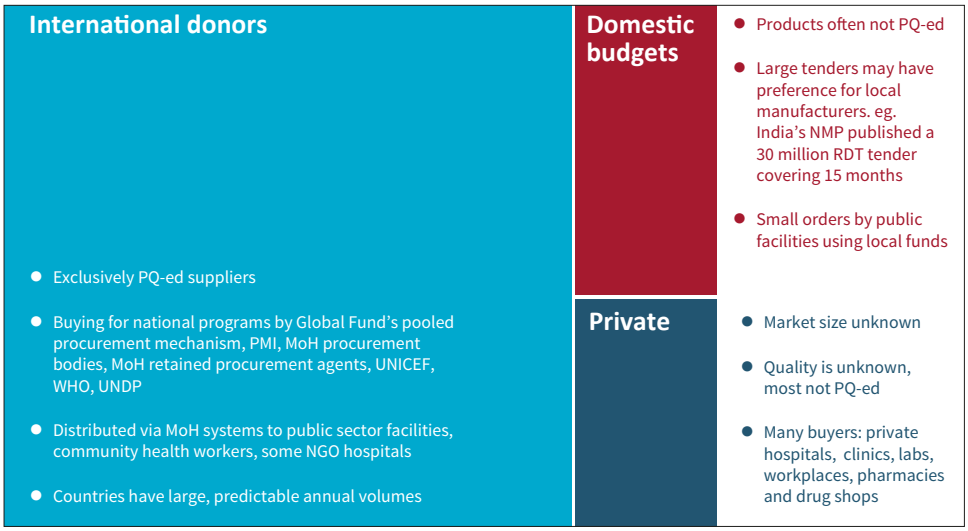
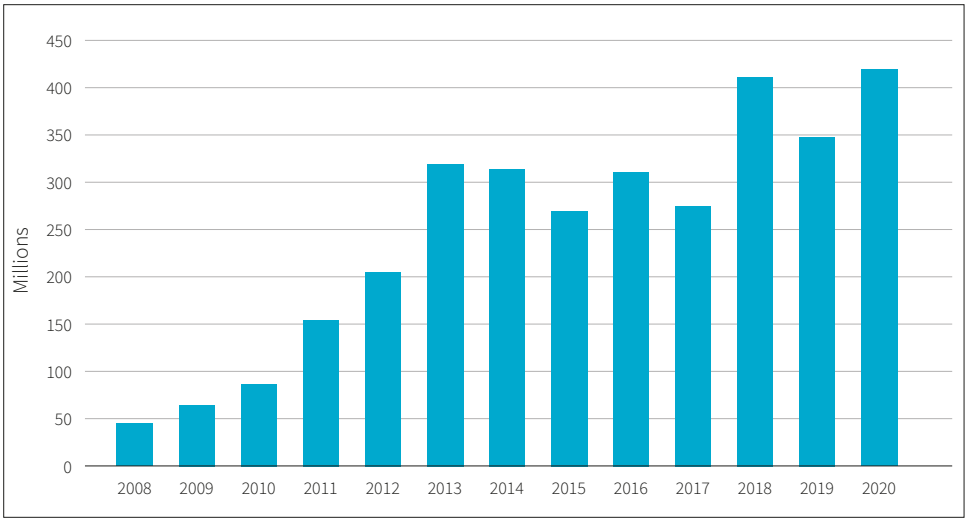


FIGURE 7. Number of malaria RDTs supplied by manufacturers eligible for the WHO procurement

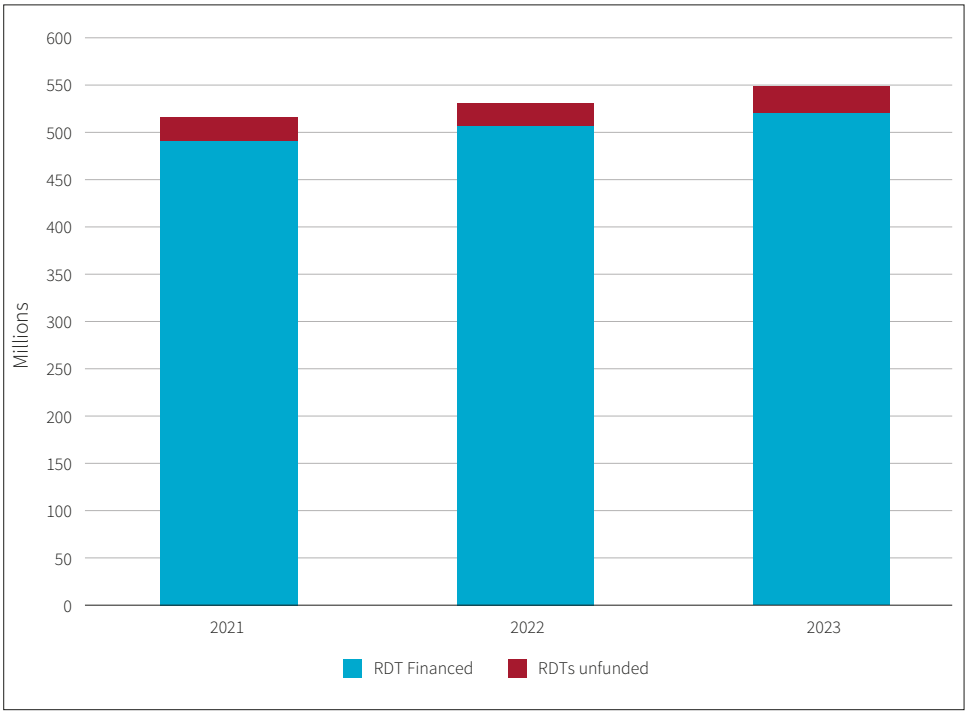


Source: WHO's annual Global malaria reports

Reporting by suppliers to the WHO indicates that annual malaria RDT volumes have increased several-fold in the past ten years. The year-to-year volume variance in part results from timing differences (i.e. transaction reporting, funding and procurement cycles). The average annual volume of RDTs supplied was 300 million annually for 2013-2017, increasing to 393 million annually for 2018-2020, and topping out at 419 million RDTs in 2020. (Figure 7) (1). While these estimates capture most of the market (Figure 6), not all suppliers report their volumes to the WHO. In particular, the WHO does not survey the many manufacturers that do not meet its quality recommendations. There is no systematic data available on this market, but conversations with suppliers suggest that these volumes are much smaller than the donor-funded sector.

Considering the pandemic's impact on supply chain and service delivery, the volume of malaria RDTs supplied in 2020 was higher than expected. There are a few potential explanations. First, as lead times lengthened (up to 75 days longer than pre-pandemic), and supply chains became less predictable, malaria programs, often following procurement agent advice (18), increased their buffer stocks and placed orders earlier in the procurement cycle. Additionally, in the current Global Fund grant-making cycle, many national malaria programs are well-funded, i.e. compared to previous years, many national programs have not felt acute pressure to limit essential interventions like testing. Moreover, even in countries where malaria funding is limited, programs tend to prioritize case management commodities, including RDTs, over other interventions, e.g. IRS. As a result, RBM is predicting minimal gaps in the 2021-23 RDT budgets (Figure 8), and PMI and Global Fund procurement volumes for the first half of 2021 suggest that 2021 malaria RDT volumes may be similar to 2020s.

FIGURE 8. 48 country commodity gap analysis by RBM

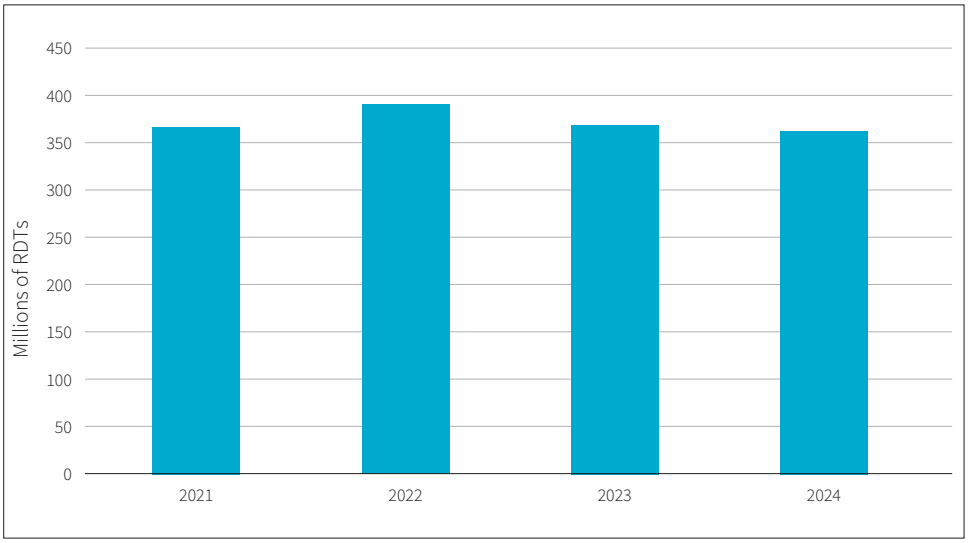


Source: RBM Partnership, Country/Regional Support Partner Committee (3)

CHAI recently forecasted steady donor-funded malaria RDT volumes, ranging from 363-390 million RDTs annually for 2021-2024 (Figure 9). Given the recent volume reported by the WHO for 2020 (419 million) the CHAI estimate may appear low. However, the two values reflect slightly different market segments. Both CHAI and WHO focus on prequalified suppliers; however, the WHO asks suppliers to report sales overall while CHAI focuses on donor-funded markets. Assuming prequalified suppliers sell 5-10% of their tests outside of donor-funded channels, the CHAI forecast would approach an average annual volume of 400m RDTs.

Several variables affect future demand. For instance, the pandemic could reduce international and domestic funding for malaria. The CHAI forecast assumes a fixed percentage of funding allocated to malaria RDTs and assumes that RDT prices are constant. Some countries, however, may require new, potentially more expensive products, e.g. tests suitable for areas with HRP2/3 deletions. Because shipping costs have increased, the total landed cost of malaria RDTs has also increased, which, if budgets are fixed could reduce the volume of tests bought. Despite these variables, there is reason to expect steady malaria RDT demand as programs typically prioritize public sector case management, and this segment already consumes most malaria RDTs. While public sector demand is likely to remain fairly steady, efforts to expand testing to new sectors (e.g. community, retail outlets) may be negatively affected by cost increases or these potential fundiwng shortages.

FIGURE 9. Forecasted donor-funded malaria RDT market



Source: CHAI forecasted donor-funded RDT procurement

MARKET GROWTH OPPORTUNITIES EXIST, YET ARE DIFFICULT TO SERVE

When RDTs came to market, malaria programs focused on scaling testing in the public sector. Although one can question its accuracy, available testing data suggests that many programs have dramatically increased testing rates in the public sector. However, reaching those who are not seeking care for fever and those who access the informal private sector is a perennial challenge. Depending on the context, the populations lacking access to quality case management can be quite substantial, indeed the majority, in some countries. Yet, evidence suggests they are not a monolithic group, and in particular a better understanding of the private sector markets is needed to prioritize and effectively reach these populations.

Private sector case management

The private sector is an important component of care-seeking for fever in countries like Nigeria, Chad, Uganda, the Democratic Republic of Congo, Ghana, and India yet quality malaria diagnosis is seldom available outside of formal health facilities. Improving case management in the retail private sector has long been a topic of interest, yet progress has been slow, likely a reflection of the complexity of "the private sector" which is heterogeneous, with business models not well understood by the public health community.

While the AMFm improved the availability of quality-assured ACTs in the private sector, it did not include diagnostics. Although the Global Fund can support private sector case management efforts, since the dedicated AMFm funding program ended, competing priorities within malaria budgets have led countries to deprioritize private sector case management.

In 2013-2016, Unitaid-funded a project implemented by Population Services International (PSI) aimed to increase private sector RDT availability in five African countries through various methods, including price-subsidies, building consumer awareness, provider training, and regulatory change support. The project highlighted many regulatory, policy, and logistical

challenges and documented several lessons. (19) (20) While it achieved moderate increases in testing, progress in sustaining and further developing these markets is unclear.

In 2020, the WHO convened a meeting with malaria programs, implementing partners, and donors to re-consider private sector case management. In 2021, the Center for Global Development led an effort among donors and policymakers to consider improvements to case management in Africa's private sector. While partners are acting on several meeting recommendations (e.g. commissioning evidence reviews, developing operational guidelines), they have not coalesced around any concrete way forward. The WHO is also developing, through universal coverage efforts, frameworks and tools for integration and strengthening private-sector care. (21) Current efforts focus on the COVID-19 response; however, the work lays a foundation for other diseases and conditions in the future.

A few partners are exploring opportunities to partner with local distributors or pharmacy networks serving segments of the retail market to improve the quality of case management in these outlets. Many of these efforts aspire to leverage point-of-sales digital technologies for program monitoring and targeting of subsidies.

Community case management

Another option for expanding malaria testing and case management access is though community-based programs. While community case management is a WHO and UNICEF priority, and there has been progress in institutionalizing community case management (22), it remains a challenge to implement Community Health Worker (CHW) programs sustainably. Furthermore, household surveys suggest that CHW contributions to malaria case management have remained modest over the years (1), although reporting systems may not adequately capture CHW contributions, because often tests used in the community are distributed through facilities and not differentiated from tests at public health facilities. In response to the pandemic, some countries did increase fever case management at the community level, for instance, in Liberia and Mozambique, while Rwanda leveraged its longstanding investment in CHWs.

Self-testing

Compared to the past, there is more global interest in self-testing, driven by increasing commercial availability and experience with COVID-19 self-testing. However, most of this experience is in high-income settings; how this translates to LMICs and malaria, an acute and potentially rapidly fatal disease remains to be seen. There is little evidence for malaria self-testing and varying expert opinions around the viability and safety of this approach. On the one hand, many patients already self-treat for malaria, and testing might improve the targeting of antimalarials in this group. Providing more diagnostics options may also chip away at the large segment of the population that is not reached by current RDTs and microscopy. However, there are concerns around self-testing, especially in children, because malaria and other acute febrile illnesses can quickly become severe, and the risks associated with misdiagnosis are higher than they may be in less acute diseases for example, HIV. There is little evidence on self-testing for malaria, apart from an initiative among forest workers in French Guyana and Suriname (23).

One malaria self-test is on the market in West Africa. In 2015, Fyodor Biotechnologies launched a urine-based malaria rapid test in Nigeria, intended for professional and self-testing. The Urine Malaria Test™ is a dipstick format, the strip is dipped into a sample cup filled with urine and allowed to stand at room temperature for 20 minutes before the results are read. Compared to a traditional RDT, the test has fewer steps (no buffer, no sample transfer device). However, limited validations suggest that performance is slightly below that of prequalified malaria RDTs (24). Online pharmacy pricing is approximately US$1.45 (3,000 Nigerian Naira for a box of five tests) (25).

Procurement practices

The largest RDT buyers, PMI and Global Fund via the Pooled Procurement Mechanism (PPM), historically sourced malaria RDTs via spot buying and sole sourcing. While spot tenders were competitive, intense rivalry among suppliers eventually resulted in unsustainable pricing. At the same time, procurers occasionally honored country preferences for a particular test, and these sole-sourced orders resulted in higher prices. As intense competition reduced margins, many suppliers exited the donor-funded market, resulting in near-exclusive reliance on two RDT manufacturers, even though several others met WHO requirements (e.g. in 2018 there were 4-5 prequalified Pf RDTs, and >20 meeting product testing requirements).

In 2018, the Malaria RDT Procurement Task Force[9] began to address this precarious market situation, meeting to align on procurement strategies to improve the health of the RDT market. Considerations included:

- 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 preferences for particular tests unless epidemiologically justified.

In 2018, PMI[10] launched a new procurement strategy, which included long-term agreements with six suppliers, fixed price solicitations, and volume allocations performed annually based on 'best value,' which includes criteria beyond ex-works price, for instance, total landed cost, supplier performance, registration coverage, shelf life, product portfolio, quality, market health considerations, and quality. PMI also limited sole sourcing except when epidemiologically justified.

In 2019, Global Fund PPM also implemented a revised procurement strategy, signing agreements with five manufacturers and anticipating the addition of other suppliers as their products became prequalified. Like PMI, the Global Fund stopped sole souring RDTs based on country requests and considers RDTs of the same type interchangeable. Additionally, the Global Fund focused on quality, competitive prices, supplier performance, sustainable markets, and a diversified supply base. To facilitate a resilient supply base, the Global Fund aimed to allocate at least 20% of volumes to "new entrants."

9 The Malaria RDT Procurement Task Force is a multilateral group, chaired by PMI, whose members include procurement organizations, donors, and NGOs. It meets as required to align on procurement policies, promote a health marketplace for quality malaria RDTs and to encourage innovation. Members include the Bill & Melinda Gates Foundation; Clinton Health Access Initiative (CHAI); FIND; Global Fund; Global Health Supply Chain Program – Procurement and Supply Management (GHSC-PSM); Médecins Sans Frontières (MSF); PATH; PMI; RBM Partnership to End Malaria; UNDP; UNICEF; Unitaid; US CDC; and WHO GMP and WHO Prequalification Programme.

10 GHSC-PSM is the procurement agent for PMI. GHSC-PSM procures malaria commodities for 30 countries and develops strategic sourcing approaches.

2020 additional tender

Just as these changes were coming into effect, in early 2020, the pandemic and other supplier events exposed the market's fragility, requiring large reallocations of demand through emergency tenders. First, in January 2020, WHO Prequalification issued a notice of concern to one dominant supplier. The notice related to several quality issues, which would take time to remedy, and as a result, procurers stopped ordering from the company and shifted volumes to other suppliers. In the two years since, the company has not remedied the WHO concerns and has focused instead on the COVID-19 market, effectively exiting the malaria RDT market.

Then, in April 2020, the other dominant malaria RDT supplier signaled that it was shifting all of its malaria production to COVID-19 RDTs. After extensive discussion, this supplier remained in the malaria market, although the temporary uncertainty and disruption increased stakeholder concern about over-reliance on suppliers.

For procurers, the sudden exit of two leading suppliers created concern and a potential shortfall of 105.8 million malaria RDTs to meet the remaining 2020 demand. However, it presented an opportunity to engage new suppliers, accelerating a diversification of the supply base that was aligned with the Global Fund and PMI's recently launched procurement strategies. The malaria RDT Procurement Taskforce met with suppliers in June 2020 to discuss the recent developments, share global donor demand, and understand how COVID-19 impacted suppliers. In July and August 2020, the procurers launched additional tenders to secure the remaining unallocated volumes through the first quarter of 2021.

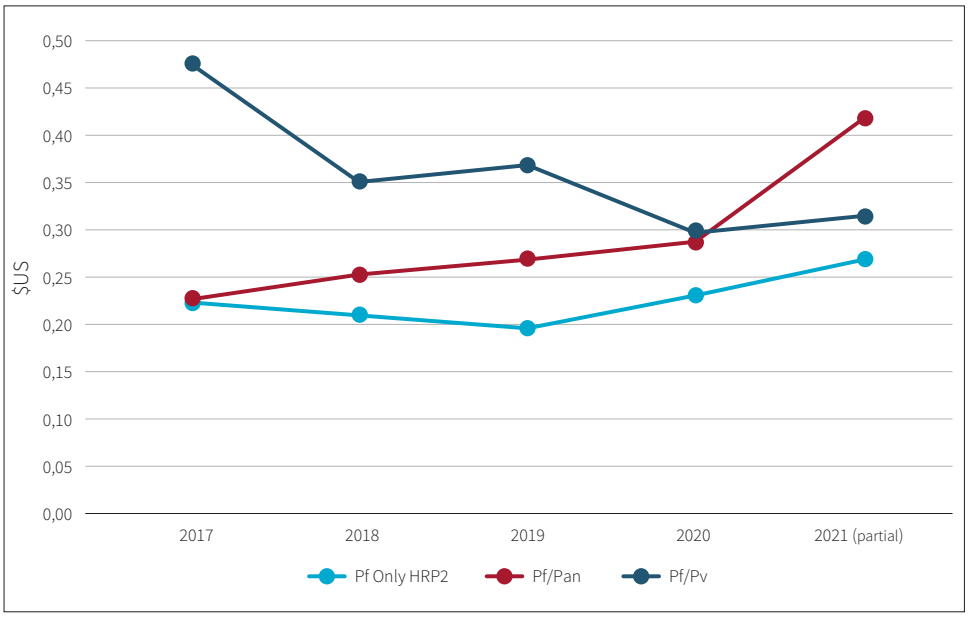
KEY MARKET INDICATORS: PRICE AND MARKET SHARE

Procurement data analysis sheds light on how the pandemic, supply base, and procurement changes have affected the malaria RDT market. This report's methods section outlines the steps taken to compile and analzye malaria RDT procurement data.

Price

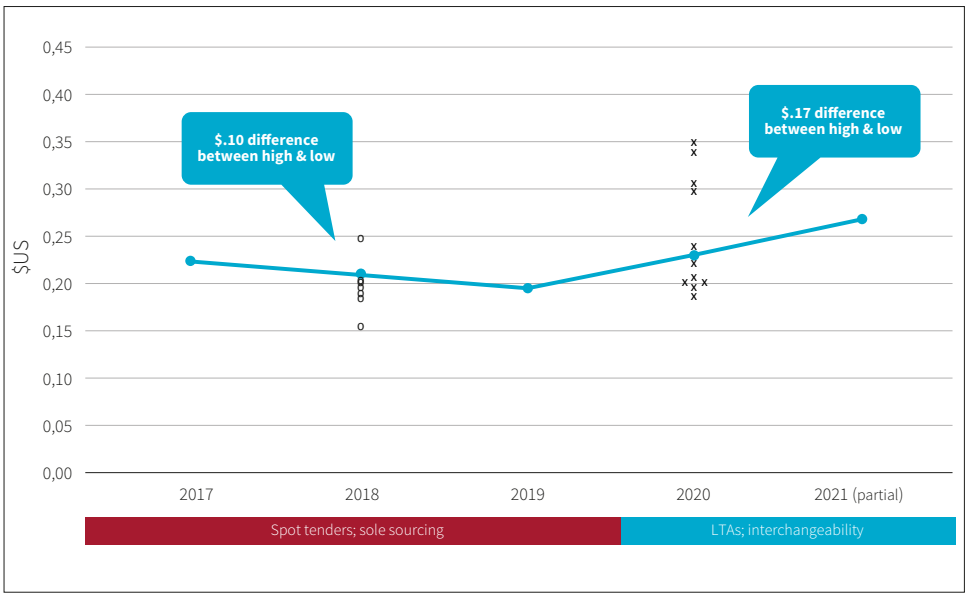
After several years of trending downwards, the weighted average ex works prices of malaria RDTs have risen slightly (Figure 10). However, analysis of price by supplier reveals more variation in 2020 than in 2018 (Figure 11). The variation seems to result from the addition of new suppliers and the events of 2020 (exit of one supplier, additional tender). Data for 2021 is partial but suggests an upward trend in prices and likely reflects inflation in the global economy.

FIGURE 10. Weighted average ex works malaria RDT price over time, by test type



Source: Procurement data analysis, data sent includes PQR and PMI.

FIGURE 11. Market ex works weighted average price for Pf-only HRP2 RDTs (line) and weighted average price by supplier Pf-only HRP2 RDTs 2018 (o) vs. 2020 (x)



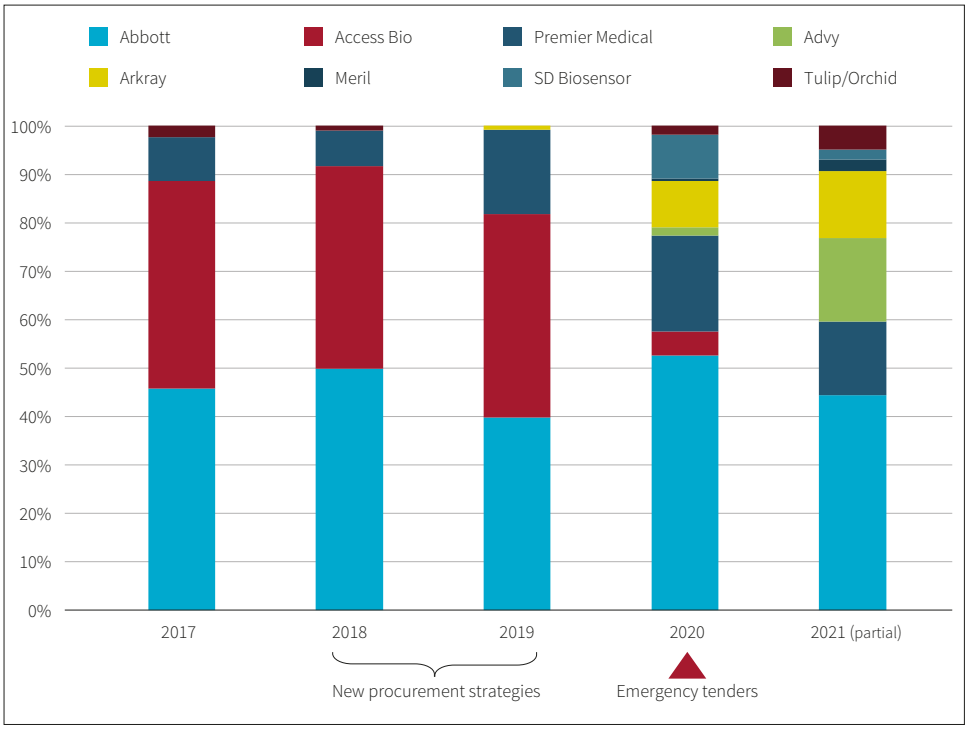
Source: Procurement data analysis, data analyzed includes PMI data and PPM orders that are reported in the PQR.

Supplier market share (by volume)

One of the incumbent suppliers, Abbott, has maintained a steady 40-50% share of RDT volumes. (Figure 12) After WHO PQ issued a Notice of Concern in January 2020, the other dominant supplier, Access Bio, left the market to pursue the COVID-19 RDT opportunity. Premier Medical, a long-time malaria RDT supplier, increased its market share in 2020.

Six other manufacturers split the remaining 30-40% of RDT volumes; the 2020 additional tenders appear to have accelerated diversification of the supply base that was underway. While some in this group are new entrants, having recently prequalified their RDTs, others are re-engaging in the market after several years of being sidelined because they were not able to compete with low prices. While new companies have started to supply the donor-funded market, concern remains about their ability to reliably and rapidly deliver at scale, and incumbent manufacturers have maintained meaningful market share.

FIGURE 12. Supplier market share, by volume



Source: Procurement data analysis. Data set includes PMI and PQR

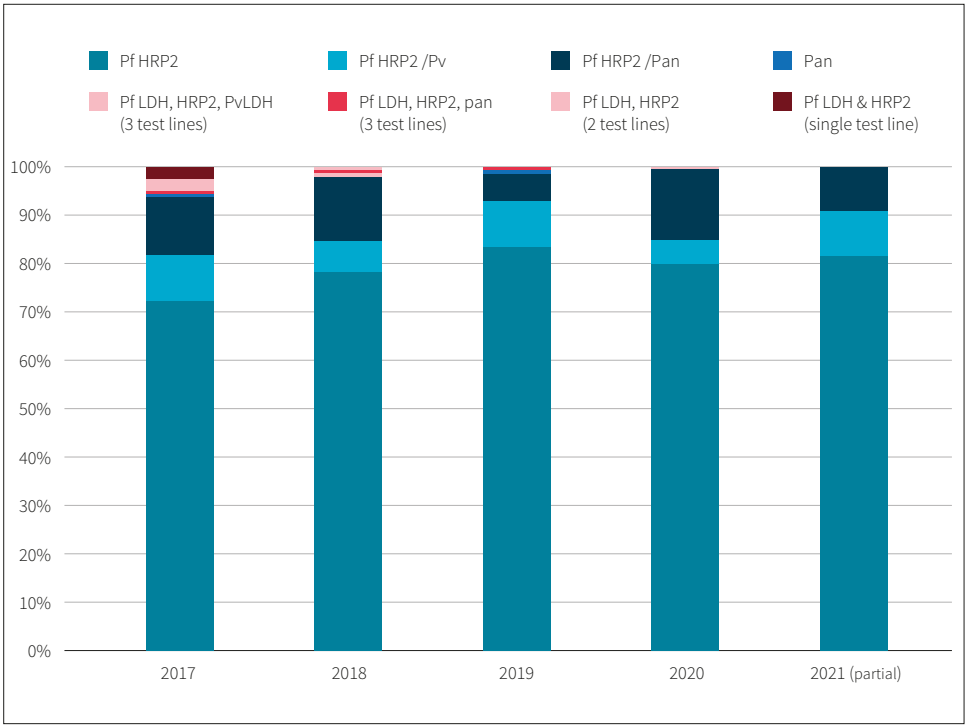
Test types

Procurement data suggests that Pf HRP2 RDTs, which have dominated historically, continue to do so (Figure 13). There are six companies with Pf HRP2 RDTs in the donor-funded market (Figure 5) and procurement data analysis shows that in 2021 each of the six received some volume of tests.

The next largest segments, Pf HRP2 / pan and Pf HRP2 / pv, each have five suppliers. (Figure 5). Procurement data analysis indicates that in 2021 two of five received volumes of Pf HRP2 / pan RDTs while four of five received volumes of Pf HRP2 / Pv RDTs.

While a few countries have procured the new Pf LDH tests with ERPd status, complete procurement data for these orders was not yet available; therefore, they are not included in this analysis.

FIGURE 13. Test type by volume

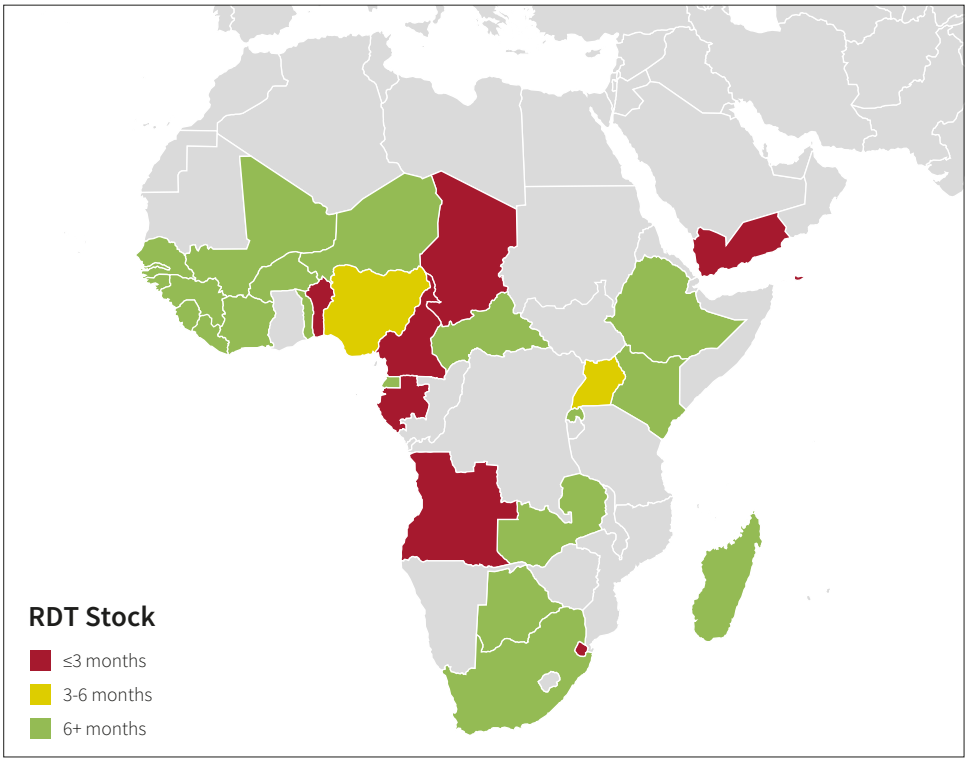


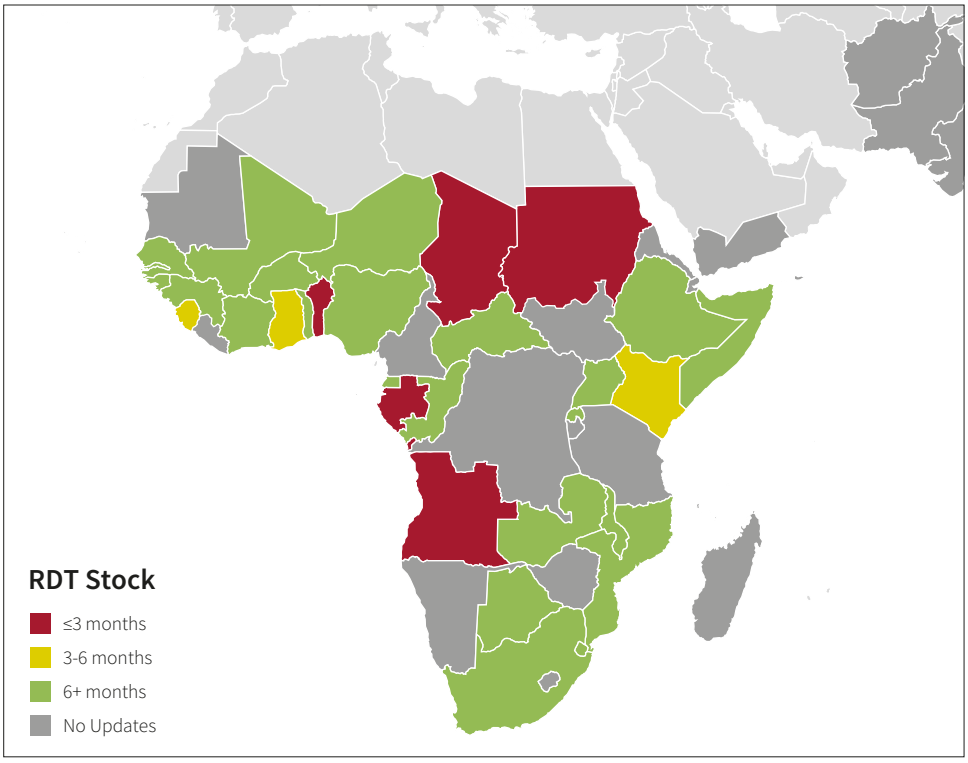
Source: Procurement data analysis. Data set is PQR and PMI

In 2020, procurers coordinated closely, reallocating supply and scheduled deliveries to countries weekly to avoid stockouts. Per their newly adopted policies, RDTs were provided interchangeability, and in some cases, multiple brands of tests were supplied within the same year by one donor to a country. This occurred for a combination of reasons, to avert a stock out or when a single manufacturer could not deliver the entire order. At times procurers suppled a slightly higher and lower priced test together, resulting in the country paying a blended price.

Overall, procurers filled country RDT needs, although not necessarily following their original allocation plans. Since then, the Global Fund, PMI, UNICEF, and UNDP have monitored RDT stocks in-country and coordinated orders and deliveries to minimize disruptions. In 2021, international freight shortages, expected to continue through 2022, became a crucial supply chain challenge. At the end of 2021, RBM reported that five African countries had fewer than three months of RDT stock (Figure 14).

FIGURE 14. RDT stock availability by country, quantity in months





Source: https://endmalaria.org/dashboard/supply-chain-dashboard (Accessed Oct 5 2021, Jan 14 2022). Updated June 2021 and December 2021.

Supplier overview

Malaria RDT suppliers vary in size and how long they have been making RDTs. Although their headquarters may be elsewhere, the current PQ-ed malaria RDT suppliers are manufacturing in Korea, China, and India. A few suppliers are large global IVD companies; several are medium-sized manufacturers primarily focused on LMICs, including India. A couple are just getting started in scaled manufacturing.

The importance of malaria RDTs to suppliers' overall business varies. For some, especially the larger companies, the business is not economically significant, and they are not pursuing it aggressively, yet, including a malaria RDTs in their product offering is important for marketing reasons (i.e. it may get them in the door to sell other tests). Other companies, especially new entrants with recently prequalified products, were encouraged by the 2020 emergency tender, and are now investing in additional capacity, country registrations, and prequalification of other tests.

Quality management systems and LMIC experience also vary. For example, some manufacturers have several PQ-ed or SRA-cleared products. Other companies' QMS systems are immature, and malaria RDT prequalification may be their first experience with a rigorous review. Only a few PQ-ed suppliers have track records for reliably fulfilling the multimillion test orders typical of African markets. These companies often have a strong presence, via their own offices or distributors, in many LMICs. Many newer companies lack distribution and presence in LMICs.

Product development expertise also varies; only a few companies have deep expertise in lateral flow technology and in developing and producing monoclonal antibodies. There is little investment in new product development unless it is donor-funded or related to rounding out their three-test portfolio of HRP2 detecting tests (e.g. Pf only, Pf/Pv, Pf/pan).

Pandemic impact

The COVID-19 pandemic has had far-reaching implications for the diagnostics industry, including malaria RDT suppliers. Historically, by volume, the malaria RDT market was among the largest rapid test markets. However, the COVID-19 RDT market is now several times the size of the malaria RDT market. Other notable changes in the industry include unprecedented product development speed; the rise of self-testing; and a large infusion of funds for diagnostics companies (e.g. government and private grants, IPOs, and COVID-19 tests sales).

In the early months of the pandemic, malaria RDT manufacturers were uncertain about their ability to deliver RDTs because of restrictions on movement, import/export restraints, and raw materials shortages. Development and production of COVID-19 rapid tests also become a global priority, placing financial and political pressure on some RDT manufacturers to prioritize COVID-19 RDTs over other product lines. All except one of the malaria RDT companies interviewed for this report sell a COVID-19 Antigen RDT. However, malaria RDT manufacturers' level of engagement in the COVID-19 market differs. While some have produced hundred-millions of COVID-19 RDTs for global distribution, others have not pursued the opportunity as aggressively and report moderate COVID-19 test business.

Unlike malaria RDTs, COVID-19 RDT demand fluctuates with pandemic waves, local policies, and government market-shaping interventions. The companies that lead the COVID-19

RDT market today invested early in product development and production capacity. While public and donor funding offset some of this risk, companies also invested significant resources without assurance of technical and market success. The performance of their RDTs on new variants and the rapidly evolving science also introduce uncertainty.

In the larger COVID-19 RDT markets, competition has increased, reducing prices and margins; however, on average, COVID-19 RDT margins are multiple times the margin of malaria RDTs even though they are similar technologies with similar manufacturing processes. Companies leading the COVID-19 testing markets are reporting strong financial performance resulting from global test sales.

LMIC COVID-19 RDT markets are growing more slowly than HIC markets. The only companies with WHO Emergency Use Listing (EUL) for COVID-19 RDTs are PQ-ed malaria RDT suppliers (e.g. Abbott, Premier Medical Corporation, and SD Biosensor), although many others are available via the Global Fund Interim Quality Assurance Requirements for the Procurement of COVID-19 Diagnostic Products. Unlike malaria, the donor-funded market for COVID-19 RDTs is smaller than the domestic and privately funded segments. The ex works price of EUL COVID-19 RDTs is $2.00-3.00, which is not always competitive with the many tests, lacking WHO EUL, available through private and domestic funding channels.

Malaria RDT manufacturing

In 2020, malaria RDT suppliers reported rising and volatile raw materials prices, especially for imported materials, components shared with COVID-19 RDTs (e.g. nitrocellulose, cassettes), and components impacted by lockdowns. In 2021, sourcing stabilized, although input prices rose due to freight and oil inflation. Generally, to control cost and ensure supply, malaria manufacturers have developed proprietary monoclonal antibodies (mAbs).

In early 2020, and during pandemic waves, lockdowns and social distancing limited malaria RDT manufacturer's production capacity, especially in India. Overall, however, the pandemic incited massive, industry-wide, investment in rapid test manufacturing capacity. The total RDT capacity of PQ-ed malaria RDT suppliers increased from 800 million RDTs a year across six suppliers before the pandemic to a capacity exceeding 2 billion RDTs a year across eight suppliers by the end of 2021.

The three Asian suppliers with PQ or ERPd status RDTs represent three-quarters of this increase; these companies are also aggressively pursuing COVID-19 RDT business. While India-based suppliers have also expanded capacity, their capacity is typically lower than Asian suppliers, e.g. a "large" Indian manufacturer might have an annual capacity of 100-250 million RDTs/year, whereas a "large" Asian supplier's capacity might range from 500-750m RDTs/year.

One new entrant is also developing an 'extreme volume manufacturing' process, capable of producing 16 million RDTs per day, to address the need for highly flexible, large scale-production of rapid tests for pandemics and epidemics. The project remains in development, with many uncertainties. However, when not needed for pandemics, the company is considering other high-volume RDTs, e.g. malaria and HIV.

Overall, the recent expansion in production capacity, combined with the more profitable but risky, COVID-19 RDT opportunity, is a notable change for the malaria RDT market. While there were concerns about having sufficient prequalified manufacturing capacity to meet demand in the past, the capacity now vastly exceeds demand. However, COVID-19

RDTs use the same manufacturing lines and effectively increase competition for the manufacturing capacity. This underscores the importance of suppliers having sufficient incentive to allocate production capacity to malaria RDTs, given other opportunities. In the future, if demand for COVID-19 RDTs subsides, overcapacity will affect all RDT markets, malaria included.

Manufacturers amortize their capacity expansion expenditures (e.g. new equipment and facilities) over time. To spread these fixed costs over a greater number of units, filling the production line becomes a priority. As seen previously in malaria RDT markets, when the incentive to fill production lines is high, suppliers may prioritize volume (i.e. spreading fixed investments over more units) over the profitability of an individual order, resulting in unsustainably low prices.

The nature of malaria RDT competition

Procurers' new strategies have changed the nature of competition in RDT markets. Broadly speaking, most malaria RDTs are now commodity products: conventional RDTs based on HRP2 detection are supplied by multiple manufacturers, interchangeably. (See below for discussion of new RDTs). Previously, the price was the key driver in open tenders. New procurement approaches encourage competition on a broader value proposition, including metrics like supplier performance and product portfolio. While strategic sourcing supports long-term market health, the metrics used are less transparent and require proactive management to adapt to changing market needs. Additionally, predictable forecasts, with quarterly detail, are essential yet often not provided by procurers. These allow manufacturers to control costs by optimizing labor and negotiating with their input suppliers.

Most malaria RDT suppliers aim to compete on having a low-cost product that they can deliver reliably. Differences in labor markets affect how companies achieve low-cost production. For example, companies in India tend to realize cost advantages through semi-automated production, affordable labor, and modest economies of scale. Companies in more expensive labor markets tend to rely on higher levels of automation and scale to achieve a low cost profile. Economies of scale contribute to low-cost manufacturing as well, including similar products that share the same components and production line as malaria RDTs. Another approach to lowering costs is shifting labor-intensive activities to competitive labor markets. For example, the assembly of strips into cassettes and the packing of the kits tend to be bottlenecks that are expensive to automate fully. Retaining the more specialized aspects requiring highly skilled labor or trade secrets (e.g. conjugation) at the original site, and shifting the downstream assembly and kitting to domestic or more competitive labor markets can optimize productivity and affordability.

It is difficult to appreciate manufacturers' pricing strategies for malaria RDTs, there is variation in the prices currently offered, and some companies appear to be testing the market after the recent changes. Although several manufacturers are concerned about inflation of input costs (e.g. higher oil prices, freight costs, general inflation), these have not risen to a level warranting price increases. Assuming they continue to receive allocations from the large procurers, many moderate-capacity manufacturers in low-cost labor markets accept current RDT prices. Several are even investing in registrations, capacity, and expansion of PQ-ed products. In contrast, some malaria RDT companies are apprehensive about the current market prices. Developers and companies lacking many years of high-volume, low-cost production experience are particularly ambivalent. Procurement data also shows some manufacturers offering substantially higher prices than in the past, even

though they are likely to have a low-cost basis (e.g. high levels of automation, production know-how, and economies of scale). This suggests that malaria RDT manufacturers have varying margin levels that they are willing to accept and varying cost structures for RDTs. The malaria business is essential for some, while others view it as a 'marginal' business, and are more apt to disengage. No doubt, the COVID-19 RDT opportunity also affects how suppliers view the malaria RDT business.

Competition based on product features, services, or new products is limited because there is little innovation in the malaria RDT market and because the policy, regulatory, and procurement structures are not conducive to product differentiation. This may become a challenge for new products and is described below.

Local manufacturing

The COVID-19 pandemic exposed vulnerabilities of LMIC reliance on imported health products. Lockdowns, import and export controls, nationalistic policies, and freight challenges disrupted the supply of essential commodities in many LMICs. To secure supply, countries and global stakeholders are exploring strategies to increase local and regional production.

Regional diagnostic test production will take time to achieve cost efficiencies. For a product like malaria RDTs, affordable pricing is a top priority, and required to compete successfully in the market. Low prices in malaria RDTs derive mostly from economies of scale and large-scale production experience or "know-how." As a result, local production of malaria RDTs may not initially be cost-competitive and there is little experience with country and donor willingness to pay (i.e. a price premium) for locally manufactured products. However, even if the ex-works cost of a locally manufactured test is higher than an imported one, the difference may be offset by the lower regional shipping costs, especially during global freight shortages.

Depending on the region, an 'ecosystem' to support local diagnostics manufacturing may take many years to develop. For example, initially, LMIC manufactures can develop local supply chains for plastics and packaging materials, allowing more components to be sourced locally, driving down cost. However, some inputs (e.g. nitrocellulose, mAbs) and the equipment used to produce RDTs, are highly specialized and usually only available from a few sources globally, so some LMIC-based manufactures would depend on importing these materials, equipment, and servicing/spare parts for many years.

Human resources are another challenge; some of the current manufacturing hubs for rapid tests (e.g. South Korea) take advantage of a large talent pool resulting from national investment in biotech higher education. Long-term efforts to ensure a critical mass of expertise in R&D, business, quality management systems, and production/operations would support local manufacturing.

Anecdotal experience to date suggests regional manufacturing of malaria RDTs can be challenging to sustain. One formerly leading malaria RDT supplier based in South Africa exited the donor-funded malaria RDT market citing excessive price competition, especially as quality standards increased. Another company successfully set up and prequalified downstream production in Africa. While some customers bought the product, others in the region preferred the more expensive "made in USA" product. Another malaria diagnostics supplier also established downstream production in Africa, but, reconsidered the project because of the large investment required to WHO-prequalify this additional site.

MALARIA RDT INNOVATION

There are a few efforts to improve malaria RDTs. While there is an acute need for RDTs that address HRP2/3 deletions, for other improvements, there are varying degrees of consensus around the need, use case, and the market. At the same time, the evidence base required to support new test introduction is uncertain. Diagnostic developers have always been responsible for laboratory validations and increasingly clinical trials to obtain regulatory clearance for tests. However, the evidence base required to inform policy and test recommendations has increased, and frequently includes utility, cost-effectiveness, and impact assessments.

Pf LDH detecting tests for areas with HRP2/3 deletions

Need and demand

WHO recommends using RDTs that do not exclusively rely on HRP2 detection in countries where more than 5% of cases would be missed due to the prevalence of Pf HRP2/3 deletions in symptomatic patients. (26) In the near term, RDTs that include Pf LDH detection are the most feasible alternative to tests exclusively detecting HRP2. Despite the availability of RDTs using Pf LDH tests twenty years ago (27), developers gravitated towards HRP2 because mAbs were readily available and easier to work with than Pf LDH which requires more technological optimization to achieve comparable performance and stability. Users came to prefer HRP2 tests for consistent performance and stability, and HRP2 detecting Pf RDTs came to dominate the market.

Most recently, countries in the Horn of Africa reported a high prevalence of deletions, and given the severity of the situation, in May 2021, WHO's Malaria Policy Advisory Group issued a statement calling for urgent action. (28) Overall, despite WHO's call to action and guidance, implementation of the recommended response (e.g. surveillance, product development, and introduction of suitable tests) has been slow.

While demand for RDTs that do not exclusively rely on HRP2 for *Pf* detection is expected to increase in the coming years, forecasting is challenging because the scope of deletions and the pace at which deletions spread are unknown. As of late 2021, 37 countries have a study documenting the presence of deletions (out of 44 that have had some type of investigation). (1) However, rarely is an initial study reporting the presence of deletions sufficiently robust and representative to inform policy. WHO has developed a generic protocol for conducting representative national surveys, which are relatively complex (e.g. conducted at multiple sites, use sophisticated molecular testing) and can take 18 months to complete. (29) (30)

Donors (e.g., GF, BMGF) are now supporting these surveillance studies; however, some countries still lack funding to conduct the studies. The number of countries running or planning studies, and the associated timelines, are not known. To improve tracking of HRP2/3 deletions surveys, WHO is developing a public dashboard.

Even when the intent to replace an RDT is made, operational factors influence the timing of switching tests. Among other factors, budgets to support new test introduction and to cover the price increase from HRP2 tests to tests that include Pf LDH tests will also influence how soon demand materializes for Pf LDH RDTs. In 2018, one estimate suggested that up to 30% of the market could be Pf LDH tests by 2021, (5) however, procurement data shows that demand is not materializing at the initially anticipated pace, and no new estimates are available.

Companies developing Pf LDH tests

There are few alternative RDTs that incorporate detection of Pf LDH, and in particular, no WHO Prequalified tests suitable for case management.[11] Technically, developing Pf LDH test can be more challenging than an HRP2 test, because LDH is less abundant in the blood and because its molecular configuration is more complicated than HRP2. Thus, improved LDH test development focuses on enhancing the sensitivity of the lateral flow test platform and optimizing the selection of monoclonal antibodies. Lab studies to date suggest that a low concentrations Pf LDH detection may never achieve the same sensitivity as HRP2 detection, however, field trials are needed to appreciate the impact. It is possible, given this limitation, that programs will favor tests that include both LDH and HRP2 for Pf detection.

Rapigen, a twenty-year old Korean company, new to the donor-funded RDT market, has three Pf LDH based products with ERPd status (2019) and, provisionally recommended by the WHO for areas with deletions. (13) Rapigen's tests use a unique lateral flow platform using black gold to enhance sensitivity. Although Rapigen did not receive donor support for product development, BMGF is now supporting several clinical trials (Table 3). Rapigen submitted three Pf LDH detecting products to PQ in 2020. (Table 2 and 4) Thus far, it has passed the laboratory evaluation component of PQ but the timelines for the dossier review and manufacturing inspection are uncertain but slower than usual due to the WHO PQ's pandemic workload.

Two additional companies, Abbott and Mologic, are developing Pf LDH tests with product development funding from BMGF. Initial development timelines have been delayed (31); currently, Abbott targets submitting to WHO PQ in early 2023 and Mologic targets a late 2023 PQ submission. (Table 2)

While Abbott is a longstanding malaria RDT manufacturer, Mologic would be new to malaria RDT markets. Known primarily as a contract product developer with deep lateral flow expertise, in 2021, it was acquired. Mologic and its manufacturing partner (Global Access Diagnostics) are now owned by Global Access Health, a not-for-profit company financed by the Soros Economic Development Fund, with support from BMGF and other philanthropic organizations and investors.(32)

Other malaria RDTs manufacturers have mixed thoughts about Pf LDH tests. While established RDT suppliers are well aware of the deletions in Africa, some are skeptical about the investment case. They doubt procurers would pay a premium for the innovation, expecting instead that any return on investment would derive from market share or volume increases. They were ambivalent about whether RDTs targeting Pf LDH are 'replacements' for Pf-only RDTs, or 'niche' products, akin to the pan category of RDTs that has never been commonly used. A few new entrants were open to developing Pf LDH tests, and at least two have done some very preliminary and exploratory work.

11 See previous section about WHO recommendations on pan test and pf LDH/HRP2 tests.

Products and use cases

TABLE 2. Four Pf-only RDTs detecting Pf LDH are in development for case management where HPP2/3 deletions are common

Manufacturer	Test line 1	Test line 2	Temperature (target)	Shelf life (target)	Design	Development stage
RapiGen	pfLDH		2-40C*	24 months*	Cassette	Design locked, ERPd approved, submitted to PQ
RapiGen	pfLDH	HRP2	2-40C*	24 months*	Cassette	Design locked, ERPd approved, submitted to PQ
Abbott	pfLDH & HRP2		2-40C targeting	24 months targeting	Cassette	Design locked, targeting early 2023 PQ submission
Mologic	pfLDH		2-40C targeting	24 months targeting	Strip	Design not locked, targeting late 2023 PQ submission
Current Pf RDTs	HRP2		2-40C**	24 months	Cassette	On market

Notes: * Real time studies completed. **One test, Paracheck, is 45C

There are notable differences in the configuration of Pf LDH products (Table 2), which suggests the RDTs could address slightly different use cases. In general, including HRP2 detection systems may be helpful in detecting the proportion of infections that still express HRP2/3, because historically HRP2 tests have a lower limit of detection and better stability than LDH. Preliminary laboratory evaluations of analytical sensitivity (i.e. RDT limit of detection) by PATH suggest that even with improved sensitivity, Pf LDH detection is less sensitive than HRP2 detection. On the other hand, Pf LDH correlates to parasite density more closely than HRP2, so over-treating persistent antigenemia, a drawback of HRP2 RDTs, is less likely.

The intended use and performance claims developers will make for these tests are unknown; however, different use cases are plausible based on the different formats. For example:

- A single-line test (either Pf LDH or both HRP2 and Pf LDH on the same line) may be easier to implement in countries accustomed to conventional Pf-only tests, as the format is similar and they would be easier for health care workers to implement. If affordable, a test with Pf LDH and HPR2 detection on the same line might be preferred because it could be deployed in settings with deletions and those without.

- Separate lines for Pf LDH and HRP2 may help with surveillance for deletions: a negative HRP2 line and a positive for LDH would suggest a deletion, so this type of test could help with surveillance as well as case management.

- Separate lines for Pf LDH and HRP2 may also support a more accurate diagnosis of active infection. A positive HRP2 line and negative LDH line could indicate persistent HRP2 antigen or an early stage/low-density infection that could become acute. In either scenario, the health care worker managing the cases needs an appreciation for these nuances and the pf-LDH test lines would need to perform as well as the HRP2 test lines for detection of clinical malaria in order to distinguish acute infection from persistent antigenemia reliably.

- The line for Pf LDH could be helpful in monitoring of response to treatment, as Pf LDH would correlate more closely with active infection, and a patient that has been treated recently would test negative more quickly with an LDH test than an HRP2 test.

Pricing is not yet available for these tests, but the BMGF target product profile (TPP) suggests <$0.50 and optimally $0.35 (ex works pricing assumed), which is above the weighted average price of current RDTs. The Global Fund recently published a reference price in the same range: for Pf HRP2 / Pf LDH tests the ex works price is $0.40 (33). Because some of the RDTs, even if only detecting Pf, use multiple detection systems (i.e. two antigens), their manufacturing cost is more akin to a combo test than an HRP2-only detecting test. TPP expectations for other key product characteristics include temperature requirements of 2-40C and a shelf-life of at least 24 months.

Evidence for regulatory approvals and policy recommendations

In terms of performance, confirming that RDTs perform on deleted parasites is necessary, particularly after the 8th round of Product Testing, when some RDTs performed inconsistently on the HRP2 expressing panel versus the non-expressing panel. The tests in development (Table 2 above) were not included in the last round of product testing; however, the WHO undertook an ad hoc evaluation of the Rapigen tests at US CDC and confirmed performance met WHO thresholds.

BMGF is supporting several lab and field evaluations of Pf LDH tests, including i) extensive lab-based validations at PATH (complete for Rapigen and Abbott) and ii) several field studies that are ongoing or commencing in early 2022 (Table 3). Presumably, these independent studies, along with manufacturers' studies and WHO PQ lab evaluations, will adequately demonstrate performance in populations with and without HRP2 deletions.

Given the varying formats of the Pf LDH RDTs and the potential for differing intended uses, they will not necessarily be 'interchangeable' commodity products. Procurers will need to adapt their approach for this new category of tests.

TABLE 3. BMGF supported studies for new Pf LDH and Pv LDH RDTs

Company and testsc	Location and type	Lead organization	Timeline for completion
RapiGen (3 tests using pfLDH)	Brazil, retrospective	PATH	May 2022
	Senegal, prospective	PATH	May 2022
	Indonesia, retrospective	FIND	June 2022
	Indonesia, prospective	FIND	June 2022
	Sudan, prospective	FIND	June 2022
	Ethiopia	Armeur Hansen Research Institute	[unk]
Abbott (Ultra-sensitive HRP2, 2 tests using pf LDH)	Brazil	PATH	To begin Q1 22
	Indonesia	FIND	To begin Q1 22
	Sudan	FIND	To begin Q1 22
	Peru	FIND	To begin Q1 22
	Ethiopia	Abbott	To begin Q1 22
	Uganda	Abbott	To begin Q1 22

Beyond Pf LDH: new biomarkers

In response to HRP2 gene deletions, FIND performed a literature and proteomics data review to identify novel biomarkers for RDTs. The paper highlights two candidate biomarkers worthy of further exploration: glyceraldehyde 3-phosphate dehydrogenase (GAPDH) and dihydrofolate reductase-thymidylate synthase DHFR-TS (34). It is not known if this review has prompted any further development, the next steps would involve the development of reagents targeting these markers and testing the reagents against a large and geographically diverse collection of plasmodium specimens.

Improved Pv detection

Need and demand

Over three billion people live at risk of *P. vivax* infection, with India, Pakistan, and Ethiopia having the largest populations at risk. Cases are predominantly rural. (35) For biological reasons, Pv doesn't respond as quickly to control interventions as Pf, therefore, in co-endemic countries, as the malaria burden reduces, Pv predominates. For example, Pv is the sole or primary cause of malaria in three-quarters of elimination countries. Even though the annual number of Pv cases is an order of magnitude smaller than Pf cases, the test market is not necessarily as small because it would still be essential to screen many febrile patients living in vivax risk areas.

On average, Pv RDTs perform less well than Pf RDTs.(36) In many vivax endemic countries microscopy is the mainstay of malaria diagnosis, partly because stakeholders have historically been concerned about the sensitivity of Pv RDTs, even though these RDTs may perform equivalently or better than some field microscopy.

In general, Pv parasitemias are lower than Pf's, suggesting that more sensitive tests would be more important in Pv than in Pf. Moreover, a recent study suggests that the amount of pv LDH antigen circulating per parasite is lower for Pv than Pf (37). Many stakeholders have called for better Pv point of care (POC) tests, and in 2017 FIND and partners published a series of target product profiles for Pv diagnostics, including a TPP for symptomatic infection. (36)

Global consensus on the need for improved vivax detecting RDTs for case management has not been reached. On the one hand, a 2015 review found few clinical Pv cases with submicroscopic parasitemia, suggesting current RDTs meeting WHO performance requirements [12] would be acceptable for most clinical cases (38). A 2015 WHO *P. vivax* technical brief (39) echoed this review but also listed among needed innovations a Pv detecting POC test with a limit of detection (LOD) of ~25p/µL for clinical case management and lower for asymptomatic detection in elimination settings. There are ongoing reviews of parasitemia in clinical *P. vivax* infections from geographically diverse settings, these results will inform any adjustments to the current Pv RDT performance recommendations for clinical case management .

12 WHO recommends Pv RDTs reliably parasite concentrations of ~200 p/µL, and the WHO Product Testing and WHO PQ evaluations use this benchmark.

Companies developing improved Pv LDH tests

Rapigen, Abbott, and Mologic, the same three companies developing Pf LDH tests described above, are also improving Pv LDH detection. No other manufacturers mentioned working in this area. The tests are on similar development timelines as the Pf LDH tests described above; Rapigen's test is on the market with ERPd status and in the WHO PQ process. Abbott and Mologic tests are further behind. As with the Pf LDH tests, Rapigen developed its test without donor support, BMGF is supporting product development at the other companies, and all three are engaged in BMGF-funded lab and field studies.

Products and use cases

All of these tests will include Pf LDH for Pf detection as well as Pv LDH, making them suitable for use in settings with HRP2/3 deletions (Table 4).

The new Pv tests target a 10x improvement in detection limit compared to existing Pv RDTs. What this translates to in terms of case management remains to be seen. Preliminary benchmarking and modeling data suggest that new Pv RDTs would detect more symptomatic and asymptomatic cases than conventional RDTs; however, these findings are based on limited data and need confirmation.

Manufacturer's pricing is not available yet, but the BMGF TPP price, <$0.75, optimally $.50, may indicate expectations. This pricing is 1.5x times the current average ex works price for conventional Pf/Pv RDTs. Without information on the clinical impact of using more sensitive tests, it is difficult to appreciate the cost-benefit of the new tests, assuming they are priced higher than conventional Pf/Pv RDTs.

From a market introduction perspective, there are two different segments to consider. The first is Pv endemic countries with HRP2/3 deletions. That Pv is common in the regions where HRP2/3 deletions have first appeared (South America, Horn of Africa), renders these tests timely because conventional tests (i.e. HRP2 detecting) could miss Pf cases. However, as noted, the pace at which this market develops is challenging to predict because deletions surveillance and policy change efforts have been slow.

The second market segment is countries without substantial HRP2/3 deletion prevalence that may desire tests with improved Pv detection. In this situation, (barring any WHO revision of the minimum performance requirements for Pv RDTs), programs may need to consider the impact of the Pf and Pv line performance on diagnosing symptomatic patients, and any potential surveillance uses. If the price of the new tests is higher, the cost / benefit may become an important consideration. There is no information yet on how developers of the new tests will position their new RDTs compared to the 'conventional RDTs' and whether these improved Pf/Pv tests would replace conventional Pf/Pv RDTs.

Evidence for regulatory approvals and policy recommendations

For vivax, PATH's lab has confirmed improved limits of detection for the new tests compared to conventional Pv LDH tests, and some of the field studies described above will directly compare the performance of the new RDTs to conventional RDTs.

From a PQ perspective, developers would need studies to back up any improved sensitivity or limit of detection claims. The WHO prequalification laboratory evaluation will confirm

that the RDT meets WHO performance recommendations (i.e. 75% panel detection score, using panels calibrated to 200 parasites/µL). The new Pv RDTs are expected to easily "pass" this evaluation; no data would be reported demonstrating superior performance over conventional RDTs. Adding International Units to the WHO PQ process could differentiate these tests. Still, the IU values for conventional RDTs would be needed for comparison, and the testing with WHO International Standards will not be extensive.

For WHO policy, the recommendations around using these new tests in settings with Pv and HRP2/3 deletions would be straightforward, likely the focus would be on confirming the tests meet existing WHO performance criteria and that they are in the PQ process. The path to a policy recommendation for the use of the improved Pv detecting tests in countries without deletions is less clear. If reviews of vivax symptomatic versus asymptomatic infections finds clinical cases are common at parasitemias lower than 200 p/µL, it would likely accelerate WHO consideration of these more sensitive Pv RDTs for settings without deletions.

For procurers, there is slight format variation in the new Pf LDH /Pv LDH tests (Table 4) because one of the tests in development includes HRP2 while the others do not, so they will not necessarily be 'interchangeable' products.

TABLE 4. Three Pf/Pv RDTs using Pf LDH and targeting improved Pv sensitivity are in development for case management

Manufacturer	Test line 1	Test line 2	Temperature (target)	Shelf life (target)	Design	Development stage
RapiGen	PfLDH	Pv LDH	2-40C*	24 months*	Cassette	Design locked, ERPd approved, submitted to PQ
Abbott	pfLDH & HRP2	pvLDH	2-40C target	24 months* target	Cassette	Design locked, targeting early 2023 PQ submission
Mologic	pfLDH	pvLDH	TBD	TBD	Strip	Design not locked, targeting late 2023 PQ submission
Current Pf/ Pv RDT	HRP2	pvLDH	2-40	24 months	Cassette	On market

Notes: * Real time studies completed. **One test, Paracheck, is 45C

High-sensitive HRP2 RDT

Since 2013, interest in low-density malaria infections and the potential role of more sensitive diagnostics, particularly for malaria elimination, has increased. Donors supported a few companies to develop improved RDTs, focusing initially on improved HRP2-based Pf detection. Only the Abbott test has come to market, and none of the other RDT manufacturers interviewed for this report mentioned product development in this area.

In April 2017, Abbott (at the time, Alere) released its ultrasensitive HRP2 detecting RDT, currently called the NxTek Eliminate malaria Pf RDT. It is marketed as having a 10-fold improvement in detection limit over conventional RDTs, enabling better identification of patients with low-density infections, including asymptomatic individuals (40). Initially priced around $1.00 (ex works), in 2020, Abbott decreased the ex works price to $0.30. Although it is now priced competitively with the traditional HRP2 RDT, in 2022 Abbott affirmed its commitment to continue supplying and supporting the traditional RDT.

In 2019, WHO PQ approved the NxTek Eliminate RDT based on its ability to detect symptomatic infection. However, WHO guidance on the use of this test is undecided: a 2017 WHO expert review of "highly sensitive tests" did not specifically consider evidence related to NxTek. Rather, the 2017 review recommended additional research on the use of highly sensitive tests more generally and supported the continued use of conventional RDTs and microscopy for routine case management and surveillance. (41) To date, Global Fund and PMI have not been supplying the test, and programs have not widely adopted the ultrasensitive RDT. Although pricing is less of a barrier, it has a shorter shelf life (12 months vs. 24 months) and requires tighter temperature controls (30C vs. 40C) than the traditional RDTs. At the same time, evidence demonstrating optimal use cases and how to operationalize these tests is needed to support wider adoption.

The potential use cases for more sensitive RDTs include case management, screening asymptomatic populations - including pregnant women, surveillance, and elimination. Despite multiple laboratory and field studies showing improvements in sensitivity (42) (43) (44) evidence-based guidance for test use in the various use cases has yet to be firmly established.

Digital technologies and malaria RDTs

Digital tools provide one or more functions: i) reading and interpreting RDT results; ii) surveillance, data capture, and monitoring; and iii) clinical decision support. The form may be a dedicated instrument or an app operating on a mobile phone or tablet. While there is no shortage of digital technologies with the potential to support malaria case management, the use cases where they add value are not well defined, nor is their cost-effectiveness.

About five years ago, studies of commercially available RDT readers found a few readers that perform as well as the human eye on Pf infections, but for fainter band lines (lower density infections) or non-Pf species, the human eye performed better than the readers. One study concluded that these test reading and data capture devices may not increase the overall accuracy of malaria diagnosis but could add value by promptly and accurately reporting results and through process monitoring (e.g. checking time elapsed before result reading, collecting images for quality control). (45) Since these studies, developers have advanced RDT reading capabilities so that apps read as well as experts. COVID-19 self-testing has also prompted additional investment and advances in the application of digital tools to RDT processing, reading, and reporting.

To ensure LMIC priorities are at the forefront of development efforts, the WHO and partners are developing a TPP for RDT readers. For example, while companies initially made proprietary RDT readers, there is growing consensus about the need for universal readers to accommodate the different types and brands of RDTs (across multiple diseases) commonly used in LMICs.

From a quality perspective, the WHO Prequalification does not review digital technologies for malaria RDTs. However, any digital tool reading RDTs would need to be validated for each RDT. Other regulatory implications depend on the functionality of the technology. For example, suppose a digital tool provides a diagnostic result. In that case, it becomes classified as a medical device under CE IVDR and FDA (WHO PQ does not review digital) and is subject to a higher standard of review. Alternatively, if the app does not provide a result, it can be classified as a medical data system.

Despite the technical promise, progress in identifying high-impact use cases for digital technologies in malaria case management has been slow. While many stakeholders, including donors, are open to digital technologies, compelling use cases scenarios need to be fleshed out in greater depth and trialed. Some stakeholders suggest digital technology target gaps or weaknesses in current practice, e.g. focus on reporting, quality, and monitoring of case management in the private sector or community where there are many gaps in current practice.

Since a digital tool would add cost to case management budgets, the benefits must be clearly defined. Assessing cost-effectiveness is complicated because many digital companies have yet to define their business models and pricing strategies (e.g. paid subscriptions, paying per test scan, or per user).

Product Development Partnership (PDP) support for RDT Innovation

PATH and FIND are supporting advancement of the pipeline, particularly around tests that can be used in countries with deletions. PATH and FIND activities support various aspects of the malaria diagnostics product development and commercialization value chain, from biobanking and prototype benchmarking to clinical trials. (Table 5)

TABLE 5. Overview of PDP support for RDT innovation

Biobank	FIND Diagnosis for all	Biobank of malaria whole blood, saliva, and urine samples, including parasites with HRP2/3 deletions, and symptomatic and asymptomatic infections.	On-going; available to developers
Benchmarking	PATH	Lab-based benchmarking studies for Pf and Pv LDH prototype RDTs; assesses analytical and clinical performance and compares the prototypes to other products. Foundational work completed included: i) developing and supporting the commercialization of a reference assay for measuring antigen concentration and ii) assessing the analytical sensitivity of current RDTs.	On-going; available to developers
Malaria innovation platform	FIND Diagnosis for all	Round 1 focused on trial-ready technologies addressing HRP2/3 deletions, detection of non-Pf species, and strengthening surveillance. The study sites mimicked intended use settings in Indonesia, Rwanda, and Sudan. Of 24 submissions 7 technologies studied included Pf LDH RDTs, digital apps, a LAMP/smartphone technology, a hemozoin based device, and automated microscopy. Results from first round of studies are forthcoming. An RFP for a second round for new malaria biomarkers (i.e. not HRP2 or LDH) will launch in Q1 2022, studies will be conducted at one site during 2022-2023.	Round 1 studies wrapping up in Q4 2021
Clinical studies	PATH	Pf and Pv LDH RDT clinical studies of RapiGen and Abbott products. Prospective and retrospective design; Brazil, Senegal, Indonesia, Sudan, and Peru.	Underway and planned
Improved fever RDT stability	FIND Diagnosis for all	In late 2021 FIND launched an RFP for product development focused on improving the stability (storage, operational temperatures and humidity range) of Covid-19 RDTs and febrile illness rapid tests, including malaria RDTs, to improve used outside of climate-controlled settings. The preliminary timeline targets regulatory submission by year-end 2022.	2021 RFP; targeting regulatory submission by year end 2022
Technical assistance	PATH	As part of BMGF China strategy, implementing a state-of-the-art educational program for Chinese manufacturers on malaria RDT product development, quality, and market introduction.	2022

4. SUPPORTING RADICAL CURE WITH G6PD TESTING

PUBLIC HEALTH BURDEN AND CONTEXT

In the past decade, the malaria community's appreciation for the burden of vivax malaria has grown. While the number of *P. vivax* cases, 4.5 million in 2020, is significantly lower than *P falciparum*, vivax is less responsive to traditional control measures. As a result, when co-endemic countries progress towards elimination, *P. vivax* emerges as the dominant species. To continue progress, programs are revisiting *P. vivax* case management, specifically deploying G6PD diagnostics to safely deliver treatments that improve individual clinical outcomes and reduce vivax transmission.

Both *P. vivax* and the less common *P. ovale* species have a dormant liver stage that causes relapses. In addition to typical antimalarial treatment (i.e. ACT or chloroquine), patients require a second treatment with primaquine or tafenoquine to prevent relapse ("radical cure"). Although these essential medicines are increasingly available, they are underutilized partly because they cause potentially dangerous hemolytic anemia in Glucose-6-phosphate dehydrogenase (G6PD) deficient patients.

Globally, G6PD deficiency is the most common enzymatic disorder, affecting an estimated 400 million people, many of them living in endemic malaria countries. To safely deploy anti-relapse treatment, policymakers and clinicians need to consider several aspects of G6PD deficiency:

- G6PD deficiency varies in type and degree of severity. There are over 200 variants of the disorder, which is genetic, and individuals with certain variants are more prone to severe reactions than others. Usually, one variant is common in any geographic region or among certain ethnicities. Geographically, the frequency of G6PD deficiency in a population varies (8); the highest prevalence (e.g. 30%) is found in specific populations in the Arabian Peninsula and Africa. While the deficiency affects less than 1% of the population in the Americas, there are groups, for example, in the Amazon region where prevalence is higher (e.g. 10-15%). (Figure 16).

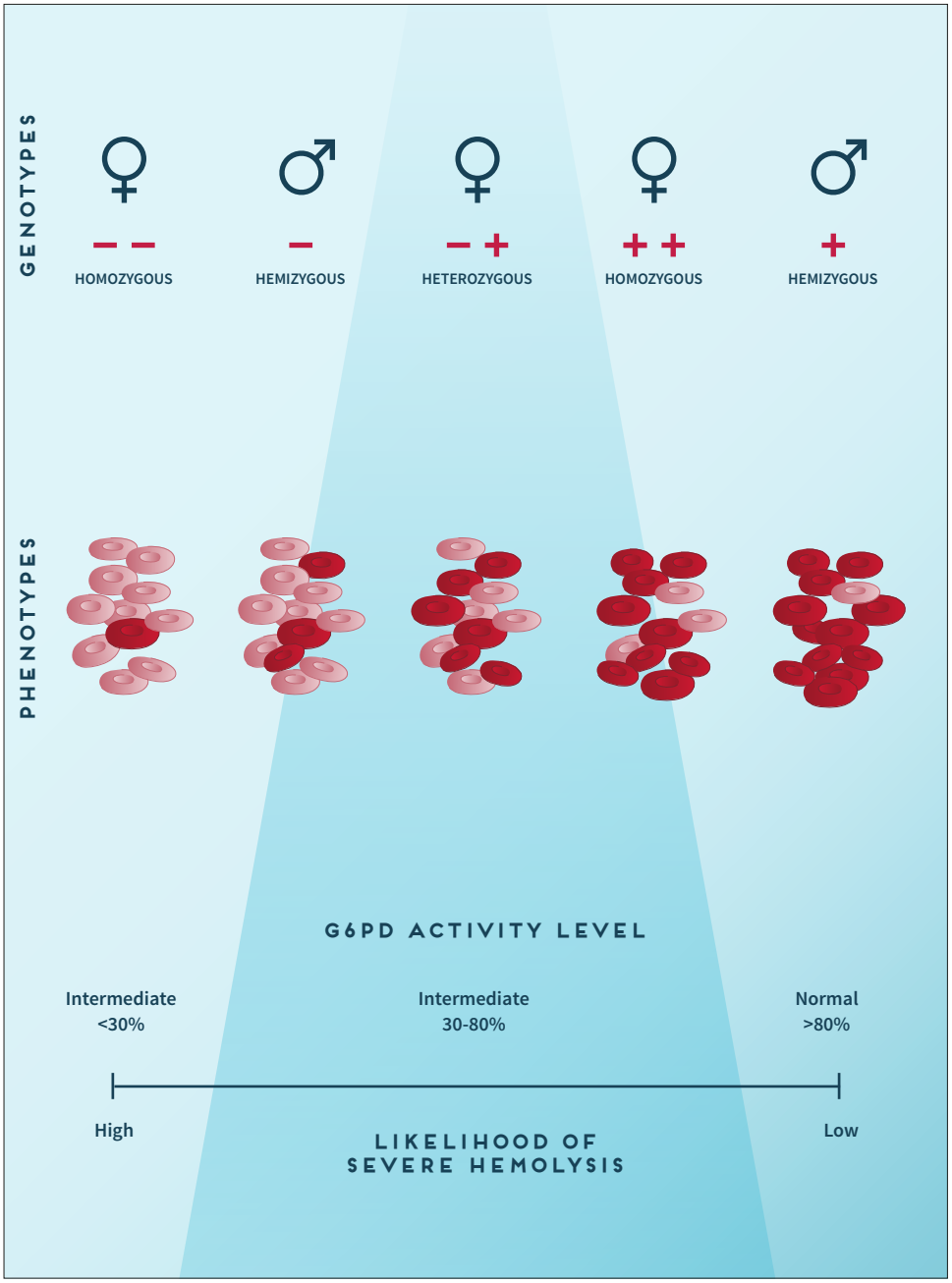
- While some G6PD deficient individuals can tolerate triggers (e.g. some medicines, foods, or infections) in small amounts, others are highly susceptible to adverse reactions. In severe cases, the reaction can be fatal or require hospitalization, transfusion, oxygen, fluids, and dialysis – which are seldom available at the lower levels of the health system caring for most malaria patients. Thus, policymakers must consider the likelihood of severe hemolysis in their populations and the local capacity to treat it.

- The gene coding for G6PD is found on the X chromosome, and as a result, the disorder behaves differently in men and women (Figure 15).

  - G6PD deficiency is more common in males; men have one copy of the X chromosome, and a mutation on the gene coding for G6PD will cause G6PD deficiency. When G6PD enzyme activity levels are measured, most men fall into two categories: normal (>80% activity) or G6PD deficient (less than 30% activity).

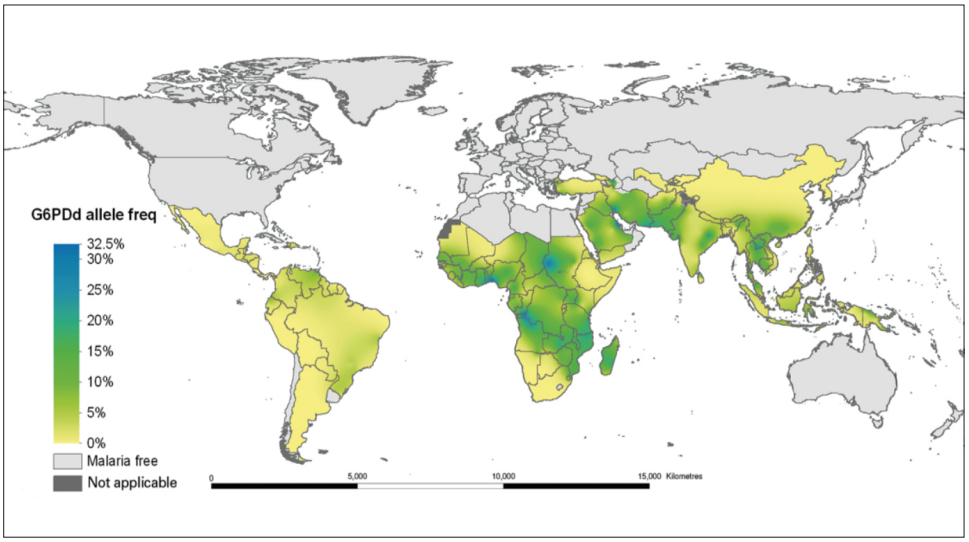
– For women, a range of G6PD enzyme activity levels is possible. While some women are clearly normal or deficient, others have an intermediate activity level. Because women have two X chromosomes, they can have a mix of cells with normal X chromosomes and cells with abnormal X chromosomes (i.e. heterozygous). When this occurs, the proportion of red blood cells that are normal versus deficient determines the overall enzyme activity level. As a result, females are classified as being deficient (<30% of activity), intermediate (30-80% activity), or normal (>80% of activity).

FIGURE 15. G6PD activity levels and risk of hemolysis in men and women



Source: adapted from Domingo, Gonzalo J et al. (46)

FIGURE 16. Estimated G6PD deficiency frequency in malaria-endemic countries



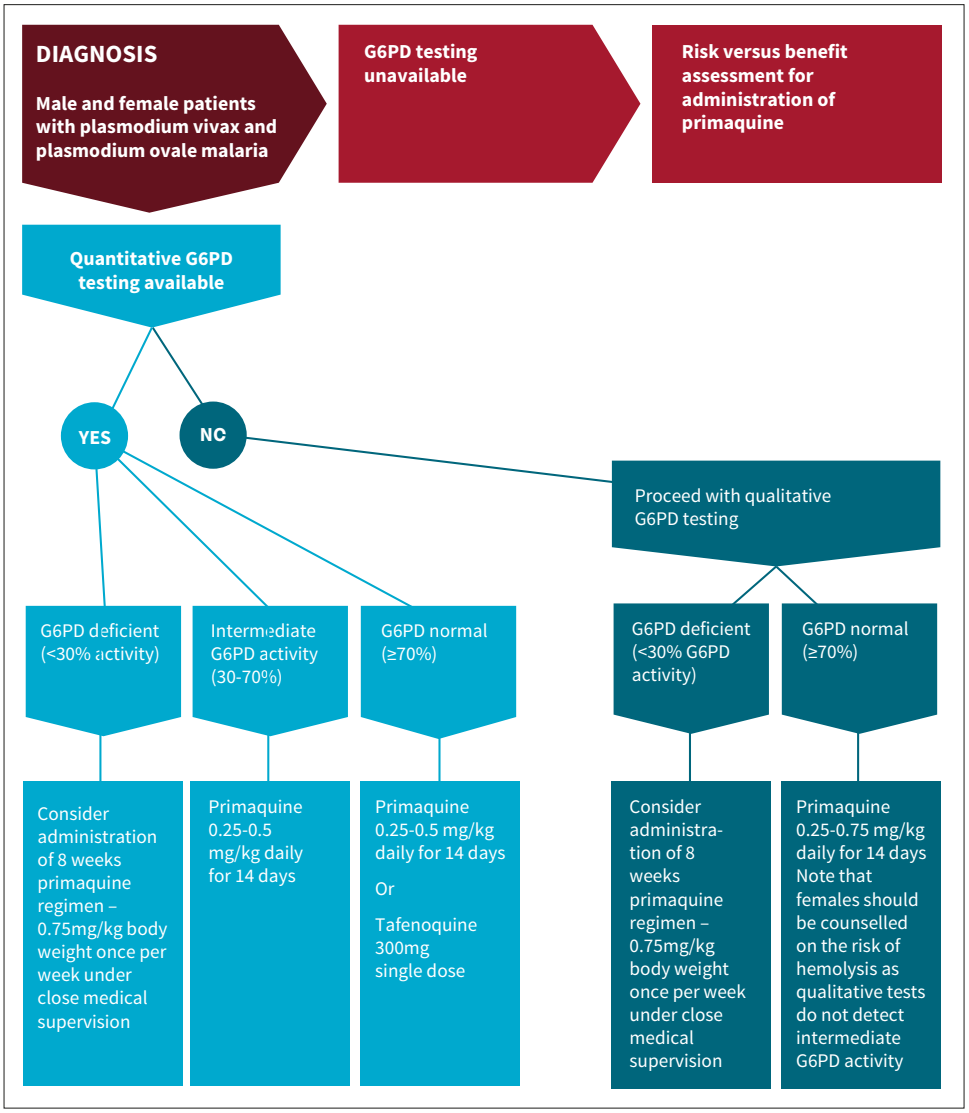
Source: Howes R. et al. (47)

Registered in 1952, primaquine predates current medicines regulation and the 1956 discovery of G6PD deficiency as a cause of sensitivity to primaquine, so its labeling does not require G6PD testing before use (48). However, since 2015, WHO recommends G6PD testing where feasible before administering a 14-day course of primaquine for radical cure.[13] When G6PD testing is not possible, WHO recommends considering the risk-benefit based on the prevalence of deficiency, the patient's ability to monitor themselves for signs of hemolysis and the health system's capacity to treat hemolysis. For patients with G6PD deficiency, WHO recommends counseling and a longer course of treatment at lower weekly doses under close medical supervision.

In 2018, a new single-dose treatment, tafenoquine, came to market. Tafenoquine belongs to the same class of medicines as primaquine (8-aminoquinolines) and is contraindicated in patients who have G6PD deficiency. While tafenoquine is advantageous because it is a single-dose treatment, there is no scope for reducing and spreading the dose over time, and treatment cannot be stopped if there are signs of hemolysis. In this context, the clinical trials supporting the drug use were conducted to minimize the risk of hemolysis, and an exclusion threshold of > 70% G6PD enzymatic activity was used. Therefore tafenoquine requires a quantitative G6PD test to confirm the patient has >70% G6PD enzymatic activity. WHO prequalification and treatment guidance is forthcoming, but tafenoquine has US FDA and Australian TGA approvals and is being piloted in Thailand and Brazil. Whether using primaquine or tafenoquine, the treatment pathway for radical cure is complex (Figure 17).

13 As G6PD testing is not required prior to administration of low-dose primaquine for blocking the infectivity of gametocytes for *P. falciparum*, such testing is only indicated prior to radical cure treatment for *P. vivax*

FIGURE 17. Potential clinical pathways for radical cure



Source: Weeratunga P et al. (49)

WHO POLICY FOR G6PD TESTING AND RADICAL CURE

In 2015, the WHO Global Malaria Program recommended G6PD testing before primaquine use where feasible. In the following years, WHO published a policy brief and a user guide for G6PD rapid testing to support radical cure (50) (51). While the latter includes guidance on ideal RDT product characteristics and generic protocols for performing a G6PD RDT, the product offering has changed since the guide was released, so in early 2022 WHO began developing a target product profile for POC G6PD tests.[14] Also in 2021-22 the WHO reviewed and updated the G6PD classification scheme related to the genetic variants and their clinical implications and the ICD-11 (International Classification of Diseases) scheme.

In 2016, WHO PQ expanded its scope to include POC G6PD tests, publishing technical specifications for G6PD tests that include enzyme activity levels (Table 6) for men and women.

14 Draft TPPs were available for comment through 5 July 2022.

TABLE 6. WHO classification of G6PD enzyme activities

Male	
G6PD deficient	G6PD activity <30% of the adjusted male median
G6PD normal	G6PD activity >30% of the adjusted male median
Female	
G6PD deficient	G6PD activity <30% of the adjusted male median
G6PD intermediate	G6PD activity 30-80% of the adjusted male median
G6PD normal	G6PD activity >80% of the adjusted male median

Source: Technical Specifications Series for submission to WHO prequalification – diagnostic assessment: in vitro diagnostics medical devices to identify Glucose-6-phosphate dehydrogenase (G6PD) activity. Geneva: World Health Organization; 2016.

POC G6PD TECHNOLOGIES

Until recently, the only reliable tests for G6PD deficiency have been laboratory-based diagnostics that require significant expertise, time, and resources to run. Since 2014, PATH has advanced a portfolio of POC G6PD tests, using target product profiles to guide its investments (Table 7). Foundational work at PATH to support the portfolio also includes market research, independent laboratory evaluations, and maintenance of a specimen repository.

TABLE 7. PATH's minimum desired features of G6PD tests

	Quantitative test	Qualitative test	Reason for desired feature
End user	Village/community health worker	Village/community health worker	The majority of malaria cases are managed at the lowest tiers of the health system
Sample type	Finger-prick	Finger-prick	Finger-prick samples are most commonly used for malaria diagnostics
Number of steps	No more than one timed step; fewer than 5 total steps	No more than two timed steps	Workflow should be minimal given the intended user
Portability	Portable; hand-held analyzer okay	Highly portable, no instrument	Lack of portability would limit ability to decentralize testing
Output	Numerical result on screen	Test line visible for "normal" and invisible for "deficient"	It is important to ensure accurate, clinically relevant G6PD status determination
Time to result	≤10 minutes	≤30 minutes	Time to result should align with patient load
Operating temperature	20°C-37°C; 30%-75% noncondensing humidity	28°C- 34°C; 30%-85% humidity	Quantitative tests can correct for operating temperature, but qualitative tests are optimized for a more limited temperature range
Target ex-factory price	Disposable: ≤US$3.00; ≤$2.50 at scale Instrumentation: reader cost of ≤$380; ≤$250 at scale	Less than US$2.00 (at volumes of 10 million)	Pricing should align with that of other malaria commodities but also recognize the need to be sustainable in a small market

POC G6PD tests use a fingerpick blood sample and have rapid turnaround times (e.g. 2-10 minutes). Technically, the main challenge is ensuring test performance in the environments where they will be used, ranging from air-conditioned laboratories to uncontrolled, tropical health posts. Because enzymatic activity is highly sensitive to temperature, developers have struggled to develop tests that perform consistently across conditions of transport, storage, and where the test is performed. In general, POC G6PD tests have narrower shelf-life, storage, and operating temperature ranges than malaria RDTs.

G6PD POC tests may be quantitative or qualitative. Tafenoquine requires a quantitative result, as does safe management of most female patients.

A few qualitative tests on lateral flow platforms have been developed, but to date, these lack evidence or have shortcomings that have hindered widespread use. Their workflows resemble that of malaria or COVID-19 Ag RDTs, and they are highly portable and less expensive than quantitative tests. The results are visually read; the entire test window often changes color as reagents react with the G6PD activity in the sample. The read-out is "normal" or "deficient," based on a threshold level of enzyme activity, e.g. deficient would be less than 30% activity.

To date, qualitative tests have several shortcomings. While the readout suits the vast majority of men, "normal" may be a misnomer for women because some would indeed have normal activity levels (i.e. >80% activity) while others could be intermediate, with 30-80% activity, and at risk of hemolysis. Thus, the actionable information gained from testing women is limited; those with "normal" results would need additional quantitative testing to determine whether they can safely take treatment. Another drawback relates to operating temperature. G6PD activity increases with temperature; if the temperature exceeds the recommended range, a deficient person's activity levels may increase, resulting in the RDT wrongly classifying them as "normal." The first RDTs on the market also required further product development because they lacked control lines. Recombinant lyophilized quality controls have also been demonstrated. (52)

Although several manufacturers have engaged in developing qualitative tests, success is challenging, and there are no WHO prequalified, WHO PQ pipeline, or ERPd status tests currently available.

- Abbott's BinaxNow G6PD test is US FDA approved but has not been used widely because it has a strict temperature range, high cost, and requires a large quantity of blood/venous blood collection.

- Access Bio has both an RDT and a handheld quantitative analyzer, however, the evidence base is limited, and neither is eligible for donor-funded procurement due to unresolved quality issues (described above). The company has prioritized pandemic related tests, however, confirms that G6PD tests are available with longer lead times. The development status of both tests is unclear: prior to the pandemic AccessBio planned additional development efforts (e.g. an improved G6PD RDT with control and test lines, versus windows that were present in the previous version). No new published evidence is available, nor progress updates on the planned improvements.

- In 2018 PATH and Mologic announced a partnership to optimize and commercialize a G6PD RDT developed by Mologic; however, it appears not to have advanced.

- Humasis, a Korean rapid test company, developed a qualitative RDT, rigorous evaluation of this product is still required.

Quantitative tests are device-based biosensors using disposable consumables for each test (e.g. capillary tubes, test strips, or cartridges). POC options include handheld or small tabletop analyzers. Although device-based platforms may be less portable and accessible than RDTs, they provide a precise measure of activity in terms of units of enzyme activity. Because they give a quantitative result, results are actionable for all, including intermediate females whose activity is above 30% but may still be below normal.

Quantitative tests have two advantages over qualitative. First, the devices accommodate a wider operating temperature range than RDTs. They recalibrate enzyme activity measurements based on the room temperature (within a range) as measured with a built-in sensor. The second advantage of quantitative tests is contextualizing G6PD activity for the number of red blood cells. Because G6PD activity occurs in red blood cells, red blood cell count variations (e.g. high or low, anemia) can affect G6PD enzyme activity values. Quantitative tests normalize these values by providing the G6PD activity per unit of hemoglobin.

Currently, only one POC quantitative test, the Standard G6PD by SD Biosensor, is available; others are in the pipeline or lack performance and quality evidence no (e.g. Care Start G6PD Biosensor Analyzer by Access Bio).

FIGURE 18. Standard G6PD analyzer by SD Biosensor

The Standard G6PD Test provides G6PD enzyme activity and hemoglobin. The hand-held device detects and quantifies enzymatic reactions using colorimetric methods to give a numerical value for G6PD activity (Figure 18). The workflow is slightly more complex than RDTs; operators insert a small test device into the analyzer, collect a fingerstick sample, mix the sample in a small tube of buffer, transfer the sample-buffer mixture to the small test device, and start the analyzer. Results are ready in 2 minutes. The read-out is a numerical value expressed as a ratio of G6PD activity units per gram of hemoglobin. The operator can use a table in the product insert to interpret these results and classify the patient as Deficient, Intermediate, or Normal (Figure 19). SD Biosensor offers quality controls for the test. The kits must be stored at 2-30C and have a 18-month shelf life. The temperature range for performing the test is 15-40C.

FIGURE 19. Standard G6PD test result patient classification

INTERPRETATION OF TEST RESULT

Male		Female	
G6PD Deficient*	≤ 4.0 U/g Hb	G6PD Deficient*	≤ 4.0 U/g Hb
G6PD Normal	≥ 4.1 U/g Hb	G6PD Intermediate**	4.1-6.0 U/g Hb
		G6PD Normal	≥ 6.1 U/g Hb

*Deficient was determined during clinical evaluation as approximately 30% of the adjusted male median of specimens tested.
**Intermediate was determined during clinical evaluation as females with activity greater than 30% and less than or equal to 70% of the adjusted male median.

CAUTION

Interpretation of the G6PD Test results should only be performed when Hb level is greater than 7g/dL.

Source: PATH (53)

SD Biosensor first registered the test in 2017 in India and Thailand. It received Australian Therapeutic Goods Administration approval in April 2021 and has provisional approval from Global Fund's Expert Review Panel Process for Diagnostic Products. WHO prequalification is underway, pending a site visit. Currently, many national programs, donors, and partners are piloting and introducing the test in connection with efforts to scale radical cure, in particular through the Partnership for Vivax Elimination (PAVE) project, primarily funded by Unitaid and BMGF. As of early 2022, SD Biosensor had registered, or made available, the test in countries comprising more than half of the global *P. vivax* burden.

PATH and BMGF are supporting another quantitative device that uses a different technology platform. Wondfo, a Chinese diagnostics company, is commercializing a G6PD POC test based on absorbance (Hb) and fluorescence (G6PD). The tabletop device is portable (Figure 20) and will provide a quantitative result normalized for hemoglobin. In 2020 Wondfo completed the technology transfer of the diagnostic. The test is design locked, and clinical evaluations are planned for 2022, with PQ submission targeted for 2023.

FIGURE 20. Wondfo G6PD test

Other device-based quantitative tests include:

- The PreQuine system, an enzymatic and colorimetric analyzer, is being developed by the US-based In Vitro Diagnostics Solutions, commonly known as "IVDS." This handheld platform will incorporate connectivity and is supported by the US National Institute of Allergy and Infectious Disease.

- SolGent, a Korean company, is developing an enzymatic and fluorescence-based tabletop platform for LMIC markets. The platform will measure G6PD activity and hemoglobin in 2 minutes. It is in early-stage development (prototype) and is supported by the RIGHT Fund.

- The Australian company ZiP diagnostics is developing a G6PD absorbance and fluorescence-based test. The developers intend to include other tests on this platform.

- In 2019 Baebies, a company targeting newborn screening, launched a microfluidic POC test for G6PD testing and their FINDER platform. The G6PD test is CE marked and was submitted to US FDA. However, given the complexity of designing and manufacturing microfluidic cartridges, this test is not likely to be affordable for LMICs.

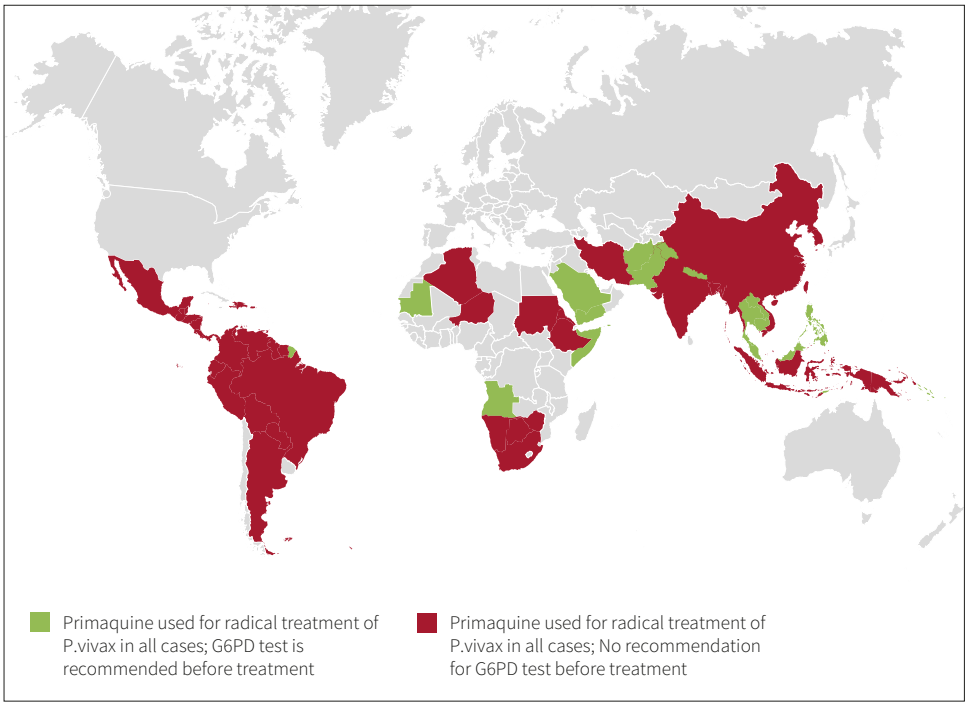
In summary, the only current option for POC G6PD testing to support radical cure in tropical settings with tafenoquine is the SD Biosensor semi-quantitative device and it will be the mainstay for the immediate future as other technologies have yet to commence regulatory review or demonstration projects. The POC G6PD pipeline is thin and attrition common: the three companies that PATH initially engaged with are no longer in the market, two dropped out for technical reasons and one for commercial reasons.

THE EMERGING POC G6PD TEST MARKET TO SUPPORT RADICAL CURE

Due to the historically limited availability of POC G6PD tests and concerns about primaquine safety, country policies for primaquine use, dosing, and the need for G6PD tests vary. (Figure 21) Differing tafenoquine adoption rates will increase divergence. Even when a radical cure policy exists, there are often significant gaps in actual implementation because testing is not available, primaquine is not available, and primaquine adherence is low (54). In some settings, primaquine is used unsafely, while in many other cases, it is underutilized.

There are no global access targets for G6PD testing or radical cure, as POC technologies suitable for LMIC use are just coming to market. However, most confirmed *P vivax* cases[15] should receive a G6PD test, an ACT or chloroquine, and radical cure. While the single-dose tafenoquine holds much promise, the G6PD testing must be in place to enable its use.

FIGURE 21. Radical cure policies by country



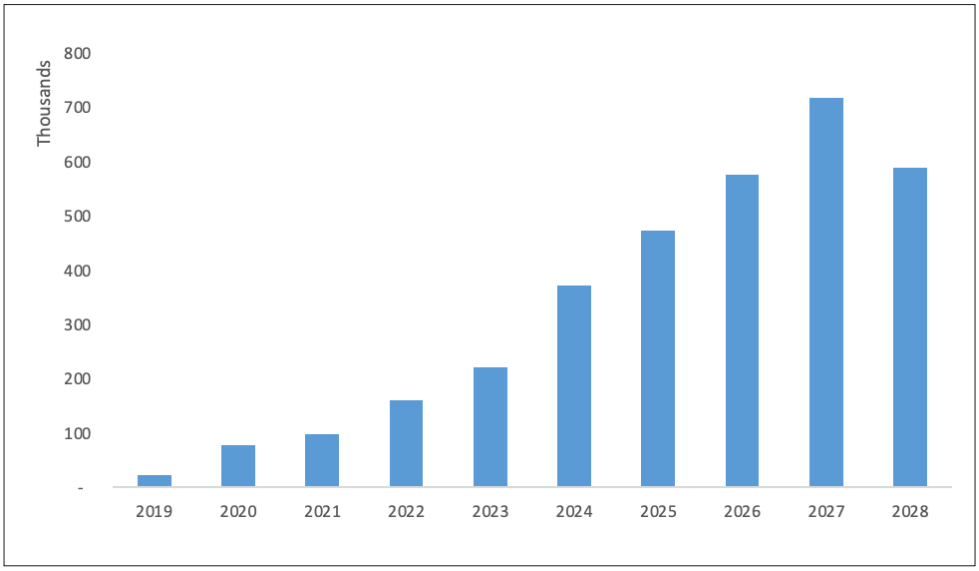
Source: P. vivax information hub website (55), based on the 2018 World Malaria Report

The POC G6PD test market to support radical cure is small and highly dependent on the number of confirmed *P vivax* cases. PATH has been estimating the market size, focusing on 20 priority Pv endemic countries and the number of patients that could be realistically reached with a POC G6PD test. They estimate an annual market size of 500,000 G6PD tests (Figure 22), with India, Ethiopia, Indonesia, Brazil, and Myanmar representing 75% of the market. Since the market is highly dependent on the number of positive Pv cases each year,

15 Exceptions include pregnant women, infants under 6 months, and women breastfeeding infants.

species-specific malaria diagnosis is a vital enabler of the market. Longer-term, assuming progress towards elimination, the market size will decline as fewer malaria tests will be vivax positive. Given modest volumes and the need for affordable pricing ($2.00-$3.50 ex works), the market value is unlikely to support many competitors. To expand the market, it is possible to consider private-sector channels (56) or other G6PD applications such as newborn screening.[16]

FIGURE 22. Estimated market size: number of G6PD tests for radical cure across 20 priority countries



Source: PATH 2017

From a policy and program perspective, the approach to radical cure and the deployment and the uptake of G6PD tests are not likely to be uniform across countries. Given starting points and the complexities of managing G6PD risk, strategies require thoughtful development, usually informed by operational research. Considerations include the prevalence of G6PD deficiency, including the frequency and the severity of variants in populations most at risk for malaria. The prioritization of Pv, for example, relative to Pf or the country's malaria elimination targets, will also factor into decision-making on deploying G6PD tests and radical cure. Decisions around tafenoquine adoption versus primaquine are also considered, as is the health system's capacity to monitor and treat hemolysis.

16 The WHO recommends screening where G6PD deficiency affects more than 3-5% of males and is implemented in the Philippines and Malaysia.

In many countries, operational research and pilots are underway to identify best practices for incorporating G6PD testing into the malaria case management workflows, including through investments by Unitaid and BMGF in the Partnership for Vivax Elimination (PAVE), described in box 2 below. The optimal testing network is also being studied: the currently available device, although portable, has a moderately complex workflow and interpretation. As a result, countries may not place them at the lowest health system level, so patients testing vivax positive in these settings may be referred for radical cure. While qualitative RDTs are more portable, tests that meet priority requirements (women, temperature) are not available or are unproven, so tradeoffs are necessary.

Many partners are working with country programs to answer the many implementation questions and support the introduction and implementation of G6PD testing and radical cure. Leading PDPs are PATH for diagnostics and MMV for medicines. Other organizations like APMEN, FIND, and CHAI are also working to support various implementations. Major donors, PMI and Global Fund, are procuring G6PD tests as well. A growing body of operatorial research results, training materials, and modeling tools are available to support decision-making and implementation.[17]

BOX 2. PARTNERSHIP FOR VIVAX ELIMINATION (PAVE).

PAVE aims to support malaria-endemic countries to accelerate elimination of P. vivax. Unitaid's investment in PAVE is led by Medicines for Malaria Venture (MMV) in collaboration with PATH, Menzies School of Health Research, and Burnet Institute with the overall goal of ensuring universal access to best clinical practices for P. vivax case management. The consortium is supporting critical activities to catalyse adoption and eventual scale-up of vivax tools by delivering on three interlinked outcomes:

OUTCOME 1: Availability of an expanded set of tools for comprehensive P. vivax case management including paediatric radical cure treatments (PQ and TQ)

OUTCOME 2: Revision of WHO and national guidelines based on feasibility evidence

OUTCOME 3: Adoption of new tools towards comprehensive P. vivax case management

The Consortium is working hand-in-hand with National Malaria Control Programmes, local researchers, and civil society organizations to assess access barriers through feasibility studies and health economic assessments and identify solutions to adapt to the varying capacities within health systems for scale-up and transition in target countries – Ethiopia, India, Indonesia, Papua New Guinea, and Peru.

17 For example, the G6PD Operational Research Community of Practice maintains a digital repository of resources, hosts meetings, and provides updates on G6PD tests (https://www.path.org/programs/diagnostics/gorcop/). MMV hosts a Vivax information hub to raise awareness and share best practices and resources with stakeholders on treatment and control of P vivax malaria (vivaxmalaria.org). Models have been developed to support countries in decision making, for example, the on-line model to estimate the cost-effectiveness of various radical cure implementation strategies. (http://lab.qmalaria.org/shiny/TFQApp/)

5. MALARIA POC DIAGNOSTIC TECHNOLOGY LANDSCAPE

An abundance of technical methods for malaria detection is possible, including direct visualization, immunoassays, biosensors, highly sensitive detection of parasite genetic material, and volatiles. As noted in the Methods above, this report does not aim to exhaustively review these technologies. Rather, it aims to identify the major approaches to diagnosing malaria, considering any major developments that might impact the malaria diagnostics market in the coming three to five years.

RECENTLY LAUNCHED AND LATE-STAGE DEVELOPMENT

Recently launched and late-stage development efforts include digital microscopy and hemozoin-based devices. While a few products have launched, none have achieved scale, and work continues to refine these assays and build the evidence base. These two categories are discussed generally below, with a few recently launched products as illustrative examples.

Digital microscopy

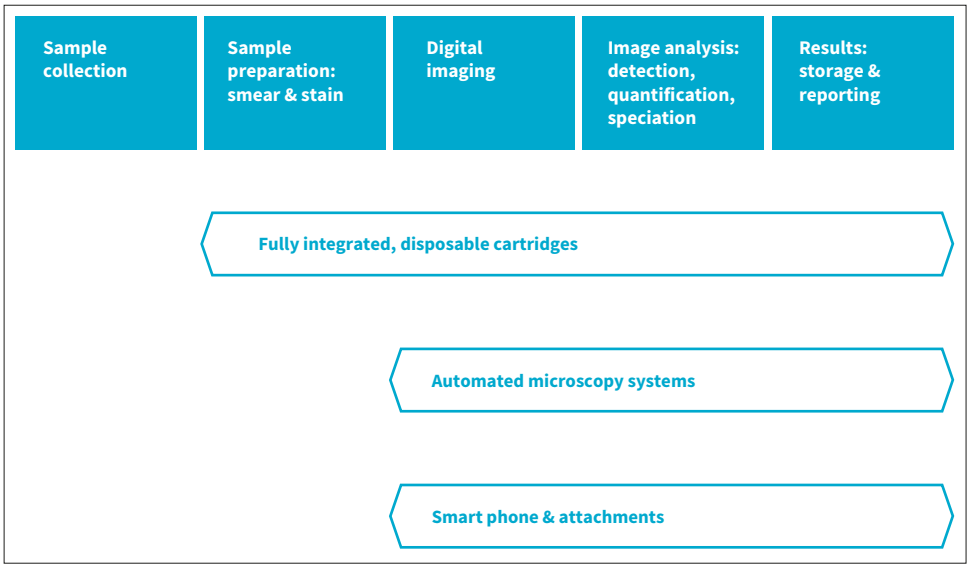
Microscopic examination of slides for the presence of malaria parasites is standard in malaria endemic countries, especially where test volumes are high and non-falciparum species common. Not only can microscopy detect disease, but it also provides speciation and quantitation (required for monitoring response to treatment).

In expert hands and ideal settings, microscopy performs well. However, under typical field conditions, the performance of microscopy is variable and compromised due to poor quality microscopes, stains and slides; insufficient training and supervision; interruptions in electricity; insufficient time; and absence of QA systems. Despite these limitations, microscopy persists as it has applications for other diseases, is relatively inexpensive, and is widely available; nearly every laboratory has a microscope, and all laboratory technicians receive training in microscopy.

For over a decade, developers have been applying technological advances in image processing and, more recently, machine learning to malaria microscopy, aiming to improve the objectiveness of slide reading and increase efficiency through automation. Although many efforts have been reported in the literature and attrition is high, a few technologies have recently come to market.

Broadly, there are three kinds of systems, fully integrated devices, automated microscopy systems using traditional slides, and smartphone attachments. These systems differ in the steps they cover (Figure 23) and in their form factor and throughput, with implications for use cases.

FIGURE 23. Steps in digital microscopy process performed by different digital microscopy systems



Digital microscopy systems differ in form. Some are free-standing benchtop devices, while others comprise an apparatus that attaches a smartphone to a standard microscope or a magnifying instrument that attaches to a smartphone. The different form factors are appropriate for different settings; for example, while some are highly portable, others are lab-based and can process multiple samples simultaneously.

A second differentiator is sample preparation. Automated microscopy systems like the Easy Scan Go by Motic/Global Good and smartphone attachments use traditionally stained slides. This has the advantage of easy integration with traditional microscopy systems; however, as with traditional microscopy, the quality of the slide preparation remains critical. In integrated systems, the test operator transfers a drop of blood to proprietary disposable cartridges that perform the sample preparation and staining. While the cartridges standardize the sample preparation and save technicians time, they are likely to cost more than slides and are not compatible with traditional microscopy.

As a category, digital microscopy is advancing. Some products have come to market, yet, there remains scope for improvement. Products claim equivalency in detection to highly trained microscopists, but evidence to date is based on limited samples sets and is not comparable across products (57). Evidence does suggest that limits of detection are unlikely to achieve levels on par with molecular testing. Speciation and quantification have lagged detection in terms of performance, but developers continue to refine this area (58).

One challenge affecting performance is accessing sizable, well-characterized microscopic image sets, including different species, to train the algorithms. AiScope is a non-profit group developing an open-source dataset of infectious disease microscopy images, the Global Disease Dataset, starting with malaria (59). The purpose is to train machine learning algorithms to diagnose malaria and other diseases. The group created an app for microscopists to photograph images; experts then analyze the images and label them.

The most advanced digital microscopes are fully integrated benchtop platforms from Sight Diagnostics and Noul.

Sight Diagnostics' first product was Parasight, an automated microscopy platform using custom cartridges inserted into a tabletop device that scans and analyses many fields using machine vision techniques. Parasight is a lab-based instrument, requiring some sample prep and accommodating multiple samples. As of the end of 2019, Parasight was available in 24 countries, and over a million malaria tests had been sold. Sight continues to pursue other tests based on digitizing and imaging blood samples, and has launched a smaller POC device, OLO, that performs complete blood count (CE mark and US FDA cleared since 2019). Presumably, malaria and sickle cell disease detection will be developed for OLO.

In 2020, Noul, a Korean start-up, launched a malaria test for its miLab (Micro-Intelligent Laboratory), the first test for its platform. The device provides results with 5 µL blood in 20 minutes; the sample is loaded into a proprietary cartridge and inserted into the machine. Smear and staining are automatically completed, followed by optical imaging and AI analysis. Currently, the device provides Pf and parasitemia levels (parasites / µL); Pv detection is in development. MiLab also performs blood counts, including a WBC five part differential and CBC estimations. A clinical validation study is ongoing in South Korea, as is an independent study in Ghana. Future plans involve developing speciation (study in Ghana underway) and cancer applications.

POC hemozoin tests

Several new platforms based on the detection of hemozoin are in development for malaria diagnosis. Hemozoin was discovered and linked to malaria in the 1800s[18]; however, it has not been used as a primary means of diagnosing malaria. While it is possible to see hemozoin in certain stages of the parasite's life-cycle using microscopy (in this case, it is commonly referred to as malaria pigment), it is not always detectable by traditional microscopy. Recent advances in sensing and lab-on-a-chip technologies have advanced hemozoin detection devices; a recent review article noted more than ten different research efforts (60). Although hemozoin detection technologies differ in how they detect hemozoin, they generally take advantage of its unique acoustic, optical, magnetic, and electrochemical properties. Hemozoin crystals scatter and uniquely depolarize light differently than red blood cells; and it is slightly magnetic due to its derivation from iron-containing hemoglobin. Most hemozoin-based technologies are hand-held devices that use fingerpick blood samples collected into a disposable sample chamber or cartridge. Reagents, if necessary, are contained within the cartridge, and results are available in 1-5 minutes. While all species produce hemozoin, speciation has been a limitation, but developers are working to see if it is possible to differentiate Pf and Pv. Non-invasive tests measuring hemozoin directly through the skin are also being developed (described below).

The most advanced hemozoin test Hemex Health's malaria test for its Gazelle platform. Gazelle is a portable, battery-operated system that uses cartridges. Academics at Case Western University licensed the technology to Hemex in 2016. It was designed for affordability, ruggedness, and ease of use. The turnaround time is 1 minute, and it does not require any cold chain. The malaria cartridge has a system for collecting a fingerstick sample and mixing it with buffer. The operator inserts the cartridge into the device, which

18 A malaria parasite produces hemozoin crystals as a by-product of its hemoglobin metabolism: after infecting a person, the parasites enter red blood cells and feed on hemoglobin. The parasite cannot use the iron-containing part of hemoglobin and sequesters it in the form of tiny crystals called hemozoin. The presence of hemozoin in a patient is a strong indication of malaria infection.

has two ports, for malaria the port uses optic-magnetic imaging to detect magnetic substances. To date, performance evaluations, while not independent, are increasingly favorable, particularly for vivax detection (61) (62). In 2020, Gazelle was tested in the FIND Innovation Platform, and results are forthcoming.

Speciation is in development, and Hemex is developing additional assays for the device, especially for the devices' second port that automates gel electrophoresis using microchips, computer vision, and AI to monitor the reaction and provide a quantitative readout. Currently, a sickle cell disease test and hemoglobin variant quantification are available, and an anemia test is in development. Hemex launched a COVID-19 test and plans to add a common diabetes indicator and immunoassays. The reader ex works price is between $800-1,200, and the cartridges are $1-$3 (63).

There is no PQ pathway for hemozoin tests, but Hemex may pursue FDA (63) . Hemex obtained regulatory clearance for the device in India and partnered with the Tata group for launch.

EARLY-STAGE DEVELOPMENT

There are many less mature efforts to advance malaria testing including work to bring molecular testing to the field level, developments using biosensors, and non-invasive sampling.

POC highly-sensitive nucleic acid detection

Many highly-sensitive techniques for detecting the nucleic acid of the malaria parasite have been developed, and multiple efforts to create affordable POC versions have been ongoing over the past decade. Efforts focus on methods that can be applied in field settings, such as reducing processing steps, avoiding expensive PCR equipment, and reducing time to result. Traditionally, nucleic acid detection comprises three steps (sample preparation, amplification, ad detection), and developers have focused on individual or multiple steps in this process.

Novel approaches include the demonstration of CRISPR technologies for ultrasensitive multi-species malaria detection (64) (65). Additionally, many groups are combining isothermal amplification methods with various approaches to sample processing, detection, and read out. For example, LAMP is combined with paper-based microfluidics for sample processing (66); with smartphone-based imaging biosensor for detection; (67) and with lateral flow tests for detection and test readout (68) (69).

While only a few of these have progressed to commercial efforts (e.g. OmniVis), the massive influx of funding for diagnostics development during the pandemic accelerated the development of disposable molecular platforms, and companies may now begin to consider how these advances can be applied to diseases other than COVID-19. For malaria, a niche use case for POC highly sensitive nucleic acid tests would be in peri-elimination situations for clearing indigenous or imported parasite reservoirs in a geography.

Biosensors

WHO expects POC biosensor-based diagnostic devices to play an increasing role in LMIC infectious disease diagnosis in five to ten years (70). Biosensors are tools that detect an analyte using specific biological receptor molecules. There are different types of biosensors

and many applications, but the glucometers launched fifty years ago, is the most familiar clinical application. Simplistically, biosensors work as follows: a bio-recognition component (antibody, DNA, enzymes) interacts with the target. This interaction produces a change in physical or chemical properties. A transducer measures the property change, and electronics turn it into a signal.

For malaria, biosensor development initiatives aim to achieve highly-sensitive detection and speciation in a field applicable POC format. A recent review described many nascent technologies targeting HRP2, Hemozoin, Pf LDH, and Glutamate dehydrogenases (GDH) analytes (71). Several bio-recognition systems for malaria analytes have been explored with various transducer technologies for measuring analyte presence and concentration. The literature describes several efforts that have achieved promising performance, yet these appear to use conceptual working prototypes that have not been engineered into self-contained devices or chips (71) (72). It is notable that so many are based on PfHRP2 detection, while its abundance in malaria infections make it an attractive target, antigen persistence and HRP2/3 deletions suggest it is no longer an optimal target for novel malaria diagnostics. One review noted an increase in focus on Pf LDH, including the use of aptamers, which are akin to monoclonal antibodies but synthetic and more stable (71).

Towards non- invasive sampling

Although fingerstick blood is generally accepted, less invasive sampling for case management with speedy turnaround time (e.g. one minute) could have advantages in increasing malaria diagnosis, especially in 'non-medical' settings, such as the private retail sector or border screening. Faster, less-invasive testing could also ease health worker workloads, particularly when suspected cases are high. If low LODs are achieved, non-invasive tests would also be helpful in elimination settings for screening asymptomatic carriers contributing to transmission.

Recent diagnostic technology advances and malaria research have increased enthusiasm about the potential to develop non-invasive malaria tests, and the WHO plans to develop a TPP for non-invasive malaria tests in 2022/2023.

Overall, efforts to use less invasive sample types are based on a variety of biomarkers and technology platforms, including lateral flow test platforms; novel biomarkers; hemozoin detection, and volatile biomarker signatures and technologies. Several efforts are described below.

In 2020, the US National Institutes of Health (NIH) held a Technology Accelerator Challenge to develop non-invasive, handheld, digital technologies to detect, diagnose and guide therapies for malaria, sickle cell disease, and anemia. BMGF is considering follow-on support. Of the six awardees/honorable mentions, four have malaria applications:

- Two efforts target a novel saliva malaria marker (PSSP17). One builds on the saliva malaria diagnostic being commercialized by ERADA (described in more detail below), aiming to incorporate ferritin and COVID-19 antigen detection. A second PSSP17 project by researchers at Cornell University in New York targets ferritin and CRP. It contemplates a smartphone attachment and an app combined with a lateral flow test.

- A third effort by CytoAstra the University of Arkansas, uses the cytophone, a smartphone-based device with laser pulses and ultrasound to detect malaria and sickle cell disease.

- Hemex, in collaboration with Medtronic, is developing a non-invasive finger cuff for its hemozoin and hemoglobin variant test.

Past attempts at saliva-based malaria diagnosis have not met performance expectations for clinical management. However, the Saliva-based Malaria Asymptomatic and Asexual Rapid Test (SMAART-1) targets a novel biomarker, PSSP17 a female gametocyte protein, present in the saliva of individuals with clinical and subclinical infections. Researchers at Johns Hopkins and the University of Florida initially developed the test and performed initial validations with prototype devices, in Cameroon, Zambia, and Sierra Leone (73). Based on promising results (83% sensitivity in symptomatic patients compared to PCR – similar to current RDTs), ERADA technology Alliance, a South African start-up, is commercializing the test under the brand name "SALVA!" The test was initially and primarily developed for epidemiological studies (i.e. using samples from patients with subclinical infection); performance will also need to be assessed in symptomatic patients. The current test is in lateral flow form and requires a fluorescent detection system.

Masimo is developing MalariSense, a technology initially developed by academics at Rice University who built a laboratory prototype demonstrating transdermal detection of malaria infection in a reagent-less 10-second procedure. The test works as follows: a short laser pulse passes through the skin to blood vessels, exciting the hemozoin and causing vapor nanobubbles to form around the hemozoin. Then the device measures the acoustic signals of these hemozoin-generated nanobubbles to detect malaria. The method may detect sub-clinical parasitemia. Although the laser is safe, research is needed to assess any impact of skin tone and long-term skin exposure to lasers. The NIH supported a proof-of-concept study in the Gambia, and a second NIH grant supported Masimo's development of a field-ready shoe-box-sized device that can screen >200,000 people each year with a per test cost below $0.10 (74).

Researchers are exploring use of volatiles for non-invasive malaria diagnosis. Recent research suggests that mosquitos can differentiate malaria-infected and uninfected people based on odor. This has motivated research into volatile biomarkers, produced by the parasite itself, its interaction with host red blood cells, or volatiles resulting from changes in a malaria-infected person, e.g. in the skin microbiome composition. Biomarker discovery research has looked at skin and breath volatiles as well as volatiles collected from samples cultured lab. Recent published reviews identified a handful of exploratory studies that successfully detected odors or volatile biomarkers from skin or breath of malaria-infected individuals (75) (76). While there were some overlapping volatile biomarkers in the different studies, there was no convergence on one promising profile. These initial studies were in small populations in specific geographies; given the variation in human odors and volatiles, the identified markers need more extensive validation across different geographies and populations to ensure the results hold. A general challenge with volatiles is the potential influence of compounds in the environment, diet, or cosmetics. Additionally, researchers strive to identify biomarkers unique to malaria, as opposed to markers associated with underlying biological conditions common in many infections and diseases. A recent malaria volatile study in Kenya however demonstrated differentiation of volatiles in malaria-infected children from volatiles in uninfected children who had similar symptoms (77).

In addition to biomarker validation, pragmatic portable volatile detection devices must be developed. The malaria signatures described thus far require detection of multiple volatile biomarkers, hence, the most promising approach is use of the "electronic nose" to detect signatures. These are in development for other applications, and use sensor arrays capable of recognizing multiple compounds, and have electronic components with algorithms that classify the detected volatiles. Volatile sample collection from breath and skin and analysis have not been standardized, and there is an absence of specimen banks or standards for product development and evaluations. Overall, despite promising early results in detecting volatiles for malaria, the efforts are at an early, pre-commercial, stage (75) (76) (78).

In addition, the kENUP Foundation is supporting several tests under development, including non-invasive malaria tests, by Magnetrap and MOJA innovations. These appear to be very upstream, as limited information was available.

Hypnozoites

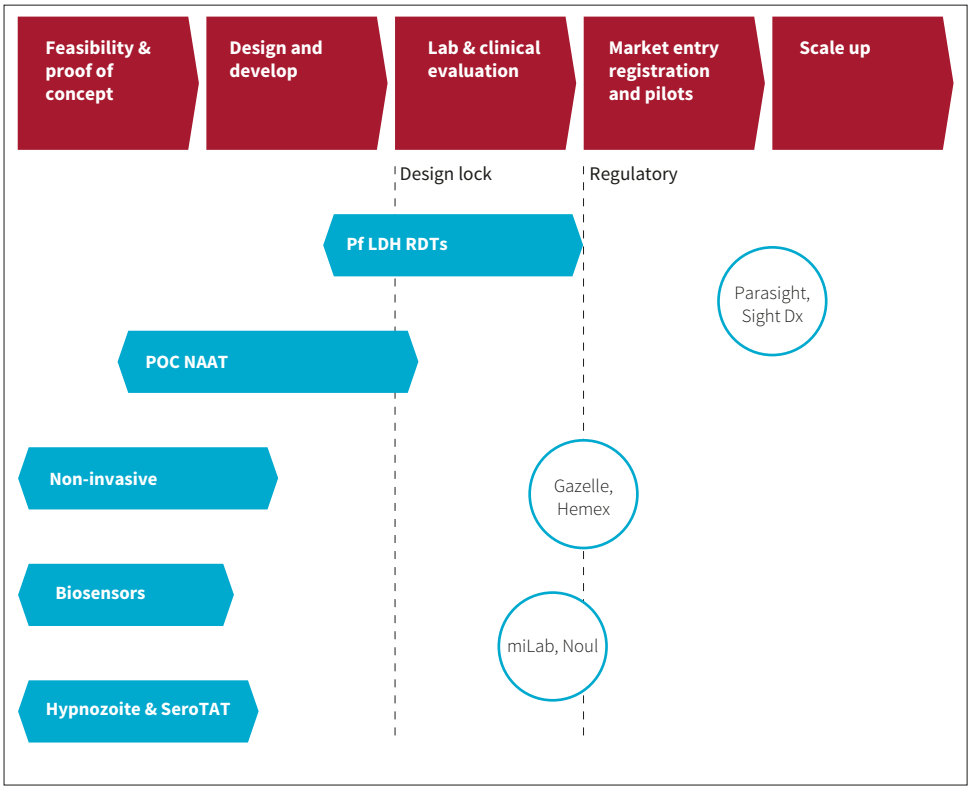
Researchers are working to develop means of identifying vivax hypnozoite-infected individuals. Hypnozoites are the undetectable vivax liver-stage responsible for relapse. There is one early-stage Japanese academic effort to identify metabolites produced by hypnozoite infection, supported by the Global Health Innovative Technology Fund.

An alternative approach detects serological markers of recent exposure to vivax, a proxy for hypnozoite carriage. Although not appropriate for diagnosing active malaria infection, tests detecting malaria antibodies can indicate exposure to malaria, because antibodies to malaria parasites remain in the body for varying periods after the active infection. The detection of exposure to malaria has a few applications. Especially in low-transmission settings it may be used for surveillance, for instance a population may be screened for exposure to malaria, which serves as a proxy for transmission.

A novel application is sero-test and treat, "seroTAT". In seroTAT the presence of a serological marker of recent exposure to vivax serves as a proxy for hypnozoite carriage, suggesting the person is at risk for relapse and requires radical cure (assuming they are not G6PD deficient). Researchers, led by Walter and Eliza Hall Institute of Medical Research and FIND, developing this approach estimate that in some settings up to half of vivax-infected individuals are asymptomatic with dormant liver stage parasites. While they are at risk for relapse, current diagnostics cannot detect them. To date, the serological biomarkers have achieved 80% sensitivity and specificity, the developers estimate that seroTAT interventions would identify 80% of vivax-infected people for radical cure. Compared to mass drug administration, overtreatment would be minimized (20%), reducing unnecessary treatments and side effects. In parallel to biomarker refinement, modeling, and studies, the researchers developing this approach have partnered with product developers to create POC versions of the test, including potentially a lateral flow assay.

Overview of the malaria diagnostics technology pipeline

FIGURE 24. Malaria diagnostics technology pipeline



While this high-level scan has identified several technology development efforts for malaria (Figure 24), assuming improvements to malaria RDTs, especially Pf LDH detection, are successful, malaria RDTs are likely to remain the mainstay for case management in the near- to medium-term. Other technologies are likely to fill specific use cases, where they uniquely add value. Longer-term, significant technical advances like non-invasive testing, if successfully developed and competitive with RDTs, could play a substantial role in the malaria diagnostics market. For all, a significant barrier will be generating a robust evidence base for the various use cases.

It is also important to acknowledge the pandemic's effect on diagnostic R&D. In early 2020, diagnostic researchers and developers shelved many projects to focus resources on COVID-19 tests. An influx of capital and the rush to launch products accelerated the development of many technology platforms. For example, disposable molecular tests are now on the market, and saliva sampling has become more common. The pandemic also increased public awareness of diagnostics. The immediate pandemic impact for malaria product development may have been a diversion of resources; however, in time the advances could be applied to malaria.

6. MALARIA RDT MARKET SHORTCOMINGS AND CHALLENGES

INNOVATION AND AVAILABILITY

Despite the malaria RDT market experiencing considerable growth over recent years, research and development has stagnated for new tests that specifically address biological threats, such as HRP2/3 deletions and tests for non-P. falciparum malaria. Some products are in development but are very upstream and have yet to reach design lock which is needed to start small-scale field validation trials and larger scale impact trials.

Incentives to drive malaria RDT innovation are limited, e.g. small profit margins and low volume purchases, leading to limited confidence on a sustainable return on investment for developers and investors. This has resulted in product development investments relying largely on donor funds and is currently exacerbated by companies focusing on larger, more profitable RDT lines such as the booming COVID-19 rapid antigen test market. While the market for HRP2 tests is relatively stable, the market progression of non-HRP2 based tests is less clear. The WHO only recommends the use of non-HRP2 tests where deletions are above a certain threshold. Manufacturers do not have reliable information to inform long-range planning and fragmented country demand for Pf LDH tests is creating an unclear picture of the real need and demand over the next 3 – 5 years, despite expert consensus that demand will shift towards non-HRP2 tests in the coming years. Without a reliable projection of the market size, manufacturers cannot commit to competitive product pricing and hesitate to engage.

At the same time, how procurers will approach these tests and adopt them into standard procurement practices is not yet clear. For example, higher prices and sole sourcing based on product differentiation may be appropriate for new products. The lack of signaling or information on how procurers will approach new products, whether they be incremental product improvements or entirely new innovative categories of tests, creates uncertainty for companies considering investing.

Demonstrating the impact and cost-effectiveness of new RDTs compared to existing tools is challenging especially as advances in the malaria RDT product landscape are mostly incremental. Guidance on the type of evidence needed to demonstrate the impact for new malaria RDTs, to build country demand, needs to be established. While TPPs and WHO PQ guidance have addressed this problem in part, suppliers have indicated that they do not have the required information to navigate the pathways, including evidence requirements, for policy recommendations.

Besides RDTs, there are many malaria diagnostics technologies in the pipeline; however, they are not advancing rapidly. In part, malaria RDTs represent a compelling value proposition, difficult for pipeline technologies to surpass. In particular, the low malaria RDT prices anchor customer expectations for diagnostic test pricing, discouraging investment in new products unless they are transformative in some way. Even though quality microscopy is challenging to maintain, the existing microscopy network contributes to technological inertia. Traditional microscopy is well entrenched, as WHO certification of elimination requires it, lab technicians are universally trained to perform it, and it has value for other

diseases. Against this backdrop, it will take time for new technology developers to identify where new products add value and to articulate and demonstrate the impact.

While newly launched digital microscopy and hemozoin platforms have begun to sell in private laboratories, additional independent performance data and demonstrated value add are needed to initiate any WHO quality or policy process. Both the digital microscopy and hemozoin device value proposition may be enhanced as additional tests are added to these platform's menus. The use cases also need consideration, especially in light of the varying product types. For example, a high throughput digital microscope may fit well in large microscopy centers, while a smaller device providing quantitative information may be more relevant in hospitals where monitoring response to treatment is needed.

POC malaria nucleic acid tests have not advanced rapidly, despite pandemic-related accelerations in POC NAAT testing platform development. Current LMIC demand for malaria NAAT tests is relatively small, limited to research and surveillance applications. For any POC NAATs, affordability is likely to be a barrier. Additionally, there is also no global consensus on the role of highly sensitive malaria tests that can detect subclinical infection. Many argue for more sensitive tests to detect and treat all infections (79). However, the feasibility of this approach and its impact on malaria and other febrile diseases is debated.

Earlier stage biosensor and non-invasive diagnostics utilize novel biomarkers and technology platforms and as a result, will require comparatively more evidence than familiar biomarkers and technologies. Therefore, trial costs and timelines are likely to be high and long. To compete with malaria RDTs, the novel device-based diagnostics will also need compelling cost, speed, ease of use, or performance advantages.

QUALITY

The donor-funded malaria RDT market relies on the WHO Prequalification Programme to quality assure products. While WHO PQ is a strong system, an increase in submissions to WHO PQ for other diagnostics, diagnostics and pandemic travel restrictions have impacted the prequalification timelines for malaria RDTs with some products experiencing long delays.

In contrast to quality assurance via WHO PQ for public sector purchases, quality assurance outside of the donor market is inconsistent and at times lacking, particularly in the unregulated private sector. For example, anecdotal evidence suggests that one LMIC procures between 20 – 30 million non-quality assured malaria RDTs annually, with minimal quality assurance or regulatory requirements. The true size of the malaria RDT private sector market is unknown, however around 40% of febrile patients in Africa seek care in this market. Drivers of limited quality products in the private sector include: lower prices of non-quality assured tests; poor awareness of the benefits of quality assured products; a preference for sourcing and procuring tests locally; and weak national or regional regulatory systems.

Despite WHO recommending post-market quality testing of malaria RDTs, quality control of in-market malaria RDTs is variable, and mostly limited in LMICs. Global efforts to develop universal quality controls were unsuccessful, national regulatory requirements are often lacking, and technical capacity to perform malaria RDT QA/QC is limited in LMICs. Additionally, while there is new WHO guidance on the development of post-purchase use of quality control materials, there is no certainty on the need and market requirements. A

myriad of use cases are possible, which could result in varying levels of demand for QCs should they be recommended. Thin margins are another disincentive for manufacturers to invest in developing controls.

AFFORDABILITY

Generally, HRP2-detecting RDTs are affordable for national programs to procure at scale and maintain coverage. While the price of malaria RDTs is very low (i.e., US$ 0.20 – 0.30 per test ex works), there are continued concerns that such low pricing could destabilize the market. Low malaria RDT prices are disincentivizing large investments and disengaging manufacturers from participating in the donor-funded market. Multilateral partners have been working to address this problem which has led to slight price increases in recent years. While the price increases have not corresponded to significant coverage shortfalls, there have been wide price variations and some countries are paying more than the average price which is unsustainable. This suggests that the equilibrium price, i.e., one that is affordable for buyers and sustainable for manufacturers has not been achieved. Additionally, the landed cost of malaria RDT testing has increased as a result of rising freight costs; if budgets are fixed this could reduce the volume of tests bought.

New Pf LDH tests will be more expensive than current malaria HRP2-detecting RDTs, which could be exacerbated by a single source or highly concentrated market. The higher price of these tests could limit coverage as they may not be affordable for countries needing to switch from HRP2 test to Pf LDH due to increasing deletions.

While the price for malaria RDTs in the public sector is low, by comparison prices for an equivalent test in the private sector are high. Higher prices deter uptake as many care seekers may not be able to afford a test as well as treatment if needed. Volumes and margins for retailers and suppliers are likely minimal, discouraging continuous stocking and distribution. Reasons for higher prices in the private sector include large distributor mark-ups, low demand due to a preference for presumptive treatment which is cheaper than purchasing both an RDT and a treatment course and limited availability due to more lucrative products dominating retail space.

DEMAND AND ADOPTION

Even if a country meets the HRP2-deletion threshold to switch to Pf LDH tests, adoption of Pf LDH tests is low. Low adoption of Pf LDH tests stems from: the lack of a quality-assured Pf LDH test; the likely high cost of a Pf LDH test compared to a HRP2-based test; the limited evidence available from investigational studies on when to switch; and the complexity and high cost of investigational studies deterring investment. Additionally, household surveys show that quality case management that includes testing in the private sector does not meet the estimated need. Often where care is provided, tests are unavailable or not offered, or caregivers don't seek care for fever in time. There is poor awareness in communities on the benefits of testing and community-based programs have limited capacity relative to the need. This leads to low uptake especially testing in the community. Similarly, there is little financial incentive for healthcare workers and retailers to test in the private sector when the cost of a test is disproportionate to the treatment. Local regulations may also prohibit diagnosis in outlets where people seek care limiting demand.

Beyond HRP2- and Pf LDH-based tests, there has been little adoption of digital tools to support effective case management and improve the delivery and quality of testing. Evidence defining use cases, impact and cost-effectiveness is lacking and limiting demand. The value proposition and investment case for scaling-up these tools alongside malaria RDTs is unclear limiting their adoption as they are seen as supplemental or enhancements of core diagnostics.

SUPPLY AND DELIVERY

Prior to 2020, significant progress was made to diversify the supply base and guide price corrections. Even with these gains, competing demand for COVID-19 diagnostics exposed the fragility of the malaria RDT market highlighting the risk to sustainable and adequate supply. At the beginning of the pandemic, a WHO PQ notice of concern for one supplier coupled with increased COVID-19 diagnostic demand caused widespread disruptions to the malaria RDT market. So, while the malaria RDT supply base is diversified, its strength is currently tenuous. Supply uncertainties can be attributed to the following: most manufacturers with large capacity for malaria RDT orders also have other strong RDT portfolios including COVID-19 rapid antigen tests, and may prioritise more profitable lines (i.e. their commitment to the malaria market cannot be assumed); their commitment to the malaria market cannot be assumed; due to COVID-19 many suppliers had unstable or longer lead-times due to manufacturing closures and shipping delays; and smaller suppliers that are willing to sell at current prices are yet to demonstrate their capacity to deliver quality RDTs at scale.

Downstream supply challenges mostly relate to the supply chain, where stock out risks have increased alongside increased supply chain costs and a greater need in coordination to monitor stock levels. Higher costs along the supply chain are putting pressure on malaria programs, while at the same time programs with large buffer stocks sitting in country could see large wastage if stock is not adequately managed.

The private sector supply chain is also failing to deliver RDTs to its potential. Linked to poor consumer/retail demand, supply chain actors can be unaware of malaria RDTs and not distribute them at all. At the global level, and for some countries, low awareness on how to successfully work with the private sector and maneuver the supply chain is limiting engagement, while cost-benefit evidence on different potential retail channels is lacking. To date, pilots and programming have demonstrated that these programs are time-consuming and resource-intense to establish. Although once established at scale the programmatic cost per diagnosis would presumably decrease, no program has achieved this yet.

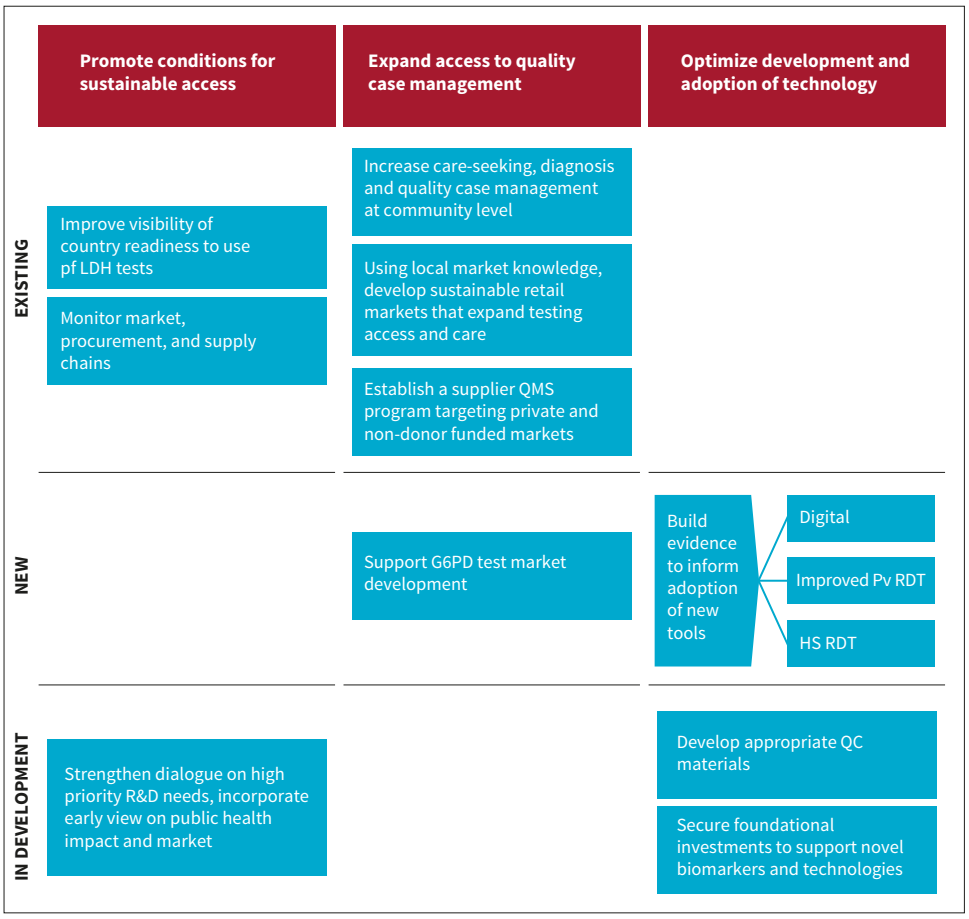
Other challenges with downstream supply are linked to low profit margins disincentivizing malaria RDT manufacturers to invest in developing their business in emerging markets.

7. OPPORTUNITIES FOR INTERVENTION

Based on the challenges and gaps, this section provides an initial view of potential market opportunities for strengthening access to the right diagnostic technologies for malaria diagnosis (Figure 25). It is not specific to the Unitad mandate and business model; rather, it represents a range of market-based interventions that different global health stakeholders could undertake. While some of these interventions could be acted on immediately, others are medium or long-term.

Many of the opportunities are time-limited interventions, for example, catalyzing new approaches to quality case management, and optimizing the development and use of new diagnostic tools. Underpinning this work are market enabling activities requiring collective work of several stakeholders, including improving visibility into Pf LDH test demand, and monitoring prices, incentives to produce, and recalibration of RDT manufacturing capacity. Secondly, forums for multistakeholder dialogue around R&D priorities would support more efficient investment in product development and commercialization of new technologies.

FIGURE 25. Opportunities for intervention



improve visibility of country readiness to use Pf LDH tests

In the near term, there is a need to improve the visibility of the potential demand for Pf LDH RDTs by compiling information on countries with reports of deletions, the timing of surveillance studies, and the associated RDT volumes. Combining this with HRP2/3 deletions risk modeling and expert opinion would better inform the potential pace of change to alternative RDTs.

Monitor the market and manage procurement and supply chains closely

As with all RDTs, the pandemic will continue to affect the malaria RDT market; in particular, fluctuation in demand and production of COVID-19 Ag RDTs will have knock-on effects on malaria RDT markets. Malaria RDTs compete for production capacity allocations with COVID-19 RDTs. If COVID-19 test demand increases, suppliers have a strong incentive to allocate capacity to COVID-19 instead of malaria RDTs. If demand for COVID-19 tests decreases, then the capacity for malaria RDTs at some suppliers will open up, and prices from these suppliers may decrease. However, suppliers may opt to shut down underutilized production lines at some point. Thus, the capacity for RDTs overall could decrease step-wise, (i.e. not gradual smooth reductions). These recalibrations of capacity will have ramifications for all RDT markets and should be monitored to ensure sufficient malaria RDT supply at affordable prices. Regular communication and expectation-setting with larger suppliers and cultivation of the new entrants could support continual supply. In-country interventions to improve visibility in the supply chain at different levels are helpful, as are 'first in, first out' inventory management practices, so that buffer stocks are consumed before expiry.

Concerning Pf LDH RDTs, closely monitoring affordability and volumes as the market develops will be important; as is monitoring the advancement of pipeline products to ensure sufficient product offering, healthy competition, and supply security. Programs may need support to conduct surveillance, accelerate studies, or operationalize any test changes. While several field studies are underway or planned for new Pf LDH RDTs, new evidence needs may emerge requiring additional support. Ensuring respective groups are appropriately resourced to provide timely quality reviews and policy recommendations is also critical. Procurers will need to define and signal the approach to new Pf LDH RDTs to the market (i.e. whether they will accept higher prices and how the tests will be sourced). A future consideration is whether standardizing on product format and types is beneficial; however, without more experience using the tests, this may be premature, discouraging innovation.

Strengthen dialogue on high priority product development needs, incorporating an early view on public health impact and market

Additional dialogue could strengthen the alignment of product development and public health priorities, stimulating innovations that address critical public health needs. Dialogue would also improve understanding of the evidence needed to support adoption - including the various quality and policy review requirements at the global and local levels.

A healthy balance between "technology in search of a problem" and "problems needing a solution" should be sought. As noted, several technologies have come to market, and their optimal use case remains undefined. It is equally important to take the reverse perspective, i.e., to identify the problems and use cases that would have the greatest public health

impact and to specify the key aspects of a solution's value proposition needed to deliver that impact. Here, human-centered design, including identifying high-priority problems to solve, is critical. Layering on market estimates and technical feasibility would further refine a problem-driven public health agenda.

Currently, global pathways to align the R&D agenda with quality and policy reviews exist (e.g. WHO R&D blueprints, WHO PQ process and TSS, and WHO MPAG). However, whether they are sufficiently resourced and comprehensive remains to be seen, as some of these systems are new.

For technologies in development, it may be helpful to explicitly incorporate analysis of the potential public health impact into early R&D discussions, including mapping how new technologies would contribute to global targets and goals, if they complement or replace existing tests. An early view of the market would also be informative, for example, comparing the new value proposition to alternative diagnostics, identifying the key use cases, and estimated market size. Smaller markets may imply higher prices, extensive PDP support, and different regulatory approaches. If WHO PQ's scope does not include the new technology, suitable alternatives that are acceptable to national programs and to donors/procurers need to be explored, including the associated timelines and cost.

INCREASING ACCESS TO QUALITY DIAGNOSIS AND CARE

Community programs targeting those who may not seek care

For those who do not seek care, formative research to understand barriers and develop human-centered-design delivery models are needed. For the employed, their families, and communities, expanding employer-supported vector control and community case management is an option, as there are several successful examples, yet the private sector remains an underutilized resource for malaria programs (80) (81) (82).

Other innovative programs that may be considered for certain contexts include self-testing and treatment for remote and hard-to-reach populations, as is being done through the Malakit in the Guiana Shield (83) (23). Additionally, China's 1-3-7 approach has been recently adapted and piloted in a high transmission area of Tanzania, where it is called the 1, 7mRCTR approach (84). In China, where the goal was elimination, the program included reporting of confirmed cases within one day, origin investigation within three days, and appropriate intervention within seven days. In Tanzania, the researchers used health facility case counts to identify hot spot villages (based on cases per population). In the following week, community health workers provided free screening and treatment in these villages.

Informed approaches to case management in the private sector

In several countries, the potential impact of improving case management in the private sector is substantial. Any effort to develop retail private sector markets must be grounded in a solid understanding of the local market, including a nuanced appreciation of where people seek care, the varied distribution and retail business models, and policy and regulation context (e.g. not only for where to test, but who can test and who can treat). Depending on the findings, various interventions might be relevant. Affordability will need to be assessed from both the patient side and the supply side, i.e. is the margin worthwhile for retailers and the various supply chain actors? The cost-effectiveness of the interventions could be modeled conceptually, and the intervention piloted.

Role of innovations in expanding case management access

It is worthwhile to consider how innovation might support improved access to testing. For example, in the retail sector researchers are piloting point-of-sale devices to target subsides, manage inventory, and monitor care. Additionally, there may be scope for self-testing, less invasive, or faster tests to reduce the burden on retailers or increase acceptance by patients.

In high-burden health facilities that already provide testing, the scope to reduce health worker workloads through facility-based self-testing could be explored, as done for HIV in some settings (85) (86). This type of task shifting might free up health care workers' time for clinical diagnosis and treatment and be coupled with a digital intervention (e.g. to capture data on the patient, test result, and treatment, to assist in testing and processing) to support quality.

QMS program focused on manufacturers selling into the private sector and domestically funded market segments

To increase the availability of quality RDTs outside of the donor-funded market, a program, targeting both supply and demand side of the market, could aim to shift market share to WHO PQ-ed (or other SRA) products. While there is uncertainty about the market size and degree of fragmentation, which could affect any effort to impact market share, it is worth exploring the potential to identify the largest manufacturers of non-PQ-ed RDTs in key markets (malaria, and other essential RDTs)[19] in order to gauge interest in strengthening quality management systems. These will include many Indian manufacturers and possibly manufacturers based in malaria endemic LMIC markets.

For suppliers the program might offer:

- Education orienting developers to the needs and expectations of global health diagnostics markets. Topics may include the state-of-the-art product development, QMS and WHO PQ, understanding the global health partner landscape, local registration/policy requirements

- Targeted technical assistance (e.g. review of mock dossiers, mock inspections, consulting support for QMS or go-to-market planning)

- Funding for capital expenditures necessary to achieve PQ (facilities, equipment)

In exchange for this support, suppliers would commit to obtaining PQ/SRA for key RDTs, registering and promoting these products in key markets, and affordable pricing. Suppliers would be expected to absorb the on-going costs of implementing higher quality standards, e.g. increasing headcount, expanded quality control sampling, changes to sourcing strategies, and implementing a culture of quality broadly.

In parallel, on the demand side, advocacy and technical support would target local regulatory institutions, programs, and procurers responsible for buying RDTs to increase awareness of the benefits and value of selecting PQ/SRA approved suppliers. Ultimately, the goal would be to increase the number of PQ-ed suppliers with low prices so that they penetrate these markets, crowding out non-quality assured products. Additionally, these suppliers could then participate in the donor-funded markets.

19 Market research could be complemented by/validated through and intervention with an expression of interest process wherein suppliers demonstrate their market share in specific markets.

Support development of POC G6PD test market

POC G6PD testing to support *P. vivax* radical cure is a small market, but critical for progress against vivax. On the demand side, implementation is not uniform, each country's context requires customization of how the test is used. Temperature requirements and shelf life are more restrictive compared to the Pv RDTs these will be paired with. While there are several grants supporting operational research and implementation of radical cure; it will be important to ensure that there are no gaps in the donor and partner support for programs. On the supply side, having more than one product is beneficial, and a proactive approach to managing the pipeline could accelerate introduction. In such a small market, until demand becomes predictable, there may be a need to support affordable pricing and manufacturers' incentive to produce. Manufacturers may also benefit from support in identifying markets for POC G6PD testing outside of radical cure applications (e.g. infant screening, potential HIV applications).

OPTIMIZING THE DEVELOPMENT AND USE OF MALARIA DIAGNOSTIC TECHNOLOGIES

Identify high-impact use cases for new tools, and develop the evidence base

Several improved diagnostic tests and supporting tools are in late-stage development or have recently been launched, including digital technologies and RDTs with improved sensitivity. Additional work is needed to identify high-impact use cases and develop supporting evidence.

Recent improvements in RDT readers (87) and increased experience with various COVID-19 apps, render it timely to revisit potential high-impact digital use cases for malaria, i.e. whether digital tools could address high-priority challenges in malaria case management. There are many potential applications of digital tools, as they can support individualized test and treatment data capture (improve surveillance), support test processing and algorithm implementation, and provide clinical decision support. Technology may also enable the targeting of financial incentives or bring visibility to stock levels. Regardless of where digital tools are implemented, they will "add cost" to the existing budgets, and even when they are time-saving or streamlining workflows, the indirect value-add will need clear articulation and the savings documented.

After developing a compelling investment case for the digital use case, field and cost-effectiveness studies will be required. In parallel, it would be important to consider the key success factors for digital implementation, and how generalizable these are to other contexts. Eventually, from a market perspective, a mechanism for understanding and staying abreast of the most promising product offerings will be beneficial.

"Next-generation" RDTs with improved sensitivity have come to market (e.g. highly sensitive HRP2 RDT) or are in late-stage development (Pf LDH + Pv LDH RDTs). The highly sensitive HRP2 RDT's performance has been evaluated in varying populations in several field studies. Use in surveillance and active case detection would result in higher prevalence and greater yield, but these are 'niche' applications and small markets. The benefits of highly sensitive HRP2 tests for clinical case management or for screening pregnant women versus the drawbacks are not clear, and, studies to generate more conclusive evidence may be fairly complex (e.g. longitudinal studies to understand antigen persistence in case management, risk of harm due to the cause of fever being erroneously attributed to malaria, the impact of

detecting lower density infections on parasite prevalence, the impact of screen-and-treat in pregnant women versus IPT).

For the improved Pv RDTs in development, a few trials in diverse populations are underway or planned. While modeling suggests the new tests could increase the detection of Pv-infected symptomatic and asymptomatic individuals, field studies will demonstrate the number of additional cases detected. Assuming compelling trial results, it may be possible for ongoing operational research studies to support the introduction of these new tests in countries or to evaluate their use in new approaches (e.g. active case finding), or in surveillance, as currently underway and planned studies focus only on symptomatic patient use cases.

Develop appropriate malaria RDT QC materials

A targeted investment may be required to support the availability of quality control materials. In the coming years, the current RDT QC program, centralized lot testing, will exhaust its sample bank and come to an end. Post-purchase quality control for malaria RDTs will need reconsideration. Given slim margins and limited financial incentives, an intervention to support QC material development, either by a third party or manufacturer might be considered. The challenge is not unique to malaria, and might be integrated across many POC tests used in global health. An intervention would likely need to support QC development, assessment to ensure the quality of the QC material, and piloting of new materials that would catalyze use.

Foundational investments to support novel biomarkers or technical approaches

Market interventions to support innovation include direct R&D funding, as well as simultaneous investments to support the evaluation and review of any novel test "category." For example, tests relying on new biomarkers such as hemozoin or volatile compounds will require biomarker reviews to understand the correlation to infection, disease, and relative performance; biobanks and standards to support product development and evaluation; and development of consensus protocols, and possibly reference assays, for evaluating the new products. This type of formative work, if already in place as products advance to trial stage could support reviews by regulators and policymakers, ultimately accelerating product introduction.

8. CONCLUSION

Competing demand for Covid 19 diagnostics exposed the fragility of the malaria RDT market, highlighting the risk to sustainable and adequate supply. Through a coordinated effort, a 100 million test shortfall was avoided, yet, as the markets settle, it will be essential to monitor the supply base: while diversified, it is also unproven. Additionally, the pandemic's far-reaching effects on the diagnostics industry could affect supplier incentives to produce malaria RDTs.

With only 27% of children receiving a diagnostic test, there is significant scope for expanding case management, especially at community levels and through retail channels. A better understanding of HRP2/3 deletions and potential demand for new RDTs incorporating Pf LDH are essential to preserving confidence in malaria RDTs. Without quality malaria testing, case management is compromised, with both over and undertreatment occurring alongside neglect for other potentially severe causes of fever. Additionally, diagnostic results underpin surveillance, thus informing the allocation of finite programmatic resources.

The introduction of tafenoquine and POC G6PD testing for radical cure represents an opportunity to transform P. vivax case management and transmission. With respect to the pipeline, it is timely to review advances in diagnostic testing and digital technologies, keeping in mind the compelling malaria RDT value proposition.

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