Global **Malaria** Programme

Analysis of research and development priorities for malaria – working paper

In collaboration with the WHO Global Observatory on Health R&D

World Health Organization

Prepared in collaboration with the Barcelona Institute for Global Health, the Malaria Eradication Scientific Alliance and WHO Global Malaria Programme

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ABBREVIATIONS

ACT	artemisinin-based combination therapy
AIM	Action and Investment to defeat Malaria
BMGF	Bill and Melinda Gates Foundation
CHMI	controlled human malaria infection
DFID	United Kingdom Department for International Development
EDL	Essential Diagnostics List
EMA	European Medicines Agency
FDA	United States Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
G6PD	glucose-6-phosphate dehydrogenase
Gavi	Gavi, the Vaccine Alliance
Global Fund	Global Fund to Fight AIDS, Tuberculosis and Malaria
GMP	WHO Global Malaria Programme
GMS	Greater Mekong Sub-region
GTS	WHO Global Technical Strategy for Malaria 2016–2030
HIV	human immunodeficiency virus
IER	WHO department of Information, evidence and research
IRS	indoor residual spraying
IPTi	intermittent preventive treatment for infants
IPTp	intermittent preventive treatment in pregnancy
ITN	insecticide-treated bed net
IVCC	Innovative Vector Control Consortium
IVR	Initiative for Vaccine Research
LAMP	loop-mediated isothermal amplification
LLIN	long-lasting insecticidal bed net
LSM	larval source management
malERA	Malaria Eradication Research Agenda
MAD-NAAT	multiplexable autonomous disposable nucleic acid amplification test
MESA	Malaria Eradication Scientific Alliance
MDA	mass drug administration
MMV	Medicines for Malaria Venture

MPAC	Malaria Policy Advisory Committee
MSAT	mass screen and treat
MVIP	Malaria Vaccine Implementation Programme
NAA	nucleic acid amplification
Observatory	WHO Global Observatory for Health R&D
PATH	Program for Appropriate Technology in Health (as of 2016, known as PATH)
PATH-MVI	PATH Malaria Vaccine Initiative
PCR	polymerase chain reaction
PDP	product development partnership
*Pf*hrp2/3	*Plasmodium falciparum* histidine-rich protein 2/3
*Pf*Kelch13	*Plasmodium falciparum* Kelch 13 propeller gene
POC	point-of-care
R&D	research and development
RDT	rapid diagnostic test
RTS,S	RTS,S/AS01 (Mosquirix)
SERCaP	single encounter radical cure and prophylaxis
SMC	seasonal malaria chemoprevention
SP	sulfadoxine-pyrimethamine
TDR	Special Programme for Research and Training in Tropical Diseases
TPP	target product profile
VCAG	Vector Control Advisory Group
VIS	Vaccine Investment Strategy
WHO	World Health Organization
WHO-PQ	World Health Organization pre-qualification
WHOPES	World Health Organization Pesticide Evaluation Scheme

EXECUTIVE SUMMARY

This document provides a prioritization framework for the R&D of malaria health products as a basis for a consultative process through the WHO Global Observatory for Health R&D. The report is relevant for stakeholders working in science and innovation to achieve a world free from malaria.

In order to meet the *Global Technical Strategy for Malaria 2016–2030* (GTS) goals, innovation is needed including new health products and strategies to implement them. Five key challenges that represent threats or barriers to achieving the GTS goals that can be alleviated with new health products were identified

- Biological adaptation, leading to resistance
- Addressing transmission
- Transforming surveillance
- Achieving universal access
- P. vivax and non-falciparum species

Potential product solutions to these challenges were identified from three existing research agendas, the Malaria Eradication Research Agenda (malERA), malERA Refresh and Action and Investment to defeat Malaria (AIM) as well as other literature. The potential solutions were overlaid with the current product development pipelines to identify gaps and opportunities. Potential product solutions were grouped based on the current status of the malaria R&D pipeline as 'improve' – tools which are improved versions of the existing core interventions e.g. new partner drugs in ACTs; 'innovate' –novel tools and technologies, e.g. a new active ingredient with insecticidal properties; and 'investigate' – novel concepts and technologies at discovery stage e.g. gene drive to prevent mosquitoes carrying malaria parasites. Lastly, a novel scoring system was constructed to rank potential product solutions based on their applicability to the challenges, the status in the research pipeline and the relative cost of bringing the potential product solution to market. The report and prioritization framework were developed by the Malaria Eradication Scientific Alliance (MESA) together with the WHO Department of Innovation, Evidence and Research (WHO IER) and the WHO Global Malaria Programme (WHO GMP) and responded to feedback from the Malaria Policy Advisory Committee (MPAC) and WHO GMP members. The outputs are summarized in Table i.

The objective of this report is to provide a prioritization framework for the R&D of malaria health products as a basis of a consultative process through WHO mechanisms. The quantitative prioritization framework presented here is one of many possible approaches and a consultation with partners is needed as a next step.

To realize the potential health products identified here, basic science is needed to advance product development. For health products to have an impact in malaria, implementation science is needed to operationalize new tools in combination with the existing core interventions for malaria, including surveillance.

Funding research and programme implementation are both critical for achieving the goals of the GTS. Finite financial resources are hindering progress towards the GTS goals and as such, prioritizing research can be a useful way to make the most of the available investments. Given that different funders have different strategic objectives and stakeholders' needs a diverse landscape of funders is needed to pursue the R&D opportunities proposed here.

Table i: Prioritization of malaria health product R&D and strength of the pipeline (last updated March 2018).

PRIORITY	PRODUCT CLASS	PRODUCT SOLUTION	PIPELINE STRENGTH		
			STRONG	WEAK	EMPTY
Top	Vector control	New insecticide classes used in combination in LLINs and IRS			
		Novel vector control tools* including endectocides and genetic approaches			
	Diagnostics	High-throughput mosquito assays			
	Drugs	Simplified therapy and prophylaxis			
		Transmission-blocking drugs			
	Vaccines	Preventive vaccines *P. falciparum*			
		Transmission-blocking vaccines *P. falciparum*			
		Preventive vaccines *P. vivax*			
		Transmission-blocking vaccines *P. vivax*			
Second	Vector control	Extended duration combination LLINs and IRS			
	Diagnostics	Validated POC diagnostics for identifying low-density infection			
		RDTs that detect and differentiate all *Plasmodium* species			
		Multiplexed POC tests of acute febrile illness			
		Non-invasive/ self-administered diagnostic tests		Non-invasive	Self-administered
		Sensitive and specific POC diagnostics for *P. vivax*			
		Diagnostics to identify hypnozoites			
		Affordable, simple and accurate POC tests for G6PD deficiency			
		POC diagnostics to identify drug-resistant parasites			
		POC/health system falsified drug screening			
	Drugs	Novel drugs for chemoprevention			
		New drug combinations suitable for use in MDA, etc.			
		Simplified therapy for *P. vivax* radical cure			
		Drugs for *P. vivax* radical cure without G6PD liability			
Third	Diagnostics	Infectivity/gametocyte diagnostics		Gametocyte	Infectivity
		Stable, valid, specific and sensitive RDTs that do not depend on Pfhrp2/3			
	Drugs	New drug classes used in combination therapies for malaria treatment			
		Novel drugs for severe malaria			

1 INTRODUCTION

Investments in health research and development (R&D) need to be aligned with global public health demands and needs. Governments, policy-makers, funders and researchers need an accurate picture of the current situation so as to ensure that priority areas of malaria R&D are responsive to both short term challenges and longer term opportunities.

In May 2013, the Sixty-sixth World Health Assembly specifically mandated the establishment of the World Health Organization (WHO) Global Observatory for Health R&D in resolution WHA66.22.[1] The 'Observatory' collates information on health R&D, with a view to contribute to the identification of gaps and opportunities for health R&D and to help define priorities for new R&D investments based on public health needs. It builds on existing data and reports from a wide range of data sources, and gathers new information (where needed and feasible) with the aim of enabling decisions on priorities in R&D, by:

- consolidating, monitoring and analyzing relevant information on the health R&D needs of developing countries;
- building on existing data collection mechanisms; and
- supporting coordinated actions on health R&D.

The Sixty-ninth World Health Assembly (May 2016) re-emphasized the Observatory's central role and the importance of expediting its development. In resolution WHA69.23 it also requested the establishment of an expert committee on health R&D to set priorities for new investments based on information primarily provided by the Observatory.[2]

In order to develop the Observatory, the WHO Secretariat:

- works closely with its technical departments and their established expert groups and committees in order to develop and/or review analyses and syntheses produced by the Observatory;
- seeks regular feedback on the Observatory's structure and outputs from potential users including national policy-makers, academia, WHO's technical experts and other international governmental organizations and global partnerships, WHO regional offices, civil society and industry stakeholders.

To identify strategic R&D needs, priorities and gaps, there is a need to consolidate all relevant data and other information to be considered for analysis by experts for specific diseases. The need for a specific R&D analysis for malaria was recognized.

This document uses the framework of the WHO Global Technical Strategy for Malaria (GTS) which sets out evidence-based goals and milestones for the period 2016-2030. It brings together the outputs of the existing consultative processes that have examined the research needs in malaria; namely the Malaria Eradication Research Agenda (malERA) in 2011, Action and Investment to defeat Malaria (AIM) 2015, and an updated malERA agenda (malERA Refresh) in 2017. This report does not tackle ffinancing for malaria R&D, nor does this report attempt an analysis on financial needs. With a focus on the malaria R&D needs and the product pipelines, this report proposes a set of priority areas for investment and provides a 'baseline' for monitoring and evaluation progress through the Observatory.

2 MALARIA TODAY

2.1 Malaria and the Sustainable Development Agenda

Malaria is a life-threatening disease caused by infection with *Plasmodium* parasites, transmitted by female *Anopheles* mosquitoes. Almost half of the world's population is at risk of malaria. In 2016, 91 countries and areas had ongoing malaria transmission.[3]

Although five *Plasmodium* species cause malaria in humans, *P. falciparum* and *P. vivax* pose the greatest public health threat.

- *P. falciparum* is the most prevalent malaria parasite on the African continent, responsible for around 99% of malaria-related deaths globally.
- *P. vivax* is the dominant malaria parasite in most countries outside of sub-Saharan Africa.

Building on the success of the Millennium Development Goals, in 2015 the United Nations Member States launched the Agenda for Sustainable Development with an overarching focus on reducing global inequalities and ending poverty.[4]

As malaria is both a major cause and consequence of poverty and inequality, the Sustainable Development Agenda is critically linked to a malaria-free world.[5] The broadening development agenda has provided an opportunity to widen the circle of engagement and investment and intensify multi-sectorial and inter-country collaboration to defeat malaria. This was captured in the Roll Back Malaria Partnership's "Action and Investment to defeat Malaria 2016–2030 (AIM) – for a malaria-free world".[5-7]

The burden of malaria is highest in the least developed areas and among the poorest members of society – particularly children, pregnant women and other vulnerable populations such as migrants, refugees and the displaced.[5] Malaria is also a frequent cause of catastrophic household health expenditure.[8, 9] In endemic countries, scaling up malaria interventions contributes strongly to reducing child mortality and improving maternal health.[5] Optimizing the access of malaria interventions is essential for achieving universal health coverage, ensuring healthy lives and promoting well-being of all ages, particularly for vulnerable and marginalized populations.

2.2 Global trends in malaria

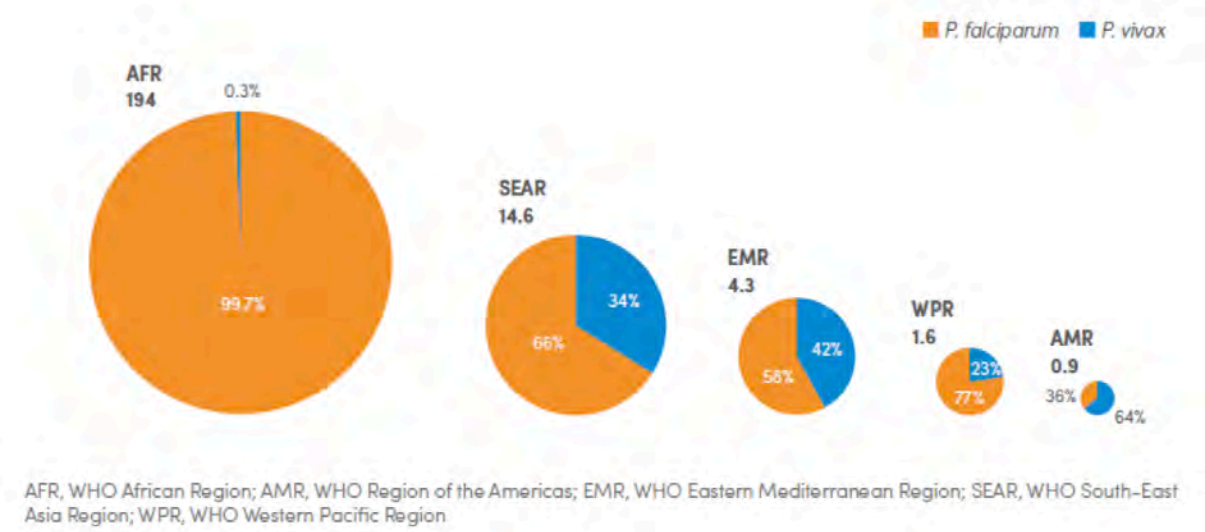
Global trends in malaria are reported annually in the WHO "World Malaria Report", produced by the WHO Global Malaria Programme, in collaboration with the WHO regional and country offices, ministries of health in endemic countries and a broad range of other partners.[10] According to the 2017 World Malaria Report, in 2016 there were 237 million cases of malaria (95%CI 218–278 million) and 445 000 deaths, mostly in children under 5 years of age.[10] This was the first World Malaria Report that showed a trend towards an increase in cases and deaths. The WHO described the situation as a 'critical juncture' since the data suggest that the burden of malaria is at a tipping point and a reversal of the gains achieved over the previous decade is possible. There is evidence that funding levels directly impact malaria burden and indeed the global trend in malaria cases and deaths parallels the trend in global investment in malaria. Add Cohen paper,[10] Since 2000, global investments had been increasing but reached a peak in 2013 of an estimated 2.7 billion US$. (WMR

2014 http://www.who.int/malaria/publications/world_malaria_report_2014/en/) Investment levels have since plateaued. The global funding target to achieve the GTS goals for 2016 was estimated to be 6.4 billion US$, whereas the investments made were estimated to be 2.7 billion US$, leaving a shortfall in funding of 41%.[6]

- The WHO African Region carries a disproportionately high share of the global malaria burden, with 90% of malaria cases and 91% of malaria deaths. *P. falciparum* is the most prevalent malaria parasite in sub-Saharan Africa (Figure 2.1).[10]
- Outside of Africa, *P. vivax* is the predominant parasite in the WHO Region of the Americas, representing 64% of malaria cases, and is above 30% in the WHO South-East Asia and 40% in the Eastern Mediterranean regions.[10] In 2016, around 8.6 million (95%CI 6.4–11.1 million) malaria episodes were caused by *P. vivax* infection (Figure 2.1).[10]

Figure 2.1 Estimated malaria cases by WHO region, 2016.[10]

The area of the circles is proportional to the estimated number of cases in each region.



AFR, WHO African Region; AMR, WHO Region of the Americas; EMR, WHO Eastern Mediterranean Region; SEAR, WHO South-East Asia Region; WPR, WHO Western Pacific Region

2.3 Impact of effective treatment and control

Malaria is preventable and curable, and increased efforts are dramatically reducing the malaria burden in many places, although as noted previously data from the WMR 2017 suggests that these gains are fragile and have stalled.

- Between 2010 and 2016, malaria incidence rate among populations at risk (the rate of new cases) fell by 18% globally.[10]
- In that same period, malaria mortality rates among populations at risk fell by 25% globally.[10]
- The Millennium Development Goal target – "to have halted and begun to reverse the incidence of malaria" – was achieved.[10]

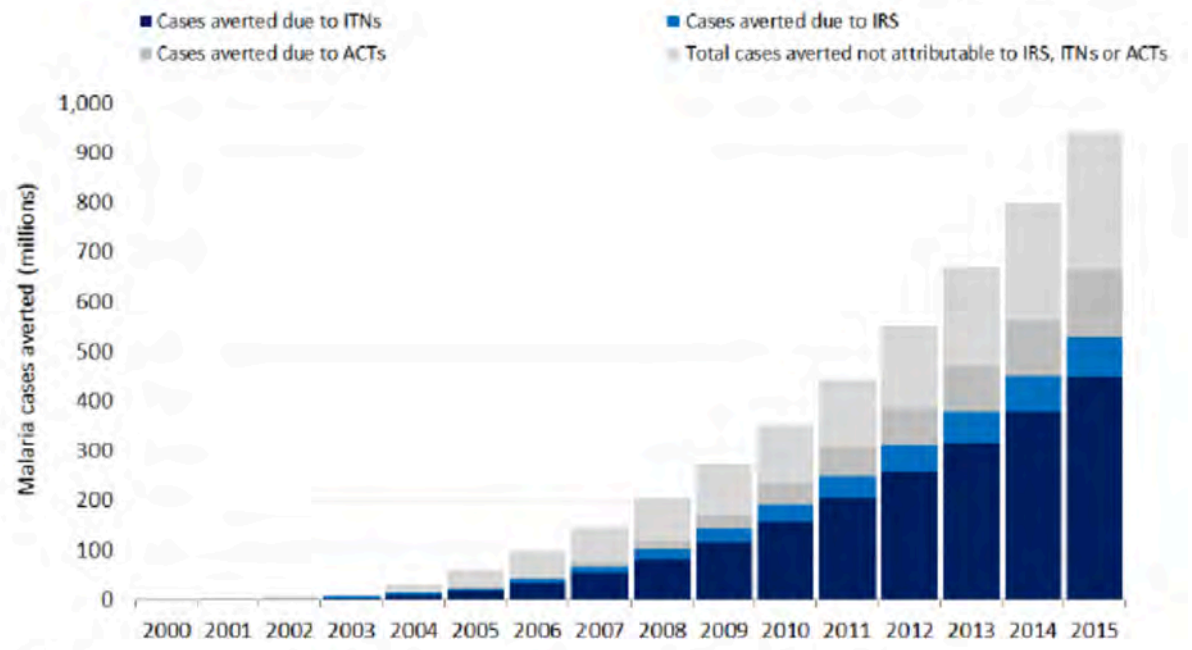
Between 2001 and 2015, it is estimated that a cumulative 1.2 billion fewer malaria cases and 6.8 million fewer malaria deaths occurred globally than would have occurred if incidence rates had remained unchanged – about 6.6 million (97%) of the deaths averted were for children aged under 5 years.[11]

The highest proportion of deaths averted was in the WHO African Region (94%).[11] An estimated 70% of the cases averted during this time resulted from the deployment of core interventions to prevent, diagnose and treat malaria (Figure 2.2):[6]

- long lasting insecticide treated nets (LLINs) and/or indoor residual spraying (IRS);
- rapid diagnostic tests (RDTs);
- artemisinin-based combination therapies (ACTs).

Although the implementation of these core interventions has expanded greatly since 2000, the gains achieved are fragile and unevenly distributed. The World Malaria Report 2017 provides evidence that the estimated number of malaria cases has increased in a number of highly endemic countries, in parallel to a plateau in funding. Investments made in 2016 were estimated to be 2.7 billion US$, whereas the funding target to achieve the GTS goals was estimated to be 6.4 billion US$.[6] This 41% shortfall in funding affects the entire spectrum of investments needed to succeed in malaria, from commodities to R&D, particularly affecting vector control. The human toll of malaria and the global risk it still poses remain unacceptably high.[6]

Figure 2.2 Predicted cumulative number of malaria cases averted by interventions in sub-Saharan Africa 2000–2015.[12, 13]



ACT, artemisinin-based combination therapy; IRS, indoor residual spraying; ITN, insecticide-treated mosquito net

2.4 Investing in malaria

Malaria interventions are highly cost-effective and demonstrate one of the highest returns on investment in public health.[5] Current methodologies suggest that the increased life-expectancy resulting from malaria mortality reductions observed between 2000 and 2015 can be valued at US$ 1810 billion in the WHO African Region (range US$ 1330–2480 billion), which is equivalent to 44% of the gross domestic product of the affected countries in 2015.[11] Globally, the malaria mortality

reductions are valued at US$ 2040 billion (range US$ 1560–2700 billion), which is 3.6% of the total gross domestic product of malaria affected countries.[11]

Consequently, in malaria endemic countries, efforts to reduce and eliminate malaria are increasingly viewed as high-impact strategic investments that have the potential to generate significant returns for public health, help to alleviate poverty, improve equity and contribute to overall development.[6] Since 2000, 18 countries and territories have been declared no longer endemic or had zero indigenous malaria cases in 2016.[10, 14] In addition, 21 countries have declared intent to eliminate malaria transmission by 2020.

There is both an opportunity and an urgent need to reduce morbidity and mortality in all countries, increase the number of malaria-free countries and identify approaches that reduce malaria transmission.[6] Progress can be hastened through expansion of existing interventions, by making the response to malaria a higher technical, financial and political priority , and by ensuring that the development and use of new tools and approaches are accelerated though strategic investment in R&D.

3 GLOBAL TECHNICAL STRATEGY FOR MALARIA 2016–2030

VISION
A world free of malaria

The WHO *Global Technical Strategy for Malaria 2016–2030* (GTS) was adopted by the World Health Assembly in May 2015 (Resolution WHA68.2).[6] The document was developed through an inclusive process under the guidance of a Steering Committee composed of leading malaria technical experts, scientists and country representatives. Oversight was provided by the Malaria Policy Advisory Committee (MPAC). The document was developed in close alignment with AIM to ensure shared goals and complementarity.[5]

During the strategy development process, WHO consulted all affected countries through a series of seven regional consultations. In July–August 2014, WHO held a public web consultation, during which members of the global health community, including non-governmental organizations in official relations with WHO, had an opportunity to comment on the draft.

The GTS includes targets and a timetable of milestones, reaching a 90% reduction in the global malaria disease burden, and the elimination of malaria from at least 35 countries, by 2030 (Table 3.1).

Table 3.1 Goals, milestones and targets for the Global Technical Strategy for Malaria 2016–2030.[6]

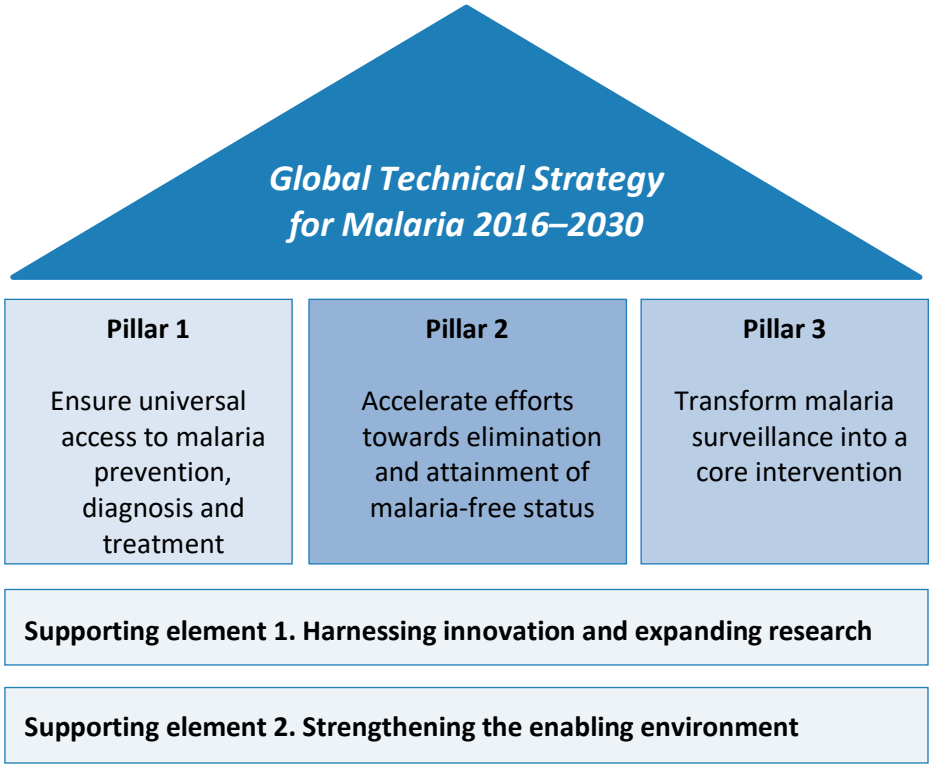
GOALS	MILESTONES		TARGETS
	2020	2025	2030
1. Reduce malaria mortality rates globally compared with 2015	At least 40%	At least 75%	At least 90%
2. Reduce malaria case incidence globally compared with 2015	At least 40%	At least 75%	At least 90%
3. Eliminate malaria from countries in which malaria was transmitted in 2015	At least 10 countries	At least 20 countries	At least 35 countries
4. Prevent re-establishment of malaria in all countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

Evidence from a modeling study helped to inform the consultative process to agree the milestones and targets in the GTS.[15] The study used a mathematical model of *P. falciparum* malaria transmission to estimate the effect of different coverage levels of interventions on case incidence and mortality. The findings indicated in quantitative terms that by increasing coverage of interventions, substantial reductions in malaria case incidence and deaths is possible. The goals encompass both *P. falciparum* and *P. vivax* malaria and will require efforts to:

- prevent and treat malaria (including the relapsing form of *P. vivax*);
- interrupt transmission of plasmodia between mosquitoes and humans.

The strategic framework is built on three pillars with two supporting elements that guide global efforts to move closer to malaria elimination (Figure 3.1).[6]

Figure 3.1 Strategic framework for the Global Technical Strategy for Malaria 2016–2030.[6]



Five principles underlie the GTS.[6]

- All countries can accelerate efforts towards elimination through combinations of interventions tailored to local contexts.
- Country ownership and leadership, with involvement and participation of communities, are essential to accelerating progress through a multisectorial approach.
- Improved surveillance, monitoring and evaluation, as well as stratification by malaria burden, are required to optimize the implementation of malaria interventions.
- Equity in access to health services, especially for the most vulnerable and heard-to-reach populations, is essential.
- Finally, innovation in tools and implementation approaches will enable countries to maximize their progression along the path to elimination.

4 RESEARCH NEEDED UP- AND DOWN-STREAM OF PRODUCT DEVELOPMENT

The focus of this report is on health products to help overcome some of the challenges to the goals set out in the GTS. However, R&D of new tools cannot happen in a vacuum. Research needed both up- and down-stream of product development.

4.1 Basic science

Up-stream, basic science and discovery unlocks the biological understanding of the parasite, mosquito and human immune response, provides the biological targets, potential new compounds and active ingredients, and new technologies. The malERA and malERA Refresh processes set out questions in basic research have been identified which would facilitate progress towards novel interventions for malaria, including robust mathematical and laboratory models of transmission, and a greater understanding the biology of parasite-host immunity and mechanisms of acquired and vaccine-induced protective and transmission-blocking immunity.[16-22]

4.1.1 Vector control

Discovery of new insecticides for use in LLINs and IRS applications has required mobilization of current resources within pesticide companies and this has so far resulted in the screening of around 4 million compounds. As a result, nine new chemical classes have been identified with significant activity against mosquitoes.[23]

4.1.2 Diagnostics

Advances in diagnostics will also require the application of new technologies and there is scope for technology transfer from other diseases.

Major advances have been achieved in molecular methods of malaria diagnosis.[24] However, highly sensitive, polymerase chain reaction (PCR) amplification requires expensive equipment, specialist facilities and expertise, and is susceptible to lab-to-lab variation.[24] Attempts have been made to produce molecular diagnostics applicable to POC testing, such as loop-mediated isothermal amplification (LAMP), and modifications of this to improve deliverability. However, it is not clear that molecular diagnostics need to be POC. A recent review compares the various molecular-based technologies.[24]

Malaria diagnostics based on dielectrophoretic and magnetophoretic methods are also being developed either to enrich samples for microscopy and conventional RDTs or as the basis of new diagnostic technologies.[25]

Serological methods are also of interest, although they cannot be used for case management as antibodies appear several days after infection and persist in the circulation so that new and previous infection cannot be differentiated. FIND is coordinating efforts to profile the immune responses of a large panel of *P. vivax* malaria patients to identify and validate markers of recent infection, with the aim of developing serological tests for *P. vivax* malaria.[26] FIND is also leading a consensus-based

process to develop TPPs for diagnostic tests using the new biomarkers, and is conducting a technology landscape assessment as well as a market analysis on the use of such tests.[26]

For non-invasive diagnostics, a number of methods and biomarkers have been reported in the literature using saliva, urine and buccal mucosa. Until recently most reported poor performance. However, a malaria urine test has reported equivalence to commercially available RDTs for malaria diagnosis.[27] Detecting very low density parasitemia is more challenging, however.

Despite validated molecular markers for parasite resistance to most available anti-malarial drugs, a point-of-care diagnostic is elusive and surveillance relies on standardized studies at sentinel sites. However, improvements in the accessibility of molecular methods are likely and could be used to identify resistant strains, relatedness, and sources of transmission.

The most formidable scientific challenge is the detection of hypnozoites, as there are no validated biomarkers of hypnozoite infection.[28] The first hypnozoite transcriptome has recently been published, providing an experimentally-derived list of molecular markers of hypnozoites.[29] Whether such markers are circulating and so accessible to diagnostic testing is unknown. However, it does suggest that hypnozoites have distinguishable molecular characteristics.

Para-diagnostics

These are not for use in humans, but support malaria treatment and control. Identifying vector species, insecticide resistance, parasite infection status and host preference are key to targeting vector control interventions and determining their effectiveness.[17] Finding the source of outbreaks and determining imported from local transmission also depends on identifying malaria transmitting mosquitoes in the field.[21] Multiplexed assays have been developed for laboratory use,[30] and translating these into field-applicable tests will require technological refinement.

4.1.3 Drugs

Scientific barriers to new drug development are centered on the need to evaluate specific product characteristics *in vitro* or *in vivo* at discovery and early stage development which predict clinical utility. Recently, there have been significant advances both in assay development for drug discovery and in animal model development for pre-clinical drug assessment.[22] In particular, the development of humanized mouse models has allowed *P. falciparum* and *P. vivax* infection to be studied in non-primate species, reducing costs and time scales and greatly increasing throughput.

However, there are still key scientific requirements that need to be addressed both to facilitate drug discovery and accelerate drug development.[17, 22]

- Lack of an *in vitro* culture system for *P. vivax* gametocytes.
- Methods to increase sporozoite availability.
- Lack of an *in vitro* culture system for *P. vivax* asexual stages.
- Poor functional annotation of genes in *Plasmodium* asexual stages.
- Validation of outcomes from animal and human infection models that predict a reduction in transmission in real-life settings.

- Development of high-throughput screening assays and evaluation assays for the identification and selection of compounds with neglected profiles (e.g. anti-relapse activity in *P. vivax)*.
- Validated *in vitro* and *in vitro* models for assessing and predicting reprotoxicity and teratogenicity.
- Poor validation of models, understanding of pathogenesis, and tools to intervene in severe malaria.

4.1.4 Vaccines

The vaccine candidate pipeline is robust, and includes novel antigens and platforms.[31] Second generation vaccines are expected to provide higher protection than RTS,S in the longer term. However, optimized tools are needed to measure incremental improvements and predict potential cost effectiveness of new candidates.[32]

The development of controlled human malaria infection (CHMI) models, efforts to harmonize elements of clinical trial design and standardization of various assays continue, and it is anticipated that these will lead to more streamlined candidate selection and more rapid advancement.

The Malaria Vaccine Technology Roadmap outlined a number of areas that would enhance the scientific feasibility of malaria vaccine development.[33]

- Develop immunological assays with standardized procedures and reagents to enable comparisons of the immune responses of vaccines.
- Standardize clinical trial design and assessment to allow comparison of data.
- Use state-of-the-art approaches to identify novel potential candidate vaccine targets.
- Confirm candidate vaccine targets and mechanisms of protection, using controlled human malaria infection models as appropriate.
- Establish a systematic approach for prioritizing vaccine candidates (including multi-antigen, multi-stage, and attenuated whole-parasite vaccine approaches).
- Develop immunological correlates of vaccine-induced protection and surrogate efficacy endpoints to advance vaccine development and licensure timelines.

4.2 Implementation science

Implementation science allows the testing of potential solutions to operational problems in the field. Here we define implementation science as ‘research which tests solutions to operational problems. It encompasses operational research which uses existing data from the disease programme, as well as research which tests novel operational strategies, or new interventions or new combinations of interventions in the field’.

Implementation science tackles questions around the optimal package of malaria interventions in a specific area, or when and how a programme can downscale a particular intervention, as well as barriers to universal access.

Unlike R&D, historically this type of research is not well tracked nor is it always documented in the scientific literature. However, the MESA Track database does capture current implementation science in malaria, providing an indication of what research is being done in this field.

There are a number of questions that need to be addressed for the implementation of any health product. These include:

1) What is the most effective combination of products and practices in the different contexts?

2) What is the most cost-effective deployment strategy to meet the operational objectives?

3) What are the needs within the health system to achieve the deployment strategy?

These issues were examined within malERA Refresh, primarily in the context of malaria elimination, but have wider applicability across the range of malaria transmission.[19, 20]

4.2.1 Combination interventions and modelling

At this time, there is no single intervention that will result in elimination of malaria. Combinations of interventions need to be delivered that are specific to the transmission setting, the human population and the health system. However, it is not feasible to test every new health product in every possible situation.

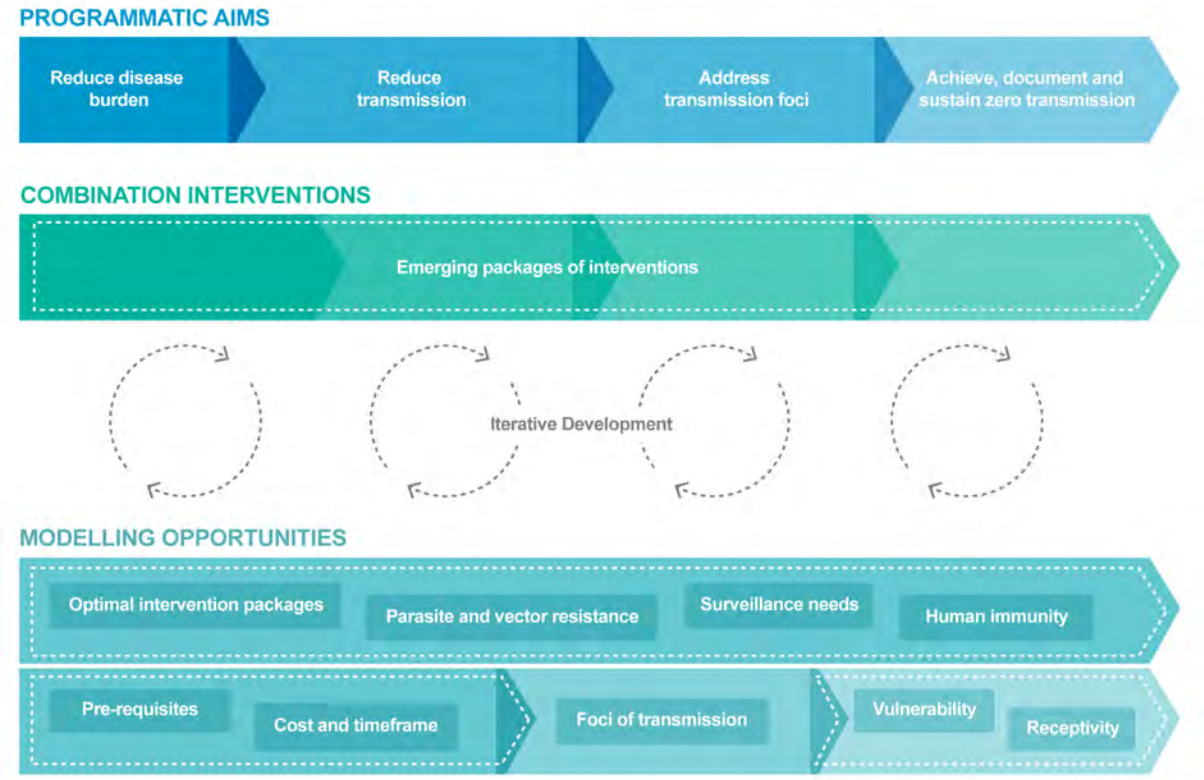
Mathematical modelling can offer an insight that allows extrapolation from the available data to varying situations across the transmission continuum.[20] Different modelling approaches can therefore be used to design intervention packages to address changing programmatic objectives (Figure 4.1).[20]

Modelling has already been used to evaluate the potential impact of introducing combination interventions of existing tools, including the need to combine MDA plus LLINs to interrupt transmission,[34] the ineffectiveness of targeting hot spots with antimalarial-drugs plus RDTs to achieve local elimination,[35] and the need to combine mass treatment with other interventions.[36] The conditions under which new interventions should be deployed has also been evaluated, for example, the high potential for reducing transmission by combining LLINs and attractive toxic sugar baits,[37] the circumstances under which ivermectin would be a useful adjunct to interrupt malaria transmission,[38] and the conditions required for maximum impact of pre-erythrocytic vaccines.[39]

However, modelling efforts will only produce relevant and meaningful findings if the data used to generate the models are available and of good quality. Thus, more effort is required to obtain outcome data from the implementation of combinations of existing and new health products as well as background surveillance information on vector populations, disease prevalence and transmission from a range of situations.[20] Predictive models can be validated with longitudinal data sets.

Finally, as combination strategies are fielded, evaluation strategies and robust surveillance systems to determine effectiveness within the specific malaria context and national strategy will be critical.

Figure 4.1 The role of modelling directed against programmatic aims. [Adapted from malERA refresh.[20]]



4.3 Health policy and systems research

WHO has defined health systems research as the purposeful generation of knowledge that enables societies to organize themselves to improve health outcomes and services.[40] People are that the centre of health systems – delivering and receiving care and health systems research looks at the system as a whole rather than an intervention-focused approach.[19]

A key issue for malaria is understanding sources of inequity in access to interventions. Are these primarily health system issues, such as lack of capacity or inadequate supply chains, or wider structural issues, such as a lack of roads, mass population movements, or language/cultural barriers?

The Alliance in Health Systems Research was established to convene national policy makers, development partners, research institutions, civil society organizations and other key actors to advance the field of health policy and systems research.[41] The Alliance works on developing and facilitating new models and approaches for the generation, synthesis and use of policy and systems research to strengthen health systems.[41]

5 R&D ANALYSIS FOR MALARIA: OBJECTIVES AND METHODS

The GTS goals and targets were developed assuming a highly accelerated scale-up of interventions. According to this scenario, it is *technically* feasible to achieve the milestones for 2020 and 2025 using existing tools, i.e. ignoring financial, operational and structural limitations. However, even with these caveats, attainment of a 90% reduction in malaria by 2030 will require innovations in both tools and approaches for their implementation that responds to local epidemiology and context.[6] The tools include new insecticides and other innovative vector control products, improved diagnostics, new and more effective medicines, new combinations of medicines and new vaccines, as well as strategies for their combination into country plans.

In order to have an impact on the GTS outcomes,[6] new health products need to be available for introduction an scale up before 2025. It will, therefore, be necessary to accelerate the development of new health products where possible, as well as encouraging innovative R&D in areas where there are gaps.

5.1 Objectives

The overall objective of this report is to provide a robust basis for prioritization of malaria R&D by the WHO Global Malaria Programme and WHO Observatory. The report also provides a 'baseline' for monitoring and evaluation of the malaria product pipeline through the WHO Observatory.

In support of the overall objective, the goals of this report are:

- To identify the R&D framework required to achieve the strategic goals set out in the GTS.[6]
- To integrate the existing research agendas for health product development across vector control, diagnostics, drugs and vaccines.
- To develop a system for prioritizing health product development that is aligned to the GTS strategic goals and technical feasibility. This resulting prioritization is presented for discussion, consultation and amending by the WHO Global Malaria Programme.
- To define R&D goals against which health product development can be monitored and evaluated.

5.2 Consultation process

This R&D analysis draws heavily on an extensive consultation process conducted over several years across multiple disciplines, settings and countries.

Between 2008 and 2010 a consultative process engaged more than 250 malaria experts on the basis that R&D will be needed to develop new products required to eliminate malaria. Product development partnerships (PDPs), researchers and funders played a leading part in the process, commensurate with their role in the development of malaria control interventions. A new generation of tools and strategies was characterized – with a focus on the interruption of transmission – and presented as The Malaria Eradication Research Agenda (malERA).

This was endorsed by another, even more extensive consultative process, engaging stakeholders from all constituencies, including affected communities, first-line service providers, aid workers, government officials, academia, private sector and multilateral organizations and culminating in the Roll Back Malaria Partnership's AIM report.[5]

A process to revise and update the research agenda can help research activities to respond to the challenges as they evolve and support the long term goals of the global malaria program. Following the international commitments to global goals and the call for collective action articulated in 2015, the process to update malERA was initiated. This was termed malERA Refresh and involved consultation with over 180 experts in six thematic panels to develop the research agenda for the next decade.[16-22]

The broader challenges in malaria were discussed within malERA Refresh and developed into actionable R&D priorities.[16-22] These priorities covered basic research, product development, understanding transmission, mathematical modeling and combination interventions and health policy and systems research. These issues were considered across a continuum from high transmission, though accelerating towards elimination, to the maintenance of elimination and containment of reintroduction and outbreaks.[16-22]

5.3 Methodology

A systematic approach was used to identify and rank potential product solutions in support of achieving the GTS goals. This work and the outputs are presented for deliberation by an expert panel in a future consultative step (see section below). The methodology for the analysis of malaria R&D Priorities is summarized in Figure 5.1.

WHO strategic objectives for malaria as defined in the GTS were used as a starting point. Using the malERA and malERA Refresh publications, the AIM and a systematic review of WHO malaria publications, overarching challenges to achieving the GTS goals were listed. The scope of those listed was limited to those where a new tool could help overcome the challenge. Using the same publications, specific technical problems were associated to the five challenges and potential product solutions were mapped to the problems (Table 7.1 in Results section).

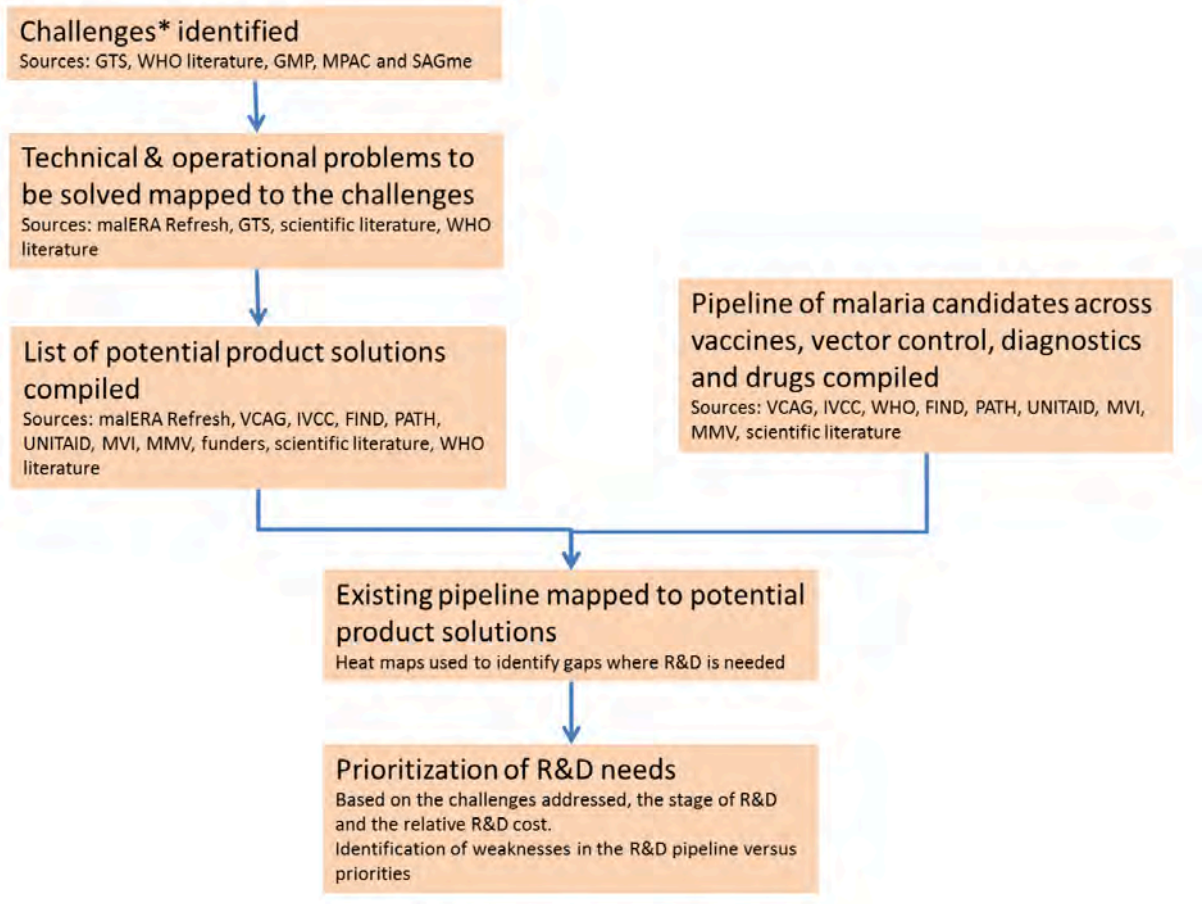
In parallel, a comprehensive pipeline of malaria vector control, diagnostics, drugs and vaccine candidates was constructed using publically available resources from the WHO, the Product Development Partnerships (PDPs) and scientific literature (Figure 5.2). In order to have an impact on the GTS goals, new health products will need to be introduced to the malaria toolbox before 2025. It will, therefore, be necessary to accelerate the development of new health products where possible, as well as encouraging innovative R&D in areas where there are gaps.

The potential product solutions and the pipeline of candidates in development were then compared. The list of potential product solutions ranged from candidates similar to existing tools (e.g. combination IRS) to novel technologies at discovery stage (e.g. monoclonal antibodies). The list of potential product solutions was sub-divided into three categories: improve – tools which are improved versions of the existing core interventions e.g. new partner drugs in ACTs; innovate – novel tools and technologies, e.g. a new active ingredient with insecticidal properties; investigate – novel concepts and technologies at discovery stage e.g. gene drive to prevent mosquitoes carrying malaria parasites.

A novel 'heat map' analysis was used whereby the authors of the report made value judgments regarding how well the pipelines of candidates were addressing the specific problems identified, their feasibility based on the current pipeline and their R&D relative cost (Annex 3). The last step to generate a ranked list of priorities was to assign scores to the different components used in the heat maps and calculate an average overall score (Tables 9.1 – 9.2 in Results section).

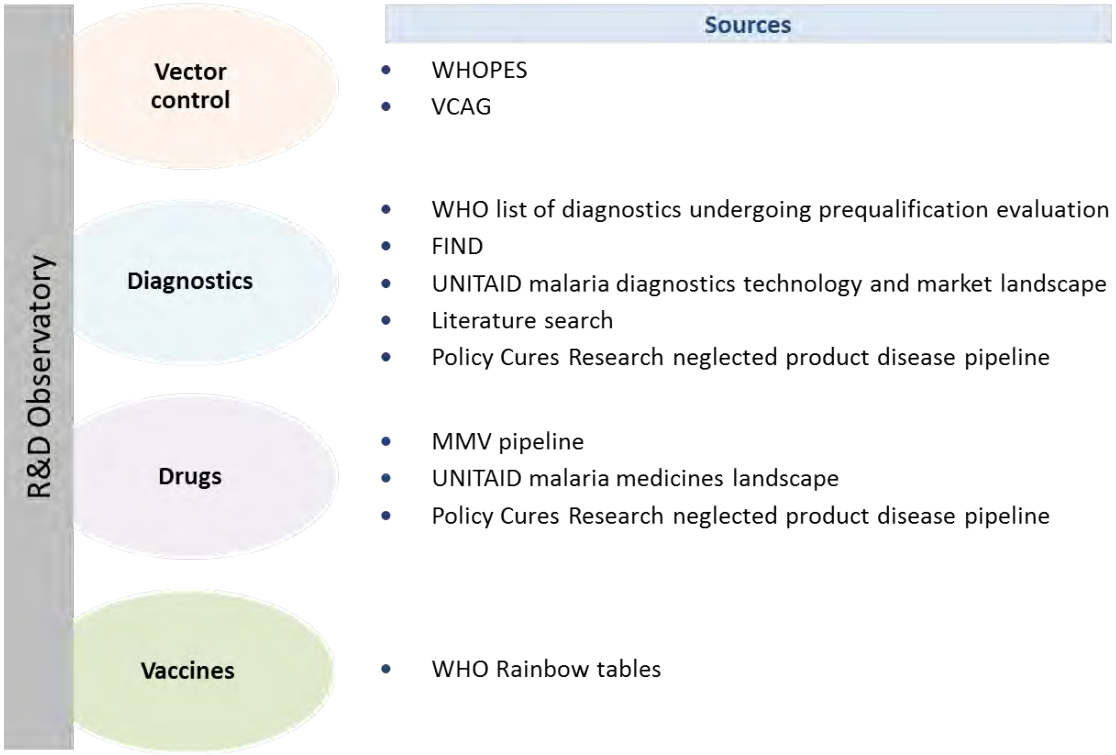
The methodological approach and outputs was presented to the WHO Global Malaria Programme, the WHO department of Information, Evidence and Research and the Malaria Policy Advisory Committee (MPAC) for inputs in 2017 and reviewed by the Malaria Eradication Scientific Alliance (MESA, the group that coordinated the malERA Refresh process). Two elements of this systematic approach need particular attention by an expert panel in a future consultative step (see section below). Namely, the heat map analysis and the fact that combinations of tools and the strategies by which they are deployed in the field have an important influence on how a potential tool can impact a problem.

Figure 5.1 Summary of the methodology for the R&D analysis of malaria.



*The scope of the challenges identified was limited to those which could be overcome with a new tool. GTS, Global Technical Strategy for Malaria; MPAC, Malaria Program Advisory Committee; VCAG, Vector Control Advisory Group; IVCC, Innovative Vector Control Consortium; FIND, Foundation for Innovative New Diagnostics; MVI, Malaria Vaccine Initiative; MMV, Medicines for Malaria Venture, MESA, Malaria Eradication Scientific Alliance/MESA Track; SAGme, WHO Strategic Advisory Group for malaria eradication.

Figure 5.2 Publications, databases and other sources used to compile the landscape of candidate tools in the malaria R&D pipeline in 2017



WHOPES, WHO Pesticide Evaluation Scheme; VCAG, Vector Control Advisory Group; FIND, Foundation for Innovative New Diagnostics; MMV, Medicines for Malaria Venture.

5.4 Considerations for priority setting and updates

The malaria R&D priorities presented in this report are based on a robust and quantitative assessment of problems and solutions in light of the current vaccine, vector control, diagnostic and drug candidates in the product pipelines. Another approach to this work would be to rank the problems to be solved in order of priority.

However it is done, an important component of any ranking should include expert deliberation. The priorities identified here are presented for consultation by the WHO Global Malaria Programme and WHO Observatory. Considerations by an expert panel could include assessment of:

- Local needs – specific kinds of new tools are likely to be more, or less urgently needed by different malaria endemic countries. Granular prioritization may be most useful at country or regional levels.
- Impact – some new tools may be well designed to help overcome one malaria problem, whereas other tools may address a range of problems. The estimated impact of a new tool on the problems and on the GTS goals may be relevant to the expert deliberations.
- Combinations - malaria tools are used in combination with one another and the strategies by which they are deployed in the field have an important influence on how a potential tool can impact a problem. The impact of a given new tool in the field can be influenced by how it

functions and adds value in combination with other tools and in different deployment strategies.

- Timeframe – priorities are strongly influenced by the timeframe of the goals. The priorities presented in this report are framed in light of the GTS goals culminating in 2030, but further prioritization could consider the range of possible short-term, medium-term and long-term gains.
- Funding – it is realistic to expect financial constraints to effect decisions regarding developing the new tools. Cost effectiveness estimates may be useful in further prioritization. As stated in malERA Refresh a diverse landscape of funders is needed to support research objectives according to their strategic plans and stakeholders' needs. (REF)

Many of the variables that effect R&D priorities will change with time. These will include the malaria burden and case incidence, levels of parasite and mosquito resistance and evasion to existing interventions, coverage levels of the core interventions, and the licensure of new tools.. The following aspects will need to be periodically reviewed to assess progress and confirm that the prioritization of malaria R&D remains relevant to reaching the GTS strategic goals.

1. Examine whether the priorities for malaria R&D have changed.

2. Update the health product pipeline and re-map against priorities.

3. Are there any new technologies that should be explored?

4. Are there any changes in technical and regulatory assessment that affect health product development?

6 CHALLENGES TO THE ACHIEVING THE GTS GOALS: LIMITATIONS OF EXISTING TOOLS AND APPROACHES

Great strides are being made towards GTS elimination goals, with 20 countries identified with the potential to achieve zero transmission by 2030. On the opposite, there are countries with reported increases in incidence and malaria mortality.[10] There are varied and evolving challenges to reaching the GTS goals globally including sufficient funding for programmes. This report focuses on those challenges which can be addressed with new tools. This section lays out the limitations of the existing core interventions and implementation strategies.

The WHO-recommended package of core interventions to prevent infection and reduce mortality comprises vector control, chemoprevention, diagnostic testing and malaria treatment plus efforts to accelerate drop in transmission and enhance malaria surveillance and response. With this existing framework, currently 20 countries are targeting elimination within their borders for at least a year by 2020, and some are already undergoing certification. In other areas, the effectiveness of these core interventions is restricted by diverse operational and technical challenges.[6]

Meeting the global malaria goals results in a range of challenges (Table 6.1). These are the variety of problems that need to be addressed, and in many cases new health products and new approaches to implementing them will be needed. A review of WHO policies and guidelines, published literature and outputs from malERA Refresh was conducted to identify a set of challenges to attaining the GTS goals which could be overcome or alleviated with a new tool to the current set of core interventions. More specific, technical problems that need to be addressed were associated to each of the challenges (Table 6.1).

Note that the key challenges and their associated techncial and operational problems were not ranked in any order by the methods used in this report. Tanking the challenges and problems (for example, by countries or regions themselves) could be a useful exercise in a future consultative process.

Table 6.1: Challenges and problems that drive the R&D framework

CHALLENGES	PROBLEMS TO BE SOLVED DRIVE R&D FRAMEWORK
Biological adaptation	• Physiological and behavioral resistance of vectors to insecticides • Parasite resistance to existing anti-malarial drugs • *Pf*hrp2/3 gene-deleted parasites evasion of diagnostics • Inability to diagnose resistant parasites at POC
Addressing transmission	• Residual transmission evading core vector control interventions • Inability to identify and/or quantify the transmission reservoir • Lack of information on vector populations • Limited strategies for accelerating elimination • Limited strategies for preventing malaria re-establishment and responding to outbreaks

CHALLENGES	PROBLEMS TO BE SOLVED DRIVE R&D FRAMEWORK
Transforming surveillance	• Sustaining surveillance where transmission is low or in the elimination setting • Limitations in diagnostic sensitivity and specificity (also impacts on addressing transmission) • Lack of capacity to conduct high--quality entomological surveillance and poor linkage with decision-making processes
Achieving universal access	• Reaching fragile, rural, mobile, and hard to access populations • Affordability of delivering national malaria programmes at scale • Lack of human capacity to implement, manage, and monitor components of the program • Weak health systems, poor infrastructure and poverty • Limited longevity of core vector control interventions • Limited shelf life of RDTs and antimalarial drugs • Training at national scale to manage introduction of new tools and strategies • Requirement for invasive diagnostic testing (blood samples) • Three-day dosing with anti-malarial drugs • Exclusion from chemoprevention and treatment because of drug contraindications • Lack of pharmacovigilance systems • Cross-border disparities; human population movement and displacement • Poor adherence on the recommended interventions by populations at risk and by the health care providers
***P. vivax* and non-falciparum species**	• Evasion of core vector control measures by *P. vivax* vectors • Insufficient sensitivity of *P. vivax* diagnostics • Limited diagnostics for differential diagnosis of *Plasmodium* spp. • Inability to detect hypnozoites and target the transmission reservoir • Lack of a WHO prequalified G6PD POC test for G6PD deficiency • Long primaquine dosing regimen • Exclusion of G6PD-deficient patients from primaquine treatment • Lack of vaccine strategies for non-falciparum malaria

6.1 Biological adaptation (resistance)

Adaptation by parasites and mosquitos to resist or evade the current set of core interventions is a major threat to achieving the GTS goals. In fact, it is one of the threats that could unravel progress made since 2000. New tools are needed, and the R&D processes as well as implementation strategies need to manage the inevitable adaptation of the parasites and mosquitoes they target.

6.1.1 Vector control

Each formulation for IRS covered by a WHO policy recommendation and listed by the WHO prequalification team contains only one insecticide, all of which belong to one of five classes: pyrethroids, carbamates, organophosphates, organochlorines or neonicotinoids.[42] All currently

available LLINs covered by a WHO policy recommendation and prequalified by WHO include only a pyrethroid insecticide, although some also contain a synergist (piperonyl butoxide) .

Sixty-one countries have reported confirmed resistance in malaria vectors to at least one insecticide class since 2010; 50 countries have reported resistance to two or more classes.[10] In some areas, resistance to the four classes of insecticides commonly used for public health has been detected.[3, 11] LLINs remain effective for now, but resistance to pyrethroids threatens the gains achieved through their widespread deployment.[10] The link between phenotypic resistance and clinical impact on insecticidal interventions is not yet fully determined.

Due to their indoor use, current core vector control interventions are most effective against indoor resting, night feeding mosquito species. Behavioral adaptation or selection of vectors, i.e. changes in their feeding and resting behavior, permits evasion of LLINs and IRS control measures. Vectors that feed outdoors and/or early in the day are not currently targeted effectively with the core interventions.[14]

6.1.2 Diagnostics

The most common RDT target for the detection of *P. falciparum* is *Pf*hrp2/3. However, clinical reports of infections with confirmed *Pf*hrp2/3 gene-deleted parasites from some countries led WHO to recommend development of alternative diagnostic methods that could be used in affected countries.[43, 44] Although in 2017RDTs based on *Pf*hrp2/3 remain effective as a diagnostic tool in many areas, there is the potential for emergence and spread of *Pf*hrp2/3 gene-deleted parasites and continued surveillance required. The WHO has issued guidance to countries on how to confirm the presence of *Pf*hrp2/3 gene-deleted parasites and the use alternative diagnostic methods.

6.1.3 Drugs

Chemoprevention in pregnancy and infants

Sulfadoxine-pyrimethamine (SP) is currently the only agent recommended for chemoprevention of malaria in pregnancy and infants. Despite the development of resistance to SP, intermittent preventive treatment in pregnancy SP (IPTp-SP) remains highly cost-effective in preventing the adverse consequence of malaria on maternal and fetal outcomes, even in areas where quintuple-mutant haplotypes of SP-resistant *P. falciparum* are prevalent.[45] However, an association between sextuple-mutant haplotypes of *P. falciparum* and decreased birth weight has been reported in observational studies in some sites in East Africa.[45]

For infants, WHO currently recommends intermittent preventive treatment with SP (IPTi-SP) in areas with moderate to high malaria transmission in sub-Saharan Africa that have less than 50% prevalence of the *P. falciparum dhps* 540 mutation.[46, 47] However, this intervention has not yet been widely implemented.

Chemoprevention in children

Seasonal malaria chemoprevention (SMC) is recommended for children aged between 3 and 59 months in areas with highly seasonal malaria transmission; amodiaquine plus SP is suitable where the efficacy of the combination remains >90%.[48, 49] However, clinical SP-resistant *P. falciparum*

observational in some areas of East Africa means that amodiaquine plus SP is suboptimal for SMC and other drug combination are needed in this area.24

Treatment of uncomplicated malaria

ACTs are first-line treatment for uncomplicated *P. falciparum* malaria in children and adults, and WHO GMP is in the process of recommending their use in women with malaria in their first trimester of pregnancy.[50]

P. falciparum artemisinin resistance was first identified in the Greater Mekong Subregion (GMS), and is defined as delayed parasite clearance following treatment with an artesunate monotherapy, or with an ACT.[51] The availability of sub-standard products and monotherapy with artemisinins or partner drugs is likely to have accelerated the development and/or spread of resistance.

Artemisinin resistance, though not on its own causing clinical failure, exposes partner drugs to higher parasite loads, increasing the risk of the selection of strains resistant to both components of the combination.[44, 51] Resistance to partner drugs in combination formulations has been documented at some level for all partner drugs, except pyronaridine, for which there are no data and which is not in general use. Artemisinin resistance plus resistance to partner drugs has severely limited the malaria treatment options in the GMS, triggering an emergency response with the aim of eliminating malaria in the region.[52]

A molecular marker for artemisinin resistance (*PfKelch13*) has been identified, and data collection on the geographical distribution of this marker is helping to improve the global surveillance of artemisinin resistance.[51] Molecular markers of resistance have been validated for mefloquine, piperaquine (Asian parasites only), chloroquine and SP and identified for lumefantrine and amodiaquine. However, there are currently no point-of-care (POC) diagnostics for identifying drug-resistant parasites.

For *P. vivax*, in many endemic areas chloroquine remains effective. With the exception of artesunate (AS)+SP, ACTs are an alternative where chloroquine-resistant *P. vivax* strains are prevalent.[53]

6.1.4 Vaccines

Resistance to malaria vaccines could occur where the target is strain specific. The theoretical concern is that parasite strains with variations in the target that cannot be recognized by the vaccine 'escape' and would be selected in the population. This concern has also been hypothesized with investigational blood stage vaccines.[54, 55]

RTS,S/AS01 (RTS,S) – also known as Mosquirix – is a pre-erythrocytic malaria vaccine and the only malaria vaccine to have received a positive opinion from a stringent medicines regulatory authority, the European Medicines Agency (EMA). RTS,S provides partial protection against malaria in young children, and is now being evaluated in sub-Saharan Africa as a complementary malaria control tool that potentially could be added to (and not replace) the core package of WHO-recommended preventive, diagnostic and treatment measures.[3, 56] The impact of resistance on RTS,S efficacy is unknown, but current analyses suggests the potential for a modest loss of efficacy with some cross protection between strains.[57] However, as the vaccine is only partially protective, any loss of efficacy will have potential clinical relevance.[58]

6.2 Addressing transmission

Malaria transmission is an important barrier to meeting the GTS goals, including elimination and prevention of reestablishment of transmission.

6.2.1 Interrupting transmission

Vector control measures are the most effective means available of interrupting mosquito to human transmission and principally comprise LLINs and IRS. In addition, larvicides are used in larval source management (LSM) as part of environmental control to reduce the number of mosquitoes. Larviciding is appropriate only under specific conditions in areas where mosquito habitats are few, fixed and findable. [42] And housing adaptations such as installing tubes to trap mosquitoes in the eaves are also used to protect inhabitants from malaria.

For interrupting human to mosquito transmission, options are limited. To target gametocytes, in low transmission areas a single dose of 0.25 mg/kg body weight of primaquine with ACT should be given to all patients with *P. falciparum* malaria (except for pregnant women, infants aged <6 months and women breastfeeding infants <6 months).[14] A single low dose of PQ (0.25 mg/kg) added to artemisinin-based combination therapy reduces infectiousness of people to mosquitoes however, it is not known whether single dose PQ could reduce malaria transmission at the community level.[59] No other drugs or vaccines are available today for transmission interruption.

6.2.2 Residual transmission

Transmission persists even with good access to and use of LLINs and/or well-implemented IRS.[14] Many malaria vector species have behaviours that circumvent these vector control strategies, such as natural or acquired avoidance of insecticide-treated surfaces, outdoor feeding and resting, daytime feeding and zoophagy.[60] Residual transmission may be intense and can contribute a large proportion of transmission including in areas with high transmission rates.[60]

6.2.3 Identifying the transmission reservoir

The contribution of low-density infections to malaria transmission at different levels of transmission intensity is not well understood. Quantifying the proportion of the population with sub-microscopic infection that is infectious is key to understanding and quantifying the transmission reservoir in a particular setting.[21]

Microscopy and currently deployed RDTs have been designed at a sensitivity for the confirmation of clinical malaria (100–200 parasites/µL) as the cause of disease, but low density infections will not be detected.[61] Suitable tools for the identification of low-density parasitemia are under development, but data to evaluate their value in the field are not yet available.[14, 44]

6.2.4 Accelerating elimination

Currently, acceleration strategies for the elimination of *P. falciparum* malaria are limited to population-wide parasite clearance by mass drug administration (MDA) and is only recommended under specific conditions.[62] MDA is the administration of a full dose of antimalarial treatment, irrespective of the knowledge of symptoms or presence of infection, to an entire population in a

given area, except those in whom the medicine is contraindicated.[62] Mass screen and treat (MSAT) nor mass test and treat (MTAT) are not currently recommended for accelerating elimination, owing to the limitations of RDTs in identifying low-density parasitemia.

To impact on transmission, MDA requires high coverage of the target population which, in turn, demands a high level of community engagement and high level of adherence. However, if the transmission of malaria is not interrupted or its importation not prevented, transmission eventually returns to its original level once MDA is terminated. The transmission 'rebound' can be lessened if there is enhanced vector control, improved case management and surviellance.[62] To minimize the risk of resistance emergence, MDA should not be started unless there is a good chance that elimination is feasible in the area where it is being administered.[62]

There are few options for MDA, particularly in areas of *P. falciparum* drug resistance and new drugs are needed.[44, 62] Medicines must not only be of proven clinical efficacy and safety, but preferably have a long half-life, differ from those used for first-line treatment and be available in a single dose. In elimination situations where the risk of malaria infection and death is very low, even rare adverse events are concerning and so drugs for community administration must have acceptable safety profiles for use in prevention.[44, 62]

P. vivax is the dominant malaria parasite in many countries that are prime candidates for malaria elimination. Each year, the parasite accounts for more than 70% of malaria cases in countries with fewer than 5000 cases of the disease.[53] Mass primaquine prophylactic treatment is not recommended for the interruption of *P. vivax* transmission because of the long treatment duration and an inadequate safety profile at the doses required to clear hypnozoites; particularly the risk of hemolysis in glucose-6-phosphate (G6PD)-deficient individuals.[53, 62] Strategies to enable use of tafenoquine (such as screening for G6PD deficiency) for community administration may facilitate targeting of *P. vivax*.

6.2.5 Preventing re-establishment of malaria

Receptivity to malaria transmission often persists after malaria elimination unless the vector itself is eliminated. If an area is also vulnerable to malaria importation transmission can be reestablished.[20, 21] There are no standard methods to assess the risk of malaria re-establishment based on receptivity and vulnerability or clear strategies that could ameliorate that risk.[20]

Rapid case detection and follow up may be difficult in hard to reach or vulnerable populations, leading to sustained transmission. Efforts to identify importation and infectious individuals are limited by the sensitivity of available RDTs and microscopy, but deployment and decisions related to use of highly sensitive tools remains controversial.[21]

6.3 Transforming surveillance

Surveillance entails tracking of vector populations, malaria cases, malaria mortality and programmatic responses, and taking action based on the data received. To enable an effective malaria response in endemic regions, to prevent outbreaks and resurgences, to track progress, and to hold governments and the global malaria community accountable, malaria surveillance systems need to be robust with timely reporting and responses.[3] Malaria surveillance systems have the opportunity to be integrated into national systems for deployment (such as HMIS) requiring trained

personnel and specialized resources. Some common weaknesses of surveillance systems include poor integration and reporting from private sector facilities, poor quality data, and a lack of trained entomologists that impairs adequate surveillance of vector populations.

Countries with weak surveillance systems, particularly in highly endemic regions, are not in a position to accurately assess disease distribution and trends, making it difficult to optimize malaria interventions in those areas.[3] Improved data is emerging from the global deployment of RDTs, increased rapid reporting from cell-phone-based systems and the extension of case detection and reporting at the community level and new systems are being created to link facility-based reporting systems to the national malaria control program.[14]

Parasite genetic epidemiological tools are being developed and can answer range of questions about malaria infections at the population level from identifying drug resistant strains to the source of importation. Genetic epidemiological tools have been powerful for other fields like Polio and use case scenarios as part of surveillance systems are being developed for discussion and testing in malaria.

6.3.1 Surveillance for elimination

In elimination settings, malaria surveillance is designed for the identification, investigation and elimination of continuing transmission, the prevention and cure of infections, and the final certification of elimination.[44] In this context, the sensitivity and specificity of surveillance systems requires upgrading to detect all cases and any foci of ongoing transmission, investigating and clearing them with appropriate treatment and possibly additional vector control.[14]

Once local elimination has been achieved, vector surveillance is the basis for defining receptivity to malaria transmission and population movement will inform vulnerability to malaria importation. Taken together, receptivity and vulnerability allow the risk of malaria re-establishment to be mapped and facilitate the design of appropriate surveillance systems.[14]

Sustaining case management, risk assessment and surveillance once elimination has been achieved requires continuous political and financial commitment.[14] Hence, more efficient and effective methods are needed to demonstrate elimination, and for identification of cases and rapid responses to importation post-certification.

6.4 Achieving universal access

The agenda for improving access is exceptionally broad and includes health systems research. Affordability is only one key component of ensuring access, but many other factors also determine whether people get the products needed to diagnose, treat and prevent malaria, such as gaps in local health systems and infrastructures, procurement practices, tax and tariff policies, mark-ups along the supply chain, and the strength of national regulatory authorities.[63] For access to lead to effective use of the tools and adherence there are also challenges to overcome and here social science, community engagement and implementation science play a role.

Malaria disproportionately affects the poorest and populations that are the hardest to reach with public health interventions, including those living in remote regions, migrants, disadvantaged populations, and persons displaced by war or other reasons. New approaches are needed that specifically address these challenges.

6.4.1 Vector control

In 2016, 54% of people at risk of malaria in sub-Saharan Africa were sleeping under an insecticide-treated mosquito net.[10] For IRS to confer significant community protection, at least 80% of homes in the targeted area should be sprayed.[3] However, IRS protection has dropped globally and in the WHO African Region, coverage dropped from 80 million people at risk in 2010 to 45 million in 2016.[10]

The limited longevity of currently available LLINs and IRS can cause interrupted access and gaps in deployment. LLINs are designed to kill mosquitoes for up to 3 years, after which time they need to be disposed of and replaced.[64] However, field studies show that the lifespan is less than 3 years and commonly, nets need replacing before this time. IRS is effective for up to 6 months, depending on the formulation used and the surface it is sprayed upon.[14] Thus, in some settings multiple spray rounds are needed to protect the population for the entire malaria season

6.4.2 Diagnostics

Between 2000 and 2015, significant progress was made in extending the coverage of malaria diagnostic testing. However, current estimates suggest that large gaps in programme coverage remain.[44] The limited longevity of current RDTs can also limit access, with the risk of deterioration and reduced sensitivity when exposed to heat and humidity for prolonged periods.[65] Even though RDTs are relatively simple to use, they cannot be self-administered as training is still required. Patients must also be willing to supply a blood sample.

6.4.3 Drugs

Availability and affordability are key requirements for access to effective anti-malarial drugs. In many settings, the public sector may not be the most important provider of drugs and the private sector or informal suppliers may not follow treatment, particularly as ACTs can be more expensive than older drugs. Also, currently recommended ACTs for uncomplicated *P. falciparum* all have a 3-day dosing regimen, which are sometimes inappropriately saved or shared among family members.

Access is also limited by drug – drug interactions and other contraindications, for example, IPTi-SP and SP-based SMC is not given to HIV-positive children already receiving co-trimoxazole.[48]

The quality of medicines is usually unverifiable, with sub-standard and counterfeit medicines available, however the global extent of this problem is not known since there is a lack of reporting.[66] Apart from being affordable and of good quality, medicines must also be safe; a system for pharmacovigilance needs to be in place, particularly if new drugs and vaccines are to be introduced.[63]

Treatment of severe malaria

For severe malaria, rectal artesunate meeting international quality standards was recently introduced as a pre-referral treatment,[67] with intravenous artesunate recommended for in-hospital treatment. Although intravenous quinine is an alternative treatment for severe malaria, it is less effective than intravenous artesunate, and there is no alternative to rectal artesunate pre-referral treatment.[68, 69]

6.4.4 Vaccines

RTS,S, the only malaria vaccine available after a positive opinion from EMA, is currently undergoing large-scale pilot studies under the malaria vaccine implementation programme (MVIP).[70] MVIP is expected to continue through 2022. During this time, the MVIP will provide data on: the programmatic feasibility of delivering the recommended 4-dose vaccine regiment outside of the routine immunization schedule in real-life settings; the safety profile of RTS,S in the context of routine use; and the vaccine's impact on child survival.[70]

6.5 *P. vivax* and non-falciparum species

P. vivax and *P. ovale* generate quiescent liver-stage parasites (hypnozoites) that can emerge to cause repeated clinical episodes of malaria from a single infectious bite. Hypnozoites present particular problems, allowing the parasite to evade vector control efforts, avoid schizonticidal anti-malarial drugs, and perpetuate an invisible transmission reservoir.[53] Following activation, hypnozoites generate gametocytes allowing human to mosquito transmission to occur spatially and temporally distant from the original infective bite. Thus, *P. vivax*-infected individuals can transport the infection to new areas.

6.5.1 Vector control

The important *P. vivax* vectors tend to rest outside during the day. *P. vivax* could therefore be considered as more resilient than *P. falciparum* to the core vector control interventions.

6.5.2 Diagnostics

Non-falciparum species present challenges to molecular detection methods. *P. vivax* frequently presents at a lower parasite density (typically 10 times lower) than *P. falciparum*, making *P. vivax* infections more difficult to detect with RDTs and microscopy.[61] The *P. vivax* hypnozoite is undetectable using currently available diagnostic methods.

Treating *P. vivax* with primaquine (and tafenoquine) can cause haemolysis in G6PD1-deficient patients and the WHO published a policy brief to guide case management G6PD1-deficient patients.[71] However, G6PD testing often not available at the point of care and the current tests are qualitative with a G6PD enzyme activity detection threshold of 30%.

RDTs are not currently evaluated for detection of *P. malariae* and *P. ovale* because of a lack of sources of suitable mono-species infections with these parasites.[14]

6.5.3 Drugs

Prevention in pregnancy

Chloroquine prophylaxis is recommended if a documented case of vivax infection has occurred in pregnancy, however routine chloroquine prophylaxis as a means of preventing vivax malaria in pregnancy in areas where transmission is high is not recommended.[53] it. Primaquine is contra-indicated in pregnancy, and there are no other drugs available for *P. vivax* relapse prevention in pregnancy.[53]

Treatment

For *P. vivax* and *P. ovale*, in addition to a schizonticide to clear the blood-stage infection (chloroquine or an ACT) anti-relapse therapy (primaquine) is required to clear hypnozoites (i.e. radical cure).[14, 50] Primaquine requires a treatment course of 7–14 days to which patients may not fully adhere, jeopardizing efficacy.[53] [72, 73]

Primaquine is contraindicated in individuals with moderate to high levels of G6PD deficiency.[50] G6PD deficiency is an X-linked genetic disorder with an estimated allele frequency of 8.0% (interquartile range 7.4–8.8%) among countries in which malaria is endemic.[74] There is no WHO prequalified POC test to exclude G6PD-deficient patients from treatment with primaquine or tafenoquine.[53]

Primaquine is contraindicated in pregnant women, lactating women with children aged <6 months, and in children aged <6 months.[50, 53] Pregnancy tests are not always available at the point of care to exclude pregnant women from primaquine treatment.

Note that *P. vivax* gametocytes are generated before malaria symptoms appear, so although primaquine is gametocytocidal, it will not prevent transmission directly. However, clearance of hypnozoites will prevent transmission that would have potentially resulted from further clinical relapses. In some studies, over 70% of vivax transmission has been estimated to be due to relapses.[75] Thus, relapse prevention is a transmission-blocking intervention, as well as preventing further *P. vivax* malaria cases.

Tafenoquine is a liver-stage drug for *P. vivax* malaria. A phase IIb clinical trial and phase III trials presented in 2017 show that with a 3 day regimen of chloroquine tafenoquine reduced the risk of relapse by around 60% compared with chloroquine alone.[76, 77] Regulatory dossiers for tafenoquine were submitted to the US Food and Drug Administration (FDA) and to the Australian Therapeutic Goods Administration in 2017.[78] In July 2018 the US FDA granted approval for tafenoquine for the radical cure of *P. vivax* malaria.[79]

6.5.4 Vaccines

There are no vaccines available or in advanced development to prevent *P. vivax* or other non-falciparum species.

7 POTENTIAL HEALTH PRODUCT SOLUTIONS TO ADDRESS THE CHALLENGES

To understand what potential health products solutions might be required to address the overall challenges and specific problems described in section 5, a review of the strategic priorities for health product development was conducted with reference to malERA Refresh,[16-22] PDP priorities and portfolios, and funding organizations as well as published literature. This was used to develop a list of potential health products that have been identified as strategically important.

Potential health products were then mapped against operational constraints to provide an integrated overview across the product classes, vector control, diagnostics, drugs and vaccines (Annex 1).

This process is summarized in Table 7.1, showing the anticipated impact of each potential health product relative to the challenges to achieving the GTS goals. Many of the potential health products identified have overlapping applications, and a rigorous prioritization processes and due diligence is generally not being applied to inform the allocation of limited resources at country-level.

Uncertainties regarding how effective different products are in different situations requires that multiple approaches be considered concurrently, with clear go-no go criteria, and that both modeling and evaluation of use scenarios be considered early in development to aid further prioritization. Moreover, no one tool will achieve malaria control or elimination. Efforts require combinations of existing and new tools that are context specific and require multi-sectorial collaboration.[17, 20]

It is important to stress that health products will not completely address all the operational constraints identified. Implementation science is needed to determine the most cost-effective, appropriate and rational deployment strategies for combinations of tools in different settings and across the spectrum of transmission. Also, health products will not be deployable unless the required health systems, processes and infrastructure exist.

Table 7.1: Anticipated impact of potential health products relative to the challenges for achieving GTS goals.

PRODUCT CLASS	POTENTIAL HEALTH PRODUCT SOLUTION	CHALLENGES				
		BIOLOGICAL ADAPTATION	ADDRESSING TRANSMISSION	TRANSFORMING SURVEILLANCE	ACHIEVING UNIVERSAL ACCESS	*P. VIVAX*
Vector control	• New insecticide classes used in combination in LLINs and IRS	■	■			
	• Extended duration LLINs and IRS		■		■	
	• Novel vector control tools*including endectocides and genetic	■	■	■	■	■
Diagnostics	• Validated POC diagnostics for identifying low density infection		■	■		
	• RDTs that detect and differentiate all *Plasmodium* species			■		■
	• Infectivity/gametocyte diagnostics		■			
	• Multiplexed POC tests of acute febrile illness		■	■		
	• Non-invasive/ self-administered diagnostic tests			■	■	
	• Sensitive and specific POC diagnostics for *P. vivax*			■		■
	• Diagnostics to identify hypnozoites		■			■
	• Affordable, simple and accurate POC tests for G6PD deficiency				■	■
	• Stable, valid, specific and sensitive RDTs that do not depend on Pfhrp2/3	■				
	• POC diagnostics to identify drug-resistant parasites	■		■		
	• POC/health system falsified drug screening	■			■	
	• High-throughput mosquito assays	■	■	■		
Drugs	• Simplified therapy and prophylaxis	■	■	■	■	
	• New drug classes used in combination therapies for malaria treatment	■				
	• Novel drugs for severe malaria	■				
	• Novel drugs for chemoprevention	■	■			
	• New drug combinations suitable for use in MDA, etc.		■		■	
	• Simplified therapy for *P. vivax* radical cure		■		■	■
	• Drugs for *P. vivax* radical cure without G6PD liability		■		■	■
	• Transmission-blocking drugs	■	■	■	■	
	•	■	■		■	■
Vaccines	• Preventive vaccines *P. falciparum*	■	■	■	■	
	• Transmission-blocking vaccines *P. falciparum*	■	■	■	■	
	• Preventive vaccines *P. vivax*	■	■	■	■	■
	• Transmission-blocking vaccines *P. vivax*	■	■	■	■	■

*New intervention vector control products. Biological, physical, environmental and personal protection, for example, products aimed larval management, including non-chemical larvicides, products for the modification of buildings, traps, biological control agents and personal protection products. G6PD, glucose-6-phosphate dehydrogenase; IRS, indoor residual spraying; LLIN, long-lasting insecticidal bed nets; POC, point of care; RDT, rapid diagnostic test; SERCaP, single encounter radical cure and prophylaxis.

8 INTEGRATED GAP ANALYSIS OF THE CURRENT PIPELINE AGAINST R&D NEEDS

8.1 Health products in the pipeline

Annex 2 lists the current development pipeline for health products in malaria.

The analysis includes:

- new products or new chemical entities of existing approved products that are currently in development;
- new products with an interim recommendation.

The following are not included:

- products that are already approved by regulatory authorities and are undergoing post-licensure trials for different combinations, regimens or formulations; (ivermectin/endectocides are an exception since these are new interventions for malaria vector control);
- products that have already reached the market (unless, as mentioned above, they are in active Phase IV clinical trials – in which case they are referred to as 'Licensed');
- products that are discontinued or on hold;
- products in the discovery Phase.

The following sources of information were used.

- The WHO Global Observatory for Health R&D.
- Reports of the WHO Vector Control Advisory Group (VCAG).
- Reports of WHOPES.
- Reports from active PDPs, such as Medicines for Malaria Venture (MMV) and Innovative Vector Control Consortium (IVCC): product pipeline for malaria.
- WHO list of diagnostics undergoing prequalification evaluation.
- UNITAID malaria diagnostics technology and market landscape.[65]
- UNITAID malaria medicines landscape.[80]
- The WHO: vaccine pipeline tracker (the 'Rainbow tables').
- Policy Cures Research neglected product disease pipeline.[81]
- PubMed.

Across diagnostics, vaccines, vector control and drugs, significant progress has been made in developing new products. However, given that malaria treatment and control interventions are used in combination, and that no single intervention will achieve the goal of malaria elimination, priorities should be examined across product areas.

8.2 Current status of health product R&D and gap analysis

In order to have an impact on the GTS goals,[6] new health products will need to be introduced to the malaria toolbox before 2025. It will, therefore, be necessary to accelerate the development of new

health products where possible, as well as encouraging innovative R&D in areas where there are gaps.

The heat maps in Annex 3 align products in development with identified R&D needs and product target applications to identify gaps in each product area.

Note that the heat maps reflect the R&D goals and do not mean that the attribute has been proven.

Attrition rates in product development are high, particularly for drugs and vaccines, and not all of the products will successfully complete registration. Thus, this should be viewed as the most optimistic outlook, and new gaps will emerge as products that fail to meet efficacy and safety criteria are discontinued. For some areas there are portfolios, others have single candidates.

Based on the analysis of the pipeline, potential health products were categorized into programmes that already have made significant progress and which can be accelerated versus those that require further innovation or proof of concept (Table 8.1).

In addition, new technologies are emerging all the time and some examples of these that could potentially be of value in malaria were identified as areas for further investigation. A scan for new technologies should be performed periodically to identify new areas for malaria R&D.

Table 8.1 Summary of the current status of potential health products compared to the status of products in the pipeline.

STATUS	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
Improve	• New insecticide classes used in combination in extended duration LLINs and IRS • Extended duration combination LLINs and IRS • Novel vector control tools including endectocides and genetic approaches	• POC diagnostics for identifying low-density infection • RDTs that detect and differentiate all Plasmodium species • Multiplexed POC tests of acute febrile illness • Sensitive and specific POC diagnostics for *P. vivax* • POC tests for G6PD deficiency • RDTs that do not depend on Pfhrp2/3 • POC diagnostics to identify drug-resistant parasites • POC/health system falsified drug screening	• Simplified therapy and prophylaxis • New drug classes used in combination therapies for malaria treatment • Novel drugs for severe malaria • Novel drugs for chemoprevention • New drug combinations suitable for use in MDA, etc. • Simplified therapy for *P. vivax* radical cure • Transmission-blocking drugs	• Preventive vaccines for *P. falciparum* • Transmission-blocking vaccines for *P. falciparum*
Innovate	• Additional novel vector control tools including endectocides and genetic approaches	• Non-invasive/ self-administered diagnostic tests • Infectivity/gametocyte diagnostics • • Diagnostics to identify hypnozoites • High-throughput mosquito assays	• Drugs for *P. vivax* radical cure without G6PD liability	• *P. vivax* targeted preventive and transmission-blocking vaccines • New targets for *P. falciparum* • Novel enhanced adjuvants
Investigate	• *Wolbachia* applications in *Anopheles spp.*	• Ultra-low cost lab-on-a-chip technology	• Alternative drug delivery systems	• Monoclonal antibodies

8.2.1 Vector control

New insecticide classes used in combination in LLINs and IRS

There is one net containing a pyrethroid plus another insecticide that has received interim approval from the former WHO Pesticide Evaluation Scheme (WHOPES) and has since been converted to a prequalified listing. It is now enerting epidemiological studies aimed at generating an evidence-base to assess its public health value. However, none of these products combine two insecticide classes that would be considered to be new. There is one new IRS insecticide in development, but this is not a combination. Other LLINs in development are single agent pyrethroid-treated nets plus or minus the synergist PBO.

Novel vector control tools: biological, physical and environmental

There are several tools under development, targeting mosquitoes in different ways indoors and/or outdoors, including: lethal house lures; spatial repellents; vector traps; attract and kill baits; house screening; eave tubes; patches for LLINs to overcome resistance; and insecticide-treated materials for specific at- risk populations. Some of these are in late-stage development. The only larvicide in development for use against malaria vectors is an extended release formulation of an insecticide used in an existing product.

Endectocides in livestock and humans

Ivermectin is a licensed product for both humans and livestock, and approved for 20 different species of endo- and ecto- parasites. To serve as a complementary malaria vector tool, the total dose and regimen are higher than the standard for some of the indications. Moreover, the delivery scheme is community administration and the drug requires specific evaluation for epidemiologic impact.

Genetic approaches to vector control

Two main approaches using gene drives for vector control are under investigation; one which reduces mosquito population numbers and one which seeks to confer resistance in *Anopheles* to *Plasmodium*, thus interrupting transmission.

Over the horizon

The alpha-proteobacterium *Wolbachia* has been used successfully to suppress *Aedes* spp. mosquito populations and to prevent transmission of dengue.[82] There is some evidence of an effect of *Wolbachia* on *Plasmodium* transmission in *Anopheles* spp.[83] This technology requires investigation, particularly given the opportunities for synergy with the dengue programme.

8.2.2 Diagnostics

POC diagnostics for identifying low-density infection

New-generation lateral flow RDTs are starting to reach the market with approximately 10x increased sensitivity than previously achieved. Ultra-high sensitivity, accessible molecular methods are becoming close to market, though cost may be an issue for routine use.

RDTs that detect and differentiate all *Plasmodium* species

Although this is possible with molecular techniques, it is currently not translatable to RDTs. Although hemozoin can be used to detect all malaria species, differentiation between species is not possible.

Multiplexed POC tests of acute febrile illness

For Asia-Pacific, one fever panel assay and a field-lab station using hydrogel are in development.

Non-invasive/self-administered diagnostic tests

The urine malaria test is already available and licensed in Nigeria and is being further developed to incorporate *P. vivax* as well as a *P. vivax* specific test. Non-invasive hemozoin-based tests are also in development. Other technologies are in early research, such as a malaria breath test. However, there is no clear candidate for a self-administered test at present.

Sensitive and specific diagnostics for *P. vivax*

Enhancement of lateral-flow RDTs and new methods are under development, including ultra-sensitive POC testing using hand-held devices or the multiplexable autonomous disposable nucleic acid amplification test (MAD-NAAT).

Affordable, simple and accurate POC tests for G6PD deficiency

New tests in development aim to be less costly and give quantitative results in order to have better performance in detecting G6PD heterozygous females than currently available tests.

Stable, valid, specific and sensitive RDTs that do not depend on *Pf*hrp2/3

Hemozoin-based testing should overcome issues of any loss of other biomarkers. However, whether early parasites can be detected remains to be proven and species differentiation is not possible. Enhanced lateral flow RDTs that are not dependent on *Pf*hrp2/3 are also in development.

POC diagnostics to identify drug-resistant parasites

There is a stated intention to develop drug susceptibility testing for the Q-POC platform and this might also be possible for MAD-NAAT.

POC/health system quality drug screening

Only one product has been launched for screening of artemisinin quality at POC.

Infectivity/gametocyte POC diagnostics

Determining infectivity at POC remains a research challenge. However, blue-laser technology has been used for the rapid sensitive detection of *P. falciparum* parasitemia and gametocytemia.

With the availability of ultra-high sensitivity parasite tests, if the objective is to identify potential sources of infection rather than currently infectious individuals, it may not be necessary to identify gametocytes. However, such technology may facilitate research into the efficacy of transmission-blocking interventions.

Diagnostics to identify hypnozoites

There are no diagnostics in development to identify hypnozoites.

High-throughput mosquito assays

Although multiplexed testing of key vector characteristics has been demonstrated, this has not yet been developed into a product. Near infrared spectroscopy has been proposed for age grading of mosquitoes.

Over the horizon

Reusable nanoparticle printed 'lab-on-a-chip' technology has been hailed as having the potential to provide ultra-low cost access to complex diagnostics.[84] The innovation brings the cost of the biochip down to US$ 0.01.

8.2.3 Drugs

Simplified therapy and prophylaxis

New drug combinations are being tested and new antimalarial drug candidates are also present in the pipeline. Single-dose therapy would have a significant market advantage and public health utility over current 3-day treatments.

New drug classes used in combination therapies for malaria treatment

There are enough new chemical entities in the malaria drug pipeline to allow combination therapies of novel classes. However, only one combination of two new agents is currently in development.

Novel drugs for severe malaria

Two agents are being specifically developed for the treatment of severe malaria, artemisone and sevuparin, the latter being an adjunctive therapy which acts by inhibiting erythrocyte adherence.

Novel drugs for chemoprevention

Many of the novel drugs for chemoprevention overlap with simplified therapy and prophylaxis above and MDA below, and several new agents with chemoprophylactic potential are in the pipeline.

New drug combinations suitable for use in MDA, etc.

It is unlikely that a drug will be developed with MDA as a primary indication, so regulatory approval would need to be granted for treatment and/or prophylaxis before this application could be investigated. Showing safety in mass treatment is a particular requirement. However, there are a number of drugs in development that may be suitable.

Simplified therapy for *P. vivax* radical cure

Tafenoquine is the only drug currently in clinical development for *P. vivax* radical cure and Phase III registration studies have been completed.

Transmission-blocking drugs

A number of new drugs have transmission blocking potential, though it is unclear whether this will be a labelled indication at this stage. Only methylene blue is being investigated specifically for transmission blocking potential in combination with an ACT.

Drugs for *P. vivax* radical cure without G6PD liability

There are no drug candidates in clinical development that address *P. vivax* without the risks of hemolysis in G6PD deficient patients.

Over the horizon

New technologies in drug delivery systems may overcome some of the pharmacokinetic/pharmacodynamic issues in developing antimalarial drugs for certain applications, such as long-duration chemoprevention.

8.2.4 Vaccines

Preventive vaccines for *P. falciparum*

There are around twenty vaccines candidates in Phase I and early Phase II trials for prevention of *P. falciparum* malaria, though the range of targets and adjuvants is limited. Vaccines against *P. falciparum* pre-erythrocytic stages and blood stages are in development. These approaches are complementary and combinations of vaccines could be possible if safety were demonstrated. If highly effective at preventing malaria, any malaria vaccine could theoretically impact on transmission.

Preventive vaccines for placental malaria

Placental malaria is a significant health risk to both mothers and their babies.[85] Current methods for protecting pregnant women rely on LLINs and IPTp, which are under threat from vector and drug resistance, respectively. There are two placental vaccines under development that have emerged based on target antigens specific to *P. falciparum* placental malaria, and will not have wider applications.

Transmission-blocking vaccines for *P. falciparum*

Sexual-sporogonic-mosquito-stage vaccines aim to interrupt parasite transmission, either by reducing the infectivity of gametocytes or disrupting sporogony within the mosquito. There are two target antigens in clinical development (Pfs25 and Pfs230).

***P. vivax* targeted preventive and transmission-blocking vaccines**

There is only one preventive vaccine for *P. vivax* in clinical development.

Over the horizon

Although there are no monoclonal antibodies in development for malaria, the cost and 'developability' of this platform have been improving in recent years.

9 PRIORITIZATION OF R&D NEEDS VERSUS THE CURRENT DEVELOPMENT PIPELINE

A matrix was formulated to evaluate the identified health product needs and the R&D necessary to deliver them (Table 9.1). Three criteria were chosen to contribute towards the prioritisation: challenge to meeting GTS goals that can be alleviated with a new health product; stage of development of product; and relative cost of subsequent development. Challenges were weighted highest if they were both a threat to gains already made and a barrier to meeting the GTS strategic goals (biological adaptation and addressing transmission) and weighted less if non R&D solutions are also needed to address the challenge. Next, transforming surveillance and achieving universal access were assessed as equally important as they are major pillars of the GTS. *P. vivax* remains the major barrier to countries outside sub-Saharan Africa achieving malaria elimination.

Development stage was also used as a criterion, favouring those products by score that are already in development and could be accelerated in time to have an impact on the GTS strategic goals.

Finally, relative R&D cost was taken into account, with vaccines and drugs assumed as classes of products to be more expensive to develop compared to most vector control products and diagnostics.

Table 9.1 Matrix of how R&D of novel tools can impact upon the key challenges.

CATEGORY		SCORE
Challenge	Biological adaptation	6
	Addressing transmission	6
	Transforming surveillance	3
	Achieving universal access	3
	P. vivax and non-falciparum species	3
Development stage	Improve	6
	Innovate	3
Relative cost of R&D	High	2
	Medium	3
	Low	5
Total		**40**

The total scores for potential health products are shown in Annex 4. These were then summarized as a first priority if the score was >20, a second priority if the score was >15 but ≤20 and third priority if the score was ≤15 (Table 9.2). Note that although potential health products have been prioritized, each was identified as potentially of strategic importance to achieving the GTS goals and the prioritization could be further prioritized by rigorous processes and criteria by GMP as R&D objectives.

Health products in the pipeline have also been mapped against this prioritization grid (Annex 5), though their attributes have not been proven in many cases. This provides an idea of the strengths

and weaknesses in the pipeline and where further R&D investment is required, as summarized in Table 9.2.

There are some important caveats to this analysis.

9.1 Changing priorities

The priorities reflect the situation today, which could change rapidly. For example, if artemisinin-resistance were to be detected in Africa, then products that addressed biological adaptation would become the priority. However, this matrix provides a basis for prompt evaluation of the existing product development landscape against a changing situation in malaria control, prevention and treatment, with reprioritization as necessary. Priorities will also change as progress is made in basic science, in the R&D pipeline and in implementation science.

9.2 Attrition

The development of any health product is difficult and many of those already in development will not reach the market, particularly at the earliest phases of development. Thus, even where the pipeline appears strong, continuing investment is needed to maintain that strength as products are lost to attrition.

9.3 Insufficient evidence of product attributes

The analysis of the current health product pipeline for malaria makes assumptions regarding the potential attributes of individual products. However, these attributes are usually unproven and health product may, therefore, not meet the criteria for the strategic product solution. This degree of uncertainty is unavoidable when looking at investigational products. Moreover, for any single pipeline in a “product class”, evaluation of use scenarios and projections of efficacy, resource use and cost – effectiveness can be useful to develop priorities. Finally, there is variation in establishment of proof of concept or proof of public health value for different classes of products, from diagnostics to vaccine strategies.

Table 9.2 Prioritization of malaria health product R&D and strength of the pipeline.

PRIORITY	PRODUCT CLASS	PRODUCT SOLUTION	PIPELINE STRENGTH		
			STRONG	WEAK	EMPTY
Top	Vector control	New insecticide classes used in combination in LLINs and IRS			
		Novel vector control tools* including endectocides and genetic approaches			
	Diagnostics	High-throughput mosquito assays			
	Drugs	Simplified therapy and prophylaxis			
		Transmission-blocking drugs			
	Vaccines	Preventive vaccines *P. falciparum*			
		Transmission-blocking vaccines *P. falciparum*			
		Preventive vaccines *P. vivax*			
		Transmission-blocking vaccines *P. vivax*			
Second	Vector control	Extended duration combination LLINs and IRS			
	Diagnostics	Validated POC diagnostics for identifying low-density infection			
		RDTs that detect and differentiate all *Plasmodium* species			
		Multiplexed POC tests of acute febrile illness			
		Non-invasive/ self-administered diagnostic tests		Non-invasive	Self-administered
		Sensitive and specific POC diagnostics for *P. vivax*			
		Diagnostics to identify hypnozoites			
		Affordable, simple and accurate POC tests for G6PD deficiency			
		POC diagnostics to identify drug-resistant parasites			
		POC/health system falsified drug screening			
	Drugs	Novel drugs for chemoprevention			
		New drug combinations suitable for use in MDA, etc.			
		Simplified therapy for *P. vivax* radical cure			
		Drugs for *P. vivax* radical cure without G6PD liability			
Third	Diagnostics	Infectivity/gametocyte diagnostics		Gametocyte	Infectivity
		Stable, valid, specific and sensitive RDTs that do not depend on Pfhrp2/3			
	Drugs	New drug classes used in combination therapies for malaria treatment			
		Novel drugs for severe malaria			

Target product profiles

Target Product Profiles (TPPs), Preferred Product Characteristics (PCCs) and Target Candidate Profiles (TCPs) describe the desirable performance attributes of a class of products. Such practical development requirements are useful for accelerating product development. Target product profiles (TPPs) are the technical documents generated by industry, PDPs and various United Nations agencies that set out the characteristics necessary if a new drug, diagnostic or vaccine is to target a particular disease.[86]

The WHO Special Programme for Research and Training in Tropical Diseases (TDR) is leading a wide consultation to create an online directory of TPPs. The directory should lead to better ways to record and communicate the R&D priorities coming out of the global health community analysis and avoid wasting valuable resources developing products that do not meet these criteria.

9.4 Vector control

The Innovative Vector Control Consortium (IVCC),[87] defines the most pressing need for malaria vector control as a credible replacement for pyrethroids on LLINs. For indoor residual spraying, IVCC advocates for at least three different classes of insecticide to which vectors are susceptible, with novel modes of action that can be used in rotation, in fine scale mosaics or in combinations. In this way, it is hoped that resistance to the new agents can be delayed. IVCC has designed TPPs for a new active ingredient, a long-lasting IRS product and an LLIN.[88]

For genetic approaches, a hypothetical TPP was published by the Committee on Gene Drive Research in Non-Human Organisms.[89]

For new insecticide-based approaches and alternative vector control methods, product-specific TPPs will be developed. However, WHO has already developed an overview of new classes in order to guide development aims and the regulatory pathway.[90]

In addition, WHO has developed Preferred Product Characteristics (PPC) for ivermectin as a complementary strategy for vector control.[91] The concept of a drug for community administration as a complementary strategy for vector control is novel, although the drug itself is repurposed from other helminth indications. MMV has also developed a Target Candidate Profile (TCP) for endectocides: TCP-6: Molecules that block transmission by targeting the insect vector (endectocides). More information on TPPs and TCPs is given below.

9.5 Diagnostics

In 2004, the WHO Evidence Review Group on Malaria Diagnosis in Low Transmission Settings recommended PPCs for this setting, based on new molecular methods.[92]

MalERA 2011 developed TPPs for diagnostics for use in case management in elimination settings and surveillance at the district level or below.[93]

In 2014, through the DIAMETER project, PATH produced the TPP for a POC malaria infection detection test for rapid detection of low-density, sub-clinical malaria infections.[94, 95]

The Foundation for Innovative New Diagnostics (FIND), through an extensive consultation process, developed three *P. vivax* malaria-specific TPPs.[96, 97]

- POC of acutely ill patients for clinical care purposes.
- POC asymptomatic and otherwise sub-patent residents for public health purposes, e.g., MSAT campaigns.
- Ultra-sensitive not POC diagnosis for epidemiological research/surveillance purposes.

9.6 Drugs

The drug development landscape in malaria has been consolidated by MMV, a PDP in the field of antimalarial drug R&D.

MMV has defined two TPPs for antimalarial drug development.[98, 99]

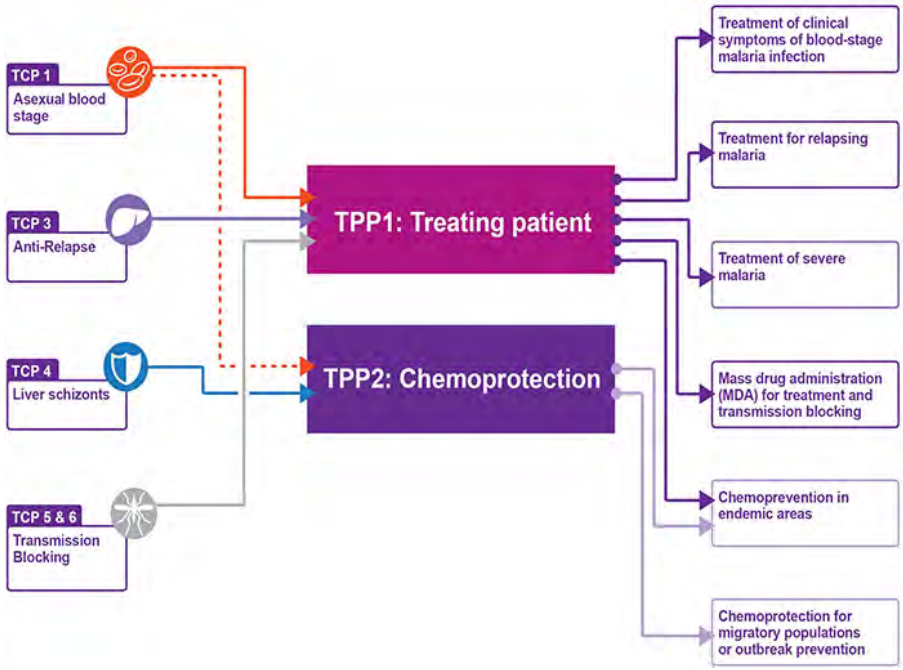
- TPP1: Case management; treatment of acute uncomplicated malaria in children or adults.
- TPP2: Chemoprotection; given to subjects migrating into areas of high endemicity, or during epidemics.

In order to meet these target profiles, a number of molecular target candidate profiles (TCPs) have been defined, which together can be combined to meet different needs (Figure 10.1).[98, 99]

- TCP-1: Molecules that clear asexual blood-stage parasitemia.
- TCP-2: (profile retired, see full article for more information).
- TCP-3: Molecules with activity against hypnozoites (mainly *P. vivax*).
- TCP-4: Molecules with activity against hepatic schizonts.
- TCP-5: Molecules that block transmission (targeting parasite gametocytes).
- TCP-6: Molecules that block transmission by targeting the insect vector (endectocides).

Full details of the TCPs have been published.[98, 99]

Figure 10.1 The inter-relationships between the two target product profiles and the individual target candidate profiles (reproduced with permission from MMV).



9.7 Vaccines

WHO published preferred product characteristics for malaria vaccines in 2014,[100] aligned to the strategic priorities of WHO and partners as articulated in the Malaria Vaccine Technology Roadmap. This aims to achieve the following two strategic goals by 2030 for licensing of vaccines targeting *P. falciparum* and *P. vivax*.[101]

- Roadmap strategic goal 1: Malaria vaccines with a protective efficacy of at least 70–80% against clinical malaria, suitable for administration to appropriate at-risk groups in malaria-endemic areas.
- Roadmap strategic goal 2: Malaria vaccines that reduce transmission of the parasite and thereby substantially reduce the incidence of human malaria infection. This will enable elimination in multiple settings. Vaccines to reduce transmission should be suitable for administration in mass campaigns.

10 POLICY AND REGULATORY PATHWAY OF NEW PRODUCTS BY CLASS

As candidate tools and approaches become available, they will be reviewed and advised upon by WHO and national regulatory bodies. Critical structural issues need to be addressed to ensure that new tools are promptly validated and adopted.[6]

- Countries should ensure the existence of a regulatory environment that facilitates rapid assessment and appropriate uptake of validated tools.
- Bottlenecks to the introduction of new tools must be identified and removed early in order to facilitate immediate use once the evidence base is available to define the appropriate conditions for their deployment.

10.1 Vector control

A meeting of stakeholders from IVCC, WHO, donor institutions, industry and other partners in 2011 plus broader consultations with more than 70 individual stakeholders from about 40 institutions in 2012, identified that all stakeholders were working towards rapid introduction of high quality insecticides. However, eight major areas for improvement in vector control innovation were identified.[102]

- Establishing a predictable and viable market.
- Protecting investments while allowing competition.
- Recognizing innovation.
- Facilitating breakthrough innovation.
- Reducing costs and improving efficiencies for time-to-market.
- Ensuring high quality products.
- Developing products that respond to the needs of end-users.
- Building strong collaboration between stakeholder groups.

WHO has responded by reviewing and replacing the mechanism for evaluating vector control products to provide clear guidance on the technical requirements and to expedite the review and recommendation process.[103] The revised evaluation process came into effect from January 2017 and transitions from WHOPES to the WHO Prequalification Team.

The new process covers ITNs, IRS, insecticidal larvicides and products providing personal protection, though the pathways for evaluation differ depending on whether there is already a WHO policy for the product class (pre-qualification pathway), or whether it is new intervention (new intervention pathway).[103] To support the latter, VCAG was jointly established in 2012 by the Global Malaria Programme and the Department of Control of Neglected Tropical Diseases to guide innovators in data and documentation requirements, and advise WHO on the public health value of new tools, technologies and approaches.[104] Guidance has been provided outlining the two pathways and their associated components, and the form of interaction between product developers/manufacturers and WHO.[103]

10.1.1 Novel vector control products

Products belonging to a class and/or having a product claim (or claims) for which there is no applicable WHO policy recommendation will be referred to VCAG. These products are assessed for their potential public health value, which will require epidemiological data on their protective efficacy against infection and/or disease.[104] Guidance has been developed on the design of epidemiological trials.[105] A review of the different product classes and the relevant pathways was developed by VCAG.[90]

10.1.2 Genetic approaches

Although this process applies to all vector control products and interventions, there have been recent advances in the methods available to genetically modify mosquitoes that require special attention in terms of the regulatory implications. These methods use homing endonuclease genes to create gene-drive systems, which work by excising genes identified as targets essential to processes relevant to malaria transmission.[106-108] The issues around gene-drive based vector control tools are complex and have been summarized in a comprehensive review by the Committee on Gene Drive Research in Non-Human Organisms.[89] No gene-drive system has ever passed through regulatory approval and the pathway to eventual release of populations into the wild is uncertain. A recent workshop examined the wide variety of approaches under development and the regulatory implications of the technology.[109] As this is rapidly developing field, WHO with the support of VCAG aims to continually review and update guidance and training documents as new approaches emerge.

10.2 Diagnostics

For malaria blood-based RDTs, there are several quality programmes in place: the WHO Product Testing Programme, the WHO–FIND Lot Testing Programme and the WHO Prequalification of In Vitro Diagnostics Programme (WHO-PQ).[65] Other regulatory programmes are challenging from a resource and cost perspective, e.g. the US Food and Drug Administration (FDA), or are largely administrative procedures that do not include a full quality evaluation.[65]

The WHO Product Testing Programme, is a laboratory evaluation that directly compares the performance of RDTs to each other using a standardized panel of specimens and procedures.[65] The programme is voluntary and is available to ISO 13458 certified companies producing blood-based RDTs targeting parasite antigens. Since 2008, seven rounds of testing have been completed.[61] The results are published in a report format and are available through an online tool that enables users to filter through large amounts of data to identify RDTs meeting specific criteria.[61, 110]

More than90% of the malaria RDTs delivered through the public sector have been prequalified by WHO-PQ. WHO prequalification involves a review of a product dossier and inspection of the manufacturing site(s), in addition to an independent performance evaluation by Product Testing. WHO-PQ also now accepts applications for the prequalification of assays intended for G6PD deficiency diagnosis.[111]

There are several areas of work, led by WHO, that could contribute to a larger number of prequalified malaria RDTs in the future, for example:

i) requiring that products submitted to Product Testing also apply for WHO-PQ;

ii) ensuring that malaria RDT manufacturers are knowledgeable about the WHO-PQ process and expectations; and

iii) closely monitoring the progress of malaria RDTs through the WHO-PQ process, and responding to major delays if warranted.[112]

As of 1 January, 2018 WHO procurement recommendations for malaria RDTs will change to require WHO prequalification designation.[112] These changes aim to encourage manufacturers to enhance their quality management systems, while avoiding unreasonable barriers to market access or undermining supply security.[112]

Another new development is that in 2017, the Expert Committee on the Selection of Essential Medicines recommended that WHO develop an Essential Diagnostics List (EDL). This will provide evidence-based guidance to countries to create their own national lists of essential diagnostic tests and tools. As a first step, WHO is creating a Strategic Advisory Group of Experts on In Vitro Diagnostics, which will advise WHO on global policies and the development of the EDL.

With the expansion of molecular methods, FIND, WHO and the UK National External Quality Assessment Service have launched the WHO Malaria external quality assessment (EQA) scheme for nucleic acid amplification (NAA) assays, targeting public health and research laboratories in malaria endemic and non-endemic settings. A repository containing enough EQA materials to allow for biannual distribution to 60 laboratories over at least two years has been established.[113]

The regulatory pathway for other types of new diagnostics is evolving to consider non-invasive diagnostic testing on a comparable platform. There is no policy or regulatory pathway for para-diagnostics not used in humans.

10.3 Drugs

Both WHO and MMV support filing all new drugs via a Stringent Regulatory Authority, i.e. FDA, EMA, Swissmedic or the WHO-PQ programme for drugs. However, there are a number of regulatory challenges (Table 11.1).[98, 99]

Table 11.1. Regulatory challenges to antimalarial drug approval.[98, 99]

OBJECTIVE	CHALLENGE
Combination therapies	Obtaining approval for a combination of two or more new compounds is complex and risky as the individual contribution of each component to efficacy and safety cannot be determined. The traditional pathway is to obtain approval for single agents, for use in combination subsequently.
Causal liver stage activity	The pathway to regulatory approval has not been defined.
Chemoprotection and chemoprevention	The pathway to regulatory approval has not been defined.
Pregnancy	Historically, this has required analysis of inadvertent exposure in early pregnancy, and gathering these data takes years, even with good post-registration safety monitoring. Early embryo-fetal development toxicity is usually done at Phase II, but can be done earlier to triage product pregnancy risk.
Children	Only adults can be enrolled in clinical trials prior to Phase II studies, so determining relevant dose and regimen for children is done subsequently.
Efficacy in non-	Only for pyronaridine-artesunate has activity against other species (*P. vivax*) been supported by clinical data in the stringent regulatory filing.

OBJECTIVE	CHALLENGE
falciparum species	
Transmission blocking	The pathway to regulatory approval has not been defined.
Treatment of asymptomatic carriers	Treating low density infections or parasite-free healthy subjects will require risk – benefit analysis akin to vaccines.
SERCaP	Meeting safety requirements while achieving a prolonged duration of drug exposure will be difficult.

Regulatory authorities have been receptive to discussions regarding development pathways. The FDA has expedited review and development mechanisms, including for drugs directed at neglected tropical diseases and malaria, and the EMA undertakes regulatory assessments and provides scientific opinion on products not intended for use in Europe through the Article 58 procedure. Thus, assuming the submitted dossier is of sufficient quality, there are opportunities for anti-malarial drugs to move relatively rapidly through regulatory review.

10.4 Vaccines

Vaccines typically require regulatory assessment and approval by a stringent regulatory authority. The regulatory requirements to developing any vaccine are substantial, requiring large numbers of subjects to demonstrate efficacy and safety, and the pathway for preventive vaccines is well established. However, vaccines developed specifically to interrupt transmission, that offers indirect protection from malaria after community administration, are a new paradigm and the concept has been reviewed favorably by the US FDA. The PATH Malaria Vaccine Initiative (PATH-MVI) and partners are exploring potential regulatory and policy approaches with the FDA and WHO.[114] A design template for a Phase III study has also been proposed.[115]

The introduction of RTS,S followed a positive scientific opinion from the EMA in 2015, but WHO advisory committees required additional pilot studies to demonstrate impact on mortality as well as operational effectiveness and safety at larger scale.[116] However, there is now a development model in place and a benchmark against which to test new protective vaccines. RTS,S clinical development generated a wave of capacity building for conducting clinical vaccine trials in endemic countries and has shown that it is possible to generate high quality evidence across a large number of sites with the subject numbers necessary to complete regulatory submission. Such programs are costly, around US$860 million plus additional funding for the pilot trials in Africa,[117] secured at around US$52 million.[116]

11 OVERVIEW OF MALARIA R&D FUNDING

11.1 Global Technical Strategy for Malaria 2016–2030 funding targets and forecasts

In 2015, annual spending on malaria was estimated at US$ 2.7 billion. The estimated total cost of delivering the Global Technical Strategy for Malaria 2016–2030 target has been calculated as US$101.8 billion (Table 12.1).[6] More than 10 million lives would be saved and over US$ 4 trillion of additional economic output generated with this investment.[5] The global return on this investment is therefore 40:1, increasing to 60:1 for sub-Saharan Africa. Conversely, failure to grasp this opportunity could see a resurgence in malaria, with increased deaths and regression of development gains.[5]

Table 12.1 Cost of implementing the Global Technical Strategy 2016–2030.[5, 6]

YEAR	GOALS	COSTS		OUTCOMES	
		INCREASED ANNUAL SPENDING	TOTAL SPEND	DEATHS AVERTED	CASES AVERTED
2020	40% reduction in malaria incidence and mortality	US$ 6.4 billion	24.5 billion	1.6 million	0.4 billion
2025	75% reduction in malaria incidence and mortality	US$ 7.7 billion	35.7 billion	4.2 million	1.3 billion
2030	90% reduction in malaria incidence and mortality	US$ 8.7 billion	41.6 billion	4.5 million	1.3 billion
		Total	**101.8 billion**	**10.3 million**	**3 billion**

In terms of R&D, additional funding of an average of US$ 673 million (range US$ 524–822 million) will be needed annually for this segment or a US$ 9.4 billion increase in total.[6] This estimate stems from a risk-adjusted portfolio model of malaria research and innovation needs until 2030. The majority of this funding is required for product development, approximately US$ 476 million per annum.[6]

There are no available estimates of the potential cost savings from more effective tools, or on the other hand, the potential costs of implementing new tools. Thus, these estimates do not consider the impact that future tools or approaches may have in the short or medium term. They are also unable to predict the degree to which drug and insecticide resistance could reduce the effectiveness of existing interventions, or how the costs of commodities or interventions may change at the global or national levels. There is therefore considerable uncertainty associated with the estimates. However, there is no doubt that even given these caveats, investing in malaria treatment and control is cost-effective.

11.2 Trends in malaria R&D funding (G-FINDER)

G-FINDER tracks and reports on global investments into neglected disease R&D. Data are collected by means of a survey of around 200 funders, intermediaries and product developers augmented with information from grant awards.[118] Survey participants were asked to enter every neglected

disease investment they had disbursed or received in their financial year 2015.[118] The scope includes funding related to drugs, vaccines, diagnostics, microbicides and vector control products and platform technologies (adjuvants, delivery technologies, diagnostic platforms).[118]

Based on 2015 data, two key conclusions of G-FINDER were:[118]

- Public sector funding in neglected disease R&D reached historic lows, though industry investment had increased, focused on malaria and tuberculosis.
- The highly concentrated nature of neglected disease funding is concerning.

Total product R&D funding in malaria was US$ 572 million in 2015, representing around 83% of the estimated annual funding required for R&D of US$ 686 million (Figure 12.1).[10]

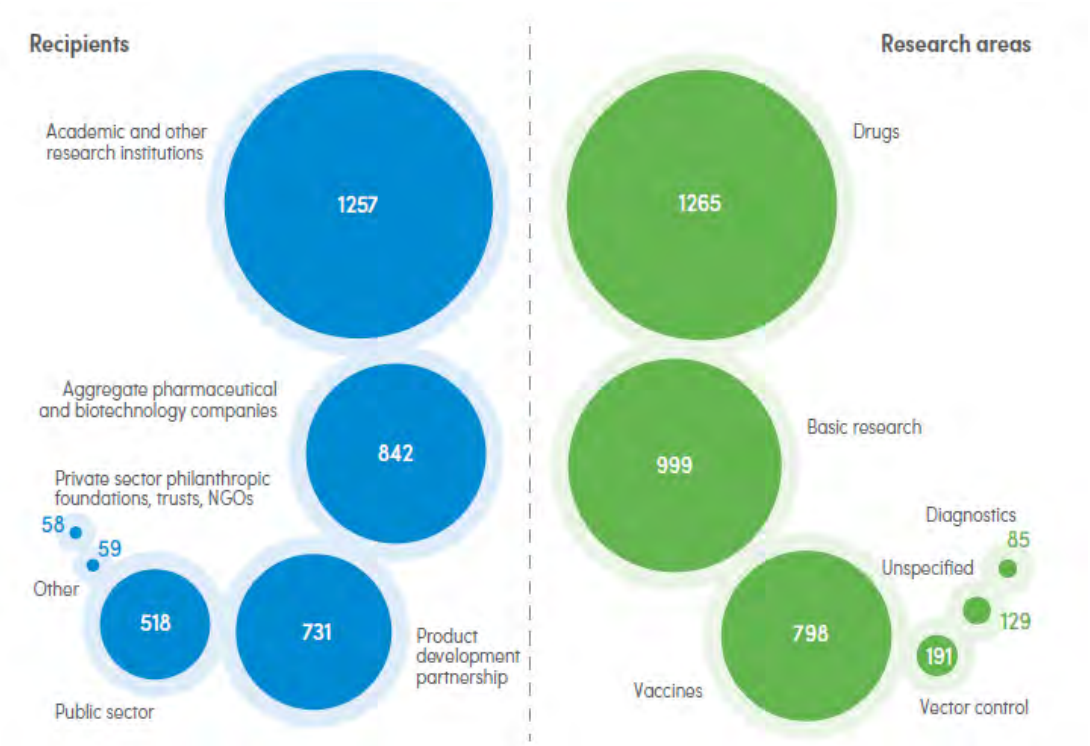
Malaria drug development attracted by far the most funding in 2015 (US$ 1265 million), followed by basic research (US$ 999 million) and vaccines (US$ 798 million). Funding for vector control products (US$ 191 million) and diagnostics (US$ 85 million) was lower (Figure 12.1).[10, 118] Funding decreased by 3% in 2015 compared with 2014, because of the large grants awarded in previous years to PATH for RTS,S clinical development.[118]

Funding was highly concentrated. Over the past three years, the three main funding channels were the US Government National Institutes of Health, the Bill and Melinda Gates Foundation (BMGF) and pharmaceutical and biotechnology companies, representing 27%, 22% and 21% of total funding, respectively.[10, 118]

The 2017 World Malaria Report documented that funding for malaria, across R&D to procurement and implementation, has dropped, and progress against malaria appears to have stalled in many countries. Overall, the funding levels are below what was indicated as necessary to reach the goals of the Global Technical Strategy.

Figure 12.1 Malaria R&D funding by recipient and by research area 2010–2015 (in US$ million).[10]

Source: G-FINDER Public Search Tool Policy Cures Research.[118]



12 MARKET STRUCTURE FOR R&D

For malaria, the commercial market is generated by global public health market mechanisms.[119] In this case, donor organizations such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and the Global Vaccine Alliance (Gavi), provide funding for commodities. This creates a visible demand once a product is developed and utilized. Along with donor funding for product development, this has resulted in a visible market that varies in robustness by product class, but depends on a small group of donor organizations.[119]

- Founded in 2002, the Global Fund is a partnership between governments, civil society, the private sector and people affected by the diseases. The Global Fund raises and invests nearly US$ 4 billion a year to support programs run by governments, civil society in countries and communities most in need.[120]
- Created in 2000, Gavi brings together public and private sectors with the shared goal of creating equal access to new and underused vaccines for children living in the world's poorest countries.[121] In 2016, GAVI received US$ 1.7 billion from donors and International Finance Facility for Immunisation investors.[122]

The disadvantage to this funding model is that although the public health market is supported, the private health sector generally functions outside of the funded programmes. The private sector includes private clinics, medical practitioners, pharmacies, unlicensed drug vendors, authorized companies, and services offered by not-for-profit organizations, such as non-Governmental organizations and faith-based organizations (although these can be funded through GFATM).[123] This sector can represent a substantial proportion of malaria case management in some countries.

The not-for-profit sector is an important provider of access to preventive measures and good quality malaria case management in some countries. However, the informal malaria market is often suboptimal due to sub-standard and counterfeit products, poor quality of care and insufficient malaria case reporting or follow up.[123] At the community level, new market challenges arise in terms of managing distributed supply chains, enhancing supportive supervision, ensuring financing for non-malaria commodities and training and retaining community health workers.[123]

The centrally directed funding model does have advantages in terms of the potential for market intervention to improve market health. In particular, management of demand, provision of a stable and assured market, the potential for economics of scale and reduced prices for payers.

The GFATM Procurement for Impact (P4I) strategy, established in 2013, changed the way the Global Fund worked across the supply chain with the following aims.[124]

- Earlier involvement and closer collaboration with manufacturers.
- Improving purchasing capability and changing contracting models (purchasing was brought in-house).
- Optimizing the international supply chain to reduce cost.
- Better planning & scheduling to support continuity of supply.
- Delivering more products at the right time and place to more people.

For manufacturers, there are advantages in financial planning and opportunities to improve sourcing and production efficiencies, while mitigating risk.

In terms of R&D funding, there are several product development partnerships (PDPs) that have been key in driving development of candidate pipelines and setting R&D goals and targets. PDPs overcome the lack of commercial incentive for malaria product development by acquiring donor funding to encourage industry and researchers to become involved in projects that would not otherwise be viable. This has proved a very effective model for malaria R&D in all product sectors, and progress in the last 10 years has been exceptional. However, donor organizations overlap between the PDPs.

By applying a portfolio approach, funds can be shifted between projects depending on the research findings. This is a major advantage given the high attrition rates during product development and encourages prioritization of projects based on their expected benefits, rather than on whether a project is associated with a particular funding stream. This encourages an efficient use of donor funds and resources targeted at developing those products that will best address the public health needs.

12.1 Vector control

UNITAID updated a comprehensive review of the malaria vector control commodities landscape in 2014.[125, 126] Since that time, the need to control Zika virus has increased the profile of the sector. Also, a small number of new insecticides have been brought to market. The continued expansion of LLIN and IRS scale-up has also grown the market significantly in the last 15 years.

In 2013, the Global Fund, UNICEF and the UK Department for International Development (DFID) brought together 13 LLIN suppliers and 10 international partners to coordinate the world's largest procurement of LLINs.[127] The aim was to ensure stability in the LLIN market by providing certainty of when budgets would be converted into funds, especially for the procurement of large quantities of nets. The industry was faced with fluctuating demand cycles and this affected lead times for delivery to programmes. This market shaping intervention was enabled by the concentration of procurement into a small number of agencies as well as their willingness to work together, and the relatively small number of manufacturers. The process was repeated in 2015 and UNITAID is supporting a market shaping intervention for the next generation LLINs. Thus, there is a highly controlled, but stable market for LLINs and this could be extended to include new vector control interventions once their effectiveness as public health interventions is demonstrated.

In terms of R&D funding, the main conduit has been the IVCC, a PDP set up in 2005. This organization has concentrated on the development of three new active ingredients for LLIN/IRS with industry support and funding from the BMGF, DFID, USAID, the Swiss Agency for Development, UNITAID and the Wellcome Trust. The IVCC remit includes development of new insecticide-based products, and more recently, the development of new vector control interventions. Over the last 3 years IVCC has evaluated five potential new interventions, including insecticide impregnated clothing and hammocks, slow release insecticide emanators that do not require heating or burning, attractive toxic sugar baits and insect repellents. The most effective of these is now being tested in village scale trials in Cambodia. However, there is scope for expanding this portfolio to translate the many novel ideas for vector control into deployable products. IVCC has been instrumental in developing capacity and tools for testing vector control interventions.

12.2 Diagnostics

A comprehensive review of the malaria diagnostics market landscape was conducted by UNITAID in 2016.[65]

After rapid growth from 2008–2013 (48% annual growth rate) the malaria RDT market size plateaued in 2014 at 314 million RDTs. In many countries, the public sector market is saturated, though some high burden countries have opportunities for market growth. In the private sector, demand is underdeveloped and growth is unlikely to be generated in this sector without significant intervention. One additional factor is that around a third of people with fever do not seek care, and there is scope for additional market growth via increasing awareness of the need for diagnosis and treatment.

Malaria RDT prices have declined, from an average of US$ 0.52 for a Pf-only RDT in 2010 to US$ 0.27 in 2014 in the public sector. Low prices may in some cases be below cost for some manufacturers and are not sustainable. Low prices also makes entry for new tests more difficult unless there are significant advantages. The market is highly concentrated with three companies (effectively two because of technology sharing) comprising 96.8% of the donor-funded market in 2014. Despite global-level harmonization efforts that have focused on labelling and instructions for use, there remain user training barriers to switching RDTs.

The characteristics of the leading suppliers are a commitment to the malaria business, high-performing tests, and sufficient production capacity to rapidly fulfil orders and a focus on cost reduction. At the global procurement level, incentives or slight price increases may be required to attract additional suppliers to the market and to encourage investment.

Current market conditions limit the business incentives for new product development with advances occurring in response to donor initiatives. New requirements for WHO PQ may create barriers to market entry, but there are also several opportunities for market intervention.[65]

- Demand-shaping interventions at the procurement level.
- Generating market growth by strategies to ensure access to those populations not seeking care or not receiving diagnostics before treatment.
- Further improvements in manufacturing quality and longevity under field conditions.
- Further development of the policy and regulatory pathway is required. This includes evaluation of highly sensitive and ultra-high sensitivity tests to allow differentiation of new products from existing RDTs, to set more clinically applicable cut-offs for the evaluation of *P. vivax* RDTs, incorporation of comparative evaluations of non-blood based RDTs, and assessment of alternative high throughput laboratory-based methods. Although G6PD tests are now included as eligible for WHO PQ, none have yet been evaluated.
- Improved alignment with technology developers and the market to make sure that the right products are being developed and that they will have a predictable market.

FIND is a PDP with the aim of enabling the development and delivery of much needed diagnostic tests for poverty-related diseases, and in malaria has particularly experience with supporting quality testing of approved diagnostics, a particularly challenging manufacturing area given the scale of production.[128] As well as product development, FIND also supports the appropriate use of

diagnostics through training programmes, quality assurance programmes and laboratory strengthening work.[129] FIND has four strategic objectives: catalyze development, guide use & inform policy, accelerate access and shape the agenda;[129] and four priorities for malaria diagnostics.[130]

- Enabling elimination of the disease and control of drug resistance through the development of new tools.
- Improving the management of fever patients with new tools and approaches.
- Maximizing the impact of existing rapid tests, especially for *P. vivax.*
- Increasing the prioritization of diagnostic solutions for malaria and fever management.

FIND also provides core resources, such as strain banks and access to its clinical trials platform for test evaluation and validation and clinical trials. Full criteria for FIND partner selection are published.[131]

The other PDP functioning in this area is the PATH Diagnostics program, which has focused on diagnostics for low density parasitemia, and developing vivax diagnostics in particular G6PD POC tests.

12.3 Drugs

A comprehensive review of the malaria medicines market landscape was conducted by UNITAID in 2015.[80]

Over the last decade, the major market issue for malaria medicines has been the need to scale up ACT use. Following adoption of ACTs as first-line therapy for uncomplicated malaria in 2006,[50] by 2013 79 malaria endemic countries had adopted ACTs as the first-line treatment for *P. falciparum* and ACT delivery volumes had increased from 11 million treatment courses in 2005 to 392 million courses in 2013. However, access is far from universal and in the private sector non-ACT medicines are still widely used.[50] Uptake of injectable artesunate was initially slow following its recommendation in 2011, despite strong evidence of its superiority over quinine.[68, 69] Thus, it is clear that there is a significant degree of market inertia in adopting new therapeutic options despite global procurement structures, public-sector mobilization, WHO treatment guidelines and strong scientific evidence.

In the private sector, adoption of new medicines is driven by price, with ACTs still several fold more expensive than SP or CQ in many markets. Although the Private Sector Co-payment Mechanism is still available via the Global Fund, allowing subsidized prices for ACTs in the private sector, it does not appear to be greatly utilized.[123]

IPTp and IPTi have also seen low adoption rates. However, SMC, which has benefitted from a large, well-funded access programme (ACCESS-SMC) has been implemented widely across sub-Saharan Africa.[132] It is not clear whether SMC will continue at such high levels after the access programme has ceased, but it may suggest a model for future policy implementation as the benefits can be directly evaluated by the community as well as health authorities.

Crucially, ACCESS-SMC will generate cost-effectiveness data. With pressure from a range of health needs, such data are needed to allow Ministries of Health to prioritize policies that address malaria, but which have demonstrable impacts on other health and socio-economic targets. These data are

often not available at product registration, and guidelines only usually consider target populations, efficacy and safety. It is not feasible to generate comprehensive cost-effectiveness data for all new antimalarial drugs. However, there is scope to use mathematical modelling to estimate the impact of interventions in different transmission settings.[20] Standardizing this approach to generate cost-effectiveness guidelines for new medicines could be a useful adjunct to the development of treatment guidelines.

A key market need for antimalarial drugs is the provision of child-friendly formulations. The recent development of pyronaridine-artesunate, which had parallel programmes for tablet and granule formulations, indicates that this is a feasible product development model. However, for dispersible artemether-lumefantrine, the issue has been supply. With only one WHO prequalified manufacturer, multiple non-prequalified pediatric formulations of unknown quality are available in local markets.

MMV was established in 1999 as a PDP with the aim of creating a pipeline for malaria drug development. At that time, the global malaria drug development pipeline was virtually non-existent, in spite of a context of increasing resistance to chloroquine and high mortality rates. Since its foundation, MMV has spent US$ 778 million to build the world's largest R&D portfolio of new and innovative antimalarial medicines.[133] The business plan estimates a minimum of US$ 420 million will be required over the period 2017–2021 to sustain this portfolio. With approximately US$ 220 million available, the organization is facing a budget gap of approximately US$ 200 million between 2019 and 2021.[133] Budget increases are required as new candidates advance to Phase III studies, the most costly stage in the drug development process. Around half of all funding for MMV has come from BMGF, around 20% from DFID and the remainder from a range of other donor organizations..[133]

12.4 Vaccines

In terms of wider market structure, in 2016, Gavi, UNICEF and BMGF jointly developed the 'healthy markets framework'. The ultimate goal is to improve the health of vaccine markets as a whole – for manufacturers, countries and partners. As a first step, Gavi developed a supply and procurement strategy 2016−2020.[134] In addition to the 'healthy markets objective', which aims to achieve moderate or high levels of healthy market dynamics in six markets, there are targets in terms of supply, price and innovation.[134] This 'innovation objective' aims to incentivize development of suitable and quality products by identifying ten innovative products, with measurable improved characteristics that advance progress on coverage and equity and meet country needs at a sustainable cost, to be included on the menu of products offered to countries.

With the market for innovative vaccines being supported, there are greater incentives for investment in malaria vaccines, though these will have to compete with vaccines against other priority diseases. Decisions on which vaccines to include in the Gavi product menu are made through the Gavi Vaccine Investment Strategy (VIS). This is an evidence-based approach to identifying new vaccines for Gavi market support.[135] It includes evidence review, analyses, stakeholder consultations, independent expert advice. The VIS aims to enable predictable vaccine programming and investment decisions (rather than first-come-first-serve). It also ensures predictability of Gavi programmes to help long-term planning by countries, industry and donors.

The next VIS cycle will be conducted in 2019 and will include the RTS,S malaria vaccine. RTS,S was evaluated in 2014, but a decision deferred until the results of pilot implementation studies were

available. There was no precendent for such large pilot implementation studies and a significant effort was made by partners to align and contribute collaboratively and support the costs. The malaria community needs to be better prepared to assure funding for such large pilot implementation studies. These pilot studies are supported by Gavi, the Global Fund, and UNITAID, but results will not be available until 2020 for the first Phase and 2022 for the second Phase.[136]

In order to include a vaccine in the Gavi market support programme, the VIS has the following data needs.[135]

- Expected demand from eligible countries over a 10-year timeframe.
- Likely vaccination strategy, including target population, dosing, schedule, and whether the programme will be national or sub-national.
- The public health impact in terms of efficacy, duration of protection, disease burden, the impact on inequity and preparedness for outbreaks.
- The cost per dose or per target person cost range.

As market entry for new malaria vaccines will depend on Gavi support, it is essential that these data needs are considered within the product development programme.

In terms of product development, PATH-MVI is a PDP focused accelerating the development of malaria vaccines and catalyzing timely access in endemic countries.[137] As well as product development, MVI is also involved in researching vaccine approaches, the development of vaccine development tools, such as mosquito-feeding assays and assay standardization, as well as influencing global policy and regulatory issues.

PATH-MVI's R&D efforts focus on two priority areas: vaccines that prevent infection, and those that block or interrupt transmission.[138] This includes pre-erythrocytic, blood-stage and transmission-blocking vaccines. MVI has four major donors (BMGF, ExxonMobil Foundation, German Federal Ministry of Education and Research [BMBF], and the Global Health Innovative Technology Fund) and a wide range of industry and academic partners.

The Malaria Vaccine Funders Group was established in order to exchange information and opinions Bbetween internationally active funding bodies for malaria vaccine development with the hope that progress can be accelerated (this include BMGF, EC, EDCTP, EVI, PATH-MVI, NIAID, USAID-MVDP, Wellcome Trust, and WHO-IVR). The group aims to coordinate vaccine research activities by defining and making use of synergies between ongoing and planned programmes/activities, structuring and prioritizing vaccine research efforts, thereby reducing unnecessary overlaps and identifying areas of research needs where support can be assembled in a complementary manner. The WHO - Initiative for Vaccine Research (IVR) serves as the secretariat of this group

13 CONCLUSIONS

Although significant gains have been made in the last decade in the prevention, control and elimination of malaria, a large proportion of the world's population remains at risk and many do not have access to key malaria interventions. The World Malaria Report documents that in some countries, progress has stalled, and in others, estimated cases of malaria have risen.[10] The emergence of vector resistance to insecticides and parasite resistance to antimalarial drugs can not only undermine progress, but threatens progress to the GTS goals.

Continued progress leading to control and elimination – and in the long term, eradication - will require innovation – including new products, tools and approaches to combining them for maximum impact, in the context of evolving health systems and competing priorities. This document examines the challenges in reaching this goal across the four main health product classes, vector control tools, diagnostics, drugs and vaccines. It sets out the requirements for malaria product R&D and prioritizes these into types of products that can be accelerated, areas where further innovation is needed.

However, this is only part of the malaria R&D landscape. Basic research will be needed to support innovation, and provide the enabling technologies to develop the malaria health products of the future. Implementation science is a key need, both to determine the most effective way to deploy existing tools and to integrate new tools into programmes once these become available.[16, 19, 20] Such implementation science is critical to achieving universal access, but unfortunately lacking.

It cannot be overemphasized that the utility of any product depends on our ability to use it wisely. Both the mosquito and the parasite will exploit any weakness in our approach and the utility of potentially transformational products will be undermined and eventually lost if they are used inappropriately. We have the opportunity to integrate the important lessons and gather key data from the deployment of existing tools, so that when new tools become available, we know how best to deploy them to maximize their impact and maintain their effectiveness.

Finite financial resources are hindering progress towards the GTS goals and as such, prioritizing research can be a useful way to make the most of the available investments. The benefits to global health and the contribution to the fight against poverty, inequity and disease will by far exceed the investment required.

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ANNEX 1: POTENTIAL HEALTH PRODUCTS IDENTIFIED AS STRATEGICALLY IMPORTANT MAPPED TO OPERATIONAL CONSTRAINTS TO THE CHALLENGES IMPEDING ACHIEVEMENT OF THE GTS GOALS.[6, 16-22]

CHALLENGES	OPERATIONAL CONSTRAINTS DRIVE R&D FRAMEWORK	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
Biological adaptation	Physiological and behavioral resistance of vectors to insecticides	• New insecticide classes used in combination in LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches • Genetic approaches to vector control	• High-throughput mosquito assays	• Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	Parasite resistance to existing anti-malarial drugs	Endectocides in livestock and humans		• New drug classes used in combination therapies for malaria treatment • Transmission-blocking drugs •	• Preventive vaccines • Transmission-blocking vaccines
	Potential resistance to malaria vaccines	• New insecticide classes used in combination in LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches • Genetic approaches to vector control		• New drug classes used in combination therapies for malaria treatment • Novel drugs for severe malaria • Novel drugs for chemoprevention • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	*Pf*hrp2/3 gene-deleted parasites evasion of diagnostics		• Stable, valid, specific and sensitive RDTs that do not depend on Pfhrp2/3		• Preventive vaccines
	Inability to diagnose resistant parasites at POC		• POC diagnostics to identify drug-resistant parasites		• Preventive vaccines
	Difficulties in controlling sub-standard and counterfeit drugs		• POC/health system falsified drug screening		•

CHALLENGES	OPERATIONAL CONSTRAINTS DRIVE R&D FRAMEWORK	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
Addressing transmission	Limited strategies for interrupting transmission beyond conventional vector control measures	• New insecticide classes used in combination in LLINs and IRS • Extended duration combination LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches		• Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	Residual transmission evading conventional vector control measures	• Novel vector control tools* including endectocides and genetic approaches •	• High-throughput mosquito assays	• Transmission-blocking drugs •	• Preventive vaccines • Transmission-blocking vaccines
	Inability to identify the transmission reservoir	• Genetic approaches to vector control	• POC diagnostics for identifying low-density infection • Infectivity/gametocyte diagnostics • Diagnostics to identify hypnozoites	• Transmission-blocking drugs • Simplified therapy for *P. vivax* radical cure • Drugs for *P. vivax* radical cure without G6PD liability	• Preventive vaccines • Transmission-blocking vaccines
	Lack of information on vector populations		• High-throughput mosquito assays	• Transmission-blocking drugs	
	Lack of RDTs for identification of sub-microscopic infection		• POC diagnostics for identifying low-density infection		
	Limited strategies for accelerating elimination	• Novel vector control tools* including endectocides and genetic approaches • Genetic approaches to vector control	• POC diagnostics for identifying low-density infection	• Simplified therapy and prophylaxis • Novel drugs for chemoprevention • New drug combinations suitable for use in MDA, etc. • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	Limited strategies for preventing malaria re-establishment and responding to outbreaks	• Novel vector control tools* including endectocides and genetic approaches	• POC diagnostics for identifying low-density infection • Multiplexed POC tests of acute febrile illness	• Simplified therapy and prophylaxis • Novel drugs for chemoprevention • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines

CHALLENGES	OPERATIONAL CONSTRAINTS DRIVE R&D FRAMEWORK	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
Transforming surveillance	Financial, structural and technological barriers to efficient surveillance where malaria burden is high	• Novel vector control tools* including endectocides and genetic approaches	• Non-invasive/ self-administered diagnostic tests • Sensitive and specific POC diagnostics for *P. vivax* • RDTs that detect and differentiate all *Plasmodium* species	• Simplified therapy and prophylaxis • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	Sustaining surveillance where transmission is low or in the elimination setting	• Genetic approaches to vector control	• Non-invasive/ self-administered diagnostic tests • POC diagnostics to identify drug-resistant parasites		• Preventive vaccines • Transmission-blocking vaccines
	Poor quality entomological surveillance	• Genetic approaches to vector control	• High-throughput mosquito assays	• Transmission-blocking drugs	
	Difficulties in defining operationally relevant metrics		• POC diagnostics for identifying low-density infection • High-throughput mosquito assays		
Achieving universal access	Affordability of delivering national malaria programmes	• Extended duration combination LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches	• Multiplexed POC tests of acute febrile illness • Non-invasive/ self-administered diagnostic tests	• Simplified therapy and prophylaxis • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
	Weak health systems, poor infrastructure and poverty	• Genetic approaches to vector control	• Multiplexed POC tests of acute febrile illness • Non-invasive/ self-administered diagnostic tests • POC/health system falsified drug screening	• Simplified therapy and prophylaxis	• Preventive vaccines • Transmission-blocking vaccines
	Limited longevity of core vector control measures	• Extended duration combination LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches •		• Simplified therapy and prophylaxis • Transmission-blocking drugs •	• Preventive vaccines • Transmission-blocking vaccines

CHALLENGES	OPERATIONAL CONSTRAINTS DRIVE R&D FRAMEWORK	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
	Limited longevity of RDTs		• Non-invasive/ self-administered diagnostic tests		
	Need for trained personnel to use RDTs		• Non-invasive/ self-administered diagnostic tests		
	Requirement for invasive diagnostic testing (blood samples)		• Non-invasive/ self-administered diagnostic tests		
	Three-day dosing with anti-malarial drugs			• Simplified therapy and prophylaxis • Transmission-blocking drugs •	• Preventive vaccines • Transmission-blocking vaccines
	Exclusion from chemoprevention and treatment because of drug contraindications	• Extended duration combination LLINs and IRS • Novel vector control tools* including endectocides and genetic approaches	• • Affordable, simple and accurate POC tests for G6PD deficiency	• New drug classes used in combination therapies for malaria treatment • New drug combinations suitable for use in MDA, etc. • Drugs for *P. vivax* radical cure without G6PD liability • Simplified therapy for *P. vivax* radical cure	• Preventive vaccines • Transmission-blocking vaccines
	Lack of pharmacovigilance				
	Human population movement and displacement	• Novel vector control tools* including endectocides and genetic approaches		• Simplified therapy and prophylaxis • Transmission-blocking drugs	• Preventive vaccines • Transmission-blocking vaccines
P. vivax	Evasion of core vector control measures by *P. vivax* vectors	• Novel vector control tools* including endectocides and genetic approaches		• Simplified therapy for *P. vivax* radical cure	• Preventive vaccines • Transmission-blocking vaccines
	Insufficient sensitivity of *P. vivax* diagnostics		• Sensitive and specific POC diagnostics for *P. vivax*		
	Lack of diagnostics for differential diagnosis of *Plasmodium* spp.		• RDTs that detect and differentiate all *Plasmodium* species		
	Inability to detect hypnozoites and target the transmission reservoir		• Diagnostics to identify hypnozoites	• Simplified therapy for *P. vivax* radical cure	• Preventive vaccines • Transmission-blocking vaccines

CHALLENGES	OPERATIONAL CONSTRAINTS DRIVE R&D FRAMEWORK	VECTOR CONTROL	DIAGNOSTICS	DRUGS	VACCINES
	Lack of a WHO prequalified G6PD POC test for G6PD deficiency		• Affordable, simple and accurate POC tests for G6PD deficiency	• Drugs for *P. vivax* radical cure without G6PD liability	
	Inconvenient primaquine dosing regimen undermines anti-relapse effectiveness			• Simplified therapy for *P. vivax* radical cure	• Preventive vaccines • Transmission-blocking vaccines
	Exclusion of G6PD-deficient patients from primaquine treatment			• Drugs for *P. vivax* radical cure without G6PD liability	• Preventive vaccines • Transmission-blocking vaccines

*New intervention vector control products. Biological, physical, environmental and personal protection, for example, products aimed larval management, including non-chemical larvicides, products for the modification of buildings, traps, biological control agents and personal protection products. G6PD, glucose-6-phosphate dehydrogenase; IRS, indoor residual spraying; LLIN, long-lasting insecticidal bed nets; POC, point of care; RDT, rapid diagnostic test; SERCaP, single encounter radical cure and prophylaxis.

ANNEX 2: MALARIA HEALTH PRODUCT PIPELINE LISTED IN THE GLOBAL OBSERVATORY FOR HEALTH R&D AND UPDATED ONLINE

Vector control

LLINs with an interim recommendation from WHO[139-145] (updated March 2018)

PRODUCT NAME	ACTIVE INSECTICIDE	INSECTICIDE CLASS	MANUFACTURER/ TRADE MARK OWNER	WHOPES INTERIM RECOMMENDATION[REF]
DawaPlus 2.0®	Deltamethrin coated on polyester	Pyrethroid	Tana Netting	2009[139]
DawaPlus 3.0®	Deltamethrin coated on polyester	Pyrethroid	Tana Netting	2017[140]
DawaPlus 4.0®	Deltamethrin coated on polyester	Pyrethroid	Tana Netting	2017[140]
Interceptor® G2	Alpha-cypermethrin + chlorfenapyr coated on polyester	Pyrethroid plus halogenated pyrrole	BASF Germany	2017[140]
LifeNet®	Deltamethrin incorporated into polypropylene	Pyrethroid	Bayer CropScience	2011[141]
MiraNet®	Alpha-cypermethrin incorporated into polyethylene	Pyrethroid	A to Z Textile Mills	2015[142]
Olyset Plus®	Permethrin + PBO incorporated into polyethylene	Pyrethroid + PBO	Sumitomo Chemical	2012[143]
Panda Net 2.0®	Deltamethrin incorporated into polyethylene	Pyrethroid	Life Ideas Biol. Tech. Co	2015[142]
PermaNet 3.0®	Deltamethrin coated on polyester side panels; deltamethrin + PBO incorporated into polyethylene roof	Pyrethroid + PBO	Vestergaard Frandsen	2008[144]
Veeralin®	Alpha-cypermethrin and PBO incorporated into polyethylene	Pyrethroid + PBO	VKA Polymer	2016[145]
Yahe® LN	Deltamethrin coated on polyester	Pyrethroid	Fujian Yamei Industry	2015[142]

Malaria chemical vector control products under WHOPES laboratory and or field testing and evaluation or reviewed by WHOPES[142, 144, 146, 147]

APPLICATION	PHASE	PRODUCT NAME	ACTIVE INSECTICIDE	INSECTICIDE CLASS	MANUFACTURER/TRADE MARK OWNER	WHOPES[REF]
IRS	II-III	SumiShield®	Clothianidin	Neonicotinoid	Sumitomo Chemical	2016[146]
	I-III	Fludora Fusion®	Deltamethrin + clothianidin	Pyrethroid + Neonicotinoid	Bayer CropScience	2016[146]
	II-III	Sylando® 240SC	Chlorfenapyr 240 SC	Halogenated pyrrole	BASF	2014[147]
LLIN	II	DuraNet Plus®	Alpha-cypermethrin incorporated into filaments	Pyrethroid	Shobikaa Impex Pvt Ltd	2016[146]
	II	Netprotect®	Deltamethrin incorporated into polyethylene fibres	Pyrethroid	Bestnet A/S Denmark	Interim recommendation withdrawn 2013[147]
	II	ICON MAXX-Net®	Lambda-cyhalothrin LN	Pyrethroid	Syngenta	2008[144]
	I	Royal Guard®	Alpha-cypermethrin incorporated into polyethylene	Pyrethroid	Disease Control Technologies	2016[146]
	I	SafeNet LN®	Alpha-cypermethrin incorporated into filaments	Pyrethroid	Mainpol GmbH	2015[142]
Larviciding	II-III	SumiLarv 2®	Pyriproxyfen (extended release)	Juvenile hormone mimic	Sumitomo Chemical	2016[146]

New intervention submissions to VCAG which may have applications in malaria[90, 148-150]

PRODUCT CLASS	PROTOTYPE AND MECHANISM OF ACTION	GOAL	DEVELOPER	VCAG STEP* (YEAR)[REF]
Lethal house lures	Eaves tubes and bricks A silicone coating binds a bioactive agent (e.g. an insecticide, biological agent (fungal spores), inert compound with insecticidal properties) to netting material affixed to tubes or "eave bricks" installed in the eaves of houses.	Overall effect on vectorial capacity and reduced infection or disease in humans	EU-FP7 project consortium consisting of five organizations	3 (2015)[148, 149]
Spatial repellents	Transfluthrin and metafluthrin passive emanators. Spatial repellents interrupt human–vector contact through vector behavior modification induced by airborne chemicals, offering protection (personal and community) from medically important vectors and nuisance pests.	Reduce pathogen transmission by interrupting human–vector contact	ECK Institute for Global Health, Notre Dame, IN, USA	3 (2015)[148]
Vector traps for disease management	Adulticidal oviposition traps (ALOT, AGO, TNK). To attract and kill gravid females seeking oviposition sites	Reduce mosquito abundance, resulting in decreased infection and disease in humans	SpringStar Inc., USA	3 (2015)[148]
Resistance targeting products	Permanet® 3.0, Interceptor G2 LLINs effective against pyrethroids-resistant vectors (See LLINs above)	Personal protection against blood meals	Vestergaard Frandsen BASF Germany	3 (2015)[148]
Attract and kill baits	Attractive toxic sugar bait (ATSB) Female and male mosquitoes need plant derived sugars and carbohydrates. The sugar-baited trap includes a toxicant	Suppressing vector insect populations sufficiently to have a beneficial impact on malaria and/or other insect-borne disease transmission	Westham Innovations Ltd	2 (2014)[149]
House screening	Pyrethroid- treated netting for full house protection using deltamethrin-impregnated netting (an LLIN) applied to the eaves, windows and doors of houses with open eaves.	To deter household entry of mosquitoes and reduce vector biting inside	Vegro Aps, Denmark	2 (2015)[148]
Mosquito population alteration strains for reducing malaria transmission	Gene drive to reduce the mosquito population	Providing a novel, cost–effective biological intervention that will contribute to the elimination of malaria in Africa	Imperial College of Science, Technology and Medicine Target Malaria	1 (2016) [90]

Mosquito population alteration strains for controlling malaria transmission	Gene drive to confer resistance to *Plasmodium*	Prevention transmission and regional, sustainable malaria elimination. It also is expected to contribute to sustainable prevention of re-establishment of malaria	University of California, Irvine Anthony A. James	1 (2016)[90]
Resistance targeting products	Smartpatch® Supplementary netting patch impregnated with non-pyrethroid insecticides placed on top of existing LLINs, transforming them into combination insecticide products to control pyrethroid-resistant mosquitoes	Personal protection against blood meals	EU-FP7 project consortium consisting of 5 organizations	1 (2014)[149]
Insecticide-treated materials for specific at risk-populations	Permethrin-treated blanket (SkinTex™) May only be of use in areas where the vectors are still susceptible to pyrethroids.	Protection of specific populations (potential for use in disaster situations) but do not contribute to community protection	Pulcra Chemicals LLC	1 (2014)[149]

*Step 1: Concept; Step 2: Entomological efficacy; Step 3: Public health/disease impact.

Diagnostics

Applications for malaria diagnostics undergoing WHO prequalification.[151] (information collected March 2018)

PRODUCT	MANUFACTURER
QuickProfile™ Malaria pf/pan Antigen Test Card 71063	LumiQuick Diagnostics, Inc.
QuickProfile™ Malaria pf/pv Antigen Test Card 71050	LumiQuick Diagnostics, Inc.

Field-applicable malaria diagnostic tests and RDTs advancing technology (not WHO prequalified)[65] (information collected March 2018)

Enhanced microscopy/	**Development stage**	**Test (developer)**	**Details[ref]**
Automated microscopy/optical	Launched 2016	Parasight® (Sight Diagnostics Ltd)	Automated microscopy platform[152]
Automated microscopy/optical	Investigational (field trials)	Autoscope (Global Good Fund at Intellectual Ventures)	Artificially intelligent low-cost, portable, automated microscope[153]
Automated microscopy/optical	Investigational (field trials)	xRapid-Malaria (xRapid)	iPhone-based slide analysis system using optical microscopy[154]
Automated microscopy/optical	Investigational (development)	(Indian Institute of Science)	Optofluidic flow analyzer for POC quantitative malaria diagnosis[155, 156]
Hematology analyzer adaptation	**Development stage**	**Test (developer)**	**Details[ref]**
Malaria diagnosis with blood count	Investigational (development)	VCS on Coulter counters (Becton Dickson, University College Hospital London and others)	Volume, conductivity, and scatter (VCS) technology applied to coulter counter with test run concurrently with blood count[157-159]
Laser technology	**Development stage**	**Test (developer)**	**Details[ref]**
Quantitative malaria diagnosis asexual and gametocytes	Investigational (development)	Sysmex XN-30 blue laser technology (Radboud University Medical Center, Nijmegen, Netherlands)	Detected asexual parasites and gametocytes at densities as low as 10 parasites/µL in a volume <100µL of whole blood within 60 seconds without any sample preparation[160]
Non-invasive tests	**Development stage**	**Test (developer)**	**Details[ref]**
Non-invasive RDT (*P. falciparum*)	Launched 2015 (Nigeria)	Urine Malaria Test™ (Fyodor Biotechnologies)	Dipstick assay using immunochromatographic technology to detect P. falciparum HRP2 in urine. No equipment, 20 min read-out[27]
Non-invasive RDT (*P. falciparum* and *P. vivax*)	Investigational (late development)	Urine *P. vivax* test (Fyodor Biotechnologies)	Dipstick assay
Non-invasive RDT (*P. vivax*)	Investigational (development)	Urine *P. vivax* test (Fyodor Biotechnologies)	Dipstick assay

Non-invasive POC (hemozoin)	Investigational (development)	(Rice University BioScience Research Collaborative)	High resolution imaging of hemozoin through skin[161]
Non-invasive POC (hemozoin)	Investigational (development)	Magneto-optical Technology (MOT) (CM Diagnostics)	Magneto-optic test using a noninvasive finger probe based on hemozoin detection. Reader $200, tests $0.25, read out 1 min[162, 163]
Non-invasive RDT	Investigational (research)	Malaria breath test (Washington University, MO, USA)	Six breath biomarkers that successfully classified infection status with 83% accuracy[164]
Next-generation lateral flow RDTs	**Development stage**	**Test (developer)**	**Details[ref]**
High sensitivity RDT (P. falciparum)	Launched 2017	Alere™ Malaria Ag P.f (Alere/FIND/PATH)	Lateral flow assay based on HRP2/3. '10-fold' increase in sensitivity versus current RDTs. 20 min read-out
High sensitivity RDT (P. falciparum)	Investigational (field trials)	(Global Good Fund at Intellectual Ventures/GE)	Lateral flow immunoassay technology plus nanoparticles tagged to key biomarkers for malaria (proteins plus pLDH). Licensed to Access Bio.[165]
High sensitivity RDT (*P. vivax*)	Investigational (development)	(Global Good Fund at Intellectual Ventures/GE)	Lateral flow immunoassay technology plus nanoparticles tagged to key biomarkers for malaria
Ultra-high sensitivity molecular tests **POC**	**Development stage**	**Test (developer)**	**Details[ref]**
Ultra-high sensitivity POC device (PCR)	Investigational (expected 2018)	Q-POC™ (Nanomal consortium) St. George's University The Karolinska Insititute Tubingen University	Hand-held battery operated PCR and sequencing platform using disposable cartridges. The entire process occurs within the cartridge after insertion into the device, read out in 20 minutes[166]
Ultra-high sensitivity POC (MAD-NAAT)	Investigational (development)	MAD-NAAT (University of Washington and others)	2-dimensional paper network (2DPN) for point-of care diagnosis of infectious disease. No training, no equipment paper-based system[167 168-170]
Ultra-high sensitivity molecular tests **field-lab**	**Development stage**	**Test (developer)**	**Details[ref]**
Ultra-high sensitivity field-lab (LAMP)	Launched 2010 Malaria assay 2016	Illumigene® Malaria (US CDC/Meridian Bioscience)	Detects Plasmodium spp; Benchtop instrument plus a kit containing reagents and consumables,[171] read out 40 min
Ultra-high sensitivity field-lab (LAMP)	Launched 2012	Loopamp™ MALARIA Pan or PAN/*Pf* Detection Kit (Eiken Chemical Company Ltd/FIND)	Isothermal DNA amplification platform.[172-176] Requires cold chain for reagents and trained technicians. Equipment cost (>$10k) plus ~UD$5.00 per test
Ultra-high sensitivity field-lab (LAMP)	Launched 2016	HTS plus Loopamp™ (Eiken Chemical Company Ltd/FIND)	High throughput LAMP[177] using HTS plus Loopamp™
Ultra-high sensitivity field-lab (PCR)	Launched 2013	Truelab Uno® (Molbio Diagnostics)	Real-time micro PCR analyzer using Truenat™ microchips

Ultra-high sensitivity field-lab (PCR)	Launched 2016	Truelab-MAG® (Molbio Diagnostics)	Stand-alone, battery-operated sample processing device for automation
Ultra-high sensitivity field-lab (PCR)	Investigational (expected 2017)	DIAGMAL (DIAGMAL Consortium)	Direct on blood PCR system nucleic acid lateral flow immunoassay (NALFIA)[178, 179]
Ultra-high sensitivity field-lab (LAMP)	Unit available, test expected 2017	Alere™ i (Alere)	Isothermal nucleic acid amplification. Cost of unit plus tests $~1.5
Ultra-high sensitivity field-lab (PCR)	Investigational (expected 2018)	Accutas (Aquila Diagnostic Systems Inc.)	Hydrogel-based POC molecular diagnostic system[180]
Ultra-high sensitivity field-lab (LAMP)	Investigational (field trials)	NINA-LAMP (PATH/University of Calgary)	Non-instrumented nucleic acid amplification (NINA) technology[181, 182]
Ultra-high sensitivity field-lab (LAMP)	Investigational (field trials)	RealAmp, (US CDC/QIAGEN)	Portable tube scanner, heating block and fluorescent reader, to perform amplification and provide a result based on fluorescence[183-186]
Ultra-high sensitivity field-lab (LAMP)	Investigational (field trials)	CZC-LAMP (Eiken/Hokkaido University, University of Zambia)	Dried-LAMP system, low sample volume, dry sample, isothermal DNA amplification platform[187]
Ultra-high sensitivity field-lab (PCR)	Investigational (development on hold)	PanNAT® (Micronics)	Fully automated PCR system
Ultra-high sensitivity field-lab (LAMP)	Investigational (development)	Loopamp™ MALARIA *Pv* Detection Kit (Eiken Chemical Company Ltd/FIND	Isothermal DNA amplification platform
Ultra-high sensitivity field-lab (PCR)	Investigational (development)	Scout (Amplino)	Targeting $250 for the device and <$2 per test
Hemozoin-based tests (blood sample)	**Development stage**	**Test (developer)**	**Details[ref]**
High sensitivity POC (hemozoin)	Investigational (field trials)	Rapid Assessment of Malaria (RAM) Device (Disease Diagnostic Group)	Highly portable unit ($2000) using cuvette blood sample ($0.25), simple 1 min read out[188]
High sensitivity POC (hemozoin)	Investigational (field trials)	Magneto-optical Device (MOD) (Hemex)	Portable hemozoin detection system. Diagnoses all species of malaria to 5 parasites/µL, $1 per test read out 1 min[189]
High sensitivity POC (hemozoin)	Investigational (development)	Magneto-optical spectroscopy (MOS) (University of Budapest)	Portable device to detect hemozoin at 0.5 ng/ml[190, 191]
High sensitivity POC (hemozoin)	Investigational (research)	(Singapore University/MIT)	Quantitative and rapid detection of Plasmodium spp.–infected red blood cells (RBCs) by means of magnetic resonance relaxometry[192]

Spectroscopy	Development stage	Test (developer)	Details[ref]
High sensitivity POC (malaria)	Investigational (development)	Attenuated Total Reflection Fourier transform infrared (ATR-FTIR) spectroscopy (Monash University)	Single test to identify malaria parasites (quantitative), blood glucose, and urea levels in whole blood samples from thick blood films on glass slides, minimal training required. Can detect early-stage parasites, read out 'in minutes'[193]
Malaria POC (malaria)	Investigational (development on hold)	Spectraphone (QuantaSpec)	Spectral system to automate the diagnosis of human blood smears[194]
Malaria POC (malaria)	Investigational (development on hold)	SpectraWave/SpectraNet (Claro Scientific)	Spectral system to automate the diagnosis of human blood smears[195, 196]
Multiplex fever tests	**Development stage**	**Test (developer)**	**Details[ref]**
Multiplex fever RDT (Asia-Pacific)	Investigational (development)	DPP® Fever Panel Assay (Chembio Diagnostics, Inc./FIND)	Chromatographic immunoassay technology to identify four Plasmodium species (pLDH/HRP2), dengue, Zika, chikungunya, leptospirosis, *Rickettsia typhi*, *Burkholderia pseudomallei*, and *Orientia tsutsugamushi*[197]
Multiplex fever field-lab (LAMP)	Investigational (development)	LabDisk system (DiscoGnosis Consortium)	POC lab-on-a-disc that tests for several febrile tropical diseases (malaria, dengue, typhoid, pneumonia) at the same time. Player and disks needed, 1 hour read out.[198]
Serology	**Development stage**	**Test (developer)**	**Details[ref]**
Serology	Investigational (research)	(Global Good Fund at Intellectual Ventures)	Licensed to Access Bio[165]
Serology	Investigational (research)	(FIND)	
Resistant parasites	**Development stage**	**Test (developer)**	**Details[ref]**
Drug sensitivity testing POC (PCR)	Investigational (unit expected 2018 assays in development)	Q-POC™ (Nanomal consortium)	Hand-held battery operated PCR and sequencing platform using disposable cartridges. The entire process occurs within the cartridge after insertion into the device, read out in 20 minutes[166]
G6PD tests	**Development stage**	**Test (developer)**	**Details[ref]**
G6PD POC RDT (qualitative)	Launched 2013	CareStart™ G6PD RDT (Access Bio Inc.)	Can be stored and performed at relatively high temperature/humidity. Visual color change read out
G6PD POC (quantitative)	Launched 2014	CareStart™ G6PD Biosensor (Access Bio Inc)	Hand-held device that utilizes strips to provide a quantitative result for G6PD enzymatic activity

G6PD POC (quantitative)	Investigative (expected 2017–2018)	(PATH G6PD Initiative)	G6PD/HbB combo quantitative platform
G6PD POC RDT (qualitative)	Investigative (expected 2017–2018)	(PATH G6PD Initiative)	RDT format with control line
Para-diagnostics	**Development stage**	**Test (developer)**	**Details[ref]**
Drug quality testing system	Launched 2017	Scio (Global Good Fund at Intellectual Ventures)	$250 near-infrared spectrometer to detect falsified or sub-standard artemisinin[199]

All costs are in US dollars.

Drugs

Candidates are those included in the MMV global antimalarial drugs portfolio.[200] **(information collected March 2018)**

PHASE	CANDIDATE(S)	DEVELOPER(S)
Marketed†	Arterolane + piperaquine	Ranbaxy
Marketed†	Artemisinin + naphthoquine	Kunming Pharmaceutical
III	Tafenoquine	GSK, MMV, US Army
III	Artemether sub-lingual spray	Malaria Research Company/SUDA Ltd.
III	Co-trimoxazole	Institute of Tropical Medicine, Belgium
II	Artefenomel (OZ439) + ferroquine	MMV; Sanofi; Monash University; Swiss TPH.
II	KAF156 + lumefantrine	MMV; Novartis
II	KAF156	MMV; Novartis, Swiss TPH.
II	Cipargamin (KAE609)	MMV; Novartis, Swiss TPH
II	DSM265	UT Southwestern; Monash Institute of Pharmaceutical Sciences; University of Washington, MMV; Takeda; Global Health Innovative Technology Fund
II	Fosmidomycin + piperaquine	MMV; Jomaa Pharma
II	Methylene blue + artesunate/amodiaquine	Heidelberg University
II	SAR97276	Sanofi
II	Artemisone	Hong Kong University of Science and Technology
II	AQ-13	Tulane University Health Sciences Center
II	Sevuparin (DF02)	Dilaforette
II	MMV048	MMV and H3D (University of Cape Town's South African Technology Innovation Agency)
II	Ivermectin	Instituto de Salud Tropical Universidad de Navarra
I	P218	MMV and BIOTEC Thailand
I	SJ733	MMV; Eisai Inc.; St. Jude Children's Research Hospital, US.; Global Health Innovative Technology Fund
I	ACT451840	Actelion
I	CDRI 97/78	Ipca

†Not yet reviewed by a stringent regulatory authority.

Vaccines (information collected March 2018)

Candidates listed below are those with active studies.[31]

TYPE/ PHASE	CANDIDATE(S) AGAINST *P. FALCIPARUM*	DEVELOPER(S)
Pre-erythrocytic		
IIb	RTS,S-AS01 delayed fractional third dose	GSK Biologicals
IIb completed	ChAd63/MVA ME-TRAP	Oxford University; Okairòs (acquired by GSK)
Ia	ChAd63/MVA ME-TRAP + Matrix M™	Oxford University; Okairòs (acquired by GSK)
IIb	PfSPZ Vaccine	Sanaria; NAID
Ia	PfCelTOS FMP012	US Army Medical Research and Materiel Command
Ia	ChAd63 CS/MVA CS (CSVAC)	Oxford University; Okairòs (acquired by GSK)
Ia	R21/AS01B	Oxford University
Ia	R21/Matrix-M1	Oxford University
Ia/IIa	R21/ChAd63/MVA ME-TRAP	Oxford University
Blood stage		
IIa/b	GMZ2	EMVI; Statens Serum Institut
Ia/Ib	PfAMA1-DiCo	Institut National de la Santé et de la Recherche Médicale, France; Biomedical Primate Research Centre
Ia/Ib	P27A	Centre Hospitalier Universitaire Vaudois
Ib/IIb	MSP3	African Malaria Network Trust
Ib	SE36	Nobelpharma Co Ltd. ; Osaka University
I/IIa	PfPEBS	Université de Lausanne
Ia	ChAd63 RH5 +/- MVA RH5	Oxford University
Ib	PRIMVAC	Institut National de la Santé et de la Recherche Médicale, France
Ib	PAMVAC	University Hospital Tubingen; University of Copenhagen
Sexual stage		
Ia	Pfs25 VLP	Fraunhofer, USA Center for Molecular Biotechnology
Ia	Pfs25-EPA/Alhydrogel	US National Institute of Allergy and Infectious Diseases (NIAID)
Ia	Pfs230D1M-EPA/Alhydrogel and/or Pfs25-EPA/Alhydrogel	US National Institute of Allergy and Infectious Diseases (NIAID)
Ia	ChAd63 Pfs25-IMX313 + MVA Pfs25-IMX313	Oxford University
P. vivax		
Ia	ChAd63 + MVA PvDBP	Oxford University

TYPE/ PHASE	CANDIDATE(S) AGAINST *P. FALCIPARUM*	DEVELOPER(S)
Other		
IIa	PfSPZ-CVac (PfSPZ Challenge + chloroquine)	Sanaria Inc.; Radboud University Medical Center, The Netherlands
IIa	PfSPZ-CVac (PfSPZ Challenge + chloroquine or + chloroquine/pyrimethamine	National Institute of Allergy and Infectious Diseases (NIAID); Sanaria Inc.
I	PfSPZ-CVAC	National Institute of Allergy and Infectious Diseases (NIAID); Sanaria Inc.
I	GAP 3KO (52-36-/sap1-) *P. falciparum* sporozoites	National Institute of Allergy and Infectious Diseases (NIAID)

ANNEX 3: HEAT MAPS FOR MALARIA HEALTH PRODUCTS IN THE PIPELINE AGAINST POTENTIAL TARGET INDICATIONS

Information on the products in the pipelines is from the WHO Global Observatory for Health R&D. Important note: Mapping is based on whether the product category is one that has been identified as a potentially strategic health product.

Note that it does not necessarily reflect the performance of the actual product as data will need to be generated for every product.

The aim is only to identify gaps where no suitable products are being developed. No endorsement of any product characteristics is implied.

Vector control

PHASE	CATEGORY	PRODUCT	NEW INSECTICIDE CLASSES USED IN COMBINATION IN LLINS AND IRS	EXTENDED DURATION COMBINATION LLINS & IRS	NOVEL VECTOR CONTROL TOOLS*	GENETIC APPROACHES TO VECTOR CONTROL
Interim	LLIN	DawaPlus 2.0®				
Interim	LLIN	DawaPlus 3.0®				
Interim	LLIN	DawaPlus 4.0®				
Interim	LLIN combination*	Interceptor® G2	Partial			
Interim	LLIN	LifeNet®				
Interim	LLIN	MiraNet®				
Interim	LLIN	Olyset Plus®				
Interim	LLIN	Panda Net 2.0®				
Interim	LLIN	PermaNet 3.0®				
Interim	LLIN	Veeralin®				
Interim	LLIN	Yahe® LN				
II-III	IRS	SumiShield®				
I-III	IRS combination*	Fludora Fusion®	Partial			
II-III	IRS new insecticide*	Sylando® 240SC	Partial			
II	LLIN	DuraNet Plus®				

PHASE	CATEGORY	PRODUCT	NEW INSECTICIDE CLASSES USED IN COMBINATION IN LLINS AND IRS	EXTENDED DURATION COMBINATION LLINS & IRS	NOVEL VECTOR CONTROL TOOLS*	GENETIC APPROACHES TO VECTOR CONTROL
II	LLIN	Netprotect®		■		
II	LLIN	ICON MAXX-Net®		■		
I	LLIN	Royal Guard®		■		
I	LLIN	SafeNet LN®		■		
II-III	Larvicide	SumiLarv 2®			■	
Step 3	Lethal house lures	Eaves tubes			■	
Step 3	Spatial repellents	Transfluthrin and metafluthrin passive emanators			■	
Step 3	Vector traps	Adulticidal oviposition traps (ALOT, AGO, TNK)			■	
Step 2	Attract and kill baits	Attractive toxic sugar bait (ATSB)			■	
Step 2	House screening	Pyrethroid- treated netting for full house protection			■	
Step 1	Mosquito population alteration	Gene-drive to reduce mosquito population density			■	■
Step 1	Mosquito population alteration	Gene-drive to confer resistance to *Plasmodium*			■	■
Step 1	Resistance targeting products	Smartpatch®			■	
Step 1	Insecticide-treated materials for specific at risk-populations	Permethrin-treated blanket (SkinTex™)			■	

Interim: interim WHOPES approval.

*Partial: either a new insecticide used alone, or a combination that does not have two new insecticides.

Diagnostics

Note that only those diagnostics that fulfil at least one product criteria are included on here.

Field-lab systems are not included, requiring greater training and resources (electricity), except for multiplex testing. However, in development some of these may become more accessible. Hand held, rapid (~20 min) stand-alone diagnostic devices are included.

L, launched; 3, field trials; 2, developmental; 1 research.

PHASE	CATEGORY	PRODUCT	POC DIAGNOSTICS FOR IDENTIFYING LOW-DENSITY INFECTION	RDTS THAT DETECT AND DIFFERENTIATE ALL *PLASMODIUM* SPECIES	INFECTIVITY/ GAMETOCYTE DIAGNOSTICS	MULTIPLEXED POC TESTS OF ACUTE FEBRILE ILLNESS	NON-INVASIVE/ SELF-ADMINISTERED DIAGNOSTIC TESTS	SENSITIVE AND SPECIFIC POC DIAGNOSTICS FOR *P. VIVAX*	DIAGNOSTICS TO IDENTIFY HYPNOZOITES	AFFORDABLE, SIMPLE AND ACCURATE POC TESTS FOR G6PD DEFICIENCY	POC TESTS FOR PREGNANCY	RDTS THAT DO NOT DEPEND ON PFHRP2/3	POC DIAGNOSTICS TO IDENTIFY DRUG-RESISTANT PARASITES	POC/HEALTH SYSTEM FALSIFIED DRUG SCREENING	HIGH-THROUGHPUT MOSQUITO ASSAYS
L	Non-invasive RDT	Urine Malaria Test™ *Pf*													
L	High sensitivity RDT	Alere™ Malaria Ag P.f													
L	G6PD test	CareStart™ G6PD POC								Partial					
L	G6PD test	CareStart™ G6PD RDT								Partial					
L	Falsified drug detection	Scio													
3	G6PD test	(PATH G6PD Initiative) RDT													
3	G6PD test	(PATH G6PD Initiative) POC													
3	Non-invasive RDT	Urine Malaria Test™ *Pf/Pv*													
3	High sensitivity RDT	Access Bio Pf RDT													
3	Ultra-high sensitivity POC	Q-POC™													
3	High sensitivity POC	Rapid Assessment of Malaria (RAM)													
3	High sensitivity POC	Magneto-optical Device (MOD)													

PHASE	CATEGORY	PRODUCT	POC DIAGNOSTICS FOR IDENTIFYING LOW-DENSITY INFECTION	RDTS THAT DETECT AND DIFFERENTIATE ALL *PLASMODIUM* SPECIES	INFECTIVITY/ GAMETOCYTE DIAGNOSTICS	MULTIPLEXED POC TESTS OF ACUTE FEBRILE ILLNESS	NON-INVASIVE/ SELF-ADMINISTERED DIAGNOSTIC TESTS	SENSITIVE AND SPECIFIC POC DIAGNOSTICS FOR *P. VIVAX*	DIAGNOSTICS TO IDENTIFY HYPNOZOITES	AFFORDABLE, SIMPLE AND ACCURATE POC TESTS FOR G6PD DEFICIENCY	POC TESTS FOR PREGNANCY	RDTS THAT DO NOT DEPEND ON PFHRP2/3	POC DIAGNOSTICS TO IDENTIFY DRUG-RESISTANT PARASITES	POC/HEALTH SYSTEM FALSIFIED DRUG SCREENING	HIGH-THROUGHPUT MOSQUITO ASSAYS
2	Quantitative asexual/sexual	Sysmex XN-30 blue laser technology													
2	Non-invasive RDT	Urine Malaria Test™ *Pv*													
2	Non-invasive POC	Hemozoin (Rice University)		Pan malaria				Pan malaria							
2	Non-invasive POC	Magneto-optical Technology (MOT)		Pan malaria				Pan malaria							
2	High sensitivity RDT	Access Bio Pv RDT													
2	Ultra-high sensitivity POC	MAD-NAAT													
2	High sensitivity POC	Magneto-optical spectroscopy (MOS)		Pan malaria				Pan malaria							
2	High sensitivity POC	ATR-FTIR		Pan malaria				Pan malaria							
2	Multiplex fever RDT	DPP® Fever Panel Assay		Pan malaria				Pan malaria							
2	Multiplex fever POC	LabDisk system (multiplex)													
2	Drug sensitivity POC	Q-POC™ drug sensitivity													
1	Non-invasive POC	Malaria breath test													
1	High sensitivity POC	Magnetic resonance relaxometry (MRR)		Pan malaria				Pan malaria							
1	Serology	Serology													

Drugs

PHASE	PRODUCT	SIMPLIFIED THERAPY AND PROPHYLAXIS (COMBINATIONS)	NEW DRUG CLASSES USED IN COMBINATION THERAPIES FOR MALARIA TREATMENT	NOVEL DRUGS FOR SEVERE MALARIA	NOVEL DRUGS FOR CHEMOPREVENTION	NEW DRUG COMBINATIONS SUITABLE FOR USE IN MDA, ETC.	SIMPLIFIED THERAPY FOR *P. VIVAX* RADICAL CURE	DRUGS FOR *P. VIVAX* RADICAL CURE WITHOUT G6PD LIABILITY	TRANSMISSION-BLOCKING DRUGS	ENDECTOCIDES IN LIVESTOCK AND HUMANS
Marketed†	Arterolane + piperaquine		*							
Marketed†	Artemisinin + naphthoquine		*							
III	Tafenoquine									
III	Artemether sub-lingual spray									
III	Co-trimoxazole				In HIV					
II	Artefenomel (OZ439) + ferroquine									
II	KAF156 + lumefantrine		*							
II	KAF156									
II	Cipargamin (KAE609)									
II	DSM265									
II	Fosmidomycin + piperaquine		*							
II	Methylene blue + artesunate/amodiaquine		*							
II	SAR97276									
II	Artemisone									
II	AQ-13									

PHASE	PRODUCT	SIMPLIFIED THERAPY AND PROPHYLAXIS (COMBINATIONS)	NEW DRUG CLASSES USED IN COMBINATION THERAPIES FOR MALARIA TREATMENT	NOVEL DRUGS FOR SEVERE MALARIA	NOVEL DRUGS FOR CHEMOPREVENTION	NEW DRUG COMBINATIONS SUITABLE FOR USE IN MDA, ETC.	SIMPLIFIED THERAPY FOR *P. VIVAX* RADICAL CURE	DRUGS FOR *P. VIVAX* RADICAL CURE WITHOUT G6PD LIABILITY	TRANSMISSION-BLOCKING DRUGS	ENDECTOCIDES IN LIVESTOCK AND HUMANS
II	Sevuparin (DF02)			■						
II	MMV048	■			■				■	
II	Ivermectin								■	■
I	P218	?			■				■	
I	SJ733	■							■	
I	ACT451840	?								
I	CDRI 97/78	?								
I	N-tert butyl isoquine	?								

*Includes an already approved drug or approved partner drug.

†Not reviewed by a stringent regulatory authority.

Vaccines

PHASE	PRODUCT	PREVENTIVE *P. FALCIPARUM*	TRANSMISSION BLOCKING *P. FALCIPARUM*	*P. VIVAX* PREVENTIVE OR TRANSMISSION BLOCKING
II	RTS,S-AS01 delayed fractional third dose	■		
II	ChAd63/MVA ME-TRAP	■		
II	PfSPZ Vaccine	■		
II	R21/ChAd63/MVA ME-TRAP	■		
II	GMZ2	■		
II	MSP3	■		
II	PfPEBS	■		
I	ChAd63/MVA ME-TRAP + Matrix M™	■		
I	ChAd63 CS/MVA CS	■		
I	PfCelTOS FMP012	■		
I	R21/AS01B	■		
I	R21/Matrix-M1	■		
I	AMA1-DiCo	■		
I	P27A	■		
I	SE36	■		
I	ChAd63 RH5 +/- MVA RH5	■		
I	PRIMVAC (placental malaria)	■		
I	PAMVAC (placental malaria)	■		
I	Pfs25 VLP		■	
I	Pfs25-EPA/Alhydrogel		■	
I	Pfs230D1M-EPA/Alhydrogel and/or Pfs25-EPA/Alhydrogel		■	
I	ChAd63 Pfs25-IMX313 + MVA Pfs25-IMX313		■	
I	ChAd63 + MVA PvDBP			■
I	PfSPZ-CVac (PfSPZ Challenge + chloroquine)	■		
I	PfSPZ-CVac (PfSPZ Challenge + chloroquine or + chloroquine/pyrimethamine	■		
I	PfSPZ-CVAC	■		
I	GAP 3KO (52-36-/sap1-) *P. falciparum* sporozoites	■		

ANNEX 4: SCORING OF POTENTIAL HEALTH PRODUCT SOLUTIONS AGAINST THE PRIORITIZATION CRITERIA.

PRODUCT CLASS	POTENTIAL HEALTH PRODUCT SOLUTION	CHALLENGE SCORE	DEVELOPMENT STAGE	RELATIVE COST	TOTAL	PRIORITY
Vector control	• New insecticide classes used in combination in LLINs and IRS	12	6	3	**21**	Top
	• Extended duration combination LLINs and IRS	9	6	5	**20**	Second
	• Novel vector control tools* including endectosides and genetic	21	6	3	**30**	Top
	•					
Diagnostics	• POC diagnostics for identifying low-density infection	9	6	5	**20**	Second
	• RDTs that detect and differentiate all *Plasmodium* species	6	6	5	**17**	Second
	• Infectivity/gametocyte diagnostics	6	3	5	**14**	Third
	• Multiplexed POC tests of acute febrile illness	6	6	5	**17**	Second
	• Non-invasive/ self-administered diagnostic tests	6	6	5	**17**	Second
	• Sensitive and specific POC diagnostics for *P. vivax*	6	6	5	**17**	Second
	• Diagnostics to identify hypnozoites	9	3	5	**17**	Second
	• Affordable, simple and accurate POC tests for G6PD deficiency	6	6	5	**17**	Second
	•	6	3	5	**14**	Third
	• Stable, valid, specific and sensitive RDTs that do not depend on Pfhrp2/3	6	3	5	**14**	Third
	• POC diagnostics to identify drug-resistant parasites	9	6	5	**20**	Second
	• POC/health system falsified drug screening	9	6	5	**20**	Second
	• High-throughput mosquito assays	15	3	3	**21**	Top
Drugs	• Simplified therapy and prophylaxis	18	6	2	**23**	Top
	• New drug classes used in combination therapies for malaria treatment	6	6	2	**14**	Third
	• Novel drugs for severe malaria	6	6	2	**14**	Third
	• Novel drugs for chemoprevention	12	6	2	**20**	Second
	• New drug combinations suitable for use in MDA, etc.	6	6	2	**14**	Third
	• Simplified therapy for *P. vivax* radical cure	12	6	2	**20**	Second
	• Drugs for *P. vivax* radical cure without G6PD liability	12	3	2	**17**	Second
	• Transmission-blocking drugs	18	6	2	**26**	Top
	•					
Vaccines	• Preventive vaccines *P. falciparum*	18	6	2	**26**	Top
	• Transmission-blocking vaccines *P. falciparum*	18	6	2	**26**	Top
	• Preventive vaccines *P. vivax*	21	3	2	**26**	Top
	• Transmission-blocking vaccines *P. vivax*	21	3	2	**26**	Top

ANNEX 5: HEALTH PRODUCT R&D PRIORITIES VERSUS THE CURRENT PIPELINE IN MALARIA.

Information on the products in the pipelines is from the WHO Global Observatory for Health R&D

Late-stage development: Phase III drugs and vaccines, step 3 vector control strategies and launched/stage 3 advanced diagnostics.

Mid-development: Phase II drugs and vaccines, step 2 vector control strategies and stage 2 advanced diagnostics.

Early development: Phase I drugs and vaccines, step 1 vector control strategies and stage 1 advanced diagnostics.

PRIORITY	PRODUCT CLASS	PRODUCT SOLUTION	PIPELINE PRODUCTS WITH POTENTIAL TO MEET CRITERIA AT LEAST PARTIALLY		
			LATE-STAGE DEVELOPMENT	MID-DEVELOPMENT	EARLY DEVELOPMENT
Top	Vector control	New insecticide classes used in combination in LLINs and IRS	• LLIN: Interceptor® G2* • IRS: Fludora Fusion®*; Sylando® 240SC*		
		Novel vector control tools including endectocides and genetic approaches	• Larvicide: SumiLarv 2® • Eaves tubes • Transfluthrin and metafluthrin passive emanators • Adulticidal oviposition traps (ALOT, AGO, TNK)	• Attractive toxic sugar bait (ATSB) • Pyrethroid- treated netting for full house protection • Ivermectin	• Smartpatch® • Permethrin-treated blanket (SkinTex™) • Gene-drive to reduce mosquito population density • Gene-drive to confer resistance to *Plasmodium*
					•
	Diagnostics	High-throughput mosquito assays			
	Drugs	Simplified therapy and prophylaxis		• Artefenomel (OZ439) + ferroquine • KAF156 + lumefantrine • Possible combinations of: KAF156; Cipargamin (KAE609); DSM265; SAR97276; AQ-13; MMV048	• SJ733
		Transmission-blocking drugs		• Artefenomel (OZ439) + ferroquine • KAF156 + lumefantrine • Possible combinations of: KAF156; Cipargamin (KAE609); MMV048 • Methylene blue + artesunate/amodiaquine	• P218 • SJ733

PRIORITY	PRODUCT CLASS	PRODUCT SOLUTION	PIPELINE PRODUCTS WITH POTENTIAL TO MEET CRITERIA AT LEAST PARTIALLY		
			LATE-STAGE DEVELOPMENT	MID-DEVELOPMENT	EARLY DEVELOPMENT
	Vaccines	Preventive vaccines *P. falciparum*	• RTS,S	• RTS,S fractionated dose • ChAd63/MVA ME-TRAP • PfSPZ Vaccine • R21/ChAd63/MVA ME-TRAP • GMZ2 • MSP3 • PfPEBS	• ChAd63/MVA ME-TRAP + Matrix M™ • ChAd63 CS/MVA CS • PfCelTOS FMP012 • R21/AS01B • R21/Matrix-M1 • AMA1-DiCo • P27A • SE36 • ChAd63 RH5 +/- MVA RH5 • PRIMVAC (placental malaria) • PAMVAC (placental malaria) • PfSPZ-CVac • GAP 3KO (52-36-/sap1-) *P. falciparum* sporozoites
		Transmission-blocking vaccines *P. falciparum*			• Pfs25 VLP • Pfs25-EPA/Alhydrogel • Pfs230D1M-EPA/Alhydrogel and/or Pfs25-EPA/Alhydrogel • ChAd63 Pfs25-IMX313 + MVA Pfs25-IMX313
		Preventive vaccines *P. vivax*			• ChAd63 + MVA PvDBP
		Transmission-blocking vaccines *P. vivax*			
Second	Vector control	Extended duration combination LLINs and IRS	• LLINs: DawaPlus 2.0®; DawaPlus 3.0®; DawaPlus 4.0®; LifeNet®; MiraNet®; Olyset Plus®; Panda Net 2.0®; PermaNet 3.0®; Veeralin®; Yahe® LN; • IRS: SumiShield®	• LLIN: DuraNet Plus®; Netprotect®; ICON MAXX-Net®;	• LLIN: Royal Guard®; SafeNet LN®
	Diagnostics	POC diagnostics for identifying low-density infection	• Alere™ Malaria Ag P.f • Access Bio Pf RDT • Q-POC™ • Rapid Assessment of Malaria (RAM) • Magneto-optical Device (MOD)	• Sysmex XN-30 blue laser technology • Access Bio Pv RDT • MAD-NAAT • Magneto-optical spectroscopy (MOS) • ATR-FTIR	• Magnetic resonance relaxometry (MRR)
		RDTs that detect and differentiate all *Plasmodium* species	• Q-POC™ • Rapid Assessment of Malaria (RAM) • Magneto-optical Device (MOD)	• MAD-NAAT	
		Multiplexed POC tests of acute febrile illness		• DPP® Fever Panel Assay (Asia only) • LabDisk system (multiplex)	