MALARIA DISEASE NARRATIVE

DECEMBER 2019

Unitaid
Innovation in Global Health

EXECUTIVE SUMMARY

This *Disease Narrative for Malaria* provides an overview of Unitaid's strategic approach to maximize the effectiveness of its contribution to the malaria response. The scope of the report is focused on malaria, but also includes integrated approaches to diagnosing and treating key childhood illnesses. Through a systematic analysis that included consultation with key stakeholders, short- and longer-term opportunities have been identified for Unitaid to actively explore to support accelerated progress towards achieving the global malaria targets.

Malaria remains a substantial global health problem that adversely affects health and development in many parts of the world, especially amongst vulnerable groups. While a substantial reduction in malaria cases and deaths took place between 2000 and 2015, progress has stalled in recent years. The World Health Organization (WHO) has warned that case incidence and mortality targets set for 2020 in the WHO Global Technical Strategy for Malaria will not be achieved on the current trajectory. Intensified efforts are needed to catalyze future progress, particularly in countries where the malaria burden remains high. In parallel, further efforts are also needed to continue to move low-burden countries towards elimination. In both contexts, innovative tools and approaches will play an important role.

Additional efforts are needed to address access barriers to malaria tools, and to support innovations

A range of challenges threaten the achievement of the global goals for malaria. Existing malaria diagnosis, prevention and treatment tools do not reach all people that require them. Insecticide-treated mosquito nets and indoor residual spraying uptake remains suboptimal in many settings, despite proven public health effectiveness. Despite progress in uptake of WHO recommended malaria chemoprevention strategies, many people who are at-risk and vulnerable to malaria transmission still do not have access. Multiple factors limit access to quality case management, including a lack of care-seeking and challenges with private sector delivery channels, such as the proliferation of substandard and falsified medicines in the private sector. Slow uptake of these WHO recommendations, as well as other initiatives such as Integrated Management of Childhood Illness and Integrated Community Case Management, are leaving the most vulnerable groups at risk.

At the same time, existing tools are also often inadequate to address the current and emerging challenges that span the malaria landscape. Challenges such as insecticide resistance to vector control products, limited effectiveness of diagnostics in specific settings, and the growing threat of drug resistance highlight the need for new tools for the malaria response.

Unitaid works closely with partners to overcome challenges in the malaria response

The malaria response benefits from a rich architecture of global, regional and country partners, many of whom play multiple complementary roles. Within a dynamic partner landscape, Unitaid has a clear role in supporting the use of innovative tools and approaches by advancing R&D and innovation, supporting normative guidance and

product quality, and catalyzing product introduction and addressing delivery challenges. Unitaid works in close cooperation with partners at different stages of the value chain to ensure that innovative tools are brought to market and scaled-up.

Unitaid is responding to key malaria challenges through a rich portfolio of projects

Unitaid has been actively expanding its malaria portfolio, which has tripled in value in the past two years. Unitaid's investments span vector control, chemoprevention, vaccines and case management, and treatment, and also includes a range of cross-cutting projects.

In vector control, Unitaid is working with partners to ensure early access to next-generation insecticides and long-lasting insecticide-treated nets, as well as supporting entirely new tools through the pipeline, such as spatial repellants and endectocides. Building on recent efforts in seasonal malaria chemoprevention, Unitaid is now working to catalyze access to preventive chemotherapy for pregnant women and has planned investments in long-acting chemoprevention regimens. Unitaid is also supporting the pilot implementation of RTS,S, the first vaccine to show partial protection against *P. falciparum* malaria in young children.

In case management, Unitaid is working to address supply-side challenges and implementation barriers to the uptake of medicines for severe malaria. As part of efforts to address malaria in the context of childhood fever management more broadly, new investments are aimed at accelerating the availability, adoption and scale-up of improved tools to identify severe disease, specifically pulse oximeters and dual/multimodal devices adapted for point-of care use in low- and middle- income countries (LMICs). Unitaid is also working on better tools for the diagnosis and treatment of *P. vivax* malaria, and plans to have investments in this area in the near future.

As its malaria portfolio matures, Unitaid will monitor progress and periodically re-evaluate the need for additional investments towards achieving maximum impact.

The malaria pipeline holds a range of promising new tools

In the short-term, new tools for the management of *P. vivax* malaria have significant potential and will be targeted under Unitaid's investments in this area. New rapid diagnostic tests that can address the emerging issue of gene deletions in malaria parasites are another important tool to monitor. By 2025, the pipeline is likely to yield new drugs to address artemisinin resistance which could also be available as a single dose. New vector control tools could include insecticide-treated nets and indoor residual sprays with new active ingredients, as well as entirely new vector control product classes such as spatial repellents, attractive toxic sugar baits and endectocides. Additional diagnostic methods, such as urine- and saliva-based rapid diagnostic tests are also in the pipeline. Beyond 2025, self-propagating gene drive technologies to control malaria-transmitting mosquitos, and new vaccines that offer a high degree of protection, could hold significant potential. Unitaid is already investing in the late-stage development of several new malaria tools and will continue to monitor research and development pipelines to identify where catalytic interventions could accelerate access to new, game-changing products.

Unitaid has identified opportunities to address key challenges in the short term

In the near-term, new tools and approaches are needed to reduce coverage gaps of existing tools and overcome key challenges such as insecticide and drug resistance. There is also a need for better evidence to support intervention prioritization and decision making. As part of the Disease Narrative update, Unitaid has identified short-term opportunities which are high priorities for further investigation over the next 6-12 months.

Malaria chemoprevention in high-risk groups is cost-effective and yields high impact, and as such has been identified as an important strategy to accelerate progress in high burden settings. Unitaid's investment in seasonal malaria chemoprevention in children played a critical role in supporting the early adoption of this intervention. A further grant is now underway to catalyze access to preventive chemotherapy in pregnant women. Unitaid has also played an important role on the supply side, supporting the availability of child-friendly formulations, a diversified supplier base, and adapted packaging. Grant development is now underway to support long-acting chemoprevention drugs. Building on this substantial footprint, Unitaid has begun exploring opportunities to support the adoption of Intermittent preventive treatment in infants (IPTi) at scale. These could include creating a proof of concept for scaled delivery approaches, and/or addressing supply side challenges to ensure availability of quality-assured infant formulations.

Towards a more integrated approach for pregnant women and newborns, opportunities could also be considered to support new tools that enable optimal case management in pregnancy, such as higher sensitivity RDTs to better detect malaria in pregnant women. Unitaid will also look at broader opportunities to integrate the management of malaria with other coinfections, such as alternative drug regimens for pregnant women with malaria who are also living with HIV. By addressing the lack of adoption of chemoprevention approaches, and the limitations of current tools that prevent optimal case management in pregnancy, Unitaid can expand its current efforts focused on decreasing the malaria burden in high-risk groups.

Additional opportunities may exist for Unitaid to support the *High burden to high impact* (HBHI) strategy, that focuses on targeted responses in countries that experience a disproportionate burden of global malaria cases. While many of Unitaid's current grants are of direct relevance to high burden settings, additional efforts could include testing combinations of tools to identify optimal packages and approaches in target countries. In parallel, enhanced surveillance and data collection innovations to assess the ideal mix of interventions in different settings would also support the implementation of the HBHI strategy. Unitaid is investigating opportunities in this area, as well as opportunities to address the low quality and availability of current malaria products, and the ongoing issue of substandard and falsified malaria products on the market.

In addition to the above, several additional technologies currently under development were identified for ongoing monitoring. These include new diagnostics for malaria and fever, single-dose treatments not based on artemisinin, and sterile insect and self-limiting mosquito technologies. Unitaid will continue to monitor these and other innovations to assess potential future opportunities to catalyze availability and early access.

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ABBREVIATIONS

AfIs	Areas for Intervention
AI	artificial intelligence
ALMA	The African Leaders Malaria Alliance
AMFm	Affordable Medicines Facility for Malaria
APLMA	Asia Pacific Leaders Malaria Alliance
AQ	amodiaquine
ASEAN	Association of Southeast Asian Nations
BMGF	Bill & Melinda Gates Foundation
DFAT	Department of Foreign Affairs and Trade
DHA-PPQ	dihydroartemisinin-piperaquine
EPI	Expanded Programme on Immunization
GM	genetically modified
GPIRM	Global plan for insecticide resistance management in malaria vectors
GTS	Global Technical Strategy
HBHI	High burden to high impact: a targeted malaria response
HRP	histidine-rich protein
iCCM	integrated community case management
IMCI	integrated management of childhood illness
IPTi	Intermittent preventive treatment in infants
IPTp	Intermittent preventive treatment in pregnancy
IRM	insecticide resistance management
IRS	indoor residual spraying
ITN	insecticide-treated mosquito nets
LMICs	low- and middle-income countries
MMV	Medicines for Malaria Venture
MVIP	Malaria Vaccine Implementation Programme
NGO	non-government organization
P. falciparum	Plasmodium falciparum
pfhrp2	*P. falciparum* histidine-rich protein 2
Pfhrp3	*P. falciparum* histidine-rich protein 3
P. vivax	Plasmodium vivax
PDPs	Product Development Partnerships
pLDH	plasmodium lactate dehydrogenase
PMI	President's Malaria Initiative
QA	quality assurance
R&D	research and development
RAS	The RBM Partnership to End Malaria
RBM	The Roll Back Malaria Partnership to End Malaria
RDT	rapid diagnostic test
SaME	Sahel Malaria Elimination Initiative
SF	substandard or falsified
SMC	Seasonal Malaria Chemoprevention
SP	sulfadoxine-pyrimethamine
UNICEF	The United Nations Children's Fund
VCAP	Vector Control Platform for Asia Pacific
WHO	World Health Organization
WHO PQP	WHO Prequalification Program

1 ANALYSIS OF THE DISEASE CONTEXT

1.1 *Disease Narrative* introduction

This *Disease Narrative for Malaria* provides an overview of Unitaid's strategic approach to maximize effectiveness of malaria interventions in the context of integrated management of childhood fevers. This document builds on Unitaid's 2015 *Disease Narrative for Malaria and Areas for Intervention* by providing updates on global progress against the goals set out in the *Global Technical Strategy for Malaria 2016 - 2030*, challenges impeding the malaria response, and Unitaid's activities in malaria. The report identifies current challenge areas where Unitaid may be well-suited to influence, and opportunities in the short- and long-term that Unitaid could consider accelerating progress towards achieving the global malaria targets. The scope of challenges assessed, and opportunities identified, is focused on malaria but also includes integrated approaches that aim to improve child health outcomes through holistic efforts to diagnose and treat key childhood illnesses (including malaria).

1.2 Disease introduction

Malaria is a curable, but life-threatening disease that causes acute febrile illness. It is transmitted to people through the bites of *Anopheles* mosquitoes, called malaria vectors, infected with *Plasmodium* parasites. Among the different species of parasites that cause malaria in humans, *Plasmodium falciparum* (*P. falciparum*) is the most prevalent; in 2017 it accounted for 99.7% of malaria cases in the World Health Organization (WHO) African Region.[1] *P. falciparum* also accounts for most of malaria deaths. *Plasmodium vivax (P. vivax)*, the second most common species of malaria parasite, differs to *P. falciparum* in that it survives in the liver for long periods, causing relapse several months to years after infection. *P. vivax* has the widest geographical distribution of all human malarias, and accounts for about half of all malaria cases outside sub-Saharan Africa.[2] *P. vivax* is also the dominant species of malaria in many countries nearing elimination, accounting for more than 70% of total cases in countries with less than 5,000 malaria cases/year.[3]

In 2017, there were an estimated 219 million cases of malaria globally, 92% of which occurred in sub-Saharan Africa. Despite a substantial reduction in malaria cases and deaths since 2000, malaria remains a substantial global health problem that adversely affects health and development in many parts of the world especially amongst vulnerable populations. The scale-up of effective malaria tools (e.g. prevention with insecticide-treated mosquito nets (ITN), treatment using artemisinin-based combination therapies (ACTs)), alongside an increase in financial investment, has been key to reducing malaria cases and deaths, but gaps and challenges persist (see Section 2).

In areas of high malaria transmission, high-risk populations include pregnant women whose immunity to malaria is decreased by pregnancy, and young children who have not yet developed partial immunity.[4] Of the approximately 435,000 malaria deaths in 2017, 61% occurred in children under five years old. Malaria infection can also cause or worsen anaemia which can be life-threatening, particularly among vulnerable populations such as pregnant women and children aged under five years. Individuals who are anaemic are also at a greater risk of mortality, including from malaria.[5]

The clinical features of malaria are variable and non-specific, and include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain. Many of these features are common to malaria, pneumonia and diarrhea, which together account for over 50% of postnatal mortality in children under five. Malaria and pneumonia are febrile illnesses, and common causes of diarrhoea in children (e.g. rotavirus, e*scherichia coli*) can also include fever. In addition, malnutrition contributes to almost half of all deaths in children under five.[6] Integrated approaches that aim to improve child health outcomes through holistic efforts to diagnose and treat key childhood illnesses (including malaria), are recommended by WHO and Unicef and are included in the scope of this narrative.

1.3 Global goals and current status

Between 2000 – 2015, the global response recorded unprecedented progress in the fight against malaria. Cases of malaria declined by 41% globally, malaria deaths declined by 62%, and 17 countries eliminated malaria with eight of these countries certified as malaria free from the World Health Organization (WHO).[7] To achieve these results, considerable efforts were made to scale-up access to high-impact, cost-effective interventions largely driven by an increase in financial investments.

In 2015 the World Health Assembly adopted a new Global Technical Strategy (GTS) for Malaria which aims to leverage past gains and accelerate progress over 15 years. The GTS sets out global targets for 2030 that all malaria partners – international agencies, non-government organizations (NGOs), the private sector, academics and others – can collectively work towards (FIGURE 1). It also provides a technical framework for countries and partners, emphasizing the importance of scaling up malaria responses and moving towards elimination. The framework is based on three pillars: 1) Ensure universal access to malaria prevention, diagnosis and treatment; 2) Accelerate efforts towards elimination of malaria and attainment of malaria-free status; 3) Transform malaria surveillance into a core intervention. All three pillars are underpinned by two supporting elements, namely harnessing innovation and expanding research, and strengthening the enabling environment.

FIGURE 1: GTS milestones and targets to accelerate progress

Vision – a world free of malaria

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 countries that are malaria-free	Re-establishment prevented	Re-establishment prevented	Re-establishment prevented

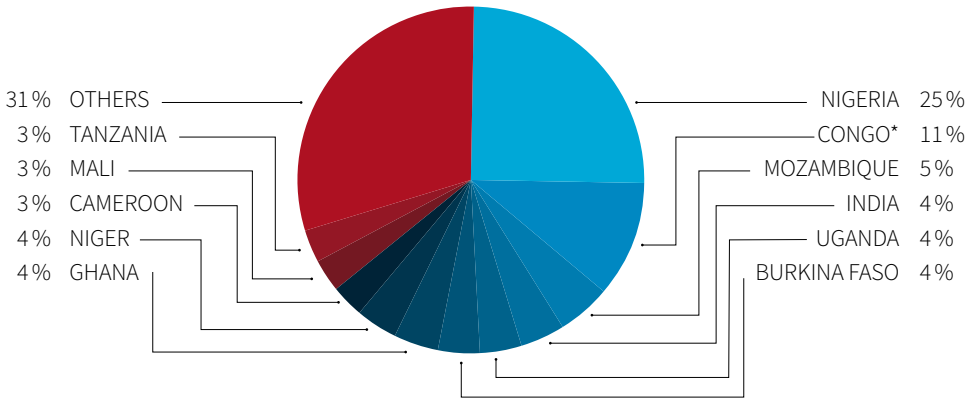
Source: WHO Global Technical Strategy for Malaria

The latest World Malaria Report highlights that the malaria community is on track for achieving the 2020 elimination milestone of the GTS[8]. Since 2015, the number of countries achieving elimination has increased to 28 in 2019, with several other countries recently requesting WHO certification.[9] However, progress towards reducing malaria cases and deaths has stalled, and the targeted reductions in case incidence and mortality will not be achieved under the current trajectory. Data for the period 2015 – 2017 highlight that no significant progress was made in reducing global malaria cases during this time.[10] Malaria mortality rates continue to decline; however, the rate of reduction has also slowed since 2015.

Eleven countries - ten countries in sub-Saharan Africa and India - together account for almost 70% of the global malaria burden (219 million cases worldwide in 2017) (FIGURE 2). Across the 10 highest burden countries in Africa, there was an overall increase in reported cases in 2017 compared with 2016. Nigeria, Madagascar and the Democratic Republic of the Congo had the highest estimated increases in cases in 2017, in each case greater than half a million cases. In contrast, India reported more than 3 million fewer cases (a 24% reduction) in the same period.[11]

Intensified efforts are needed to catalyze future progress, particularly in countries where the malaria burden remains high. In parallel, further efforts are also needed to continue to move low-burden countries towards elimination. In both contexts, innovative tools and approaches will play an important role. Two recent reports examining the potential for malaria eradication have emphasized the important role of innovative tools to achieve this goal[12,13].

FIGURE 2: Estimated share of total malaria cases in the 11 highest burden countries, 2017



*Democratic Republic of the Congo

Source: Adapted from High burden to high Impact: A targeted malaria response, World Health Organization and RBM Partnership to End Malaria, 2018

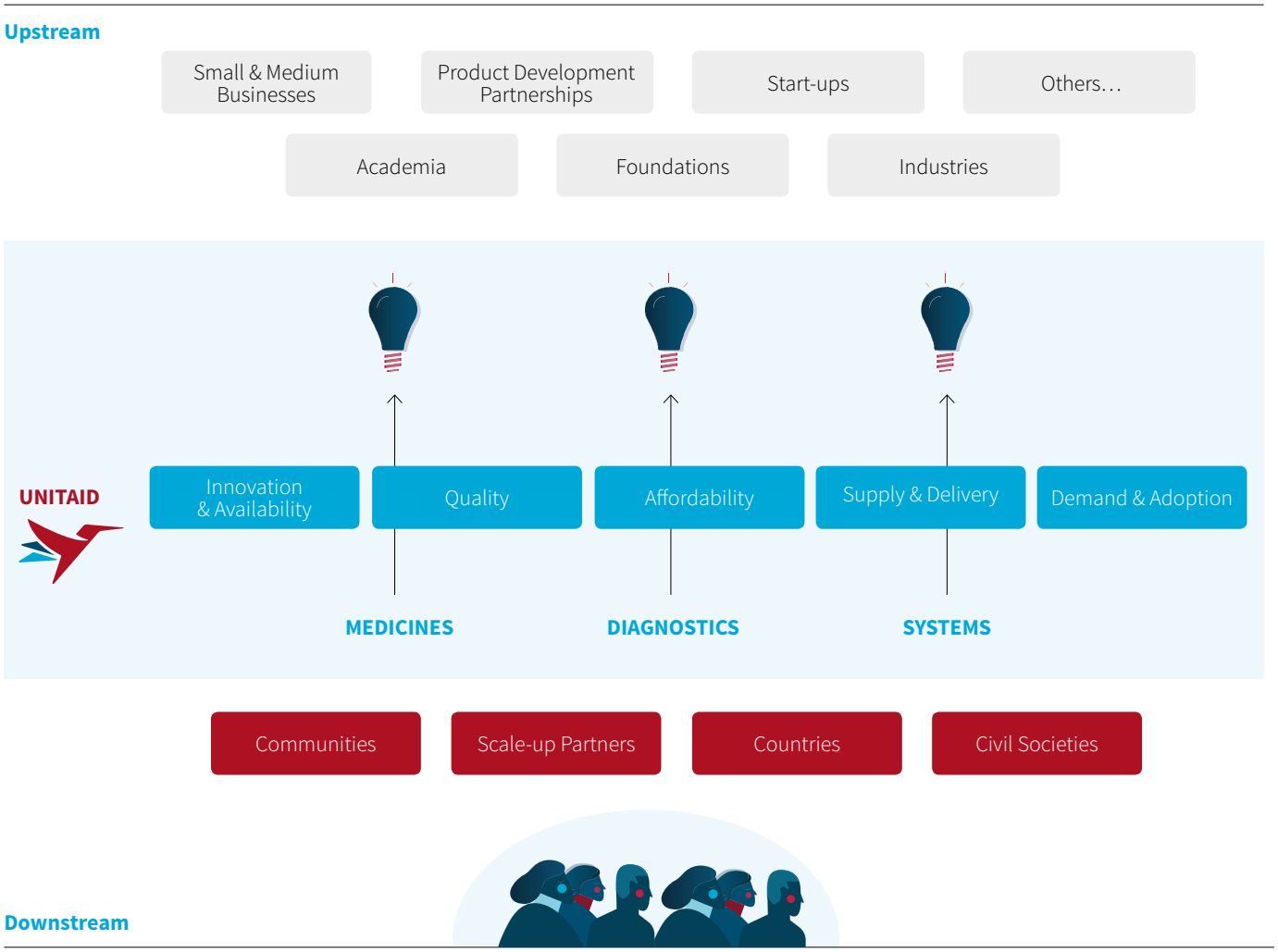
1.4 Collective action and the partner landscape

The malaria response benefits from a rich architecture of global, regional and country partners, many of whom play multiple complementary roles. Partners focused on upstream innovation include the Bill & Melinda Gates Foundation (BMGF), other private foundations such as the Institut Pasteur, the US Government (Center for Disease Control, National Institute of Allergy and Infectious Diseases) and other funders/bilaterals. Several Product Development Partnerships (PDPs) also work to ensure there is a rich pipeline of malaria tools e.g. Medicines for Malaria Venture (MMV), IVCC and FIND. NGOs, private industry and academia also have a critical role to play in upstream innovation and research and development (R&D). Further downstream, multiple players are working on normative guidance (WHO), quality assurance (WHO, FIND), and advocacy (The RBM Partnership to

End Malaria (RBM), African Leaders Malaria Alliance (ALMA), Asia Pacific Leaders Malaria Alliance (APLMA), civil society). With respect to downstream delivery and scale-up, national malaria control programs are at the heart of the response, supported by a range of partners involved in all aspects of delivery including procurement, programme implementation, and research. This includes not only large funders of malaria programs such as the Global Fund to Fight Aids, Tuberculosis and Malaria (Global Fund), the President's Malaria Initiative (PMI) and the UK Department for International Development, but also selected activities of partners such as WHO and BMGF, and a wide range of international, national and local NGOs and civil society organizations.

Unitaid works with partners at all stages of the value chain, connecting upstream partners such as academia and PDPs with downstream implementation partners such as countries and procurement agencies (FIGURE 3). Within a dynamic partner landscape, Unitaid has a clear role in supporting the use of innovation tools and approaches by advancing R&D and innovation, supporting normative guidance and product quality, and catalyzing product introduction and addressing delivery challenges.

FIGURE 3: Unitaid's role in global health – connecting the upstream with the downstream to unlock access



In support of collective action and to guide partner activity, several global initiatives have been developed to accelerate progress towards the goals set out in the GTS. In 2016, WHO launched the E-2020 initiative by identifying 21 countries spanning 5 regions that could defeat malaria by 2020. Through E-2020, these focus countries have scaled up their elimination efforts, with a view to "getting to zero" within the 2020 timeline. Regional specific elimination responses have also been established including the Elimination Eight which is an effort by eight countries in the southern African region to foster regional collaboration, and the Sahel Malaria Elimination Initiative (SaME), a platform for co-ordination on malaria elimination between eight countries in the Sahel region.

To intensify efforts in high burden countries, in November 2018 WHO and the Roll Back Malaria (RBM) partnership launched a new country-led approach: High burden to high impact: a targeted malaria response to accelerate progress in high burden countries (HBHI).[14] The approach is anchored by 4 pillars for success: 1) translation of political commitments into resources and tangible actions; 2) strategic use of data to pinpoint where to deploy the most effective malaria control tools for maximum impact; 3) improved and targeted global policies and strategies to support countries in delivering an optimal mix of tools for its unique setting; and 4) coordinated country responses that align partners and engage sectors beyond health.[15] The 11 countries that currently carry the highest burden of malaria are early adopters of this approach.

2 INTERVENTION COVERAGE, KEY CHALLENGES AND STATUS OF THE RESPONSE

As a starting point for identifying potential future Areas for Intervention (AfIs), Unitaid has compiled an inventory of challenges that threaten the achievement of the global goals for malaria (FIGURE 4). Beginning with the challenge inventory developed for the 2015 Malaria Disease Narrative, updates were considered based on consultation with partners and input from multiple sources. Many challenges are interlinked, and there may be multiple root causes contributing to a single challenge. In some cases, similar or related challenges have been merged to reach an inventory that can be used as a workable framework for considering corresponding opportunities.

This inventory of challenges has been grouped according to three key categories:

- **Prevention**: challenges relating to vector control strategies and preventive therapies, the latter of which includes both preventive chemotherapy and vaccines

- **Case management**: challenges relating specifically to either the diagnosis or treatment of malaria, or to integrated approaches to fever case management

- **Cross-cutting:** Challenges which affect the disease response as whole. This includes infrastructure challenges, such as weak health systems, as well as social and environmental challenges, such as social unrest or climate change. Given the focus of Unitaid on commodities, some cross-cutting challenges may be partially or indirectly addressed through a Unitaid intervention.

FIGURE 4: Overview of key challenges threatening the malaria response

KEY CHALLENGES TO OPPORTUNITIES

Prevention

VECTOR CONTROL (VC)	Moderate lifespan & Implementation challenges with ITNs/ IRS	Moderate efficacy of tools for indoor biting	Complexity of insecticide resistance mgmt	Slow uptake of new VC products	Lack of tools to address key challenges	Limited pre/ post market QC systems	Lack of data for targeting interventions
PREVENTIVE TREATMENT	Low demand & adoption of chemoprevention	Expansion to greater target populations lacks evidence	Poor quality SP and low supply of quality-assured SP	No alternative regimens to address resistance	RTS,S/AS01 partial efficacy & complex dosing	No highly effective vaccine	

Case management

TREATMENT	Limited tools to manage biological threats & to support adherence	Proliferation of substandard/ falsified products and limited QC measures	Poor quality case mgmt in private sector	Poor adoption of IMCI/iCCM; limited tools for inte-grated mgmt of childhood fever	Current tools limit optimal case mgmt. in pregnancy	Low adherence to guidance on severe malaria		Lack of operational evidence on elimination strategies	Complexity of *P. vivax* case mgmt. & limitations of current tools
DIAGNOSTICS						Limitations of RDTs & microscopy	RDT supply challenges		

Cross-cutting

DELIVERY/ IMPLEMENTATION	Weak surveillance systems	Lack of data for decision making to deploy new tools	Weak health systems: HR, supply chain, etc.	Lack of financing, political commitment	Challenges of regional collaboration	Limited delivery for the prevention and treatment of malaria related anaemia
SOCIAL / ENVIRON./ POLITICAL	Social unrest & conflicts, humanitarian disasters	Food security	Climate and environmental change	Population growth		Disproportionate malaria in vulnerable and hard-to-reach groups

Challenges to continue monitoring Unitaid past and active grants

The following sections summarise the key challenges in each category, with more detailed descriptions provided in the Annex 1. As context, prevention and case management challenges are preceded by an overview of recommended interventions and current coverage status. These categories also include a summary of the global response and in particular, relevant Unitaid interventions.

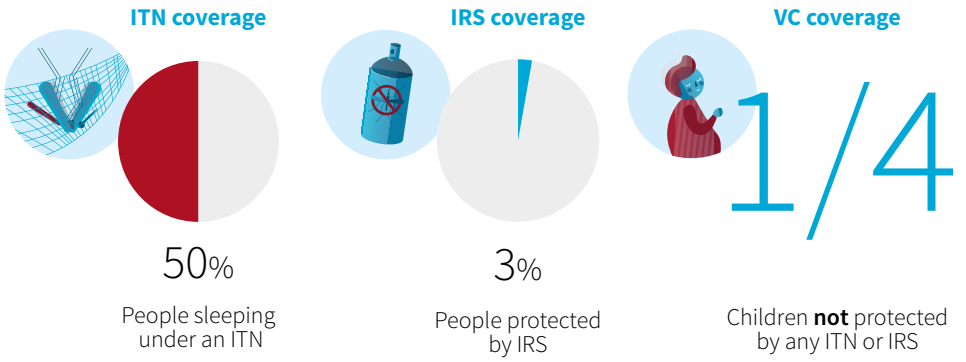
2.1 Prevention

2.1.1 Vector control

Overview of existing tools and coverage gaps

Vector control is a key tool for preventing malaria as part of broader control and elimination efforts. The two, core, broadly applicable vector control measures are insecticide-treated mosquito nets (ITN) and indoor residual spraying (IRS). Their public health impact has been proven, especially for ITNs which, in areas with high coverage rates, can reduce malaria cases by 40–60%.[16] Despite this, coverage of ITNs varies considerably between countries and by geographic area, with some countries/areas having very low coverage while others achieving high levels of coverage e.g. in sub-Saharan Africa in 2017, only half the people at risk of malaria (50%) slept under an ITN, and around 40% of households have at least one ITN for every two people.[17] Coverage of IRS is significantly lower than that of ITNs and is declining: in 2017, only 3% of the global population at risk was protected by IRS, decreasing from more than 5% in 2010.[18] Overall, approximately one in four children in sub-Saharan Africa are still living in a household without any protection from an ITN or from IRS.[19]

FIGURE 5: ITN and IRS coverage gaps in 2017



Adapted from *World Malaria Report 2018*, World Health Organization 2018

Key challenges

There are several challenges limiting access to ITNs and IRS and limiting the protection provided from these tools. Among these are the **moderate lifespan and implementation challenges with ITNs and IRS.** Both tools require regular and repeated implementation campaigns due to their moderate lifespans. In real-world settings, appropriate use and the durability of ITN's varies and IRS campaigns are expensive and complex to implement. Even when these tools are deployed and used correctly, they only have moderate efficacy meaning that they only provide partial protection to people at risk. Despite the **moderate efficacy of tools for indoor biting**, the impact of ITNs and IRS on mortality across sub-Saharan Africa has been marked. But, this challenge is still a concern especially in settings with high pyrethroid insecticide resistance and new strategies are needed to ensure continued protection against indoor biting.[20] Resistance to all four classes of insecticides used for public health is widespread. To address insecticide resistance, several strategies include rotating insecticides used in ITNs and IRS, using insecticide combinations or mosaic spraying contributes. The coordination and management needs of these strategies contribute to the **complexity of insecticide resistance management** (IRM). A further challenge for implementing IRM is that it is unknown whether these strategies are more effective than sequential use of insecticides.

Innovative products that have recently been evaluated and recommended for malaria control (e.g. ITNs with insecticide combinations) can help address some of the challenges for existing tools. However, there is a **slow uptake of new vector control products** due to their higher-price; a lack of impact data; and limited availability of funds, that are often already insufficient to maintain/achieve high coverage of existing, lower-cost tools. At the same time, there is also a **lack of tools to address key challenges** such as insecticide resistance, outdoor biting and residual transmission, and the geographic migration of new vectors. While ITNs and IRS target indoor biting mosquitos, they do not protect people outside, when they are away from their houses or not under nets. Mosquitoes can therefore evade these interventions leading to residual malaria transmission. Another emerging challenge is the spread of *An. Stephensi*, an urban vector. Generally, malaria is prevalent in rural areas in Africa, but as urban development rapidly expands, the spread of *An. Stephensi* across Africa could lead to malaria outbreaks of unprecedented size. Some tools are in the pipeline to overcome these challenges (see Section 2.4), but key barriers to accelerating R&D include: the cost and complexity of late-stage R&D; the need to generate cost-effectiveness data; the relatively small size of the public health market compared to the agricultural market; and investing in a high-risk market that is price driven.

Countries and manufacturers of vector control tools also face several ongoing quality control (QC) constraints due to **limited pre/post market QC systems**. These include no commonly defined quality benchmarks/thresholds to guide product development, limited pre- or post-shipment quality assurance (QA) systems and post-marketing controls in the field; and a lack of clarity on how data informs changes or updates to a product listing. There is also the broader challenge of a **lack of data for targeting interventions** to support evidence-based decision making.[21,22] As more tools become available, countries lack the necessary resources, systems and skilled workers required to generate the evidence needed to support their malaria prevention strategies and guide context-specific packages of interventions.

Global action and Unitaid's response

To address the key challenges described above, several global strategies and responses have been initiated. To support resistance management, the WHO *Global plan for insecticide resistance management in malaria vectors (GPIRM)* was released in May 2012 as a call to action to tackle the threat of insecticide resistance. Since its launch, 40 countries have completed their insecticide resistance monitoring and management plans in line with the GPIRM.[23] To strengthen IRM, WHO also launched the Malaria Threats Map in 2018 to provide up-to-date data on the magnitude and spread of three biological challenges for malaria control and elimination. This platform is a rich database for countries to use and inform their IRM plans.[24]

Moreover, in 2017, WHO launched a new vector control strategy – The Global Vector Control Response 2017-2030 to strengthen vector control worldwide through increased capacity, improved surveillance, better coordination and integrated action across sectors and diseases. In the same year, the World Health Assembly adopted a resolution calling on Member States to develop or adapt national vector control strategies and operational plans to align with this strategy.

Bolstering the innovation pipeline, the ZERO by 40 initiative was launched by IVCC and BMGF at the London Malaria Summit in 2018. This initiative brings together agrochemical companies alongside global health partners to strengthen industry's commitment to research and to develop innovative vector control tools to help end malaria.

Unitaid is playing an active role in addressing vector control challenges. Over the last four years, Unitaid has been working to catalyse the uptake of new vector control tools. In 2016, Unitaid launched the NgenIRS project, led by IVCC (US$65 million), to catalyze the uptake and availability of three new next-generation IRS products at more affordable prices and facilitate the market introduction of two new IRS insecticides. NgenIRS accelerated the availability of alternative insecticides that have better efficacy and can support resistance management. The project has protected 50 million people from malaria in 28 countries and the median price/unit of one product, Actellic®300CS, reduced from US$23.50 in 2016 to US$19.11 in 2018. As the NgenIRS grant ends in 2019, a key component of the project's transition plan is managing the rotation of insecticides taking into consideration the active ingredients in IRS as well as the active ingredients in new ITNs that will be entering the market in the coming years (see Section 4 - Annex for detailed information of new innovations).

More recently Unitaid and the Global Fund announced a joint project, the New Nets Project (US$66 million), to fund pilots that will test the performance of ITNs treated with new insecticide combinations under real conditions in sub-Saharan Africa. The pilots will generate data to guide international policy on their use, assess the cost-effectiveness of the nets under pilot conditions and generate demand making these new nets more affordable. Further, recognizing a gap in funding for vector control R&D, particularly for the epidemiological trials needed to determine public health value, Unitaid has invested in two projects to evaluate potential new product categories and generate the evidence needed for a WHO policy recommendation: the AEGIS project is a US$37 million grant with the University of Notre Dame to evaluate slow-release spatial repellents that can be easily deployed in houses and temporary shelters. The project incorporates an integrated response to vector control by also testing the impact of spatial repellents for other vector borne diseases such as dengue fever; the BOHEMIA project, led by ISGlobal (US$25 million), will evaluate the impact of mass-distribution of the anti-parasitic drug ivermectin in reducing malaria transmission by killing mosquitoes. In parallel to BOHEMIA, Unitaid is developing a grant on long-acting ivermectin. The current R&D trajectory suggests that this product could be available in the next 5 years.

In June 2018 Unitaid, in collaboration with Asia Pacific Leaders Malaria Alliance (APLMA), launched the Vector Control Platform for Asia Pacific (VCAP) to accelerate access to vector control innovations. VCAP links national regulators, policy-makers, industry, academia and the global health community to boost development and use of antimalarial tools, such as ITN and insecticides.

Looking forward, more efforts are needed in the response to reduce coverage gaps of existing tools, overcome key challenges and accelerate progress towards the global goals. There is a need for new tools alongside better evidence to support intervention prioritization and decision making. To maintain the momentum of vector control tools in the pipeline, anticipated investment needs and market barriers for new innovations should be scoped (see Section 2.4). There are currently eight compounds from five chemical classes for ITNs and IRS in the pipeline with some expected to become available in the next 3 – 5 years. New approaches such as sterile insect techniques are also in the pipeline and could be available in the next five years. If early data confirm the potential of these tools, funding will be needed for large-scale field trials to demonstrate their public health impact with epidemiological endpoints, as well as operational research and market interventions to support rapid adoption.

As the malaria toolbox expands, countries will need locally-driven evidence to guide the prioritization of interventions from amongst current tools and new tools as they become

available. With more tools to choose from, scaling-up access and achieving high-coverage will continue to be a challenge, especially in the context of resource constraints. Country-driven prioritization is a key component of the HBHI approach, and for elimination strategies. An important element of prioritization is the availability of quality regional- and country-level surveillance data. These data are needed to support national malaria programs as well as IRM strategies that are based on robust sub-national evidence. In additional, IRM transcends borders, so strong regional coordination is required. Several new technologies that can support surveillance efforts, including digital technologies that use artificial intelligence (AI) and robotics, have been developed but are expensive and not robust for long-term use in low- and middle-income countries (LMICs). Financing of these technologies will be needed to improve the evidence base and improve decision-making. Moreover, as a part of prioritization, countries will require guidance, both impact and operational guidance, to develop and deploy tailored packages of interventions that are specific for various transmission settings. Funding is needed to test packages of interventions, across malaria interventions - not just within vector control tools, to inform practical guidance, achieve impact and accelerate progress towards the GTS targets.

2.1.2 Preventive therapies

Overview of tools and coverage gaps

WHO recommends targeting pregnant women, infants and children in areas of moderate to high malaria transmission with intermittent chemoprevention strategies, using sulfadoxine-pyrimethamine (SP) alone (pregnant women and infants) or in combination with amodiaquine (AQ) (children).

Intermittent preventive treatment in pregnancy (IPTp) is the provision of at least three SP doses, starting in the second trimester of pregnancy, to prevent malaria transmission in pregnant women. The WHO recommendation to provide IPTp in areas of medium to high malaria transmission is supported by evidence on its effectiveness in reducing maternal malaria episodes, maternal and fetal anemia, placental parasitemia, low birth weight, and neonatal mortality.[25] The primary delivery channel for IPTp is routine antenatal care (ANC) visits. Nearly 90% of pregnant women in sub-Saharan Africa attended at least one ANC visit in 2017. However, of the 35 million pregnant women in sub-Saharan Africa, only 54% received at least one dose of IPTp, and only 22% received the recommended three or more doses.[26]

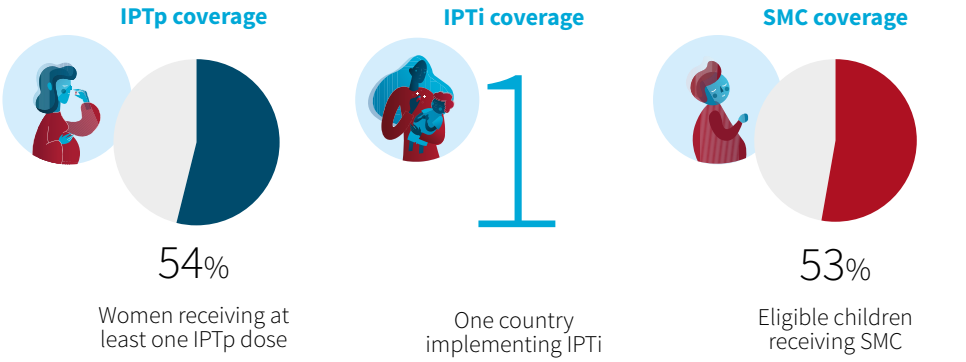
Seasonal malaria chemoprevention (SMC) is the monthly administration of SP+AQ to children under 5 years of age during malaria season (approximately 4 months per year) in areas of the Sahel sub-region in Africa where *P. falciparum* is sensitive to both antimalarials.[27] SMC can be 75% protective against malaria in the target group. While significant progress has been made in its scale-up, only 15.7 million out of 29.3 million eligible children received SMC in 2017.[28] Despite this gap, SMC uptake to date has been able to demonstrate the impact that effective chemoprevention initiatives can have on malaria transmission in vulnerable groups. As a result, the global malaria response is revisiting opportunities to increase IPTi uptake - the third pillar of chemoprevention.

SP delivered to infants at point of care through IPTi at around 10 weeks, 14 weeks, and 9 months of age has been found to have a protective efficacy of 30% against clinical malaria, 21% against episodes of anemia, and 23% against all-cause hospital admissions.[29] WHO has recommended IPTi for malaria prevention since 2010 but only one country, Sierra Leone, has adopted this recommendation.[30]Studies are currently underway in Sierra Leone to evaluate

the effectiveness of the Expanded Program on Immunization (EPI) as an IPTi delivery channel, and the impact of adding the antibiotic azithromycin to SP for IPTi on all-cause mortality in children under 18 months.[31]

These preventive strategies are safe and cost-effective, but notwithstanding the WHO recommendations to implement them as part of routine ANC or childhood vaccinations, there are challenges that impede high-uptake in groups that are most vulnerable to malaria transmission.

FIGURE 6: Preventive therapy coverage gaps in 2017



Adapted from *World Malaria Report 2018*, World Health Organization, 2018.

Key challenges

For all WHO recommended malaria chemoprevention interventions there is **low demand and adoption.** Low uptake of IPTp results from a disconnect between maternal/child health and malaria programs, negative perceptions of drug use in pregnancy, and practices of deprioritizing preventive interventions in ANC. Even though SMC has recently been scaled, there are ongoing behavioral challenges (e.g. adherence to all four doses; caregivers' negative perceptions of SMC) slowing the pace of uptake, as well as resource limitations to fund SMC programs. Additionally, some studies show that SMC is well tolerated in children outside of the current recommended under-five age group and for longer periods,[32,33] but **expansion to greater target populations lacks evidence**.

Only one country (Sierra Leone) has adopted IPTi since WHO recommended it in 2010. Contributing factors are being investigated and are likely to include a lack of IPTi implementation guidance alongside a lack of quality-assured drugs in strengths appropriate for infants. **Poor quality SP and low supply of quality assured SP** is an ongoing problem stemming from the low demand of chemoprevention interventions. Manufacturers are reluctant to invest in supplying quality assured SP and SP+AQ, as well as the active pharmaceutical ingredients, due to the small market size, low unit sale prices and the high costs of regulatory processes.

A major uptake barrier for IPTp, IPTi and SMC is ongoing perceptions of SP resistance despite demonstrated efficacy of SP when used for chemoprevention and not for first-line treatment. While SP is efficacious for chemoprevention, its widespread availability for treatment coupled with varying levels of quality does call for the need of alternative options, but currently there is **no alternative regimen to address resistance.**

In addition to chemoprevention strategies, vaccination against malaria could be a low-cost, effective way to prevent disease and save lives. However, the first malaria vaccines',

RTS,S/AS01, partial effectiveness and complex dosing may limit uptake. RTS,S/AS01 only provides partial protection against *P. falciparum* malaria in young children and has a relatively complex dosing schedule, meaning it may be challenging to implement at scale. There is therefore a need for a better vaccine, but to date there is **no highly effective vaccine** expected to become available in the next 10 years.

Global action and Unitaid's response

Between 2015 and 2018, Unitaid funded the ACCESS-SMC project. ACCESS-SMC ran across seven countries, with an aim to overcome the supply and demand side challenges that prevented SMC uptake in the Sahel sub-region. The key objectives of the project were to work with market actors to strengthen policy and regulatory frameworks, build the capacity building of health systems for SMC inclusion, and increase uptake in the target areas.

ACCESS-SMC showed that large-scale administration of SMC is feasible, has a strong public health impact, and is cost-effective. In addition, the cost of delivering SMC treatment per child fell more than 20 percent over the life of the ACCESS-SMC project. The project also worked with suppliers to support the market entry of child-friendly, palatable, easy-to-administer medicines for SMC.

In response to the low uptake of IPTp in sub-Saharan Africa, in 2015 the RBM Partnership issued a Global Call to Action to increase IPTp coverage, highlighting the need to scale up IPTp access, and update national guidelines and practices in accordance with WHO recommendations. Key recommendations of the Call to Action were to explore innovative opportunities for IPTp delivery in the community, as well as increased operational research to improve the quality of service delivery for IPTp.[34] The Unitaid TIPTOP project aims to address IPTp access challenges by demonstrating effectiveness of IPTp delivery by community health workers in four target countries. Led by Jhpiego, evidence delivered by TIPTOP will stimulate market demand for SP and accelerate use of the intervention during ANC visits in countries outside of the TIPTOP trial, where SP uptake for IPTp is low.

To respond to the growing market-need for QA SP, and to complement investments in the ACCESS-SMC and TIPTOP projects, Unitaid is funding MMV to overcome supply-side barriers. MMV's activities include: the prequalification of a second dispersible SP+AQ product for SMC; the prequalification of one sulfadoxine AI product and at least one SP African-manufactured product; and the development of user-friendly SP packaging for IPTp. Unitaid anticipates that the availability of more quality assured sulfadoxine and SP sources, alongside growing demand, will increase country uptake of IPTp.

Unitaid also has a recently-approved AfI on long-acting drug technologies across all its disease portfolios. For malaria this could be applied to long-acting chemoprevention regimens, which would improve adherence and decrease implementation costs and complexity.

Building on its work in SMC and IPTp, Unitaid has begun exploring opportunities to support the adoption of IPTi at scale. These areas could include funding a proof of concept study for integrating delivery of IPTi with the Expanded Programme on Immunization, addressing supply chain challenges, and/or assessing whether azithromycin can be delivered alongside SP to reduce child mortality. Unitaid could also explore opportunities to build on its investment that led to the development of dispersible SP, and develop dispersible SP formulations in infant strengths, along with packaging appropriate for IPTi use.

Unitaid, along with Gavi and The Global Fund, is currently co-funding The Malaria Vaccine Implementation Programme (MVIP) project. Led by WHO (with PATH) MVIP is a six-year project that will evaluate key questions related to RTS,S's impact, safety, and operational feasibility,

through pilots in in Ghana, Kenya and Malawi. The ultimate goal of the MVIP is to enable a WHO policy recommendation on the use of the vaccine. WHO committees recently endorsed a step-wise approach to policy consideration, with a recommendation possible as early as 2021 based on 1) satisfactory resolution of safety signals observed in the Phase 3 trial, and 2) severe malaria or mortality trends consistent with a beneficial impact of the vaccine.[35]

2.2 Case management (diagnostic tests and treatments)

Overview of tools and coverage gaps

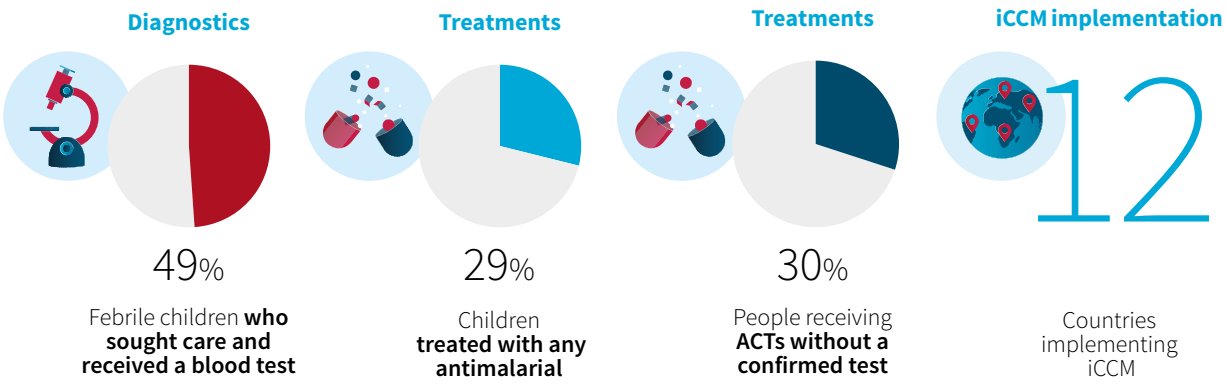
Prompt diagnosis and effective treatment are the cornerstones of malaria case management. If diagnosed and treated early, patients have a better chance of rapid recovery. A negative malaria diagnosis, rather than presumptive treatment (i.e. based on symptoms alone) can also help health workers to investigate other possible causes of febrile illness. Accurate diagnoses of febrile illness can reduce the unnecessary use of antimalarial drugs and associated side-effects and mitigate the rapid emergence and spread of drug resistance.

All cases of suspected malaria should have a parasitological test (microscopy or rapid diagnostic test (RDT)) to confirm diagnosis. WHO recommends artemisinin-based combination therapies (ACTs) as the first-line treatment of uncomplicated *P. falciparum* malaria. Five different ACT treatments are recommended.[36] For pregnant women with uncomplicated *P. falciparum*, the treatment recommendation during the first trimester is seven days of quinine + clindamycin, and for HIV co-infected patients WHO recommends avoiding artesunate + SP if being treated with co-trimoxazole, and to avoid artesunate + AQ if being treated with efavirenz or zidovudine.

For treatment of *P. vivax* malaria, WHO recommends two treatments: one to treat the acute (blood-stage) infection and a second to clear the malaria parasite from the liver to prevent relapse ("radical cure"). The first-line treatments for acute *P. vivax* are chloroquine and ACTs. For radical cure, the current recommendation is a 14-day, daily treatment course of primaquine. Testing for deficiency of the enzyme glucose-6-phosphate dehydrogenase (G6PD) is recommended prior to administration of primaquine (and other 8-aminoquinolines), as these drugs can cause acute haemolytic anaemia in patients with this deficiency.

In recent years, there has been significant progress in scaling-up malaria RDTs and ACTs. In 2017 around 320 million ACT treatment courses were procured, and 276 million RDTs were sold. Despite this progress, coverage gaps persist. Current RDT volumes are still largely insufficient to deal with the estimated 656 million malaria-like fevers per year in African children between 0 – 4 years and around 40% of sick children are not brought for care at all.[37,38] Household survey data from sub-Saharan Africa show that between 2015 – 2017 only 49% of febrile children who sought care received a blood test (suggesting that a malaria diagnostic test may have been performed). Testing rates drop considerably in the informal private sector, where only 10% of children <5 years receive a blood test for fever. Over the same period, only 29% of children <5 years with a fever received any antimalarial drug,[39] and around 30% of patients that receive ACTs were not tested for malaria. The current demand for ACT treatments in the African region would be reduced by more than half if only malaria cases confirmed with diagnostic testing were treated with ACTs.[40] This speaks to the need for better targeting of ACTs at confirmed malaria cases, alongside expanded scale-up efforts.

FIGURE 7: Case management coverage gaps in 2017



Adapted from *World Malaria Report 2018*, World Health Organization 2018

Since 2010, WHO has recommended injectable artesunate as treatment for adults and children with severe malaria (including pregnant women and infants). If artesunate is not available, only then is quinine conditionally recommended to treat severe malaria.[41] WHO also recommends that in situations where injections are not possible, children be given rectal artesunate suppositories (RAS) as pre-referral treatment.[42] Pre-referral treatment for severe malaria, administered correctly at the community level can prevent malaria related deaths. While progress has been made, coverage of recommended treatments for severe malaria remain low.

To bridge diagnostic and treatments gaps among children, WHO and UNICEFF have developed two integrated strategies that address the leading causes of childhood mortality including pneumonia, malaria and diarrhoea: integrated management of childhood illness (IMCI) and integrated community case management (iCCM). Integrated management can contribute to reduced childhood morbidity and mortality and can mitigate the threat of drug resistance by improving the rational use of antimalarials and antibiotics, e.g. a recent review showed that 69% of patients who tested negative with malaria RDTs received an antibiotic.[43] However, while in 2015 over 100 countries had adopted IMCI, implementation varies widely across settings. For iCCM, in 2017, of 21 African countries with high malaria burden, 20 had iCCM policies in place, of which only 12 had national coverage.[44]

Key challenges

Many of the case management challenges cut across both treatments and diagnostics. Firstly, there are **limited tools to manage biological threats and to support treatment adherence**. Antimalarial drug resistance includes partial resistance to artemisinin (the key active ingredient in ACTs) and ACT partner drug resistance – both of which have been identified in the Greater Mekong region.[45,46] New non-artemisinin single-dose treatments are needed but will not be available in the short term. Another threat requiring urgent action is the emergence of *P. falciparum* strains that cannot be detected with the most common RDTs used in primary care across Africa and beyond.[47] The malaria parasites are evolving without the genes expressing the P. falciparum histidine-rich protein 2/3 (pfhrp2/pfhrp3), where the most commonly available RDTs work by detecting a specific protein expressed only by P. falciparum, called HRP2, leading to false-negative tests results. The availability of non-HRP2 based RDTs is currently limited, and these RDTs are less sensitive and less heat stable than HRP2-based RDTs.[48]

One of the factors contributing to drug resistance is the **proliferation of substandard and falsified (SF) products and limited quality control measures.** Approximately 50% of reported SF cases are antimicrobials, with antimalarials and antibiotics most frequently reported. Key barriers to reduce SF products include: weak regulation and limited regulatory capacity; weak quality control measures and post market surveillance systems; poor supply chains with inadequate storage conditions; and limited availability of quality assured tracking/verification technologies suitable for use in LMICs. The private sector is an important source of malaria care in many high-burden countries, and poor-quality drugs often proliferate in this sector. More broadly, **poor quality case management in the private sector** is common and can be attributed to low availability/demand for diagnostic testing and ACTs and the availability/use of non-quality ACTs or non-recommended treatments that are usually cheaper but ineffective.

Integrated approaches to treating common causes of childhood fever can increase care seeking and malaria treatment rates and reduce ACT wastage.[49] However, there is **poor adoption of IMCI and iCCM alongside limited tools for integrated management of childhood fever**. IMCI/iCCM adoption is limited by the cost and complexity of implementation at scale, weak political leadership, a lack of community engagement, poorly-resourced health facilities and community health worker networks, unreliable supply chains, demand side barriers, weak monitoring and evaluation systems, and weak supportive government policies and engagement.[50,51] The limited availability of tools to support IMCI/iCCM implementation also contributes to poor adoption. Easy to use, point-of-care devices and diagnostics to improve identification of severe disease, identification of risk factors that can cause severity and bacterial vs non-bacterial are being developed but are not validated for use in LMICs, and targeted treatments, e.g. dispersible amoxicillin, are often unavailable when needed.

Effective case management of high risk groups has not been widely adopted due to multiple challenges. Pregnant women have a higher risk of contracting malaria,[52] but **current tools limit optimal case management in pregnancy**. Diagnosis of clinical malaria in pregnant women can be difficult with current tools due to lower parasite density in the blood that is undetectable with current malaria RDTs. In children under 5 who account for 61% of malaria deaths, appropriate management of severe malaria is sub-optimal. Over the last five years, the global response has been active in scaling-up tools to manage severe malaria, but there is still **low adherence to guidance on severe malaria**.

Specific challenges for malaria diagnostics include **limitations of microscopy and RDTs** and **RDT supply challenges**. Microscopy is the gold standard diagnostic for malaria but is compromised in field settings, and while RDTs have many advantages and widely accepted (i.e. they are inexpensive, portable and disposable, and require limited infrastructure), there are some important challenges such as poor heat stability. In addition, they only provide a simple interpretation of infection. There are also RDT supply challenges caused the by market consolidation around two suppliers and the low price of existing RDTs which threatens the sustainability of the market and discourages new market entrants. Also, for alternative tests that are needed to address HRP2 deletions as well as to detect other malaria species, product selection is quite limited or nonexistent.

In elimination settings, a key challenge is a **lack of operational evidence on effective strategies**. Specifically, there is a lack of operational research on the feasibility, safety and cost-effectiveness of elimination tools/strategies (e.g. active case detection, reactive case detection, asymptomatic infections/low parasite density detection, MDA etc[53]) needed

to support decision-making. *P. vivax* accounts for over 70% of malaria cases in countries approaching elimination,[54] and the **complexity of *P. vivax* case management and limitations of current tools** is another key challenge in these settings as well as in higher-burden settings. Treatment of *P. vivax* requires two drugs – one to clear the acute blood stage parasites and another for the dormant liver parasites that can cause relapse. Treatment of the liver stage also requires diagnostic testing to identify and exclude patients with G6PD deficiency who can suffer from adverse events due to liver-stage treatment. Other challenges for *P. vivax* case management include: adherence with the 14-day treatment course of primaquine, low blood parasite concentrations of *P. vivax* making it harder to detect with RDTs, and the absence of a diagnostic tool to detect and treat individuals at risk of relapsing.

Global action and Unitaid's response

The global response has made significant inroads to increase access to quality diagnostics and treatments for case management. At the global level, the WHO Prequalification Program (WHO PQP), initiated in 2001, has been instrumental in increasing the availability of quality-assured malaria products. In 2007, WHO Member States adopted a resolution calling for the progressive removal of oral artemisinin-based monotherapies from markets, which has been highly effective. In 2012, to accelerate the scale-up of recommended case management tools, WHO launched an initiative called *T3: Test. Treat. Track*, urging malaria-endemic countries, donors and the global malaria community to scale-up diagnostic testing, treatment and surveillance for malaria. Since this time, there has been a shift away from presumptive fever treatment, but access to a malaria diagnostic test is still below 50%. Another step was taken to improve the availability of diagnostics, including malaria diagnostics, when WHO launched the first Essential Diagnostics List in 2018. The list acts as a guide for manufacturers on where there is a commodity need and gaps exist.

To address the availability of poor quality products more broadly, in 2013 WHO launched the Global Surveillance and Monitoring System to encourage countries to report incidents of SF medical products in a structured and systematic way and to help develop a more accurate and validated assessment of the problem. Through the Government of Cambodia's leadership and strong partner support, regional momentum in South-East Asia to address SF products is mounting. In 2018, the International Institute of Research Against Counterfeit Medicines together with the Government of Cambodia held the Regional Conference on Combating Falsified and Substandard Medicines. As a result, the Government of Cambodia has led the Greater Mekong Sub-region to commit to the Phnom Penh Declaration against Substandard and Falsified Medicines. Other regional initiatives are now in development, for example, the Association of Southeast Asian Nations (ASEAN) is currently scoping potential opportunities to work with stringent regulatory authorities and NGOs to tackle this problem. Digital technologies are beginning to play an important role in detecting and monitoring the quantity and movement of SF medicines. However, these tools have not been tested at scale, and their scale-up will depend on strong political will and multisectoral participation.

Unitaid has previously invested in multiple projects to improve malaria case management in the private sector. The Affordable Medicines Facility for Malaria (AMFm) was designed to expand affordable access to ACTs in the private sector through a co-payment mechanism and other supportive interventions. Hosted by the Global Fund, AMFm was launched as a pilot in 2010 in eight malaria endemic countries and was integrated into the Global Fund's grant mechanism at the end of 2013. That same year, Unitaid invested

US$34 million to increase the appropriate use of quality-assured malaria RDTs in private sector markets in five malaria-endemic countries. Based on the project outcomes, in 2019 PSI published *A Roadmap for Optimizing Private Sector Malaria Rapid Diagnostic Testing*,[55] in collaboration with WHO and other partners. Separately, Unitaid also supported ACT and RDT forecasting across both public and private sectors, as well as co-funding the ACTwatch project which collected and disseminated market intelligence on antimalarials and RDTs in both public and private sectors. In 2015, the Unitaid Executive Board considered an AfI on malaria case management in the private sector and requested that future work in this area be considered in the broader context of and access to quality case management more generally. Recently, there has been renewed partner interest in private sector case management for malaria. In May 2019, WHO held a technical consultation on malaria case management in the private sector in high-burden countries. Unitaid continues to monitor developments in this area in discussion with key partners, to assess any potential future opportunities.

Unitaid's support to WHO PQP supports the global availability of quality-assured medicines and diagnostics. Unitaid also funded FIND to conduct product testing of malaria RDTs and to develop positive control wells to test RDT quality at the national level.[56] RDT product testing has now transitioned to the WHO PQP and lot testing has transitioned to malaria RDT procurers. While quality control efforts have improved the availability of quality RDTs, gaps remain including; limited insights into quality at the manufacturing level and varying access to quality controls for checking the performance of RDTs in the field. Future opportunities for additional standalone interventions on RDT quality are likely to be minimal considering Unitaid's previous investments to support RDT quality.[57] However, any interventions to expand access to RDTs should include efforts to ensure product quality.

Through the Malaria RDT Procurement Task Force, Unitaid and other partners have been working to identify strategies to improve the health of the RDT market. Considerations include: moving away from spot procurements to long term agreements to help stabilize pricing and provide suppliers with visibility into demand; allocating demand to multiple suppliers, based on factors other than price; and limiting country requests for restricted procurement unless epidemiologically justified. Both PMI and The Global Fund have recently made changes to their RDT procurement practices, for example, PMI has launched a new procurement strategy which includes long term agreements, allocates across multiple suppliers using criteria beyond price, and limits sole sourcing of RDTs.[58] Unitaid will continue to monitor trends in the RDT market and will continue to engage with core partners to determine if additional actions are needed to ensure market stability and availability of different product categories.

Unitaid has also invested in two grants to support better access to medicines for severe malaria. Unitaid targeted the slow uptake of injectable artesunate by funding the Improved Severe Malaria Outcomes (ISMO) project. Led by MMV, ISMO implemented several market-shaping activities from 2013 – 2016 to switch the use of injectable quinine to injectable artesunate for severe malaria cases in several high-burden countries,[59] alongside paving the way for prequalification of RAS – the recommended pre-referral measure. A recent follow-up study to the intervention found that the use of injectable artesunate for treatment of severe malaria increased in at least two of the ISMO project countries three years after the study closure. The ISMO project supported the availability of RAS by accelerating two RAS products through WHO prequalification, which is now being utilized in the Unitaid funded RAS project (CARAMAL). CARAMAL, led by CHAI, aims to responsibly introduce QA RAS in select geographic areas, and to generate high-quality evidence on RAS implementation. If successful in demonstrating

the operational feasibility of using RAS at the frontline, evidence from the CARAMAL intervention will be used to develop operational guidance on rational scale-up of quality-assured RAS.

Several global efforts over the last two decades have aimed to strengthen IMCI/iCCM and accelerate the adoption of febrile-management tools e.g. between 2014 – 2017 The Global Fund allocated approximately US$125 million towards iCCM in 38 countries, and UNICEF and The Global Fund have a Memorandum of Understanding on the alignment of Maternal, Neonatal, and Child health Interventions, with a focus on strengthening IMCI and iCCM. The WHO also launched an initiative in 2013 to plan for the sustainability of integrated iCCM programmes supported by the Rapid Access Expansion (RAcE) Programme in five African countries. In 2017, a final program evaluation was conducted and found that iCCM can measurably decrease child mortality.[60]

In 2017 Unitaid's Executive Board endorsed the AfI "Better tools for integrated management of childhood fever" As a first step, in 2019, Unitaid signed two new grants aimed at accelerating the availability, adoption and scale-up of improved tools to identify severe disease, specifically pulse oximeters and dual/multimodal devices adapted for point-of care use in LMICs. Through the TIMCI project, PATH will pilot the use of adapted pulse oximeters at primary health care alongside the use of a digital support algorithm and catalyze the development of point-of-care tools that have broader functionality e.g. tools that can identify oxygen concentration, respiratory rate and hemoglobin at the same time. The AIRE project, led by ALIMA, will also pilot the introduction of pulse oximeters and the improve the usability of a digital IMCI platform, IeDA.

Unitaid's most recent efforts in malaria case management relate to *P. vivax*. Because of its lower mortality and a lack of effective tools, historically *P. vivax* has not been the main focus of international efforts to combat malaria. However, the *P. vivax* response has gained in momentum in recent years due to increase evidence of its significant morbidity and mortality, the important role of *P. vivax* in countries nearing malaria elimination, and the promise of new tools on the horizon. Countries and partners working to achieve malaria elimination in Asia-Pacific, such as the Asia Pacific Malaria Elimination Network (APMEN) and APLMA, have identified *P. vivax* as a key barrier to this objective. P. vivax is also closely linked to HBHI, as approximately half of all cases of *P. vivax* globally occur in India (an HBHI focus country).[61] Several new tools are becoming available that have significant potential to improve *P. vivax* case management. In December 2018, The Unitaid Executive Board approved an Area for Intervention to support better tools for the diagnosis and treatment of *P. vivax*. Grant development is currently underway focused on 1) piloting the implementation of radical cure tools in a selection of countries and 2) establishing a supply of quality-assured paediatric treatments.

2.3 Cross-cutting

Key challenges

Cross-cutting challenges to the malaria response can be divided into two categories. The first category is delivery and implementation challenges, which captures barriers at various levels of the health service. The other is social, environmental and political challenges, which are external mechanisms outside of the health system that affect the malaria epidemic and access to care. These external challenges are broader social issues, which a strong health system can often respond to, but they occur outside of health architecture.

Despite substantial improvements in recent years, a lack of national surveillance body oversight, variable population testing and treatment seeking rates, and a lack of validated surveillance systems has led to **weak surveillance systems** that are otherwise needed to drive the malaria response. These poor surveillance systems, despite new tools across the malaria innovation pipeline and new ways of service delivery at a country level, are often unable to provide robust **data for decision making to deploy new tools**. More broadly, **weak health system infrastructure**, including poor management of supply chains, lack of regulation in the private health sector, and a lack of technical and human resource capacities create barriers for implementation of malaria interventions and new tools. In addition to health system difficulties, the lack of predictable and **sustained international and domestic financing** for malaria interventions restricts appropriate responses to the difficulties faced by health systems. Malaria responses at the country level also require strong **regional collaboration** across borders, yet links between countries in elimination efforts are generally weak. Lastly, successful malaria case management should include the management of malaria-related anaemia. Anaemia is a direct and indirect consequence of malaria, it carries its own burden in areas of high malaria transmission, and if present it should be managed in addition to the malaria infection. Despite this, recent years have seen a decline in awareness of the burden of malaria-associated anaemia leading to **limited prevention and treatment delivery for malaria-related anaemia**.

Outside of the health system, **social unrest & conflicts, and humanitarian disasters** contribute to the spread of malaria in populations that are already at risk. **Food insecurity** at an individual level, such as malnourishments leaves vulnerable patients unable to mount an immune response against a malaria infection, which influences malaria transmission and mortality. At a population level, agricultural practices linked to food production can encourage vector breeding sites and influence vector mosquitoes' reproduction. Similarly, **climate and environmental change** arguably has an influence on malaria distribution, which can influence malaria transmission. **Population growth** in areas of high malaria transmission require increased resources for malaria intervention coverage, despite being in an environment of decreased funding globally. Within endemic populations, **vulnerable and hard to reach groups**, such as mobile or migrant populations and other groups with limited access to health services suffer a disproportionate burden of malaria.

While Unitaid does not directly invest in health system strengthening, it does invest in products that can impact health systems by delivering ease of use at the point of care, promoting integrated approaches to health, or freeing up resources and improving efficiencies. Where Unitaid does support health system enhancements, they are funded as a component of delivery for new tools, such as surveillance and health worker training to accompany introduction of innovations in the IMCI fever management "toolbox".

Unitaid will continue to explore innovative opportunities to improve malaria surveillance that will help address the current lack of available data, which is vital to prioritize use of new and existing tools. There may be opportunities for Unitaid to respond to key delivery and implementation challenges in the context of the WHO's recent HBHI malaria strategy update. As Unitaid explores opportunities to test intervention packages in the 11 countries where 70% of the world's malaria burden is disproportionately concentrated,[62] it will also monitor innovations for enhanced surveillance systems, and mechanisms to address weaknesses in health systems to support these packages.

2.4 Malaria Innovation Pipeline

The R&D pipelines for malaria drugs, diagnostics, vector control tools and vaccines hold a range of promising new tools, particularly in the medium- to longer-term. In the short-term, a single-dose treatment for the liver-stage of *P. vivax* ("radical cure") offers significant advantages over the current 14-day regimen. Tafenoquine has been approved by two stringent regulatory authorities and should be considered by WHO for a policy recommendation in the next year or two. Paediatric products for *P. vivax* radical cure are also in the late-stage pipeline. A quantitative G6PD diagnostic test needed for tafenoquine use has recently become conditionally available through the Global Fund Evidence Review Panel (ERP) process,[63] with additional products in late-stage development. The short-/medium- term pipeline also includes a more sensitive RDT for *P. vivax* malaria which could improve case management by detecting lower-density infections. *P. falciparum* RDTs which are not based on the antigen most commonly detected in current RDTs (HRP2) are also under development to address the emerging issue of HRP2/3 gene deletions in malaria parasites. These new RDTs are expected to enter the market in 2020/2021.

By 2025, R&D pipelines are likely to yield new drugs to address artemisinin resistance which could also be available as a single dose, offering advantages to current 3-day regimens. Long-acting drug formulations for use in malaria vector control, could also become available. New vector control tools could include ITNs and IRS with new AIs, as well as entirely new vector control product classes such as spatial repellents, attractive toxic sugar baits and endectocides. Efforts are underway to improve both microscopy as well as RDTs and their underlying monoclonal antibodies. Additional diagnostic methods, such as urine- and saliva-based RDTs that may offer alternatives are in the pipeline. Unitaid is monitoring developments in this space and liaising with WHO to understand the potential use cases of new/improved products.

Other promising innovations like self-limiting genetically modified (GM) mosquitoes that rely on sterile insect techniques could also become available. This method propagates mosquitoes that contain a "self-limiting" gene. When this gene is passed on to offspring, they do not survive adulthood resulting in a reduction in the mosquito population. These mosquitoes are called self-limiting mosquitoes because the insects that are released, as well as their offspring, are designed to die and disappear from the environment. Because this approach is designed to disappear, they require continuous mass release that may be challenging across large geographic regions or in areas where vector and parasite populations are high.[64]

Beyond 2025, self-propagating (or "self-sustaining") gene drive technologies to control malaria-transmitting mosquitos could hold significant potential. Self-sustaining gene drive technologies differ from self-limiting mosquitoes in that the genetic modification is designed to persist and even spread within the target population. These technologies can potentially reduce malaria transmission in hard to reach places as they do not require continuous or mass release, or heavy infrastructure and resources.[65]

New vaccines that offer a high degree of protection against malaria in young children, and vaccines that can block transmission of the malaria parasite from humans to mosquitoes and prevent the onwards spread of malaria in the population, may also become available in the longer-term.[66] Unitaid monitors R&D pipelines on an ongoing basis to identify where catalytic interventions could accelerate access to new game-changing products (see FIGURE 8).

Detailed information on these emerging innovations can be found in Section 4 - Annex.

FIGURE 8: Selected tools in the innovation pipeline (non-exhaustive)

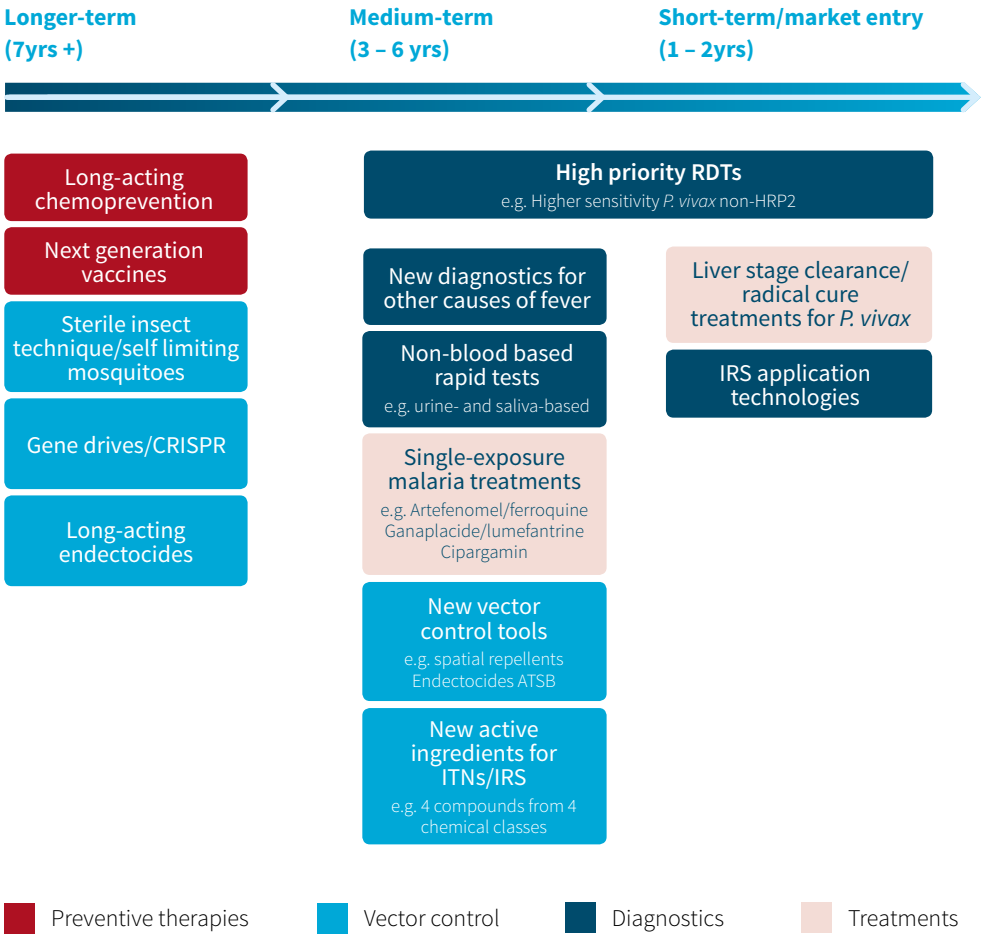


FIGURE 9: Malaria research and development framework[67]

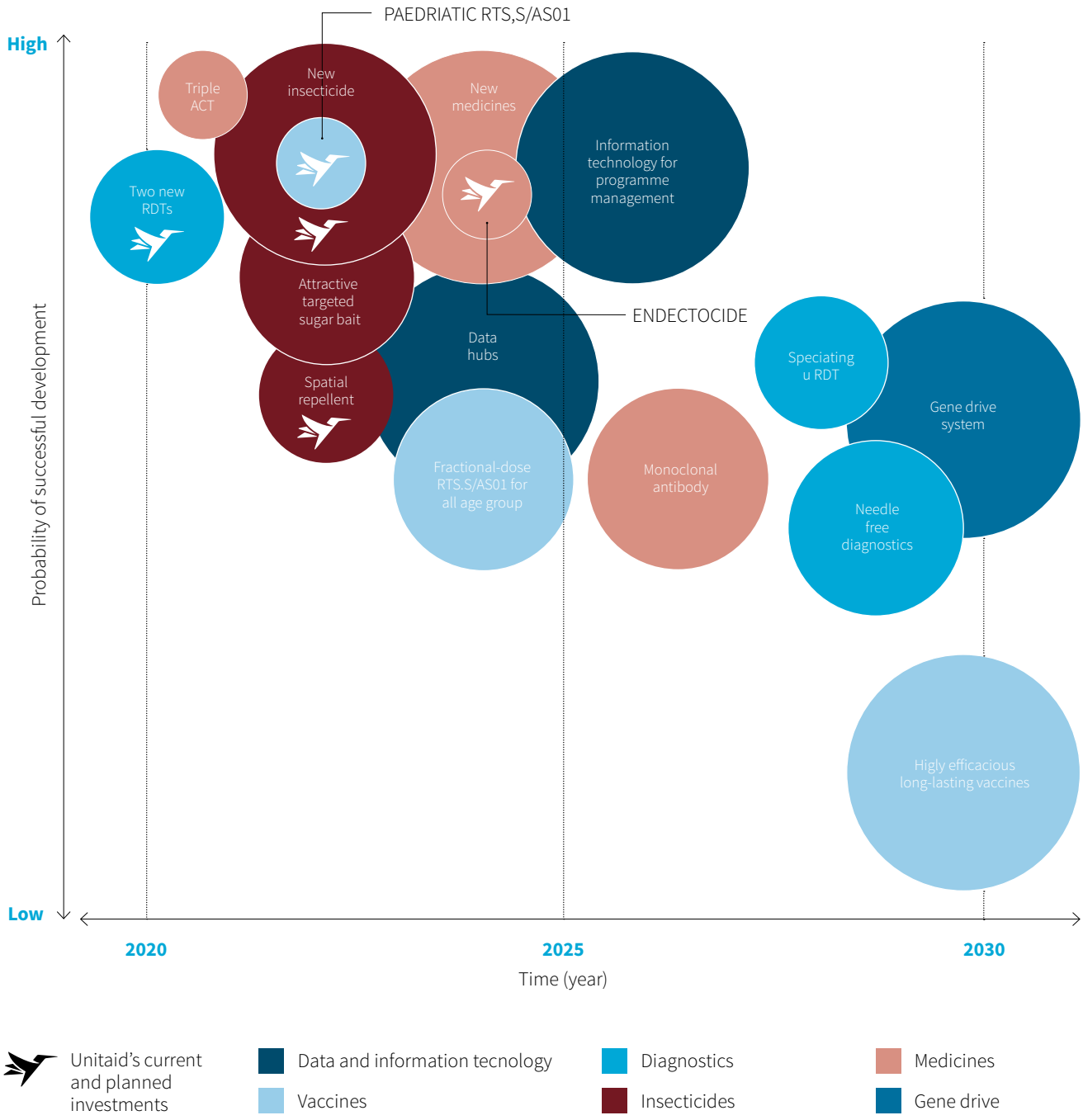


FIGURE 9, adapted from *The Lancet's* publication *Malaria eradication within a generation: ambitious, achievable, and necessary*, shows innovations according to the probability of successful development (vertical axis), the timeline of availability (horizontal axis), and their relative effect on accelerating eradication efforts (size of coloured circle). The starred innovations show areas that Unitaid has either current or planned investments. This chart demonstrates Unitaid's commitment to high impact, diverse investments in the robust malaria pipeline.

3 POTENTIAL OPPORTUNITIES

Following the development of the inventory of challenges affecting the malaria response and a review of the innovation pipeline, Unitaid's criteria were applied to assess potential fit for Unitaid:

a. Unitaid's expertise: focus on challenges that are inherently commodity access issues
b. Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact
c. Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe
d. Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible

These criteria were used as filters to identify a shortlist of challenges that represent the highest potential for Unitaid intervention (FIGURE 10). Based on the filtering exercise undertaken by the Secretariat and validated with key partners, a small number of short-term opportunities were identified which are high priorities for further investigation over the next 6-12 months. In addition, several additional opportunities were identified for active exploration and/or ongoing monitoring. These are described further in the following section. It should be noted that these opportunities are subject to change in light of the dynamic nature of commodity markets, changes in partner activities, or other factors. In addition, Unitaid has several new grants in the malaria portfolio which are in early stages of implementation (FIGURE 11). As these investments mature, they will inform future opportunities in related areas.

FIGURE 10: Overview of outcomes of Unitaid's filtering process

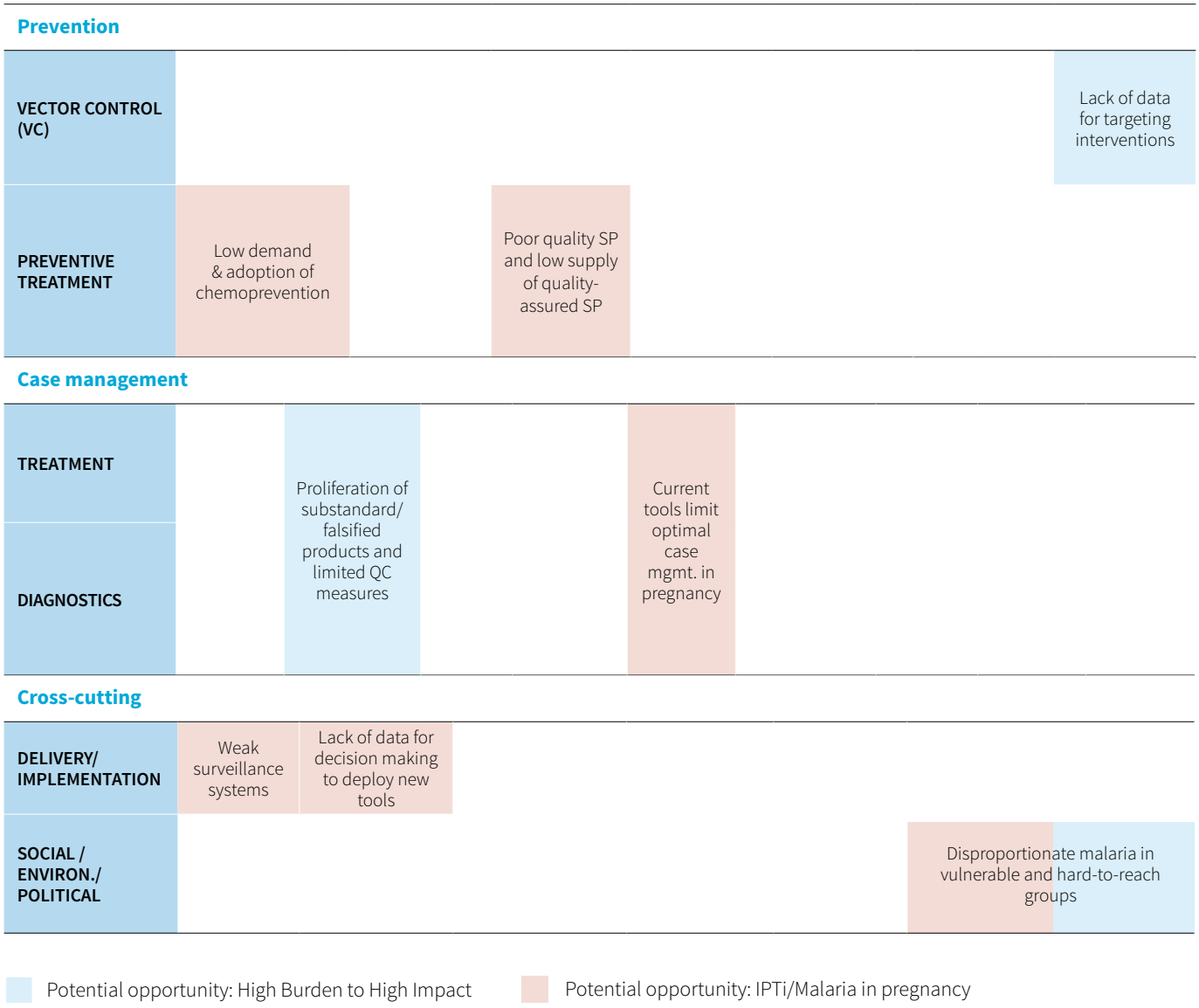
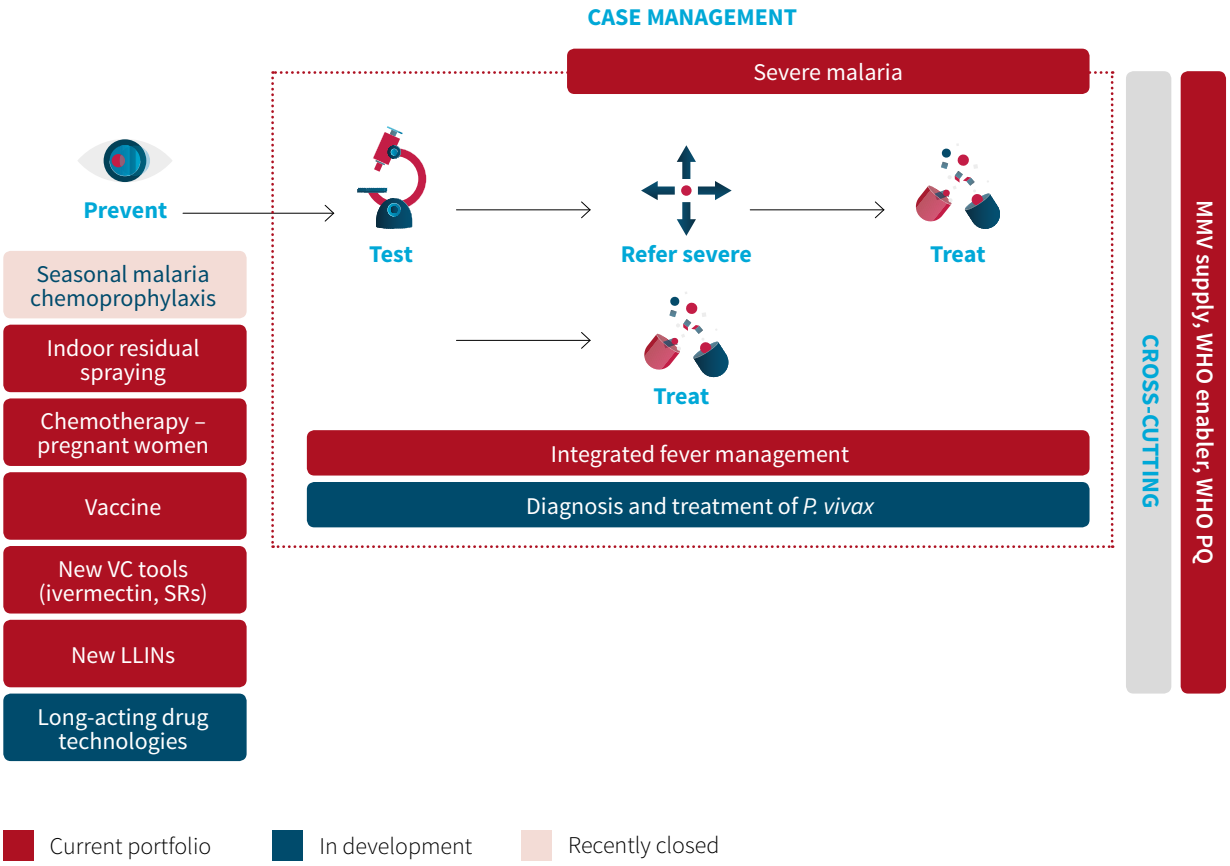


FIGURE 11: Overview of Unitaid's malaria portfolio (≈US$ 350 million)



3.1 Potential opportunities in the next 12 months

Short-term opportunities include targeted approaches to catalyze uptake of IPTi. Testing integration of IPTi delivery with the Expanded Programme on Immunization and/or weigh-in visits would provide a proof of concept for effective delivery of IPTi at scale. Other interventions could include infant-friendly strengths and packaging of SP, longer-acting chemoprevention drugs for use in IPTp, IPTi and SMC, or testing a combination of IPTi with other interventions such as mass distribution of single-dose azithromycin that has been shown to reduce childhood mortality.[68]

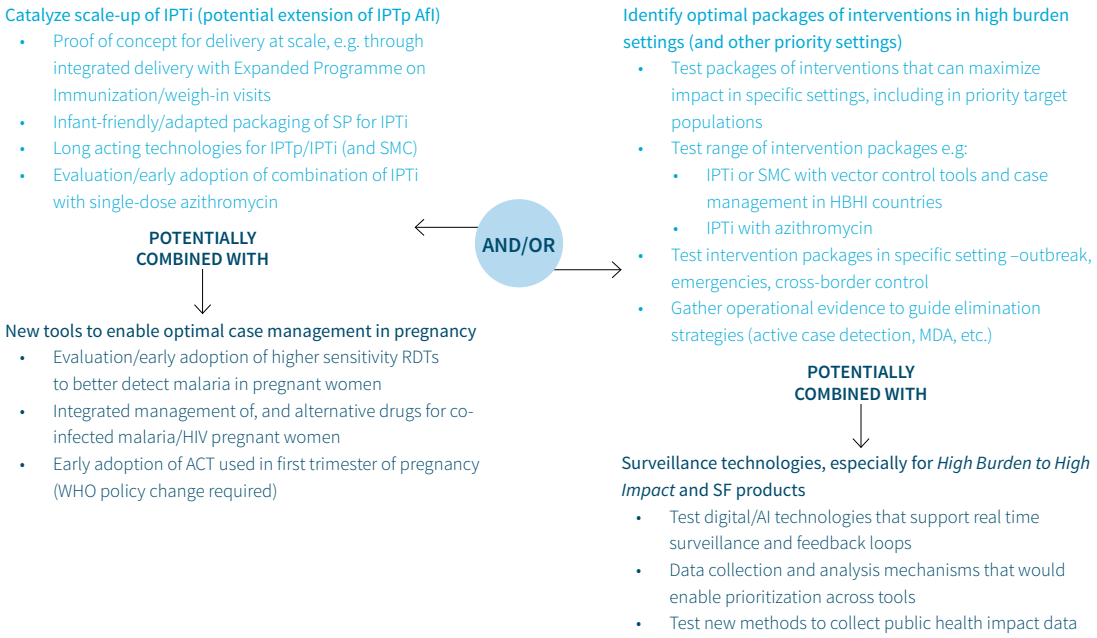
Towards a more integrated approach for pregnant women and newborns, and building on Unitaid's existing AfI in IPTp, IPTp opportunities could be considered alongside new tools that enable optimal case management in pregnancy, such as the evaluation and early adoption of higher sensitivity RDTs to better detect malaria in pregnant women, and/or early adoption of ACT use in the first trimester of pregnancy should this become a WHO policy recommendation. Unitaid will also look at broader opportunities to integrate management of malaria with other coinfections, such as alternative drug regimens for pregnant women with malaria who are also living with HIV.

In parallel, Unitaid is exploring ways to contribute to the HBHI strategy for countries that experience a disproportionate burden of global malaria cases. While many of Unitaid's current grants are of direct relevance to high burden settings, additional efforts could include testing combinations of intervention (new and existing tools) to identify optimal

intervention packages in HBHI countries. Intervention packages for these settings could include combining IPTi or SMC with different vector control tools, together with quality case management. Unitaid could also consider testing packages of interventions for other high priority settings, such as elimination settings, outbreaks or humanitarian emergencies.

New surveillance technologies could support prioritization of different tools for HBHI countries. This could include, for example, innovations that can collect data to prevent disease outbreaks, analyze public health impact and operational data, and enable feedback loops in real time. Innovative surveillance tools such as Microsoft Premonition robots, ZZAPP, or other digital and AI technologies aim to predict disease outbreaks and improve response planning. Some technologies in the pipeline can efficiently find and collect live specimens from the environment, generate real-time sub-national data and prevent disease. They can contribute to improved efficiencies in national malaria control programs by supporting more targeted interventions and reducing the level of labor currently required. Enhanced surveillance technologies could also be used to respond to the use of SF malaria products, developing antibiograms for antimicrobial resistance,[69] and to guide approaches in other priority settings, such as areas of disease outbreak, humanitarian or environmental emergency, or in cross-border regions.

FIGURE 12: Potential near-term opportunities



3.2 Further innovative areas for exploration

There are new innovations also emerging in the medium-to-long-term that Unitaid will continue to monitor. New vector control tools that respond to insecticide resistance, outdoor and indoor biting behaviors, and residual transmission could be integrated into testing packages for HBHI countries and other high priority settings. Whilst continuing to support the development and early introduction of new tools, Unitaid will also explore opportunities to support integrated vector control approaches that address other vector-borne diseases.

As they approach late stage development, GM mosquito innovations have potential to target vector populations. Sterile insect and self-limiting mosquito technologies have been able to suppress mosquito populations in laboratory settings and could be utilized in the real-world.

To address biological threats to current tools that challenge case management, Unitaid will look for opportunities to support product development, pre-qualification, and introduction of new diagnostics, such as non-HRP2 RDTs.

New fever diagnostic innovations will be able to support scale-up of IMCI and iCCM adherence, such as point of care anaemia and hemoglobin tests, host response biomarkers for bacterial infection, and RDTs for combinations of conditions. Other innovative approaches, such as mass drug administration of single dose azithromycin for underlying causes of illness, dispersible amoxycillin, and increased access to treatments for anemia and malnutrition could also support the fever response.

Further work on testing and early adoption of new tools and approaches for *P. vivax* could include evaluation of serological markers to detect hypnozoite carriers, mass drug administration to clear hypnozoites in latent vivax carriers, screening new-born infants and maintaining G6PD registries, and exploratory work to investigate co-drugs opportunities for 8-aminoquinolones that lower risk of acute hemolytic anemia in G6PD deficient patients.

Some tools to detect SF products exist such as Minilab, and new digital solutions are currently in development. These innovations could offer quality control measures to enhance access to QA medicines in response to the proliferation of SF malaria products.

Given the potential of new innovations on the longer-term horizon, Unitaid will continue to monitor opportunities, even though there is limited scope for the organisation's involvement in the near-term. Unitaid will monitor opportunities to support early adoption of single dose treatment regimens not based on artemisinin to encourage treatment adherence and address drug resistance. Also, in the longer-term, innovations that use gene drive/ CRISPR* technology to genetically modify self-propagating mosquitoes that can boost the frequency of non-transmission traits across a vector population are showing promise.

* Clustered regularly interspaced short palindromic repeats (CRISPR) is a method of genome editing encompassing the deletion, insertion, or modification of specific DNA sequences in the genome.

PLEASE NOTE: Further analysis and partner consultation is needed before these exploratory areas can be presented to the Board of Unitaid for funding-decisions.

4 ANNEX

This Annex provides a detailed description of the malaria response challenges, which are presented briefly in Section 2 of the *Disease Narrative for Malaria*. The challenges have been identified through a thorough assessment of the current malaria landscape, including engagement with key stakeholders. Using the filters outlined in Section 3, Unitaid has identified the challenges that fit best within the scope of the organization, and will be actively explored in the near- and longer-term. Although Unitaid will direct attention to these priority challenges (FIGURE 10), the organization will also continue to monitor the status of all challenges below, and assess future opportunities for potential involvement.

Vector control key challenges

Moderate lifespan and implementation challenges with ITNs/IRS

ITNs have a lifespan of approximately three years, and next-generation IRS products provide protection for one malaria peak transmission season (3 – 6 months), so both require regular and repeated implementation campaigns. IRS campaigns are expensive and complex to implement as they are labor intensive and require major planning, training, operations and cooperation from households. The implementation success of IRS also varies depending on the sprayed surface. New IRS application technologies are in the pipeline and could become available in the next 2 – 3 years (see Section 2.4).

ITNs delivery is less complex compared to IRS. However, under operational conditions the durability and appropriate use of vector control tools varies. While guidelines exist for monitoring use under operational conditions, operationalizing monitoring programs is resource-intensive, and countries lack the resources, systems and skilled workers required to implement them. Other challenges include the high-cost of products and unclear demand, which limits supplier incentives to develop more durable/longer lasting tools. Suppliers are also not required to monitor tools once they are deployed.

Moderate efficacy of tools for indoor biting

ITNs have had a marked impact on malaria mortality across sub-Saharan Africa.[70] However, coverage of ITNs is low in some settings, and where they are utilized, they are approximately 45% effective at reducing uncomplicated malaria cases. Pyrethroid resistance is also a concern.

Available evidence to support new tools and approaches is weak, surveillance and cost effectiveness data of product combinations are lacking, and programmatic coordination is complex. More guidance is also needed on which tools are best suited to a specific setting, and how to best rotate products to slow the spread of resistance and to protect the efficacy of existing tools. Mixes of interventions alongside the rapid introduction of new, efficacious tools are also needed for increased impact, e.g. ITNs with novel AI.

Complexity of insecticide resistance management

Current strategies for insecticide resistance management (IRM) include rotating the insecticides used in IRS, use of interventions in combination (e.g. use of a pyrethroid ITN in combination with IRS using a non-pyrethroid insecticide), and mosaic spraying (using

different chemicals in different geographic areas). In 2017, WHO also recommended that ITNs that include both a pyrethroid insecticide and the synergist piperonyl butoxide be considered in areas of confirmed pyrethroid resistance of moderate intensity conferred (at least in part) by monooxygenase-based resistance mechanism.[71]

These strategies are more complex to implement than traditional ITNs or IRS programs, and their effectiveness compared to sequential use of insecticides is unknown. The evidence base for resistance management in vector control is weak and the monitoring and management of insecticide resistance is currently insufficient and inconsistent in most settings. As such, informed decision-making on managing insecticide resistance is often challenged by a lack of reliable routine monitoring data.[72]

Slow uptake of new VC products

Innovative products that have recently been evaluated and recommended for malaria control have achieved very poor market penetration due to their higher-price, a lack of impact data, and a funding pool that is often already insufficient to achieve or maintain high coverage of existing, lower-cost tools.

Innovators and procurement market-entry barriers also include the need to establish the cost-effectiveness of new products, articulating the unique selling point of novel interventions, reaching sustainable price points so products are profitable but also affordable, ensuring procurer and consumer acceptance, and deploying new tools into malaria programs that have complicated and resource-intensive implementation requirements. For example, new versions of ITNs that contain insecticide combinations that address pyrethroid resistance cost more than pyrethroid-only nets, and real-world deployment/cost-effective evidence for these new tools is unavailable. As a result, countries are not willing to purchase these more expensive tools, as they would generally have to come at the cost of cutting current net coverage levels.

Lack of tools to address key challenges such as insecticide resistance, outdoor biting

Despite the gains achieved using cost-effective vector control interventions, multiple challenges continue to threaten future progress. Critical among these are insecticide resistance, outdoor biting and residual transmission whereby disease transmission persists despite good coverage with high-quality vector control interventions.

Insecticide resistance is a key threat to the effectiveness of current core vector control tools. Resistance to all four classes of insecticides used for public health is widespread in all major malaria vectors, and 68 out of 80 malaria endemic countries reported resistance to at least one of the four insecticide classes.[73]

ITNs counter late-night and indoor-biting mosquitoes, and IRS targets indoor-resting mosquitoes. Mosquitoes that bite in the early evening, or which are outdoor biting or resting, can therefore evade these interventions and lead to residual malaria transmission. Transmission can also continue when people are away from houses or not under nets at the times when and where malaria vectors prefer to bite.[74]

The spread and geographic migration of new vectors is another emerging challenge. In Africa, malaria is generally prevalent in rural areas with strong seasonal variation and a malaria vector is not adapted to urban centers. However, in 2016, *An. stephensi* mosquitoes that are native to southern and western Asia were detected in Ethiopia for the first time following earlier reports of the species in Djibouti. *An. stephensi* is an

efficient malaria vector that can transmit both *P. falciparum* and *P. vivax.* It is found in rural areas and is well adapted to urban cities and infrastructures where they breed in manmade water containers.[75] As urban development rapidly expands, the spread of this vector across Africa could lead to malaria outbreaks of unprecedented size.

Currently, there are limited tools to address these challenges, though multiple products are in the pipeline (see Section 2.4). Challenges threatening the vector control pipeline include: the cost and complexity of late-stage R&D, specifically large-scale field trials to demonstrate impact on reducing infection and/or disease, and long and expensive country registration processes required for countries to begin using new tools. These challenges can delay the availability of new innovations and deter investments in R&D. Entering the public health market is relatively new for some vector control manufacturers and in doing so they can also encounter operational challenges adapting to the different market conditions. Other disincentives include the relatively small size of the public health market compared to the agricultural market and the high-risk, price-driven nature of the public health market where funding envelopes and willingness-to-pay are uncertain.[76]

Limited pre/post market QC systems

In 2017, the WHO PQP expanded to include vector control tools allowing for systematic, independent pre- and post-marketing manufacturing site inspections for vector control products. While the harmonization of a global quality control mechanism has accelerated the availability of quality products, there are several ongoing limitations with the current quality assurance (QA) systems for vector controls including: no commonly defined quality benchmarks and thresholds for manufacturers to follow, limited pre- or post-shipment QA systems (though some agencies, such as PMI, conduct their own pre- or post-shipment QA), limited post-marketing controls in the field, and a lack of clarity on how data informs changes or updates to a product listing.

Lack of data for targeting interventions

Malaria prevention strategies should be developed through evidence-based decision making that is guided by operational research, cost-effectiveness data, epidemiological impact evidence and surveillance.[77] Some tools also require entomological data e.g. vector control products. As more innovations become available, countries often lack the necessary resources, systems and skilled workers required to undertake these activities. In most malaria-endemic countries, four interventions—case management (diagnosis and treatment), vector control (ITNs and IRS) and chemoprevention, make up the essential package of malaria interventions. But as countries move to develop more context specific control and elimination strategies, they need strong data to guide product prioritization, product mixes, and decisions on where and when to deploy the most effective malaria tools for maximum impact.

Preventive therapies key challenges

Low demand & adoption of chemoprevention

WHO has recommended the provision of SP for IPTp as a component of routine ANC in areas of medium to high malaria transmission since 2012. Despite the WHO recommendation, demand for IPTp remains low in community and primary care settings.[78] Low uptake results from a combination of factors, including “falling through the cracks” between maternal child health and malaria programs, negative perceptions of drug use in pregnancy and of the efficacy of SP, and lack of prioritization of preventive interventions in ANC.

Although SMC uptake has progressed, several factors impede caregiver decisions to provide it to children including physical access to medication, the burden of the drug regimen, trust issues with healthcare providers, and perceived norms around malaria prevention strategies.[79]

Only Sierra Leone has adopted IPTi since WHO recommended it in 2010. Long-standing concern over increasing drug resistance to SP has been suggested as a possible reason for the low uptake for IPTi.[80] Efforts are underway to better understand the barriers to IPTi adoption and to identify strategies to catalyze scale-up.

Expansion to greater target populations lacks evidence

Currently SMC is only recommended in children under five in the Sahel, where *P. falciparum* is sensitive to both antimalarials.[81] Recent studies conducted with children under ten years of age in Senegal have found that SMC is well tolerated in children outside of the current recommended under-five age group,[82] and for longer periods than the recommended four months. [83] Use of SMC outside of the recommended age group could help reduce malaria transmission in areas of Africa where there is high malaria burden for children over five years old, however evidence to support this approach is currently lacking. SMC expansion beyond the Sahel to other regions with seasonal transmission could have significant impact. However, this would require alternative drug regimens. Long acting malaria chemoprevention regimens not based on SP are under development but will not be available in the next few years.

Poor quality SP and low supply of quality assured SP

There are a limited number of suppliers of QA SP on the global market. Reasons for low QA product supply include manufacturer reluctance to invest due to low sale price, small market size due to low IPTp and IPTi coverage, and the requirements and costs of achieving international QA.

No alternative regimen to address resistance

While evidence shows that SP remains highly effective for IPTp, concerns over resistance is prompting development and evaluation of alternate regimens for chemoprevention. Both azithromycin-chloroquine and mefloquine were recently considered as alternatives to SP for IPTp, however these have now been excluded.[84]

The latest evidence on efficacy and safety of dihydroartemisinin-piperaquine (DHA-PPQ) as an alternative is promising,[85] but currently there are insufficient data to allow for a full evaluation. Additional considerations in the use of DHA-PPQ for IPTp will be its higher cost as well the need for 3-day dosing.

RTS,S/AS01 partial effectiveness and complex dosing

RTS,S is the first vaccine to show partial protection against *P. falciparum* malaria in young children. During clinical trials, the efficacy of RTS,S/AS01 against clinical malaria was found to be 36% in young children and 26% in infants when a booster dose was administered.[86] RTS,S/AS01 has a relatively complex dosing schedule (3 doses plus a booster dose), which does not fully align with the EPI schedule and may be challenging to implement at high coverage. While RTS,S has already received a positive scientific opinion from the European Medicines Agency, WHO Expert Committees have recommended pilot implementation to further evaluate its public health use as a complementary malaria control tool.[87]

No highly effective vaccine

Vaccination against malaria could be a low-cost, effective way to prevent disease and save lives. While RTS,S is already undergoing pilot implementation and may be recommended by WHO in the coming years, next-generation malaria vaccines that are able to provide a higher level of protection and reduce transmission will be required. Next-generation vaccine candidates in the R&D pipeline but are not expected to be available in the next 10 years.

Case management key challenges

Limited tools to manage biological threats and to support adherence

A key biological threat to the malaria response is antimalarial drug resistance. *P. falciparum* resistance to previous generations of medicines – such as chloroquine and SP – became widespread in the 1970s and 1980s, undermining malaria control efforts and reversing gains in child survival. ACT partner drug resistance has been identified and partial resistance to artemisinin (the key active ingredient in ACTs), defined as delayed parasite clearance, has been confirmed in five countries of the Greater Mekong region.[88,89,90]

Prompt diagnosis and treatment with good quality medicines will delay the spread of resistance and the loss of ACTs. This includes improved adherence with the three-day ACT treatment regimen, and the removal of oral artemisinin-based monotherapies and substandard or falsified (SF) drugs from the market. Increased surveillance and monitoring is also critical to detect changes in therapeutic drug efficacy and to update policy in a timely manner.[91]

New single-dose treatments without artemisinin are being developed. These new products could be effective against resistant strains of malaria, but they will not be available in the short-term. Triple artemisinin combination therapies, which use combinations of existing antimalarial drugs, are also under investigation.[92]

Another emerging biological threat is increasing levels of *phfrp2*/*pfhrp3* gene deletions in some countries. Malaria parasites are evolving without the gene expressing the HRP2 antigen targeted by the most commonly available RDTs, leading to false-negative tests results. As a result, in some areas commonly used RDTs have lost their ability to reliably detect malaria. In areas where *phfrp2*/*pfhrp3* deletions have been well documented e.g. the Amazon region of South America, HRP2-based tests are not recommended. Recently, there have been documented deletions and reports of potential *phfrp2* deletions in several African countries and India. WHO recommends using alternative RDTs in countries where *phfrp2* deletion prevalence exceeds 5% among symptomatic patients. As a result, demand for non-HRP2 RDTs for P. falciparum detection is expected to increase in the coming years. However, there are few options for detecting *P. falciparum* using RDTs based on other target antigens (e.g. plasmodium lactate dehydrogenase (pLDH), aldolase), and alternatives are less sensitive and less heat stable than HRP2-based tests.[93] Limited efforts are underway to develop high-performing non-HRP2 *P. falciparum* RDTs which should become available in the next 1-2 years.

Proliferation of SF products and limited quality control measures

Poor quality medicines are often categorized as either falsified, which are deliberately and fraudulently mislabeled with respect to the identity and/or source, or substandard which are authorized medical products that fail to meet either their quality standards or specifications, or both.[94] Medicines distributed in public and private markets can also be unregistered/unlicensed or diverted. Unregistered drugs, which may be of good quality, are those that are not granted market authorization in a country. Approximately

50% of reported SF cases are antimicrobials, with antimalarials and antibiotics being the most prevalent.[95]

Key challenges to reduce SF products include weak regulation and surveillance systems, poor supply chains with inadequate storage conditions, and limited availability of quality assured tracking/verification technologies suitable for use in LMIC settings. As more technologies emerge, such as digital technologies that use artificial intelligence and blockchain, their high cost will make them prohibitive in LMICs. These technologies will require long term maintenance and monitoring and have limited interoperability with existing national systems.

The abundance of SF products, both treatments and diagnostics, is related to limited regulatory capacity, as well as weak quality control measures and post market surveillance systems. For instance, there are ongoing quality control concerns with malaria RDTs and no mechanisms in place to reliably check that RDTs are working in the field.

Poor quality case management in the private sector

The private sector plays an important role in delivering malaria care in urban areas and in remote rural areas of many high-burden countries. A large proportion (~40%)[96] of patients with fever in malaria-endemic countries first seek treatment through private health care providers, especially pharmacies, authorized and informal drug shops, and other medicine sellers. The quality of case management in these facilities, especially in terms of access to quality ACTs and malaria testing before treatment varies widely and is often poor.

Several factors can affect the quality of malaria case management in the private sector, including low availability/demand for diagnostic testing, low availability/demand for ACTs, and the availability/use of poor quality ACTs or non-recommended treatments. The higher-cost of ACTs, combined with the widespread availability of cheaper but ineffective antimalarial medicines, some of which are of substandard quality, is a key issue.

In the case of RDTs, low uptake results from several factors including regulations that do not allow or encourage the sale or use in the private sector, unaffordable prices (particularly combined price of RDT plus ACT), low awareness and/or acceptance of diagnostic testing, and lack of incentives for retailers to stock and sell RDTs (potential to lose medicine sales, lack of clarity on how to handle negative tests). Overall, there can be low demand for RDTs and ACTs from patients seeking treatment in the private sector, which limits the stocking and sale of these products and leads to lack of availability. Another key challenge to appropriate case management in the private sector is the large, unregulated informal sector, where non-recommended and often poor-quality drugs proliferate.

Poor adoption of IMCI/iCCM; limited tools for integrated management of childhood fever

Over three-quarters of children who seek care at health facilities and in the community in LMICs present with fever.[97] Many fevers are presumptively treated with antimalarials and antibiotics particularly in the private sector where monotherapies and SF medicines are widely available. Some studies also show that children who test positive for malaria often simultaneously have other infections, such as pneumonia.[98] Missed opportunities to effectively treat sick children can result in severe disease (including severe malaria), which is often overlooked and contributes to increased child mortality.

The recent scale-up of malaria RDTs, together with decreasing malaria incidence, have resulted in an increasing number of fevers diagnosed as malaria-negative. A recent modelling exercise suggests that as malaria has declined in sub-Saharan Africa, in a two-week period 25% of children will have a non-malaria fever whereas 3% of children will have a fever caused by malaria.[99] Poor fever management can lead to inappropriate treatment causing overuse and wastage of antimalarials and antibiotics, increased drug pressure leading to resistance, and high costs related to the management of drug-resistant patients.

Evidence suggests that many non-malarial fevers are not appropriately managed due to poor adoption of integrated approaches such as IMCI/iCCM alongside a lack of appropriate tools. When fully implemented, IMCI can reduce childhood mortality by 15% and iCCM algorithms for community health workers aim to extend care to areas without adequate access to health facilities.[100] However, the degree of implementation of these platforms is variable. Challenges for IMCI include a lack of child health leadership and funding, systems issues (e.g. staff turnover, motivation, retention), a lack of accountability and targets, as well as a lack of commitment to appropriately resource community health workers that are vital to ICMI/iCCM implementation. Additional shortcomings include a need for on-going, systematic evidence generation, review, and integration as well as improved flexibility for local customization (e.g. add/remove diseases according to local epidemiology).[101,102] The major challenge with iCCM is the need for government stewardship and investment in CHW systems, which are chronically underfunded.

A lack of appropriate tools has contributed to poor adoption of IMCI/iCCM. Easy to use, point-of-care diagnostics, such as tools for triaging severe disease or distinguishing between bacterial vs non-bacterial infection, are needed to better guide treatment practices. Some diagnostic tools are in the pipeline, but they are still being validated for use in LMICs, and targeted treatments are often unavailable when needed. Dispersible amoxicillin with child-dose packaging has been developed, but coverage is low despite scale-up efforts as first-line of pneumonia treatment and phase out co-trimoxazole. Co-packaged oral rehydration solutions and zinc has recently been listed on essential medicines lists, as only about 7% of diarrhoea cases are treated with both.[103]

Current tools limit optimal case management in pregnancy

Pregnant women have a higher risk of contracting malaria.[104] Malaria infection during pregnancy is associated with severe illnesses, including anemia, and can contribute to low birth weight among newborn infants, which is a leading risk factors for sub-optimal growth and development, and infant mortality.[105]

The WHO currently recommends treating women with uncomplicated malaria in second or third trimester of pregnancy with ACT.[106] In the first trimester treatment with quinine and clindamycin is recommended, as there has been challenges establishing the safety of ACT use in the first trimester. However, recent studies have found no evidence that artemisinin treatment increases adverse outcomes in first trimester of pregnancy compared to quinine treatment. [107,108] The availability and tolerability of ACTs, along with likely reduced future availability of quinine has led to recommendations for treatment guideline updates on ACT use in the first trimester.[109]

Moreover, due to the complex behavior of the malaria parasite, pregnant women with malaria may not carry the parasite in their blood at a density that can be detected with current RDTs. This adds to the difficulty of malaria case management in pregnancy, as malaria infections may not be diagnosed as clinical malaria, or may even be asymptomatic, and thus remain untreated.

Low adherence to guidance on severe malaria

Sixteen countries in Africa include the use of RAS in their treatment guidelines,[110] however these guidelines vary widely by country, and none fully align with the WHO recommendations. A lack of operational guidance from the WHO, in addition to the lack of commercially available QA RAS raises implementation concerns for countries that have adopted the WHO recommendation.

A study commissioned by Unitaid found that adoption of WHO recommendations on severe malaria case management has been slow.[111] As of June 2019, only seven of the 60 countries that have available guidelines on severe malaria treatment recommend injectable artesunate as the preferred first line treatment (or treatment option), specify dosing for children under 20kg, and recommend use of artemether over quinine when artesunate is not available, as per the WHO recommendations. The study also found persistent issues for injectable artesunate use in study countries, including a lack of health worker supervision and training, misuse at point of care, and unauthorized use at lower levels of the health system. Quinine is still the preferred treatment for severe malaria in some countries due to its affordability, ample supply, and preference by health care workers.

Limitations of microscopy and RDTs

In ideal settings, microscopy is highly sensitive and specific. However, under typical field conditions, performance can be compromised by poor quality microscopes, stains and slides, insufficient training and supervision, interruptions in electricity, insufficient time to stain and examine slides, and absence of QA systems. Staining and interpretation are labor intensive (30 minutes per slide), and require considerable expertise, particularly for species identification, and in cases of low parasite density.

Malaria RDTs have several advantages. They are inexpensive, portable and disposable, and require no laboratory infrastructure, electricity or instruments. Operationally, low-skilled health workers with limited training can use RDTs. However, malaria RDTs also have several limitations. These include poor heat stability, with risk of deterioration and reduced sensitivity when they are exposed to heat and humidity for prolonged periods, the inability to distinguish between current and past infections, and the inability to quantify parasite density to monitor a patient's response to treatment.

RDT supply challenges

The RDT market has been evolving in the past few years, yet several key challenges remain largely unchanged. Recent public-sector procurement data shows that the RDT market remains consolidated around two suppliers that have captured 85% of the market since 2013. This has created a risk to supply security. Prices also remain at low, unsustainable levels (as low as US$0.15/test) which, together with competitive advantages around high volume production (ability to fill large orders with short lead times), create barriers to entry for other suppliers. This has resulted in formerly dominant malaria RDT manufacturers exiting the public-sector market and has discouraged potential new entrants.

HRP2-based *P. falciparum* RDTs remain the dominant malaria RDT, comprising approximately 60-80% of the donor market. However, there have been recent shifts in demand from HRP2 *P. falciparum*-only RDTs to HRP2/pLDH pf tests to address *pfhrp2/pfhrp3* deletions, and *P. falciparum/P. vivax* and pan (multispecies) tests that can detect different malaria species. While some prequalified HRP2 *P. falciparum*-only RDTs exist, product selection is quite limited or nonexistent for these other product categories.

Lack of operational evidence on elimination strategies

Malaria elimination is defined as the interruption of local transmission (reduction to zero incidence of indigenous cases) of a specified malaria parasite species in a defined geographical area because of deliberate activities.[112] Core malaria interventions such as vector control and case management should be maintained in settings with low or very low transmission. However additional interventions can also be considered in these settings to accelerate elimination. These include:

- Active case detection - diagnostic testing in population groups considered to be high risk, to find malaria cases among people who do not present to health facilities
- Reactive case detection - active response to a confirmed case or cluster of cases, in which a population potentially linked to such cases is screened and tested
- Detecting asymptomatic infections with very low parasite densities using more sensitive diagnostic methods, such as molecular techniques or a new higher-sensitivity RDT that has recently become available
- Population-wide parasite clearance by mass drug administration to accelerate transmission reduction[113]

In addition, in low-transmission settings WHO recommends that treatment of *P. falciparum* malaria include a single low-dose of primaquine alongside ACTs to reduce transmission.[114]

Operational research on the feasibility, safety and cost-effectiveness of the above tools/strategies is limited. Evidence is needed to evaluate their potential wide-scale use, and to support national decision-making and WHO policy recommendations/guidelines.[115]

Complexity of P. vivax case management and limitations of current tools

P. vivax malaria differs to *P. falciparum* as dormant forms of the parasite, known as hypnozoites, can remain in the liver after treatment and relapses can occur as a result. Treatment is therefore more complex as it requires two drugs – a first to treat acute (blood-stage) illness, and a second to clear the dormant liver parasites. In addition, treatment of liver stage requires diagnostic testing to identify and exclude patients with G6PD deficiency, as available treatments can cause adverse effects (hemolysis) in cases with this gene deficiency. A further challenge is the 14-day treatment course of primaquine, which can limit adherence.

Another complexity in *P. vivax* case management relates to the fact that clinical cases can occur at lower blood parasite concentrations than for *P. falciparum*. This makes it harder to detect all symptomatic cases with currently-available RDTs or field quality microscopy. In addition, there are currently no diagnostic tools capable of detecting hynozoites to identify (and treat) individuals who are at risk of relapse.

Cross-cutting key challenges

Weak surveillance systems

The malaria response needs strong surveillance systems to provide reliable data that can inform decision making for targeted interventions. Despite significant improvements since 2010, surveillance systems for monitoring malaria remain weak due to a lack of health care facility oversight by national surveillance bodies, variable testing and treatment seeking rates at a population level, and a lack of reliable processes for measuring the surveillance systems themselves.[116] Currently, the WHO is working with the RBM Partnership to develop

national surveillance assessment tools to better define testing and reporting rates, whilst developing improved tools and standards for surveillance.[117]

Lack of data for decision making to deploy new tools

Without strong surveillance systems, adequate data that are needed to guide the most appropriate use of new tools for malaria are not available. Robust data are particularly vital for making decisions on utilization of new technologies as more tools become available. Donors, countries and implementing partners rely on reliable information for programmatic guidance, yet often lack the necessary resources, systems and skilled workers required to generate the evidence that is needed.[118] Moving forward, comprehensive data, delivered in real-time will be an important element for planning, delivering and evaluating context-specific packages of interventions in response to the HBHI strategy.[119]

Weak health systems: HR, supply chain etc

Weak health system infrastructure includes issues such as management of supply chains, lack of regulation in the private health sector, poor surveillance, monitoring and evaluation systems, and a lack of adequate technical and human resource capacities.[120] These factors pose impediments to planning, delivery and evaluation of malaria response tools.

Lack of financing, political commitment

Lack of predictable and sustained financing from countries and international donor is a key challenge to progress in the malaria response. These financial threats are compounded by difficulty in maintaining political commitment at the highest levels, such as opinion leader engagement from the political and private spheres.[121] Maintaining this commitment is particularly difficult, and poses a significant threat in countries that are progressing towards elimination.[122]

In high-burden countries malaria interventions rely predominantly on external funding. International investment into malaria programs in 2017 fell US$1.3 billion short of the US$4.4 billion funding target set by the GTS.[123]

Challenges of regional collaboration

Malaria responses at a country level also require regional collaboration across country borders. However, this can be challenging to establish and coordinate. Specific issues that require regional collaboration include movement of populations, such as laborers or refugees across countries, and malaria transmissions that cross or occur along international land boundaries. Regional collaboration is particularly important in the context of artemisinin resistance in the Greater Mekong Sub-region.

Countries that are approaching elimination often find that malaria cases occur along international borders shared with countries that do not have strong control programs and have not reached malaria elimination stage. To address this challenge, neighboring countries should explore opportunities for scaling up cross-border coordination and enhancing collaboration to optimize shared malaria elimination efforts.[124]

Limited delivery for the prevention and treatment of malaria related anaemia

In malaria endemic areas of Africa, malarial anaemia is most common in young children and pregnant women. Estimates suggest that severe anaemia is related to more than 50% of all malaria-related childhood deaths in Africa,[125] and approximately 30-40% malaria deaths in adults.[126] Given this trend, there is significant overlap with malaria challenges in populations at highest risk.

Malarial anaemia is primarily prevented by preventing malaria. Preventing repeated or recurrent malarial infections is important for preventing malarial anaemia, as repeated malaria episodes can have a cumulative impact.[127] IPTi can reduce malarial anaemia by up to 50% in children,[128,129] and IPTp has been shown to reduce maternal anaemia in pregnant women.[130]

Diagnosis and treatment of malarial anaemia also has its own challenges. If a patient is diagnosed with an active malarial infection, their anaemia cannot be treated with WHO recommended iron supplementation unless the malaria infection is effectively managed,[131] as the iron will not be effectively absorbed by the patient, and the iron may act as growth factor for parasites, bacteria and viruses. Current diagnostics for anaemia lack the capacity to indicate a patient's readiness to uptake iron.

Blood transfusions may be needed in cases of severe malarial anaemia. This is often challenging in resource-constrained environments, as access to blood transfusion remains unavailable to a large proportion of population in sub-Saharan Africa.[132]

Social unrest & conflicts, humanitarian disasters

Military conflicts and humanitarian disasters contribute to the spread of malaria by forcing people into new areas of exposure and by limiting access to malaria prevention and treatment. For example, during the 2014–2016 outbreak in West Africa, an increase in malaria cases and deaths was observed, as people with fever were reluctant to visit health facilities in fear of being quarantined, fear of being treated as suspected Ebola, or fear of contracting Ebola.

Food security

A lack of food security can have a negative impact on malaria and other health problems. Malnourished children are less able to mount an immune response and withstand malaria infection, and children who are infected are at increased risk of mortality.[133] Malnutrition can result in iron deficiency, which along with malaria is one of the most common causes of anemia in children. WHO recommends the intermittent use of iron supplements to improve iron status and reduce the risk of anaemia among children, including in conjunction with malaria prevention and treatment tools in malaria-endemic areas.[134]

In addition, agricultural practices aiming to improve food security, such as intense farming, irrigation and drainage need to be well managed, or they can result in increasing vector breeding sites.[135]

Climate and environmental change

Some analyses suggest that weather and climate may have an influence on malaria distribution, seasonality and on longer-term trends. For example, periods of high rainfall or warmer temperatures can result in increased malaria transmission.[136] The Intergovernmental Panel on Climate Change concluded that "changes in temperature and rainfall will affect the natural habitats of mosquitoes, changing the prevalence of the vector or prolonging transmission seasons (or both) in some areas, and potentially exposing new regions and populations to malaria and other vector-borne diseases".[137]

Other modelling suggests that climate change will not consistently exacerbate malaria incidence, but rather have a disproportionate effect, making different geographic environments more or even less hospitable to malaria carrying mosquitoes. This shift will need to be considered when planning strategies for climate adaptation in areas of high malaria burden.[138]

Environmental change can also have an impact on malaria transmission. For example, deforestation,[139] large-scale irrigation, urbanization,[140,141] the establishment of rubber plantations,[142,143] soil salinification,[144] and extractive activities can all influence malaria transmission.[145,146]

Population growth

Many malaria endemic countries are also countries with high levels of population growth.[147] Countries in Africa have the highest rate of population growth, and this is where the highest burden of malaria is. Growing populations require increased resources to achieve universal coverage of malaria interventions, but the average funding available per person at risk of malaria globally declined between 2015 and 2017, compared with 2012 to 2014.[148]

Disproportionate malaria in vulnerable and hard to reach groups

Hard-to-reach groups at risk of malaria include the poor, who tend to live in rural areas where there is a high risk of malaria, in poorly-constructed housing that have little, if any, barriers against mosquitoes.[149] Other hard-to-reach groups include high-risk occupational groups, mobile or migrant populations, stigmatized population groups, and people in conflict areas.[150]

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