Disease Narrative for Malaria and Areas for Intervention

ADAPTED FROM CONTENT DEVELOPED FOR PRESENTATION TO UNITAID EXECUTIVE BOARD FOR ITS 23 MEETING (11/2015)

Executive Summary

In the past 15 years, substantial progress has been made in reducing malaria incidence and mortality. The number of cases worldwide has been reduced by 30%, leading to a total of 670 million fewer cases between 2001 and 2013. Despite recent gains, approximately half of the world's population is still at risk of malaria, and in 2013 an estimated 198 million malaria cases and 584 000 malaria deaths occurred globally.

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 the next 15 years. The GTS outlines a set of ambitious goals that all malaria partners – international agencies, NGOs, the private sector, academics and others – can collectively work towards. Namely, to reduce malaria mortality rates and incidence rates by 90% versus 2015 as well as eliminate malaria from at least 35 countries and prevent re-establishment in all malaria-free countries. The goals are ambitious, but technically feasible. Substantial additional gains could be achieved through the dramatic scale-up of existing cost-effective tools, which would require not only increases in funding, but also innovative approaches to delivery/implementation. Innovative tools are also needed to address key challenges such as insecticide and drug resistance. Malaria R&D pipelines contain a range of new tools that could "bend the curve" towards achieving the global goals, some of which will be available in the next few years.

UNITAID has identified a comprehensive list of challenges the response is facing to reach these global goals. These challenges were identified through the following steps:

- Analysis of partners' strategies
- Review of relevant UNITAID's landscapes
- Engagement with partners

Based on this list, challenges were then assessed according to the following criteria:

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

This has resulted in the identification of four high-priority Areas for Intervention (AfIs), to be considered by the UNITAID Executive Board for validation:

1. Accelerate adoption of innovative vector control tools

This AfI will address a key threat to the achievement of the global goals: mosquito resistance to the insecticides used in vector control. Specific challenges to be addressed include the lack of tools to combat resistance, the low uptake of innovative vector control products and limited pre- and post-market quality controls for vector control products. The aim of this AfI is to accelerate the timelines for innovative products to reach the market by supporting a more streamlined global evaluation process and generating evidence on the use of new tools to guide normative guidance and implementation support. The expected impact of this AfI is that much-needed vector control innovations will reach the market more quickly and will be able to be deployed more rationally to maximize their impact.

2. Expand private sector access to diagnosis and treatment

This AfI aims to improve access to appropriate malaria case management in the private sector. Given that 40% of malaria patients seek care in the private sector, improve access to diagnostic testing and treatment in this sector is necessary to achieve a step change in universal coverage.

By addressing key barriers to private sector case management in a selection of countries, this AfI would unlock the potential of the Global Fund Private Sector Co-payment Mechanism and generate lessons and models that could be applied more broadly. These learnings would also inform the inclusion of private sector case management in future Global Fund malaria Concept Notes. Interventions would build on UNITAID's past and ongoing investments in private sector case management, as well as other related initiatives, in order to leverage the lessons learnt, challenges and opportunities of these projects.

Better malaria case management in the private sector would result in improved outcomes for patients with malaria as well as other sources of fever; better targeting of resources, and reduced risk of drug resistance caused by the use of ineffective and poor quality drugs.

3. Expand access to preventive chemotherapy in pregnant women

This AfI will aim to address the low coverage of intermittent preventive therapy in pregnant women (IPTp), a highly cost-effective intervention targeting a high-risk group for malaria. The focus will be on challenges related to the current low demand for IPTp and the limited supply of quality assured SP for IPTp and SMC. Specifically, innovative approaches to IPTp delivery and demand generation will be generated to support global guidance and scale-up. Current challenges related to the supply of quality SP, the drug regimen used in IPTp, will also be addressed to ensure that quality products are available to support future scale-up efforts. Interventions that address both supply-side and demand-side challenges would provide the necessary foundation for a significant expansion of IPTp coverage.

4. Optimize introduction of tools for the treatment of severe malaria

Severe malaria that goes untreated causes death in nearly 100% of cases, and the great majority of these deaths are in children under 5 year of age. This AfI will aim to address key challenges related to the treatment of severe malaria. To address expected barriers to the introduction of rectal artesunate once it is available for donor procurement in 2016, the implementation of rectal artesunate would be piloted in order to ensure controlled introduction due to concerns of misuse, as well as provide proof of concept that this community-based intervention can be implemented at scale. Future opportunities will also be monitored and evaluated, particularly with respect to further scale-up of injectable artesunate, and facilitating access to new treatments for severe malaria.

Further interventions in severe malaria would serve to optimize the impact of UNITAID's current project, *Improving Severe Malaria Outcomes*. The broader impact of the increased use of tools for the treatment of severe malaria would be a reduction in under 5 mortality.

Table of Contents

1 Analysis of the disease context

1.1 Disease introduction

Malaria is a curable, but life-threatening disease that causes febrile illness. It is transmitted to people through the bites of *Anopheles* mosquitoes, called malaria vectors, infected with *Plasmodium* parasites. In areas of high malaria transmission, high-risk populations include pregnant women whose immunity is decreased by pregnancy, and children under 5 years of age who have not yet developed partial immunity to malaria[1]. Among the five different species of parasites that cause malaria among humans, *P. falciparum* and *P. vivax* are the most prevalent. *P. falciparum*, the most common species in Sub-Saharan Africa, is the most deadly. *P. vivax*, the most common species in Asia and Latin America, differs to *P. falciparum* in that it survives in the liver for long periods, causing relapse several months after infection. Full cure of *P. vivax* therefore requires treatment of the acute illness as well as a second treatment to clear dormant liver parasites.

1.2 Global goals and associated strategy

In the past 15 years, substantial progress has been made in reducing malaria incidence and mortality. The number of cases worldwide has been reduced by 30%, leading to a total of 670 million fewer cases between 2001 and 2013. Global mortality rates have also dropped by 47% - 54% in the African Region – resulting in 4.3 million fewer deaths between 2001 and 2013 (3.9m fewer deaths in children under 5 in Sub-Saharan Africa)[2]. However, these gains remain fragile and have been unequally distributed[3].

Despite recent gains, approximately half of the world's population is still at risk of malaria, representing approximately 3.2 billion people in 97 countries in 2013. In 2013 it is estimated that 198 million malaria cases occurred globally, of which 80% were in Sub-Saharan Africa alone. In the same year it is estimated that there were 584 000 deaths from malaria, 78% of which occurred in children under 5[4].

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 the next 15 years. The strategy sets global goals for 2030 and provides a technical framework for countries and development partners for the next 15 years, emphasizing the importance of scaling up malaria responses and moving towards elimination. Concurrently, the Roll Back Malaria Partnership published Action and Investment to defeat Malaria 2016-2030 (AIM), a companion document to the GTS that provides a guide for collective action in the fight against malaria.

The GTS and AIM have outlined a set of ambitious goals that all malaria partners – international agencies, NGOs, the private sector, academics and others – can collectively work towards (see figure 1).

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[1] Centers for Disease Control and Prevention. Impact of Malaria (website). Available from: http://www.cdc.gov/malaria/malaria_worldwide/impact.html (accessed 17 Oct. 2015).

[2] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[3] Roll Back Malaria Partnership. Action and Investment to defeat Malaria 2016–2030. Geneva: World Health Organization; 2015.

[4] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

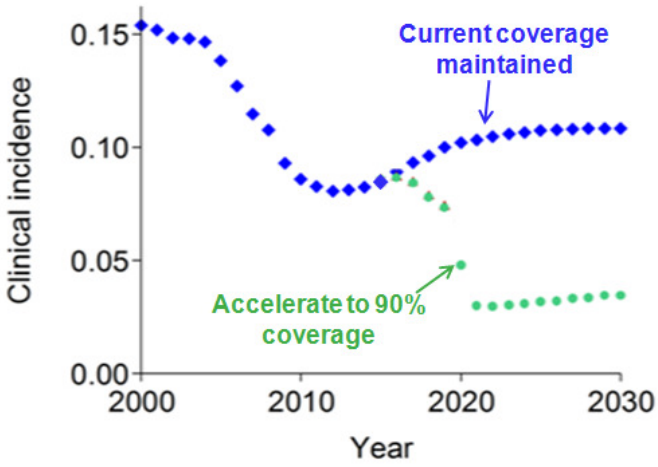
Figure 1. Global goals

	2020	2025	2030
Reduce malaria mortality rates vs. 2015	≥40%	≥75%	≥90%
Reduce malaria case incidence vs. 2015	≥40%	≥75%	≥90%
Eliminate malaria from countries	≥ 10 countries	≥ 20 countries	≥ 35countries
Prevent re-establishment in all malaria-free countries		Prevented	

Source: WHO Global Technical Strategy & RBM AIM

The goals and targets set out in the GTS and AIM are ambitious, but technically feasible. The figure below projects malaria incidence between 2015 and 2030 under two coverage scenarios. The blue line projects malaria case incidence if current coverage of key interventions was continued at 2012 levels. Under this scenario there is a risk that incidence increases over the coming years, due primarily to decreased immunity. The green line projects malaria incidence at 90% coverage of key interventions. This projection demonstrates that substantial additional gains could be achieved through the dramatic scale-up of existing interventions. Achieving such widespread coverage will require not only increases in funding, but also innovative approaches to delivery/implementation. Given current trends in malaria incidence, achieving the milestones set out in the GTS will require further efforts to "bend the curve", through increased commodity access and innovation (see figure 2).

Figure 2. Global projection of clinical incidence



Source: Adapted from Alonso P. *P. vivax* in the context of the GTS for malaria 2016-2030 (presentation). *Plasmodium vivax* Global Meeting, New Delhi, 29 – 30 July 2015.

Key messages:

- There has been substantial progress in the fight against malaria in the past 15 years, however malaria still results in nearly 600,000 deaths/year, 78% of which are in children under 5
- A new Global Technical Strategy (GTS) for Malaria was adopted in 2015 which aims to leverage past gains and accelerate progress over the next 15 years, including expanding malaria elimination
- Achieving the goals and targets set out in the GTS requires innovative strategies to increase access to existing, cost effective tools, as well as the rapid uptake of new, game-changing tools

1.3 Cost-effective tools to prevent, diagnose and treat malaria, but significant coverage gaps and current tools at risk

Cost-effective tools exist to prevent, diagnose and treat malaria. These tools can be classified into four categories: vector control, medical prevention, diagnosis and treatment.

1.3.1 Vector control

Vector control is a key tools 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%[5]. In Sub-Saharan Africa, less than one-third (29%) of households had enough ITNs for all household members, and one third of households did not own a single ITN[6]. However, coverage of ITNs varies considerably between countries and by geographic area, with some countries/areas achieving high levels of coverage. Coverage of IRS is significantly lower than that of ITNs: in 2013, only 4% of the global population at risk was protected by IRS, decreasing from more than 5% in 2010[7].

In addition to coverage gaps, the effectiveness of vector control is threatened as malaria mosquitoes develop resistance to the insecticides used in ITNs and IRS. In some areas, resistance to all 4 classes of insecticides used for public health has been detected. The *Global plan for insecticide resistance management in malaria vectors*[8] was launched by WHO in 2012 to address this issue and is starting to be implemented at country level. The threat of insecticide resistance is one of the main challenges to future progress against malaria; new products and chemicals to fight resistance is therefore a key priority for research and development.

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[5] Roll Back Malaria Partnership. Global malaria action plan for a malaria-free world. Geneva: World Health Organization; 2008.

[6] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[7] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[8] WHO. Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization; 2012.

1.3.2 Preventive therapies

WHO recommends targeting pregnant women, infants and children with chemoprevention strategies. Preventive treatment with sulfadoxine-pyrimethamine (SP) is recommended for pregnant women and infants in areas with moderate to high transmission. In highly seasonal transmission areas of the Sahel sub-region in Africa, seasonal malaria chemoprevention (SMC) is recommended for children aged 3-59 months.

Of the 35 million pregnant women in sub-Saharan Africa, it is estimated that 15 million did not receive a single dose of intermitted preventive treatment in pregnant women (IPTp) in 2013. [9]The primary delivery channel for IPTp is antenatal care (ANC). While nearly 90% of pregnant women in sub-Saharan Africa attend ANC at least once, in 2013 only 57% received at least one dose of IPTp and only 17% received the recommended three or more doses[10]. Coverage of preventive chemotherapy in infants and seasonal malaria chemoprevention (SMC) in children in the Sahel are also low, though in the past year there has been significant interest from both countries and donors to expand the coverage of SMC.

In 2015, the first malaria vaccine – RTS,S/AS01 – was approved by the European Medicines Agency. The RTS,S/AS01 vaccine has been found to provide partial protection against clinical malaria (26% efficacy in infants and 36% in young children[11] who received all planned doses). A WHO policy recommendation regarding the RTS,S/AS01 vaccine is expected in late 2015. Other malaria vaccine candidates are at various stages of the R&D pipeline, with four vaccines currently undergoing field trials[12].

1.3.3 Diagnosis

Prompt diagnosis and effective treatment are the cornerstones of malaria case management; patients recover rapidly if diagnosed and treated early. In most areas of Africa today, less than half of the malaria diagnostic tests performed are positive. Presumptive treatment of malaria (i.e. based on symptoms alone) therefore leads to the widespread use of antimalarial drugs for non-malaria fevers. It is estimated that current demand for ACT treatments in the African region (479million) would be reduced by more than 60% if only malaria cases confirmed with diagnostic testing were treated with ACTs[13]. Scaling-up diagnostic testing is therefore critical to ensuring the optimized use of ACTs.

In 2010, the World Health Organization (WHO) recommended diagnostic testing of all suspected cases of malaria before treatment. However, in sub-Saharan African, the proportion of all febrile children that receive a parasitological test for malaria is only 17%. Moreover, the proportion of children aged under 5 years who received a blood test for fever is lower in the private sector (median 9%) than in the public sector (median 31%)[14].

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[9] Roll Back Malaria Partnership. Global Call to Action to Increase National Coverage with Intermittent Preventive Treatment of Malaria in Pregnancy. Available from: http://www.rollbackmalaria.org/files/files/resources/call_to_action_report_v5d_EN.pdf (accessed 17 Oct. 2015)

[10] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[11] RTS,S Clinical Trial Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized, controlled trial. Lancet, 386(9988):31–45, 4 July 2015.

[12] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[13] WHO. World Malaria Report 2013. Geneva: World Health Organization; 2013.

[14] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

1.3.4 Treatment

WHO recommends artemisinin-based combination therapies (ACTs) as the first-line treatment of uncomplicated *P. falciparum* malaria. Overall in sub-Saharan Africa, the estimated proportion of children aged under 5 years with confirmed *P. falciparum* malaria that received an ACT was less than 20% in 2013 (range 9–26%)[15]. This translates into 56–69 million children with malaria that did not receive an ACT in 2013. Lack of access to ACTs by those who have malaria therefore co-exists with treatment of non-malarial fevers with ACTs and other antimalarials.

The public sector has been instrumental in scaling-up access to malaria case management, including both diagnostic testing as well as treatment with ACTs However, access to case management in the private sector remains low, despite the fact that 40% of malaria patients seek care in this sector. Ensuring diagnostic testing and effective treatment of malaria in the private sector is therefore a key component of universal access[16].

For severe malaria, intravenous artesunate is the first choice of treatment in adults and children[17]. Pending transfer to a heath care facility, in situations where injections are not possible, WHO also recommends that children be given rectal artesunate as pre-referral treatment[18]. Coverage of recommended treatments for severe malaria remains low, though scale-up of injectable artesunate is being catalyzed under an ongoing UNITAID project, *Improving Severe Malaria Outcomes (ISMO)*. The introduction of rectal artesunate has been impeded by the lack of a stringent regulatory authority (SRA)-approved/WHO Prequalified product and its coverage today is close to zero. Under the ISMO project, support is being provided for the development of rectal artesunate products for submission to WHO prequalification (PQ).

An important challenge in malaria treatment is drug resistance, which could trigger an upsurge in cases and deaths if left unaddressed. In recent years, parasite resistance to artemisinins has been detected in 5 countries of the Greater Mekong region: Cambodia, Laos, Myanmar, Thailand and Viet Nam. New drugs are under development which are not cross-resistant with current artemisinin-based treatments, however these are not yet available. Current efforts to contain artemisinin resistance, as recommended in the *Global Plan for Artemisinin Resistance Containment*[19], include malaria control and elimination measures to stop the spread of resistant parasites, routine monitoring of antimalarial drugs for changes in therapeutic efficacy, and improved access to diagnostics and rational treatment with ACTs to limit opportunities for resistance.

Key messages:

[15] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.

[16] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

[17] WHO. Guidelines for the treatment of malaria. Third edition – 2015. Geneva: World Health Organization; 2015.

[18] WHO. Guidelines for the treatment of malaria. Third edition – 2015. Geneva: World Health Organization; 2015.

[19] WHO. Global Plan for Artemisinin Resistance Containment. Geneva: World Health Organization; 2011.

- Coverage of key interventions for high-risk populations remains poor: chemoprevention in pregnant women and treatment for children with severe malaria
- Insecticide and artemisinin resistance are major risks to current tools and are therefore key priorities for research and development
- Expanded access to appropriate diagnostic testing and treatment in the private sector will be critical to achieving universal access

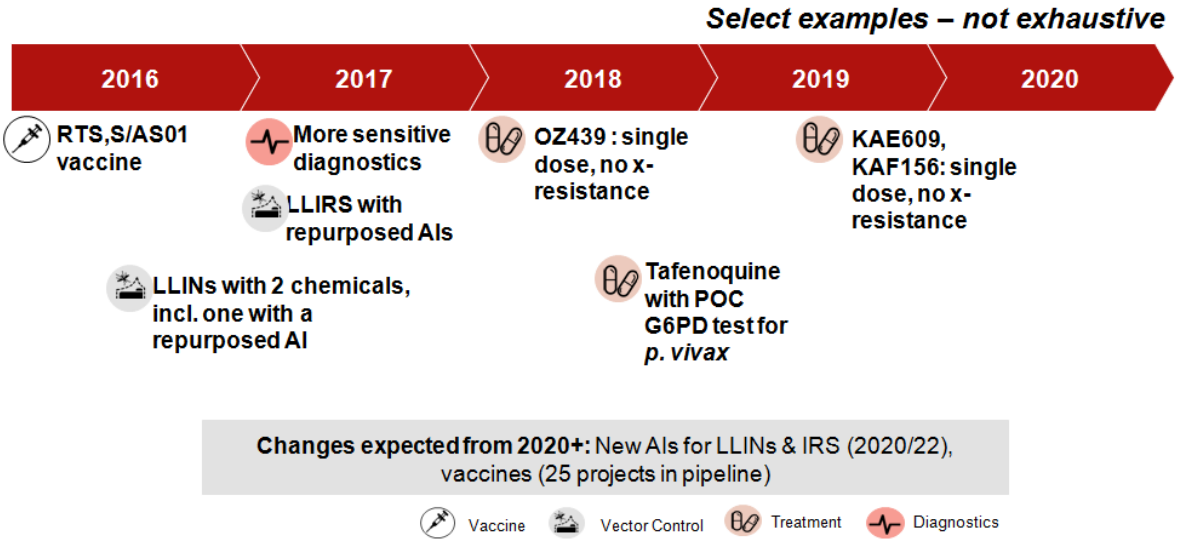
1.4 Innovations will accelerate the pace of change in the coming years

There are several products in the innovation pipeline for vector control, preventive therapies, diagnostics and that have the potential to influence the pace of progress towards the global goals. In 2016, it is expected that rectal artesunate, used in pre-referral treatment of severe malaria, will become eligible for donor procurement. The vaccine RTS,S/AS01 received a positive scientific opinion from the European Medicines Agency (EMA) in 2015, and a WHO policy recommendation on its use is expected in late 2015. By 2020, R&D pipelines are likely to yield new drugs to address artemisinin resistance, LLINs with combinations of chemicals, a chemical repurposed from agriculture that could be used for LLINs and IRS, and more sensitive diagnostics that can detect carriers of malaria parasites who are not sick but contribute to the spread of malaria[20]. Beyond 2020, promising innovations include vaccines that can offer a high degree of protection against malaria in young children; vaccines that can block transmission of the malaria parasite from humans to mosquitoes, thereby preventing the onwards spread of malaria in the population; and new chemicals that can be used for malaria vector control[21]. UNITAID monitors the R&D pipelines on an ongoing basis to identify where catalytic interventions could accelerate access to new game-changing products (see figure 3).

[20] UNITAID. Malaria medicines technology and market landscape. 2nd Edition. Geneva: UNITAID; 2015. UNITAID. Malaria diagnostics landscape update. Geneva: UNITAID; 2015. UNITAID. Malaria Vector Control Commodities Landscape. 2nd Edition. Geneva: UNITAID; 2014.

[21] PATH. Reimagining global health. 30 high-impact innovations to save lives. Available from: http://ic2030.org/wp-content/uploads/2015/07/ic2030-report-2015.pdf (accessed 17 Oct. 2015).

Figure 3. Innovation pipeline



Key messages:

- A range of new tools and technologies are under development that can mitigate resistance and support elimination efforts.
- New vector control tools to fight insecticide resistance are expected in the next two years.
- New drugs to address artemisinin resistance will be available as early as 2018.

2 Partner landscape in Malaria

A clear vision of the role of all organizations acting against malaria is key to ensuring that UNITAID's strategy is consistent and coordinated with the global response to the disease. The image below maps out key players in the global response against malaria and their primary areas of focus, bearing in mind that this list of partners is not exhaustive and that each partner generally plays several complementary roles.

Figure 4. Partners mapping

As illustrated in figure 4, in the upstream space, malaria innovation is benefitting from the efforts of the Bill & Melinda Gates Foundation, 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, as well as several public private partnerships (MMV, IVCC, FIND, MVI). NGOs such as PATH, private industry and academia also have a critical role to play in upstream innovation and R&D. In between upstream innovation and downstream delivery, multiple players are working on normative guidance (WHO), quality assurance (WHO, FIND), and advocacy (RBM, ALMA, civil society). With respect to downstream delivery, 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, PMI and DFID, 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.

Within this 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. In countries and regions where the malaria burden remains high, efforts are primarily needed to expand access to existing tools using innovative approaches, while in countries nearing elimination the deployment of new strategies and tools will be needed[22].

[22] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

3 Challenges threatening progress towards global goals

UNITAID identified a comprehensive inventory of challenges that threaten achievement of global goals, as a framework for articulating and refining its focus in potential Areas for Intervention. This analysis was based on consultation with partners and input from multiple sources, as mentioned in the box.

List of sources used to develop list of challenges:

- UNITAID strategic insight and market intelligence resources (e.g. landscapes, dashboard)
  Countries' implementing strategies
- Global Technical Strategy for Malaria 2016-2030 of the Global Malaria Programme
- Action and Investment to Defeat Malaria 2016-2030 from the Roll Back Malaria Partnership
- The Global Fund's strategies and analyses
- The 2015-2020 Strategy of the President's Malaria Initiative (PMI)
- PATH report: Innovation Countdown 2030
- WHO/UNICEF report: Achieving the malaria MDG target (2015)
- Bill & Melinda Gates Foundation, United Nations Secretary-General's Special Envoy for Financing the Health Millennium Development Goals and for Malaria report: From Aspiration to Action: what will it take to end malaria? (2015)
- Innovation pipelines of the private sector

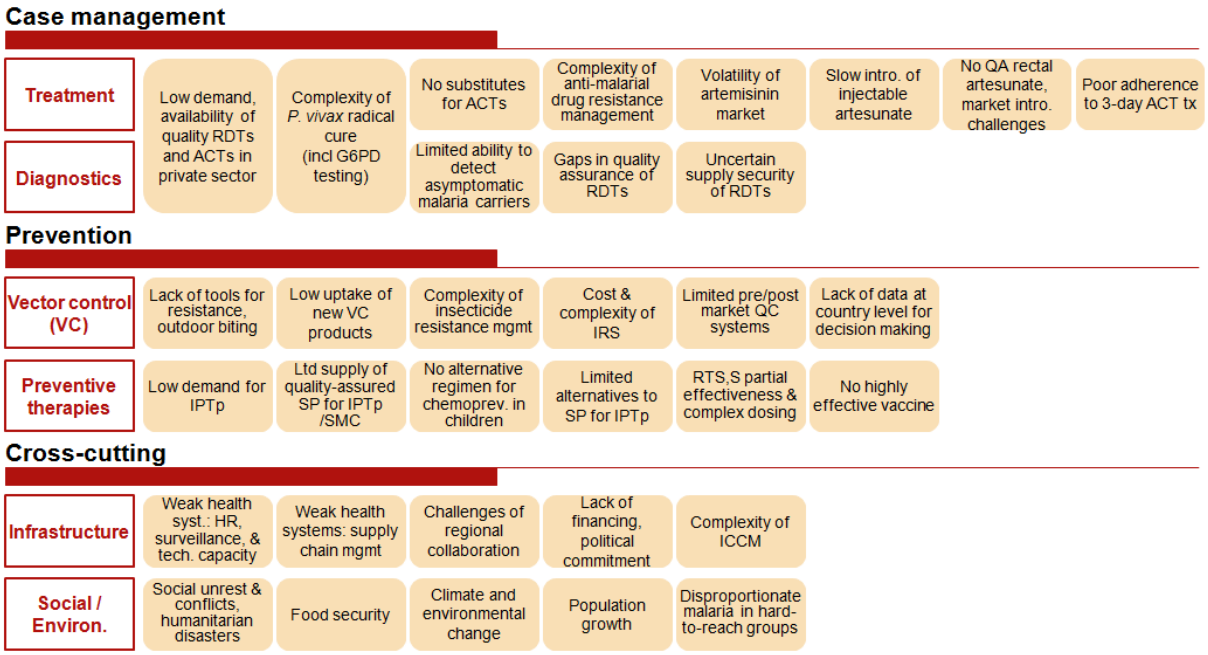
Each input was checked, and partners consulted, to avoid missing potential opportunities. Many challenges are interlinked, and there may be many root causes contributing to a single challenge. In some cases, similar challenges have been merged to reach an inventory that can be used as a framework for action.

This comprehensive inventory of challenges was grouped according to three key categories:

- **Case management**: challenges relating specifically to either the diagnosis or treatment of malaria, or to the holistic approach of malaria case management
- **Prevention**: challenges relating to vector control strategies and preventive therapies, the latter of which includes both preventive chemotherapy and vaccines
- **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.

The complete inventory of challenges is shown below. Description of challenges is available in Appendix 1.

Figure 5. Challenges inventory



Four criteria were then applied to the inventory of challenges:

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. This final list of challenges provided the basis for the identification of Areas for Intervention for UNITAID.

4 Priority challenges to be addressed by UNITAID

The objective of this section is to describe the results of the filtering process through which challenges were prioritized as potential focus areas for UNITAID, leading to potential Areas for Intervention.

4.1 Challenge prioritization process

4.1.1 UNITAID's expertise: focus on challenges that are inherently commodity access issues

This first criterion is designed to ensure UNITAID focuses on areas where it has expertise and strength in addressing gaps in access to products used to test, treat, and prevent disease. By doing that, UNITAID will leverage its market-shaping experience.

As such, challenges that are not directly linked to commodity access issues, or are primarily programmatic- and/or funding-related, have been removed at this stage:

- All infrastructure and social/environmental challenges[23]
- Complexity of antimalarial drug resistance management and insecticide resistance management
- Lack of monitoring systems and data needed to inform vector control decisions
- Cost and complexity of IRS spray campaigns

4.1.2 Potential public health impact: focus on challenges for which there is strong evidence of high potential public health impact

The second criterion is designed to focus on those areas where UNITAID action will have the greatest impact on the global response. Under this criterion, the challenge related to the partial effectiveness & complex dosing schedule of RTS,S/AS01 vaccine has been removed due to the current lack of policy guidance on its use. Such guidance will be available from WHO in the coming months, which will enable a further examination and consideration of this area.

4.1.3 Feasibility: focus on challenges for which the necessary technology can be available in the relevant timeframe

The third criterion is largely pragmatic, focusing on challenges for which the necessary technology is available, or can be expected to be available, in the timeframe needed.

Challenges for which new products are needed but will not enter the market in the next two years, have been removed:

- Lack of alternatives to ACTs[24]
- Poor adherence to 3-day dosing of ACTs
- Alternative regimens for chemoprevention in children
- Highly efficacious malaria vaccine

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[23] While weak supply chain management is an underlying component of many commodity-based interventions, it is primarily a health system strengthening activity.

[24] The most advanced candidate OZ439, which is not expected to reach the market until 2018.

4.1.4 Optimized use of resources: focus on challenges for which critical gaps exist in the global response and where scale up is possible

The fourth and final criterion is the most critical to ensuring UNITAID's added value in the global response. Under this criterion, the ongoing/planned activities of partners (including UNITAID's projects) are evaluated to see whether the landscape either a) leaves limited opportunities for UNITAID, or conversely, b) provides opportunities for UNITAID to leverage and build upon the activities of others.

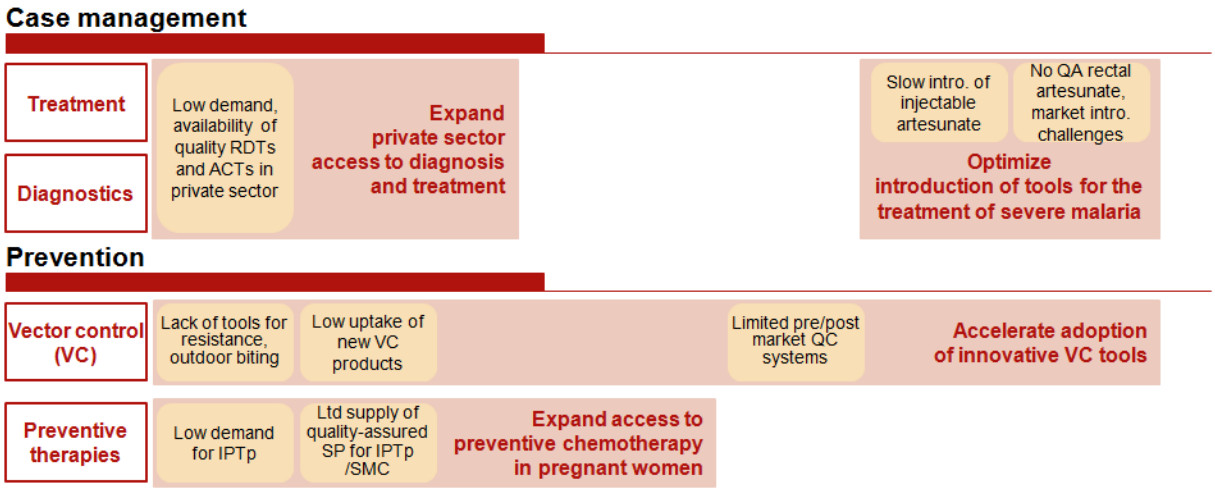
The following challenges have been removed under this criterion, recognizing that the landscapes of partner activities requires ongoing monitoring to periodically reassess critical gaps and opportunities for UNITAID:

- **Limited ability to detect asymptomatic malaria carriers:** Limited near-term opportunities for UNITAID as highly sensitive diagnostics are still under development, notably by PATH with support from Bill and Melinda Gates Foundation (BMGF). While opportunities may exist in the future in relation to market introduction, it is too early to determine whether these diagnostics, developed primarily for use in elimination settings, represent a critical gap where UNITAID could optimize its added value.
- **Complexity of *P. vivax* radical cure (including G6PD testing):** Limited near-term opportunities for UNITAID as the feasibility of implementation of the only point-of-care G6PD test currently available, is unclear (currently being evaluated as part of field evaluations supported by PMI). PATH is undertaking a range of activities on G6PD diagnostics with support from BMGF and DFID, including working with manufacturers on product development. Multiple products are in the pipeline, and as such future opportunities may exist for UNITAID to support the introduction of G6PD testing. In particular, G6PD diagnostic testing infrastructure will be needed to facilitate the launch of tafenoquine, a drug being developed by GSK and MMV for the radical cure of *P. vivax* which may be available as early as 2018.
- **Volatility of the artemisinin market:** There is agreement among key partners that additional interventions are not required in the short-term aside from maintaining the market intelligence activities on artemisinin supply and demand that UNITAID is currently supporting. However, this is an areas to monitor closely to ensure that artesminin supply does not pose a threat to meeting ACT demand in the future.
- **Gaps in quality assurance of RDTs:** opportunities for additional standalone interventions on RDT quality are perceived as minimal in light of UNITAID's ongoing investments to support RDT quality[25]. However, any interventions to expand access to RDTs should include efforts to ensure product quality.
- **Uncertain supply security of RDTs:** UNITAID's primary role related to this challenge is part of its ongoing engagement with the Global Fund and other partners, for example participating in discussions on the structure of the upcoming Global Fund RDT tender.

[25] The *WHO Prequalification of Diagnostics Programme* and the *WHO/FIND Product and Lot Testing Programmes*

4.2 Overview of the priority challenges to be addressed by UNITAID in the next 24 months

Figure 6. Priority challenges to be addressed by UNITAID in the next 24 months



Based on the filtering exercise undertaken by the Secretariat and validated with key partners, the above challenges can be grouped into four Areas for Intervention, which are high priorities for the next 24 months:

Expand private sector access to diagnosis and treatment: This AfI is focused on improving access to malaria case management through a key delivery channel, the private sector. Specifically, this AfI would aim to unlock the potential of the Global Fund Private Sector Co-payment Mechanism in selected countries and generate lessons and models that could be applied more broadly. As a result, this AfI would contribute to a step change towards universal access to case management, leading to improved treatment of malaria and other sources of childhood fever. This AfI would also contribute to reduce overtreatment with antimalarials, allowing ACTs to be targeted to those people who actually have malaria.

Optimize introduction of tools for the treatment of severe malaria: Under this AfI, the implementation of rectal artesunate would be piloted in order to ensure controlled introduction due to concerns of misuse, as well as provide proof of concept that this community-based intervention can be implemented at scale. The broader impact of increased use of tools for the treatment of severe malaria will be a reduction in under 5 mortality. Future opportunities will also be monitored and evaluated, particularly with respect to further scale-up of injectable artesunate, and facilitating access to new treatments for severe malaria. Further interventions in severe malaria would serve to optimize the impact of UNITAID's current project, *Improving Severe Malaria Outcomes*.

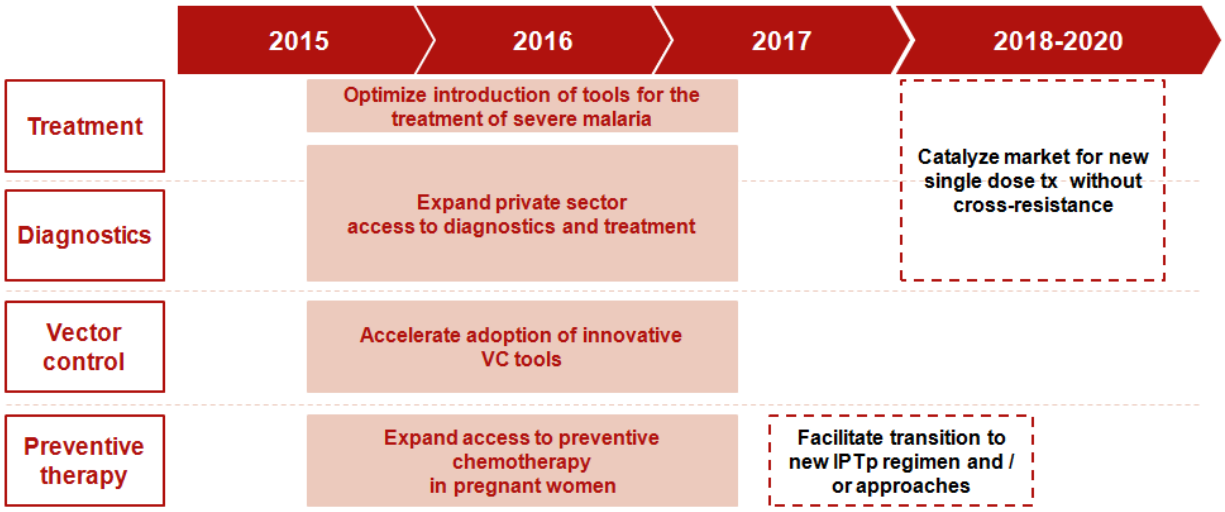
Accelerate adoption of innovative vector control tools: The aim of this AfI is to accelerate the timelines for innovative products to reach the market by focusing specifically on a more streamlined global evaluation process, and by generating evidence on the use of new tools to guide normative guidance and implementation support. The expected impact of this AfI is that much-needed vector control innovations will reach the market more quickly and will be able to be deployed more rationally to maximize their impact.

Expand access to preventive chemotherapy in pregnant women: This AfI is focused on generating innovative approaches to IPTp delivery and demand generation to support global guidance and scale-up. Current challenges related to the supply of quality SP, the drug regimen used in IPTp, will also be addressed to ensure that quality products are available to support future scale-up efforts. Interventions that address both supply-side and demand-side challenges would provide the necessary foundation for a significant expansion of IPTp coverage.

Related to the scope of these AfIs, other challenges and opportunities will be monitored and could result into Areas for Intervention to be launched beyond this 24 months period:

- Catalyzing the market for new, single-dose treatments that are effective against artemisinin-resistant strains of malaria
- In coordination and cooperation with partners, catalyze the transition to new regimens and/or delivery models for IPTp

Figure 7. Potential timing



The following sections of the report will describe each AfI in greater detail.

5 APPENDIX 1: Description of challenges

5.1 Challenges related to case management

Low demand, availability of quality ACTs and RDTs in the private sector

Low demand for appropriate case management in the private sector includes both low demand for ACTs as well as demand for ACTs and other antimalarials without a positive diagnostic test. Low demand is due to a number of interconnected challenges. 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/encourage the sale or use of RDTs 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 is 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 overall private sector is the large, unregulated informal sector that is a key source of antimalarials where non-recommended and often poor quality drugs proliferate.

Complexity of P. vivax radical cure (including G6PD testing):

P. vivax, the malaria species most common in Asia and Latin America, differs to *P. falciparum* in that relapses can occur due to dormant liver forms of the parasite known as hypnozoites. Two stages of treatment are therefore required for full cure – acute to treat initial illness, and a second (primaquine) to clear the dormant liver parasites. Treatment of liver stage requires diagnostic testing to identify and exclude patients with G6PD deficiency, as this deficiency leads to adverse events (hemolysis) with primaquine treatment. Experience with G6PD testing in advance of radical cure of *P. vivax* malaria is variable across countries, as has been limited by the fact that a point-of-case test has only recently become available. A further challenge is the 14-day treatment course of primaquine, which can limit adherence.

5.1.1 Treatment

No substitutes for ACTs

An important challenge in treating malaria is drug-resistance, which could trigger an upsurge in deaths if left unaddressed. Resistance of *P. falciparum* to previous generations of medicines – such as chloroquine and sulfadoxine-pyrimethamine (SP) – became widespread in the 1970s and 1980s, undermining malaria control efforts and reversing gains in child survival. In recent years, parasite resistance to artemisinins has been detected in 5 countries of the Greater Mekong region: Cambodia, Laos, Myanmar, Thailand and Viet Nam[26]. New drugs are under development which could be effective against artemisinin-resistant strains of malaria, however these are not yet available.

[26] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

Complexity of anti-malarial drug resistance management

A further challenge related to antimalarial drug resistance is the complexity of resistance management strategies. Given the emergence of artemisinin resistance in the Greater Mekong subregion and the threat of its spread to other areas, and the fact that new treatments will not be available in the next few years, resistance containment activities are required to prevent the loss of ACTs as effective treatment. This includes stopping the spread of resistant parasites through intensified prevention and control measures, including efforts to ensure compliance with ACT treatment and removal of oral artemisinin-based monotherapies and substandard and counterfeit drugs from the market. In some cases, interventions such as focused screening and treatment, active case detection, mass screening and treatment or mass drug administration, may also be employed. Increased surveillance and monitoring is also critical to detect changes in drug therapeutic efficacy[27].

Volatility of artemisinin market

ACTs rely largely on an agricultural starting material – artemisinin – which has a long and complex production cycle. Since the introduction of ACTs as first-line treatment for malaria, the agricultural artemisinin market has been characterized by cycles of tight supply and high prices, followed by oversupply and low prices. Undersupply of artemisinin could lead to ACT supply shortages and/or higher prices. The recent introduction of semi-synthetic artemisinin offers an additional supply of non-agricultural starting material with a shorter lead time. This, combined with an expected stabilization of demand for ACTs due to leveling-off of funding, should bring greater stability to the artemisinin market, though ongoing monitoring of supply and demand estimates is required to ensure sufficient artemisinin is available to meet global demand for artemisinin-based drugs (ACTs, injectable artesunate, etc.)[28].

Slow introduction of injectable artesunate

Since its recommendation as first-line treatment for severe malaria, the uptake of injectable artesunate has been hampered by its higher cost compared to injectable quinine (three times more than injectable quinine). Additional barriers include buyer concerns over a single prequalified supplier, commercial interests around injectable quinine, and poor acceptance by patients and providers. Between 2010–2013, approximately 12M prequalified injectable artesunate vials were procured, representing around 25% of the total volume needed to treat global annual cases[29]. While demand for injectable artesunate is growing due in part to the volumes being procured under UNITAID's Improving Severe Malaria Outcomes project, it is too early to tell whether additional interventions will be required to ensure full market introduction and increased number of suppliers.

No quality-assured rectal artesunate and market introduction challenges

Despite being recommended by WHO for the pre-referral treatment of severe malaria, the lack of a prequalified rectal artesunate product has meant that the market for this product has remained nascent. As a result of a UNITAID investment, it is expected that at least one rectal artesunate product will be available for donor procurement in 2016. However, concentrated efforts will be

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[27] WHO. Global Plan for Artemisinin Resistance Containment. Geneva: World Health Organization; 2011.

[28] UNITAID. Malaria medicines technology and market landscape – 2nd edition. Geneva: UNITAID; 2015.

[29] Artesunate injection (updated December 2013). Geneva: Medicines for Malaria Venture; 2013 (www.mmv.org/achievements-challenges/achievements/artesunate-injection-32-million-vials-lifesaving-medicine-deli (accessed June 2014).

required to introduce this product which may face a range of implementation challenges (risks of misuse as monotherapy, need for community based delivery infrastructure, cultural barriers to suppository use, etc.).

Poor adherence to 3-day ACT regimen

The dosing regimen of current ACTs requires one or two pills to be taken each day for a total of three days. When patients do not adhere to the full regimen, not only do they remain infected with malaria and can contribute to onwards transmission. Importantly, lack of adherence contributes to the development of drug resistance. A three-day dosing regimen also makes current ACTs less suitable for strategies such as chemoprevention or mass drug administration. A single-dose treatment is under development but is not yet available.

5.1.2 Diagnostics

Limited ability to detect asymptomatic malaria carriers

Efforts to eliminate malaria include identifying and treating the asymptomatic human reservoir to prevent onwards transmission. People that harbour parasites in their blood at low densities do not have clinical malaria, but should they be bitten by a mosquito these parasites in the blood can be transmitted to mosquito and then to another human. More sensitive diagnostics are under development to enable identification of sub-clinical malaria, particularly for use in elimination settings.

Gaps in quality assurance of RDTs

Despite the efforts to improve RDT quality, gaps remain including limited insight into quality at the manufacturing level, lack of quality controls for checking the performance of RDTs in the field, and lack of clear regulatory pathway for new malaria diagnostics. To address these issues the WHO is currently considering an expanding role of Prequalification for malaria RDTs and FIND is leading efforts to develop positive control wells to test RDT quality at the point-of-care[30].

Uncertain supply security of RDTs

The donor RDT market is currently consolidating around a small number of suppliers, creating risk to supply security. In 2012, three manufactures comprised 90% of the market and, in 2013, four had 98% of the market. However, since one of the three highest-volume manufacturers procures semi-finished product from one of the others, 90% of the public sector supply is actually dependent on two manufacturers. It is thought that this market consolidation is due in part to current low prices, which have precipitated supplier exit from the market[31].

[30] UNITAID. Malaria diagnostics landscape update. Geneva: UNITAID; 2015.

[31] UNITAID. Malaria diagnostics landscape update. Geneva: UNITAID; 2015.

5.2 Challenges related to prevention

5.2.1 Vector control

Lack of tools for resistance, outdoor biting

Currently there are limited vector control tools to address key challenges such as insecticide resistance or outdoor transmission, though several products are in the pipeline. For innovative products, a key challenge is the long timeline for global evaluation, normative guidance, and country registration that is required for countries to begin using these tools. Extended timelines not only delay the availability of strongly needed innovations, but also act as a disincentive for manufacturers to continue to invest in R&D. Other disincentives include the fact that the public health market is small compared to the agricultural market, high risk and price driven, with uncertain willingness-to-pay for higher-cost, innovative products[32].

Low uptake of new VC products

Recent innovative products that have been evaluated and recommended for malaria control have achieved very poor market penetration due to their higher-price and, in some cases, a lack of information on where products can be best deployed. One example is Actellic CS, a next-generation organophosphate insecticide used in indoor residual spraying. Despite evidence of high effectiveness when compared with pyrethroids, in 2013, 2 years after product launch, coverage with Actellic CS represented only 3.8% of the total IRS coverage. A key barrier to product uptake has been a much higher price ($23.50/unit) than other insecticides ($13.50/unit for carbamates, $2-4/unit for widely resisted pyrethroids)[33].

Complexity of insecticide resistance management

Insecticide resistance is a major threat to the effectiveness of current primary vector control tools. Current strategies for insecticide resistance management (IRM) include rotating the insecticides used in IRS from one year to the next, the use of interventions in combination (e.g. use of a pyrethroid LLIN in combination with IRS using different chemicals), and mosaic spraying (using different chemicals in different geographic areas). A key challenge in implementing current IRM strategies is that these interventions are more complex to implement than traditional LLIN or IRS programs.

Cost & complexity of IRS

The cost and complexity of IRS campaigns contributes to low uptake, as the application of IRS requires major planning, training and operations.

Limited pre/post market QC

Limitations in current quality assurance systems for vector control tools include:

[32] UNITAID. Malaria Vector Control Commodities Landscape. 2nd Edition. Geneva: UNITAID; 2014.

[33] IVCC. Market Intervention to accelerate uptake of new vector control tools. Project Proposal. January 2015.

- limited systematic, independent global pre-marketing manufacturing site inspections for vector control products, with no commonly defined 'Good Manufacturing Practices' standards that would allow for manufacturing inspections;
- limited pre- or post-shipment quality assurance (QA) systems (though some agencies, such as PMI, conduct their own pre- or post-shipment QA); and
- limited post-marketing controls in the field.

Moreover, products currently do not need to go through any periodic re-evaluation for quality once they obtain a WHOPES recommendation[34].

Lack of data at country level for decision making

Evidence-based decision making in vector control should be guided by operational research and entomological and epidemiological surveillance and evaluation[35], however often countries lack the necessary systems and skilled human resources required to undertake these activities. For example, currently the monitoring of insecticide resistance is inadequate 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[36].

5.2.2 Preventive therapy

Low demand for IPTp

Malaria infection during pregnancy is associated with severe anemia and other illness in the mother and contributes to low birth weight among newborn infants — one of the leading risk factors for infant mortality and sub-optimal growth and development[37]. However, demand for IPTp remains low among antenatal care workers, the primary delivery channel for IPTp, and among pregnant women. This results from a combination of factors, including IPTp "falling through the cracks" between maternal child health and malaria programs; negative perceptions of drug use in pregnancy and of the efficacy of SP; lack of prioritization of preventive interventions in ANC, with a focus on time of delivery; and stock-outs of SP at facility level.

Limited supply of quality-assured SP for IPTp (and SMC)

There are a limited number of suppliers of quality-assured SP on the global market. In 2015, the only prequalified supplier of sulfadoxine API exited the market, leading to a shortage of SP needed for SMC campaigns. While efforts are underway to develop dispersible formulations of SP-AQ needed for SMC, achieving a dramatic increase in scale of SP would require greater volumes of quality assured product. Reasons for low supply include procurement using domestic resources for

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[34] Bill & Melinda Gates Foundation. Achieving Innovation to Impact in Vector Control. Draft Vision Statement Executive Summary (version 48). 2015.

[35] WHO. Integrated Vector Management (IVM) (website). Available from: http://www.who.int/neglected_diseases/vector_ecology/ivm_concept/en/ (accessed 17 Oct. 2015).

[36] WHO. Global plan for insecticide resistance management in malaria vectors. Geneva: World Health Organization; 2012.

[37] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).

which international quality assurance is not required; low IPTp coverage and resulting small market size, low cost of SP, and the requirements and costs of achieving international quality assurance.

No alternative regimen for chemoprevention in children

Seasonal malaria chemoprevention is only recommended in the Sahel sub-region in Africa, due SP resistance in other regions with seasonal malaria transmission. Currently there are no other options for chemoprevention in children outside of this sub-region.

Limited alternatives to SP for IPTp

While the latest evidence shows that SP remains highly effective for IPTp, concerns over resistance is prompting the development/evaluation of alternate regimens. Both azithromycin-chloroquine and mefloquine were recently considered as alternatives to SP for IPTp, however these have now been excluded[38]. The latest evidence on the use of DHA-PPQ is promising, 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

In phase 3 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[39]. RTS,S/AS01 also has a relatively complex dosing schedule (3 doses plus a booster dose), which does not align with the EPI schedule and is therefore likely to make implementation more complex. In 2015, the European Medicines Agency (EMA) has adopted a positive scientific opinion for RTS,S/AS01, and a WHO policy recommendation on the use of RTS,S/AS01 is expected in late 2015[40]. Given its partial efficacy, RTS,S/AS01 is like to play a complementary role to other preventive interventions for malaria, rather than replace them.

No highly effective vaccine

There are multiple vaccine candidates in the R&D pipeline, however these will not be available for several years.

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[38] UNITAID. Malaria medicines technology and market landscape – 2nd edition. Geneva: UNITAID; 2015.

[39] RTS,S Clinical Trial Partnership. Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomized, controlled trial. Lancet 2015;386(9988):31–45.

[40] PATH Malaria Vaccine Initiative. RTS,S malaria vaccine candidate (website). Available from: http://www.malariavaccine.org/rd-rtss.php (accessed 17 Oct. 2015).

5.3 Cross-cutting challenges

5.3.1 Infrastructure

Weak health systems: surveillance, HR, technical capacity & supply chain management

Weak health system infrastructure includes issues such as the weak 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[41].

Challenges of regional collaboration

Progress in malaria will require regional collaboration across countries, which can be challenging to establish and coordinate. Specific issues requiring regional collaboration include the movement of populations such as laborers or refugees across countries, and efforts to contain artemisinin resistance in the Greater Mekong Subregion.

Lack of financing, political commitment

Lack of robust, predictable and sustained international and domestic financing is a key challenge to future progress. This is compounded by the difficulty in maintaining political commitment and ensuring regional collaboration at the highest levels[42]. As countries make progress towards malaria elimination it may be particularly challenging to maintain political commitment and funding.

Complexity of integrated community case management of malaria (iCCM)

Integrated Community Case Management (iCCM) is a strategy whereby diagnosis and treatment of malaria, pneumonia and diarrhea is provided to populations with limited access to facility-based health care providers, and especially to children under five[43]. A range of challenges to scaling up iCCM have been identified: 1) the need for a strong network of community health workers 2) maintaining reliable supply chains; 3) demand side barriers; 4) weak monitoring and evaluation systems, and 5) the need for supportive government policies and engagement[44].

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[41] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

[42] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

[43] WHO. Integrated community case management of malaria (website). Available from: http://www.who.int/malaria/areas/community_case_management/overview/en/ (accessed 17 Oct. 2015)

[44] UNICEF. Review of Systematic Challenges to the Scale-up of Integrated Community Case Management. United Nations Children's Fund: New York; 2012 .

5.3.2 Social / Environmental

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. During the recent Ebola outbreak, an increase in malaria cases and deaths was observed as people with fever were afraid to visit health facilities for fear of being quarantined/treated as suspected Ebola/contracting Ebola.

Food security

A lack of food security can have a negative impact on malaria, as malnourished children are less able to mount an immune response and withstand malaria infection. Malnourished children who are infected with malaria are also at increased risk of mortality[45]. In addition, agricultural practices aiming to improve food security, such as including intense farming, irrigation and drainage, need to be well managed or they can result in increasing vector breeding sites[46].

[45] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).

[46] Roll Back Malaria Partnership. Action and Investment to defeat Malaria 2016–2030. Geneva: World Health Organization; 2015.

Climate and environmental change

Weather and climate have a significant influence on malaria distribution, seasonality and longer-term trends. For example, periods of high rainfall or warmer temperatures can result in increased malaria transmission. The Intergovernmental Panel on Climate Change has 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"[47]. Environmental change also has an impact on malaria transmission. For example, deforestation[48], large-scale irrigation, urbanization[49], the establishment of rubber plantations[50], soil salinification[51], and extractive activities can all influence malaria transmission[52].

Population growth

Many malaria endemic countries are also countries with high levels of population growth[53]. Growing populations require increased resources in order to achieve universal coverage of malaria interventions.

Disproportionate malaria in hard-to-reach groups

Hard-to-reach groups for 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[54]. Other hard-to-reach groups include high-risk occupational groups, migrants, and people in humanitarian crises[55].

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[47] Van Lieshout M et al. Climate change and malaria: analysis of the SRES climate and socio-economic scenarios. Glob Environ Change 2004;14:87-99.

[48] Imai N et al. Transmission and control of Plasmodium knowlesi: a mathematical modelling study.PLoS Negl Trop Dis 2014;8:e2978.

[49] Tatem AJ et al. Urbanization and the global malaria recession. Malar J 2013;12:133. Hay SI et al. Opinion – Tropical infectious diseases: urbanization, malaria transmission and disease burden in Africa. Nat Rev Microbiol 2005;3:81-90.

[50] Bhumiratana A et al. Malaria-associated rubber plantations in Thailand. Travel Med Infect Dis 2013;11:37-50. Yasuoka J & Levins R. Impact of deforestation and agricultural development on anopheline ecology and malaria epidemiology. Am J Trop Med Hyg 2007;76:450-460.

[51] 7. Temel, T. Malaria from the gap: need for cross-sector co-operation in Azerbaijan. Acta Trop 2004;89:249-259.

[52] Ali H et al. Climate change and health in Sudan. Capacity strengthening in the least developed countries (LDCs) for adaptation to climate change (CLACC) (2008). Patz JA et al.Effects of environmental change on emerging parasitic diseases. Int J Parasitol 2000;30:1395-1405.

[53] The World Bank. Population growth (annual %) (website). Available from: http://data.worldbank.org/indicator/SP.POP.GROW (accessed 17 Oct. 2015).

[54] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.

[55] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).