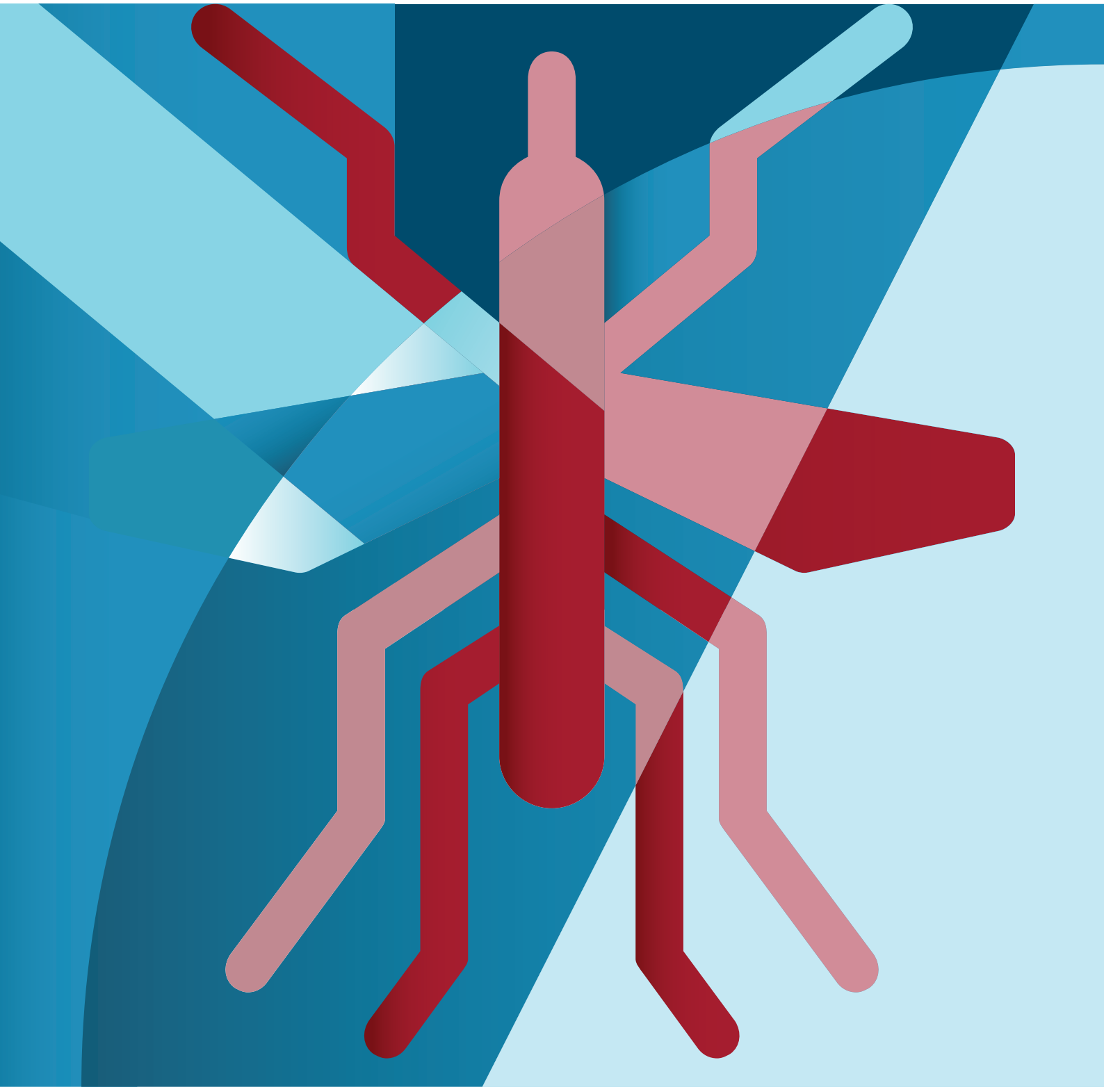
Unitaid
Innovation in Global Health



EXECUTIVE BOARD MEETING

STRATEGIC NARRATIVE FOR MALARIA AND AREAS FOR INTERVENTION

23RD MEETING, NOVEMBER 2015

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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 RandD 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:

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

- **Unitaid's expertise:** focus on challenges that are inherently commodity-access issues
- **Potential public health impact:** focus on challenges for which there is strong evidence of high potential public health impact
- **Feasibility:** focus on challenges for which the necessary technology can be available in the relevant timeframe
- **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, better 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 sulfadoxine-pyrimethamine (SP) for IPTp and seasonal malaria chemoprevention (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 years 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 (3.9 million 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].

[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.

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).

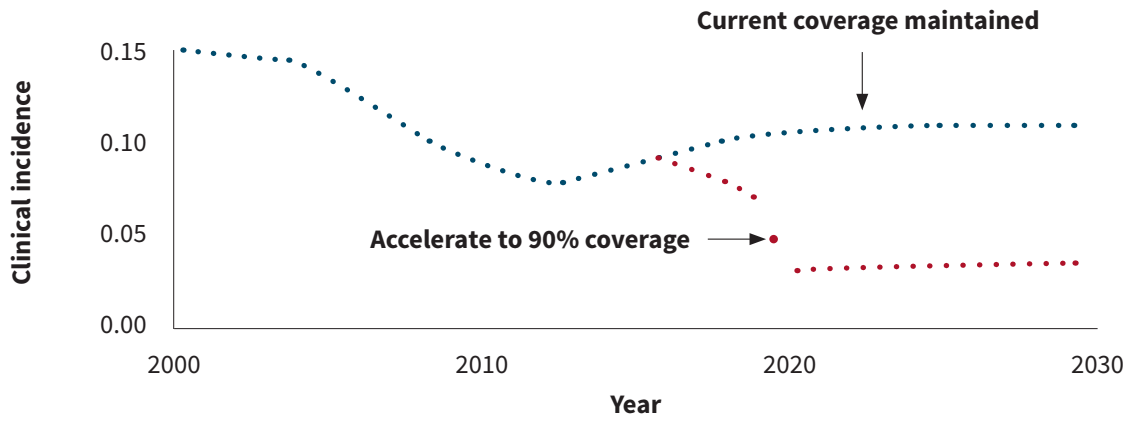
FIGURE 1.
GLOBAL GOALS

Global Technical Strategy for Malaria 2016 - 2030			
	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	≥ 10 countries	≥ 10 countries
Prevent re-establishment in all malaria-free countries	Prevented		

Source: WHO Global Technical Strategy and 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 red 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 and 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 per year, 78% of which are in children under 5 years old*
- *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

1.3.1. Vector control

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%[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; developing new products and chemicals to fight resistance is therefore a key priority for research and development.

[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

The World Health Organization (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 subregion 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 RandD 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 (479 million) 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 WHO recommended diagnostic testing of all suspected cases of malaria before treatment. However, in sub-Saharan Africa, the

[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.

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].

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 five countries of the Greater Mekong region: Cambodia, Laos, Myanmar, Thailand and Vietnam. 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*

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

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

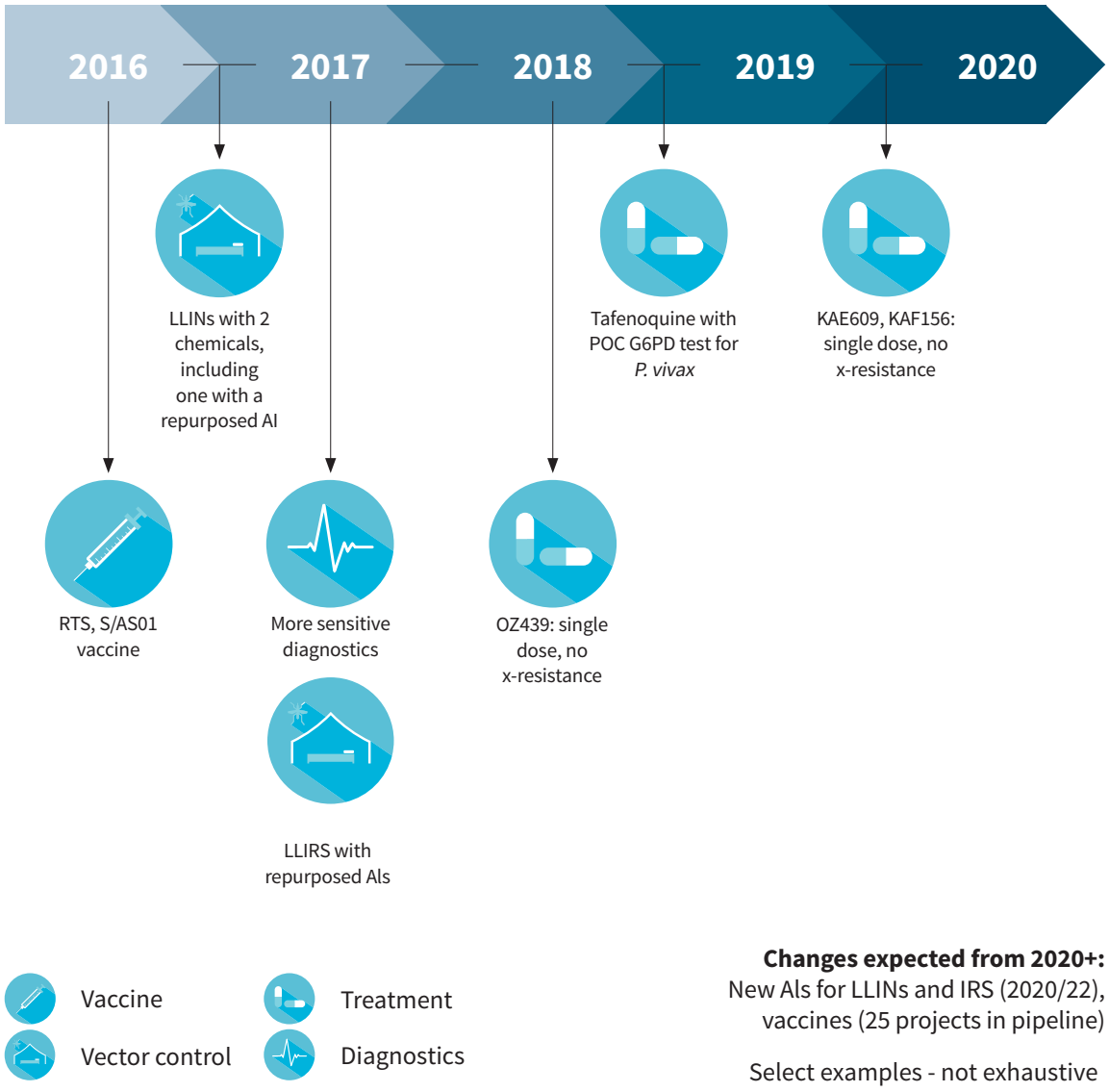
- *Coverage of key interventions for high-risk populations remains poor: chemoprevention in pregnant women and treatment for children with severe malaria*
- *Insecticide and artemisinin resistance are major risks to current tools and are therefore key priorities for research and development*
- *Expanded 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 and diagnostics. Among them are products 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, RandD 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 onward spread of malaria in the population; and new chemicals that can be used for malaria vector control[21]. Unitaid monitors the RandD 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.



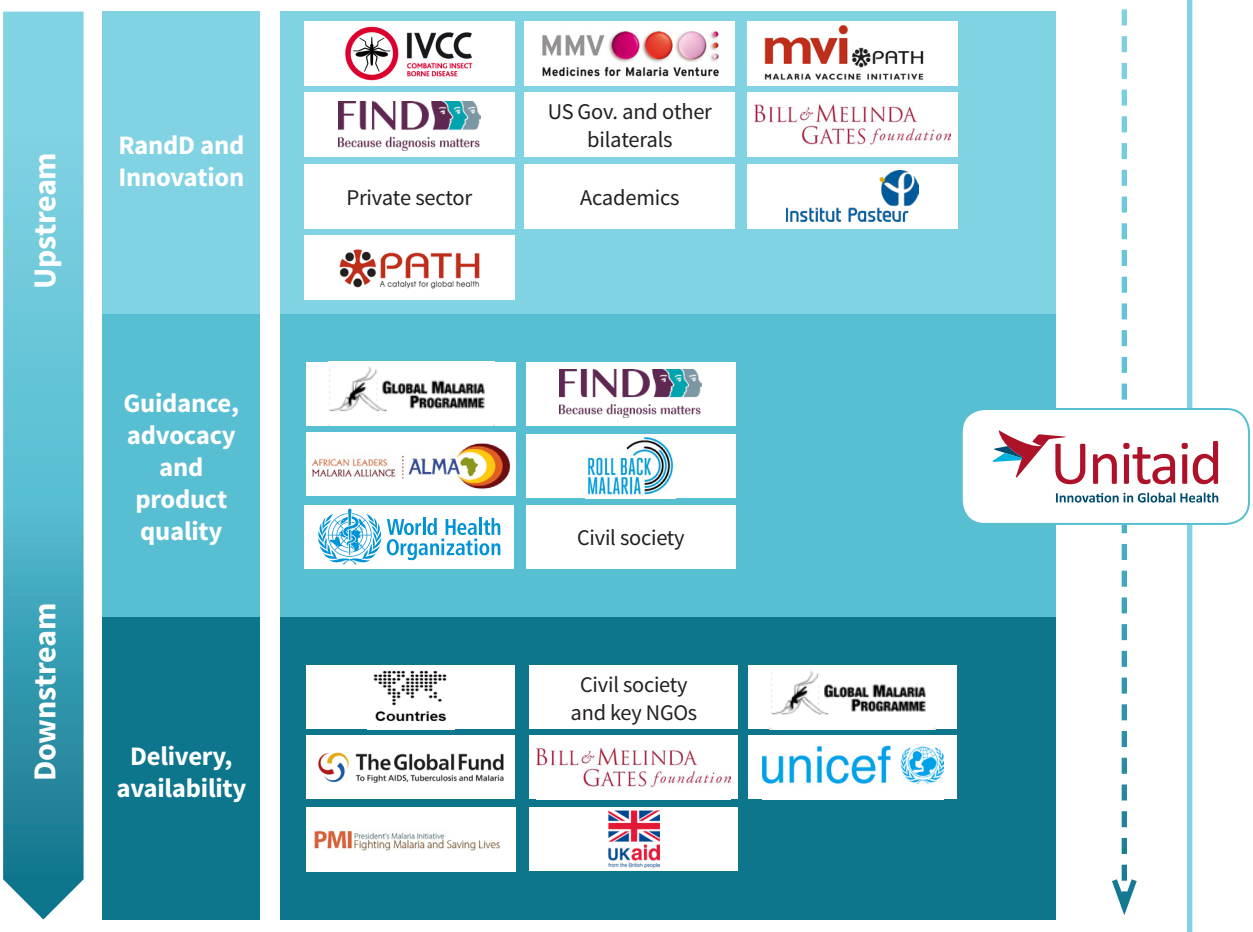
KEY MESSAGES

- *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 and Melinda Gates Foundation, other private foundations such as the Institut Pasteur, the US Government (Centers for Disease Control and Prevention, 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 RandD. 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 programmes 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 programmes 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 RandD 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 and plans*
- *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 and 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 in Figure 5, below. Description of challenges is available in Appendix 1.

FIGURE 5.

Case management

<table>
<tr><th>DIAGNOSTICS</th><th colspan="2">TREATMENT</th></tr>
<tr><td colspan="3">LOW DEMAND, AVAILABILITY OF QUALITY RDTS AND ACTS IN PRIVATE SECTOR</td></tr>
<tr><td>Limited ability to detect asymptomatic malaria carriers</td><td></td><td>No substitutes for ACTs</td></tr>
<tr><td colspan="3">COMPLEXITY OF P. VIVAX RADICAL CURE (INCL G6PD TESTING)</td></tr>
<tr><td>Gaps in quality assurance of RDTs</td><td></td><td>Complexity of antimalarial drug resistance management</td></tr>
<tr><td rowspan="4">Uncertain supply security of RDTs</td><td></td><td>Volatily of artemisinin market</td></tr>
<tr><td></td><td>Slow introduction of injectable artesunate</td></tr>
<tr><td></td><td>No QA rectal artesunate, market intro. cghallenges</td></tr>
<tr><td></td><td>Poor adherence to 3-days ACT treatment</td></tr>
</table>

Prevention

Vactor control (VC)	Preventive therapies
Lack of tools for resistance, outdoor biting	Low demand for IPTp
Low uptake VC products	Ltd supply for quality-assured SP for IPTp/SMC
Complexity of insecticide-resistance mgmt	No alternative regimen for chemoprevention in children
Cost and complexity of IRS	Limited alternatives to SP for IPTp
Limited pre/post market QC systems	RTS.S partial effectiveness and complex dosing
Lack of data at country level for decision making	No highly effective vaccine

Cross-cutting

Infrastructure	Social/Environment
Weak health systems: HR, surveillance, and technical capacity	Social unrest and conflicts, humanitarian disasters
Weak health systems: supply chain mgmt	Food security
Challenges of regional collaboration	Climate and environmental change
Lack of financing, political commitment	Population growth
Complexity of integrated community case management	Disproportionate malaria in hard-to-reach groups

Four criteria were then applied to the inventory of challenges:

- **Unitaid's expertise:** focus on challenges that are inherently commodity-access issues
- **Potential public health impact:** focus on challenges for which there is strong evidence of high potential public health impact
- **Feasibility:** focus on challenges for which the necessary technology can be available in the relevant timeframe
- **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

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

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 and 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

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.

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

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

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-month period:

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.

FIGURE 6.

PRIORITY CHALLENGES TO BE ADDRESSED BY UNITAID IN THE NEXT 24 MONTHS

Case management

	AREA FOR INTERVENTION	CHALLENGES
TREATMENT	Expand private-sector access to diagnosis and treatment	Low demand, availability of quality RDTs and ACTs in private sector
TESTING		
TREATMENT	Expand private-sector access to diagnosis and treatment	Slow introduction of injectable artesunate No QA rectal artesunate, market intro. challenges
TESTING		

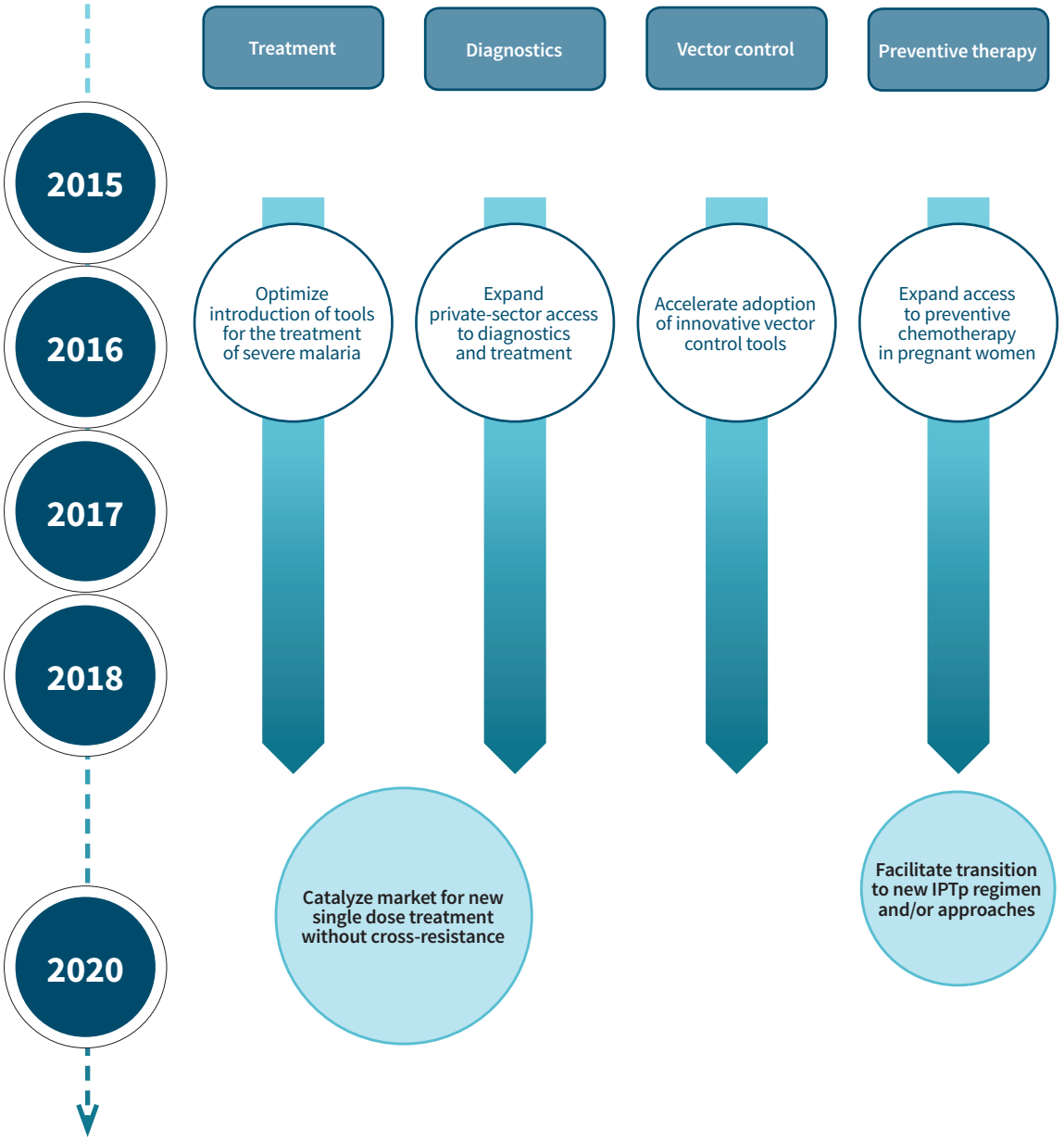
Prevention

	AREA FOR INTERVENTION	CHALLENGES
VECTOR CONTROL (VC)	Accelerate adoption of innovative VC tools	Lack of tools for resistance, outdoor biting Low uptake of new VC products Limited pre/post market QC systems
PREVENTIVE THERAPIES	Expand access to preventive chemotherapy in pregnant women	Low demand for IPTp Ltd supply of quality-assured SP for IPTp/SMC

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-month 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.Areas for intervention for decision by the Board

5.1. Area for intervention 1: Expand access to preventive chemotherapy in pregnant women

5.1.1 Why now and what are the key issues?

5.1.1.1 Coverage gap of IPTp results in significant morbidity and mortality for both mother and child

Pregnant women are a high-risk group for malaria: there are approximately 32 million[26] pregnancies per year in malaria-endemic areas in sub-Saharan Africa (SSA) with an estimated 8 million[27] pregnancies presenting evidence of malaria infection at time of delivery. Despite the existence of a highly effective and low-cost prevention tool, malaria in pregnancy results in significant morbidity and mortality for both mother and child:

- 400,000 cases of maternal anemia yearly related to malaria in pregnancy[28] and 10,000 maternal deaths[29]
- 900,000 low birth-weight newborns per years in SSA attributable to malaria[30] and up to 200,000 neonatal deaths likely related to malaria infections during pregnancy[31]

In addition, as malaria transmission is reduced as part of elimination efforts, decreases in level of acquired immunity could lead to increases in severe malaria and deaths from malaria in pregnant women. This is relevant not only to countries in the elimination phase, but also to many African countries where there are increasing proportions of the population living in urban areas with low malaria transmission but surrounded by highly endemic areas[32].

Intermittent preventive therapy in pregnant women (IPTp) is a preventive intervention that has been recommended by WHO since 1998: doses of the drug SP (sulfadoxine-pyrimethamine) are given to pregnant women

[26] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
[27] Desai MD et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007;7(2):93-104.
[28] Desai MD et al. Epidemiology and burden of malaria in pregnancy. Lancet Infect Dis 2007;7(2):93-104.
[29] Mendelez C. Overview of the burden and impact of malaria in pregnancy on maternal and infant's health (presentation). 07 July 2015.
[30] Walker PGT, ter Kuile FO, Garske T, Menendez C, Ghani AC. Estimated risk of placental infection and low birthweight attributable to Plasmodium falciparum malaria in Africa in 2010: a modelling study. Lancet Glob Health 2014;2(8):e460-e467.
[31] Steketee RW, Nahlen BL, Parise ME, Menendez C. The Burden of Malaria in Pregnancy in Malaria-Endemic Areas. In: Breman JG, Egan A, Keusch GT, editors. The Intolerable Burden of Malaria: A New Look at the Numbers: Supplement to Volume 64(1) of the American Journal of Tropical Medicine and Hygiene. Northbrook (IL): American Society of Tropical Medicine and Hygiene; 2001 Jan.
[32] Mendelez C. Overview of the burden and impact of malaria in pregnancy on maternal and infant's health (presentation). 07 July 2015.

at multiple points throughout their pregnancy to prevent malaria. In 2012, WHO revised its recommendations for IPTp, moving from two doses to at least three doses, given at least one month apart beginning as early as possible during the second trimester of pregnancy[33]. Despite recent concerns regarding the impact of SP resistance on IPTp effectiveness, an Evidence Review Group convened by WHO in 2015 has determined that SP remains highly effective and cost-effective for IPTp[34].

Despite long-standing WHO recommendations on IPTp, coverage remains extremely low and has lagged behind other malaria interventions. While the GTS emphasizes the need for universal coverage of preventive therapies for populations at risk in high/moderate transmission settings[35], currently only 17% of women receive 3+ doses of IPTp[36].

5.1.1.2 Low coverage can be explained by low demand and lack of adequate supply and delivery

There are multiple interconnected reasons for the low coverage rate of IPTp. Firstly, IPTp is a malaria intervention which is primarily delivered as part of antenatal care (ANC), and often tends to "fall through the cracks" between the malaria and maternal child health programming. Because IPTp is a low-cost intervention that is not delivered through National Malaria-control Programmes, donor funding is often not requested for this intervention under the assumption that this will be covered through domestic financing, which does not systematically occur. This is evidenced by the fact that the Global Fund receives very few requests for IPTp as part of malaria grants.

While the large majority (89%) of pregnant women in sub-Saharan Africa attend one ANC visit[37], many do not attend multiple visits. Further, women often present late in their pregnancy, leaving limited opportunities for multiple doses of IPTp. Even when pregnant women do attend multiple ANC visits, only about one-quarter receive two or more doses of IPTp[38]. Although WHO has signaled the opportunity to deliver IPTp through community-based programming[39], to date this has only been explored through small-scale pilot studies[40].

A key barrier to IPTp is therefore **low demand** for this intervention from health workers and pregnant women. ANC visits are often focused on the time of delivery, with preventive interventions receiving less attention, though even when compared to other preventive interventions IPTp coverage is still low[41]. Negative impressions of taking medications during pregnancy, as well as health

[33] Updated WHO Policy Recommendation (October 2012). Intermittent Preventive Treatment of malaria in pregnancy using Sulfadoxine Pyrimethamine (IPTp-SP). Available from http://www.who.int/malaria/iptp_sp_updated_policy_recommendation_en_102012.pdf (accessed 17 Oct. 2015).
[34] Malaria in pregnancy. WHO Evidence Review Group meeting report. 13-16 July 2015. Malaria Policy Advisory Committee Meeting. 16-18 September 2015, Geneva, Switzerland. Background document for Session 4.
[35] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.
[36] Among the nine countries that have reported to WHO on 3+ doses. WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
[37] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
[38] Hodgins S, D'Agostino A. The quality-coverage gap in antenatal care: toward better measurement of effective coverage. Glob Health Sci Pract. 2014 Apr 8;2(2):173-81.
[39] WHO. A strategic framework for malaria prevention and control during pregnancy in the African region - Opportunities for community-based programming. Brazzaville: WHO Regional Office for Africa; 2004.
[40] Manguyu W. Accelerating MiP: Improving Access to and Quality of Care – Community Engagement (presentation). Roman E. Testing the feasibility of community delivery of intermittent preventive treatment during pregnancy with IPTp-SP in Burkina Faso (presentation). RBM MIP Working Group 2015 Annual Meeting in Geneva.
[41] Hodgins S, D'Agostino A. The quality-coverage gap in antenatal care: toward better measurement of effective coverage. Glob Health Sci Pract. 2014 Apr 8;2(2):173-81.

workers' perceptions of SP as a "failing drug", both contribute to low demand. Low demand for IPTp is both a cause and an effect of **stock-outs of SP at facility level**. Bulk packaging of SP is also seen as a barrier to uptake[42]. Blister packaging of multiple SP doses, possibly in chewable format to eliminate the need for water, with adapted labeling and information for use in IPTp, could all be explored as options to improve the presentation of SP and facilitate its use in IPTp.

Moreover, there is a **lack of adequate supply of quality SP**, both at global level and at healthcare facilities. At global level, there are limited incentives for manufacturers to continue to produce quality-assured SP, due to low demand, low cost of the drug and resulting limited return on investment, and concerns that resistance will result in a termination of the use of SP in the near future[43]. This is evidenced by the market exit of the only prequalified sulfadoxine API supplier in 2014, leading to shortages of SP combination for in seasonal malaria chemoprevention. PMI has also observed large increases in lead time for SP orders, from 3-4 months to 8-12 months[44]. On local markets, there are numerous suppliers of SP, with **many products of poor-quality**. In a study conducted by WHO in six African countries on the quality of selected antimalarial medicines in both public and private sectors[45], the results for SP are striking:

- Of the samples collected, there were a high number of different SP products available (up to 23 products in Nigeria)
- 16% of all SP samples were products that were not registered in the country where the sample was taken
- The quality control failure rate was 30% of all SP samples tested, and 17% of all SP samples showed extreme deviations from quality standards

While a recent expert review has reconfirmed that SP remains highly effective for preventive chemotherapy in pregnant women[46], it remains a high priority to ensure that alternatives exist should it become necessary to replace SP. An additional need is to find an alternative drug for IPTp in HIV-infected women, in whom SP is contraindicated. The ACT DHA-PPQ is currently the only drug under investigation, and while initial results are positive, more research is needed on its use in IPTp[47].

Should DHA-PPQ be recommended as an alternative to SP for IPTp, reinforcing and expanding the delivery infrastructure for IPTp would facilitate its introduction, particularly as this regimen is likely to face additional implementation challenges related to its higher cost and 3-day regimen (vs. one dose for SP).

[42] RBM MIP Working Group 2015 Annual Meeting in Geneva.
[43] SP is no longer recommended for malaria treatment, but is still recommended for preventive interventions.
[44] Susan Youll, USAID/PMI, Personal communication, 21 September 2015.
[45] WHO. Survey of the quality of selected antimalarial medicines circulating in six countries in sub-Saharan Africa. Geneva: World Health Organization; 2011.
[46] Malaria in pregnancy. WHO Evidence Review Group meeting report. 13-16 July 2015. Malaria Policy Advisory Committee Meeting. 16-18 September 2015, Geneva, Switzerland. Background document for Session 4.
[47] Malaria in pregnancy. WHO Evidence Review Group meeting report. 13-16 July 2015. Malaria Policy Advisory Committee Meeting. 16-18 September 2015, Geneva, Switzerland. Background document for Session 4.

5.1.2 Who is doing what?

While IPTp is a malaria intervention, its primary delivery mechanism is through antenatal care and as such it often tends to "fall through the cracks" between the two areas of programming. Partners involved in IPTp therefore include not only malaria donors/stakeholder/implementers, but also equivalent counterparts from maternal and child health (MCH). In light of the resulting gaps in funding and activities for IPTp, it will be critical for Unitaid to work closely with key partners to ensure transition and ultimate sustainability of interventions targeted under this AfI.

In 2015 the Roll Back Malaria Partnership published a *Global Call to Action to increase national coverage of intermittent preventive treatment of malaria in pregnancy for immediate impact*[48]. While many of the barriers to IPTp uptake result from issues of health systems and the lack of sufficient collaboration and coordination between malaria and MCH programmes, opportunities exist for Unitaid to contribute to specific recommendations outlined in the Call to Action:

- Explore innovative opportunities in the community for IPTp delivery, both to extend ANC-based programmes and to serve women where ANC services are under-developed;
- Evaluate alternative strategies for the delivery of IPTp in hard-to-reach populations or communities;
- Provide support for operational research to increase IPTp coverage;
- Facilitate private-sector engagement with increased financial and technical support that will translate into improved IPTp coverage;
- Meet the demand for SP procurement and register quality SP in all malaria-endemic countries.

5.1.3 What is the cost of inaction and the potential value for money?

The cost of inaction can be summarized as four major effects:

- Inability to reach universal coverage of pregnant women with 3+ doses of IPTp by 2025, resulting in substantial morbidity and mortality.
- Continued reliance on drugs of uncertain quality. Poor-quality drugs can decrease the preventive effects of IPTp, thereby reinforcing low demand for IPTp; can result in adverse events; and can contribute to the spread of drug resistance[49].

[48] 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)
[49] Newton PN, Green MD, Fernandez FM. Impact of poor-quality medicines in the 'developing' world. Trends Pharmacol Sci. 2010; 31(3-3): 99–101.

- Lack of increased supplier base for quality-assured SP could lead to further shortages as were experienced in the context of SMC, as well as an insufficient quality-assured supply to support future scale-up efforts.
- Low coverage limiting manufacturers' incentives to invest in alternative chemotherapy regimens, especially for pregnant women in whom clinical research is more challenging and costly.

The value for money of such interventions needs to be evaluated in terms of public health and market impacts:

- Public health impact: Increasing coverage of IPTp could result in a 40% decrease in malaria cases in pregnant women, i.e. 3.2 million cases per year at full coverage and more than 60% decrease in neonatal mortality, i.e. more than 72,000 infants per year at full coverage[50].
- Market impact: Proposed interventions would result in increased demand for IPTp as well as improved supply capacity and security for quality-assured SP. In addition, economic benefits include averted treatment costs for malaria in pregnancy, infants with low birth weight and maternal anemia, making IPTp a highly cost-effective intervention[51]:

5.1.4 Fit with the current portfolio and suggested interventions

5.1.4.1 Fit with the current portfolio

This AfI would address prevention of malaria in pregnant women and market shortcomings for SP.

To date, Unitaid's malaria portfolio has not included any investments targeting pregnant women despite the fact that they are a high-risk group for malaria. An intervention in this area would therefore address a current gap in the portfolio, and would be complementary to Unitaid's current investment to expand coverage of seasonal malaria chemoprevention (SMC) through the *Access-SMC* project. One expected outcome of this project is the expanded supply of quality-assured SP-amodiaquine for use in SMC, in dispersible form to facilitate its use in young children. Expanding supply of SP-amodiaquine will also serve to reinforce the supply of SP for use in IPTp. However, given that current coverage of IPTp is so low, an aggressive expansion in the coverage of IPTp would require additional supply of quality-assured SP, ideally in packaging adapted for this use.

Projects on both SMC and IPTp would be complementary and mutually reinforcing, sending a strong signal to manufacturers that ensuring

[50] Mendelez C. Overview of the burden and impact of malaria in pregnancy on maternal and infant's health (presentation). 07 July 2015.
[51] Desai M. et al. Epidemiology and burden of Malaria in pregnancy. Lancet Infect Dis. 2007 Feb;7(2):93-104. USAID/PMI. Malaria protection in pregnancy: A lifesaving intervention for preventing neonatal mortality and low birth weight. Briefer. March 2013. Eisele TP et al. Malaria prevention in pregnancy, birth weight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. Lancet Infect Dis. 2012 Dec;12(12):942-9.

an adequate supply of quality SP remains a priority for the malaria community. Indeed, there is increasing recognition of the need to ensure a quality-assured supply of older, inexpensive antimalarial drugs such as SP, chloroquine and primaquine, for which manufacturers have limited incentives to continue to produce. In addition to SP shortages, in the past year there have also been shortages of quality-assured chloroquine[52]. Maintaining adequate supplies of these needed products is therefore a priority.

5.1.4.2 Suggested interventions in the next 24 months

Generate evidence for innovative approaches to delivery and demand generation, to support global guidance and scale-up.

- While ANC remains the primary delivery channel for IPTp, WHO has also recommended community-based delivery of this intervention. While innovative approaches are needed to increase demand for IPTp by both health workers and pregnant women as part of ANC, other delivery channels should also be explored if the dramatic increases in coverage called for in the GTS are to be achieved. In particular, community-based delivery could provide a platform for expanded delivery of IPTp, and could also serve to strengthen ANC services (e.g. through referrals of pregnant women in the community to ANC).
- Specific interventions could include developing and testing models of cost-effective delivery in a number of countries, which if successful, could be replicated more broadly. The focus would be on evaluating innovative approaches to IPTp, which could cover innovative delivery channels and approaches, private-sector engagement, demand generation including incentives for health workers and/or women, and logistics and stock management.

Support adequate supply of quality SP, including adapted packaging.

- Currently there are multiple supply issues with quality-assured SP that would need to be resolved in order to meet universal coverage of IPTp called for in the GTS. Firstly, as with other older, inexpensive drugs such as chloroquine and primaquine, there are few suppliers of quality-assured SP on the global market. The severity of this issue is evidenced by the recent supply shortages of quality-assured SP that limited the scale-up of SMC in the 2015 season, as well as with the dramatic increase in SP lead times in recent months. While Unitaid's SMC project will bring sufficient supply of dispersible SP-AQ needed for SMC, it would be insufficient for a parallel scale-up of IPTp. Additional suppliers of quality-assured SP that meet donor procurement requirements would therefore be needed for scale-up

[52] Dr Andrea Bosman, WHO GMP, personal communication, 01 October 2015.

efforts. Emphasis should also be placed on developing packaging that would promote SP's specific use in IPTp.

- Specific interventions are likely to include working with existing SP manufacturers to meet international quality standards and providing support/incentives for the activities needed to achieve WHO Prequalification. Expanding the production capacity of existing quality-assured SP manufacturers could also be considered.

Beyond 24 months, potential intervention could consist in supporting rapid introduction and scale-up of alternative therapies, in coordination with partners, (e.g. DHA-PPQ) or approaches (e.g. community-based delivery), should these be recommended.

5.1.5 Resolution n°2

"Having considered the analysis presented by the Secretariat during EB23, the Executive Board supports the need for Unitaid to focus strategically on "Expand access to preventive chemotherapy in pregnant women" with a view to securing a substantial impact on the Global goals for access to malaria preventatives for pregnant women.

The Executive Board requests the Secretariat to launch appropriate calls for proposal within this area for intervention and to present progress on implementation to the PSC.

The Board's endorsement of this area for intervention has no budgetary implications."

5.2. Area for intervention 2: Accelerate adoption of innovative vector control tools

5.2.1 Why now and what are the key issues?

5.2.1.1 Insecticide-resistance threatens current tools, and new tools are needed to address outdoor transmission

Vector control is a central component of recent gains made in malaria, and a keystone of the potential to achieve future goals. It is estimated that the distribution of insecticide-treated nets accounts for 68% of the gains made against malaria in the last 15 years[53]. However, mosquito resistance to the insecticides used in vector control products threatens the effectiveness of these tools and is therefore one of the major challenges to achieving the global goals set out in GTS/AIM. Insecticide-resistance has already developed and is present in varying intensities in all four classes of insecticides used in malaria vector control. Widespread resistance to pyrethroids - the only insecticide class that can be used in LLINs - is a particular risk[54].

[53] UNICEF, WHO. Achieving the malaria MDG target. Reversing the Incidence of Malaria 2000-2015. Geneva: World Health Organization and the United Nations Children's Fund; 2015.
[54] WHO. Global plan for insecticide-resistance management in malaria vectors. Geneva: World Health Organization; 2012..

Due to the major threat of insecticide-resistance, accelerating the development and introduction of tools for managing insecticide resistance, including new active Ingredients, is a high priority.

Efforts to streamline the market entry pathway for vector control tools is critical to combat insecticide-resistance, and would also have a beneficial effect on tools to address outdoor mosquito biting. These tools are particularly important in Asia where outdoor transmission is a leading cause of malaria infection[55]. They are also important in elimination settings, to protect population groups such as forest workers who work outdoors at biting times and/or near mosquito breeding sites[56].

5.2.1.2 Innovative vector control tools face challenges to market entry and introduction

Currently there are limited vector control tools to address the issues above, though several products are in the RandD pipeline. For innovative products, a key challenge to market entry is the long timeline for global evaluation, normative guidance, and country registration that is required for countries to begin using new tools. Extended timelines delay the availability of strongly needed innovations, and act as a disincentive for manufacturers to continue to invest in RandD. Other barriers to RandD 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[57]. Once available, new tools may also face limited or slow uptake. Recent innovative products that have been evaluated and recommended for malaria-control have achieved very poor market penetration due to their higher prices and, in some cases, a lack of information on where products can be best deployed[58].

An additional challenge that can limit the uptake of new products is a lack of normative guidance on when, where and how to use new vector control tools. The WHO Vector Control Advisory Group (VCAG) is charged with assessing the public health value, "proof of principle" (epidemiological impact) of new vector control tools, approaches and technologies[59]. Once a new tool is recommended by VCAG, however, policy guidance on the use of this new tool may be limited or delayed due to a lack of evidence. For example, an LLIN designed to address mosquito resistance received a positive VCAG review in February 2014[60], however normative guidance on its use is still pending. Even once normative guidance is available, product introduction may be limited by a lack of practical experience on how these new tools can be effectively deployed at country-level.

[55] Bill and Melinda Gates Foundation, United Nations Secretary-General's Special Envoy for Financing the Health Millennium Development Goals and for Malaria. From Aspiration To Action: what will it take to end malaria? 2015. Available from: http://endmalaria2040.org/assets/Aspiration-to-Action.pdf (accessed 17 Oct. 2015).
[56] Malaria Elimination: Targeting High-Risk Populations (ASTMH Symposium abstract). Available from: http://www.abstractsonline.com/Plan/ViewSession.aspx?sKey=8971af18-b58a-4205-8582-af2e372b598aandmKey=%7B52AE2426-7F12-4D2B-9404-C0D0B5A8EB5A%7D (accessed 17 Oct. 2015).
[57] Unitaid. Malaria Vector Control Commodities Landscape. 2nd Edition. Geneva: Unitaid; 2014.
[58] IVCC. Market Intervention to accelerate uptake of new vector control tools. Project Proposal. January 2015.
[59] WHO. Vector Control Advisory Group (VCAG) on new paradigms (website). Available from: http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/ (accessed 17 Oct. 2015).
[60] WHO. Second meeting of the Vector Control Advisory Group (VCAG). Geneva; World Health Organization: 2014.

The lack of policy and operational guidance on the use of new vector control tools to guide their deployment in countries has been identified by both the Global Fund and PMI as a key challenge to product introduction and uptake, which is compounded by the higher cost of innovative tools compared to traditional products such as standard LLINs. A range of new paradigms are expected to be evaluated by VCAG over the next few years; it will therefore be important to ensure that the necessary guidance is available on the optimal, most cost-effective deployment of this range of tools.

5.2.1.3 Reforms to global processes underway to accelerate time to market and improve quality assurance

The WHO Pesticide Evaluation Scheme (WHOPES) was established in 1960 and is responsible for the testing and evaluation of public health pesticides through laboratory and field trials. It issues recommendations for use in product registration and procurement[61]. Currently the product evaluation process can be long and variable, and is based on minimum standards which makes it difficult for manufacturers to demonstrate innovation. There is broad stakeholder agreement on the need to increase the transparency and timelines of the evaluation process, as well as the technical requirements for evaluation[62].

The following reforms to the current pesticide evaluation system have been agreed in order to ensure that critical new vector control tools reach the market more quickly, and manufacturers are incentivized to continue to invest in RandD for innovative products:

- Pesticide evaluation system moved and harmonized to the WHO Prequalification Programme;
- Efficient global evaluation system based on manufacturer's own data, enabled by Good Lab Practice (GLP) compliant sites for safety and efficacy trials;
- Product evaluation based on dossier reviews by an independent committee, with pre-submission guidance to developers;
- Establishment of pre−marketing manufacturing site inspections and post−marketing quality assurance.[63]

It is expected that these reforms will reduce the time required for dossier evaluation to < 100 days[64].

Efforts are also underway to improve the efficiency of normative guidance processes for vector control tools, with a target timeline for normative guidance to be produced following a VCAG recommendation of six months[65].

[61] WHO. WHO Pesticide Evaluation Scheme: "WHOPES" (website). Available from: http://www.who.int/whopes/en/ (accessed 17 Oct. 2015).
[62] Bill and Melinda Gates Foundation. Achieving Innovation to Impact in Vector Control. Draft Vision Statement Executive Summary (version 48). 2015.
[63] Innovation to Impact (I2I) in Vector Control. Stakeholder Convening – Plenary sessions. June 24, 2015.
[64] Innovation to Impact (I2I) in Vector Control. Stakeholder Convening – Plenary sessions. June 24, 2015.

However, while some efficiencies to the process for generating normative guidance may be possible, availability of the evidence needed to inform policy recommendations will still be a critical determinant of the overall timeline.

5.2.2 Who is doing what?

Reforms to the current pesticide evaluation system and normative guidance activities are taking place under the Innovation to Impact (I2I) Framework. I2I is a global vision for improving the value chain for vector control tools. It outlines a comprehensive strategy that covers product innovation, efficacy, safety and quality evaluation, country-level product registration, global and local procurement and health impact. Led by the Bill and Melinda Gates Foundation, I2I began in Fall 2013 and has developed as a collaborative and consultative process with all key stakeholder groups including industry, global evaluation and regulatory bodies, procurers, national and local representatives, and donors[66].

A range of partner activities underway to accelerate the adoption of innovative vector control tools, both within the I2I and more broadly. WHO has a central role in the implementation of reforms to both product evaluation and normative guidance processes. Such reforms are a foundation upon which other activities depend, and as such the timely implementation of these reforms is critical. IVCC, the public-private partnership for vector control, plays a critical role in supporting development of new products. The Global Fund and PMI are both supporting efforts to improve normative guidance on the use of new tools through desk and operational research. Procurement bodies also have a key role in terms of basing procurement decisions on product performance traits beyond price. Industry also has a key role in terms of maintaining robust RandD pipelines and participating in reforms to the global evaluation process (e.g. participating in pilot dossier reviews)[67].

Within this landscape, Unitaid is uniquely positioned to support both product evaluation and the introduction of new tools in an effort to generate evidence, market intelligence and implementation models that can enable further scale-up.

5.2.3 What cost of inaction and potential value for money?

This AfI aims to combat insecticide resistance with new tools, for maximum public health impact. Pyrethroids are currently the only insecticides used in LLINs, however 64 countries have reported resistance to pyrethroids including most of sub-Saharan Africa. At current coverage levels, the failure of pyrethroids could result in:

[65] Innovation to Impact (I2I) in Vector Control. Stakeholder Convening – Plenary sessions. June 24, 2015.
[66] Bill and Melinda Gates Foundation. Achieving Innovation to Impact in Vector Control. Draft Vision Statement Executive Summary (version 48). 2015.
[67] Innovation to Impact (I2I) in Vector Control. Stakeholder Convening – Plenary sessions. June 24, 2015.

- 120,000 additional deaths in children in Africa per year
- 26 million additional malaria cases, with diagnostic and treatment costs of US$ 30–60 million
- US$ 30–60 million in additional costs due to increased malaria cases[68].

Delayed access to new tools to control outdoor transmission could also have a negative impact on the pace of elimination, particularly in Asia where outdoor transmission is a leading cause of malaria transmission[69].

Market impacts targeted under this AfI include:

- Acceleration of the speed at which innovations reach markets and are introduced
- Catalyzed uptake of new products, leading to accelerated global scale-up and price reductions
- Incentives for manufacturers to continue investing in research and development
- Improved product quality resulting from the establishment of pre-marketing and post-marketing quality assurance

5.2.4 Fit with the current portfolio and suggested interventions

5.2.4.1 Fit with the current portfolio

Support for improved global evaluation processes for vector control tools would be closely aligned with Unitaid's strategic focus on global product evaluation programmes as a critical component of product quality: *Prequalification Programmes for medicines and diagnostics*, and the *WHO/FIND Product Testing Programme for malaria RDTs*.

In addition, interventions to accelerate the market entry of innovative vector control tools would be complementary to the anticipated Unitaid investment to support the scale-up of third-generation insecticides (3GIRS) for indoor residual spraying (IRS). This project aims to increase the use of 3GIRS products, of which several are still in the RandD pipeline. By supporting a more efficient global evaluation process, these tools could reach the market more quickly.

5.2.4.2 Suggested interventions in the next 24 months

Streamline product evaluation through support for reforms to the current pesticide evaluation system, including the transition of WHOPES to the *WHO Prequalification Programme.*

[68] WHO. Global plan for insecticide-resistance management in malaria vectors. Geneva: World Health Organization; 2012.
[69] Bill and Melinda Gates Foundation, United Nations Secretary-General's Special Envoy for Financing the Health Millennium Development Goals and for Malaria. From Aspiration To Action: what will it take to end malaria? 2015. Available from: http://endmalaria2040.org/assets/Aspiration-to-Action.pdf (accessed 17 Oct. 2015).

- An opportunity exists for Unitaid to support the planned reforms to the current pesticide evaluation system. These reforms have been described above and include the creation of a new unit under the WHO Prequalification Programme for the evaluation of vector control tools. During the transition, there will be a gradual shift towards product dossiers based on data generated by manufacturers. In parallel, an infrastructure of GLP sites will be built to enable data generation owned by manufacturers. Systems will also be developed for pre- and post-marketing quality assurance (e.g. factory inspections).

- It is expected that the transition process will be complete by the end of 2018[70], however this timeline is ambitious and is dependant upon funding availability. Unitaid support could therefore play a key role in ensuring the completion of the transition within the required timeframe. A rapid and smooth transition is critical to maintain the momentum that has been generated from the I2I process, and to ensure that the transition process represents the principles of efficiency and transparency which are the ultimate objectives of the reforms.

- Ensuring that global pesticide evaluation processes are as efficient and streamlined as possible will be critical to ensure that strongly needed tools, particularly those to address insecticide-resistance but also those to address outdoor biting, reach the market as quickly as possible. It is also anticipated that a more streamlined system will improve the incentives for manufacturers to continue to invest in RandD for vector control tools. This enabler will also serve to strengthen pre-marketing and post-marketing quality assurance systems for existing vector control tools.

- In coordination with partners, support selective deployment of new vector control products: 1) to generate data to support normative guidance and market research; 2) to support rapid introduction and scale-up of new tools (e.g. combination nets, nets with new AIs) (e.g. combination nets, nets with new active ingredients).

- In cases where the required normative guidance on the use of new vector control tools is limited due to a lack of data, Unitaid can accelerate market introduction by supporting the selective deployment of these products including research activities to generate missing evidence. This evidence would serve as a critical input into normative guidance processes and recommendations. In cases where data is sufficiently robust to enable the rapid generation of normative guidance, a further opportunity exists to support the initial introduction of these tools and catalyse their uptake, generating important learnings on how these tools can be implemented as part of national programmes.

[70] Innovation to Impact (I2I) in Vector Control. Stakeholder Convening – Plenary sessions. June 24, 2015.

- Under the planned reforms to the global evaluation process for vector control tools, it is expected that an interim recommendation will be provided that will enable the deployment of new tools before the completion of the evaluation process. Once this interim approval process is established, an opportunity will exist for Unitaid and others to support the initial deployment of new tools. This would not only provide initial volumes to manufacturers and send a signal that there is interest in the uptake of new innovations, but it would also serve to generate lessons and models for product introduction in other settings, as well as generate market research such as potential market size that could assist both manufacturers (production planning) and procurers (price negotiations).

5.2.5 Resolution n°3

"Having considered the analysis presented by the Secretariat during EB23, the Executive Board supports the need for Unitaid to focus strategically on "Accelerating adoption of innovative vector control tools" with a view to securing a substantial impact on the Global goals for access to Malaria innovative vector control tools on a timely manner.

The Executive Board requests the Secretariat to launch appropriate calls for proposal within this area for intervention and to present progress on implementation to the PSC.

The Board's endorsement of this area for intervention has no budgetary implications."

5.3. Area for intervention 3: Expand private-sector access to diagnostics and treatment

5.3.1 Why now and what are the key issues?

5.3.1.1 Remarkable progress made in improving access to diagnosis and treatment in the public sector, but up to 40% of patients seek care in the private sector

Dramatic progress has been made in the fight against malaria in the past 15 years, largely due to the scale-up of proven interventions such as treatment with artemisinin-based combination therapies (ACTs). The public sector has played a key role in expanding access to malaria case management, including both diagnostic testing and ACT treatment.

However, up to 40% of patients seek care for malaria through the private-sector, where access to appropriate case management remains low. Access to ACTs in the private sector has increased in recent years, but remains low in many countries: the proportion of febrile children treated with an ACT in the private sector ranges from 9 to 75%[71]. Access to diagnostic testing,

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

specifically malaria Rapid Diagnostic Tests (RDTs), is minimal in the private-sector. A lack of diagnostic testing leads to large rates of overtreatment of non-malaria fevers with antimalarial drugs. This is evidenced by the fact that the overall size of the private sector for antimalarials in Africa has been estimated at 655 million treatments[72]. Further, demand for ACTs based on current rates of diagnostic testing is 480 million treatments, compared to only 163 million malaria cases[73]. Thus, widespread overtreatment co-exists with a lack of access to ACTs by people who have malaria.

The WHO Global Technical Strategy 2016-30 is built on three pillars, one of which includes universal access to malaria diagnosis and treatment in both public and private sectors as well as at community level. Specifically, the coverage scenarios used to guide the development of the GTS targets includes 50% of confirmed malaria cases are treated with an ACT in the private sector by 2020[74].

The global goals therefore require that immediate efforts are made to expand access to appropriate case management in the private sector.

5.3.1.2 Multiple barriers exist to the scale-up of RDTs and ACTs in the private sector

Lack of access to ACTs and RDTs in the private sector 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[75].

The private sector is a heterogeneous construct that includes multiple types of sales points, from licensed pharmacies to street vendors. A 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.

5.3.2 Who is doing what?

Multiple initiatives have taken place, or are currently ongoing, in order to expand access to appropriate malaria case management

[72] Cohen JM et al. Optimizing Investments in Malaria Treatment and Diagnosis. Science. 2012 ; 338(6107) :612-614.
[73] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
[74] WHO. Background brief on the proposed targets and estimated costs of implementation of the draft global technical strategy for malaria (2016-2030). 19 December 2014. Available from: http://www.who.int/malaria/areas/global_technical_strategy/WHO_HTM_GMP_2014.11_eng.pdf?ua=1 (accessed 17 Oct. 2015)
[75] Unitaid. Malaria medicines technology and market landscape. 2nd Edition. Geneva: Unitaid; 2015. Unitaid. Malaria diagnostics landscape update. Geneva: Unitaid; 2015.

in the private sector. The *Affordable Medicines Facility–malaria* (AMFm), supported by multiple donors including Unitaid, has been the largest effort to date to improve the availability and use of ACTs in the private sector. In November 2012, the Global Fund Board decided to incorporate the AMFm in the Global Fund grant management and financial processes, and as such co-payments for commodities distributed through the private sector are now open to all countries eligible to Global Fund financing[77]. The Global Fund is now considering making a private-sector strategy a mandatory component of case management in future malaria Concept Notes, and has signaled their enthusiasm for further Unitaid investments that could support and complement their strengthened focus on the private sector.

This AfI will not only benefit target countries, who will be in a better position to utilize the Global Fund Private Sector Co-payment mechanism in the future, but will also have broader impact by providing important lessons and models that can be employed by other countries. These learnings will also be critical to inform the inclusion of private-sector case management into future Global Fund Concept Notes, particularly if this becomes mandatory.

Other ongoing initiatives of high relevance include the *Creating a Private-sector Market for Quality-Assured RDTs* project being undertaken by Population Services International and partners with Unitaid support, which aims to introduce RDTs in the private sector in five countries. The BMGF is funding a greater Mekong elimination project that promotes RDT use in the private sector, and DFID support includes a project to promote greater access to ACTs and RDTs in the private sector in Kinshasa, Democratic Republic of the Congo. PMI is also engaged in private-sector malaria-control activities.

The landscape of partner activities to promote greater use of RDTs and ACTs in the private sector therefore includes multiple relevant initiatives. However, there is a strong recognition that given the challenges and risks involved in private-sector engagement, additional complementary work is needed to improve access to both RDTs and ACTs in this sector. In particular, there are limited efforts to expand the use of the private sector in Western African countries where the malaria burden remains high and where the private sector represents a key source of antimalarials.

5.3.3 What is the cost of inaction and potential value for money?

Poor case management in the private sector (low demand for ACTs, demand for ACTs without a positive diagnostic test) can have several negative public health consequences:

[76] The Global Fund. Board Approves Integration of AMFm into Core Global Fund Grant Processes (website). 15 November 2012. Available from: http://www.theglobalfund.org/en/news/2012-11-15_Board_Approves_Integration_of_AMFm_into_Core_Global_Fund_Grant_Processes/ (accessed 17 Oct. 2015).

- Lack of access to ACTs by people who have malaria, leading to increased morbidity and mortality
- Use of ACTs by people who do not have malaria, leading to wasted resources and increased morbidity and mortality from other causes of fever
- Continued use of ineffective drugs and drugs of substandard quality, which can increase the risk of drug resistance

The value for money of a private-sector intervention is two-pronged, with an impact on both public health as well as the market. In terms of public health impact, such an intervention would result in reduced malaria morbidity and mortality, delayed resistance to artemisinin in the region, as well as possible reduced morbidity and mortality from other common sources of fever (pneumonia, diarrhea). With regards to market impact, an intervention targeting the private sector would increase demand for ACTs and RDTs, decrease prices and decrease the market share of poor-quality and non-recommended medicines.

5.3.4 Fit with the current portfolio and suggested interventions

5.3.4.1 Fit with the current portfolio

Investing in further interventions to increase appropriate case management in the private sector is a strong fit with Unitaid's current portfolio and has high potential to leverage past and ongoing projects. In particular, new investments would be able to leverage the activities and lessons learnt from the ongoing project *Creating a Private-sector Market for Quality-Assured RDTs* being implemented by PSI and partners, as well as from the *Affordable Medicines Facility-malaria* (AMFm). Both projects have faced implementation challenges which would be important to consider in the design of new interventions. All five target countries in Unitaid's current RDT project are also former AMFm pilot countries; this was done purposefully to ensure that access to affordable ACTs were available to treat patients with a positive RDT result. However, it has resulted in a concentration of Unitaid's investments in malaria case management in a small number of countries. There is therefore a strong rationale to increase efforts outside of these countries, particularly to investigate different approaches to expanding private-sector case management in countries with differently structured pharmaceutical systems.

5.4.3.2 Suggested interventions in the next 24 months

To expand access to recommended, quality-assured diagnostics and treatment in the private sector, it is proposed that interventions be undertaken in a selection of countries to address key barriers to case management in the private sector. The investment would specifically

serve as a bridge to accessing the Global Fund Private Sector Co-payment Mechanism, or other sources of funding, in the future. Even with the availability of a commodity co-payment to improve affordability to patients, multiple other changes will be needed at country-level to enable uptake. These include the creation of a conducive policy and regulatory environment, functioning supply chains, appropriate quality assurance, the necessary incentives for retailers, affordable pricing and the creation of demand for these commodities by patients who seek care in the private sector.

Interventions are likely to include a commodity co-payment in order to address affordability barriers and kick-start demand. Building on lessons learned from other projects, interventions should address RDTs and ACTs holistically and should be country-specific in order to address key barriers and leverage key opportunities, to improve private-sector uptake of RDTs and ACTs. In addition to efforts at country-level, regional activities such as regulatory harmonization efforts or regional efforts to promote product quality, would serve to reinforce the private-sector environment and should be explored.

High-priority countries would include those with an ongoing high malaria burden, a high rate of care-seeking in the private sector and a large private sector market for antimalarials, and critically, evidence of strong political commitment for expanding malaria treatment in the private-sector, including a commitment to sustainability/transition (e.g. through the Global Fund Private Sector Co-payment Mechanism). Countries moving towards elimination (e.g. pre-elimination stage) are also important to target as many will need to engage the private sector in order to reach their objectives. Francophone countries in Western Africa are of particular interest given their malaria burden, high use of the private sector, and lack of investments in the private-sector to date.

5.3.5 Resolution n°4

"Having considered the analysis presented by the Secretariat during EB23, the Executive Board supports the need for Unitaid to focus strategically on "Expanding private-sector access to diagnostics testing and treatment" with a view to securing a substantial impact on the Global goals for access to Malaria innovative vector control tools on a timely manner.

The Executive Board requests the Secretariat to launch appropriate calls for proposals within this area for intervention and to present progress on implementation to the PSC.

The Board's endorsement of this area for intervention has no budgetary implications."

5.4. Area for intervention 4: Optimize introduction of tools for the treatment of severe malaria

5.4.1 Why now and what are the key issues?

5.4.1.1 If left untreated, severe malaria causes death in nearly 100% of cases, but effective treatments exist

There are approximately 2 million cases of severe malaria per year. Severe malaria is a serious medical condition that can lead to convulsions, respiratory distress, coma, and death[79]. If left untreated, severe malaria causes death in nearly 100% of cases[80]. In 2013, there were 584,000 deaths from malaria, 80% of which occurred in children under 5 years of age[81]. Severe malaria is most commonly caused by infection with *Plasmodium falciparum* malaria, and usually[82] results from delayed treatment of uncomplicated malaria. However in some cases, particularly in children, severe *P. falciparum* malaria may develop so rapidly that early treatment of uncomplicated malaria is not possible[83]. About 90% of the world's severe and fatal malaria is estimated to affect young children in sub-Sahara Africa[84].

Severe malaria is a medical emergency that requires treatment as soon as possible to reduce the risk of death and brain damage. WHO recommends treatment with injectable artesunate (intravenous (IV) or intramuscular (IM)) for at least 24 hours and until oral medication can be tolerated, following which patients should receive a complete treatment course of ACTs. Pending transfer to a heathcare facility, in situations where it is not possible to provide intramuscular artesunate as pre-referral treatment, WHO also recommends that children under 6 years of age be given a single rectal dose of artesunate as pre-referral treatment[85]. Rectal artesunate interrupts disease progression but is not a cure; it can be used in the community to buy time while patient is transported to a health facility.

Pre-referral treatment of severe malaria is important as malaria is common in many rural areas where people have to travel for several hours to reach clinics and hospitals. In a study in Ghana and Tanzania, only 56% of severe malaria patients reached a secondary healthcare facility within six hours, and of these half had still not reached a facility after more than 15 hours[86].

5.4.1.2 New, life-saving products for severe malaria face a number of market introduction challenges

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 QN). Additional barriers include buyer concerns over a single prequalified supplier, commercial interests around injectable QN, and poor acceptance by patients and providers. Between 2010–2013, procurement volumes of

[79] WHO. Management of Severe Malaria. A practical handbook. Third edition. Geneva: World Health Organization; 2012.
[80] WHO. Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015.
[81] WHO. World Malaria Report 2014. Geneva: World Health Organization; 2014.
[82] WHO. Management of Severe Malaria. A practical handbook. Third edition. Geneva: World Health Organization; 2012.
[83] WHO. Management of Severe Malaria. A practical handbook. Third edition. Geneva: World Health Organization; 2012.
[84] Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 2010;375:1969–1987.
[85] WHO. Guidelines for the treatment of malaria, third edition. Geneva: World Health Organization; 2015.
[86] Gomes MF et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009; 373: 557–66.

injectable artesunate represented only 25% of the total volume needed to treat global annual cases[87]. 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 an increased number of suppliers. As a result, the remainder of this section will focus on rectal artesunate, though Unitaid will continue to monitor opportunities to further support scale-up of injectable artesunate.

Today, the coverage rate of rectal artesunate is close to zero. While rectal artesunate is available in some countries on a limited basis, the lack of a WHO prequalified product has limited the ability for the use of this product on a large scale through international donor programmes. Under the *Improving Severe Malaria Outcomes* project, MMV is supporting the development of a rectal artesunate product for pre-referral treatment of severe malaria. As a result, at least one rectal artesunate product is likely to be available for donor procurement in 2016.

However, once rectal artesunate is available for more widespread deployment, it is still likely to face a number of implementation challenges, such as:

- **Concerns over misuse** of rectal artesunate, a monotherapy, for treating uncomplicated malaria and other fevers that could participate in developing resistance
- **Complex distribution through community health worker (CHW) networks**: this pre-referral treatment can be delivered at first point of care, usually at community level, to reach the isolated rural populations that most need this window of opportunity to be transported to health facilities where they will receive the appropriate treatment
- **Lack of cultural acceptance** among community health workers and patients and inadequate product knowledge
- **Difficulty targeting children or communities** where health facilities cannot be reached within six hours
- Administration of rectal artesunate may **discourage onward transport to health facilities**
- **Time lag for updates to national policies and guidelines**: to be adopted at community level, rectal artesunate need to be included in national strategic plans
- **Competition for funding** with other malaria priorities

[87] 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).

5.4.2 Who is doing what?

Some small-scale deployment of rectal artesunate is currently under way, however widespread use is hampered by the lack of a WHO prequalified product. Large scale funders such as Global Fund and PMI have acknowledged that even once a prequalified product is available, uncertainty regarding optimal implementation of rectal artesunate is going to be a key challenge to its deployment.

Unitaid is well positioned to fill this coverage gap for rectal artesunate, by showing — through proof–of–concept — that scaled implementation is possible for this treatment in different settings, with due consideration of potential misuse. This will enable larger and more effective scale-up by the global response and thereby ensure access to this life-saving product by large number of people in the most vulnerable settings.

5.4.3 What cost of inaction and potential value for money?

Without a targeted intervention, rectal artesunate is likely to face slow adoption due to the various implementation challenges described above. This would have multiple negative consequences:

- The global response will be unable to reach universal coverage, resulting in preventable mortality in children under 5 years of age.
- The rectal artesunate market will remain nascent in its first years, limiting incentives for suppliers to stay in the market or for new suppliers to enter the market. There is also the potential that slow market growth results in a price increase, as was experienced with injectable artesunate[88].
- In the context of a small market size, slow initial growth may serve as a disincentive for the development of alternative pre-referral products for severe malaria.

The potential public health impact of rectal artesunate is significant. When combined with onward referral and treatment, the use of rectal artesunate has the potential to reduce mortality in children with severe malaria by 50% as compared to referral treatment alone[89].

With respect to market impact, early growth of this small-market product will be an important outcome. Forecasts conducted under the Unitaid project, *Improving Severe Malaria Outcomes* (ISMO), estimate expected demand as 1.5 million treatments in 2016 (range 1.2 - 1.5 million), growing to 3.6 million treatments (range 1.2 – 7.9 million) in 2018.[90] These estimates represent demand based on severe malaria cases in which rectal artesunate could be used, however they do not take into account other

[88] MMV. Improving Severe Malaria Outcomes Project Proposal. 2012.
[89] Gomes MF et al. Pre-referral rectal artesunate to prevent death and disability in severe malaria: a placebo-controlled trial. Lancet 2009; 373: 557–66.
[90] Johnson BG, Larson PS, Yadav P. Global Demand Forecast for Intra-Rectal Artesunate (IR AS) 2016-2018. William Davidson Institute, December 2014.

influences on demand such as funding availability. As rectal artesunate is a new product, resources will need to be allocated to it from within fixed budget envelopes, i.e. it will need to compete for resources against other malaria interventions. Given the uncertainties around feasibility of implementation, as well as concerns over its misuse, the volumes of this product may in fact be smaller in its first years on the market.

A Unitaid project would therefore serve to accelerate market growth, by providing a larger volume in its first years on the market than could be expected through traditional donors alone.

It would also "unlock" a larger future market size by enabling scale-up by other donors. Other effects may include additional entrants, (however given the small market size a large number of suppliers would not be expected), as well as optimized pricing related to higher volumes. Finally, by supporting the creation of an infrastructure for the pre-referral treatment of severe malaria, it is expected that the introduction of other products currently in the pipeline would be facilitated. One example is ArTiMist™, a sub-lingual spray formulation of artemether for the treatment of severe malaria in children[91] which, in certain contexts, may be more socially acceptable to patients and caregivers than rectal administration.

5.4.4 Fit with the current portfolio and suggested interventions

5.4.4.1 Fit with the current portfolio

This intervention will build on Unitaid's current project *Improving Severe Malaria Outcomes* being undertaken by MMV and partners. This project's objectives are to:

- Increase market uptake and appropriate use of injectable artesunate for the treatment of severe malaria.
- Support additional generic manufacturers of injectable artesunate to attain WHO prequalification.
- Provide technical support to artesunate suppository manufacturers to attain WHO prequalification.

Unitaid's current investment will address a key barrier to the pre-referral treatment of severe malaria, namely the lack of a WHO prequalified rectal artesunate product. However, this alone will not be sufficient to ensure its uptake due to the implementation challenges described previously. As such, a follow-on investment will serve to increase the impact of the *Improving Severe Malaria Outcomes* project by addressing the key barriers to product introduction that rectal artesunate is likely to face once available for donor procurement.

[91] SUDA Ltd. Artimist™: Malaria (website). Available from: http://sudaltd.com.au/index.php/malaria (accessed 17 Oct. 2015).

5.4.4.2 Suggested interventions in the next 24 months

Demonstrate the possibility of scaling up use of rectal artesunate in a controlled environment in different settings.

The key objective of this intervention would be two-fold:

- Ensure that rectal artesunate is introduced in a controlled manner, with close monitoring of potential misuse;
- Provide a proof of concept that scaled implementation of rectal artesunate is feasible.

Specifically, interventions would be aimed at introducing rectal artesunate at scale in a selection of countries, including supportive interventions related to procurement, supply chain, storage, community health worker training, behavior change and communication and demand generation. The feasibility of implementing this community-based intervention under a range of different country systems and contexts, which could include integrated community case management of childhood diseases (iCCM) or other integrated platforms, would be evaluated in order to provide lessons and models for broader scale-up efforts. In particular, experiences regarding mitigating potential product misuse, as well as promoting referral to healthcare facilities and addressing situations where cases are not referred, will be critical to future scale-up.

Country selection would focus on settings with high malaria mortality rates to maximize impact; existence of an infrastructure for community-based delivery would also be a key consideration.

Guidance on best practices in the implementation of rectal artesunate, as well as adaptable tools that could be used in further scale-up (e.g. training kits), would expand on Unitaid's current "offer" of a prequalified rectal artesunate product, to provide a more comprehensive package of supportive resources necessary for country adoption.

Future opportunities may include additional investments to secure the scale-up of injectable artesunate, as well as investments to support new products for severe malaria that offer an advantage over existing tools. The Unitaid Secretariat will continue to monitor the progress of injectable artesunate uptake, as well as products for severe malaria in the pipeline, to evaluate additional near-term opportunities.

5.4.5 Resolution n°5

"Having considered the analysis presented by the Secretariat during EB23, the Executive Board supports the need for Unitaid to focus strategically on "Optimizing introduction of tools for the treatment of severe malaria" with a view to securing a substantial impact on the Global goals for access to Malaria innovative vector control tools on a timely manner.

The Executive Board requests the Secretariat to launch appropriate calls for proposals within this area for intervention and to present progress on implementation to the PSC.

The Board's endorsement of this area for intervention has no budgetary implications."

6. APPENDIX 1: Description of challenges

6.1. 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-care test has only recently become available. A further challenge is the 14-day treatment course of primaquine, which can limit adherence.

6.1.1 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 five countries of the Greater Mekong region: Cambodia, Laos, Myanmar, Thailand and Vietnam[92]. New drugs are under development which could be effective against artemisinin-resistant strains of malaria, however these are not yet available.

Complexity of antimalarial 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 the therapeutic efficacy of drugs[93].

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.)[94].

[92] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.
[93] WHO. Global Plan for Artemisinin Resistance Containment. Geneva: World Health Organization; 2011.
[94] Unitaid. Malaria medicines technology and market landscape – 2nd edition. Geneva: Unitaid; 2015.

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 12 million prequalified injectable artesunate vials were procured, representing around 25% of the total volume needed to treat global annual cases[95]. 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 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, but they can also contribute to onward 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.

6.1.2 Diagnostics

Limited ability to detect asymptomatic malaria carriers

Efforts to eliminate malaria include identifying and treating the asymptomatic human reservoir to prevent onward transmission. People

[95] 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).

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 the 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 a 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[96].

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[97].

6.2. Challenges related to prevention

6.2.1 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 RandD. 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[98].

[96] Unitaid. Malaria diagnostics landscape update. Geneva: Unitaid; 2015.
[97] Unitaid. Malaria diagnostics landscape update. Geneva: Unitaid; 2015.
[98] Unitaid. Malaria Vector Control Commodities Landscape. 2nd Edition. Geneva: Unitaid; 2014.

Low uptake of new vector control 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, two 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 (US$ 13.50 per unit) than other insecticides (US$ 23.50 per unit for carbamates, US$ 2-4 per unit for widely resisted pyrethroids)[99].

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 programmes.

Cost and 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 quality control both pre- and post-market

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

- 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

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

- 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[100].

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[101], 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[102].

6.2.2 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[103]. 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 programmes; 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 which international quality assurance is not required; low IPTp coverage and

[100] Bill and Melinda Gates Foundation. Achieving Innovation to Impact in Vector Control. Draft Vision Statement Executive Summary (version 48). 2015.
[101] WHO. Integrated Vector Management (IVM) (website). Available from: http://www.who.int/neglected_diseases/vector_ecology/ivm_concept/en/ (accessed 17 Oct. 2015).
[102] WHO. Global plan for insecticide-resistance management in malaria vectors. Geneva: World Health Organization; 2012.
[103] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).

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 subregion in Africa, due to SP resistance in other regions with seasonal malaria transmission. Currently there are no other options for chemoprevention in children outside of this subregion.

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[104]. 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[105]. 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[106]. 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 RandD pipeline, however these will not be available for several years.

[104] Unitaid. Malaria medicines technology and market landscape – 2nd edition. Geneva: Unitaid; 2015.
[105] 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.
[106] PATH Malaria Vaccine Initiative. RTS,S malaria vaccine candidate (website). Available from: http://www.malariavaccine.org/rd-rtss.php (accessed 17 Oct. 2015).

6.3. Cross-cutting challenges

6.3.1 Infrastructure

Weak health systems: surveillance, human resources, technical capacity and 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[107].

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[108]. 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 healthcare providers, and especially to children under five[109]. 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[110].

[107] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.
[108] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.
[109] 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)
[110] UNICEF. Review of Systematic Challenges to the Scale-up of Integrated Community Case Management. United Nations Children's Fund: New York; 2012 .

6.3.2 Social / Environmental

Social unrest and 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 a suspected Ebola case, or 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 dying[111]. 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[112].

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"[113]. Environmental change also has an impact on malaria transmission. For example, deforestation[114], large scale irrigation, urbanization[115], the establishment of rubber plantations[116], soil salinification[117], and extractive activities can all influence malaria transmission[118].

[111] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).
[112] Roll Back Malaria Partnership. Action and Investment to defeat Malaria 2016–2030. Geneva: World Health Organization; 2015.
[113] 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.
[114] Imai N et al. Transmission and control of Plasmodium knowlesi: a mathematical modelling study.PLoS Negl Trop Dis 2014;8:e2978.
[115] 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.
[116] Bhumiratana A et al. Malaria-associated rubber plantations in Thailand. Travel Med Infect Dis 2013;11:37-50. Yasuoka J and Levins R. Impact of deforestation and agricultural development on anopheline ecology and malaria epidemiology. Am J Trop Med Hyg 2007;76:450-460.
[117] 7. Temel, T. Malaria from the gap: need for cross-sector co-operation in Azerbaijan. Acta Trop 2004;89:249-259.
[118] 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.

Population growth

Many malaria-endemic countries have rapidly growing populations[119]. 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[120]. Other hard-to-reach groups include high-risk occupational groups, migrants, and people in humanitarian crises[121].

[119] The World Bank. Population growth (annual %) (website). Available from: http://data.worldbank.org/indicator/SP.POP.GROW (accessed 17 Oct. 2015).
[120] WHO. Global Technical Strategy for Malaria 2016-2030. Geneva: World Health Organization; 2015.
[121] UNICEF: Malaria (website). Available from: http://www.unicef.org/health/index_malaria.html (accessed 17 Oct. 2015).

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