Malaria eradication: marching to the beat of the global drum

Message from the Chairman and CEO

Last year saw a step-change in the global march to malaria eradication, as the world transitioned from the Millennium Development Goals to the bolder and more comprehensive targets of the Sustainable Development Goals (SDGs) for 2030. It also marked the first year of action under the guidance of the World Health Organization (WHO)’s strategic roadmap⁷ to maximize health outcomes. By 2030, WHO aims to reduce malaria infections and deaths by 90% and eliminate the disease in an additional 35 countries.

MMV is proud to play an important role in the global march to a malaria-free world. MMV-supported drugs are estimated to have already saved the lives of over one million people in 50 malaria-affected countries between 2009 and 2016. This number continues to rise as more and more people have access to the effective and affordable medicines we have developed with our partners.

In 2016 alone, MMV’s partner Guilin Pharmaceutical shipped over 73 million courses of sulfadoxine-pyrimethamine plus amodiaquine (SP+AQ) to countries in the Sahel region of West Africa, enough to provide 18 million children with Seasonal Malaria Chemoprevention (page 36).

Pyramax® (pyronaridine-artesunate) paediatric granules, an important treatment for children suffering from Plasmodium falciparum or Plasmodium vivax malaria, was added to WHO’s List of Prequalified Medicinal Products in 2016. This will facilitate its delivery to the very young – the population hardest hit by malaria (pages 30–31).

Supported by UNITAID funding, we worked intensively with partners to complete the Improving Severe Malaria Outcomes project by the agreed deadline of June 2016. This 3-year project set out in 2013 to transition six high-burden African countries to the use of injectable artesunate for severe malaria. The outcome was impressive: by the end of the project, more than 90% of health facilities in these countries had switched from quinine to injectable artesunate. We estimate that the overall uptake of injectable artesunate since prequalification may have saved between 450,000 and 500,000 young lives (pages 33–35).

Another exciting development for the management of severe malaria occurred in December. The Expert Review Panel of The Global Fund to Fight AIDS, Tuberculosis and Malaria issued a 12-month authorization for procurement of rectal artesunate suppositories developed by Cipla in partnership with MMV. While the WHO prequalification review of this product continues, the interim authorization will allow countries to procure this life-saving medicine for pre-referral management of children with severe malaria (page 32).

Multidrug-resistant P. falciparum malaria has now emerged in the Greater Mekong Subregion resulting in high levels of treatment failure with artemisinin-based combination therapy (ACT).² Signs of potential reduced sensitivity,³ and/or treatment failure with ACTs⁴ have also been detected in Africa. With this firmly in mind, our priority continues to be the development of novel, easier-to-take, next-generation cures for the ever-mutating malaria parasite. These medicines will not only improve patient compliance but could also potentially counter current and future parasite resistance (pages 12–18).

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In 2016, with an eye on the long march ahead, MMV focused on discovering and developing transformative medicines designed to support malaria control and eradication. The goal is for these medicines to be well tolerated in populations most vulnerable to malaria as well as in patients with other co-infections. Together with our partners, we are populating the pipeline with promising new antimalarial compounds to block transmission, protect against infection and stop the relapse of *P. vivax*. These include compound classes with novel mechanisms of action that will ultimately be partner drugs in combination therapies. The carefully selected compounds are being rigorously tested and are progressing through the pipeline; they will contribute to the achievement of the SDGs, to WHO’s strategic goals, and ultimately help to defeat malaria.

MMV’s global partnership network continues to expand. We worked actively with 24 industry partners and established new collaborations with Zydus Cadila, India, S Kant Healthcare, India and Novartis, Switzerland.

Alongside delivering on our promises from the previous business plan, in 2016 we charted our priorities for the next 5 years with the development of a new 2017–2021 business plan. With a 15-year horizon in sight and in close alignment with global malaria elimination goals, the new plan describes MMV’s longer-term view and the important contribution of new medicines to help defeat malaria (page 8).

As the Chairman and the CEO of MMV, it is with pride that we continue this march together with the dedicated team at MMV. It is the solid beat of their progress that we report here. Furthermore, as we reflect on 2016, it is clear that this progress, guided by the wider malaria community, is amplified by our partners, donors and Board of Directors. For this support, we are immensely grateful. We will rely on it all the more as we edge closer to the global goal of stamping out malaria for good.

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Key achievements

First potential new medicine for relapsing malaria in more than 60 years, **tafenoquine**, completes phase III trials with GSK.

**MMV048** progresses to phase Ila as new formulation with 3x greater exposure identified.

9 potential new medicines in clinical development prioritizing treatment for vulnerable populations and supporting malaria eradication.

180 Pathogen Boxes shipped free of charge to scientists around the world to boost neglected diseases drug discovery.

19 new malaria drug targets validated since 1999.

1 donor dollar creates an estimated 3.5 dollars of investment impact thanks to direct and in-kind support from partners.
160 active partners in MMV’s network, working to help defeat malaria

18,000 health-care workers across 2,082 health-care facilities trained to administer injectable artesunate for severe malaria, via CHAI and the Malaria Consortium in the MMV-led Improving Severe Malaria Outcomes (ISMO) project funded by UNITAID

12,000 episodes of malaria in almost 5,000 patients assessed in first trial investigating the real-life safety and effectiveness of four ACTs (WANECAM) – data provides reassurance of safety when re-dosing patients with the same drug

>90% of severe malaria cases now treated with injectable artesunate in preference to quinine across 6 countries through the MMV-led ISMO project

75 million vials of Artesun® (Guilin Pharma’s injectable artesunate) delivered to treat children with severe malaria, saving an estimated additional 450,000–500,000 lives compared to quinine treatment

1st rectal artesunate suppository to be quality assured: with MMV’s support, Cipla received a 12-month authorization from the Global Fund for procurement of their suppositories for pre-referral management of severe malaria

73 million courses of SP+AQ were shipped to countries in West Africa’s Sahel region in 2016, by MMV’s partner Guilin Pharmaceutical, enough to provide 18 million children with Seasonal Malaria Chemoprevention

New medicine for children, Pyramax® granules (pyronaridine-artesunate), co-developed with Shin Poong, added to the WHO list of prequalified medicines

1 million lives saved by MMV co-developed medicines since 2009
MMV’s mission is to treat and protect people from malaria today, and develop next-generation medicines for tomorrow that will contribute to the eradication of the disease. In line with global frameworks from the World Health Organization and the United Nations, MMV will seek to maximize the impact of medicines for malaria control and elimination over its next business-planning period (2017–2021) by focusing on three strategic areas of activity:

1. Facilitating equitable access to quality antimalarials to maximize the use and health impact of existing products (near-term).
2. Developing better medicines for case management, including patient-adapted new combinations to overcome drug resistance, to facilitate deployment of shorter treatment courses and to protect vulnerable populations like children and pregnant women (medium-term).
3. Bringing forward new tools for resistance and elimination to help countries reduce transmission and ultimately become malaria free (long-term).

To facilitate access (1), MMV works with partners and key global and country-level stakeholders. This effort includes gathering data on the tolerability of new medicines specifically in vulnerable populations and in ‘real-world’ settings to support their registration and adoption into relevant policies and guidelines; securing sustainable supply by diversifying the manufacturing base of existing medicines; and scaling-up use in-country.

For MMV’s research and development (R&D) work (2 & 3), given the 12 to 15-year timeline from discovery to launch of a new medicine, it is important to define, at the very outset, the characteristics of the medicines needed. This is described by two Target Product Profiles (TPPs).

The first TPP, a Single Encounter Radical Cure and Prophylaxis (SERCaP) as proposed by the malERA Consultative Group on Drugs in 2011, remains a priority. Such a single-dose treatment would be effective against resistant strains of malaria, cure clinical malaria, stop transmission and prevent relapses. It would also simplify case management and improve compliance.

The second TPP is for chemoprotection drugs for non-infected people entering an area of high-malaria endemicity. The goal is to develop a Single Exposure Chemoprotection (SEC). Compounds used for this indication would need to have distinct mechanisms of action compared to those used for treatment.

Ideally, both groups of medicines would be universally well-tolerated, including in vulnerable populations and those with co-infection, and thus be suitable for Mass Drug Administration (MDA) – an approach that could help accelerate the trajectory to elimination and eradication by depleting the human parasite reservoir on a regional basis. Additional pharmacovigilance studies of medicines post launch will be required to confirm this level of safety.

Although 3 days is the minimum acceptable regimen, we continue to work towards the development of a single exposure medicine. However, this goal places an extraordinary demand on a molecule in terms of the required pharmacokinetics, potency, absolute dose, safety, tolerability and formulation.

Consequently, we recognize that a trade-off might have to be navigated between single- and multiple-dose therapies, particularly when the latter show activity against known resistant strains and isolates.

The development of SERCaP or SEC will require the combination of at least two molecules. Thus, we have defined five Target Candidate Profiles (TCPs; see first column of Figure 1), corresponding to different clinical attributes needed for the TPPs, and built a strong portfolio of molecules with diverse or competing mechanisms to combat resistance. As we hunt for molecules for SERCaP and our understanding of their characteristics grows, some of these molecules could be reprioritized and developed for the treatment of severe malaria; chemoprevention for vulnerable groups living in endemic regions; or as endectocides, which reduce survival of the mosquito vector and thereby malaria transmission.

MMV is currently working with 160 partners around the world to put this strategy into action. In 2016, our partner network was augmented by the addition of Janssen Pharmaceuticals, Zydus Cadila, India and S Kant Healthcare, India. Our partners are critical to our work to discover, develop and deliver antimalarials to treat and ultimately help eradicate malaria for good.

Figure 1: Connecting the TCPs, TPPs and goals of the resultant medicines

NB Previous TCP 1 (fast clearance) & TCP 2 (long duration) have been combined as TCP 1 (asexual parasite clearance).
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## MMV-supported projects

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## Target Product Profiles

- 3-day cure, artemisinin-based combination therapies
- Combinations aiming at a new Single Encounter Radical Cure (SERC), TPP-1
- Intermittent/Seasonal Malaria Chemoprevention
- Severe malaria and pre-referral treatment
- Products targeting prevention of relapses for P. vivax

*There are currently no products in the development portfolio meeting the Single Exposure Chemoprotection (SEC) TPP-2*

| **Brand names:** | 1. Coartem® Dispersible; 2. Artesun®; 3. Eurartesim®; 4. Pyramax® tablets or granules; 5. ASAQ/Winthrop®; 6. SP-AQ-COTM |

## To develop the individual compounds for combination into the TPPs, MMV has defined five Target Candidate Profiles (TCPs):**

- Asexual parasite clearance 
  - TPP-1
- Targeting Plasmodium hypnozoites
  - TCP-3
- Targeting liver schizonts
  - TCP-4
- Transmission blocking (gametocytocidal or sporontocidal)
  - TCP 5 & 6

*Global product development is being reviewed by Access and Product Management.*

- *A single dose of 500/25mg SP on Day 1, 150mg AQ given once daily on Day 1, 2 and 3.*
- *A single dose of 250/12.5mg SP on Day 1, 75mg AQ given once daily on Day 1, 2, and 3.*