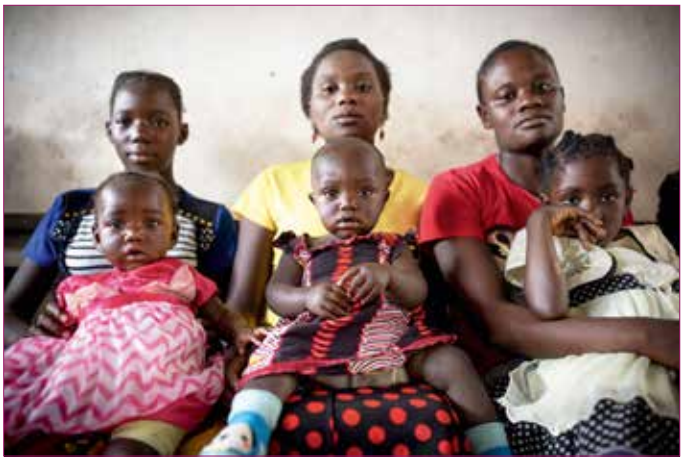
Medicine for malaria: setbacks and successes on the road to eradication

The search for solutions against the multiple facets of malaria is not simple. David Reddy assesses progress

We are at a critical juncture in the fight against malaria. After almost two decades of success in reversing the incidence of the disease, the World Health Organization (WHO) reports that progress is stalling. In 2016, around 216 million people fell ill from malaria, 445,000 of whom lost their lives. In comparison with 2015, that's almost 5 million more cases of people who became ill.

Maintaining or bettering the pace of progress witnessed during the last one and a half decades is the objective of the entire malaria community. For our part, MMV is focused on strengthening successful efforts to facilitate access to quality antimalarials while developing new measures to counter the challenges ahead. This includes a new road map of the medicines needed to defeat malaria and the tools to realise it.



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MMV's efforts to date have delivered eight new medicines, which are estimated to have saved the lives of more than 1.5 million people. Let me tell you about just one of them: 16-month-old Inness's story of survival. MMV has been working with a consortium of partners led by the NGO Transaid, in Zambia, to provide access to severe malaria medicines. When Inness fell ill in early 2017 her mother brought her to a community health volunteer who had been trained to recognise severe malaria danger signs. The volunteer quickly administered a rectal artesunate suppository (RAS), provided by the project for pre-referral management of severe malaria. She was then referred to a clinic and treated with injectable artesunate followed by Coartem® Dispersible when she was able to hold down oral medicine. The combination of these medicines helped save her life. Unfortunately, we received word at the same time that others in her community who did not receive early enough intervention did not survive.

For MMV, Inness's story has huge significance and, in particular, is a testament to the power of our partnerships to save lives, as well as our need to expand our access work to make sure that all children in need get these life-saving interventions. All the projects that enabled the medicines to reach Inness at the right time were conducted in partnership, harnessing the strength of numerous individuals and organisations. Our work with Indian pharmaceuticals company Cipla to develop RAS and achieve a successful review by The Global Fund in 2016 paved the way for the first-ever batch of approximately 500,000 quality-assured suppositories to be delivered to the field. In 2010, with Chinese pharmaceutical company Guilin, we obtained prequalification of injectable artesunate: to date, 100 million vials have been delivered. In 2009, MMV launched Coartem Dispersible with partner Novartis: to date 350 million treatments have been delivered. We are moving deeper and deeper into the last mile with the medicines required to save the lives of people most vulnerable to malaria.

Our focus is not only on treatments for these at-risk populations. MMV is also increasingly working with partners to use medicines to protect pregnant women and young children from getting malaria in the first place. For example, seasonal malaria chemoprevention administered to children under 5 in Africa's Sahel region during the rainy season has dramatically reduced disease incidence. As part of the Unitaid-funded ACCESS-SMC consortium, MMV is supporting the scale-up of the intervention in 12 countries. In 2017, more than 68 million courses of sulfadoxine-pyrimethamine + amodiaquine (SPAQ) had been delivered to the Sahel, enough to provide 17 million children with protection.

These consortium-based approaches to scale up access draw on the strengths of different organisations to understand the issues, develop data-driven solutions, pilot these solutions and then run with them. The success of this approach has led us to explore how it could be applied to other projects in the pipeline. One such exciting project is the potential roll-out of tafenoquine. In 2018, international regulatory approvals for tafenoquine, for the prevention of relapse of P. vivax malaria, were obtained, first by the US Food and Drug Administration in July and then by the Australian Therapeutic

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Goods Administration in September. With these, tafenoquine became the first medicine to be approved for this indication since 1952. Further, as a single dose, the medicine could be an important tool in helping some countries move towards malaria elimination.

With one eye on the shifting malaria landscape and another on the development of future antimalarials, MMV has taken a leadership role in coordinating the thinking of the antimalarial drug discovery and development community. We have helped define standards, target candidate profiles and target product profiles, contributing to a road map for product development: the update of the Malaria Eradication Research Agenda (malERA Refresh).[1]

Part of this planning also includes keeping a view on antimalarial drug resistance, particularly in the Greater Mekong Sub-region. As attempts are made to contain artemisinin resistant malaria in Cambodia, we continue to see partner drugs succumbing to resistance – another setback causing concern in our global efforts to defeat malaria. Thus, the deployment of newer artemisinin combination therapies such as Shin Poong's co-developed Pyramax® (pyronaridine-artesunate) remains critical.

We also need to be ready with new drugs should resistance gain a greater hold. We have two new combinations in phase II trials in adults and children: artefenomel and ferroquine with Sanofi, and KAF156 in combination with a new formulation of lumefantrine with Novartis. In addition, we have three other new medicines being tested in patients, as well as promising new compounds in human volunteer infection studies. Moreover, we are ready to accelerate development of these medicines through trials in patients with drug-resistant malaria should more cases occur and/or resistance emerge in Africa.

With one eye on the shifting malaria landscape and another on the development of future antimalarials, we remain committed to maintaining the focus that has already helped us successfully deploy our co-developed medicines. Furthermore, together with our partners, we will do everything in our power to help save the lives of children like Inness and turn recent setbacks to success on the road to malaria eradication.

References

1 malERA Refresh Consultative Panel on Insecticide and Drug Resistance. 'An updated research agenda for insecticide and drug resistance in malaria elimination and eradication.' PLoS Med. 30;14(11):e1002450 (2017).
2 As proposed 7 years ago by malERA Consultative Group on Drugs. 'A research agenda for malaria eradication: drugs'.PLoS Med. 8(1):e1000402 (2011).
3 Burrows JN et al. Designing the next generation of medicines for malaria control and eradication. Malar J 12:187 (2013).
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MMV strategic focus

MMV's mission is to develop and deliver the medicines needed to support malaria-endemic countries in their quest to control and eventually eradicate malaria. In line with global frameworks from the WHO and the United Nations, MMV is focused on three strategic areas of activity:

1. Facilitating equitable access to quality antimalarials to maximise their health impact and control malaria
2. Developing easy-to-administer, next-generation medicines that can improve case management, overcome drug resistance and protect vulnerable populations, such as children and pregnant women
3. Bringing forward new tools to counter resistance, achieve elimination and help countries reduce transmission and ultimately eradicate malaria

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

In its R&D effort (areas 2 & 3), MMV has applied a new approach that focuses on the need for accelerated, efficient and appropriate drug discovery and development via an integrated model. Given the 12-15-year timeline from discovery to launch of a new medicine, it is important to invest in only those promising compounds that can potentially meet identified unmet medical needs. This is described by two Target Product Profiles (TPPs).

TPP1 defines the characteristics of drugs for treatment, prevention and transmission blocking, also known as a Single Encounter Radical Cure and Prophylaxis (SERCaP).[2] Drugs that meet TPP1 would be effective against resistant strains of malaria, cure clinical malaria, stop transmission and prevent relapses. They would also simplify case management and thus improve compliance.

TPP2 describes drugs that can protect non-infected people entering an area of high malaria endemicity, also known as Single Exposure Chemoprotection (SEC). Compounds that meet this profile would need to provide a long duration of protection and have a distinct mechanisms of action compared to those used by TPP1 drugs.

The development of a new treatment (SERCaP) or new protection (SEC) requires the combination of at least two active candidate drugs. Thus, MMV has defined five Target Candidate Profiles (TCPs) corresponding to different clinical attributes compounds will contribute to the TPPs, and built a strong portfolio of molecules with diverse or competing mechanisms to combat resistance.[3,4]

MMV is currently working with a nuber of active partners around the world on research and development projects. Innovative approaches are being used to enhance speed and efficiency, including Volunteer Infection Studies and the Combo Tool. Together with our partners we will continue to rethink and optimise the development of new antimalarials to help control and ultimately eradicate malaria.

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