

# Antimalarial development: a step forward in the global fight against antimicrobial resistance



It's hard to imagine that common infections might one day have no cure, but many medicines have already become—or are slowly becoming—ineffective. Microbes naturally evolve to beat the drugs that are used to fight them. If no action is taken, this phenomenon, known as antimicrobial resistance,<sup>1</sup> could kill as many as 10 million people per year by 2050.<sup>2</sup> According to the World Health Organization (WHO), antimicrobial resistance threatens the public health response to many diseases, including malaria.<sup>3</sup> Research and development (R&D) into new medicines is the best insurance policy against the risk of antimalarial resistance; at the same time, it is yielding promising new compounds to fight other diseases at risk of resistance. Furthermore, the product development partnership (PDP) model as applied by Medicines for Malaria Venture (MMV) has been successful at replenishing the malaria drug pipeline and bringing new medicines forward, and its lessons learned continue to be relevant to the effort to contain all forms of antimicrobial resistance. Some important lessons learned include:

**1.** The development of children's formulations is an important strategy for reducing resistance. MMV invests in patient-friendly medications, including paediatric formulations, which enhance palatability and increase the accuracy of dosing, leading to better adherence to treatment by children and improved clinical effectiveness, which in turn reduce the probability of resistance.

**2.** MMV has developed expertise in ensuring that only high-quality, WHO-prequalified medicines are developed and delivered. To achieve this, MMV and its partner network have developed and adhere to stringent target product profiles that define the characteristics required of new malaria medicines, along with standardized R&D protocols that ensure candidate drugs meet these profiles. MMV's R&D protocols include testing all new compounds against drug-resistant malaria strains.

**3.** MMV has developed, as part of its core business, discovery networks and assay platforms, based as much as possible on open data sharing, thereby accelerating the identification of the most promising compounds against malaria. MMV has also established processes by which compounds and know-how are made available to researchers to facilitate the discovery of compounds against drug-resistant strains of many other pathogens.

**4.** MMV has developed expertise in ensuring that the right medicine gets to the right patient at the right time, which helps to minimize the risk of drug resistance. Working with national malaria programmes, manufacturers and other partners, MMV invests in the development of suitable education materials and packaging to promote appropriate antimalarial administration and use; gathers data on the tolerability and safety of new medicines to inform national policy; and helps secure the sustainable supply of antimalarials.

“Research and development (R&D) into new medicines is the best insurance policy against the risk of antimalarial resistance.”

1. The World Health Organization (WHO) defines antimicrobial resistance (AMR) as “the resistance of bacterial, viral, parasitic and fungal microorganisms to antimicrobial medicines that were previously effective for treatment of infections.”  
What is antimicrobial resistance? Online Q&A. World Health Organization. July 2017.

2. *No Time to Wait: Securing the future from drug-resistant infections*. Interagency Coordination Group on Antimicrobial Resistance. April 2019.

3. *Global Action Plan on Antimicrobial Resistance*. World Health Organization. May 2015.



Since 2000, progress against malaria has been remarkable. Malaria death rates among children under five years fell by 65% between 2000 and 2015,<sup>4</sup> mainly thanks to the increased provision of various malaria control tools, including artemisinin-based combination therapies (ACTs), today's first choice of drugs against malaria. Over these years, 6.2 million lives have been saved.<sup>5</sup>

Unfortunately, concerns have emerged that the parasite's growing resistance to these medicines could threaten progress. In July 2019, scientists reported that drug-resistant strains of malaria had spread substantially across Cambodia, Laos, Thailand and Vietnam in the past decade.<sup>6</sup> Clinical data from these countries indicate that, on average, half of patients are not being cured with a standard ACT.<sup>7</sup> The possible expansion of artemisinin resistance to areas of high malaria burden could kill as many as 116,000 additional people per year.<sup>8</sup>

To prevent and respond to treatment failure, there is an urgent need to adopt new and effective tools. R&D efforts for new ACTs have paid off so far in the region, with ongoing therapeutic efficacy studies confirming that artesunate-pyronaridine, co-developed by MMV and partners and currently registered for use in Cambodia, Myanmar, Vietnam and Thailand,<sup>9</sup> is more effective than the failing drug DHA-PPQ.<sup>10</sup> New and effective non-artemisinin based antimalarials are also necessary as resistance to partner

drugs is emerging in areas where artemisinin resistance has taken hold.<sup>11</sup>

This is not the first time that the global fight against malaria is compromised by drug-resistant strains of the parasite. While WHO was coordinating the project to eradicate malaria in all countries of the world, a rise in resistance to chloroquine, the standard of care at the time, started in the 1960s, which resulted in disease resurgence and millions of lives lost. MMV was established in 1999, when resistance to chloroquine had fully spread across South East Asia and sub-Saharan Africa,<sup>12</sup> the investment in new malaria medicines was virtually non-existent, and it was widely recognized that new approaches to product development were needed to replenish the pipeline.

Over the last 20 years, MMV-supported partnerships have brought forward 13 new antimalarial interventions and delivered 600 million medicines to people who needed them, saving more than 2.2 million lives. MMV's successful experiences show that with partnership, purpose, and the power of innovation, it is possible to achieve impact against this major public health problem and disease of poverty. But to preserve these gains and contain the perpetual risk of malaria resurgence, we must always keep the momentum—and ensure that the R&D effort is fully funded. These and a number of other lessons learned from experiences with malaria could be helpful to the global fight against drug-resistant microbes. ■

“MMV develops affordable new medicines by building alliances and forging trust among a wide range of stakeholders.”

## 1. Public-private partnerships stimulate innovation in the fight against resistance

As it once was for malaria, there are now few replacement or alternative products in the drug development pipeline for most microbial infections. Typically, long drug development cycles and high probabilities of failure present a major financial risk to manufacturers, which prevents them from investing in the discovery and development of new antimicrobials.

New, partnership-based approaches for R&D have proven successful in driving the

development of new antimicrobials. MMV, for example, develops affordable new medicines by building alliances and forging trust among a wide range of stakeholders. Currently, MMV has around 150 active partners, including governments, research institutions, pharmaceutical firms and non-governmental organizations.

MMV reduces financial risk and adds value for money by gathering contributions from governments, pharmaceutical industries as

well as philanthropic organizations. These joint investments—also known as syndicated investments—mean that a donor's investment of one dollar creates 3.5 dollars of investment impact thanks to direct and in-kind support from MMV partners.

Collaboration has been crucial in securing tangible results, as this operating model allows partners to share not only risks, but also costs, ideas and efforts, which helps incentivize the discovery of new medicines. ■

4. Achieving the Malaria MDG Target Reversing the Incidence of Malaria 2000–2015. World Health Organization and the United Nations Children's Fund. 2015.  
5. *Ibid.*  
6. van der Pluijm RW, et al. "Determinants of dihydroartemisinin-piperazine treatment failure in *Plasmodium falciparum* malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study." *Lancet Infect Dis.* v19, n.9 (2019).

7. Ménard, D et al. "Accelerated evolution and spread of multidrug-resistant *Plasmodium falciparum* takes down the latest first-line antimalarial drug in southeast Asia." *Lancet Infect Dis.* v19, n.9 (2019).  
8. Lubell Y, et al. "Artemisinin resistance – modelling the potential human and economic costs." *Malaria Journal.* v13, n. 452 (2014).  
9. MMV: Countries where Pyramax® is registered.

10. Artemisinin resistance and artemisinin-based combination therapy efficacy. Global Malaria Programme, World Health Organization. August 2018.  
11. Ashley, Elizabeth et al. "Drugs in development for malaria." *Drugs.* v78, n. 9 (2018).

12. *The World Health Report, 1999.* World Health Organization. 1999.

## 2. To contain resistance, begin with the end in mind

To focus R&D efforts among a wide range of partners, MMV defines and regularly updates its strategy against resistance and target product profiles, which serve as the blueprint for new medicines it seeks to develop. In MMV's product development model, systematic attention is paid to resistance from the onset of the research path.

MMV's partners are developing several molecules with new mechanisms of action that have the potential to serve as alternative treatments when first-line antimalarials fail.

For example, as mentioned above, in addition to many other compounds currently in the pipeline, studies confirm that artesunate-pyronaridine, developed by MMV and Shin Poong Pharmaceutical, is a promising alternative treatment in many areas where resistance to other ACTs is increasing. Artesunate-pyronaridine has received a positive scientific opinion from the European Medicines Agency, and WHO also indicates that countries can consider including this medicine in their national treatment guidelines.<sup>13</sup>



### Pioneering technologies for next-generation drug combinations to combat resistance

Combinations of different active compounds help preserve the efficacy of the drug and combat resistance. Understanding how different candidate compounds interact is a highly complex process. MMV and its partners are using pioneering technologies to accelerate the selection of next-generation drug combinations. These include the severe combined immuno-deficient (SCID) mouse model, and human volunteer infection studies. The SCID mouse model is a laboratory model of malaria that provides the most accurate prediction of drug response in humans working with a non-human host. Human volunteer infection studies involve the inoculation of human volunteers with a low level of malaria parasites in a tightly controlled environment, followed by the administration of a study drug a few days later, after a certain threshold of parasites is reached. The evaluation of combination therapies before they are tested in patient trials reduces the risk, time, and costs of developing a product and bringing it to market.

MMV is also working on developing compounds that can improve patient compliance and will help protect against the development of drug resistance. Compounds are studied to ensure rapid clearance of all

parasites, including resistant strains, from the blood, have a simple dosing regimen to ensure correct dosing, and present a good safety and tolerability profile.

### Containing the risk of resistance with child-friendly formulations

Ensuring correct dosing, compliance, and tolerability of medicines for children is particularly important to minimize the development of drug resistance. Children bear the brunt of the disease: in 2017, they accounted for 61% (266 000) of all malaria deaths worldwide. But many children still receive adult formulations – usually tablets that need to be crushed and taste bitter, causing children to either refuse the medicine or vomit on administration. This can lead to inappropriate dosing, which can also promote drug resistance. MMV and partners invest in new and effective antimalarial drugs for children—that taste sweet, are easily administered and well-tolerated. In the first studies of a combination therapy, carried out by MMV and partners in malaria patients, children are enrolled as soon as the risk or benefit of the combination has been assessed in a small population of adults, to enable inclusion of paediatric dossiers for the first regulatory submission. MMV has already supported the approval of several child-friendly medicines, and more are in product development as of today.

“Studies confirm that artesunate-pyronaridine, developed by MMV and ShinPoong Pharmaceutical, is a promising alternative treatment in many areas where resistance to other ACTs is increasing.”

13. World Health Organization. *The use of artesunate-pyronaridine for the treatment of uncomplicated malaria*. October 2019.



As the best protection against antimalarial drug resistance, the ideal treatment would be a drug taken only once, that could also block transmission. A single exposure radical cure and prophylaxis (SERCaP) would transform the case management of

malaria and strongly support population-wide elimination efforts. There are currently several projects in clinical development with MMV and partners targeting a single-dose cure.

### Studying the emergence of resistance as it occurs in the field

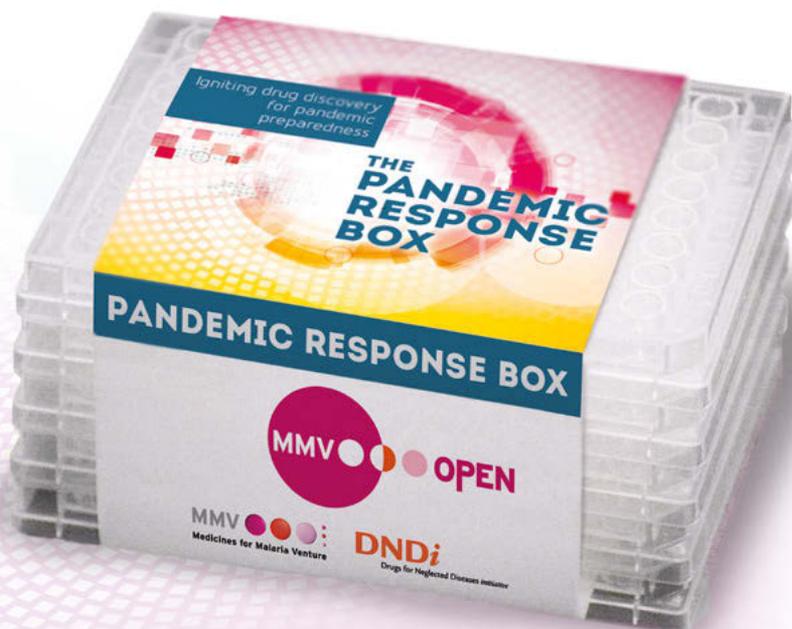
At MMV, all new molecules are tested for their ability to overcome strains of the parasite that are known to be resistant. They are also tested for their robustness against the potential of generating resistance in the future. Since the malaria parasite is constantly evolving, MMV has developed a new approach which allows it to test, *in vitro*, the efficacy of compounds against the parasite, including resistant strains, in high-burden areas. Today, MMV is collaborating with laboratory teams based in Brazil, Burkina Faso, Cambodia and Uganda to study the parasite in the field and provide a better understanding of the compound's activity in real conditions before human trials start.

Until these compounds are actually approved by regulatory authorities and available for use, current strategies to protect first-line therapies include using ACTs in combination with single low-dose primaquine to reduce transmission, or with a second partner drug in triple ACTs. These approaches are based on the principle that combinations of different active compounds help preserve the efficacy of the drug.

MMV is currently supporting pilot studies on multiple first-line therapies, which involve the concurrent use of different ACTs in a geographic area to diminish drug pressure on a single overused ACT. MMV is also involved in a dialogue with partners on what combinations of triple ACTs would best combat drug resistance, before a new non-artemisinin drug is available for use globally. ■

“MMV invests in paediatric formulations, which enhance palatability and increase the accuracy of dosing. These lead to better adherence by children and improved clinical effectiveness, which in turn reduce the probability of resistance.”





The MMV Boxes are helping researchers identify hits and leads against malaria and a wide range of other pathogens at risk of, or currently experiencing, resistance.

### 3. Open approaches to find new drugs can help the effort to contain resistance

MMV has pioneered open approaches to boost early stage drug discovery for malaria and other infectious diseases by promoting collaboration and transparency among project partners, giving scientists free access to data and materials, and encouraging them to deposit their data and findings in the public domain. MMV puts data and compounds into the public domain wherever possible.

For certain projects, MMV uses an 'Open Innovation' approach, sharing data and assays among a subset of partners only. In other cases, MMV supports 'Open Source' initiatives where all project data and structures are laid bare and the wider community is invited to fully engage and offer support e.g. advice, synthesis, testing and in-kind technology. This includes the Open Source Drug Discovery (OSDD) programme, which aims to share all information, data and ideas openly with fellow researchers. For example, one of these Open Source projects, led by the University of Sydney, resulted in finding a better way to make the praziquantel molecule for schistosomiasis.<sup>14</sup>

MMV also supports an 'Open Access' approach, which makes data, compounds, publications available to the wider research

community to maximize their possible use across diseases. For example, in 2011, MMV launched the Malaria Box, a collection of 400 diverse compounds with antimalarial activity. Between 2011 and 2015, 250 malaria boxes were packaged and shipped free of charge to researchers in 30 countries around the world to help them discover new malaria treatments. The only condition was that they put their results in the public domain.

The Malaria Box identified mechanisms of action for 135 promising compounds against malaria.<sup>15</sup> In addition, the Malaria Box resulted in the discovery of compounds that could be effective against other diseases caused by bacteria, as there is a significant overlap in the activities of antimalarials and antibacterials due to structural similarities in the malaria parasite and in bacteria. And indeed, while scientists screening compounds in the Malaria Box found hits against a wide range of drug-resistant bacteria, they also found hits against 16 different protozoa, seven helminths, the dengue fever mosquito vector and human cancer (including *Acinetobacter baumannii*, *Staphylococcus aureus*, *Mycobacterium abscessus*, *Wolbachia* and *schistosomiasis*).<sup>16</sup> The Malaria Box has been cited in at least 81 publications.

Based on this successful experience, MMV launched the Pathogen Box, and, more recently, the Pandemic Response Box, which has been developed together with the Drugs for Neglected Diseases initiative (DNDi). These boxes are helping researchers identify hits and leads against malaria and a wide range of other viral, fungal, bacterial and parasitic diseases, including tuberculosis, neglected tropical diseases, as well as pandemic fever viruses and multiple pathogens at risk of, or currently experiencing, resistance.

The MMV Boxes are also likely to help us find promising compounds against pathogens responsible for current or, potentially, future health emergencies, such as Ebola. Research on the Pathogen Box had led to 32 publications by the end of 2018 and, based on the experience with the Malaria Box, the number of publications is expected to rise over time.

The MMV Boxes are proving to be crucial in the development of new tools for a wide range of diseases. They are helping maximize the impact of efforts to contain antimicrobial resistance, while reducing costs and duplication of efforts. ■

14. MMV: Drug discovery with a difference.

15. van Voorhis W, et al. "Open Source Drug Discovery with the Malaria Box Compound Collection for Neglected Diseases and Beyond." *PLoS Pathogens*. v12, n.7 (2016)

16. *Ibid.*



#### 4. Get the right drug to the right patient at the right time

MMV aims to develop treatments of the highest quality by meeting the rigorous guidelines of stringent regulatory authorities and works with national malaria programs to ensure that the people who need these medicines have access to them.

The irresponsible or inappropriate use of medicines can result in drug resistance, and MMV also invests in the development of suitable packaging and educational materials to ensure that antimalarials are administered and used appropriately.

Low tolerability can lead to low compliance, which in turn can contribute to drug resistance. With partners and key global and country level stakeholders, MMV gathers data on the tolerability and safety of new medicines, specifically in vulnerable populations and in 'real world' settings. This evidence supports their adoption into relevant national policies and guidelines.

Substandard or fake medicines can prolong illness, result in treatment failure and contribute to drug resistance. As a founding member of Fight the Fakes, MMV engages

with manufacturers on anti-counterfeiting packaging, which helps consumers identify and select quality medicines, and pushes out the use of low-quality medicines.

Supply chain collapse can result in drug shortages, which can lead to disease outbreaks and the emergence of antimicrobial resistance. MMV works with manufacturers to secure sustainable supply, by diversifying the manufacturing base of existing medicines and scaling up their use. ■

#### Conclusion

The R&D effort for malaria is essential because malaria control and elimination, major global public health objectives, are once again facing the threat of untreatable infections due to resistance.

R&D into new malaria tools can help save lives and protect achievements against malaria. This effort is also supplying powerful and promising solutions for global health, as well as strategies that are relevant to the fight against various forms of antimicrobial resistance. These include specific drug development targets that can drive the development of novel compounds;

fixed-dose combinations and patient-friendly formulations, particularly for children; open approaches that help boost early drug discovery; a wide partner network that allows for the standardized clinical development of new, high-quality medicines; and the promotion of the effective and appropriate use of medicines, combined with the removal of fake and substandard drugs from the marketplace. In combination with the strengthening of health services and surveillance systems, these activities are essential to reduce the risk of antimicrobial resistance.

If all health and development partners continue working together, steadfast towards our joint vision of health for all by 2030, our strengths and successes are likely to add up in ways we may not even be able to imagine. Continued leadership, broad product-development oriented partnerships, and a fully funded malaria R&D effort will help safeguard and build upon recent gains made against malaria as well as other major threats to global health security. ■