2 Improving case management of uncomplicated malaria

Targeting unmet medical needs

MMV and partners are dedicated to the research and development of next-generation medicines needed for the regional elimination and eventual global eradication of malaria, in line with global frameworks from the World Health Organization (WHO) and the United Nations. Given the long timeline from discovery to launch of a new medicine, it is important to invest in compounds that have the potential to satisfy the unmet medical needs in malaria. These are described by two target product profiles (TPPs) published by MMV,1,2 which build on the global research agenda published by the Malaria Eradication Research Agenda (maiERA) Consultative Group on Drugs in 2017.3

TPP1 defines the characteristics of a combination of drugs for the treatment of uncomplicated malaria by targeting all stages of the malaria parasite’s life cycle. The ultimate goal is to shorten or simplify the treatment course, with medicines that also address emerging drug resistance. Such a combination should provide post-treatment protection for as long as possible and also reduce transmission. In the best case, it would be what is known as a single-exposure radical cure, administered as one or more doses in a single day, thus simplifying case management and helping to improve compliance.

TPP2 describes the characteristics of drugs for the protection of populations entering an area of high malaria endemicity. Ideally, these drugs are administered as a single dose repeated over a long period (monthly). This is described as single-exposure prophylaxis and would include at least one molecule with activity against the liver stage of the parasite life cycle, which precedes the blood stage.4 To reduce the risk of drug resistance emerging, for a given geographic area, combinations used for protection should not contain the same components as those used to cure malaria. Given the long duration of protection required for TPP2, MMV is exploring a variety of approaches, such as new formulations, prodrugs and monoclonal antibodies.5

The development of a new treatment for uncomplicated malaria or a new prophylactic regimen requires the combination of at least two active drugs. MMV has defined five target candidate profiles (TCPs), corresponding to different attributes needed in the molecules that will form new combination therapies (Figure 2).1,2 TCP1 describes a candidate compound’s activity against the blood stage of the parasite life cycle, and TCP3 describes its activity in preventing relapses of malaria, caused by the hypnozoite liver stage of P. vivax and P. ovale malaria (hypnozoites can lie dormant in the liver for long periods, reactivating periodically to cause relapses). Two TCPs describe a candidate’s ability to block transmission of malaria, either by killing the malaria parasite in the human host (TCP5), or by killing the mosquitoes that carry it (TCP6). All molecules with blood-stage activity are also profiled for their potential to become new injectable treatments for severe malaria.

Central to everything is that all new molecules must be highly active against all existing resistant isolates, and be tested for their robustness against generating resistance in the future. MMV places a priority on compounds that are ‘irresistible’ in discovery, in other words those for which it is not possible to generate resistant strains in the laboratory when the compound is incubated with large numbers of malaria parasites.

Figure 2: Linking the TPPs to the TCPs
Antimicrobial resistance

Microbes evolve naturally to resist the drugs that are used to fight them. This phenomenon, known as ‘antimicrobial resistance’, threatens the public health response to many infectious diseases, including malaria. The best insurance policy against the risk of antimalarial drug resistance is to replenish the pipeline and bring new and novel-acting medicines forward, which MMV has been successfully enabling for over 20 years. Furthermore, the product development partnership (PDP) model, which brings together the expertise and knowledge of both the private and public sectors, continues to play an important role by stimulating innovation in antimalarial drug discovery, catalysing the development of next-generation combination therapies to combat resistance (pp. 12–13, 18, 30–33), and promoting open-source approaches to identify promising drug candidates with irresistible mechanisms of action (p. 35).

Dr Stephanie Williams tells us more about the threat of antimicrobial resistance and what can be done to tackle it.

How much of a threat to global health and the world’s economy is antimicrobial resistance?

- Antimicrobial resistance remains a significant immediate and long-term threat to global health and the world’s economy. Currently, around 700,000 people die each year due to drug-resistant disease, and if we do not act now to minimize the further spread of resistance, the number of deaths could rise to 10 million per year by 2050. Antimicrobial resistance also poses a serious economic threat: by 2050, it could force up to 24 million people into extreme poverty, and the cost in terms of lost global productivity between now and 2050 could be as high as USD 100 trillion. It is therefore clear that without urgent action, antimicrobial resistance will continue to threaten the public health gains we have made so far.

What effect could drug resistance have on malaria control efforts?

- The success of malaria control and elimination efforts depends largely on the sustained efficacy of artemisinin-based combination therapies (ACTs). The evolution of treatment failure to ACTs in the Greater Mekong Subregion needs to be monitored closely, as well as the possible emergence of artemisinin resistance in other areas of high malaria burden, which, according to modelling studies, could kill as many as 116,000 additional people per year.

In economic terms, the predicted medical costs associated with artemisinin resistance (resulting from retreatment of clinical failures and non-artemisinin-based management of severe malaria) exceed USD 32 million per year, while productivity losses resulting from excess morbidity and mortality are estimated at USD 385 million for each year in which failing ACTs are in use as first-line treatments. However, the true impact of drug resistance on malaria control efforts is likely to vary between regions, depending on complex factors such as health system infrastructure, population dynamics and the state of each country’s economy.

What can be done to anticipate and mitigate the emergence of further drug resistance in malaria?

- Combating antimicrobial drug resistance requires a highly collaborative approach between different stakeholders, at a national and regional level. From a scientific perspective, we need to implement comprehensive surveillance studies to identify and track resistant strains, as well as monitor the therapeutic efficacy of existing treatments, using the results from these studies to inform national treatment policy and provide early warnings for treatment failures. Scientific networks such as the Asia Pacific Malaria Elimination Network are key to exchanging knowledge, building capacity, and expanding the evidence base to support regional elimination efforts. Raising political awareness is also crucial, so that recommendations from the scientific community can be implemented in a timely and sustained manner, and adequate funding mobilized at a domestic and global level.

How do you see the role of MMV in terms of open-source innovation to accelerate the development of next-generation medicines?

- MMV is one of the most established PDPs working in global health, and is therefore well placed to catalyse international research and development efforts to find effective and affordable drugs for malaria. Today, in April 2020, there is an urgent global need to identify potential drugs for the treatment of COVID-19. Several compounds from MMV’s Pandemic Response Box are currently being tested against SARS-CoV-2 – the virus responsible for COVID-19, highlighting the value of open-source libraries for the international community. Collective resources and collaborative initiatives such as these will maximize the impact of efforts to contain antimicrobial resistance and identify treatments for new diseases, while reducing costs and duplication of efforts.

10 Cambodia, China (specifically Yunnan Province and the Guizhou Zhumai Autonomous Region), Laos, Myanmar (Burma), Thailand, and Vietnam.
Beyond ACTs: next-generation therapies to counter resistance

As noted on page 11, antimicrobial resistance threatens the effective prevention and treatment of an ever-increasing range of infectious diseases, including malaria. ACTs are the first-line treatment for acute, uncomplicated malaria in approximately 80 countries. However, because they require administration over 3 days, patients may not always adhere to the complete treatment regimen, which can expose parasites to suboptimal doses and lead to the development of drug resistance. Several ACTs are now failing against *Plasmodium falciparum* malaria in parts of South East Asia, where both artemisinin and partner drug resistance have been identified, and most recently, markers of partial artemisinin resistance have been reported in Rwanda. If resistance to artemisinin (or partner drugs such as lumefantrine and pyronaridine) were to take hold in sub-Saharan Africa, where the malaria burden is highest, it could lead to failure of the ACTs, which would pose a major threat to malaria control and elimination efforts.

Over the last decade, MMV and partners have brought a wide range of fixed-dose, 3-day ACTs through clinical development, with a focus on making them child-friendly and affordable. These ACTs are all manufactured to fixed-dose, 3-day ACTs through clinical development, with a focus on making them child-friendly and affordable. Above all, any new combination must be effective, have an acceptable safety profile, be fully active against emerging drug-resistant parasite strains, and offer the potential for more convenient therapy.

Currently, MMV has two combinations being tested in Phase II studies in Africa – artefenomel-ferroquine and ganaplacide-lumefantrine. The clinical plan is to show good activity in children as young as 2 years old, with regimens varying from 1 to 3 days. In drug development, there is always a high risk of clinical failure at this stage of development, as it is the first time the medicines are tested in their intended target population. What is important is to have other drugs in the pipeline that could be used to pair up and form new combinations. MMV and partners already have two such compounds, cipargamin and MMV048, and each year one or two more join this list, with Zydus Cadila’s MMV253 joining in 2019 (p. 19). Above all, any new combination must be effective, have an acceptable safety profile, be fully active against emerging drug-resistant parasite strains, and offer the potential for more convenient therapy.

Table 2: Activity of MMV-supported molecules in development, 2019

<table>
<thead>
<tr>
<th>Target indication</th>
<th>MMV/Partner (former partner)</th>
<th>Stage of development</th>
<th>Asexual blood-stage activity</th>
<th>Potential to block transmission</th>
<th>Potential to prevent relapse</th>
<th>Potential for prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Artesunate-mefloquine</td>
<td>MMV* (Sanofi, Monash Univ./Univ. of Nebraska/ Swiss TPH)</td>
<td>Patient exploratory (Phase Ib)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Novartis</td>
<td>Patient exploratory (Phase II)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>Cipargamin</td>
<td>Novartis</td>
<td>Patient exploratory (Phase II)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV048</td>
<td>MMV* (Univ. of Cape Town)</td>
<td>Patient exploratory (Phase IIa)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>M5717 (DD0486)</td>
<td>Merck KGaA (Univ. of Dundee)</td>
<td>Human volunteers, (Phase I)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>P218</td>
<td>Janssen (Biotec Thailand)</td>
<td>Human volunteers</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV253</td>
<td>Zydus Cadila (AstraZeneca)</td>
<td>Human volunteers, (Phase I)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV533 (SAR121)</td>
<td>MMV* (Sanofi)</td>
<td>Human volunteers, (Phase I)</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV370/MMV371</td>
<td>Janssen (Calibr)</td>
<td>Preclinical</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV183</td>
<td>(TropIQ)</td>
<td>Preclinical</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>MMV646 (LPC3210)</td>
<td>Jacobus</td>
<td>Preclinical</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>INE963</td>
<td>Novartis</td>
<td>Preclinical</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
<tr>
<td>Aboguanil</td>
<td>Ipca</td>
<td>Preclinical</td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td><img src="image" alt="image" /></td>
<td></td>
</tr>
</tbody>
</table>

* MMV listed where we have assumed operational responsibility.
Ganaplacide/lumefantrine is a novel combination currently being assessed for its potential use in acute, uncomplicated malaria. Ganaplacide is a fast-acting compound with a novel mechanism of action, capable of killing both *P. falciparum* and *P. vivax* parasites, and is active against parasites that are resistant to currently-used antimalarial drugs. Its partner lumefantrine clears any remaining parasites (a new formulation of lumefantrine has made once-daily administration possible). Importantly, both components also have the potential to block onward transmission of parasites from humans to mosquitoes.

In 2017, MMV and Novartis initiated a Phase IIb clinical trial of ganaplacide/lumefantrine in nine countries across Africa and Asia. Results from part A of the study, in 349 adults and adolescents aged ≥ 12 years treated for between 1–3 days, showed rapid killing of parasites and a low rate of treatment failure. In part B of the study, the combination will be tested in children aged 2–12 years. One further study is currently planned to begin in 2020 – a paediatric study to evaluate the efficacy, safety and pharmacokinetics of ganaplacide/lumefantrine in very young children (from 6 months).

Artefenomel/FQ is also a novel combination. It consists of the fast-acting compound artefenomel, which kills most parasites in the blood and alleviates the clinical symptoms of malaria within a short timeframe, and the longer-acting compound FQ, which destroys any remaining parasites. As a single-dose treatment, artefenomel/FQ has the potential to reduce dosing frequency, thereby improving patient compliance and, crucially, slowing down the development of resistance. In 2019, MMV took over operational responsibility from Sanofi for Phase II clinical development of artefenomel/FQ. The “FALCI” trial, a Phase IIb combination study to determine the efficacy and safety of a single dose in patients aged 6 months to 70 years, completed interim analysis in October 2019 with ~250 patients (children ≤ 5 years in Africa) but did not show expected efficacy results. Consequently, following review of the interim data by an independent data monitoring committee, further patient recruitment for this study was stopped. To ensure that key insights are carried forward, final results from the trial will be analysed, along with modelling and simulation data, to explore whether a two-dose or three-dose cure would have been effective, and to identify a potential new partner for FQ.
Providing treatment options for uncomplicated malaria today

Since its inception in 1999, MMV has worked with over 400 partners in 50 countries to bring forward 11 new antimalarial medicines, including five new treatments developed especially for children. However, international regulatory approval is only the first step in achieving patient access to these medicines. Before a product can be used at national level, it must first be registered by that country’s drug authority. National Malaria Control Programmes (NMCPs) consider the available scientific evidence, in conjunction with current WHO guidance, before changing their policy and reallocating finances to include a new treatment. MMV works closely with both the WHO and NMCPs to ensure that peer-reviewed evidence about its medicines informs policy and guideline changes. In addition, MMV supports post-launch studies to generate real-world safety data on new drugs, and develops innovative packaging solutions and easy-to-follow instructions to support product use at the community level.

Medicines brought forward by MMV and partners

Coartem® Dispersible

Coartem Dispersible (artemether-lumefantrine), developed by MMV and Novartis and approved in 2009, was the first artemisinin-based combination therapy developed specifically for children and approved by a stringent regulatory authority. It is indicated for the treatment of children weighing between 5 kg and <25 kg with acute, uncomplicated P. falciparum malaria, and quickly became the leading quality-assured dispersible product for this patient population. The development and approval of Coartem Dispersible has paved the way for WHO prequalification (WHO-PQ)17 of generic versions of dispersible artemether-lumefantrine by five companies, further increasing the availability and uptake of the product. Since its launch in 2009, over 390 million Coartem Dispersible treatments have been distributed to more than 50 countries, which is estimated to have saved >840,000 lives. The product is now approved in 40 malaria-endemic countries.

As part of MMV’s efforts to expand coverage to the smallest and most at-risk children, a new formulation of dispersible artemether-lumefantrine specifically for infants <5 kg is currently under development in collaboration with Novartis.18

Pyramax®

Pyramax (pyronaridine-artesunate), developed by MMV and Shin Poong Pharmaceutical Co. Ltd., is the only ACT specifically approved by a stringent regulatory authority for the treatment of acute, uncomplicated malaria caused by both P. falciparum and P. vivax, in adults and children. In 2012, Pyramax tablets were approved under the European Medicines Agency’s (EMAs) Article 58 procedure, initially receiving a restrictive label due to a lack of real-world safety data to support repeat dosing, and concerns about liver safety signals. Since then, an extensive programme of post-approval, Phase IV studies in Africa have generated the evidence to support a less restrictive label, and the final study requested by the EMA completed recruitment in 2019, showing positive preliminary results.19 Today, Pyramax is available in both tablet (for adults and children >20 kg) and granule (for children from 5 kg to <20 kg) formulations, both of which are included in the WHO’s list of prequalified medicines20 and the Essential Medicines Lists for adults and children. Based on this strong evidence, Pyramax has been launched in 13 countries; four countries have already added it to their National Treatment Guidelines, and over 400,000 patients were treated in 2019.

In October 2019, the WHO issued an information note on Pyramax, stating that “artesunate-pyronaridine can be considered a safe and efficacious ACT for the treatment of uncomplicated malaria in adults and children weighing 5 kg and over in all malaria-endemic areas”, and stated that “in due time the Global Malaria Programme will revise the Guidelines for the Treatment of Malaria” to reflect this.21 This clarification from the WHO should support further uptake of this important medicine.

Eurartesin®

Eurartesin (dihydroartemisinin-piperaquine) is a once-daily, fixed-dose ACT developed by MMV and Alfasigma S.p.A. for the treatment of acute, uncomplicated P. falciparum malaria in adults, children and infants weighing >5 kg. It received marketing authorization from the EMA in 2011, WHO-PQ in 2015, and was added to the WHO Essential Medicines List in 2017. The approval of Eurartesin led to the development and WHO prequalification of the first generic version of dihydroartemisinin-piperaquine – available in two formulations, including the first dispersible paediatric formulation – in 2019.22 Alfasigma S.p.A. is currently developing its own paediatric formulation that, if approved, would further increase the child-friendly treatment options for endemic countries.

ASAQ Winthrop® and ASMO

In addition, MMV has taken on the access stewardship of two additional ACTs, artesunate-amodiaquine (ASAQ) and artesunate-mefloquine (ASMO), originally developed by the Drugs for Neglected Diseases initiative and partners, which includes support for product adoption and use in endemic countries. This brings the total number of quality-assured ACTs in MMV’s portfolio to five, two of which are designed specifically for use in children. MMV is now engaging with multiple industry partners to increase access to these vital ACTs. Over the past 20 years, the treatment landscape for uncomplicated malaria has evolved dramatically, thanks largely to the efforts of MMV and partners.

On World Malaria Day, the Swiss Agency for Development and Cooperation and the Swiss Malaria Group hosted an event to reflect on 20 years of successful Swiss collaborations for new antimalarial medicines, such as Coartem Dispersible, and to discuss the way forward for malaria elimination.
Multiple first-line therapy options

Diagnostic testing and prompt treatment – within 24 hours of onset – is required for the effective case management of malaria. In line with WHO recommendations, most countries have adopted ACTs, typically administered over 3 days, as the first-line treatment for acute, uncomplicated malaria. However, sustainable treatment strategies are needed to protect these valuable ACTs against the threat of resistance (alternatives to artemisinin derivatives are not expected to enter the market for several years). One such strategy is the use of multiple first-line therapies (MFTs), which are made available in both the public and private sectors for physicians to choose from. By deploying multiple therapies – compared with only a single therapy – across the population, resistance to ACTs may develop at a slower rate.\(^{23-25}\)

MMV and partners are implementing two operational feasibility studies involving MFTs. Following completion of an initial pilot study in Burkina Faso, a second study is now underway; and in Kenya, a pilot study is expected to begin in 2020.\(^{26}\) It is hoped that results from these studies will answer questions about the feasibility and logistics of MFT and eventually support broader policy changes in endemic countries.

Dr Bernhards Ogutu tells us about the case management of uncomplicated malaria in Kenya, and the potential value of MFTs.

How has the treatment landscape for uncomplicated malaria changed in Kenya over the last 20 years?

- The malaria treatment landscape in Kenya has changed considerably. The transition from monotherapy with quinine to combination therapies is gaining traction, and health worker compliance has increased over time. Currently, artemether-lumefantrine is used as first-line treatment and dihydroartemisinin-piperaquine as second-line treatment for acute, uncomplicated malaria.\(^{27}\) Child-friendly, taste-masked products such as Coartem Dispersible\(^ {28}\) have really helped to ease administration and improve paediatric case management. However, prescription patterns are not consistent. In the public sector, global funding mandates that quality-assured treatments are dispensed in accordance with international guidelines; however, in the private sector, which is less strictly regulated, older, less effective therapies may still be used.

What are the advantages of having MFTs available in malaria-endemic countries?

- The biggest advantage of MFTs is that they can reduce the risk of resistance to currently available ACTs. MFTs can also prevent the use of outdated drugs. For example, artemether-lumefantrine, which is the first-line treatment in Kenya, is effective at clearing the blood-stage infection, but only provides a short duration of post-treatment protection. This means that if a patient shows symptoms of infection after completing a 3-day course of artemether-lumefantrine, physicians may perceive that the drug is not effective, and might switch to a more familiar, but outdated, treatment. If MFTs are available, physicians can choose another combination therapy and stay within the guidelines.

How has MMV helped to improve the case management of uncomplicated malaria in Kenya?

- By bringing together various stakeholders from both endemic and non-endemic countries, MMV has changed the way new antimalarial drugs are developed. For paediatric medicines in particular, MMV has shifted the whole paradigm by establishing partnerships to bring forward palatable, child-friendly formulations, such as Coartem Dispersible. Without MMV, such progress would have been very difficult to achieve. In Kenya, we are now starting to explore MFT pilots in partnership with the public and private sectors. MMV’s support in helping us prepare for an MFT feasibility study has been very valuable, and we look forward to seeing whether this new approach could help to improve the case management of malaria in Kenya.

\[\text{“...MMV has shifted the whole paradigm by establishing partnerships to bring forward palatable, child-friendly formulations...\text{“}}\]
In 2018 alone, 11 million pregnancies in sub-Saharan Africa were exposed to malaria, resulting in high levels of maternal anaemia and 872,000 low-birthweight babies. Pregnant women infected with malaria are at increased risk of cerebral malaria and severe anaemia, as well as outcomes such as miscarriage, prematurity delivery and low-birthweight babies.

To protect pregnant women, the WHO recommends intermittent preventive treatment in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP), starting as early as possible in the second trimester. Beyond SP, there are currently no alternative options for IPTp, which is especially problematic for pregnant women living in areas of SP resistance, and for HIV-positive pregnant women who are not eligible to receive SP. Despite increased mobilization from countries in recent years, only 31% of eligible pregnant women receive SP. Despite increased mobilization from countries in recent years, only 31% of eligible pregnant women receive the recommended three doses. For pregnant women who become infected with malaria during their second or third trimester, the WHO recommends ACTs, which are the first-line treatment for patients with uncomplicated malaria.

New medicines that can be used to treat and prevent malaria in all stages of pregnancy are therefore urgently needed, but drug development is a long and complicated process, particularly when it involves pregnant women. Women of child-bearing age are systematically excluded from clinical trials to protect the potential mother and foetus, but ironically this prevents the generation of data to assess the risks and benefits in pregnant women. As a result, most drugs become available to pregnant women 5–10 years later than for non-pregnant women – only after completion of post-approval pregnancy registries or other studies. In this timeframe, drug resistance can develop, further limiting the options available to pregnant women. Furthermore, the paucity of data can lead to uninformed decision-making by practitioners and patients, who might be taking medicines, nonetheless.

Increasing options for pregnant women

For several years, MMV has been committed to providing informed therapeutic choices for malaria treatment and prevention across all genders and age categories, including pregnant women. As part of this commitment, MMV collaborated with Pfizer between 2013 and 2016 to investigate the safety and efficacy of azithromycin plus chloroquine (AZ+CQ) as an alternative to SP for IPTp in an open-label, Phase III study in countries where SP is the current standard of care, but resistance is evident. Although AZ+CQ did not show any clinical benefit, the study highlighted the significant protective benefit of IPTp with SP, in conjunction with controlled usage of insecticide-treated bed nets – a finding that supported the WHO’s ongoing recommendations for IPTp using SP. In addition, unexpected tolerability findings in the AZ+CQ arm of this study, such as vomiting, underscored the need for new medications for this population.

While new drugs are being discovered and developed, MMV is working with partners to fill the data gap on the use of existing antimalarial drugs in pregnancy. MMV and the Liverpool School of Tropical Medicine, UK, recently completed an analysis of retrospective and prospective data from pregnant women exposed to dihydroartemisinin-piperaquine (DHA-PQP) as compared to quinine, during their first trimester in Indonesia. No congenital abnormalities were found and the safety profile of DHA-PQP was similar to that of quinine. In collaboration with the London School of Hygiene & Tropical Medicine, UK, MMV is also evaluating the cardiac safety of a single course of IPTp with DHA-PQP in Tanzania. It is hoped that the findings from these studies will generate the evidence needed to increase antimalarial treatment options for pregnant women. Lastly, to help address the issue of low IPTp uptake, MMV is working with industry partners, Unitaid, and the WHO to ensure an adequate supply of quality SP for use in IPTp.

In 2020, the Roll Back Malaria, Malaria in Pregnancy Working Group, which includes MMV, will launch the ‘Speed-up, Scale-up’ campaign to bring SP to all eligible pregnant women in sub-Saharan Africa in need. So far, IPTp has been delivered primarily in healthcare facilities, during antenatal care visits. However, because these visits typically cost money to attend, pregnant women often skip them due to limited resources. The ‘Speed-up, Scale-up’ campaign should help to establish new delivery channels in the community to increase the coverage of IPTp and protect as many pregnant women as possible.

“In 2018 alone, 11 million pregnancies in sub-Saharan Africa were exposed to malaria.”
In 2019, MMV laid the foundations for a new initiative – Malaria in Mothers and Babies (MIMBa, meaning ‘pregnancy’ in the Swahili language) – which aims to address the needs of pregnant women and their newborn babies affected by malaria. Dr Wiweka Kaszubska tells us more.

**How did the MIMBa initiative start out?**

It was really a spontaneous movement among different experts from the MMV team, who started to ask what more we could do to ensure equitable access to medicines by pregnant women with malaria. We recognized that malaria elimination will not fully succeed without the intentional inclusion of women who are, or might become, pregnant. Even in the absence of supportive epidemiological data, it is easy to imagine that in Africa, pregnant women must represent a large proportion of the population that carry malaria parasites. Currently, too few medicines can be safely used by pregnant women, particularly in the first trimester, and by women who might become pregnant. We formalized the MIMBa initiative and extended it to include women who are breastfeeding, and babies, thereby covering the whole continuum.

**What does the MIMBa initiative aim to achieve?**

In the near-term, we aim to fill data gaps on the use of current antimalarial medicines, which relate mostly to safety, but also to efficacy. In many cases, we don’t have the pharmacokinetic data to support the doses of currently-used antimalarials, which might need to be adjusted in women who are pregnant or who are breastfeeding. There are also gaps on how to increase the coverage of antimalarials for these populations, so our APM team will conduct relevant operational research. As we develop new antimalarial medicines for the general population, the R&D team has the challenge of collecting data to help policymakers evaluate the risk–benefit profile of medicines for use in pregnant or lactating women.

**What can MMV do to bring forward new medicines for pregnant women and babies?**

MMV is operating within a broader movement rooted in gender equity to address gaps for pregnant women. Recognizing that gaps in adequately tolerated and effective therapies exist across all diseases, the US National Institutes of Health established a global task force (PRGLAC), which identifies the gaps in knowledge and research, and proposes recommendations that we intend to follow. A similar effort is underway by the European Innovative Medicines Initiative’s ConCePTION project. MMV’s contribution is to bring malaria, a disease of the developing world, into this global movement.

MMV’s drug discovery strategy already includes an early focus on admitting drug candidates to the development portfolio that have a promising safety profile for future use in pregnancy. To strengthen our approach to non-clinical studies, we plan to work even closer with our ESAC team to select the most predictive in vitro and laboratory models, standardize interpretation of data, and ensure consistency in ranking and prioritization of compounds with a favourable profile. MMV and partners are also establishing modelling approaches to predict if a compound is likely to cross the mother’s placenta, and how much of it might be found in her breast milk. Based on supportive data, it may be possible to conduct pharmacokinetic studies in pregnant women in parallel to Phase III development of a new drug, giving patients and physicians early and reliable information regarding its potential use during pregnancy.

**Has the MIMBa initiative led to any specific projects yet?**

We are establishing a pregnancy registry with the Liverpool School of Tropical Medicine, UK, covering several malaria-endemic countries in Africa. This multicentre, prospective, observational study will provide insights on the safety profile of a range of ACTs used during pregnancy in a real-world setting. We plan to collect data on the health of mothers and babies in the next few years, to support evaluation of the benefit-risk profiles of selected ACTs and inform decision-making on their use, particularly in the first trimester of pregnancy.

With our long-standing partner, Novartis, MMV is also developing what could become the first medicine for the treatment of acute, uncomplicated malaria in neonates weighing under 5 kg. This is a new ratio of artemether plus lumefantrine (the components of Coartem Dispersible, p. 14), which we hope will enter clinical testing in 2021.

---

35 Access & Product Management, 36 The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), was convened in response to US Congress legislation, the 21st Century Cures Act of 2016. This cross-cutting group, in consultation with the public, has produced 15 recommendations for the Secretary of Health and Human Services on how to close the gap in knowledge and research on well-tolerated and effective therapies for pregnant women and lactating women.

37 Expert Scientific Advisory Committees are external bodies of experts that help to identify the best projects worthy of inclusion in MMV’s portfolio and continue to monitor progress through an annual review of all projects.

38 Contract development in progress at the time of writing.
Maintaining a healthy pipeline of candidate antimalarial drugs

Any candidate compound or combination in the pipeline has the potential to fail at any stage of clinical development due to reasons of formulation, safety, tolerability or efficacy. Even in the post-approval setting, medicines can fail due to resistance in the field. To mitigate against this risk, MMV strives to continuously maintain and enrich the malaria drug development pipeline with compounds that meet its target candidate and target product profiles (p.10). In 2019, several of MMV’s portfolio compounds progressed in their clinical development.

Cipargamin

Cipargamin (KAE609), developed by Novartis in collaboration with MMV and with financial and technical support from the Wellcome Trust, has the potential to become part of a fast-acting combination treatment for uncomplicated malaria, or a next-generation treatment for severe malaria. Cipargamin targets a cell membrane channel in the parasite, the first validated new molecular target for severe malaria. Cipargamin rapidly cleared parasites from the blood of adults with uncomplicated *P. falciparum* or *P. vivax* malaria. A subsequent study demonstrated the compound’s longevity in the blood, where a 75 mg dose resulted in blood concentrations above the level needed to kill parasites for over 8 days. In addition to its asexual blood-stage activity, cipargamin also has the potential to block transmission of malaria. Potential combination partners for cipargamin are being evaluated, and Phase I testing of a new formulation of cipargamin for intravenous use in severe malaria is planned for 2020.

MMV048

MMV048 was discovered and developed by an international team led by scientists at the University of Cape Town, South Africa, and was the first antimalarial candidate compound to enter a Phase I study in Africa. MMV048, which works by inhibiting a key enzyme in the parasite, is active against the asexual blood stage and liver stage of the parasite life cycle, and thus it could be used for both treatment and prophylaxis. MMV048 also kills gametocytes, which means it has the potential for transmission blocking. An 80 mg dose of MMV048 is predicted to stay in the blood above the concentration needed to kill parasites for over 8 days, indicating good longevity. Non-clinical studies have indicated that MMV048 is not a suitable candidate for use in non-pregnant women and children. A Phase IIa study in Ethiopia to further explore the efficacy of the compound in patients with *P. falciparum* and *P. vivax* malaria is on hold but should resume once the COVID-19 crisis has been brought under control.

M5717

M5717 (formerly DDD498), in development with Merck KGaA, shows activity against all stages of the parasite life cycle (except for the dormant liver stage of *P. vivax* malaria). As such, this compound has the potential to both treat and protect at-risk populations. M5717 has a novel mechanism of action, targeting the protein-making machinery of the malaria parasite. In a Phase I study in 2018, the compound was shown to be well tolerated, and an 800 mg dose of M5717 completely cleared a blood-stage infection in a volunteer infection study (VIS) – a type of study in which healthy volunteers are injected with a low number of drug-sensitive parasites before receiving an experimental drug 8 days later to assess its blood-stage activity. The next stage for M5717 is a VIS to evaluate its prophylactic activity in humans. In parallel, ongoing activities are being conducted to select the best combination partner and to start combination studies in humans.

P218

P218 is a potential long-acting, single-administration, injectable drug for prophylaxis that is being developed in collaboration with Janssen and is currently in Phase I development (p. 33). The compound acts via a clinically validated pathway and has shown efficacy against known drug-resistant malaria parasites. The prophylactic activity of P218 has been demonstrated using a variant of the VIS model, in which healthy volunteers receive an experimental drug before being injected with a low number of drug-sensitive sporozoites. These studies enable MMV and partners to assess the potential of experimental drugs, such as P218, to protect against an infection taking hold in humans. If successful, P218 in its long-acting, injectable formulation could provide protection with a low-frequency dosing schedule, making it a valuable tool for malaria prophylaxis in highly endemic areas.
Originally discovered in India as part of MMV’s collaboration with AstraZeneca in Bangalore, MMV253 is now being developed by Zydus Cadila, an Indian Pharmaceutical company (p. 30). MMV253 has the potential, when combined with the right partner, to become a single-exposure, blood-stage treatment for acute, uncomplicated *P. falciparum* and *P. vivax* malaria. MMV253 has shown a good safety profile in both non-clinical toxicology studies and Phase I studies in humans, a low susceptibility to resistance, and a profile that suggests it may eventually be suitable for use in pregnancy. The next step for this promising molecule will be to develop a combination strategy for further clinical development.

**New drug candidates**

MMV’s current portfolio includes three preclinical candidates: MMV533 (transferred from SanoEq), two prodrugs\(^44\) of atovaquone for use in a potential injectable drug for prophylaxis (MMV370/MMV371; one to be selected to enter GLP-compliant preclinical safety studies\(^45\)), and a novel compound from GSK, GSK701.\(^46\) Furthermore, in 2019, MMV’s Expert Scientific Advisory Committee\(^47\) recommended three new candidates for progression to preclinical testing: MMV183, MMV646 and INE963 (pp. 36–37), each with its own unique and exciting profile. Together, these candidates represent MMV’s strongest and most diverse portfolio to date. Behind these in the pipeline are 33 different chemical series being worked on by MMV and its partners, with a view to approving two new preclinical candidates each year from the studies that MMV finances. In addition, MMV envisages that one new preclinical candidate each year will come from projects for which MMV is providing advice, but not direct funding.