ANNUAL REPORT 2022

MMV

Medicines for Malaria Venture

Malaria

- takes a child's life every minute of every day
- killed an estimated 619,000 people in 2021
- can kill within 24 hours of symptom onset
- is both a cause and consequence of poverty

Medicines for Malaria Venture (MMV)

is recognized as a leading product development partnership in the field of antimalarial drug research and development. It was established as a foundation in 1999 in Switzerland.

MMV's mission

is to reduce the burden of malaria in disease-endemic countries by discovering, developing and delivering new, effective and affordable antimalarial drugs.

MMV's vision

is a world in which these innovative medicines will cure and protect the vulnerable and underserved populations at risk of malaria, and help to ultimately eradicate this terrible disease.

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↖ Young malaria patient and mother, Bagamoyo, Tanzania

Message from the Chairman and CEO

Medicines for Malaria Venture's (MMV's) mission is to bring forward antimalarials to protect and cure the world's most underserved populations, enhancing control efforts, leading to local and regional malaria elimination and contributing to the eventual eradication of the disease.

Achieving this mission requires working with our partners to address key unmet medical needs in prevention and clinical management, while simultaneously addressing long-standing challenges to equitable access to healthcare, ensuring the tools and technologies we develop are suitable for diverse populations, and ensuring inclusion in research and knowledge sharing. COVID-19 brought many of these challenges to the fore, with low-income countries experiencing significant delays in access to COVID-19 interventions (personal protective equipment, diagnostic tests and vaccines) versus high-income countries. These challenges negatively impacted ongoing public health programmes which, in the case of malaria, led to an overall increase in infections and deaths.

This 23rd edition of our Annual Report highlights how, in 2022 and over the past years, we have worked tirelessly towards the goal of a malaria-free world, tackling these issues along the way.

The fruit of research for diverse populations

MMV's end-to-end '3D' (discover, develop, deliver) strategy continues to prioritize the search for antimalarials to protect and treat vulnerable populations at highest risk of malaria. Due to safety issues with new compounds and a dearth of evidence, these populations – mainly children and pregnant women – have insufficient treatment options. Other research priorities include therapies for people with *Plasmodium vivax* malaria (often indigenous populations, forest workers and displaced persons) and those at risk of drug-resistant malaria. In 2021–2022, MMV celebrated several triumphs in these areas:

- **48 million children protected by seasonal malaria chemoprevention (SMC) in 2022**. Since 2013, over 700 million doses of SMC have been distributed to young children in Africa's Sahel region, safeguarding their lives. Today, 14 countries are implementing regular SMC campaigns in the rainy malaria season and are considering ways to broaden the reach of this cost-effective intervention (p. 27).
- **Paediatric tafenoquine approved**. The work of MMV and partners resulted in approval from the Australian Therapeutic Goods Agency for single-dose tafenoquine for the radical cure of *P. vivax* malaria in children over 2 years of age (p. 31).
- ***P. vivax* protocol assessed in Brazil**. The protocol, deploying tafenoquine and quantitative glucose-6-phosphate dehydrogenase (G6PD) testing concomitantly, was studied in the Amazon region in Brazil over 18 months via the landmark MMV-backed Tafenoquine Roll-Out Study (TRuST). As a next step, Brazil's Ministry of Health will evaluate the evidence and make a policy decision on nationwide roll-out (p. 31).
- **Ganaplacide/lumefantrine to progress to Phase III clinical trials**. This decision was based on its highly promising efficacy reported in Phase IIb. If all goes to plan, this novel non-artemisinin combination therapy for both adults and children will offer a once-daily alternative to current malaria treatments, and to artemisinin combination therapies (ACTs) should they succumb to resistance (p. 11).

Collaborating on equitable access and uninterrupted drug supply

Through the year, World Health Organization (WHO) guidelines and strategies helped us accelerate access to vital antimalarial treatments and preventions for people who need them most.

- **Inclusion in the WHO Malaria Treatment Guidelines.** In 2022, we celebrated the inclusion of two vital antimalarials – **Pyramax®** (pyronaridine-artesunate) for uncomplicated malaria and **artemether-lumefantrine** for pregnant women in the first trimester, with strong recommendations for broader use. This is an important way to increase uptake and procurement of quality malaria medicines.
- **Strategy to stop the spread of resistance**. WHO's antimalarial drug resistance strategy for Africa recognized the value of new tools like *Pyramax* and the new combination ganaplacide/lumefantrine (in development), as well as multiple first-line therapies (MFTs) designed to reduce drug pressure on ACTs. MMV has long advocated for MFTs and, in 2021, supported pilots of this approach in Kenya and Burkina Faso (p. 10).
- **Diversity of suppliers**. With MMV's support, Kenya's Universal Corporation Ltd (UCL) became the first African manufacturer to gain WHO prequalification of sulfadoxine-pyrimethamine (SP) that protects pregnant women from malaria (p. 25). Two other SP manufacturers in Nigeria are awaiting WHO approval. To further fortify supply security and equitable access to antimalarials, MMV and the Africa Centres for Disease Control and Prevention (Africa CDC) signed a Memorandum of Understanding to strengthen and increase the quality-assured drug production capability of African manufacturers (p. 25).

Prioritizing the needs of women

Equity issues can be a matter of life and death, especially where access to antimalarials for pregnant women and adolescents is concerned, as they have insufficient treatment options. This is one of our priorities. We produced a patient-centred film[1] and co-authored several articles on malaria in pregnancy to raise awareness of the disease's impact on this group.

With the recent inclusion of artemether-lumefantrine in the WHO Malaria Guidelines, women in early pregnancy now have the very first WHO-approved treatment option for uncomplicated malaria. This is a welcome step towards preventing adverse outcomes of malaria for first-trimester pregnant women and their unborn babies. However, much more needs to be done.

The effect of antimalarials in pregnancy is still largely unknown. A key part of MMV's response to this issue, and of its MiMBa (Malaria in Mothers and Babies[2]) strategy, is to collect and analyse evidence for existing antimalarials via pregnancy registries. These will provide insight into expanding the range of malaria treatment options for pregnant women. Registries have been established in Kenya and Burkina Faso. Almost 58,000 women of child-bearing potential had consented to enter the registry by end 2022, with 11,200 pregnancies already recorded. Analysis is expected by end 2024 (p. 22).

Furthering access to knowledge

Bolstering the case for greater sharing of knowledge, MMV-led projects, such as the West African Network for Clinical Trials of Antimalarial Drugs (WANECAM) and PAMAfrica[3] are investing in workshops and studentships for next-generation African scientists. PAMAfrica is supporting five PhD students and six MSc students attached to consortium partners. In addition, the newly instituted Prof. Ogobara K. Doumbo Fellowship will provide hands-on training and skills to young African scientists in the field of malaria-related research.

R&D through open innovation

Meanwhile, MMVOpen[4] continues to take drug discovery to the next level (p. 19). The wealth of data, findings and results emanating from its Open Box initiatives is as diverse as the connections and collaborations they have inspired.

Our open access tool for early dose and pharmacokinetics prediction, MMVSola, has been awarded Project of the Year 2022. Its expansion holds significant promise for use in drug development for underserved populations in other therapeutic areas besides malaria (p. 34).

Gender parity on the Board

Spurred by the 2018 Global Health 50/50 Report,[5] MMV continues to develop and deploy appropriate gender-related policies and practices in-house. As a result, the 2022 report[6] rates MMV a 'very high performer' and a 'fast riser', highlighting the gender parity achieved on our Board. This year we were delighted to welcome three new Board members, all from malaria-endemic countries: Dr Lucille H Blumberg, Dr Ngashi Ngongo and Mr Gustavo Murgel. MMV's Board comprises equal numbers of men and women.

Bridging troubled waters

Global health is currently in troubled waters. It urgently needs improved health systems for greater resilience and a robust R&D pipeline to serve diverse at-risk populations. This requires continued funding from the global community, at a time when countries are stretched economically. It was heartening to see that the Global Fund replenishment raised USD 15.7 billion for the next 3 years through increased commitments from an expanded donor base that included malaria-endemic countries. This critical work must continue and we, at MMV, are just as committed to playing our part in the drive to eliminate malaria (SDG3.3[7]).

Despite COVID-19 and the numerous challenges encountered in 2022, our work has borne fruit. MMV's focus on diversity, equity and inclusion at so many levels is seen as a source of unity, trust and inspiration leading to creative dialogue, decisions, and outcomes. Ever grateful for the sustained support and guidance of our partners and donors, we aspire to build on our strengths as we bring forward high-quality, affordable antimalarials, and facilitate their delivery to those most in need. Stronger, broader trusted partnerships are the way forward.

1.
2. "MiMBa" means "pregnancy" in Swahili.
3. https://www.pamafrica-consortium.org/
4. MMVOpen. http://www.mmv.org/mmv-open
5. Global Health 50/50 Report (2018). https://globalhealth5050.org/report/
6. Global Health 50/50 Report (2022). https://globalhealth5050.org/2022-report/
7. SDG Target 3.3 Communicable Diseases. https://www.who.int/data/gho/data/themes/topics/sdg-target-3_3-communicable-diseases

Mr Alan Court ↙
Chairman of the Board

Dr David Reddy ↖
CEO

MMV achievements in 2022

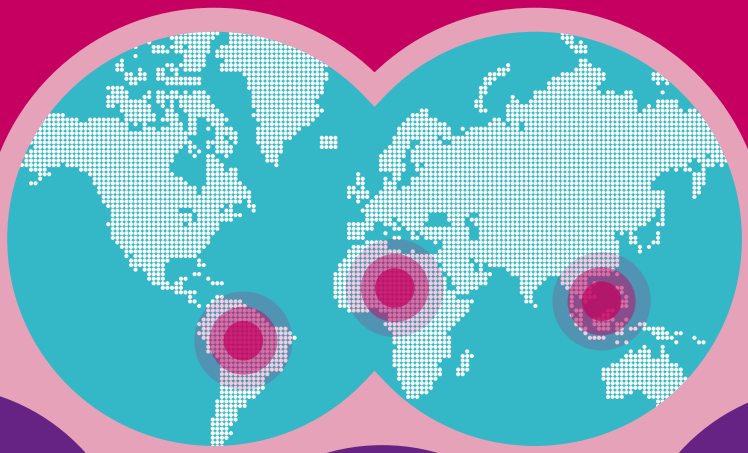
Working for equitable health in a diverse world

- Extensive reach and impact

Cumulatively,

~640 million people effectively treated or protected by MMV products[1]

~13.6 million deaths averted in absolute terms (compared to no treatment)



In 2022,

~84 million people effectively treated or protected.

>48 million children protected by seasonal malaria chemoprevention in 17 countries in Africa's Sahel region.

~235,500 deaths averted with MMV products compared to alternative treatments (~1.9 million compared to no treatment).

- Fruits of our research for diverse populations

Single-dose paediatric tafenoquine approved by Australia's Therapeutic Goods Administration to prevent *Plasmodium vivax* malaria relapse in children >2 years old, opening doors to further approvals in the region.

Feasibility of deploying tafenoquine with **point-of-care quantitative G6PD testing**[2] assessed in Brazil via the TRuST study. A policy decision on nationwide roll-out is expected in 2023.

Single-dose ganaplacide/ lumefantrine for uncomplicated malaria in adults and children (in development with Novartis) to progress to Phase III.

1. It is estimated that 1.1 billion people have received an MMV-supported product and that 640 million of these were appropriately treated, excluding use in non-malaria cases or (for products indicated for severe malaria) in uncomplicated malaria. For details, see: https://www.mmv.org/how-mmv-estimates-impact

2. Measurement of G6PD (glucose-6-phosphate dehydrogenase) is needed before treatment with tafenoquine because the drug can cause haemolytic anaemia (destruction of red blood cells) in people deficient in this enzyme.

Accelerating equitable access and diversifying supply

First African manufacturer (Kenya's Universal Corporation Ltd) gained **WHO prequalification** for sulfadoxine-pyrimethamine, the drug of choice for protecting pregnant women.

Two vital MMV-supported products included in 2022 WHO Guidelines for Malaria: **artemether-lumefantrine** for use in first-trimester pregnancy and **Pyramax®** (pyronaridine-artesunate) for uncomplicated malaria.

MMV's co-developed ***Pyramax*** and **ganaplacide/lumefantrine** recognized by WHO's antimalarial drug resistance strategy for Africa as important in tackling the spread of resistance.

Promoting equity and inclusion

MMV is pioneering the use of **modelling and simulation** in early development to prioritize drugs potentially suitable for pregnant and lactating individuals.

First data on first-trimester exposure to dihydroartemisinin-piperaquine and pyronaridine-artesunate obtained through the **Malaria in Mothers and Babies (MiMBa)** programme's pregnancy registry, established by MMV, KEMRI and LSTM[3] in Kenya and Burkina Faso.

mimba

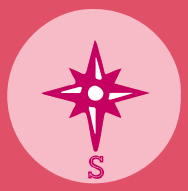
MMV-led consortia like PAMAfrica are promoting access to knowledge sharing and mutual capacity development.

Inclusive R&D through open innovation

Global Health Priority Box, a new compound collection available to researchers worldwide free of charge, launched by **MMVOpen.**

MMVSola, a free and publicly available open-source tool, awarded MMV Project of the Year 2022 for its promise in early dose prediction.

In 2022, nearly 40% of both Global Health Priority Box recipients and participants in MMVSola user groups and trainings have been **researchers in the Global South.**



Gender equity and diversity at MMV and in our work

MMV rated a 'fast riser' and 'very high performer' across 9 indicators in the 2022 Global Health 50/50 Gender and Health Index, placing it in the top 10% of the 147 global health organizations assessed.

In a campaign to prioritize and expand intermittent preventive treatment in pregnancy, MMV connected with more than 300 organizations in Africa, resulting in more than 1,000 signatures supporting further scale-up and investment for this intervention.

3. Kenya Medical Research Institute and Liverpool School of Tropical Medicine.

Powering towards a vibrant pharmaceutical manufacturing sector in Africa

2

↖ Pharmacy, Uganda

Message from Dr Stella Chinyelu Okoli, Founder and CEO, Emzor Pharmaceutical Industries Limited, Nigeria

In 1977, fresh from my training and work as a pharmacist in the UK, I set up Emzor Chemists Limited, a small retail pharmacy shop in Lagos, Nigeria. Today, Emzor manufactures over 190 different products across 26 therapeutic classes, ranging from antimalarials, analgesics and antibiotics to vitamins, and employs over 2,000 people. However, Nigeria's home-produced supply of quality medicines still remains inadequate, and we need to become less reliant on imports.

Africa's population is growing at a rate of 2.7% a year and is expected to double to 2.5 billion by 2050. Meeting the health needs of this growing population will require a strong supply chain of quality therapies to cure and prevent disease. The current situation is also untenable, with African countries spending around USD 14 billion a year of donor funds to import more than 80% of our drug and vaccine needs from overseas.

In 2017, before COVID-19 undermined progress in global health, a McKinsey report positioned Nigeria, Africa's largest economy, as 'Pharma's next frontier', forecasting growth in overall household consumption of USD 94 billion by 2026. This is undoubtedly an exciting prospect for global companies, but stockouts of critical healthcare interventions during the pandemic highlighted continuing drug insecurity in Nigeria, accentuating the need for local solutions to local problems and thus the need to boost local manufacturing capacity.

This was also true for all other countries on the continent, and impelled the Africa Centres for Disease Control and Prevention (Africa CDC) to support African Union (AU) Member States like Nigeria in strengthening their health systems, and improving surveillance, emergency response and prevention and control of diseases.

Nigeria's local pharmaceutical sector

Today, Emzor is part of a multibillion-dollar Nigerian pharmaceutical sector, which represents a third of West Africa's pharma manufacturing capacity and is vital to enhancing our citizens' quality of life and strengthening the country's economy.

In 2005, the revised Nigerian National Drug Policy aspired to fulfil 70% of the country's needs for medicines through local manufacturing by 2015. It also sought to promote pharmaceutical R&D using local products and to increase the availability of high-quality, effective, affordable and safe medicines. However, progress has been very slow.

Only 30% of medicines in Nigeria are produced locally while 70% are imported. Experts believe that strengthening local pharmaceutical manufacturing will enable it to meet up to 75% of national medicine requirements and fortify Nigeria's drug security by reducing dependence on pharmaceutical imports.

The call to expand local manufacturing

The good news is that, in the wake of COVID-19, Africa's pharmaceutical manufacturing is on the move. In 2021, the African Union mandated the Africa CDC to promote the development of vaccine manufacture in Africa, as a health security imperative. The goal is to develop, produce and supply over 60% of Africa's total vaccine requirements by 2040, that is to say, 1.5 to 1.7 billion doses each year.

This ambitious vision for scale-up of African vaccines will improve not only Africa's public health response to epidemics/pandemics but also its capacity to produce medicines for preventing and treating infectious diseases like malaria. In 2021, malaria was responsible for 619,000 deaths globally, of which 96% were in sub-Saharan Africa; this is more than three times the number of COVID-19 deaths reported in Africa in 2022.[1,2]

Production and regulation challenges

Undeniably, Nigeria's and Africa's pharmaceutical supply chains must be reinforced. Only five[3] of the 375 drug manufacturers in sub-Saharan Africa[4] produce drugs that have attained internationally recognized quality standards. The AU established the African Medicines Agency (AMA) in 2019 to develop a robust and efficient regulatory system for health products, raise the quality of local medicine production to meet stringent regulatory standards, and displace substandard medicines from the supply chain. The AMA has also been tasked with harmonizing regulations on medical products marketed across Africa, as well as coordinating and supporting pharmacovigilance to monitor the safety and effectiveness of these products.

Drivers of change

In 2012, the Pharmaceutical Manufacturing Plan for Africa (PMPA)[5] business plan was devised to build a vital, self-sustaining African pharmaceutical sector that satisfies international quality standards. This is now supported by a World Health Organization (WHO) 2021 resolution to improve access to quality medicines and health technologies by strengthening local production.[6]

Nigeria, other African countries and partnerships like MMV are committed to the implementation of this WHO resolution. Emzor, too, is part of this movement. We are working with MMV to develop and produce a key antimalarial drug, sulfadoxine-pyrimethamine (SP), to WHO prequalification standards – with approval expected in 2023. As part of this initiative, Emzor has conducted many training workshops, particularly for quality control and quality assurance staff, and has procured state-of-the-art equipment to enable testing of raw materials and finished product in compliance with pharmacopoeial standards. SP is used to protect an estimated 13 million pregnant women annually in sub-Saharan Africa. When coupled with amodiaquine, it is used as seasonal malaria chemoprevention for the young: SP + amodiaquine (SPAQ) protected over 48 million children from malaria in 2022.

MMV has already had some success in diversifying the supply chain for this vital drug in partnership with a Kenyan company, and is also supporting another Nigerian company. Establishing quality SP production on the continent in this way will ensure a sustainable and secure supply of this life-saving intervention.

Strategic collaboration and coordination are the key to success

To build a robust pharmaceutical sector, countries will need to bolster healthcare infrastructure, procurement processes, access to finance and skills on the ground to meet the challenge. Coordination among AU Member States and sectors is also vital. A self-sustaining pharmaceutical sector is key to securing the supply chain. It will not only help to grow the capacity of African drug manufacturers and secure the drug supply chain but will also power economic growth across multiple sectors, ensure equitable access to life-saving and life-enhancing interventions and improve public health outcomes in Africa.

> Experts believe that strengthening local pharmaceutical manufacturing will enable it to meet up to 75% of national medicine requirements...

When I started Emzor over 40 years ago, the pharmaceutical sector in Nigeria was struggling to grow. Today, the country holds the potential to deliver quality pharmaceutical products for domestic and regional therapeutic needs.

Emzor Pharmaceutical has witnessed tremendous growth over the years, becoming one of the largest of Nigeria's more than 115 pharma companies. And this is just the beginning! In partnership with organizations like MMV, and in collaboration with our national and African partners, Emzor aims to produce and ensure access to locally-made, quality-assured medicines for malaria, like SP. We are committed to playing our part in realizing Nigeria's potential to produce the high-quality, affordable medicines that the country and region deserve.

Dr Stella Chinyelu Okoli
Founder and CEO,
Emzor Pharmaceutical Industries Limited,
Nigeria

1. COVID-19 deaths in African region to fall by nearly 94% in 2022: WHO analysis. https://www.afro.who.int/news/covid-19-deaths-african-region-fall-nearly-94-2022-who-analysis
2. Number of coronavirus (COVID-19) deaths in the African continent as of November 18, 2022, by country. https://www.statista.com/statistics/1170530/coronavirus-deaths-in-africa/
3. Medicines for Malaria Venture Joins African Manufacturing Initiative. https://healthpolicy-watch.news/medicines-for-malaria-venture-joins-african-manufacturing-initiative/
4. Should sub-Saharan Africa make its own drugs? https://www.mckinsey.com/industries/public-and-social-sector/our-insights/should-sub-saharan-africa-make-its-own-drugs
5. The PMPA was devised by AUDA-NEPAD (African Union Development Agency New Partnership for Africa's Development) See https://www.nepad.org/news/pharmaceutical-manufacturing-plan-africa
6. Strengthening local production of medicines and other health technologies to improve access. https://apps.who.int/gb/ebwha/pdf_files/WHA74/A74_ACONF1-en.pdf

Developing the next generation of medicines

3

↖ Schoolchildren, Mangalore, India

Meeting the challenge of antimalarial drug resistance

Progress against malaria has plateaued in recent years, and the global disease burden remains high, with some 247 million cases and 619,000 deaths annually.[1] To get back on track, multiple tools and approaches will be needed, including new antimalarial medicines to help manage the emergence and spread of resistant parasites.

Evolution of microbes to resist the medicines used to fight them threatens the public health response to many infectious diseases, including malaria. To delay the emergence of resistance, malaria treatment combines drugs with different mechanisms of action, so parasites resistant to one component remain vulnerable to another. Decreased sensitivity to artemisinin derivatives, the mainstays of treatment, has been observed for two decades in South-East Asia, and more recently in Africa.[2,3,4] However, resistance has not yet developed to all partner drugs, leaving several key compounds including lumefantrine and pyronaridine largely unaffected. The emergence of parasites completely resistant to artemisinins or to all their partner drugs would mean loss of the first line of defence in Africa – artemisinin-based combination therapies (ACTs[5]). This would pose a major threat to control and elimination efforts.

In November 2022, the World Health Organization (WHO) released its 'Strategy to respond to antimalarial drug resistance in Africa'.[6] This Strategy is based on four pillars, each comprising a set of interventions to be adapted to specific contexts and implemented at local, regional and global levels: 1) strengthening surveillance of antimalarial resistance; 2) optimizing and better regulating the use of medicines and diagnostics to reduce selection for resistance; 3) limiting the spread of drug-resistant parasites; and 4) stimulating research and innovation to develop new tools against resistance and to better leverage existing ones.

Before discussing the role of new medicines, the WHO Strategy highlights the need to optimize the use of existing ones. MMV exemplifies this approach in several ways. Firstly, by advocating use of multiple first-line treatments (MFTs) within a population: we have been leading pilot implementation studies in Burkina Faso and Kenya that aim to prolong the useful lives of medicines by delaying development of resistance to individual components.[7] Secondly, we are partnering with Fosun Pharma, Marubeni Corporation and the Mahidol Oxford Tropical Medicine Research Unit (MORU) to develop triple-drug artemisinin combination therapies as fixed-dose combinations – effectively MFTs in a single pill.

> "The earlier we have new medicines ready to be deployed and the faster the world is prepared to introduce them, the better chance we stand of beating resistance."
>
> — **Dr Sujata Vaidyanathan**, Head Global Health Development Unit, Novartis

1. World Malaria Report 2022: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022
2. Uwimana A *et al.* "Emergence and clonal expansion of *in vitro* artemisinin-resistant *Plasmodium falciparum* kelch13 R561H mutant parasites in Rwanda" *Nat Med.* 26(10):1602–8 (2020), doi: 10.1038/s41591-020-1005-2
3. Balikagala B *et al.* "Evidence of Artemisinin-Resistant Malaria in Africa" *N Engl J Med.* 385(13):1163-71 (2021), doi: 10.1056/NEJMoa2101746
4. Artemisinin resistance is linked to specific mutations in the parasites, notably affecting the gene kelch13; the presence of these mutations is being closely monitored by WHO. For further information about geographical distribution of artemisinin resistance, see https://apps.who.int/malaria/maps/threats/
5. Consisting of an artemisinin derivative and a partner drug. Combinations of three different drugs are also being investigated.
6. World Health Organization. Strategy to respond to antimalarial drug resistance in Africa (2022). https://www.who.int/publications/i/item/9789240060265
7. Boni MF *et al.* "Benefits of using multiple first-line therapies against malaria" *Proc Natl Acad Sci USA.* 105(37):14216–21 (2008), doi: 10.1073/pnas.0804628105

Finally, we are working to prevent the spread of resistant parasites by making the WHO-recommended transmission-blocking medicine primaquine available at doses small enough for use in children.

Our response to antimalarial resistance also includes monitoring for resistance and changing treatments when it arises; delivering only high-quality, WHO-prequalified medicines to ensure efficacy; advocating against use of substandard or counterfeit drugs;[8] developing discovery networks and assay platforms to identify the most promising compounds for fighting malaria and other pathogens;[9] giving researchers open access to compounds and knowledge to facilitate drug discovery;[10] and supporting National Malaria Control Programmes (NMCPs) and other partners in delivering medicines to the people who need them most.[11]

The best defence against antimalarial resistance is a robust pipeline of medicines to replace those losing their efficacy. To date, MMV's partnerships with pharmaceutical and biotech companies, research institutions, governmental, international and non-governmental/non-profit organizations, donors and clinical centres in malaria-endemic countries have resulted in 15 medicines now in clinical use, with 13 further compounds in clinical development.[12]

MMV prioritizes molecules that are highly active against existing resistant strains, with low potential to generate future resistance – particularly compounds for which no resistant strains can be developed in the laboratory or isolated clinically. We aim to develop potent combination medicines that are unlikely to produce resistance to other drugs, have good safety profiles, and can both cure infection and manage the risk of resistance, as well as compounds that can block transmission and/or protect against infection.

Because incomplete cure also contributes to the development of resistance, we and our partners seek to improve treatment adherence by developing patient-friendly medicines with shorter and simpler treatment regimens, ideally requiring only a single dose.

8. See Chapter 5 and https://fightthefakes.org
9. See Chapter 4.
10. Including compounds active against drug-resistant strains of other pathogens; see Chapter 4.
11. See Chapters 5 and 6.
12. See portfolio on page 15.
13. Ogutu B *et al.* "Safety and efficacy of KAF156 (ganaplacide) in combination with lumefantrine-SDF in children 2–12 years with uncomplicated *Plasmodium falciparum* malaria. Part B of a phase 2 clinical trial." Presented at American Society of Tropical Medicine & Hygiene 2022 Annual Meeting (30 October–3 November 2022; Seattle, Washington, USA). Abstract no. 1472. See also https://clinicaltrials.gov/ct2/show/NCT03167242
14. Ganaplacide is the result of a Wellcome Trust, MMV and Singapore Economic Development Board-supported joint research programme with the Novartis Institute for Tropical Diseases (NITD), the Genomics Institute of the Novartis Research Foundation, and the Swiss Tropical and Public Health Institute (Swiss TPH). Phase II and III studies of this compound are funded by the European and Developing Countries Clinical Trials Partnership (EDCTP), which is supported by the European Union.
15. Yipsirimetee A *et al.* "Assessment *In Vitro* of the Antimalarial and Transmission-Blocking Activities of Cipargamin and Ganaplacide in Artemisinin-Resistant *Plasmodium falciparum*" *Antimicrob Agents Chemother.* 66(3):e0148121 (2022), doi: 10.1128/AAC.01481-21

Ganaplacide/lumefantrine advancing to Phase III

In November 2022, MMV and Novartis announced the decision to advance to Phase III (confirmatory studies in patients) with a novel non-artemisinin combination, ganaplacide/lumefantrine, for treatment of acute, uncomplicated *Plasmodium falciparum* malaria. This decision was based on promising results in a Phase IIb study in adults and older children.[13]

Ganaplacide,[14] a fast-acting compound with a new mechanism of action, has been combined with a new formulation of lumefantrine optimized for once-daily dosing, as opposed to twice daily with artemether-lumefantrine. Ganaplacide is active against both *P. falciparum* and *Plasmodium vivax* parasites, including those resistant to current medicines. The combination not only has potential to cure patients with 3 days of treatment but may also block parasite transmission from humans to mosquitoes.[15]

A large Phase III trial, planned to start in late 2023, will compare the efficacy of ganaplacide/lumefantrine solid dispersible formulation (SDF) to the current gold standard, artemether-lumefantrine (Coartem® *Dispersible*). It will be conducted in collaboration with the West African Network for Clinical Trials of Antimalarial Drugs-2 consortium (WANECAM-2; funded by the European and Developing Countries Clinical Trials Partnership (EDCTP)), and will include partner clinical sites in Burkina Faso, Gabon, Mali and Niger as well as other sites in sub-Saharan Africa and India.

> We are increasingly seeing parasites with decreased sensitivity to artemisinin, even in Africa. This new combination will increase the number of options available to countries facing artemisinin resistance and play a key role in slowing down its spread. It is urgently needed to treat children in malaria-endemic countries.
>
> — **Dr Timothy Wells**, Chief Scientific Officer, MMV

Intravenous cipargamin (KAE609) in severe malaria

Severe malaria is a life-threatening condition resulting from complications of malaria infection. Patients may develop anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which can result in death within hours.[16] Every minute counts when treating severe malaria, particularly in young children. However, in many endemic areas, access to diagnosis and treatment is limited. In remote settings, community healthcare workers can provide initial diagnosis and basic medications, referring patients to more advanced facilities when necessary. WHO currently recommends using injectable artesunate for severe malaria.[17]

Cipargamin (KAE609), discovered by a Novartis-led consortium funded by MMV and other partners,[18] targets *Plasmodium falciparum* Ca^{2+} ATPase (*Pf*ATP4), a parasite cell membrane channel that is the first validated new molecular target for malaria in more than 20 years. In a proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated *P. falciparum* or *P. vivax* malaria.[19] Subsequent studies have established its effective dose and demonstrated its rapid onset of effect, as well as confirming a good safety profile.[20]

Novartis is investigating a new intravenous cipargamin formulation for treatment of severe malaria, with funding from the Wellcome Trust. A study of this formulation in healthy volunteers (Phase I), completed in 2020, demonstrated good tolerability. A Phase II study of intravenous cipargamin is being conducted in several African countries and India, in collaboration with the PAMAfrica[21] consortium (which is led by MMV and funded by the EDCTP). The study aims to identify a well-tolerated and effective dose for treatment of adults and children with severe malaria.

→ Young patients, Nchelenge, Republic of Zambia

16. Trampuz A *et al.* "Clinical review: Severe malaria" *Crit. Care* 7(4):315-23 (2003), doi: 10.1186/cc2183
17. World Health Organization. WHO Guidelines for Malaria, 25 November 2022. WHO/UCN/GMP/2022.01 Rev.3. https://apps.who.int/iris/handle/10665/364714
18. This consortium is funded by MMV, the Wellcome Trust and the Singapore Economic Development Board in collaboration with the Swiss TPH. Cipargamin is being developed by Novartis in collaboration with MMV and EDCTP, with financial and technical support from the Wellcome Trust.
19. White NJ *et al.* "Spiroindolone KAE609 for *Falciparum* and *Vivax* Malaria" *N Engl J Med.* 371(5):403–10 (2014), doi: 10.1056/NEJMoa1315860
20. Schmitt EK *et al.* "Efficacy of Cipargamin (KAE609) in a Randomized, Phase II Dose-Escalation Study in Adults in Sub-Saharan Africa with Uncomplicated *Plasmodium falciparum* Malaria" *Clin Infect Dis.* 74(10):1831-9 (2022), doi: 10.1093/cid/ciab716
21. A group of nine public and private-sector research and development partners across Africa and Europe, led by MMV and including IRSS (*Institut de Recherche en Sciences de la Santé*, Burkina Faso), IDRC (*Infectious Diseases Research Collaboration*, Uganda), GRAS (*Groupe de Recherche Action en Santé, Burkina Faso*), Fundação Manhiça (Mozambique), ISGlobal (Barcelona Institute for Global Health), CERMEL (*Centre de Recherches Médicales de Lambaréné*, Gabon), Eberhard Jarls Universität Tübingen, Novartis and Merck KGaA and with funding from the EDCTP as well as from the consortium partners. See https://www.pamafrica-consortium.org

Chemoprevention: a continuing need

Preventing infection is always a better option than treating disease. The present mainstays of malaria prevention involve either targeting the vector (mosquito) with bed nets or larvicides or protecting people using medicines (chemoprevention). Chemoprevention has proven to be efficacious and cost-effective, particularly in children where malaria transmission is seasonal. In 2022, almost 50 million children under 5 years old were protected by seasonal malaria chemoprevention (SMC), and almost 20 million pregnant women took some form of malaria prophylaxis.[22]

> "Preventing infection is always a better option than treating disease."

SMC for children requires 3 days of medicine every month. Anything that would be simpler, such as a long-acting injectable (LAI) formulation for chemoprevention or a new oral medicine with once-monthly dosing, would represent a valuable alternative. Long-acting medicines have already proven their practicality and effectiveness with HIV and show considerable promise for use against malaria.

Two newer approaches to long-acting protection involve vaccines or monoclonal antibodies. The current vaccine, RTS,S (Mosquirix™) from GSK, is only partially protective, and is relatively expensive. Recent studies have shown that it is most effective when given in addition to SMC in small children.[23] New vaccines are under development, but because the immunity resulting from natural malaria infection cannot completely prevent future infection, it is unlikely that any new vaccine will produce a paradigm shift in terms of protection. It will therefore remain essential to be able to offer multiple levels of protection: nets, vaccines *and* medicines. The other new area of development over the last year is the potential use of monoclonal antibodies as once-per-season injections to protect children; MMV is partnering with the US National Institutes of Health to explore this possibility.

Long-acting injectables for chemoprevention

Long-acting chemoprevention is an important area of research and development for MMV, and has the potential advantages of high efficacy, simplicity and low cost.

Working originally with Calibr (a non-profit research institute in San Diego), Oregon Health & Science University, and subsequently Janssen Pharmaceuticals, MMV is continuing development of a long-acting injectable combination with potential to protect children – and possibly adults – for several months.

The first component, MMV371, is a prodrug[24] of atovaquone, one of the two active ingredients of the travellers' drug Malarone®. Once released into the circulation, MMV371 is rapidly converted to the active molecule, atovaquone. A slow-release formulation for injection has completed preclinical safety testing, and a first-in-human study is planned to start in 2023. The current prediction is that a single injection corresponding to the proposed human dose could provide protection for more than 3 months.

An important consideration with a long-acting injectable is to prevent the selection of resistant parasites by including a second active molecule. MMV tested all currently registered medicines to find potential partner compounds, but none was suitable. However, a drug discovery candidate known as MMV055 (previously published as ELQ300; discovered in an MMV-supported collaboration with Oregon Health & Science University) has suitable physico-chemical properties and meets all other necessary criteria.

Both compounds work by binding to mitochondrial cytochromes, disrupting energy production and thereby killing both blood-stage and liver-stage parasites. Crucially, they bind to their target at different sites, so parasites that become resistant to either compound will remain sensitive to the other. Moreover, cell biology studies show that there is synergy between the two molecules: the impact of the combination is greater than would be predicted from the two used separately.

If the slow-release MMV371 injection shows acceptable safety and suitable pharmacokinetics[25] in Phase I, then the plan is to complete the preclinical package for MMV055, both alone and in combination with MMV371, to allow clinical assessment as soon as possible.

Pyronaridine/piperaquine combination

The burden of malaria chemoprevention is currently carried by two medicines: sulfadoxine-pyrimethamine (SP), used for chemoprevention during pregnancy, and SP + amodiaquine (SPAQ), used for SMC in children.[26] As these medicines are used to protect tens of millions of women and children in Africa, the threat of resistance is omnipresent and new options for chemoprevention are urgently needed. This is particularly true for protection of women during pregnancy: chemoprevention with SP can be used only after the first trimester, there are no data to support use of vaccines during pregnancy, and current monoclonal antibodies are unlikely to be cost-effective for adults.

MMV's strategy for addressing this challenge includes the re-combination of compounds that are now used individually for malaria treatment. A review of approved products was conducted as part of a WHO/MMV workshop in 2020 to prioritize combinations potentially suitable for malaria chemoprevention in pregnancy, leading to the selection of a pyronaridine/piperaquine combination. Pyronaridine and piperaquine have been in clinical use for more than 20 years for uncomplicated malaria, as part of the ACTs Pyramax® (pyronaridine-artesunate) and Eurartesim® (dihydroartemisinin-piperaquine) respectively, but have not been administered in combination previously. The new combination has potential for requiring only a single dose per month. Current clinical safety data from the two ACTs suggest that a pyronaridine/piperaquine combination may be suitable for use in pregnant women.

The safety and pharmacokinetics of the combination were tested in a study in healthy volunteers of sub-Saharan African origin, which finished in September 2022.[27] A Phase II study to assess the duration of protection in African adults is planned in 2023.

22. See Chapter 5.
23. The combination further reduced the risks of clinical malaria, hospitalization for severe malaria and death from malaria by approximately 60%, 70% and 75% respectively, compared to the vaccine alone; Chandramohan D *et al.* "Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention" *N Engl J Med.* 385(11):1005-17 (2021), doi: 10.1056/NEJMoa2026330
24. A precursor of a drug that is converted to its active form by metabolic processes.
25. Characteristics describing how a drug is absorbed, distributed, metabolized and excreted from the body.
26. See Chapter 5.
27. Conducted in collaboration with Richmond Pharmacology and PharmaKinetic Ltd; a summary can be found at https://clinicaltrials.gov/ct2/show/results/NCT05160363

Promising candidates in early development

Thanks to the success of our discovery collaborations, there are now several highly promising molecules in early clinical development that could form part of a next-generation cure for uncomplicated malaria. The current plan is to combine up to three molecules, with a view to shortening treatment and providing protection against future emergence of resistance.

- **MMV533 (discovered in partnership with Sanofi)** is fast-acting, with a low predicted human dose (around 1 mg/kg)[28] and a long half-life[29] in humans. No resistance against MMV533 has been observed in cell biology studies or in clinical isolates. The first-in-human study and a volunteer infection study[30] were completed in September 2022.

- **GSK701 (GSK)** is fast-acting, with an intermediate predicted human dose (>5 mg/kg) and half-life, and is highly active against resistant strains. Its mechanism of action has been identified as inhibition of the *P. falciparum* enzyme acyl-CoA synthetase 10/11. The first-in-human study has been completed, and the compound will be tested for activity in a volunteer infection study at QIMR Berghofer (Brisbane, Australia) in 2023.

- **INE963 (Novartis)** is fast-acting, with an intermediate predicted human dose (>5 mg/kg) and half-life (around 150 hours). No resistance has been observed in cell biology studies or in clinical isolates. The first-in-human study has completed dosing, and the compound will be tested for activity in a Phase II study in African adults, as monotherapy and in combination with cipargamin, in 2023.

Two further compounds, both of which would form part of a multiple-drug treatment-shortening combination, are currently in preclinical development:

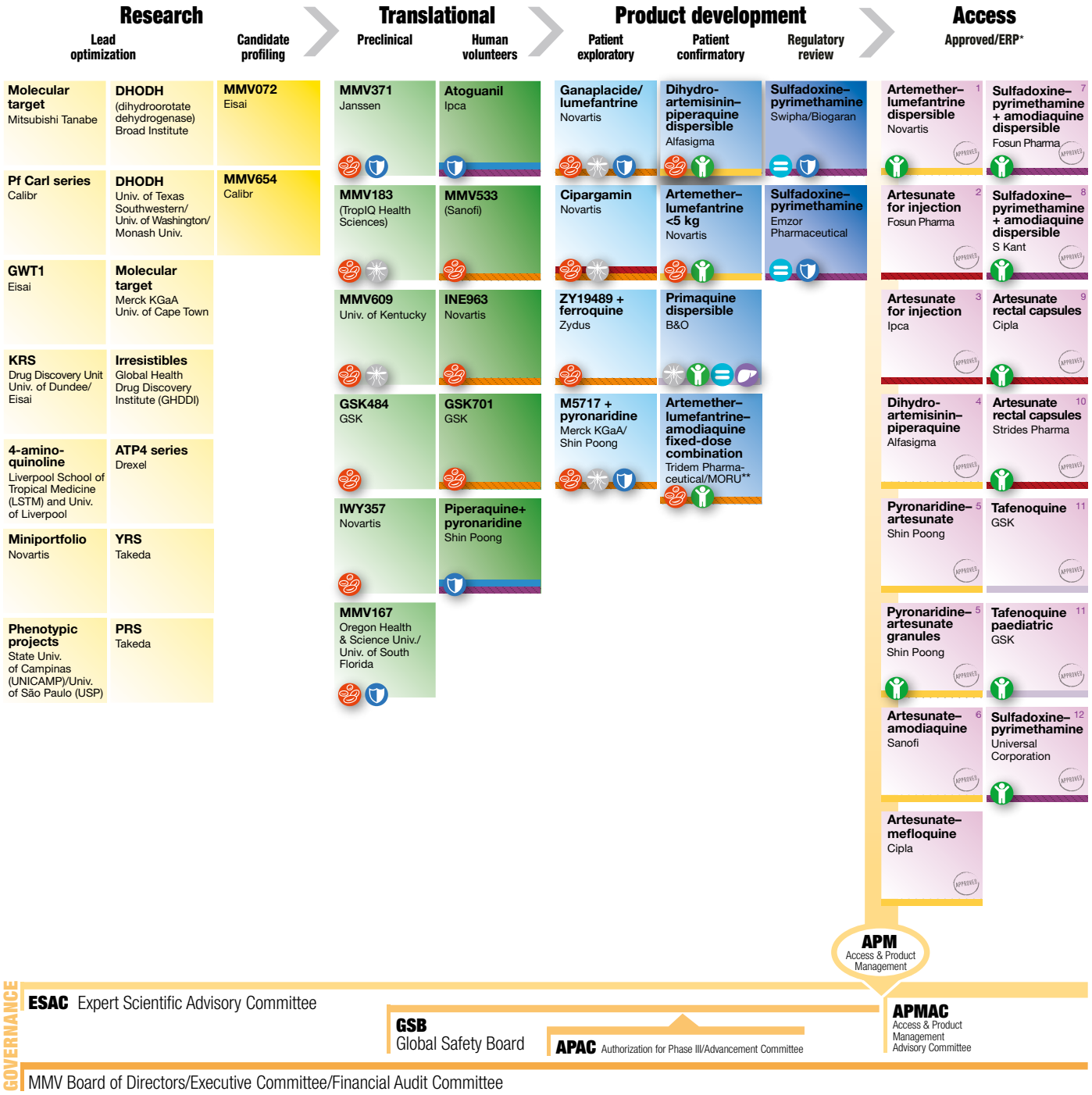
- **GSK484 (GSK; 2021 Project of the Year)** is a fast-acting compound with a low predicted human dose (1 mg/kg) and a long predicted human half-life (around 200 hours). No resistance has been observed in cell biology studies. A first-in-human study is planned in 2023.

- **MMV183 (discovered in partnership with TropIQ Health Sciences)** is a fast-acting compound with a low predicted human dose and short predicted half-life. It has a novel mechanism of action: inhibition of the enzyme acetyl-CoA synthetase. It is presently being scaled up in preparation for a first-in-human study.

→ In a hospital laboratory in Kilifi, Kenya

28. Burrows JN *et al.* "New developments in anti-malarial target candidate and product profiles" *Malar J.* 16(1):26 (2017), doi: 10.1186/s12936-016-1675-x. Erratum in: *Malar J.* 16(1):151 (2017).
29. Meaning that the compound stays in the blood for a long time.
30. Studies 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.

MMV-supported projects



Target product profiles (TPPs)

- 3-day cure, artemisinin-based combination therapies (TPP1)
- Non-artemisinin therapy for uncomplicated malaria treatments and resistance management (TPP1)
- Intermittent preventive treatment (TPP1)
- Severe malaria treatment/pre-referral intervention (TPP1)
- Products targeting prevention of relapse for *P. vivax* (TPP1)
- Chemoprophylaxis (TPP2)

Brand names: 1. Coartem® *Dispersible*; 2. Artesun®; 3. Larinate® 60 mg; 4. Eurartesim®; 5. Pyramax® tablets or granules; 6. ASAQ Winthrop®; 7. SPAQ-CO™; 8. Supyra®; 9. 100 mg Artesunate Rectocaps; 10. Artecap™; 11. *Krintafel/Kozenis* (Trademarks owned or licensed by GSK); 12: Wiwal®

Target candidate profiles (TCPs)

Asexual blood stages	(TCP 1)
Relapse prevention	(TCP 3)
Causal prophylaxis	(TCP 4)
Transmission reduction	(TCP 5, 6)

- Paediatric formulation
- WHO prequalified OR approved/positive opinion by regulatory bodies who are ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) members/observers
- Via a bioequivalence study
- (-) Past partners are in brackets

* ERP: Global Fund Expert Review Panel
** MORU: Mahidol Oxford Tropical Medicine Research Unit

Leveraging data to maximize the global health impact of MMV's assets

4

↖ Scientist using computer application

Exploring new approaches to R&D

Changes in the way potential new medicines are identified and optimized have dramatically increased both the number and the diversity of molecules in MMV's early development portfolio.[1] MMV and our partners are exploring new artificial intelligence[2] (AI)-based approaches to better focus our efforts. We are also harnessing open innovation to advance global health priorities by giving scientists free access to data and materials, encouraging them to make results publicly available so they can build on one another's work.

Using AI to streamline optimization of new compounds

Researchers must sift through vast datasets to identify promising new molecules and biological targets (proteins on which a medicine is meant to act), and AI has the potential to greatly facilitate this task.

MMV is partnering with a wide range of AI researchers and companies to design compound libraries for screening against prioritized targets, identify promising starting points (called hits) with the desired activity on their targets, and modify the most promising compounds to improve their drug-like properties[3] (called lead optimization). In each case, the partnership is enabling the company to propose a small number of compounds that MMV can then make and test. This helps to validate the new technology, as well as providing an efficient way to design new compounds.

Using AI to identify patterns from existing chemical and associated biological data, the European Bioinformatics Institute (EBI), in collaboration with MMV and partners, developed an *in silico*[4] model – the first in antimalarial drug discovery – to predict a molecule's potential blood-stage activity against malaria. This model is now publicly available[5] through the malaria inhibitor prediction platform.[6,7]

The AlphaFold database of 3D protein structures from DeepMind and EBI[8] now includes AI-predicted structures for various *Plasmodium* biological targets, a potential game changer already being used in MMV's target-based projects. For phenotypic drug discovery,[9] which is based on cell biology data and does not need an identified target, our partners at Novartis have developed an impressive model,

> AI works best when there are a lot of data, and MMV has a lot of antimalarial data. Our partners know that if their technology finds exciting new molecules, we can talk about the results openly, and that is a real advantage for them.
>
> — **Benoît Laleu**, Associate Director of Drug Discovery, MMV

1. Burrows JN *et al.* "New developments in anti-malarial target candidate and product profiles" *Malar J.* 16(1):26 (2017), doi: 10.1186/s12936-016-1675-x. Erratum in: *Malar J.* 16(1):151 (2017).
2. Artificial intelligence: a branch of computer science encompassing machine learning and deep learning, as well as natural language processing and image recognition.
3. Physical and chemical properties (e.g., solubility, permeability, metabolic stability and transporter effects) suggesting that a compound is likely to have acceptable toxicity and absorption, distribution, metabolism and elimination (ADME) profiles.
4. Conducted or produced by means of computer modelling.
5. Available at https://www.ebi.ac.uk/chembl/maip/
6. Verras A *et al.* "Shared Consensus Machine Learning Models for Predicting Blood Stage Malaria Inhibition" *J Chem Inf Model.* 57(3):445–53 (2017), doi: 10.1021/acs.jcim.6b00572
7. Bosc N *et al.* "MAIP: a web service for predicting blood-stage malaria inhibitors" *J Cheminform.* 13(1):13 (2021), doi: 10.1186/s13321-021-00487-2
8. This database includes more than 200 million 3-dimensional protein structures predicted by AI based on amino acid sequences.
9. Phenotypic screening is a drug discovery strategy for identifying molecules that can alter a cell's observable features (phenotype). See Martin EJ & Jansen JM "Biased Diversity for Effective Virtual Screening" *J. Chem. Inf. Model.* 60(9):4116-19 (2020), doi: 10.1021/acs.jcim.9b01155

called pQSAR,[10] that can predict activity based on data from other compounds in their vast database. We are considering using this and other data-informed models to design our next screening library, which should enrich it with compounds active against malaria.

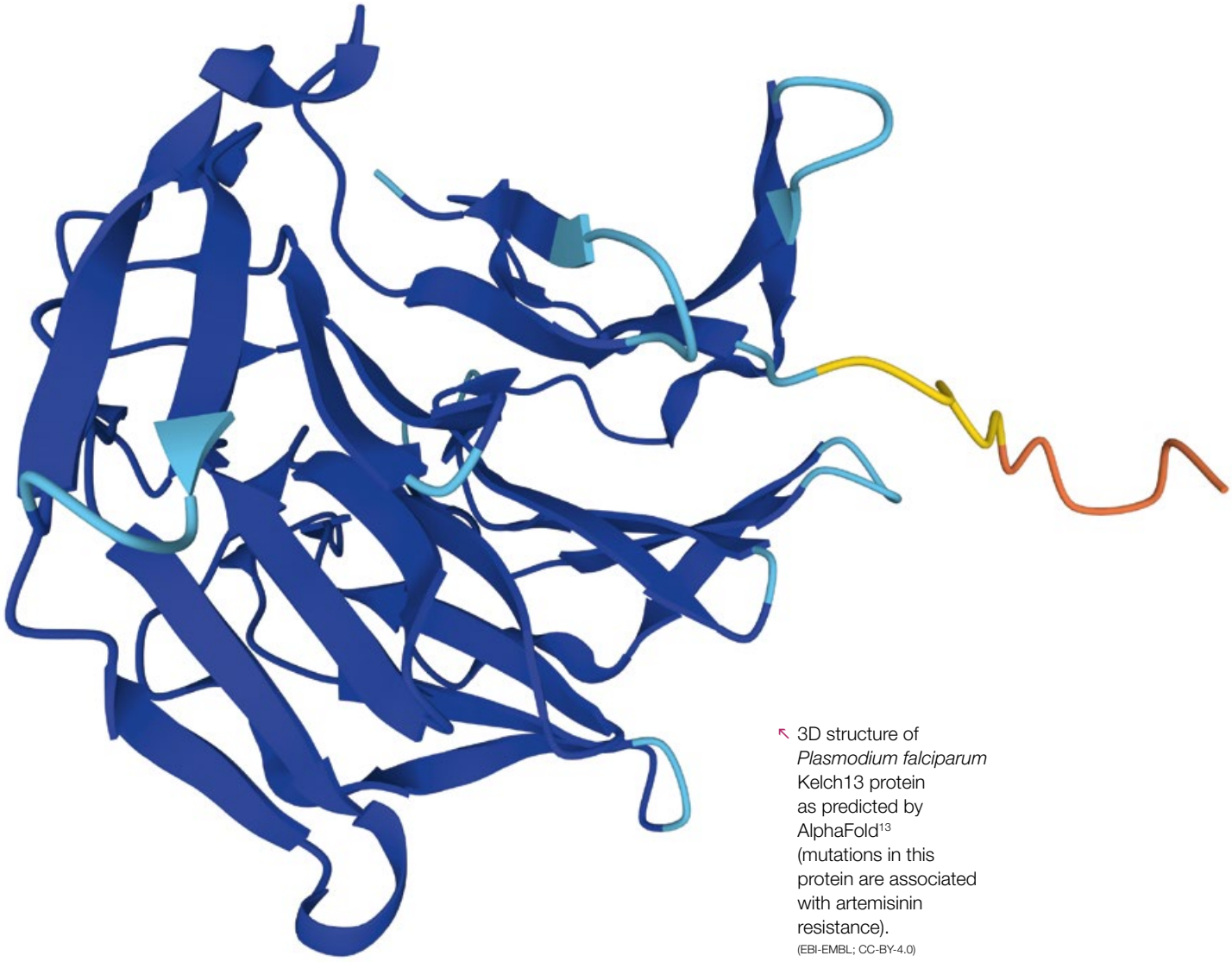
We are partnering with the Bill & Melinda Gates Foundation on two hit identification projects. San Francisco-based Atomwise used neural networks to model five malaria proteins that MMV prioritized as biological targets, then used proprietary algorithms to find the best fits for each amongst some 16 billion compounds: 72 candidates were identified for testing. Exscientia, a company based on technology developed by our partners at Dundee University, is using its algorithms to detect bispecific antimalarials. These compounds act on two distinct molecular targets, reducing the likelihood of selecting a resistant parasite. This is a very challenging but extremely exciting possibility, which would overcome the Achilles' heel of compounds designed for a single target.

MMV has been partnering with Schrödinger, a leader in development of state-of-the-art chemical simulation software, for several years. Their data-informed models allow scaffold-hopping (moving from one chemical series to another based on structural information) to enable new ways of thinking.

In November 2022, MMV and the generative modelling company Iktos announced a partnership to apply their new DockAI technology[11] to deliver novel hit compounds using a molecular target we identified.

In another new collaboration, the Ersilia Open Source Initiative, a tech non-profit organization supporting research in low- and middle-income countries,[12] is using open-source AI to speed up antimalarial drug discovery. This will be our first AI collaboration intended to be led by African scientists – hopefully the first of many.

> "Ersilia is leveraging MMV's data on new antimalarial candidates to build AI models, and is fostering innovation and AI development from within the African continent by partnering with research institutions like the Holistic Drug Discovery and Development (H3D) Centre in Cape Town, which is training local scientists in the use of AI tools. H3D now has a local AI expert, whom we trained, who takes care of the use, implementation and development of new models."
>
> — **Dr Gemma Turon**, CEO, Ersilia Open Source Initiative



↖ 3D structure of *Plasmodium falciparum* Kelch13 protein as predicted by AlphaFold[13] (mutations in this protein are associated with artemisinin resistance).
(EBI-EMBL; CC-BY-4.0)

10. Martin EJ *et al.* "All-Assay-Max2 pQSAR: Activity Predictions as Accurate as Four-Concentration IC_{50}s for 8558 Novartis Assays" *J Chem Inf Model.* 59(10):4450-59 (2019), doi: 10.1021/acs.jcim.9b00375
11. For ultra-large-scale combined with cloud-based high-performance computing (HPC).
12. See https://www.ersilia.io/
13. Jumper J *et al.* "Highly accurate protein structure prediction with AlphaFold" *Nature* 596:583-89 (2021), doi: 10.1038/s41586-021-03819-2
    Varadi M *et al.* "AlphaFold Protein Structure Database: massively expanding the structural coverage of protein-sequence space with high-accuracy models" *Nucleic Acids Research* 50(D1):D439-44 (2021), doi: 10.1093/mar/kgab1061

↘ Family on the road in Zambia

Launch of the Global Health Priority Box

14. Transmitted from animals to humans.
15. Dr Mary Mader rejoined the ESAC in 2023 after a pause in 2021–2022.

One of the most successful MMV programmes has been the assembly and distribution of standardized high-quality, open-access compound collections, starting with the Malaria Box in 2011. Since then, over 500 boxes have been distributed, resulting in many new drug discovery collaborations and over 200 publications.

On 20 August 2022 (World Mosquito Day), MMV and the Innovative Vector Control Consortium (IVCC) launched the Global Health Priority Box, providing scientists with free access to a collection of 240 compounds with confirmed activity against pathogens and vectors of global concern. The structurally diverse collection contains three sets of 80 compounds in various stages of development:

- Compounds active against drug-resistant malaria, selected by MMV.
- Compounds for screening against neglected and zoonotic[14] diseases and diseases at risk of drug resistance, from a compound library donated by Bristol Myers Squibb.
- Compounds active against vector species, selected with input from IVCC.

The box provides confirmed starting points for the development of tools to combat antimicrobial resistance and communicable diseases, two priorities defined by the World Health Organization in late 2021.

MMV's open source work is highly cost-effective, and has led to the identification of promising compounds to treat cryptosporidiosis, leishmaniasis, toxoplasmosis, trypanosomiasis and drug-resistant candidiasis as well as malaria. ●

> MMV's Open Access collections provide invaluable access to pre-plated sets of compounds together with annotations of their activity, with the aim of facilitating hypothesis testing in target identification and validation. The demand for the prior offerings, including the Malaria Box and Pandemic Response Box, has been very strong, and we are looking forward to seeing the impact of the newest box, the Global Health Priority Box.
>
> — **Dr Mary Mader**, Vice-President of Molecular Innovation, Indiana Biosciences Research Institute, and Co-Chair (Discovery), MMV Expert Scientific Advisory Committee[15]

INTERVIEW

Larry Norton, Senior Project Manager, IVCC (UK) and **Dominique Besson**, Associate Director, Discovery Data Research & Development, MMV (Switzerland) discuss the vision and aspirations behind the Global Health Priority Box.

Could you briefly describe the objective of the Global Health Priority Box?

DB: Like other MMVOpen boxes, the Global Health Priority Box is intended to stimulate research on diseases affecting vulnerable populations by granting any scientist in the world free-of-charge access to samples and information to support their research. It's specifically targeting research on vector control, and drug research for malaria and other neglected or zoonotic diseases with a high risk of drug resistance.

What is the vision behind this project?

LN: The goal is to improve collaboration among public and private organizations in developing new tools to combat public health threats, and to improve communication among scientists to speed up research. Emerging resistance to current mosquito and malaria interventions has increased the urgency of finding effective alternatives. A major objective is to spark interest in developing interventions for managing current and future public health threats. The key drivers here are novelty, structure-guided diversity and, for the malaria set, staying away from resistance. This new box was developed not only to stimulate research, but to provide meaningful starting points that could lead to drug discovery programmes to fight diseases that affect the poorest people.

What has it been like to work with MMV?

LN: The Product Development Partnership model that IVCC and MMV share has led to a strong working relationship over the past two decades. By understanding this mutual way of working, we're better able to share relevant knowledge and expertise for addressing the threats of drug and insecticide resistance. Working with MMV on the Global Health Priority Box has been an opportunity to widen and deepen our partnership, and to stimulate innovation among a more diverse group of stakeholders to achieve our common goal of eradicating malaria.

What do you hope this project will achieve?

DB: Our ambition is to stimulate the scientific community's interest and involvement in global health. The box provides an opportunity to reach researchers who might not have been targeted or impacted by our previous MMVOpen boxes. Similarly, we hope that Bristol Myers Squibb's donation might inspire other pharmaceutical partners to propose compound libraries or submit discovery projects to fuel our pipeline. Overall, we believe that this collection will help us identify new partners who can propose novel, interesting ideas or research strategies.

Making malaria prevention and treatment more equitable

5

↖ New mother and child in hospital, Bagamoyo, Tanzania

Prioritizing the needs of mothers and children

In addition to new medicines, continued progress against malaria will require reaching vulnerable and underserved populations with suitable options for prevention and treatment. MMV is devoting particular attention to the needs of pregnant and lactating mothers and their babies, for whom options are currently limited.

In 2021, more than 13.3 million pregnant women in Africa contracted malaria, mainly in the World Health Organization (WHO) sub-regions of West and Central Africa.[1] Consequences of malaria in pregnancy (MiP) can be catastrophic. A mother's immunity to the parasite is reduced by the biological and physiological changes of pregnancy, increasing her susceptibility to infection and her risk of severe illness and death.[2] Furthermore, the accumulation of parasites in the placenta can lead to adverse outcomes for the child. *Plasmodium falciparum* malaria is associated with a shocking one in ten maternal deaths in malaria-endemic countries, as well as a three to fourfold increase in the risk of miscarriage.[3] MiP can also result in low birth weight and premature birth, which increase the risk of neonatal mortality and can have lasting developmental consequences for the growing child.

To protect pregnant women from infection, WHO recommends intermittent preventive treatment in pregnancy (IPTp), consisting of three or more doses of sulfadoxine-pyrimethamine (SP) that can be given monthly until the baby arrives.[4] However, IPTp is recommended only from the second trimester, leaving mothers unprotected when unborn babies are most vulnerable. SP is also unsuitable for people living with HIV who are taking cotrimoxazole.

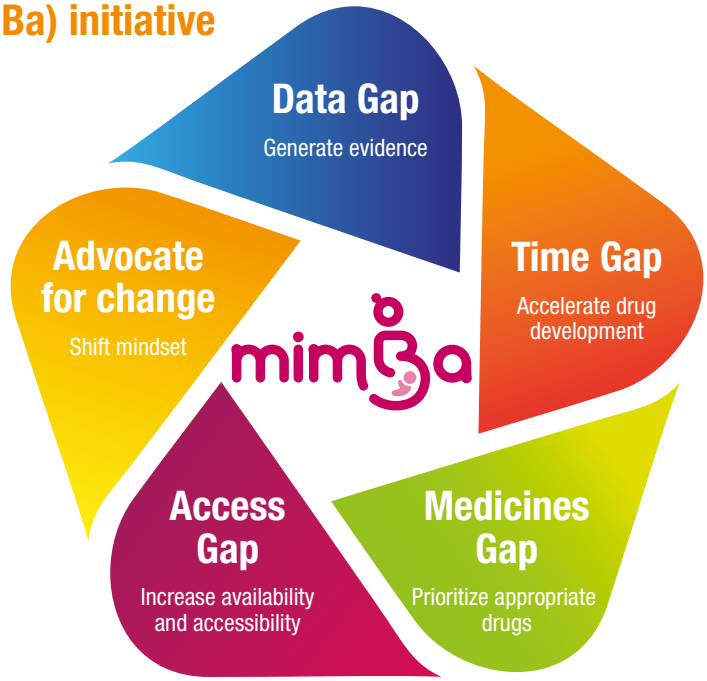
WHO-recommended options for treatment of MiP are also limited, particularly in the first trimester. Moreover, during the first trimester women may not yet realize they are pregnant, effectively broadening the population of concern for both prevention and treatment to include anyone who can become pregnant. There is also little information available on antimalarial use in nursing mothers.[5]

> Every woman deserves to live her pregnancy without the fear of getting malaria.
>
> — **Maud Majeres Lugand**, Associate Director, Social Research, Access & Product Management MMV; Co-leader of MiMBa initiative

1. World Malaria Report 2022: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022
2. Schantz-Dunn J & Nour NM "Malaria and pregnancy: a global health perspective" *Rev Obstet Gynecol.* 2(3):186–92 (2009), PMCID: PMC2760896
3. Saito M *et al.* "Deleterious effects of malaria in pregnancy on the developing fetus: a review on prevention and treatment with antimalarial drugs" *Lancet Child Adolesc Health.* 4(10):761-74 (2020), doi: 10.1016/S2352-4642(20)30099-7
4. Al Khaja KAJ & Sequeira RP "Drug treatment and prevention of malaria in pregnancy: a critical review of the guidelines" *Malar J.* 20(1):62 (2021), doi: 10.1186/s12936-020-03565-2
5. Saito M *et al.* "Antimalarial drugs for treating and preventing malaria in pregnant and lactating women" *Expert Opin Drug Saf.* 17(11):1129-44 (2018), doi: 10.1080/14740338.2018.1535593

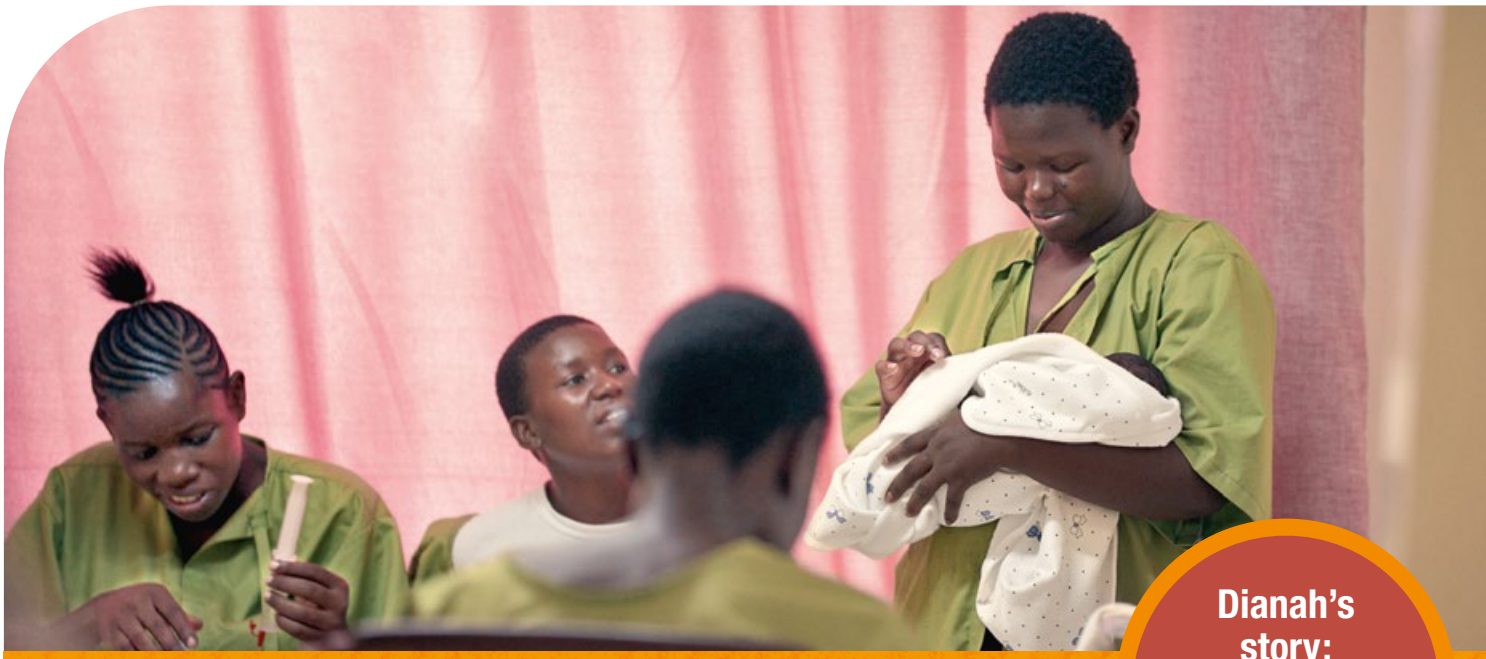
MMV's Malaria in Mothers and Babies (MiMBa) initiative

The MiMBa initiative is central to our strategy for addressing the needs of people who are or could become pregnant, or who are breastfeeding. Progress towards MiMBa's objectives is described in the following pages.



> We recognized that malaria elimination will not succeed without the intentional inclusion of women who are, or might become, pregnant. … In response, we established the MiMBa initiative to address the needs of pregnant and breastfeeding women and their babies.

— **Dr Wiweka Kaszubska**, Vice-President and Head of Product Development, MMV



Dianah's story: an expectant mother with malaria

Story

Dianah Otiend (pictured at right) – like millions of other women – lives with the real and constant fear of what malaria can do to her and her baby if she falls ill while pregnant.

Dianah, who lives in Homa Bay on the south shore of Lake Victoria in Kenya, experienced an expectant mother's worst nightmare: she became ill with malaria twice while pregnant with her baby girl. "When a mother is sick with malaria," she observed, "it affects the entire family, because a pregnant woman is carrying a life beside her life."

Dianah's doctor recommended a caesarean section to save both her life and the life of her baby. Consequently, baby Elizabeth was born premature and significantly underweight, weighing around 1 kg (globally, newborns average between 2.5 and 4 kg at birth).

Thanks to the care that they received, Dianah is optimistic about her family's future: "I can say that today I have peace in my heart, I've come out of it. My baby is alive. I'm also alive. Elizabeth, I really wish a lot of great things in her life."

It is difficult to know which medicines are suitable for pregnant and lactating women, as they are often excluded from clinical research for fear of causing harm, resulting in a lack of essential data. Including pregnant women in clinical trials will contribute to generating the robust evidence needed on the safety and efficacy of medicines that could save the lives of mothers at risk like Dianah whilst keeping their babies safe.

Closing the data gap by generating evidence for existing antimalarials

MiMBa pregnancy registry

A woman's first trimester of pregnancy is crucial for the development of the baby she is carrying, so healthcare providers are cautious about prescribing medicines to prevent or treat illness.

To gather data about current malaria treatments and to expand the range of options for pregnant women, particularly during the critical first trimester, the MiMBa pregnancy registry was established in 2021 by MMV, the Liverpool School of Tropical Medicine (LSTM) and the Kenya Medical Research Institute (KEMRI), with expertise on data management and analysis from the Worldwide Antimalarial Resistance Network (WWARN).

This long-term prospective observational study[6] provides a framework to proactively collect safety data on exposure to antimalarial drugs during pregnancy, to support evaluation of the risks and benefits of different medicines. Its ultimate goal is to help reduce gender disparity in the availability of antimalarial interventions.

Three sites are open in Kenya, and in 2022 the registry was expanded to Burkina Faso where two sites are now open. By the end of December 2022,

- in Kenya, 45,486 women had consented to be followed and 9,461 pregnancies had been recorded. Of 2,105 antimalarial drug exposures, 231 occurred during the first trimester and roughly 50% involved artemether-lumefantrine. Pregnancies and infants will be followed until Q3 2024.
- in Burkina Faso, 12,236 women had consented and 1,711 pregnancies had been recorded. Enrolment is expected to continue until Q2 2023.

In November 2022, WHO updated its guidelines for malaria[7] to include a strong recommendation for the artemisinin-based combination therapy (ACT) artemether-lumefantrine to treat malaria during the first trimester, based in part on a meta-analysis[8] supported by MMV.[9] This is a significant milestone. However, there is still work to be done to identify other ACTs potentially suitable for use in early pregnancy, particularly given the threat of emerging resistance to artemether-lumefantrine.

In Q3 2022, the MiMBa registry obtained the first data on first-trimester exposure for dihydroartemisinin-piperaquine and pyronaridine-artesunate – an important first step, although considerably more safety data will be needed by policymakers, clinicians and patients.

A better understanding of which medicines may be suitable for use in early pregnancy will help to expand the range of treatment options, providing additional tools for mitigating resistance – a strong argument for continuing the registry and expanding clinical research on other ACTs in the first trimester.

> MiMBa for the first time put the first-trimester treatment of malaria on the map, and will expedite this process of finding out whether these newer antimalarials that are coming to the market now are safe to use in the first trimester.
>
> — **Prof. Feiko ter Kuile**, Clinical Epidemiologist, LSTM

Artemether-lumefantrine in babies <5 kg

Medicines developed for adults may not be ideal for children, who absorb and metabolize medicines differently: children need medicines adapted for their age and weight. Children are included in Phase III of MMV's development programmes, and we prioritize the development of paediatric formulations. However, data are still lacking to support antimalarial use in the smallest infants.

In collaboration with Novartis and other PAMAfrica consortium members and with funding from the European and Developing Countries Clinical Trials Partnership (EDCTP), we are developing what could become the first medicine to treat uncomplicated malaria in babies weighing <5 kg. Pharmacokinetic (PK)[10] studies conducted by MMV and Novartis showed that the proportion of artemether to lumefantrine used in older children is not appropriate for newborns. Consequently, a new dispersible tablet formulation was developed containing artemether and lumefantrine in adapted proportions.

A Phase II/III study evaluating this new formulation in babies <5 kg, known as CALINA, is ongoing in Burkina Faso, Democratic Republic of Congo (DRC), Kenya, Mali, Nigeria, and Zambia.[11] The study started in December 2020 and is expected to finish in 2023.

6. Meaning that participants are followed over a period of time to see whether they become pregnant and if so, whether they are exposed to antimalarial drugs during pregnancy.
7. World Health Organization. WHO Guidelines for Malaria 25 November 2022. WHO/UCN/GMP/2022.01 Rev.3. https://apps.who.int/iris/handle/10665/364714
8. An analysis combining results from multiple studies or sources.
9. Saito M *et al.* "Pregnancy outcomes after first-trimester treatment with artemisinin derivatives versus non-artemisinin antimalarials: a systematic review and individual patient data meta-analysis" *The Lancet* 401(10371):118-30 (2023), doi: 10.1016/S0140-6736(22)01881-5 This analysis was coordinated by LSTM, with funding from MMV, WHO and WWARN (funded by the Bill & Melinda Gates Foundation). It included 34,178 pregnancies, of which 737 were exposed to artemisinin; 525 of these were exposed to artemether-lumefantrine.
10. Pharmacokinetics is the study of how a drug is absorbed, distributed, metabolized, and excreted from the body.
11. Led by Novartis in collaboration with the PAMAfrica consortium, MMV and the Swiss Tropical and Public Health Institute (Swiss TPH).

Closing the time gap by accelerating development of new drugs for pregnant women

Exclusion of pregnant or lactating women from clinical research is intended to protect them, but prevents generation of the safety and dosing data needed to inform recommendations on use of new medicines. Consequently, most medicines become available to pregnant and lactating individuals only after completion of pregnancy registries or other post-approval studies, making them the last to benefit from new therapies.

In April 2022, *Malaria Journal* published a commentary by MMV authors proposing changes to antimalarial drug development to better integrate the needs of pregnant women, based on innovations by MMV and partners.[12] MMV, as a recognized leader in malaria drug development, is well positioned to ensure that these changes are applied concurrently to other diseases of the Global South, which disproportionately affect women and particularly mothers.

> The malaria community has ambitious elimination goals, and the only way to meet them is by designing solutions that are suitable for everyone, and working together towards a more inclusive drug development.

— **Dr Myriam El Gaaloul**, Senior Director, Clinical Sciences, MMV; Co-leader of MiMBa initiative

← Researcher at Kenya Medical Research Institute, Kisumu, Kenya

Closing the medicines gap by prioritizing new drugs that could serve everyone from the start

In antimalarial development, MMV and our partners aim to prioritize compounds demonstrating low potential for risk to a developing embryo or breastfeeding infant. We have incorporated developmental safety assays[13] before selection of candidates for further development to detect any potential adverse effects as early as possible.

This early evaluation increases the probability of advancing candidates that are potentially suitable for women who are or could become pregnant.

Our strategy includes conducting standard dose-range finding and embryo-foetal development studies in two animal species in parallel with Phase I (healthy volunteer studies). To ensure consistent decision-making, MMV and our Expert Scientific Advisory Committee (ESAC) are working with the Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC[14]) to promote a balanced evaluation of these compounds that considers both benefits and risks in pregnancy.

Physiologically-based pharmacokinetic (PBPK[15]) simulations have been used to predict blood exposures (levels) during pregnancy and milk exposures for several different antimalarials,[16] permitting validation of the pregnancy and lactation models by comparing the simulations with available clinical data. A publication on the PBPK lactation simulations is planned in early 2023.

When a compound's profile is appropriate and its risk/benefit balance has been established in non-pregnant individuals, we are investigating how pharmacokinetic and pharmacodynamic[17] studies might be safely conducted in pregnant or lactating women in parallel with confirmatory studies (Phase III) in the general population.[18] Findings from these studies could be included in a new medicine's initial prescribing information, giving patients and physicians early access to reliable information about use during pregnancy and lactation, whilst data collection would continue after approval.

> Physiological changes during pregnancy can affect pharmacokinetics, and hence efficacy. We plan to use PBPK modelling to explore the potential need for dose adjustment in pregnant women, and to predict the extent of passage into breast milk.

— **Dr Nada Abla Geiser**, Director, Drug Disposition and PBPK Modelling, MMV

12. El Gaaloul M *et al.* "Re-orienting anti-malarial drug development to better serve pregnant women" *Malar J.* 21:121 (2022), doi: 10.1186/s12936-022-04137-2
13. For example, the zebrafish and human induced pluripotent stem cell (hiPSC) assays. The zebrafish assay has been shown to be a reliable predictor of embryotoxicity in mammals. This model's advantages include similar genetic structure to humans, small size, and transparency in the larval stage. The hiPSC assay, a human test system, enables observation of the development of heart, liver, and neural tissues and key cellular events of early embryonic development, detecting disruption of these processes through morphological and molecular read-outs.
14. PRGLAC was established by the US National Institutes of Health in 2016. This global task force, in consultation with the public, has produced 15 recommendations for closing the gap in knowledge and research on well-tolerated and effective therapies for pregnant and breastfeeding women. MMV participates in PRGLAC through the Teratology Society.
15. Physiologically-based pharmacokinetic modelling uses mathematical modelling to predict how a drug or other chemical will be absorbed, distributed, metabolized and excreted from the body, taking into account the physiological functions involved in these processes.
16. Blood exposures have been predicted for artemether-lumefantrine, piperaquine, artesunate/dihydroartemisinin, atovaquone and proguanil, and milk exposures for piperaquine, chloroquine, pyrimethamine, primaquine and mefloquine.
17. Pharmacodynamics is the study of how a drug affects the body.
18. In accordance with US Food and Drug Administration guidance (US Food and Drug Administration (2018). Guidance for Industry: "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials", Revision 1).

→ Lucy, a data manager for the MiMBa pregnancy registry, with a study participant at Ngodhe Island dispensary, Homa Bay, Kenya

Closing the access gap by increasing availability and accessibility of high-quality antimalarials

Despite increases in IPTp coverage over the last decade, only a third of pregnant women in Africa receive the full recommended chemoprevention regimen.[19] MMV and our partners are working to improve access to the WHO-recommended medicine SP for IPTp.

Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP)[20] was a 5-year pilot project in DRC, Madagascar, Mozambique and Nigeria aiming to substantially increase the number of expectant mothers receiving IPTp, presently provided at antenatal care (ANC) clinics. TIPTOP implemented community intermittent preventive treatment for malaria in pregnancy (c-IPTp), a promising approach to increasing access and adherence to IPTp through delivery by trained community health workers (CHWs). Data were also collected on drug resistance and on cost-effectiveness.

TIPTOP concluded in April 2022, and underwent WHO technical review in late June. In November, WHO updated its guidelines for malaria to recommend exploring the use of CHWs to reinforce delivery of ANC and IPTp where access is challenging.[21]

With TIPTOP, MMV and our lead partners Jhpiego and ISGlobal have set the stage for scale-up of c-IPTp. The resulting demand must now be matched by a continuous supply of high-quality SP.

> Ensuring the availability and accessibility of quality treatment for underserved communities, particularly women, newborns and children who are disproportionately at high risk of death from malaria, is a critical component to the full realization of the right to health.
>
> — **Joy Phumaphi**, Executive Secretary, African Leaders Malaria Alliance, and MMV Board member

Boosting local drug manufacturing

Only a handful of Africa's nearly 400 drug makers[22] have achieved international quality standards. Inadequate supply of quality-assured local products results in dependence on imported or poor-quality drugs, as was highlighted when COVID-19 disrupted global supply chains, leaving Africa with limited access to vital medicines. Concerns about quality and supply have slowed implementation and scale-up of numerous disease control programmes, including IPTp.[23] Until 2022, there was no quality-assured SP manufactured in Africa.

To close this gap, MMV, with funding from Unitaid, has engaged with three African manufacturers to help them achieve stringent regulatory approval of their SP products for IPTp.

In August 2022, Kenya's Universal Corporation Ltd became the first African manufacturer to receive WHO prequalification[24] for SP, enabling them to support regional efforts to combat malaria by producing quality-assured medicine locally. Nigeria's Emzor Pharmaceutical Industries Ltd and Swiss Pharma Nigeria (Swipha) Ltd/Biogaran are expected to achieve prequalification in 2024.

MMV ended the year by signing a memorandum of understanding with Africa Centres for Disease Control and Prevention focused on strengthening African manufacturing of quality-assured malaria medicines. This is crucial not only for the safety of Africa's people, regional supply chain security, and local healthcare autonomy, but for the struggle against antimicrobial resistance.[25]

Advocating for change beyond the field of antimalarial R&D

To close the data and medicines gaps for pregnant and lactating women, MMV is working to bring malaria, a disease of the Global South, into a broader global movement rooted in gender equity. We have undertaken initiatives to energize the greater malaria community and researchers in other fields to join this movement towards greater inclusion. We are also facilitating conversations with other organizations working across diseases of poverty to jointly explore ways to address this major historical blind spot in public health.

> It is important to include women in clinical trials to find drugs that are safe for them, that are efficacious for this particular population of women. When we do clinical trials in populations that actually need it, then we are adhering to the principle of justice.
>
> — **Dr Hellen Barsosio**, Senior Clinical Research Scientist, Kenya Medical Research Institute (KEMRI)

In November 2022, MMV hosted a consultation on gender-inclusive R&D with pharmaceutical industry partners to identify barriers and opportunities to better address women's health needs throughout their life cycle, particularly during pregnancy and lactation.

In 2022, we also initiated a cross-disease advocacy coalition with other product development partnerships and advocacy organizations to promote the equitable inclusion of people of childbearing potential in R&D processes.

19. World Malaria Report 2022. Global messaging briefing kit, https://cdn.who.int/media/docs/default-source/malaria/world-malaria-reports/world-malaria-report-2022-global-briefing-kit-eng.pdf?sfvrsn=5ec7ec5c_6&download=true
20. Led by Jhpiego and ISGlobal, with collaboration from MMV and WHO and funding from Unitaid. See https://www.tiptopmalaria.org/
21. World Health Organization. WHO Guidelines for Malaria 25 November 2022. WHO/UCN/GMP/2022.01 Rev.3. https://apps.who.int/iris/handle/10665/364714
22. IFC Insights: Africa's Shot at Local Pharma Production. https://www.ifc.org/wps/wcm/connect/news_ext_content/ifc_external_corporate_site/news+and+events/news/insights/africa-local-pharma-production
23. Roman E *et al.* "Determinants of uptake of intermittent preventive treatment during pregnancy: A review" *Malar J.* 18(1):372, doi: 10.1186/s12936-019-3004-7
24. Set up in 2001, WHO's prequalification programme is designed to "facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis".
25. World Health Organization. Strategy to respond to antimalarial drug resistance in Africa (2022). https://www.who.int/publications/i/item/9789240060265

INTERVIEW

Dr Julie Gutman, Co-chair of the Malaria in Pregnancy Working Group, RBM Partnership to End Malaria (USA), discusses the working group and the importance of MiMBa.

Could you briefly describe the RBM Malaria in Pregnancy Working Group (MiPWG)?

The working group is a diverse partnership made up of Ministry of Health leaders from both national reproductive health programmes and National Malaria Control Programmes (NMCPs), technical partners, researchers and donors that come together to bridge the gap between global policy and country practice, with the goal of accelerating malaria in pregnancy (MiP) programme implementation.

What are the functions of the working group?

The MiPWG aims to align RBM partners on best practices and lessons learnt in MiP programming to help achieve higher coverage for MiP interventions globally. This is done through advocacy at national and global levels, fostering partnerships between national reproductive, maternal, newborn and child health and national malaria control partners, disseminating country experiences and best practices related to scaling up MiP interventions and ensuring linkages between researchers and NMCPs so that research is used to guide policy.

How does the MiMBa strategy align with the goals of the working group?

MiMBa's goals of broadening access to current antimalarials and investing in new molecules for the future are perfectly aligned with the working group's goals of optimizing treatment and prevention of MiP.

What is it like to work with MMV in this working group?

MMV has been a wonderful partner and has provided an immense amount of support to the working group to help us achieve our objectives of highlighting the low uptake of IPTp. With respect to ensuring optimal treatment for MiP, we are excited about working with countries to support implementation of the new WHO recommendation to provide ACTs for treatment of malaria in the first trimester. We believe that this transition will improve malaria case management both by providing more effective treatment for pregnant women and by simplifying guidance for healthcare workers, thus improving adherence. We look forward to working with MMV to support this shift, and to generate additional evidence on the safety of ACTs other than artemether-lumefantrine.

→ Emmah, Port Loko, Sierra Leone

→ Community health volunteer with Ramatou, age 6, one of the first children in Niger to benefit from MMV's SMC-Impact project (Damagaram Takaya, Niger)

Broadening the reach of seasonal malaria chemoprevention (SMC) to protect more children from malaria

Children are at the greatest risk of dying from malaria.

Young children are particularly vulnerable to infection due to their developing immune systems and lack of previous exposure. Children under 5 years old represented nearly 80% of lives lost to malaria in 2021.[26] The disease's detrimental effects can follow surviving children throughout their lives, affecting neurological, cognitive and physical development.

Where malaria transmission is seasonal, notably in the Sahel region, children are protected through SMC. This intervention consists of full antimalarial treatment courses administered at regular intervals during the high-transmission period (typically the rainy season), generally for up to 4 months per year. SMC can be deployed relatively easily across a large population, and is highly cost-effective,[27] making it an important tool for malaria control. In clinical trials, SMC using SP + amodiaquine (SPAQ) was highly effective, providing up to 88% protection against infection in the first 28 days and 61% reduction in clinical malaria 29–42 days after administration.[28]

Expansion of SMC programmes resulted in more than 48 million children being protected from malaria in 2022 alone. However, many children in Africa are still not receiving SMC. Until recently, WHO recommended SMC only for children from 3 months to 5 years old. However, in June 2022, WHO updated its guidance to recommend this intervention for any child at high risk of severe malaria.[29]

> "SMC's efficacy and good tolerability have given communities and health workers new hope of winning the battle against malaria in seasonal transmission areas."
>
> — **Prof. Jean-Louis Ndiaye**, Director of Research and Scientific Innovation, Department of Medical Biology, University of Thiès, Senegal

26. World Malaria Report 2022: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022
27. ACCESS-SMC Partnership. "Effectiveness of seasonal malaria chemoprevention at scale in west and central Africa: an observational study" *The Lancet* 396(10265):1829-40 (2020), doi: 10.1016/S0140-6736(20)32227-3
28. Cairns M *et al.* "Effectiveness of seasonal malaria chemoprevention (SMC) treatments when SMC is implemented at scale: Case–control studies in 5 countries" *PLoS Med.* 18(9):e1003727 (2021), doi: 10.1371/journal.pmed.1003727
29. World Health Organization. Updated WHO recommendations for malaria chemoprevention among children and pregnant women (2022), https://www.who.int/news/item/03-06-2022-Updated-WHO-recommendations-for-malaria-chemoprevention-among-children-and-pregnant-women

Sarah's story: protecting older children in Niger by extending SMC

Story

Sarah Hamissou is 9 years old and lives in Damagaram Takaya, a village in the Zinder region of southern Niger. Like other children her age, she goes to school, plays with her friends and spends time with her family, including her 5-year-old brother Rayan and her mother Mariama.

All of that stopped last year when Sarah fell ill from malaria, suffering from a high fever and other symptoms. Mariama knows that malaria can be fatal if untreated, so she sought and received care for her daughter. But she also worries that Sarah and her other two children will fall ill again, like some 7 million others in Niger each year. In a country of only 25 million people, this disease takes an enormous toll, getting in the way of learning, playing and growing.

SMC is a vital intervention that has been implemented in 17 African countries[30] to protect children in areas where malaria is highly seasonal. In 2021, nearly 4.5 million children in Niger were protected with SMC;[30] this number increased to 4.7 million in 2022.

The updated WHO recommendation means that in some locations, SMC can now be extended to protect older children – like Sarah and Rayan.

30. World Malaria Report 2022: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2022
31. SMC-Impact project: Project overview. https://www.smc-alliance.org/smc-impact-project
32. Malaria Research and Training Centre (MRTC), Bamako, Mali; Gamal Abdel Nasser University of Conakry, Guinea; *Centre de Recherche Médicale et Sanitaire* (CERMES), Niamey, Niger; and the Medical Research Council Unit The Gambia (MRCG) at LSHTM.

Nurturing and adapting SMC implementation: updates on MMV-supported initiatives

SMC-Impact[31] is a 4-year project (launched in 2021) that aims to provide evidence for expanding SMC to children 5–10 years old and extending SMC administration to five cycles where the peak malaria season is longer. It is led by the NMCPs in The Gambia, Guinea, Mali, Niger and Nigeria, with support from Catholic Relief Services (CRS), the Malaria Consortium, the London School of Hygiene and Tropical Medicine (LSHTM) and MMV and with funding from the Korea International Cooperation Agency Global Disease Eradication Fund (KOICA-GDEF).

In 2022, SMC-Impact was launched in Niger. SMC was extended to children 5–10 years old in one district in Niger and one in The Gambia (for the second year), and a fifth SMC cycle was implemented in one district in Guinea (for the second year), two in Mali, one in Niger and two in Nigeria.

LSHTM and local research organizations[32] are currently evaluating the project's cost and impact in Guinea, Mali and Niger. Evaluation will be extended to The Gambia in 2023 pending availability of funding. Research will also be needed to evaluate the optimum duration of SMC on an ongoing basis, in light of climate change and shifts in malaria seasonality.

SMC-Impact is working with manufacturers to develop SPAQ dosage, formulation and packaging for children 5–10 years old. In the absence of WHO recommendations, an expert committee, established in 2022, reviewed dosages currently used in Mali and Senegal and presented its conclusions to the WHO Global Malaria Programme in November.

SMC implementation and expansion require high-quality data collection. In Nigeria, SMC-Impact used the application KoboCollect.[33] Data recorded directly in the application are synchronized to an online platform, where they can be consulted in real time. CRS, who have been at the forefront of electronic data collection in SMC campaigns, coordinated SMC-Impact implementation in The Gambia, Guinea, Mali and Niger, and identified key benefits as increased accuracy, faster access to data for evaluation and planning, and reduced workload.

In June 2022, WHO introduced new chemoprevention guidelines recommending adaptation of the number of SMC cycles and age range of protected children to local epidemiology, increasing opportunities to support countries in expanding SMC's impact.

Optimizing SMC (OPT-SMC)[34] is a 4-year project (launched in 2020) that aims to support NMCPs in conducting operational research on adapting SMC to local contexts, improving delivery and maximizing impact, notably through grants, technical assistance and facilitating the sharing of knowledge between countries. OPT-SMC is led by the University of Thiès, Senegal, in partnership with MMV, LSHTM, the WHO Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and the NMCPs of 13 West African countries,[35] and with funding from the EDCTP.

Three completed OPT-SMC projects were presented at the American Society of Tropical Medicine and Hygiene's 2022 conference.[36] Five projects[37] collected data during the year's SMC campaigns, and two further projects[38] are in preparation. ●

33. Based on the open-source application ODK Collect; see https://getodk.org/ and https://www.kobotoolbox.org/
34. OPT-SMC: Optimising the impact of SMC. https://www.lshtm.ac.uk/research/centres-projects-groups/opt-smc
35. Benin, Burkina Faso, Cameroon, Chad, The Gambia, Ghana, Guinea, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Togo.
36. 30 October – 3 November 2022; Seattle, Washington, USA. Projects presented were "SMC coverage and factors associated with uptake and adherence" (Ghana); "Barriers to SMC uptake in mining areas in Guinea and an improved delivery approach"; "Barriers and facilitators of SMC uptake in Nigeria: a qualitative study in 5 states".
37. "Evaluating the determinants of variations in SMC coverage in Burkina Faso"; "Effectiveness and cost of using Community Household Leaders to improve SMC adherence in northern Cameroon"; "Evaluating three approaches to improve uptake and adherence of SMC in Koulikoro Region, Mali"; "Monitoring effectiveness of SMC in northern Benin during the 2020 & 2021 campaigns, using the case-control method" (data management/analysis ongoing); "Applying updated WHO SMC guidelines in Niger: timing, number of cycles, and age ranges at risk of severe malaria" (data collection ongoing).
38. "Estimating the delivery costs and cost effectiveness of SMC in southern Senegal" (awaiting ethics committee approval) and "Defining optimal SMC strategies in Togo: timing and number of cycles, and age ranges at risk of severe malaria".
39. https://www.smc-alliance.org/

INTERVIEW

Dr Djermakoye Hadiza Jackou, former Coordinator of Niger's National Malaria Control Programme (NMCP), and **Dr André-Marie Tchouatieu**, Director, Access & Product Management, MMV (Switzerland) discuss the expansion of SMC.

How has the expansion of SMC helped in the fight against malaria?

DHJ: Post-campaign evaluation and epidemiological analysis have shown significant impact of SMC scale-up on malaria incidence amongst children aged 3 months to 5 years, although this is not uniform across implementation areas. We are investigating the reasons for this lack of uniformity.

SMC, like most other interventions in place, prioritizes children in this age group, whilst older children are left pretty much on their own. After a few years we noticed an increasing trend in the number of cases in children aged 5 to 10 years, which led us, with MMV's help, to initiate a pilot project administering SMC to children in this age group based on the experience of countries like Senegal who have done this since 2013. This will allow us to determine the added value of extending SMC to these children.

Niger was amongst the first countries to graft other interventions onto SMC implementation. Since 2016, we have been screening for malnutrition (which is almost as much of a public health issue as malaria and affects the same age bracket), verifying immunization records, and doing research on acute flaccid paralysis in parallel with SMC.

What was it like to work with MMV?

DHJ: MMV has been a major actor in SMC since the beginning. Not only by providing campaign planning tools and adapted SPAQ formulations, but also – and especially – through its capacity to bring together different stakeholders through the SMC Alliance,[39] to perpetuate what countries put in place at the outset. In 2018, Niger was honoured to host the first annual SMC review and planning meeting under the Alliance's new approach. We hope that this collaboration will continue, for the benefit of children in Niger.

What value has the SMC Alliance brought in terms of knowledge sharing among partner countries?

AMT: The SMC Alliance is a group of SMC stakeholders, including implementing countries, that serves as a platform for discussion and problem-solving. The spirit of collaboration within the Alliance has been commendable, with all members sharing information for the benefit of others, reinforcing collaboration and generating new initiatives.

In 2022, the Alliance's monitoring and evaluation subgroup developed a framework for harmonizing practices across implementing countries. The research subgroup focused on defining research questions for improving SMC implementation. The communication subgroup organized several webinars to promote SMC, with the goal of increasing interest in this intervention and ultimately diversifying funding, especially from local sources. As the Alliance includes a large pool of SMC experts, it took part in the review of the SMC implementation guide after revision of WHO guidance in June 2022, as well as the interpretation and dissemination of these new guidelines.

SMC Alliance

Driving inclusion of vulnerable populations to reduce the burden of relapsing malaria

6

↖ Kellen with her children Thaemilly and Maria (Manaus, Brazil)

Simplifying radical cure for *Plasmodium vivax*

The malaria parasite *Plasmodium falciparum*, which dominates in Africa, is responsible for the majority of malaria deaths worldwide. The parasite *Plasmodium vivax*, responsible for relapsing malaria, dominates in Central and South America, South and South-East Asia and the Horn of Africa, where it presents a different set of challenges. In these regions, often-neglected populations such as migrant workers, displaced people and indigenous communities are disproportionately affected.

Unlike *P. falciparum*, *P. vivax* can cause both a blood-stage infection (causing an acute malaria episode) and a liver-stage infection, which can lie dormant and then reactivate if not treated, causing relapses that may occur weeks or months after the initial infection. This makes *P. vivax* a particular challenge for elimination efforts, with transmission driven largely by relapses from dormant liver stages.[1]

For many years, *P. vivax* malaria was considered relatively benign. However, evidence has emerged that it can also lead to severe disease and death,[2] with young children and pregnant women at highest clinical risk.[3] Children are especially vulnerable to cumulative anaemia from repeated relapses, and to chronically swollen spleens (splenomegaly), which may rupture and cause internal haemorrhaging. Moreover, children experiencing repeated infections are likely to suffer physical and cognitive impairment,[4,5,6] with adverse consequences for their development and education. *P. vivax* malaria in pregnancy is also a major cause of morbidity and mortality, with potential consequences like those of *P. falciparum* disease.[7]

Achieving 'radical cure' for *P. vivax* involves treating both the blood stage and the liver stage of infection. The current standard of care involves 3 days of chloroquine or an artemisinin-based combination treatment (ACT) to treat the blood stage and either 7 or 14 days of primaquine for the liver stage. Adherence to the primaquine regimen is problematic, as symptoms improve rapidly once the blood-stage infection is cleared. In addition to the obvious risk to patients, poor adherence fuels transmission, as dormant liver-stage parasites become a reservoir for infection.

Tafenoquine (*Krintafel/Kozenis*),[8] developed in partnership between GSK and MMV with the support of endemic-country partners, represents a significant advance in treatment of liver-stage infection because of its single-dose administration, which eliminates the problem of poor adherence.

Both tafenoquine and primaquine are generally well tolerated but can cause severe haemolytic anaemia (destruction of red blood cells) in people deficient in the enzyme glucose-6-phosphate dehydrogenase (G6PD).[9] Testing for G6PD deficiency is therefore important for patient safety, but has previously presented a logistical challenge for National Malaria Control Programmes (NMCPs).

A quantitative point-of-care G6PD diagnostic test has been developed by SD Biosensor with support from the global non-profit organization PATH.[10] The portable, battery-operated device can distinguish deficient, intermediate and normal levels of G6PD enzyme activity which is essential for the prescription of tafenoquine. The test received regulatory approval from the Australian Therapeutic Goods Administration (TGA) in 2021, certifying that it is appropriate for use in point-of-care settings and meets rigorous quality standards.[11]

1. Chu CS, White NJ. "Management of relapsing *Plasmodium vivax* malaria" *Expert Rev Anti Infect Ther.* 14(10):885-900 (2016), doi: 10.1080/14787210.2016.1220304
2. Price RN *et al.* "*Vivax* malaria: neglected and not benign" *Am J Trop Med Hyg.* 77(6 Suppl):79–87 (2007), PMCID: PMC2653940
3. Phyo AP *et al.* "Clinical impact of *vivax* malaria: A collection review" *PLoS Med.* 19(1): e1003890 (2022), doi: 10.1371/journal.pmed.1003890
4. Fernando D *et al.* "Cognitive performance at school entry of children living in malaria-endemic areas of Sri Lanka" *Trans R Soc Trop Med Hyg.* 97(2):161-5 (2003), doi: 10.1016/s0035-9203(03)90107-6
5. Vorasan N *et al.* "Long-term impact of childhood malaria infection on school performance among school children in a malaria endemic area along the Thai-Myanmar border" *Malar J.* 14:401 (2015), doi: 10.1186/s12936-015-0917-7
6. Brasil LMBF *et al.* "Cognitive performance of children living in endemic areas for *Plasmodium vivax*" *Malar J.* 16(1):370 (2017), doi: 10.1186/s12936-017-2026-2
7. See Chapter 5.
8. Tafenoquine is approved for patients at least 16 years old in Australia, Brazil, Colombia, Peru, Thailand, and the USA, with additional submissions pending review in endemic countries. Approvals in Colombia and the Philippines were obtained in 2022. It is marketed as *Kozenis* in Australia and *Krintafel* in the USA; trademarks are owned or licensed by the GSK group of companies.
9. The label for tafenoquine restricts its use to patients with at least 70% G6PD activity; however, primaquine can be given to people with at least 30% G6PD activity.
10. See www.path.org.
11. The test is approved in countries including Cambodia, Djibouti, India, Indonesia, Myanmar, Pakistan, the Philippines, Saudi Arabia and Thailand.

An implementation study assessing the feasibility of providing tafenoquine or primaquine based on G6PD test results at different levels of the health system was completed in 2022 in Brazil (the TRuST study),[12] and a second was started in Thailand in May 2022 (the ARCTIC study).[13] In 2023, additional studies are planned in Ethiopia and Peru with tafenoquine, as well as in Indonesia and Papua New Guinea where only primaquine will be used.[14]

Approval of novel paediatric relapse-prevention treatment

In March 2022, the Australian TGA approved use of single-dose tafenoquine in combination with chloroquine for radical cure of *P. vivax* malaria in children at least 2 years old. A child-friendly dispersible formulation was developed in a partnership between GSK and MMV. The submission was supported by a Phase IIb study[15] evaluating tafenoquine dosages based on weight for children aged from 2 to 15 years and weighing ≥10 kg, which showed pharmacokinetics,[16] safety and efficacy similar to those previously observed. Moreover, 95% of the 60 participants showed no recurrence of *P. vivax* malaria over 4 months of follow-up.[17]

TGA approval is supporting registrations in endemic countries where tafenoquine could contribute to malaria elimination goals. Tafenoquine for paediatric use represents a step towards addressing the needs of children in these countries, who are particularly vulnerable to repeated *P. vivax* episodes.

Brazil: Tafenoquine Roll-out STudy (TRuST) updates

The Brazilian Amazon region accounts for 99% of malaria cases in the country. The disease has considerable economic and social impact, perpetuating cycles of poverty.[18]

One of the main challenges to malaria control in Brazil is the difficulty of accessing remote populations, notably indigenous communities. Adherence to treatment is another major challenge, as failure to complete treatment leads to relapses and continued transmission.

The first real-world study of tafenoquine and quantitative point-of-care G6PD testing, known as TRuST, was launched in Brazil in September 2021. The study, a collaboration between the Brazilian Ministry of Health (MoH) and MMV, was led by malaria experts from the Dr Heitor Vieira Dourado Tropical Medicine Foundation (*Fundação de Medicina Tropical Doutor Heitor Vieira Dourado*; FMT-HVD) and the Tropical Medicine Research Centre (*Centro de Pesquisa em Medicina Tropical*; CEPEM).[19]

TRuST assessed the feasibility of providing appropriate relapse-prevention treatment with tafenoquine or primaquine based on G6PD test results. Within the framework of TRuST, a qualitative study known as QualiTRuST was conducted by FMT-HVD to assess the understanding and acceptability of the new tools amongst health workers and patients.

The first phase was conducted in nine higher- and medium-level health facilities (hospitals) in Porto Velho and Manaus, in the Amazon region.[20] In February 2022, the study was expanded to 40 lower-level facilities in the same municipalities. Enrolment finished in August 2022, and in November the second interim analysis showed that more than 99% of patients treated with tafenoquine had been treated appropriately based on quantitative G6PD test results.

In December 2022, the MoH submitted a dossier on tafenoquine and quantitative G6PD testing to the National Committee for [health] Technology Incorporation (CONITEC[21]). This dossier, based on consolidated results from the TRuST first and second interim analyses, QualiTRuST, a cost-effectiveness analysis and a budget impact analysis, will inform the decision on the incorporation of tafenoquine and quantitative G6PD testing into the Brazilian health system for patients at least 16 years old.

Analysis of full safety and efficacy data is ongoing, with a report expected in March 2023 and publications thereafter.

← A woman holds her *Cartão Malaria* and primaquine prescription (Manaus, Brazil)

12. Tafenoquine Roll-out Study. See also the video "From science to real life: Tackling relapsing malaria in the Amazon":
13. Assessing Radical Cure Treatment In routine Care. See also the video "The ARCTIC study: optimizing *P. vivax* radical cure in Thailand":
14. These additional studies are supported by funding from Unitaid.
15. TEACH – Tafenoquine Exposure Assessment in Children.
16. Characteristics describing how a drug is absorbed, distributed, metabolized and excreted from the body.
17. Vélez ID *et al.* "Tafenoquine exposure assessment, safety, and relapse prevention efficacy in children with *Plasmodium vivax* malaria: open-label, single-arm, non-comparative, multicentre, pharmacokinetic bridging, phase 2 trial" *Lancet Child Adolesc Health.* 6(2):86-95 (2022), doi: 10.1016/S2352-4642(21)00328-X
18. Adults may be too ill to work or carry out family responsibilities, or may lose jobs after multiple absences; children may be unable to attend school or suffer from cognitive problems.
19. In Amazonas and Rondônia, respectively.
20. An estimated 5% of the population in this region is G6PD-deficient. (Dombrowski JG *et al.* "G6PD deficiency alleles in a malaria-endemic region in the Western Brazilian Amazon" *Malar J.* 16(1):253 (2017), doi: 10.1186/s12936-017-1889-6
21. National Committee for [health] Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde – CONITEC).

Revisiting Raquel: Single-dose tafenoquine for *P. vivax* malaria

Story

Raquel da Silva, shown here with her son Camilinho, has lived in Manaus in Brazil's Amazonas State since her childhood. Today she shares her home on the banks of the Rio Negro with her husband Camilo, their three children, her mother-in-law and her grandmother-in-law. On the weekends, she works in a restaurant.

As a mother of three, Raquel needs her energy to keep up with her children, but living in one of the most malaria-affected areas in the country she has been ill with the disease many times. She has lost track of how many times she has contracted malaria but estimates it must be at least a dozen. In 2022 alone, she got sick with malaria at least three times: twice with *Plasmodium falciparum* malaria and once with *P. vivax* malaria, which is more common in Latin America.

The first time MMV met Raquel in 2020, she was unwell. At the time, *P. vivax* malaria required a full 7-day treatment to cure and prevent relapse, and since she had a 6-month-old baby at home and her husband was away working, she felt unable to complete the full treatment course. **"I took just enough so my symptoms would improve."** She dealt with many bouts of the illness, accompanied by low energy, chills and fever.

In 2022, however, things were different. When she got malaria, she received a new drug: tafenoquine. Developed in partnership between GSK and MMV, this drug is a single-dose radical cure for *P. vivax* malaria, meaning that it prevents relapse when accompanied by chloroquine, an antimalarial drug already widely distributed and used in Brazil's health system.

Manaus, where Raquel lives, and Porto Velho are the only cities in Brazil authorized by the Brazilian Ministry of Health to prescribe tafenoquine after quantitative point-of-care G6PD testing as part of a temporary implementation plan in the national public health system. This implementation is accompanied by the MoH and MMV-co-sponsored Tafenoquine Roll-out STudy (TRuST), described above.

For patients with normal G6PD enzyme activity, the new treatment protocol with tafenoquine is much simpler, something that makes a big difference in the lives of patients like Raquel.

Raquel is optimistic about the new possibilities that the drug provides. She says that, although she also takes preventive measures such as using bed nets, the drug provides a sense of security in case she or her family members do fall ill again.

Tackling relapsing malaria in Thailand

In the Mekong region of Southeast Asia, as NMCPs have substantially reduced the incidence of *P. falciparum* malaria, *P. vivax* malaria has become more dominant and is threatening elimination targets due to the challenges of effective radical cure.

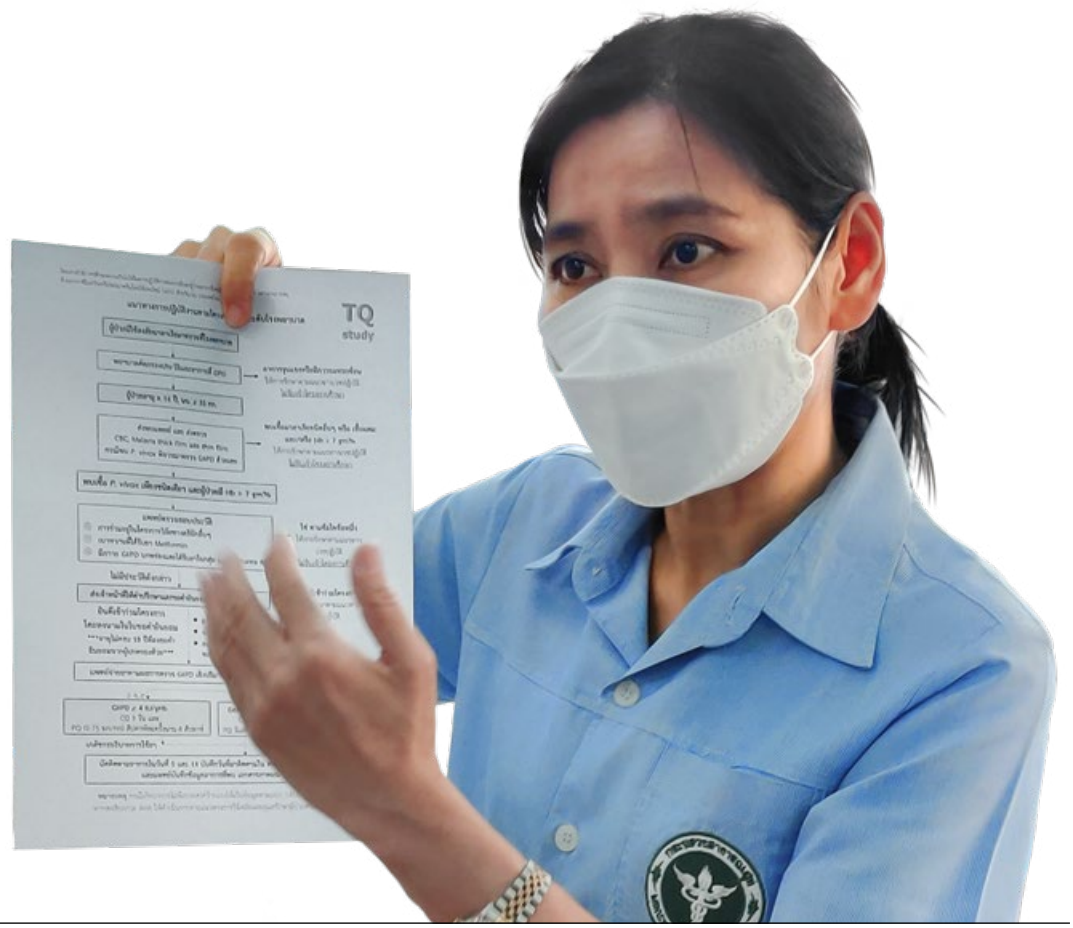
In Thailand, people living in forested border areas are the main population at risk of *P. vivax* malaria, as transmission is associated with two vectors found in these settings.[22] This population includes migrant workers, whose occupations[23] increase their risk of contact with infectious mosquitoes, as well as people displaced by conflict and economic hardship who are at risk due to poor healthcare access. Conflict and economic disruption can also undermine malaria control efforts, and migration can re-establish the parasite where it has been previously eliminated. These populations – and *P. vivax* patients in general – face substantial challenges to adherence to the 14-day primaquine regimen, which single-dose tafenoquine could potentially overcome.

In May 2022, the Thai Ministry of Public Health's Division of Vector-Borne Diseases, with the support of MMV, enrolled the first patients in the ARCTIC study. This feasibility study, similar to TRuST, is investigating real-world use of quantitative point-of-care G6PD testing to determine appropriate relapse-prevention treatment with tafenoquine or primaquine. This is the first such study with tafenoquine in the Asia-Pacific region and should provide evidence of its potential role in achieving Thailand's 2024 malaria elimination goal.

ARCTIC is being conducted in Mae Hong Son and Yala provinces, where quantitative G6PD testing has been available in district hospitals since 2020.[24] Mae Hong Son province, near the Thai-Myanmar border, has experienced a significant rise in malaria cases with the increase in refugees crossing the border.

In November 2022, an interim analysis showed that all of the first 50 patients had received appropriate treatment (tafenoquine or primaquine) based on G6PD test results. An independent study oversight committee approved expansion from high-level health facilities (hospitals) to lower-level malaria clinics in December 2022. Enrolment is expected to continue until June 2023. ●

> We are thrilled to be working hand in hand with the Thai Ministry of Public Health on the ARCTIC study, assessing whether tafenoquine can be integrated into routine care in Thailand. Single-dose tafenoquine has great potential to reduce the burden of *P. vivax* by increasing treatment adherence, taking us one step closer to eliminating this particularly challenging species.
>
> — **Dr Elodie Jambert**, Senior Director, Access & Product Management, MMV



↖ A Thai MoH representative presents the ARCTIC study to Mae Hong Son hospital staff

22. Specifically, *Anopheles dirus* and *An. minimus*. See "Thailand, LAO PDR and Regional Malaria Operational Plan FY 2018", President's Malaria Initiative, USAID (2018), p. 6: https://reliefweb.int/report/thailand/presidents-malaria-initiative-thailand-malaria-operational-plan-fy-2018
23. Notably mining, forestry and agriculture.
24. Prevalence of G6PD deficiency ranges from 3% to about 18% in Thailand, varying with region and ethnic group.

Project of the Year 2022

MMVSola – shining light on new molecules to optimize clinical outcomes

MMV's Project of the Year 2022 is awarded to a team of scientific experts led by Dr Stephen Brand, MMV Associate Director of Drug Discovery, for the development of the dose prediction tool 'MMVSola'.

MMVSola is an innovative, open-access, user-friendly and free-of-charge application that combines information on the chemical, physical and biological properties of a compound to estimate the dose needed to cure a patient with malaria, or to protect someone from infection. It was named in memory of the microbiologist Suresh Solapure, a friend of MMV and an early champion of pharmacokinetic/pharmacodynamic[1] (PK/PD) data modelling for dose prediction. Key to the project, alongside MMV team members, were Dr Peter Webborn, an independent drug metabolism and pharmacokinetics (DMPK) and PK/PD consultant; Dr Ghaith Aljayyoussi, a postdoctoral fellow at Liverpool School of Tropical Medicine; and Dr Venelin Mitov, a modelling and simulation scientist and programmer with IntiQuan GmbH.

MMV's independent Expert Scientific Advisory Committee (ESAC) recommended MMVSola for this award owing to its ability to help discovery teams evaluate the PK and dose of their frontrunner compounds, identify the key parameters on which to focus lead optimization efforts and ultimately advance the best possible candidate from a series.

MMV applies a strict dose criterion at candidate selection, consistent with our goal of delivering new single-dose drugs for malaria prevention and treatment that minimize cost whilst maximizing adherence and therefore cure. MMVSola has been transformational in helping our discovery collaborators achieve this challenging goal and is making it possible to design medicines that can be given as infrequently as once a month rather than once or more per day.

1. Pharmacokinetics is the study of how drugs are absorbed, distributed, metabolized and excreted by the body, and pharmacodynamics is the study of how drugs affect the body and/or organisms causing disease.

INTERVIEW

Dr Stephen Brand, MMV Associate Director of Drug Discovery, Dr Peter Webborn, Independent DMPK & PK/PD Consultant, and Prof. Dennis Smith, DMPK expert and ESAC member, discuss the MMV 2022 Project of the Year.

How does MMVSola contribute to antimalarial drug discovery?

SB: In essence, it predicts human PK from preclinical data and combines it with malaria pharmacodynamics to predict antimalarial doses.

PW: Using MMVSola, you can predict what dose of a novel compound is likely to be effective in patients based on preclinical information. MMVSola also calculates a range of PK parameters such as half-life and bioavailability.[2] Together, these allow you to ask "what if" questions like "What would be the impact if we improved this parameter twofold?" And that really helps to focus on the key issues in the design of new long-lasting molecules.

Why was MMVSola introduced, and what has been its impact?

DS: Teams traditionally moved compounds through various stages of the drug discovery process using cut-off values for potency, selectivity,[3] solubility, and at later stages *in vivo*[4] parameters such as clearance,[5] half-life and bioavailability. But these were often considered in isolation. The key lessons come from combining all these properties, and this requires not only new computational tools, but also systematic collection of the right data. MMVSola holistically links all the relevant preclinical data into a simple property: the effective dose. The benefits of its use across MMV discovery projects, which are conducted at a diverse range of research centres, are substantial.

These include:

- Ability to focus on clinical efficacy from an early stage;
- Alignment of methodology, data recording and use in order to achieve common standards; and
- Holistic use of the data so multiple parameters can be balanced correctly against desired clinical outcome.

The development of regular user group workshops has considerably broadened discovery teams' knowledge and expertise, facilitating universal uptake of the tool.

Who has been involved in the delivery of MMVSola?

SB: This project has been a real team effort. The key point is that MMVSola required expertise in several different areas. There's DMPK, which is about being able to predict human exposure for a compound. There are pharmacodynamic studies using data from a laboratory model of malaria.[6] PK/PD modelling is about combining those data to predict the dose needed to have a desired effect in humans. Then there's computer programming and software design for implementing this methodology as a usable tool. Finally, there's an expert group that trains MMV discovery teams to use the tool and interpret the information.

How does MMVSola help discovery teams?

PW: MMVSola enables teams to evaluate early in a project what the predicted doses of their compounds are, without needing a PK/PD modeller on the team. If it turns out that predicted doses are too high, which they usually are in early stages of lead optimization,[7] it lets them get a handle on which parameters will be the most impactful to optimize, so they can adopt an appropriate medicinal chemistry strategy.

How have you and your team further developed this tool since its launch?

PW: We've added a few new modules recently after discussions with the users. One is enabling allometric scaling[8] to be used to predict clearance. We've also added the ability to incorporate renal clearance[9] in human predictions.

SB: Another important new functionality is the prediction of a prophylactic (or chemoprevention) dose. It's a different way of defining how much drug you need: the tool originally focused on the dose you would need to kill all the blood-stage parasites in someone with malaria. The prophylactic dose is about achieving concentrations above what's called the minimum inhibitory concentration[10] to provide protection for as long as 28 days. MMVSola calculates how much drug you would need to get above that level for that amount of time.

What are your plans for future upgrades?

SB: We will continually assess MMVSola's performance and will apply preclinical and clinical data from future compounds to update the tool's algorithms and improve predictions. We are also aiming to enhance the user interface and to develop this tool to be able to make dose predictions for other diseases, using the expertise within the MMV network and IntiQuan – while of course maintaining it as an open-access resource.

How do I access MMVSola?

SB: It's available at the web address (https://www.mmvsola.org), and it's free of charge, secure and does not retain data. Training and user group workshops are provided regularly and are also free of charge.[11]

2. Half-life is the time needed for the amount of drug in the body to decrease by half. Bioavailability is the amount of an administered drug that enters the circulation and can therefore have a pharmacological effect.
3. How closely the compound's effects are focused on the proteins it is meant to target in the malaria parasite.
4. Obtained within a living organism.
5. How rapidly a drug is eliminated from the body.
6. Jiménez-Díaz MB *et al.* "Improved Murine Model of Malaria Using *Plasmodium falciparum* Competent Strains and Non-Myelodepleted NOD-scid IL2RγnullMice Engrafted with Human Erythrocytes" *Antimicrob Agents Chemother.* 53(10):4533-6 (2009), doi: 10.1128/AAC.00519-09
7. Lead optimization is the modification of identified lead molecules to improve their target specificity and selectivity (i.e., to confirm desired effects on the target and minimize potential undesired effects) and PK while preserving their desired activity on their targets.
8. Allometric scaling uses relationships between body size and physical, anatomical and biochemical changes (which tend to be slower in larger organisms) to predict human dose and exposure based on results in animals.
9. How fast a substance is removed from the body by the kidneys.
10. The lowest concentration able to inhibit growth of the parasite.
11. If you would like a demonstration or training in the use of MMVSola, please contact Stephen Brand at brands@mmv.org.

Financial view

Financial year to 31 December 2022

8

Legal status
MMV is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 15 November 1999. The summary consolidated financial statements of MMV also include the accounts of the United States entity MMV North America, Inc., which is registered in the United States as a section 501(c)(3) organization (please refer to note 2.c of the summary consolidated financial statements).

Revenue
Total revenue in 2022 amounted to USD 74.7 million. This, and every contribution over the years, has helped to advance our mission and the ultimate goal of defeating malaria together.

MMV is very grateful for these and previous commitments from all of its donors and partners.

Expenditure
Total expenditure in 2022 amounted to USD 89.1 million. Research & development (R&D) expenditure amounted to USD 56.3 million.

Access & product management (APM) expenditure amounted to USD 16.6 million. Other portfolio expenditure amounted to USD 1.7 million.

Report of the auditor

to the Board of Directors of Medicines for Malaria Ventures

Meyrin

Report of the auditor on the summary consolidated financial statements

Opinion

The summary consolidated financial statements, which comprise the consolidated balance sheet as at 31 December 2022, and the consolidated statement of changes in capital, the consolidated statement of operations, the consolidated cash flow statement, for the year then ended, and notes to the consolidated financial statements, including a summary of significant accounting policies.

In our opinion, the accompanying summary consolidated financial statements are consistent, in all material respects, with the audited consolidated financial statements, in accordance with Swiss GAAP FER and the provisions of Swiss law.

Summary Consolidated financial statements

The summary consolidated financial statements do not contain all the disclosures required by Swiss GAAP FER and the provisions of Swiss law. Reading the summary consolidated financial statements and the auditor's report thereon, therefore, is not a substitute for reading the audited consolidated financial statements of Medicines for Malaria Ventures and the auditor's report thereon. Those consolidated financial statements, and the summary consolidated financial statements, do not reflect the effects of events that occurred subsequent to the date of our report on those consolidated financial statements.

The Audited Consolidated financial statements and Our Report Thereon

We expressed an unmodified audit opinion on those consolidated financial statements in our report dated April 26, 2023.

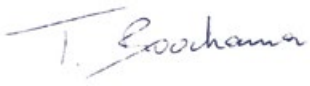
Board of Directors' responsibility

The Board of Directors is responsible for the preparation of the summary consolidated financial statements in accordance with the requirements of Swiss GAAP FER and the provisions of Swiss law.

Auditor's responsibility

Our responsibility is to express an opinion on whether the summary consolidated financial statements are consistent, in all material respects, with the audited consolidated financial statements based on our procedures, which were conducted in accordance with International Standard on Auditing (ISA) 810 (Revised), *Engagements to Report on Summary financial statements*.

PricewaterhouseCoopers SA



Marc Secretan

Tarik Bouchama

Licensed audit expert

Geneva, May 26, 2023

Enclosure:

- Summary consolidated financial statements (consolidated balance sheet, consolidated statement of changes in capital, consolidated statement of operations, consolidated cash flow statement, notes)

PricewaterhouseCoopers SA, avenue Giuseppe-Motta 50, case postale, 1211 Genève 2, Switzerland
Téléphone: +41 58 792 91 00, www.pwc.ch

MMV CONSOLIDATED STATEMENT OF FINANCIAL POSITION

ASSETS		Notes	31 Dec 2022 USD	31 Dec 2021 USD
Current assets				
	Cash and cash equivalents	3	26 726 317	35 376 192
	Donations receivable	7	4 047 024	4 954 481
	Accounts receivable	8	9 474 064	8 869 203
	Tax receivable		51 420	8 973
	Prepaids		735 167	644 143
	Prepaid portfolio commitments	10	2 665 158	6 696 570
Total current assets			**43 699 149**	**56 549 562**
Long-term assets				
	Long-term receivables	8	-	8 309 966
	Investment portfolio - Foundation Fund	5	22 146 748	15 592 585
	Rental deposits	17	156 814	249 399
	Fixed assets, net	4	228 194	126 143
Total long-term assets			**22 531 755**	**24 278 093**
TOTAL ASSETS			**66 230 904**	**80 827 655**
LIABILITIES, CAPITAL & RESERVES				
Current liabilities				
	Accrued portfolio commitments		9 058 747	7 619 406
	Other creditors		3 136 532	1 234 129
	Accrued expenses		2 758 855	2 657 891
	Short-term provisions	6	983 468	1 135 606
	Foreign exchange contracts	12	-	88 063
Total current liabilities			**15 937 603**	**12 735 095**
	Restricted operating funds		9 375 164	16 511 914
Total restricted funds			**9 375 164**	**16 511 914**
Unrestricted funds				
	Paid-in capital	1	4 000 000	4 000 000
	Foundation Fund	5	30 519 199	32 212 537
	Unrestricted operating funds		6 398 938	15 368 110
Total unrestricted funds			**40 918 137**	**51 580 647**
TOTAL LIABILITIES, CAPITAL & RESERVES			**66 230 904**	**80 827 655**

MMV CONSOLIDATED STATEMENT OF CHANGES IN CAPITAL

	Balance at 1 January 2021	Allocation of funds	Use of funds	Internal funds transfers	Gain/(loss) for the period	Balance at 31 December 2021	Allocation of funds	Use of funds	Gain/(loss) for the period	Balance at 31 December 2022
Restricted operating funds	16 936 831	27 948 646	(27 509 621)	(863 943)	439 025	16 511 914	25 860 371	(32 997 121)	(7 136 750)	9 375 164
TOTAL RESTRICTED OPERATING FUNDS	**16 936 831**	**27 948 646**	**(27 509 621)**	**(863 943)**	**439 025**	**16 511 914**	**25 860 371**	**(32 997 121)**	**(7 136 750)**	**9 375 164**
Paid-in capital	4 000 000	-	-	-	-	4 000 000	-	-	-	4 000 000
Foundation Fund	31 758 024	783 340	(328 828)	-	454 513	32 212 537	62 465	(1 755 803)	(1 693 338)	30 519 199
Unrestricted operating funds	10 781 336	56 806 778	(53 083 947)	863 943	3 722 831	15 368 110	48 741 063	(57 710 234)	(8 969 172)	6 398 938
TOTAL UNRESTRICTED FUNDS	**46 539 360**	**57 590 119**	**(53 412 775)**	**863 943**	**4 177 344**	**51 580 647**	**48 803 528**	**(59 466 038)**	**(10 662 510)**	**40 918 137**
TOTAL	**63 476 192**	**85 538 764**	**(80 922 395)**	**-**	**4 616 369**	**68 092 561**	**74 663 899**	**(92 463 159)**	**(17 799 260)**	**50 293 301**

The internal funds transfers between restricted and unrestricted funds in fiscal year 2021 concern allocation of 2020 expenditures (originally covered by an unrestricted grant) to a restricted grant based on donor request.

MMV CONSOLIDATED STATEMENT OF OPERATIONS FOR THE PERIOD ENDED

		Notes	31 Dec 2022 USD	31 Dec 2021 USD
REVENUE				
Donation revenue				
	Restricted donation revenue	7	25 880 371	27 948 646
	Unrestricted donation revenue	7	47 299 733	56 128 805
Total donations revenue		**7**	**73 180 104**	**84 077 451**
	Restricted revenue from partnerships		-	-
	Unrestricted revenue from partnerships		1 236 416	932 622
	Other unrestricted revenue	8	247 379	133 697
Total other revenue			**1 483 795**	**1 066 319**
TOTAL REVENUE		**8**	**74 663 899**	**85 143 770**
EXPENDITURE				
Portfolio expenditure				
	Discovery project expenditure	9	14 610 150	16 906 596
	Integrated Sciences project expenditure	9	7 019 667	10 183 875
	Development project expenditure	9	34 660 998	23 335 117
	Access & Product Management project expenditure	9	16 555 269	14 774 879
	Other portfolio expenditure		1 664 937	562 556
Total portfolio expenditure			**74 511 021**	**65 763 022**
Support of portfolio expenditure				
	Board meetings expenditure	15	247 870	57 426
	Corporate Affairs expenditure		4 498 808	7 013 255
	Administration & Finance expenditure		9 827 284	6 101 798
Total support of portfolio expenditure			**14 573 962**	**13 172 480**
	Other expenditure		9 510	-
Other expenses			**9 510**	**-**
TOTAL EXPENDITURE			**89 094 493**	**78 935 502**
RESULT FROM OPERATING ACTIVITIES			**(14 430 594)**	**6 208 268**
	Financial income	12	334 800	477 334
	Financial expenses	12	(3 703 466)	(2 069 232)
	Net financial result		(3 368 666)	(1 591 899)
	Of which are related to the Foundation Fund		*(1 755 803)*	*66 167*
NET SURPLUS PRIOR TO ALLOCATIONS TO RESTRICTED FUNDS			**(17 799 260)**	**4 616 369**
Transfer (to) donor restricted operating funds			**7 136 750**	**(439 025)**
NET SURPLUS/(DEFICIT) PRIOR TO ALLOCATIONS TO UNRESTRICTED FUNDS			**(10 662 510)**	**4 177 344**
ALLOCATIONS				
Transfer (to)/from unrestricted operating funds			**8 969 172**	**(3 722 831)**
Transfer (to)/from Foundation Fund			**1 693 338**	**(454 513)**

MMV CONSOLIDATED CASH FLOW STATEMENT AS OF 31 DECEMBER

	Notes	2022 USD	2021 USD
(LOSS)/SURPLUS FOR THE YEAR		**(17 799 260)**	**4 616 369**
Cash flow from operating activities			
Depreciation	4	100 016	81 924
(Increase)/decrease in donations receivable		907 457	(4 315 235)
(Increase)/decrease in accounts receivable	8	(604 862)	(7 994 883)
(Increase)/decrease in tax receivable		(42 447)	(1 522)
(Increase)/decrease in portfolio-related prepaid expenses	10	4 087 751	3 759 986
(Increase)/decrease in prepaid expenses		(89 843)	(87 960)
(Increase)/decrease in long-term receivable	8	8 309 966	7 921 621
Increase/(decrease) in accrued portfolio-related commitments		1 383 453	(6 109 426)
Increase/(decrease) in deferred revenue	7	-	(2 800 000)
Increase/(decrease) in other creditors		1 899 365	(1 090 309)
Increase/(decrease) in accrued expenses		32 907	(409 845)
Increase/(decrease) in provisions	6	(152 138)	(241 875)
Unrealized foreign currency (gain)/loss		(1 095 344)	236 688
Unrealized (gain)/loss on investment portfolio - Foundation Fund	12	-	(399 589)
(Increase)/decrease in investment portfolio - Foundation Fund	5	(6 554 163)	333 422
Cash flow resulting from operating activity		**(9 617 141)**	**(6 500 635)**
Cash flow from investment activity			
(Increase)/decrease in guarantees		92 585	8 583
(Increase)/decrease in foreign exchange contracts		(88 063)	29 112
(Increase)/decrease in fixed assets	4	-	-
CASH FLOW RESULTING FROM INVESTMENT ACTIVITY		**4 523**	**37 695**
NET INCREASE/(DECREASE) OF CASH AND CASH EQUIVALENTS		**(9 612 618)**	**(6 462 940)**
Cash & cash equivalents at beginning of year		**35 376 192**	**41 857 848**
Effect of exchange rate fluctuations on cash held		1 164 807	(18 716)
Cash & cash equivalents at end of year		**26 928 381**	**35 376 192**

1. GENERAL INFORMATION

a) Organization

MEDICINES FOR MALARIA VENTURE (MMV) is a Swiss foundation, established as a not-for-profit legal entity, registered in Geneva under statutes dated 15 November 1999. It is managed by a foundation council, a chief executive officer and seven senior managers.

The aim of MMV is to bring public and private sector partners together to fund, and provide managerial and logistical support for, the discovery and development of and access to new medicines for the treatment and prevention of malaria. The products should be affordable and appropriate for use by populations in developing countries. The MMV head office is located in Geneva.

Medicines for Malaria Venture is monitored by the Swiss Federal Supervisory Board for Foundations.

The consolidated financial statements for the year ended 31 December 2022 were approved for issue by the MMV Board on 26 April 2023.

b) Paid-in capital

The paid-in capital is fully subscribed at USD 4,000,000 as stipulated under the original legal statutes. Under normal circumstances, paid-in capital may be used during the year to meet cash flow shortfalls, but should be replenished before closing at year end. Paid-in capital, together with the residual operating funds, serves to maintain the viability of the organization until other funding sources can be found.

c) Operation funds

The accumulated restricted and unrestricted operation funds represent the excess of donor grants over expenditure since the inception of MMV. These funds are available to be utilized for future operations and project funding costs in accordance with the donors' requirements.

d) Foundation Fund

In 2019, the MMV Board of Directors approved the establishment of a directly controlled quasi-endowment structure (the Foundation Fund, described in Note 5 below) to invest the revenues from the GSK *Krintafel* (tafenoquine) partnership described in Note 8 below, as well as any possible and similar future extraordinary revenue.

2. ACCOUNTING PRINCIPLES APPLIED IN THE PREPARATION OF THE FINANCIAL STATEMENTS

a) Basis of preparation

The consolidated financial statements have been prepared in accordance with the articles of incorporation of MMV and the Swiss Generally Accepted Accounting Principles (Swiss GAAP FER/RPC), in particular FER 21.

The consolidated financial statements have been prepared on a historical cost basis, except where a standard requires a different measurement basis.

Fair value is the amount for which a financial asset, liability or instrument could be exchanged between knowledgeable and willing parties in an arm's length transaction.

The consolidated financial statements give a true and fair view of the organization's financial position, the result of operations and cash flows.

Certain prior-year amounts have been reclassified to conform with the current year's presentation.

b) Foreign currency translation

The consolidated financial statements are presented in US dollars (USD), since the majority of MMV's activities are conducted in this currency (group functional and presentation currency).

Transactions in foreign currencies are translated at the foreign exchange rate in effect on the date of the transaction. Monetary assets and liabilities denominated in foreign currencies are translated at the foreign exchange rate in effect on the date of the balance sheet. Foreign exchange differences arising on translation are recognized in the consolidated statement of operations. Non-monetary assets and liabilities that are measured at historical cost in a foreign currency are translated using the exchange rate on the date of the transaction.

The following exchange rates were used at year end:

2022

- CHF 1 = USD 1.08135
- EUR 1 = USD 1.06985
- GBP 1 = USD 1.20897
- AUD 1 = USD 0.68164

2021

- CHF 1 = USD 1.095356
- EUR 1 = USD 1.134199
- GBP 1 = USD 1.351043
- AUD 1 = USD 0.726113

2022

- USD 1 = CHF 0.924769
- USD 1 = EUR 0.934710
- USD 1 = GBP 0.827150
- USD 1 = AUD 1.467050

2021

- USD 1 = CHF 0.912945
- USD 1 = EUR 0.881679
- USD 1 = GBP 0.740169
- USD 1 = AUD 1.377196

c) Basis of consolidation

MMV has established a special purpose entity (SPE) for fundraising in North America (MMV North America, Inc.). MMV does not have any direct or indirect shareholdings in this entity. An SPE is consolidated if, based on an evaluation of the substance of its relationship with MMV and the SPE's risks and rewards, MMV concludes it controls the SPE. The SPE was established under such terms and conditions that it imposes strict limitations on the decision-making powers of the SPE's management, with the result that MMV receives the majority of the benefits related to the SPE's operations and net assets while being exposed to the majority of risks incident to the SPE's activities, and retaining the majority of the residual or ownership risks related to the SPE or its assets. MMV appoints the board members of the SPE.

On this basis and in accordance with Swiss GAAP FER 30, MMV North America, Inc. has been fully consolidated on a line-by-line basis into the consolidated financial statements since 2011.

Organizations consolidated in 2022 and 2021:

Country	United States of America
Name and domicile	MMV North America, Inc. Delaware
Functional currency	USD
% controlled by MMV	N/A
Direct/Indirect	N/A

All intra-group balances and transactions, and any unrealized gains and losses arising from intra-group transactions, are eliminated in preparing the consolidated financial statements.

d) Accounting estimates and judgements

The preparation of consolidated financial statements in conformity with Swiss GAAP FER requires management to make judgements, estimates and assumptions that affect the application of policies and reported amounts of assets and liabilities, income and expenditure. The estimates and associated assumptions are based on historical experience and various other factors that are believed to be reasonable under the circumstances, the results of which form the basis of the judgements made about carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates. If, in the future, such estimates and assumptions, which are based on management's best judgement on the date of the consolidated financial statements, deviate from the actual circumstances, the original estimates and assumptions will be modified as appropriate in the year in which the circumstances change.

Significant accounting judgements in applying MMV accounting policies pertain to:

Revenue recognition
MMV enters into complex grant contracts that contain numerous provisions related to performance, reporting and spending. These criteria are monitored by both the scientific programme and finance teams to assess progress according to grant milestones and objectives. The evaluation of progress requires judgement, as it is based on subjective evaluations and discussions with programme participants and sponsors. When MMV has submitted the report and associated expenditures, the associated donation is considered as a revenue of the year and as receivable as of year-end.

Research and development expenditure
MMV's research and development expenditure is generally not direct expenditure, but is in the form of grants and contracts with external parties who perform certain tasks at their request. These requests are formalized by contracts and agreements that outline the requested services and development effort. Progress against expectations is difficult to measure, and measurement criteria are generally not defined in grant agreements. We review research plans and activities regularly to adjust annual funding levels prospectively. Additionally, actual research and development timing and execution are often different from those of the original plans. These factors lead to subjectivity in the timing and recognition of research and development expenditure.

3. CASH AND CASH EQUIVALENTS

Cash and cash equivalents comprise cash balances and short-term deposits with maturity of 3 months after the closing date.

	2022 USD	2021 USD
Petty cash	14 339	7 065
Bank balances	22 220 622	27 831 094
Money market deposits	491 355	-
Time deposits	4 000 000	7 538 033
Total cash and cash equivalents	**26 726 317**	**35 376 192**

4. FIXED ASSETS

Fixed assets are stated at cost net of accumulated depreciation. Depreciation is charged to the consolidated statement of operations on a straight line basis over the estimated useful life of the assets. The following depreciation rates are used depending on the fixed asset category:

- office furniture 20%
- fixtures and installations 33%
- computers and equipment 33%

2022	Fixtures & installations USD	Office furniture USD	Computers & equipment USD	Total USD
Costs at 1 January	1 039 637	392 363	302 346	1 734 345
Additions	39 776	6 778	155 513	202 067
Disposals	-	-	-	-
At 31 December	**1 079 413**	**399 141**	**457 859**	**1 936 412**
Accumulated depreciation at 1 January	928 395	391 965	287 842	1 608 202
Charge for the year	69 104	736	30 176	100 016
Disposals	-	-	-	-
At 31 December	**997 499**	**392 701**	**318 018**	**1 708 218**
Net book value at 31 December	**81 914**	**6 440**	**139 841**	**228 194**

5. INVESTMENT PORTFOLIO – FOUNDATION FUND

In 2019, the MMV Board of Directors approved the establishment of a directly controlled quasi-endowment structure (the Foundation Fund) to invest the revenues from the GSK *Krintafel* (tafenoquine) partnership described in Note 8 below, as well as any possible and similar future extraordinary revenue. The long-term strategic objective of the Foundation Fund is to improve the conditions for MMV business sustainability, and/or to pursue possible future opportunities that are consistent with its humanitarian mission, but may be restricted by the current business model of the foundation. In 2019, the Board also approved the related investment policy and appointed an investment manager for the Foundation Fund, following a competitive selection process, and approved the transfer to the investment manager. The investment is classified as a long-term asset, as the intention of MMV is to keep these investments in the foreseeable future. Originally, this deposit was invested in a varied portfolio (shares, bonds and money market funds). This investment was liquidated on 2 November 2022 following the important hike in interest rates on the markets, and the subsidies were reinvested in fiduciary deposits.

The value of this investment portfolio as of 31 December was the following:

	2022 USD	2021 USD
Money market funds	-	356 019
MSCI World ESG index	-	2 132 820
Fixed interest portfolio (discretionary mandate)	-	13 103 746
Fiduciary deposits	22 146 748	-
Total	**22 146 748**	**15 592 585**

6. SHORT-TERM PROVISIONS

A provision is recognized in the balance sheet when MMV has a present legal or constructive obligation as a result of a past event, and it is probable that an outflow of economic benefits will be required to settle the obligation.

	Unused vacation provision USD	Total provisions USD
Balance at 1 January 2021	**1 377 481**	**1 377 481**
Use/release	(1 377 481)	(1 377 481)
Allocation for the year	1 135 606	1 135 606
Balance at 31 December 2021	**1 135 606**	**1 135 606**
Use/release	(1 135 606)	(1 135 606)
Allocation for the year	983 468	983 468
Balance at 31 December 2022	**983 468**	**983 468**

7. REVENUE AND DONATIONS RECEIVABLE

Revenue recognition

Unrestricted grants

An unrestricted grant is recognized as revenue in the consolidated statement of operations when the grant becomes receivable. Any other grant which has performance, timing or other conditions is recognized in the balance sheet as revenue once the foundation has complied with the stipulated conditions. If the conditions have not yet been fully complied with, then this grant component is reported as a contingent asset as disclosed in Note 14. At year end, if the unrestricted grants have not been fully used, they are presented as unrestricted operating funds in the balance sheet.

Restricted grants

When the donor wishes to see a donation allocated to a specific cause, the donation is considered to be a restricted grant. Restricted grants that have not been used at the end of the year are presented in the restricted operating funds in the balance sheet.

Deferred revenue

When a grant associated to a specific project is paid to MMV prior to the start of this project, this revenue is considered as deferred and will be recognized only during the fiscal year in which the project starts.

Contributions in kind

Occasionally, MMV receives donations in kind, primarily in the form of free use of goods or services or preferential discounts. These in-kind contributions are not stated in the statement of operations as this type of contribution is difficult to quantify.

Summary of donations received or committed during 2022:

	Cash received 2022	Revenue recognized during previous year	Donations receivable	Revenue deferred from previous year	Revenue deferred to following year	Unrealized foreign exchange (gain)/loss	Total revenue as per statement of operations
Bill & Melinda Gates Foundation (BMGF; Core grant)	36 020 000	-	-	-	-	-	36 020 000
UK Foreign, Commonwealth & Development Office (UK FCDO)	8 615 655	-	-	-	-	-	8 615 655
Swiss Agency for Development and Cooperation (SDC)	1 626 606	-	-	-	-	-	1 626 606
Irish Government Department of Foreign Affairs and Trade (Irish Aid)	1 056 959	-	-	-	-	-	1 056 959
Individual donors	514	-	-	-	-	-	514
Total unrestricted donations	**47 299 733**	**-**	**-**	**-**	**-**	**-**	**47 299 733**
Unitaid (Vivaction Plan grant)	2 290 977	-	-	-	-	-	2 290 977
Unitaid (Supply grant)	776 752	-	-	-	-	-	776 752
Bill & Melinda Gates Foundation (BMGF; Antimalaria drugs novel formulation evaluation grant)	239 775	-	-	-	-	-	239 775
European and Developing Countries Clinical Trials Partnership (EDCTP; PAMAfrica grant)	1 067 648	(1 145 690)	3 453 555	-	-	78 042	3 453 555
European and Developing Countries Clinical Trials Partnership (EDCTP; Sindofo grant)	-	-	94 642	-	-	-	94 642
UK Foreign, Commonwealth & Development Office (UK FCDO; Pyramax Phase III)	12 812 290	-	-	-	-	-	12 812 290
Ministry of Foreign Affairs of the Netherlands – Directorate-General for International Cooperation (DGIS)	148 054	-	-	-	-	-	148 054
German Federal Ministry of Education and Research (BMBF)	2 664 289	-	-	-	-	-	2 664 289
Global Health Innovative Technology Fund (GHIT)	544 630	-	-	-	-	-	544 630
United States Agency for International Development (USAID)	4 248 277	(3 560 098)	-	-	-	-	688 179
Swiss Agency for Development and Cooperation (SDC; Pregnancy registry)	273 471	-	-	-	-	-	273 471
PATH (VivAccess grant)	641 529	(248 692)	498 827	-	-	-	891 664
European and Developing Countries Clinical Trials Partnership (EDCTP; SMC grant)	12 175	-	-	-	-	-	12 175
The RIGHT Foundation	43 636	-	-	-	-	-	43 636
Newcrest Mining	176 282	-	-	-	-	-	176 282
Korea International Cooperation Agency Global Disease Eradication Fund (KOICA-GDEF)	750 000	-	-	-	-	-	750 000
Total restricted donations	**26 689 786**	**(4 954 481)**	**4 047 024**	**-**	**-**	**78 042**	**25 860 371**
TOTAL DONATIONS	**74 009 520**	**(4 954 481)**	**4 047 024**	**-**	**-**	**78 042**	**73 180 104**

Of the total donations recognized in the consolidated statement of operations, USD 514 were received through MMV North America, Inc.

8. ACCOUNTS RECEIVABLE & TOTAL OTHER REVENUE

Revenues from partnerships

GSK

MMV has been collaborating with pharmaceutical partner GSK on the co-development of *Krintafel* (tafenoquine) since 2008. On 20 July 2018, the United States Food and Drug Administration (FDA) granted regulatory approval, under priority review, of single-dose *Krintafel* for the radical cure (prevention of relapse) of *Plasmodium vivax* malaria in patients aged 16 years and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.

Under US law, following approval by the FDA of a treatment for a neglected or rare paediatric disease, the developer may receive a Priority Review Voucher (PRV) that entitles the recipient to a priority review by the FDA for a different drug. This voucher can either be used by the developer or sold to a third party. Upon approval of *Krintafel*, the FDA granted a PRV to GSK. In October 2018, GSK used this PRV for a new drug application to the FDA by ViiV Healthcare, an affiliate of GSK.

GSK and MMV have both contributed to the cost of development of *Krintafel* during the period 2008–2022. Under the terms of the co-development agreement, as GSK has used the PRV, MMV is entitled to the refund of its share of the co-development costs from GSK. GSK agreed to reimburse 50% of MMV's cumulative costs, of which USD 62,465 in 2022 (2021: USD 388,345). The last payment, in the amount of USD 9,357,290, is due at the end of July 2023.

The *Krintafel* trademark is owned by or licensed to the GSK group of companies.

In 2022 and 2021, MMV also recognized revenues of USD 984,959 and USD 385,900 respectively from GSK in relation to the co-development of the project GSK701 (or MMV367).

Others

In 2022, in addition to the above-mentioned revenues from GSK, MMV booked the following revenue from partnerships: USD 189,092 (2021: USD 91,500) from Janssen in relation to the co-development of P218 and IM-atovaquone.

MMV plans to use the above-mentioned revenues from partnerships in support of its charitable mission.

	2022	2021
	USD	USD
GSK receivables	9 357 290	8 695 866
Other receivables	116 775	173 337
OTHER REVENUE	**9 474 064**	**8 869 203**

Other unrestricted revenue includes:

	2022	2021
	USD	USD
Tax at source commission	32 977	37 899
Honorarium	7 094	16 044
Reimbursement from grantees	52 626	70 062
Intellectual property cost sharing	126 151	-
Carbon tax reimbursement	17 872	-
Other	10 659	9 692
OTHER REVENUE	**247 379**	**133 697**

9. PORTFOLIO EXPENDITURES

Expenditure and grants allocated for research and development activities undertaken with the prospect of gaining new scientific or technical knowledge and understanding are recorded on the basis of contracts with grantees. In the event that a portion of a grant is unpaid at year end, it is included under current liabilities. Expenses paid before year-end for the following period are recorded as prepaid portfolio commitments.

Regulatory and other uncertainties inherent in the development of new products in this sector preclude MMV from capitalizing on development costs.

Project-related variable expenditure includes all legal advice/services for contract negotiations (IPR), organization and travel for project meetings/reviews, and MMV scientific personnel compensation. Expenditure for this MMV support totalled USD 17,547,894 in 2022 and USD 19,951,735 in 2021.

Project reimbursements receivable

These refer to unused balances of project grants previously committed, which are returned to MMV by the project partners as stipulated in the individual contractual agreements on termination or reorganization of R&D projects.

10. PREPAID PORTFOLIO COMMITMENTS

Prepaid portfolio commitments are payments made to grantees or suppliers for goods or services which will only be delivered during the next fiscal years.

As of 31 December 2022, there are the following major categories of prepayments in relation to MMV portfolio projects:

	2022 USD	2021 USD
Chloroquine prepayment	-	2 575 125
EDCTP PAMAfrica prepayments to subgrantees	91 230	2 850 763
VivAction project prepayment	1 029 108	630 586
KOICA-GDEF SMC project prepayment	43 085	-
Discovery related	155 016	146 755
Translational related	280 941	130 080
Product Development related	1 044 528	206 249
Access and Product Management related	21 250	101 810
Other prepaid portfolio commitments	-	55 202
Total prepaid portfolio commitments	**2 665 158**	**6 696 570**

11. PERSONNEL EXPENSES

As of 31 December 2022, there were 88 full-time equivalent employees with a permanent contract (2021: 71.5), as well as 13.2 full-time equivalent temporary staff members with a fixed-term contract ranging between 1 and 3 years (2021: 31.8).

The pension plan covers all employees for death and disability benefits. Cover for retirement benefits begins in the year following each employee's 24th birthday. The retirement pension is based on the amount of the retirement credits, the interest rate to be credited and the conversion rate to be applied at retirement age. Risk benefits are related to pensionable salary.

Occupational benefits are provided by a collective foundation, Profond, according to a defined contribution benefit plan: investment yield has no impact on premiums; the employer does not guarantee the benefit amount. The plan is funded by the contributions of MMV and the employees.

	2022	2021
Capital ratio	104.4%	116.1%
Amount (receivable)/payable to pension fund	(1 110)	4 596

12. FINANCIAL RESULT

Financial income	2022 USD	2021 USD
Unrealized gain on portfolio investments	-	399 589
Bank interest	324 507	11 757
Exchange gain from CHF	-	-
Exchange gain from EUR	-	-
Exchange gain from AUD	10 294	-
Exchange gain from GBP	-	65 988
Total	**334 800**	**477 334**

Financial expenses	2022 USD	2021 USD
Loss on foreign exchange forward contracts	-	88 063
Bank charges	43 283	62 908
Exchange loss from GBP	700 000	-
Exchange loss from CHF	666 519	1 304 538
Exchange loss from EUR	301 184	327 612
Exchange loss from AUD		38 377
Exchange loss from JPY	29 163	8 528
Exchange loss from KRW	3 545	-
Unrealized loss on money market deposit	1 917	239 207
Realized loss on portfolio investment	1 957 856	-
Total	**3 703 467**	**2 069 233**

In order to minimize the potential adverse effect of foreign exchange fluctuations, MMV liquidity is regularly deposited in bank accounts denominated in foreign currencies in proportion to the breakdown of total expenditure by currency (natural hedging). At the end of fiscal year 2021, MMV had some foreign exchange forwards opened which took place in 2022. There were no foreign exchange forwards opened at the end of fiscal year 2022.

	2022			2021		
	Positive value	Negative value	Purpose	Positive value	Negative value	Purpose
Foreign exchange forward contracts	-	-	N/A	-	(88 063)	Hedging
Total financial instruments	**-**	**-**	**-**	**-**	**(88 063)**	**-**

13. LEASES

Non-cancellable operating lease rentals are payable as follows:

	2022 USD	2021 USD
Less than 1 year	580 068	733 044
Between 1 and 5 years	2 320 272	76 359
More than 5 years	386 712	-
Total	**3 287 052**	**809 403**

MMV has several operating leases. These leases generally run for a period of 6 years, with an option to renew the lease after that date. During the year ending 31 December 2022, USD 951,769 was recognized as an expense in the consolidated statement of operations in respect of operating leases (2021: USD 1,012,399).

14. CONTINGENT ASSETS

As per current contractual agreements, and depending on satisfactory reporting to donors, contingent assets related to donations are as follows:

	2022 USD	2021 USD
Less than 1 year	64 787 465	78 827 294
Between 1 and 5 years	34 886 347	90 055 460
Total	**99 673 812**	**168 882 754**

15. RELATED PARTIES

MMV has related-party relationships with its Board members, executive officers and MMV North America, Inc.

Board members serve on a voluntary basis and receive no remuneration. They are compensated for travel and accommodation for participation in board meetings and receive a *per diem* allowance to cover incidental expenses during these events.

	2022 USD	2021 USD
Board members & meetings	247 870	57 426

There were no loans to directors or executive officers for the years ending 31 December 2022 and 31 December 2021.

Some donors are represented in the foundation council. MMV management considers that their presence in the foundation council does not affect the nature of the relationship between MMV and these donors. These donors are therefore not considered related parties. Therefore, all MMV donors have been considered as third parties.

MMV performs an annual evaluation to identify potential related parties, which is done at senior management level and with Board members. The nature and volume of transactions with the identified related parties are summarized in the following table.

	2022		2021	
	Transactions during the year	**Receivable/(payable) at year end**	**Transactions during the year**	**Receivable/(payable) at year end**
Strategic partnership	57 121	**(20 654)**	270 577	**-**
Schooling fees	-	-	84 373	**-**
Total	**57 121**	**(20 654)**	**354 950**	**-**

16. RISK MANAGEMENT

The foundation council has overall responsibility for organizing and supervising risk management. The audit committee monitors management's approach to risk management in compliance with the organization's principles and procedures and verifies that risks are managed appropriately in light of the current risks faced by the organization. Based on a risk identification carried out periodically, MMV's essential risks are assessed with respect to likelihood and impact and documented in a risk analysis report. Management is responsible for monitoring and supervising the substantial risks.

For risks related to accounting principles and financial reporting, an annual risk analysis is carried out. Controls in line with the internal control system have been defined, and resulting measures have been implemented in order to minimize risks related to accounting principles and financial reporting.

17. RENTAL DEPOSITS

Rental deposits concern office rental only and are recoverable on vacating the premises subject to the prevailing contracts.

18. CAPITAL COMMITMENTS AND CONTINGENCIES

MMV encounters certain risks and uncertainties in conducting its affairs. These risks and uncertainties have financial statement implications. In all instances, these have been considered in the consolidated financial statements, despite the fact that the outcomes of these uncertainties cannot be predicted with absolute certainty. Management has concluded that provisions for these risks are appropriate, and that any adverse resolution of these uncertainties will not have a material impact on the financial position or results of the foundation.

19. AUDITORS

PWC SA, Geneva, have been appointed as MMV's statutory auditors since the fiscal year 2022, following a competitive bid in 2022. The current lead auditor, Marc Secretan, has acted in this capacity since 2022.

During fiscal year 2022, MMV incurred the following expenses:

- → Statutory audits: USD 85,758 (2021: USD 67,546)
- → Special audit reports to donors: USD 149,898 (2021: USD 75,996) - not all of these audit reports are performed by MMV statutory auditors.
- → Other services: nil (2021: USD 36,040)

20. SUBSEQUENT EVENTS

No events have occurred between the balance sheet date and the date of this report that require adjustment to, or disclosure in, these financial statements.

9 Behind the scenes 2022

MMV Board

First line left to right

Mr Alan Court[1]
Chair of MMV Board; Senior Adviser to the WHO Ambassador for Global Strategy, USA; former Director of the UNICEF Programme Division in New York; former Director of the UNICEF Supply Division in Copenhagen

Dr David Reddy[1]
CEO, MMV, Switzerland

Dr Aileen Allsop
Former Vice-President and Head of the Infection Therapy area and Vice-President Science Policy, both with AstraZeneca; former Council member and Review Panel chair with the Royal Society of Biology in the UK and former Trustee of the Primary Science Teaching Trust; Chair of the UK government review of Science and Society; member of Expert Scientific Advisory Committee for over 8 years and former chair of Emerging Technology Reviews for MMV

Ms Jennifer Cain Birkmose
Senior Principal, IQVIA; Co-founder and CEO of VivaValet; former Head of Access, Region Europe, Roche; former Vice-President, Global Head of Patient Access Swedish Orphan Biovitrum (SOBA); *Institut Européen d'Administration des Affaires* (INSEAD) lecturer; former Project Officer, European Observatory on Health Systems and Policies, WHO Regional Office for Europe

Prof. Lucille H Blumberg *
Former Deputy Director, National Institute for Communicable Diseases, National Health Laboratory Service; founding Head of Division of Public Health Surveillance and Response; Medical Consultant to the Centre for Emerging, Zoonotic and Parasitic Diseases; Consultant in Infectious Diseases at 'Right to Care', South Africa

Dr David Brandling-Bennett
Former Senior Advisor, Malaria, Bill & Melinda Gates Foundation, USA

Prof. Sir Michael Ferguson
Regius Professor of Life Sciences and Associate Dean for Research Strategy, University of Dundee, Scotland, UK

Ms Yuli Ismartono
Co-founder and Managing Editor of the weekly online *AsiaViews* portal; formerly with the weekly current affairs *TEMPO* magazine; Board member of Nature Resources Governance Institute (NRGI), the Coral Triangle Center (CTC), the Prestasi Junior Indonesia (PJI) foundation and the Alternative Association of Southeast Asian Nations (ALTSEAN), Indonesia

Second line left to right

Mr Gabriel Jaramillo[2]
Former General Manager of the Global Fund to Fight AIDS, Tuberculosis and Malaria, Switzerland

Dr Dominique Limet[1]
Former CEO, ViiV Healthcare, London, UK

Ms Elizabeth J Linder
Founder & CEO, Chief Diplomatic Officer, Brooch Associates, UK; Co-Chair, St. James's Roundtable, Chatham House; Chair, Kinross House Meetings; Member, Ditchley Park Programme Committee; former Facebook Spokesperson and Politics & Government Specialist (California and EMEA region); former Google & YouTube Global Communications & Public Policy (California), USA

Mr Gustavo Murgel *
Former senior executive for financial groups, including ING, Santander and Itaú, in Brazilian and international markets; currently serves on several executive boards for education-related NGOs in Brazil

Dr Robert Newman
Director, Aspen Management Partnership for Health, The Aspen Institute, USA; former Vice-President, Global Head, TB Programs, Johnson & Johnson; former Director of Global Malaria Programme, World Health Organization

Dr Ngashi Ngongo *
Executive Director, International Centre for Health Systems Strengthening (ICHESS), USA; former Team Leader UNICEF Global Malaria Program, New York; former Team Leader, UNICEF Ebola Health Response, Liberia and DRC; Principal Advisor, Child Survival and Development for West and Central Africa; Board Member, PROSAMI, Virginia; Lecturer, University of Lubumbashi, DRC

Ms Joy Phumaphi
Co-Chair of the Independent Expert Review Group for Every Woman Every Child; Chair of the Global Leaders Council for Reproductive Health; Executive Secretary of African Leaders Malaria Alliance, USA

Dr Wendy R Sanhai
Deloitte Consulting LLP (Federal Strategy and Operations); Associate Professor (adj), Duke University, School of Medicine; former Senior Scientific Advisor, Office of the Commissioner, US Food and Drug Administration (FDA); former Senior Director, Global Regulatory Affairs, GSK, USA

Dr Elisabeth Svanberg
former Vice-President of Established Products, Johnson & Johnson, USA; former Vice-President of Medical Affairs Intercontinental Region, Bristol-Myers Squibb, USA; Board member of Galapagos, Belgium; Board member of Swedish Orphan Biovitrum (SOBI); based in Geneva, Switzerland

* New Board member named in 2022

1. Member of the Audit & Finance Committee
2. Chair of the Audit & Finance Committee

MMV North America Inc. Board

Ms Sylvie Fonteilles-Drabek
Chair of MMV North America Board; General Counsel and Executive Vice-President, MMV, Switzerland

Mr Alan Court
Chair of MMV Board of Directors; Senior Adviser to the WHO Ambassador for Global Strategy, USA; former Director of the UNICEF Programme Division in New York; former Director of the UNICEF Supply Division in Copenhagen

Ms Andrea Lucard
Executive Vice-President, Corporate Affairs, MMV, Switzerland

Dr David Reddy
CEO, MMV, Switzerland

Dr Dennis Schmatz
Former Vice-President, Head of Tsukuba Research Institute, Merck-Banyu Research Laboratories, Japan; now based in USA

Expert Scientific Advisory Committee (ESAC)

Dr Lynn Marks
Co-chair MMV ESAC (Development); Former Senior Vice-President GSK R&D, USA

Dr Michael Witty
Co-Chair MMV ESAC (Discovery); former Vice-President Pfizer R&D; Drug Discovery Consultant, UK

Dr Jane Achan Senior Research Advisor, Malaria Consortium, UK/Uganda

Dr Nick Cammack
Head, Priority Area, Wellcome Trust, UK

Sir Simon Campbell Former Senior Vice-President for Worldwide Discovery and Medicinals R&D Europe, Pfizer, UK

Dr Robert Clay
Former Vice-President of Global Regulatory Affairs, AstraZeneca; Consultant, Regulatory Science, Drug Development and Business Strategy, UK

Dr Anne Cooper
Director, AEC Scientific Consulting, UK

Prof. Brian Cox Emeritus Professor of Pharmaceutical Chemistry, University of Sussex, School of Life Sciences, UK

Ms Delese Mimi Darko
Chief Executive Officer, Food and Drugs Authority, Ghana

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