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.

Malaria
- takes a child’s life every 2 minutes
- kills an estimated 409,000 people each year
- can kill within 24 hours of symptom onset
- is both a cause and consequence of poverty

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.

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.

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Staying true to our malaria mission in a time of global uncertainty

Message from the Chairman and CEO

It is 2021, and the world is still striving to emerge from the long, dark shadow of SARS-CoV-2, searching, as American poet Amanda Gorman¹ says to find “find light in this never-ending shade”.

In 2020, Medicines for Malaria Venture (MMV) joined that search wholeheartedly. While keeping a strong focus on our core mission to discover, develop and deliver effective antimalarials for underserved populations, we expanded our work to include efforts to respond to COVID-19 in areas where we could make a unique contribution.

All hands on deck: contributing to the global pandemic response

Six years after the launch of the Global Health Security Agenda² the world was nonetheless caught off guard by the rapid spread of SARS-CoV-2. At MMV, we contributed our core R&D and access strengths to the global effort (pp. 10-11). In response to supply chain issues, raised initially by our drug manufacturing partners, and given the intense interest in existing antimalarials as potential treatments for COVID-19, we joined forces with the World Health Organization (WHO), partners and major suppliers, advising on linkages with industry and coordinating efforts to monitor the supply chain and safeguard access to critical malaria commodities.

In addition, we swiftly sent antimalarial compound collections with potential SARS-CoV-2 activity to testing centres and distributed our open access compound collections to researchers free of charge. Since initiating the distribution of these compound collections, 125 copies of the Pandemic Response Box and 50 of the newly launched COVID Box, have been distributed, and shipments continue. We also supported clinical studies to repurpose existing medicines, including launching a Phase II clinical study in South Africa (p. 11).

Prevention

Young children urgently need protection from malaria, as they are the hardest hit by this disease. Despite challenges brought on by the COVID-19 pandemic, we helped ensure that the seasonal malaria chemoprevention (SMC) (pp. 25-28) programme for young children stayed on track in 13 implementing countries, helping protect 30 million children.

COVID-related disruptions did not unduly delay the distribution of this lifesaving intervention thanks to the exceptional effort of healthcare workers, government officials and political leadership. It is heartening that this success has also encouraged the expansion of SMC into new areas in the Sahel – in one example, three times as many children were reached in Nigeria in 2020 than in 2019.

Management of severe malaria

In Malawi, a study led by MMV on artesunate rectal capsules (ARC) generated important evidence demonstrating the role of toolkits and a formalized referral slip protocol in increasing the likelihood of a positive treatment outcome for patients. ARC is a pre-referral, lifesaving intervention for the very young with severe malaria. It halts the progression of the disease, giving time for patients to be transported to a health facility where they can be treated with injectable artesunate. Another exciting development on the horizon is the novel injectable compound KAE609 (cipargamin), which is in Phase II trials in collaboration with Novartis as an alternative

¹ Amanda Gorman was America’s first National Youth Poet Laureate (2017) – this phrase is from her poem The Hill We Climb that she read out at President Biden’s inauguration on 20 January 2021.

² www.ghsagenda.org: a group of 70 countries and public and private sector organizations whose vision “is to achieve a world safe and secure from infectious disease threats” by improving country capacity and leadership to prevent, detect and effectively respond to infectious diseases.
treatment for severe malaria. This is particularly important in view of the recent identification of partial artemisinin resistance in Rwanda and several other African countries.

Radical cure
Our work to introduce and support the integration of tafenoquine (TQ) into P. vivax clinical management bore fruit – the first country in South East Asia to grant TQ marketing authorization approval, Thailand, also marked the first step to open up access to TQ across the Asia-Pacific, where P. vivax is becoming the more dominant malaria species. TQ was also submitted for approval in Myanmar, Vietnam, Philippines and Peru, while the paediatric dossier was submitted to the Australian Therapeutic Goods Administration (TGA).

Preparing for the next big global health crisis — Antimicrobial Resistance (AMR)
In 2020, reports of de novo artemisinin resistance in Rwanda were an urgent reminder of the need to step up surveillance for antimalarial drug resistance indicators both in the lab and the field. Although the artemisinin-based combination therapies (ACTs) AL and DHA–PQP continued to show cure rates of > 95%, it is likely only a matter of time before ACTs, too, begin to lose their effectiveness as a treatment for uncomplicated P. falciparum malaria in the endemic regions of sub-Saharan Africa.

As with all forms of antimicrobial resistance, three things are required to prevent its rapid spread: to protect existing treatments, monitor their efficacy, and accelerate the development of next-generation medicines (pp. 12-17).

In the race against resistance, MMV’s strategy is to work with partners to develop simpler, effective, high-quality, patient-friendly medicines for adults and children that improve treatment adherence. Ganaplacide–lumefantrine is a leading combination currently in Phase IIb with Novartis for uncomplicated malaria. Behind that we have a healthy pipeline of compounds being assessed in various combinations, including for chemoprevention, through our Malaria Drug Development Catalyst. The Catalyst provides a legal and scientific platform to promote effective collaboration between industry partners, to facilitate decision-making on the most appropriate compounds for combination therapies and to accelerate the development of new drug combinations.

When it comes to finding ways to accelerate the discovery of new compounds, MMV continues to be a pioneer. We have established discovery networks and assay platforms to expedite identification of the most promising compounds against malaria as well as drug-resistant strains of other pathogens. In 2020, we developed two new tools to support the selection and dosage of compounds for combination therapies (pp. 38-39): the ACPR28 mathematical model and a mathematical application, MMVSola, named after the late Suresh Solapure, an MMV partner and an early champion of using pharmacokinetic/pharmacodynamic modelling to predict dosage, who tragically passed away in 2020.

Redressing the fatal gender imbalance
This year, MMV shone a stronger light on the unmet needs of pregnant women. Each year, malaria causes over 10,000 maternal and 200,000 newborn deaths. MMV and partners have committed to exploring innovative R&D strategies to identify new medicines that serve the needs of this population.

As a first step, we designed a far-sighted strategy, ‘MMBa’, (p. 22) to generate more data on the impact of existing antimalarials on pregnant women, enrich the R&D pipeline with appropriate new drugs deemed low risk to mother and foetus, and advocate for earlier inclusion of pregnant and breastfeeding women in clinical trials than currently practiced. In 2020, this led to the launch of MMV and LSTM’s pregnancy registry (pp. 22-23) in three African countries to capture safety and exposure data on the real-life use of ACTs during all stages of pregnancy. Its aim is to support policy change through robust data, thereby improving treatment options for pregnant women suffering from malaria.

Prepared for an uncertain future...

2020 was an unprecedented year for global health. The MMV team, our Board, donors, indispensable partners and stakeholders demonstrated exemplary agility and adaptability at every level. We are grateful and inspired by their commitment and support.

As the SARS-CoV-2 virus continues to disrupt the economic, political, social and health systems of the world, the critical value of scientific research to global health security, and the preparedness, resilience and flexibility of the partnership model have been recognized. Both will continue to be needed.

Since 2009, the 13 malaria therapies that we have brought forward, together with our partners, have saved an estimated 2.7 million precious lives. While we remain resolute in our commitment to a malaria-free world, we also commit to sharing our expertise and experience when global health crises occur in the future. In this hyper-connected 21st century, we will work with partners to pursue the end of malaria and help ensure preparedness for the next impending global health crisis, for it will affect us all.
The WHO Global Technical Strategy for Malaria 2016–2030 provides a framework and key targets for all malaria-endemic countries working towards control and elimination. Reaching these targets will contribute to achieving Sustainable Development Goal 3 ‘Ensure healthy lives and promote well-being for all at all ages’. In 2020, MMV and key partners made important strides towards meeting these targets by:

### Ensuring universal access to malaria prevention and treatment
- 2.7 million lives estimated to have been saved to date through MMV-supported medicines
- 536 million courses of SPAQ delivered since its launch in 2014 for seasonal malaria, protecting over 30 million children in 2020. Six new combinations of licensed molecules have been evaluated and ranked as alternatives to SPAQ for SMC.
- 430 million paediatric treatment courses of Coartem® Dispersible (artemether–lumefantrine) distributed to over 50 countries since 2009, saving an estimated 926,000 lives
- 7.9 million Eurartesim® (dihydroartemisinin–piperine) treatments distributed since approval with registration in 24 countries
- 1.73 million patients treated with Pyramax® (pyronaridine–artesunate); tablets approved in 29 countries and granules in 19 countries
- Three new regulatory approvals for Krintafel/Kozenis (tafenoquine), including in Thailand, the first South East Asian country to grant marketing authorization approval
- 209 million vials of injectable artesunate delivered since launch, estimated to have saved 1.36 million additional lives compared to treatment with injectable quinine
- 3.8 million doses of artesunate rectal capsules delivered to date with registration in 17 countries, saving an estimated 443,000 lives
- 4.4 million Coartem® (artemether–lumefantrine) treatment courses of SPAQ distributed to over 50 countries since 2009, saving an estimated 926,000 lives

### Strengthening the enabling environment
- European and Developing Countries Clinical Trials Partnership (EDCTP)-funded PAMAFrika training to strengthen research capacity at trial sites and research capability of next-generation African scientists

### Harnessing innovation and expanding research
- 11 compounds in preclinical and clinical development including 10 with novel biological pathways compared with existing ACTs
- Four new late leads approved in 2020
- Two compounds active against Plasmodium cynomolgi liver stages identified through screening
- Two potent compounds against P. vivax liver stages identified through screening

### Accelerating efforts towards elimination and attainment of malaria-free status
- Marketing authorization application of tafenoquine paediatric submitted to Australian Therapeutic Goods Administration
- Investigation of next-generation combinations for uncomplicated malaria through the Malaria Drug Development Catalyst
- Three new regulatory approvals for Krintafel/Kozenis (tafenoquine), including in Thailand, the first South East Asian country to grant marketing authorization approval
- A new pregnancy registry has been established to monitor the impact of different antimalarials on mother and child, inform policymakers and strengthen healthcare systems

### Ensuring universal access to malaria prevention and treatment
- Over 100 Pandemic Response Boxes shipped in 2019–2020 to facilitate drug discovery in other disease areas
- Implementing measures to support supply chains for chloroquine to treat malaria in P. vivax-endemic countries and mitigate stockouts
- Over 50 COVID Boxes shipped to enable standardization of testing results across various laboratories
- Promoted healthcare awareness in rural communities adapting existing malaria educational initiatives, e.g. training community health volunteers on danger signs and protocols around COVID-19

### Working beyond our scope: Response to the COVID-19 pandemic
- Over 100 Pandemic Response Boxes shipped in 2019–2020 to facilitate drug discovery in other disease areas
- Over 50 COVID Boxes shipped to enable standardization of testing results across various laboratories
- Promoted healthcare awareness in rural communities adapting existing malaria educational initiatives, e.g. training community health volunteers on danger signs and protocols around COVID-19
- Working with partners on COVID-19 clinical studies, including the ReACT and ANTICOV studies
- Over 50 COVID Boxes shipped to enable standardization of testing results across various laboratories
- Promoted healthcare awareness in rural communities adapting existing malaria educational initiatives, e.g. training community health volunteers on danger signs and protocols around COVID-19
- Working with partners on COVID-19 clinical studies, including the ReACT and ANTICOV studies

1. WHO Global Technical Strategy for Malaria 2016–2030
3. Tafenoquine is marketed as Krintafel in the USA and as Kozenis in the EU
4. Over 100 Pandemic Response Boxes shipped in 2019–2020 to facilitate drug discovery in other disease areas

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**Milestones 2020**

1. Staying true to our malaria mission in a time of global uncertainty
The dual challenge of COVID-19 and malaria

Message from Dr Soumya Swaminathan, Chief Scientist, WHO

In 2020, global health weathered a turbulent year. Once again, a new, lethal virus caused disruption worldwide and brought global health security back into the limelight. From the moment the World Health Organization (WHO) classified SARS-CoV-2 as a Public Health Emergency of International Concern, the virus began to stress test the resilience of all health systems. Hundreds of compounds, including antimalarials, continue to be investigated as potential treatment and prevention for this disease, some with initial success. Crucially, an increasing number of SARS-CoV-2 vaccines are now being deployed to millions of people across the world.

Throughout 2020 and into 2021, health professionals struggled with the excessive load of COVID-19 patients, and of people with untreated emergencies and non-infectious diseases like cancer, heart disease and diabetes. We have had to learn and continue to relearn how to manage the impact of the disease not only on people, but also on societies and economies.

Malaria was not forgotten

Throughout this upheaval, malaria and other deadly diseases remained high on the WHO’s list of priorities. As caretakers of the world’s health, the WHO lost no time in sending out both an immediate call for countries to keep a close watch on their malaria control programmes and guidelines to jointly address malaria and the COVID-19 pandemic. The concern was that in a worst-case scenario, a 75% simultaneous reduction in long-lasting insecticidal net distribution campaigns and antimalarial drug coverage could double malaria deaths in 2020 compared to 2019, and possibly lead to greater increases in the years ahead. Countries were thus urged to prioritize case-management interventions, while taking care to protect their healthcare workforce and patients from COVID-19.

Gains in malaria control in jeopardy

The World Malaria Report issued in November 2020 outlined the significant gains made in malaria control since 2000 – 1.5 billion cases and 7.6 million malaria deaths have been averted, and malaria deaths in Africa have been reduced by 44%. However, this unprecedented progress has since tapered off (see Figure 1). The major concerns highlighted were the deceleration of progress and insufficient support to R&D, as well as access to proven tools, due to a recent shortfall in both international and domestic funding (in 2019, total funding reached $3 billion vs the targeted $5.6 billion). With the additional burden of COVID-19, the report’s authors predict that the global 2020 target for reducing malaria cases and mortality will be missed by 37% and 22% respectively, killing more people than COVID-19 in sub-Saharan Africa in 2020. To avoid a reversal of two decades of progress, and avert this looming public health disaster it is imperative to maintain malaria as an integrated priority alongside the response to COVID-19.
Invaluable partnerships

In March 2020, the need to mitigate the negative impact of COVID-19 and build a coordinated, integrated response to both COVID-19 and malaria, led the WHO Global Malaria Programme to quickly establish a cross-partner effort. Seven workstreams comprising malaria specialists from around 20 organizations met regularly to share updates on a variety of issues. Medicines for Malaria Venture (MMV), a non-state actor in official relations with the WHO since 2018, joined three of these workstreams: malaria supply-chain, clinical trials with antimalarials (and product development,) and communications, with experts providing invaluable advice and input. This partnership was invaluable to Member States as they sought to maintain essential health services and care for their people.

With the help of existing surveillance systems and networks of community health workers (CHWs), trained by partners in integrated community case management and malaria treatment and control procedures, countries swiftly mobilized resources to tackle the dual challenges of the COVID-19 pandemic and endemic malaria. Experiences in Mozambique, Uganda and Rwanda bear testament to this. In Zambia, CHWs trained for the MMV-supported Mobilizing Access to Maternal Health Services in Zambia (MAMaZ) (pp. 30-31) project, to improve the treatment and case management of severe malaria, and received further training in COVID-19 health and safety procedures. They were then able to disseminate vital information on safety measures to prevent the spread of the pandemic. Meanwhile, MMV’s assiduous support of the implementation of seasonal malaria chemoprevention campaigns in the Sahel helped protect 12 million children in Nigeria, three times more than in 2019.

A new era of partnerships has begun. Our hyper-connected world worked together in 2020 in a time of urgent global need, with partners old and new committed to ensuring access to healthcare interventions for as many people as possible. At the WHO, we recognize that the next pandemic could be caused by another virus or antimicrobial drug resistance and we must be fully prepared to meet it head on with new tools and interventions. It can only be tackled holistically, using a coordinated, multisectoral One Health\(^8\) approach, in which global health programmes, policies, legislation and research are designed and implemented by multiple sectors. The WHO relies on strong partnerships, such as the one with MMV, as the only way forward if we are to successfully steer global health through future turbulent pandemic events, achieve universal healthcare, and make the world malaria free.

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\(^6\) Source: WHO estimates.
\(^7\) Jointly addressing endemic malaria and pandemic COVID-19: https://www.who.int/malaria/areas/epidemics_emergencies/covid-19/who-gmp-response-covid-19.pdf?ua=1

\(^8\) ‘One Health’ is an approach to designing and implementing programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better public health outcomes.
Global health security and malaria

Keeping a focus on malaria in a global health crisis

The vulnerability of the malaria drug supply chain to disruption by COVID-19 became obvious in late January 2020, when manufacturing partners first alerted the Medicines for Malaria Venture (MMV) team to looming shortages in key starting materials for malaria drug production. Our concerns intensified with the almost immediate global focus on certain antimalarials, such as chloroquine, as possible treatments for COVID-19. These developments underscored that maintaining supply of medicines to malaria patients must be a primary focus for MMV and the wider malaria community during the pandemic.

Beginning in March 2020, MMV and the World Health Organization (WHO) co-led a workstream ensuring global supply chain security for malaria commodities amid the COVID-19 pandemic. This work involved continuous coordination amongst country funders, partners and major suppliers, with a focus on safeguarding access to malaria diagnostics, long-lasting insecticide-treated nets, indoor residual spraying, and medicines. Critical work included the early identification of possible risks and bottlenecks in the upstream and downstream supply flows for all malaria commodities. MMV and partners closely monitored for unexpected shifts in product demand, and mapped the sources and supply chains of key starting materials and active pharmaceutical ingredients. This was essential and allowed for the development of risk-mitigation strategies.

As part of this work, MMV, with support from the Bill & Melinda Gates Foundation, initiated mechanisms to stabilize the supply chain and help secure chloroquine stocks for Plasmodium vivax-endemic countries, thereby mitigating the risk of treatment stockouts. Chloroquine remains widely used for treating the blood stage of P. vivax infections in many malaria-endemic countries.

In another critical area for global health security, MMV and partners closely tracked the planning and procurement cycles that were vital in ensuring limited or no disruptions in the 2020 seasonal malaria chemoprevention (SMC) campaigns across the Sahel region of Africa. Remarkably, all countries could pursue their planned SMC campaigns, estimated to have reached at least 30 million children in 2020. SMC involves the administration of the antimalarial sulfadoxine–pyrimethamine plus amodiaquine (SPAQ) to children during months of high malaria transmission (usually during the rainy season, lasting 3–4 months). SPAQ supply is essential to the success of SMC campaigns, which help keep children malaria free and thus reduce patient demands on healthcare settings overloaded with COVID-19 case management. MMV monitored the manufacturing, shipment, and delivery of SPAQ to keep access and distribution on target throughout 2020 and into 2021. SMC partners also provided guidance to countries on how to satisfy WHO-recommended personal protective equipment measures during the distribution campaigns.

Using existing expertise to help lessen the impact of COVID-19

In 2020, MMV used its expertise to support the COVID-19 pandemic response. In March, MMV sent a diverse set of drugs and compounds (including antimalarials) to test centres across Europe and the USA to investigate their potential activity against SARS-CoV-2. MMV has also provided modelling, simulation and data screening expertise to progress projects, including an antimalarial 4-aminoquinoline project that screened compounds in parallel on malaria and on in vitro SARS-CoV-2 assays.

Throughout 2020, MMV continued distribution of its Pandemic Response Box, with 125 copies distributed free of charge so far. This is one of several open-access compound libraries used by researchers globally (others...
include the Malaria and Pathogen Boxes). In 2020, MMV also launched a new open-access ‘COVID Box’ including 160 compounds with known or predicted activity against SARS-CoV-2 and already 50 copies have been distributed. In addition, MMV set up a new drug discovery programme to address infections by drug-resistant malaria parasites in which project compounds were also tested in parallel for their activity against SARS-CoV-2.

In support of efforts to repurpose available medicines against COVID-19 and meet the needs of low-resource settings, MMV and Shin Poong Pharmaceuticals worked with investigators at Ezintsha, a research institute of the University of the Witwatersrand, South Africa, to initiate a Phase II exploratory study “ReACT” in September 2020. The trial is exploring the safety and efficacy of four different repurposed anti-infective drugs compared to standard of care in adults with mild COVID-19 infection. It will help to determine which drugs have potential benefit for COVID-19 that warrant further evaluation in larger trials. MMV also became a member of the COVID-19 Clinical Research Coalition and the ANTIcov consortium. In November 2020, the consortium launched the ANTIcov clinical trial to identify treatments early for mild and moderate cases of COVID-19, thereby avoiding spikes in hospitalizations that could overwhelm already overburdened health systems in Africa.

Dr Meera Venkatesan and Dr Lisa Hare discuss their work and that of others in securing global health supply chains in 2020.

Shortly after COVID-19 was declared a pandemic, global health experts predicted it could significantly disrupt malaria programmes and supply chains for malaria commodities, reversing years of hard-won progress. PMI and others have taken exceptional measures to address this situation. What are these measures and what lessons has PMI learned so far?

The pandemic has taught us that global collaboration and commitment is essential in securing malaria supplies and commodities. Critically, the global community came together early in the crisis to identify pandemic-related threats to malaria efforts. Priorities included streamlining importation requirements and estimating demands for continued production and distribution. Endemic countries also responded quickly to maintain mosquito net delivery, insecticide spraying and seasonal malaria chemoprevention.

How have countries managed malaria despite disruption from COVID-19?

To maintain progress, countries have adapted to ensure safe delivery of lifesaving malaria interventions, administering SMC through caregivers and prioritizing health worker protection. Despite these incredible efforts, there are still challenges, such as dips in availability and use of routine services, including testing, treatment, and addressing malaria in pregnancy. These disruptions can have devastating and long-lasting impacts on malaria. We need all hands on deck to protect progress.

The USA, like many countries, is facing its most devastating infectious disease pandemic in over a century. Why is it important to continue supporting the work of product development partnerships (PDPs) like MMV at the same time as dealing with a national health crisis?

COVID-19 has made it clear that a health threat anywhere is a health threat everywhere. It is important to invest in any such global threat, especially one as deadly and infectious as malaria. For example, in the Republic of Guinea during the Ebola outbreaks of 2013–2014 there were likely more malaria deaths than Ebola deaths, largely due to disrupted services. PMI is dedicated to providing support to countries, so they do not need to choose between fighting COVID-19 or malaria.

The pandemic has shown how important it is to continuously develop new tools to fight infectious disease as well as expand access to existing ones. What role does MMV play in helping partner countries and PMI to fight malaria?

PMI and MMV have synergistic roles in the fight against malaria. Today we have medicines to treat and prevent malaria, but we know that resistance to artemisinin-based combination therapies (ACTs) can spread. Therefore, we will require new antimalarial tools in future. MMV is critical for adding more tools to the box. With the PDP model, MMV has strong relationships with manufacturers and brings much-needed knowledge to the table, helping us prepare for the malaria of tomorrow.

Although COVID-19 poses a serious threat to malaria progress, what gives you hope we can eliminate this disease?

Malaria can be eliminated within our lifetimes. El Salvador is the most recent example and we are seeing similar progress elsewhere, including in the Mekong sub-Region, where PMI supports implementation of national elimination strategies. Thailand and Cambodia are aiming to eliminate malaria in the next five years, which is incredibly exciting. Despite COVID-19, countries have continued many of their lifesaving malaria prevention campaigns and are gearing up to do the same in 2021. Even though there are serious threats to malaria progress, there are also many reasons to have hope.
Antimicrobial resistance, malaria and next-generation medicines

Exposing microbes to drugs leads to selection for mutants that can survive, which is a natural process known as ‘antimicrobial resistance’. This process is a fact of life in infectious disease research and, to minimize the spread of resistance, malaria is treated with combination therapies such as ACT. Partial resistance to artemisinin derivatives has been present for two decades in South East Asia and has now been reported in several sites in Africa. MMV is piloting ways of slowing the spread of artemisinin partial resistance in Africa using multiple first-line therapies (MFTs; p. 18). However, what is urgently needed are new classes of medicines that are fully active against all clinical strains of malaria and have a low propensity for malaria parasites to generate resistance. This is a key goal for MMV and, through its PDP model, MMV works with partners to fast-track innovation in antimalarial drug discovery and development.

We must communicate that malaria is not only a disease that kills around 400,000 people per year, but also has massive economic consequences in countries that can least afford such challenges.

Dr Timothy Wells discusses MMV’s research and development strategy in 2020 in the context of global health security and antimicrobial resistance.

How did COVID-19 affect the discovery and development of new antimalarials?

COVID-19 slowed our operations slightly, but MMV has adapted to the challenges and found new ways of working. MMV has a world-class compound logistics system, which operated continuously during 2020, transferring compounds from their manufacturing sites to testing sites. Although some of our partners had to shut down activities in the short term in response to the pandemic, we were still able to maintain delivery and produce results. At the clinical development stage, we have benefitted from teams working tirelessly to keep sites open through collaborations with our partners. We also developed new ways of ensuring clinical trial quality, despite travel restrictions.

What lessons can we learn from COVID-19 about how to do things better in the treatment of malaria?

The rapid development of COVID-19 vaccines was only achievable through the significant upfront work that developed a solid foundation for innovation in new areas, such as messenger RNA (mRNA) vaccines and adenovirus vaccines. Funding was made available rapidly, governments took funding decisions quickly, and the pathway to approval by regulators and the WHO was streamlined extensively. For malaria, we can see how communicating a pathway to policy change is critical. We must communicate that malaria is not only a disease that kills around 400,000 people per year, but also has massive economic consequences in countries that can least afford such challenges.

What is your take on the emergence of partial artemisinin drug resistance in Africa?

The challenge is to contain emerging resistance geographically, preserve the lifespan of our current medicines and prevent emergence of more resistant strains. There is a need for new classes of medicines and our most advanced are already in Phase II clinical studies. All the new medicines in our portfolio are active against existing resistance mutations in the field and we also check to see whether resistance can be generated in laboratory conditions. We prioritize those that can eliminate parasites with a low risk of resistance mutations developing. It’s important to highlight that two of our ACTs have partners that have had no resistance mutations detected (lumefantrine and pyronaridine), even after decades of clinical use in the case of lumefantrine.

What are the key priorities in malaria drug research and development?

There are currently three priority areas: developing new medicines for uncomplicated malaria, developing new medicines for severe malaria, and finding new ways to protect people from getting malaria (prophylaxis). For uncomplicated malaria, the challenge is to have medicines that do not produce resistant parasites and also offer the chance of a simplified, shortened regimen. The single-dose cure will be difficult to achieve but would be transformative for malaria treatment. Since more than two drugs are likely to be needed, new molecules must be more and more potent. Regarding severe malaria, MMV is in partnership with the European and Developing Countries Clinical Trials Partnership and Novartis on the development of cipargamin, which is ready to be tested in patients. Prophylaxis is a key emerging area and we co-sponsored a workshop with the WHO on the ideal prophylactic medicines in December 2020. Last year, 30 million children were protected with drugs as part of SMC. In future, this may be done with an antibody therapy given once per season. Additionally, we need new therapies that are known to be safe in women at all stages of pregnancy. There is excitement regarding monoclonal antibody therapy for malaria in pregnant women as it is very specific (i.e. lower chances of off-target effects), has minimal transfer to the developing foetus and may be safe even in early stages of pregnancy.

MMV-supported projects

Target product profiles (TPPs)

- 3-day cure, artemisinin-based combination therapies (TPP1)
- Uncomplicated malaria treatments for single-exposure radical cure (SERC) and/or resistance management (TPP1)
- Intermittent preventive treatment (TPP1)
- Severe malaria treatment/pre-referral intervention (TPP1)
- Products targeting prevention of relapse for P. vivax (TPP1)
- Prophylaxis (TPP2)


ESAC Expert Scientific Advisory Committee
GSB Global Safety Board
APAC Authorization for Phase III/Advancement Committee
APM Access & Product Management

To develop the individual compounds for combination into the TPPs, MMV has defined five target candidate profiles (TCPs):

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

- Included in MMV portfolio after product approval and/or development
- Global Fund Expert Review Panel reviewed product – permitted for time-limited procurement, while regulatory/WHO prequalification review is ongoing
- Paediatric formulation
- WHO prequalified OR approved/positive opinion by regulatory bodies who are ICH* members/observers
- Via a bioequivalence study
- Past partners are in brackets

* International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Tackling resistance in uncomplicated malaria

In response to emerging partial artemisinin resistance, next-generation combinations are being investigated to eventually replace existing therapies. One frontrunner combination is ganaplacide–lumefantrine, currently being investigated in Phase II clinical trials.

**Ganaplacide–lumefantrine (Novartis)**

Ganaplacide–lumefantrine is a leading combination being assessed for its potential to treat acute, uncomplicated malaria. Ganaplacide is a fast-acting compound with a novel mechanism of action that can kill both *Plasmodium falciparum* and *P. vivax* parasites and is active against parasites resistant to current antimalarials. A longer-lasting formulation of lumefantrine – a component of Coartem® (artemether-lumefantrine) – has been developed for this new combination and clears remaining parasites. Both components also have the potential to block transmission from humans to mosquitoes. In 2017, MMV and Novartis initiated a Phase IIb clinical trial across Africa and Asia. Results from Part A of the study in 349 adults and adolescents aged ≥12 years treated for 1–3 days showed rapid killing of parasites and a low treatment failure rate. Part B started in October 2020 and aims to include 175 patients between the ages of 2 and 12 years.

Other ongoing studies include a paediatric ‘KALUMI’ study investigating ganaplacide–lumefantrine in children aged between six months and 12 years, which began in the first quarter of 2021. It aims to include at least 224 patients from sites in Mali, Burkina Faso, Gabon and the Republic of Guinea. Depending on current studies, the Phase III study investigating ganaplacide–lumefantrine could be initiated in 2022 and a stringent regulatory authority filing could be made in late 2024.
Maintaining a healthy pipeline of candidate antimalarial drugs

Antimalarial drug failure is an ongoing risk throughout the drug development pipeline, and resistance can lead to drug failure in the clinical setting. To protect the pipeline against these risks, MMV aims to maintain a strong and continuous pipeline of candidate drugs. In 2020, several key molecules were moved forward in clinical development.

**Ferroquine**

Ferroquine is a member of the 4-aminoquinoline family. Following the termination of the artefenomel–ferroquine combination due to poor tolerability, the rights of ferroquine were transferred to MMV from Sanofi in October 2020. This allows it to be further investigated in new Phase II combination studies.

**M5717 (Merck)**

M5717, originally discovered as part of an MMV-led collaboration with the Dundee Drug Discovery Unit and now in development at Merck, shows activity against all stages of the parasite life cycle (except for the dormant liver stage of *P. vivax* malaria) and targets the protein-making machinery of the malaria parasite. In a Phase I study in 2018, M5717 was well tolerated and an 800 mg dose completely cleared blood-stage infection in a volunteer infection study (VIS). Embryofetal and fertility studies in laboratory models of malaria were completed in 2020 showing a clean profile. A VIS evaluating the prophylactic activity of M5717 in humans is ongoing. Merck is working with MMV to prioritize partners for a potential combination Phase II study for treatment of malaria.

**ZY19489 (Zydus Cadila)**

ZY19489, in development with Zydus Cadila, has shown a good safety profile in both non-clinical toxicology studies and Phase I studies in humans, a low susceptibility to resistance, and a profile that suggests it may eventually be suitable for use in pregnancy. A blood-stage VIS and an embryofetal development study were completed in 2020, with a formulation development study still underway. ZY19489 in a combination therapy has the potential to become a single-exposure, blood-stage treatment for acute, uncomplicated *P. falciparum* and *P. vivax* malaria.

**MMV533**

MMV533 was recommended by MMV’s ESAC as a preclinical development candidate due to its rapid parasite killing and a long half-life. A Phase Ia safety and tolerability study of MMV533 was initiated in the third quarter of 2020.

2020 saw the termination of two development compounds. MMV048, originally discovered and developed by an international team led by Prof. Kelly Chibale at the University of Cape Town, South Africa, was the first antimalarial candidate compound to enter a Phase I study in Africa. Extensive non-clinical toxicology studies determined that MMV048 is a potent teratogen, and the programme has been discontinued. The lessons learned on the safety of this molecule have been passed on to other groups focusing on the same molecular target with the hope that a second-generation compound can be designed to overcome these weaknesses. Another compound that was discontinued called P218 is a *P. falciparum* dihydrofolate reductase inhibitor that was developed in collaboration with Biotec, Thailand. Phase I studies showed that it had a short half-life and, therefore, would need to be given daily to provide prophylaxis. In collaboration with Janssen, long-acting formulations have been investigated but none have been able to reach the current target product profile.

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5 Volunteer infection study (VIS): A type of study where healthy volunteers are injected with a low number of drug-sensitive parasites before receiving an experimental drug 8 days later to assess blood-stage activity.

6 A substance that may cause birth defects through toxic effects on an embryo or fetus.
Characterizing resistance

Given the urgent need to develop new antimalarial treatments, it is important to have a defined and consistent way of characterizing the risk of resistance emergence to a specific compound, and ranking them compared to one another. We can then make fully informed decisions regarding the choice of compounds to take forward.

Dr Maëlle Duffey discusses her work to characterize resistance as part of MMV’s Drug Discovery team.

Can you describe your work and how it will help MMV identify drugs that combat resistance?

My work focuses on the identification of new drugs with blood-stage efficacy and manageable or no resistance. I oversee various parasitology and pharmacology platforms supporting the discovery of new antimalarial compounds.

Based on clinical observations, various partner testing platforms and expert input, we have developed a new strategy that allows us to detect and characterize the risk of resistance at each step of the pipeline. We use known modes of action and mechanisms of resistance, genetic testing, detailed in vitro analysis and in vivo experiments. This allows us to identify and deprioritize early- and late-lead series exhibiting a very high risk of resistance, and have a comprehensive assessment of the resistance risk at the level of candidate selection.

What drew you to work on malaria drug resistance, and why is this work important?

Drug resistance is fascinating because it demonstrates the idea that “evolution always wins”. A number of years ago, partial resistance to artemisinin derivatives emerged in South East Asia, with worrying signs also recently detected in Africa. Fortunately, when artemisinin is used in combination with other drugs, such as lumefantrine or pyronaridine, efficacy is maintained. Having a well-characterised picture of the risk of resistance of an antimalarial compound early in its development helps us make better-informed decisions across the whole MMV pipeline.

How does this work fit in with MMV’s research and development strategy and the resistance work being conducted by David Fidock and his team who were awarded MMV Project of the Year 2020 (pp. 40-41)?

With its unparalleled expertise in molecular parasitology, the Fidock Lab has profiled over 180 compounds and discovered 18 new modes of action and mechanisms of resistance. David and his team have been a central pillar in our resistance work. In addition to being key contributors to the in vitro experiments that support our strategy, their research has interrogated drug resistance in the malaria parasite, increasing our understanding of malaria parasite biology. This understanding has informed our new resistance strategy that investigates resistance risk throughout the drug development process.

What has been the impact of your project on MMV’s portfolio?

Once the strategy has been validated using clinical data on the advanced compounds in our profile, the impact is likely to be an increase in the down prioritization of projects presenting an unacceptable resistance risk, freeing up resources to focus on more promising projects. We are expected to deliver preclinical candidates with a comprehensive resistance risk assessment, ultimately leading to fully informed decisions regarding compound prioritization and partner drug selection.
Multiple first-line treatment options for uncomplicated malaria

In 2001, the WHO recommended ACTs as first-line therapy for uncomplicated malaria, a decision largely driven by the devastating emergence of resistance to existing therapies (chloroquine and sulfadoxine–pyrimethamine) in Asia, Africa and Latin America. In addition to increased efficacy, a key benefit of using drugs with different mechanisms of action in combination, such as in ACTs, is delaying the emergence of resistance. Currently, the WHO recommends six ACTs for the treatment of uncomplicated *P. falciparum* malaria, creating a pool of antimalarial medicines for uncomplicated malaria which healthcare workers in the public and private sectors can choose from. This is referred to as a multiple first-line treatment (MFT) policy and is a pre-emptive approach to drug-resistance management. By providing MFT options, it is possible to further delay the emergence and spread of resistance by challenging malaria parasites with many different types of drugs (rather than with a single combination). An MFT approach quickly replaces discontinued options and limits the risk of single medicines becoming out of stock.

At the national level, the WHO recommendation of ACTs has led to malaria-endemic countries positioning ACTs as first-line therapy options, however, often only one ACT is routinely used. Over the last 15 years, the work of MMV and others in developing multiple ACTs, and supporting innovation and optimization of how these treatments are used has led to some countries progressing effective MFT policies and programmes. Countries adopting this strategy include Angola, Brazil, Burkina Faso, Nigeria and Myanmar.

MMV is supporting two pilot studies investigating the operational use of an MFT approach: a pilot evaluation in Burkina Faso that included dihydroartemisinin–piperaquine, pyronaridine–artesunate and arteether–lumefantrine has recently been completed, with analysis still ongoing, and an additional evaluation in Kenya was initiated in June 2020.

MMV continues to support the research and development of novel antimalarials for uncomplicated malaria, including the following ACTs:

- **Pyramax®, Eurartesim® and Coartem®**

  *Pyramax* (pyronaridine–artesunate) was brought forward by MMV and Shin Poong Pharmaceuticals to treat acute, uncomplicated *P. falciparum* and *P. vivax* malaria. It is available as tablets and granules for adults, children and infants, with both formulations included in the WHO’s prequalified medicines and the Essential Medicines Lists for adults and children. Eight sub-Saharan African countries had adopted Pyramax in their national treatment guidelines by the end of 2020. An additional three countries are expected to do the same by the end of 2021.

  **Eurartesim** (dihydroartemisinin–piperaquine) was brought forward by MMV and Alfasigma S.p.A to treat acute, uncomplicated *P. falciparum* malaria in adults, children and infants > 5 kg. It received WHO prequalification in 2015 and was added to the WHO Essential Medicines List in 2017. Eurartesim is included in the national treatment guidelines of five African countries.

  **Coartem** (artemether–lumefantrine) is used to treat uncomplicated *P. falciparum* malaria. Its tablet formulation developed by Novartis and dispersible tablet (Coartem Dispersible) formulation, brought forward by MMV and Novartis, are suitable for adults and children between 5 and 24 kg. In 2008, Coartem Dispersible became the first child-friendly ACT to be approved by a stringent regulatory authority. Currently, an artemether–lumefantrine formulation suitable for infants < 5 kg is being developed in order to meet the need of an approved ACT for this patient population. Coartem Dispersible is approved in 50 countries.
What are the inherent challenges and advantages of an MFT approach for the treatment of uncomplicated malaria?

MFT reduces pressure on the use of a single ACT and increases the therapeutic life of multiple ACTs, which are both critical in the fight against malaria. MFTs also improve access to a range of ACTs in endemic settings. In terms of challenges, acquisition of sufficient ACTs for use in MFT can be difficult in a real-world setting. Managing ACT distribution and prevention of stockouts are other required considerations. The training of health workers and setting up supportive monitoring at a health facility level can also be challenging.

Could you briefly describe the formative phase of the MFT pilot evaluation in Burkina Faso?

The formative phase of the pilot evaluation included the generation of baseline information and development of tools for implementation. Baseline information included perception and expectation of MFT strategy by health system stakeholders and community members. In addition, it aimed to document any perceived/existing obstacles to implementation, treatment-seeking behaviour for febrile episodes/malaria, and morbidity and mortality rates in the pilot evaluation area. ACTs were delivered according to patient category (e.g. pregnant women) and age (adults/children).

Who were the partners you worked with and how was it conducted?

In Burkina Faso, a consortium was set up to conduct this pilot evaluation. The leading research institute in the consortium is the Groupe de Recherche Action en Santé. The Institut de Recherche en Sciences de la Santé is a second research institute that evaluates the effects of the programme through its health and demographic surveillance system that covers part of the pilot evaluation area. An additional partner is the Ministry of Health of Burkina Faso through its technical department, the National Malaria Control Programme. This serves as the main link between the researchers, the central drug store in the country and the national health system. This work is possible with the financial and technical support (i.e. protocol development and monitoring of activities) of MMV.

How easy/difficult was it for the health workers to accept the MFT protocol?

It was relatively easy in the evaluation area. Malaria is one of the top 10 diseases in Burkina Faso, so health workers are familiar with the management of uncomplicated malaria. Health workers included in the evaluation were retrained on malaria diagnosis, prescription of ACTs (especially the newer combinations), pharmacovigilance and management of ACTs prior to deployment. The health workers benefited from supportive monitoring visits from the health district management and research teams. The main difficulty was the turnover of health workers involved in implementation, which could have affected their compliance with the evaluation protocol. Fortunately, this has been mitigated by hands-on training for the new staff.

What has the pilot evaluation revealed so far?

We have just completed the evaluation phase of the pilot. According to preliminary data, approximately 81,000 malaria episodes in children under five years old benefitted from pyronaridine–artesunate treatments, 4,700 malaria episodes in pregnant women benefitted from artemether–lumefantrine, and 90,000 malaria episodes in individuals five years and older benefitted from dihydroartemisinin–piperaquine administration. So far, no serious adverse drug reactions have been reported.

From your perspective, how could the use of MFTs benefit Burkina Faso’s malaria control programme? How could it support the country’s efforts to eliminate malaria?

Currently, the Burkina Faso malaria treatment guidelines recommend three ACTs – amodiaquine–artesunate, artemether–lumefantrine and dihydroartemisinin–piperaquine. Only artemether–lumefantrine is available at the health facility level for treating uncomplicated malaria. Our pilot evaluation offers additional ACTs at this level and is the first opportunity for distributing two additional ACTs (dihydroartemisinin–piperaquine and pyronaridine–artesunate). National guideline revision is underway, and our evaluation has been instrumental in promoting future adoption of pyronaridine–artesunate. Pilot evaluation data will be made available to policy makers and we hope this data will be used to scale up MFT if results are positive.

What has it been like to work with MMV on this pilot evaluation?

This has been my first opportunity to work with MMV and I greatly appreciate our collaboration. We look forward to reporting successful results and continuing our work with MMV on future research in Burkina Faso.
Malaria through the lens of gender and age

‘Women hold up half the sky’ – yet there is a fatal gender imbalance on the ground

Malaria disproportionately impacts infants, young children and women of child-bearing age. The biological and physiological changes that occur throughout pregnancy reduce a woman’s immunity to the malaria parasite, leading to greater susceptibility and an increased risk of severe illness and death. Malaria during pregnancy can result in anaemia and severe anaemia, increasing the risk of stillbirth, premature birth and low birthweight.

Globally, in 2007, an estimated 54.7 million and 70.5 million pregnancies were at risk of *Plasmodium falciparum* and *Plasmodium vivax* malaria, respectively.1 However, these numbers will have changed since then due to the shrinking malaria map. Staggeringly, one in ten maternal deaths in malaria-endemic countries are estimated to result from *P. falciparum* malaria, with pregnant women at a 3–4 times increased risk of miscarriage.2 Malaria is the fifth leading cause of death for girls between 10 and 14 years of age and accounts for 7.4% of deaths in adolescent women globally.3 In addition, adolescent pregnant girls are more likely to have malaria and anaemia compared with adult pregnant women.3 Regarding lactating women, there is a lack of robust data to inform recommendations on antimalarials, making this a neglected area of research.4 MMV is working with partners, including the Liverpool School of Tropical Medicine and the WorldWide Antimalarial Resistance Network to increase access to antimalarial treatment, develop lifesaving tools, and generate new data.

Repeated exposure to malaria infections can help build immunity over the course of several years. For this reason, newborn and young children are particularly vulnerable due to their developing immune system and lack of earlier exposure. The detrimental effects of malaria can also manifest in other ways, following an individual throughout their entire life. For example, malaria infection is thought to affect neurological, cognitive and physical development in children, perpetuating an inescapable cycle of poverty and disease.

Since its inception, MMV has maintained a strong focus on women and children to help alleviate the disproportionate effects of malaria in these vulnerable populations. Maintaining this focus is a key imperative to help protect the reproductive and educational rights of women and children, respectively.

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Eileen Buxton works as a nurse in Ghana, where malaria causes more than 3% of all maternal deaths each year. Through her job she meets many malaria patients and is well aware of the potentially fatal nature of this disease. Thus, when she got sick during her third trimester of pregnancy, she imagined the worst.

Suffering from severe nausea as well as vomiting, uneasiness and a high temperature, Eileen realized something was wrong. “I was scared. I was actually very scared…I knew how being sick during pregnancy could affect the mother and the child too.” said Eileen.

Eileen’s worst fears were confirmed when she was diagnosed with malaria. She says, “I was put on some intravenous fluids and was also given artemether-lumefantrine.” She was admitted to the hospital for three days and then discharged. But before she could recover fully, the fever came back within a couple of days. Further tests revealed that Eileen was now suffering from severe malaria and she was admitted to the hospital again, this time for about three weeks. “I was given intravenous quinine for about five days… It took a long time for me to recover some strength,” she recalls.

Fortunately, three weeks after her recovery from malaria, Eileen delivered a healthy child. However, this incident impacted her deeply. “Having malaria during pregnancy is like you’ve signed your death sentence… Apart from you being anxious about your health, you are also anxious for the health of the baby you are carrying,” she explains.

Eileen says, “Some people survive, like myself, but others don’t.” She adds, “my experience has actually made me educate people more about malaria in pregnancy.”

Malaria in pregnancy is a serious public health issue. MMV and partners are intensifying efforts to address this issue by raising the standard of care for pregnant women and newborn babies through inclusive drug development and deployment strategies.

Having malaria during pregnancy is like you’ve signed your death sentence… Apart from you being anxious about your health, you are also anxious for the health of the baby you are carrying...
Treating and preventing malaria in pregnancy

During the development of new therapeutics, including antimalarial drugs, women of childbearing age, pregnant women, and lactating women are actively excluded. The goal of this practice is to ‘protect’ the expectant mother and developing foetus, but it also prevents the generation of crucial safety data required for real-world implementation. Consequently, when a new drug is registered, it remains unknown whether it can be given safely to these women. In the context of malaria-endemic countries, this means that most drugs only become available to pregnant women several years after their first approval. Many women in their first trimester of pregnancy may also be unaware that they are pregnant, placing them at even greater risk of exposure to potentially harmful therapies. This highlights a need for research to identify and implement interventions that can be safely prescribed to women of childbearing age, pregnant women, and lactating women.

Through the Malaria in Mothers and Babies (MiMBa) initiative, MMV has committed to accelerate innovative drug development and deployment strategies to identify and deliver new medicines that better serve the needs of pregnant and lactating women. For the development of new antimalarials, MMV strives to prioritize molecules that are deemed low risk to the developing foetus and MMV is investigating new models to detect adverse effects as early as possible. During the early phases of drug development, MMV will use pharmacometric tools to predict the passage of molecules to the placenta and breast milk. Once efficacy is established in clinical trials, molecular levels in pregnant women can be tested before licensing. This will help to generate data to support earlier use of new medicines in pregnant women, that is, shortly after launch.

MiMBa also aims to generate more evidence on existing treatments. MMV has collaborated with the Liverpool School of Tropical Medicine to establish a registry to monitor the use of different antimalarials during pregnancy with an emphasis on the first trimester. The registry was launched in Kenya in February 2021, with the selection of a second country before the end of the year. The data gathered will inform policymakers regarding decisions that will ultimately benefit pregnant women at risk of malaria.

The intervention currently recommended by the World Health Organization (WHO) to prevent pregnant women from getting malaria is intermittent preventive treatment in pregnancy (IPTp). This approach implies one course of sulfadoxine–pyrimethamine (SP) administered during routine antenatal care visits, with doses given at least one month apart, starting as early as possible in the second trimester of pregnancy. MMV and its manufacturing partners are aiming to enhance supply security and global access to quality-assured SP for IPTp and are working to secure WHO prequalification of SP products for African manufacturers.
Dr Stephanie Dellicour discusses malaria in pregnant women and the malaria pregnancy registry.

**What are the main gaps in the treatment and prevention of malaria in pregnant women?**

A clear gap in treating this population is the limited number of interventions available. Pregnant women are typically excluded from clinical studies and it can take several years for enough real-world data to accumulate to support the use of an antimalarial during pregnancy. The most critical gap is providing safe and effective interventions during the first trimester, as this is a key period for foetal development. Today, preventative antimalarials used during pregnancy are only recommended from the second trimester, leaving pregnant women unprotected against malaria when their unborn babies are most vulnerable. In addition, women usually attend their first antenatal clinic after the first trimester in malaria-endemic countries, meaning protective insecticide-treated nets are not provided earlier in pregnancy. Malaria in the first trimester is now recognized as an important risk factor for adverse pregnancy outcomes (including miscarriage, foetal growth restriction, low birthweight, and maternal anaemia). There is an urgent need to obtain the necessary data to enable a full risk-benefit assessment of the most suitable antimalarials for this high-risk group.

**What is the benefit of setting up a pregnancy registry? Why does the use of antimalarials need to be monitored?**

In most high-income countries, there are robust systems that allow monitoring of drug safety using electronic health records (e.g. prescriptions and outcomes for pregnant women); however, these systems are not available in most malaria-endemic countries. The pregnancy registry addresses this gap, giving us a proactive system, which can be used to collect safety data on the use of antimalarial drugs during pregnancy. These exposures need to be monitored so we can evaluate the risks and benefits of different antimalarials, ultimately helping pregnant women get access to new and more effective treatments faster.

**What is being done to collect quality data to help address these gaps? What are the main challenges?**

We are taking several steps to ensure the data we collect for the pregnancy registry are robust, including introducing obstetric ultrasound to help determine the exact gestational period as well as implementing training to improve the quality of congenital anomaly assessments. The main challenge is capturing accurate exposure information, as malaria can be a commonplace, forgettable event in areas of high transmission where antimalarials are widely available over the counter. This requires linking multiple data sources for confirmation of exposure.

**How will the evidence generated be used?**

The goal is to generate robust data that can be reviewed by regulators and policymakers, and then be used by healthcare providers and expectant mothers to make informed decisions on treatment.

**How will the registry contribute to the control and ultimate elimination of malaria?**

To eliminate malaria, it is crucial to reduce overall transmission, and pregnant women represent a small but important reservoir of infection. The safety data generated by the registry will help to expand the use of the tools at our disposal for the elimination of malaria.

**What has it been like to work with MMV on this project? What do each of the partners bring?**

It has been a true partnership and there is real synergy between all collaborators. MMV brings extensive industry knowledge, the team at Liverpool School of Tropical Medicine brings technical and field experience, and the WorldWide Antimalarial Resistance Network provides expertise for data management, curation, and analysis.
Improving management of uncomplicated malaria in neonates

After birth, newborn children are at considerable risk from severe diseases, particularly malaria. Antimalarial treatments developed for adults are not ideal for use in very young children due to differences in metabolism. Furthermore, antimalarial tablets for adults need to be broken up for children, making it difficult to ensure correct dosing, and the bitter taste can cause very young children to spit out lifesaving medicines.

In collaboration, Novartis and MMV launched Coartem® Dispersible (artemether–lumefantrine) in 2009, setting a new standard for child-friendly antimalarial treatments in children weighing 5 kg or more. Coartem Dispersible is a flavour-masked formulation, readily taken by children, and has helped improve dosing accuracy and compliance.

Since its launch in 2009, over 430 million treatments of Coartem Dispersible have been distributed in more than 50 countries.

“For newborn children under 5 kg, Novartis, in collaboration with MMV, is developing a new formulation of artemether-lumefantrine designed specifically for use in the youngest of patients. A Phase II/III study aiming at evaluating pharmacokinetics, safety, tolerability, and efficacy of a new dose ratio of artemether-lumefantrine dispersible tablets in <5 kg neonates and infants. The study is ongoing and is co-funded by the European and Developing Countries Clinical Trials Partnership (EDCTP) under the PAMAfrica project. The study, which started in December 2020, plans to include 42 patients from Burkina Faso, Kenya, Mali, Nigeria, and Democratic Republic of Congo. It is expected to be completed by 2023.”

Expectant mothers and their newborn children are at risk from malaria in its severest manifestations. The risk for the mother diminishes soon after pregnancy, however, children remain disproportionately affected up until the age of five. These patients represent one of the most vulnerable and, to date, neglected groups affected by malaria. MMV and Novartis are working together to change that.
Children: seasonal malaria chemoprevention (SMC)

In the Sahel and sub-Saharan regions of Africa, malaria transmission rates are particularly high during and immediately after the rainy season. Approximately 39 million children across Africa live in areas affected by seasonal malaria, and have little or limited immunity to malaria, making them most at risk. Almost 275,000 children under five years of age died from malaria in 2019, with an additional 60% of malaria cases during the rainy season, usually 3–5 months of the year. SMC is the administration of full antimalarial treatment courses to children aged 3 months to 5 years at regular intervals during periods of seasonal transmission to prevent malaria infection.

The SMC medicine sulfadoxine–pyrimethamine plus armodiaquine (SPAQ) has helped prevent millions of cases of malaria among children. In a recent study investigating SMC in 2015–2016 in Burkina Faso, Chad, The Gambia, Guinea, Mali, Niger, and Nigeria, results showed an estimated reduction in confirmed malaria cases at outpatient clinics during the high transmission period, ranging from 25.5% in Nigeria to 55.2% in The Gambia. In 2019, 85 million treatments were delivered by manufacturers to 13 countries, and approximately 22 million children in total were reached with SMC programmes. In 2020, the target was increased to 30 million children.

Fosun Pharma is the only WHO-prequalified supplier of SPAQ. To diversify the supplier base, MMV has been supporting S Kant Healthcare Ltd. (India) in the development of a second child-friendly, dispersible SPAQ product Supyra®. In April 2021, Supyra reached the significant milestone of achieving WHO prequalification. Prior to prequalification, countries were able to purchase Supyra using international donor funds after positive opinion from the Global Fund Expert Review Panel was renewed in August 2020. S Kant Healthcare now has the capacity to supply up to 100–120 million courses annually. Market authorization of Supyra has been achieved in five countries and review is ongoing in a further five.

Progress towards achieving the WHO Global Technical Strategy for Malaria 2016–2030 goal of reducing global malaria incidence and mortality by 90% has plateaued in recent years. In 2018, the ‘High burden to high impact’ initiative was implemented to reignite the pace of progress in the global malaria fight. Speaking at the ‘Getting the most from SMC: New learnings from Niger, Nigeria and Benin’ webinar in 2020, Dr Pedro Alonso, Director of the WHO Global Malaria Programme, highlighted that “SMC is a great success story and we must not just preserve it but nurture it. I believe also, that we must adapt it, as per the principles of the High Burden, High Impact (HBHI) initiative.”

To expand the reach of SMC, MMV has recently secured a major new grant from the Korean government’s Global Disease Eradication Fund to support five countries in covering 5–10-year-old children and to explore an additional month of SMC. This upscaling will also require detailed forecasts to ensure on-time distribution of SPAQ during the peak malaria transmission season. MMV is supporting the development of a web-based forecasting platform to assist operational planning and monitoring. Additional support comes from the Optimizing the impact of SMC (OPT-SMC) project, launched in 2020. This project supports national malaria programmes in conducting implementation research to optimize SMC delivery, providing grants, technical assistance and facilitating knowledge-sharing between countries. It is led by the University of Thès, Senegal, as a collaboration between several partners, including MMV, with funding from the EDCTP.

The SMC working group ‘SMC Alliance’ is formally endorsed by Roll Back Malaria’s Country/Regional Support Partner Committee with MMV as the host-organization and secretariat. It serves as an umbrella body between partners and countries interested in, and currently implementing, SMC. SMC Alliance, national malaria programme teams, and local healthcare workers have ensured continued delivery of SMC during the COVID-19 pandemic. Additionally, SMC Alliance and OPT-SMC have developed tools and created platforms to support good practice for SMC implementation during the pandemic.

6. WHO World Malaria Report 2020: https://www.who.int/publications/i/item/9789240015791
As SMC protects children from malaria and reduces hospitalization, it became an even more critical tool during the COVID-19 pandemic, yet there were also pandemic-related challenges. Can you talk us through the actions undertaken to address these challenges?

In response to the recent Ebola crisis, people began avoiding health facilities, refusing drugs and not receiving healthcare providers. SMC Alliance and partners anticipated these issues during the COVID-19 pandemic and, to mitigate them, provided additional funding for personal protective equipment for health workers as well as extensive training on social distancing.

In addition, SMC Alliance and countries that implement SMC quickly began reviewing their planning and included additional preparations for SMC. A tracker was developed to share information between partners to track drug deliveries, including weekly updates. As amodiaquine was being investigated as a COVID-19 therapy, drugs were also secured for SMC campaigns to help prevent stockouts.

What was the role of partnerships in making this happen?

Solidarity has been key. Partners shared information widely on drug procurement, quantities and ordering. At the country level, collaboration allowed for the exchange of stocks to benefit those in need. SMC Alliance was very important in offering a platform for collaboration between all stakeholders during the COVID-19 pandemic crisis.

How is SMC contributing to the global effort to eliminate malaria?

SMC reduces the incidence of clinical attacks and severe malaria by about 75% in clinical trials, and it can be deployed across a large population relatively easily. SMC therefore has a huge role in malaria control.

Why is MMV developing alternatives to SPAQ?

Drug resistance is a key concern. Today, some countries that could benefit from SMC do not implement it due to the presence of resistance to SP. In addition, it is important to anticipate the emergence of resistance in countries already implementing SMC. SMC is a very cost-effective intervention and would be of great benefit if deployed more widely. The challenge will be having new treatments that are as low cost as SPAQ.
Protecting children from malaria despite COVID-19

Mohammed Sani Muftaw is a paediatric nurse and sub-district leader in Savelugu, located in the Northern Region of Ghana. He leads a team of volunteers that go house to house to administer seasonal malaria chemoprevention to children aged three months to five years living in the community. The team has been implementing SMC since 2015 when the intervention was first introduced in 23 districts in the Upper East and Upper West Regions of Ghana.

In 2015, approximately 366,000 children were protected with SMC. By 2019, that figure had almost trebled, with an estimated 965,000 children receiving SMC. The onset of the COVID-19 pandemic, however, threatened to disrupt this lifesaving programme, putting many young lives at risk during the rainy season.

Nevertheless, Mohammed and his team rose to the new challenge and quickly adapted to deliver SMC in the context of the pandemic. Mohammed proudly notes that “All volunteers and health workers wore face masks and were required to maintain a distance of at least two metres. On entering the house, we washed our hands with water and soap and disinfected our tools and materials before interacting with the household.” He adds, “Unlike in previous years when volunteers gave the first dose of the SMC medication to children, we gave the medicines to the caregivers to dissolve and give to the children while we instructed and observed from a distance.”

Due to social distancing measures, implementers also used non-conventional channels such as mobile vans, radio announcements and social media platforms to communicate with local communities and coordinate the roll-out of the intervention.

According to Dr Keziah Malm, the programme manager of the National Malaria Control Programme, despite the challenges posed by the COVID-19 pandemic, Ghana was successfully able to reach an estimated 1.05 million children in the Northern Region with SMC, exceeding the number reached in 2019 despite the challenges.
New products for malaria prophylaxis

MMV has a three-pillar strategy underpinning the development of new prophylaxis tools to protect vulnerable populations, such as young children and pregnant women. The first pillar focuses on interventions that can be delivered in the short term (2020–2024) with emphasis on repurposing existing products such as dihydroartemisinin–piperaquine.

The second pillar focuses on using approved antimalarials in new combinations to tackle resistance, in particular to SP, with a target for the launch of these products in 2025–2029. MMV’s Seasonal Malaria Chemoprevention Extension 2 (SEAMACE2) programme is evaluating how SMC can be extended through the development of new, non-SPAQ combinations using existing antimalarials that can provide long-term protection. In December 2020, MMV and the WHO co-hosted a consultation meeting to explore the preferred product characteristics of next-generation chemoprevention drugs and to prioritize potential combinations of existing antimalarials. Furthermore, MMV is exploring opportunities to complement SMC with the provision of approved transmission-blocking medicines, administered either before or alongside SMC. The aim is to achieve an overall reduction in malaria in the community and decreased reinfection rates in areas of high malaria transmission.

The third pillar to MMV’s prophylaxis strategy is to deliver new molecules, combinations and formulations (injectable, as well as oral) as new products to be launched after 2030, seeking direct approval for prophylaxis, for example:

- MMV has explored the potential of P218 as a single-administration, long-acting injection in collaboration with Janssen Pharmaceutical Companies of Johnson & Johnson. Difficulties in achieving adequate duration of drug exposure resulted in the termination of P218 activities in 2020.
- MMV370 and MMV371 in collaboration with Janssen, as well as prodrugs of atovaquone designed for intra-muscular injection, licensed from Calibr USA, underwent preclinical studies in 2019, showing promising long-duration profiles. Work on the formulation of MMV371 is ongoing and toxicology studies are planned for 2021 to inform the decision to progress to Phase I trials.
- ELQ331 (Oregon Health Sciences University), a novel chemical entity, was approved as an oral candidate for further investigation following a positive review by MMV’s Expert Scientific Advisory Committee.
Lifting the burden of severe malaria: studying existing and novel therapies

Saving more lives from severe malaria

Severe malaria occurs as a result of complications during malaria infection, including multiple organ failure or abnormalities in a patient’s blood or metabolism. Symptoms may include anaemia, hypoglycaemia, respiratory distress, convulsions and coma, which can progress rapidly and result in death within hours or days. In 2019, an estimated 409,000 lives were lost to malaria, 67% (274,000) of which were children under five years of age. If development of severe malaria is suspected, patients must be treated immediately, however, access to appropriate diagnostics and medicines can be limited in endemic areas, making assessment and treatment of patients challenging. MMV and its partners are working hard to optimize access to currently available treatments and expand the range of novel antimalarial medicines available for the treatment of severe malaria.

Rectal artesunate

When treating cases of severe malaria, every minute counts. This is particularly true in young children. In their latest guidance (2017–2018), the World Health Organization (WHO) recommends the use of artesunate rectal capsules to help manage the complications of severe malaria in children. The administration of artesunate rectal capsules can reduce malaria progression in patients, giving them more time to seek more advanced care at a healthcare facility. For example, improved access to artesunate rectal capsules in rural Zambia through the Mobilizing Access to Maternal Health Services in Zambia (MAMaZ) Against Malaria (MAM) project contributed to a 96% reduction in reported malaria case fatality rates in children under six years of age in intervention sites. This illustrates the value of such treatments in remote settings where the burden of malaria often falls heaviest.

In remote settings, community healthcare workers provide an initial diagnosis, prescribe basic medications and, if necessary, refer patients to more advanced facilities. As part of efforts by MMV and partners to support the continuum of care from the community level to referred health centres, the Rectal Artesunate Information Education and Communication (RASIEC) study was conducted in Malawi. The overall goal of this cohort case control study was to evaluate the introduction of the RASIEC toolkit (consists of information pamphlet, poster, indication and step-by-step administration of artesunate rectal capsules) alongside appropriate training. The study investigated whether these measures could increase early presentation at village clinics for pre-referral administration of artesunate rectal capsules. Additional metrics investigated include increased acceptability of artesunate rectal capsules by caregivers, improvement in community healthcare worker diagnosis and treatment, as well as enhanced, prompt compliance with referral instructions by caregivers.

After completion of the study in 2020, findings indicated that providing healthcare workers with RASIEC toolkits and a formalized referral slip protocol successfully increased the likelihood of a positive treatment outcome for patients. These findings have now been disseminated to key stakeholders in
Injectable artesunate

Artesun®, developed by Fosun Pharma at Guilin Pharmaceutical Co. Ltd., was the first injectable artesunate product to receive WHO prequalification. The milestone was achieved in 2010 with the support of MMV, and 34 million vials were distributed in 2020 alone. As part of ongoing efforts, MMV supported the refurbishment of Guilin’s manufacturing site, ensuring uninterrupted supplies via the US President’s Malaria Initiative and The Global Fund. To help maintain supply security, MMV supported the WHO prequalification of a second drug called Larinate® 60mg, which was developed by Ipca Laboratories. Cumulatively, 209 million vials of Artesun and Larinate 60 have been distributed to 37 million people, saving an estimated 1.36 million additional lives compared with quinine (assuming patients would have received injectable quinine in the absence of injectable artesunate). As COVID-19 creates numerous risks for malaria efforts, MMV has worked closely with partners to help address bottlenecks and to secure global supply of injectable artesunate with limited disruptions.

In 2020, MMV continued supporting the upscaling of the MAM project in collaboration with an international consortium and Zambian partners, with support from the FIA Foundation for the Automobile and Society (FIA Foundation), Grand Challenges Canada® and match-funding partners. The pilot project in Serenje District increased rural access to commodities such as artesunate rectal capsules for the case management of severe malaria, helping to reduce the reported malaria case fatality rate in children under six years of age in intervention sites. Based on its success, the MAM@Scale project expanded to five districts in Zambia, with the aim of increasing access to artesunate rectal capsules in areas of high disease burden. Importantly, the National Malaria Elimination Centre within the Zambian Ministry of Health have agreed to scale up artesunate rectal capsules at the community level, with a goal to cover 10 districts in 2021.

Rapid assessments of severe malaria case-management practices were completed in Angola and Mali, supporting the National Malaria Control Programmes by addressing areas for improvement, based on recommendations.

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Dr Michael Kayange discusses severe malaria in Malawi and the RASIEC cohort case control study.

What is the burden of malaria and, in particular, severe malaria in Malawi and what impact does the disease have on individuals, communities, and the country as a whole?

Each year there are about six million cases of malaria (one third of the total population) in Malawi, resulting in approximately 2,300 deaths. Patients tend to travel to hospital with at least one guardian, meaning at least 12 million people could be attending hospital due to malaria each year. This keeps adults away from work and children away from school, sometimes for days at a time, which leads to economic and educational impacts on local communities and the country as a whole.

What is Malawi’s national strategy to manage severe malaria? What is the role of injectable artesunate and rectal artesunate?

Our policy for severe malaria includes entry at the health facility or community levels. At the health facility level, patients are assessed by a clinician or nurse and admitted for microscopy diagnosis and treatment if there are signs of severe malaria. Patients with a positive diagnosis receive intravenous artesunate for a minimum of three doses before switching to oral antimalarial drugs. Most patients improve within 24 hours after the first three doses, they are then given oral drugs and discharged. At the community level, health surveillance assistants manage mild malaria but are trained in detecting severe malaria and administering rectal artesunate. They then refer cases to the health facility. This means that severe malaria signs can be detected quickly and drugs can be given at the community level.

What are the main challenges you face in the management of severe malaria?

At the health facility level, delayed diagnosis is a challenge. Some patients admitted with signs of severe malaria do not get a diagnosis within 24 hours, however, this does not stop us managing cases by starting treatment with intravenous artesunate. If the result is positive, we continue with intravenous artesunate and, if not, we stop and move to other treatments. At the community level, compliance with pre-referral management is a challenge. We train health surveillance assistants in severe malaria management, but most cases are still referred without rectal artesunate administration.

Last year, together with MMV you conducted the RASIEC study. What were the key findings?

The greatest impact was observed in health surveillance assistants. The study showed that additional training of health surveillance assistants was needed to maintain correct administration of rectal artesunate. With the RASIEC toolkit, acceptability and use of rectal artesunate increased compared with the control district, and the capacity to identify symptoms of severe malaria also increased, leading to appropriate care. There was no difference in referrals compared with the control district, showing that health surveillance assistants referred patients appropriately. However, the introduction of a referral slip did improve the reception of patients and caregivers at the next healthcare level.

What are the next steps to implement changes based on these findings?

We plan to present study findings to the Case Management Technical Working Group and Malaria Social and Behaviour Change Communication Technical Working Group for possible inclusion in the upcoming community engagement campaign. Unfortunately, this has been delayed due to the COVID-19 pandemic.

What has it been like to work with MMV on this study?

We were privileged to work with MMV on this project and appreciate their support. We would like to engage with them again on future projects targeting the same or different malaria issues in Malawi.
Akullo and Aboli’s story

Buying time to save a life with artesunate rectal capsules

Akullo Conny lives with her little daughter Aboli Patricia in Oyam, Northern Uganda. Mother and daughter love to be in each other’s company and often share domestic chores. However, it was not long ago that Akullo almost lost her only child to an episode of severe malaria.

One night, Akullo woke up to the cries of Aboli who was convulsing and had a burning fever. Akullo was overcome with fear and remembered thinking that her daughter might be dying. She rushed her to the community health worker, who quickly diagnosed that Aboli was suffering from severe malaria and administered artesunate rectal capsules. “The quick actions of the health worker helped lower the fever and the convulsions stopped soon after,” recalls Akullo. Though the administration of artesunate rectal capsules brought immediate relief to Aboli, the community health worker urged Akullo to take her daughter to the nearest town hospital to ensure full treatment for severe malaria. Upon reaching the hospital, Aboli was taken to the children’s ward and started on IV treatment: over the course of her 24-hour stay, she received three doses of injectable artesunate followed by a three-day treatment with an oral artemisinin-based combination therapy. Soon after completion of the parenteral treatment, Aboli’s health improved significantly, and she was able to return home with her mother.

Akullo says, “These medicines saved my daughter’s life. After my experience, I am encouraging fellow mothers to take their children to the community health workers when they notice symptoms of severe malaria, and then follow the referral advice to go to a hospital for further treatment.”

Today, Aboli is a healthy and happy girl who continues to love playing outdoors and being in the company of her mother.

Cipargamin for severe malaria

Cipargamin (KAE609) was discovered and developed by Novartis in collaboration with MMV and the Swiss Tropical and Public Health Institute, together with Wellcome Trust funding. Cipargamin has the potential to become part of a fast-acting treatment in combination for uncomplicated malaria, or a next-generation parenteral treatment for severe malaria. Cipargamin targets a cell membrane channel in the parasite, the first validated new molecular target for malaria in more than 20 years. In a Phase II proof-of-concept study in Thailand, cipargamin rapidly cleared parasites from the blood of adults with uncomplicated \textit{Plasmodium falciparum} or \textit{Plasmodium vivax} malaria. The fast onset of effect was reconfirmed in a Phase II study in Africa of cipargamin monotherapy, which also demonstrated a good safety profile. Cipargamin will be further investigated in combination with other agents.

A new intravenous formulation is also being investigated by Novartis for the treatment of severe malaria, supported by funding from the Wellcome Trust. A Phase I study of the intravenous formulation was completed in 2020, which supported progression to a Phase II study that is expected to start in the third quarter of 2021. This study will be conducted by the PAMAfrica consortium® with funding from the Wellcome Trust and the MMV-led European and Developing Countries Clinical Trials Partnership.
New tools to stop relapse

Preventing malaria relapse for adults and children

While the incidence of *Plasmodium falciparum* malaria infections is highest, *Plasmodium vivax* is the most geographically widespread species of malaria. Although there has been a significant reduction in malaria incidence in malaria-endemic countries recently, the proportion of malaria due to *P. vivax* has been increasing. In 2019, *P. vivax* caused between 5.9 and 7.1 million clinical infections worldwide, many of which were relapses of existing infections that occurred in the absence of a new infective mosquito bite.1 This happens because *P. vivax* parasites can lie dormant in the liver in a form known as hypnozoites, reactivating to trigger multiple episodes of malaria, weeks, months or even years after the initial mosquito bite.

Tafenoquine (Krintafel/Kozenis),2 developed in partnership with GlaxoSmithKline (GSK), became the first new treatment for the prevention of relapse of *P. vivax* malaria in more than 60 years and the first ever single-dose treatment of its kind. In 2019, tafenoquine received its first *P. vivax* endemic-country market authorization approvals in Brazil and Thailand, followed by Peru in January 2021 (see interview below). A further five endemic countries are currently reviewing tafenoquine submissions.

Prior to 2019, primaquine had been the only available treatment for preventing relapses of *P. vivax* malaria. Low patient compliance with the 7–14 days treatment regimen of primaquine has been shown to compromise its therapeutic efficacy, which underscores the need for new, shorter-course treatments and strategies, such as tafenoquine.

Tafenoquine is currently approved for use in patients aged 16 years and older, however, *P. vivax* can be particularly dangerous for children, not only due to the individual periods of illness, but also to cumulative morbidity and indirect mortality. For example, in Papua, Indonesia, children under the age of five years have been shown to be at significant risk of multiple *P. vivax* relapses leading to death within one year of the initial malaria episode.3 To help alleviate this burden, MMV and GSK have developed a new paediatric formulation for children weighing less than 35 kg. Evidence has also been generated to support the use of tafenoquine in children and adolescents under 16 years old.

The TEACH4 study, conducted in Vietnam and Colombia, studied the pharmacokinetics5 of tafenoquine in children and adolescents to provide information on correct dosing and GSK and GSK have developed a new paediatric formulation for adolescents under 16 years old.

Dr Veronica Soto Calle discusses the challenges Peru faces in managing malaria, particularly in the context of COVID-19, and some possible solutions.

**What is the main challenge Peru faces in eliminating malaria?**

Dr Veronica Soto Calle
Executive Director of the Directorate for the Prevention and Control of Metaxenic Diseases and Zoonoses, Ministry of Health of Peru

"The main challenge is securing political support. Malaria has existed in Peru for many years, so people assume it will always be there. Ensuring the political authorities understand that elimination is possible will be critical, because they need to commit to the elimination plans and ensure that the necessary funds are disbursed from the Ministry of Economy and Finance. Sustaining this commitment will be a huge challenge. The Malaria Zero Plan (MZP) has been programmed to last until we achieve malaria elimination, estimated to be in the next 15–20 years. With around 15,000 cases it is not difficult to justify the budget spend, but if we are successful in reducing case numbers, we will need to maintain substantial spending to ensure complete elimination of the malaria parasites. It will be a real challenge to keep the political and financial commitment for elimination when there are very few cases."
What additional challenges has the COVID-19 pandemic brought to malaria control in Peru in 2020 and how have you overcome them?

“One of the major challenges has been patient follow-up. It has been even more difficult during the COVID-19 pandemic in terms of reaching patients in remote areas and ensuring treatment follow-up. Many of the primary healthcare facilities closed during the pandemic, so access to medical care was greatly affected. Fortunately, community health workers have been an invaluable support, especially during 2020. They have continued diagnosing and treating patients in remote rural areas and have led the activities of the MZP. We have also been able to maintain a dedicated team for the MZP, despite many resources having been reallocated to COVID-19 activities. Keeping this dedicated human resource helped us a lot. Another challenge has been the lack of reporting in the national surveillance system. In a non-pandemic year, around 5% of cases do not get reported. Last year this number increased.”

What benefit do you feel single-dose tafenoquine and the quantitative glucose-6-phosphate dehydrogenase (G6PD) test could bring to malaria control and elimination efforts in Peru?

“Most malaria patients have P. vivax, which means that they receive treatment for at least seven days. Currently, treatment adherence is only around 60%, partly due to patients living in remote areas far from health facilities. If we could have a single-dose treatment, it would be wonderful in terms of adherence. The next phase of the MZP aims to reduce malaria by 99%. We need tools that allow us to achieve that objective. Drugs such as tafenoquine could really boost adherence in future years, combined of course with a safety test such as the G6PD test.”

The burden of relapsing P. vivax malaria on families

Nossa Senhora de Fatima is a remote village located in the middle of the Brazilian Amazon. In addition to being one of the most beautiful places in Brazil, the Amazonian region also accounts for 99.5% of all national malaria cases.

Raquel da Silva lives in Nossa Senhora de Fatima with her family. For Raquel, the burden of P. vivax malaria is heavy. Not only has she been ill with P. vivax malaria many times, but she has to care for each member of her family who have been infected one after the other. “My family and I had malaria five times, for 5 consecutive months last year,” she says. “When I got malaria, my baby was 6 months old, so I couldn’t take the full treatment regimen for 7 days. I took just enough so my symptoms would improve, so it always relapsed. My husband works so he had to leave the house and I didn’t have energy to do anything. It was hard.”

In addition to transmission through mosquito bites, P. vivax malaria can relapse causing multiple episodes of malaria from a single infectious mosquito bite. It impacts efforts to achieve global goals like zero poverty and gender equality. Research shows that each episode of malaria requires at least two days of care, the burden of which is almost always borne by women and girls, preventing them from pursuing economic and social activities like going to work and school.

There is an urgent need to improve access to new tools for relapsing P. vivax malaria in these remote villages so that Raquel, and women like her, are relieved of the burden of care, and children can go to school and play fearlessly.

The Ministry of Health, in partnership with MMV, plans to conduct a study to understand the feasibility of implementing quantitative point-of-care G6PD testing with tafenoquine in real-world settings before treatment is made available in Brazil. This study, known as Tafenoquine Roll-out Study (TRuST), is due to take place in 2021. Mathematical modelling work conducted by the Pasteur Institute in partnership with the Oswaldo Cruz Institute in Brazil estimates that single-dose tafenoquine could lead to a 38% reduction in transmission and over 214,000 cumulative averted cases within the first five years of introduction in Brazil.6

Raquel da Silva’s story

Raquel and her son, Carlos

6. New tools to stop relapse

Selecting the best combinations: pioneering developments to accelerate R&D

Innovation is critical to achieving Medicines for Malaria Venture’s (MMV’s) long-term goal of eradicating malaria, and therefore it is our priority to create tools that accelerate the research and development of new antimalarial drugs.

Malaria Drug Development Catalyst

Successful drug discovery efforts over the last decade mean that MMV and partners now have an increasing portfolio of new drug candidates. To achieve optimal efficacy and reduce the chance of resistance emerging to antimalarial medicines, it is important that they are administered as combination therapies. Ideally, the drugs within these combinations should be complementary in terms of their antimalarial activity and when they are active in the body after administration. Additionally, these drugs should be well tolerated when given together and, preferably, not show signs of generating resistant parasites in laboratory conditions.

At MMV, understanding how different preclinical candidate molecules interact is a crucial, complex and extensive process that allows us to identify the best drug combinations for further development. It is important that all combinations are reviewed through the same lens. In 2019, MMV launched the Malaria Drug Development Catalyst – a scientific platform that helps to provide that lens and promote collaboration between industry partners to accelerate the development of next-generation drug combinations for uncomplicated malaria (Figure 3). The Catalyst is both curated and led by MMV and assesses single molecules that have entered translational development. Through the Catalyst, MMV provides funding and preclinical data (pharmacological assays, pharmacokinetic models and assessments of safety and tolerability), thereby accelerating decision-making for combination partners. Decisions are based on the complementary characteristics of the drug candidates, irrespective of who owns the compounds. The Catalyst also opens a dialogue between MMV’s industry partners, helping to promote the exchange of knowledge and increase the efficiency of drug development. Ultimately, the aim of MMV’s Malaria Drug Development Catalyst is to support the identification and progression of the best drug combinations for clinical testing, enabling members to optimize and de-risk their clinical development plans. This helps to get lifesaving medicines to patients whilst making the best use of the resources available.

The Catalyst is open to all of MMV’s pharmaceutical partners with drugs within 12 months of entering Phase I studies. In 2019, Merck, Novartis, and Zydus Cadila joined the platform with their respective assets. Shin Poong Pharmaceuticals joined in 2020 and Sanofi is currently an observer. In July of 2020, MMV’s Expert Scientific Advisory Committee endorsed a strategy to progress lead combinations, identified from data generated under Catalyst activities, into the clinic. Entry into Phase II is projected for 2022. Future Catalyst research will include more recently approved preclinical candidates, many of which are completely refractory to resistance selection in the laboratory, including compounds from MMV, Novartis and GlaxoSmithKline, along with new candidates approved by MMV’s Expert Scientific Advisory Committee in 2020.
Monotherapies go in, combination candidates come out.

VIS: volunteer infection studies / SCID: a laboratory model of malaria that provides a prediction of drug response in humans / CPRR: in vitro checkerboard assays.

Ultimately, the aim of MMV’s Malaria Drug Development Catalyst is to support the identification and progression of the best drug combinations for clinical testing, enabling members to optimize and de-risk their clinical development plans.

Figure 3: Malaria Drug Development Catalyst
Why do we need these new modelling tools? What are their advantages and what challenges do they help us overcome?

The new mathematical model we have developed allows us to predict how combinations may behave in patients before clinical trials, which would be much more expensive than establishing and running a model. These models enable us to incorporate all the knowledge available on compounds from different sources and predict the clinical outcome. Based on simulations for six combinations, four are being progressed to clinical trials. We hope that these tools will help select the most promising combinations for further development.

Who did MMV partner with to develop them?

We worked with the mathematical modelling company IntiQuan based in Basel, Switzerland, to develop our algorithm, with additional support from Daniel Lill, a student from the University of Freiburg, Germany. We built our pharmacokinetic/pharmacodynamic models in collaboration with Prof. Sebastian Wicha from the University of Hamburg. To obtain information on the pharmacological interaction, Claudia Demarta-Gatsi from the MMV team worked closely with the Swiss Tropical and Public Health Institute to set up in vitro assays, and with The Art of Discovery in Spain to set up laboratory experiments.

Now that you and your team have developed these tools, what are the next projects in the pipeline?

In the future, we aim to look at combinations of three or more compounds using similar models. This would allow us to explore the combination of additional characteristics in one medicine, such as transmission-blocking and parasite clearance. We would also like to extend the model to look at chemoprophylaxis.

ACPR28 modelling for combinations

Antimalarial drugs can be combined to increase efficacy, delay resistance and prolong their clinical utility, but how can we better understand how individual drugs will interact when administered together? The World Health Organization (WHO) and regulatory authorities assess drug combinations by looking at the number of people who achieve an adequate clinical and parasitological response 28 days from the start of treatment (ACPR28). For a drug to be approved, ≥ 95% of patients must achieve ACPR28. To help MMV decide which drug combinations have such potential, pharmacometric1 scientists use in vitro experiments, laboratory models and clinical trials.

Mathematical models are built from this data to characterize drug combinations and predict the drug dose required. This information helps MMV and partners make decisions driven by data, prioritizing combinations that can feasibly be combined to reach the required target efficacy. These predictive models are becoming an important tool for efficiently identifying new antimalarial drug combinations. For example, in 2020, ACPR28 modelling was successfully used by MMV’s Malaria Drug Development Catalyst to analyse and rank six drug combinations. Notably, this helped prioritize four promising combinations, saving resources and time.
In 2020, MMV developed the innovative, free, user-friendly application ‘MMVSola’. MMVSola combines information on the chemical, physical and biological properties of a compound to predict the human dosage required to clear all malaria parasites from a patient. It uses state-of-the-art mathematical modelling to consolidate data from different preclinical experiments, seamlessly translating the results into predictions on the clinical activity of different drug candidates in humans. This means that, for the first time, an accessible application can be used to predict dosing and treatment durations for potential antimalarial candidates as early as the discovery phase. This helps identify the best possible candidates, and design better and more informative clinical trials. It also removes the need for animal efficacy studies, saving crucial resources, reducing animal usage and expediting drug development timelines. MMVSola will also help standardize malaria drug discovery data, so that laboratories can collaborate more effectively. MMVSola is a powerful and innovative tool, which can be used to select drug candidates and transform early drug development.

Could you briefly introduce us to MMVSola?

MMVSola is a free, web-based tool based on a well-established methodology developed by MMV and launched in 2020. It performs human exposure and dose predictions for antimalarial compounds using preclinical data. We have specific dose and parasite-reduction criteria for our clinical candidates – aiming for a single-dose combination treatment of less than a gram to cure a typical adult. MMVSola allows teams to confirm compounds are in line with these criteria from the early discovery stages and, if not, identifies which of the compound properties are best to focus optimization on. Beyond malaria drug discovery, MMVSola’s human pharmacokinetic prediction capability can be freely used for drug discovery in any other therapeutic area.

What are the main advantages of MMVSola?

The tool allows researchers to take early (and limited) data and perform a preliminary estimation of the efficacious dose in humans by the discovery teams without the need for an expert. As predictions are made using in vitro and limited animal data, MMVSola can be used early, before investing in expensive and time-consuming experiments. It also identifies key compound properties for further development during the lead optimization phase, including potency, metabolism and protein binding. By using this tool for all our discovery projects, we also aim to standardize the comparison of compounds across projects.

Where does the name MMVSola come from and who did you partner with to develop it?

MMVSola was named to commemorate Suresh Solapur, who tragically passed away recently and was an early champion of using pharmacokinetic/pharmacodynamic modelling to predict dosage at MMV. He also contributed to the discovery and development of one of our key candidates (ZY19489 – Zydus Cadila, p. 16). For the pharmacokinetic aspects of the tool, we partnered with Peter Webborn (an independent pharmacokinetic consultant) to develop our predictions of human exposure using well-established and robust methodology. For pharmacodynamic modelling and tool construction, we worked with Ghaith Aljayoussi (Liverpool School of Tropical Medicine, UK), who also developed the in vitro methodology, which replaces animal efficacy studies. Key members of the MMV modelling team were Nathalie Gobeau, Aline Fuchs and Mohammed Cherkaoui, who supported Ghaith and validated the methodology.

Now that you and your team have developed this tool, what are the next projects in the pipeline?

We will now focus on further developing the tool and creating new capabilities. We are aiming to use real-world pharmacokinetic/pharmacodynamic population data to enable predictions for ACPR28 and, importantly, to predict a dose in children and a dose for prophylaxis. We are also providing continuous support to users of the tool and working towards publishing this work.
Project of the Year 2020

The brilliance of resistance profiling

Each year, a project is selected by Medicines for Malaria Venture’s (MMV’s) independent Expert Scientific Advisory Committee (ESAC) as Project of the Year. This highlights an exciting drug discovery and development project in the MMV portfolio and recognizes the scientific excellence of partners involved. The winner of Project of the Year 2020 is the malaria drug resistance profiling project, led jointly by Prof. David Fidock (Columbia University, USA) and Dr Didier Leroy (MMV). This project profiles potential new antimalarials to discern their potential to select for resistance – and to characterize any resistance – before projects are progressed into human studies.

Resistance to antimalarial medicines is an ongoing concern in malaria, leading to failure of frontline therapies. Broadening our understanding of resistance mechanisms is key to addressing this major issue. By investigating new antimalarials in the laboratory, the project team can better predict how resistance can develop in a real-world setting. This profiling also improves efficiency in drug discovery by identifying drug candidates exhibiting higher risks early and characterizing favourable compounds that can progress into more advanced and costly studies. Such an approach has also increased our understanding of resistance mechanisms in older drugs including chloroquine, piperaquine and artemisinin.
Could you briefly describe the profiling project? When did it begin and how has it evolved?

**Dr Leroy:** The drug discovery profiling project is central to MMV’s drug development pipeline. Its purpose is to interrogate the biology of the malaria parasite in terms of drug resistance, using laboratory-based techniques to predict the risk of resistance in the field. The Fidock lab started coordinating with MMV in 2008 to investigate the drug discovery and development portfolio and identify resistance risks.

**Prof. Fidock:** Profiling is done throughout drug development, from early drug discovery to lead compounds and candidate selection, allowing for de-prioritization of series with unacceptable risks. Through whole-genome sequence analyses of cultured, drug-pressured resistant parasites, we can investigate the genetic basis of *Plasmodium falciparum* resistance. This increases our understanding of the parasite’s biology and helps us identify novel mechanisms of action that won’t be compromised by resistance mechanisms already existing in the field. Our technology has evolved to allow for accelerated processes in the laboratory, whole-genome sequencing analyses and reverse-genetic approaches to confirm the impact of point mutations or copy number variations on resistance. In addition, data accumulated in recent years has shown that our laboratory results closely match what is seen in human volunteer infection studies, humanized mouse models and clinical trials, showing that the drug discovery profiling project can accurately predict paths to resistance.

Why is it an exciting project?

**Dr Leroy:** This project is exciting because, for the first time, we are at a point in malaria drug discovery where we can investigate compounds and relate resistance data to the real-world setting. In turn, discovery can be guided by clinical data, effectively ‘closing the loop’ in malaria drug development.

**Prof. Fidock:** Beyond this, our project has interrogated key pathways in the malaria parasite and helped to increase our understanding of its biology, particularly its vulnerabilities from a therapeutic perspective.

How does the project fit into MMV’s overarching strategy on resistance risk assessment?

**Dr Leroy:** This profiling project is integrated into MMV’s overarching strategy as a key tool in assessing the risk of resistance throughout the pipeline. Resistance could be interrogated in clinical trials, however, the ability to identify resistance risks during the drug development process allows MMV to make strategic decisions much earlier to deliver higher-quality antimalarial candidates and combinations.

Why is it important to define the resistance risks of antimalarials?

**Dr Leroy:** It is highly cost-effective to have a platform that can predict the risk of resistance early. Re-prioritization through defined risk criteria allows resources to be used more efficiently and results in higher-quality products. In addition, our understanding of resistance can be used to inform future antimalarial development, particularly the choice of combination partners.

What led you to develop this project and decide to work together?

**Prof. Fidock:** This project presented a very appealing convergence of interests. Our lab was initially focused on understanding clinical resistance of first-line antimalarial medicines, but it became clear that investigating drug resistance in antimalarial candidates is key to helping guide drug discovery and development efforts. In this way, MMV and our lab were motivated to work together to develop and deliver next-generation medicines for malaria. This has been, and continues to be, an extremely enriching partnership that benefits from the extensive experience of all partners.

What has the impact of this project been on MMV’s portfolio and the drug discovery process?

**Dr Leroy:** So far, 180 compounds have been investigated and 18 drug targets and mechanisms of resistance have been identified. This has had an extensive impact on the development and quality of compounds in MMV’s pipeline. MMV is a global leader in coordinating malaria drug discovery and development, and this project has benefited academia, industry and pharmaceutical research by streamlining development and highlighting the need to identify resistance early.

This profiling project is integrated into MMV’s overarching strategy as a key tool in assessing the risk of resistance throughout the pipeline.
Financial view

Financial year to 31 December 2020

Legal status
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. The 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 consolidated financial statements).

Business model
MMV receives funding and support from government agencies, private foundations, international organizations, corporations, corporate foundations and private individuals. These funds are used to finance MMV’s portfolio of R&D projects (historically 70–80% of total expenditure), as well as specific, targeted access & product management (APM) interventions that aim to facilitate increased access to malaria medicines by vulnerable populations in disease-endemic countries and support their appropriate use (historically 5–15% of total expenditure). Since its foundation in 1999, MMV has brought forward eleven new antimalarial drugs and taken over the access stewardship of two more. Together, these medicines have saved an estimated 2.73 million lives. With partners, MMV has also established the world’s largest R&D pipeline of innovative, new antimalarial medicines, designed to address remaining unmet medical needs and support the push towards malaria elimination and eradication. MMV’s private sector partners support joint projects through co-investment and by contributing expertise and facilities. We estimate that for every United States dollar (USD) invested, MMV leverages approximately USD 1 in matched funds for external costs, plus USD 1.5 of in-kind contributions through its partners, resulting in a total investment impact of USD 3.5.

Tax status
As a not-for-profit Swiss foundation, MMV is exempt from Swiss cantonal and federal taxes and is the equivalent of an exempt organization within the meaning of section 501(c)(3) of the United States Internal Revenue Code. Furthermore, from 1 January 2011, the Swiss Federal Council granted MMV the status of ‘Other International Organization’ conferring certain privileges and immunities including exemption from VAT in Switzerland – representing an estimated additional contribution from Switzerland to MMV of approximately 1 million Swiss francs (CHF) per annum.

Financial management
The philosophy underlying MMV’s financial management is that of prudent, conservative control, including appropriate return on interim treasury investments. Forecasting various long-term funding and income scenarios enables MMV to manage its growing R&D portfolio more effectively. It also provides a baseline analysis for fundraising activities aimed at financing the portfolio in line with long-term projections. Given the current unsteady financial environment and market conditions, it is evident that the portfolio, cash flow and new potential fundraising opportunities must be managed dynamically and seamlessly. As an ethical healthcare organization, MMV maintains sufficient funds to support the managed close-out of ongoing clinical studies, related publication of clinical data, reporting and regulatory obligations, including those outlined by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH).

Figure 4: Total donations received in 2020

<table>
<thead>
<tr>
<th>Private Foundations</th>
<th>43.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation (BMGF)</td>
<td></td>
</tr>
<tr>
<td>Governments</td>
<td></td>
</tr>
<tr>
<td>UK Foreign, Commonwealth &amp; Development Office (FCDO, ex-DFID)</td>
<td>27.2%</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP)</td>
<td>11.2%</td>
</tr>
<tr>
<td>Ministry of Foreign Affairs of the Netherlands (DGIS)</td>
<td>3.8%</td>
</tr>
<tr>
<td>German Federal Ministry of Education and Research (BMBF)</td>
<td>3.2%</td>
</tr>
<tr>
<td>Australian Government Department of Foreign Affairs and Trade (DFAT)</td>
<td>3.1%</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (SDC)</td>
<td>2.6%</td>
</tr>
<tr>
<td>Ireland Department of Foreign Affairs (Irish Aid)</td>
<td>1.3%</td>
</tr>
<tr>
<td>United States Agency for International Development (USAID) and National Institutes of Health (NIH)</td>
<td>1%</td>
</tr>
<tr>
<td>Principality of Monaco Direction de la Coopération Internationale (DCI)</td>
<td>0.1%</td>
</tr>
<tr>
<td>Others (Other donors, partnerships, individual donations)</td>
<td></td>
</tr>
<tr>
<td>Global Health Innovative Technology Fund (GHT)</td>
<td>1.5%</td>
</tr>
<tr>
<td>Bristol Myers Squibb Foundation</td>
<td>0.6%</td>
</tr>
<tr>
<td>Program for Appropriate Technology in Health (PATH)</td>
<td>0.3%</td>
</tr>
<tr>
<td>Newcrest Mining Limited</td>
<td>0.2%</td>
</tr>
<tr>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
Banking relationships
Cash and cash equivalents represent the largest portion of MMV’s total assets. Relationships with four major Swiss banks allow MMV to effectively manage cash resources and diversify risk. The banks provide services such as current accounts, investment and cash management facilities in multiple currencies. The Foundation Fund explained below is managed by an investment manager, which is part of a major US investment banking group, under the terms of a discretionary portfolio management mandate and under the supervision of the Board of Directors of MMV.

Foreign exchange exposure
MMV operates in a multi-currency environment. Cash inflows from donors are largely received in US dollars and British pounds sterling (GBP), and a smaller portion in other currencies, such as Swiss francs (CHF), euros (EUR), Australian dollars (AUD) and Japanese yen (JPY). Cash outflows for R&D and APM projects are mostly in USD, which is the standard currency used in the various contractual agreements signed with each project partner and therefore a natural cover for financial exchange risk. Being a Swiss-based organization, many operational expenses are in CHF. Throughout the financial year, MMV’s management strives to maintain a natural hedged position, whereby the breakdown of cash available by currency mirrors the estimated breakdown of expenditure by currency. At the end of 2020, MMV entered into a forward agreement with one of its relationship banks to fix the monthly conversion of USD into CHF at a predefined exchange rate throughout 2021. The reference currency for accounting at MMV is USD.

Financial reporting standards
The consolidated financial statements (including MMV North America Inc.) are prepared in compliance with Swiss GAAP FER, as well as the requirements of the Swiss Code of Obligations. The organization’s operating procedures are constantly updated in line with evolving requirements. MMV also issues stand-alone financial statements, which are prepared in compliance with the Swiss Code of Obligations (articles 957 to 963b, in force since 1 January 2013).

Foundation capital
By 31 December 2003, the stipulated foundation capital of USD 4 million was fully subscribed (in a Swiss foundation it is a legal requirement that foundation capital be constituted without delay, to provide a degree of financial security). The foundation capital has since remained unchanged.

Revenue
Total revenue in 2020 amounted to USD 88.4 million (2019: USD 93.4 million), thanks to the continued commitment of our donors.

In 2020, the Bill & Melinda Gates Foundation (BMGF) contributed a total of USD 32.5 million as part of the USD 180 million five year unrestricted grant for the period between 1 July 2019 and 30 June 2024 – the largest single donation pledged to MMV since its foundation in 1999. Furthermore, BMGF provided a one-off USD 5.5 million restricted grant related to COVID-19 activities. In 2020, BMGF’s contributions to MMV represented 44% of total MMV revenue. The UK Foreign, Commonwealth and Development Office (FCDO, ex-DFID) contributed a total of GBP 15 million (equivalent to USD 19.1 million) as part of the 2017–2021 unrestricted grant for the period between 1 July 2019 and 30 June 2024 – the largest single donation pledged to MMV since its foundation in 1999. Furthermore, BMGF provided a one-off USD 5.5 million restricted grant related to COVID-19 activities. In 2020, FCDO’s contributions represented 27% of total MMV revenue.

In 2020, MMV was awarded two new grants: a new USD 10 million grant from the Korea International Cooperation Agency Global Disease Eradication Fund (KOICA GDEF) related to the four year period 2021–2024; and (through MMV North America Inc.) a USD 0.5 million grant from the Bristol Myers Squibb Foundation.

In 2020, MMV received funding support from the European and Developing Countries Clinical Trials Partnership (EDCTP), the Directorate-General for International Cooperation (DGIS) of the Netherlands, the Australian Government Department of Foreign Affairs and Trade (DFAT), the German Federal Ministry of Education and Research (BMBF), the Swiss Agency for Development and Cooperation (DEZA/SDC), the Global Health Innovative Technology Fund (GHIT), the Irish government’s programme for overseas development (Irish Aid), the United States Agency for International Development (USAID), PATH, Newcrest Mining Limited, and the Direction de la Coopération Internationale (DGI) of the Principality of Monaco. When comparing 2020 to 2019, it should be noted that 2019 revenue included a one-off restricted indemnity payment of EUR 17 million (equivalent to USD 19.4 million) from our pharmaceutical partner Sanofi for completion by MMV (under MMV’s operational responsibility and leadership) of a Phase II artefenomel–ferroquine drug combination development programme from 1 January 2019 onwards.

MMV is extremely grateful for these and previous commitments from all its donors and partners.
Expenditure

Capital & reserves
The total unrestricted funds of the organization as of 31 December 2020 amounted to USD 46.4 million (31 December 2019: USD 59.4 million), of which USD 4.0 million was paid-in capital, and USD 10.7 million unrestricted operating funds. There is an additional USD 31.8 million represented by the Foundation Fund (see below). As of the same date, total restricted funds amounted to USD 17.0 million (31 December 2019: USD 1.5 million).

Cash and cash equivalents
MMV’s total cash balance as of 31 December 2020 amounted to USD 41.9 million (2019: USD 57.2 million).

Foundation Fund
The Foundation Fund is a directly controlled quasi-endowment structure to invest the revenues from MMV’s contractual share of the priority review voucher (PRV) received by our pharmaceutical partner GlaxoSmithKline (GSK) upon approval of Krintafel (tafenoquine) from the US Food and Drug Administration (FDA) in July 2018, 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, which are consistent with its humanitarian mission, but may be restricted by the current business model of the foundation.

Financial commitments
MMV maintains sufficient funds to support the appropriately managed close-out of ongoing clinical studies in compliance with ICH requirements.

Financial forecasts
Management estimates that MMV’s current portfolio will require an investment of approximately USD 85 million per annum over the five year period 2021–2025. With approximately USD 276 million available at the start of 2021 (USD 41.9 million cash as of 1 January 2021, USD 218.2 million committed pledges over the period 2021–2025 and a residual USD 16.2 million receivable from pharmaceutical partner GSK payable 50% in July 2022 and 50% in July 2023), the organization has sufficient funds for 2021, but is currently tracking a shortfall of approximately USD 150 million over the five year period 2021–2025. Although fundraising activities in 2020 were successful and significant additional funds were sourced, major fundraising efforts will be required in 2021 and beyond, as MMV continues to strive to meet the projected financial requirements of its growing portfolio.

Financial tables
The following financial tables and notes are extracted from the Swiss GAAP FER-compliant accounts.

Figure 6: MMV income and expenditure to date and scenario 2020–2024
Report on extracted elements of consolidated financial statements to the management of

**MMV MEDECINES FOR MALARIA VENTURE, Meyrin**

We have audited the consolidated financial statements of the MMV MEDECINES FOR MALARIA VENTURE for the year ended 31 December 2020 from which the extracted elements of consolidated financial statements were derived, in accordance with Swiss law and Swiss Auditing Standards. In our report dated 29 April 2021, we expressed an unqualified opinion on the consolidated financial statements from which the extracted elements of consolidated financial statements were derived.

In our opinion, the accompanying extracted elements of consolidated financial statements are consistent, in all material respects, with the consolidated financial statements from which they were derived.

For a better understanding of the organisation’s financial position and the results of its operations for the period and of the scope of our audit, the extracted elements of consolidated financial statements should be read in conjunction with the consolidated financial statements from which the extracted elements of consolidated financial statements were derived and our audit report thereon.

KPMG SA

Hélène Béguin
Licensed Audit Expert
Auditor in Charge

Jordan Chassard

Geneva, 29 April 2021

**Enclosure:**
- Extracted elements of the consolidated financial statements (page 47 to 55 included)
## MMV CONSOLIDATED STATEMENT OF FINANCIAL POSITION

<table>
<thead>
<tr>
<th>ASSETS</th>
<th>Notes</th>
<th>31 Dec 2020 USD</th>
<th>31 Dec 2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Current assets</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cash and cash equivalents</td>
<td>3</td>
<td>41,857,848</td>
<td>57,233,655</td>
</tr>
<tr>
<td>Donations receivable</td>
<td>7</td>
<td>645,911</td>
<td>426,174</td>
</tr>
<tr>
<td>Accounts receivable</td>
<td></td>
<td>874,321</td>
<td>788,720</td>
</tr>
<tr>
<td>Tax receivable</td>
<td></td>
<td>7,451</td>
<td>263,992</td>
</tr>
<tr>
<td>Prepaids</td>
<td></td>
<td>555,643</td>
<td>735,240</td>
</tr>
<tr>
<td>Prepaid portfolio commitments</td>
<td>11</td>
<td>10,646,546</td>
<td>907,157</td>
</tr>
<tr>
<td><strong>Total current assets</strong></td>
<td></td>
<td><strong>54,587,720</strong></td>
<td><strong>60,354,938</strong></td>
</tr>
<tr>
<td><strong>Long-term assets</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term receivables</td>
<td>8</td>
<td>16,231,586</td>
<td>15,567,566</td>
</tr>
<tr>
<td>Investment portfolio - Foundation Fund</td>
<td>5</td>
<td>15,526,418</td>
<td>14,431,325</td>
</tr>
<tr>
<td>Guarantees</td>
<td>18</td>
<td>257,882</td>
<td>234,067</td>
</tr>
<tr>
<td>Fixed assets, net</td>
<td>4</td>
<td>208,067</td>
<td>256,722</td>
</tr>
<tr>
<td><strong>Total long-term assets</strong></td>
<td></td>
<td><strong>32,224,053</strong></td>
<td><strong>30,489,700</strong></td>
</tr>
<tr>
<td><strong>TOTAL ASSETS</strong></td>
<td></td>
<td><strong>86,811,773</strong></td>
<td><strong>90,844,638</strong></td>
</tr>
</tbody>
</table>

| LIABILITIES, CAPITAL & RESERVES | | |
| Current liabilities | | |
| Accrued portfolio commitments | | 13,728,350 | 15,103,931 |
| Deferred revenue | 9 | 2,800,000 | 9,793,333 |
| Other creditors | | 2,296,771 | 1,502,687 |
| Accrued expenses | | 3,072,030 | 2,748,345 |
| Short-term provisions | 6 | 1,377,481 | 838,540 |
| Foreign exchange contracts | 13 | 58,950 | - |
| **Total current liabilities** | | **23,335,582** | **29,986,846** |
| Restricted operating funds | | 16,936,831 | 1,506,750 |
| **Total restricted funds** | | **16,936,831** | **1,506,750** |
| Unrestricted funds | | | |
| Paid-in capital | | 4,000,000 | 4,000,000 |
| Foundation Fund | 5 | 31,758,024 | 29,998,911 |
| Unrestricted operating funds | | 10,781,336 | 25,352,131 |
| **Total restricted funds** | | **46,539,360** | **59,351,042** |
| **TOTAL LIABILITIES, CAPITAL & RESERVES** | | **86,811,773** | **90,844,638** |

### MMV CONSOLIDATED STATEMENT OF CHANGES IN CAPITAL

<table>
<thead>
<tr>
<th></th>
<th>Balance at 1 January 2019</th>
<th>Internal funds transfer</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2019</th>
<th>Prior year adjustments</th>
<th>Gain/(loss) for the period</th>
<th>Balance at 31 December 2020</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricted operating funds</td>
<td>11,265,709</td>
<td>(7,296,894)</td>
<td>(2,462,065)</td>
<td>1,506,750</td>
<td>-</td>
<td>15,430,081</td>
<td>16,936,831</td>
</tr>
<tr>
<td><strong>TOTAL RESTRICTED OPERATING FUNDS</strong></td>
<td>11,265,709</td>
<td>(7,296,894)</td>
<td>(2,462,065)</td>
<td>1,506,750</td>
<td>-</td>
<td>15,430,081</td>
<td>16,936,831</td>
</tr>
<tr>
<td>Paid-in capital</td>
<td>4,000,000</td>
<td>-</td>
<td>-</td>
<td>4,000,000</td>
<td>-</td>
<td>-</td>
<td>4,000,000</td>
</tr>
<tr>
<td>Foundation Fund</td>
<td>28,426,969</td>
<td>-</td>
<td>1,571,942</td>
<td>29,998,911</td>
<td>-</td>
<td>1,759,113</td>
<td>31,758,024</td>
</tr>
<tr>
<td>Unrestricted operating funds</td>
<td>19,505,608</td>
<td>7,296,894</td>
<td>(1,450,371)</td>
<td>25,352,131</td>
<td>1,420,653</td>
<td>(15,991,448)</td>
<td>10,781,336</td>
</tr>
<tr>
<td><strong>TOTAL UNRESTRICTED FUNDS</strong></td>
<td>51,932,577</td>
<td>7,296,894</td>
<td>121,571</td>
<td>59,351,042</td>
<td>1,420,653</td>
<td>(14,232,335)</td>
<td>46,539,360</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>63,198,286</strong></td>
<td>-</td>
<td>(2,340,494)</td>
<td><strong>60,857,792</strong></td>
<td><strong>1,420,653</strong></td>
<td><strong>1,197,747</strong></td>
<td><strong>63,476,192</strong></td>
</tr>
<tr>
<td>REVENUE</td>
<td>Notes</td>
<td>31 Dec 2020 USD</td>
<td>31 Dec 2019 USD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------</td>
<td>-------</td>
<td>----------------</td>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donation revenue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted donations</td>
<td>7</td>
<td>29 143 260</td>
<td>12 561 313</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrestricted donations</td>
<td>7</td>
<td>57 709 230</td>
<td>58 830 438</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total donations revenue</strong></td>
<td>7</td>
<td>86 852 490</td>
<td>71 391 751</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restricted revenue from partnerships</td>
<td>8</td>
<td>–</td>
<td>19 351 128</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unrestricted revenue from partnerships</td>
<td>8</td>
<td>1 362 337</td>
<td>2 562 760</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other unrestricted revenue</td>
<td>8</td>
<td>164 603</td>
<td>118 474</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total other revenue</strong></td>
<td></td>
<td>1 526 940</td>
<td>22 032 362</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL REVENUE</strong></td>
<td>8</td>
<td>88 379 430</td>
<td>93 424 113</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| EXPENDITURE                                   |       |                |                |
| Portfolio expenditure                         |       |                |                |
| Discovery project expenditure                 | 10    | 24 144 192     | 22 266 240     |
| Translational project expenditure             | 10    | 24 976 098     | 20 122 690     |
| Development project expenditure              | 10    | 12 499 688     | 23 622 642     |
| Access & product management project expenditure | 10  | 12 239 427     | 15 271 157     |
| Other portfolio expenditure                   |       | 2 286 135      | 3 021 284      |
| **Total portfolio expenditure**               |       | 76 145 540     | 84 302 013     |
| Support of portfolio expenditure              |       |                |                |
| Board meetings expenditure                    | 16    | 219 031        | 329 817        |
| Corporate affairs expenditure                 |       | 6 148 532      | 5 834 979      |
| Administration & finance expenditure          |       | 6 600 129      | 6 084 948      |
| **Total support of portfolio expenditure**    |       | 12 967 692     | 12 249 744     |
| Other expenditure                             | 7 000 | –              | –              |
| Funding reimbursements                         |       | 62 805         | 36 640         |
| **Other expenses**                            |       | 69 805         | 36 640         |
| **TOTAL EXPENDITURE**                         |       | 89 183 037     | 96 590 397     |
| RESULT FROM OPERATING ACTIVITIES              |       | (803 607)      | (3 166 284)    |
| Financial income                              | 13    | 2 520 140      | 1 005 032      |
| Financial expenses                            | 13    | (518 786)      | (179 243)      |
| Net financial result                          |       | 2 001 354      | 825 789        |
| Of which related to Foundation Fund           |       | 1 095 092      | 217 861        |
| **NET SURPLUS PRIOR TO ALLOCATIONS**          | 1 197 747 | (2 340 495) |

| ALLOCATIONS                                   |       |                |                |
| Transfer (to)/from unrestricted operating funds |       | 15 991 447     | 1 450 371      |
| Transfer (to)/from Foundation Fund            |       | (1 759 113)    | (1 571 942)    |
| Transfer (to)/from donor restricted operating funds |       | (15 430 081)  | 2 462 065      |
| **NET SURPLUS AFTER ALLOCATIONS**             | –     | –              | –              |
### MMV CONSOLIDATED STATEMENT OF CASH FLOW FOR THE PERIOD ENDED

<table>
<thead>
<tr>
<th>Notes</th>
<th>USD 2020</th>
<th>USD 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(LOSS)/SURPLUS FOR THE YEAR</strong></td>
<td>1 197 747</td>
<td>(2 340 495)</td>
</tr>
<tr>
<td><strong>CASH FLOW FROM OPERATING ACTIVITIES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in provisions</td>
<td>6</td>
<td>538 941</td>
</tr>
<tr>
<td>Depreciation</td>
<td>4</td>
<td>84 302</td>
</tr>
<tr>
<td>(Increase)/decrease in donations receivable</td>
<td></td>
<td>(219 737)</td>
</tr>
<tr>
<td>(Increase)/decrease in accounts receivable</td>
<td>8</td>
<td>(85 601)</td>
</tr>
<tr>
<td>(Increase)/decrease in tax receivable</td>
<td></td>
<td>256 541</td>
</tr>
<tr>
<td>(Increase)/decrease in portfolio-related prepaid expenses</td>
<td></td>
<td>(9 739 389)</td>
</tr>
<tr>
<td>(Increase)/decrease in prepaid expenses</td>
<td></td>
<td>179 597</td>
</tr>
<tr>
<td>Increase/(decrease) in donations receivable</td>
<td></td>
<td>(219 737)</td>
</tr>
<tr>
<td>(Increase)/decrease in accounts receivable</td>
<td>8</td>
<td>(85 601)</td>
</tr>
<tr>
<td>(Increase)/decrease in tax receivable</td>
<td></td>
<td>256 541</td>
</tr>
<tr>
<td>(Increase)/decrease in portfolio-related prepaid expenses</td>
<td></td>
<td>(9 739 389)</td>
</tr>
<tr>
<td>(Increase)/decrease in prepaid expenses</td>
<td></td>
<td>179 597</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued portfolio-related commitments</td>
<td></td>
<td>(1 311 095)</td>
</tr>
<tr>
<td>Increase/(decrease) in deferred revenue</td>
<td>9</td>
<td>(6 993 333)</td>
</tr>
<tr>
<td>Increase/(decrease) in other creditors</td>
<td></td>
<td>681 151</td>
</tr>
<tr>
<td>Increase/(decrease) in accrued expenses</td>
<td></td>
<td>304 919</td>
</tr>
<tr>
<td>(Increase)/decrease in long-term receivables</td>
<td>8</td>
<td>(664 020)</td>
</tr>
<tr>
<td>Increase/(decrease) in reserves due to reimbursement of prior years’ expenditure</td>
<td></td>
<td>1 420 652</td>
</tr>
<tr>
<td>Unrealized foreign currency (gain)/loss</td>
<td></td>
<td>(616 062)</td>
</tr>
<tr>
<td><strong>CASH FLOW FROM INVESTMENT ACTIVITIES</strong></td>
<td></td>
<td>(14 965 385)</td>
</tr>
<tr>
<td>(Increase)/decrease in guarantees</td>
<td></td>
<td>(16 044)</td>
</tr>
<tr>
<td>(Increase)/decrease in derivative financial instruments</td>
<td></td>
<td>58 950</td>
</tr>
<tr>
<td>Unrealized (gain)/loss on investment portfolio - Foundation Fund</td>
<td>13</td>
<td>(1 142 056)</td>
</tr>
<tr>
<td>(Increase)/decrease in investment portfolio - Foundation Fund</td>
<td>5</td>
<td>46 963</td>
</tr>
<tr>
<td>(Increase)/decrease in fixed assets</td>
<td>4</td>
<td>(35 647)</td>
</tr>
<tr>
<td><strong>CASH FLOW RESULTING FROM INVESTMENT ACTIVITIES</strong></td>
<td></td>
<td>(1 087 834)</td>
</tr>
<tr>
<td><strong>NET INCREASE/(DECREASE) OF CASH AND CASH EQUIVALENTS</strong></td>
<td></td>
<td>(16 053 219)</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at beginning of year</td>
<td></td>
<td>57 233 655</td>
</tr>
<tr>
<td>Effect of exchange rate fluctuations on cash held</td>
<td></td>
<td>677 412</td>
</tr>
<tr>
<td>Cash &amp; cash equivalents at end of year</td>
<td></td>
<td>41 857 848</td>
</tr>
</tbody>
</table>

9. Financial view
NOTES TO THE CONSOLIDATED FINANCIAL STATEMENTS AS OF 31 DECEMBER 2020

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 eight senior managers.

With its head office in Geneva, 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 new medicines for the treatment and prevention of malaria. The products should be affordable and appropriate for use by populations in developing countries.

As with all Swiss foundations, Medicines for Malaria Venture is monitored by the Swiss Federal Supervisory Board for Foundations.

The consolidated financial statements for the year ending 31 December 2020 were approved for issue by the MMV Board on 29 April 2021.

c) Operating funds

The accumulated restricted and unrestricted operating funds represent the excess of core 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, the applicable provisions of the Swiss Code of Obligations and the Swiss Generally Accepted Accounting Principles (Swiss GAAP FER/RPC), in particular RPC 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 ruling on the date of the transaction. Monetary assets and liabilities denominated in foreign currencies on the balance sheet date are translated to USD at the foreign exchange rate ruling on that date. Foreign exchange differences arising on translation are recognized in the consolidated statement of operations. Non-monetary assets and liabilities that are measured in terms of historical cost in a foreign currency are translated using the exchange rate on the date of the transaction.

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. 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 (MMV, North America Inc.). MMV does not have any direct or indirect shareholdings in this entity. An SPE (MMV, North America Inc.). MMV does not have any direct or indirect shareholdings in this entity. The following exchange rates were used at year end: 2020

<table>
<thead>
<tr>
<th>Currency</th>
<th>Exchange Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF 1</td>
<td>USD 1.33052</td>
</tr>
<tr>
<td>EUR 1</td>
<td>USD 1.226373</td>
</tr>
<tr>
<td>GBP 1</td>
<td>USD 1.364900</td>
</tr>
<tr>
<td>AUD 1</td>
<td>USD 0.770745</td>
</tr>
</tbody>
</table>

2019

<table>
<thead>
<tr>
<th>Currency</th>
<th>Exchange Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF 1</td>
<td>USD 1.033428</td>
</tr>
<tr>
<td>EUR 1</td>
<td>USD 1.121473</td>
</tr>
<tr>
<td>GBP 1</td>
<td>USD 1.318462</td>
</tr>
<tr>
<td>AUD 1</td>
<td>USD 0.701275</td>
</tr>
</tbody>
</table>

In accordance with the Swiss GAAP FER 30 and based on the facts above, MMV North America Inc. is fully consolidated in these consolidated financial statements and has been, on a line by line basis, since 2011.

List of organizations consolidated in 2020:

<table>
<thead>
<tr>
<th>Country</th>
<th>Name and domicile</th>
<th>Functional currency</th>
<th>% controlled by MMV</th>
<th>Direct/Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States of America</td>
<td>MMV North America, Inc., Delaware</td>
<td>USD</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

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 the 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 making judgments 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.

Certain critical accounting judgements in applying MMV accounting policies are described below.
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.

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 to that 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 one month after the closing date.

<table>
<thead>
<tr>
<th></th>
<th>2020 USD</th>
<th>2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Petty cash</td>
<td>6 475</td>
<td>10 265</td>
</tr>
<tr>
<td>Bank balances</td>
<td>33 689 235</td>
<td>40 129 307</td>
</tr>
<tr>
<td>Time deposits</td>
<td>8 162 138</td>
<td>17 094 083</td>
</tr>
<tr>
<td><strong>Total cash and cash equivalents</strong></td>
<td><strong>41 857 848</strong></td>
<td><strong>57 233 655</strong></td>
</tr>
</tbody>
</table>

4. FIXED ASSETS
Fixed assets are stated at cost less accumulated depreciation. Depreciation is charged to the consolidated statement of operations on a straight line basis over the estimated useful life of the assets.
→ office furniture 20%
→ fixtures and installations 33%
→ computers and equipment 33%

<table>
<thead>
<tr>
<th></th>
<th>2020 USD</th>
<th>2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixtures &amp; installations</td>
<td>1 019 140</td>
<td>392 362</td>
</tr>
<tr>
<td>Office furniture</td>
<td>392 362</td>
<td>287 196</td>
</tr>
<tr>
<td>Computers &amp; equipment</td>
<td>287 196</td>
<td>15 150</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1 698 698</td>
<td>35 647</td>
</tr>
</tbody>
</table>

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, which 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 of the initial 50% received from GSK (described in Note 8). The investment of this initial amount is accounted for in MMV’s 2019 consolidated statement of financial position as a “long-term investment portfolio”, as the intention of MMV is to keep these investments over the long-term. In compliance with the investment policy approved by the Board, the above-mentioned assets were invested in:
→ a discretionary fixed interest portfolio (USD-denominated, investment-grade bonds, 87.5% of total);
→ a well-known exchange-traded fund, or ETF, (the MSCI World ESG Index) reflecting the performance of the global equity markets (10% of total); and
→ a money market fund (2.5% of total).

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

<table>
<thead>
<tr>
<th></th>
<th>2020 USD</th>
<th>2019 USD</th>
<th>2020 performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Money market funds</td>
<td>357 577</td>
<td>357 486</td>
<td>0.03%</td>
</tr>
<tr>
<td>MSCI World ESG index</td>
<td>1 737 825</td>
<td>1 480 200</td>
<td>17.42%</td>
</tr>
<tr>
<td>Fixed interest portfolio (discretionary mandate)</td>
<td>13 431 016</td>
<td>12 593 819</td>
<td>6.65%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>15 526 418</td>
<td>14 431 325</td>
<td>7.59%</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th></th>
<th>Unused vacation provision USD</th>
<th>Total provision USD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Balance at 1 January 2019</strong></td>
<td>703 624</td>
<td>703 624</td>
</tr>
<tr>
<td>Use/release</td>
<td>(703 624)</td>
<td>(703 624)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>838 540</td>
<td>838 540</td>
</tr>
<tr>
<td><strong>Balance at 31 December 2019</strong></td>
<td>838 540</td>
<td>838 540</td>
</tr>
<tr>
<td>Use/release</td>
<td>(838 540)</td>
<td>(838 540)</td>
</tr>
<tr>
<td>Allocation for the year</td>
<td>1 377 481</td>
<td>1 377 481</td>
</tr>
<tr>
<td><strong>Balance at 31 December 2020</strong></td>
<td>1 377 481</td>
<td>1 377 481</td>
</tr>
</tbody>
</table>

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 15.

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.

**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 valorize.

Below is a summary of donations received or committed during 2020:

<table>
<thead>
<tr>
<th>Donor</th>
<th>Cash received 2020</th>
<th>Revenue recognized during previous year</th>
<th>Donations receivable</th>
<th>Revenue deferred from previous year</th>
<th>Revenue deferred to following year</th>
<th>Unrealized foreign exchange gain/(loss)</th>
<th>Total revenue as per statement of operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bill &amp; Melinda Gates Foundation (BMGF, Core grant)</td>
<td>32 505 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32 505 000</td>
</tr>
<tr>
<td>UK Foreign, Commonwealth &amp; Development Office (FCDO)</td>
<td>19 132 955</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19 132 955</td>
</tr>
<tr>
<td>Australian Government Department of Foreign Affairs and Trade (DFAT)</td>
<td>2 673 518</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 673 518</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC)</td>
<td>1 752 797</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 752 797</td>
</tr>
<tr>
<td>Irish Government Department of Foreign Affairs (Irish Aid)</td>
<td>1 144 926</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 144 926</td>
</tr>
<tr>
<td>Bristol Myers Squibb Foundation</td>
<td>500 000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 000</td>
</tr>
<tr>
<td>Individual donors</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>35</td>
</tr>
<tr>
<td><strong>Total unrestricted donations received</strong></td>
<td>57 709 230</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>57 709 230</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP, PAMAfrica grant)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bill &amp; Melinda Gates Foundation (BMGF, Vivax supply security)</td>
<td>5 529 649</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5 529 649</td>
</tr>
<tr>
<td>UK Foreign, Commonwealth &amp; Development Office (FCDO, South Africa ReACT study)</td>
<td>4 493 637</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 493 637</td>
</tr>
<tr>
<td>Netherlands Ministry of Foreign Affairs (DGIS)</td>
<td>3 279 745</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 279 745</td>
</tr>
<tr>
<td>German Federal Ministry of Education and Research (BMBF)</td>
<td>2 790 331</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 790 331</td>
</tr>
<tr>
<td>Global Health Innovative Technology Fund (GHIT)</td>
<td>1 176 701</td>
<td>154 905</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 331 606</td>
</tr>
<tr>
<td>United States Agency for International Development (USAID)</td>
<td>935 889</td>
<td>(426 174)</td>
<td>368 369</td>
<td></td>
<td></td>
<td></td>
<td>878 084</td>
</tr>
<tr>
<td>Swiss Agency for Development and Cooperation (DEZA/SDC, Antimalarial Treatment Options for Pregnant Women)</td>
<td>543 793</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>543 793</td>
</tr>
<tr>
<td>Program for Appropriateness Technology in Health (PATH, VivAccess grant)</td>
<td>257 454</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>257 454</td>
</tr>
<tr>
<td>Principality of Monaco Direction de la Coopération Internationale (DCI)</td>
<td></td>
<td></td>
<td>122 637</td>
<td></td>
<td></td>
<td></td>
<td>122 637</td>
</tr>
<tr>
<td>Newcrest Mining Limited</td>
<td>180 696</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>180 696</td>
</tr>
<tr>
<td>European and Developing Countries Clinical Trials Partnership (EDCTP, OPT-SMC grant)</td>
<td>37 210</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>37 210</td>
</tr>
<tr>
<td>Korea International Cooperation Agency (KOCICA)</td>
<td>2 800 000</td>
<td></td>
<td></td>
<td>(2 800 000)</td>
<td></td>
<td>(94 914)</td>
<td>29 143 260</td>
</tr>
<tr>
<td><strong>Total restricted donations received</strong></td>
<td>22 026 104</td>
<td>(426 174)</td>
<td>645 911</td>
<td>9 793 333</td>
<td>(2 800 000)</td>
<td>(94 914)</td>
<td>29 143 260</td>
</tr>
<tr>
<td><strong>TOTAL RECEIVED</strong></td>
<td>79 734 335</td>
<td>(426 174)</td>
<td>645 911</td>
<td>9 793 333</td>
<td>(2 800 000)</td>
<td>(94 914)</td>
<td>86 852 490</td>
</tr>
</tbody>
</table>

Of the total donations recognized in the consolidated statement of operations, USD 500,035 have been received through MMV North America Inc.
8. LONG-TERM RECEIVABLES & TOTAL OTHER REVENUE

Revenues from partnerships

GlaxoSmithKline

MMV has been collaborating with pharmaceutical partner GlaxoSmithKline (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 antimarial 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 2008–2018. 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 for the period from 2008 to 31 December 2018 in Q1 2019, 25% in July 2022 and the residual 25% in July 2023. The two latter payments are subject to amendments to reflect any additional Krintafel development costs incurred by MMV after 1 January 2019.

The cumulative costs incurred by MMV on the development of Krintafel from 2008 and up to 31 December 2018, amounted to USD 28,426,969. Therefore, MMV recognized this amount as revenue from the GSK partnership during the fiscal year 2018. MMV also booked in its consolidated statement of financial position as of 31 December 2018, 50% of the above amount, i.e. USD 14,213,484, as a short-term account receivable due in March 2019; and USD 14,213,484 as a long-term account receivable (to account for two residual payments of USD 7,106,742 each, due in July 2022 and July 2023).

In March 2019 MMV received from GSK a USD 14,213,484 cash payment in respect of the above-mentioned short-term account receivable. In 2020 MMV incurred additional net expenditure of USD 664,021 (2019: USD 1,354,081) in the co-development of Krintafel. As the two parties had agreed that GSK would refund any additional expenditure incurred by MMV after 1 January 2019, by increasing the two residual payment amounts, MMV recognized USD 664,021 (2019: USD 1,354,081) as revenue from the GSK partnership during the fiscal year 2020. MMV also increased the long-term receivable by the same amount, so that the total of the two residual payments due in July 2022 and July 2023 increased to USD 16,231,587 (2019: USD 15,567,566).

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

Others

In 2020, in addition to the above-mentioned revenues from GSK, MMV booked the following revenues from partnerships: USD 140,970 from Janssen in respect of the co-development of P218 and IM-atovaquone (2019: USD 1,028,556), and USD 292,968 from Shin Poong (2019: USD 180,123). In 2019 MMV had also received USD 19,351,128 from Sanofi in respect of an indemnity payment of EUR 17,014,000 for the completion by MMV of the above-mentioned Phase II studies, from 1 January 2019 onwards.

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

All other types of revenues which are not considered donations are presented in other unrestricted revenues as follows:

<table>
<thead>
<tr>
<th>2020</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>USD</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Tax at source commission</td>
<td>41,520</td>
</tr>
<tr>
<td>Honorarium</td>
<td>35,373</td>
</tr>
<tr>
<td>Consulting fees</td>
<td>12,908</td>
</tr>
<tr>
<td>Reimbursement from grantees</td>
<td>30,370</td>
</tr>
<tr>
<td>Other</td>
<td>44,432</td>
</tr>
<tr>
<td>OTHER INCOME</td>
<td>164,603</td>
</tr>
</tbody>
</table>

9. DEFERRED REVENUE

In late December 2020, MMV received the first payment from Korea International Cooperation Agency (KOICA) as a pre-financing grant of USD 2,800,000. Considering the project financed by this grant will start in 2021, this payment was recognized as deferred revenue and will be booked as revenue in the fiscal year 2021.

In 2019 a deferred revenue of USD 9,793,333 was recorded in respect of a pre-financing grant received from EDCTP as described in Note 7 and Note 11.

10. PROJECT GRANTS

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 the 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 19,422,922 and USD 16,428,039 in 2020 and 2019, respectively.

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.
11. PREPAID PORTFOLIO COMMITMENTS

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

As of 31 December 2020, there were the three following major categories of prepayments in relation to MMV portfolio projects:

<table>
<thead>
<tr>
<th>Category</th>
<th>2020 USD</th>
<th>2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine prepayment</td>
<td>4,500,000</td>
<td>–</td>
</tr>
<tr>
<td>EDCTP PAM Africa prepayments to sub-grantees</td>
<td>4,199,643</td>
<td>–</td>
</tr>
<tr>
<td>Discovery related</td>
<td>453,167</td>
<td>491,740</td>
</tr>
<tr>
<td>Translational related</td>
<td>214,236</td>
<td>137,622</td>
</tr>
<tr>
<td>Product development related</td>
<td>662,163</td>
<td>12,255</td>
</tr>
<tr>
<td>Access &amp; product management related</td>
<td>561,395</td>
<td>210,707</td>
</tr>
<tr>
<td>Other prepaid portfolio commitments</td>
<td>55,942</td>
<td>54,833</td>
</tr>
<tr>
<td>Total prepaid portfolio commitments</td>
<td>10,646,546</td>
<td>907,157</td>
</tr>
</tbody>
</table>

The significant increase in prepaid portfolio commitments is mainly due to the two following items:

a) Use of a restricted donation of USD 4,984,000 received from the Bill & Melinda Gates Foundation in 2020 and aimed at the procurement and distribution of 120 million tablets of chloroquine phosphate 250 mg.

Chloroquine is a generic oral medication initially used in the treatment and prevention of all malaria species (Plasmodium falciparum, P. vivax, Plasmodium ovale, and Plasmodium malariae). It is no longer used for P. falciparum, as there is widespread resistance to it and artemisinin-based combination therapies are now the standard of care, but it is still the main treatment against the blood stage of P. vivax malaria.

The above-mentioned restricted grant from the Bill & Melinda Gates Foundation was accounted for as ‘revenue’ in 2020. As pharmaceutical products to be donated in the context of MMV’s mission can only be accounted for as ‘expenditure’ upon physical and legal transfer of ownership to the final beneficiaries (in this specific case, the Ministries of Health of India and Ethiopia and other similar entities), MMV has accounted for the entire stock of 120 million tablets as ‘prepaid’. MMV will book as ‘expenditure’ the value either of part, or all of the stock, as soon as the organization either partly or wholly transfers its ownership.

b) Use of a restricted donation from the EDCTP as a pre-financing grant equivalent to USD 9,698,419, which was recognized as a revenue in the fiscal year 2020. In the first quarter of 2020, MMV (as leader of the consortium) released advance payments to other consortium members for a total amount equivalent to USD 5,848,430 to cover the costs of activities supported by the EDCTP grant for the period 2020–2021. As of 31 December 2020 the total amount of outstanding prepaid portfolio commitments related to 2021 activities funded by the EDCTP grant was equivalent to USD 4,199,643.

12. PERSONNEL EXPENSES

Salaries and related charges are included under project expenditure and support of portfolio expenditure in the consolidated statement of operations.

As of 31 December 2020 there were 67.8 full-time equivalent employees with permanent contracts (2019: 60.7), as well as 37.6 full-time equivalent temporary staff members with fixed-term contracts ranging from one to three years (2019: 42.6).

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 level 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.

The 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 made by MMV and its employees.

13. FINANCIAL RESULT

In order to minimize the potential adverse effect of foreign exchange fluctuations, MMV liquidity is deposited in bank accounts denominated in foreign currencies pro rata to the breakdown of total expenditure by currency (natural hedging).

Furthermore, MMV is entered into foreign exchange forward contracts with a bank to cover its CHF purchases for 2021. These forwards are used for hedging balance sheet items, and are recognized at a fair value on the date a derivative contract is entered into; they are recorded as other receivables or other current liabilities.
14. LEASES
Non-cancellable operating lease rentals are payable as follows:

<table>
<thead>
<tr>
<th></th>
<th>2020 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>1,028,830</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>2,732,081</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>3,760,911</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>2020 USD</th>
<th>2019 USD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than one year</td>
<td>73,957,503</td>
<td>70,274,379</td>
</tr>
<tr>
<td>Between one and five years</td>
<td>130,715,668</td>
<td>165,956,820</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>204,673,171</td>
<td>236,231,199</td>
</tr>
</tbody>
</table>

16. RELATED PARTIES
MMV has a related-party relationship 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.

There were no loans to directors or executive officers for the years ending 31 December 2020 and 31 December 2019.

Some donors are represented in the foundation council. Given the foregoing, these donors could be considered as related parties. However, MMV management considers that their presence in the foundation council does not affect the nature of the relation between MMV and these donors.

Therefore, all MMV donors have been considered third parties.

17. RISK MANAGEMENT
The foundation council has overall responsibility for organizing and supervising risk management. The audit committee monitors the 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 exercise carried out periodically, MMV’s essential risks are assessed in respect of likelihood and impact and documented in a risk analysis report. The management has the responsibility to monitor and supervise the substantial risks.

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

18. GUARANTEES
Guarantees concern office rentals only and are recoverable on vacating the premises subject to the prevailing contracts.

19. CAPITAL COMMITMENTS AND CONTINGENCIES
MMV encounters certain risks and uncertainties in conducting its work. 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 any adverse resolution of these uncertainties will not have a material impact on the financial position or results of the foundation.

20. AUDITORS
KPMG SA, Geneva, have been MMV’s statutory auditors since the fiscal year 2003. Following a competitive bid in 2017, KPMG were reappointed as the statutory auditors. The current lead auditor, Hélène BEGUIN, has acted in this capacity since 2017.

During the fiscal year 2020, MMV paid:

- Special audit reports to donor: USD 62,445 (2019: USD 36,033) - These audit reports to donors are not all performed by MMV statutory auditors.

21. 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.

MMV has several operating leases. These leases generally run for a period of six years, with an option to renew the lease after that date. During the year ending 31 December 2020, USD 1,075,537 was recognized as an expense in the consolidated statement of operations in respect of operating leases (2019: USD 794,236).
Mr Per Wold-Olsen
Chairman of the Audit & Finance Committee; Chairman GN Store Nord A/S, Denmark; Board Member of Gilead Sciences Inc., USA; Chair of Oncopeptides AB, Sweden

Dr David Reddy
CEO, MMV, Switzerland

Mr Alan Court
Vice-Chairman 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

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

Dr Winston Gutteridge
Former Chief, Product R&D, Special Programme for Research and Training in Tropical Diseases (TDR), WHO, Switzerland; served as full MMV Board Member from 1999–2003 and again from March 2009; Chairperson, MMV Expert Scientific Advisory Committee (ESAC) from 2003–2009, 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), Coral Triangle Center (CTC), Prestasii Junior Indonesia (PJI) and Alternative Association of Southeast Asian Nations (ALTSEAN), Indonesia

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

Dr Dominique Limet
Former Chief Executive Officer, ViiV Healthcare, London, UK

Ms Elizabeth J. Linder
Founder & CEO, Chief Diplomatic Officer, Brooch Associates; 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/UK

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

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 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; former Senior Director, Global Regulatory Affairs, GSK, USA

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

Ambassador Dr Konji Sebatii
CEO, Innovative Pharmaceutical Association of South Africa (IPASA), Johannesburg, South Africa

Ms Jennifer Cain
Birkmose
Vice President, Global Head of Patient Access and Community Engagement, Swedish Orphan Biovitrum; INSEAD lecturer; former Project Officer, European Observatory on Health Systems & Policies, WHO Regional Office for Europe, Switzerland

Dr Aileen Allsop
Former VP and Head of Infection Therapy area and VP Science Policy, both with AstraZeneca; former Council member and Review Panel Chair with Royal Society of Biology, UK, and former Trustee of the Primary Science Teaching Trust; Chair of the UK government review of Science and SSociety; member of ESAC for over 8 years and former Chair of Emerging Technology Reviews for MMV

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), Sweden. Now based in Geneva, Switzerland

* Member of the Audit & Finance Committee
** Chair of the Audit & Finance Committee

Behind the scenes 2020
**MMV North America Inc. Board**

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

- **Mr Andrea Buscaglia**
  - Chief Financial Officer, MMV, Switzerland

- **Mr Alan Court**
  - 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**
  - CEO, MMV, Switzerland

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

- **Dr Dennis Schmatz**
  - Former Vice President and Head of Tsukuba Research Institute, Merck-Banyu Research Laboratories, Japan. Now based in USA

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**Expert Scientific Advisory Committee (ESAC)**

- **Dr John Pottage**
  - Co-Chairman MMV ESAC (Drug Development); Chief Scientific and Medical Officer, Vivid Healthcare, USA

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

- **Dr Tesfaye Bitlu**
  - Distinguished Professor, National Institute of Pharmaceutical Sciences, Adama Science and Technology University, Ethiopia

- **Sir Simon Campbell**
  - Former Senior Vice President for WW Discovery, Pfizer, organic chemist, UK

- **Dr Nick Cammack**
  - Former Senior Vice President and Head, Medicines Development Campus for Diseases of the Developing World at GSK, Tres Cantos, Spain

- **Dr Robert Clay**
  - Consultant/Managing Director, Highbury Regulatory Science Limited; Board Member (President 2017) at TOPRA, UK

- **Dr Anne Cooper**
  - Programme Director, Sosei Heptares, UK

- **Dr Brian Cox**
  - Professor of Pharmaceutical Chemistry, University of Sussex, School of Life Sciences, UK

- **Ms Delese Mimi Darko**
  - Chief Executive Officer, Safety Monitoring & Clinical Trials Division, Food and Drugs Authority, Ghana

- **Dr Rick Fairhurst**
  - Pharmacovigilance Medical Director, Chief Medical Office, Oncology R&D, AstraZeneca

- **Prof. Daniel Goldberg**
  - Professor and Co-Chief, Division of Infectious Diseases, Department of Medicine, Washington University, USA

- **Dr Tim Hammond**
  - Independent Pharmaceutical Preclinical Safety Consultant at Preclinical Safety Consulting Ltd, UK

- **Dr Monica Hemben**
  - Emunjezo Director, Registration & Regulatory Affairs Directorate, National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria

- **Dr Laurent Hennequin**
  - Research Director, Galderma R&D by Nestlé Skin Health/ Galderma R&D, Sophia Antipolis, France

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  - Public Health Specialist, Fiocruz, Brazil

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  - Chief Medical Officer, Global Head Medical Affairs and Consulting, PAEXEL International – Early Phase, UK

- **Dr Mary Mader**
  - Research Fellow, Discovery Chemistry Research and Technologies, Eli Lily and Company, USA

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- **Dr Esperança Sevane**
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- **Prof. Dennis Shanks**
  - Director, Australian Defence Force Malaria and Infectious Disease Institute, Australia

- **Dr Peter Siegl**
  - Siegl Pharma Consulting, USA

- **Dr Shailja Singh**
  - Associate Professor, Special Centre for Molecular Medicine, Jawaharlal Nehru University, India

- **Dr Sodiomon Sirima**
  - Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso

- **Dr Dennis Smith**
  - Former Vice President, PGRD, Pfizer, Kent, UK

- **Dr Jane Stewart**
  - Reproductive Toxicology Associate, ApconX, UK

---

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- **Elizabeth Juma**
  - WHO Inter-country Support Team for Eastern and Southern Africa

- **Dr Corine Karembe**
  - Swiss TPH, Switzerland; Malaria Expert on Global Fund Technical Review Panel; former Director NMCP, Rwanda

- **Ms Maeye Magner**
  - Supply Chain Expert, USA/Ireland

- **Dr Wilfred Mbacham**
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- **Dr Karimni Mendis**
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  - Professor of Global Health at the Menzies School of Health Research, Australia

- **Dr Frank Richards Jr. M.D.**
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---

**Global Safety Board (GSB)**

- **Dr Stephan Duparc**
  - Co-Chairman MMV Global Safety Board; Chief Medical Officer, MMV, Switzerland

- **Dr Trevor Gibbs**
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- **Prof. Tim Hammond**
  - Pharmaceutical Preclinical Safety Consultant, UK

- **Prof. Pieter Joubert**
  - Clinical Pharmacology Consultant, UK

- **Dr John Pears**
  - Director, Woodhouse Green, UK
# Executive Leadership Team & Support

Andrea Buscaglia, 
CFO, FA  
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EVP, APM  
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Helen Weir, 
PA to the CEO  
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Elodie Jambert  
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Murchana Roychoudhury  
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Lindsay Seth  
Ivana Sirovic-Aplon  
Mylène Vincent

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Lorena Gesto Gende  
Eric Justafre  
Aleksandra Kalentic  
Simona Mag Valigova  
Allison Neapole  
Dragana Obrenovic  
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Tareq Sunderji  
Lily Tian

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Elodie Chenu  
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Angelique Doy  
Maëlle Duffey  
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Benoit Laleu  
Didier Leroy  
Zaira Rizopoulos  
Mélanie Rouillier  
Paul Willis

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Yves Beret  
Benoit Bestgen  
Mohammed Cherkaoui  
Helen Demarest  
Claudia Demarta-Gatsi  
Ilaria Di Resta  
Cristina Donini  
Emilie Escoffier  
Aline Fuchs  
Nathalie Gobeau  
Jacques Hervé  
Jorge Liz  
Nicolas Martinier  
Jörg Mährle  
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Anouchka Smits Bayala  
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Florian Wartha
#UniteFor Malaria
MMV is also grateful for the support received from private individuals.