Shining a light on the most at risk

Malaria is still a leading cause of death in many least-developed countries. Even though anyone may be infected by malaria, there are some groups that are at greater risk than others. In 2020, a staggering estimated 11.6 million pregnant women were infected with malaria in sub-Saharan Africa, with devastating consequences for both mothers and babies. Pregnancy reduces a woman’s immunity to the parasite, making her more at risk of developing infection and exposing her unborn baby to the adverse effects of an infection during pregnancy, effects that can include premature delivery or stillbirth, and low birth weight. Children under 5 years of age are another segment of the population at high risk of being infected by malaria and developing complications, accounting for about 80% of all malaria deaths in sub-Saharan Africa. Besides these groups, malaria is among the top killers of adolescent girls, and contributed to 7.4% of deaths among this population, with younger pregnant adolescents being at a higher risk of malaria and anaemia. Programmes that take these populations into consideration and invest in research and development of therapies that are well tolerated by pregnant women are necessary to better serve these populations.

MMV’s MiMBa strategy: meeting the needs of pregnant and lactating women

The Malaria in Mothers and Babies (MMBa) initiative aims to improve care for pregnant and lactating women and their newborns. First, by ensuring that the right quality-assured medicines are available and accessible to them. Then, by prioritizing and accelerating the development of new antimalarial medicines that are appropriate for use in all stages of pregnancy and promoting an earlier inclusion of pregnant women in drug development. This ensures that innovative and appropriate medicines for pregnant and lactating women are developed to adequately serve them.

Closing the data gap: a step towards better antimalarials for pregnant women

Little information is currently available on malaria drug safety in the first trimester of pregnancy. As part of the MMBa strategy, MMV and the Liverpool School of Tropical Medicine (LSTM) are collaborating to establish a pregnancy registry in malaria-endemic countries. Using the registry, the team is collecting information on the use of over-the-counter drugs and prescription medicines (including artemisinin-based combination therapies: ACTs) by pregnant women to treat uncomplicated and severe malaria. This information is added to the registry and linked to any outcome observed in the mother and newborn babies. One of the main goals of this project is to produce evidence-based information on the safety of first and second-line ACTs to treat uncomplicated malaria in pregnant women, particularly in the first trimester.

The project is about to complete its first full year and the women who provided the initial data have already delivered their babies. The health profile of these babies is being closely monitored and documented. Only by knowing what pregnant women experience when taking antimalarial drugs, especially new drugs such as the most recently approved ACT, Pyramax® (pyronaridine-artesunate), and how their babies then develop, will it be possible for agencies such as the World Health Organization (WHO) to update their guidelines on well-tolerated drugs that can be used to treat and prevent malaria in this population.
Why are pregnancy registries so important?

Pregnancy registries are vital in providing safety information on drugs and vaccines used during pregnancy, particularly within the first trimester, a critical period for the growing baby. There is usually limited data on the safety of drugs by the time they come to the market, and little if any data at all about the safety in pregnancy; therefore, pregnancy registries are crucial to monitor safety in the early post-marketing phase. This information also helps to update drug labelling.

How is the data from the registries collected?

We collect information on exposure to prescription and over-the-counter drugs used to treat malaria and other illnesses from women of reproductive age, and link this to information we collect about pregnancies and pregnancy outcomes of interest, such as miscarriage and stillbirths, and from newborn babies at the end of pregnancy including any congenital malformations. We use multiple data sources to ascertain drug exposure, such as data from health facility registers, and interview women attending antenatal clinics at each visit, and at delivery, to inquire about recent drug exposure. We screen newborn babies at delivery and at 6 weeks of age for congenital anomalies. In addition, we will follow a sub-cohort of infants who were exposed to antimalarials in utero at 6 months and 1 year of age to screen for congenital anomalies not detected at birth, including congenital heart defects, and assess their neurodevelopment.

What challenges did COVID-19 pose?

The COVID-19 pandemic posed multiple challenges. First, we noted reduced antenatal clinic attendance among pregnant women, especially during the 3rd and 4th waves of the pandemic in Kenya. During these periods, we had to adapt the implementation of the study to ensure that staff, participants, and community health workers (CHWs) remained safe, breaking up the field teams to work in cohorts, restricting meetings, and providing masks and hand sanitizer to all staff, including all of the 400 CHWs working closely with the study. Second, we had multiple industrial strikes that interrupted the registry’s data collection activities in government hospitals, but we ensured our presence in private health facilities to which patients were diverted, to minimize gaps in the data. Third, some of our staff, research participants, CHWs and community health volunteers also fell ill. Thankfully, we now have free COVID-19 vaccines available to CHWs and the general population including pregnant women, in local health facilities. The cost of personal protective equipment has also substantially fallen and is now more readily available at hospitals and to the public, which has improved working conditions in medical facilities.

What are the next steps?

As of February 2022, we are entering the 11th month of data collection, with one big push for recruitment and pregnancy detection for the last few months of another multiple first-line ACT study – conducted in parallel in the same region as the pregnancy registry – and ending in June 2022. We have also started active data cleaning and merging multiple data sources, including exploring integration with newly introduced electronic medical record systems’ in the study area. Some of our research participants have delivered their children, so we have started to document the babies’ health, including screening for congenital anomalies such as heart defects, and will shortly begin assessing neurocognitive development in a sub-cohort. By October 2023, we should have completed data collection and soon after we will analyse the data and share our findings.

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

I have to say that this has been one of my favourite collaborations of my career so far. MMV has been a true partner, and it has been an equitable and supportive collaboration. MMV has been hands on and supportive with the field teams led by the Kenya Medical Research Institute and LSTM, sharing their ideas, expertise, and checking in on our progress through joint project meetings. Dr Stephan Duparc from MMV recently visited our project sites in rural Homa Bay and on the islands in Lake Victoria involved in the study, meeting our staff, CHWs and field workers, experiencing the fieldwork that goes into the MiMBa Pregnancy Registry. This was special for us as we rarely experience this level of hands-on collaboration from Global North collaborators and funding partners.
Strategies to improve access of preventive options for pregnant women

MMV has prioritized the unmet needs of pregnant women and their babies. The WHO recommends the use of intermittent preventive treatment in pregnancy (IPTp) with three or more doses of sulfadoxine-pyrimethamine (SP) given to all pregnant women living in areas of moderate-to-high malaria transmission in Africa. The preventive treatment should start as early as possible in the 2nd trimester and can be administered at monthly intervals up to the time of delivery, to prevent the complications caused by malaria during pregnancy. There is a great lack of quality-assured SP for IPTp that is produced anywhere on the continent of Africa. To ensure that all pregnant women have access to quality-assured SP, MMV is engaged with three African manufacturers, Emazor Ltd. and Swipha Ltd. in Nigeria and Universal Corporation Ltd. in Kenya to support their efforts to achieve WHO prequalification of their SP product for IPTp.

Studies have shown that despite an increase in coverage of WHO-recommended IPTp over the last decade, only a third of pregnant women in Africa have access to full (repeated) chemoprevention treatment over the course of their pregnancies. This lifesaving antimalarial treatment is given during antenatal care (ANC) visits to the ANC clinics. A promising approach to increase adherence to IPTp has been the delivery of preventive treatment by trained CHWs (C-IPTp). Transforming Intermittent Preventive Treatment for Optimal Pregnancy (TIPTOP) is a pilot project – in Democratic Republic of Congo, Madagascar, Mozambique and Nigeria – that aims to dramatically increase the number of pregnant women in malaria-affected countries in sub-Saharan Africa receiving antimalarial preventive therapy, thus saving the lives of thousands of mothers and newborns. With TIPTOP, MMV and project lead partners have set the stage for the scale-up of community distribution of IPTp with quality-assured SP to make sure the high demand is matched by a continuous and high-quality supply of the medicine. The TIPTOP project also involves carrying out research and household surveys to produce data on drug resistance and the cost-effectiveness of the initiative. It is hoped that data obtained with these studies will provide evidence to inform WHO’s implementation guide.

To ensure that all pregnant women have access to quality-assured SP, MMV is engaged with three African manufacturers... to support their efforts to achieve WHO prequalification of their SP product for IPTp.”
What is the goal of the TIPTOP pilot project?

We aim to build evidence for C-IPTp so that WHO and countries can review and potentially adopt C-IPTp as a delivery mechanism as part of malaria in pregnancy programming, helping achieve higher coverage of interventions globally. We also aim to set the stage for scale-up across the countries we target and with influence across sub-Saharan Africa.

How does the project break down barriers between pregnant women and the malaria medicines they need?

TIPTOP was designed as a ‘no missed opportunities approach’ so that eligible pregnant women have access to IPTp with quality-assured SP in the communities in which they live as well as at antenatal care clinics. To gain the trust of pregnant women, their families and the broader community, we worked with health workers who were selected by the community, along with local organizations. Pregnant women were counselled through CHWs and messaging about ANC, whilst malaria prevention, including IPTp, was reinforced through civil society organization platforms and other communication channels.

How will the evidence generated through this project be used?

The WHO will assess the data to determine whether it can be used to update its implementation recommendations (the “how to”). Countries will apply the learning to expand and scale up C-IPTp as well as introduce C-IPTp in countries where it has not yet been started.

What key challenges do you face?

The first challenge we face is keeping our CHWs and volunteers motivated. We also have the task of maintaining strong data systems that link community- and facility-level monitoring. Outside of TIPTOP (since we supplied the drug), but across sub-Saharan Africa, we face the challenge of availability of quality-assured SP at antenatal care clinics. With continued country and partner commitment, I believe these barriers can be overcome.

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

While MMV’s scope in the TIPTOP project was specific to the drug, we have (from the conceptualization phase) worked hand in hand to design, problem solve and meet the needs of the countries we support. It has been a true privilege to work with MMV.
Sustainable severe malaria case management

If not treated within 24 hours, malaria can progress to severe illness, sometimes with fatal consequences. It continues to take the life of a young child every minute of every day.13

In 2011, the World Health Organization recommended injectable artesunate as the preferred treatment for severe malaria in adults and children. With support from MMV, Fosun Pharma (China) became the first manufacturer to achieve WHO prequalification for this formulation in 2010. However, even with this breakthrough, patients continued to die because they lived too far from health facilities where healthcare professionals could administer injectable artesunate. With funding from Unitaid, MMV has worked in partnership with two Indian manufacturers – Cipla and Strides – to develop artesunate rectal capsules (also known as rectal artesunate – RAS),14 an easy-to-administer pre-referral intervention that can be administered by community health workers, buying enough time to transfer patients to a health facility to receive injectable treatment.

In parallel to developing RAS, in 2017 MMV joined forces with partners15 on a pilot project – MAMAZ Against Malaria (MAM) – in the Serenje District, Zambia,16 to improve severe malaria case management in children less than 6 years old. The project initially introduced RAS 100 mg, covering Serenje’s population of 54,000 people. By 2018, this project had successfully reduced severe malaria case fatality by 96% (from 96 anticipated deaths to three).17,18 This was achieved not only through increased access to key medicines for severe malaria but also through effective community engagement, a functioning drug supply chain and an innovative emergency transport system for patients using bicycle ambulances.

The dramatic reduction in case fatality demonstrated the undeniable benefit of using RAS in tandem with emergency transport, creating a bridge to follow-up care with injectable artesunate followed by a full course of an ACT.

In 2019, the Zambian National Malaria Elimination Centre (NMEC) designed a new strategic malaria elimination plan that aligned the case management of severe malaria with WHO recommendations.19 Following the success of the 1-year MAM project funded by MMV and Transaid, the NMEC, together with MMV and partners Development Data, DAI Global Health, and Disarcare, began working on scale up with additional funding from the FIA Foundation, Grand Challenges Canada and the government of Canada.20

By mid-2021, the NMEC began to scale up RAS to a further 26 districts,21 putting the government on course to reach approximately 22% of the country’s population. Training continues to be a key part of this expansion. For maximum coverage, the NMEC hopes that one day, initiatives similar to MAM will be present in all 114 districts of Zambia.24

MAM and MAM@Scale have shown the value of investing in communities and have empowered rural Zambian families to reduce the mortality risk to their children from severe malaria.25 Interventions implemented to generate community ownership and ensure the health system is responsive to community needs, have far-reaching and sustainable benefits. This approach changes the way a health system operates – it becomes truly people-centred, as envisioned in the Sustainable Development Goals.

In addition to the scale-up of RAS to treat severe malaria, MMV’s work in field stability testing of the drug has also borne fruit: the evidence led WHO to change their guidelines (2021)26 and recommend that CHWs can use the product for up to 6 months even if the ambient temperatures exceed 30°C. This is excellent news for the case management of severe malaria patients.

In 2021, observational research funded by Unitaid (The CARAMAL Project27) raised concerns about the effectiveness of RAS in real-life settings, particularly when referral processes and quality of care could not be assured. Subsequently, WHO issued an information note28 in 2022 that advised countries employing RAS to ensure that its minimal use conditions were met, including: (i) correct diagnosis and administration of RAS; (ii) immediate referral; and (iii) treatment with injectable artesunate followed by a three-day ACT. For countries not yet using RAS, WHO advised waiting for further guidance from themselves. WHO will conduct a formal evidence review and develop detailed guidance on the conditions under which the use of this tool can be implemented safely and effectively. These recommendations point to the need to strengthen referral systems, inpatient care, and post-discharge planning. These critical elements of the “severe malaria patient journey” highlight the essential need for integrated health system planning and coordination to assure minimum standards of quality care under demanding real-life conditions.

13 Malaria kills more children than previously estimated according to WHO Malaria Report: https://www.who.int/news-room/mediacentrefactsheets/sf/28
14 Cipla’s Artesunate Rectocaps and Strides’s Artecap™ both received WHO prequalification in 2018.
15 The consortium of partners included Transaid and the Zambian National Malaria Elimination Council.
16 Key Results from MAM@Against Malaria – A Pilot Project Focused on Increasing Rural Community Access to Rectal Artesunate: https://www.td.gov.ge/2021/mamscale/
17 Children and malaria: treating and protecting the most vulnerable: https://www.who.int/malaria/resources/publications/pr/18
19 MAM Initiative: increasing access to rectal artesunate in Zambia: Final results from MAM@Scale: https://www.transaid.org.uk/newsroom/interviews/mam-initiative-increasing-access-rectal-artesunate-rural-communities
20 Scaling up rectal artesunate in a community-based initiative in Zambia: Final results from MAM@Scale: https://www.transaid.org.uk/newsroom/interviews/mam-initiative-increasing-access-rectal-artesunate-rural-communities
21 Use of rectal artesunate for severe malaria at the community level, Zambia: https://apps.who.int/iris/bitstream/handle/10665/330125/PMO883271.pdf?sequence=1&isAllowed=y
22 Loop M, Jakata J, Chanda C, Congdon P: “Use of rectal artesunate in Zambia: Final results from MAM@Scale: https://www.transaid.org.uk/newsroom/interviews/mam-initiative-increasing-access-rectal-artesunate-rural-communities
23 Scaling up rectal artesunate in a community-based initiative in Zambia: Final results from MAM@Scale: https://www.transaid.org.uk/newsroom/interviews/mam-initiative-increasing-access-rectal-artesunate-rural-communities
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26 Between 2018 and 2021, the MAM@Scale project was implemented in 10 districts in seven provinces, reaching a population of 900,000 people living in rural Zambia.21,22 With a major expansion in the project’s training activities.
27 By mid-2021, the NMEC began to scale up RAS to a further 26 districts,21 putting the government on course to reach approximately 22% of the country’s population. Training continues to be a key part of this expansion. For maximum coverage, the NMEC hopes that one day, initiatives similar to MAM will be present in all 114 districts of Zambia.24
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Justina and her husband, Kelvin, are farmers who grow maize and soya beans in the Serenje District in Zambia’s Central Province. The malaria burden here is high which is why it was selected as the location for the MAMaZ Against Malaria project.

One day while Kelvin was out, Annette, one of the couple’s five children, developed a high fever. Later that day, her symptoms worsened: she began vomiting and having diarrhoea. “I was very scared because that day I was alone. My husband had gone to a funeral, so I was the only one that remained with the kids,” Justina says.

The next morning, Justina took Annette to visit the local community health volunteer (CHV), Charity. Justina says that by the time she reached Charity’s house, “my child was unconscious. She had no energy... I did not know if she would survive.”

Charity examined Annette and discovered that she was suffering from severe malaria. She gave Annette RAS and an oral rehydration solution, and to her mother, a referral slip to a health facility. Justina rushed Annette to the health facility by bicycle ambulance. When they arrived, Annette was taken straight to the clinical officer who admitted her immediately. She was given injectable artesunate and other therapies at the clinic, where Annette and Justina remained for 4 days. The treatment was concluded with a 3-day course of ACT.

This was the first time that any of Justina and Kelvin’s children had suffered from malaria, and they are grateful for lifesaving interventions, especially RAS and the bicycle transport, that are provided to the community by CHVs.

“Without the CHV,” Justina says, “my child would have died. The challenge is how do you move a sick child from here in the community to the facility? With the help of RAS and the CHVs, it is easier now. We feel confident as parents that our children will survive episodes of malaria.”
Seasonal malaria chemoprevention: protecting more children from malaria

Children under 5 are among the most vulnerable to malaria infection and its associated complications. To protect this population, WHO recommends seasonal malaria chemoprevention (SMC) – the administration of a combination therapy of sulfadoxine-pyrimethamine plus amodiaquine (SPAQ) to children aged 3–59 months in a 3-day regimen; it is typically administered at monthly intervals for up to 4 months during the rainy season when malaria transmission spikes.

When tested in clinical trials, SMC proved highly effective, providing up to 88% protection against malaria infection within the first 28 days after its administration, as shown in a recent case-control study with 2,126 malaria cases.

SMC-Impact, a project implemented by MMV and partners, seeks to assess the efficacy and cost-effectiveness of increasing the reach of SMC from children aged 3–59 months to children aged between 5 and 10 years in the Sahel region. Data from Senegal suggest that SMC in children up to 10 years of age is as effective, and as cost effective, as for children under 5 years of age.

As a result, at least three countries are now considering increasing the age limit: Mali, Burkina Faso and The Gambia. Among other objectives, the project also aims to evaluate the impact of adding an extra month of SMC coverage (from the typical 3–4 months) during the transmission season. This proposal is partly attributed to climate change, which is causing a shift in rainfall patterns and thus extending the malaria transmission season or causing a shift in malaria geographies. Beyond the SMC-Impact project, investments in research and modelling tools to determine shifts in rainfall patterns and their impact on malaria epidemiology are needed.

OPT-SMC: to ensure optimal delivery and effectiveness of SMC, MMV teamed up with key partners on the “Optimizing Impact of SMC” project. The project, led by the University of Thies in Senegal, aims to strengthen the capacity of National Malaria Control Programmes to conduct implementation research, to adapt SMC to the local context, and to improve its delivery and impact.

By 2020, MMV and its partners had established an SMC data capture tool to help countries plan and coordinate their campaigns and reach as many eligible children as possible. The data from this tool have since been used to compile the annual WHO World Malaria Report. In 2021, thanks to the remarkable efforts of the SMC Alliance partners, the SMC programme reached over 44 million children.

In addition, in October 2021, WHO recommended the world’s first malaria vaccine, RTS,S, developed by GSK, for use in children at risk in sub-Saharan Africa and other malariaous regions. A recent study showed that combining RTS,S with SMC in high transmission areas was markedly superior to either intervention alone at preventing severe malaria, and could further reduce malaria deaths by 70.

This integrated approach could be key to saving many more young lives.
How effective has SMC been in reducing child morbidity and mortality from malaria in Nigeria?

No formal impact assessment has been done in the country. However, a case-control study in five countries, including Nigeria, looked at the reduction in clinical malaria during the 4 weeks after receiving SMC with SPAQ. The protective effect reported from the Nigerian study arm was 83.1%. However, a landmark publication in *The Lancet* puts the reduction in confirmed malaria cases at outpatient clinics during the high transmission period at 55.2% in Nigeria.

Can you talk us through Nigeria’s expansion of the SMC programme?

In 2020, the nationally-led ‘high burden to high impact’ approach recommended by WHO to jump-start progress against malaria led to an expansion of SMC-eligible states; from nine states within the Sahelian region to 20, plus the Abuja Federal Capital Territory. In addition, in some of the new states, the cycles were increased from four to five due to extended annual rains.

What key challenges did you face in 2021 with regard to SMC implementation?

The COVID-19 pandemic posed new challenges affecting how we implemented SMC; personal protective equipment was required as well as specific training, which increased the unit cost of implementation.

How did you overcome these challenges?

We have mainstreamed COVID-19 preventive measures into the SMC training modules. Caregivers were asked to administer SPAQ with community distributors observing the process; supervisors also ensured physical distancing was respected, as well as adherence to precautionary actions by people and communities to help slow down the spread of COVID-19.

What has it been like to work with MMV on SMC?

The cooperation with MMV has been rewarding. Regular calls provide the opportunity for cross learning amongst SMC countries and this has provided information about new developments within the malaria sector.