Prioritizing the needs of mothers and children

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

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

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

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


Every woman deserves to live her pregnancy without the fear of getting malaria.”

— Maud Majeres Lugand, Associate Director, Social Research, Access & Product Management MMV; Co-leader of MiMBa initiative
MMV’s Malaria in Mothers and Babies (MiMBa) initiative

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

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

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

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

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

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

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

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

Story

Dianah’s story: an expectant mother with malaria

5. Making malaria prevention and treatment more equitable
Closing the data gap by generating evidence for existing antimalarials

MiMBa pregnancy registry

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

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

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

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

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

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

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

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

“

MiMBa for the first time put the first-trimester treatment of malaria on the map, and will expedite this process of finding out whether these newer antimalarials that are coming to the market now are safe to use in the first trimester.”

— Prof. Feiko ter Kuile, Clinical Epidemiologist, LSTM

Artemether-lumefantrine in babies <5 kg

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

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

A Phase II/III study evaluating this new formulation in babies <5 kg, known as CALINA, is ongoing in Burkina Faso, Democratic Republic of Congo (DRC), Kenya, Mali, Nigeria, and Zambia. The study started in December 2020 and is expected to finish in 2023.
Closing the time gap by accelerating development of new drugs for pregnant women

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

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

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

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

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

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

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

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

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

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

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

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

5. Making malaria prevention and treatment more equitable
Lucy, a data manager for the MiMBa pregnancy registry, with a study participant at Ngoothe Island dispensary, Homa Bay, Kenya.
Closing the access gap by increasing availability and accessibility of high-quality antimalarials

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

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

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

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

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

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

Advocating for change beyond the field of antimalarial R&D

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

Ensuring the availability and accessibility of quality treatment for underserved communities, particularly women, newborns and children who are disproportionately at high risk of death from malaria, is a critical component to the full realization of the right to health.\(^{26}\)

— Joy Phumaphi, Executive Secretary, African Leaders Malaria Alliance, and MMV Board member

Boosting local drug manufacturing

Only a handful of Africa’s nearly 400 drug makers\(^{27}\) have achieved international quality standards. Inadequate supply of quality-assured local products results in dependence on imported or poor-quality drugs, as was highlighted when COVID-19 disrupted global supply chains, leaving Africa with limited access to vital medicines. Concerns about quality and supply have slowed implementation and scale-up of numerous disease control programmes, including IPTp.\(^{28}\) Until 2022, there was no quality-assured SP manufactured in Africa.

It is important to include women in clinical trials to find drugs that are safe for them, that are efficacious for this particular population of women. When we do clinical trials in populations that actually need it, then we are adhering to the principle of justice.\(^{29}\)

— Dr Hellen Barsosio, Senior Clinical Research Scientist, Kenya Medical Research Institute (KEMRI)

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

In 2022, we also initiated a cross-disease advocacy coalition with other product development partnerships and advocacy organizations to promote the equitable inclusion of people of childbearing potential in R&D processes.
Dr Julie Gutman, Co-chair of the Malaria in Pregnancy Working Group, RBM Partnership to End Malaria (USA), discusses the working group and the importance of MiMBa.

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

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

What are the functions of the working group?

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

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

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

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

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

— Prof. Jean-Louis Ndiaye, Director of Research and Scientific Innovation, Department of Medical Biology, University of Thiès, Senegal

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

Children are at the greatest risk of dying from malaria.

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

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

Expansion of SMC programmes resulted in more than 48 million children being protected from malaria in 2022 alone. However, many children in Africa are still not receiving SMC. Until recently, WHO recommended SMC only for children from 3 months to 5 years old. However, in June 2022, WHO updated its guidance to recommend this intervention for any child at high risk of severe malaria.
Sarah Hamissou is 9 years old and lives in Damagaram Takaya, a village in the Zinder region of southern Niger. Like other children her age, she goes to school, plays with her friends and spends time with her family, including her 5-year-old brother Rayan and her mother Mariama.

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

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

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

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

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

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

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

SMC-Impact is working with manufacturers to develop SPAQ dosage, formulation and packaging for children 5–10 years old. In the absence of WHO recommendations, an expert committee, established in 2022, reviewed dosages currently used in Mali and Senegal and presented its conclusions to the WHO Global Malaria Programme in November.
SMC implementation and expansion require high-quality data collection. In Nigeria, SMC-Impact used the application KoboCollect. Data recorded directly in the application are synchronized to an online platform, where they can be consulted in real time. CRS, who have been at the forefront of electronic data collection in SMC campaigns, coordinated SMC-Impact implementation in The Gambia, Guinea, Mal, and Niger, and identified key benefits as increased accuracy, faster access to data for evaluation and planning, and reduced workload.

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

**INTERVIEW**

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

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

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

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

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

**What was it like to work with MMV?**

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

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

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

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

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

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

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1. Based on the open-source application ODK Collect, see https://getodk.org/ and https://www.smc-alliance.org/
2. OPT-SMC: Optimizing the impact of SMC
3. Lions, Bunkalal Faye, Cameron, Chad, The Gambia, Guinea, Senegal, Guinea-Bissau, Mali, Niger, Nigeria, Senegal and Togo.
4. 20 October – 3 November 2022, Seattle, Washington, USA. Projects presented were “SCM coverage and factors associated with uptake and adherence” (Senegal), “Barriers to SMC uptake in mobile areas in Guinea and an improved delivery approach” (Gambia, “Barriers and facilitators of SMC uptake in Guinea; a qualitative study in 5 areas” (Nigeria), “Estimating the determinants of variations in SMC coverage in Burkina Faso”, “Effectiveness and cost of using Community Household Leaders to improve SMC adherence in northern Cameroon”; “Evaluating three approaches to improve uptake and adherence of SMC in Koulikoro Region, Mali”, “Monitoring effectiveness of SMC in northern Benin during the 2020 & 2021 campaigns, using the case-control method” (data management/analysis ongoing); “Applying updated WHO SMC guidelines in Niger: timing, number of cycles, and age ranges at risk of severe malaria” (data collection ongoing); “Evaluating the delivery costs and cost effectiveness of SMC in southern Senegal” (awaiting ethics committee approval and “Defining optimal SMC strategies in Togo: timing and number of cycles, and age ranges at risk of severe malaria” (data collection ongoing).
5. Making malaria prevention and treatment more equitable