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. 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. 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. In addition, adolescent pregnant girls are more likely to have malaria and anaemia compared with adult pregnant women. Regarding lactating women, there is a lack of robust data to inform recommendations on antimalarials, making this a neglected area of research. 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.
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.
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.

The safety data generated by the registry will help to expand the use of the tools at our disposal for the elimination of malaria.

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 <5kg 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. Among 275,000 children under five years of age died from malaria in 2019, with an additional 25 million deaths, although the impact on childhood education and development is not fully quantified. Since 2012, in the absence of a highly effective vaccine, the WHO has recommended seasonal malaria chemoprevention in eligible countries (countries that experience at least 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 amodiaquine (SPAQ) has helped prevent millions of cases and thousands of deaths 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 Thiès, 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.

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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. Over a single season we can see its effect in reducing incidence, parasite prevalence and mortality. It is important to note that investment will continue to be key for the success of SMC. Governmental and private sector investment can have a huge impact on malaria elimination and is essential for efforts to continue.”

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.”

Dr André-Marie Tchouatieu discusses SMC and the global effort to eliminate malaria.

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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.