



MALARIA IN MOTHERS AND BABIES

AN MMV INITIATIVE

Problem Statement

Malaria is caused by a parasite, transmitted from one person to another through the biting of certain species of mosquitos in parasite-endemic regions. Those at greatest risk of severe forms of the disease, and death, are children under the age of 5 years, and pregnant women.

An estimated 125 million pregnancies per year are at risk of malaria around the world.¹ For both mother and child malaria is potentially life-threatening. Common risk factors are maternal anaemia, premature labour and poor birth outcomes such as low birth weight, which are associated with a negative impact on early childhood development.² WHO reported³ that in 2018 around 11 million pregnancies were exposed to malaria, resulting in high levels of maternal anaemia (see figure below from WHO World Malaria Report 2019) the delivery of around 872,000 children with low birthweight.

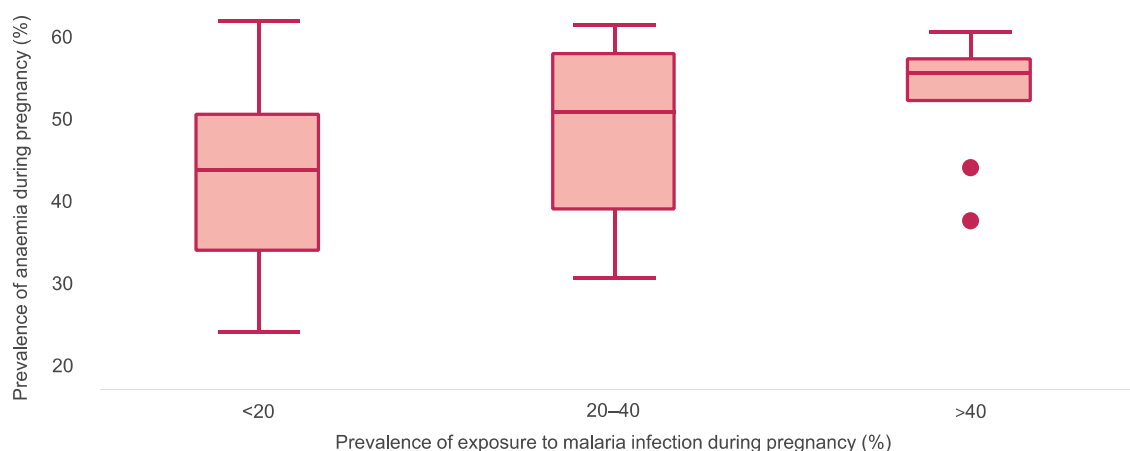
¹ Dellicour S *et al.* "Quantifying the Number of Pregnancies at Risk of Malaria in 2007: A Demographic Study". *PLoS Med*; 7(1): e1000221 (2010).

² Schantz-Dunn J & Nour NM. "Malaria and Pregnancy: a global health perspective". *Rev Obstet Gynecol*; 2(3):186–192 (2009).

³ WHO World Malaria report 2019. <https://www.who.int/publications-detail/world-malaria-report-2019>.

Estimated maternal anaemia (20)^a versus exposure to malaria infection in pregnancy in 2018 in moderate to high transmission countries in sub-Saharan Africa

Source: Imperial College, UNICEF-WHO estimates.



UNICEF: United Nations Children's Fund; WHO: World Health Organization.

^a Prevalence of all cause low birthweight used in this analysis were those estimated for 2015 as shown in this source.

Unfortunately, during the clinical development of most new medicines, including anti-malaria drugs, pregnant women are actively excluded from trials and if pregnancy occurs during the trial, treatment is discontinued and follow-up on the pregnancy outcomes is ensured. This practice aims to protect women and the foetus, but it also prevents generation of data.

Data to support the use of medicines during pregnancy is typically collected only after the product is marketed and its efficacy is established, in order to balance potential risks if used in pregnancy. Data on drug exposure in lactating women, is also collected in a post-approval setting, if at all. In the context of malaria endemic countries, this means that there is often a long delay in access to medicines by pregnant and lactating women. The paucity of data leads many patients and practitioners to uninformed decision making during this lag-period. Similarly, there is a lack of data to support the use of malaria medicines in the youngest of infants.

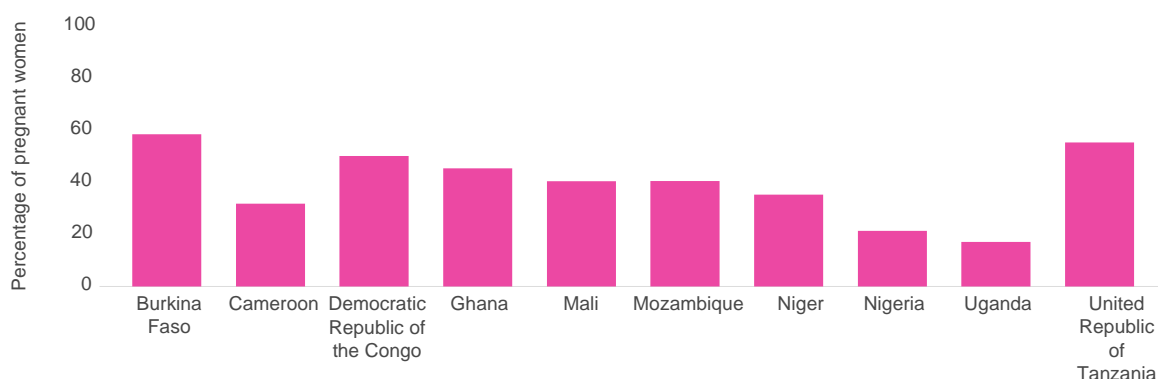
Another key issue is that many women in their first trimester of pregnancy may be unaware that they are pregnant, placing them at even greater risk and effectively broadening the high-risk category to include all sexually active women of reproductive potential.

Off-label use is common and data capture on safety and efficacy in pregnancy or birth outcomes is challenging for many national health systems. Furthermore, the lack of acceptable treatments for pregnant women limits the scope and effectiveness of preventive treatment / mass drug administration (malaria elimination) campaigns aimed at preventing infecting and reducing malaria prevalence levels. There is a need for effective, well-tolerated and affordable anti-malaria medicines for pregnant and lactating women.

In addition, in the few cases where there are recommended therapeutic options for pregnant women drug supply is often not guaranteed in malaria endemic countries. The issue of limited access to appropriate drugs for pregnant women is illustrated with the example of sulfadoxine-pyrimethamine (SP), which is recommended to be taken by pregnant women, at a curative dose, each trimester, beginning as early as possible during the first trimester or pregnancy. This is referred to as intermittent, preventive treatment during pregnancy, or IPTp. Latest data from the 2019 WHO World Malaria Report³ indicates that, in the 10

countries with the highest burden of malaria, the percentage of pregnant women who received the recommended 3 doses of IPTp remains moderate to low.

Percentage of pregnant women who received IPTp3, 2018

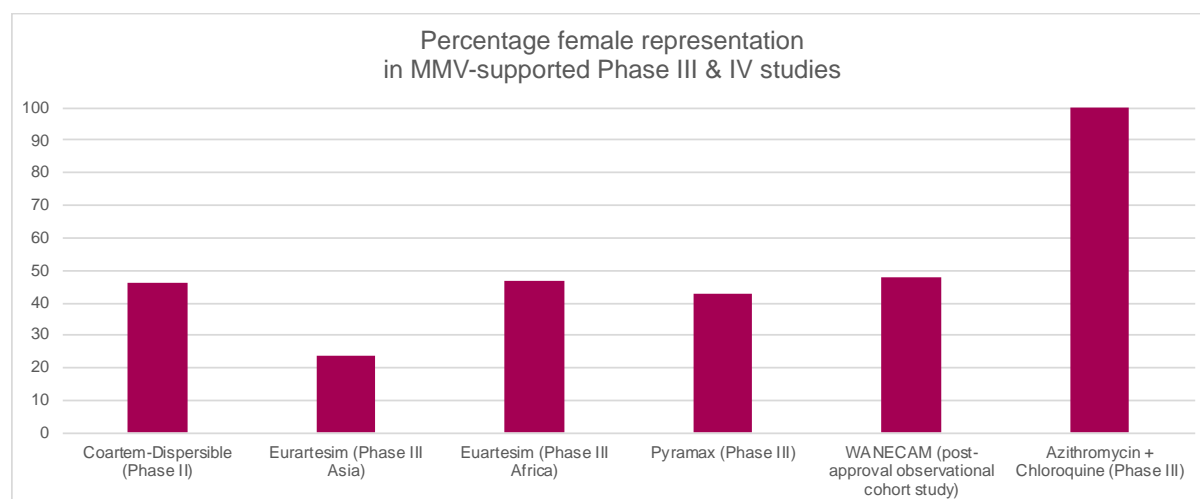


IPTp3: third dose of intermittent preventive treatment in pregnancy
World Malaria Report 2019

Addressing the Needs of Pregnant Women and Babies

As a recognized leader in anti-malarial drug discovery, development and delivery, MMV aims to provide informed therapeutic choices for malaria treatment and protection across all genders and age categories, including pregnant and lactating women.

As a first principle, MMV’s agreements with its partners ensure that MMV-partnership medicines are launched in malaria endemic countries and are priced affordably. In order to achieve the broadest possible access, MMV and its partners include women in their confirmatory safety and efficacy studies, to ensure that the drug can be accessed by both males and females following regulatory approval and launch. MMV-supported post-approval evidence generation studies also include women.



Similarly, MMV works to include paediatric patients in its development programs during Phase III, and prioritizes the development of paediatric formulations. To date, MMV and its partners have developed paediatric formulations of all drugs developed through its collaborations. However, there continues to be a lack of data to support the use of malaria

medicines in the youngest of neonates (<5 kgs). MMV is actively working to address this deficiency.

Furthermore, as outlined above, current approaches to drug development do not address the needs of **pregnant women**, who are generally systematically excluded from mainstream drug development programs. As pregnant women are particularly at-risk from malaria, MMV is actively engaged in increasing drug coverage, providing information and generating data on safety of existing anti-malaria medicines in pregnancy. Furthermore, MMV is well positioned as a custodian of the anti-malarial pipeline, to begin aligning the development of new anti-malaria medicines with emerging thinking by global regulatory and advocacy groups on earlier inclusion of pregnant women into clinical trials, to ensure more timely and equitable access of medicines for pregnant and lactating women after drug approval.

Key Elements of MMV's MiMBa Strategy

MMV's MiMBa strategy aims to raise the standard of care for pregnant women and their new-borns affected by malaria. Key elements of the strategy include:

1. Ensuring drug supplies for children and pregnant women;
2. Generating data on existing compounds to inform on their use in pregnant women and neonates;
3. Developing new anti-malaria medicines to address the needs of pregnant women and neonates;
4. Strengthening the capture of safety data from routine clinical use of anti-malaria medicines during pregnancy;
5. Advocating for changes in drug development that promote the safe inclusion of pregnant women into clinical studies, with the aim of generating data to support earlier access to innovative medicines for this population.

Ensuring drug supply

MMV is working with partners to enhance access to the WHO-recommended medicine sulphadoxine-pyrimethamine (SP) for intermittent preventive treatment for pregnant women by:

1. working with manufacturers to improve the quality of global supplies of SP;
2. working, as a partner in the UNITAID-funded and Jhpiego-led consortium [TIPTOP](#), to support improved coverage of SP by strengthening the supply of WHO-prequalified SP in Africa;
3. collecting information on barriers to access to SP for IPTp.

Generating data on existing compounds to support use during pregnancy

Since 2010, MMV has been actively working to identify alternatives to SP for IPTp, in areas where drug resistance is a concern. Between 2010 and 2013 MMV collaborated with Pfizer to investigate the safety and efficacy of azithromycin plus chloroquine (AZ-CQ) as an alternative to SP for pregnant women. Unfortunately, the study was discontinued in 2013 after a planned interim analysis showed no clinical benefit for AZ-CQ over SP, and significantly poorer tolerability. While this study did not provide a viable alternative to SP, it highlighted that, when used in conjunction with insecticide treated bednets, IPTp with SP provided significant protective benefit to pregnant women, including those living in areas of SP resistance. This supported the WHO's recommendation for all pregnant women living in malaria-endemic areas to receive IPTp. Furthermore, the unexpected tolerability findings in pregnant women underscored the need for dedicated studies to be undertaken in this population.

For women who become infected with malaria during pregnancy, the WHO currently recommends artemisinin combination therapies (ACTs) in the second or third trimesters, and quinine with the antibiotic, clindamycin, in the first trimester. MMV is working with the Liverpool School of Tropical Medicine's Timika Research Facility in Indonesia to analyse historical data to generate evidence regarding safety and tolerability of the ACT dihydroartemisinin-piperaquine (DHA-PQP) in the first trimester of pregnancy. MMV is also working with the London School of Hygiene and Tropical Medicine in Tanzania on a study to evaluate the cardiac safety of a single course of IPTp with the drug DHA-PQP.

MMV and partner Shin Poong Pharmaceutical have registered a new ACT pyronaridine-artesunate (Pyramax) for the treatment of uncomplicated malaria which is being rolled out in Africa and Asia. In order to make this new combination available to pregnant women as quickly as possible, MMV is providing key inputs to the design of an EDCTP-funded study PYRAPREG to assess the safety and efficacy of Pyramax in 2nd and 3rd trimester of pregnancy. This study will compare Pyramax to either AL or DHA-PQP and the pregnant women will be followed up until day 63 post-treatment, at delivery, and at 4-6 weeks post-delivery.

Developing new anti-malarials to address the needs of pregnant women and neonates

The long-standing practice that most drugs are tested for safety in pregnancy post approval, whilst the clinical development strategies are designed to address the medical needs of the greater patient population, has come under scrutiny partly in response to global gender equity movement. Pregnant women are generally classified as vulnerable and therefore protected from biomedical research. This classification has recently been removed from the "Common Rule", which is the code of federal regulations in the US governing the ethics of biomedical research involving human subjects.

Furthermore, a task force on research specific to pregnant women and lactating women, "PRGLAC", was convened in response to US Congress legislation, the 21st Century Cures Act of 2016. This cross-cutting group, in consultation with the public, has produced 15 recommendations in 2018 for the Secretary of Health and Human Services on how to close the gap in knowledge and research on well-tolerated and effective therapies for pregnant women and lactating women.

In malaria, the medical needs of pregnant women are compelling and will be addressed expeditiously only if pregnant women are included in the target population during new drug development. MMV, as a recognized leader in malaria research, is well positioned to ensure that these changes are applied concurrently to diseases of the developing world, where pregnant women and lactating women are disproportionately affected.

MMV's drug discovery strategy includes an early focus on admitting drug candidates to the development portfolio that might have an acceptable safety profile in pregnancy. This includes conducting standard dose-range finding developmental studies and embryo-foetal development studies in two animal species in parallel with phase I human studies. Moving forward, MMV intends to be even more rigorous in prioritizing compounds in chemical series to progress only those that have a favourable profile in such non-clinical studies. It is important to standardize as much as possible what data constitutes a favourable profile in non-clinical studies, so that consistency in decision making in the development of anti-malaria medicines for pregnant women can be ensured. To this effect, MMV and its Expert Scientific Advisory Committee members, participating in the "PRGLAC" task force through the Teratology Society, are working towards consistent interpretation of non-clinical studies and their relevance to pregnant women and lactating women.

Furthermore, MMV recently supported a review of published data to help guide the prioritization of drugs for development. It detailed the non-clinical safety of all non-

artemisinin anti-malarial drugs.⁴ The article summarized data that was previously not easily accessible to health experts and is helping to guide the development of next-generation anti-malarial medicines with an appropriate safety profile in pregnant women.

In keeping with the US-FDA updated Guidance, MMV is investigating how it could safely conduct PK/PD studies in pregnant women, in parallel to phase III development, when the candidate drug profile is appropriate. Such PK/PD studies in pregnant women would generate data that could be reflected in the medicine label on initial registration. Data collection in pregnant women would continue post-marketing but both patients and practitioners would have early access to reliable information concerning the use of a new drug during pregnancy.

MMV has also initiated a program leveraging cutting edge modelling and simulation platforms to predict the concentrations of drug in breast milk to inform the use of medicines in lactating women.

Lastly, in addition to its efforts to develop medicines for pregnant and lactating women, MMV is also working with partners to develop medicines for neonates (infants <5kg). Several years ago, MMV and Novartis undertook studies to investigate the pharmacokinetics of artemether plus lumefantrine in this special population. The study indicated that the ratio of artemether to lumefantrine used in older children is not appropriate for the youngest of neonates. In response, a new formulation has been developed to meet the needs of this population, and clinical development, supported by MMV and Novartis, is ongoing.

Strengthening the capture of safety data from routine clinical use of anti-malaria medicines during pregnancy

In line with the WHO and regulatory recommendations on the need to generate high quality data on a continuous basis, MMV plans to help support setting up pregnancy registries in a number of countries. In partnership with researchers and local regulatory authorities responsible for pharmacovigilance, MMV envisages developing a standard protocol and a network of sites to collect safety data from all anti-malarial drugs circulating in relevant endemic regions. This effort will contribute to health systems strengthening and encourage a sustainable pharmacovigilance culture.

In addition to funding and leading specific projects as part of normal pipeline development activities, MMV will undertake a set of initiatives aimed at energizing the greater malaria community to join the movement to integrate pregnant women and lactating women in biomedical research. Such activities might include the following:

- agreeing and standardizing clinical study protocols to relax the requirements to exclude pregnant women and the requirements on the use of contraception;
- agreeing and standardizing post-approval study protocols in lactating women, pregnancy registry protocols and pharmacovigilance activities;
- convening a pharmaceutical industry CMO round table to help establish a new approach to inclusion of pregnant women and lactating women in research conducted in their organizations according to the “PRGLAC” task force recommendations;
- training and improving educational opportunities for non-clinical and clinical researchers through our partnerships to shift the mind set;

⁴ Clark RL. “Animal Embryotoxicity Studies of Key Non-Artemisinin Anti-malaria medicines and Use in Women in the First Trimester.” *Birth Defects Res.* 109(14):1075-1126 (2017).

- establishing a clinical studies network to encourage public-private partnerships in including pregnant women earlier in drug development and co-accountability of associated potential risks;
- use of cutting-edge modelling and simulation platforms to predict concentrations of anti-malaria drugs in breast milk;
- proposing novel mechanisms to address some of the legal risks for pharma partners;
- influencing and supporting the “PRGLAC” task force in the implementation of their recommendations and finalization of the Report to the highest governance levels;
- sharing learnings with “sister” organizations (e.g. GAPf, IAS, others) by participating in their discussions and generation of work products for other diseases of the developing countries;
- advocating for the cause in appropriate arenas outside of R&D.

Conclusion

Pregnant women and lactating women are disproportionately affected by malaria and have fewer therapeutic options than general population. This situation can be remedied by adapting drug development strategies to provide earlier access to safety and tolerability data that can inform the selection of medicines for use during pregnancy.

MMV is committed to work with partners to improve the way pregnant women and lactating women as well as health practitioners deal with risks of malaria infection in endemic regions.

“...pregnant women should not be protected from research but through research...”⁵



⁵ Kristen Sullivan, PHASES Project Director, University of North Carolina Center for Bioethics, 2018 US Conference on AIDS.