Malaria in pregnancy is associated with serious health risks to the mother and unborn child. Although 125 million pregnancies around the world are at risk of malaria each year, treatment and prevention options for this population are limited. Most antimalarial treatments currently indicated for adults are not suitable for pregnant women due to a lack of safety data.

The global target set by the World Health Organization to end malaria by 2030 cannot be achieved if the prevention and treatment needs of pregnant women and their babies are neglected. These populations represent a large proportion of total malaria cases and deaths, and are a significant source of transmission. 11 million pregnant women were exposed to malaria infection in 2018, resulting in high levels of maternal anaemia and the delivery of around 872,000 children with low birthweight. Malaria causes around 10,000 maternal deaths and 200,000 newborn deaths a year.

Pregnant women are particularly susceptible to malaria infection mainly due to immunological changes occurring in pregnancy and the ability of the parasite to accumulate in the placenta. Common consequences of malaria in pregnant women are maternal anaemia, premature labour and poor birth outcomes. Even when death is averted, low birthweight has adverse consequences on children’s growth and cognitive development. Malaria is life-threatening for both the mother and the child.

Malaria causes around 10,000 maternal deaths and 200,000 newborn deaths a year.

Nancy’s story

Nancy lives in a rural settlement just outside Kisumu, on the shores of Lake Victoria, Kenya. Malaria transmission is high in this area owing to a combination of factors: the lake is a rich breeding ground for mosquitoes and the area is poor, mainly supported by fishing and small farms. Nancy is 19 years old and pregnant with her first baby. Having lived in this area all her life she is well aware of the risks, especially for her baby.

Diligently, Nancy attends the antenatal clinic at Kombewa District Hospital for her check-up and medicines. She receives a dose of sulfadoxine-pyrimethamine (SP) to protect her and her baby from malaria, an intervention known as Intermittent Preventive Treatment in pregnancy (IPTp) – ideally repeated at least three times during the 2nd and 3rd trimesters of pregnancy.

Nancy is one of the luckier ones. Many mothers-to-be across sub-Saharan Africa simply do not attend antenatal clinics; those that do often do not receive the complete course of preventive treatment. This is partly due to the poor perception of the medicine as parasite resistance is rendering SP ineffective in many parts of Africa as a treatment of acute bouts of uncomplicated malaria. However SP remains effective as a preventive treatment.

Although Nancy is doing all she can to protect her baby from malaria, there are certainly no guarantees. There is an urgent need to increase the number of antimalarial treatment and prevention options to protect women like Nancy and their babies from the threat of malaria. The establishment of pregnancy registries will help to meet this need by providing critical safety information about the use of antimalarial medicines throughout each trimester of pregnancy.
Artemisinin-based combination therapies (ACTs), the first-line treatment for uncomplicated malaria, are not recommended in the first trimester of pregnancy, except in life-threatening circumstances, because animal studies have shown that artemisinin is toxic to embryos in animals and there is insufficient data on artemisinin's safety and tolerability in the first trimester of a woman's pregnancy.*

WHO currently recommends quinine and clindamycin for treatment of malaria during the first trimester of pregnancy. However, this treatment is reported to be poorly tolerated and to increase the risk of adverse pregnancy outcomes such as miscarriage and stillbirth.6

Pregnancy registries are observational studies specifically designed to collect clinically relevant data related to pregnant women's use of medicines or vaccines. This data can help improve safety information for medicines used during pregnancy and can be used to update drug labeling.7

Pregnancy registries can be prospective or retrospective, collecting data pertaining to medical interventions before or after the outcome of the pregnancy is known. They are highly reliant on well-kept medical records, which are not always available in malaria affected countries.

Pregnancy registries are particularly useful to gather data on the use of medicines in pregnancy when:

1. Prior knowledge of the product suggests a safety concern based on the pharmacological or chemical class, or on data from animal studies or clinical trials; or
2. The product is expected to be indicated for use during pregnancy (e.g. medications for chronic illnesses or pregnancy-related conditions); or
3. There is a high likelihood that women of reproductive age will use the product and therefore be inadvertently exposed during pregnancy if they become pregnant. 

Why are pregnancy registries needed for malaria?

During the clinical development of new antimalarial drugs, pregnant women are systematically excluded from clinical trials. This practice aims to protect the mother and the baby, but it also prevents the generation of data that could optimize pregnancy outcomes, and deprives pregnant women of existing, potentially well-tolerated and efficacious treatments.

Because antimalarials are not tested during pregnancy before marketing authorization, they are contra-indicated in the package inserts. Even after marketing authorization, a largely unmet need remains—that is to collect data through clinical trials or pregnancy registries to provide evidence on whether to keep the contra-indication or lift it. Yet data on pregnant women’s use of existing antimalarials for prevention and treatment are not systematically collected and reported, and there is insufficient evidence on their safety and tolerability during all trimesters of pregnancy.

For example, most of the current data on artemisinin exposure in the first trimester of pregnancy are based on artemether-lumefantrine; more data are needed on the effects of pregnant women’s use of artemisinin combinations with other partner drugs. There is a need for continued monitoring and pharmacovigilance to evaluate the impact of drug exposure in early pregnancy, including congenital malformations.

Most information about the safety and risk profile of medicines during pregnancy is collected after regulatory approval, when pregnant women can be exposed to them. Pregnant women may be prescribed a contra-indicated medicine because their life is at risk, or they might take a contra-indicated drug unintentionally ignoring they are pregnant.

* 1025 documented cases of artemisinin exposure in 1st trimester of pregnancy, of which 544 concern A-L use are available; this evidence supported an expert recommendation that policy should be updated for A-L use in all trimesters of pregnancy. It is currently under review by WHO-GMP: https://www.who.int/malaria/mpac/mpac-sept2015-erg-mip-report.pdf

Based on the review of this same recommendation, CDC has recommended A-L for use in 1st trimester when other treatment options are unavailable: https://www.cdc.gov/mmwr/volumes/67/wr/mm6714a4.htm


...collect information on the effects of antimalarials on pregnant women, in particular the newest ACTs...”
MMV’s approach to pregnancy registries

Working with partners to collect safety data for policy-makers on anti-malarial drugs circulating in endemic countries and helping to determine their benefit-risk profile in pregnant and lactating women.

MMV’s mission is to reduce the burden of malaria in disease-affected countries by discovering, developing and delivering innovative, effective and affordable antimalarial drugs. As part of its mandate, MMV is prioritizing data collection to increase the number of appropriate antimalarial options for women throughout pregnancy.

MMV has been facilitating the establishment of pregnancy registries in malaria-endemic countries across sub-Saharan Africa in collaboration with the Liverpool School of Tropical Medicine (LSTM), and the Worldwide Antimalarial Resistance Network (WWARN), with initial financial support from the Swiss Agency for Development and Cooperation. These registries aim to collect information on the effects of antimalarials on pregnant women, in particular the newest ACTs, dihydroartemisinin-piperaquine (DHA-PQP, Eurartesim®) and pyronaridine-artesunate (Pyramax®), to generate high-quality safety data, and to improve therapeutic options for this population. The evidence gathered is intended to support policy change and inform WHO guidelines.

Objectives of the Malaria in Pregnancy Registries

- Provide a rich and reliable source of safety data on the use of ACTs in pregnancy to support policy change and ultimately avoid preventable adverse drug-related pregnancy outcomes.
- Establish a network of sites to collect safety data on all antimalarials circulating in endemic regions, in partnership with researchers and local regulatory authorities responsible for pharmacovigilance.
- Promote the development of standard protocols and build capacity for pharmacovigilance.
- Support a culture of drug safety awareness among pregnant women and their care providers.
In Kenya, prevalence of exposure to malaria infection during pregnancy was >20% in 2018. Setting up a pregnancy registry in Kenya

Malaria remains a significant public health concern in Kenya. Prevalence of exposure to malaria infection during pregnancy was >20% in 2018. The Kenyan Malaria Strategic plan 2019 – 2023 for malaria in pregnancy is focusing on increasing uptake of IPTp at antenatal care (ANC), and use Community Healthcare Volunteers to identify cases of missed IPTp opportunities for referral to ANC1.

Using data from pregnancy registries in Indonesia

In 2019, MMV and LSTM used retrospective and prospective pregnancy registries to conduct two studies in Indonesia, the first country to have introduced ACTs to treat malaria in 2006, and where data records on pregnant women were available for a ten-year period. The aim was to obtain additional safety data on exposure to DHA-PQP in the first trimester of pregnancy.

Data between 2006-2017 were extracted from electronic and manual records. These data were compared to the risk of miscarriages, stillbirths and congenital anomalies in women treated with quinine. The collected data concluded that DHA-PQP in first trimester does not increase significantly the risk of pregnancy loss compared to quinine. This study added to the growing evidence on the safety of DHA-PQP for use in first trimester of pregnancy and could support the revision of the antimalarial recommendations for use in the initial period of pregnancy.

In the longer-term, in partnership with researchers and pharmacovigilance authorities in countries, MMV is planning to build up the capacity of this initial network with the objective of collecting safety data from all antimalarial drugs that are currently used in endemic countries.

This will be achieved step by step by:

- Developing standard protocols for the registries, aligned to the local realities in high-burden, malaria-endemic countries and to the protocols of stringent regulatory authorities like the European Medicines Agency (EMA)/ and the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) and the US Food and Drug Administration (FDA).

- Facilitating exchanges between researchers with experience in collecting safety information for malaria medicines during pregnancy.

- Gradually broadening the network of sites and linking them to each other and with the countries’ pharmacovigilance systems as well as the WHO Collaborating Centre for International Drug Monitoring in Uppsala.

- Promoting learning of lessons among the members of the network and local health system services.


Conclusion

Pregnancy registries are crucially needed to help meet the health needs of the populations hardest hit by malaria. By supporting the establishment of pregnancy registries in a number of countries in sub-Saharan Africa, MMV and its partners envisage to improve the collection of critical health information which can help increase the number of antimalarial treatment and prevention options available to pregnant women, improve the quality of care, and strengthen national health systems. With better data, a commitment towards innovation, and strong partnerships, the global health community can contribute towards reducing the burden of malaria and improving health outcomes among the most at-risk populations by 2030.

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Medicines for Malaria Venture (MMV)
International Centre Cointrin - Route de Pré-Bois 20
PO Box 1826 - 1215 Geneva 15 - Switzerland
T +41 22 555 03 00 - F +41 22 555 03 69
www.mmv.org | communications@mmv.org

http://www.facebook.com/medicinesformalaria/ Twitter @MedsforMalaria
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