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Plasmodium vivax malaria

A case for primaquine in breastfeeding women

- *Plasmodium vivax* malaria is a serious health burden, and breastfeeding women are among those at increased risk of multiple relapses and anaemia.
- A radical cure – one that prevents relapse – exists with the drugs primaquine and tafenoquine, but the World Health Organization (WHO) currently restricts the use of primaquine in breastfeeding women and there are no recommendations for tafenoquine.
- Recent primaquine clinical data and modelling studies show that the benefits of primaquine in breastfeeding women outweigh the potential risks.
- Dr Nada Abla from Medicines for Malaria Venture (MMV) gives an overview of a recent position paper arising from a multiple-party collaboration. The paper highlights key data as evidence to re-examine the recommendations around primaquine as a radical cure for *Plasmodium vivax* in breastfeeding women.

Plasmodium vivax is the most common malaria-causing parasite outside of sub-Saharan Africa, responsible for 75% of all cases in Latin America, 51% in South-East Asia, 42% in the Eastern Mediterranean, and 27% in the Western Pacific, with an estimated 6.9 million cases in 2022. In Africa, only 0.5% of reported malaria cases are caused by *P. vivax* with Ethiopia shouldering 95% of the burden.

Some *Plasmodium* species, including *P. vivax*, can form hypnozoites – that is, dormant *Plasmodium* parasites that remain inside liver cells. They can cause repeated malaria episodes, or relapses, by reactivating weeks or months after the initial infection. Multiple relapses can trigger chronic anaemia that may become severe and life threatening. Pregnant and breastfeeding women are particularly vulnerable to multiple relapses, and clinical *P. vivax* infection is associated with an increased risk of maternal anaemia.

A treatment dilemma

A radical cure (one that treats blood-stage infection, eliminates hypnozoites and therefore prevents relapse) for *P. vivax* malaria is achievable with primaquine given in combination with chloroquine or artemisinin-based combination therapies (ACTs), or tafenoquine given in combination with chloroquine. However, these medications belong to a class of drugs known as 8-aminoquinolines, which can cause haemolysis (breakdown of red blood cells) in people with the genetic disorder glucose-6-phosphate dehydrogenase (G6PD) deficiency, potentially causing anaemia.

Adverse events in mothers were mild, and there was no evidence of drug-related haemolysis in infants compared to age-matched controls.

The World Health Organization (WHO) currently has no recommendations for tafenoquine in breastfeeding women. It restricts the use of primaquine if their child is younger than 6 months, or older than 6 months with G6PD deficiency (or unknown G6PD status), for fear of causing anaemia in the infant. Since the WHO recommends that infants should be breastfed exclusively in the first 6 months after birth, with continued breastfeeding until the age of 2 years, women face potential health risks from repeated *P. vivax* relapses if they choose not to pause breastfeeding to receive the radical cure. Repeated pregnancies could leave women vulnerable to relapses over several years, leading to increased malaria burden and transmission, and obstructing the fight against malaria.

Despite 70 years of experience with primaquine, there has been no systematic assessment of its benefits versus its risks during breastfeeding. However, data from recent studies suggest primaquine can be used without safety concerns in breastfeeding women.

Primaquine clinical studies in breastfeeding

A 2018 clinical study by Gilder and colleagues evaluated primaquine in 21 healthy women with previous *P. vivax* infection and their breastfed infants aged 28 days to 2 years. Both mothers and infants

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had normal G6PD levels. Adverse events in mothers were mild, and there was no evidence of drug-related haemolysis in infants compared to age-matched controls. The researchers conducted a pharmacokinetic (PK) analysis to understand what happens to the drug within the body. With the standard treatment dose of 0.5 mg/kg/day for 14 days, plasma levels of primaquine in breastfeeding women were similar to those reported for non-pregnant or non-breastfeeding adults. In infants, plasma primaquine concentrations were all below the limit of quantification except for one patient.

In a follow-up analysis, Wattanakul and colleagues used a PK model simulation based on these clinical data to predict drug concentrations in infants at the different dosing schedules currently recommended for *P. vivax* radical cure. Infant primaquine plasma concentrations were predicted to be low, in line with the clinical data, demonstrating that infants received less than 1% of the weight-adjusted dose in mothers for all primaquine dosing schedules.

Pregnant and breastfeeding women are particularly vulnerable to multiple malaria relapses, caused by dormant *Plasmodium* parasites that remain in the body.

Physiologically based PK modelling in breastfeeding

Clinical studies do not account for all breastfeeding scenarios, such as the changes in the composition of breast milk during the first 2 months after birth. Additionally, the Gilder et al. study did not include neonates (< 28 days of age). Physiologically based PK (PBPK) modelling can address these limitations by considering factors such as drug properties, human physiology and age-related changes in newborns and infants to predict the PK profiles of drugs in women and their breastfeeding infants.

In a 2024 study (Pan and colleagues), MMV collaborators from Certara Ltd used an adult primaquine PBPK model to predict the PK properties of primaquine in mothers and their breastfeeding newborns and infants (those over 28 days old) using the standard primaquine treatment dose (0.5 mg/kg/day) for 14 days. Predicted primaquine plasma concentrations in infants were consistent with clinical data that were reported. In all infant (including newborn) scenarios, the predicted concentrations were less than 1% of that in the mothers' plasma.

Using this PBPK model, the authors performed an additional analysis to investigate a dosing schedule of 0.75 mg/kg/week for 8 weeks, used for patients with G6PD deficiency (or where G6PD testing is unavailable). The simulated concentrations of primaquine in newborns and infants were again found to be less than 1% of that in the mothers' plasma throughout the 8 weeks.

Although PBPK modelling has some limitations, the model used by the MMV collaborators was conservative in its design and provided valuable information about primaquine in neonates, a population that is difficult to recruit for clinical studies.

A way forward

Based on the available evidence, Abla and colleagues from MMV and partner organisations have summarised the clinical and modelling evidence for a favourable benefit-risk evaluation of *P. vivax* radical cure with primaquine for breastfeeding women in a perspective paper. The evidence of low primaquine exposures in breastfed newborns and infants suggests that primaquine can be given without safety concerns to breastfeeding women regardless of their child's G6PD status. Adjusting current treatment guidelines would support health equity in regard to effective interventions to protect women and their children, enhance malaria control strategies, and advance *P. vivax* elimination.

Personal response

What do you think are the remaining knowledge gaps that need to be filled to strengthen the case for the use of primaquine in breastfeeding women?

I believe there is enough evidence to support the use of primaquine in breastfeeding women, even in the case of neonates. An ongoing clinical study with primaquine in lactating women and their breastfed neonates (ClinicalTrials.gov Identifier NCT06191458, sponsor: University of Oxford) will allow us to bridge predictions with additional data and will provide further confidence in PBPK modelling as a tool to speed up breastfeeding mothers' access to highly needed antimalarial treatments.

What are the main challenges in obtaining malaria treatment data in breastfeeding women and how can these be addressed?

It is often challenging to obtain ethical approval for a clinical lactation study, and even when such a study is performed, it cannot include all the scenarios that can happen in the real world, such as different infant ages and limits to the number of blood samples that can be collected. Performing PBPK simulations before a clinical lactation study can give a preliminary assessment of whether a given drug could be administered to breastfeeding mothers (based on the predicted dose their infants will receive from the milk and their estimated plasma exposure) and help clinical study design and data interpretation.

How robust is physiologically based pharmacokinetic modelling in the context of antimalarial treatment in breastfeeding women?

In the case of primaquine, PBPK simulations are quite robust because the model has been verified with clinical lactation data. We have been working with colleagues from Certara to address this question for other antimalarials and will publish the results of this analysis shortly. Overall, for antimalarials for which clinical lactation data are available, predictions are in line with the observations. There are, however, limitations to the models that we have highlighted, and sensitivity analyses should be performed alongside any PBPK modelling when no clinical data are available. We will also be providing a strategy using PBPK modelling to decide on the need for a clinical lactation study.

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Bio

Dr Nada Abla is a pharmacist by training. She obtained her PhD in pharmaceutical sciences from the University of Geneva before completing postdoctoral training at UCSF. Before joining MMV in 2014, she worked for Merck Serono as a drug metabolism and pharmacokinetics (DMPK) scientist. She is the PBPK strategy lead at MMV, supporting antimalarial drug development by addressing specific pharmacokinetic questions related to drug-drug interactions and special populations.

Further reading

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Competing interest statement

NA, ACM, EJ, SD, JJM and MEG are employees of MMV. PZ and JC are employees of the Bill & Melinda Gates Foundation. LA, KRY and XP are employees of Certara Ltd and may hold shares in the company. NR is a paid consultant for MMV. SK is employee of Montpellier University. CW is funded by Wellcome Clinical Research Career Development Fellowship (222075_Z_20_Z). CK is funded by the Gates Foundation (INV-023795). AB and SC work for the Medicines and Healthcare Products Regulatory Agency and are funded by the Gates Foundation (INV-009383). JT declares no competing interests.