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Addressing health equity for breastfeeding women: primaquine for *Plasmodium vivax* radical cure

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Abstract

Plasmodium vivax malaria remains a global health challenge, with approximately 6.9 million estimated cases in 2022. The parasite has a dormant liver stage, the hypnozoite, which reactivates to cause repeated relapses over weeks, months, or years. These relapses erode patient health, contribute to the burden of malaria, and promote transmission. Radical cure to prevent relapses requires administration of an 8-aminoquinoline, either primaquine or tafenoquine. However, malaria treatment guidelines updated by the World Health Organization (WHO) in October 2023 restrict primaquine use for women breastfeeding children < 6 months of age, or women breastfeeding older children if their child is G6PD deficient or if the child's G6PD status is unknown. Primaquine restrictions assume that 8-aminoquinoline exposures in breast milk would be sufficient to cause haemolysis in the nursing infant should they be G6PD deficient. WHO recommendations for tafenoquine are awaited. Notably, the WHO recommends that infants are breastfed for the first 2 years of life, and exclusively until 6 months old. Repeated pregnancies, followed by extended breastfeeding leaves women in *P. vivax* endemic regions potentially vulnerable to relapses for many years. This puts women's health at risk, increases the malaria burden, and perpetuates transmission, hindering malaria control and elimination. The benefits of lifting restrictions on primaquine administration to breastfeeding women are significant, avoiding the adverse consequences of repeated episodes of acute malaria, such as severe anaemia. Recent data challenge the restriction of primaquine in breastfeeding women. Clinical pharmacokinetic data in breastfeeding infants ≥ 28 days old show that the exposure to primaquine is very low and less than 1% of the maternal exposure, indicating negligible risk to infants, irrespective of their G6PD status. Physiologically-based pharmacokinetic modelling complements the clinical data, predicting minimal primaquine exposure to infants and neonates via breast milk from early post-partum. This article summarizes the clinical and modelling evidence for a favourable benefit:risk evaluation of *P. vivax* radical cure with primaquine for breastfeeding women without the need for infant G6PD testing, supporting a change in policy. This adjustment to 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.

Keywords *Plasmodium vivax*, Radical cure, Primaquine, Physiologically-based pharmacokinetic modelling, Breastfeeding, Pregnancy, Malaria

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Background

Globally, there were an estimated 6.9 million cases of *Plasmodium vivax* malaria in 2022 [1]. *Plasmodium vivax* is dominant in Latin America and South-East Asia, causing 75% and 51% of all malaria cases, respectively [1]. *P. vivax* is also a key pathogen in the Eastern Mediterranean (42% of cases), Western Pacific (27% of cases) and the horn of Africa [1]. Chloroquine is the first-line treatment for acute uncomplicated *P. vivax* malaria in most countries, though artemisinin-based combination therapy (ACT) is also used [2].

The *P. vivax* lifecycle is complicated by the ability of the parasite to form hypnozoites. This arrested or dormant stage shelters in the liver, is not susceptible to treatment with chloroquine or ACT, and cannot be detected symptomatically. Although serological testing to assess prior exposure to *P. vivax* has been suggested as a presumptive test for hypnozoites to support test and treat strategies for malaria elimination, there is no direct diagnostic available for the presence of hypnozoites [3].

Hypnozoites become reactivated within weeks or months of the initial infection causing repeated malaria episodes (relapses) and onward transmission (Fig. 1). Multiple relapses are damaging to patient health, causing chronic anaemia with associated morbidity and an increased mortality risk [4–6]. Short-latency tropical strains of *P. vivax* have relapse intervals of approximately 3 weeks [7]. The contribution of relapses to the burden of *P. vivax* malaria varies but often represents more than half of cases and can be over 80% of cases in endemic countries [8–10]. Thus, it is essential to break the cycle of repeated *P. vivax* relapses by not only treating the acute infection but also eliminating hypnozoites, termed radical cure.

Plasmodium vivax radical cure requires the administration of a blood schizonticide (chloroquine or artemisinin-based combination therapy) to eliminate the blood-stage parasites and an 8-aminoquinoline to eliminate hypnozoites. Two 8-aminoquinolines are approved for radical cure of *P. vivax*—primaquine and tafenoquine—and both can cause haemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency [11–15]. Haemolysis may be severe, causing acute haemolytic anaemia requiring hospitalisation, blood transfusion and potentially renal dialysis [16–20]. The haemolytic risk depends on the dose and duration of 8-aminoquinoline

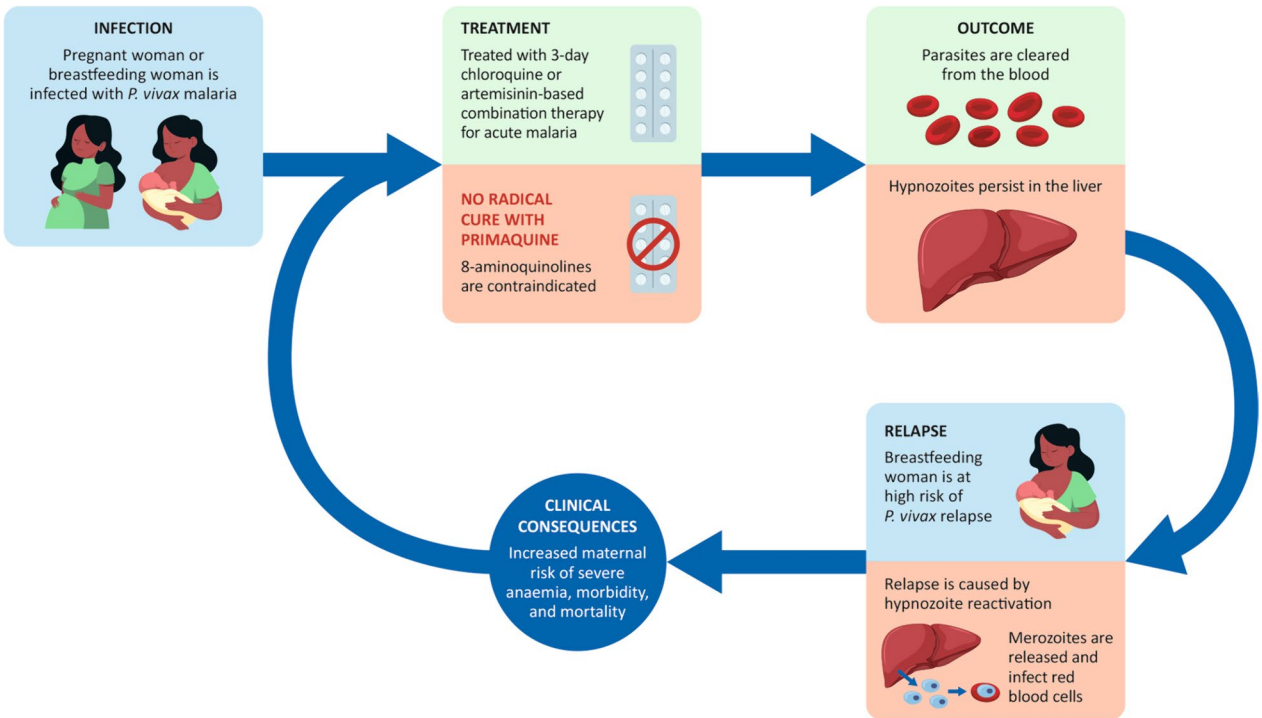

Fig. 1 Breastfeeding women remain at risk of multiple *P. vivax* relapses without access to primaquine. Following a single infectious bite from a mosquito during pregnancy or when breastfeeding, without access to effective radical cure with primaquine breastfeeding women are at high risk of repeated *P. vivax* malaria relapses. Relapses are damaging to a patient's health, causing chronic anaemia with associated morbidity and an increased mortality risk. Although chloroquine prophylaxis during pregnancy and while breastfeeding is recommended, it is not deployed in endemic regions so most women will be trapped in this cycle of repeated relapses until they complete breastfeeding or until their child is ≥ 6 months old and proven not to be G6PD deficient

administration and the level of G6PD enzyme activity [11–13, 16, 21].

G6PD deficiency is the most common X-linked enzymopathy worldwide, and prevalence is highest in populations that are exposed currently or historically to malaria, with the allelic frequency averaging around 8%, but as high as 33% in some populations [22]. The high prevalence of G6PD deficiency and the potential adverse consequences have hampered *P. vivax* radical cure using 8-aminoquinolines. To address the challenge of G6PD deficiency diagnosis, point-of-care quantitative G6PD tests have recently become available, with the potential to direct appropriate therapy and expand access to *P. vivax* radical cure [23–26]. This permits single-dose tafenoquine treatment for patients ≥ 2 years old with normal G6PD activity, a daily primaquine regimen (7 or 14 days) for patients ≥ 6 months of age who have G6PD normal or intermediate activity, and a weekly primaquine dose (0.75 mg/kg/week) for 8 weeks for G6PD-deficient patients [2]. Potentially, the extended weekly regimen can also be used where G6PD testing is not available.

Access to *P. vivax* radical cure is restricted in pregnant and breastfeeding women. Updated in October 2023, the World Health Organization (WHO) guidelines prohibit primaquine during pregnancy or to women breastfeeding infants aged < 6 months or women breastfeeding infants aged ≥ 6 months if their child is G6PD deficient or has unknown G6PD status [2]. As a relatively new treatment option, the inclusion of tafenoquine in the WHO malaria guidelines is currently under review. However, the product insert states that breastfeeding women should not take tafenoquine if they have a child who is known to have G6PD deficiency or who has not been tested for G6PD deficiency and women should not breastfeed for three months following the last dose of tafenoquine [14].

Historically, restrictions on the administration of 8-aminoquinolines during breastfeeding have been based on infant safety. However, primaquine has been in clinical use for around 70 years, and yet there has been no systematic effort to assess the primaquine risk:benefit during breastfeeding. Although a weekly primaquine regimen is recommended for G6PD-deficient adults, this regimen appears to be contraindicated in women breastfeeding children of any age [2].

Lactating women are underserved with limited options and resources to adequately meet their needs for malaria prevention and treatment [27]. Recent studies supporting the administration of primaquine to breastfeeding women for *P. vivax* radical cure have prompted calls for policy change [28–32]. Here, the totality of the available evidence is presented, emphasising the urgent need and supporting equitable access to primaquine to better serve the health of breastfeeding women.

Limitations for prevention of *P. vivax* relapses in breastfeeding women

A study at the Thailand–Myanmar border found that a history of *P. vivax* infection during pregnancy dramatically increased the risk of subsequent *P. vivax* malaria by 1398% [33]. This 14-fold increase in risk for *P. vivax* malaria is likely because pregnant women who experience an acute *P. vivax* malaria episode subsequently experience repeated *P. vivax* relapses. Figure 1 illustrates the impact of restricting primaquine in pregnant and breastfeeding women on the prevention of *P. vivax* relapses. Extending the availability of *P. vivax* radical cure to breastfeeding women would likely greatly decrease the burden of malaria in this population.

To prevent *P. vivax* infections in women who are pregnant or breastfeeding and not eligible for primaquine, the WHO recommends weekly chemoprophylaxis with chloroquine (300 mg base adult dose) [2, 8, 34–36]. However, in low transmission areas, where the risk of a new infection is lower than the benefit of weekly chloroquine chemoprophylaxis, the intervention could be used following an acute *P. vivax* malaria episode in women who are at risk of relapse [8, 34–36]. The presence of therapeutic concentrations of chloroquine in the blood should prevent both newly acquired blood-stage infections and suppress most acute *P. vivax* malaria episodes caused by relapses [8, 34]. However, hypnozoites will persist and the probability of a relapse increases if adherence is sub-optimal.

The operational feasibility and cost-effectiveness of chloroquine chemoprophylaxis for relapse suppression have not been investigated. There are no data on the adherence of breastfeeding women to the regimen in operational settings or its long-term safety. Information on its deployment and accessibility in *P. vivax* endemic regions is also lacking. The effectiveness of this regimen in suppressing relapse in areas with chloroquine-resistant *P. vivax* is unknown, though artemisinin-based combination therapy has been suggested [2, 37]. Thus, once infected with *P. vivax,* it is likely that most women will remain vulnerable to multiple *P. vivax* relapses while breastfeeding (Figs. 1, 2A).

Breastfeeding versus protection from *P. vivax* relapse

To promote infant and child health and development, the WHO recommends exclusive breastfeeding for the first 6 months of life with continued breastfeeding until at least 2 years of age [38]. Although WHO guidance does not advocate that women should pause breastfeeding in order to receiving primaquine, clinicians may advise suspending breastfeeding, with harmful effects on breastfeeding outcomes [39]. Women must either

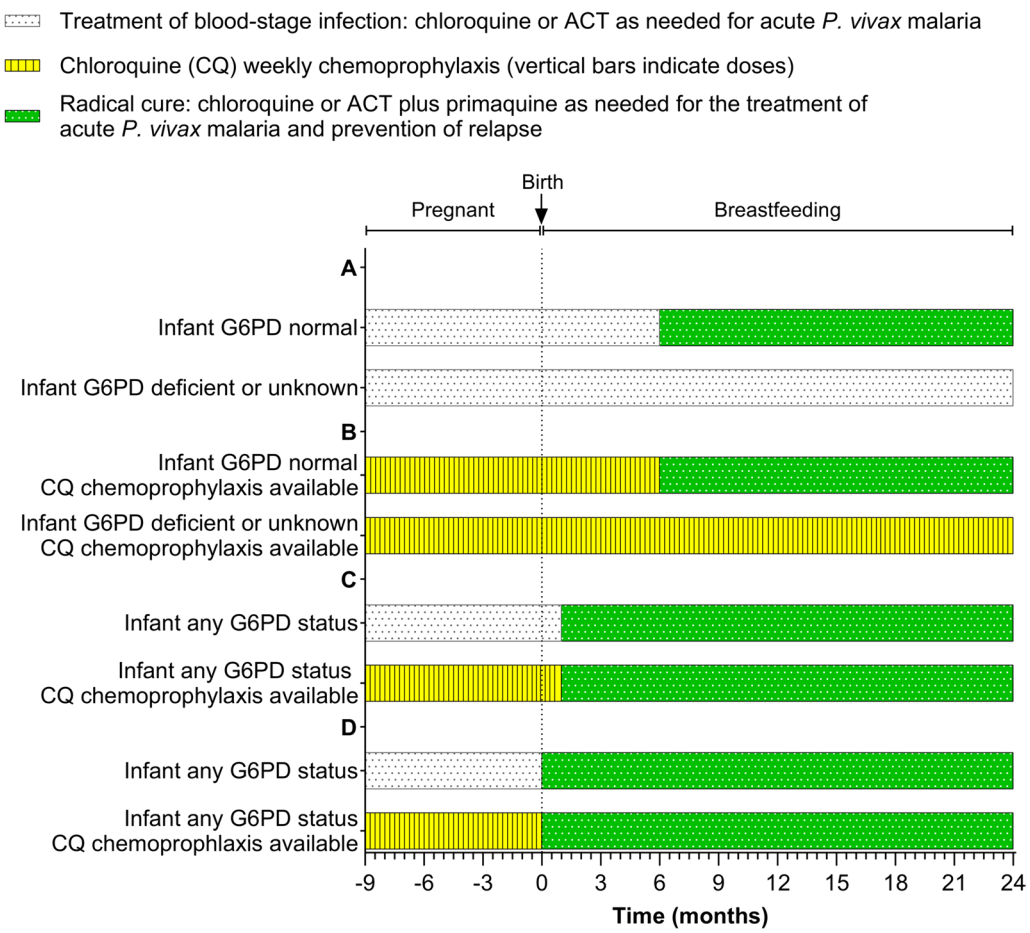

Fig. 2 *Plasmodium vivax* radical cure with primaquine during pregnancy and breastfeeding. Different possible scenarios for employing radical cure (green bars) for the management of *P. vivax* malaria and prevention of relapse for a single pregnancy in terms of the timing of restrictions to drugs during pregnancy and breastfeeding for 24 months. (A) and (B) are based on the WHO recommendations updated in October 2023, (C) is based on clinical pharmacokinetic data and (D) on PBPK modelling. The aim is to maximize the time during which *P. vivax* radical cure could be administered (green bars) and negate the need for infant G6PD testing. Thus, scenario D is preferred, followed by C, whereas scenarios B and A restrict the availability of radical cure to breastfeeding women unless their child is ≥ 6 months old and shown not to be G6PD deficient. (A) The most common scenario where chloroquine or an artemisinin-based combination therapy (ACT) is available as needed for the treatment of uncomplicated acute *P. vivax* malaria, and chloroquine chemoprophylaxis is not available. Radical cure, which is chloroquine or an ACT plus primaquine to treat uncomplicated *P. vivax* malaria and prevent relapse, can only be given to women breastfeeding infants ≥ 6 months old if the child is known to not be G6PD deficient. (B) Chloroquine chemoprophylaxis is not usually available and is unlikely to be cost-effective in low transmission zones unless the mother has had acute *P. vivax* malaria [2]. However, the October 2023 recommendations are for weekly chloroquine for *P. vivax* malaria prevention for at least 15 months (~ 65 chloroquine doses) while pregnant and while breastfeeding if radical cure is contraindicated. Once the child is ≥ 6 months old, radical cure, which is chloroquine or an ACT plus primaquine to treat uncomplicated *P. vivax* malaria and prevent relapse, can be given to women only if their child is known to not be G6PD deficient. (C) Based on clinical pharmacokinetic data of primaquine exposures in breast milk and plasma in infants ≥ 28 days old, radical cure with chloroquine or ACT plus primaquine could be given from 28 days post-partum to breastfeeding women, regardless of the G6PD status of the child (normal, deficient or unknown). If available, chloroquine chemoprophylaxis could be given while pregnant and for the first month of breastfeeding. If chloroquine chemoprophylaxis is not available, treatment with chloroquine could be given during pregnancy and during the first month of breastfeeding. (D) PBPK modelling of infant exposure via breast milk in children < 28 days old supports radical cure with chloroquine or ACT plus primaquine for breastfeeding women soon after birth, regardless of the G6PD status of the child (normal, deficient or unknown). If available, chloroquine chemoprophylaxis could be given while pregnant. If chloroquine chemoprophylaxis is not available, treatment with chloroquine could be given during pregnancy

face the uncertainty of repeated *P. vivax* relapses and the attendant health risks or pause breastfeeding and risk the health of their child (Fig. 1).

Assuming chloroquine chemoprophylaxis is available, to simultaneously follow the WHO requirements for breastfeeding, as well as the recommendations for *P. vivax* prevention throughout pregnancy until

breastfeeding is completed would require 15 to 33 months of weekly chloroquine chemoprophylaxis per pregnancy. The regimen would potentially be shorter if started following an acute episode of *P. vivax* malaria, which may occur later in the pregnancy (Fig. 2B).

For women breastfeeding for the 2 years recommended by the WHO, assuming they have three children (based on fertility rates in Indonesia and Pakistan of 2.4–3.4), this represents 2.25 years of pregnancy and 6 years of breastfeeding [30]. Thus, a woman could be excluded from primaquine treatment and potentially vulnerable to *P. vivax* relapse for more than 8 years if her children were G6PD-deficient or if their G6PD status was unknown [30]. A study conducted on the Thailand–Myanmar border reported that one woman was excluded from radical cure of *P. vivax* malaria for > 10 years due to consecutive cycles of pregnancy and breastfeeding [28].

Even if the child has been tested and is not G6PD deficient, the restriction on primaquine for breastfeeding mothers of infants < 6 months old would still exclude the mother from radical cure for a total of 3.75 years over three pregnancies (Fig. 2A, B). However, this would be reduced to as little as 2.25 years in total if primaquine was only contraindicated during pregnancy and could be given post-partum regardless of the G6PD status of the child (Fig. 2C, D).

Substantial risks to women from *P. vivax* relapse

The greatest risk to post-partum women with *P. vivax* malaria is anaemia, which can be severe or life-threatening [40, 41]. Maternal anaemia is common in many malaria endemic countries, but pregnant women with symptomatic *P. vivax* infection are over five times more likely to be anaemic compared with non-infected pregnant women [42]. Even asymptomatic *P. vivax* malaria during pregnancy can increase the risk of maternal anaemia [40]. Consequently, during post-partum, women who are at risk of *P. vivax* relapse are likely to be already anaemic. Repeated *P. vivax* relapses compound their anaemia, causing morbidity and leaving the individual susceptible to other diseases [18, 27]. Severe *P. vivax* malaria is also a risk, particularly in breastfeeding women who may be malnourished or have additional co-morbidities [4, 27, 41, 43]. It is, therefore, essential to provide radical cure for new mothers who have had *P. vivax* malaria during pregnancy as soon as possible following birth to prevent relapse, allowing haematological recovery and preventing severe anaemia [27].

It is also necessary to ensure that women who have had *P. vivax* during pregnancy or while breastfeeding receive radical cure before their next pregnancy. If there is no opportunity for administration of 8-aminoquinolines between children, women remain vulnerable to relapses during pregnancy, with potentially serious consequences for the mother, foetus, and newborn [40, 41, 44–47].

Malaria elimination requires access to *P. vivax* radical cure

To accelerate malaria elimination, the greatest proportion of the population possible must have access to *P. vivax* radical cure. The persistence of the hypnozoite reservoir significantly contributes to malaria morbidity, mortality and transmission [48, 49]. To deplete this reservoir requires effective radical cure with high coverage of the population at risk. Where dosing is inadequate, adherence sub-optimal, or coverage is insufficient, the hypnozoite reservoir will continue to fuel relapses and transmission [8, 9, 30, 50, 51].

There has been considerable progress in modelling *P. vivax* transmission dynamics to consider the impact of the hypnozoite reservoir on malaria control and elimination. In a recent model, increasing *P. vivax* radical cure coverage reduced disease prevalence, with high coverage (82% of *P. vivax* infections) driving the parasite to near elimination over a period of 10 years, even without the use of mass drug administration [52]. A different model based on data from the Republic of Korea showed a decline in *P. vivax* prevalence with increasing coverage of radical cure [53]. Any new strategies for *P. vivax* malaria elimination based on radical cure will need to achieve high coverage to be effective and must therefore include breastfeeding women [3, 54].

Around 13% of women are excluded from radical cure because they are pregnant or breastfeeding [30]. This is a substantial fraction of the population in need of treatment and will sustain the hypnozoite reservoir, potentially hindering *P. vivax* control and elimination. However, if breastfeeding women could receive primaquine, then only around 4% of women would be excluded from radical cure [30]. Thus, extending primaquine radical cure to breastfeeding women is crucial to successfully support *P. vivax* malaria control and elimination.

Primaquine exposure in breastfeeding infants

Restrictions on the use of primaquine in breastfeeding mothers assumes that primaquine concentrations in breast milk may be sufficient to provoke haemolysis in a G6PD-deficient infant. However, the available clinical data for primaquine provide strong evidence that this is not the case [28].

Conducted in the Thailand–Myanmar border region, primaquine pharmacokinetics and haematological safety parameters were evaluated in 21 healthy G6PD-normal women with previous *P. vivax* infection and their healthy,

breastfeeding, G6PD-normal infants aged between 28 days and 2 years [28]. Primaquine was administered to the mothers for 14 days at the standard dose of 0.5 mg/kg/day. The nursing infants showed no differences in haematological findings versus age-matched controls [28].

Drug concentrations of primaquine and its major metabolite carboxyprimaquine were measured in maternal plasma, breast milk and infant plasma [28]. Plasma pharmacokinetic parameters for primaquine and carboxyprimaquine in the breastfeeding women were similar to those reported for non-pregnant or non-breastfeeding adults [55–58]. The median values for the maximum primaquine concentration (C_{max}) and the area under the concentration time curve 24 h after dosing (AUC_{0-t}) were around threefold lower in breast milk than in maternal plasma, i.e., median (range) C_{max} was 44.0 (31.4–99.0) ng/mL versus 139 (66.1–215) ng/mL, and AUC_{0-t} was 420 (179–1150) ng·h/mL versus 1220 (499–2360) ng·h/mL, respectively (Fig. 3) [28]. For carboxyprimaquine the difference in C_{max} and AUC between maternal plasma and breast milk was more pronounced, being at least 113-fold and 163-fold lower in breast milk, respectively (Fig. 3) [28].

In the clinical lactation study, infant plasma primaquine concentrations were all measured to be below the lower limit of quantification (1.14 ng/mL), except for one sample that was 2.59 ng/mL on day 7 [28]. The resulting infant plasma carboxyprimaquine concentrations were negligible (0–25.8 ng/mL) compared to observed maximum plasma concentrations in mothers

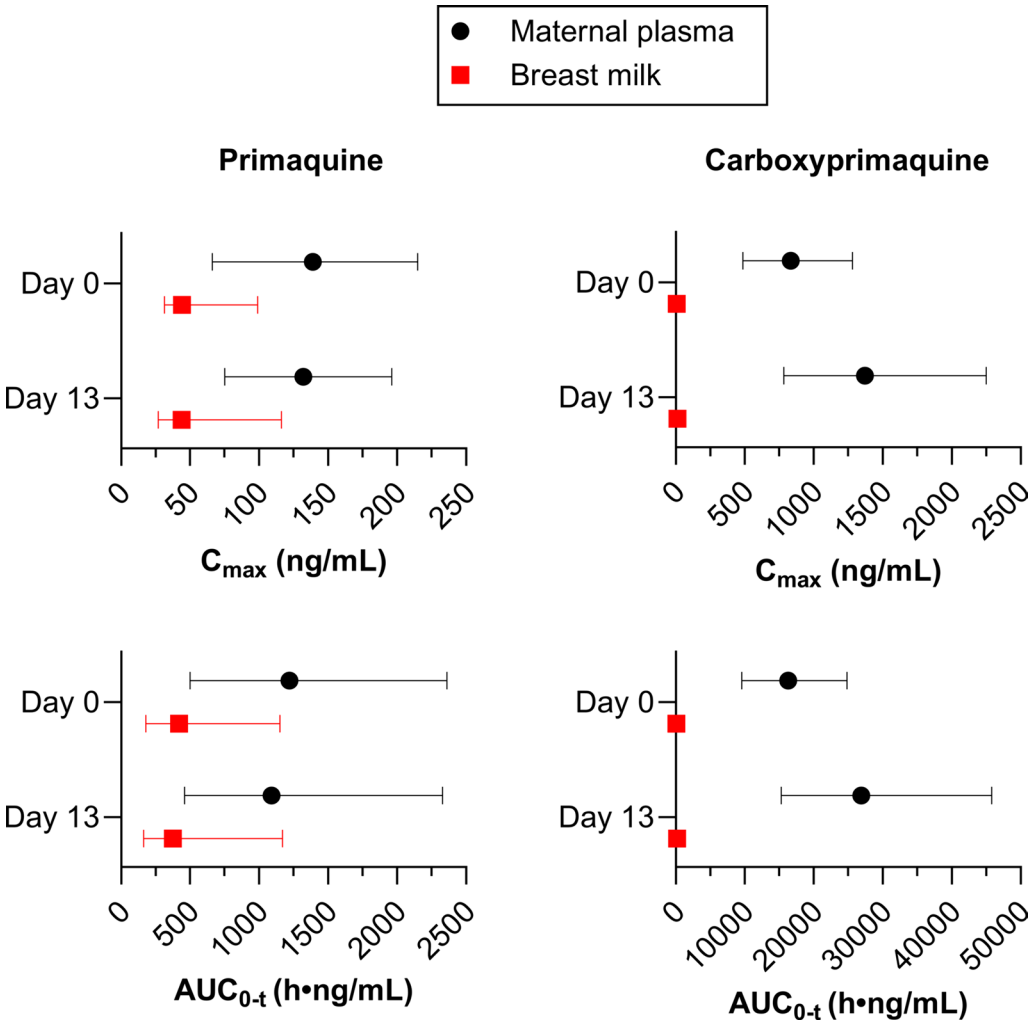

Fig. 3 Pharmacokinetic parameters for primaquine and carboxyprimaquine in maternal plasma and breast milk [28]. Primaquine dose in mother was 0.5 mg/kg/day for 14 days; data are presented as median ± range. AUC_{0-t}, area under the concentration – time curve until the last sampling point (24 h after administration); C_{max}, maximum drug concentration. The lower limit of quantification was 1.14 ng/mL for primaquine and 4.88 ng/mL for carboxyprimaquine

receiving the treatment (486–2250 ng/mL) [28]. To put this in context, the single 0.25 mg/kg dose of primaquine, which is recommended to block transmission in patients with falciparum malaria without the need for G6PD testing [2], had a median (range) plasma primaquine C_{max} of 103 (38–174) ng/mL and an AUC_{0-last} of 730 (297–1251) ng·h/mL in children with acute falciparum malaria aged > 6 months to 1 year [59].

In a follow-up analysis, the clinical pharmacokinetic plasma and breast milk data from the mothers were evaluated using a simultaneously fitted population pharmacokinetic model. The data did not allow for developing a model for the infant plasma data as almost all of the observed concentrations were below the lower limit of quantification. However, based on breast milk concentrations and a mechanistic breastfeeding model, primaquine and carboxyprimaquine concentrations in infant plasma were simulated [31]. These simulations showed an infant primaquine plasma concentration below 1 ng/mL and carboxyprimaquine plasma concentrations below 2 ng/mL, comparable to that of the observed infant data. The simulations also demonstrated that for all of the currently recommended and used primaquine dosing regimens for radical cure and transmission blocking (0.5 mg/kg/day for 14 days, 1 mg/kg/day for 7 days, 0.5 mg/kg/day for 7 days, 0.75 mg/kg/week and 0.25 mg/kg single dose), breastfeeding infants received less than 1% of the weight-adjusted maternal dose [31].

Based on the clinical findings for the 0.5 mg/kg/day primaquine dose for 14 days, the relative primaquine dose in infants versus mothers was estimated to be between 0.23 and 1.82% on day 0 and 0.21% to 1.64% on day 13 [28]. A relative infant dose surpassing 10% of the maternal dose is conventionally regarded as a threshold warranting concern [60, 61], but as a fixed threshold, this overlooks the potential toxicity of the drug [61]. However, it has been demonstrated that a single 0.25 mg/kg primaquine dose does not cause clinically significant haemolysis in G6PD-deficient adults [62]. In comparison, infants in this study received a total dose via breast milk of 0.042 mg/kg spread over 14 days [28]. The very low calculated relative infant dose, along with the negligible primaquine and carboxyprimaquine concentrations in infant plasma, are highly unlikely to pose a haemolytic risk to a G6PD-deficient infant and should not prevent the administration of primaquine to breastfeeding women of nursing infants between 1 and 24 months of age [28].

These clinical data are compelling and support the use of primaquine in women with acute *P. vivax* malaria who are breastfeeding, without the requirement to determine the infant's G6PD status. This would reduce the period for which women are vulnerable to relapse to 10 months for any pregnancy and negate the risk of carrying that risk to subsequent pregnancies (Fig. 2C).

The role of physiologically-based pharmacokinetic modelling

Although highly reassuring, the clinical findings do not include all circumstances for breastfeeding mothers. For example, the results cannot be generalised to newborns (< 28 days) because the composition of breast milk in the first days after birth (colostrum) differs significantly from mature milk. To complement clinical studies, researchers are addressing the challenges of drug development in breastfeeding women by using PBPK modelling [29, 63–73]. PBPK modelling combines information on human physiology and known drug properties to understand and predict the pharmacokinetic properties of a drug in a target population. Drug factors within the model include physicochemical properties and metabolism, and intrinsic physiological factors include bodyweight, height, age, organ sizes and the expression of metabolising enzymes. Extrinsic factors such as food intake and co-medications can also be considered.

This approach allows exploration of various drug dosing regimens under different scenarios that are challenging to test clinically. Relevant demographic and physiological factors can be incorporated in PBPK models to simulate drug pharmacokinetics in different populations of interest. For example, virtual populations of women at different stages of breastfeeding or infants with different feeding patterns can be incorporated into the model and exposures estimated in neonates and infants via breast milk [29, 63–72].

PBPK modelling is used routinely in drug development and is well accepted by regulatory authorities, with clear guidance on the factors that must be considered, such as the uncertainties and bias [74–77]. For example, a credibility assessment framework has been developed with the aim of standardising regulatory evaluation of PBPK models across therapeutic products [78]. Similarly, a structured framework has been proposed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) conceptual approach, for integrating model-derived evidence into health decision-making processes [79]. PBPK models can be verified against existing clinical pharmacokinetic data for drugs, with integration of clinical and model-derived data for optimal decision-making.

Simulated primaquine concentrations in breast milk, neonates and infants

A recent paper used a previously verified primaquine PBPK model to estimate the pharmacokinetics and variability of primaquine in breastfeeding

women and in their infants via breast milk [29]. The model was optimized using the reported observed milk to plasma (M/P) ratio and verified using the data from the clinical lactation study described above, with the virtual infant population defined based on the heights and weights of the clinical population [28, 29]. The simulated primaquine dose (0.5 mg/kg/day for 14 days) was the same as in the clinical lactation study [28, 29].

Model-predicted primaquine plasma concentrations in virtual infants were below 2 ng/mL across the duration of 14-day primaquine dosing in breastfeeding women [29]. These predicted concentrations were consistent with the reported clinical data for infants (≥ 28 days old) who had primaquine exposures below the lower limit of quantification [28] (Fig. 4A).

The model was also used to simulate primaquine concentrations in neonates (< 28 days old), where no clinical data are available, given the difficulty in recruiting neonates into clinical trials. Primaquine is mainly metabolised by monoamine oxidase (MAO), and different scenarios were modelled considering varying degrees of maturation of MAO activity in the neonate. In all scenarios, the predicted exposures of primaquine in neonates were < 1% of those reported in maternal plasma (Fig. 4A).

Using the published PBPK model, an additional analysis was performed for this paper investigating the 0.75 mg/kg/week for 8 weeks primaquine dosing regimen, which is used clinically for G6PD-deficient patients or where G6PD testing is not available [2]. In this case, the simulated concentrations of primaquine in infants and neonates were below 3 ng/mL, which is less than 1% of the maternal plasma levels, throughout the 8-week dosing period (Fig. 4B).

Another factor to consider is the impact of changes in composition of human milk (from colostrum to mature milk) in the first 2 months post-partum on the primaquine intake of infants via breast milk. Using the composition of mature milk, the predicted M/P ratio was 0.47, similar to the observed value of 0.34 [28, 29]. A sensitivity analysis was performed within the PBPK model, varying breast milk fat content (2–5%) and pH (7.2–7.6) to simulate the fluctuations in milk composition [29]. These indicated a range of M/P ratios of 0.2 to 0.48, with the predicted primaquine exposures via breast milk to infants receiving colostrum being lower than with mature milk [29].

There are limitations to the PBPK model, including limited understanding of drug absorption processes in young children and of the degree and effect of protein

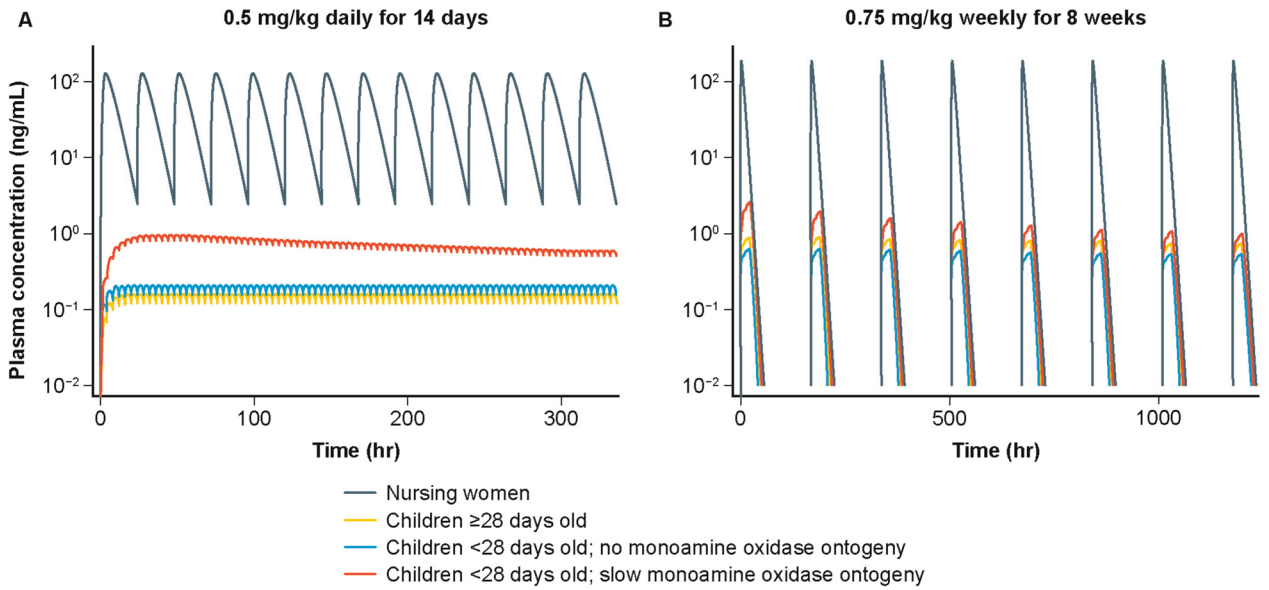

Fig. 4 Simulated primaquine plasma concentrations in breastfeeding infants relative to mothers [29]. Simulated mean plasma concentration–time profiles of primaquine in breastfeeding women (black line) and their infants aged ≥ 28 days (yellow line) and neonates aged < 28 days assuming no ontogeny for monoamine oxidase (MAO) (blue line) and a slow ontogeny following birth (red line). **A** Based on a maternal dose of 0.5 mg/kg/day for 14 days and infant dose of 2.98 µg/kg/day (six feeds every 4 h at 0.497 µg/kg/feed). Originally published as Figure 5b in Pan et al. [29], permission by creative commons license. **B** Analysis conducted for this paper using the same PBPK model using the maternal primaquine dose of 0.75 mg/kg/week for 8 weeks and infant dose of 9.42 µg/kg/week (six feeds every 4 h at 1.57 µg/kg/feed). In both cases, the simulations account for the rapid physiological and biochemical changes occurring in neonates and infants during the simulation period. In the absence of any information defining the ontogeny of MAO following birth, simulations were done for no ontogeny and slow ontogeny, which is the most conservative assessment. All simulations were performed using the clinically observed milk to plasma ratio (0.34) [28]

binding within breast milk, as well as the sparse clinical data available for model verification in children, particularly in neonates [67]. There is also uncertainty regarding the sensitivity of neonates and infants to primaquine-induced oxidative toxicity. However, the model was conservative in its design. It incorporated the clinically reported M/P ratio in infants, assumed complete drug absorption from the gastrointestinal tract and a slow maturation of metabolising enzymes, representing a 'worst-case' scenario. Simulated variations in milk composition and the degree of metabolising enzyme maturation consistently indicated very low predicted exposures to primaquine in breastfeeding infants which were congruent with the available clinical data [28, 29].

The findings from the PBPK model support and supplement the clinical lactation study and population pharmacokinetic modelling. Taken together, the evidence of low primaquine exposures in breastfeeding neonates and infants suggests that primaquine could be safely given to breastfeeding women, regardless of the G6PD status of the child. This would allow administration of radical cure soon after birth, further reducing the period during which women are vulnerable to *P. vivax* relapse to just the duration of the pregnancy (Fig. 2D). It would also ensure that women received treatment with primaquine before being potentially 'lost to follow up' post-partum.

Conclusion: health equity for *P. vivax* radical cure

Addressing health equity for *P. vivax* radical cure is a public health priority, with significant societal and economic implications associated with inadequate access [5, 6, 18, 27, 41, 80, 81]. Women living in areas where *P. vivax* malaria is endemic may be excluded for many years from radical cure with primaquine while breastfeeding, threatening their health. Additionally, the indirect benefits to children when their mothers are treated appropriately versus the harmful effects of repeated relapses must be considered. There are also public health consequences, with healthcare systems having to choose between supporting adherence to many months of chloroquine chemoprophylaxis and managing the clinical consequences of repeated relapses, such as anaemia and potentially severe malaria [5, 6, 18, 27, 41]. Moreover, there are uncertainties around the prolonged use of chloroquine chemoprophylaxis, in terms of feasibility, adherence and potential safety risks to the mother and child. Additionally, the persistence of the hypnozoite transmission reservoir in the approximately 9% of women who are breastfeeding in endemic populations undermines malaria elimination and control activities [30].

The individual and societal benefits of being able to administer radical cure among breastfeeding women are likely to be substantial. The health of breastfeeding women should not be jeopardised when clinical data and population and PBPK modelling provide consistent evidence of very low primaquine exposures in breastfeeding infants, suggesting negligible haemolytic risk, regardless of the child's G6PD status [28, 29, 31]. *P. vivax* radical cure in this population should be integrated with strategies to provide comprehensive care for maternal and infant health [27, 82].

Despite there being no evidence of risk, the treatment guidelines have restricted breastfeeding women from using primaquine presumably because of the perceived risk that exposures through breast milk could be sufficient to cause haemolysis should the infant be G6PD deficient. However, the health interests of breastfeeding women should not be secondary to an unproven assumption of risk to the infant. Even considering the complex regulatory environment for the approval of drugs for breastfeeding women [83], it is unacceptable that primaquine, which has been used for more than 70 years, has been withheld from breastfeeding women [84].

Although robust, the clinical pharmacokinetic data are limited to one study including 21 mother and infant pairs [28]. However, more than 5 years after publication, neither a change in guidelines nor additional clinical studies occurred. Plans for a clinical trial evaluating the impact of different breast milk composition on primaquine and tafenoquine concentrations in breast milk in the early post-partum period were recently withdrawn because of challenges in obtaining ethical approval (ClinicalTrials.gov Identifier: NCT04984759). Although the study is being redesigned (NCT06191458), it highlights the difficulty in progressing clinical studies in breastfeeding women and the knowledge gaps that need addressing. Support for studies investigating the safety and efficacy of drugs in lactating women needs to come from all levels of the research continuum, starting with drug development to clinical trials implementation, with sufficient funding and appropriate regulatory and ethical oversight [82, 85, 86]. Where clinical data are limited, the integration of clinical data and PBPK modelling can be used to strengthen the evidence base and inform treatment recommendations and policy change. Similar approaches should become best practice for studying underserved populations, such as breastfeeding women, in an efficient manner to achieve equitable access for other medicines [29, 63, 82, 84–86].

Breastfeeding women should have access to primaquine without the need for G6PD testing of their infant. The evidence supports primaquine 0.5 mg/kg/day for 7 or 14 days in breastfeeding women from early post-partum, unless the woman is G6PD deficient or if G6PD testing is not available, in which case primaquine 0.75 mg/kg/week for 8 weeks can be administered.

Based on the totality of evidence, it is of paramount importance to re-examine the recommendations around primaquine for *P. vivax* radical cure in breastfeeding women, and thus provide health equity for this critically important intervention.

Abbreviations

ACT	Artemisinin-based combination therapy
G6PD	Glucose-6-phosphate dehydrogenase
MAO	Monoamine oxidase
MDA	Mass drug administration
M/P	Milk to plasma
PBPK	Physiologically-based pharmacokinetic modelling
WHO	World Health Organization

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Availability of data and materials
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
NA, ACM, EJ, SD, JJM and MEG are employees of MMV Medicines for Malaria Venture. PZ and JC are employees of the Bill & Melinda Gates Foundation. LA, KRY and XP are employees of Certara Ltd and may hold shared in the company. NR is a paid consultant for MMV Medicines for Malaria Venture. 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 Bill & Melinda Gates Foundation (INV-023795). AB and SC work for the Medicines and Healthcare products Regulatory Agency and are funded by the Bill & Melinda Gates Foundation (INV-009383). JT declares no competing interests.

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