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Expanding the Use of Primaquine for the Radical Cure of *Plasmodium vivax*

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There is currently strong impetus for global malaria eradication, with many national malaria control programs setting ambitious elimination targets. While intensified malaria control efforts have reduced the burden of falciparum malaria significantly, the fragile gains made thus far remain vulnerable to the threat of emergence and spread of multidrug-resistant parasites. Outside of sub-Saharan Africa, the decline in falciparum malaria has also been shadowed by a rise in the proportion of malaria due to *Plasmodium vivax*, which is now the predominant cause of malaria in these regions [1]. Vivax malaria is more difficult to eradicate than *Plasmodium falciparum* because it can form dormant liver stages (hypnozoites) that reactivate periodically, causing recurrent infections (relapses) and further transmission [2].

The primary objective of antimalarial treatment is to kill the pathogenic asexual parasite stages as rapidly as possible and thereby prevent or alleviate clinical symptoms and organ dysfunction. Schizontocidal agents have little efficacy against the mature sexual stages (gametocytes) of *P. falciparum* or the hypnozoites of *P. vivax* or *Plasmodium ovale*. Gametocytes and hypnozoites do not cause clinical disease directly, but they are critical for ensuring ongoing transmission of the parasite. Furthermore, reactivation of *P. vivax* hypnozoites results in recurrent episodes of malaria that can have a profound negative impact on health, particularly in women and infants from poorly resourced communities [3, 4].

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If malaria elimination targets are to be achieved, there will need to be more aggressive use of “radically curative” drug regimens that are capable of eliminating all parasite stages from the body, including gametocytes and hypnozoites. Both patients with clinical disease and the large numbers of apparently healthy individuals who harbor transmissible malaria parasites need to be targeted [5]. The only widely available drug to treat the mature gametocytes of *P. falciparum* and the hypnozoites of *P. vivax* is primaquine (PQ), a drug which can cause severe hemolytic anemia when administered to patients with glucose-6 phosphate dehydrogenase (G6PD) enzyme deficiency. G6PD deficiency is the most common enzymopathy worldwide, affecting an estimated 400 million people. Recent World Health Organization guidelines advocate that, where possible, all patients should be tested for G6PD deficiency prior to administration of PQ; however, few malaria-endemic countries have yet to incorporate this into national guidelines [6, 7]. While PQ has been shown to be well tolerated in G6PD-normal children aged >12 months, there are almost no safety data for its use in young infants. Moreover, it is not possible to diagnose G6PD deficiency in utero or before the age of about 6 months using standard G6PD assays available in resource-poor countries. For these reasons, prescription of PQ is currently contraindicated during pregnancy and for at least the first 6 months that mothers are lactating [6]. Since women in many malaria-endemic settings are either pregnant or breastfeeding for most of their reproductive years, they may be denied radical cure for many years, and potentially decades. The ongoing carriage of hypnozoites puts subsequent pregnancies at risk from relapsing vivax malaria, contributing to preterm delivery, maternal anemia, and perinatal mortality [4].

In this issue of *Clinical Infectious Diseases*, Gilder and colleagues report the results of the first pharmacokinetic study to determine whether PQ is excreted into breast milk and therefore whether PQ should be contraindicated during lactation [8]. The authors enrolled 20 G6PD-normal mothers from northern Thailand, who required PQ for radical cure of *P. vivax* infection and who were breastfeeding infants >28 days old. Serial venous blood and breast milk samples were taken from the mothers during a 14-day high-dose PQ regimen (7 mg/kg total dose) along with capillary blood samples from their breast-fed infants. The estimated dose of PQ received by the infants from breast milk was <3 µg/kg/day, equivalent to approximately 0.5% of that which would be administered directly during a standard weight-based PQ regimen. Only 1 of the infant blood samples had a PQ level above the limit of detection and the concentration measured was negligible. While there are few data on the safety of PQ in infants, there is no evidence that PQ is more toxic to infants than adults. Because a single dose of 0.25 mg/kg has been shown to cause no significant hemolysis even in G6PD-deficient individuals, it is highly likely that a total dose >6-fold lower would be safe, even in deficient individuals. These results are extremely reassuring. Further data are needed to confirm tolerability in infants <28 days of age, but in the meantime, treatment policy should be changed so that G6PD-normal mothers with a history of *P. vivax* malaria can be treated with a radically curative course of PQ provided they are at least 4 weeks postpartum. Such a strategy will reduce the risks to mother and baby of malaria in future pregnancies and reduce parasite transmission. Expanding the eligibility of radical cure to include lactating mothers has potential to reduce the global burden of malaria.

The authors should be applauded for addressing a neglected area that, over the last 60 years, has effectively denied millions of lactating women appropriate antimalarial treatment. The

study also highlights the importance of defining antimicrobial policy through detailed pharmacokinetic studies in vulnerable populations. Collecting relevant samples from pregnant women and young children is particularly challenging, and thus recommended dosing regimens are frequently extrapolated from studies in older children and nonpregnant adults, assuming that the pharmacokinetic profiles are similar; often this assumption is patently invalid. Malaria treatment guidelines derived by such means have resulted in underdosing of sulfadoxine-pyrimethamine in children [9], of artemether-lume-fantrine in pregnant women [10], and of dihydroartemisinin-piper-aquine in low-weight children [11]. Technological advances have enabled quantification of antimicrobial agents and their metabolites reliably from increasingly smaller sample volumes, allowing carefully designed and conducted studies, like the one by Gilder and colleagues, to define optimal treatment strategies in those who need them most.

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