Higher-Dose Primaquine to Prevent Relapse of *Plasmodium vivax* Malaria

TO THE EDITOR: Chamma-Siqueira et al. (March 31 issue)[1] report that the 6-month efficacy of primaquine against relapse of *Plasmodium vivax* malaria was better at a total dose of 7 mg per kilogram of body weight than at a total dose of 3.5 mg per kilogram, both given 2 weeks after the completion of chloroquine treatment, in patients 5 years of age or older. Given the assumption that primaquine exposure at the 3.5-mg-per-kilogram total dose was adequate, this result is important. In Cruzeiro do Sul, Brazil, the reported recurrence rates among patients who received the 3.5-mg-per-kilogram total dose of primaquine (approximately 40%) are higher than the combined rates from Brazil, Peru, and Colombia among the recipients of primaquine (approximately 34%) or tafenoquine (approximately 33%)[2] and higher than the reported rates in primaquine studies from Peru (approximately 10 to 13%),[3] Colombia (approximately 18%),[4] and the Brazilian Amazon overall (approximately 14%).[5]

Nevertheless, the study by Chamma-Siqueira et al. raises the question of whether primaquine at a total dose 7 mg per kilogram may be more efficacious in other countries (i.e., outside Southeast Asia and Oceania) where "temperate climate" *P. vivax* exists. Now may be the time to abandon the traditional guidelines recommending the use of primaquine for *P. vivax* malaria at a total dose of 3.5 mg per kilogram in temperate climates and a total dose of 7 mg per kilogram in tropical climates and focus instead on developing evidence-based, pharmacokinetically sound primaquine regimens for all ages using suitable tablet strengths to inform drug policy. Brazilian guidelines recommend a 7-day regimen of the 3.5-mg-per-kilogram total dose of primaquine that incorporates six weight- and age-based dosing bands and uses only 5-mg and 15-mg tablets. The paucity of studies involving young children and lack of quality-assured, child-friendly primaquine formulations present challenges but are being addressed.[6]

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TO THE EDITOR: The unusual sequential "radical cure" treatment regimen for *P. vivax* malaria reported by Chamma-Siqueira et al. from western Brazil complicates interpretation of the trial result. Usually chloroquine and primaquine are given together to treat *P. vivax* malaria. Both drugs have activities at the asexual stage of parasite development, but only primaquine kills the dormant liver-stage parasites (hypnozoites) that cause relapse.[1] Although long-latency *P. vivax* malaria occurs in the Americas,[2] most relapses emerge from the liver approximately 14 days after presentation of the initial illness. The slowly eliminated chloroquine suppresses the relapsing blood-stage infection for several weeks. Chamma-Siqueira et al. delayed administration of primaquine for a median of 17 days. Because each study group received the same dose of chloroquine, the authors were therefore comparing the asexual-stage antimalarial effects of primaquine against early relapse and the hypnozoitocidal effect against later relapses. Primaquine has relatively weak activity against asexual-stage parasites,[3] so, unsurprisingly, the 2-week course was superior to the 1-week course. Clinical trials comparing radical curative activity in *P. vivax* and *P. ovale* malaria should assess concurrent — not sequential — treatment (i.e., hypnozoitocidal efficacy and not activities at the asexual stage of parasite development should be assessed).

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THE AUTHORS REPLY: Some caution is warranted in comparing the studies mentioned by Taylor et al. with ours. Two are antimalarial efficacy trials conducted in 2003 and 2008 — years before our study. The third study is a retrospective analysis of national surveillance data from Brazil. Retrospective analyses of surveillance data have inherent limitations in accurately assessing treatment efficacy and are not the first option the World Health Organization (WHO) would recommend to evaluate antimalarial efficacy and guide policy.[1] In addition, other studies that also use the 3.5-mg-per-kilogram total dose of primaquine in the Americas have shown percentages of patients with recurrence of *P. vivax* malaria in the range of 23 to 40%, findings that are similar to what we observed.[2,3] These findings underscore the need to conduct efficacy trials in other countries in the region to accurately evaluate the efficacy of primaquine in preventing recurrence.

The synergism of concomitant use of chloroquine and primaquine is more prominent against blood-stage parasites.[4] Although the synergistic effect of chloroquine on primaquine against hypnozoites has been described, its clinical effect and relevance are not well established. Taking into consideration the need for the measurement of glucose-6-phosphate dehydrogenase activity before primaquine use, we decided to delay primaquine until those results became available, which is in line with WHO recommendations.[1]

In Brazil, relapses of *P. vivax* malaria have been reported between the 4th and 13th week after treatment of the acute infection, a time range for relapse that is similar to that of other strains in the Americas.[2,5] Indeed, we noted that the recurrence episodes in the study group that received the 7.0-mg-per-kilogram total dose (in which primaquine was administered over a 14-day period) started approximately 2 weeks after the recurrence episodes in the other two study groups that received the 3.5-mg-per-kilogram total dose of primaquine over a 7-day period (one in which administration was observed and the other in which administration was unobserved). We performed some supplementary analyses in which the data regarding recurrence episodes that occurred before day 56, when the first recurrence in the 7.0-mg-per-kilogram group was documented, were censored. By doing so, the probability of freedom from recurrence of *P. vivax* malaria by day 168 was 64% (95% confidence interval [CI], 49 to 75) among the patients who received the 3.5-mg-per-kilogram total dose of primaquine with unobserved administration and 64% (95% CI, 52 to 74) among those who received the 3.5-mg-per-kilogram total dose with observed administration — results that were different from the probability among patients who received the 7.0-mg-per-kilogram total dose of primaquine (86%; 95% CI, 76 to 92). Therefore, it is unlikely that our findings are the result of an effect of primaquine on blood-stage parasites (i.e., prevention of early relapses through a schizonticidal effect) alone but probably also reflect an effect on hypnozoites (i.e., prevention of later relapses).

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Since publication of their article, the authors report no further potential conflict of interest.

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