EDITORIAL

Radical Cure of *Plasmodium Vivax* Malaria: How can we Improve 8-Aminoquinoline Implementation?

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Plasmodium vivax is expected to be a greater obstacle to malaria elimination than *Plasmodium falciparum.* Radical cure of *P. vivax* malaria requires drugs for the treatment of blood and liver stages of the parasite. The 8-aminoquinolines (primaquine and tafenoquine) are the known drugs that have been used to treat the liver stage of *P. vivax* malaria. However, effective implementation of 8-aminoquinolines has been a challenge in most malaria endemic settings due to the safety concern mostly related to risk of hemolysis with use of these drugs specifically in glucose-6-phosphate dehydrogenase (G6PD) deficient individuals.

World Health Organization recommends G6PD testing prior to primaquine administration for radical cure treatment of *P. vivax* malaria (1). However, access to laboratory-based assays G6PD testing is unavailable or limited in most malaria endemic settings. The recent development and emergence of qualitative and quantitative G6PD point-of-care (POC) tests has shown promise for routine use and implementation studies are ongoing in most malaria endemic settings (2).

Evidence has shown that the antirelapse efficacy of primaquine is related to the total dose of primaquine whereas the risk of hemolysis is related to the daily dose administered (3). Most national malaria control programs recommend a total dose of 3.5 mg/kg primaquine administered over 14 days, allowing the daily dose to be reduced to 0.25 mg/kg to minimize hemolysis as G6PD test is not easily accessible. However, an unsupervised 14-day regimen is associated with a significantly reduced primaquine adherence and effectiveness (4) and, daily supervision of a prolonged treatment regimen is not practical in most malaria-endemic settings. The higher primaquine total dose mg/kg is most effective but the risk of serious adverse events (gastrointestinal disturbance and hemolysis) increases. Some malaria endemic countries use seven-day primaquine regimens of higher daily doses (0.5 mg/kg). Although primaquine related serious hemolysis is less commonly reported, most of the reports were observed from malaria endemic setting that used higher daily doses (0.5 mg/kg) and mostly in G6PD deficient individuals (5).

Tafenoquine has an advantage over primaquine in improving treatment adherence as it is single dose. However, tafenoquine is long-acting drug and requires quantitative G6PD testing prior to administration to prevent risk of hemolysis. Besides, tafenoquine can reduce the risk of recurrence of *P. vivax* malaria when co-administered with chloroquine but the clinical benefit was not seen when co-administered with dihydroartemisinin–piperaquine. This raises a concern of its use in chloroquine resistance settings (6).

Therefore, there are multiple factors to be taken into considerations in identifying the effective and safe 8-aminoquinoline regimen for radical cure treatment of *P. vivax* and for enhancing its effective implementation. One of the considerations to note is the frequency and risk of relapse and its consequences which are mostly related to host immunity, background transmission intensity, and geographic location. It is also important to note the presence of co-endemicity of *P. vivax* and *P. falciparum* in the setting as an increased risk of *P. vivax* parasitaemia following *P. falciparum* malaria have been observed. Recent evidence also indicated the benefits of expanding radical cure for *P. falciparum* in co-endemic settings to reduce *P. vivax* parasitaemia (7). The other important concern that should be well assessed in the setting is the risk of hemolysis and serious adverse events with use of 8-

aminoquinoline and the capacity of health system to monitor, early detect and manage. This requires looking at the prevalence of G6PD deficiency in the population and the health system infrastructure including the access to G6PD testing and availability of robust pharmacovigilance system.

In general, *P. vivax* radical cure implementation in malaria endemic settings can be improved by understanding the health system, local malaria and G6PD epidemiology and using tailored approach to the context to decide on effective radical cure regimen as there is not a one size fits all. National malaria programmes need to use local data and evidence, weigh the risks and benefits of different radical cure regimens and conduct implementation research to design safe and effective radical cure treatment and enhance its effective implementation.

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