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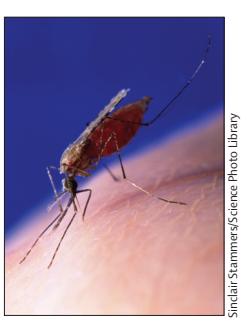
Single low-dose primaquine to reduce malaria transmission

The WHO Evidence Review Group's August, 2012 report about the safety and effectiveness of a single dose of primaquine as a *Plasmodium falciparum* gametocytocide[1] and WHO's new policy recommendation about low-dose primaquine[2,3] generated much interest for malaria control programmes seeking additional methods to reduce malaria transmission, especially in settings in which elimination of malaria is pursued. A single dose of primaquine at 0·75 mg base per kg has long been recommended as an adjunct therapy to reduce malaria transmission of *P falciparum*. However, the drug is often not used because of concerns about dose-dependent haemolytic effects in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency and the low availability of G6PD tests in the field. WHO's expert review group reviewed the available scientific literature, which suggested that one low dose of 0·25 mg base per kg of primaquine could be used widely and safely in people with malaria infection, including those with G6PD deficiency,[1] to help reduce the duration of circulating late-stage gametocytes (the sexual transmissible stage of the parasite) by roughly half and contribute to malaria transmission reduction. The authors of the report noted that additional effectiveness and safety evidence would be welcome to characterise the optimum dose and help countries to establish policies and strategies for single low-dose primaquine.[1]

In *The Lancet Infectious Diseases*, Alice Eziefula and colleagues describe the results of the first formal dose-finding study to assess the *P falciparum* gametocytocidal efficacy (measured as duration of gametocyte carriage) of a single dose of primaquine when given with artemisinin combination therapy.[4] The study included 468 Ugandan children younger than 10 years with normal G6PD function and uncomplicated malaria who received standard doses of artemether–lumefantrine and one low dose of primaquine at doses of 0·75 mg/kg, 0·4 mg/kg, and 0·1 mg/kg. The aim was to establish the lowest efficacious dose in people with normal G6PD enzyme function. All doses of primaquine were safe and very well tolerated. The 0·4 mg/kg dose and the standard 0·75 mg/kg regimen had similar gametocytocidal efficacy (mean duration of gametocyte carriage: 6·6 days in the 0·75 mg/kg group and 6·3 days in the 0·4 mg/kg group), but an efficacy gradient was apparent from 0·4 mg/kg to 0·1 mg/kg to placebo. As Eziefula and colleagues note, this work preceded the choice of 0·25 mg/kg in the WHO report,[2] but the WHO-recommended dose falls between the 0·4 mg/kg and 0·1 mg/kg doses



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assessed. In malaria control programme settings, children are likely to receive a specific number of tablets within prespecified age or bodyweight bands, whereby actual doses will range above and below the intended target dose of 0·25 mg/kg (eg, 0·15–0·35 or 0·1–0·4 mg/kg).[5] Eziefula and colleagues' study clarifies, for the first time, that doses greater than 0·4 mg/kg are not needed but, as the authors note, further attention should be given to the efficacy gradient between 0·4 mg/kg and 0·1 mg/kg, including the assessment of their safety in patients with G6PD deficiency to define the most efficacious and safest primaquine treatment regimen. Several studies are planned or in progress, and although protocol changes can be difficult, investigators should strongly consider including groups that would allow assessment of the dosing based on these new findings and WHO's recommendations.

The investigators gave the primaquine dose to the participants on day 2, which is common practice.[6] Nevertheless, national malaria control programmes might be more inclined to give primaquine with the first dose of the ACT to ensure that both drugs are given under observation. Although the authors acknowledged the limitation of delaying the primaquine dose, this approach was used to minimise potential interference of the malaria-attributable haematological effects during the acute phase of illness. However, the optimum timing of the single dose deserves further study. Primaquine has a very short half-life and delay of its administration has been suggested to enhance its efficacy because gametocyte densities often peak several days after the start of artemisinin treatment.[7,8] Delayed dosing might also improve safety because the risk of haemolysis in G6PD-deficient patients could be lower in afebrile patients.[9] However, it is unclear whether this benefit is outweighed by the additional days of potential infectivity before primaquine administration[6] and the reduced opportunity to give primaquine under observation.

A final programmatic consideration is the adherence to the full 3 day course of the artemisinin combination therapy. Artemether–lumefantrine, which resulted in clearance of the asexual parasites, was also an effective treatment for the sexual stage of the parasites, which is consistent with earlier studies with other artemisinin combination therapies.[6] A substantial decrease was recorded in the nucleic acid sequence-based amplification-measured gametocyte prevalence from roughly 82% at day 0 to roughly 40% at day 2 before primaquine administration, and to 15% by day 14 in participants who received artemether–lumefantrine plus placebo. Although complete gametocyte clearance was not achieved, this finding emphasises the importance of effective artemisinin combination therapy treatment, since slow or incomplete clearance of the asexual stages of the parasite could fuel gametocyte numbers and viability.[6,10] Mass malaria treatment campaigns must focus on ensuring that full dosing of artemisinin combination therapy is achieved. To this end, we will all welcome a safe and highly effective single-dose treatment that can be combined with one dose of primaquine and can be given as directly observed treatment for malaria.

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