Low-dose primaquine for falciparum malaria

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[A: We have edited your paper to avoid repetition, enhance readability, reduce length, and achieve consistency with *Lancet* style.]

Low-dose primaquine for falciparum malaria: authors' reply

We read with interest the Correspondence by Kapil Goyal and colleagues[1] on primaquine resistance and Eyal Meltzer and Eli Schwartz[2] on primaquine metabolism by CYP2D6 in relation to our report on primaquine for transmission reduction of *Plasmodium falciparum*.[3] The development of resistance has two discrete phases: de-novo emergence and subsequent spread. Resistance arises during asexual reproduction and not in non-replicating gametocytes. Although primaquine has been used widely for more than 60 years, including in mass drug administrations of single-dose formulations,[4] no conclusive evidence exists of primaquine resistance[5] in *P falciparum* gametocytes. Goyal and colleagues state that drug sensitivity assays are needed to monitor gametocyte resistance to primaquine and refer to an in-vitro screening system for gametocytocidal drugs.[6] This approach is unfeasible and uninformative for primaquine because the active metabolites of primaquine are unknown and the parent compound has very little activity in vitro.[6] Moreover, the assay relies on a small number of gametocyte-producing laboratory parasite isolates that are unlikely to represent those in natural infections.

Primaquine might exert a strong selective advantage to the small proportion of surviving gametocytes. Meltzer and Schwartz use the term failure rate for these surviving gametocytes, linking this to the slow drug metabolism by CY2D6 in some individuals. The densities of surviving gametocytes were markedly lower than those before primaquine,[3] and the drug might further affect their viability.[7] Further evidence of this finding with mosquito infectivity assays would allow the investigation of primaquine failure. We agree that more data are needed for the geographical differences in CYP2D6 metaboliser phenotype, and we are establishing CYP2D6 status in our Ugandan cohort to inform primaquine policy considerations.

We declare no competing interests.

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