

Malaria Policy Advisory Committee

Evidence Review Group on the Safety and Efficacy of Gametocytocidal Doses of Primaquine for *Plasmodium falciparum* malaria

Terms of Reference

1. Background:

Primaquine is widely used for radical cure of vivax malaria, increasingly used as a gametocytocide in falciparum malaria, and recommended by some agencies for primary prophylaxis of all forms of malaria. Other uses of primaquine include “presumptive anti-relapse therapy” (PART or terminal prophylaxis) in persons with extensive exposure to relapsing parasites, and “mass primaquine prophylactic treatment” (MPPT) involving the administration of 15 mg primaquine on a daily basis for 14 days during the pre-transmission season to eliminate both short and long-incubation strains of *P. vivax*. All these benefits have to be weighed against the principal toxicity of the 8-aminoquinolines, i.e. potentially life-threatening haemolysis in people who are glucose-6-phosphate dehydrogenase (G6PD) deficient. As G6PD deficiency has a prevalence of between 5 and 15% in many malaria endemic areas this has severely limited the use of primaquine in some areas, as simple inexpensive screening tests for G6PD deficiency are not available. The human G6PD gene is highly polymorphic; there are more than 200 different G6PD phenotypic variants, and more will undoubtedly be discovered. Many of these result in reduced enzyme activity and consequent increased susceptibility to oxidant stresses induced by fava beans and various medicines (such as primaquine). The urgency underlying the need for a safety review of primaquine, an 80 year old problem, is because of the increasing interest for using of primaquine as a single dose gametocytocide for transmission control, including reducing the transmission of artemisinin resistant falciparum malaria.

2. Questions to be addressed by the ERG on gametocytocidal doses of primaquine for *P. falciparum* malaria:

1. What is the haemolytic risk of a single gametocytocidal dose of primaquine in different phenotypes/genotypes of G6PD deficiency?
2. What is the haemolytic risk of radical curative dose regimens of primaquine by different phenotypes/genotypes and gender of patients with G6PD deficiency?
3. What is the haemolytic dose response relationship of primaquine when used for radical cure of malaria?
4. How can the haemolytic risk of G6PD deficiency be best estimated in field use of the drug?
5. How can the primaquine haemolytic reaction in patients with unknown G6PD status be best assessed in the field?
6. What is the best clinical management of haemolytic reactions following primaquine exposure?
7. What is the dose response relationship for gametocytocidal activity in falciparum malaria?
8. What is the minimal gametocytocidal dose of primaquine?
9. When should single dose primaquine be given (Day 1, 2, 3 or as split doses)?

10. Can the administration of single-dose primaquine be made safer?

In addition, based on the review of the evidence available, the ERG will be requested to also address the following 2 questions:

11. Based on the review of available evidence, including unpublished reports, which key recommendations (if any) could be proposed for a GRADE assessment?
12. Which priority research gaps need to be addressed to clarify the role of primaquine as a gametocytocide for falciparum malaria?

The main reason limiting current use is a concern over safety, so there is a need for an Evidence Review Group which will focus primarily on collating and reviewing all evidence on the safety of primaquine and its 8-aminoquinoline predecessors. Primaquine, and before it plasmoquine, has been used extensively in mass treatments, and often in areas where severe variants of G6PD deficiency were prevalent. Much of this information *may* be available in WHO documents as unpublished reports unavailable to the general public. Thus commissioning researchers to conduct a detailed literature search and assist with review of internal WHO and League of Nations documents is a necessary prelude to a meeting. The main output of the meeting would be an extensive safety and efficacy review of primaquine with primary attention to the single-day gametocytocidal use in falciparum malaria.

3. Suggested timetable:

February: identify suitable researcher(s), March-June: compile and analyse literature, August (week of 13): Meeting in Bangkok, 1st September: submission of evidence review and report of the meeting to the Malaria Policy Advisory Committee.

4. Declaration of Interests:

All ERG members to complete a DoI form which will be evaluated, summarized, and published on the MPAC website for public record.