Reviewer's report

Title: Single low-dose primaquine for blocking transmission of Plasmodium falciparum malaria - a proposed model-derived age-based regimen for sub-Saharan Africa

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Reviewer: Miles Davenport

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Taylor and colleagues report on an anticipated primaquine dosing schedule for their planned trial of primaquine for transmission blocking in Pf in sub-Saharan Africa. This is very similar to a paper by many of the same authors published in BMC Medicine last year, based on Cambodian demographic data. They analyse the expected dosing range based on five age-dosing groups, and demographic data on weight for age. The article provides a detailed background discussion of the risks and benefits of low-dose primaquine, and suggests optimal dose ranges and maximal levels. They then divide dose by observed weight distribution (from the demographic data) to see how their proposed dosing regime performs in staying within these limits. However, other than reporting the proportion of subjects expected to have under-dosing and overdosing, it provides little information to help us understand whether these doses / groups are optimal, or what the expected risk / benefit tradeoffs are.

1) This manuscript is very similar to one recently published in BMC Med by many of the same authors (ref 16). However, it uses slightly different age classes (for <1 yr). The reasons for this are not well explained. Is this because of the different weight for age in the SSA data, different Hb, or different perceived risk of G6PDd (frequency / severity of defect)? In the 'explanation' for the dosing regime (p9, l17-21), the authors state the upper limits they choose for the older age groups. However, for children 6-11 months they just state the dose. Given that the maximal tolerated levels they suggest in SSA is higher than in Cambodia for all older ages, it seems slightly unexplained why the dose for <1yr is half that recommended in Cambodia. Is this now also the preferred regime for Cambodia? The authors mention low Hb in children, but children <1yr have higher Hb than older children (table 3). Some explanation would be helpful.

2) Although this is a primarily quantitative study, it does not provide a quantitative basis for its starting points. That is, the rationale for choosing the particular dosing regime studied appears to rely on qualitative arguments. The authors state (p11, line 17) "Setting the upper therapeutic range of PQ is crucial for safety". However, all of the subsequent arguments for dosing are qualitative. There is a good discussion of the potential risks of primaquine for G6PDd individuals in the introduction. However, there seems no calculation of the clinical
effects of the expected dosing regime. The authors report the predicted extent of under-dosing (proportion of patients with low dose). They also report the upper limits they are trying to avoid (p9, l 17-21) - but simply as a threshold to keep under - and the proportion exceeding this, but do not estimate the potential impact of normal or overdosing.

Data exist on the predicted Hb losses in G6PDd and G6PDn individuals, for different primaquine doses. For example, Eziefula et al (ref 38), Goncalves et al (ref 35 - on supple table 4 &5), and Shekalaghe (ref 39) provide information on expected hemoglobin drops for G6PDd and G6PD normal individuals for different primaquine doses. This could be used to predict the proportion of patients with hemoglobin drops of different levels, given the proposed dosing regime and predicted proportion of individuals receiving a given mg/kg dose. This then allows a quantitative estimate of the (for example) total Hb drop across the population for a given dosing regime. As it stands, there is no measure of the 'trade-off' against higher primaquine doses, as only the proportion over-dosed is reported. The threshold for 'overdose' is 0.5 for children >6 years, and some estimate of the Hb drop for 0.4 mg / kg is provided in the references above (even if in some cases it is not significantly different from placebo). Predicting the 'penalties' (in terms of Hb loss) of increasing the dose, and therefore better justifying the choice of dose would be helpful.

3) The children who receive the highest doses are the youngest in the age bracket, and those on the lowest centile for body weight. There is likely a link between weight for age and haemoglobin, which might affect the impact of any subsequent (primaquine-dose-induced) hemolysis. Exploring the relationship between weight, dose, starting hemoglobin, and expected Hb drop may indicate children at particular risk.

4) A side-by-side table of the SSA and Cambodian dosing regimes would be helpful, as well as proportion under / over dosed in each.

5) In figure 4 and 5, a horizontal bar indicating the therapeutic range and upper limits proposed for each age group (p9, l 17-21) would be helpful

As it presently stands, the manuscript reproduces (for SSA) the approach recently applied in Cambodia. However, the justification for the regime change from the Cambodian regime seems largely qualitative. A more quantitative assessment of the risk / benefit tradeoff for different regimes (which would seem to be the major issue that is being optimized here) would greatly strengthen the manuscript.

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