Reviewer’s report

Title: Pregnancy-specific malarial immunity and risk of malaria in pregnancy and adverse birth outcomes: a systematic review

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Reviewer: Alfredo Mayor

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The MS by Cutts et al entitled "Pregnancy-specific malarial immunity and risk of malaria in pregnancy and adverse birth outcomes: a systematic review" reports results from a systematic review and meta-analysis of studies examining antibody responses to pregnancy-specific P. falciparum antigens and pregnancy/infant outcomes. Authors conclude that antibody responses are increased in women with placental infection, suggesting the potential role of pregnancy-specific malarial antibody responses as markers of exposure to placental malaria. Substantial heterogeneity in antibody and birth outcome associations may be explained by differences in the recombinant VAR2CSA antigens tested and the epidemiological settings of included studies. The manuscript is very well written and structured, and clear in its main messages.

Major comments:

Only 14 studies contributed estimates in a format enabling inclusion in meta-analysis and 12 were included in narrative form only. May this relatively low number of studies have limited the meta-analysis of associations between antibodies and infant outcomes? Authors argue that "Randomized controlled trials of interventions against P. falciparum malaria and vaccine efficacy trials were excluded because rigorous inclusion and exclusion criteria are applied in these studies, such that the participants are, typically, not representative of the general population". It would be worth to explain what do authors mean by "general population" and how authors consider if the women included in a study are representative of that general population.

Some of the 14 studies included in the systematic review either applied strong selection criteria (even more stringent than those applied in clinical trials) or resulted from clinical trials. For example:
Babakhanyan et al: When referring to the third set of plasma samples included in the study, "all samples from placental malaria positive women and randomly selected samples from PM− women were selected from women who had ≥3 pregnancies, ≥20 years of age, and had term or premature deliveries. All PM− women had been exposed to malaria since they had Ab to DBL5".

- Fowkes et al and Mc Lean et al: women participated in a placebo randomized controlled trial of chloroquine prophylaxis against P. vivax infection during pregnancy

- Guitard et al: "Women pregnant for less than 6 months were enrolled if they were not infected with malaria parasites at that time, declared not to have had malaria since being pregnant, and were likely to be exposed to infective mosquito bites during their pregnancy".

- Teo et al: "In the latter period, women were randomized to receive 3 courses of intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine (SP) and azithromycin (AZ) during pregnancy or to receive a single course of SP and chloroquine (CQ)"

- Staalose et al (2004): "Sample selection was done on the basis of HIV-1 status, gravidity (primigravid, 2-3 gravid, or >3 gravid), and placental histology (no malaria infection, acute infection, chronic infection, or past infection). We aimed to investigate 25 samples or more from HIV-1-negative women in all 12 categories of gravidity and histology, but could not always do so".

- Staalose et al (2001): Authors included 4 groups of pregnant women from these 2 sites. The first comprised 33 primigravid women; the second group consisted of 45 multigravid women; group 3 comprised 36 primigravid women and the final group comprised 55 primigravid and 58 multigravid women.

Also, any study conducted at antenatal clinics or maternity wards (as is the case of most studies reported) has inherent biases with respect to the general community, as the use of ANC clinics may be linked to demographic characteristics (e.g. place of residence, educational level, socioeconomic status or parity) that could also be related to malaria risk (women who do not attend antenatal clinics are often more rural, less literate, and older than women who utilize antenatal clinics).
Overall, inclusion of women participating in clinical trials might not introduce a bias greater than the biases inherent to the 14 papers included in the systematic review and would rather increase the breadth of study designs and antigens examined to be able to pool estimates for the association between a specific antibody response and clinical outcome across different populations, as well as to assess the effect of transmission intensity. I think authors could consider this possibility and provide more clear arguments to assess if the study can be used as representative or not of the general population.

Minor comments:

- Several articles have already shown the increase of pregnancy-specific antibodies in women with placental infection and would be worth to mention them in the discussion.
- Line 281: "IgGs against" or "antibody responses" is missing in the sentence.
- Line 294: Check reference 67, as it is a review and does not provide the OR mentioned in that line of the discussion
- "The association of antibodies to pregnancy-specific pRBC, measured at delivery, and low birthweight was examined in three studies (Figure 6) [51, 57, 58]". Why only two of these 3 studies were included in Figure 6?
- "Pooled analyses indicated that compared to non-responders, IgG responders to CSA-binding pRBC, measured at delivery, had a 26% reduction in the odds of low birthweight delivery (pooled OR using random effects (reOR)=0.74, 95% CI 0.51-1.06) (Figure 6) [57, 58]". Do authors consider this as statistically significant? If not, the sentence may need some change, including the sentence in the abstract ("Antibodies to pregnancy-specific pRBC, but not recombinant VAR2CSA antigens, were associated with protection from low birthweight").
- Reference 55 is incomplete

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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Not applicable
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