Reviewer’s report

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

Version: 0 Date: 29 Jul 2019

Reviewer: Diane Taylor

Reviewer's report:

The manuscript by Cutts et al. provides a systematic review and met-analysis of the literature on epidemiologic evidence for protection antibodies (Ab) to VAR2CSA in preventing pregnancy-associated malaria and adverse pregnancy outcomes. As noted by the authors, information in the literature is inconsistent and confusing. Thus, an un-biased, detailed synthesis of the literature is a great service to the research community. The review and analysis was a huge undertaking and narrowed down the literature to 26 studies that met the inclusion criteria. In addition to a solid summary of the literature, the authors obtained raw data (or re-analysis) from 11 studies and calculated estimates that had not been originally published. Thus, the meta-analysis has new information and begins to make a clearer picture of the role of Ab to VAR2CSA in protection (of lack thereof) of pregnant women from placental malaria (PM).

Overall, the manuscript (MS) is very written and logically put together. I have no concerns with how the data were analyzed, the outcome measures selected, the studies included, or the conclusions drawn. Thus, I find the overall presentation of the manuscript very well done!

Because of the amount of conflicting information in the literature, the task at hand was daunting. In reading the MS I sometimes got bogged down in "pieces of information" and couldn't "follow the story line." This problem is inherent in the topic, but the suggested changes below might help.

1. Put a summary at the end of each Results section. For example, I got to Line 316 and thought "So? What am I supposed to think?" My brain was begging for a summary or some indication about the bottom-line message. The same was true for the section on peripheral parasitemia and the other sections as well. When several studies that found Ab were beneficial are mentioned, but a lot of studies showed the Ab were not, are we supposed to dismiss the first two studies or focus on them?
2. Discuss the data for Ab presence/absence measured at the time of delivery. Then, present a section for the influence of Ab measured during the first and second trimesters on PM and peripheral malaria at delivery. To me, these are two different topics and combining them made it difficult to sort out the information. The presence of Ab at delivery is associated with an increased risk of PM, which makes sense because women with PM are more likely to make Ab to VAR2CSA. However, when Ab are present early in pregnancy (e.g., T2), the question becomes, are the Ab effective in clearing PM by the end of pregnancy? So, the two types of studies, seem to address two questions. Thus, I found combining the data to be confusing.

FYI (comment only - Lines 321-324): In the study by Tutterrow et al. all women in the study were diagnosed as having malaria early in the second trimester and then followed to term. Since the study was conducted before implementation of IPTp, the primary question was, did Ab to VAR2CSA help clear placental parasites during the second half of pregnancy? Ndam et al. also measured Ab at enrollment (<24 weeks), but then IPT-p was used, making it somewhat difficult to interpret the results, but they also finding reduced PM in Ab+ women. I'm not sure one would actually see the effect in a longitudinal study (e.g., the other two reported studies) unless transmission was high and sample size was very large.

3. Discussion point: Was something missed by including secundigravidae with multigravidae (MG)? Duffy and Fried found Ab to VAR2CSA were associated with improved birthweight and length of pregnancy in secundigravidae (only). They may represent a "transition" group? Should they have been considered as a separate group? Likewise, Laar's group found that Ab to VAR2CSA were effective in women with history of past infections. So, in the early literature it appeared that Ab to VAR2CSA were effective in ONLY a subgroup of women. I am not suggesting a full re-analysis, but telling the reader you have taken these points into consideration (Discussion?) might strengthen the MS.

The remaining specific comments are minor (or trivial), but could provide more clarity for the reader (remember, we are not all well versed in doing statistics or meta-analysis).

1. Trivial point - Line 72: How solid are the data that malaria increases miscarriages? These often occur in the first trimester, before malaria parasites sequester there. I know the literature about reduced blood vessel formation, but …… .

2. Line 109 - or elsewhere: Please define "severe malaria". I'm not sure what the term includes.
3. Line 148 - Do you want to include CS2 as a source of VAR2CSA-expressing cells?

4. Line 197: As an American, I am not sure what a performa is. Is it a data-entry template? The only way I have heard the word used refers to an invoice for a commercial company.

5. Line 235 (and Abstract): "...referred in narrative terms only ..." I'm not sure what this means. Does it mean that the data were extracted from the original publication? Please explain/define.

6. Line 243: The abbreviation FV2 appears without explanation. FV2 does not appear in the list of abbreviations. I assume anyone who is reading the manuscript will know it refers to full-length VAR2CSA, but ..... Terms is defined on line 273

7. Line 267: data were (I said some of the comments were trivial).

8. Line 284-286: LOVE the summary. A similar statement for the other result sections would be useful for clarify.

9. Line 341: Is the conclusion that Ab to VAR2SA do not appear to reduce prevalence or level of peripheral parasitemia ... i) at delivery or ii) at the time the blood was drawn?

10. Line 355: "... T2/T3 had reduced odds of severe malaria (versus uninfected controls) ..." Does this make sense? Uninfected controls don't have malaria. Maybe part of the problem is not being sure how severe malaria was defined.

11. Line 369: "... because only one primigravid women was positive for ....... ." Is this worth mentioning? Maybe the wording could be changed, because it sounds like the authors reported a conclusion based on only 1 person. Is that what you meant?
12. Line 394-395: "… Ab to ID1-ID2a had an increased odds of PTB…" This point sounds scary for the on-going vaccine trials. So, in the Discussion, you might address this concern. It is likely that the ID1-ID2a domain in the intact molecular is weakly immunogenic and presence of Ab to it may indicate a rather high parasitemia took place that induced the Ab. As far as I know, there is no evidence that Ab to ID1-ID2a actually might do harm. Just a suggestion.

13. Figures 2 and 3: Information on % weight (from random effect analysis) is presented. What does this mean? As a non-bio-statistician, I'm not sure how to interpret the information.

14. Line 444: FYI only: With respect to the two Tutterrow papers, I would argue that the association with reduced placental parasitemia at delivery was also not associated with Ab to a single domain, but rather to either i) a multiple domains and variants, and ii) high avidity Ab to FV2. The Ab may not be directly involved in protection, but merely serve as a surrogate marker of the maturation of the immune response of the pregnant women to either the entire FV2 molecule or to malaria in general.

15. Final comment: Since several of our publications were mentioned, I checked the Tables for accuracy. Table 1: Lloyd et al. [55] studied 1377 women (not 137); Table 2: Siriwardhana [63] studied 1337 women not 1377; Table 2: Tutterrow et al. [66] "… PM- had higher Abs to FV2 and 7G8 than …" should be changed to "… PM- had higher Abs to FV2 (FcR3) than …".

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

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Not applicable

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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