Reviewer’s report

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

Version: 0 Date: 05 Aug 2019

Reviewer: Anna Van Eijk

Reviewer's report:

Review Cutts et al 2019

This review aims to summarize information on antibodies to pregnancy-specific P. falciparum antigens and malaria in pregnancy/delivery and pregnancy outcomes. This is an interesting and courageous but tricky review, given the absence of uniformity in laboratory study designs, testing, tests and antibodies used. However, showing the lack there-off and showing the limited unstandardized information available that is used for decision-making is also the strength of this review.

The review is long because all outcomes are spelled out: perhaps the authors can focus on a few outcomes and put the description of the others in the supplement. Maternal or placental malaria must be used as outcomes, and to confirm detection by microscopy or histology in the case of placental malaria is reported in the quality criteria. I am not sure if I would have included PCR in the quality criteria, because that brings up the issue of submicroscopic malaria, and its unclear impact on malaria in pregnancy. LBW, preterm delivery, and anaemia can have other causes than malaria. Perhaps LBW and anaemia can be used best as additional outcomes given their common reports in malaria studies, and preterm and severe malaria can be moved to the supplement.

Abstract

Methods: dates of last update differ throughout text: in abstract 07jun19, in methods section: "databases were searched for studies published in all years up to and including 12 July 2018", in suppl 2 pubmed search: to 07 june 2018.

Number of studies and number of participants need to be reported for each outcome presented where possible, e.g. for these sentences: "Estimates were mostly from cross-sectional data …" and "Antibody responses to pregnancy-specific pRBC and VAR2CSA antigens, measured at delivery, were associated with placental malaria and may therefore represent markers of infection, rather than correlates of protection. Antibodies to pregnancy-specific pRBC, but not recombinant VAR2CSA antigens, were associated with protection from low birthweight".

Conclusion: perhaps also add something on standardization of laboratory methods?
Methods

Was the review registered in prospero?

Searching databases: how was Google scholar searched, given that it generally gives an unwieldy output of over &gt;1,000,000? It is a missed opportunity that the malaria in pregnancy database was not used (http://library.mip-consortium.org), which could have helped with assessment of completeness.

"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."

Why were trials excluded? Generally, the inclusion criteria are not much different from surveys and you could also opt to only use the data from the control arm. In addition, this was not consistently maintained, given that e.g. Staalsoe 2004 was included which was part of a trial (IPTp, Salanti 2004 used women from the same study), same for Fowkes 2012 for participants from the Thai-Burmese border (CQ prophylaxis). A study like Cox 2005 could have provided useful information; you could have restricted to only using the control arm. Case-control studies can be not representative as well, given their selection criteria, and they often go for women with laboratory test results available. Some of these case-control studies may have been matched for one or more potential confounders. It would be good to indicate in the table (1 &amp; 2) where that was the case for case-control studies, and which characteristics were matched for.

The inclusion criteria are extensive and have two parts: inclusion criteria and quality criteria. I tried to summarize them here:

1) Inclusion criteria: The primary criterion for study inclusion was pregnant women living in areas endemic for P. falciparum infection. All geographical locations were included. Studies that measured immunoglobulin G (IgG) responses to pregnancy-specific parasite strains or placental isolates and/or recombinant or synthetic defined pregnancy-specific variant surface antigens were considered. We also included studies that measured functional antibody responses to pregnancy-specific pRBC, including CSA binding inhibition (anti-adhesion assay), pRBC cell-agglutination, and phagocytosis. Studies in which antibodies were measured in peripheral blood taken during pregnancy and/or the immediate postpartum period were considered.
2) The minimum quality criteria for inclusion of studies were: for placental malaria, confirmation of P. falciparum placental infection by slide microscopy of placental blood, PCR, or placental histology for the examination of P. falciparum parasites; for peripheral parasitaemia, detection by slide microscopy or PCR; for low birth weight, defined as less than 2500 grams and birth weight was measured within 72 hours of birth; and for preterm birth, defined as delivery at less than 37 weeks gestation, where gestational age must have been confirmed using Crown Rump Length (CRL) from Ultrasound and Robinson's chart or date of last menstrual period (LMP). Antibody levels must have been determined in maternal peripheral blood samples preceding or at the same time as outcome measurement. Studies in which antibodies were measured in cord blood, placental blood or infant peripheral blood were excluded. Cut-offs for positive antibody responses by ELISA or other means must have been defined using unexposed (malaria-naïve) controls or men/children from the malaria-endemic area.

I tried to check if the inclusion is complete, but that is hard to do when it is not clear which studies were rejected and why; e.g. why are the following studies not appearing: Mount 2004 Lancet, Fievet 2006 Infection Genetics and Evolution, Keen 2007. I must admit I am not an immunologist, so there are probably very good reasons, but it would be nice if this is clear. Perhaps the authors can list the studies rejected and the reasons why in the supplement.

Another concern is the lack of information on potential confounders. Although timing of the assessment of the antibodies is presented in most forest plots (trimester or delivery), and plots by gravidity are available, other confounders have not been presented. Young age is one of them, and level of transmission another. The authors could have linked study site and time with information from the malaria atlas project to have an indicator of malaria transmission level in the area (P. falciparum prevalence among children age 2-10 years of age: https://map.ox.ac.uk/explorer/#/). Are there other potential confounders of the antibodies, e.g. is there an effect of medication on antibody development (quantity), on which studies may have reported? HIV-status? Use of antimalarial prevention (ITNs, IPTp)?

Risk of bias assessment; how was this incorporated in the review?
Standardization

The study only uses responders/no responders for the presence or absence of antibodies. Was there a specific reason that the authors choose not to use continuous data for their study, e.g. the concentration of antibodies, or is this opening another can of worms because of the lack of standardization?

"when the I2 statistic was $>75\%$ and/or the lower 95% confidence limit was between 50%-100%, the studies were not combined [47]." I could not find a guideline regarding to this method in the quoted reference. It may be good not to combine or pool the results if the number of studies were low, or if the comparability of exposures was doubtful (or from the same study); Forest plots are still an excellent way to visualize data.

Results

Flow chart: Preferably there would be more information on why studies were not included. E.g. what were common reasons among the 81 excluded studies? Animal studies? Not the right tests etc?

For 19 studies data was not available in required format for meta-analysis or data did not meet inclusion or quality criteria. What was the reason to exclude these 6 studies; was this for quality? If 12 studies were described, there is still one study not accounted for?

Numbers flow chart and text of results don't match.

Table 1 &amp; 2: it would be nice if more information could be presented, e.g. time period or study, number of primigravidae per study, mean or median age, HIV status, (use of antimalarial prevention: not sure if this would be relevant), level of malaria transmission. Table 1: perhaps make a separate column for timing of assessment of response, so it is clearer (T1/T2/T3 or delivery). Now you have to search for it. Definition of anaemia would be good (I assume it is all $<11$ g/dl)?

This sentence in the footnote is not clear: "Similarly, where categorical data for peripheral parasitaemia was available we used that, if not we reported parasitaemia as a continuous variable." Was parasite density used in that case? Does that mean that all women included had parasitemia?
Footnote d and I: "Women were enrolled up to T3; also measured antibodies at T3 (weeks 30-32), but these estimates are not presented in this review" and footnote i: "Time points correspond to first- (6-29 weeks) and third- (25-41 weeks) antenatal visits; antibodies were also measured at second visit (16-951 36 weeks) but data is not included in this review." Perhaps for studies with follow up over time, these outcomes can be graphed? Here we have real cohort studies, but the results are not fully utilized (as a comment on the conclusion of the abstract).

Figure 2 Forestplot

Although I understand the challenges with making them, they are a bit difficult to read with the differences in line spacing and only clear from the last columns which studies were pooled and which were not.

It would be nice if the numbers could be added to the forestplot, so you can check where the numbers are coming from (can be done in stata). Odds ratio can be added as the effect estimate where applicable.

Results text

"4 were cohort (two of which contributed only cross-sectional data)". As far as I can see, all of them were used as cross-sectional data?

Please add numbers of participants/studies for each outcome, and I2 for each pooled outcome.

The discussion covers most of my concerns so nothing to add. My main concern is (that I cannot check) completeness of inclusion.

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

No

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.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English  
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests  
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests
Statement on potential review bias
Please complete a statement on potential review bias, considering the following questions:

1. Did you co-author any publication with an author of this manuscript in the last 5 years?
2. Are you currently or recently affiliated at the same institution as an author of this manuscript?

If you can answer no to all of the above, write 'I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria”. If your reply is yes to any, please give details below.

I declare that I did not publish with these authors in the last 5 years and also meet the affiliation criteria

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal