Reviewer's report

Title: Iron deficiency during pregnancy is associated with a reduced risk of adverse birth outcomes in a malaria endemic area in a longitudinal cohort study.

Version: 0 Date: 04 Apr 2018

Reviewer: Chandy John

Reviewer's report:
This is a well conducted and beautifully written study, typical of the high-quality work produced by this research group. The findings that iron deficiency is strongly associated with a decrease in low birth weight and (less strongly) with a decrease in preterm birth, and that these protections do not appear to be primary mediated by protection from malaria or anemia, are striking, novel and important to public health.

The study was very well designed, and the analysis is clear and well described and presented. I did not identify any obvious deficiencies, and only have a few comments and questions.

MAJOR COMMENTS
1. PTB presented in tables and noted in Discussion, but not discussed in Results section. Iron deficiency protective only in subgroup analysis (primigravidae) against PTB, 95% CI close to 1, so statements in the Discussion about substantial protection against PTB should be modified, and restricted to primigravidae
2. All mothers received iron during pregnancy, as per national guidelines. Did the authors assess prevalence of iron deficiency in women at time of delivery, and if not, could they? It would be very informative to know if iron supplementation change prevalence of iron deficiency in women by end of pregnancy, and whether iron status at delivery related to birth outcomes?
3. I wonder what the authors think the next steps should be in studies on this issue, now that they have presented these very striking findings. In this study, most women had iron deficiency, but all received iron supplementation during pregnancy, and the findings of
protection from iron deficiency are in that context. I presume the authors do not think withholding iron during pregnancy is a good idea. So what should be done next to try improve birth weight of infants, in the context of these findings?

4. Maternal iron deficiency could lead to worse cognitive outcomes in their children - some studies suggest this, while others suggest no relation. Child cognitive testing would need to be included in future studies in which iron supplementation is altered. LBW is associated with worse neurocognitive outcomes, so the two might cancel each other out - maternal iron deficiency is likely not good for developing brain, but better weight and nutrition are definitely good for it. This aspect would have been great to study in this cohort, but should definitely be considered in future studies.

MINOR COMMENTS

1. This population has very high rates of baseline malaria infection, and extremely high rates of iron deficiency. Therefore these findings may not be extrapolatable to other populations with malaria in pregnancy.

2. Do the authors have any information on infections during pregnancy in this cohort? This would start to answer some of the questions about protection from infection. I assume they do not, or would have presented it, but thought I should ask anyway, as any information in this regard would be useful.

3. I understand the mediation analysis, but am not qualified to comment on the accuracy of methods used, so a statistician should review this section.

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.
Yes

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