Reviewer’s report

Title: Modulation of innate immune responses at birth by prenatal malaria exposure and association with malaria risk during the first year of life

Version: 1 Date: 08 Jul 2018

Reviewer: Prasanna Jagannathan

Reviewer's report:

In this revised manuscript, Natama and colleagues address many of the issues raised in the previous review. This reviewer appreciates details included re: parent COSMIC trial and revised figure 1 as well as the revised abstract. I have some suggestions that might increase interpretability of this revised manuscript.

Table 1: Would consider reorganizing this table into columns based on the main groupings used throughout the manuscript (non-exposed, exposed No PM, past PM, chronic PM, acute PM). Would be much more informative.

Discussion remains too long and rather unwieldy at present. Would try to shorten. Some suggestions below:

Discussion paragraph 1: Unfortunately, the 2nd -4th sentences do not make sense as written (appears to potentially have been a copy/paste error with one of the limitations sentences with run-on sentences as a result)

"Overall, we found that PME has a profound effect on the fetal immune Second, in this study, the measurement of white blood cells population… thus influence TLR-mediated innate immune responses. system and that the …"

Discussion paragraph 2: Line 388: "However other approaches, regarding the categorization of PME and/or the stimulation assays, have been previously used to…"

Unclear what this clause (regarding the categorization of PME and/or the stimulation assays) means. Suggest you remove it.

Discussion paragraph 3: Agree that "trained" innate immunity could explain the heightened responsivity observed in this study among PM-exposed cord blood samples - the paragraph should state that more directly. However, the main counter to this hypothesis is within the last
Discussion paragraph 4: This paragraph could be combined with the prior paragraph. First three sentences describing categories of PM redundant and unnecessary. Starting at line 420 (It has been previously shown…) - could be moved up to prior paragraph and condensed.

Line 424, Line 434 - "probably" should be re-written as "possibly."

Discussion paragraph 5, 6 read too long. Could remove repetition of results in sentence 2 of paragraph 5 (line 439) and sentence 2-3 from paragraph 6 (455-457).

Line 470: "consisting on" - unclear what this means. Perhaps: "Altogether, our findings are consistent with the hypothesis that PME results in down-regulation of cytokine production that can affect all important functional classes of cytokines…"

Line 474: "...then also more prone to pathogenesis upon infection." - would remove or state that this is speculative as no data was presented to support this hypothesis.

Line 522: "Overall, these results demonstrate that PME has a clear impact on malaria risk." As these are associations would temper this statement and change the word "demonstrate" to "suggest."

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If not, please specify what is required in your comments to the authors.

Yes

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If not, please specify which controls are required in your comments to the authors.

Yes

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