Reviewer’s report

Title: Peripheral blood monocyte-to-lymphocyte ratio at study enrolment predicts efficacy of the RTS,S malaria vaccine: analysis of pooled phase 2 clinical trial data

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Reviewer: Denise Doolan

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Warimwe et al. present a brief but interesting report associating the ratio of peripheral blood monocytes to lymphocytes with the efficacy of the RTS,S malaria vaccine candidate, by retrospective analysis of data from two of 11 Phase 2 test sites in Africa: Kenyan children 5-7 months old at time of first vaccination with RTS,S or rabies control (n=421) and Gabonese infants 6-10 weeks at time of first vaccination with EPI vaccines with or without RTS,S (n=189). The authors have previously reported that the ratio of peripheral blood monocytes to lymphocytes correlates with increased susceptibility to clinical malaria in Kenyan children. Here, they associate an increase in ratio of monocytes to lymphocytes at time of pre-vaccination screening with a decrease in efficacy of RTS,S, using time to first clinical malaria episode as the primary endpoint. They conclude that variation in RTS,S vaccine efficacy can be attributed to the monocyte to lymphocyte ratio in vaccinees. The RTS,S vaccine candidate is currently undergoing Phase 3 testing in Africa, so this finding may have important implications for vaccine deployment. The authors do not speculate as to a potential mechanistic basis of their finding.

- Major Compulsory Revisions

1. There are a number of limitations to the study, as acknowledged by the authors, but the most significant is the availability of baseline monocyte and lymphocyte numbers in only two of the 11 Phase 2 studies, and then only at some sites within those two studies. However, according to the original report of the Phase 2 study in Kenya and Tanzania (ref 11; Bejon et al. N Eng J Med. 359:24) authored by the senior author of the current manuscript, a full blood count was done for all participating children at the time of first vaccination. Why, therefore, was the Tanzanian cohort not included in the current analysis?

2. The two cohorts included in this analysis were Kenyan children aged 5-17 months at first vaccination (0,1,2 schedule) and Gabonese infants aged 6-10 weeks at first vaccination (0,1,2 or 1,2,7 schedule). RTS,S efficacy is known to vary between individuals according age at vaccination, as noted by the authors, and the numbers of lymphocytes and monocytes could also be expected to vary with age. Also, the definition of clinical malaria differed between the two study sites (>250 parasites/ul versus > 500 parasites/ul). The manuscript must present separate analyses for each of the two sites, as well as the combined analysis.
Particularly since the authors note (page 7) that “ML ratio was significantly correlated with age at vaccination.”

3. Why did the authors choose not to identify the association in one cohort and confirm the finding in the second independent cohort?

4. The authors should speculate as to a potential mechanistic basis of the observed relationship between ML ration and RTS,S vaccine efficacy. They should also note whether similar outcomes have been observed for other vaccines.

- Minor Essential Revisions

1. Please clarify the time interval between screening (when the full blood count was done) and the time of vaccination. Was this consistent between study sites and would it be expected to reflect the blood count (and hence M:L ratio) at the time of vaccination?

2. The statement that “ML ratio did not directly influence clinical malaria risk in the RTS,S group ... but there was a strongly significant interaction between ML ratio and vaccine efficacy” is confusing as written. Please rewrite for clarity.

3. References – correct the errors in capitalization of journal names.

- Discretionary Revisions

1. The authors should consider presenting the data showing that ML ratio correlated positively with peak anti-CS protein IgG antibody response, since this would be of interest to the readers.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests