Reviewer’s report

Title: Antibody responses to merozoite antigens after natural Plasmodium falciparum infection: kinetics and longevity in absence of re-exposure

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Reviewer: Julius Hafalla

Reviewer's report:

The manuscript addresses the dynamics of antibody responses to malaria infection. The authors aimed at looking at the longevity of responses following a single infection and measuring antibody responses and ASCs.

It is not clear what the authors meant by a 'single' infection. In their inclusion criteria, the authors recruited European individuals with no prior history of malaria infection but with a reported cumulative time of residency in an endemic region of 0-3 years. I can understand short visits but residency of more than 2 weeks is a bit iffy. Are these individuals taking anti-malarial drugs during visits of more than 2 weeks? How can the authors ensure that they did not have prior infection? These need to be clarified. I think mentioning the comparison between 'likely naïve' vs 'previously exposed' is good enough.

When reading the title, it seems that the authors measured ASCs. However, no cellular analysis was done. This is very misleading, particularly for experimental scientists. Analysis was based on mathematical modelling relating to referred literature indicating that the number of bone marrow ASCs correlates with circulating antibody levels. This issue - experimental vs mathematical modelling - should be reflected clearly in the title, abstract and introduction as not to mislead readers.

Despite the above confusions, the results presented in Figures 2, 3 and 4 are quite interesting. However, the authors tend to highlight the 'negative' sides of the data - by focusing on the poor modelling results for IgG2 and IgG4 responses, as well as the differences with TTd responses. For the former, the IgG2 and IgG4 response are mostly still above LLoQ. Furthermore, total IgGs, IgG1 and IgG3 show robust responses - way above LLoQ - that follow expected kinetics of antibody responses, which then persist to memory. One can deduce that malaria infections develop long-lived memory responses.

For Figure 3, while it is expected that previously exposed individuals should mount a higher secondary response, the results are interesting for malaria that long-lived components of the memory response are developed after exposure that are capable of being boosted following exposure. I was trying to compare/associate the half-lives presented versus the time of residency
in endemic area to see timing of boosting, etc but was I was not able to infer anything with the limited data available.

While it is obvious that from the capped error bars (Figure 3) that the responses to malaria antigens have shorter half-lives, the range for many antigens still overlapped with responses to TTd.

The discussion should include why protection is scarce despite long-lived components of the memory response.

The manuscript should refer to original papers that experimentally measured ASCs against malaria antigens - one by Dorfman et al, one by Wipasa et al, and one by Weiss et al - and discuss the results accordingly.

**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?**
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Yes

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