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: Julie Simpson

Reviewer's report:

The paper provides a nice comparison of antibody responses between two groups of adults infected with malaria: a group without any previous infection (previously naïve group) and a group with a previous history of infection (previously exposed group). The work uses a mathematical model (Figure 1) that describes the antibody level in the blood in terms of the populations of short- and long-lived Antibody Secreting Cells (ASCs). The results show that the model is able to provide a good fit (Figure 2) to the measured total and subclass (IgG1-4) antibody responses to several P. falciparum merozoite antigens. The fitted responses show that the level and breadth of antibodies are significantly higher in the previously exposed group compared with the previously naïve group (Figures 4 and 5). The work then provides estimates for some parameters, such as half-lives of antibody responses, short- and long-lived ASCs, as well as the proportion of the two ASCs types (Figure 3). It is shown that the previously exposed group has a significantly higher proportion of long-lived ASCs, which leads to persistence of antibodies over a longer period. (though, the response is not persistent enough like that to tetanus, challenging the development of an antimalarial vaccine). This is not a novel finding, however, estimation of the values of the aforementioned parameters may be helpful in the efforts of antimalarial vaccine development.

Major comments:

The antibody data are only measured for 12 months of follow-up, and there are only a few measurements to capture the decline, thus it doesn't seem there are the data available to support confident estimation of half-lives beyond 1 year (half-life estimates provided are 1.7 to 3.7 years).

The mathematical model is not properly explained (the explanation in the supplementary material also requires more detail). Yes the model is developed and explained in reference [5], but the authors should still briefly explain what each term in the equation represents in this manuscript.
The equation for A(t) does not reflect the stated fact by the authors that there is an antibody boosting only after a new infection at time $t=0$, as the second term on the RHS of the model is nonzero for $t<0$ (the heaviside function is needed as in [5]).

Seeing the antibody responses in Figures 2-5, as well as not discussing $\pi_0$ anywhere later on in the manuscript, makes me believe that you have set $\pi_0 = 0$. If this is true, then you are assuming that the malaria infection, that has caused the antibody boosting within the patients, has happened at the time of getting the first blood sample, $t=0$, and this is not right, as this primary infection must have happened (maybe many days) before the first blood sample.

Following on this, the infographics of the antibody responses in Figure 1 are confusing, as in the left one $\tau_0 =0$ unlike the right one.

The paper does not discuss the effect of other parameters such as $A_0$ and $\beta$, and their estimated values are not reported in the manuscript.

The supplementary tables do not have a caption explaining what the columns represent.

I think the sections "Half-life of IgG antibody responses to P. falciparum schizont extract, recombinant antigens, and tetanus toxoid" and "Dynamics and longevity of the antigen-specific IgG subclass response to eight recombinant P. falciparum antigens" need a revision, as you discuss the half-lives of the antibodies in both sections, and it's not clear to me why these are presented under different sections.

Please do not provide only p-values from Mann Whitney U tests in the results for comparing antibody levels at time of diagnosis between the two exposure groups. It is more informative to actually give the median values for the two groups, or even better the ratio of geometric means (95% CIs), since you analyse the logged antibody levels using linear regression when investigating associations with time of residency (and for this analysis also give estimates (95% CIs) as opposed to just $p>0.05$, a p-value of 0.051 is very different to a p-value of 0.9).

Minor comments:

You can overlay the geometric mean of the samples of experiments on the panels of Figure 2, to be able to compare them with those of the model.

There is a problem with typesetting of the equation on page 9.

Supplementary Tables do not have caption.

Table S1 is very large, which makes it difficult to make sense of. There needs to be more explanation of what the parameter values represent, and units given, and the _low and _high represent the limits of the credible intervals. I'd suggest you put a smaller table (maybe in the
manuscript), e.g. only for the estimated parameters of total IgG to all or some of the antigens, as these estimated parameters are important for future work.

Some sentences are very long and unclear, for instance: sentences in lines 79-83, 187-189, 196-200, In many occasions, "previously naïve/exposed" is used without a noun, i.e. it should be e.g. "previously naïve/exposed group/individuals".

There is a missing "respectively" in line 205. TTd is written TTD in line 212. Line 223, should "between" be "with"? The sentence in lines 295-296 is not clear. Line 390-392: "Because of their rapid decay in short-lived ASCs …" needs thorough revision. In line 355, there is a missing "of". Line 393: "proportional to the frequency of", I guess number is better than frequency. Lines 481-482: "… inefficient acquisition" -> "… inefficient acquisition of immunity".

Discussing antibody breadth seems a bit out of place on page 10, as you will discuss it again later on page 14. Discussion, 1st paragraph - should be in past tense "We investigated, …", etc.

In line 254, you say "Geometric mean malaria specific IgG levels increased rapidly after malaria diagnosis", which is confusing, as IgG levels naturally increases after malaria infection/recurrence, not diagnosis.

On page 12 in lines 275-277 you say "For IgG to TTd the half-lives of secreted IgG molecules and short-lived ASCs (estimated by the model by design) were 20 and 5 days, respectively (Figure 3B).", but the means (dots) are slightly different from these numbers in the Figure. Lines 289 - 291: "For TTd, the proportion of long-lived ASCs was similar in both exposure groups and was estimated to be 96% (Figure 3B), consistent with a non-boosted antibody response maintained entirely by long-lived ASCs." I guess the horizontal bars for TTd lie on each other, hence, one can't be seen. I suggest you add a sentence to the figure caption and explain that, otherwise, it would be a bit confusing.
On page 14, lines 331: "... but the subclass specific breadth was estimated to be slightly lower (Figure 5)." Isn't this obvious, because total IgG is sum of the subclass IgG's?

The estimated decay rates of antibodies are compared with the previous findings, e.g. on page 16, but there is not any similar comparison for ASCs. Is there any previous estimation for the parameters of these cells in the literature? If yes, please make a comparison.

Are the methods appropriate and well described?
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