Reviewer’s report

Title: Induction and decay of functional complement-fixing antibodies by the RTS,S vaccine in children, and a negative impact of malaria exposure

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Reviewer: Elke Bergmann-Leitner

Reviewer's report:

Kurtovic et al report in their manuscript "Induction and decay of functional complement-fixing antibodies by the RTS,S vaccine in children, and a negative impact of malaria exposure on their profiling of serological responses. This in-depth analysis revealed that the functional activity of CSP-specific responses declines with age. It is not clear whether this is solely linked to age or also impacted by the higher malaria exposure in older children.

Overall, the manuscript is carefully compiled and investigates the kinetics of functional activity in sera. There are few issues, if addressed, could enhance the manuscript:

(1) the authors do not capitalize on the fact that they have two cohorts that could determine the impact of the functional activity and the serological profile (fine specificity, isotype, avidity) on protection either against clinical disease (cohort Manhica) or against new infection (cohort Ilha Josina).

(2) Statistical tools such as multivariate analysis should be used to determine the level of correlation between fine specificity (repeat, full length CSP, C-terminal peptide, C1q, isotypes) - see Figure 4.

(3) The ELISA data are reported as OD when sera were diluted to 1/4000 for IgG and IgG subclasses or 1/500 for IgM. It is difficult, given the differences in binding efficiency and use of the different secondary antibodies, to make conclusions about the interaction and the prevalence of the different isotype. While comparisons within the isotypes are appropriate (to evaluate differences in responses between the study subjects), it may not be appropriate to study the kinetic of a low-prevalence isotype such as IgG2 and IgG4. Have the authors considered of addressing this by a quantitative assay using standard curves for the respective isotypes or multiplexed assays?

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?
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Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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