Reviewer's report

Title: The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using Phase III data and simulation models

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Reviewer: Steffen Borrmann

Reviewer's report:

Penny et al. embark on an ambitious effort to predict the future public health impact of the anti-malarial RTS,S vaccine candidate, which is now completing a large phase III trial in >17,000 African children. They use available data for the first 1.5 of up to 4 years of follow-up for simulating vaccine effects (maximum and decay) against infections and then, parameterize the model with country-specific estimates of known effect modifiers (parasitological, demographic, public health parameter etc) for arriving at predictions for a total of 43 countries. This is a formidable challenge and I trust that this team of very experienced authors is uniquely positioned to take such a challenge on board. The complex modeling efforts yield such a wide range of prediction that it is difficult to highlight the most salient ones here. Even the authors appear to struggle in condensing their huge set of analytical outcomes in the abstract, mixing findings with interpretations.

Unfortunately, I lack the adequate scientific background for a full appraisal of the statistical methods at the core of the paper. However, looking back at quite a few years in malaria research, I suppose I should belong to a target group of readers of the paper. Still I found it harder than expected to follow the paper (although being well written) – in fact, at times I felt overwhelmed by the sheer scope of it! Therefore, my key recommendations for improving the manuscript (see below) are mainly meant to increase its value for a broader audience.

Also, because of the pending publication of the 3-4 year follow-up data from the RTS,S trial, this manuscript ought to be published rapidly.

Main points:

1. I would have liked to see a better description of the virtual “cohorts”. I think I can understand the concept yet in particular a graphical representation/cartoon would facilitate interpretation of everything downstream in the paper.

2. The analytical concept requires a very detailed simulation of the available phase III clinical trial data. Even the authors freely admit that the model fits poorly to the rather important 5-17 month cohort… the fit for the EPI cohort appears to be reasonable, even greater uncertainties are introduced by using country-wide estimates that are known to be very rough estimates (and in particular, do not reflect the extreme heterogeneity in transmission for instance)... I kept wondering how much weight the analytical exercise can have for guiding decisions (the authors elude to upcoming WHO recommendations). Therefore, I would have
liked to see a box summarizing the key points and (!) a box for identifying the major gaps (according to the authors) that for instance WHO needs to be aware of when basing decisions on clinical trial data and statistical predictions based on them.

3. The third point has more to do with (at least from my perspective) a misbalance between a huge wealth of information on technical statistical details and an often missing link to malaria biology and supposed vaccine mechanisms. For instance, I found it hard to follow the frequent shifts between infection and malaria as disease. The authors of course have made key contributions to our understanding between exposure, infection and malaria but in the paper this only occurs at rare moments. So, an upfront explanation of the exposure-infection-disease model together with a better description of what RTS,S is supposed to do (preventing liver stage infection – this word is not occurring a single time – yet it’s so essential to understand how RTS,S works) would go a long way in improving the value of the manuscript for a larger audience. In particular, when discussing RTS,S against the backdrop of the epidemiological model (and their complex interactions) many analytical aspects may become more intuitive. One example: “age-shifting of susceptibility” is quickly mentioned on page 5. This evokes a complex concept and without further explanation, it may remain an enigma for most readers. Saying a few words on how a vaccine that partially prevents liver stage and subsequent, blood stage infections may interfere with the natural acquisition of anti-blood stage immunity (that shapes the epidemiology of malaria) would be very helpful. Another example: the seeming oddity of a higher initial vaccine efficacy against infections compared to malaria episodes can (in my view) be best explained by the fact that it is impossible to get malaria for every infection (mosquito-transmitted infections can occur every night).

4. I was also missing a discussion of the “real-life” performance of RTS,S (when administered outside a stringent clinical trial setting). I understand that this would complicate the modeling effort even further… still, for medicines this is a non-negligible aspect.

5. A polite, naive question: do we really expect that a full public health impact can be modeled? Is an honest word helpful? When do we need to decide that uncertainty remains too large for the predictions to provide a robust guidance?

Minor points:

Page 2: “a vaccine whose efficacy decays quickly may be of public health importance”: public health “benefit”?

Page 2: “mathematical models are essential to predict long term outcomes of vaccination programs when delivered to populations outside trial settings”: effectiveness studies are also needed!

Page 7: “likely implementation of the 5 to 17 months cohort in the Phase III trials[21] which demonstrated higher clinical efficacy compared to 6-12 week cohort in trial data”: I was wondering whether this is not another (inverse) representation of the above mentioned “age-shifting of susceptibility”? The effect
of maternally transmitted immunity (antibodies) starts to wane around 6 months. Again, even a simple cartoon may be helpful to guide readers through these rather complex issues.

Page 9: There appears to be an inconsistency. On the one hand “Uncertainty about vaccine properties will have the greatest impact on the level of predictions.” Yet a bit later on the same page “he best fitting models with lowest DIC was obtained when models fit for site-specific variation in incidence”.

On the same page: “Our optimum model fit, with lowest DIC and narrowest posterior distributions for half-life and efficacy (model 18), estimated vaccine properties as follows…”: what is the endpoint/time interval? 6 months?

Again on the same page: “assuming a half-life of 1 year or fitting for half-life …” This estimate appears to be in line with published data on the kinetics of vaccine-induced IgM serum concentrations (a point for the discussion).

On page 11: “However, the prediction of 6 monthly period efficacy against clinical cases…”: VE against first episode or against multiple episodes? More generally, for someone more attuned to clinical trial descriptions I found some of the definitions lacking in precision.

Same page: “The proportions of malaria events averted by the simulated vaccination programs are low, ranging from 1-4% for clinical events”. Wow. Who would want to use such a vaccine? Perhaps a better initial description of the virtual cohorts could prevent a blatant misinterpretation of these figures?

On same page: “….Figure S14-S15), depending on immunisation schedule.”: I couldn’t understand the figure legend. What is “…effectiveness of events averted…”?

On page 12: “EPI vaccination is predicted to avert more deaths than vaccination of 6-9 month old children”: There appears to be a mix-up. It should be 5-17 month old children? (it occurs at other instances too)

On page 14: “we infer that the efficacy measured against clinical malaria in the trial is declining over time even more rapidly than the underlying effect in preventing new infections”: expected from a vaccine that prevents liver and subsequent blood stage infections? (“This is an unavoidable property of a leaky vaccine combafing recurrent challenges from a pathogen that stimulates partial immunity.” seems awkward). To understand RTS,S it seems essential to differentiate between the two developmentally differentiated stages in the human host.

Quality of written English: Acceptable

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

I have no competing interests.