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: Philip Bejon

Reviewer's report:

The paper presents an analysis of the currently available data on RTS,S to predict cases averted and lives saved across a range of scenarios. This adds value to the already published analyses and will be of interest to decision making regarding the use of the vaccine.

Given the scale of the problem and the imminent licensing of the first malaria vaccine I would expect this paper to be of general interest.

I have no major methodological comment, all the comments below relate to clarifications or presentational issues. I think the authors could be left to make these changes without my further review and can be regarding as discretionary revisions.

Introduction

The paper uses site-specific Phase III data. It references a previous combined analysis (White et al, ref 27). Could the authors justify the non-inclusion of these Phase II data?

Later discussion and methods descriptions describe the difference between efficacy against infection and against clinical disease - this is particularly important to distinguish, as the authors demonstrate, in the case of a pre-erythrocytic vaccine that may result in reduced exposure over time and therefore delayed acquisition of blood-stage immunity.

There is some prior literature on this issue, including measurement of antibody responses to blood stage antigens, and the background might benefit from a short mention of this to introduce the idea before it appears in methods and reference previous work.

Methods

Why are there so many simulations of vaccination and only a few comparator simulations?

"Results for an EIR of 0.1 were not simulated but calculated by interpolation between the comparators and the results for EIR 1"

I don't understand how interpolation is done at this range - it must assume a
particular functional form which would be hard to predict below 1?

Are the mean results of these ensemble models dependent on the distribution of scenarios chosen?

"Within-site variability in EIR was estimated from the pixel-specific posterior distributions of the Malaria Atlas Project MAP 2010 prevalence surfaces for each trial site"

Does this reflect within-site variability or simply the uncertainty in the estimate? I can't see how any of the data used for MAP would help inform us about within-site heterogeneity, although I see that some sort of estimate has to be made.

It is mentioned that Kilifi and Manhica data were used for a preliminary validation but it isn't described how this was done and how the results of it were used subsequently. (Or how Kilifi/Manhica were chosen - or were these the Phase II data? Which would make logical sense, except that the Manhica trial was using a different adjuvant).

Results

After rereading I thought the difference between table 4 and 5 is that table 4 assumes continuous policy at a country-wide level and includes indirect effects whereas table 5 includes individual-level data on cases prevented without indirect effects. Neither table are clearly referenced in the results and this could be clearer in the text and in the table footnotes.

Discussion

"The estimate of the initial efficacy of RTS,S/AS01 against infection is around 63–79%"

Actually this is quite a lot higher than CHMI studies done in the first month after vaccination. (Perhaps the intensity of challenge is relevant there but this should be discussed) and probably best to quote the point-estimate from the most relevant study - Aponte et al, 66% (43 to 80%) - which was in fact with AS02 not AS01. Also the co-administration may not have been taken into account here, which is likely to reduce efficacy.

"The underlying vaccine profile of efficacy against infection and decay, is most likely the same across the trial sites, even though the measured clinical efficacy appears to be lower in sites with higher exposure[5]"

Could the authors also comment on whether the half-life of efficacy against infection is likely to be similar across trial sites, albeit with efficacy against clinical malaria waning more rapidly in sites where exposure is higher and therefore immunity against blood-stage parasites more rapidly acquired.

Finally could the authors speculate on how much greater precision they expect to achieve once the full data are released?
Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I have received funding from MVI to conduct studies evaluating RTS,S vaccinations. I have no other competing interests.