Author's response to reviews

Title: The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up Phase III data and simulation models

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Basel, 5 May 2015

Revision of manuscript: The public health impact of malaria vaccine RTS,S

Dear BMC Medicine,

We would like to thank you for the review of our manuscript “The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using Phase III data and simulation models” and for giving us the opportunity to revise the manuscript for publication in BMC Medicine.

A detailed point-by-point response to each of the reviewers’ comments is included below. Included with this revision are new drafts of the manuscript and supplementary information, and versions of these documents with full Track Changes.

We request the journal consider the following change to the manuscript title

The public health impact of malaria vaccine RTS,S in malaria endemic Africa: country-specific predictions using 18 month follow-up Phase III data and simulation models

Best regards,

Melissa Penny and Tom Smith

(Swiss Tropical and Public Health Institute)
Referee 1

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.

We thank the reviewer for their helpful comments and hope they are satisfied with the point-by-point responses below.

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?

We have not included Phase II data in this analysis as most Phase II trials of RTS,S used a different adjuvant to that in the final Phase III trial. In addition the site- and time-specific data for which the analysis in this paper depends are not available for the Phase II trials. We have added to the text in the methods section “Fitting of vaccine properties” (page 5, last paragraph):

Due to availability of site- and time-specific data from Phase II, we restrict trial data to Phase III sites using adjuvant AS01”.

We do note that our results seem consistent with data from Phase II trials of RTS,S/AS01.

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.

We have added the following 2 paragraphs into the introduction, directly after the leading paragraph. This also addresses a similar comment from referee 2; the need to introduce to the reader to further biology, nuances of RTS,S action, antibodies and blood-stage immunity, clinical disease and age shifts:

“Plasmodium falciparum malaria is transmitted to humans through bites from infected mosquitoes and has a complex life-cycle in the human host. An infected mosquito injects sporozoites into subcutaneous tissue of the host, which then travel to the liver. Successful invasion of hepatocytes depends on the circumsporozoite protein (CSP) of the sporozoite [7]. Following replication in the liver the parasite enters the blood stream, infecting erythrocytes and multiplying. It is the erythrocytic cycle of Plasmodium falciparum that causes clinical disease.

The RTS,S vaccine induces antibodies in the host against CSP and thus, with high enough antibody titer, prevents liver infection and subsequent clinical malaria that would have resulted from a blood stage infection. RTS,S has shown to be efficacious and safe [5], but as antibody titers to CSP wane so does protection against successful infection of the liver [8] and observed efficacy against clinical disease decays
relatively rapidly in the trial [5]. Repeated malaria infections induces natural, but not complete, immunity in the host to all stages of the parasite life-cycle, including the blood stage causing clinical disease. There is a tendency for efficacy against clinical malaria to wane more rapidly in sites where exposure is higher [5], which is to be expected, because natural exposure to blood-stage parasites is more rapidly acquired by non-vaccinated individuals. Any partially protective malaria infection blocking intervention, such as RTS,S or Seasonal malaria chemoprophylaxis, aimed at infants and young children will give rise to ages-shifts of burden and susceptibility to infection for this reason.

**Methods**

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

The vaccine scenarios were larger in number than comparator as we simulated a wide range of vaccine properties (efficacy, half-life, decay) to cover all possible vaccine profiles for fitting and projections. Only a few non-vaccine scenarios are required as the baseline estimates to calculate events averted by the vaccine scenarios.

"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?

Non-linearity in the relationship between the outcomes and the EIR arises because of effects of superinfection. We assume a linear interpolation because at very low EIR, reinfection of the same host is infrequent, based on Nunes et al 2013. In the methods we have added “linear” to the following sentence in the methods (page 4 paragraph 2):

“Results for an EIR of 0.1 were not simulated but calculated by **linear** interpolation between the comparators and the results for EIR 1 (as done previously [17]).”

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

The approach assumes that linear interpolation between simulated scenarios, which will gives a good approximation to the predictions for intermediate values of the sampled parameters when many different levels are simulated, or when the estimated levels are close to one of those simulated. For the parameters estimated in this paper, the main uncertainty surrounds the estimated half-life, for which the best fitting parameter estimate is close to one of the simulated levels. We changed the text to read:

“All the fitted models had estimates of the half-life of vaccine efficacy against infection of approximately one year. This estimate does not depend much on the linear interpolation between simulated scenarios since one year is among the values of half-life simulated (Table 1)”

"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.
The uncertainty in the MAP surfaces (captured by the imprecision of the posterior densities) results mainly from heterogeneity between sampled data points that is not captured by environmental predictors or by the modelled spatial process, and only partly from binomial sampling variation. We explain elsewhere Penny et al (2015) the logic of our procedure and have also expanded the text to read:

“For each site, we allowed for within-site variability in EIR by defining a limited number of EIR bins. For any specific EIR bin, we used as estimate of the proportion of the site population exposed at that level, population-weighted averages of the pixel-specific posterior distributions corresponding to that bin, derived from the Malaria Atlas Project MAP 2010 prevalence surfaces.”

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).

The sites were chosen for validation because they presented particular challenges for fitting because of missing data. but could still be used to ensure the predictions were still in the range of the estimates for the other sites. In the results section of the submitted version of the paper we write:

“Two sites, Manhica and Kilifi were not used in the fitting. Access to effective care for uncomplicated cases for these two sites was fit to the control data and predictions of clinical efficacy given these access to care estimates, adjusted transmission levels by site and resulting vaccine parameters fits were produced. These are provided in Figure S8 for the 5-17 month and EPI cohorts. There are reported wide confidence bounds for both sites and outliers with estimates of clinical efficacy less than 0, and thus limited data to validate the model with any certainty. The validation thus provided no reason to reject the new parameterisations, but had only very limited statistical power.”

The reference is to the Phase III data, not to the Manhica Phase II trial that used adjuvant AS02. We expect with further data of the trial appropriate validation can be undertaken.

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.

The authors apologize that the tables were not referenced correctly. Table 4 reflects the absolute numbers of events averted (in thousands) over all countries for 10 year follow-up. Whereas Table 5 details the events averted per 100,000 fully vaccinated. The last paragraph on page 11 (section “Predictions of public health impact.”) has been altered, see below. This also addresses a comment from Referee 2 in regards to percentage of events averted over entire population.

“A substantial number of clinical events are predicted to be averted 10 years following introduction (total over endemic countries in Table 4 or per fully vaccinate Table 5). Under the immunisation schedules of targeting only the young, and considering the protection from the vaccine wanes relatively rapidly, this translates into relatively low proportion of malaria events averted over the entire population (range from 1-4% for clinical events and up to 10% for deaths (Figure S14-S15), depending on immunisation schedule). These low proportions are to be expected since malaria disease can occur at any age, but only the youngest cohorts will be targeted by vaccine. The proportion of events averted for under five is much higher.”
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.

We agree we should discuss why this is higher than some of challenge studies, however the results are consistent the Aponte et al study of 66% for infant immunisation. We have altered the second paragraph of this discussion to be:

The estimate of the initial efficacy of RTS,S/AS01 against infection is around 63% (95% CI 39.5-80.3%) for infants and 79.2% (95% CI 67.3-84.8%) for children, and is slightly higher than the efficacy in challenge trials which directly estimate the same quantity. In challenge trials with RTS,S in adults, 42% (kester2007_phase) and 47% (kester2008_phase2) protection against an infection challenge was observed with adjuvant AS02, and 50% observed when using adjuvant AS01B (kester2009_randomized). Consistent with our results is the almost equivalent estimate obtained with natural challenge of 65.9% (95% CI 42.6-79.8%) protection against first infection in a Phase I/IIb trial immunising infants with RTS,S/AS01 (aponte2007_safety). The model estimates for RTS,S/AS01 initial efficacy against infection in this work are substantially higher than those previously estimated by modelling from the initial Phase II RTS,S/AS02 data of 52% (maire2006_predictions), and, as expected, higher than the directly measured efficacy against clinical episodes at 18 months followup \cite{RTSSphaseIII}. However there is considerable uncertainty around them, especially for the 6-12 week cohort.”

"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.

The half-life of efficacy against infection is expected to be the same across all trial sites regardless of the protection against clinical efficacy because this is a characteristic of the induced pre-erythrocytic immunity, not of the secondary effect on blood stage immunity. The word decay was to reflect both half-life and decay shape. We have now added this explanatory text.

Finally could the authors speculate on how much greater precision they expect to achieve once the full data are released?

Given more data by trial site of the same temporal detail or finer, then further investigations of vaccine efficacy against infection waning can be undertaken, namely further precision of half-life of decay and shape of decay of vaccine efficacy against infection. We do not expect the initial efficacy against infection to change. We have addressed this in the discussion “Data are still being accrued that will be crucial for estimating the shape of the efficacy decay, and the estimation will be repeated when the results from the full follow-up of 32 months are available. This analysis will also enable us to assess whether a different efficacy for the boosting dose is expected compared to the third
dose given 18 months prior to boost. This will considerably reduce the uncertainty in predictions of the effect of boosting.”
Referee 2

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.

We thank the reviewer for their helpful comments to improve the paper’s readability and summarized results. We hope they are satisfied with the point by point responses below.

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.

A lexis diagram has now been provided to explain how events averted are calculated for the virtual cohorts used in the vaccine properties parameterization and the for population projections of events averted.

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.

We agree that there are important points in the paper of note for WHO, and some gaps from the trials. These are discussed and listed in the discussion. At this point we have not added a box re-iterating these, as it would replicate that text.

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).

To address the referee’s concerns, the authors have included an explanation in the introduction of malaria biology, RTS,S action, and impact of pre-erythrocytic vaccines, including age-shifts (see changes to introduction for comment 2 of referee 1)

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.

The authors have tried to account for some of the real-life use of RTS,S by including a sensitivity analysis of implementation relevant parameters (coverage of vaccination and transmission) and vaccine properties (such as initial efficacy). This allowed us to account for lower coverage than DTP3 and for missed doses of the vaccine. The broad conclusions are still relevant. We do feel any more analysis is outside the scope of this already very full analysis, but do agree further investigations, such as different immunization schedules, boosters and ages is of importance. Further important investigations are the potential use of the vaccine as a transmission blocker when applied in low transmission areas with mass vaccination (Penny et al 2008). This has been included in the discussion”

“Indeed, the high initial efficacy of RTS,S/AS01 is similar to the profile aimed at for vaccines aiming to interrupt transmission [33], and mass administration of a vaccine with such a high efficacy would have substantial transmission effects [9]. However the current strategy for licensure of RTS,S does not envisage mass vaccination, and this is outside the scope of this paper, but previous efforts have indicated the potential benefits in low transmission settings [8] Post-registration use of the vaccine will be important, as will further modeling investigations.”

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 to large for the predictions to provide a robust guidance?

The models aim to make predictions based on as much relevant data as practicable. All predictions are associated with uncertainties, and all evidence-based policy decisions face the need to face this. The uncertainties associated with our predictions of RTS,S impact are arguably considerably less than those associated with most public health decisions.

Minor points:
Page 2: “a vaccine whose efficacy decays quickly may be of public health importance”:
public health “benefit”?
We changed this to read 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!

This is a good point, so have change the sentence to:

“and, prior to Phase IV follow-up studies, mathematical models are essential to predict long term outcomes of vaccination programs when delivered to populations outside trial settings.”

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.

We didn’t address co-administration, interaction with hep b explicitly, but did briefly address maternal immunity.

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 “the best fitting models with lowest DIC was obtained when models fit for site-specific variation in incidence”.

“Uncertainty about vaccine properties” refers to the fact that vaccine properties (efficacy, half-life and shape of decay) have greatest impact on the prediction of events averted in the population. The second phrase “the best fitting models with lowest DIC was obtained when models fit for site-specific variation in incidence” indicates in the fitting process, that when the Bayesian MCMC model allowed the variation parameter in the log-likelihood to be determined for each trial site, rather than assume the same fitted value for all sites, then better fits to the data were obtained, indicating that allowing for the inter-site variation in transmission provided improved estimates of the vaccine properties, even though these estimates had the same values for all sites.

We now added the explanation that the ‘estimates have the same values for all sites.’

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?

The properties are those pertaining to efficacy against infection in time, in this case initial efficacy against infection at completion of third dose, half-life and decay shape. We have made this clearer in the text.

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).

We have entered this statement into the discussion

"but is in line with published data of IgM serum concentrations (White 2014 et al)"

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.

This paragraph has been improved to:
“Predictions of expected clinical efficacy by 6 monthly time points, namely percentage of clinical events averted in the previous 6 monthly period, and expected cumulative efficacy in time over all trial sites for the two cohorts are shown in Figure 4. The overall efficacy against clinical disease in time is predicted to be sustained for both the 6-12 week and 5-17 month cohorts, even up to four year follow-up. However, the prediction of efficacy against clinical cases (including repeated episodes in the same individuals) for six month time intervals, indicates that the proportion of cases averted in each 6 monthly period will decrease to 10% towards the end of the final followup of the trial.

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?

As indicated above we have altered the text of this paragraph to read:
“A substantial number of clinical events are predicted to be averted 10 years following introduction (total over endemic countries in Table 4 or per fully vaccinate Table 5). Under the immunisation schedules of targeting only the young, and considering the protection from the vaccine wanes relatively rapidly, this translates into relatively low proportion of malaria events averted over the entire population (range from 1-4% for clinical events and up to 10% for deaths (Figure S14-S15), depending on immunisation schedule). These low proportions are to be expected since malaria disease can occur at any age, but only the youngest cohorts will be targeted by vaccine. The proportion of events averted for under five is much higher.” In addition the virtual cohort is explained via Lexis diagrams in the supplementary methods.

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

We have changed the figure legends to say “effectiveness in terms 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)

Two cohorts were vaccinated in the Phase III trials, 6-12 weeks and 5-17 months. However the implementation of the 5-17 month vaccination schedule being considered is a schedule immunizing 6-9 month olds. In the methods we write:
“We considered a 3 dose regimen of vaccination via the Expanded Program on Immunization (EPI) given with a standard Diphtheria-Tetanus-Pertussis (DTP) schedule of 3 doses between 6 and 12 weeks of age. In addition, an extended routine schedule beginning with the vitamin A visit at 6 months and subsequent doses at 7.5 months and ending with measles containing vaccine at 9 months is examined (this is a schedule considered as the 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 [3,21].”

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 combatting 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.

We have addressed this by adding more introduction of action of pre-erythrocytic vaccine into the introduction; as indicated above in comment 2 to referee 1