Author's response to reviews

Title: Sixty years trying to define the malaria burden in Africa: have we made any progress?

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Author's response to reviews: see over
Dear Sabina

We thank the reviewers for their positive response to the opinion piece entitled "Sixty years trying to define the malaria burden in Africa: have we made any progress?". Overall the comments were those requiring expansion of the debate and we've indicated in the response below where we have tackled this, or feel expansion in some directions would alter the broad message and purpose of the opinion. Overall I felt that both reviewers were happy with the piece and wonder whether you need delay final review further by re-sending to Professors Maitland and Beeson?

Reviewer's report 1: Kathryn Maitland
Major compulsory Revisions
None
Minor Essential Revisions
None
Discretionary

1) For the non-specialist it may not be apparent that in order to gain immunity from malaria disease (and even infection) that annual exposure and multiple episodes of malaria are required –before achieving disease specific immunity ie no more febrile events and finally full immunity from malaria (anti-parasite)- if ever. And that this is different across each level of endemicity (exposure) and possibly poorly understood in populations experiencing an epidemiological transition. Hence the focus of the article - how to tease this out using existing data.

This is the enigma of malaria - one that if we could solve would provide the framework for vaccine discovery. This is a similar comment to that made by Professor Beeson (see below) and we have expanded the required sentence in paragraph 1 page 4.

2) I thought the section highlighting the use of disparate data to calculate predictions of disease burden for Swaziland and Rwanda giving misleading results could go one step further. The authors may or may not want to expand on how this diverts funding to areas where the predications are clearly not contemporaneous – and if possible give example of this?

A useful observation, and hopefully, the "one step further" is implicit. This is a politically charged area, if a country opts to go for elimination in will cost considerably more than simply sustaining the low, endemic stability that supports a low disease burden. Countries like Swaziland and Rwanda could not afford an end game themselves and will seek funding from communities, including Gates, to support their ambitions. Whether this is right at global funding level or not is the subject of a much bigger debate. While I am sympathetic to Professor Maitland’s position we feel its not the place of this opinion to tackle this debate,
3) The section on indirect morbidity, they may want to quote the recent systematic review of bacteraemia complicating severe malaria, which give a more accurate estimate published this year (2014) in BMC Medicine by, errrrr....., this reviewer!

Done...... with apologies to Professor Maitland and BMC Medicine

4) Conclusions- I was hoping that at the end there would be a summary ‘wishlist’/roadmap for future funding / epidemiological studies – but the authors don’t quite do this, despite hinting at it in the last line of the abstract. It would certainly invite comment if they went the extra mile?

The "extra mile/wish list" is now presented as a new paragraph concluding the paper on page 9.

Reviewer's report 2: James Beeson
Minor Essential Revisions
The manuscript is clear and interesting to read and I only have minor comments:

1) ..... I think it would be valuable to add some comments on the clinical and public health value of having estimates of morbidity and mortality due to malaria, and why these data are valuable. Perhaps future malaria burden estimates should be presented in two ways, based on parasitemia and based on case reports of morbidity and mortality? Is that what the authors are suggesting, or are they proposing shifting to parasitemia-based estimates only?

We are opening (or rather resurrecting) the debate on whether under stable endemic conditions which support the highest disease risks in Africa morbidity and mortality due to malaria can be measured at all. Our concluding section speaks to the last sentence of the reviewers comments above, rather than using both.

As with reviewer 1 we are now more specific about what should now be done, or rather should have been done when we launched RBM (!) over next 15 years. This now is included in the last, new paragraph of the paper.

2) ... clarify that P falciparum is by far the major cause of malaria in Africa (with very little due to other species)

Now corrected in main MS on page 3, second para

It might also be helpful to clarify that by the term ‘malaria’ they mean clinical illness with fever (this is often a point of confusion, and clarity around this point is essential to their subsequent arguments)

This we have checked throughout MS and are confident that distinctions made correctly at each stage
3) Page 2, sentence ‘how immunity confounded any reliable estimations…..’ Some clarification or details about what is meant here would be helpful

This we tackle later in MS when discussing presence of infection not equivalent to prevalence of disease; last sentence para 1 page 4

4) P4, 1st para. I think it is debatable whether malaria immunity does develop quickly – what is meant by ‘quickly’? The term is a bit vague.

As with reviewer 1 this is now more elaborately spelt out and an honest statement to the effect that we don’t know, other than it all happens when someone is a young child (hence "quick"); paragraph 1 page 4

I think it would be worth noting that the clinical and public health significance of very low parasitemias is somewhat unclear with many reports of asymptomatic low grade parasitemias (not exclusively in immune individuals) and lack of clarity about the transmission potential of people with low grade parasitemias, something that we need more research on. So, measuring parasitemia rates and using those to estimate burden does have some limitations.

We acknowledge the issues around parasite detection sensitivity in para 3 page 7 and reference 72. I agree with Professor Beeson that the precise role of exceptionally low grade infections on broader health outcomes is interesting and has both an immunological and public health value. I also agree that we don’t have enough research in this area. However, for the purposes of the present opinion piece we have proposed that infection is easier to measure routinely than a complete picture of malaria specific deaths and that infection per se might contribute to a wider health burden. To elaborate further on sub-microscopic infections and outcomes of low grade infections would take the opinion piece into a new territory, double the word count and take us off point. So while I agree with Prof Beeson, this would in fact be the subject of a separate, and important, review and/or opinion piece.