Author's response to reviews

Title: Parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania

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Version: 2 Date: 8 July 2009

Author's response to reviews: see over
Cover letter

8th July 2009.

Dear Editor,

Re: MS 2021230647268477.
Attached is a revised manuscript entitled - Parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania.

We have gone through all comments which were raised by reviewers and where possible addressed comments raised. In response to the reviewer letter, we have under each query explained the changes that we made in the text.

Other changes that we have done but not included in under response to reviewer are:

1. Shorten the abstract where we omitted some texts which we found not very important for the section
2. More elaboration on data description by including village and district names to make it easy for readers to know the study site

We look forward to your response.

On behalf of all authors,

Bruno P. Mmbando

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Enclosure:
Responses to reviewers
Reviewer's report 1

Title: Parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania

Version: 1 Date: 11 May 2009

Reviewer: jean Gaudart

Reviewer's report:

Title : parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania

Ref. : 2021230647268477

Journal : BMC Medical research Methodology

I. Generalities :

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The presented work aimed to find a threshold of parasite density associated with fever. As the author know, the literature on the subject is already significant. However, the authors present an interesting approach, using different statistical models and simulations to estimate parameters. Nevertheless, there are many points to clarify, particularly the different models.

II. Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached):

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1/ the aim of this work was to find a threshold of parasite predicting fever. Fever is defined as axillary temperature >= 37.5°C. How this fever has been defined? It is not clear that this threshold temperature is adequate to define a fever. The choice of this threshold will modify the parasite threshold.

Response: It is true that change of the fever threshold will also change the parasite threshold. The fever cut-off we are using is the common one used in definition of malaria fever.

2/ in the “Method” section, subsection “Parasite threshold models formulation”, sub-sub section “threshold model”:

2.1/ The definition of alpha seems to be wrong. Indeed, the probability of clinical malaria in individuals with parasite below tau is F(alpha), not alpha.

Response: This is now corrected

2.2/ the function F() is not defined.

Response: At this subsection, it is just defined as a function, without mentioning the assumed probability distribution. However, in the following subsections it is clearly defined as inverse-logit.

2.3/ Statistical models 1 and 2 have to be rewritten. Indeed, it seems that these models are logistic models with a noisy parameter tau.
In the first model, the parasite density $P$ is defined as a binary variable.
In the second model, the parasite density $P$ is defined as a quantitative truncated variable.
Logit (gamma)=$\alpha$+$\beta$ $P$
This formulation is preferable.
Note that if $P=0$ then logit(gamma)=$\alpha$.

Response: It is true that the models are logistic, but we have put it as general models, where one could be interested to use other model from same family such as negative-binomial. We outlined logistic formulation immediately after model 2, where relation (3) build-up to logistic model as you suggested.

2.4/ For parameter estimations and inferences, it is not necessary to translate the parasite density $P$; ie, use $\pi$ (where $P$ is a quantitative truncated variable) instead of ($\pi$-tau).
Response: We think that it is important to keep it translated since “tau” is the important parameter we are interested in.

3/ in the “Method” section, subsection “Parasite threshold models formulation”, sub-sub section “estimation of threshold by regression”:
3.1/ Here are presented another cofactor (age). Please write models as logistic regressions (see 2.3). Furthermore, this logistic formulation will introduce a basic probability depending on age, which is a classical point.
Response: This is now considered and model is formulated as logistic regression

3.2/ It is not clear why authors used means of age group instead of individual ages. Please clarify.
Response: In principal this was supposed to be done for individual’s ages, but because we wanted to compare with the previous results where we had grouped thresholds into different age groups, that is why we used the same age category, but this time with mean age of each age group.

3.3/ Note that the function $\tau = \theta_0 + \theta_1 A + \theta_2 A^2$ is still a linear function, over the parameters.
Response: This part is now excluded together with what was eqn. 6 since it doesn’t change the method. Instead, we have added a sentence stating that “if $\theta_2$ is not significant then the effect of $A^2$ will be excluded from estimation of $\tau$ parameter” just before eqn 4.

4/ in the “Method” section, subsection “Simulation studies”:
4.1/ “The simulated samples were multiplied by 40”. Please argue.
Response: The simulated samples were multiplied by 40 for the purpose of generating realisations resembling unit used in quantification of malaria parasites (which is parasites/µL). The simulation could also do fine even if there was no multiplication by 40. This is also explained in the text.

4.2/ there are confusing notations: between $\pi$ and gamma as well as $\alpha$ and $\pi$.
Response: We have now changed notations in this section to resemble once used in the previous subsections, where $p_i$ is now strictly for parasite density and $\gamma$ for probability of fever.
5/ in the “Result” and “Discussion” sections:
5.1/ the numbering of the models is very confused: why 8 models? Only 6 are defined?
Response: We have now reduced numbering of models to only 6, and corrected in the results and discussion sections.

5.2/ As the model 2 used a quantitative truncated variable, and then used more information than model 1 (with the same number of parameters), information criteria will be obviously better for model 2 than model 1.
Response: Main purpose of this comparison was to compare with the classical one (model 6) which use only quantitative variable, since through simulation it was already shown that model 2 better than 1.

III. Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct):

1/ in the “Result” section, page 9 line 24: “prevalence of of fever”
The repeated word “of” is now deleted

IV. Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore):

1/ In order to compare different diagnostic method, authors should use the Diagnostic Odd Ratio (DOR):
Noted, I will consider them in further discussion of the materials to be presented as appendix elsewhere.

2/ why did not you used the ROC curves?
We had interests in alternative method (maximum likelihood), however we are aware of ROC which has been presented elsewhere as referenced in the background section.

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests
Reviewer's report 2
Title: Parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania
Version: 1 Date: 12 May 2009
Reviewer: Lawrence Ndekeleni Kazembe

Reviewer's report:

I have considered the paper by Mmbando et al on Parasite threshold associated with clinical malaria in areas of different transmission intensities in north eastern Tanzania. The paper describes and compares two methods of estimating parasite thresholds that may be used to describe the relationship of malaria fever and parasite density. The technique may be useful in assessment of interventions in clinical trials. The techniques are applied to simulated and real data. An the conclusion offered is able to summarize the appropriate model to consider. The paper is well written with minimum mathematical treatise. The introduction provides a good background and justification for the study. The methodology can be replicated and the paper is of interest to those within this area of study.
The paper should be accepted after the authors have revised some small typos and discretionary revisions, as indicated below:

Abstract
i) Akaike should have a capital A.
This is now omitted in the abstract, however in the main text it is changed to capital “A”

ii) Results subsection: the authors use the phrase "... mean age squared by 1". I don't understand what they mean.
We have slightly shortened the abstract, and have excluded the text you are referring. However, in the results section we have taken care of your concern and rephrased the sentence in a way that it will be understood to readers. In short, this is an interpretation of model where we fitted a linear term (mean age) quadratic term (mean age squared), so, the effect of age on threshold should be derived from the two terms (mean age and mean age squared) where the units are years and years squared, respectively.

Introduction
i) page 3, first para, last sentence which states that "some vaccines ..." needs rephrasing.
The sentence is now rephrased

Methods
i) page 7: some connecting sentence is missing to introduce eqn (8).
This equation now read as 6. We have now introduced a connecting sentence.

ii) page 7: Reference for Box-Tidwell methods would be beneficial.
Reference is now included

iii) page 7: last line. I dont understand the notation p_i=expit(\alpha).
expi is not clear to me. Same on page 8 first line. 
This is now changed to “exp” which is well known to readers

iv) page 8: small w on "where" immediately after the MSE equations. 
This is now changed

Results
i) page 9: line 7 from top: repeat of "parasite". 
The repeated word is now deleted