Author’s response to reviews

Title: Analysis of human immune responses in longitudinal settings: Tutorial in Biostatistics

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Title: Analysis of human immune responses in longitudinal settings: Tutorial in Biostatistics

Dear Editor,

We thank the reviewers for their thorough review and insightful comments on the revised version of the manuscript. We find these comments extremely helpful for our paper. Please find enclosed herein the comments by each reviewer and our response (marked in red in both the cover letter and the text).

I hope that you will find our response satisfactory and consider the manuscript favourably for publication in your journal.

Sincerely,
Elena N. Naumova

Reviewer: Freedom Nkhululeko Gumedze

Reviewer's report: None

Reviewer: Joanna Stewart

Reviewer's report:

The authors have responded to the concerns I had previously with their paper. However I have a remaining concern over a change that was made. Although I strongly feel a change needs to be made I am listing it under a minor concern as I believe the authors can be relied on to either remove it or give a better explanation of what is occurring.

We find the comments extremely helpful and believe they help to improve our manuscript.

Minor:

1. I have a concern about the new information presented in the new fig 4, and its interpretation. Given the structural relationship between change and baseline the authors have changed to looking at the relationship between change and mean. I agree this is the standard thing to do and what I probably would have also done with most data. However with the very different spread of the data at the two time points this has introduced a new problem. Because of the much greater spread in the final value it dominates the initial one, meaning the variation of both the mean and the difference is dominated by the final value. This results in a false relationship. The authors then present this same graph, based on the logged values, which largely overcomes the difference in variation. However by taking the difference of the logged values it is now the ratio of the actual values that is being examined. The reader needs to be made aware of what this means – very small absolute differences could result in quite large (or even very large if the baseline is very small) ratios. Of course the same absolute
difference in larger values will result in a very small ratio. Given the nature of immune response data this may be considered highly appropriate. However if these 2 graphs are to be presented there needs to be some explanation of the effects being seen. The whole paper is attempting to illustrate that analysis of data needs to be done with considerable thought rather than following a set formula. This is well illustrated by the problems encountered here.

We agree with the reviewer’s comments that small absolute differences in IR values can result in large differences in the log-transformed values and vice versa. We have now added a statement clarifying this point in our manuscript (Page 7, lines 9-12).

2. P6 3rd line, correct the spelling of Wilcoxon

The spelling of Wilcoxon has now been corrected

3. P6 last paragraph, 4th line – remove ‘or the change in IR’

We have removed the phrase “or change in IR” from that sentence.

4. Delete fig 4A and renumber 4B and 4C as A and B in accordance with the text and legend.

We are sorry for the oversight. We have now deleted Fig. 4A and renamed Fig. 4B as 4A & Fig. 4C as 4B.

5. The horizontal line and CI on these graphs does not seem to be mentioned in the legend or text so would be better removed.

We have now added the interpretation of the horizontal line and the 95% CI on Figs. 4A and 4B to the legend.

6. P10 4th paragraph. An explanation is given 2 paragraphs earlier for the false impression of a raise pre disease. The reference to it in this final paragraph, implying there is a real increase in response should be removed.

As suggested by the reviewer, we have now modified the sentence by removing “and finally, the onset of increase in responses that occur slightly prior to a diarrheal episode” from it. We hope that by doing so, the readers will not get a false impression about an increase in immune response pre-event (Page 10, lines 26-28).