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**DUE MARCH 17**

To Dr. Temime

Healthcare-associated infection control editorial board member

February 15

Dear Dr. Temime,

We would like to thank the associate editor and the reviewers for their constructive feedback on our manuscript titled "A comparison of five epidemiological models for transmission of SARS-CoV-2 in India" (INFD-D-20-03634) by Soumik Purkayastha, Rupam Bhattacharyya, Ritwik Bhaduri, Ritoban Kundu, Xuelin Gu, Maxwell Salvatore, Swapnil Mishra, Bhramar Mukherjee and for giving us an opportunity to address the concerns through a revision. We would like to clarify that we are submitting this manuscript as a review article and not as an original research article. Following are itemized responses (shown in blue) to the reviewer and editor comments (shown in *italics*).

The main changes that we have incorporated are:

-A

-B

-C

Thank you for your consideration of our revised manuscript. We hope you find the revised manuscript suitable for publication in *BMC Infectious Diseases.*

Sincerely,

[Bhramar Mukherjee](mailto:bhramar@umich.edu)

Department of Biostatistics

**LETTER FROM EDITOR FOR REFERENCE - DELETE**

Dear Dr. Mukherjee,

Your manuscript "A comparison of five epidemiological models for transmission of SARS-CoV-2 in India" (INFD-D-20-03634) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Infectious Diseases.

Their reports, together with any other comments, are below. Please also take a moment to check our website at <https://www.editorialmanager.com/infd/> for any additional comments that were saved as attachments.

If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Infectious Diseases.

Once you have made the necessary corrections, please submit online at:

<https://www.editorialmanager.com/infd/>

If you have forgotten your password, please use the 'Send Login Details' link on the login page at <https://www.editorialmanager.com/infd/>. For security reasons, your password will be reset.

Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.

Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Submission Guidelines on the journal homepage.

A decision will be made once we have received your revised manuscript, which we expect by 17 Mar 2021.

Please note that you will not be able to add, remove, or change the order of authors once the editor has accepted your manuscript for publication.

Any proposed changes to the authorship must be requested during peer-review, and adhere to our criteria for authorship as outlined in BioMed Central's policies.

To request a change in authorship, please download the 'Request for change in authorship form' which can be found here - <http://www.biomedcentral.com/about/editorialpolicies#authorship>.

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Your request will be taken into consideration by the editor, and you will be advised whether any changes will be permitted.

Please be aware that we may investigate, or ask your institute to investigate, any unauthorized attempts to change authorship or discrepancies in authorship between the submitted and revised versions of your manuscript.

I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Laura Temime, Ph.D.

BMC Infectious Diseases

<https://bmcinfectdis.biomedcentral.com/>

Technical Comments:

Editor Comments:

Assessing and comparing different models of SARS-CoV-2 transmission is certainly useful in the current context. However, this comparison needs to be performed in the most robust way possible. This requires major revisions to the current version of the paper. In particular, I strongly support the suggestion made by the two reviewers to add uncertainty estimates to model predictions in order to be able to determine whether differences are significant. I also agree with Reviewer 2's suggestion to try and assess whether the conclusions reached in terms of model comparison still hold under conditions other than those of the first epidemic wave in India. In other words, some kind of sensitivity analysis is missing from the paper.

We operate a transparent peer review process for this journal where reviewer reports are published with the article but the reviewers are not named (unless they opt in to include their name).

**^^^ LETTER FROM EDITOR FOR REFERENCE - DELETE**

**Response to Reviewer Panel: Reviewer 1**

Summary of the paper: *The paper is overall well written. The authors implement and compare five epidemiological models and assess their predictive accuracy on real COVID-19 data from India. Under reporting of cases which has been a major hurdle is taken into account by three of the models. Data from March 15 to June 18 is used as training set while June 19 to July 18 data as a test set. The models are presented in a clear manner and so are the results stemming from them. While no new extension is proposed to the existing models used, their comparison and performance on real data offer interesting insights. However, some parts of the paper need clarification (see below for more details).*

1. **The terms "unascertained" and "asymptomatic" seem to be used interchangeably throughout the paper. Do unascertained cases consist of mild symptomatic and asymptomatic cases or do both terms refer to the same thing? If the latter is true, wouldn't it be simpler to use only one of the terms?**

**c.f pg 19, line 116: "In the previous subsection we have seen an extension which includes the 'asymptomatic infectious' compartment (people who are infected and contributing to the spread of the virus, but do not show any symptoms)." However, in the previous subsection, there is only mention of unascertained infectious.**

RESPONSE

1. **Page 7 line 128: "an" exponential process**

We thank the reviewer for noticing this error and note that we have made the appropriate correction.

1. **Page 2 line 33: 23. ? eSIR. It seems that something is missing here.**

We thank the editor for noticing this error. The correct sentence should have read

“23.10 (for eSIR)”

in accordance with Table 2. We add that we have re-fit all five models on a training period from March 15 – October 15 and test how well the projections match with observed case and death-counts on testing period from October 16 till December 31.

1. **Page 18 line 307: "using data from Singapore". Can you provide a reference for this?**

We apologise for leaving out an important reference from the text. In order to obtain an initial estimate of ascertainment rate, we followed the approach outline in Wang et al., 2020 (*Hao, X., Cheng, S., Wu, D., Wu, T., Lin, X., & Wang, C. (2020). Reconstruction of the full transmission dynamics of COVID-19 in Wuhan. Nature, 584(7821), 420-424*). Tracking more research in this context, we obtained a more recent prior distribution for the ascertainment rate (specifically, we now assume the ascertainment rate follows a Beta(10, 90) prior distribution) as described in a study by Rahmandad et al., 2020 (*Rahmandad, H., Lim, T. Y., & Sterman, J. (2020). Estimating COVID-19 under-reporting across 86 nations: implications for projections and control. Available at SSRN 3635047*) on under-reporting in 86 nations including India. The modified manuscript reflects this information.

1. **Why use the term "node" in section 2.1.d when compartment has been used throughout the paper? It would be less confusing to keep to the same convention here.**

We agree with the reviewer – interchangeably using ‘node’ and ‘compartment’ is confusing. Further, we thank the reviewer for raising this point and note that the modified manuscript is consistent in using ‘compartment’ instead of ‘node’ for all the compartmental models.

1. **page 29 line 485: yields instead of yield**

We thank the reviewer for spotting this grammatical error and apologise for our oversight. The modified manuscript reflects the appropriate correction.

1. **page 30 line 492: "we do not include the same in this specific comparison method". What do you mean by this statement?**

We apologise for the lack of clarity in the sentence being discussed. What we meant to say is as follows

*Since the ICM projections are total counts (sum of reported and unreported), we do not tally them with reported COVID-counts – thereby leaving ICM projections out of this comparison method.*

We note that this modified manuscript reflects this change.

1. **In Figure 6, SAPHIRE is mentioned in the legend but not shown on the graph.**

We thank the reviewer for this comment – the projections from SAPHIRE are indeed included in the figure, but given how closely the projections from SAPHIRE and SEIR-fansy agree with each other, the deeper colour for the SEIR-fansy curve makes it very hard to read the SAPHIRE curve from the figure. We note that the new figures (generated with new projections from each of the models) are more informative and easy to read.

**Reviewer 1, Major remark:**

*It is problematic to properly compare the performances of the methods without confidence intervals on the predictions to quantify uncertainty.*

RESPONSE

**Reviewer 2**

*In this paper, the authors consider five mathematical models that aim to describe the population-level transmission of SARS-CoV-2 and provide forward projections of various epidemiological quantities of interest. The authors provide a useful exploration of the main features of each model considered, as well as the methods each model uses to produce forward projections. The study focuses on the context of the SARS-CoV-2 outbreak in India, using data from a test period between March and June 2020 to inform the various models considered. The forward projections resulting from each model are compared with data on what happened during the following period between June and July 2020. The authors use various metrics to assess the accuracy of the five models in making forward projections and also to estimate the extent of underreporting in the Indian context considered.*

*There is clearly utility in comparing different epidemiological modelling approaches and improving our understanding of which models provide the best predictive ability in which contexts. The work done so far by the authors is able to assess the predictive ability of the models under consideration, but it lacks strong conclusions about which modelling approaches are preferable and why. My view is that this kind of comparative modelling assessment will be significantly strengthened if the authors can make stronger conclusions about the models considered and their use and suitability in different contexts. Further, the work will be significantly strengthened by repeating the model comparisons in a couple of different contexts.*

*Firstly, it would be useful to repeat the same assessment across the five models during different phases of the epidemic. For example, various countries around the world are now experiencing second and third waves of SARS-CoV-2 outbreaks, with much data available during various epidemic phases such as exponential growth and decay, low but sustained prevalence and high and sustained prevalence. I think this work would be improved by assessing the abilities of the models under consideration during various phases of transmission. Further, the current assessment would be strengthened by providing more context to the reader on the epidemic dynamics that India was experiencing during the test and project periods considered (March - July 2020), earlier on in the text. A second comparison which I believe would strengthen the work is a cross-country comparison. The authors note that the degree of underreporting has been a major concern in India and in many other countries. Therefore, it would also seem sensible to compare these five models in a context where the degree of underreporting is lesser, to see if the same model hierarchy emerges in terms of predictive ability.*

RESPONSE

*In addition to my overall comments above, I have some more general comments which I think the authors need to address:*

1. The authors only provide point estimates and do not discuss the uncertainty estimates produced by the models. It would certainly make sense to include uncertainty in their assessment of the various models' performance

RESPONSE

1. The authors discuss the lockdown introduced in India, and refer to four different lockdown periods considered. More work needs to be done in the text to link the policies introduced in India with the four phases under consideration, as well as to define clearly what you mean by these four periods.

RESPONSE

1. For one of the models considered (ICM), the authors are not able to compare the model performance using all of the metrics used for the other models. Why is this model included if the authors cannot assess its performance in line with the other models? Are there any other metrics the authors can use that would enable a comparison across all five models? Further, I think that the authors should provide more justification for why they have chosen particular models.

RESPONSE

1. Figure captions should define model parameters and variables

RESPONSE

1. Equation (2) - why is there an l subscript on the left hand side?

RESPONSE

1. Page 13, line 224 - define the adaptation number

RESPONSE

1. Page 14, line 226 - start with 4 chains but end with what?

RESPONSE

1. Page 14, line 234 - define what is meant by COVID-19 counts. Same comment on page 18, line 305

RESPONSE

1. Ensure that justification and/or references are provided for parameterizations. In fact, I think this element would be strengthened if parameter values were justified/motivated across all models in the text, before introducing each model

RESPONSE

1. The authors do not allow for population movement between the Indian states. This seems like a key limitation, especially since there were reports during the early stages of the outbreak in India of migration of workers from urban to rural locations. Can the authors discuss the implications of not considering population movement on the results? Or incorporate population movement into the results as a sensitivity analysis?

RESPONSE

1. It is not clear what is meant by active case counts -> please define

RESPONSE

1. Page 16, lines 263-267 - please define n and N here

RESPONSE

1. The authors assume that unascertained cases have lower transmissibility than ascertained cases (lines 275-6). Intuitively, I would assume the opposite (i.e. ascertained cases would have lower transmissibility relative to unascertained cases, due to increased awareness). I would suggest that the authors consider doing sensitivity analysis on this aspect

RESPONSE

1. Page 17, lines 284-285 - the authors assume an isolation period of 30 days, but don't provide justification for this assumption (this seems a long period to assume). Further, the authors say that this choice has no effect on model fitting or estimates. Can the authors explain why?

RESPONSE

1. Page 17, line 290 - strange phrasing where the authors talk about the assumed value for r\_0

RESPONSE

1. Page 18, line 307 - the authors parametrize the ascertainment rate using data from Singapore. I assume that the ascertainment rate in Singapore is going to differ from India. Can the authors instead use an estimate more relevant to the Indian context considered? This links back to my earlier point about doing this analysis for a different country context -- perhaps Singapore would be a good country to choose for this comparison.

RESPONSE

1. Section 2.1.d. SEIR-fansy model - the authors use the 'node' terminology multiple times but I think 'compartment' would be a more appropriate term

RESPONSE

1. Page 19, lines 324-329 - the authors discuss modelling of false negatives but don't mention consideration of false positives. Please outline what assumptions/considerations are made here

RESPONSE

1. Page 20, line 333 - do the authors mean exponentially distributed times?

RESPONSE

1. Page 20, lines 336-337 - alpha\_p is a ratio and then alpha\_u is a scaling factor - why the difference in terminology?

RESPONSE

1. Page 20, line 340 - "disease times" -> "disease multiplied by"

RESPONSE

1. Page 20, lines 349-350 - the authors talk about their assumption of testing being instantaneous as being reasonable. I feel this statement is a bit strong.

RESPONSE

1. Figure 4 - labelling of transitions needs improving, it's not clear which quantities related to which transition e.g. alpha\_u\*beta. In fact, it seems that a slightly different Figure has been uploaded separately to the one included in the text? Perhaps the in text Figure is missing arrows

RESPONSE

1. Page 22 - line 373 - what does daily differences mean? Are you using a time step of one day?

RESPONSE

1. Page 23 - lines 380-382 - can the authors explain this working?

RESPONSE

1. Page 27 - line 436 - define the star superscript notation

RESPONSE

1. Page 27 - lines 446-447 - make the notation for R\_t,m consistent across these lines

RESPONSE

1. Page 28 - lines 450-451 - make the notation here consistent with what you have used in equation (16)

RESPONSE

1. Page 28 - section 2.2.a Choice of parameters - seems like this section should come before introducing and discussing the parameterization of each model

RESPONSE

1. Page 29 - equation (18) - define the norm notation used

RESPONSE

1. Page 29 - equations (18) and (19) - the right hand side of both measures seems to be calculated from t=1 to t=T but the left hand side are defined as being relevant to time t only

RESPONSE

1. Page 30 - lines 501-502 - can the authors provide some context as to what values of the Rel-MSPE mean? E.g. are smaller / larger values better?

RESPONSE

1. Page 30 - lines 504-505 and equation (20) - it seems that the left hand side of the equation doesn't match the right hand side. As far as I can tell, the right hand side would calculate the Rel-MSPE of model A with respect to model B

RESPONSE

1. Page 31 - lines 523-524 - over what time period is the data taken?

RESPONSE

1. Page 31 - lines 525-526 - how is the interactive dashboard relevant to this work?

RESPONSE

1. Page 32 - lines 540-542 - how do these results compare with data on population movement / behaviour? It would be useful to compare these results with contextual information on what was happening during the various lockdown stages considered

RESPONSE

1. Page 35 - lines 600-603 - how do these results compare to another country with a different degree of underreporting?

RESPONSE

1. Page 35 - lines 608-609 - if the authors assume that there are no changes in either interventions or behaviour of people during the four lockdown periods considered, then why is there a need to divide the lockdown into these four periods at all?

RESPONSE

1. Page 35/36 - lines 612-614 - I think the authors need to be more explicit about the limiting assumptions of the modelling approach, e.g. that there is no age structuring so individuals of all ages mix homogeneously, and also that you do not allow for movement between Indian states considered.

RESPONSE

1. Page 36 - lines 615-617 - it is not clear what the authors mean by this sentence: if the uncertainty estimates play a key role in model choice, then why don't you report them?

RESPONSE

1. Figure 6 - use numbers for vertical axis, consider providing a zoomed in segment of the lines for observed, baseline and SAPHIRE and SEIR-fansy - as you can't see the difference between these lines easily

RESPONSE

1. Figure 7 - it is hard to see the red line for observed, would be helpful to provide a zoomed in segment, similar to comment above

RESPONSE

1. Figure 9 - use numbers for axes

RESPONSE

1. Figures 9, 10, 11 - difficult to interpret the densities plotted horizontally and vertically - these may look better if the authors provide their own separate axes. It is also difficult to see the various model's density plots when they are plotted on top of each other

RESPONSE

**Editor’s Comments**

*Assessing and comparing different models of SARS-CoV-2 transmission is certainly useful in the current context. However, this comparison needs to be performed in the most robust way possible. This requires major revisions to the current version of the paper. In particular, I strongly support the suggestion made by the two reviewers to add uncertainty estimates to model predictions in order to be able to determine whether differences are significant.*

RESPONSE

*I also agree with Reviewer 2's suggestion to try and assess whether the conclusions reached in terms of model comparison still hold under conditions other than those of the first epidemic wave in India. In other words, some kind of sensitivity analysis is missing from the paper.*

RESPONSE

*We operate a transparent peer review process for this journal where reviewer reports are published with the article but the reviewers are not named (unless they opt in to include their name).*

RESPONSE