Author’s response to reviews

Title: Modelling the impact of chest X-ray and alternative triage approaches prior to seeking a tuberculosis diagnosis

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RESPONSE TO REVIEWERS

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"Modelling the impact of chest X-ray and alternative triage approaches prior to seeking a tuberculosis diagnosis"

The authors would like to thank the reviewers and the editor for their time and effort in reviewing our manuscript. We thank them for their support of our paper and for their inciteful and helpful comments which we believe we have addressed fully in the attached revised manuscript and ‘point by point’ in the responses below (the points made by the editor and reviewers are shown and our responses immediately). We have also labelled our responses (A to X) to facilitate referencing.

We sincerely hope that with these revisions the manuscript can now be accepted for publication.

Thank you
Technical Comments:

- Please include email addresses of all authors.

A. The email addresses have been added

Editor Comments:

Dear Authors, Thank you for the submission, this was an interesting paper on an area of great interest and potential impact.

The reviewers have raised a number of key points that should be addressed before your submission can progress.

Thank you for these encouraging comments. We have addressed each comment ‘point by point’ below.

I agree with Reviewer 1, that it is difficult to properly interpret the implications of this work when false positive diagnoses and treatment costs have not been considered.

These points have been fully addressed in manuscript and by response F and I to reviewer Menzies below.

The costing data is very limited and does not appear to account for costs associated with the testing process, which I would think an operational model could handle easily.

B. Thank you for this observation. The unit costs used in the model do in fact include all the variable operational costs associated with completing the tests including staff time, consumables, running costs and equipment depreciation. They do not include fixed overheads which are assumed will remain the same whatever tests are used. This has now been clarified in the manuscript – see the ‘Costing’ sub-section within the ‘Methods’ section.
As it stands the conclusions drawn from the economic modelling should be downplayed. False positive diagnoses represent unnecessary treatment and potentially adverse events along with increased costs.

C. Following the revisions made we believe the manuscript does provide valuable insight into operational modelling and the yield and diagnostic cost impact of alternative triage.

We agree that in considering the overall impact of alternative diagnostic algorithms, clinical judgement and the level of false positive diagnosis is important. Indeed, the authors have made this point previously in a number of their publications 1, 2. In relation to including false positive treatment in this study we have made changes to the Results section and in the detailed response to Menzies, point I below.

As raised by reviewer 2 the methodology is not easily understood, particularly for non-modellers, and would benefit from clarifications.

This point has been addressed by changes to the manuscript and response O to reviewer Shaikh below.

For example, it begins as though you are looking at 6 different triage approaches, but then you add two diagnostic approaches so you are looking at 12 different options and then you look at those 12 options with and without CXR, is this correct? It would help to be more explicit about this approach from the beginning.

D. For clarity this statement has now been added to the last paragraph of the background-

This study investigates the use of operational modelling to predict the impact of seven potential alternative approaches to triage (including no triage – base case), with or without X-ray and in combination with the Xpert diagnostic test. The projected outcomes were compared to a base case of sputum smear microscopy without triage or X-ray.

i.e. 7 triage approaches x 2 X-ray approaches = 14 compared to a base case of sputum smear microscopy.

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Reviewer reports:

Nicolas Menzies (Reviewer 1): Summary:

This is a well-written paper on an aspect of TB control that warrants greater attention - how individuals are identified to receive TB diagnostic tests. My major concern with the analysis is that the issue of false positive diagnosis does not appear to be considered, and this may bias the evaluation towards more sensitive approaches at the expense of specificity.

E. Thank you for these comments – they are really helpful and have been fully addressed below and by changes to the manuscript.

Major points:

1. Page 4, Costing: I find it difficult to interpret the cost implications if treatment costs are not considered, as changes in sensitivity and specificity will have predictable consequences for treatment costs.

F. We agree that an important cost to the TB programme is the cost of TB treatment. We have added treatment costs to our overall projections of costs – see Results section and Tables 2, 3 and 4.

2. Page 5, Operational Model: for a sequence of diagnostic tests, the sensitivity and specificity of the algorithm is not necessarily a function of the sensitivity and specific of the individual tests alone. It seems that the analysis assumes conditional independence of all tests - is this correct? At the least I think this warrants discussion, and it may need investigation in the sensitivity analyses, even if there is little data to say whether this assumptions holds.

G. Yes the assumption used is that the tests are conditionally independent and we agree this assumption needs discussing so we have added this to the Discussion section.

3. Page 5, Operational Model: in an earlier section there is discussion of clinical diagnosis for the smear/Xpert negatives, but I cannot see the performance characteristics for clinical diagnosis included in Table 2. I realize that the sensitivity and specificity of clinical diagnosis is difficulty to judge (and potentially setting-specific), but I am not sure it can be ignored.
H. This has been added to table 2. As the reviewer implies the accuracy and use of clinical judgement are extremely variable depending on the individuals making the judgement and the context in which they are exercised.

4. Page 6, Results: Results are reported in terms of various performance measures, but I don't see how one algorithm can be judged better than another if false-positive diagnosis is not considered. It appears that the only penalty for reduced specificity in the triage test is increased costs for other subsequent tests.

I. This is a very interesting observation and we have addressed your comments below: -

• We accept that low specificity of a triage test might increase the levels of over diagnosis compared to a triage test with higher specificity and have added the false-positive projections to tables 3 and 4 and the Results section. Note that no triage, which is the base case, in effect is a triage test with 0% specificity and 100% sensitivity. Therefore, any triage test should at worst leave over diagnosis unchanged – the impact will depend significantly on the clinical judgement used following a negative diagnostic test and how this correlates with the triage approach used.

• The focus of an effective triage test must be to identify all the true TB cases (or as many as possible). This implies high sensitivity to avoid true cases of TB not being tested and therefore not treated. For a triage test to maximise on sensitivity it is almost inevitable that specificity will be compromised as can be seen from table 1 (excluding the theoretical TPP alternatives).

• To clarify, the emphasis of this study is on triage of individual patients presenting at a diagnostic centre for testing (it is not about active case finding). The result of the triage test is to support the decision on whether to use an ‘expensive’ diagnostic test (e.g. Xpert), or not to use the test and therefore not to treat for TB. All patients with a negative triage will not be treated for TB. In this context triage cannot increase the number of patients being tested and treated as currently all these patients are tested and those that test positive, or where clinical judgement suggest TB treatment is required, are treated for TB. Therefore, the focus of this study is on positive diagnosis of patients with TB and the impact on diagnostic costs. The manuscript has been amended in the Methods – Operational Modelling section to make the context clearer.

• Clinical judgement following a negative smear or Xpert test is the most critical decision that effects the level of false positive diagnoses. Note, both diagnostic tests considered here (Xpert and sputum smear microscopy) have very high specificity therefore false positives from these tests themselves are not a significant issue.
Minor points:

1. **Figure 2:** this figure should be very useful for understanding the model, but at present is hard to read, and some icons appear to be unexplained.

J. We point out text was provided that should accompany Figure 2 and gave more detail to explain each of the figures including Figure 2 (see below). Additional keys to icons have also been added to Figure 2 in the revision sent.

**Figure 2 – Example screenshot of operational model of TB diagnostics in Porte Alegre**

The screen shot of the model illustrates presumptive-TB cases arriving at 1 of 10 health clinics where they undergo the triage test followed in some cases by X-ray. Patients who are triage positive then proceed for sputum collection. When microscopy is used for diagnosis the patients then go home and return the next day with a second sputum sample. Sputum samples are tested in the laboratory using either microscopy or Xpert MTB/RIF. A red patient icon indicates the patient has active TB and a green icon indicates a patient with no TB. Sputum samples and results are shown as circles. Circles with brown centres represent initiation of the diagnostic test and TB positivity unknown, red and yellow centres indicate samples that tested positive and negative respectively. Patients who are tested positive, undertake initiation of TB treatment and those who are tested negative go for clinical assessment and then TB treatment if clinically diagnosed. Some patients are also shown as lost to follow up (LTFU) and no treatment is initiated. Three types of resources are also shown in the model to represent Clinicians (Orange and Black), Nurses (Pink and Yellow) and Lab Assistants (Green and Brown).

2. **Page 4, line 46-47:** The sentence beginning "The two diagnostic algorithms…" might need to be rephrased.

K. This sentence has been reworded – thank you
Nabila Shaikh, MSc (Reviewer 2): This is a very interesting paper and certainly shows the potential uses for mathematical modelling in TB control and treatment.

Overall, this paper requires some clarifications and improvements to make it more suitable as an academic paper.

We thank the reviewer for her comments and have addressed all her concerns below.

My two main concerns would be as follows:

- The introduction requires essential strengthening to show the contextual importance of this paper e.g. it is well understood that SSM has limitations as a diagnostic method and that GeneXpert has a better sensitivity but is expensive. Some connection between these facts and the local context in further detail would make this paper more relevant to the current field.

L. The Background section has been updated to take account of the points raised above.

Similarly, the relevance of the triage methods and diagnostic methods used in the model would benefit from further justification - The method is not very clear and requires multiple read throughs to understand the process. I would suggest reconsidering the order and making the methodology succinct with sufficient justifications.

M. Thank you for your comments. We have added further details justifying the triage and diagnostic methods considered and modified the order in which the information in the Methods section is presented.

- There is no consistency in the way the results are presented in the body of writing. An effort is needed to make it more academically sound i.e. include the case detection rate for all of the interventions mentioned.

N. The results section has been significantly revised to take account of treatment costs as requested by reviewer 1. We have also taken on board the reviewers comment above in the revised Results section.

- Further detail of the model should be outlined in the written text (introduction or methods) rather than relying on the reader to look to the appendices. It will then also attract readers who may not have a background in mathematical modelling.
O. We have added some more detail in the Methods to address this point. However, we believe to avoid cluttering up the paper with all the detail of the model itself the free online appendix is the right solution. For many readers this detail will not be of interest, the free online appendix is therefore the appropriate place for some of this detail for this journal. This has certainly been our experience previously with other health based and equally impactful journals. The information will easily be available free online to all readers.

- The discussion requires some further analysis of the results and links into the detailed context of the study location.

P. Additional discussion of the results relevant to the context of the study have been added in the Discussion section.

Some minor amendments are suggested as follows:

Abstract - Reconsider the objective statement, not consistent with the rest of the paper and conclusions

Q. An additional objective has been added to bring in line with conclusions

Background - Suggest defining triage.

- Page 3, line 29 suggest rephrasing to "if a diagnosis of TB could be excluded using a triage approach" or "some of the non-TB cases could be excluded"

R. The background has been modified and now contains a definition for triage

Methods - In paragraph 1 I suggest removing phrase "which potentially could be performed.....allocated to individual or combination of characteristics."

S. The phrase has been deleted

- It may be helpful to clarify the flow of TB cases through the system at a hospital i.e. hospital attendees with symptoms > triage > presumptive TB > diagnostic test > case and started on treatment
T. Some additional comments have been added in the Methods. This is also detailed in the description that goes with Figure 2.

- State how many different triage and diagnostic algorithms were tested in total

U. For clarity this statement has now been added to the last paragraph of the background-

This study investigates the use of operational modelling to predict the impact of seven potential alternative approaches to triage (including no triage – base case), with or without X-ray and in combination with the Xpert diagnostic test. The projected outcomes were compared to a base case of sputum smear microscopy without triage or X-ray. -

i.e. 7 triage approaches x 2 X-ray approaches = 14 compared to a base case of sputum smear microscopy.

- Suggest moving information regarding data from PROVE-IT study to earlier in the section on Operational Model so the section is outlined as such: type of model, the data required to set up model, the various interventions tested Results - Consider rephrasing sentence on page 6, line 6-9

V. The Methods section has been totally restructured. The reviewer’s comments have been taken into account in this restructure – thank you.

- Suggest moving phrase on page 7, line 4/5 for further investigation to the discussion

Discussion - Page 8, line 44/45, suggest rephrasing to "add-on test for all with positive SSM"

W. The first comment above has been moved.

We have often seen Xpert used as an add-on test for smear negatives so we don’t think the suggested change suggested is appropriate.

- Page 8, line 50/51/52, it would be interesting if the author included a clarification as to why the number of TB patients starting treatment would be reduced rather than just stating the fact.

X. This has been added.
REFERENCES

