Author’s response to reviews

Title: Investigating spillover of multidrug-resistant tuberculosis from a prison: a spatial and molecular epidemiological analysis

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Version: 1 Date: 04 Jun 2018

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It below and formatted version is uploaded as supplementary file 1 or revision1

Response to Reviewers’ Comments:

We thank Editor Diana Samuel and the two expert referees for providing valuable feedback to our manuscript. The updated version of the manuscript is greatly improved due to the changes suggested by the reviewers. Below, we provide a point-by-point discussion of the revisions. We have uploaded a tracked changes version of both the main manuscript and the supplement in order to facilitate review of the proposed changes.
Diana Samuel:

Comment #1: In your “Authors’ contributions” declaration, authors JLZ and JRA are solely credited with revising the initial draft. Please note that, in accordance with guidelines set out by the International Committee of Medical Journal Editors (ICMJE), this is not sufficient to qualify for authorship.

Response #1: We apologize for this oversight. We have updated this information to fully reflect each coauthor’s contribution to this manuscript. Please see the “Authors’ contributions” Section for full details.

Comment #2: Could you please include the reference/approval numbers for both your institutional- and ethical approval.

Response #2: This information has been added to the text in “Ethics approval and consent to participate” Subsection of the “Declarations” Section.

Reviewer 1:

Comment #1: (pg.10) Prior specification involves default priors, e.g., inverse gamma (0.01,0.01) that is not consensual for variance components. Thus, a sensitivity analysis of the hyperparameters is welcome (see comments in Gelman, 2006).

Response #1: Thank you for this suggestion. Following the guidelines of Gelman (2004), we have rerun the final model (Gaussian Spillover Risk) using Uniform(0, 100) prior distributions for the two standard deviation parameters (σ_δ and σ_w). Please see the “Prior specification” Subsection of the “Methods” Section for full details.

The main results were robust to the choice of prior distributions for these parameters. The spatial range of spillover of MDR-TB risk from the prison was estimated to be 5.29 kilometers in the sensitivity analysis versus 5.47 kilometers in the main analysis. The range of residual spatial correlation was estimated to be 0.11 kilometers in the sensitivity analysis and 0.13 kilometers in
the main analysis. Overall, the results suggest that our understanding of the impact of the prison and of potential local transmission on MDR-TB risk in the community is relatively consistent across both sets of prior distributions. Please see the “Molecular analysis” Subsection of the “Results” Section for full details.

Comment #2: (pg.10) Have you used any R-package for executing MCMC sampling? If so, inform us about it/them at least in the supplementary material.

Response #2: No, we did not use any specific Markov chain Monte Carlo (MCMC) packages to perform posterior sampling outside of the usual random number generators for specific probability distributions. Instead, we developed our own R code to fit the model due to the complexities of including a spatial change point in the model specification (i.e., standard MCMC packages within R could not be easily adapted for our use).

Comment #3: (pg.11 or Table S1) Spillover risk analysis is made from a model that was selected based on only one measure (WAIC). That is limited since other measures are easily implemented via MCMC sampling and are more suitable for evaluating the model predictive power; e.g. Conditional Predictive Ordinate (CPO) (see e.g. Gelfand, 1996).

Response #3: Thank you for this suggestion. We now include Dk alongside Watanabe-Akaike information criterion (WAIC) in Table S1 (Additional file 1) for making model comparisons. Dk is a posterior predictive model comparison tool that focuses on the predictive performance of competing methods, while WAIC focuses more on the explanatory ability of different models. Overall, the two metrics provided consistent conclusions regarding the improvement of the Exponential and Gaussian Spillover Risk models over the other competing options. We have updated the text in a number of locations to reflect these changes:

“Spillover risk analysis” Subsection of the “Methods” Section;

“Spillover risk analysis” Subsection of the “Results” Section;

Table S1 of “Additional file 1”.

Comment #4: (pg.12 or Table 2) There is no information about inferential results on variance components. That is important for assessing the spatial unobserved heterogeneity indeed present in the data.

Response #4: Thank you for this suggestion. We now add inference for the variance component for the spatial random effects as well as for the regression parameters in Table 2.

Comment #5: (pg.13-14) I wonder if your identification of eight unique spatial clusters makes sense as six of them have only two patients (Table S2).

Response #5: Our identification of eight unique clusters was driven by the statistical inference for the spatial random effects and the estimated spatial range of residual spatial correlation. The primary benefit of this definition is that it is completely automated and data driven, rather than including a subjective component. However, if a user was interested in clusters with more than two patients, then the original findings could easily be subset to those clusters of interest. Clusters that include only two patients could still represent cases of multidrug-resistant tuberculosis (MDR-TB) transmission, and therefore, be of interest to some readers.

Comment #6: (pg.15-16) I welcome the authors in stating several limitations of the study. But I expect to read some discussion about the ecology fallacy since this spatial data analysis focuses on both individual-level and patient-city-block observed information (see e.g. references within Banerjee et al., 2014).

Response #6: Thank you for this suggestion. We have added some information about this potential limitation in the “Discussion” Section.
Reviewer 2:

Comment #1: Control group. The control group in this analysis is patients who have tuberculosis that is not MDR, presumably as a proxy for the general distribution of the population. Does this therefore assume that the spillover risk from the prison is confined only to MDR patients and not to other types of TB? Or, if we assume that this spillover effect is being shown over and above any spillover effect from all types of TB, then the MDR effect is more striking. The limitations of using other TB patients as the denominator population should at least be raised in the discussion.

Response #1: Thank you for this comment. The reviewer is correct that the control group is the group of TB patients who do not have MDR-TB. However, we do not intend for this control group to represent the general non-TB population. Instead, our interest was in identifying factors that are associated with increased risk of MDR-TB among individuals with active TB. Therefore, this work does not address questions about the general spread of TB from the prison location (and in identified hotspots across the community). The focus of the statistical modeling is on MDR-TB risk, conditional on the fact that a person has TB.

Comment #2: Table 1 - summary of patient characteristics. This table should include the numbers of patients in each group, rather than just the proportions. The numbers calculated form the proportions do not tally up with numbers quoted in the text - the results state that "among the 40 inmates with TB, 17.5% have MDR-TB compared to 10.2% of individuals in the general population." However, the table implies that there are 0.04*164=6.5 prisoners with MDRTB and 0.02*1423=28.5 prisoners with non-MDRTB. 6.5+28.5. This gives us a total of 35 prisoners, not 40?

Response #2: Thank you for this suggestion. We have added the requested numbers to Table 1. The issue you observed is due to the rounding of the presented proportions. Now that the counts are included in the table, this confusion should be removed.
Comment #3: The figures should have a scale in km, not just the lat/long values - this would help when interpreting the ~5 km estimated spillover effect from the prison.

Response #3: Thank you for this suggestion. We now include a kilometer scale to each of the spatially referenced figures (Figures 1-3, Figures S3-S5) to improve interpretation of the plots.

Comment #4: In figure 1, the selected colours (red/ grey/ blue) are (at least for me) quite difficult to look at. The legend should explain what the black lines represent (city block?).

Response #4: Thank you for this comment. We have updated the colors in Figure 1 to avoid (as much as possible) color combinations that may be difficult for colorblind readers: red/gold/blue. We have also added the information about the black lines in the Figure 1 legend (they represent within region district boundaries).

Comment #5: Figures 2 and S4 are the same but one for patients with previous TB treatment and one for patients without previous TB treatment. The results say that these figures highlight the large difference in risk between patients with and without history of TB treatment. However, I found the differences between these two figures hard to interpret because the colour scales are different.

Response #5: Thank you for this comment. We have updated Figure S4 so that it is on the same scale as Figure 2.

Comment #6: Results - molecular analysis section. If I have understood this correctly, this section compares: a. Number of MDR-TB patients residing within the spillover region who share a strain type with an MDR-TB patient in the prison as a proportion of number of TB patients living in the spillover region = 9/467; b. Number of MDR-TB patients residing outside the spillover region who share a strain type with an MDR-TB patient in the prison/ number of TB patients living outside the spillover region = 7/1080. I think that a more natural comparison
would be to restrict the denominator to MDR-TB patients as well - i.e. to compare the proportion inside and outside spillover areas of MDR-TB patients who had prison links. The current analysis looks at two factors - MDR and prison links - whereas restricting to MDR patients would enable investigation of prison links specifically.

Response #6: Thank you for this comment. You are correct about the test currently being performed in the manuscript (9/467 vs. 7/1,080). Based on your suggestion, we also subset the denominator to only those patients with MDR-TB. The new comparison becomes 9/35 (25.71%) vs. 7/89 (7.87%) with a p-value from a two-sample test of proportions equal to 0.008. Therefore, there is a statistically higher proportion of MDR-TB patients residing inside the estimated prison spillover buffer who share a common strain with an inmate compared with MDR-TB patients residing outside of the prison spillover buffer. This information has been added the Abstract as well as the “Molecular analysis” Subsection of the “Results” Section.

Comment #7: Background, first sentence - this should be referenced.

Response #7: We have added the following reference for this sentence: “Global tuberculosis report 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NCSA 3.0 IGO”. Please note that we have also changed the relevant statistic to 490,000 estimated incident cases for 2016 based on updated information. This information can be seen in the “Background” Section.

Comment #8: Average socioeconomic status of city block. I think that this has been included in the model as an individual-level effect. Could the authors discuss if they considered it as a group (city block) level effect.

Response #8: Thank you for this comment. Yes, we included a categorical version of city block-level average socioeconomic status in the models. While this variable differed for individuals in separate city blocks, individuals residing in the same city block received the same value for this predictor. So effectively the variable has been included as a group-level predictor of an individual-level response. As mentioned by Reviewer #1 (Comment #6), this could lead to
ecological bias. Therefore, we have included this as a potential study limitation in the “Discussion” Section.

Comment #9: Table 1 - are population density and distance to prison the mean values?

Response #9: Yes, the presented values are means of the variables. We have added this information to the Table 1 caption.

Comment #10: How many of the MDR-TB patients shared residences?

Response #10: In our study population, 115 patients out of 1,587 share a residence with another patient. There are 40 prisoners located at the same prison location, one group of 4 co-located patients, one group of 3 co-located patients, and 34 groups of 2 co-located patients. Some of this information has been added to the “Data description” Subsection of the “Methods” Section.

References: