Reviewer’s report

Title: The impact of drug resistance on the risk of tuberculosis infection and disease in child household contacts: a cross sectional study

Version: 0 Date: 21 Feb 2017

Reviewer: Sanghyuk Shin

Reviewer’s report:

Overall, this is a well-written manuscript about an important public health topic. However, a number of major issues need to be addressed:

1. Page 9, Lines 42-43. TB disease among child contacts is defined as multiple categories, but the Results section reports only disease vs. no disease. Please explain whether how the final binary variable was defined.

2. The statistical analysis section does not mention accounting for household-level clustering (e.g. using GEE or mixed effects modeling). Assuming there are some households with multiple children exposed, one cannot assume independence between observations. Please explain why within-household clustering was not accounted for in your analysis.

3. Page 10, line 17 states that a DAG was used to identify variables a priori for the multivariable models. Typically, this implies that all of the variables that conceptually should be included in the final models were, in fact, included. However, not all of the variables reported are included in Table 2. Please clarify the process by which variables were selected for inclusion.

4. Please justify the inclusion of smear positivity in the final model for infectivity. It seems that application of DAG would have identified smear positivity as a descendent of MDR TB and, therefore, in the causal pathway between MDR TB and infection. Conditioning on smear positivity could, therefore, attenuate the overall relationship.

5. IPT is mentioned in the statistical analysis section (page 10, line 30), but not described in the results or the table. While this should not affect the findings (presumably, children exposed to MDR TB were not given IPT), it would be of interest to include this data in Table 1. Please also mention clinical care, if any, provided to children exposed to MDR TB (i.e. preventive therapy, active follow-up, etc.)

6. Please explain why children with previous TB treatment were included in the analysis for infection. It seems that it would be difficult to interpret TST results among such children. Many of those would, presumably, be misclassified as new infection.

7. The Discussion section provides too much detail about HIV infection and other factors, and not enough discussion about the main finding pertaining to the relationship between MDR TB and infection/disease. Please expand your discussion of the relevant literature listed in page
15. lines 27-45 to improve contextualizing your results. For example, how is the design of your study similar or different than the previous ones? How do your findings extend current knowledge? What are possible reasons for disparate findings in the different studies and settings?

8. Page 15, lines 7-10. Why did you choose not to include incident TB?

9. Page 16, lines 17-22. Please discuss the possible impact of the different inclusion criteria on the infection analysis. It seems that it could have led to differences in length of exposure, which could have biased the infection analysis towards increased effect.

10. In the Limitation section, please include the following:

   a. Was time since symptom onset of the index patient recorded? This information would help better understand the causal pathway by which MDR TB affects infectivity.

   b. It seems that MDR TB and DS-TB patients were drawn from different neighborhoods/populations that could have had different levels of TB transmission (as suggested by higher prevalence of previous TB among child contacts). Please describe how this could have affected the results.

   c. Related to above, was there information about previous TB history among other household members?

   d. While controlling for BCG is appropriate, given that nearly 100% of DS-TB group and >80% of MDR TB group had BCG, I don't think controlling for this in the analysis eliminates the possibility of spurious findings introduced by misclassification.

11. Given the limitations described above, please remove the statement about implications in the Conclusions (Page 17). Instead, please describe how your findings inform the development of future studies that can more definitively answer this question.

12. Figure 2 seems redundant and not helpful. I suggest removing it from the manuscript.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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