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: 19 Feb 2017

Reviewer: Ian Kitai

Reviewer’s report:

This study examines the influence of sensitivities of the source case strain on the prevalence of tuberculosis infection and disease in young childhood contacts of adults with confirmed drug sensitive (DS) and multidrug-resistant (MDR) tuberculosis. The authors combine data from two community-based contact investigation studies. At the time of evaluation, 6.6% of MDR-TB and 8.7% of DS-TB contacts had TB disease. After adjusting for co-variables, MDR-TB exposure was associated with less disease. In addition TB infection seemed less likely following exposure to drug sensitive cases than after MDR exposure. The authors use these data to suggest potential differences in "relative fitness" of drug-sensitive and drug-resistant organisms as applies to both infection and disease in young children.

Overall, while these data may be subject to a number of confounding factors, they are likely the best possible data available in this field for a while, and I believe are certainly worthy of publication. Accumulating these cohorts and evaluating them in a standardized way using clinicians from a single center would be difficult in most settings. The authors also qualify and discuss the limitations in detail. While the conclusions are not definitive they add to the limited literature in this field. They also help point to the fact that MDR strains are probably, at a minimum, no more likely to cause disease in young children than DS-strains.

I have a few general comments:

INTRODUCTION

The introduction could be worded more concisely. For instance the first sentence could read "in 1953 Middlebrook and Cohn demonstrated that mycobacteria....

Page 7 lines 1- 30 could be reworded to make the points a little more clearly. As far as I can ascertain the major points are:

1. Mathematical models that assume fix fitness cost suggest that drug resistant TB will remain a localized problem.

2. Models that include heterogeneity in levels of fitness point to global spread of the drug resistant TB epidemic.
3. Understanding fitness of drug-sensitive and drug resistant organisms is therefore important.

Methods: it's unclear to me whether the clinicians assessing the different cohorts were the same or different. Some indication of this could be given in the methods or the results. If they were significantly different that is a potential confounder that should be acknowledged in discussion.

RESULTS:

Children suspected disease had undergone microbiological testing. Although differences would be subject to a very large number of confounders and the numbers will be small it would be worth noting what proportions of DS and MDR contacts with suspected disease had cultures and how many had positive cultures. This is NOT essential if the data are difficult to retrieve but would be helpful. Certainly equal proportions of culture-positive disease in both cohorts or more culture positive disease in the DS-exposed children would help make the authors' case around fitness.

Discussion.

The authors discuss limitations in detail. One limitation not discussed is that the clinicians were not blinded to the sensitivities of the index strain. Since treatment of DS-disease is shorter and involves less toxicity than treatment of MDR disease it is possible that clinicians would be unconsciously more inclined to label children with questionable radiographic abnormalities as having disease if the strain was DS than if it was MDR. This, again, is a limitation that does not argue against publication of these data but it should be acknowledged in some brief form.

Tables.

Table 1 notes a * for p<0.05, but there are no characteristics that are flagged as attaining this significance. Is this an omission? Perhaps it should be dropped if there are no variables where the differences attain this level of significance.

OVERALL:

Overall I think this is an important study and the analysis significantly adds to the limited literature in this field, and the authors should be complemented on doing the secondary analysis.

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

Yes

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

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**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

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

'I declare that I have no competing interests
I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.