Reviewer's report

Title: Dose-Response Models for Selected Respiratory Infectious Agents: Bordetella pertussis, group A Streptococcus, rhinovirus and respiratory syncytial virus

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Reviewer: Carl Morrow

Reviewer's report:

The authors gather together data to generate dose response curves for four respiratory illnesses that are relevant to human public health.

The paper is clearly written and I feel that it is important to publish weak to negative findings as these highlight the gaps in our current knowledge. There are, however, some serious limitations to the work that would need to be resolved prior to the paper being acceptable for publishing. The authors do need to be careful not to oversell the results presented.

As a general comment and disclaimer, I am not an expert in the field of modelling and QMRA and also am not in a position to comment on the mathematics and statistical treatment of the data.

Major Compulsory Revisions:

General comments:

1. The authors are rather cursory in their comments about the airborne route of infection of humans which I feel should be expanded as it is evident that very little is known about the mechanisms of airborne transmission and, in many cases, it is even unclear with many of the microbes being discussed whether this is indeed the route of transmission. Further, it seems to me that the study of dose response curves becomes very complicated when there are multiple routes of infection (contact, large droplets and small droplets that are airborne) and this complexity is not discussed. With the diseases being studied there is a range of infection mechanisms at play (eg. Results, Respiratory Syncytial Virus, paragraph 1) and the differences between the different infective agents are not explained.

2. QMRA involves four steps (Hazard identification, Dose response, Exposure assessment and Risk Characterisation) this paper is only focusing on step two which is an important contribution to understanding but it needs to be carefully stated that these results as they stand are not going to allow for quantitative assessment of workers and community members as well as the effectiveness of infection control interventions.

3. The acceptability of use a mouse model respiration to assess dose response on humans concerns me. What evidence is there that this assertion is
supported?

Major Compulsory Revisions:
Specific comments:

Abstract
4. The abstract needs to be rewritten to more accurately align with the content of the paper. I feel that the limitations of the results are poorly reflected in the abstract.

Abstract, Background, sentence 1
5. I would add “and exposures” to “Dose response functions are needed…”

Background, paragraph 1
6. Other reasons for the limited application of QMRA to respiratory diseases are the lack of base data and understanding of the mechanisms of transmission.

Background paragraph 3
7. The last sentence is a very broadly sweeping statement of the range of routes that respiratory infections can occur. Some references to support this would be good and clarity on whether this is describing tuberculosis transmission or respiratory infections more generally.

Results, Bordetella pertussis, paragraph 2
8. The authors talk about excluding data from aerosolised B pertussis due to its lack of relevance to human transmission but accept that instillation into a mouse’s nose is a good surrogate for human modelling. Evidence or discussion around the appropriateness of this opinion would help a somewhat uninformed sceptic like me.

Results, Rhinovirus
9. This whole section highlights the complexity being investigated (Respiratory tract temperature, contact and airborne routes of infection and host serum antibody levels) but this does not get discussed once the models have been defined nor is the relevance of the models in the light of the complexity being faced.

Results, Respiratory Syncytial Virus, paragraph 1
10. Evidence is clearly provided that RSV does not use the airborne route for infection but then the authors appear to ignore this evidence and go ahead with their analysis.

Discussion
11. I feel an explanation is needed for the observation that models derived from different experiments on the same disease organism were dramatically different. Using B pertussis as an example, in figure 1 the 50% probability of infection occurs for an inoculation of between $1e+06$ and $1e+08$ CFU while in figure 2 50%
infection occurs at approximately 1e+02 to 1e+04. Why does there not seem to be a general dose response for each organism and what does this mean in terms of QMRA? This limitation needs to be taken into account in the last sentence of the discussion that claims that “With the new dose response functions presented herein QMRA can be applied…”

12. There is no review of the limitations or confounders of the results presented. These need to be discussed. This would include routes of infection; diversity of models for the same infectious agent; limited understanding of exposure assessment and so these results may provide progress towards the QMRA of these diseases but we are still not in a position to have them defined.

Conclusions

13. This section is just a review of the issues at hand and does not provide any answers as a result of the work presented in the paper. I think it needs to be written again to draw out the most important observations made in the paper.

Minor Essential Revisions

Abstract, Methods, second sentence

14. Should “fit” rather be “fitted”?

Background Paragraph 2

15. The first sentence needs rewriting

Background Paragraph three

16. Another limitation of the Wells-Riley model is the assumption of steady state conditions. This is discussed and resolved in Rudnick SN, Milton DK (2003) Risk of indoor airborne infection transmission estimated from carbon dioxide concentration. Indoor Air 13(3): 237–45

Methods, Dose-response model fit and evaluation, First sentence

17. Should “fit” rather be “fitted”?

Methods, Dose-response model fit and evaluation

18. This study relies on advanced statistical analysis but no details of the statistical packages used for the analysis are given. Please supply these.

Methods, Data Selection

19. No details are given on how the studies used in the analyses were identified. Please provide information on search criteria used in which databases and how exhaustive this search process was. Was there a systematic review process, were all identified studies accessed and assessed for the conditions of inclusion and did each author review the papers independently?

Discussion, paragraph 2, line 4

20. “does” should be “doses”
References, 3
21. Incomplete, no volume number of page numbers

References, 52
22. Incomplete, no volume number of page numbers

Discretionary revisions
Discussion, last sentence
23. “With the new dose response functions presented herein QMRA can be applied...” should have the comma added “With the new dose response functions presented herein, QMRA can be applied...”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests