Reviewer’s report

Title: Modeling the impact of tuberculosis interventions on epidemiologic outcomes and health system costs

Version: 2  Date: 17 November 2014

Reviewer: Ashleigh Tuite

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Major Compulsory Revisions

1. The background section lacks references.

2. Overall, I think the model description would benefit from additional description (this could be included in the supplementary material). In particular, additional details on how primary active cases are generated should be provided. It seems that annual risk of infection is held constant over the 20-year period and that there is no direct feedback between active cases and incident cases, which is why the projected active cases in the cohort is constant regardless of intervention (except for the scenario where reactivation in HIV-infected individuals is reduced). Is this correct? Active cases are able to generate secondary cases, which are another model output, but these cases do not in turn enter the model (in terms of costs and outcomes)?

3. Related to the previous point, additional details about the contagiousness/secondary cases part of the model are needed; specifically, how are people getting infected? There are estimates of period of contagiousness for active cases who aren’t diagnosed and those who start treatment but die/cure spontaneously, but there doesn’t seem to be a parameter describing the amount of transmission/number of secondary cases generated per active case/per unit of time.

4. Probabilities of patients experiencing delays of 1 year are calculated by dividing average delay time in days by 365. I do not understand the logic behind these calculations and no reference is provided to suggest that this is a valid approach. It is typical to assume an underlying distribution (e.g., exponential, Weibull) and use this to calculate probabilities. Although the distribution of delays is undoubtedly skewed, assuming such an extreme distribution seems unwarranted in the absence of supporting data. For instance, assuming that the majority of cases experience no delay in seeking care for active disease, while some percentage experience a 1-year delay would seem to have very different implications for preventing TB transmission than a scenario where most individuals experience a modest (but non-zero) delay.

5. Given that most of the time delays presented are of the order of days or months, it seems like using a monthly time-step might be more appropriate for this model. Is there a reason that the authors opted for a one-year time step?
6. The authors should provide some sort of validation as part of the results. Baseline conditions show ~2/3 of cases die and very low cure rates – how does this compare with reality? Are these baseline estimates realistic?

Minor Essential Revisions

7. The definition of drug resistant TB in the methods is unclear and seems inconsistent with what is presented in the tables of parameter values. It seems that the authors are considering MDR-TB cases only (based on the parameters presented), but this does not seem to be what is stated in the methods. This should be clarified.

8. In Table S1: The “probability of dying if not undiagnosed” parameter, should be “probability of dying if not diagnosed”? For the TB pathogenesis /natural history of active TB parameters, there are no units provided.

9. It’s unclear how the delays are implemented. As I understand, an active case has a certain probability of experiencing a delay during different stages of the diagnosis and treatment process, during which time they remain contagious. Are these delays additive? That is, if a case has a delay in seeking care, and delay in diagnosis, does that mean he will be contagious for two years?

10. I’m not sure how meaningful it is to present intervention costs without taking into account cases averted – for instance, the results show that enhanced diagnosis will result in the greatest increase in health system costs in Indonesia, due to more people being on treatment, but will also reduce secondary cases, which will have downstream impacts on costs. This should be included as a limitation.

11. Results refer to figure 2, but there’s no figure 2 included.

12. Some additional explanations of cost would be helpful. How are treatment costs for those lost to follow-up calculated? Was discounting used and if not, why?

Discretionary Revisions

13. Given the complexity of model, I think it would be useful to present a schematic of the possible decisions made during a patient’s trajectory from initial infection to possible diagnosis and treatment. Although it is possible to piece together the process from the parameter tables, I think having a schematic of the decisions and branch points would greatly help readers understand the processes being modeled.

14. The listing of the intervention names in the text of the methods isn’t very informative. The authors could either expand upon how the specific interventions map onto points in the model/model parameters, or just refer to Table 1, where this is laid out nicely. It’s also doesn’t seem necessary to explain in the methods why additional interventions weren’t evaluated – this text could be moved to the discussion.
15. Could combine Tables 2 and 3 (and Supplementary tables 8 and 9) – lots of repeated information.

16. Why not include the (combined) results of Tables S8 and S9 in the main text? It’s interesting to compare the results in a high HIV burden country to the other countries. Why did the authors not look at the impact of progressive addition of interventions in Mozambique as they did for the other countries?

17. The authors present seven different programmatic interventions in the methods, some of which include combinations of interventions that impact multiple model parameters, but the results mostly focus on the impacts of individual components of the bundled interventions. I found this a bit puzzling. It might be helpful to explain why this approach was taken.

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

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.