Reviewer's report

Title: Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost analysis

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Reviewer: Kevin Schwartzman

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This is a very nicely written manuscript which compares the costs of several screening strategies for latent tuberculosis infection (LTBI) in TB contacts, using a decision analysis model. The key finding is that cost savings related to dual testing (i.e. tuberculin skin test followed by interferon-gamma release assay) vs. single testing (TST or an IGRA) are attenuated once costs of future active TB and isoniazid-related hepatotoxicity are considered in the analysis. It is surprising to note that as stated by the authors, most earlier analyses have not considered these “downstream” costs, which should be essential to any such evaluation.

Major Compulsory Revisions

1. The key limitation of this analysis is that it is a pure cost comparison (“cost minimization analysis.”) This would be more appropriate if clinical outcomes related to the various strategies were equivalent, which is not the case. The consequence is that cheaper strategies may be associated with poorer clinical outcomes, but this cannot be formally captured with the current analysis. In other words, the fewer cases of LTBI detected, the lower the cost—but the fewer cases of active TB prevented. Indeed, the most extreme interpretation would be that it is cheapest to not screen contacts at all. The authors hint at some concerns of this nature: for example, on p. 9, they state that “A lower test sensitivity…reduces the cost of that strategy as fewer cases of LTBI are detected and treated.”

In their discussion section, the authors need to state very clearly that a cost minimization analysis, when clinical outcomes are not in fact equivalent, can potentially lead to distorted recommendations. On p. 16, they do mention that a full cost-effectiveness analysis was not performed, but they need to better identify the limitations of their current approach. Notwithstanding the authors’ comment on p. 17, it is in fact possible to model the “effectiveness” of the IGRA by adding assumptions about future likelihood of active TB to those already made about costs and test properties. Indeed, Marra and colleagues have just published such an analysis in the December 2008 issue of the International Journal of Tuberculosis and Lung Disease, and this would be a relevant addition to the reference list.

2. One would anticipate that any serial testing strategy involving two tests with imperfect sensitivity will identify fewer cases of LTBI than will a single test, so it will be cheaper from that standpoint. However, the most often cited advantage of
the dual testing strategy is the reduction in “false positives” related to the relatively poor specificity of the TST alone, particularly in BCG-vaccinated individuals. This point should be emphasized in the discussion.

3. Some clarification is needed with respect to Figure 3. As submitted, the figure suggests that the probability of true LTBI after 1) a positive TST and then 2) a positive IGRA is simply the positive predictive value of the IGRA. In fact, it must be the positive predictive value of the IGRA, GIVEN A POSITIVE TST, which is higher than the PPV of the IGRA alone. This point needs to be clarified, with parallel considerations for the other branches of that tree.

4. Finally, the authors limit the time frame of their analysis to two years—the period of greatest risk after acquisition of TB infection. On the one hand, the analysis assumes that all persons with true LTBI have acquired it as a consequence of their recent TB contact, and hence have a 2.5% annual risk of active disease. This assumption is difficult to justify, as many foreign-born contacts will have longstanding LTBI acquired in their countries of origin. This assumption would tend to overestimate the probability and cost of active TB among the target population, and should be acknowledged as such. On the other hand, benefit accruing from prevention of TB cases further into the future is not modeled. There are certainly sufficient data to permit this type of modeling, as other authors have done. The analysis would benefit from a better accounting of future active TB cases and related costs, with suitable discounting, although the present authors do acknowledge this limitation (p. 13).

Minor Essential Revisions

1. The perspective of the cost analysis (UK health care system) should be stated explicitly.

2. The analysis should inflate/deflate costs to a single, common year; that year should be stated, and the indicator used to inflate/deflate costs should be cited.

3. The description of the methods should indicate the software used for the model.

4. The sensitivity analysis assumes equivalent efficacy for 6 and 9 month courses of isoniazid. North American treatment guidelines are based on Comstock’s reanalysis suggesting superior efficacy for 9 months vs. 6, but comparable efficacy for 9 and 12 months. If the authors disagree with this premise, then they should state this up front. But in that case it seems pointless to model (or prescribe) a 9 month treatment course--with assumed equivalent efficacy to 6 months, but increased cost and toxicity risk.

Level of interest: An article of importance in its field

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.