Author's response to reviews

Title: Tuberculosis screening of travelers to higher-incidence countries: A cost-effectiveness analysis

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Version: 2 Date: 5 May 2008

Author's response to reviews: see over
May 5, 2008
BMC Public Health
Editorial Office

Re: MS: 8601798761798094--Tuberculosis screening of travelers to higher-incidence countries: A cost-effectiveness analysis

Michael Tan, Dick Menzies and Kevin Schwartzman

To the Editor:

We are submitting a revised version of the above-named manuscript, which incorporates the suggestions and comments of the three reviewers. As before, this manuscript has not been submitted elsewhere for publication, and none of the authors has any conflict of interest with respect to its contents. All authors have read and approved the final version of the manuscript.

We thank the reviewers for their excellent and constructive comments. We have pasted their comments in bold type, with our responses immediately below. Please see the following pages.

Sincerely,

Kevin Schwartzman MD, MPH [Corresponding author]
On behalf of Michael Tan, MSc and Dick Menzies MD, MSc
Reviewer 1:

1. Given the levels of drug resistance and MDR-TB in the three high burden countries included in the cost-effectiveness analysis of the screening strategies, why was the decision taken only to consider drug susceptible TB? For example, Ferdinand et al (2003) reported 8.9% MDR in Haiti, 1995 survey data in Dominican Republic reported 19.7% MDR, and 1997 survey data from Mexico reported 22.4% MDR. This could have a significant impact on the cost of treatment, effectiveness of treatment of cases, as well as prophylaxis. Reasons for exclusion of drug resistance data should be discussed.

We did in fact account for drug resistance in all three countries, although we did not make this point clearly enough in our methods section. We assumed that persons who became infected in those countries would have the same probability of resistance to isoniazid as the local population, based on drug resistance data for active TB cases. The efficacy of isoniazid treatment for latent infection was assumed to be zero in the presence of isoniazid resistance (whether the underlying resistance pattern is isoniazid mono-resistance or MDR). This point has been further clarified in table 2 (Model Assumptions), and references for drug resistance prevalence are provided. We have also added a sentence to this effect to the Methods section, under the heading “Travelers.”

The US cost survey on which we based our cost estimates for inpatient treatment of active TB in fact included a mixture of drug-sensitive and MDR cases the exact proportion of MDR cases was not explicitly stated by the authors. (See Taylor et al, Causes and costs of hospitalization of tuberculosis patients in the United States. *Int J Tuberc Lung Dis* 2000; 4:931-939). We agree that the survey by Taylor and colleagues may have underestimated the impact of MDR cases on overall TB costs, depending on the prevalence of MDR in their patient sample compared to that expected among travelers. However, there are limited data on the cost of MDR cases, so we felt it reasonable to use the data from the Taylor survey and account for the potential contribution of MDR cases in this manner.

Finally, with an increasing prevalence of drug resistance, all the strategies considered become less effective, and less cost-effective, but the single post-travel test remains the preferred option.
Reviewer 2:

1. Is the question posed by the authors well defined?
The question of cost-effectiveness in terms of identifying currently infected individuals who travel to other countries is well-defined in this paper due to the careful assessment of the epidemiological and clinical features of tuberculosis in the Americas. Nevertheless, one of the features, the costs of the TST test in the U.S.A., renders this investigation "restricted" to the U.S.A. and can not be viewed as a global interest.

We entirely agree with the reviewer that the perspective used was not a global one; we did not intend to suggest otherwise. Our goal was to consider potential approaches for screening of travelers from high-income, low-TB incidence countries who make prolonged visits to high-incidence countries. This issue has been a point of debate for Canadian public health and infectious disease authorities. We in fact ran the analysis for both Canada and the US, using entirely Canadian cost data on the one hand (for skin testing, TB care, and all other elements of the algorithm), and then US cost data on the other hand, as reported in the manuscript. We elected to focus on the US data because we felt this would be relevant to a broader readership than the Canadian data. We did not report detailed assumptions and results for both countries simultaneously, as we felt this would be overwhelming to readers. Similarly, to substitute the estimated cost of the TST in other countries would also imply the substitution of all other cost data (for other tests, TB care, etc.) and we did not have these cost data at hand (e.g. for European countries). Again, we did not wish to overwhelm readers. In principle, the analysis could be rerun with an alternate set of cost data. See further discussion below.

5. Are the discussion and conclusions well balanced?

From the points of view of travel on the American continent, this is a well balanced study. Nevertheless, there is a severe danger that the conclusions about the low cost-efficacy of TB-screening by TST are not relevant -- and might remain disappointingly misleading -- for other parts of the globe for two reasons.

(i) In spite of the impressive algoritm and the high intellectual value of considering small details as well (for example discussing the potential loss of earnings due to attending the diagnostic service facility while undergoing TST and other diagnostic investigations), important wider significant issues (such as the loss of earning due to tuberculosis and the spread of infection in host environment within the local communities) remain incalculable and therefore do not feature in the equations.

In the manuscript as originally submitted, the discussion section included the following text:

“We limited the analysis to the perspective of the health care system, since we did not have reliable estimates for productivity losses and out-of-pocket costs associated with screening. Adoption of this perspective meant that lost productivity and patient costs related to active TB were ignored, but it also meant that we did not consider time lost from work to undergo
screening. Given the small number of active cases prevented, relative to the number of travelers screened, it is possible that incorporation of time lost from work would actually increase costs per case prevented.“ [p. 14]

We agree with the reviewer; we explicitly acknowledge the use of the health care system perspective as a limitation of our analysis, precisely because it ignores costs borne by patients such as lost earnings, often termed “lost productivity” as in the above paragraph. To make this point clearer, we have changed this term to “lost earnings” in the revised text. As for the spread of infection, we again agree with the reviewer. This is difficult to capture precisely, but we did model secondary transmission from returning travellers to other community members, as described on p. 8 of the manuscript, in the section entitled “Secondary Transmission.”

(ii) the high-cost of testing can lead to epidemiologically unjustified positions and conclusions. Two points are here: first, the costs in the U.S.A. are very high and these are unlikely to be repeated in Africa, Asia and Russia. Therefore in other countries the TB screening might become cost-effective. Second, these authors should publish this current paper in the U.S.A. -- and continue in collaboration with the World Health Organization to analyse the question where the TST (and interferon) costs are regarded as one of the crucial variables. This is to investigate that how low the bulk laboratory service costs need to drop in order to render the (essential and much wanted) TB surveillance cost-effective IN THE DIFFERENT REGIONS of the world.

The focus of this paper was purely on travellers returning to low-incidence countries—in particular, the US for reasons noted above. Our goal was not to evaluate the yield, cost, or cost-effectiveness of TB screening and surveillance activities in other populations or contexts. We agree that in higher-incidence countries the dollar costs of TB screening tests and TB care (in particular) will be substantially lower. In assessing various TB control activities in those countries, costs must be considered relative to income and buying power, and also in light of priorities for TB control. For example, abundant evidence indicates that screening for latent TB—even in persons at high risk for infection and for progression to active disease—should only be considered once prompt and effective treatment of persons with active TB can be guaranteed.

6. Are limitations of the work clearly stated?

Not. The author do not place sufficient emphasis to explain that their results are cost-dependent and therefore strictly U.S.A.-relevant (see comments above)

We have added the following as a limitation, in our discussion section (pp. 15-16):

“Our analysis was limited to travelers leaving from and returning to the United States or Canada, and used cost estimates from those countries. The expected costs of the four screening strategies for travelers from other low-incidence countries would vary according to the costs of the individual screening components and of TB care in those countries. However, if the relative costs of screening versus TB care are similar to those in the US and Canada, then the single post-trip test would likely remain the preferred option.”
7. Do the authors clearly acknowledge any work upon which they are building?

Yes. Still, a bit more emphasis (and hints about cost-comparisons) between the TST and the interferon-based assays published in their previous paper (Intern.J.Tb Lung Dis. 2007; 11: 16-26) is recommended.

We have added more explicit discussion about this issue to the discussion section, as follows:

“Use of an interferon-gamma release assay would be most relevant, and potentially cost-effective, for travelers born in countries where the BCG vaccination is administered repeatedly, as in Eastern Europe and the former Soviet Union. A single post-trip test with one of the newer-generation interferon-gamma release assays might be considered as an alternative in such travelers, to avoid potential confounding by BCG vaccination after infancy. However, a formal cost-effectiveness evaluation of this option was beyond the scope of the current analysis. Interested readers are referred to a recently published cost-effectiveness analysis which compared interferon-gamma release assays with tuberculin tests and chest X-rays for TB screening, among close contacts and immigrants. The analysis highlighted the potential utility of interferon-gamma release assays as confirmatory tests for latent infection, after positive tuberculin tests in persons from countries where BCG is repeatedly administered. [32]” [pp. 17-18]

8. Do the title and abstract accurately convey what has been found?

Yes, but the restricted relevance to the U.S.A. - with potentially opposite conclusions in other areas of the globe - should be a stated warning signal there.

We have reworded the abstract to emphasize that the analysis relates to travelers departing from and returning to the United States or Canada. We agree that the original wording did not make this point clearly enough.

9. Is the writing acceptable?

Excellent.

This reviewer suggests that this excellent and sensibly important paper should be published as an accompanied paper to their previous work in an American journal or in Intern.J.Tb Lung Dis. Then, as a next phase of investigation, they should alter the design and re-investigate the parameter "COST" as a variable in order to define the level of laboratory costs (as a potential 'higher volume' investigation) in order to render TB surveillance a cost-effective reality. This is a more sensible approach to the countries with restricted finances accompanied by devastating disease-patterns than regarding the 'COST' parameter in its artificially high level position as a standard "un-alterable" feature of this
epidemiological problem.

We are grateful for the positive feedback. We felt that BMC Public Health would be an accessible and relevant venue for our analysis.

We fully agree that TB control in high-incidence countries is a much more pressing problem. We have previously published other work addressing this issue, and will continue to do so in the future. Indeed, ongoing work by our group explicitly addresses the expected cost and yield of various diagnostic testing strategies for active and latent TB in high-incidence countries.

The present analysis was designed to tackle the specific question of screening for travelers, as outlined in our earlier comments. We believe we have addressed this question, in a manner that will hopefully be relevant to readers who provide medical care or guidance for travelers in this context.
Reviewer 3:

Reviewer's report:

This paper tries to answer a frequent question related to the risk of acquiring tuberculosis infection for travelers from low-incidence countries to high-incidence countries. Several policies have been proposed, but none was assessed in term of cost-effectiveness. This report clearly demonstrates that screening for latent infection (or disease) after the travel only is the most cost-effective policy. In this respect, it can help decision makers responsible for the surveillance of travelers, in particular professional travelers like health-care workers, members of technical cooperation agencies, Red Cross delegates, and others, who may have frequent contacts with potential TB index cases.

The only major limitation of this paper is the fact that the model is applicable mainly for travelers from countries where adults were not vaccinated with BCG, as it considers only the use of the tuberculin skin test (TST). The authors have mentioned in the discussion that, at least for travelers from countries where most adults were vaccinated with BCG, the use of Interferon-Gamma Release Assays (IGRA) would avoid the false positive test responses observed with the TST. This should also be stated in the abstract. Therefore, the model cannot be generalized and used, for instance, for travelers from European Countries, where most adults have been vaccinated at least once with BCG (even if the policies have changed during the last 20 years). The authors should clearly state that their model is not generally applicable without adaptations.

The abstract has been modified to reflect the reviewer’s suggestion, as follows:

“Conclusions: A single post-trip tuberculin skin test was the most cost-effective strategy considered, for travelers from the United States or Canada. The analysis did not evaluate the use of interferon-gamma release assays, which would be most relevant for travelers who received BCG vaccination after infancy, as in many European countries. Screening decisions should reflect duration of travel, tuberculosis incidence, and commitment to treat latent infection.”

We have also modified the discussion as follows:

“Our analysis was limited to travelers leaving from and returning to the United States or Canada, and used cost estimates from those countries. The expected costs of the four screening strategies for travelers from other low-incidence countries would vary according to the costs of the individual screening components, of TB drugs, and of TB care in those countries. However, if the relative costs of screening versus TB care are similar to those in the US and Canada, then the single post-trip test would likely remain the preferred option.” [pp. 15-16]

“Use of an interferon-gamma release assay would be most relevant, and potentially cost-effective, for travelers born in countries where the BCG vaccination is administered after infancy, as in many European countries. A single post-trip test with one of the newer-generation
interferon-gamma release assays might be considered as an alternative in such travelers, to avoid potential confounding by BCG vaccination after infancy. However, a formal cost-effectiveness evaluation of this option was beyond the scope of the current analysis. Interested readers are referred to a recently published cost-effectiveness analysis which compared interferon-gamma release assays with tuberculin tests and chest X-rays for TB screening, among close contacts and immigrants. The analysis highlighted the potential utility of interferon-gamma release assays as confirmatory tests for latent infection, after positive tuberculin tests in persons from countries where BCG is repeatedly administered. [32]” [pp. 17-18]

Minor comments:

1. Method: Screening by Chest X-ray is only useful for the detection of active disease. Why are clinical symptoms not integrated in this procedure (maybe asking the travelers for symptoms after return could also detect active disease).

We assumed that 27% of travellers with active TB would return from travel with symptoms (as cited in Table 2), and that any post-travel screening intervention would pick up all symptomatic travelers. We did not model a strategy involving a post-travel visit solely for symptom questionnaire, as the main goal of the analysis (and screening strategies) was the potential detection of latent tuberculosis.

2. It seems clear from the discussion that all travelers with a positive TST will be offered a course of preventive therapy. This should be mentioned in the Method section.

We have modified the first paragraph of the Methods section to make this point clearer; it is also addressed explicitly in Table 1. The added text to the Methods section is as follows:

“Depending on the strategy, some or all travelers diagnosed with latent TB were prescribed a nine-month course of isoniazid (Table 1).” [p. 6]

3. Do the authors consider offering a preventive therapy to travelers discovered with a positive TST BEFORE travel?

One of the TST screening strategies did involve the provision of treatment for latent infection identified before travel, as described in Table 1.

4. Results: The cost for older travelers increases also because the available time for a potential reactivation is shorter in elderly people compared with 21-year old travelers, as in the model.

We agree. The analysis used a 20-year time frame for all scenarios. The impact of screening and treatment of latent infection in older travelers is reduced because of competing mortality risks. Over a 20-year period, they are more likely to die of other causes before developing active TB, so the available time for potential reactivation is less, as stated by the reviewer. Older
travelers are also at higher risk of isoniazid toxicity. These points are addressed in our results section (p. 12):

“With older traveler age, the cost per case prevented increased. This reflected the increased background mortality rate, and the higher risk of side effects with treatment of latent infection.”

5. The authors consider that the completion rate for preventive treatment does not change the results of their model. What about the cost-effectiveness if the completion is zero?

As shown in Table 4 of the manuscript, the sensitivity analysis indicated that the lower the completion rate, the higher the incremental cost-effectiveness ratio for each screening strategy (i.e. the higher the cost per additional TB case prevented). Among the competing screening options, however, the single post-trip test remained the most cost–effective (lowest cost per case prevented, relative to no screening), across the range of completion rates. In the extreme case of zero completion of isoniazid treatment, the cost per case prevented would be infinite. In that case, the single post-trip test would be cheaper than the other screening interventions, while no screening would be cheaper still; none of these options would reduce TB morbidity.

6. Table 2: In many countries, 9 months of isoniazid cost much more than $25.- (this is a prize for generic drugs, which is not applicable in all countries).

We appreciate and agree with this point. In the discussion section, we have emphasized that the analysis focuses on travelers from the United States and Canada. As described above, we have also indicated that an analysis focusing on travelers from other countries would need to incorporate testing, drug, and TB care costs from those countries.