Reviewer’s report

**Title:** How much is TB Screening Worth? Estimating the Value of Active Case Finding for Tuberculosis in South Africa, China, and India

**Version:** 1  **Date:** 29 August 2014

**Reviewer:** Kevin Schwartzman

**Reviewer’s report:**

In general, this is an elegant modeling study that is clearly written and described. It addresses the potential role of active case-finding for TB in a manner that advances and expands current thinking on this topic, and that will hopefully provoke renewed attention from those setting the TB research and policy agenda in public health.

The major conclusions from this analysis are important, from both the substantive and the methodologic standpoints. From the substantive point of view, the authors’ key finding is that active case-finding (ACF) is likely to be highly cost-effective, when the metric of cost per disability-adjusted life year (DALY) averted is considered—using national per-capita GDP as a threshold.

From the methodologic point of view, the authors’ findings are arguably even more influential: namely, that clinical trials designed to evaluate the impact of active case-finding will predictably underestimate any benefits that in fact accrue, largely because of the time lag before much of the ensuing reduction in TB incidence and TB-related mortality. Hence it is reasonable to consider the disappointing results of the ZAMSTAR study in that light.

The compartmental model used for this analysis is similar to those previously used by these authors and other groups. Clinical and epidemiologic parameters are well described and referenced, as are the differential equations underlying movement between model states. The approach to modeling HIV infection and treatment appears reasonable for the context and study question. Model calibration also appears suitable.

**Major Compulsory Revisions**

1. My main question or concern relates to the putative effect of active case-finding, and the mechanism by which it is expected to avert DALYs. In the base case scenario, the authors assume that in the first year of such an intervention, the number of TB diagnoses would increase by 25%, as compared to the number expected without the intervention, i.e. passive diagnosis/status quo. This is based on the proportion of cases in ACF communities which were in fact diagnosed through ACF activities, in the ZAMSTAR study. It cannot be known from that study’s design and data how many such cases would otherwise have been diagnosed passively, and over what time frame. One suspects that at least some of these cases would have been diagnosed passively instead.
There is little discussion of this point in the main manuscript. In the Supplement, Section S4, there is a much more targeted description. There, the authors acknowledge that a 25% increase in diagnosis may be a very ambitious figure, and may well overstate the true impact on diagnosis in the ZAMSTAR study. I would like to see some of this text moved to the main manuscript, in the Methods and/or the Discussion section.

The sensitivity analysis related to this parameter is a key one, I think. The ensuing results are described briefly in the main manuscript, and more fully in the Supplement. I was surprised to see that marked variation in the number of additional cases diagnosed had minimal impact on cost per DALY (Figure S2), and find this result difficult to understand. Presumably the downstream impact of ACF on TB incidence and mortality must relate to accelerated diagnosis of contagious/ill patients, so why is the impact on cost per DALY so limited? The reasons for this unexpected finding [in my view] should be reviewed and then clearly explained by the authors—briefly in the main text, and more fully in the Supplement, and in their response to reviewer comments.

2. In the Discussion section, it would be appropriate to list (and reference) any available cost data for reported active case-finding interventions, so that readers may place the authors’ findings in this context. It seems highly likely that program costs per case detected will come in below the thresholds shown in Figure 3, particularly when a longer time horizon is considered. Nonetheless, any available “real-world” cost estimates of this parameter would be very informative for readers.

Minor Compulsory Revisions:

1. A more minor point again related to the ACF intervention involves the description of its modeling in section S4. The authors indicate that the modeling involved a 25% increase in Asp, Asn, and Aep, if I understood correctly. Wouldn’t this instead involve an increase in theta [#], resulting in a higher rate of shift from the A to the Tx states? Please clarify.

2. Supplement Figure S2: There is an error with the axis labels. In its current form, the figure shows proportion (not percent) increases in number of cases detected, i.e. the base case is 0.25, or 25 percent [not 0.25 percent, as the X-axis label implies]. The same point holds for the Y-axis of this figure. Please correct.

3. There is a minor typographical error that recurs throughout the Supplement: please correct “presymtomatic” to “presymptomatic.”

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.