Author's response to reviews

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

Authors:

Andrew S Azman (azman@jhu.edu)
Jonathan E Golub (jgolub@jhmi.edu)
David W Dowdy (ddowdy1@jhmi.edu)

Version: 2
Date: 26 September 2014

Author's response to reviews: see over
Dear Dr. Lee,

We thank you and the referees for your prompt and careful attention to this manuscript. Attached are our revisions to “How much is TB Screening Worth? Estimating the Value of Active Case Finding for Tuberculosis in South Africa, China, and India” (MS: 1380752981388541). In this revised version we have responded to all referee comments in point-by-point fashion as detailed below and in the marked up manuscript. We believe that these revisions have made this paper stronger and clearer and hope you do too. Please pass along our gratitude to the referees for their excellent comments as well.

If you have any further questions about this please feel free to contact us.

Sincerely,
Andrew S. Azman and David W. Dowdy
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
615 N. Wolfe Street
Baltimore, MD 21205
Referee 1:

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.

First, in response to the question about the putative effect of active case-finding, our model incorporates two different mechanisms; the direct and indirect effect. The direct effect involves diagnosing and treating the actively detected individuals before they can suffer additional morbidity and mortality. The indirect effect involves reducing the amount of time that those individuals remain infectious, thereby reducing the number of people they infect. The direct effect occurs rapidly; the indirect effect occurs gradually over time (both because duration from infection to active disease can be long, and because it can include secondary, tertiary, etc. rounds/generations of infection). In our model, the magnitude of the indirect effect diminishes over time – that is, in each subsequent year, the number of cases prevented that year by the ACF campaign (in the past becomes smaller and smaller but many lives can be saved in the interim.

When considering the size of the study, it is important to understand that larger interventions do have a bigger effect. Our goal was not to elucidate the relationship of cases detected at a given program cost to cost per DALY – this would, as the reviewer states, have a strong dependence on study size. Rather, our goal was to elucidate the relationship of cost per additional case detected and treated to cost per DALY. This relationship is not a perfectly linear one, because the indirect effect per additional case detected and treated is slightly higher in large campaigns than in small ones. That is, an
extra case detected and treated in a large campaign will avert slightly more transmission over time than an extra case detected and treated in a small campaign. But direct effects and first-order indirect effects drive the impact of ACF in our model, such that the DALY impact per additional case detected and treated is roughly the same, regardless of the size of the study. As long as the relationship between number of additional cases detected and treated and number of DALYs averted is roughly linear [as it is in our model], the relationship between cost per additional case detected and treated and cost per DALY averted will also be roughly linear – and this relationship is the key finding of this manuscript.

Finally, we agree with the reviewer that there is no way to know how many cases would have been detected and treated in ZAMSTAR (or any other ACF intervention) in the absence of the intervention itself. Unfortunately, the absolute number of cases detected and treated (the more measureable quantity) bears no easily-described relationship to the number of DALYs averted – at the extreme, a program that diagnosed and treated all of their cases and completely interrupted transmission would have very few cases detected in subsequent years, but would avert a sizeable number of DALYs. Thus, we chose a measure (incremental cases diagnosed and treated in the first year) that should be estimable – through comparison with prior notification trends (or in a trial, a suitable control) – and does have a clear relationship with the number of DALYs averted. But as per the discussion above (and Figure S2), our estimates of the relationship between cost per additional case diagnosed and treated and cost per DALY averted is fairly stable across a range of case finding intensities.

In response to this comment, we have added the following text to the Results, Discussion, and Supplement:

“Varying the increase in number of cases detected in year one from 5% to 50% had little effect (<3.5% change, Supplement S4 and Figure S2) on the estimated cost per DALY averted, as long as the cost per additional case detected and treated remained constant. Thus, while larger ACF campaigns had greater impact (and greater cost), the relationship between cost and impact was not strongly dependent on campaign size.” [lines 211-214]

Discussion: “While we based the main intervention on an estimate from a large trial in South Africa (7), this is likely an upper limit on its impact. In sensitivity analyses (Supplement S4 and Figure S2) we show that cost per DALY averted is relatively constant for different ACF campaign sizes, as long as the cost per additional case detected and treated remains constant. Campaigns that detected more cases had greater impact, but (for a given cost per additional case detected and treated) also had greater cost, and the relationship between cost per additional case detected/treated and cost per DALY averted was robust to the campaign size (Figure S2). Thus, we expect that our findings would hold even if our estimate of ZAMSTAR’s impact was overly optimistic.” [lines 265-272]

Supplement: “As seen in Figure S2, the relationship between cost per additional case diagnosed and treated and cost per DALY averted is robust to the size of the ACF campaign. In many cases, there may be efficiencies of scale that reduce the cost per additional case diagnosed and treated in larger campaigns. In such cases, the cost per DALY averted would be smaller for a larger campaign, but that cost could still be
estimated from Figures 2 and 4 (i.e., the larger campaign would fall at a different place on the cost-per-case-diagnosed axis).” [Section S4, page 6-7]

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.

We have added a reference to the average cost per additional smear positive case detected, summed over 28 different ACF programs implemented under TB REACH throughout the world. The following text has been added to the Discussion section:

“A recent summary of 28 different active case finding programs across 12 high-burden countries estimated that 17,236 additional smear-positive cases (relative to control populations) were detected at a cost of 14.9 million USD, or an average cost per smear positive case detected of $865 (32). If these cases were linked to treatment, our model suggests that the average ACF campaign would be highly cost-effective in a setting like India within a five-year horizon, and in settings like China or South Africa within a two-year horizon. To the extent that additional smear-negative cases were also diagnosed and treated without additional expense, ACF would be even more cost-effective.” [lines 251-257]

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.

You are correct, that the intervention involves an increase in theta, which will result in an increase in the number of people moving from A (Asp, Asn, and Aep) to the Tx compartments. We chose the increase in the rate theta such that 25% more cases are found in the first year as compared to the counterfactual. To clarify this point, we changed the first sentence of S4 to read:

“We modeled the ACF intervention in main manuscript as a 25% increase in the number of cases (Asp, Asn, and Aep) that would have been found in the first year in the absence of ACF (through increasing the rate of diagnosis and detection, θ).”

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.

We have updated the figure axes so that they are now expressed as a percent rather than proportion.
3. There is a minor typographical error that recurs throughout the Supplement: please correct “presymtomatic” to “presymptomatic.”

We corrected these spelling errors in the revised Supplement
Referee 2:

Major revisions:

1. I cannot see in the methods how the cost of the case finding intervention and treatment is obtained. What are the assumptions about case finding costs - what methods of case finding are proposed to be used?

Our intention was not to model a specific active case finding campaign but to provide a tool to allow readers to convert cost per additional case detected and treated in an active case finding campaign (something readily measurable by program implementers) into cost per DALY averted, an important measure for decision making but one that isn’t easily estimable. For example, following major revision 2 suggested by Reviewer 1, we now cite a summary of TB REACH activities, where a number of additional cases detected (17,236) and overall programmatic costs (14.9 million USD) were estimated in each of 28 different ACF campaigns. Our findings do not instruct readers how to collect such data, but given such data, they inform an estimate of cost per DALY averted (for example, $1600 per DALY averted under a 5-year horizon in India and China, Figure 3B). We do not specify specific active case finding activities since there is great diversity in approaches to ACF, and such approaches should be tailored to local needs. Instead, we model the relationship between (cost per additional case detected and treated) and (cost per DALY averted), under the simple assumption that ACF campaigns can be modeled as proportionally decreasing the time between the onset of infectiousness and treatment initiation among the additional cases detected and treated. This can allow program officials (e.g., those in TB REACH projects) to convert their estimates of cost per case detected into estimates of cost-effectiveness, to better ascertain whether their ACF campaigns provide good value for money under international standards.

The final line of the Introduction now reads:

“By modeling generic interventions, we create a tool for converting data that are easily estimable by people considering specific case-finding programs (i.e., program costs and number of additional TB cases detected from ACF campaigns using a specific approach) into data that are important for decision-making (i.e., cost per disability adjusted life year averted). We use these results to provide guidance as to how much donors and in-country TB control programs should be willing to pay to find one additional case of active TB.” [line 71-74]

We now also state in the Methods:

“We assume that the cost of an ACF campaign, as well as the additional number of TB cases diagnosed and treated, can be locally measured (or estimated) for any given campaign.” [lines 116-118]

Minor revision:

2. You assume all values of TB risk are the same for an individual on ART as one who is HIV+ with a CD4 count >350. Is this true? Could you make some statement to this effect and why you chose to adopt this parameter.
TB risk following ART initiation is obviously a dynamic and complex phenomenon. However, for purposes of this model, we attempted to capture the key elements of TB/HIV overlap without including excess complexity. Our approach of assuming TB risk on ART similar to that of someone with HIV but CD4 count >350 is both similar to other published, high-profile TB/HIV models (e.g., Menzies et al, PLOS Medicine 2012, e1001347) and high-level, data-driven publications (e.g., Figure 1 of Havlir et al, JAMA 2008; 300:423). We now mention this in the Methods:

“Our approach to parameterizing HIV states within this model is similar to previously published data-driven and modeling analyses. [14,15]” [lines 101-103]

3. Figure 3 is difficult to read which figure relates to what in panel A – can this be improved? It may be better in colour but often this will be read in black and white.

We made added labels to the cost effectiveness thresholds in Panel A to the reader identify what country each line pertains to. In addition, we slightly decreased the font size below each panel identifying the exact highly cost effective threshold to have less physical overlap between numbers. We anticipate publishing all figures in color but are happy to work with the journal to make this figure more ‘black-and-white friendly’ if desired.

4. Figure 3 is the title correct? I think these are the costs per case detected but the title seems to imply the costs need to be increased by 1000x?

We apologize for this confusion; the cost per case detected as displayed in small font on the x-axis needed to be multiplied by 1000, but the cost as displayed in larger font (and color) did not. We rescaled the x-axis so that everything is reported in actual dollar figures (not requiring multiplication by 1000) in order to avoid this confusion.

5. I do not fully understand how the rates of getting onto ART for CD4<350 have been derived. As I understand it there seems to be a lower rate of progression in South Africa than in India or China- is this correct? Can you reference the source?

Thanks for catching this! We reviewed the model and parameters thoroughly and found that there was a mistake in the model code that has quantitatively (though not qualitatively) affected many of the numbers reported in the main text and Supplement. We have re-run all analyses, including sensitivity and uncertainty analyses to make sure all numbers match the newly corrected model outputs. In general, the numbers from China and India, where HIV prevalence is low, were either not affected or affected very little. The results from South Africa changed slightly more. All changes are highlighted in the marked up version of the manuscript. The new rates of ART initiation are 0.04 (India), 0.06 (China), and 0.19 (South Africa) as shown in the revised Table S1.