Author's response to reviews

Title: Estimating the magnitude and direction of bias in tuberculosis drug resistance surveys conducted only in the public sector: a simulation study

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Author's response to reviews: see over
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Dear BMC Public Health Editor:

Thank you for allowing us the opportunity to respond to the reviewers’ comments and suggestions and submit a revised version of our manuscript entitled “Estimating the magnitude and direction of bias in tuberculosis drug resistance surveys conducted only in the public sector: a simulation study.” We appreciate the reviewers’ time, and believe that the paper is strengthened in changes made in response to their comments. We provide a point-by-point response to the reviews below.

Reviewer’s report
Title: Estimating the magnitude and direction of bias in tuberculosis drug resistance surveys conducted only in the public sector: a simulation study
Version: 1 Date: 7 March 2010
Reviewer: Emilia Vynnycky

Reviewer’s report:
The authors use modelling to discuss the extent to which surveys of tuberculosis cases attending public sector facilities provide reliable indicators of the proportion of cases that are drug-resistant. This was generally an interesting paper and discussed important questions.

My main concerns were that at times, it was not clearly written, and this was not helped by the way in which the paper was organized (see below). More importantly, in places, the paper seemed unnecessarily complicated, with the authors sometimes using modelling and mathematics to reach conclusions that did not appear to need modelling. At the other extreme, the authors used a model which seemed over-simplistic and did not adequately reflect the natural history of TB. It is unclear as to whether their conclusions would still hold if they were to account for these complications (see below).

Thank you for these general comments. We reply to these in our responses below.

Major comments
Some of the conclusions seemed to be stating the obvious and it felt that modelling was not required to prove them, e.g. the first 3 sentences of the results section, where the authors state that, for surveys of TB cases attending public sector facilities to reliably reflect the proportion of cases that are drug-resistant in the population, then either all cases would need to attend public sector facilities or equal proportions of drug-sensitive and drug-sensitive cases would need to attend public sector facilities. The same applies for para 2 of page 7.

We agree that these are intuitive points, but attempted to make these statements explicit to introduce the meaning and to establish the face validity of model parameters. We have now revised the text to make it clear that the model results
support general intuition and the mathematical results.

We also agree that paragraph describing the common error of failing to properly weight stratum specific estimates makes a point that is not difficult to understand and probably does not, in and of itself, require a model to demonstrate. However, the fact that this error is commonly made in practice (and even has an eponym -- Simpson's paradox) indicates this is a point worth emphasizing since combined (new + retreatment) estimates are frequently reported from drug resistance surveys.

Appendix: the model used is generally simple and does not reflect the natural history of TB. For example, cases are assumed to result from cases in the previous generation after a fixed time step, which is assumed to be identical for both drug-sensitive and drug-resistant cases. In reality, cases can occur following reactivation of an infection acquired many years previously or following new infection or reinfection. Since the proportion of disease resulting from these different mechanisms is age-dependent, the proportion of TB cases that are drug-resistant should also, in theory, be age-dependent. For example, older individuals in some settings are likely to be experiencing disease as a result of reactivation of an infection acquired many previously, when the prevalence of drug-resistance was low. In contrast, young individuals are most likely to be experiencing disease due to new infection and the prevalence of drug-resistance in these cases should reflect recent trends, and may well be higher than that for older individuals. It is plausible that the proportion of young and old cases who take up treatment in the public and private sectors differs. The authors should account for these factors in their analyses, or at the very least, discuss these complications.

Because our main objective for this work was to explore the performance of surveys, we chose to focus this model on the treatment outcomes and health-seeking behavior of symptomatic tuberculosis patients. For this reason, as the reviewer notes, this model is of a different form than previous models that include the natural history of disease as the major focus. Since our model does not include this type of detail (and the reviewer is most certainly right that the inherent time dynamics of DR and DS tuberculosis may not be the same and that the risks of re-infection and reactivation disease are age dependent), we also do not focus on the dynamic behavior of this model. Instead we focus on equilibrium properties of the system that, while certainly influenced by, should be much less dependent on the simplifying assumptions we made (specifically with regard to the equivalence of the time steps between treatment episodes for a new and a retreatment episode of TB). To address the concern that these assumptions were not clear, we have added a paragraph to the Discussion of the paper to point out the limitations of this modeling approach. However, it is important to note, as we now do in the paper, that the conclusions we make under these simple models would be even more important in models with increased complexity.
The organization of the main paper was very odd and needs to be improved. For example, most of the methods were in an appendix and there was a long section discussing methods for combining estimates from multiple sources in the results section. This section should be moved to the methods section.

In response, we moved the methodological details to the Methods section of the text and removed the Appendix entirely. Also, we moved the description of the methods/rationale for the stratified sampling/weighted estimation approach to the Methods section and left the actual results of the 2 cases we consider in the Results section. We also moved the discussion of methods for getting the data necessary to combine estimates in the Discussion. We agree that these are more appropriate places for the presentation of these parts of the manuscript.

The authors discussed a method for combining estimates of the proportion of TB cases from the private and public sectors to obtain estimates of the overall proportion of TB cases that were drug-resistance. It is unclear as to how much of this is new and how much it overlaps with the unpublished paper by Hedt and Pagano that they cited.

The Hedt and Pagano paper provide theoretical justifications for using routine program data and targeting special activities to measure populations (in this case the private sector) to achieve unbiasedness. This paper is general, with reference to HIV prevalence estimates, and so does not overlap with this application. We believe this is now clarified, in large part by the changes made to respond to the next comment.

The authors referred to this approach as “annealing estimates”. This terminology seems over-complicated. From their description, it seems that the authors are simply taking a weighted average of the proportion of TB cases in the private sector and public sectors that are drug-resistant, where the weights are the proportion of TB cases that seek treatment in the public and private sectors. If this is the case, the authors need to state this clearly.

We have removed the use of the term “anneal” throughout the paper. This was originally included as a link to the work cited by Hedt and Pagano with the intention of emphasizing that we were suggesting that small targeted surveys be annealed to existing survey activities. Based on this comment (and those of the second reviewer) we realize this was not clear and have now described this only as weighted averages.

At present, the application of the “annealing” process seems somewhat theoretical. It could be made much more interesting and relevant for most readers if the authors used actual data from many different settings (e.g. India, China, Russia etc), and discussed how specific estimates of the prevalence of drug resistance among TB cases would change if different proportions of TB cases in the private sector were found to be drug-resistant.
This is a good suggestion, but we do not have the necessary data to model these other settings. One of the central reasons we chose to focus on model on India as a case study was because there are several existing studies of how patients access the health system for the diagnosis/treatment of new and retreatment TB in India. This is obviously a much more difficult property of the system to assess than the size of the private sector (which some people have tried to estimate in these other settings). However, we know of no other locations with an important private sector for which this type of health sector seeking and switching behavior data has been reported. We have also replaced figures 5 and 6 in the main text to show how the weighted survey estimates perform in different scenarios where varying fractions of new and retreatment cases are treated in the hidden (private) sector.

Whilst the introduction to the manuscript was generally clear, the methods and results were not clearly written and likely to be difficult to follow, particularly for readers who do not have a mathematical background. This description of the methods and equations seemed unnecessarily complicated and could be improved considerably. Specifically:

1. Use of the letter Z with a subscript in the range 1-8 denoting whether the case was attending the public/private sector, drug-sensitive/resistant, new/retreatment etc. It would be helpful to use a different (and meaningful) letter or subscript for these various subcategories.

We have moved the model equations to the main text. Before the appearance of these equations we have included a description of what these 8 treatment categories of patients represent. We had tried several abbreviations in early versions of this manuscript, but we found them even more confusing than this current formulation because of the unfortunate fact that some first letters occur repeatedly such as Public and Private; Resistant and Retreatment; New and NTP.

2. Some of the subscripts were unnecessary. For example, the proportions of cases that are lost to follow up, failed treatment or acquired resistance were denoted by l_i, f_i, a_i, where i was in the range 0-1. However, it seems that in subsequent figures, these parameters were assumed to be identical for all categories in the model.

We have now changed the parameter subscripts to include only indices that are unique. This has been corrected in the model equations, the parameter table, and the figure captions.

Figure 1 – this was somewhat cryptic. Could the authors use words, rather than symbols, to describe what the different categories in the model represent? Some clarification of what the dotted arrows represent is needed. Presumably they
represent drug-sensitive cases becoming resistant?

We have attempted to make this Figure clearer by adding a legend within the figure itself that lists what the categories of patients that are represented by the eight Z states. As mentioned above, we think that replacing the Z states with names or abbreviations actually makes the notation more confusing. We have also modified the figure caption to describe the meaning of the dotted arrows; the reviewer is correct that this was supposed to represent the acquisition of resistance.

Figure 2 (and likewise Figure 3 & supplementary figures) – this figure was unclear. The authors state that the figure shows the bias as a function of the proportion of drug-sensitive and resistant cases presenting in the public sector. How are they measuring the bias and what values for the bias are represented by the red and blue areas? What do the black lines with the numbers next to them represent? Also, the notation used in the caption was inconsistent with that provided in Table 1. For example, the parameters (e.g. a, f_s, f_r, l) either had no subscripts accompanying them or differed from those provided in Table 1. The parameter rf did not appear to be defined anywhere but apparently took the value 0.6.

We have changed the captions corresponding to each of these figures to indicate that we are reporting percent bias, the meaning of the colors, and what the values actually represent; we also describe our approach for reporting bias in our new Methods section. The parameter rf actually was supposed to be labeled “q” – it refers to the relative transmissibility of the drug resistant compared with the drug sensitive strain and is described in Table 1. We thank the reviewer for catching this mistake.

Figures 5 & 6: the thick black line is easily confused with the green line. It could be made clearer by adding a right hand y-axis and plotting the proportion of all TB cases that are drug-resistant on that axis.

We have replaced the previous versions of Figures 5 and 6 with a new version in which we think it is easier to distinguish the green and black line. If this is still not acceptable, we can figure out another way to present this.

Appendix, page 2, end of para 2: the authors need to clarify the basis of the equation that they present. The statement that this is equation is consistent with the data from India is insufficient.

The two mathematical statements (now appearing in the Methods) are only intended to constrain the values of the parameters to be consistent with two facts about tuberculosis patients utilization of TB services in India: 1) The majority of new patients first present for treatment in the private sector and 2) The majority of retreatment cases present for treatment in the public sector. We have now
provided citations to the literature to support these statements.

Minor comments
p6, para 2, 4th line: the term “susceptible case” is odd and not one that is used in infectious disease modelling.

We agree that this was confusing use of that word. We have modified this to read:
“…the proportion of all new drug-sensitive cases that present to the public sector ($S_x$) must be equal to the proportion of all drug-resistant cases that present to the public sector ($R_x$).”

p7, 1st para, penultimate sentence – this is unclear.

We have removed this sentence entirely.

p8, bottom para – it would be helpful to define $n_s$ before it is used.

We have now defined this parameter prior to using it, and have changed the subscript to be consistent with the rest of the paper.

p8, 2nd line from the bottom: presumably the decision to sample 50 additional cases in the private sector is arbitrary? The authors should state this.

To clarify, we have added this sentence to that paragraph:
“The choice of 50 additional samples is arbitrary and was chosen only for illustrative purposes.”

Level of interest: An article whose findings are important to those with closely related research interests
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare I have no competing interests.

Reviewer's report
Title: Estimating the magnitude and direction of bias in tuberculosis drug resistance surveys conducted only in the public sector: a simulation study
Version: 1 Date: 18 December 2009
Reviewer: Patrick Phillips
Reviewer’s report:
Overall I think this is a paper that is clearly written and the methods seem correct and reasonable as best as I can tell (I don’t have much experience with mathematical modelling, so I haven’t got anything to compare it with). I have been through the appendix and the methods sections and checked the formulae and what has been said and that is all correct. It all seems to accurately depict what I would think is the movement of patients between the public and private sectors and from sensitive to resistant.

I just have a few specific comments:

* Second formulae on page 8. It would be useful if they defined what \( n_s \) and \( n_s^{\text{bar}} \) are

We have now defined these terms before using them in the main text, and have changed the subscripts to be consistent with the rest of the paper.

* The figure caption for Figure 2 refers to 'the percent of', but I think this should be 'the fraction of' in each case as in the figure itself

We have modified the caption to correct this.

* According to the captions, Figure 2 seems to be showing absolute bias, where Figure 3 is showing percentage bias. Is this correct? It's not clear from the captions. It might be clearer if they both showed absolute bias or both show percentage bias.

We have now clarified that we are reporting percentage bias in both figures and have modified the text in the caption to this effect.

One small point about wording. the use of teh word annealed seems slightly unusual in this context. Could thr authors consider an alternative?

In response to this comment, and the one from the other reviewer, we have not changed the wording so that these estimators are called "weighted estimators". The original use of the word "annealing" and reference to the Hedt and Pagano paper is to emphasize that we want to supplement routine activities, not eliminate them. We now think that this new draft emphasizes these points more clearly.

The Discussion is short, more could be said which draws together some of the conclusions from the individual figures.

We have expanded the Discussion and made the links between our conclusions and the figures presented in the text. We have attempted to emphasize that our central conclusion is that:

1) It is difficult to ensure that public-sector surveys validly estimate resistance and the data necessary to support a claim of unbiasedness is never met in practice.

2) Small targeted surveys in the private sector promise to improve the validity
of these activities.
We have also added some text to the Discussion in which we mention some of
the challenges (and opportunities) associated with trying to design these private
sector surveys.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests