Reviewer’s report

Title: The cost-effectiveness of incentive-based active case finding for tuberculosis (TB) control in the private sector Karachi, Pakistan

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Reviewer: Justin Ingels

Reviewer's report:

1. The article rests on the idea that ACF strongly dominates PCF due to lower costs and more effects. On the surface the greater incremental effects per person makes sense. However, the entirety of the cost savings (lower incremental costs for ACF relative to PCF) rests on the parameter "Cost of no TB symptom". This can be determined by calculating the expected value of costs using the decision tree and parameters provided in Table 1. For,

ACF this looks like the following:

0.978*$2.15 = $2.10 (No TB)
0.022*0.39*$2.15 = $0.02 (No test)
0.022*0.61*0.92*$7.15 = $0.09 (Test -)
0.022*0.061*0.08*0.06*$82 = <$0.01 (No Treatment)
0.022*0.061*0.08*0.94*X = ? (Treatment)

X in the final equation is dependent upon the Markov model but based on the expected value of costs provided in Table 3, the result of the final equation is about $0.40 which would allow the above values to sum to $2.61, making X roughly $392. Regardless of the result of the final equation, 80% ($2.11/$2.61) of the final cost is based solely on this part of the model. The same holds for PCF as the probabilities are different but not that different (70% rather than 80% and $305 for X rather than $392).

The problem for me is that it is not apparent how these estimates were made from anything provided in the remainder of the article. Total program and participant costs are provided in Table 2 and these seem to be in the model as "Cost of successful TB treatment". In every part of this table other than "Before diagnosis" patient costs, the costs for ACF are larger. Therefore, I assume that the cost estimate for "Cost of no TB symptom" is based solely on the "Before diagnosis" part of Table 2. If that is the case, the primary driver seems to be the cost of medication. My question then would be why are the per person costs for PCF so much higher for medication than for ACF. My assumption is that active case finding identifies far more
individuals due to the "active" part of the strategy and many of these individuals are not on medication because they are not symptomatic, thereby decreasing the per person cost in that specific category. However, any decision model should be presenting two or more arms where a cohort of individuals (the exact same individuals) move through each arm of the model (two different and potential realities for the exact same cohort) experiencing a different set of circumstances dependent on each arm. Further evidence for this situation exists in the smaller probability in ACF for persons presenting with TB, the larger proportion testing negative, and the greater number of visits before diagnosis. These results from the data alone show that these two cohorts of individuals are not actually equivalent. My concern is that these additional people found in ACF are not being appropriately included on the PCF side. If you took the 1858 that were identified and included on the ACF side and in a separate reality could "see" what happened to them in a PCF world, there is a good chance the costs per person before diagnosis would decrease for the PCF group. Something like this would be remedied by an additional chance node in the start of the model for PCF that splits the cohort between those in the cohort who are never "found" in the PCF strategy but would be found in ACF strategy. The response to this cannot be that the "uncertainty" around the parameter did not change the results in the one-way sensitivity analysis. The +/-20% is arbitrary and if my above statements are true would not be large enough to correct for these issues.

For all of the parameters under "Cost" in Table 1, something more than "Primary data" is needed to justify these numbers as only the estimates for "Cost of successful TB treatment" are clear.

It's unclear how any of the parameters in Table 1 that cite Reference 33 come from this reference as it is entirely focused on costs and is only referenced with respect to probabilities. Looking at Reference 17 it is also difficult to tell where these parameters come from. (I also cannot tell from Reference 32 if that's what was actually intended for the table)

2. The formatting of Table 1 makes it difficult to read, I think some of it has to do with the vertical justification within table cells. For example, the ref. # 24 is much higher than the words "Probability of dying from nature causes" and as the numbers cannot be included in the table, some placeholder should be there below PCF and ACF such as "Life table" or something similar. Also the reference for the last two rows of the cost section do not seem to align with the titles and costs to the left. The headings should not say "Probability ACF" and "Probability PCF" as only the numbers in the first two sections are actually probabilities. More detail is needed somewhere in the Methods to describe what is meant by "Primary data (loss to follow up at 3 month of treatment)" and "Primary data (Death at 4 month of treatment)"
3. There are several pieces in Table 1 that seem to be based on "loss to follow-up" but there is nothing in the decision model (Figure 1a) or either of the Markov models (Figures 1b and 1c) that indicate where loss to follow-up comes in.

4. How are the treatment cost parameters in Table 1 incorporated into the model? The model is running in 6 month cycles and patients can leave and reenter the "TB Treatment" state. Are the costs in Table 1 applied each cycle (I assume this is the case based on the statement on page 11 near lines 19 and 21)? Are they only applied once an individual transitions out of the "TB Treatment" state? Does this mean that an individual leaving "TB Treatment" via the "Cured" route would have $223 applied in the ACF arm and leaving through the "Death" route would have $149 applied? What about leaving through "Treatment Failure" because there is no parameter titled similarly in Table 1? I also think that the titles of the parameters in Table 1 need to correspond very closely to the titles used in Figures 1a, 1b, and 1c. As it is now they do not and it takes some time to determine where probabilities and costs are applied (and is impossible in some cases).

The above statements and questions also lead me to the question of "how was this model evaluated?" Was this a cohort simulation or a microsimulation? This was not specified in the Methods.

5. The presentation of Table 3 is a little problematic without some additional notes. The average reader who knows a little about incremental cost-effectiveness will be quickly confused as to why a positive incremental cost and positive incremental effect would indicate strong dominance. Because the DALYs here are presented as a loss in quality of life, more is not better as would be expected if these were presented as QALYs or life-years. Some notation indicating this would be helpful to an average reader.

6. The threshold analysis is meaningless as the parameter that was selected is far down the list of important parameters according to the tornado diagram and as I mention above the majority of the costs per person in the model are a result of the "Cost of no TB symptom" parameter and not this parameter. There is also no justification for the 150/DALY WTP threshold used in the threshold analysis.

7. With respect to the author's comments to Reviewer 1 (question 5) they did not perform a probabilistic sensitivity analysis which requires assigning a distribution of uncertainty (i.e. uniform, normal, beta, etc.) around each parameter and then running a process where values for each parameter are randomly selected from these distributions and the model is run, the result saved, and the process repeated. If the statement on page 12 lines 39 and 41 mean that this was done based on a standard error calculation of an arbitrary +/-20% uncertainty around each
parameter then more information is needed. What distributions were selected? How many iterations were completed? Nothing in the results suggests that this was actually done or what an ICER plot or CEAC resulting from this process might reveal about the uncertainty in the model. If a PSA is completed it should be based on mean and standard error estimates from the actual data (to which the authors cite they have access) which is explained in detail in Chapter 4 of the book the authors cite as Reference 31.

8. On page 9 around line 56, Reference 31 is not an appropriate reference as a guideline for selecting a discount rate. As far as I'm aware the examples in this text may use 3% but this may not be appropriate for this study. There are many other actual CEA guidelines, including for international settings, that have recommendations for discount rates.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

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