Reviewer's report

Title: Counting the lives saved by DOTS in India: a model-based approach

Version: 0 **Date:** 18 Nov 2016

Reviewer: Peter Dodd

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SUMMARY

This paper tackles the important question of estimating the lives saved through reformed & improved tuberculosis service provision in India, the country with the largest number of TB cases. This is done via a transmission modelling approach that can account for and separate out the direct benefits from patient-level improvements in outcome from the indirect population benefit from TB cases averted.

This is an important question and the approach has many of the right ingredients. In my opinion however, major revisions are required before publication.

MAJOR COMMENTS

I think there needs to be a more careful framing of the question throughout. The ways in which RNTCP explicitly changed and complied with DOTS guidance needs to be made more explicit in the introduction (the non-NTP sector also needs to make a first appearance here with some discussion, and it needs to be clearer how the separation between NTP, non-NTP and not-treated is made). A more careful definition of the comparison made is needed, with consistent terminology throughout (DOTS services, DOTS treatment, 'vs no intervention'). This definition should make clear that the comparator has the outcome characteristics the service achieved in 1997 projected forward without change. This needs to be mentioned in the Discussion as a limitation since clearly aspects may have in reality improved without the RNTCP revision. Even DOTS-based treatment in the title might bear some thought, as it sounds like it is considering something more specific than the whole strategy (perhaps correctly).

Update calibration data and consider trends. Why only calibrate to one year's estimate? Surely the incidence trend will be important in determining the main outcome? There is a throwaway comment about data quality, but the same data that is currently used is used over more years. It is unclear how the shift to absolute numbers has been made and how the 30% change in India's population over this period has been accounted for. If not important, approximations should be flagged and justified. Model features omitted & their potential effects (like age and smear status) should be discussed in limitations. Also, things like the model initialisation and accounting for population size should be in the main paper. Also the data can now be updated to use the most recent estimates.

Comparison with other estimates. The authors cite in the introduction other approaches to this question, but then do not compare their results or discuss the reasons for differences. I felt like the discussion could contain more information to bolster face validity, e.g. comparison of overall mortality rate outputs with WHO estimates, comparing implied mean change in CFR with known changes in treatment outcomes (see below).

Technical detail. Perhaps most importantly, not enough detail is provided on the Bayesian approach for assessment to be possible, to such an extent I suspect a section was omitted from the Appendix in error. To a much lesser extent, the model structure needs some extra details (e.g. a table of state definitions).

MINOR COMMENTS

ABSTRACT

DOTS services/programme/... I think the DOTS strategy needs to appear in the background of the abstract

reliable data -- India VR data situation needs a bit more detail in the Intro.

reviewed the literature -- I would drop this phrase or boost the detail given to the search approach (see below).

Bayesian evidence synthesis -- this doesn't seem to be described anywhere (see below).

INTRODUCTION

DOTS -- as a strategy, the acronym is a bit irrelevant and should be dropped

'DOTS-based treatment' may not be unambiguously understood. I think you need to define what treatments are recommended in the DOTS strategy and choose a consistent terminology for them. DOTS-based sounds odd to me, but a bit subjective.

last para pg 4 'no intervention' -- this is a bit ambiguous, the basecase is not scaling up DOTS and assuming no change in treatment outcomes from that period. Would also suggest comparator or basecase rather than baseline, which may be taken to refer to a point in time.

In switching to discuss the RNTCP here, it is left implicit that this programme runs according to DOTS principles whereas the previous programme did not.

'DOTS treatment' -- see above comment

METHODS

Literature search for untreated TB outcomes -- this seems pointless as phrased there is the painstaking *systematic* review of Tiemersma et al on this topic already (as used).

Also: mortality rates could be a bit confusing as it's really survival characteristics (duration, CFR) that are sought rather than population-level numbers.

X_2 seems an unnecessarily opaque terminology for a model parameter (& similarly the other parameters X_n)

p6 (i) - (iv): I think the use of the term rate here for all these items, as well as for X_2 invites unnecessary confusion

p7 para 1 is probably as clear without the equations

'upto' here and below should be 'up to'

p7 'modeled' - two ls are used elsewhere

'Bayesian melding' -- was Bayesian melding ~ Poole & Raftery really used? No details are provided.

Why only calibrate to one year's estimate? Surely the incident trend will be vital in determining the main outcome? Also (sorry, bad timing I know) this number can now be updated to use the most recent estimates.

'Owing to challenges with vital registration data' -- this is crucial to the motivation but only appears here in the Methods. Needs to be flagged in the Introduction.

p8 -- perhaps just change terminology to 'hazard' which means what you want and bypasses confusion and obviates explanation?

p9 -- if you're going to sell having searched the literature, I think it would be as well to include some gist of the search terms in the appendix, even if not attempting to be fully systematic

No information given about model initialisation in methods?

RESULTS

p9 'key parameters ...' - actually just all parameters?

'CI' is not defined, but in any case is not likely to be a confidence interval

2/3 of 380K per year = 250 K with current incidence at 2.2 mn implies a difference in CFR of around 10%. I guess this is plausible. It might be worth discussing this in terms of known improvements in treatment outcomes.

p10 indirect effect on MDR deaths - quantify?

DISCUSSION

p11 para 2: 440 USD. I can't easily work out where this number comes from using Results and suggest including the denominator there explicitly; USD 2267mn / (6.8mn deaths averted - 1.19 MDR deaths averted) = 404 USD per DSTB death averted. Also -- why DSTB?

Private sector -- this makes an appearance for the first time in the Discussion. Should be discussed in the Introduction already and approach to it touched on in Methods. It should be clearer how the separation between NTP/non-NTP and not treated is made.

p11 last para -- it wasn't at all clear to me why having a large private sector was a pre-requisite to employ this methodology. Poor or absent VR systems seem more relevant.

P12 para 2 'absence of adequate data on secular trends' -- given that the data used is the WHO estimate of incidence, why do the authors believe that the time series provided (from 1990 for that round of estimates, from 2000 in the new update) is less valid as a calibration target than a single year?

P12 - X_2 adds nothing here

Comparison with other work -- the authors cite other work estimating lives saved by RNTCP (using a static approach) and mention in the Intro this found 1.2mn lives saved, but do not compare their answer or discuss reasons for differences (⅔ of 6.8 mn is still much bigger). Similarly, the WHO also estimate overall TB mortality for India -- it would be worth making a quick sanity check comparison (with the understanding that it won't be identical).

Another limitation I'm curious about is the absence of smear status in the model. Given that the CFR for untreated smr -ve TB is around 30% but 70% for smr +ve TB, and given the emphasis of DOTS on smear as a diagnostic, what is the implication for your estimates of ignoring this heterogeneity and assuming a 50% average CFR (or whatever)?

CONCLUSIONS

'...the nation's TB epidemic...' -- think 'nation' needs to be 'India'

'...valuable noting...' -- 'valuable to note'?

TABLES

Table 1

It is worth noting that the beta inferred (bearing in mind it is an average over smr+/-) and also the high primary progression assumed mean that quite a high proportion of incident TB will be due to recent transmission. I don't know India well, so maybe this is the case, but this proportion recent will be a key driver of the level of indirect benefit. Might be worth cross checking a model estimate of this quantity against direct estimates from molecular epidemiology if there are any.

NSP, NEP, NSN = ??

Table 2

I think it would be useful to include the row totals in this table, and potentially have DS-TB lives saved and MDR-TB lives saved so that one could also have column totals and make the table look like a contingency table with all marginals. Potentially easier for the reader to follow.

FIGURES

Figure 1 -- I think S'_RNTCP needs to be explained briefly in the legend. Progression following reinfection is not shown in this figure.

Figure 2 -- surely it would be better to rescale the y-axis to explicitly convey the saturation coverage and avoid any readers thinking that you assume 100% of patients are RNTCP?

Figure 3 -- perhaps more relevant to report absolute incidence, as more directly relevant to your main outcome and the changing population size is surely a big factor.

ADDITIONAL FILE

I think we need a table of state variables and their interpretation before the ODEs -- I'm still only guessing at the meaning of S'_RNTCP for example.

Only at this point (ODEs) is it evident that a closed population assumption has been used. This is not a minor detail, and needs to be in the main paper. Given that the Indian population has increased by ~30% over 1997-now, how have the authors included this effect?

At this point from the FOI formulae, I infer that all state variables are in fact fractions?

Equilibrium initial condition also needs to be in main text

Weighting smr+/- mortality -- state the weightings.

Missing section on MCMC?! Given the paper and earlier in the Appendix ('see section on Bayesian MCMC below') I'd been expecting a section that describes the calibration approach: i.e.

the construction of the likelihood, the algorithm used, sufficient outputs to assess convergence etc. This seems entirely absent, which is not acceptable.

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

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

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I hold and have applied for research funding in the area of using dynamic models for TB burden estimation, but have no ongoing work applying to India or to the question of lives saved through DOTS. I have no other competing interests.

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