Author's response to reviews

Title: Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost-effectiveness analysis

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To the Editor of BMC Pulmonary Disease

Thank you for the opportunity to make a revision to the manuscript 1685559911229299 entitled: “Different screening strategies (single or dual) for the diagnosis of suspected latent tuberculosis: a cost-effectiveness analysis”

We found the reviewers’ comments were very helpful in making a more coherent analysis. We have attempted to address all the concerns made by the reviewer by preparing a point-by-point response to each comment.

Reviewer comment (in bold) is followed by our response (in plain text). Each comment and response is numbered in the same order as given in the reviewer’s report. Text that has been changed or added in the manuscript (in response to the reviewer’s comments) is shown in red text. The order of the responses is as follows:

Reviewer 1 – Kevin Schwartzman

Major Essential Revisions

1. The presentation of the cost-effectiveness results in table 4 and the related description in the text, need some improvement. In particular, the number of expected TB cases is compared with a "no screening" scenario, to derive the number of cases prevented. In the same way, the authors need to compare the cost of each screening strategy with that of the same "no screening" scenario--because not screening creates downstream costs of treating active TB cases. At present, it does not appear that the authors have done this, and it would actually reduce the cost per case prevented by every screening strategy, relative to "no screening."

1. We accept the reviewer’s comments highlighting the fact that not screening incurs downstream costs due to active TB cases. As such the cost of not screening has been calculated as £57,148 over the 2 year period of the model, which has now been
included in table 2 and has been stated in the results section on page 9-10 of the main manuscript:

‘Additionally, no screening incurs downstream costs due to treatment of active TB cases; this amounts to £57,148 per 1000 contacts screened over the 2 year period of the model.’

A related point is that in the base case scenario, the T-SPOT alone strategy dominates all others, i.e. it prevents the most cases and is cheapest. This is the key finding. The relative ”savings per case prevented” are less important. If the most expensive strategy also was the most effective, it would be appropriate to show an incremental cost per additional case prevented, relative to the next most expensive/next most effective strategy, but that is not the case here.

Screening with T-SPOT.TB only does prevent the most cases, but it is not the cheapest strategy. We have expressed the cost-effectiveness as the cost per active TB case prevented. Whilst we accept the reviewer’s comments that negative ICERs are not usually presented, we do think it helpful to make it clear to the reader that using IGRA based strategies actually save money compared to using the incumbent methodology, the TST.

2. If I understood the manuscript and supplement correctly, the authors assume that 80% of contacts with positive test results will begin preventive treatment with INH, and all those who start will complete it, unless they develop severe hepatitis. This is an extremely optimistic base case scenario, as most program evaluations have demonstrated substantially lower completion rates, often on the order of 50-60%. The authors get at this issue in sensitivity analysis by examining a 55% treatment initiation scenario, but the base case strikes me as too optimistic in this respect. At minimum this warrants explicit discussion.

2. We acknowledge the reviewer’s concerns but while our model does assume that 80% of contacts with a positive result start INH treatment, it does not assume that all individuals will complete the treatment. The efficacy of INH treatment (associated with the branches “LTBI fully cured” in the decision tree) is given as 65%, taken from the IUAT trial. This estimate of efficacy accounts for varying degrees of adherence to and completion of INH treatment, as stated in the Comstock reanalysis. If all persons undergoing INH treatment were ‘completer-compliers’ i.e. both adhered to and completed treatment, then the efficacy of INH would be greater. Thus these lower completion rates seen in other program evaluations are actually accounted for in the estimate for INH efficacy used in our analysis.

In order to make this point clearer, we have included the following statements on page 7 of the supplemental data attachment:

‘These estimates assumed heterogeneity in the adherence and completion rates of those taking INH treatment. Estimates were higher in those who complied to and completed treatment’
3. The base case scenario assumes 100% specificity for the T-SPOT, based on 2 UK studies, while other studies have estimated somewhat lower specificity. One might consider adopting a slightly more conservative estimate for the base case scenario (e.g. the midrange). Again, I realize this issue was addressed secondarily, in sensitivity analysis. At minimum a) a threshold specificity below which T-SPOT alone is no longer cheaper AND more effective than all other strategies should be reported, and b) this point should be mentioned in the discussion.

3. A recent review by Pai\textsuperscript{iii} showed that in 5 studies conducted in low incidence TB countries reported T-SPOT.TB specificity to be 100%. This is the reason that this specificity was used as our estimate. We do acknowledge the fact that one other study\textsuperscript{iv} did estimate a lower specificity, but this study was conducted in a medium endemicity setting where the background rate of LTBI infection was estimated to be 15% (incidentally the same as the positivity rate in the cohort detected by T-SPOT.TB). Interestingly, a recent publication on the specificity of T-SPOT.TB in a low endemicity setting\textsuperscript{v} shows T-SPOT.TB specificity to be 98.9%, a value not inconsistent with our assumption. Consequently, we chose to only use estimates from those studies that reflected our study population. This is mentioned on page 5 of the additional data supplement:

‘In order to best approximate a UK study population, estimates of IGRA sensitivity and specificity were used from studies conducted in the UK or with similar population dynamics to the UK (low TB burden, moderate to high levels of immigration, BCG vaccination).’

However, as suggested, we have added a threshold specificity in our analysis below which the T-SPOT.TB single strategy is the least cost effectiveness. This is included in the results section on pg 12 of the main manuscript:

‘The T-SPOT.TB single strategy became the least cost-effective when T-SPOT.TB specificity fell below 85%.’

\textsuperscript{i} Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. Bull World Health Organ 1982, 60(4):555-564