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 insightful and contributed to making a more thorough, meaningful analysis. In response to the reviewer’s comments, the manuscript has been substantially rewritten, particularly the results and discussion sections. The title of the manuscript has been slightly altered and new tables are also included. We have prepared a point-by-point response to the concerns of the reviewers and editor.

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
Reviewer 2 - Laurent P Nicod
Editorial Request

REVIEWER 1

1. The key limitation of this analysis is that it is a pure cost comparison (“cost minimization analysis.”) This would be more appropriate if clinical outcomes related to the various strategies were equivalent, which is not the case. The consequence is that cheaper strategies may be associated with poorer clinical outcomes, but this cannot be formally captured with the current analysis. In other words, the fewer cases of LTBI detected, the lower the cost—but the fewer cases of active TB prevented. Indeed, the most extreme interpretation would be that it is cheapest to not screen contacts at all. The authors hint at some concerns of this nature: for example, on p. 9, they state that “A lower test sensitivity...reduces the cost of that strategy as fewer cases of LTBI are detected and treated.”

In their discussion section, the authors need to state very clearly that a cost
minimization analysis, when clinical outcomes are not in fact equivalent, can potentially lead to distorted recommendations. On p. 16, they do mention that a full cost-effectiveness analysis was not performed, but they need to better identify the limitations of their current approach. Notwithstanding the authors’ comment on p. 17, it is in fact possible to model the “effectiveness” of the IGRA by adding assumptions about future likelihood of active TB to those already made about costs and test properties. Indeed, Marra and colleagues have just published such an analysis in the December 2008 issue of the International Journal of Tuberculosis and Lung Disease, and this would be a relevant addition to the reference list.

1. We have addressed the reviewer’s concerns by adding new effectiveness measures into the model (such as modelling of the numbers of downstream active TB cases resulting from each screening strategy) as well as cost-effectiveness measures (cost per active case of TB). The results and discussion sections have also been substantially rewritten to highlight the various trade-offs between the screening strategies in terms of total costs, clinical effectiveness and cost-effectiveness (Results on pg 9-14 and Discussion on pg 14-22 of the main manuscript). We have also included the Marra et al paper in the discussion (pg 16) and reference lists.

Discussion pg 16

‘Marra et al. [16] found the QFT alone strategy was most cost effective in BCG vaccinated contacts (not necessarily in other cohorts) followed by QFT dual strategy, in a screening population of contacts stratified by ethnicity and BCG vaccination status.’

2. One would anticipate that any serial testing strategy involving two tests with imperfect sensitivity will identify fewer cases of LTBI than will a single test, so it will be cheaper from that standpoint. However, the most often cited advantage of the dual testing strategy is the reduction in “false positives” related to the relatively poor specificity of the TST alone, particularly in BCG-vaccinated individuals. This point should be emphasized in the discussion.

2. We have added more granularity to the results tables (tables 2-4 on page 35-36 of the main manuscript), highlighting the proportion of the total costs of each screening strategy that goes into the test costs, treatment costs and into false-positive or otherwise erroneous results. We have also included commentary in the discussion (pg 19-20 of the main manuscript – see below) that compares and contrasts where the costs go with each screening strategy to allow more rational discussion of the actual cost savings of the dual testing strategy.

Discussion pg 19-20

‘The conclusion that is consistent in our study and previous cost analyses is that screening with the TST alone is not cost-effective compared to strategies using the IGRA. However, whether IGRAs should be used as a replacement to the TST or in conjunction with it remains debatable. IGRA single screening does cost more (higher testing costs) but less money is spent on false negatives. Less false negatives means fewer people will progress to active disease, resulting in these strategies being the most effective (prevents most cases of post-primary TB). In terms of cost effectiveness, the single strategies are ranked higher than the dual strategies as they have the lowest cost per case of active TB prevented.’
3. Some clarification is needed with respect to Figure 3. As submitted, the figure suggests that the probability of true LTBI after 1) a positive TST and then 2) a positive IGRA is simply the positive predictive value of the IGRA. In fact, it must be the positive predictive value of the IGRA, GIVEN A POSITIVE TST, which is higher than the PPV of the IGRA alone. This point needs to be clarified, with parallel considerations for the other branches of that tree.

3. This was an error in the previous version which has now been corrected. As the reviewer has pointed out, the prevalence of LTBI in the TST positive cohort is clearly higher than that in the original cohort of 1,000 contacts; consequently this will affect the PPV and NPV of the subsequent IGRA test. We have recomputed the PPV and NPV of the IGRA, following a positive TST, taking into account this fact. Page 4-5 of the supplemental data makes this clear.

Supplemental data file pg 4-5

‘In the dual screening strategies, the prevalence of LTBI in the TST positive cohort will be higher than the background prevalence. As such, the probability of a positive and negative result, as well as the PPV and NPV, of the IGRA given a positive TST is different than these estimates in the IGRA only strategies. These values are shown in table 1.’

We have also changed the labelling of the branches in Figure 3 to make this clear (see below)

IGRA true positive given a + TST
IGRA true negative given a + TST
IGRA true positive given a + TST
IGRA true negative given a + TST

These values (for T-SPOT.TB and QFT-GIT) have also been added to table 1 (pg 37 of the main manuscript).

4. Finally, the authors limit the time frame of their analysis to two years—the period of greatest risk after acquisition of TB infection. On the one hand, the analysis assumes that all persons with true LTBI have acquired it as a consequence of their recent TB contact, and hence have a 2.5% annual risk of active disease. This assumption is difficult to justify, as many foreign-born contacts will have longstanding LTBI acquired in their countries of origin. This assumption would tend to overestimate the probability and cost of active TB among the target population, and should be acknowledged as such. On the other hand, benefit accruing from prevention of TB cases further into the future is not modelled. There are certainly sufficient data to permit this type of modelling, as other authors have done. The analysis would benefit from a better accounting of future active TB cases and related costs, with suitable discounting, although the present authors do acknowledge this limitation (p. 13).

4. The reviewer has raised two countervailing points:
a) The analysis uses a rate of progression of 2.5% per year and that this may be an overestimate given that many foreign-born contacts may have longstanding infection that is less likely to reactivate than recently acquired infection. Consequently the analysis tends to overestimate the number of downstream active TB cases.
b) The analysis does not include a time period longer than 2 years and this will tend to underestimate the number of downstream active TB cases.

We have answered each of these in turn.

a) The analysis used a total rate of progression of 2.5% over the 2 year period (not 2.5%/year), which reduces any extent of overestimation. We accept that many contacts may be foreign-born, but firstly, even if they were carrying a prior longstanding infection, they may have incurred new recent bacterial load as a result of contact (with an index case) that would make their rate of progression similar, if not identical, to any other recently exposed contact without prior longstanding infection. Secondly, it is well documented that recent immigrants, even if they have a longstanding prior infection, have a markedly increased risk of progression to active disease within the first few years of entry into their new country of residence. So it is not entirely clear that the rate of progression chosen is inappropriate.

b) We accept that a longer time horizon may more accurately reflect downstream active TB cases. However, introducing a Markov type process to adequately model this would add considerable complexity to the model. We chose a 2 year period as we wanted to examine costs and effectiveness over a fairly narrow time window that is more appropriate to the narrow decision-making time horizons of most healthcare institutions. Secondly, a shorter time period also increases the accuracy of certain assumptions (e.g. the assumption that there are no re-infections).

Notwithstanding the above points, we devote more space in the discussion (pg 22-23 – see below) of the revised manuscript to the relative merits and drawbacks of our model construction and the effects on accurate estimation of downstream active TB cases.

Discussion (pg 20-21)

‘There are several limitations of this study. Our analysis used a shorter timeframe of 2 years (other analyses used Markov modeling over a 20 year period [9-11, 14, 16]) and excluded wider transmission. We used this timeframe as Markov modeling would have added considerable complexity to the model. Additionally, healthcare institutions prefer to examine how implementation of a new clinical intervention affects their annual budget rather than long term overall costs over a 20 year period. However, a shorter timeframe underestimates the number of downstream active TB cases. Thus the more effective strategies in our model (T-SPOT.TB and QFT-GIT only) will become even more cost effective if a longer timeframe was used. Similarly wider transmission underestimates the costs of less effective strategies. If included, single IGRA strategies would become more cost-effective as more future TB cases will be avoided. Nonetheless, it is reassuring that the results of our model in terms of ranking of the screening strategies are similar to analyses that have included Markov processes [10].

Health assessment agencies typically use Quality of Life Years (QALYs) as their outcome measure when conducting cost-effectiveness analysis. Our analysis did not include this measure due to limited UK data. However given that the main source of quality of life losses is active TB cases (as the risk of hepatitis is small) then strategies which prevented the most active TB cases would be even more cost effective if QALYs were included. Additionally, we only included costs from the narrow perspective of the UK healthcare provider and did not include costs to the wider society i.e. costs incurred on patients, costs due to death, etc.’
Minor Essential Revisions

1. The perspective of the cost analysis (UK health care system) should be stated explicitly.

   1. We have now included the following phrase ‘from a UK healthcare perspective’ in the abstract (page 3) and background (page 6) of the main manuscript to make this point clear.

2. The analysis should inflate/deflate costs to a single, common year; that year should be stated, and the indicator used to inflate/deflate costs should be cited.

   2. All costs were inflated, as appropriate to 2008 numbers using the UK Bank of England consumer price index inflation calculator, which was also done in Marra et al. IJTLID 2008. As such, we have now included the following statement on page 7 in the main manuscript and page 8 in the supplemental data attachment: “All costs were updated to 2008 GBP using the Bank of England Consumer Price Index”. The new costs are now listed in table 1 (pg 34 of the main manuscript). The Bank of England CPI calculator has been appropriately referenced in the main manuscript and supplemental data attachment. There was no time discounting of future costs as the time period of the model was only 2 years. The only significant cost incurred in year 2 (rather than year 1) in any case would be the costs of treating cases of active TB resulting in year 2. Given that the costs would have to be inflated by the price index and then discounted back at a rate similar to this, it was considered an acceptable approximation not to discount these costs back to 2008 pounds. We have made these points clearer in the supplemental data attachment (pg 9-10).

   Supplemental Data File (pg 9-10)

   ‘Despite the costs of active TB being incurred in the second year after initial infection, we chose not to discount these costs back to 2008 GBP as the rate of inflation used by the consumer price index (3.9%) is similar the rate of discounting typically used in cost analyses (3.5%).’

3. The description of the methods should indicate the software used for the model.

   We have now added the following statement to indicate the software used for our analyses on page 7 of the Methods section: ‘Construction of the decision tree and analysis was performed using TreeAge Pro 2009 (TreeAge Software Inc., Williamston, MA, USA) and Microsoft Excel 2003 (Microsoft, USA)”

4. The sensitivity analysis assumes equivalent efficacy for 6 and 9 month courses of isoniazid. North American treatment guidelines are based on Comstock’s reanalysis suggesting superior efficacy for 9 months vs. 6, but comparable efficacy for 9 and 12 months. If the authors disagree with this premise, then they should state this up front. But in that case it seems pointless to model (or prescribe) a 9 month treatment course--with assumed equivalent
efficacy to 6 months, but increased cost and toxicity risk.

4. We accept the authors’ concerns, but in contrast to the American Thoracic Society, the British Thoracic Society recommends treatment with 6 months of INH\textsuperscript{ii}. Consequently, our basecase analysis uses assumptions and costs based on 6 months of INH therapy. We have estimated efficacy of treatment for LTBI from the IUAT study\textsuperscript{iii}, [a large, multi-centre, randomised controlled trial which investigated isoniazid treatment duration] using 6 months of therapy.

We accept that longer durations of treatment are more effective (e.g. the same IUAT trial estimated that the efficacy of 12 months INH was 75% in contrast to 65% for 6 months). To account for the uncertainty over INH cure rates, we have varied the success rate of INH therapy in the sensitivity analysis and we discuss the results of this more fully in the discussion (pg 22 – see below).

Discussion (pg 22)
‘Other LTBI treatment regimens (3 months isoniazid and rifampicin) have been recommended by the British Thoracic Society [19] as alternatives to the currently used 6 months of INH. Furthermore, other countries, such as the USA, recommend the use of either 9 months INH or 4 months of rifampicin for treating LTBI [38]. However these effects are complex to model. Different regimens will affect certain parameters in the model, including effectiveness and costs of LTBI treatment, compliance (shorter regimens will be tolerated better), risk of hepatotoxicity and other adverse drug effects. Modelling these different treatment regimens was beyond the scope of this study but would be a fruitful area of future research.’

REVIEWER 2

Major comment

1. Most experts think that the risk of active TB will be at least as great in the rest of life as during the initial first two years after a primo-infection. This should be considered as this might improve the balance toward a sensitive test compared to a less sensitive one.

1. We agree with the reviewer’s comments that a longer time period would better account for the true number of downstream active TB cases. However, introducing a markov type process to adequately model this would add considerable complexity to the model. We chose a 2 year period as we wanted to examine costs and effectiveness over a fairly narrow time window more appropriate to the narrow decision-making time horizons of most healthcare institutions. Secondly, a shorter time period also increases the accuracy of certain assumptions (e.g. the assumption that there are no reinfections).

The reviewer is right to point out that a more sensitive test may detect more cases of LTBI and therefore prevent more downstream cases of TB. Consequently, we have included effectiveness measures in the model (table 3 on pg 39) and subsequent results sections of the revised manuscript (pg 11-12) now better highlights the benefits of a more sensitive screening strategy.

Results section pg 11-12
In our model, test sensitivities and specificities were varied according to the range of values reported in the literature. A lower test sensitivity (TST, QFT-GIT or T-SPOT.TB) reduces the cost of that strategy as fewer cases of true LTBI are detected and treated. However, these missed LTBI cases result in a greater number of post-primary TB cases for the 2 year screening period. As a result, lowering test sensitivity decreases the cost effectiveness of that strategy. CE rankings changed in favour of the QFT-GIT based strategies if QFT-GIT sensitivity is ~ 4% higher than T-SPOT.TB sensitivity. Similarly, screening with TST only becomes more cost-effective than IGRA single test options (QFT-GIT or T-SPOT.TB only) if the sensitivity of the TST is ~20% more than the sensitivity of T-SPOT.TB and ~17% greater than the sensitivity of QFT-GIT.

2. Rifampicin is a more efficient, shorter to apply and probably safer prophylaxis than Isoniazid. This should be evaluated to really bring perhaps some real improvement in this field. The higher price is likely offset by the improved observance, the lower hepatitis rate, and the fewer late reactivation of tuberculosis.

2. We accept the reviewer’s comments and have made this point in the discussion section of the revised manuscript. We have also suggested in the discussion that it might be fruitful area of subsequent research using this, or other, economic models to assess the costs, effectiveness and side effect sequelae of different LTBI treatment regimens. Please see the response to point #4 of the minor comments section of Reviewer 1.

Discretionary revisions

1. The authors should try to display with a graph the costs comparing TST and one or the other combined therapy to improve the comprehension of their reasoning in function at least of the sensitivity and specificity of the tests.

1. We have revised the manuscript to more clearly demonstrate the costs and effectiveness of the screening strategies so that the trade-offs between sensitivity and specificity of the three tests and five screening strategies can be more clearly seen.

EDITORIAL REQUEST

Please state the name of the ethics committee, which granted you permission to perform this investigation, in the Methods section of your manuscript.

Due to the nature of the study where we did not use any patients or patient information therefore it was not necessary to obtain ethical approval for the study. We have now stated this in the methods section (pg 7 of the main manuscript) – ‘No ethical approval was required for this study.’

\[\text{For example, see Tuberculosis Section. Health Protection Agency Centre for Infections London “Annual report on tuberculosis cases reported in 2002 in England, Wales and Northern Ireland” March 2005}\]