Author's response to reviews

Title: The benefits and risks of bacille Calmette-Guerin vaccination among infants at high risk for both tuberculosis and severe combined immunodeficiency: assessment by Markov model

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Author's response to reviews: see over
Dear BioMed Central Editorial Team,

We received a response to our submission “The benefits and risks of bacille Calmette-Guérin vaccination among infants at high risk for both tuberculosis and severe combined immunodeficiency: assessment by Markov model.” We wish to thank the referees for their excellent comments and suggestions. Upon careful review of their concerns, we have decided to revise and re-submit the paper for your review and re-consideration.

Please find attached the revised version of the paper, along with all associated files. We have also formatted the paper according to the instructions referred to in your communication. Below we have responded to all specific recommendations provided by the two referees, in an addendum.

Please do not hesitate to contact us if any additional information or revisions are necessary.

Kind regards,

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Referee 1

Annual risk of infection for TB should be determined: this should be a recommendation of the authors as conclusion based on an ARI.

This is a valid suggestion. Reference is already made to one example of an attempt to determine the ARI in a region, but the ARI in most areas has yet to be determined. We have recommended in the Conclusions section of the paper that efforts to determine the ARI in areas where BCG is in use be a priority.

Figure 5 should be better explained.

We have added a legend to this figure to explain the nature of the analysis being depicted, and the meaning of the terms displayed in the graph.
Statistical review important as I do not have sufficient knowledge to critically evaluate the methodology.

We believe that the second referee has raised many important statistical issues in the study, and hope that this suffices as an adequate statistical review.

Referee 2

Although it is stated that the primary outcome modelled is quality-adjusted life expectancy, the model has a time horizon of 15 years. As it is believed there may be differences in mortality rate between the intervention, it may be more appropriate to have a life-time horizon for the model, maybe using life-tables to estimate life-expectancy beyond 15 years of age.

The model did not consider a lifetime horizon, which has been recommended for decision analyses (1). As described in the Methods section, the study considered a time horizon of 15 years. This is consistent with other modelling studies on BCG benefits and risks (2, 3). Available evidence indicates that BCG protection last for 10-15 years (4, 5). There is no good evidence that neonatal BCG protects into adulthood, whether it protects against pulmonary disease, or whether it has any secondary herd immunity benefits resulting from reduced transmission (6, 7). For these reasons, using a lifetime horizon would not have changed any of the key outcomes in the model.

To avoid confusion, we have removed the term ‘quality-adjusted life expectancy’ from the paper, and replaced it with ‘quality-adjusted life-years.’ The latter is a more accurate description of the outcome modelled in each cohort until age 14 years. We have also commented on this issue in the Discussion section (page 18).

As the focus of the analysis is decision-analysis I would suggest concentrating on the selection of the option that maximises expected QALE consistent with a risk neutral decision maker (as in the threshold analysis shown in figure 5) rather than the significance tests shown in table 4. For instance, in the abstract it is stated that ‘QALE is not significantly improved by BCG unless SCID incidence is 0’. However is could also be stated that ‘QALE is not significantly approved by withdrawing BCG unless SCID incidence is 23’. To provide an indication of uncertainty it may useful to provide estimates of the probability that BCG is optimal for a range of SCID incidence. Maybe a graph or a table giving the probability that BCG is optimal as a function of SCID incidence for a range of ARI values. This would be analogous to a cost-effectiveness acceptability curve. I think this would make better use of the work done to make the decision-analytic model probabilistic.

We agree that results from sensitivity analyses would perhaps be of greater importance to the risk neutral decision maker. Upon reviewing the text, we believe the difference between sensitivity and uncertainty analyses may have been difficult to comprehend for
the reader. For this reason, we have modified certain parts so that results of both analyses are presented more clearly. In the Abstract, results of sensitivity analyses are presented before uncertainty analyses. We also clarify here that uncertainty analyses were done in the form of Monte Carlo simulations. In the Discussion section, a comment on the value of both sensitivity and uncertainty analyses to different readers has been added (page 17).

We also agree that results of uncertainty analyses could be better depicted graphically. Thus, Table 4 has been replaced by a new figure (Figure 6), showing the results of Monte Carlo simulations with varied risks of TB infection and SCID incidence.

If significance tests are used I would suggest using phrases such as ‘BCG results in a statistically significant increase in QALE (p=0.05)’ rather than ‘BCG significantly increases QALE’ which might be taken to imply that the magnitude of the change is clinically significant. I would also question the statement in the results section of the abstract: ‘with this ARI (0.1), BCG is contraindicated if SCID incidence exceeds 23 per 100,000’ as figure 5 indicates that expected QALE is reduced by BCG where SCID exceeds 4 per 100,000.

We agree with all of the above, and the text in the Results section has been modified accordingly. In particular, terms such as ‘contraindicated’ have been removed and replaced by phrases that describe the statistical association between factor and effect. Unfortunately, p values are unavailable from the program used for analyses. Statistical differences were determined when 95% confidence limits for different options (e.g. BCG or no BCG) did not overlap for a given parameter, as discussed in the Methods section.

The latter part of the above comment reflects a confusion similar to the concern in the former comment, namely the difference between sensitivity and uncertainty analyses. We believe that changes made to the paper will correct for this, particularly the presentation of Figures 5 and 6.

It would be useful if we were provided with some values of expected QALYs for the different strategies as a function of SCID and ARI so we have some indication of the magnitude of the differences between the options. This may be useful if decision-makers are not risk neutral. Currently we are given an indication of which is the optimum strategy and some indication of significance but no indication of the magnitude of the differences in the primary modelled outcome.

At the population level, the impact of an intervention designed to prevent a rare event (e.g. pediatric TB) may appear small when presented numerically. This would be the case if the number of QALYs among vaccinated and unvaccinated cohorts were presented. Nonetheless, this seemingly small magnitude of difference reflects the numbers faced by policy-makers in reality. Outcomes in the form of TB case tallies and mortalities have been presented in the paper (Figure 4, Table 3). However, we maintain that presenting the number of QALYs in various cohorts would be of little use to the reader – what we believe is important is that at certain parameters the QALY tally is higher or lower for a given BCG decision.


