Reviewer’s report

**Title:** The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention

**Version:** 3  **Date:** 13 February 2014

**Reviewer:** Koen Vanden Driessche

**Reviewer’s report:**

Most of my comments are essential revisions (not Major Compulsory Revisions, but also not minor). The article addresses an important concept:

TB care for children is often not considered a priority by TB programs because children do not contribute much to the epidemic: Children are most of the time not infectious. TB infection and disease in a child should however be considered as a sentinel event for ongoing transmission in the community. Children also make up the reservoir from which future infective cases may arise. It is very important that articles like this one that consider shortcomings in TB care and prevention for children are being published. The authors should make an important effort to improve the focus/message and fluency of the article. This process should be guided by their major findings (presented in the tables and figures) while avoiding distraction from less important findings. Also some data analysis should be repeated: who missed the opportunity to give a BCG vaccine? Was this opportunity missed in The Netherlands or in the home country? You have to take into account that the timing of the BCG vaccine is important: Best in newborns. Not so effective above the age of 5. I think the best way to approach this is by stratifying between children that lived abroad when they were infants versus children that lived in the Netherlands as an infant. But additional expert advise should be sought to come to a decision how to approach this best.

**Abstract:**

Not all conclusions can be made based on the presented results in the abstract. The results section does not cover BCG vaccination rates while the conclusion section does. Similarly the results section does not compare LTBI treatment between Dutch and foreign-born children. Overall the abstract does not read fluently.

**Introduction:**

Well organized. Key elements of the TB program and childhood TB are being discussed.

Maybe also briefly describe the difference between active and passive case finding in the introduction.

Some background info about BCG (you should include some but not all in the introduction):

BCG offers best protection if offered at a young age. Apparently the timing of
BCG vaccination in relation to the other childhood vaccines is crucial with BCG offering a non-specific protective effect beyond TB prevention. It appears that BCG also protects against bacterial sepsis and all-cause mortality. This benefit will likely be less pronounced in developed countries.

Methods:
Please include references to support the selection of program indicators.

Results:
Trend analysis
Was there no decline in incidence before 2001? Please specify.
I would stick to the term “native Dutch” instead of “native”.
Figure 2 shows 6 curves but the legend only shows 3

Characteristics of children with TB
I would include the one-year-olds with the less than one year olds and call them “infants less than 2 year old”.
What do you mean with primary TB infection and how does this discriminates from pulmonary TB. Please clarify.
I would not include a multivariate analysis to demonstrate an association between passive case finding and culture performance. Does not seem necessary to me.

Opportunities for prevention
Table 3 gives a very clear overview of missed opportunities. But the corresponding paragraph in the body of the text does not read fluently. Please simplify (the reader can find the details in the table).

I would add the timeframe in the title or the legend of table 3.

The usefulness of the last column of table 3 is not clear to me.

This is my most important specific comment:
You should clarify who missed the opportunity to give a BCG vaccine: was this opportunity missed in The Netherlands or in the home country? You have to take into account that the timing of the BCG vaccine is important: Best in newborns. Not so effective above the age of 5. If the opportunity to give BCG vaccines was mainly missed in The Netherlands, than there is room for TB program improvement. Figuring this out will require digging in the data again and new statistical analysis. I think the best way to approach this is by stratifying between children that lived abroad when they were infants versus children that lived in the Netherlands as an infant. If you don’t address this comment, the article will be much less solid but still publishable if you acknowledge this shortcoming in the discussion.

In table 3, third indicator: according to the body of the article the denominator
consists of children with disseminated TB and TB meningitis, but in the table TB meningitis was left out.

I don’t understand the meaning of the sentence “The majority of the latter children (149 (81%)) had been detected through SCI or screening.”

Table 4 contains a “#”, but this is not explained in the legend (I assume that the authors intended to specify the covariates for which the OR was adjusted).

Please clarify that the OR in table 4 means the OR to be detected through passive case finding

Please include the OR for the subtotal foreign-born in table 4

In table 4, I would not group culture negative together with unknown (i.e. leave unknown out). Please specify how patients are classified who are at the same time ETB and PTB. Consider using the abbreviation EPTB instead of ETB.

In table 4 the reference value for the OR for the types of TB does not make sense to me. You might consider leaving “Type of TB” and “Culture” out of this table or simplify to PTB (the reference) and EPTB (for which you can give an OR)

Consider presenting an adj-OR for BCG (because the crude-OR is likely to be confounded by ethnic origin)

Did you get any info on MDR in children?

Can you predict how many TB cases could have been prevented? Taking into account the effectiveness of the different preventive opportunities that were missed?

Discussion:

Please specify the international standards. Consider including data from neighboring countries as a comparison.

“clinical case” does not mean “hospitalized patients” in some English speaking countries

Typo: “more likely not to be missing”

In general 3 limitations are discussed in the discussion section: other limitations would be that while you identify risk factors, there is no guarantee that an intervention aiming at tackling those will actually reduce the incidence of TB.

You write “Universal coverage of BCG vaccination in target groups would have most impact on the occurrence of TB”. Is this truly the measure with the highest impact? Does this target group consist of newborns (with an immigrant parent)? New immigrant children above the age of 5? If this target group consists of the latter: How effective is BCG at a later age (i.e. for new immigrant children that were not vaccinated before) and what is the downside / are the dangers associated with BCG vaccination? Who will screen for these risk factors?
Another measure (other than LTBI treatment) to consider for immigrants would be follow-up to detect TB cases early.

What about patient/parent education. Another intervention that might help with detecting future cases early.

Overall the discussion should read a bit more fluently.

Conclusion:
I don’t think that you can conclude that TB treatment in the Netherlands is well managed, because your results do not cover management issues or how much health care providers know about TB treatment: You probably mean that most patients have a successful treatment outcome or that the TB program is well organized with intensified active case finding?

In the conclusion you suggest that risk groups are well screened, but in the table 4 you demonstrate the opposite. A major finding of this article is the low active case finding proportion in the immigrant population, but this is not discussed in the conclusion.

The conclusion should be more focused, guided by the major findings of the different tables and figures.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests