Author's response to reviews

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

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Version: 5 Date: 4 April 2014

Author's response to reviews: see over
Dear editor,

Thank you and the reviewers for the critical review of this paper. The comments and suggestions have improved the quality of our paper. Below we have responded to each point and we explain how we have addressed them in the paper. We have also copyedited the paper to improve the written English as you have suggested. For convenience of the reviewers, we have marked alterations in the original text in red text.

With kind regards,
Connie Erkens

Reviewer's report 1
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.

Author’s response:
We intended to evaluate the opportunities for prevention in the Netherlands, according to current Dutch policies. Therefore, in all children eligible for BCG, the opportunity was missed in the Netherlands. To answer to the point raised that BCG vaccination is most effective among children < 5 years, we have calculated the rates in the different age groups and included the results in the results section.

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.

Author’s response:
Thank you for pointing this out. We have rephrased some of the results and the conclusions in the abstract to address your points.
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.

Author’s response:
In line 72 we have specified ‘early case finding as ‘active case finding’ through screening and contact investigation.

- 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.

Author’s response:
In line 63 we have added a sentence on the effectiveness of BCG-vaccination:
“BCG offers best protection if offered at a young age [1]. We have also added more information on the BCG-policy in the Netherlands in line 84-88: “In the Netherlands to new-born children with a parent born in a TB endemic country (defined as an estimated incidence according to WHO >50 per 100,000 population). Not previously vaccinated immigrant children are offered BCG-vaccination until an age of 12 years.”

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

Author’s response:
In line 117 we defined the outcome indicators for missed opportunities in TB prevention. These indicators were defined for the purpose of this study, and are not generally used as program indicators in TB control. For instance for BCG-coverage WHO guidelines recommend for treatment outcome: 85% successful completed. However for the purpose of this study, we have used 100% treatment completion as objective.

Results:
Trend analysis: Was there no decline in incidence before 2001? Please specify.

Author’s response:
From 1993 until 2000 there was no clear change in the annual incidence. We have added this information in the text.

I would stick to the term “native Dutch” instead of “native”.

Author’s response:
Thank you for pointing this out. We have corrected this in the text.

Figure 2 shows 6 curves but the legend only shows 3

Author’s response:
Thank you for pointing this out. We have corrected this in the figure.

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”.

Author’s response:
Thank you for pointing this out. We have corrected this in the text.
What do you mean with primary TB infection and how does this discriminates from pulmonary TB. Please clarify.

Author’s response:
Primary TB are TB cases notified with ICD-9 codes 010. For clarification we have added in the introduction (line 59-60) ‘In children TB typically presents by the formation of a primary complex in the lungs consisting of a small peripheral pulmonary focus and hilar or paratracheal lymph node involvement’ We have also clarified this in Table 1.

I would not include a multivariate analysis to demonstrate an association between passive case finding and culture performance. Does not seem necessary to me.

Author’s response:
We do believe it is important to control for potential confounders like type of TB. After adjustment, this association was still present.

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).

Author’s response:
We have shortened and simplified the text in order to make it more readable.

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

Author’s response:
We have added the time frame in the title following your advice.

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

Author’s response:
We have removed the last column following your advice.

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.

Author’s response:
The opportunity was missed in the Netherlands, as these children belong to the target group for BCG-vaccination in the Netherlands. All children <12 years either born in a TB endemic area or with a parent born in an TB endemic are targeted for BCG-vaccination. Foreign born children should be checked for proof of BCG-vaccination when being screened for active TB after entry in the Netherlands. If no proof of BCG is found, they receive a tuberculin skin test. We have described this policy more in detail in the introduction. However, following your advice we also have reanalyzed the data, and have added information in the results section on the percentage of Dutch-born children in the target group for BCG who were not BCG vaccinated (line 197-199) and the percentage of children who were not vaccinated with BCG upon entry screening by age group.

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.

Author’s response:
Thank you for pointing this out. We have corrected this in the table.

I don’t understand the meaning of the sentence "The majority of the latter children (149 (81%)) had been detected through SCI or screening."
Author’s response:
When children are detected through contact investigation, this usually happens in the household setting. In these cases investigation of the child’s contacts is usually not needed. We have rephrased the sentence: ‘When no SCI was performed the majority of the child TB patients (149 (81%)) had been detected through SCI or screening themselves’ (line 206).

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).
Author’s response:
Thank you for pointing this out. We have corrected this in the table.

Please clarify that the OR in table 4 means the OR to be detected through passive case finding
Author’s response:
Thank you for pointing this out. We have corrected this in the table.

Please include the OR for the subtotal foreign-born in table 4
Author’s response:
The OR for the subtotal of foreign born was 4.6 (2.4-8.8). We have added this to the table.

In table 4, I would not group culture negative together with unknown (i.e. leave unknown out).
Author’s response:
We have chosen to group culture negative together with unknown, to avoid too many categories in this variable and because culture negative cases are fewer compared to culture unknown cases. Moreover, we know from another study validating the NTR data, that culture unknown results, are likely to be negative or culture not done.

Please specify how patients are classified who are at the same time ETB and PTB. Consider using the abbreviation EPTB instead of ETB.
Author’s response:
We have chosen to group patients with combine ETB and PTB disease among the group with PTB disease and renamed this category PETB to clarify. We have clarified this in the table. As EPTB may be confused with PETB, we opted to keep the abbreviation 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)
Author’s response:
As replied to your comment above, we believe it is important to control for potential confounders like Type of TB, which are independently associated with passive case finding. We have specifically chosen the categories for Type of TB to illustrate the distinction in severity of disease between children found actively and passively.

Consider presenting an adj-OR for BCG (because the crude-OR is likely to be confounded by ethnic origin)
Author’s response:
In the model including BCG (with non-BCG vaccinated as the reference category) the adj OR for BCG was not significant any more: 1,5 ( 95% CI 0.815-2.6). Also the fit of the model did not decrease after removing BCG from the model. Therefore we chose not to include BCG in the model.
Did you get any info on MDR in children?
Author’s response:
There were 2 children aged 10-14 year with MDR TB. We have added this to the results (line 153).

Can you predict how many TB cases could have been prevented? Taking into account the effectiveness of the different preventive opportunities that were missed?
Author’s response:
For children completing preventive treatment we estimate how many cases were prevented based on a reported life time risk for progression to TB disease of on average 10%, and effectiveness of preventive treatment with 6 months of isoniazid of 70%: 962 (n completing preventive treatment)*0.7(effectiveness)*0.1(life time risk)=65.7. We have added this calculation in the discussion (line 234-236).

Discussion:
Please specify the international standards.
Author’s response:
WHO recommends a treatment completion rate of at least 85%. We have clarified this in the text.

Consider including data from neighboring countries as a comparison.
Author’s response:
We have referred to a range of the culture confirmation rates cited in studies from Western settings (Denmark, UK, EU, Israel). ‘This is comparable or higher than rates reported in other studies ranging from 40%-64% among cases from whom material for culture was obtained [2, 3].’

“clinical case” does not mean “hospitalized patients” in some English speaking countries
Author’s response:
’Clinical case’ in our study means ‘symptomatic case” detected through passive case finding, and treated in the ‘non-public health sector’. For more clarity we have rephrased the sentence: ”The data represent both symptomatic cases detected in the curative sector as cases detected and managed ambulatory in the public health sector by the MPHSs.”

Typo: “more likely not to be missing”
Author’s response:
Thank you for pointing this out. We have corrected this in the text.

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.
Author’s response:
We agree with the author that an intervention does not guarantee reduction in incidence, for this reason we focused on identifying missed opportunities and have refrained to state what the impact of ‘not missing” the opportunities could have been, other than in the group non-BCG vaccinated children.

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?
Author’s response:
Missed opportunity for BCG vaccination is the largest group. IN this group, according to BCG studies at least 50% of child TB cases could have been prevented and at least 80% of serious forms of TB.
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?

Author’s response:
The majority -61%- of these children was younger than 5 years of age. We have added this information to the results.

Another measure (other than LTBI treatment) to consider for immigrants would be follow-up to detect TB cases early.

Author’s response:
Follow-up screening for TB is indeed a possibility, but not a feasible option in the Netherlands. However, in a retrospective study among 46 424 asylum seekers Van Burg et al. showed that < 50 per 100,000 children <12 years were likely to have incident pulmonary TB within approximately one year TB after entry. For this reason biannual follow-up TB screening of children<12 years was abolished in 2003. Another study in the Netherlands based on data from the screening of immigrants 1998-2002 (unpublished) showed that the follow-up screening was not cost-effective, even among immigrants from high-endemic countries.

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

Author’s response:
Indeed parent education could help to raise awareness from parents to seek health care timely when TB symptoms occur. However, this intervention would help to reduce patient delay, and not necessarily prevent incident TB cases.

Overall the discussion should read a bit more fluently.

Author’s response:
We have rephrased some sections of the discussion and emphasized the main findings.

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?

Author’s response:
Yes indeed, this is what we mean to state, we have clarified this in the text. We do believe that based on these results we are able to state that TB treatment in children is well managed, as treatment success rates are regarded as a proxy for case management by WHO. Another indicator for the quality of treatment is the relapse rate. Relapses were not reported in our study. We have added this observation in line 153.

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.

Author’s response:
We have indeed reported in the study that foreign born children are less likely to be found through active case finding. In the conclusion we come back to this finding when state: ‘However, excess mortality and morbidity may be further prevented through improved implementation of existing preventive measures such as targeted BCG vaccination and diagnosis and treatment of LTBI among foreign born children, and exploring feasibility and (cost) effectiveness of screening and preventive
treatment of LTBI in children from TB high endemic countries.’ We have adjusted the wording slightly to emphasize the relation to case finding and prevention in foreign-born children.
Reviewer's report 2
Title:The epidemiology of childhood tuberculosis in the Netherlands: still room for prevention
Version:3Date:19 February 2014
Reviewer:Andrea Cruz

General:
• This is a very interesting longitudinal article on the epidemiology of TB in a low-incidence nation. While much of the existing literature focuses on high-burden nations, there are lessons to be learned from the management of TB in low-incidence settings (many of which were high incidence settings 50 years ago). The fact that almost two-thirds of cases are detected actively is a testament to the efficacy of TB control in the Netherlands.

Title:
• Accurately reflects manuscript content.

Abstract:
• Results section: if you could elaborate in the text (not the abstract) if culture confirmation rates were lower in the children who were actively detected because cultures were not attempted in these children. Alternatively, you could present these data as # with + cultures / # in whom cultures were attempted to help control for the bias in terms of which children we attempt to obtain cultures from.

Author’s response:
We have added the information as suggested in the results section and elaborated on the results in the discussion (line 253): "In this group the culture-confirmation rate was low because culture was not performed in 65% of the cases, but it was also low in cases where culture was attempted. This reflects the difficulty to obtain culture confirmation in early TB disease in children as well as the Dutch consensus that the combination of obvious exposure, etc......"

• Results section: please clarify what is meant by ‘... a more pronounced decline among foreign born adults.’ I ask because when reading the bottom of page 4, the proportionate decline was higher among native adults than foreign-born adults.

Author’s response: We meant that the decline in TB incidence among foreign born adults was not observed among foreign born children. We have taken out this part of the sentence from the abstract to avoid confusion.

• What % of passively detected cases may have been candidates for LTBI testing? I ask this specifically because a recent US paper by Winston and Menzies (Pediatrics 2012) described that almost three-quarters of all US pediatric TB cases represented potential missed preventive opportunities.

Author’s response:
According to the current guidelines target groups for LTBI testing are - TB contacts, children more than 1 year of age before BCG/vaccination, Dutch born children who have traveled to TB endemic areas for more than 3 months and all foreign born non BCG vaccinated children younger than 12 years at post/entry screening. From our data, we could only evaluate the missed opportunities in LTBI-screening of TB contacts. We proposed as a further opportunity for prevention all children who developed TB shortly after immigration. As we have explained in the text, we presume they could have been detected with TB infection at post/entry screening.

Winston and Menzies use presence of a foreign born parent or residence in a foreign country as a proxy for possible missed opportunities. Based on this they estimate that three quarters of pediatric patients with TB in the US have potential TB exposures. However, they do not evaluate whether actual possibilities have occurred. In the Netherlands, a similar proportion -74%- of the child TB population is foreign born or 2d generation immigrant, and in 37% of the cases we found a possible missed opportunity for prevention within the present possibilities of TB control. However, being foreign born and longer than 6 months in the Netherlands was independently associated with being found passively, suggesting missed opportunities in this population.

Introduction:
2nd paragraph: please provide more details as to the primary preventive therapy to child contacts: is this done as directly observed preventive therapy?

Author’s response:
We have information on DOT in TB cases, but we do not have information whether preventive treatment was administered under DOT in children. From what we know from the general practice, if the index case is treated with DOT, preventive treatment of household child contacts is often given at the same time. In other cases, treatment will be administered by the well instructed parent or guardian. We have entered some information on the DOT practices in children in the introduction (Line 75 and 164) and the results and entered the proportion of child TB cases treated with DOT in Table 1.)

Would suggest mentioning the Netherlands’ BCG vaccination practices in the introduction, as there is variation in how the vaccine is utilized in different nations (e.g., is it given to native Dutch children in addition to foreign born and 2nd generation children?).

Author’s response:
In line 83 we have added a sentence on the BCG-vaccination policy:
“In the Netherlands BCG vaccination is targeted to new-born children with a parent born in a TB endemic country (defined as an estimated incidence according to WHO >50 per 100,000 population). Not previously vaccinated immigrant children are offered BCG-vaccination until an age of 12 years.”

Which IGRA is utilized for the 2-step testing?

Author’s response:
There is no specific preference for the IGRA test. We have specified this now in the text (line ....)

Methods:
Is INH available only through the MPHS, or is it commercially available?

Author’s response:
INH is only available on prescription of a medical doctor.

Do private practice physicians also voluntarily report new LTBI cases? (getting at possible biases in what’s reported; despite this, it is still far better than US policy, where LTBI cases are not reportable)

Author’s response:
In the Netherlands health care is organized in three different settings: 1) public health care, provided by the Municipal Public Health Services, which generally deals with hygiene and infectious disease control; 2) Family health care, provided by general practitioners; 3) Clinical care (either hospital or outpatient based), provided by specialized physicians. The GP will normally refer suspected TB patients to either MPHS or hospital for further diagnosis. LTBI can be diagnosed in the public health care and hospital setting. Since the main reason for examination for LTBI is contact investigation, most children with LTBI will be diagnosed in the public health sector. Rare cases diagnosed by hospital specialists are usually not notified to the NTR.

Also, do you think reporting among foreign-born children is higher because they are screened in venues where providers report cases (MPHS)?

Author’s response:
As we explained in the answer above, LTBI screening in children is typically performed in the context of contact investigation (see table 2). Only non-BCG vaccinated immigrant children are screened for LTBI at entry screening. Out of 1120 reported cases only 42 were reported as detected by screening.

Bottom of page 3: does the patient management portion also query adverse events?

Author’s response:
Yes, adverse events are reported in as far they cause delay or require adjustment of the treatment regimen. However, they occur rarely. We have entered information on the total of adverse events in Table 1. In 4 children <5 years 2 children with a drug allergy and 2 children with adverse events were reported. In 12 children 5-14 years the nature of adverse events was: hepatic dysfunction (4), neurological symptoms (1), psychic symptoms (1), allergy (4), joint pains (1), other non-specified (2). No children were reported with visual dysfunction.
Results:
- Top of page 5: would change from ‘active TB’ to ‘TB disease.’
  
  Author’s response:  
  We have corrected ’active TB’ to ’TB disease’ throughout the document.’

- How many foreign-born children with disease came from countries considered to be high prevalence nations by WHO?  
  - This could potentially be added to table 1.
  
  Author’s response:  
  99 children came from countries with an WHO/estimated incidence more than 200 per 100,000 population. We have added this information in Table 1, based on estimated WHO incidence in 2008.

- Page 5, 1st paragraph: please clarify what is meant by ‘primary TB infection (35%),’ as this term ordinarily is used to describe the pathophysiology, not the disease site per se. Are you referring to a Ghon complex or intrathoracic adenopathy? If so, for purposes of clarity, would recommend stating it as such.
  
  Author’s response:  
  Primary TB are TB cases notified with ICD-9 codes 010. For clarification we have added in the introduction ‘In children TB typically presents by the formation of a primary complex in the lungs consisting of a small peripheral pulmonary focus and hilar or paratracheal lymph node involvement.’ We have also clarified this in Table 1.

- If you have the % for CNS, miliary, and skeletal disease, would suggest adding those numbers.
  
  Author’s response:  
  We chose to display these serious forms of TB separately. Since the table is already rather large, we choose not to show a subtotal for these categories.

- None of the children had peripheral lymphadenitis?
  
  Author’s response:  
  This cases are categorized under ICD9 code ‘Other specific forms of TB’. Since this is a indeed a rather large disease category, especially among older children, with have added a separate category for this diagnosis in Table 1 ‘TB of peripheral lymph nodes’

- If you have the data, would suggest breaking down the culture-confirmed cases by radiographic finding. Given the frequency of diagnosis by active surveillance in the Netherlands, I suspect many children had isolated intrathoracic adenopathy, where the culture yield will be abysmal. However, many of the children identified passively likely have more impressive radiographic findings and we may expect that culture yield will be higher in these children.
  
  Author’s response:  
  We do not have information on radiographic findings.

- The culture yield in the passively identified children is one of the highest I have ever seen. How many cultures are recommended by the national guidelines?
  
  Author’s response:  
  There are no official guidelines recommending the number of cultures in the case of children suspected with TB. The national guidelines for laboratory diagnosis of tuberculosis date from 2008. In this guideline it is stipulated that induced sputum may yield better results than gastric lavage. However, we do not now from our database what body material is used for culture.

- If you change the denominator for culture yield to those in whom cultures were obtained, as opposed to the entire population; for the passively identified children, this brings the yield to 84%.
  
  Author’s response:  
  Thank you for pointing this out. We have now indeed added this information in the results.

- Treatment outcome: a minority of children was admitted, yet cultures were obtained in the majority. The beginning of the study period predates sputum induction. How were so many specimens obtained in the outpatient setting, especially given that almost 40% of cases occurred in the <5 yr old group?
Actually the definition of hospital admission in the NTR is 'admitted for more than 1 week', as it is intended to capture cases that are managed on a clinically basis after diagnosis. We have added this information to Table 1. It is well possible that an (unknown) proportion of the children was admitted for a short period until TB diagnosis was made and the treatment was started.

Page 5, last paragraph: 'notified' is duplicated in the first sentence.
Author’s response: Thank you for pointing this out.

Was there a change in acceptance or completion rates for LTBI therapy after integration of IGRA into LTBI diagnostic guidelines to confirm a positive TST?
Author’s response: This is an interesting question, but it is difficult to answer from the registration data. IGRA were gradually introduced since 2008. In the guideline for LTBI diagnosis, endorsed in 2010, it is stipulated the diagnosis LTBI in non/BCG/vaccinated children younger than 5 years should either be based on a TST\(\geq\)10mm or a TST\(<\)10mm and a positive IGRA. In BCG/vaccinated children the diagnosis is based on a positive IGRA. On the other hand acceptance is also a matter of believe from the physician that a positive reaction can be attributed to recent exposure. Indeed, in another study published recently in the International Journal for Lung Disease and Tuberculosis,[4] we have shown that more LTBI cases are eligible and given preventive treatment when IGRA is used in BCG/vaccinated populations.

Regarding source case investigation: in what % of passively detected children was a source case identified after the child's diagnosis?
Author’s response: According to the registration in total 76 SCIs were performed among 19 children with sputum smear positive TB, 28 with smear negative TB and 29 with extra pulmonary TB. Respectively 4, 8 and 10 contacts with TB were identified among 4, 7 and 5 index cases. This adds up to 21% of all SCIs among passively detected children. Since this is rather detailed information, we chose not to include this information in the paper.

Discussion:
Page 7, 2nd full paragraph: may want to note that up to 20% of children who receive the BCG vaccine do not have a scar. Am also curious as to what % of children had BCG status verified by immunization record vs scar.
Author’s response: In the registration system BCG vaccination is recorded as 'yes' both when a scar is present or when other evidence of vaccination is present such as a vaccination card. This means we have no specific information on the proportion of children that actually had a scar. As is argued in the discussion, passively detected children may also not have been thoroughly checked for the presence of a scar or other evidence of BCG vaccination.

The last paragraph before the conclusions is key; modification of LTBI screening in immigrants is going to be key to decrease the number of cases in the Netherlands and other low-incidence nations.
Author’s response: Thank you for this observation. Presently we are indeed considering to move to LTBI screening in immigrants. We hope this paper will provide the evidence to do so at least in the case of children.

Conclusion paragraph: extra word is added in the last sentence: 'access'
Author’s response: Thank you for pointing this out.

References:
• Appropriate and current.

Tables:
• Table 1: The #s for culture-confirmed cases in table 1 and the text do not seem to match. Please
clarify. The numbers in the table are more in line with published literature.

Author’s response:

*In the text we state* `Overall, 32% of childhood TB diagnoses were bacteriologically confirmed` *as is displayed in Table 1. This percentage is low, since 64% of the children are detected actively, and the confirmation rate is only 12% as is explained in the text. We have edited the text to make this more clear to the reader.*

- **Table 2**: were completion rates higher in children identified with LTBI during contact investigations?

Author’s response:

*As explained earlier, the largest proportion of children with LTBI – 83% -were diagnosed through contact investigation. Of 185 children with LTBI diagnosed for other reasons than contact investigation 93% completed the treatment successfully, which is slightly better than the contacts/ 89%.*

- **Table 3**: please clarify what is meant by ‘target group.’ I really like this table, but think that clarifying it a bit would be incredibly high yield.

Author’s response:

*We mean ‘target group for the intervention listed in the first column.’ We have added this to the heading of the column in the table. We also removed the last column of the table following the advice of reviewer 1.*

Figures:

- **Figure 2**: The coloring of the lines in figure 2 is somewhat difficult to read; consider modifying if possible (especially the top line). Additionally, the figure legend does not include all the lines in the figure, but only 3 of the 6.

Author’s response:

*Thank you for pointing this out, we have adjusted the lines and legend accordingly.*


