

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population-based cohort study
<b>AUTHORS</b>	Winje, Brita; Groneng, Gry; White, Richard; Akre, Peter; Aavitsland, Preben; Heldal, Einar

### VERSION 1 – REVIEW

<b>REVIEWER</b>	David Roth British Columbia Centre for Disease Control Vancouver, BC, Canada
<b>REVIEW RETURNED</b>	07-May-2018

<b>GENERAL COMMENTS</b>	<p>Objective of paper: “to use Norwegian immigration and TB surveillance data to measure the effectiveness of the immigrant LTBI screening program, using estimates of the NNS and the number needed to treat for different immigrant screening strategies.”</p> <p>Summary of Work: Winje et al. analyze the Norwegian LTBI screening policy by using: 1) aggregate data from the Norwegian Directorate of immigration, 2) country specific incidence estimates from the WHO, and 3) individual level case and treatment data from the Norwegian Surveillance System for Diseases (MSIS). Within-Norway incidence (notification rate) for each country-of-birth group is calculated using the aggregate immigration data to calculate person-time estimates, with diagnoses and treatment data coming from MSIS. The authors also calculate the number needed to screen (NNS) and number needed to treat (NNT) by dividing the screening and treatment totals by the preventable TB cases (those diagnosed after 1 and 6 months) diagnosed in Norway. Finally, the Winje et al. compare the NNT with both the incidence in the home country and incidence in Norway.</p> <p>Results show that incidence in the home country is not as good a predictor of TB outcomes as is incidence in Norway. The NNS/NNT remains high for many immigrant groups. Results also show that early treatment of LTBI is a requirement in order to reduce TB incidence in low incidence countries where TB occurs primarily in the foreign-born.</p> <p>Reviewer Comments:</p>
-------------------------	---

	<p>General/Writing</p> <ul style="list-style-type: none"> <li>□ The article is well written with few typos or grammatical errors. Kudos to the authors for providing such a clean, concise and well written document.</li> <li>□ Tables are well laid out and concise, with footnotes providing the needed information for interpretation.</li> </ul> <p>Abstract</p> <ul style="list-style-type: none"> <li>□ The abstract reads well. No major issues.</li> <li>□ Page 2 line 21 - use of “sensitivity” twice in same sentence. Consider re-writing.</li> </ul> <p>Introduction</p> <ul style="list-style-type: none"> <li>• LTBI screening and treatment is a key approach to the reduction of TB incidence in low-incidence regions where a high percentage of total TB may result from reactivation of LTBI in recent immigrants.</li> <li>• Effectively evaluating regional LTBI screening programs in regions with low TB incidence is extremely important, as targeted approaches are often required.</li> <li>• The introduction provides a clear, concise summary as to the research objectives, and why such work is important. Both the topic of study, as well as the study objectives, are worthy of study.</li> <li>• Page 4 line 7: “treatment of LTBI in groups at high-risk groups” <ul style="list-style-type: none"> <li>o Sentence reads strangely. Consider re-writing</li> </ul> </li> </ul> <p>Methods:</p> <ul style="list-style-type: none"> <li>• The use of country specific incidence, NNS and NNT estimates are all appropriate for a study of this kind.</li> <li>• The paper could be improved by better describing the nature of the MSIS system. Would help clarify what data is captured within the surveillance system for each client, and what information is instead estimated from other studies.</li> <li>• The use of national estimates of group specific emigration data provides a strong estimate of the person-time experienced by recent immigrants. The resulting regional incidence estimates are therefore expected to be stronger than those done in regions lacking such emigration estimates.</li> <li>• The inability to determine the total number of people with LTBI is a common challenge of research of this kind. The authors attempt to estimate this number based on previously published IGRA positivity estimates. Some of these estimates come from outside of Norway (the UK specifically), which could in theory influence the accuracy of LTBI estimate. However, Winje et al. also refer to a previous regional study focused on a cohort of immigrants in Norway to provide regional estimates that likely improve the accuracy of subsequent calculations.</li> <li>• Primary Issue: In many ways, this work represents a modelling exercise that on initial reading is presented as a retrospective cohort study. As a result, I found the methods somewhat challenging to understand in initial readings, especially the section outlining the “Assumptions and definitions”. It took me many reading to begin to understand exactly how certain numbers were arrived at. Specifically: <ul style="list-style-type: none"> <li>o Page 5 line 19 – I don’t understand the NNT correction presented here. Unclear why 1/risk of preventable TB in case of no</li> </ul> </li> </ul>
--	---

	<p>emigration from Norway. Some additional explanation may be warranted.</p> <ul style="list-style-type: none"> <li>o page 5 line 21 - unclear what "probability" refers to here? Doesn't seem to be a probability calculation, should be able to directly calculate given a patient's Date of Birth and immigration arrival date. If that latter piece of information is missing, it may be worth explicitly stating so.</li> <li>o page 5 line 28 - methods are unclear regarding how to calculate the "total number of individuals with TB or LTBI treatments" - again related to use of the word "probability"<sup>[SEP]</sup> <ul style="list-style-type: none"> <li>□ Could this be better described as the "percentage of total cases"? Or am I not understanding this concept?</li> <li>□ A more detailed description of how it was determined if a client immigrated to Norway</li> </ul> </li> <li>o Page 5 line 29 - I did not understand the nature of the "adjusted probability" that was described here.</li> <li>o page 6 line 13 – unclear exactly how the “subsequent risk of preventable TB in different time periods” was calculated.<sup>[SEP]</sup> <ul style="list-style-type: none"> <li>• I believe that a re-write and re-framing of the methods, or at least a more detailed discussion of the calculations and assumptions, could improve the clarity of the methods and the understandability of the paper as a whole. The authors could also focus on providing a rationalization for some of the “corrections” and “adjustments” made.</li> <li>• That said, I fully admit that my lack of understanding may stem from a limited understanding of the particular datasets.</li> </ul> </li> </ul> <p>Results:</p> <ul style="list-style-type: none"> <li>- As discussed, I had some problems following the exact calculations that were described in the methods. That said, the results as calculated were presented clearly and concisely. Perhaps additional effort could be placed in clearly describing how the three tables relate to each.</li> <li>- The NNS provided in table 2 is not as described in text. The text (page 5 line 44) describes the calculation as “the ratio of the number of arriving immigrants to the number of incidence TB cases observed in Norway within 5 years”. I believe the value presented in table 2 is in fact the number of arriving immigrants divided by the number of “preventable” TB cases, and not incident TB cases.</li> <li>- The information provided in figure 1 could more clearly be presented in a table. That said, the use of a figure is acceptable and should not limit publication.</li> </ul> <p>Discussion:</p> <ul style="list-style-type: none"> <li>- The authors do a good job of discussing the potential limitations of the work, and most importantly, clearly identify the public health value of this work.</li> <li>- The discussion of how classifying immigrant groups on the basis of country alone may mask important socioeconomic differences (perhaps better captured by the TB notification rate in Norway) was appreciated.</li> <li>- The authors conclude that the high NNT/NNS suggests alternative screening approaches are needed: 1) reduce pool of those screened by focusing on those with additional risk factors, and 2) engage screening and treatment earlier. While point two will undoubtedly decrease TB, it still requires screening a huge</li> </ul>
--	---

	<p>number of immigrants and may be unfeasible in most settings. I suspect a combination of the two approaches would be needed in many settings.</p> <p>Reviewer Conclusions:</p> <ul style="list-style-type: none"> <li><input type="checkbox"/> I believe this is an important area of research. Evaluating TB screening in recent immigrants in low-incidence countries can be difficult to evaluate because of limited post-arrival data. This study is not alone in lacking refined denominator estimates when estimating post-landing incidence and does an admirable job of refining these estimates using emigration data. Similarly, this is not the only study that does not have access to all IGRA screening data, and appropriately uses published literature values to estimate these hard-to-get values.</li> <li><input type="checkbox"/> As discussed, I did experience some confusion with the methods and assumptions described in section titled “Assumptions and definitions” section of the Methods. However, I fully admit this may result from my limited experience with these types of calculations and approaches. That said, I would suggest the authors focus on clarifying the methods/calculations as much as possible to aid the reader. The addition of a table in the appendix that explicitly outlines the nature of each calculation could help improve the readers understanding.</li> <li><input type="checkbox"/> Overall, I feel that this article is worthy of publication given the minor modification described above. It effectively provides additional evidence on the challenges scaling up LTBI screening and treatment, and provides novel data clearly showing the value of early LTBI treatment if the preventative aim is a reduction in the total number of active TB cases within a low-incidence setting.</li> </ul>
--	--

<b>REVIEWER</b>	Iacopo Baussano International Agency for Research on Cancer, Lyon, France
<b>REVIEW RETURNED</b>	18-May-2018

<b>GENERAL COMMENTS</b>	<p>The findings reported in the manuscript entitled "Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population- based study" are potentially very relevant for Norway and other high-income countries with low incidence of TB. However, I am unable to judge on the validity of the findings because the definition of the objectives of the study is only partially clear and the methods are difficult to follow.</p> <p>The authors state the following objectives: a) to use Norwegian immigration and TB surveillance data to measure the effectiveness of the immigrant LTBI screening programme, b) to assess the impact of LTBI treatments in a 4-year cohort of immigrants to Norway, and c) to measure the effect of timely follow-up of screening results.</p> <p>It is not clear however, how these objectives relate to each other. Are they independent or not? If they are independent, I strongly suggest to address them in separate manuscripts (or at least sections of the manuscript). If not, it should be clarified how they relate to each other. Incidentally, both objective b) and c) are not formally defined. What measure of impact of LTBI treatments is going to be provided? How is measured the effect of timely follow-up of screening results? Please define measures of impact and effect.</p>
-------------------------	---

	<p>Methods section.</p> <ul style="list-style-type: none"> <li>- Are the administrative data on the number of immigrants (line 41) used to define the population at risk? If so, why this is not also stratified by age and gender? Are these administrative data exhaustive? Do they accurately capture migration events occurring in Norway?</li> <li>- It is not clear how date of emigration of refugees and asylum seekers was calculated based on a percentile distribution of the number of days before final application rejection. Please clarify.</li> <li>- The authors state that untreated LTBI is not reported, so how was the number of individuals testing positive for LTBI (a key competent on NNT) calculated? I suspect that this is described in the section "Assumptions and definitions", see lines 14 to 20. Please clarify. As I understand, the number of LTBI in Norway among immigrants was calculated by multiplying the number of arriving immigrants by the estimated percentage of immigrants with a positive IGRA was based on published literature. This is a very serious limitation which needs to be carefully discussed in the limitation section. How (in)accurate can the calculated number of LTBI be? What biases in the available information can distort the estimate and in which direction?</li> <li>- In the "Assumptions and definitions" section, the authors provide a narrative description of methods to calculate different quantities (see lines 14, 21, 28, and 34). I suggest to provide more formal definitions, accompanied with formulas and a list of indexes. I also suggest to clarify where the calculated values are subsequently used and what for. In the current version of the manuscript the text is difficult to interpret. For example, at lines 28-29 it is stated "We then calculated the total number of individuals with TB or LTBI treatment by multiplying the number of patients by the adjusted probability that they immigrated to Norway in 2008-2011". What is the "adjusted probability"? It is also unclear whether for the calculated values some range of uncertainty is provided or not.</li> <li>- In the section entitled "NNS and NNT" it should be clarified what "This NNT can be interpreted as a combined effect of emigration and TB risk" (lines 47 and 48) exactly means?</li> <li>- As emigration censors individuals (i.e. they remain at risk of TB but can not be observed), the authors provide a measure which can be interpreted as the TB risk corrected for the effect of migration. However, I am not sure they are using the most correct approach. A statistician should address this key issue.</li> <li>- At lines 6 and 7 of page 6 it should be explicitly stated what effect is measured with the correlation between NNT and TB-NR and TB-IR.</li> <li>- Again, in section "Prevented TB and timing of LTBI treatment", at lines 11 and 17 the authors provide a narrative description of methods to calculate different quantities. Also, in this case the use of formulas and indexes would streamline and clarify the text.</li> </ul> <p>At moment, I am unable to interpret and comment upon the results of this manuscript because the method section needs to be significantly clarified and streamlined. In my opinion, the methods are not sufficiently well described to allow the study to be repeated.</p>
--	---

<b>REVIEWER</b>	Mirjam Heinen University College Dublin, Republic of Ireland
<b>REVIEW RETURNED</b>	09-Jul-2018

<p><b>GENERAL COMMENTS</b></p>	<p>This study examined prospectively the effectiveness of the Norwegian immigrant latent tuberculosis infection (LTBI) screening programme by estimating numbers needed to screen (NNS) and treat (NNT) to prevent one tuberculosis (TB) case, and measure the effect of timely follow-up of screening results. The authors observed that NNSs and NNTs were overall high, with substantial variation. NNTs were affected substantially by emigration and the definition of incident TB. Estimates were lowest for Somali [NNS 99 (70-150), NNT 27 (19-41)] and highest for Thai immigrants [NNS 585 (413-887), NNT 111 (79-116)]. Implementing LTBI treatment in immigrants sooner after arrival may improve the effectiveness of the programme, although the overall high NNT challenges the scale-up of preventive LTBI treatment for significant public-health impact.</p> <p>The manuscript is very well written, and there are only minor issues that need to be addressed to strengthen this report.</p> <p>Minor comments</p> <p>Results section</p> <p>1. Page 6, lines 42-43: Estimates for Somalia are given: “screening of 70-105 and treatment of 14-28 Somali immigrants was required to prevent one incident TB case”. Where can these estimates be found in table 2? If these are not presented in table 2, suggest to either include them in the table or to state in the results section that results are not shown.</p> <p>2. Page 6, lines 44-46: The authors state that “estimates were lowest when we corrected for the effect of emigration and applied the 1-month threshold to define incident TB (table 2)”. Which estimates are meant by this exactly? All countries or Somalia or other? And compared to what? Suggest to add more detail to make this sentence clearer.</p> <p>3. Page 6, lines 51-55: The authors state that they “found a stronger numerical correlation between the TB NR in Norway and NNT to prevent one incident TB case [correlation coefficient (CC) -0.75 (95% CI -1.05 to -0.44)] than between the NNT and WHO-estimated IR in the country of origin [CC -0.32 (95% CI -0.93 to 0.29)] for the top 10 source countries for TB in Norway”. The stronger correlation between the TB NR in Norway and NNT makes sense, however, as both the NRs and the NNT estimates are both derived from the same ‘real-time’ Norwegian data, whereas the WHO IRs are not. This has to do with the WHO IRs being IRs from the countries of origin from where the people migrate from, whereas the Norwegian NRs are based on the immigrants arriving in Norway, which might be certain sub-populations of a country and not necessarily a representative sample of the people in the country of origin. Suggest to rephrase this and address the differences in the Discussion section. Another note, how can the correlation coefficient’s 95% CI be lower than -1?</p> <p>4. Page 8: In table 1, the number of notified TB should be 380, not 418 for the ‘Horn of Africa’.</p> <p>Discussion section</p> <p>5. Page 11, lines 53-54: The authors state that “the estimated NNTs for source countries were considerably higher in Norway than in the UK”. Could maybe the range for both could be given as comparison?</p>
--------------------------------	---

	<p>6. In the 'Public health implications' section, suggestions are given on certain strategies on what to do next. Is there any cost-effectiveness data available? As the number of people to screen or number to treat to prevent one TB case is high.</p> <p>7. According to the authors, "the programme has the potential to prevent additional TB cases if more immigrants with LTBI are offered treatment, and this treatment starts sooner after arrival". What do the authors suggest to do? Which groups should be included that are not at the moment?</p>
--	---

<b>REVIEWER</b>	Augusto Filippo Di Castelnuovo IRCCS NEUROMED, Pozzilli, Italy
<b>REVIEW RETURNED</b>	03-Sep-2018

<b>GENERAL COMMENTS</b>	The authors prepared a good manuscript. In particular, concerning my expertise, study design and statistical methods are very satisfactory.
-------------------------	---

### VERSION 1 – AUTHOR RESPONSE

#### Reviewer: 1

##### General/Writing

☐ The article is well written with few typos or grammatical errors. Kudos to the authors for providing such a clean, concise and well written document.

☐ Tables are well laid out and concise, with footnotes providing the needed information for interpretation.

##### Abstract

☐ The abstract reads well. No major issues.

☐ Page 2 line 21 - use of "sensitivity" twice in same sentence. Consider re-writing. *We have now rephrased this sentence, replacing the use of "test sensitivity" with "test performance", page 2*

##### Introduction

- LTBI screening and treatment is a key approach to the reduction of TB incidence in low-incidence regions where a high percentage of total TB may result from reactivation of LTBI in recent immigrants.
- Effectively evaluating regional LTBI screening programs in regions with low TB incidence is extremely important, as targeted approaches are often required.
- The introduction provides a clear, concise summary as to the research objectives, and why such work is important. Both the topic of study, as well as the study objectives, are worthy of study.
- Page 4 line 7: "treatment of LTBI in groups at high-risk groups"
- o Sentence reads strangely. Consider re-writing *This was a typing error and is now corrected*

##### Methods:

- The use of country specific incidence, NNS and NNT estimates are all appropriate for a study of this kind.
- The paper could be improved by better describing the nature of the MSIS system. Would help clarify what data is captured within the surveillance system for each client, and what information is instead estimated from other studies. *We have now included a paragraph in the text with data and sources and listed the content of the information from each source under separate headings, page 5. We have further presented this information in table format in appendix 1a. We hope this improves the readability of the paper.*

- The use of national estimates of group specific emigration data provides a strong estimate of the person-time experienced by recent immigrants. The resulting regional incidence estimates are therefore expected to be stronger than those done in regions lacking such emigration estimates.
- The inability to determine the total number of people with LTBI is a common challenge of research of this kind. The authors attempt to estimate this number based on previously published IGRA positivity estimates. Some of these estimates come from outside of Norway (the UK specifically), which could in theory influence the accuracy of LTBI estimate. However, Winje et al. also refer to a previous regional study focused on a cohort of immigrants in Norway to provide regional estimates that likely improve the accuracy of subsequent calculations.

• **Primary Issue:** In many ways, this work represents a modelling exercise that on initial reading is presented as a retrospective cohort study. As a result, I found the methods somewhat challenging to understand in initial readings, especially the section outlining the “Assumptions and definitions”. It took me many readings to begin to understand exactly how certain numbers were arrived at. *We thank the reviewer for this comment. In this study we have combined aggregate numbers from Norwegian immigration data (i.e. information on the entire cohort) and individual level TB surveillance data (i.e. information on the people of interest, i.e. individuals with TB or LTBI treatment) to create a unified dataset for modelling and analysis. We have substantially edited the methods section and tried to present all steps included to create the unified dataset (in text). In addition, we have presented this information in table format in appendix 1a-d. We hope this has improved the clarity and transparency of our methods.*

Specifically:

o Page 5 line 19 – I don't understand the NNT correction presented here. Unclear why 1/risk of preventable TB in case of no emigration from Norway. Some additional explanation may be warranted. *We used the information on person years lost for observation due to emigration to calculate corrected NNT, i.e. in a hypothetical world where all immigrants stayed in Norway for 5 years with zero emigration. This was calculated as 1/(risk of preventable TB in 5 years). We have added information to this in the manuscript, page 7*

o page 5 line 21 - unclear what "probability" refers to here? Doesn't seem to be a probability calculation, should be able to directly calculate given a patient's Date of Birth and immigration arrival date. If that latter piece of information is missing, it may be worth explicitly stating so. *Immigration arrival date was not available in our dataset. What we had available was “time in Norway prior to diagnosis” reported from clinicians as categorical information: <1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years. Based on this information, we estimated the probability distribution for each case's arrival year in Norway. Examples: “a case received a diagnosis in December 2010 and has been in Norway for <1 month, therefore they have 100% probability that they arrived in Norway in 2010”, or “a case received a diagnosis in March 2012 and has been in Norway for 1-6 months, therefore they have a 50% probability that they arrived in Norway in 2011, and 50% probability that they arrived in Norway in 2012”. We have tried to explain this clearly in the revised manuscript, page 5*

o page 5 line 28 - methods are unclear regarding how to calculate the "total number of individuals with TB or LTBI treatments" - again related to use of the word "probability" *As described above, date of arrival was not available, and we calculated a probability for each case for arrival in 2008-2011. We then estimated the number of individuals with TB or LTBI treatment who belonged to the 2008-2011 cohort of immigrants by multiplying the number of cases by the probability that they immigrated to Norway in 2008-2011. We have included additional text to clarify on this in the methods section, page 5 and in appendix 1b.*

☐ Could this be better described as the "percentage of total cases"? Or am I not understanding this concept? *Please see the response above*

☐ A more detailed description of how it was determined if a client immigrated to Norway *The number of immigrants is based on number of asylum applications and number of residence permits for other immigrant groups. We assumed that immigrants who received residence permit or applied for asylum actually immigrated to Norway and that immigrants that later were registered as emigrated, or had a final rejection of application for asylum, actually emigrated. This has been clarified in the text, page 4*

o Page 5 line 29 - I did not understand the nature of the "adjusted probability" that was described here. *We have added detail to how we calculated the probability that a TB/LTBI treatment*



case immigrated to Norway in 2008-2011, page 5, lines 170-181. We hope this add clarity as requested by the reviewer.

o page 6 line 13 – unclear exactly how the “subsequent risk of preventable TB in different time periods” was calculated. *For each time period after arrival to Norway (<1 month, 1-6 months, 7-12 months, 1-2 years, 3-4 years, 5-9 years, and >10 years) we obtained the number of preventable TB cases and then calculated the risk of preventable TB per time period. This was calculated as the number of cases divided by number of people under observation in each period (corrected for TB, LTBI or emigration). We have added detail to this in the manuscript, page 7*

• I believe that a re-write and re-framing of the methods, or at least a more detailed discussion of the calculations and assumptions, could improve the clarity of the methods and the understandability of the paper as a whole. The authors could also focus on providing a rationalization for some of the “corrections” and “adjustments” made. *We have revised the Methods section of the manuscript substantially and we hope that the readability and transparency of our adjustments and assumptions are improved.*

• That said, I fully admit that my lack of understanding may stem from a limited understanding of the particular datasets.

#### Results:

- As discussed, I had some problems following the exact calculations that were described in the methods. *That said, the results as calculated were presented clearly and concisely. Perhaps additional effort could be placed in clearly describing how the three tables relate to each. We have tried to clarify on this by rephrasing the objectives, page 4*

- The NNS provided in table 2 is not as described in text. The text (page 5 line 44) describes the calculation as “the ratio of the number of arriving immigrants to the number of incidence TB cases observed in Norway within 5 years”. I believe the value presented in table 2 is in fact the number of arriving immigrants divided by the number of “preventable” TB cases, and not incident TB cases. *Thank you. We have corrected this.*

- The information provided in figure 1 could more clearly be presented in a table. *That said, the use of a figure is acceptable and should not limit publication. We see the point from the reviewer. However, the manuscript already contains four comprehensive tables, so for this reason we believe it is nice to keep this as a figure.*

#### Discussion:

- The authors do a good job of discussing the potential limitations of the work, and most importantly, clearly identify the public health value of this work.

- The discussion of how classifying immigrant groups on the basis of country alone may mask important socioeconomic differences (perhaps better captured by the TB notification rate in Norway) was appreciated.

- The authors conclude that the high NNT/NNS suggests alternative screening approaches are needed: 1) reduce pool of those screened by focusing on those with additional risk factors, and 2) engage screening and treatment earlier. While point two will undoubtedly decrease TB, it still requires screening a huge number of immigrants and may be unfeasible in most settings. I suspect a combination of the two approaches would be needed in many settings. *We agree with the reviewer and we have added a comment on this in the discussion, page 15. We have also included a recent BMJ reference, related to this comment (Behr MA, Edelstein PH, Ramakrishnan L. Revisiting the timetable of tuberculosis. BMJ, 2018), and one Thorax reference (Winje BA, White R, Syre H, et al. Stratification by interferon-gamma release assay level predicts risk of incident TB, Thorax 2018)*

#### Reviewer Conclusions:

☐ I believe this is an important area of research. Evaluating TB screening in recent immigrants in low-incidence countries can be difficult to evaluate because of limited post-arrival data. This study is not alone in lacking refined denominator estimates when estimating post-landing incidence and does an admirable job of refining these estimates using emigration data. Similarly, this is not the only study that does not have access to all IGRA screening data, and appropriately uses published literature values to estimate these hard-to-get values.

☐ As discussed, I did experience some confusion with the methods and assumptions described in section titled “Assumptions and definitions” section of the Methods. However, I fully admit this may result from my limited experience with these types of calculations and approaches. That said, I would

suggest the authors focus on clarifying the methods/calculations as much as possible to aid the reader. The addition of a table in the appendix that explicitly outlines the nature of each calculation could help improve the readers understanding. *Please see previous comments, we have substantially edited the methods section in the manuscript and added information in table format in appendices 1a-d.*

☑ Overall, I feel that this article is worthy of publication given the minor modification described above. It effectively provides additional evidence on the challenges scaling up LTBI screening and treatment, and provides novel data clearly showing the value of early LTBI treatment if the preventative aim is a reduction in the total number of active TB cases within a low-incidence setting. *I hope the modifications of our manuscript have improved the readability and transparency of our work.*

Reviewer: 2

Reviewer Name: Iacopo Baussano

Institution and Country: International Agency for Research on Cancer, Lyon, France Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below The findings reported in the manuscript entitled "Immigrant screening for latent tuberculosis infection – numbers needed to test and treat: A Norwegian population- based study" are potentially very relevant for Norway and other high-income countries with low incidence of TB. However, I am unable to judge on the validity of the findings because the definition of the objectives of the study is only partially clear and the methods are difficult to follow.

The authors state the following objectives: a) to use Norwegian immigration and TB surveillance data to measure the effectiveness of the immigrant LTBI screening programme, b) to assess the impact of LTBI treatments in a 4-year cohort of immigrants to Norway, and c) to measure the effect of timely follow-up of screening results.

It is not clear however, how these objectives relate to each other. Are they independent or not? If they are independent, I strongly suggest to address them in separate manuscripts (or at least sections of the manuscript). If not, it should be clarified how they relate to each other. Incidentally, both objective b) and c) are not formally defined. What measure of impact of LTBI treatments is going to be provided? How is measured the effect of timely follow-up of screening results? Please define measures of impact and effect. *We believe the three objectives are clearly related, they are based on the same data and assumptions, and should be published in one manuscript. To clarify the objectives and how they relate to each other, we have rephrased the objectives of the manuscript and presented them as primary and secondary objectives. We have further replaced the terms impact and timeliness with more direct wording of what we have actually done. We hope this adds clarity to the readers.*

Methods section.

- Are the administrative data on the number of immigrants (line 41) used to define the population at risk? If so, why this is not also stratified by age and gender? Are these administrative data exhaustive? Do they accurately capture migration events occurring in Norway?

*In this study we have combined aggregate numbers from Norwegian immigration data (i.e. information on the entire cohort) and individual level TB surveillance data (i.e. information on the people of interest) to create a unified dataset for modelling and analysis. We obtained administrative data on immigration by year, country of origin, and reason for immigration in Norway in 2008-2011.*

*The number of immigrants reflects number of asylum applications and number of residence permits for other immigrant groups. Asylum seekers make their applications after entering Norwegian territory and is therefore a valid proxy for immigration. Other immigrant groups may receive a residence permit prior to entry, but checking with UDI, it is rare that immigrants with a residence permit do not immigrate. Thus, the definition of immigration should not cause substantial bias.*

*Immigrants are screened soon after arrival. There has been a substantial delay in the provision of residence permits and the 11 digit personal ID number for arriving asylum seekers. Therefore, we obtained immigration data from two separate sources, to capture the number of arriving immigrants eligible for screening. The age-distribution was obtained as proportions by reason for immigration. We used this to identify the number of immigrants younger than 35 years (and therefore eligible for LTBI screening) and to calculate the cumulative prevalence of LTBI separately for immigrants 0-14 years and 15-35 years. We did not obtain data on sex.*

*With the high mobility in the immigrant groups, we have made substantial efforts to measure observation time in Norway. The national estimates of group specific emigration data provides a strong estimate of the person-time experienced by recent immigrants, which we believe is unique for this study. We believe the immigration data are sufficiently exhaustive and accurate for this analyses, and probably better for Norway than most other countries. Individuals may arrive without documentation or overstay after refusal of asylum application. The size of this population is not known. However, NGOs offer low threshold health services to this group who in case of TB have the right to delay in deportation until end of treatment.*

- It is not clear how date of emigration of refugees and asylum seekers was calculated based on a percentile distribution of the number of days before final application rejection. Please clarify. *For asylum seekers, data on emigration was obtained as percentile distributions of number of days from application date to date of final rejection of application. Example: among the 421 asylum seekers from Somalia who arrived in Norway in 2008 and whose application for asylum later was rejected, 10% were rejected within 62 days, 20% were rejected within 87 days and so on up until the 90% percentile. We used this information to calculate the number of person-years of observation lost due to emigration within the first five years after arrival in Norway. This was done separately by country, TB IR in country of citizenship and by year.*

- The authors state that untreated LTBI is not reported, so how was the number of individuals testing positive for LTBI (a key competent on NNT) calculated? I suspect that this is described in the section "Assumptions and definitions", see lines 14 to 20. Please clarify. As I understand, the number of LTBI in Norway among immigrants was calculated by multiplying the number of arriving immigrants by the estimated percentage of immigrants with a positive IGRA was based on published literature. This is a very serious limitation which needs to be carefully discussed in the limitation section. How (in)accurate can the calculated number of LTBI be? What biases in the available information can distort the estimate and in which direction? *We thank the reviewer for this comment and we see that this was not sufficiently commented on the original manuscript. The estimated number of LTBI in the immigrant cohort was based on published literature and calculated separately by age-group (0-14 years and 15-35 years) and by TB IR in country of origin. As there is no source where we may obtain this information, we had to turn to the literature. We included data from a Norwegian publication on asylum seekers which provides some added validity. We have added a paragraph on this potential bias in the discussion, page 13. We have also included this in the Strengths and limitations in the beginning of the manuscript.*

- In the "Assumptions and definitions" section, the authors provide a narrative description of methods to calculate different quantities (see lines 14, 21, 28, and 34). I suggest to provide more formal definitions, accompanied with formulas and a list of indexes. I also suggest to clarify where the calculated values are subsequently used and what for. *We have substantially edited the methods section and included a more thorough description. We have also provided this information in appendix 1a-d in table format. In the current version of the manuscript the text is difficult to interpret. For example, at lines 28-29 it is stated "We then calculated the total number of individuals with TB or LTBI treatment by multiplying the number of patients by the adjusted probability that they immigrated to Norway in 2008-2011". What is the "adjusted probability"? We created a new section called "Construction of analysis dataset". This explains the methodology in much more detail, with examples. We used the term "adjusted probability", which is now corrected to "probability". None of the calculations in this study included uncertainty. Our model was primarily deterministic. The only source of uncertainty in our study came from running our deterministic model with alternative IGRA sensitivities and treatment efficacies (extreme value approach) and the two separate definitions of incident TB (1 month and 6 months). This is now presented in its own section called "Uncertainty in the calculations."*

In the section entitled "NNS and NNT" it should be clarified what "This NNT can be interpreted as a combined effect of emigration and TB risk" (lines 47 and 48) exactly means? *This means that we did not correct for person-years lost due to emigration. If someone emigrates from Norway they cannot receive a TB diagnosis in Norway, thus the more emigration the lower the risk for TB observed in Norway. We have commented on this in the manuscript, page 7 and in appendix 1a-d*

- As emigration censors individuals (i.e. they remain at risk of TB but can not be observed), the authors provide a measure which can be interpreted as the TB risk corrected for the effect of migration. However, I am not sure they are using the most correct approach. A statistician should address this key issue. *We believe this is a correct approach and this is supported by the statistician on our team. However, we have tried to clarify how we reached at these estimates, to clarify the methods.*

- At lines 6 and 7 of page 6 it should be explicitly stated what effect is measured with the correlation between NNT and TB-NR and TB-IR.

*We have now written the following about the purposes of the analysis. "We then explored correlation with 95% confidence intervals (CIs) of the NNT with the TB NR in Norway and WHO-estimated TB IR. The purpose of this analysis was to identify which data source (TB NR in Norway or WHO-estimated TB IR) had a stronger association with public health implications in Norway (NNT)." See page 7*

- Again, in section "Prevented TB and timing of LTBI treatment", at lines 11 and 17 the authors provide a narrative description of methods to calculate different quantities. Also, in this case the use of formulas and indexes would streamline and clarify the text. *We agree with the reviewer that this needed some clarifications. We hope our revised methods section in combination with appendix 1a-d adds clarity and transparency*

At moment, I am unable to interpret and comment upon the results of this manuscript because the method section needs to be significantly clarified and streamlined. In my opinion, the methods are not sufficiently well described to allow the study to be repeated. *We thank the reviewer for the comments and hope the modifications to the manuscript are sufficient to clarify the methodology.*

Reviewer: 3

Reviewer Name: Mirjam Heinen

Institution and Country: University College Dublin, Republic of Ireland Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This study examined prospectively the effectiveness of the Norwegian immigrant latent tuberculosis infection (LTBI) screening programme by estimating numbers needed to screen (NNS) and treat (NNT) to prevent one tuberculosis (TB) case, and measure the effect of timely follow-up of screening results. The authors observed that NNSs and NNTs were overall high, with substantial variation. NNTs were affected substantially by emigration and the definition of incident TB. Estimates were lowest for Somali [NNS 99 (70-150), NNT 27 (19-41)] and highest for Thai immigrants [NNS 585 (413-887), NNT 111 (79-116)]. Implementing LTBI treatment in immigrants sooner after arrival may improve the effectiveness of the programme, although the overall high NNT challenges the scale-up of preventive LTBI treatment for significant public-health impact.

The manuscript is very well written, and there are only minor issues that need to be addressed to strengthen this report.

Minor comments

Results section

1. Page 6, lines 42-43: Estimates for Somalia are given: "screening of 70-105 and treatment of 14-28 Somali immigrants was required to prevent one incident TB case". Where can these estimates be found in table 2? If these are not presented in table 2, suggest to either include them in the table or to state in the results section that results are not shown. *The numbers were wrong and are corrected. Thank you.*

2. Page 6, lines 44-46: The authors state that "estimates were lowest when we corrected for the effect of emigration and applied the 1-month threshold to define incident TB (table 2)". Which estimates are meant by this exactly? All countries or Somalia or other? And compared to what? Suggest to add more detail to make this sentence clearer. *We apologize for being unclear on this. This was related to all countries for estimates corrected for the effect of emigration and was compared to the crude NNT. We have added information to this in the text, page 8*

3. Page 6, lines 51-55: The authors state that they "found a stronger numerical correlation between the TB NR in Norway and NNT to prevent one incident TB case [correlation coefficient (CC) - 0.75 (95% CI -1.05 to -0.44)] than between the NNT and WHO-estimated IR in the country of origin [CC -0.32 (95% CI -0.93 to 0.29)] for the top 10 source countries for TB in Norway". The stronger correlation between the TB NR in Norway and NNT makes sense, however, as both the NRs and the NNT estimates are both derived from the same 'real-time' Norwegian data, whereas the WHO IRs are not. This has to do with the WHO IRs being IRs from the countries of origin from where the people migrate from, whereas the Norwegian NRs are based on the immigrants arriving in Norway, which might be certain sub-populations of a country and not necessarily a representative

sample of the people in the country of origin. Suggest to rephrase this and address the differences in the Discussion section. *We now address this in the discussion under the section “Comparing NNT to TB NR in Norway and WHO estimated IRs in countries of origin”, page 15*

Another note, how can the correlation coefficient's 95% CI be lower than -1? *Some statistical equations for the calculation of confidence intervals for correlation coefficient can go below -1. It is then either left as a number below -1 or truncated at -1 for the ease of interpretation. We have now truncated it at -1.*

4. Page 8: In table 1, the number of notified TB should be 380, not 418 for the ‘Horn of Africa’. *Thank you. We found an error in the data from the Horn of Africa and these are now corrected, tables 2, 3 and 4.*

Discussion section

5. Page 11, lines 53-54: The authors state that “the estimated NNTs for source countries were considerably higher in Norway than in the UK”. Could maybe the range for both could be given as comparison? *We have added information on this on page 14*

6. In the ‘Public health implications’ section, suggestions are given on certain strategies on what to do next. Is there any cost-effectiveness data available? As the number of people to screen or number to treat to prevent one TB case is high. *For now, we have no cost-effectiveness data available. We have added a sentence in the manuscript where we recommend to do cost-effectiveness estimates, page 16*

7. According to the authors, “the programme has the potential to prevent additional TB cases if more immigrants with LTBI are offered treatment, and this treatment starts sooner after arrival”. What do the authors suggest to do? Which groups should be included that are not at the moment? *We have added a comment where we suggest a combination of the two approaches (page 15) and we suggest cost-effectiveness estimates which could also guide this decision.*

Reviewer: 4

Reviewer Name: Augusto Filippo Di Castelnuovo Institution and Country: IRCCS NEUROMED, Pozzilli, Italy Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below The authors prepared a good manuscript. In particular, concerning my expertise, study design and statistical methods are very satisfactory. *Thank you*

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Mirjam Heinen University College Dublin, Republic of Ireland
<b>REVIEW RETURNED</b>	20-Oct-2018

<b>GENERAL COMMENTS</b>	The authors have responded well to the questions raised by the reviewers, in a very detailed and clear way. I have no further comments.
-------------------------	---

<b>REVIEWER</b>	Augusto Filippo Di Castelnuovo IRCCS NEUROMED, Pozzilli, Italy
<b>REVIEW RETURNED</b>	18-Oct-2018

<b>GENERAL COMMENTS</b>	The authors provided a satisfactory revision
-------------------------	--

#### VERSION 2 – AUTHOR RESPONSE

Thank you for your kind respons. We have edited the Strengths and Limitations section of the manuscript. The five bulletpoints are now shorter and related specifically to the methods.

I hope they are revised according to the request from the editor.

I have tried to edit my name as I would prefer my whole name to be used. I have changed it, but it goes back.