Author’s response to reviews

Title: The impact of migration on tuberculosis epidemiology and control in high-income countries: a review

Authors:
Manish Pareek (mp426@le.ac.uk)
Christina Greenaway (ca.greenaway@mcgill.ca)
Teymur Noori (Teymur.Noori@ecdc.europa.eu)
Jose Munoz (jose.munoz@isglobal.org)
Dominik Zenner (Dominik.Zenner@phe.gov.uk)

Version: 1 Date: 04 Mar 2016

Author’s response to reviews:
Corresponding Author: Dr. Manish Pareek
Senior Clinical Lecturer in Infectious Diseases
Department of Infection, Immunity and Inflammation
Maurice Shock Medical Sciences Building
University of Leicester
University Road
Leicester
LE1 9HN
UK
Email: manish.pareek@leicester.ac.uk
Telephone: 0116 2586952
Dr Sabina Alam
BMC Medicine

2nd March 2016

Re: The impact of migration on tuberculosis epidemiology and control in high-income countries: a review

Dear Dr. Alam,

Thank you for recognizing the value of our work and for inviting us to submit a revised version of the above manuscript as a letter.

We are extremely grateful for the insightful and appreciative comments made by the Associate Editor and the two expert peer reviewers. We were pleased in particular that the peer-reviewers valued the comprehensive nature of our work, the areas covered in the review and the appeal of the work we have conducted. By incorporating their recommendations we feel we have significantly improved the manuscript and hope that it is now suitable for publication.

Please find attached a detailed, point-by-point, response to the comments/suggestions made by the Associate Editor and the two peer reviewers.

Thank you.

Yours sincerely,

Dr Manish Pareek
Senior Clinical Lecturer in Infectious Diseases
Authors’ response to comments from Associate Editor

Comment: Your manuscript "The impact of migration on tuberculosis epidemiology and control: a review" (BMED-D-16-00141) has been assessed by our reviewers. They have raised a number of points which we believe would improve the manuscript and may allow a revised version to be published in BMC Medicine.

Response: Thank you for the positive comment. We have responded point-by-point to the comments made by the Associate Editor and two Reviewers. We have made the changes recommended by the Reviewers including rewriting sections of the manuscript and adding additional tables and figures. These changes have significantly improved the manuscript and we hope that the manuscript is now able to be accepted for publication.

Comment: Their reports, together with any other comments, are below. Please also take a moment to check our website at http://bmed.edmgr.com/l.asp?i=27179&l=7ANE30EU for any additional comments that were saved as attachments. Please note that as BMC Medicine has a policy of open peer review, you will be able to see the names of the reviewers.

Response: Thank you for the comment. We have responded point-by-point to the comments made by the Associate Editor and two Reviewers.

Comment: We believe strengthening the unique angle of your work, and take home message would be appropriate in your revised manuscript.

Response: Thank you for the comment. The issue of migration and tuberculosis is highly topical and is at the forefront of research, clinical and policy priorities. Previous work in this area has, in general, been limited as it has only focused on a single aspect of tuberculosis and migration be it epidemiology, methods of screening or outcomes of screening. The value, novelty and strength of our work is that it brings together all aspect of tuberculosis and migration and provides the general readership of BMC Medicine detailed information in each of these areas.
As Reviewer 2 outlines there are many aspects to migration and tuberculosis. We have focused on specific aspects and made the unique angle of our work much clearer in the revised manuscript. In the abstract we now highlight the focus, and novelty, of our work:

“Tuberculosis (TB) causes significant morbidity and mortality in high-income countries with foreign-born individuals bearing a disproportionate burden of the overall TB case burden in these countries. In this review of tuberculosis and migration we discuss the impact of migration on the epidemiology of TB in low burden countries, describe the various screening strategies to address this issue, review the yield and cost-effectiveness of these programs and describe the gaps in knowledge as well as possible future solutions.”

In the summary we now state:

“In this review we have comprehensively brought together the literature with respect to all aspects of tuberculosis and migration.”

We agree that the take home messages could be made clearer. We have therefore significantly rewritten several sections of the manuscript to take account of the Reviewer’s comments as detailed below.

Firstly, we have added a clearer introductory paragraph which structures the review and the areas covered:

“Introduction

In this review (see figure 1) we first analyse the burden of tuberculosis (TB) in foreign-born, migrant populations before going on to discuss the drivers of the current TB epidemiology in these populations focusing on migration patterns, the importance of reactivation of latent tuberculosis infection as compared to the burden of imported active TB and molecular genotyping data underpinning these studies. We then go on discuss, in detail, the methods, outcomes, and cost-effectiveness of the different TB control strategies in place for migrant populations.”
Secondly, we have summarised the key take-home messages for the readers which are set out in the new figure 1. In particular we want the reader to take away the following information:

- Tuberculosis continues to be a public health concern in high-income countries

- Tuberculosis burden in high-income countries is primarily amongst the foreign-born, migrant population

- The reasons underlying this burden are the interaction of migration from high TB burden countries and the reactivation of remotely acquire latent tuberculosis infection in the first five years after arrival

- Genotyping data suggests that there is relatively little transmission in migrant communities in the receiving country

- Methods of TB control in migrant population have historically focused on identifying active tuberculosis but the yields for this remain relatively low

- Screening migrants for latent tuberculosis infection may have a higher yield although implementation may be difficult

- The health economics of screening migrants for active and/or latent tuberculosis is a topic of much debate

- Targeted pre-arrival screening for active TB and post arrival screening for latent tuberculosis infection in migrants from intermediate/high TB burden settings is likely to provide the most cost-effective solution
• Implementation of programmatic screening is limited by uptake, acceptance and completion of therapy

Thirdly, the paragraph sub-headings in the review are linked to each of these take home messages as recommended by the Reviewer.

Fourthly, we have revised the summary paragraph to link it to the key take-home messages:

“In this review we have comprehensively brought together the literature with respect to all aspects of tuberculosis and migration. Tuberculosis in high-income countries continues to be a cause of morbidity and mortality – particularly amongst individuals who have been born overseas in high TB burden, low-income countries and migrated to high-income countries. The reasons for the burden of disease in the foreign-born, migrant, population are primarily due to migration from high TB burden settings and the reactivation of remotely-acquired latent TB infection. As a consequence there is increasing focus on how best to enhance TB control through the coordinated screening of migrants for TB. Whilst most countries focus on screening migrants for active TB, this has a relatively low yield on its own and it is likely that the most effective and cost-effective means of screening migrants for TB will comprise multiple, inter-linking elements: pre-arrival screening for active TB and targeted post arrival screening for LTBI in migrants from intermediate/high TB burden settings. However, the programmatic implementation of migrant screening is potentially hampered by limited uptake, acceptance and completion of therapy. There is an urgent need for further coordinated research in this area to inform future national and international guidance.”

Fifthly, we have revised the abstract to outline the key messages for the reader:

“Tuberculosis (TB) causes significant morbidity and mortality in high-income countries with foreign-born individuals bearing a disproportionate burden of the overall TB case burden in these countries. In this review of tuberculosis and migration we discuss the impact of migration on the epidemiology of TB in low burden countries, describe the various screening strategies to address this issue, review the yield and cost-effectiveness of these programs and describe the gaps in knowledge as well as possible future solutions.
The reasons for the TB burden in the migrant population are likely to be the reactivation of remotely-acquired latent tuberculosis infection (LTBI) following migration from low/intermediate-income high TB burden settings to high-income, low TB burden countries.

TB control in high-income countries has historically focused on the early identification and treatment of active TB with accompanying contact-tracing. In the face of the TB case-load in migrant populations, however, there is ongoing discussion about how best to identify TB in migrant populations. In general, countries have generally focused on two methods: identification of active TB (either at/post-arrival or increasingly pre-arrival in countries of origin) and secondly, conditionally supported by WHO guidance, through identifying LTBI in migrants from high TB burden countries. Although health-economic analyses have shown that TB control in high income settings would benefit from providing targeted LTBI screening and treatment to certain migrants from high TB burden countries, implementation issues and barriers such as sub-optimal treatment completion will need to be addressed to ensure program efficacy.”

Comment. If you are able to fully address these points, we would encourage you to submit a revised manuscript to BMC Medicine. Once you have made the necessary corrections, please submit online at:

http://bmed.edmgr.com/

If you have forgotten your username or password please use the "Send Login Details" link to get your login information. For security reasons, your password will be reset.

Response: We have submitted the point-by-point response and revised manuscript at http://bmed.edmgr.com/

Comment. Please include a cover letter with a point-by-point response to the comments, describing any additional experiments that were carried out and including a detailed rebuttal of any criticisms or requested revisions that you disagreed with. Please also ensure that all changes to the manuscript are indicated in the text by highlighting or using track changes.
Response: We have responded point-by-point to the comments and also submitted a manuscript with the changes highlighted using track changes.

Comment. Please also ensure that your revised manuscript conforms to the journal style, which can be found at the Instructions for Authors on the journal homepage.

Response: We will ensure that the revised manuscript conforms to the journal style.

Comment. A decision will be made once we have received your revised manuscript, which we expect by 23 Mar 2016.

Response: We will submit the revised manuscript by 23 March 2016.

Comment: I look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Response: Thank you for your help with the submission of the manuscript.

Authors’ response to comments from Reviewers

Reviewer: 1

Comment. Page 4, line 40: Please refer already here to table 1 (which I cannot find somewhere in the text).

Response: Thank you for the comment. We have now added a reference to table 1. The reviewed sentence now states:
Surveillance data, and findings from previous meta-analyses (see table 1), have shown that the proportion of migrants with active TB present at the time of migration is relatively small (0.35%).

Comment. Page 5, line 6 f.: "Whilst the literature has expanded rapidly in respect of cross-sectional data on LTBI prevalence, longitudinal data on the risk of migrants with untreated LTBI progressing to active TB disease remain limited partially due to low numbers of chemoprophylaxis-naïve patients (due to recommendations to treat)…". In which countries routine screening for LTBI among immigrants is recommended? Please provide some examples!

Response: We apologise if this section was not clear. The point we were trying to make was that undertaking a randomised, placebo-controlled, clinical trial to longitudinally follow patients to document outcomes is difficult in this population due to ethical concerns of withholding chemoprophylaxis if an individual has been identified with latent TB. Whilst we appreciate that routine migrant screening (such as recently commenced in the UK) is very limited, in a research context it would be difficult to withhold chemoprophylaxis. We have made this section clearer which now states:

“Whilst the literature has expanded rapidly in respect of cross-sectional data on LTBI prevalence, longitudinal data on the risk of migrants with untreated LTBI progressing to active TB disease remain limited partially due to low numbers of chemoprophylaxis-naïve patients (due to recommendations to treat, and not withhold treatment from, individuals identified with latent TB such as in the UK) and because studies to answer this research question need a large sample size and long duration of follow-up.”


Response: We have added the reference to the manuscript (reference 54).
Authors’ response to comments from Reviewers

Reviewer: 2

Comment: This manuscript is a narrative review of the literature on the impact of migration on the epidemiology of tuberculosis (TB). The manuscript is well-written and comprehensive in its coverage of the topic.

Response: Thank you for the positive comment.

Comment: However, I do have a number of major concerns regarding this manuscript, described below:

Response: We have responded point-by-point to the comments made by the Reviewer and made all the changes recommended by the Reviewer. These changes have significantly improved the manuscript and we hope that the manuscript is now able to be accepted for publication.

Comment: The title of this manuscript suggests that the topic is broader than is actually the case. This manuscript primarily focuses on the role of migration on TB epidemiology and control in high-income countries. The role of migration in lower-income countries (e.g., cross-border migration for work in African mines, internal migration from rural to urban China) is not discussed in detail. On one hand, I find this a shame - as the topic of migration in high-burden countries is one that is in need of a review like this (while the topic of migration in low-burden countries has been discussed before, see below). On the other hand, to include this would require a complete reframing of this manuscript. As such, I would recommend that the authors include a note in their title that this review is restricted to TB epidemiology and control in high-income countries (the abstract is clear on this), and then remove any discussion (if any) that falls outside that scope.

Response: Thank you for the excellent point. We too agree that TB and migration is an extremely broad topic and, therefore, made a decision, for the purposes of this review, to focus on migration to high-income countries rather than migration in lower-income countries. Whilst we agree that reviewing the literature in lower-income countries would be useful in future work, this was outside of the scope of the current manuscript. This is primarily due to the fact that, in general, migration still, for the present at least, occurs from lower-income countries to high-
income countries which we state in the manuscript. We agree that the scope of the review could have been made clearer in the title of the review and we have therefore revised the title:

“The impact of migration on tuberculosis epidemiology and control in high-income countries: a review”

Comment: Similarly, is this about "the impact of migration on TB epidemiology" or "TB epidemiology in foreign-born populations”? I don't see too much on the impact of migration per se.

Response: Thank you for the comment. The manuscript is about the impact of migration on tuberculosis epidemiology and control in high-income countries. We discuss in detail the issues of migration, patterns of tuberculosis notifications in migrants (who are by definition foreign-born and have migrated from overseas) and the specific methods of TB control for this population.

Comment. As the authors themselves note, this is a topic that has been covered in detail before, just in smaller scope.

Response: Thank you for the comment. The issue of migration and tuberculosis is highly topical and is at the forefront of research, clinical and policy priorities. Previous work in this area has, in general, been limited as it has only focused on a single aspect of tuberculosis and migration be it epidemiology, methods of screening or outcomes of screening. The value, novelty and strength of our work is that it brings together all aspect of tuberculosis and migration and provides the general readership of BMC Medicine detailed information in each of these areas.

As Reviewer 2 outlines there are many aspects to migration and tuberculosis. We have focused on specific aspects and made the unique angle of our work much clearer in the revised manuscript. In the abstract we now highlight the focus, and novelty, of our work:

“Tuberculosis (TB) causes significant morbidity and mortality in high-income countries with foreign-born individuals bearing a disproportionate burden of the overall TB case burden in these countries. In this review of tuberculosis and migration we discuss the impact of migration on the epidemiology of TB in low burden countries, describe the various screening strategies to address
this issue, review the yield and cost-effectiveness of these programs and describe the gaps in knowledge as well as possible future solutions.”

In the summary we now state:

“In this review we have comprehensively brought together the literature with respect to all aspects of tuberculosis and migration.”

Comment: The authors appropriately reference meta-analyses of clustering (ref 53), pre-arrival screening (refs 18 and 66), and screening for LTBI (ref 45).

Response: Thank you for noting the appropriate referencing of previous meta-analyses.

Comment: But by the same token, it raises the question of whether this topic is too broad for a single review.

Response: We do not believe that the topic is too broad for a review. We have, within, the word limit covered all aspects of tuberculosis and migration and provided the reader with a critical review of the literature with respect to TB epidemiology, the impact of migration, reasons underlying the burden of TB in migrants, methods of TB control and the health-economics of screening. Our work brings together, for the first time, all aspects of tuberculosis and migration and thus provides a reference point for the reader and other researchers.

Comment. In general, I found that the coverage of any one topic here was (necessarily) superficial - there's much more to be said about each of the sub-headings here. As a result, this piece largely reads as something of a "meta-meta-analysis", where individual detailed systematic reviews are referenced for each specific topic. But arguably, as a result, the manuscript ends up having too much breadth, at the expense of insufficient depth.

Response: We respectfully disagree with the esteemed Reviewer and feel our work provides the first comprehensive review of this topic. It is important that our work references previous meta-analyses and not to do so would weaken the manuscript. Overall, the aim of this review is to
provide a comprehensive overview of tuberculosis and migration as a whole. We feel that we do this and, by referencing the appropriate literature, we give interested readers from the general readership of BMC Medicine the opportunity to look further into this topic.

We also note the positive comments from Reviewer 2 who commended us on the comprehensive review of the topic. In addition Reviewer 1 did not comment that our work was superficial.

We do not, therefore, feel that the manuscript is superficial and indeed it is a comprehensive review of the literature on tuberculosis and migration.

Comment: In a similar vein, I worry that there is no unifying theme or "take-home message" from this review. The abstract essentially states that most TB in migrant populations (probably more appropriately called foreign-born populations) results from reactivation, and calls for a combination of pre-arrival and post-arrival screening for LTBI (plus more research), but leaves out many of the other topics discussed. What do the authors hope for the reader to take away after reading this manuscript?

Firstly, we have added a clearer introductory paragraph which structures the review and the areas covered:

“Introduction

In this review (see figure 1) we first analyse the burden of tuberculosis (TB) in foreign-born, migrant populations before going on to discuss the drivers of the current TB epidemiology in these populations focusing on migration patterns, the importance of reactivation of latent tuberculosis infection as compared to the burden of imported active TB and molecular genotyping data underpinning these studies. We then go on discuss, in detail, the methods, outcomes, and cost-effectiveness of the different TB control strategies in place for migrant populations.”
Secondly, we have summarised the key take-home messages for the readers which are set out in the new figure 1. In particular we want the reader to take away the following information:

- Tuberculosis continues to be a public health concern in high-income countries

- Tuberculosis burden in high-income countries is primarily amongst the foreign-born, migrant population

- The reasons underlying this burden are the interaction of migration from high TB burden countries and the reactivation of remotely acquire latent tuberculosis infection in the first five years after arrival

- Genotyping data suggests that there is relatively little transmission in migrant communities in the receiving country

- Methods of TB control in migrant population have historically focused on identifying active tuberculosis but the yields for this remain relatively low

- Screening migrants for latent tuberculosis infection may have a higher yield although implementation may be difficult

- The health economics of screening migrants for active and/or latent tuberculosis is a topic of much debate

- Targeted pre-arrival screening for active TB and post arrival screening for latent tuberculosis infection in migrants from intermediate/high TB burden settings is likely to provide the most cost-effective solution
• Implementation of programmatic screening is limited by uptake, acceptance and completion of therapy

Thirdly, the paragraph sub-headings in the review are linked to each of these take home messages as recommended by the Reviewer.

Fourthly, we have revised the summary paragraph to link it to the key take-home messages:

“In this review we have comprehensively brought together the literature with respect to all aspects of tuberculosis and migration. Tuberculosis in high-income countries continues to be a cause of morbidity and mortality – particularly amongst individuals who have been born overseas in high TB burden, low-income countries and migrated to high-income countries. The reasons for the burden of disease in the foreign-born, migrant, population are primarily due to migration from high TB burden settings and the reactivation of remotely-acquired latent TB infection. As a consequence there is increasing focus on how best to enhance TB control through the coordinated screening of migrants for TB. Whilst most countries focus on screening migrants for active TB, this has a relatively low yield on its own and it is likely that the most effective and cost-effective means of screening migrants for TB will comprise multiple, inter-linking elements: pre-arrival screening for active TB and targeted post arrival screening for LTBI in migrants from intermediate/high TB burden settings. However, the programmatic implementation of migrant screening is potentially hampered by limited uptake, acceptance and completion of therapy. There is an urgent need for further coordinated research in this area to inform future national and international guidance.”

Fifthly, we have revised the abstract to outline the key messages for the reader:

“Tuberculosis (TB) causes significant morbidity and mortality in high-income countries with foreign-born individuals bearing a disproportionate burden of the overall TB case burden in these countries. In this review of tuberculosis and migration we discuss the impact of migration on the epidemiology of TB in low burden countries, describe the various screening strategies to address this issue, review the yield and cost-effectiveness of these programs and describe the gaps in knowledge as well as possible future solutions.
The reasons for the TB burden in the migrant population are likely to be the reactivation of remotely-acquired latent tuberculosis infection (LTBI) following migration from low/intermediate-income high TB burden settings to high-income, low TB burden countries.

TB control in high-income countries has historically focused on the early identification and treatment of active TB with accompanying contact-tracing. In the face of the TB case-load in migrant populations, however, there is ongoing discussion about how best to identify TB in migrant populations. In general, countries have generally focused on two methods: identification of active TB (either at/post-arrival or increasingly pre-arrival in countries of origin) and secondly, conditionally supported by WHO guidance, through identifying LTBI in migrants from high TB burden countries. Although health-economic analyses have shown that TB control in high income settings would benefit from providing targeted LTBI screening and treatment to certain migrants from high TB burden countries, implementation issues and barriers such as sub-optimal treatment completion will need to be addressed to ensure program efficacy.”

Comment: Linked to this issue is the lack of "structuring" elements in this review. I would recommend that the authors include some sort of outline in their introduction - something to say, essentially, "here is what we are going to cover in this review" - then at least a box or other illustration to illustrate those major points, and then a summary statement in the end that better highlights the key points raised. Without this, the reader is left thinking, "what did I learn from reading this article?" The authors should state the main messages up-front, call it out in a box/table/figure, structure sub-headings to reinforce those main messages, and then summarize those messages in the conclusion.

Firstly, we have added a clearer introductory paragraph which structures the review and the areas covered:

“Introduction

In this review (see figure 1) we first analyse the burden of tuberculosis (TB) in foreign-born, migrant populations before going on to discuss the drivers of the current TB epidemiology in these populations focusing on migration patterns, the importance of reactivation of latent tuberculosis infection as compared to the burden of imported active TB and molecular
genotyping data underpinning these studies. We then go on discuss, in detail, the methods, outcomes, and cost-effectiveness of the different TB control strategies in place for migrant populations.”

Secondly, we have summarised the key take-home messages for the readers which are set out in the new figure 1. In particular we want the reader to take away the following information:

- Tuberculosis continues to be a public health concern in high-income countries

- Tuberculosis burden in high-income countries is primarily amongst the foreign-born, migrant population

- The reasons underlying this burden are the interaction of migration from high TB burden countries and the reactivation of remotely acquire latent tuberculosis infection in the first five years after arrival

- Genotyping data suggests that there is relatively little transmission in migrant communities in the receiving country

- Methods of TB control in migrant population have historically focused on identifying active tuberculosis but the yields for this remain relatively low

- Screening migrants for latent tuberculosis infection may have a higher yield although implementation may be difficult

- The health economics of screening migrants for active and/or latent tuberculosis is a topic of much debate
• Targeted pre-arrival screening for active TB and post arrival screening for latent tuberculosis infection in migrants from intermediate/high TB burden settings is likely to provide the most cost-effective solution

• Implementation of programmatic screening is limited by uptake, acceptance and completion of therapy

Thirdly, the paragraph sub-headings in the review are linked to each of these take home messages as recommended by the Reviewer.

Fourthly, we have revised the summary paragraph to link it to the key take-home messages:

“In this review we have comprehensively brought together the literature with respect to all aspects of tuberculosis and migration. Tuberculosis in high-income countries continues to be a cause of morbidity and mortality – particularly amongst individuals who have been born overseas in high TB burden, low-income countries and migrated to high-income countries. The reasons for the burden of disease in the foreign-born, migrant, population are primarily due to migration from high TB burden settings and the reactivation of remotely-acquired latent TB infection. As a consequence there is increasing focus on how best to enhance TB control through the coordinated screening of migrants for TB. Whilst most countries focus on screening migrants for active TB, this has a relatively low yield on its own and it is likely that the most effective and cost-effective means of screening migrants for TB will comprise multiple, inter-linking elements: pre-arrival screening for active TB and targeted post arrival screening for LTBI in migrants from intermediate/high TB burden settings. However, the programmatic implementation of migrant screening is potentially hampered by limited uptake, acceptance and completion of therapy. There is an urgent need for further coordinated research in this area to inform future national and international guidance.”

Fifthly, we have revised the abstract to outline the key messages for the reader:

“Tuberculosis (TB) causes significant morbidity and mortality in high-income countries with foreign-born individuals bearing a disproportionate burden of the overall TB case burden in these countries. In this review of tuberculosis and migration we discuss the impact of migration on the
epidemiology of TB in low burden countries, describe the various screening strategies to address this issue, review the yield and cost-effectiveness of these programs and describe the gaps in knowledge as well as possible future solutions.

The reasons for the TB burden in the migrant population are likely to be the reactivation of remotely-acquired latent tuberculosis infection (LTBI) following migration from low/intermediate-income high TB burden settings to high-income, low TB burden countries.

TB control in high-income countries has historically focused on the early identification and treatment of active TB with accompanying contact-tracing. In the face of the TB case-load in migrant populations, however, there is ongoing discussion about how best to identify TB in migrant populations. In general, countries have generally focused on two methods: identification of active TB (either at/post-arrival or increasingly pre-arrival in countries of origin) and secondly, conditionally supported by WHO guidance, through identifying LTBI in migrants from high TB burden countries. Although health-economic analyses have shown that TB control in high income settings would benefit from providing targeted LTBI screening and treatment to certain migrants from high TB burden countries, implementation issues and barriers such as sub-optimal treatment completion will need to be addressed to ensure program efficacy.”

Comment: I found the treatment of health economics to be a little disjointed. There is so much other ground to cover already. I feel that this section could probably be removed (or reduced to just 1-2 paragraphs), without making it such a large portion of the review. Better to talk about the control strategies themselves, the data to support them, and their strengths and limitations. Then list cost-effectiveness (and limitations of cost-effectiveness analyses) as one of those strengths (and limitations), but no need to give health economics such a large section on its own.

Response: Thank you for the comment. We think it is important to explore health economics because cost-effectiveness is a key concern when considering implementing migrant screening programmes and to not discuss this in some detail would significantly weaken the review and lessen its potential impact. In the health economics section we comprehensively review the available literature for the cost-effectiveness of screening migrants for active and latent tuberculosis. Nonetheless, we agree that this section could be shortened and have therefore revised the health economics sections as detailed below:
“Health economics of migrant screening

Whilst the programmatic outcomes of migrant screening are important, a key consideration for policy-makers and clinicians is cost-effectiveness. Several studies have explored the cost-effectiveness of migrant screening for TB although they have focused on different aspects of screening including whether to screen for active or latent TB, which migrant groups to screen and how to screen.41,42,73-82

Cost-effectiveness of screening for active and latent tuberculosis

Screening migrants for active TB is widely implemented by high-income countries albeit with different models of care. However there are few studies formally examining the cost-effectiveness of this intervention. Previous studies have come to differing conclusions about the cost-effectiveness of screening migrants for active TB. Schwartzman and colleagues modelled the comparative cost-effectiveness of migrant screening using chest radiography versus tuberculin skin test (versus no screening) and found that in migrants with a high prevalence of infection that chest radiography was the most cost-effective screening modality although the TST strategy prevented the most cases of TB. By contrast, Dasgupta et al constructed a Markov model informed by empirical data to compare the cost effectiveness of screening migrants with chest radiography pre-arrival followed by TST (if the CXR showed any abnormalities) with screening close contacts of index sputum smear-positive cases (with TST followed by CXR).73 The authors found that migrant screening using chest radiography was not cost-effective due to difficulties with operationalising screening.73 The lack of research in this area highlights the need for further health-economic analyses to objectively assess, and make conclusions about, the cost-effectiveness of screening migrants for active TB.

A larger number of published studies from high-income countries have focused on evaluating the cost-effectiveness of screening migrants for LTBI.74-82 These studies, which have evaluated different aspects of LTBI screening including which migrants to screen and how to screen, have generally concluded that LTBI screening of migrants from high burden countries, mainly Asia and Africa is a cost-effective intervention in high-income countries.41,42,74-82

Methods for diagnosing LTBI have evolved over the last decade with IGRAs increasingly replacing the TST.83 This is reflected by the several studies which have explored the relative cost-effectiveness of different screening modalities and algorithms for LTBI.41,42,75-80 These health-economic analyses have, in general, found that IGRA are more cost-effective than TST.41,42,75,77,80 However, in the absence of robust longitudinal data as for TST, there
remains ongoing debate about the use of IGRA as a screening tool with certain national guidelines instead advocating the use of TST.13”

In line with the Reviewer’s suggestion we have added further detail about the potential weakness of active TB screening:

“Previous work has shown that the current models of active TB screening have weaknesses including: individuals not completing the screening processes, limited yields for active disease and an inability to identify active TB occurring through LTBI reactivation.13“

The manuscript already discusses the potential limitations of latent TB screening:

“However, there is less data on the other elements of the screening pathway – including uptake, and completion, of chemoprophylaxis. A Canadian group recently reviewed the data on LTBI screening effectiveness and found that migrants dropped out at each step of the screening pathway so that overall only 31% of the cohort completed the programme successfully highlighting the need for research into interventions to optimise the LTBI screening pathway.75”

Comment. I feel like the discussion around reactivation could be much more nuanced. Specifically, reactivation of latent TB is likely a spectrum - with high rates in the first 1-2 years following infection, then progressively lower risks in the next 3-5 years, then a persistent non-zero annual risk of reactivation (that may decline further with time) thereafter. As a result, much reactivation occurs in the first year or two after arrival, almost certainly reflecting infection acquired in the year or two prior to immigration. The authors refer to this as being "for as yet undetermined reasons" (top of p. 5), but I feel that the "undetermined" reason has more to do with the natural history of TB (we know that these rates decline with time since infection, we just don't know why), not migration itself. This risk of reactivation may also be modulated by factors in the new country of residence - things like nutritional status, etc. More nuanced discussion of this is important, especially if we are to think about targeted strategies for TB control in these populations - if we don't focus some of our additional effort on people who have recently arrived, then we will miss out on a large amount of potential impact.

Response: We agree that a more nuanced discussion around reactivation is required. We have therefore significantly revised the section entitled “High prevalence of latent TB infection and risk of progression to active disease” which now states:
Latent TB prevalence figures in migrants are primarily derived from cross-sectional studies where, depending on the specific population tested and the diagnostic tool used, 5-72% of migrants test positive for LTBI; 20-43 this is independently associated with increasing age and TB incidence in country-of-origin.41,42,44 One can therefore infer that it is both the cumulative duration of exposure and the TB burden in the source country which determines whether individuals will have LTBI.29,41,42,44,45 Migrants with LTBI are coming to lower incidence settings and in the initial years following arrival in the destination country, have a higher risk of LTBI reactivation which decreases slowly over time but remains higher than rates in the host population.12,46-48 This higher rate of reactivation in the initial one to two years after migrants arrive likely reflects latent tuberculosis infection which has been acquired in their country of origin shortly before migration although there is also likely to be an ongoing complex interplay, in the destination country, of host (such as age, and comorbidities including diabetes mellitus) and environmental factors (such as nutritional status) which contribute to the observed epidemiology. Understanding the natural history of TB in recently arrived migrants is important when we are considering how best to implement TB control in this population.

Comment: There is relatively little discussion about recent trends in other risk factors (e.g., diabetes, age) in foreign-born populations. What are the implications of these trends for the future epidemiology of TB in these populations, and the control thereof?

Response: Thank you for the comment. In the manuscript we allude to the importance of comorbidities in determining the risk of reactivation and the importance of concomitant medical conditions:

"Further work is needed to determine both the overall risk of progression from LTBI to active TB disease in migrants as well as the contribution of different risk factors such as concomitant medical co-morbidities or re-exposure during travel back to their countries of origin."

We agree that this should be discussed in more detail. We have, therefore, revised this section significantly which now states:

“Further work is needed to determine both the overall risk of progression from LTBI to active TB disease in migrants as well as the contribution of concomitant medical co-morbidities and demographics such as diabetes mellitus, chronic kidney disease and age. Diabetes mellitus and
chronic kidney disease are more common in migrant populations and significantly increase the risk of reactivation from LTBI to active TB. This is likely to result in increasing TB notifications in the foreign-born, migrant populations, particularly as the migrant population ages, and this will, therefore, need to be taken into consideration when developing TB control programmes.

We also agree that it is important that the implication of medical risk factors on TB control is discussed in the manuscript. We have therefore significantly revised the TB control section to take account of the Reviewer’s comments. This section now states:

“For reasons of practicality and cost-effectiveness, most high-income countries attempt to limit the eligible population to refugees or asylum seekers or those individuals arriving from high TB burden settings. However, countries vary considerably in their definition of a high TB burden setting for the purposes of migrant screening: the UK has taken a decision to screen migrants arriving from countries in Sub-Saharan Africa or those countries with a TB incidence above 150 per 100,000 whereas Canada screens at a lower threshold of 30/100,000 but only migrants with increased risk of reactivation. Given the prevalence of comorbidities in the migrant population (such as diabetes mellitus) which increase the risk of reactivation, these factors will likely need to be taken into account when determining which migrants to screen. At the present time, however, the variation between guidelines could reflect uncertainty about the optimal screening threshold which balances the need to identify the majority of LTBI with cost effectiveness.”

Comment: The issue of frequent returns home to the country of origin is a fascinating one, and one that I would love to see covered in a bit more depth here. How much of the incidence we see in foreign-born populations represents infection acquired before the initial immigration event, versus during returns home (which can often be months at a time)?

Response: We agree with the Reviewer that the issue of individuals acquiring latent TB infection following travel to their country of origin is extremely interesting. However, research in this area is very limited. Nonetheless we have expanded this section of the manuscript to take into account the available literature. This section has been significantly revised and now states:

“An additional issue which is likely to play a part in determining TB epidemiology in migrant populations is the acquisition, and subsequent reactivation, of LTBI following re-exposure
during travel back to their countries of origin. Previous work in this area has indicated that travel to high TB burden countries increases the risk of acquiring LTBI with the risk increasing with more prolonged travel and a higher TB burden in the country visited. Although there is a paucity of data on the proportion of TB acquired through travel, published work suggests this could be anywhere between 20% and 50%. However further prospective research in this area is needed to more accurately quantify the risk.”

Comment: Similarly, I didn't see much coverage of the role of immigration policy, and the difficulty in collecting data on/performing interventions in undocumented populations that do not go through standard screening procedures. (This also should be considered when making the blanket statement on p. 4 that "surveillance data...have shown that the proportion of migrants with active TB present at the time of migration is relatively small.")

Response: In the current manuscript we did not specifically discuss the immigration policies in place in high-income countries as the number of countries is very large and the policies in place likely to be highly divergent. Summarising this information would require a separate review and we felt that other areas were more important to cover. We would point out that we do discuss, in some detail, the screening policies in place in high-income countries. Nonetheless we accept the point made by the Reviewer and have therefore added the following statement:

“It should, however, be borne in mind that much of the available data relates to documented migrants and there remains ongoing difficulty in collecting data on undocumented migrant who bypass standard screening protocols.”

Comment: While I think the figure provided is helpful, I think a real opportunity is missed to have another figure that synthesizes many of the concepts here. Perhaps a diagram that illustrates the country of origin, destination country, ways in which incident TB can occur in the destination country, and points at which TB control interventions can have an impact? A map of TB incidence among the foreign-born versus native-born in low-incidence countries? I would strongly urge the authors to consider adding a summary figure or two.

Response: Thank you for stating that the figure is helpful. In line with the Reviewer’s comments we have added a figure (figure 1) which provides key take home messages for the reader. We
agree that a schematic diagram would be useful and have therefore added this to the manuscript (figure 3).

Comment: Similarly, I feel that a table (or series of tables) to synthesize and summarize existing data on this topic could be very helpful.

Response: We have already incorporated a table (table 1) which summarises the outcomes of screening for active TB. On balance we did not want to include too many tables as they would, in some cases, be replicating previous work undertaken by the authors or others. However we do agree that a further summary table would be useful and have therefore included a table (table 2) summarising the strengths and weaknesses of different screening methods.

Comment: The TB epidemiology section (introduction) is very useful - if anything, I would recommend that the authors expand this section somewhat (ideally at the expense of the health economics section, as above). It is difficult to appreciate the dynamics of immigration without first understanding the epidemiology of TB in high-income countries. Perhaps choosing two or three countries with a lot of data and somewhat different epidemics (e.g., Netherlands, UK, USA), then using a figure to compare and contrast these dynamics, could be useful?

Response: Thank you for the positive comment. The aim of the manuscript is to provide a review of tuberculosis and migration. Whilst we agree that the section on TB epidemiology is important, there are additional sections which are also equally important and likely to be of interest to the general readership of BMC Medicine. We feel that we have cogently summarised the epidemiology of TB in high-income countries, the burden of disease in the local-born population, the burden of disease in the foreign-born population, temporal changes in notifications and the factors which are associated with an increased risk of TB. We therefore believe that the manuscript provides the reader with clear and comprehensive information. Nonetheless, we have expanded the section a little as per the Reviewer’s comment and now state:

“Tuberculosis epidemiology in high-income countries

Tuberculosis (TB) remains a ‘global health emergency’.1 Although much of the burden is concentrated in high-burden settings in Asia and Africa (which make up 58% and 28% of all cases respectively),2 TB continues to be of concern in high-income nations. In the 34 high-income Organisation for Economic Cooperation and Development (OECD) countries, TB
incidence fell by a median of 4.7% per year (between 1995 and 2004) decelerating to 3.0% per year between 2005 and 2014 – making TB elimination more difficult to attain.4

Yet the overall changes seen in TB incidence in high-income countries hide an important disparity: while local-born cases have remained static or decreased, foreign-born cases have decreased more slowly or increased. From 2000 to 2013, local-born TB cases decreased by half (median 51.3%; IQR -64.3 – -35.3%) whilst foreign-born case notifications increased marginally (median 2.3%; IQR -36.7 – +40.4%).5-10 In just under half of the high-income OECD countries foreign-born TB cases increased.5-10 Consequently foreign-born individuals, in 2013, made up over half of all TB cases (median 52.0%; IQR 31.4–73.9%)5-11 with incidence rates 8.7-18.4 times that seen in the local-born population.7,9,10,12

Drilling down further into the patterns TB notifications in the foreign-born population in high-income countries reveals information about key risk groups with the highest incidence and risk of active TB following migration: migrants from Asia and Africa, recent migrants (within 5 years of arrival), refugees and individuals with comorbidities (such as HIV infection and diabetes mellitus).7,9,10,12,13

We have not made any further changes to this section (particularly as we are mindful of word count limits) and would leave it to the Editor’s discretion whether any further changes are warranted.

Comment. Another important point to stress in this regard is that immigrants are not a representative sample of the population in the home country - the demographics of immigrants are important to consider.

Response: We agree with this point and have revised the manuscript appropriately to take account of this:

This has resulted in more permanent migrants moving from low/medium income, higher TB burden, countries to high-income developed, lower TB burden, countries including USA, Canada, Australia and Western European nations although migrants are not necessarily representative of the population in the country of origin.15
Comment: Thank you for the opportunity to review this manuscript, and I would like to commend the authors on putting together such a comprehensive review of a very broad and difficult topic to cover!

Response: Thank you for your positive comment. We would also like to specifically thank the Reviewer for their excellent, cogent and helpful comments. By incorporating the suggestions/changes we have significantly improved the manuscript and hope that the manuscript is now suitable to be published.