Author’s response to reviews

Title: MDR-TB treatment adherence in migrants: a systematic review and meta-analysis

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To Alessandro Recchioni, Associate Editor BMC Medicine,

Thank you for your kind consideration of our manuscript “MDR-TB treatment adherence in migrants: a systematic review and meta-analysis” (BMED-D-17-01258), and for the opportunity to revise our submission based on the constructive and positive comments of the reviewers.

We are pleased to submit a revised manuscript and point-by-point response to your comments, which we hope you will find acceptable for publication. We also include a version of the manuscript in which changes are highlighted using the track-changes mode.

We look forward to hearing from you in due course.

Best Regards,

Jon Friedland, on behalf of all the authors

Editor’s comments:

Thank you very much for considering our manuscript.

Please provide the appendix containing your search strategy.

This appendix has been uploaded as an attachment alongside the revised manuscript.

Reviewer 2 – Kevin Schwartzman:

Thank you for your positive and constructive comments, and we are pleased you found this to be a “well-written systematic review and meta-analysis.”

1. With respect to the rationale for the study, what is already known about adherence (and non-adherence) to treatment for drug-sensitive TB in migrants? I was surprised not to see any explicit reference to data in this regard, beyond assumptions and policy documents. If no such data exist, this would be a key topic for further investigation, particularly since poor
adherence to treatment for drug-sensitive TB fosters the further emergency of MDR strains. However, I believe that some data are available from national surveillance systems (e.g. the US CDC), and these should be cited and discussed – in the introduction and the discussion sections.

Thank you for highlighting this important consideration. Unfortunately, there is also insufficient data collected on migrant status and treatment completion for drug sensitive TB, limiting efforts to comprehensively examine this association. We agree that this is a key topic for further investigation, and warrants its own systematic review and meta-analysis. We have highlighted the need for further research in this area in the discussion (lines 347-352, page 16). In addition, we have cited relevant data from the UK available on treatment outcomes in non-UK born TB patients (Lines 67-69, page 4). Thank you for suggesting we look into what data are available from the US CDC. We have looked through their data and found that treatment completion is typically stratified by ethnicity rather than migrant status as is often the case (https://www.cdc.gov/tb/statistics/reports/2015/pdfs/2015_Surveillance_Report_FullReport.pdf). Therefore, we have not referenced this in the manuscript, but have discussed this issue in line 389, page 17.

2. The methods are appropriate and well-described.

Thank you for this positive feedback.

3. As mentioned by the authors, treatment failures may not reflect poor adherence, and it is appropriate that they conducted a sensitivity analysis where failures were excluded. On line 231 the authors should include the results of this sensitivity analysis for non-migrants as well as migrants, to permit suitable comparison. It is also worth noting that attributing treatment failure to poor adherence may be viewed as stigmatizing or “blaming the victim.”

We agree this is useful to include to permit comparison, and have added this data where requested (line 252, page 12). Excluding failures, treatment non-adherence in non-migrants was 3% (95% CI: 0-8%; I² = 9.92%). We have also acknowledged here that attributing treatment failure to poor adherence may be stigmatising (line 250, page 12).

4. In interpreting their results, the authors could also consider the fact that treatment adherence may be viewed by some migrants as necessary to obtain status in the destination country (e.g. permanent residence or citizenship), and conversely they may believe that any perception of poor adherence will jeopardize their prospects in this regard – particularly
since poor adherence may lead to enforced treatment and hospitalization, or even imprisonment (for contempt of court) in some settings.

This is an interesting consideration, and we have included a discussion of this (Lines 275-287, pages 13-14). It is also interesting to note the context in the UK where migrant patients may be avoiding presenting for care or dropping out of treatment because of patient data sharing with the Home Office, which is being used for immigration enforcement purposes. As a result, adhering to treatment and continuing to access health services may in fact put them at risk of being identified by the Home Office and deported.

5. In their interpretation and discussion of their results, the authors should further emphasize the heterogeneity of studies reviewed – e.g. setting, treatment regimen, patient characteristics. Also important is the often small sample sizes – in the individual studies, and (in fact) overall, in the meta-analysis. [As an aside, I was surprised to note that a case report of a single patient (reference 52) received a quality score of 8/9]. More generally, there is enormous potential for publication bias, given the nature of the observational studies reviewed (primarily case series). This may not entirely invalidate the results of the analysis, but this point deserves a much more forthright discussion as an important limitation of this work – as does the marked heterogeneity of some of the individual study results.

We have added further detail in our discussion regarding the heterogeneity of the studies included. In addition, we have added a discussion point regarding the small sample sizes across the included studies, and thus in the review. We have also added further discussion about the potential for bias. (See lines 398-410, pages 18-19).

The data available on migrant treatment outcomes in TB may be reflective of settings in which migrants are a particular interest group, leading to the collection of data on and stratification by migrant status. This is a limitation across migrant health research, as data on migrant status are not consistently or systematically collected in clinical settings.

We also clarify that across the studies that were originally labelled as ‘case series’, the papers were reporting all cases in that clinical setting over a period of time, and thus were not selective case studies. We have now labelled these studies more correctly as ‘cohort studies’ (with the exception of studies which explicitly describe themselves as ‘case series’ to respect their own designation). This acknowledges the systematic inclusion of all cases in each data set for the relevant study period. We have updated Table 1, and conducted a quality assessment for all relevant studies using the CASP cohort study quality appraisal tool. The quality remains very high. We have also updated the methods and results accordingly (line 155-6, page 8; line 203, page 10). It is worthwhile to note that those studies still labelled as ‘case series’ are systematic and inclusive of all cases during the relevant study period for each data set (see lines 204-5, page 10).
With regards to the comment on the quality score for reference 52, the single patient was actually the only relevant data that could be extracted for this review, but the study was evaluated using the validated quality appraisal tool, and assessed as a whole study (e.g. the assessment does not relate to the specific data that were extracted, but rather the quality of the research overall).

6. There is unnecessary repetition in the discussion section of the manuscript, e.g. repeated statements that the findings contradict earlier assumptions about poorer adherence in migrants, need for better quality evidence.

Thank you for pointing this out, and we have rectified this.

7. The conclusion is appropriate and well written.

Thank you for this positive feedback.

Minor comments:

1. In the abstract, lines 35-6, the authors state: “The estimated rate of adherence to MDR-TB treatment across migrant patients was 71% (95% CI: 0.58 – 0.84%),” i.e. there is a typographical error in the 95% CI, where the numbers are expressed as proportions rather than percentages. This occurs at other places in the full text manuscript, e.g. line 209. Please correct throughout.

Thank you, and we have addressed this.

2. Line 54: change to “has become a major focus.” More generally, there are scattered minor typographical and syntax errors; please proofread carefully and correct accordingly.

We have corrected this, and proofread the manuscript again.

Reviewer 4 – Claudia Dobler

The paper is well written and the research methodology is sound.

Thank you for this positive feedback.
Major comments:

1. Data analysis: The authors use treatment outcomes as proxy for treatment adherence. The manuscript would be clearer if the authors would address the following points:

   a. Explain that success of treatment is only a proxy indicator for treatment adherence, often used in pragmatic population-based assessments.

      We have included this in the manuscript (Line 122-127 page 7; Line 169-171, page 9).

   b. Was the definition of adherence based on treatment outcomes for this review chosen because information on quantity and timing of the medication taken by the patients in the included studies was not available? Other reasons?

      We sought to comprehensively identify and synthesise any data available on MDR-TB treatment adherence migrant populations, and elected to use as broad a definition as possible given the heterogeneity across studies in how adherence or treatment outcomes were reported. In addition, treatment outcomes are more routinely reported than data on quantity and timing of medication taken in the literature, in part because of the clinical relevance of this, and it was also felt that examining treatment adherence with respect to its relationship with treatment outcomes within the scope of the review would benefit its translation to clinical care.

2. Line 239: “…increased adherence rates among patients in specialist institutions, which may be better equipped to support treatment adherence…” Was all treatment given as DOT? Were some programs community-based (versus institution-based treatment)? If yes, what was the association with adherence?

      Not all treatment across the included papers was given as DOT, and indeed some treatment was community-based. However, it was not feasible to systematically examine whether treatment was provided in a community setting, or whether and for what period of time patients were hospitalised/institutionalised. Our comment referred to a trend of improved adherence and treatment outcomes in studies which indicated treatment was provided at specialist TB centres or centres that specialised in infectious and pulmonary diseases. We have sought to provide clarification regarding these issues in the manuscript (lines 288-297, page 14).

3. Line 282: “The comparable rates of adherence (and non-adherence) between migrants and non-migrants challenge assumptions that adherence to MDR-TB treatment is likely to be worse in migrants…though this group [migrants] is a key focus of TB strategies in high
income low TB incidence countries…” The authors seem to imply that concerns about treatment adherence are the reason for the focus of TB control measures on migrants in low TB incidence countries. However, the major reason why migrants are targeted for TB control measures is the high relative risk of TB in migrants compared to the general population, not the assumption that they are less adherent to treatment. This should be clarified.

We have clarified this in the manuscript (see lines 345-6, page 16).

4. Line 312: “Further research is needed to improve understandings of drivers of MDR-TB treatment adherence and non-adherence within migrant populations…” This sentence seems to contradict an earlier statement, where the authors state that health systems and services within which MDR-TB is diagnosed and treated may be a significant determinant of treatment adherence, and may mediate the effects that social and cultural barriers may have.” I suggest that the authors modify their statement.

We have modified our statement (lines 352 - 356, page 16).

Minor comments:
1. Line 24: foci should be focus (singular).

This has been amended.

2. Line 57: “…with poor treatment adherence in TB patients thought to be a driver of this emerging resistance.” Increasingly, MDR-TB is no longer primarily acquired through poor adherence to first line TB treatment, but direct transmission in the community (e.g. Nsofor CA et al, Sci Rep 2018, PMID: 28794425, Dobler CC et al., Emerg Inefct Dis 2015, PMID: 26196504). I suggest the authors discuss this and emphasize the importance of adherence to MDR-TB treatment to prevent transmission of MDR-TB.

We have cited these two references in background section of the manuscript, and have also brought attention to this issue.

3. Methods Line 102: Assessment of MDR-TB treatment is mentioned as only study aim, which seems inconsistent with the aim in abstract: “to identify and synthesise data on MDR-TB treatment adherence and outcomes (loss-to-follow up, default, treatment, failure, death)
in migrant patients”. Only later do the authors mention that treatment outcomes were used as proxy outcomes for adherence (see also major comment #1). The aim in the introduction and methods should be worded consistently.

Thank you and we have amended this to be consistent in the manuscript.

4. Line 301 A reference for guidelines/policies should be provided.

This has been included.

5. There is quite a bit of repetition in the discussion. Repetitions should be avoided and the discussion streamlined.

Thank you for pointing this out, which was also helpfully done by another reviewer. We have removed repetition and streamlined the discussion.

Reviewer 5 – Dominik Zenner

It is a systematic review and meta-analysis on a very important topic – that of MDR treatment completion, on this occasion amongst migrants. On the whole this is a very well designed study with all the attributes one would expect from a systematic review…

Thank you for your positive comments.

I am, however, slightly concerned about the inclusion/exclusion of papers, which resulted in a systematic review of only 15 papers of which 13 are case-series studies. It may be possible that important data/papers are missing, and that is my main concern here – reasons are described further below.

This is an important consideration in any systematic review and we have responded to your specific points below. However, we also wanted to summarise several key points here. First, an important and significant limitation of the current evidence-base on migrant health is that data on migrant characteristics are not consistently collected in a rigorous or systematic way in either research or clinical data. Furthermore, even where these data are collected, key outcome data (e.g. treatment adherence or drug sensitivity) are not disaggregated by migrant status. As a result, and as highlighted in this review, there is very limited evidence available which can be included in data syntheses such as the one we present in this manuscript. With regards to your mention of the large number of included case-series, the majority of these papers reported all cases in the relevant clinical setting over a period of time, and thus were not selective case series,
but rather representative and systematic. In order to ensure this is transparent in our manuscript, these studies are now labelled as cohort studies over a defined period of time (with the exception of those which are self-labelled as case series, for which we have retained this label). We have also carried out a quality assessment using the validated CASP cohort study quality assessment tool for the relevant papers.

Introduction:

In general the introduction is a fairly broad summary of reasons for non adherence. Would suggest to limit introduction to setting the scene and some robust well referenced introduction to the topic and move some of the hypotheses about reasons to the discussion.

Thank you for this suggestion, and we have moved some of the content regarding reasons for low adherence to the discussion.

Minor points:

P4 154 …a major focus
This has been corrected.

P4 159 But the reason for the lower who completion target is not lfu alone (higher mortality for example not necessarily adherence driven)
We have clarified this (line 62, page 4).

L61 – 244 million International migrants…many more internal
This is an important clarification, which we have made.
L 69 – yes but now 9m Bangladesh regimen available for many…should at least mention. Point still stands as often not applicable.
Thank you and we have now mentioned this.

P5 176 – social risk factors among migrants – contentious point – migrants are very heterogeneous – some may be socioeconomically deprived, many not. Need to qualify and reference pls.
We have added references, and reworded this in light of this feedback.

L79-83 – highly context specific. E.g. In some U.K.-based Somali populations this may partly apply, in many others not. Please rephrase or take out.
Methods:

Methods overall robust but does not include Web of Science and grey literature. Reviewing abstracts of important conferences (union, ers, ats, bts etc) could avoid that important findings from countries which publish less (but may be high-MDR) or that aren’t published yet are retrieved.

Thank you for your positive feedback that the methods overall are robust. Whilst we did not elect to use Web of Science, we did include four key databases for this field, including Embase, Global Health, MEDLINE, and PubMed. In addition, we did seek additional relevant papers through hand searching, and relevant information sources including the Global Fund, Public Health England, the World Health Organization, and the International Union Against Tuberculosis and Lung Disease, in addition to consulting key experts in the field. Whilst you highlight that there may be relevant grey literature, conference abstracts, country reports, and surveillance data that may be accessible disaggregating MDR-TB treatment adherence data by migrant status, the aim of our search was to systematically identify peer-reviewed papers reporting primary data on MDR-TB treatment adherence in migrants. We sought to systematically examine the evidence available in the published peer-reviewed literature in order to provide a comprehensive synthesis of this ‘academic’ evidence-base (and gaps/publication bias in this evidence), which is often prioritised in the development of health services and health policy. The systematic aggregation and analysis of available data on MDR-TB treatment adherence in migrants would be a separate and interesting piece of work, which was beyond the scope of the current review.

In the analysis – I assume mortality was excluded as part of treatment outcome? What about those still on treatment? Please clarify.

Mortality was not one of the treatment outcomes reported on in this review. However, we carried out analyses for both successful treatment outcomes/adherence and unsuccessful treatment outcomes/non-adherence as individuals who died are not represented in either, and thus non-adherence is not necessarily the inverse as adherence. Patients still on treatment were excluded from the adherent categorisation as it is not a definitive outcome measure. We have ensured that this is clarified in the methods and results (Line 173-5, page 9; line 243, page 12).

Included studies – did they include RCTs? They may not be representative as likely better outcomes, but need to specify.

Our study included peer-reviewed papers reporting primary data on MDR-TB treatment adherence and outcomes in migrants, and thus RCTs were not explicitly excluded. However, no
RCTs were ultimately included in the review, as none were identified which met the inclusion criteria. We have clarified our inclusion criteria for study type on line 131, page 7.

Results:

I am surprised at the low number of studies included for full text. I’m also surprised as countries report on this WHO indicator annually and in the Public Health England reports for example there are lots of details on outcomes. At least in countries with robust surveillance systems such data may be of similar or even better quality than some included studies. For example there is good outcome data stratified by U.K./non U.K. born from the UK, including peer-reviewed (Anderson LF et al, Euro Surveill., 2013 vol. 18(40)), and of course annual reports. It’s a cohort study and I’m sure there are many more from other countries, so I’m not sure why the review found mainly case series…Please clarify.

Thank you for these helpful considerations. As mentioned in response to your comment above, the review included peer-reviewed papers reporting primary data on MDR-TB treatment adherence and outcomes in migrants. The low number of peer-reviewed studies identified through our search thus highlights the need to strengthen the peer-reviewed evidence base in this area. This does highlight a few key issues in the literature base, however, and consequently with attempts to formally or informally synthesise and interpret this evidence base.

First, the majority of papers excluded in the full-text screening were excluded because data were not disaggregated by migrant status or drug-susceptibility status in relation to treatment outcomes. The Anderson LF et al paper to which you referred us is one example of this where the data desired on treatment adherence and migrant status were not available in the reported data. More specifically, data were only available on adverse or successful treatment outcomes by migrant status, however the category ‘successful treatment outcomes’ only referred to treatment completed at 24 months or longer, whilst adverse treatment outcomes referred to: treatment completed at 12 months (which does not imply lack of adherence), treatment completed at 24 months or longer but patient relapsed (again, which does not imply lack of adherence), patient died (which may not be attributed to poor adherence), treatment stopped (for any reason including clinician decision), or lost to follow-up. Such adverse treatment outcomes may be attributed to many factors other than lack of adherence, and as a result this paper does not meet the specific inclusion criteria of the review and could not be included. There were many examples of other papers where this was also the case, though they may provide valuable insight into other aspects of MDR-TB treatment in migrants. A future piece of research could be carried out to request all such data from authors, and conduct an individual level meta-analysis, though this was beyond the scope of this review.

Another key reason why potentially relevant papers may not have been identified through our systematic search of the literature is attributed to how migrant status is reported in clinical data
and in the research. There is significant heterogeneity and a lack of consistency in reporting of migrant status. Our search terms were selected to comprehensively identify any papers reporting data on migrants, migrant workers, migration, immigration, refugees, asylum seekers, foreigners, foreign workers, foreign born, non-native, overseas born, emigrants, immigrants, foreign students, international students, or individuals who have been trafficked (see Appendix 1 provided with this revision). We acknowledge that there may be papers which may not include these routinely used terms, and thus were not included. We have noted this in our limitations section (Lines 387-392, page 18).

With regards to your query about the large number of case series included in the review, and the potential for there to be other relevant cohort studies (such as the Anderson paper), we have now labelled case series which were inclusive of all cases in a data set as ‘cohort studies’. However, we also acknowledge that there may be other cohort studies that included migrants with MDR-TB but which were not included either because they did not disaggregate data by migrant status and treatment adherence, and thus were excluded, or did not utilise any of the routine migrant key words.

The study quality is high – again a surprising finding given inherent problems with case series…or does this refer to the two CCS only?

As we have now clarified, most of the studies previously categorised as case series were inclusive of all cases in a data set, and thus were not selective case series. These have now been described as ‘cohort studies’ in the manuscript, and the quality has been assessed using the validated CASP cohort studies quality assessment tool. We did find that across the included studies, quality was high, though this assessment refers to the study in its own right, and not the data specifically extracted in line with the aims of this review.

I note from the flowchart that the commonest reason for non study inclusion was that data could not be disaggregated in an analysable way. Whilst in itself this is reasonable – did the authors make attempts to contact the authors / find publicly available data to answer this? For example, in the Anderson paper above, most (and very granular data is available in PHE reports…).

The aims of this review were to systematically identify and synthesise peer-reviewed primary research in this area to comprehensively examine the available published evidence-base. Though it was outside the scope of this research, a separate and interesting piece of research would be an individual-level meta-analysis or integrative data analysis, in which the original data is acquired and synthesised, for example by contacting authors going to original sources of surveillance data etc, though in many cases the original clinical or surveillance data is still limited in terms of what has been collected by migrant status.
Discussion:

It may be worth summarising the main results in the first sentence. As it reads it launches into the comparison with the literature, as for example specialised and other clinics outcomes were not formally compared.

We have revised the discussion, and no open with a summary of the main results (see line 259, page 13).