

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

TITLE (PROVISIONAL)	Effectiveness of service models and organisational structures supporting tuberculosis identification and management in hard-to-reach populations in countries of low and medium tuberculosis incidence: A systematic review
AUTHORS	Heuvelings, Charlotte C.; Greve, Patrick F.; de Vries, Sophia G.; Jelle Visser, Benjamin; B�elard, Sabine; Janssen, Saskia; Cremers, Anne L.; Spijker, Ren�e; Shaw, Elizabeth; Hill, Ruaraidh A.; Zumla, Alimuddin; Sandgren, Andreas; van der Werf, MJ Grobusch, Martin Peter

VERSION 1 – REVIEW

REVIEWER	Akiko Kowada Ota City Office, Japan
REVIEW RETURNED	28-Oct-2017

GENERAL COMMENTS	<p>General comments:</p> <p>TB prevails in the big cities where vulnerable and hard-to-reach populations are concentrated in many low TB incidence countries. Health care services need to be organized effectively. This systematic review aim was to answer the question : ‘Which service models and organizational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations in low and medium incidence countries?’ The authors demonstrated that the systematic review combined with the original NICE review provides limited evidence, due to the lack of high quality studies. The authors concluded that identification and management of TB in hard-to-reach populations is suboptimal and that service models and organizational structures to identify and manage TB in hard-to-reach populations and countries should be improved and evaluated regularly.</p> <p>The article was well written and needs minor revision.</p> <p>Minor comments:</p> <ol style="list-style-type: none">1. Abstract, Design; Page 3, line 4; Please revise (20017). → (2017)2. Result: It is somewhat difficult to understand the whole results of this review. The results section in this paper focuses on the evidence of the five studies identified in the updated review of the authors. Six studies of the NICE review were written in the detail in the Tables.
-------------------------	--

REVIEWER	Anthony Byrne University of Sydney, Australia
REVIEW RETURNED	23-Dec-2017

GENERAL COMMENTS	<p>This is a well planned systematic review on an important topic. The search strategy seems extensive and potentially appropriate. However, there are some questions that I had in reading the manuscript which require clarification. The main problem is the scope of the review seems to be too large and its objective is not sufficiently defined, thus the inclusion criteria seems vague and the conclusions unclear/non-informative.</p> <p>Major points</p> <ol style="list-style-type: none"> 1. There are several previous reviews that have been performed on this topic. These included the NICE review and several that were excluded in their search strategy. What was different about the author's review to that which was done previously (other than being an update on NICE). 2. The inclusion criteria for articles is not clear. Other than the participants, the type of studies or interventions and the outcome measures seem very broad. 3. The primary and secondary outcome measures are not clearly defined, at least in the way that they are presented in the article (I note that PROSPERO is included but the article should include the most important details to allow the reader a sufficient understanding of what was done). By "effectiveness" do the authors mean "case detection rates" or "treatment outcomes" or both? What are the comparisons? I think this is the main problem with this review. The types of interventions for improving case detection and those for treatment completion are quite distinct and I think can not be adequately covered in one review. 4. The PRISMA flow diagram of results should mention the reason/s for exclusion of the 81 full text articles that were considered but not included in the review. 5. Whilst the data is far too heterogenous for meta-analysis, the results are too vague. I think this is a consequence of the (excessively large) scope of the review and point 3. 6. The conclusion of the abstract is too long. Also a consequence of the objective being unclear. <p>Minor points; Abstract design line 8 should read "2017" not "20017" Abstract line 8 "extent" should read "extend"</p>
-------------------------	---

REVIEWER	Monica Sane Schepisi National Institute for Infectious Diseases, Rome, Italy
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	<p>This review addresses the question: "which service models and organisational structures are effective and cost effective for delivering TB services to hard to reach populations in low-medium incidence countries", in order to update the base for the guidance document by the ECDC on controlling TB in hard to reach and vulnerable populations. The methods are accurately reported, sound and complete. The results are based on the evidence reported by 5 studies.</p> <p>As a minor revision I would suggest the following:</p>
-------------------------	--

	<p>- contextualize the results of the topic addressed, including - but not only as a continuation of the NICE review- the previous six studies identified by the NICE review in the text: the NICE review is cited several times, but in my opinion a general reader should be able to read this review without knowing the NICE review</p> <p>- report the results (of the 11 studies) by population (i.e. drug users - migrants - homeless people - prisoners) or by type of intervention (i.e. TB education - screening (pre or post) - treatment)</p> <p>- please check if the following studies on drug users could be included in your review: 1. "Rüütel K, Loit HM, Sepp T, Kliiman K, McNutt LA, Uusküla A. Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. BMC Research Notes 2011, 4:192" which reports results of a case management intervention aimed at increasing TB screening and entry among IDUs referred from a methadone drug treatment programme; 2. "WHO Regional office Europe. Accessibility and integration of HIV, TB and harm reduction services for people who inject drugs in Portugal. A rapid assessment, April 2012." which reports existing models of integrated TB and HIV care for PWID in Porto, Portugal, and 3. "IMPACT Guide Manual on HIV and TB Testing for DUs and migrants in low-threshold services. 2012", which reports the results of a TB clinical screening among DUs and migrants DUs attending low- threshold facilities (street units, drop-in centres, needle exchange points, substitution treatment facilities) in Rome, Turin, Bratislava and Prague.</p> <p>- please check if the following study on migrants could be included in your review: Schepisi MS, Gualano G, Piselli P, et al. Active Tuberculosis Case Finding Interventions Among Immigrants, Refugees and Asylum Seekers in Italy. Infectious Disease Reports. 2016;8(2):6594. doi:10.4081/idr.2016.6594.</p> <p>- please check if reference 12 (line 25 page 9) is correctly cited</p>
--	---

VERSION 1 – AUTHOR RESPONSE

Editorial Request:

- Please thoroughly proofread the manuscript before submitting your revision e.g. abstract: “and extent “ (=> and extend).

Reply: We have thoroughly read the manuscript again and checked for correct English grammar.

Reviewer: 1

Reviewer Name: Akiko Kowada

Institution and Country: Ota City Office, Japan

Competing Interests: None declared.

General comments:

TB prevails in the big cities where vulnerable and hard-to-reach populations are concentrated in many low TB incidence countries. Health care services need to be organized effectively. This systematic review aim was to answer the question: ‘Which service models and organizational structures, including different types of healthcare workers and settings, are effective and cost-effective for delivering TB services to hard-to-reach populations in low and medium incidence countries?’ The authors demonstrated that the systematic review combined with the original NICE review provides limited evidence, due to the lack of high quality studies. The authors concluded that identification and management of TB in hard-to-reach populations is suboptimal and that service models and organizational structures to identify and manage TB in hard-to-reach populations and countries should be improved and evaluated regularly.

The article was well written and needs minor revision.

Reply: Dear Akiko Kowada, thanks for reviewing our manuscript and for your comments, the replies to your comments can be found below.

Minor comments:

1.1 Abstract, Design; Page 3, line 4; Please revise (20017). →(2017)

Reply: Thanks for noticing this, we changed this accordingly.

1.2 Result: It is somewhat difficult to understand the whole results of this review. The results section in this paper focuses on the evidence of the five studies identified in the updated review of the authors. Six studies of the NICE review were written in the detail in the Tables for information but are not further described nor interpreted.

Reply: Since we conducted an update on the NICE commissioned reviews, as we explain in the methods section, we felt that it would not be appropriate to include the results of others (NICE) in the results section. This is also the approach that was used for two other papers of our research group that were published in *Lancet Infectious Diseases* covering other aspects of prevention and control of tuberculosis in vulnerable and hard-to-reach populations.

Our suggestion is to leave the presentation of the data from the NICE review in the discussion section and the supplementary material as our approach is explained in the methods section, and the previous NICE review papers are properly referenced. Also, this ensures proper and open citation of the NICE review.

Reviewer: 2

Reviewer Name: Anthony Byrne

Institution and Country: University of Sydney, Australia

Competing Interests: None declared

This is a well planned systematic review on an important topic. The search strategy seems extensive and potentially appropriate. However, there are some questions that I had in reading the manuscript which require clarification. The main problem is the scope of the review seems to be too large and its objective is not sufficiently defined, thus the inclusion criteria seems vague and the conclusions unclear/non-informative.

Reply: Dear Antony Byrne, first of all thank for reviewing our manuscript and for your comments. You mentioned that the search strategy seems extensive, and we agree that we conducted a scope-wise very wide search. This manuscript is part of a review series that served as the evidence base for the ECDC guidance document on TB in hard-to-reach populations; supplementing the work commissioned by NICE previously. We used the same search as was used for the review, "Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review" by Heuvelings et al. previously published in the *Lancet Infectious Diseases*. As this was an update of the reviews series previously commissioned by NICE, we used a very similar search strategy (the search was slightly extended as explained in the methods section) as was used in these reviews, for consistency.

Secondly, you mention that the scope of this review is too large and that the objective is not sufficiently defined. As mentioned in the manuscript this is a review with a scoping component,

evaluating the effectiveness of service models and organisational structures to improve identification and management of TB cases in hard-to-reach populations. We agree that the term service models and organisational structures are a bit vague but we did not want to miss any essential models or structures that could be effective in improving TB identification or management.

To clarify the scope a bit more in the manuscript, we added the following sentence to the methods section: “TB identification tools, TB diagnostics, incentives, social support, directly observed therapy and treatment of co-morbidities are discussed in another review.¹³ In this review we aim to identify the effectiveness of the type of health worker and setting, to identify and manage TB in hard to reach and vulnerable populations.” (last paragraph page 4).

Major points

2.1 There are several previous reviews that have been performed on this topic. These included the NICE review and several that were excluded in their search strategy. What was different about the author’s review to that which was done previously (other than being an update on NICE).

Reply: As we wanted to supplement the NICE review we used the same methodology, the only differences are that we added two extra hard-to-reach populations (people living with HIV and children within vulnerable and hard-to-reach populations), included more countries; all countries that are part of the EU/EEA, EU candidate countries and OECD countries and we excluded latent TB.

In our systematic search of the literature we have not come across reviews that cover the same topic as covered by our systematic review.

2.2 The inclusion criteria for articles is not clear. Other than the participants, the type of studies or interventions and the outcome measures seem very broad.

Reply: We did not want to miss any relevant studies; therefore, we reviewed all studies that discussed an intervention focussing on a service models and/or organisational structures. As these interventions might vary widely we did not want to restrict our search and inclusion to a certain pre-defined type of intervention as we wanted to evaluate which interventions are most effective/cost-effective. In the second paragraph of “Selection of studies and data management” we provide a few examples: “Predefined interventions were using more convenient locations (like specialised TB centres, shelters for homeless people or drug users, needle exchange/methadone programme locations, port of arrival, schools or mobile clinics) and peers or health care workers with the same ethnic or cultural background; however, other interventions could also be included if they supported TB identification or management in hard-to-reach populations.”

Regarding the outcomes, the studies had to report on the (cost)effectiveness (first paragraph page 5: “Outcomes were defined as any measure of TB identification and management (for example, number of people screened, screening coverage, proportion receiving treatment and treatment completion rate).”

We agree with the reviewer that to assess effectiveness different outcome measures were evaluated. All outcome measures included in the review are directly or indirectly supporting TB prevention and control in hard-to-reach populations and were therefore included in our systematic review with a scoping component.

2.3 The primary and secondary outcome measures are not clearly defined, at least in the way that they are presented in the article (I note that PROSPERO is included but the article should include the most important details to allow the reader a sufficient understanding of what was done). By

"effectiveness" do the authors mean "case detection rates" or "treatment outcomes" or both? What are the comparisons? I think this is the main problem with this review. The types of interventions for improving case detection and those for treatment completion are quite distinct and I think cannot be adequately covered in one review.

Reply: Thank you for this comment. In the methods section we provide the outcomes of interest 'Outcomes were defined as any measure of TB identification and management (for example, number of people screened, screening coverage, proportion receiving treatment and treatment completion rate)'. We clarified the effectiveness definition by adding a line in the "Selection of studies and data management" part: "Effectiveness was defined as an improvement in any measure of TB identification and/or management."

Thanks for commenting on the comparator. We did not pre-define the comparator group, as we did not want to exclude studies beforehand but during the review process we redefined the comparator to a relevant comparator to the intervention, like usual care, no intervention, another intervention or historical comparison. We should have reported this in the first version of the manuscript. This can now be found in the last paragraph of page 4.

We do think that the review presented offers a comprehensive assessment of evidence across TB detection and TB management. We are not sure that separating the TB identification and TB management parts would make the review any more decisive.

2.4 The PRISMA flow diagram of results should mention the reason/s for exclusion of the 81 full text articles that were considered but not included in the review.

Reply: Thank you for this comment. We updated the flow diagram; 16 studies were included in the second review of this review series published in the Lancet ID, Heuvelings et al., the other 65 studies did not meet the inclusion criteria for this review. We could give a reason for every excluded study but that would be a lot to include in a flow diagram. We hope this is satisfactory.

Additionally, we added a line in the methods section under the Selection of studies and data management part that the same search was used for the review published in the Lancet Infectious Diseases (Heuvelings et al.): "The same search strategy as for the previous NICE review¹⁵ and the previous published review by Heuvelings et al.¹³ was used..." To clarify that some studies were discussed in the other review.

2.5 Whilst the data is far too heterogenous for meta-analysis, the results are too vague. I think this is a consequence of the (excessively large) scope of the review and point 3.

Reply: A meta-analysis would indeed not be possible as the interventions vary too much and only limited data is available per intervention. However, several studies showed improved screening uptake and treatment completion, what in our opinion is a pretty clear result. As we write in the conclusion section only a limited number of studies evaluated the same intervention with the same outcome measure and therefore no hard conclusion can be drawn.

2.6 The conclusion of the abstract is too long. Also a consequence of the objective being unclear.

Reply: We do agree that the conclusion might be a bit long but as the results are heterogeneous but informative we prefer to provide the main findings that could be obtained from the results in the conclusion.

Minor points;

2.7 Abstract design line 8 should read "2017" not "20017"

Reply: Thanks for noticing this, we changed this accordingly.

2.8 Abstract line 8 "extent" should read "extend"

Reply: Thanks for noticing this mistake, we changed this accordingly.

Reviewer: 3

Reviewer Name: Monica Sane Schepisi

Institution and Country: National Institute for Infectious Diseases, Rome, Italy

Competing Interests: None declared

This review addresses the question: "which service models and organisational structures are effective and cost effective for delivering TB services to hard to reach populations in low-medium incidence countries", in order to update the base for the guidance document by the ECDC on controlling TB in hard to reach and vulnerable populations. The methods are accurately reported, sound and complete. The results are based on the evidence reported by 5 studies.

As a minor revision I would suggest the following:

3.1 contextualize the results of the topic addressed, including - but not only as a continuation of the NICE review- the previous six studies identified by the NICE review in the text: the NICE review is cited several times, but in my opinion a general reader should be able to read this review without knowing the NICE review

Reply: Our systematic review is a supplement to the NICE review. Therefore we feel that it is not appropriate to repeat the findings of the NICE review in the results section, since these are not the results of our work. We do acknowledge that the reader should have easy access to the results of the NICE review. Therefore, we have chosen to provide the results of both our review and the NICE review in table 1 and 2 and in the supplementary material.

3.2 report the results (of the 11 studies) by population (i.e. drug users - migrants - homeless people - prisoners) or by type of intervention (i.e. TB education - screening (pre or post) - treatment)

Reply: Thanks for this comment, we changed the order of table 2 by intervention.

3.3 please check if the following studies on drug users could be included in your review:

1. "Rüütel K, Loit HM, Sepp T, Kliiman K, McNutt LA, Uusküla A. Enhanced tuberculosis case detection among substitution treatment patients: a randomized controlled trial. BMC Research Notes 2011, 4:192" which reports results of a case management intervention aimed at increasing TB screening and entry among IDUs referred from a methadone drug treatment programme;

Reply: This study is included in the review published in the Lancet Infectious diseases (Heuvelings et al.), "Effectiveness of interventions for diagnosis and treatment of tuberculosis in hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review".

2. "WHO Regional office Europe. Accessibility and integration of HIV, TB and harm reduction services for people who inject drugs in Portugal. A rapid assessment, April 2012." which reports existing models of integrated TB and HIV care for PWID in Porto, Portugal.

Reply: As we included studies documented in PubMed and Embase this study did not come up in our search. Also, this paper did not report on effectiveness or cost-effectiveness, one of our inclusion criteria.

3. "IMPACT Guide Manual on HIV and TB Testing for DUs and migrants in low-threshold services. 2012", which reports the results of a TB clinical screening among DUs and migrants DUs attending low- threshold facilities (street units, drop-in centres, needle exchange points, substitution treatment facilities) in Rome, Turin, Bratislava and Prague.

Reply: Thanks for this suggestion, it looks like a very interesting study; however, we did not see an evaluation of effectiveness or cost-effectiveness on TB in this study. This was one of the criteria for inclusion in our review.

4. please check if the following study on migrants could be included in your review: Schepisi MS, Gualano G, Piselli P, et al. Active Tuberculosis Case Finding Interventions Among Immigrants, Refugees and Asylum Seekers in Italy. *Infectious Disease Reports*. 2016;8(2):6594. doi:10.4081/idr.2016.6594.

Reply: The same applies for this study; we did not see an evaluation of effectiveness or cost-effectiveness on TB in this study, what is one of the criteria for inclusion in our review.

5. please check if reference 12 (line 25 page 9) is correctly cited

Reply: Thank you for checking this mistake, the reference on page 9 should be: de Vries SG, Cremers AL, Heuvelings CC, et al. Barriers and facilitators to the uptake of tuberculosis diagnostic and treatment services by hard-to-reach populations in countries of low and medium tuberculosis incidence: a systematic review of qualitative literature. *Lancet Infect Dis* 2017. We changed this accordingly.

VERSION 2 – REVIEW

REVIEWER	Akiko Kowada Ota City office, Tokyo, Japan
REVIEW RETURNED	18-Mar-2018
GENERAL COMMENTS	Minor issues are satisfactorily addressed.
REVIEWER	Monica Sane Schepisi National Institute for Infectious Diseases INMI L Spallanzani
REVIEW RETURNED	04-Apr-2018
GENERAL COMMENTS	The authors have addressed all of my comments and I recommend to accept the paper.