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

<table>
<thead>
<tr>
<th>TITLE (PROVISIONAL)</th>
<th>Protocol for systematic review and meta-analysis of treatment success rate among adult tuberculosis patients in sub-Saharan Africa</th>
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<tbody>
<tr>
<td>AUTHORS</td>
<td>Izudi, Jonathan; Semakula, Daniel; Sennon, Richard; Tamwesigire, Imelda; Bajunirwe, Francis</td>
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</tbody>
</table>

VERSION 1 – REVIEW

| REVIEWER | Ram Bajpai  
|          | Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore |
| REVIEW RETURNED | 27-Jun-2018 |

GENERAL COMMENTS

Authors have chosen the time period from 2007 – 2018. However, it is not justified that why 2007 was considered as starting point. How authors concluded that it’d be adequate?

Primary and secondary objectives (if any) should be presented before the method section in a subheading to give clear idea to the readers.

How missing data will be handled during data acquisition and analysis? Will primary author be contacted? Then, how many times?

Add reference to Cochrane Q test and I² statistic classification which is usually Cochrane Handbook.

For funnel plot asymmetry using Egger’s test, p<0.1 should be considered as level of significance for the any evidence of publication bias.

Authors should also consider to add prediction interval, when they perform meta-analysis. Prediction interval will help them to understand the direction of evidence in future studies. Lots of useful resources are available online to understand this concept. Authors did not explain their plan for analysis by the study design. For example, it is not recommended to combine cross-sectional and randomised studies together in meta-analysis. So, it is recommended to elaborate on the meta-analysis plan by their design. It is important as confliction results due to various study designs may affect the study findings.

Some additional subgroups analysis such time cut-off etc. needs to think at this stage to avoid any bias due to the post-hoc analysis.
Need to add (policy) implication of this review in one paragraph as discussion heading at the end, so readers would know the future benefits/implications from this study.

**REVIEWER**
Jean Joel Bigna  
Department of Epidemiology and Public Health, Centre Pasteur of Cameroon  
**REVIEW RETURNED**
10-Jul-2018

**GENERAL COMMENTS**
The authors plan to conduct a systematic review with meta-analysis of the proportion of successful TB treatment in sub-Saharan Africa. Sub-Saharan Africa is among the regions with the highest burden of tuberculosis, mainly due to HIV infection. The method chosen to answer the research question is adequate, but requires important considerations for improvement.

**Highly important comment**

1) As sources of data, the authors should mandatory contact the health authorities of each country in charge of the national tuberculosis program. Each country has data for the outcomes of patients undergoing TB treatment. It would therefore be an important source of study selection bias to do not consider data from countries with national representativeness. Moreover, I would have proposed, as is done in other areas, to consider only the data collected by the programs of each country. It is only in the absence of data from different countries that subnational data published in other databases should be considered. In addition, data on the success of TB treatment can be found on the World Bank website (https://data.worldbank.org/indicator/SH.TBS.CURE.ZS?view=chart) and WHO (http://www.who.int/tb/data/en/)

**Major comments**

2) I suggest that the authors also look at other outcomes of TB treatment as defined by the WHO to have a more authoritative review.

3) The authors do not tell us why they chose to limit the search for studies in 2007. Perhaps there is a reason, this should be clearly stated.

4) In lines 112-113, the authors say that they will consider observational studies, but in lines 130-131, interventional studies appear. Authors should be consistent throughout the manuscript about what will be done. Please also look at Lines 194-195, when listing study design, authors not listed interventional studies.

5) For comparative studies with two or more arms, authors should consider each arm as a single study. This needs to be clarified. In addition, they should specify that they will only consider the arm for which TB patients have the outcome of interest. For example, one may have a case-control study in which the cases are TB patients and the controls are not TB patients.

6) I wonder if it is really necessary to consider interventional studies. Interventional studies may overestimate treatment success rate because subjects are often best followed-up in trials. This is not
going to represent real life and may not be useful for health policy makers.


8) Search strategy. In addition to the consideration of the term sub-Saharan Africa and its variants, I propose to the authors to better capture all the studies of each country, to add in the search strategy with the term boolean "OR", the name of each country of Sub-Saharan Africa and its variants (example: "... Nigeria OR Côte d'Ivoire OR Ivory Coast OR ....").

9) I do not understand why the authors use the NOS and Cochrane risk of bias tool to evaluate the methodological quality of the studies. What interests the authors in the studies is the prevalence / proportion data. The authors are not interested in whether an interventional study was conducted without bias, but that the prevalence data are of good quality in included studies even if these studies are interventional, cohort or case control studies. It is only this aspect that interests the authors and therefore it is only this aspect that should be assessed.

10) I do not understand why the authors qualify “Metaprop” as “newly developed” tool. I propose to delete this part.

11) Line 270-271: “However, in instances of low heterogeneity, we will use Mantel Haenszel (M-H) fixed effects model to pool TSR”. The decision to use random effect model or fixed-effect model should not be based on the results of quantified heterogeneity I² or the Cochran Q test results. Authors already acknowledged that they will a-priori be heterogeneity due to study design, study participants... Therefore, only random effect model should be used for all analyses. I propose to delete this sentence.

12) I propose to also consider sex (female versus male), setting (urban versus rural), human development index (very high, high, medium, low) in subgroup analysis.

13) Lines 310-311. “We also plan to share the results with the Uganda Ministry of Health, Division of National TB and Leprosy”. I do not understand why the authors specify that they will share data with Uganda Ministry of Health. Authors are planning to conduct a systematic review for sub-Saharan Africa, not only for Uganda.

14) Abstract should be revised according to all above comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. Authors have chosen the time period from 2007 – 2018. However, it is not justified that why 2007 was considered as starting point. How authors concluded that it’d be adequate?
Response. We appreciated this comment. Ideally, our aim was to review data that spanned one decade, hence we selected 2007 as the starting point for convenience. We believe a decade was sufficient time frame for a demonstrable trend of events. We have restated the review period as July 01, 2008 to June 30, 2018, exactly a decade (10 years).
2. Primary and secondary objectives (if any) should be presented before the method section in a subheading to give clear idea to the readers.
Response. We have inserted the sub-heading for the primary objective before the methods section, and consequently re-stated the primary objective of the study. We do not have any secondary objective.

3. How missing data will be handled during data acquisition and analysis? Will primary author be contacted? Then, how many times?
Response. We have included a text detailing how missing data will be handled in the revised manuscript: 1) during data extraction by contacting primary authors, 2) at data analysis by conducting sensitivity analysis, and 3) by discussing the potential impact of missing data on the review findings.

4. Add reference to Cochrane Q test and I2 statistic classification which is usually Cochrane Handbook.
Response. We thank the reviewers for this comment and have now inserted an in text citation as advised.

5. For funnel plot asymmetry using Egger’s test, p<0.1 should be considered as level of significance for the any evidence of publication bias.
Response. We have corrected the p-value from p<0.05 to p<0.1 as recommended.

6. Authors should also consider to add prediction interval, when they perform meta-analysis. Prediction interval will help them to understand the direction of evidence in future studies. Lots of useful resources are available online to understand this concept.
Response. We have inserted added a new text on prediction interval in this study.

7. Authors did not explain their plan for analysis by the study design. For example, it is not recommended to combine cross-sectional and randomised studies together in meta-analysis. So, it is recommended to elaborate on the meta-analysis plan by their design. It is important as confliction results due to various study designs may affect the study findings.
Response. We are grateful for this observation. In the revised manuscript, we have included a sub-group analysis plan, where we will determine TSR for each study design.

8. Some additional subgroups analysis such time cut-off etc. needs to think at this stage to avoid any bias due to the post-hoc analysis.
Response. We have specified all the necessary sub-group analysis. We do not have a rationale for time specific cut-offs in this study. As a result, time cut-off sub-group analysis was not included in the revised manuscript.

9. Need to add (policy) implication of this review in one paragraph as discussion heading at the end, so readers would know the future benefits/implications from this study
Response. This suggestion is much appreciated. We have included the likely implications of the review for practice, policy, and research in the revised manuscript under the subsection “Implications of the review”.

Reviewer: 2
The authors plan to conduct a systematic review with meta-analysis of the proportion of successful TB treatment in sub-Saharan Africa. Sub-Saharan Africa is among the regions with the highest burden of tuberculosis, mainly due to HIV infection. The method chosen to answer the research question is adequate, but requires important considerations for improvement.

1. Highly important comment
As sources of data, the authors should mandatory contact the health authorities of each country in charge of the national tuberculosis program. Each country has data for the outcomes of patients undergoing TB treatment. It would therefore be an important source of study selection bias to do not consider data from countries with national representativeness. Moreover, I would have proposed, as is done in other areas, to consider only the data collected by the programs of each country. It is only in the absence of data from different countries that subnational data published in other databases
should be considered. In addition, data on the success of TB treatment can be found on the World Bank website (https://data.worldbank.org/indicator/SH.TBS.CURE.ZS?view=chart) and WHO (http://www.who.int/tb/data/en/)

Response. Thank you for bringing this to our attention. We are concerned that it will be practically and logistically impossible to contact all the Ministries of Health in sub Saharan Africa (SSA) in an attempt to acquire data on treatment success rate, especially for adult bacteriologically confirmed TB patients. We have considered the inclusion of data provided on TSR from the World Bank and World Health Organization websites.

Please note that we have planned to use grey literature (published reports, conference proceedings, dissertations/thesis, and so forth) which will supplement data from published studies. In the manuscript, the use of grey literature has been well described.

Major comments
2) I suggest that the authors also look at other outcomes of TB treatment as defined by the WHO to have a more authoritative review.
Response. This suggestion is appreciated. In addition to cure and treatment completion, we will extract data on other TB treatment outcomes: number of TB patients who died, defaulted, got lost, and failed treatment.
3) The authors do not tell us why they chose to limit the search for studies in 2007. Perhaps there is a reason, this should be clearly stated.
Response. We appreciated this comment. Ideally, our aim was to review data that spanned one decade, hence we selected 2007 as the starting point for convenience. We believe a decade was sufficient time frame for a demonstrable trend of events. We have restated the review period as July 01, 2008 to June 30, 2018, exactly a decade (10 years).
4) In lines 112-113, the authors say that they will consider observational studies, but in lines 130-131, interventional studies appear. Authors should be consistent throughout the manuscript about what will be done. Please also look at Lines 194-195, when listing study design, authors not listed interventional studies.
Response. We thank the reviewers for this observation. In the revised manuscript, we have corrected this throughout the manuscript to state that both observational and interventional studies will be considered.
5) For comparative studies with two or more arms, authors should consider each arm as a single study. This needs to be clarified. In addition, they should specify that they will only consider the arm for which TB patients have the outcome of interest. For example, one may have a case-control study in which the cases are TB patients and the controls are not TB patients.
Response. We thank the reviewers for this comment and agree that we will only extract data from arms for which TB patients have the outcome of interest from RCT, case-control, and cohort studies as a single study. We have explained this process in the revised manuscript under data extraction section.
6) I wonder if it is really necessary to consider interventional studies. Interventional studies may overestimate treatment success rate because subjects are often best followed-up in trials. This is not going to represent real life and may not be useful for health policy makers.
Response: We agree the results might vary by study design. We believe it is a good idea to include interventional studies so that a comparison can be done between interventional versus observational studies. Any differences therein will present an opportunity for practitioners, healthcare managers, and policy makers in SSA to recognize needed strategies in real life.
Response. We thank the reviewers for pointing this out. In the revised manuscript, we have explicitly defined the age category for children as being below 15 years.

8) Search strategy. In addition to the consideration of the term sub-Saharan Africa and its variants, I propose to the authors to better capture all the studies of each country, to add in the search strategy with the term boolean “OR”, the name of each country of Sub-Saharan Africa and its variants (example: "... Nigeria OR Côte d’Ivoire OR Ivory Coast OR ....). Response. Thank you for this feedback. The search strategy for this study has been revised and improved over time. We aimed at developing and using a more sensitive search strategy that will identify all the eligible studies. Presently, we have developed a highly sensitive search strategy that is included in the revised manuscript. Regarding the selection of countries, we will do this manually. We realized that the inclusion of list of the SSA countries in the search strategy tends to reduce its sensitivity, and we are convinced it is better to screen the countries manually. Please note that we have included a new search strategy for PubMed/Medline in the supplementary material as well.

9) I do not understand why the authors use the NOS and Cochrane risk of bias tool to evaluate the methodological quality of the studies. What interests the authors in the studies is the prevalence / proportion data. The authors are not interested in whether an interventional study was conducted without bias, but that the prevalence data are of good quality in included studies even if these studies are interventional, cohort or case control studies. It is only this aspect that interests the authors and therefore it is only this aspect that should be assessed.
Response: It is true that we are interested in proportion data in each of the analytic study designs (case-control, cohort, and RCT). We propose to use the Newcastle-Ottawa Scale (NOS) for assessing the appropriateness of the study designs and conduct of studies. To have also noted that the NOS is widely used in systematic review and meta-analytic studies that are similar to ours. However, we welcome your suggestions for improvement.

10) I do not understand why the authors qualify “Metaprop” as “newly developed” tool. I propose to delete this part.
Response: We have addressed this issue. The word “newly developed” has been deleted in the revised manuscript version.

11) Line 270-271: “However, in instances of low heterogeneity, we will use Mantel Haenszel (M-H) fixed effects model to pool TSR”. The decision to use random effect model or fixed-effect model should not be based on the results of quantified heterogeneity I² or the Cochran Q test results. Authors already acknowledged that they will a-priori be heterogeneity due to study design, study participants. Therefore, only random effect model should be used for all analyses. I propose to delete this sentence.
Response: Thank you for this critical observation. We have deleted the Mantel Haenszel (M-H) fixed effects approach, and maintained the D+L approach in the revised manuscript.

12) I propose to also consider sex (female versus male), setting (urban versus rural), human development index (very high, high, medium, low) in subgroup analysis.
Response: We have revised the sub-group analysis plan. We have included analysis based on study setting (rural, urban, and both urban and rural), and human development index per 2018 World Bank classification (very high, high, medium, low). However, we did not include sub-group analysis based on sex as most studies do not summarize the outcome (TSR) based on sex categorization.

13) Lines 310-311. “We also plan to share the results with the Uganda Ministry of Health, Division of National TB and Leprosy”. I do not understand why the authors specify that they will share data with Uganda Ministry of Health. Authors are planning to conduct a systematic review for sub-Saharan Africa, not only for Uganda.
Response: The statement “We also plan to share the results with the Uganda Ministry of Health, Division of National TB and Leprosy” has been deleted. We acknowledge by publishing the results of this meta-analysis in a peer-reviewed journal and presenting the findings in conferences, these avenues will be appropriate for reaching the wider scientific community.

14) Abstract should be revised according to all above comments.
Response: The abstract has been revised taking into consideration all the needed changes in the review comments.

**VERSION 2 – REVIEW**

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<tr>
<th>REVIEWER</th>
<th>Ram Bajpai</th>
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<tr>
<td>REVIEW RETURNED</td>
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<td>GENERAL COMMENTS</td>
<td>I have just minor comments: -</td>
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<td></td>
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<tr>
<td>GENERAL COMMENTS</td>
<td>I am satisfied with the revised version of the manuscript.</td>
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**VERSION 2 – AUTHOR RESPONSE**

Reviewer: 1

Comment #1. In the abstract, please replace word ‘STATA’ with ‘Stata” as it is not acronym. Same to follow in the statistical analysis section.

Response. Thank you. We have replace the word “STATA” with “Stata”.

Comment #2. The Newcastle-Ottawa Scale is much simplified and brief. I’d suggest to use NIH tool for observational studies which is more comprehensive. The link is given below: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools

Response. Thanks. We have adopted the NIH tool for assessing quality of all included studies.

Reviewer: 2

Comment #1. I am satisfied with the revised version of the manuscript.

Response. Thank you for the high quality review.