

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Prevalence of latent TB infection and TB disease among adolescents in high TB burden countries in Africa: a systematic review protocol
AUTHORS	Bunyasi, Erick; Schmidt, Bey-Marrie; Abdullahi, Leila; Mulenga, Humphrey; Tameris, Michele; Luabeya, Angelique; Shenje, Justin; Scriba, Thomas; Geldenhuys, Hennie; Wood, Robin; Hatherill, Mark

VERSION 1 - REVIEW

REVIEWER	Angela Oyo-Ita University of Calabar, Nigeria
REVIEW RETURNED	11-Nov-2016

GENERAL COMMENTS	ABSTRACT: The authors list BCG vaccination as one of preventive measures. Its effectiveness in the reduction of transmission of the disease is uncertain. It may, therefore, not be technically appropriate to list it as such.
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REVIEWER	Lisa V. Adams Geisel School of Medicine at Dartmouth, USA
REVIEW RETURNED	01-Dec-2016

GENERAL COMMENTS	<p>This is a protocol for a proposed systematic review to describe the evidence on the prevalence of latent TB infection and TB disease in adolescents living in high TB-burden countries. Given the history of neglect of TB in children, this is an important and emerging topic that is definitely worthy of further study.</p> <p>Major Comments</p> <p>1. In the Introduction, the authors include global data from the 2015 World Health Organization's Global TB Report, which may have been the most recent report available at the time they were first drafting the protocol. Given that the 2016 report is now available, it would be advisable, and relatively easy, for the authors to update the background data, which would make this section more relevant, especially given that it may be many months before they conclude the systematic review and it is published.</p> <p>2. The authors state that they will assess studies of adolescent LTBI or TB prevalence that were conducted in one or more of the 22 high TB-burden countries. While there is some logic to this choice of target countries, it does exclude some smaller countries that have very high rates of TB, such as Swaziland and Lesotho. It would seem that data from these high incidence countries could be very</p>
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	<p>useful to the authors' overall objective. Such countries could be added to (rather than replace any of) the 22 high TB-burden countries. If the authors have clear justification/reasoning to limit their review to data from the 22 high TB-burden countries and exclude these others, they should provide this. The authors will have to decide if they want to update the list based on the new classification of high-burden countries in the 2016 report.</p> <p>3. The authors describe the apparent paradox in adolescent TB, namely that there is an apparent increase in latent TB infection in the adolescent age group but an observed decrease in TB disease cases (or at least TB case notifications). The authors need to clarify that they will be able to quantify the prevalence but not be able to explain the reasons for this paradoxical yet persistent observation across many countries and settings.</p> <p>4. The authors say they will include articles published between 1990 and 2016 because this timeframe is reflective of the mature HIV epidemic. However, antiretroviral treatment for HIV was not readily available in most of these same countries during the 1990s. While this may be less relevant when assessing an adolescent age group, nonetheless, the authors should mention what significance (if any) they anticipate including studies from the pre-ART era will have on their review and why they are extending their timeframe to 1990, rather than starting with articles published in 2000 and beyond.</p> <p>5. I think the search strategy and selection of studies are well described, as is the assessment of risk of bias.</p> <p>6. I was unclear as to how the authors will incorporate HIV status data (including unknowns) into their data analysis and descriptions of LTBI and TB disease prevalence.</p> <p>Minor Comments</p> <p>1. I suggest the authors define the term force of infection, as it is a less commonly used term.</p> <p>2. I think the Introduction contains a blast of data and either could be shortened or better tied to the overall purpose of the review.</p> <p>3. In the Primary Objectives section, the authors list that they are using the 22 high TB-burden countries as defined by the WHO 2014 Global TB Report, but I think they mean this list is from the 2015 report based on 2014 data.</p> <p>4. In the Definitions section, I suggest revising "with a LTBI positive or negative result" to "with a positive or negative result from a diagnostic test for LTBI".</p> <p>5. There is a typo in the Dealing with Missing Data section (should be "no response" not "none response").</p> <p>6. The authors may want to add "teen" to their search terms, which I believe would capture more than "teenage".</p> <p>7. Is the Language field necessary in the Data Extraction Form since only English language articles will be selected?</p>
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	<p>8. On the Diagnostic Modality for TB disease or latent TB infection form, what is meant by X-ray, if yes, state type – do the authors mean what views were obtained?</p> <p>9. It was unclear if only one author will complete the quality assessment forms or whether 2 authors will complete it and the mean score will be calculated.</p>
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VERSION 1 – AUTHOR RESPONSE

REVIEWER #1

1) Reviewer feedback: “ABSTRACT: The authors list BCG vaccination as one of preventive measures. Its effectiveness in the reduction of transmission of the disease is uncertain. It may, therefore, not be technically appropriate to list it as such.”

Author response: The following text in the abstract has now been deleted: “universal infant vaccination with Bacille-Calmette Guerin in all high TB burden countries; and ...”.

REVIEWER #2

MAJOR COMMENTS

2) Reviewer feedback: “In the Introduction, the authors include global data from the 2015 World Health Organization’s Global TB Report, which may have been the most recent report available at the time they were first drafting the protocol. Given that the 2016 report is now available, it would be advisable, and relatively easy, for the authors to update the background data, which would make this section more relevant, especially given that it may be many months before they conclude the systematic review and it is published.”

Author response: Changes have been incorporated as pointed out. The statement, “TB remains a key public health problem, especially in Africa, which reported almost a third of the 9.6 million incident TB cases in 2014: 5.4 million among men, 3.2 million among women and approximately 1.0 million among children...” has been changed to “...TB remains a key public health problem especially in Africa which reported almost a third of the 10.4 million incident Tuberculosis [TB] disease cases globally in 2015.” This is on page 6, lines 89-90.

Furthermore, all references to the 2015 report have been revised to reflect the changes as reported in the 2016 World Health Organization’s [WHO] Global TB Report.

3) Reviewer feedback: “The authors state that they will assess studies of adolescent LTBI or TB prevalence that were conducted in one or more of the 22 high TB-burden countries. While there is some logic to this choice of target countries, it does exclude some smaller countries that have very high rates of TB, such as Swaziland and Lesotho. It would seem that data from these high incidence countries could be very useful to the authors’ overall objective. Such countries could be added to (rather than replace any of) the 22 high TB-burden countries. If the authors have clear justification/reasoning to limit their review to data from the 22 high TB-burden countries and exclude these others, they should provide this. The authors will have to decide if they want to update the list based on the new classification of high-burden countries in the 2016 report.”

Author response: We made two key changes on consideration of this feedback. We adopted the new classification categories for high TB burden countries reported in the 2016 WHO Global TB Report because this classification approach will be used by the WHO to monitor milestones in the global TB targets for the period 2016-2020. However, we will limit our analysis to high TB burden countries found on the African continent. We believe this will be more relevant to our core objective and to policy in high TB burden countries on the African continent. Additionally, most of the other countries were from Eastern Europe and Asia [e.g. Tajikistan and Ukraine] and we anticipated significant language bias besides key differences in the socioeconomic position or GDP of most of these countries as compared to those in Africa.

Our new list of countries is now on page 10 lines 181-191 and reads as follows: “In 2016, unlike

before, the WHO defined 'high TB burden countries' along three broad categories that included; [1] countries with the highest burden of TB/HIV coinfection, [2] countries with the highest burden of multi-drug resistant TB and [3] countries with the highest burden of TB in general. This classification takes consideration of both the absolute number of cases of TB disease and the relative burden of TB disease after factoring the population size or denominator [i.e. estimated incidence rate]. In this study, we will restrict our review to the 25 countries from across these three WHO high TB disease burden categories that are found on the African continent.(2) These include: The Democratic Republic of Congo, Ethiopia, Kenya, Uganda, United Republic of Tanzania, Zimbabwe, South Africa, Mozambique, Angola, Sierra Leone, Central African Republic, Congo, Lesotho, Liberia, Namibia, Zambia, Botswana, Cameroon, Chad, Ghana, Guinea-Bissau, Malawi, Swaziland, Somalia and Nigeria."

4) Reviewer feedback: "The authors describe the apparent paradox in adolescent TB, namely that there is an apparent increase in latent TB infection in the adolescent age group but an observed decrease in TB disease cases (or at least TB case notifications). The authors need to clarify that they will be able to quantify the prevalence but not be able to explain the reasons for this paradoxical yet persistent observation across many countries and settings."

Author response: the following sentence has been added on pages 7-8 lines 135-138 "Our study will quantify prevalence of LTBI and TB disease among adolescents in high TB burden countries in Africa and highlight this pattern across these countries. However, we appreciate that our study design, or rather a systematic review, may not provide definitive reasons for this paradoxical yet persistent observation across many countries and settings."

5) Reviewer feedback: "The authors say they will include articles published between 1990 and 2016 because this timeframe is reflective of the mature HIV epidemic. However, antiretroviral treatment for HIV was not readily available in most of these same countries during the 1990s. While this may be less relevant when assessing an adolescent age group, nonetheless, the authors should mention what significance (if any) they anticipate including studies from the pre-ART era will have on their review and why they are extending their timeframe to 1990, rather than starting with articles published in 2000 and beyond."

Author response: We have opted to stratify our analysis along three strata, contingent on data availability: we will perform an analysis along the strata of the periods 1990-1999, 2000-2016 and 1990-2016. This will enable us to obtain deeper insight on differences in burden across these key periods, compare the burden pre- and post-ART wide availability era and, in addition, review data for the entire period. We agree that the impact of HIV on adolescent TB may not be as substantial as that among adults [on comparison of pre- and post- era of wide availability of ART] who bore the brunt of the HIV epidemic. This was the basis for us having one unified analysis for the entire period of 1990-2016. Nonetheless, prevalence of HIV is generally very low among adolescents as compared to young adults or adults in general. However, we believe that stratification of our analysis along the defined strata will provide deeper insight and useful information to our core objectives and also account for impact, if any, attributable to wide ART availability and use.

The above changes have been incorporated on Page 18 line 372-375.

6) Reviewer feedback: "I think the search strategy and selection of studies are well described, as is the assessment of risk of bias."

Author response: Feedback appreciated.

7) Reviewer feedback: "I was unclear as to how the authors will incorporate HIV status data (including unknowns) into their data analysis and descriptions of LTBI and TB disease prevalence."

Author response: We appreciate that HIV prevalence among adolescents is very low and that this is generally not done for most prevalence studies, as informed by a preliminary review of articles meeting our inclusion criteria. Therefore, stratification along HIV test result has been excluded from our analytical plan.

MINOR COMMENTS

8) Reviewer feedback: "I suggest the authors define the term force of infection, as it is a less commonly used term."

Author response: the following definition has been revised and incorporated on Page 5 lines 93 to 95: "The force of TB infection, defined as the proportion of susceptible individuals [i.e. individuals without LTBI] who become latently infected with *Mycobacterium tuberculosis* per annum, is a key measure of TB transmission in a defined population."

9) Reviewer feedback: "I think the Introduction contains a blast of data and either could be shortened or better tied to the overall purpose of the review."

Author response: The introduction section of the manuscript has been revised and shortened for clarity and focus to our core objectives.

10) Reviewer feedback: "In the Primary Objectives section, the authors list that they are using the 22 high TB-burden countries as defined by the WHO 2014 Global TB Report, but I think they mean this list is from the 2015 report based on 2014 data."

Author response: We corrected this and factored feedback from item number [2]. This primary objective, now on page 7-8 lines 153-156 reads as follows: "To determine prevalence of latent TB infection in adolescents in the 25 high TB burden countries in Africa as defined by the WHO in the 2016 Global TB report."; and "To determine prevalence of TB disease among adolescents in the 25 high TB burden countries in Africa, as defined by the WHO in the 2016 Global TB report."

11) Reviewer feedback: "In the Definitions section, I suggest revising "with a LTBI positive or negative result" to "with a positive or negative result from a diagnostic test for LTBI".

Author response: we revised this sentence as advised. This is on page 8 line 164; i.e. "... with a positive or negative result from a diagnostic test for LTBI."

12) Reviewer feedback: "There is a typo in the Dealing with Missing Data section (should be "no response" not "none response")."

Author response: Corrected as pointed out. This is on page 13 line 283.

13) Reviewer feedback: "The authors may want to add "teen" to their search terms, which I believe would capture more than "teenage"."

Author response: Corrected as pointed out [i.e. "... OR "teen*" ...". This is in our "Search strategy" supplementary file.

14) Reviewer feedback: "Is the Language field necessary in the Data Extraction Form since only English language articles will be selected?"

Author response: The "language" option on our data extraction form has been deleted.

15) Reviewer feedback: "On the Diagnostic Modality for TB disease or latent TB infection form, what is meant by X-ray, if yes, state type – do the authors mean what views were obtained?"

Author response: We have modified the sentence in question in our data extraction form to only state the number of individuals with pulmonary TB diagnosed via "X-ray" film, regardless of view of the film.

16) Reviewer feedback: "It was unclear if only one author will complete the quality assessment forms or whether 2 authors will complete it and the mean score will be calculated."

Author response: This section on scoring for quality has been modified to read as follows on page 14 line 294-295: "Two authors [EB and BS] will independently score the risk of bias using this tool and the mean score calculated."

VERSION 2 – REVIEW

REVIEWER	Lisa V. Adams Dartmouth's Geisel School of Medicine, USA
REVIEW RETURNED	29-Jan-2017

GENERAL COMMENTS	<p>The authors have effectively addressed my comments. The Introduction, including the justification for the review, is more focused and the Methods are clearly described. I have only a few minor, grammatical edits to suggest.</p> <ol style="list-style-type: none"> 1. Under Strengths and Limitations on page 4 – the authors say “...our study will provide key insight on this relationship” – assuming there may be several insights provided, I suggest making insight plural and I think their original use of “into” rather than “on” is preferred though I think either is grammatically acceptable. Would defer to the journal’s copyeditor on this. 2. I wasn’t sure why “South Africa” was in brackets on page 7, line 132. Shouldn’t it be “Although adolescents in Cape Town, South Africa appear to ...”. 3. When listing the 25 countries you use for your review on page 11, I suggest alphabetizing the list for easier reading. 4. I would suggest changing the subheading “Dealing with missing data” to “Approach to missing data”. I think the last portion of the last sentence can be simplified to read “if no communication or response is established” instead of “would have been established”. Again defer to journal’s copyeditor. 5. There is a typo under Assessment of reporting biases, line 395, space is missing between “least” and “10”. 6. Under Subgroup analysis, line 424 where the strata are listed and include the years 1990-1999, 2000-2016 and 1990-2016, the authors should specify if these are years of publication of the studies or years of data collection. 7. Under the Author contributorship statement, the authors revert to using initials in the last sentence whereas full names (even ones repeated) are used in the preceding sentences. This should be adjusted for consistency.
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VERSION 2 – AUTHOR RESPONSE

REVIEWER #1

None

REVIEWER #2

Reviewer Name: Lisa V. Adams

Institution and Country: Dartmouth's Geisel School of Medicine, USA

Competing Interests: None declared

The authors have effectively addressed my comments. The Introduction, including the justification for the review, is more focused and the Methods are clearly described. I have only a few minor, grammatical edits to suggest.

MINOR COMMENTS

1) Reviewer feedback: "Under Strengths and Limitations on page 4 – the authors say "...our study will provide key insight on this relationship" – assuming there may be several insights provided, I suggest making insight plural and I think their original use of "into" rather than "on" is preferred though I think either is grammatically acceptable. Would defer to the journal's copyeditor on this.

Author response: On page 4 line 73, "insight" has been changed to "insights", "on" has been changed to "into".

2) Reviewer feedback: "I wasn't sure why "South Africa" was in brackets on page 7, line 132. Shouldn't it be "Although adolescents in Cape Town, South Africa appear to ..."

Author response: The recommended edit has been incorporated and is now on page 5 line 104.

3) Reviewer feedback: "When listing the 25 countries you use for your review on page 11, I suggest alphabetizing the list for easier reading."

Author response: The 25 countries have now been alphabetized and are on page 9 lines 183-188.

4) Reviewer feedback: "I would suggest changing the subheading "Dealing with missing data" to "Approach to missing data". I think the last portion of the last sentence can be simplified to read "if no communication or response is established" instead of "would have been established". Again defer to journal's copyeditor".

Author response: The two changes have been made as advised on page 13 lines 281 and 286, respectively.

5) Reviewer feedback: "There is a typo under Assessment of reporting biases, line 395, space is missing between "least" and "10"".

Author response: The typo has been revised as pointed out and is now on page 17 line 344.

6) Reviewer feedback: "Under Subgroup analysis, line 424 where the strata are listed and include the years 1990-1999, 2000-2016 and 1990-2016, the authors should specify if these are years of publication of the studies or years of data collection".

Author response: The strata has been revised to reflect the years are for years of data collection. This change is found on page 18 line 371.

7) Reviewer feedback: "Under the Author contributorship statement, the authors revert to using initials in the last sentence whereas full names (even ones repeated) are used in the preceding sentences. This should be adjusted for consistency.

Author response: The change has been revised as recommended on page 20 and 21 lines 416 and 420, respectively.

Prevalence of latent TB infection and TB disease among adolescents in high TB burden countries in Africa: a systematic review protocol

Erick Wekesa Bunyasi, Bey-Marrie Schmidt, Leila Hussein Abdullahi, Humphrey Mulenga, Michele Tameris, Angelique Luabeya, Justin Shenje, Thomas Scriba, Hennie Geldenhuys, Robin Wood and Mark Hatherill

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