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

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ABSTRACT

Introduction

Almost a third of the world population has latent TB infection [LTBI], approximately 10 million of whom develop TB disease annually, despite universal infant vaccination with *Bacille-Calmette* Guerin in all high TB burden countries; and existence of effective, but lengthy, preventive and curative drug regimens. Although adolescents appear to have a very high force of LTBI, their reported incidence of TB disease is less than that of their corresponding general population. The few available studies on adolescent TB infection and disease prevalence are not sufficient to address the apparent discordance between rates of infection and disease in high TB burden countries. Therefore, we aim to perform a systematic review to examine the relationship between adolescent LTBI and TB disease, benchmarked against national TB disease burden data.

Methods and analysis

A comprehensive literature search will be performed for cross-sectional studies and screening data in cohort studies to determine prevalence of LTBI and TB disease among adolescents in high TB burden countries in the following databases; *Pubmed*, *Scopus*, *Cochrane* library, *Web of Science, Africa Wide, CINAHL and Africa Index Medicus*. This will be supplemented by a search of reference lists of selected articles for potentially relevant articles. We will restrict our search to articles published in English language between 1990 and 2016 among adolescents in order to obtain estimates reflective of the mature HIV epidemic in most high TB burden countries that occurred over this critical period. Primary end-points are; prevalence of LTBI and TB disease. We will use the random-effects or fixed effects modelling for our meta-analysis based on heterogeneity estimates.

Ethics and dissemination

No ethics approval is required given this is a systematic review. Findings will be disseminated in a peer-reviewed journal in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* [PRISMA].

Registration details

This protocol is registered with the *International Prospective Register of Ongoing Systematic Reviews* [PROSPERO], registration number CRD42015023495.

Key words

Prevalence; latent TB infection; TB disease; adolescents; protocol; systematic review.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review to conduct and compare adolescent LTBI and TB disease prevalence in high TB burden countries.
- By examining the relationship between adolescent LTBI and TB disease benchmarked against national TB disease burden data, our study will provide key insight into this relationship.
- Data reporting adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] guidelines for reviews [PRISMA] and protocols [PRISMA-P].
- Our choice of period for review is driven by the need to provide findings reflective of the mature HIV epidemic in high TB burden countries that occurred over this critical period, thus we appreciate that our estimates will not provide old or historical trends in TB burden.
- Our restriction of analysis to articles published in English language may introduce publication and language bias, respectively.

INTRODUCTION

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.[1] In the same year, TB caused 1.5 million deaths worldwide and was the leading cause of death by an infectious agent [including an estimated 1.1 million HIV-negative people; 0.4 million HIV-positive people; 890,000 men, 480,000 women and 140,000 children]. However, a relatively small proportion [5–15%] of the estimated 2–3 billion people worldwide who are infected with *Mycobacterium tuberculosis* will develop TB disease during their lifetime. The probability of developing TB is much higher among people infected with HIV, especially those recently infected who have not received antiretroviral therapy.[1] The incidence rate of TB disease in Africa [281 cases for every 100,000 people] is more than double the global average of 133 cases per 100,000 in the global population.[1] 80% of the global TB burden is borne by the 22 countries referred to as 'high TB burden countries' by the World Health Organisation [WHO].[1] The WHO "End TB Strategy" [2016-2035], is a key global target linked to the Sustainable Development Goals, which aim to reduce the number of TB deaths by 95% and to cut incident TB cases by 90% by 2035 compared with 2015 levels. This is part of a goal to end the global TB epidemic, defined as achieving a TB incidence of fewer than 10 cases per 100,000 people by 2035.[1]

Force of infection, the proportion of susceptible individuals who become infected, is a proxy measure of TB transmission. A cross-sectional tuberculin skin test [TST] prevalence study in a South African township near Cape Town showed a high annual force of infection that increased throughout childhood from 3.9% at 5 years and peaked at 7.9% at 15 years of age.[2] However, the true force of infection may be obscured by test reversion in cross-

sectional prevalence studies. A longitudinal interferon-gamma release assay study, also near Cape Town, showed a much higher annual force of TB infection among adolescents [14.0%] when all test conversions and reversions were considered.[3]

Unfortunately, very few longitudinal cohort studies of child or adolescent latent TB infection [LTBI] exist. There is paucity of data on prevalence of LTBI among adolescents in high TB burden countries, with most studies coming from South Africa. A nationally representative Kenyan survey of children aged 6-14 years showed a prevalence of LTBI of 10.2% [95% CI: 9.0-11.3], a figure that has not significantly changed over 2 decades, between 1986 and 2006.[4] A cross-sectional South African study showed an increase in prevalence of LTBI from 26% at 5-8 years to 53% at 14-17 years to 75% at 25 years.[5-9] Prevalence rate of LTBI for men and women in a South African city [Cape Town] reached a maximum of 92% at the age of 32 years and 84% at the age of 27 years among men and women, respectively.[2,8]

Although adolescents in Cape Town [South Africa] appear to have a very high force of TB infection,[3] their reported incidence of TB disease is less than that of their corresponding general population.[9,10] A South African study [in Cape Town] showed a very high incidence rate of TB disease in children aged below 5 years which decreased rapidly in childhood to a nadir between 10-14 years of age and was followed by a rapid increase till the second peak that occurs just after adolescence, at 20-24 years, among HIV negative individuals.[9] The decline in cases of TB disease after the age of 5 years occurs despite a high force of LTBI that increases throughout childhood. These two highest peaks of incidence of TB disease [0-5 years and 20-24 years] in the life-course of HIV-negative individuals are followed by a third peak of high TB incidence between the ages of 45-49

years.[9,10] In Cape Town, overall TB notification rates for both HIV negative and HIV positive individuals exceeded 1,400 per 100,000 population among young adults in 2009.[9]

A new TB infection in an infant or young child is a sentinel signal of active transmission from a person, usually an adult, with active pulmonary TB disease. Thus, we would expect high rates of childhood LTBI to be associated with high prevalence of adult TB disease in the same community. However, there is little research describing settings from which adolescents acquire TB infection,[11] which makes it difficult to explain the apparent discordance between very high rates of adolescent TB infection and low rates of adolescent TB disease in the same communities. In a South African township, prevalent TB infection among children aged 5 to 14 years was directly and significantly associated with residential exposure to an adult case of TB disease within their residential plot. However, a non-significant association was observed for individuals aged 15-22 years despite their high force of TB infection.[11] This finding suggests increasing significance of settings other than residence as a determinant of TB infection and subsequent disease from mid-adolescence onwards.[12,13] Glynn et al recently [2015] demonstrated via whole genome sequencing that, overall, known smear positive prior contacts accounted for less than 10% of tuberculosis cases in a Malawian community, and that even for those with a prior contact with smear positive tuberculosis in their family, there was a higher than 50% chance that they acquired their tuberculosis elsewhere, similar to our own previous finding.[11,14,15] Andrews et al used statistical modeling techniques to estimate that up to a half of TB transmission among individuals aged 15-19 years occurs in the school setting, with this figure being 25% in individuals aged 0-14 years.[8] If this hypothesis were true, we would expect to observe high prevalence of TB disease in parallel with high force of TB infection among high school-aged adolescents in the same high burden communities. The fact that this apparently reasonable observation does not appear to hold true deserves further investigation.

This study aims to quantify prevalence of LTBI and TB disease among adolescents [aged 10-19 years] in the 22 high TB burden countries that together bear 80% of the global TB burden.[1] Due to lack of a systematic review on prevalence of LTBI and TB disease among adolescents, this systematic review will provide useful data for policy by consolidating and synthesising available data regarding a key sub-population with the highest force of TB infection[3] and a relatively low reported prevalence of TB disease. These data will not only contribute to our understanding of TB transmission in adolescence, the findings will be key to inform policies, such as the school health policy, in high TB burden countries. The data will also be useful for monitoring future TB transmission trends in the wake of the global efforts to end the TB epidemic. Our findings will also be useful for novel TB vaccine research efforts. In 2015, 15 investigative vaccine candidates were in clinical trials, with increasing focus on conduct of novel TB vaccine trials among adolescents.

METHODS AND ANALYSIS

This protocol was developed in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P],[16,17] see Supplementary File 1 for a PRISMA-P checklist of the recommended bare minimum items to be included.

Objectives

Primary objectives

- To determine prevalence of latent TB infection in adolescents in the 22 high TB burden countries as defined by the WHO in the 2014 Global TB report.
- To determine prevalence of TB disease among adolescents in the 22 high TB burden countries, as defined by the WHO in the 2014 Global TB report.

Secondary objective

- To explore the relationship between age-specific risk of LTBI and age-specific prevalence of TB disease, benchmarked against published estimates of national TB disease incidence and notification rates.

Definitions

Prevalence of LTBI is defined as the number of individuals with LTBI divided by total number of individuals in a cross-sectional, population-based study or screening database in cohort studies with a LTBI positive or negative result. We will consider LTBI diagnosed by the Tuberculin Skin Test [TST] and/or the Interferon Gamma Release Assay.

Prevalence of TB disease is defined as the number of individuals with TB disease divided by total number of individuals in a cross-sectional, population-based study, or screening database in cohort studies. We will consider the following diagnostic modalities for TB disease: solid and liquid mycobacterial culture, Xpert MTB/RIF assay, sputum smear for acid fast bacilli and clinical diagnosis. Studies restricted to one or more forms of non-pulmonary TB disease only e.g. Koch's disease, TB lymphadenitis or disseminated TB, will not be included. Studies reporting on respiratory diseases in general and not clearly defining the prevalence of LTBI or TB disease will not be eligible.

Adolescents will be defined as individuals aged between 10 to 19 years, as defined by the World Health Organisation [WHO].[18]

WHO defines 'high TB burden countries' as a group of 22 countries that together account for 80% of the global TB burden.[1] These include: Africa-The Democratic Republic of Congo, Ethiopia, Kenya, Uganda, United Republic of Tanzania, Zimbabwe, South Africa, Mozambique and Nigeria; Americas- Brazil; Eastern Mediterranean- Afghanistan and Pakistan; Europe- Russia; South East Asia- Bangladesh, India, Indonesia, Myanmar and Thailand; Western Pacific- Cambodia, China, Philippines, and Vietnam.

Criteria for consideration of studies for this review [Eligibility criteria]

(i) Study designs

We will consider cross-sectional or prevalence study designs and screening data in cohort studies that report primary data on prevalence of LTBI or TB disease. Statistical or mathematical modelling articles, cost-effectiveness studies, opinion pieces, narrative reviews, case studies, case series and letters to editors will not be considered. Grey/unpublished literature will also be excluded.

(ii) Participants

Adolescent participants should be representative of the general adolescent population in the setting in which the study was conducted. Studies conducted among the general school-going population will also be considered provided that age is reported. For studies that report on age ranges that extend beyond the 10-to-19-year age bracket, data on individuals aged 10 to 19 years will be extracted, if possible. Otherwise, these data will be sought from corresponding authors. If extraction is not possible and these data are not obtainable from corresponding authors, at least 75% of participants should fall between the ages of 10 to 19 years. Studies reporting prevalence of TB infection or TB disease in sub-populations that are not representative of the general adolescent or school-going population in a specific study setting will be excluded e.g. studies reporting prevalence of TB restricted to HIV positive adolescents only.

(iii) Outcome measures

Outcome measures of interest will include: prevalence of LTBI and TB disease. Studies which do not measure any of our primary outcomes; do not clearly state the case definition of

LTBI or TB disease; do not report primary data; or lack explicit description of methodology, will be excluded.

(iv) Time frame

We will consider studies reported between 1st January 1990 and 1st July 2016 because this period will also reflect the TB burden in mature or generalised Human Immunodeficiency Virus [HIV] epidemics across the high TB burden countries.

(v) Study setting

Studies should have been performed in at least one of the 22 high TB burden countries as defined above.[19] Studies not conducted in one of these countries or, for multi-country studies, if data pertaining to the listed high TB burden countries is not obtainable, they will be excluded.

(vi) Language

We will only consider articles published in English language because of limited time and financial resources available to this study.

Search strategy

We will systematically search for articles published between 1990 and 2016 using a combination of database specific medical subject headings [MeSH terms] and a range of free text or key words that will include the following, among others: adolescents, persons, latent, tuberculosis, LTBI, epidemiology, prevalence, morbidity and burden. Our draft *PubMed* search-term is provided in Supplementary File 2. The specific search strategies will be

finalised with guidance from a health sciences librarian with expertise in systematic review searching with input from the project team. After the *PubMed* strategy is finalized, it will be adapted to the syntax and subject headings of the other targeted databases. We will review reference lists of selected articles to identify potentially relevant articles to our research questions that would have been missed by our search term in specified bibliographic databases. Our search will be limited to the following electronic databases due to limited time and financial resources; *PubMed, Scopus, Web of Science, Cochrane library, Africa Wide, Africa Index Medicus* and *CINAHL.* This review will not include grey/unpublished reports due to the low likelihood of peer-review and potential practical difficulties of obtaining supplementary or missing data. We appreciate that this may lead to publication bias and acknowledge this as a limitation of our planned review.

Selection of studies

The first author [EB] will perform a systematic search for articles by employing the search strategy. For duplicate articles or publications reporting the same data in multiple articles, only the more recent and/or complete version of the publication will be considered. EB will review references of selected articles to identify articles relevant to our review which would have been missed by the search strategy. EB and BS will independently classify articles as either; [i] 'included', [ii] 'excluded' or [iii] 'pending'. A 'pending' status shall imply the reviewer is unsure on whether to include or exclude an article. This classification will be done by applying the inclusion and exclusion criteria, and will initially be based on the title and abstract, and then a quick scan, assessment or reading of the full text of the articles. Articles that both reviewers classify as 'excluded' will be excluded from further consideration whereas those that both reviewers classify as 'included' will be included in the review. We will obtain full reports for all 'included' titles and those with contradictories in

classification between the two reviewers. We will seek additional information from study authors where necessary to resolve questions about eligibility. A discussion will be held between EB and BS to resolve differences or contradictories in classification of articles by reviewing full text. A third reviewer [LA] will be consulted to resolve persistent disagreements following discussion. We will present a flow chart, in keeping with PRISMA guidelines as much as practicable, to summarise the search process and selection of studies for the review and document reasons for exclusion of studies [see Supplementary File 3]. We will include a table of all selected studies in the final review and document reasons for exclusion of articles.

Data management

Data management will be done by the first author [EB] in liaison with the second author [BS]. A google drive electronic folder will be maintained for the review and will contain; the protocol, a record of obtained articles and documentation of steps in data synthesis and analysis [including records included and excluded], risk of bias and quality scoring, among others. A back-up of the electronic records will be stored on a laptop and on a memory flash drive. '*Refworks'* bibliographic management software[20] will be used to manage references.

Data extraction

EB will read, extract and collate data from selected articles on to a standardised Data Extraction Form [see Supplementary File 4]. This form will be piloted on at least 4 randomly selected studies meeting the criteria for consideration. BS will verify abstracted data in order to reduce bias and reduce errors in data extraction. Data to be abstracted will include: study characteristics- title, year of publication, authors, study design; study setting and population- country, socio-demographics [age and gender]; study conduct- number of study participants [total in the study and those participants with TB, by diagnostic approach and number with

LTBI], number of adolescents that are HIV positive. Reviewers will resolve disagreements by discussion, with arbitration by LA for unresolved disagreements. We will contact study authors for data that may resolve any uncertainties.

Dealing with missing data

In the event of missing data that are key, we will attempt to contact the corresponding authors of the studies to obtain the relevant missing data via email. A second email will be sent after one week of the first email in the event of none response to the first email. A two-week wait period from the date of submission of the second email will be allowed for responses, failing which these studies will be excluded, if no communication or response would have been established.

Assessment of risk of bias of included studies

Risk of bias and assessment of quality will be evaluated using an assessment tool adapted from Hoy et al[21] by Werfalli et al who included a scoring system for evaluation of prevalence studies.[22] The tool helps evaluate internal and external validity [see table 1]. This tool was preferred over others because it was designed via an expert consensus exercise then tested, retested, validated and thus optimised for evaluation of quality of prevalence studies via a rigorous published process that included a review of limitations of existing tools.[21,23] The tool was shown to have a high inter-rater agreement.[21] Two authors [EB and BS] will independently score the risk of bias using this tool. Agreement between the two raters will be assessed for each item in the tool and overall using proportion of agreement [P_0] and the Kappa [κ] statistic. For the Kappa statistic, its values range from -1 to +1. Values of 0 or less will be regarded as poor agreement, 0.01 to 0.20 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 0.99 almost perfect agreement.[24] Raw agreement and Kappa values [including their 95% confidence intervals] will be calculated

using *STATA* version 14.0 for windows.[25] Neither of the review authors will be blinded to the journal titles or to the study authors or institutions.

Table 1: Risk of bias and quality assessment criteria for prevalence studies

Item under review	**Quality score [Points]**
External Validity	
Was the study's target population a close representation of the national population in relation to relevant variables?	1
Was the sampling frame a true or close representation of the target population?	1
Was some form of random selection used to select the sample, OR was a census undertaken?	1
Was the likelihood of non-response bias minimal?	1
Total	**4 points**
Internal validity	
Were data collected directly from the participants [as opposed to a proxy]?	1
Was an acceptable case definition used in the study?	1
Was the study instrument that measured the parameter of interest shown	1

to have validity and reliability?	
Was the same mode of data collection used for all subjects?	1
Was the length of the shortest prevalence period for the parameter of interest appropriate?	1
Were the numerator[s] and denominator[s] for the parameter of interest appropriate?	1
Total	**6 points**
Summary item on the overall risk of study bias [low, moderate or high]	

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10 items. This approach is consistent with the Cochrane and GRADE [GRADE=Grading of Recommendation, Assessment, Development and Evaluation] working group[26] recommendation or approaches. Furthermore, as summarized in the PRISMA [PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses] elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful,[27] hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low [1] or high risk of bias [0]. If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item.[21,28,29]

Data analysis

We hypothesise that there will be substantial statistical heterogeneity in study results because prevalence of LTBI and TB disease varies by distribution of socioeconomic determinants of health and HIV prevalence within and across settings, among other factors. *A priori*, random effects meta-analysis will be preferred due to the anticipated heterogeneity. However, choice of random-effects or fixed effects modelling will be based on observed statistical heterogeneity. For the latter, we will not pool the results but summarise findings in a narrative format. Additionally, we will derive Annual Risk of LTBI using the formulae: 1-[1-Prevalence] $^{1/[\text{mean age}]}$ for every year of adolescence. We will then describe the relationship between the annual risk of TB infection and observed TB prevalence from our review. Alternatively, for countries with insufficient data, we will describe the relationship between the Annual Risk of TB Infection and reported TB notification [or incidence rates estimates] by National TB Programs or estimates from the WHO.

In random effects modelling, effect measures are assumed to vary between studies and the summary effect is the weighted average of the effects reported in different studies.[30] This model directly adjusts for inverse of the standard error, and thus indirectly for the sample size reported in studies. Thus, studies with smaller standard error and larger sample sizes will be given more weight in the calculation of the pooled prevalence and 95% confidence intervals.

Data synthesis

Our outcome will be combined and calculated using the Cochrane Review Manager [*RevMan*] statistical software,[31] according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions.*[28] If statistical heterogeneity is observed, the random effects model will be chosen over the fixed effects model. If there is substantial statistical heterogeneity, we will not perform a meta-analysis; a narrative, qualitative summary will be done supported by a table [Supplementary File 5] and figures,

where appropriate. This will be done by the first reviewer and checked by the second reviewer for accuracy.

Assessment of reporting biases

The potential for publication or reporting bias will be explored by funnel plots if we obtain at least10 articles. This will be done by visually assessing asymmetry of funnel plots. As suggested by Egger et al, asymmetry of funnel plots will indicate presence of publication bias.[32] We appreciate that our choice of considering articles reported in English only [language bias] and the fact that we are only searching in a sample of bibliographic databases may be a source of reporting bias.

Assessment and management of heterogeneity

We anticipate clinical and statistical heterogeneity in prevalence rate estimates within and across settings and countries. Statistical heterogeneity will be quantified using the I^2 test statistic to determine the extent of variation in effect estimates that is due to heterogeneity rather than chance. Statistical heterogeneity will be explored graphically by inspection of forest plots [i.e. the 'eyeball test']. Non-overlap of 95% confidence intervals will suggest remarkable heterogeneity. A formal test for statistical homogeneity, the Cochran's χ^2 Q test statistic, will be performed using an alpha cut-off level of 10% as suggested by Higgin's et al[33] and Cochrane[34], due to the test statistic's low power in detecting heterogeneity, particularly when the number of studies is low. The I^2 test statistic will be used to quantify statistical heterogeneity between studies i.e. provide percentage of observed total variation across studies that is due to real heterogeneity rather than chance. This will provide a quantitative measure of heterogeneity. Cochrane provides the following rough guide to interpretation of heterogeneity: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75%

to 100%: considerable heterogeneity.[35] If substantial heterogeneity is observed, we will try to explain the source of heterogeneity by subgroup analysis and/or sensitivity analysis.

Subgroup analysis

Subgroup analysis will be done in order to obtain estimates that are reflective, and thus potentially more useful and applicable, for specific sub-population groups or settings, and will be conducted along the following strata, subject to availability of sufficient data; [1] geographic region using WHO classification of high TB burden countries i.e. Africa, South East Asia, Western Pacific and Eastern Mediterranean; [2] schooling status- adolescents in school vs those not in school; [3] country of study participants; [4] age [5] gender and [6] diagnostic modality of LTBI and TB disease.

Sensitivity analyses

Sensitivity analyses will be conducted to explore the source of heterogeneity i.e. determine impact of specific studies on pooled prevalence estimate, by exclusion of studies with low quality scores and thus higher risk of bias. We will also explore exclusion of studies with deficiency in specific items on the 10-point modified Hoy et al quality assessment tool, in order to evaluate impact of this exclusion on pooled prevalence estimates.

Ethics

Given that we will utilise published anonymised data, which is publicly available and peer-reviewed, ethical approval is not required for this study.

Dissemination [Reporting of this review]

Our review will be reported, as much as possible, in keeping with the Preferred Reporting Items for Systematic reviews and Meta-Analyses [*PRISMA*] Statement,[36] and will include

the PRISMA check-list [or adapted as practicable]. Our findings will be published in a peer-reviewed journal and as part of a doctoral thesis at the University of Cape Town.

Synthesis of evidence

The *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P][16,17] recommends gauging of overall judgement of quality of evidence from obtained articles and indicates increasing support and use of *the Grading of Recommendations Assessment, Development and Evaluation* [GRADE] working group[26] methodology. We will consider methodological quality of included studies and strength of evidence and adapt the basic principles of the GRADE approach.

Competing interest statement

None. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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those of the authors and are not necessarily attributed to the NRF. EWB initiated the research. This research is not done on behalf of or commissioned by the NRF. The first author [EB] would also like to appreciate supplementary departmental scholarship and support towards his PhD studies from the University of Cape Town [SATVI programme@UCT], of which this publication is a part of. No specific sponsor is associated with our review.

Author contributorship statement

Erick Wekesa Bunyasi and Leila H. Abdullahi conceptualised and designed the study. Erick Wekesa Bunyasi, Bey-Marrie Schmidt, Leila H. Abdullahi, Humphrey Mulenga, Michele Tameris, Angelique Luabeya, Justin Shenje, Thomas J. Scriba, Hennie Geldenhuys, Robin Wood and Mark Hatherill were involved in development of the study protocol. Erick Wekesa Bunyasi prepared the first draft of the manuscript with supervision from Hennie Geldenhuys, Robin Wood and Mark Hatherill. Erick Wekesa Bunyasi, Bey-Marrie Schmidt, Leila H. Abdullahi, Humphrey Mulenga, Michele Tameris, Angelique Luabeya, Justin Shenje, Thomas J. Scriba, Hennie Geldenhuys, Robin Wood and Mark Hatherill critically reviewed, revised and approved the subsequent and final version of the protocol. EWB is the guarantor. EWB and BS will perform the study search, screening and extraction of data under the guidance of Hennie Geldenhuys, Robin Wood and Mark Hatherill.

Provenance and peer review: Not commissioned; externally peer reviewed.

Amendment procedure

In the event that amendment to this protocol is required, we will describe the change and give the rationale in the methods section of the published review. EB will ultimately be responsible for approving, documenting, and implementing any amendments.

Data sharing

The authors declare that this research protocol is an original work. Results from the study completed using this protocol will be published in a peer-reviewed journal.

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Domain	Line item & PRISM-P code	Page
Section 1: Administrative information		
1. Title:		

PRISM-P checklist of items to be reported in a systematic review

	Identification [1a]	1
	Update [1b]	NA
2. Registration	Registration [2]	4
3. Authors:		
	Contact [3a]	1
	Contributions [3b]	21
4. Amendments	Amendments [4]	21
5. Support:		
	Sources [5a]	20-21
	Sponsor [5b]	21
	Role of sponsor or funder [5c]	21
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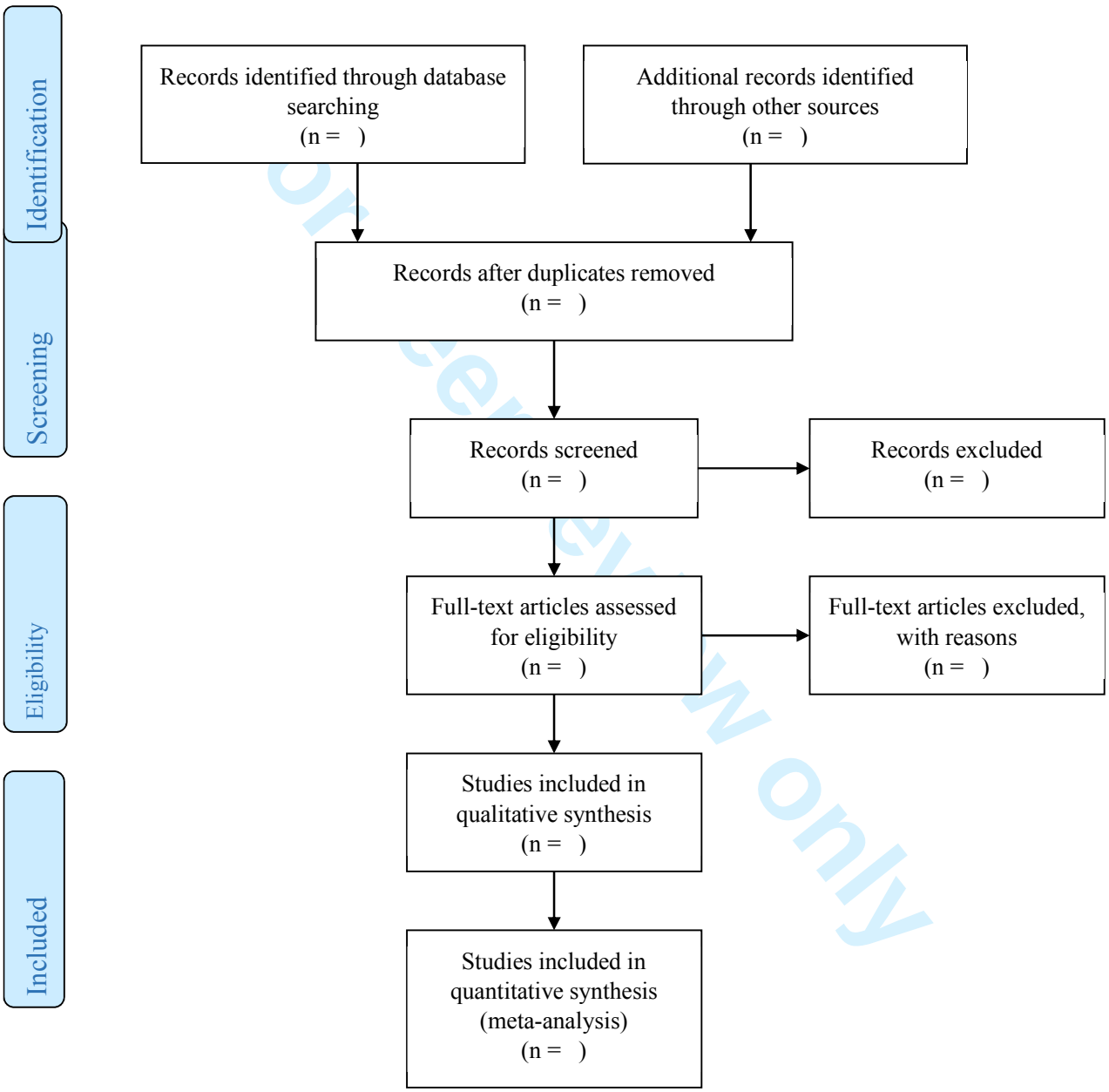
6. Rationale	Rationale [6]	8
7. Objectives	Objectives [7]	8, 9
Section 3: Methods		
8. Eligibility	Eligibility criteria [8]	10, 11
9. Information	Information sources [9]	12
10. Search	Search strategy [10]	11
11. Study records:		
	Data management [11a]	13
	Selection process [11b]	12
	Data collection process [11c]	12, 13
12. Data	Data items [12]	13
13. Outcomes	Outcomes and prioritization [13]	10
14. Bias	Risk of bias in individual studies [14]	14-16
15. Data synthesis		
	Quantitative synthesis criteria [15a]	17-18
	Appropriateness of data for synthesis [15b]	17-18
	Sensitivity and subgroup analyses [15c]	19
	Qualitative synthesis? [15d]	17-18
16. Meta-bias(es)	Meta-bias(es) [16]	14
17. Confidence in cumulative evidence	Assessment of strength of cumulative evidence [17]	14

(PRISM-P=Preferred Reporting Items for Systematic Review-Protocol)

Search strategy

Item	Search term	Boolean operator
Adolescents	("adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescent" [MeSH Terms] OR "adolescence" [MeSH Terms] OR "teenage"[All Fields] OR "child" [All Fields] OR "person" [All Fields] OR "persons" [MeSH Terms] OR "people" [All Fields])	AND
Tuberculosis	("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "TB"[All Fields] OR "TB"[MeSH Terms] OR "LTBI"[MeSH Terms] OR "LTBI"[All Fields] OR "latent"[MeSH Terms] OR "latent"[All Fields])	AND
Countries	("Africa" [All Fields] OR "Africa" [MeSH Terms] OR "east*" [All Fields] OR "south*" [All Fields] OR "Congo" [All Fields] OR "Zaire" [All fields] OR "Ethiopia" [All Fields] OR "Kenya" [All Fields] OR "Uganda" [All Fields] OR "Tanzania" [All Fields] OR "Zimbabwe" [All Fields] OR "South Africa" [All Fields] OR "Mozambique" [All Fields] OR "Nigeria" [All Fields] "Brazil" [All Fields] OR "Afghanistan" [All Fields] OR "Pakistan" [All Fields] OR "Russia" [All Fields] OR "Bangladesh" [All Fields] OR "India" [All Fields] OR "Indonesia" [All Fields] OR "Myanmar" [All Fields] OR "Thailand" [All Fields] OR "Cambodia" [All Fields] OR "China" [All Fields] OR "Philippines" [All Fields] OR "Vietnam" [All Fields])	AND
Prevalence	("epidemiology"[Subheading] OR "epidemiology"[MeSH Terms] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]	AND
Time period	Between 1st January 1990 and 1st July 2016	

PRISMA 2009 flow diagram



Data Extraction Form

Part A: Cover sheet summary

Study ID …… Initials of eligibility assessor ……..

Title of the study ……..

……..

Language …… Publication year ……..

Part B: Study characteristics

Outcome: Note: if other is selected, study is excluded. □ TB disease prevalence □ LTBI prevalence □ Other ……

Country of study Note: if non-high-TB burden country is selected, study is excluded.

□ High-TB burden country (state)…… □ Non-high-TB burden country

Study design Note: if other is selected, study is excluded.

□ Cross-sectional study

□ Cohort study

□ Other. State if other ……

Population

□ Non-students

□ Students

□ Both {(General population including students and non-students) state proportion that is students, if defined/obtainable ……..

□ Undefined ……

Diagnostic modality for TB disease or latent TB infection

TB disease	**Prevalence**
	n/N
Clinical	
Sputum smear for AFB	
Solid or liquid culture	
Xpert MTB/RIF assay	
Other microbiological. If yes, state ……. ……	
X-ray. If yes, state type ……..	
Latent TB infection	
Interferon Gamma Release Assay	
Tuberculin Skin Test	
Other. If yes, state & exclude ……..	

Age range of study participants (Please include percentage aged 10-19 years. If disaggregated data are not obtainable and proportion of individuals aged 10-19 years is less than 75%, the study will be excluded) ……..……...……

Gender of study participants

Gender	**n/N**	**%**	**No. with LTBI**	**No. with TB disease**	**No. with HIV**
Male					
Female					
Total		**100%**			

Legend: No=Number

Decision on inclusion/exclusion

□ Included

□ Excluded. Primary reason ……

□ Unsure. Reason (including need to contact authors) ……

……...

Other comments ……

……..

Part C: Quality assessment

Item under review	Score awarded (Yes=1 or No=0)
External Validity	**…**
Was the study's target population a close representation of the national population in relation to relevant variables?	…
Was the sampling frame a true or close representation of the target population?	…
Was some form of random selection used to select the sample, OR was a census undertaken?	…
Was the likelihood of non-response bias minimal?	…
Internal validity	**…**
Were data collected directly from the participants (as opposed to a proxy)?	…
Was an acceptable case definition used in the study?	…
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	…
Was the same mode of data collection used for all participants? (1 point)	…
Was the length of the shortest prevalence period for the parameter of interest appropriate?	…
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	…
Total	**…**

Summary item on the overall risk of study bias: low, moderate or high risk of bias

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10 items. This approach is consistent with the Cochrane and GRADE (GRADE=Grading of Recommendation, Assessment, Development and Evaluation) working group (26) recommendation or approaches. Furthermore, as summarized in the PRISMA (PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses) elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful (27), hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low (1) or high risk of bias (0). If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item (21,28,29).

Data Summary Table

Country	Author	TB or LTB		Sampling	Sampling	Sampling	Age range	Prevalence (%: 95% CI)			Diagnostic method	Overall quality score
		TB	LTBI	Size	Strategy	Response rate		Male	Female	Total		

BMJ Open

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

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Manuscript ID	bmjopen-2016-014609.R1
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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Evidence based practice, Global health, Public health, Research methods
Keywords:	Tuberculosis < INFECTIOUS DISEASES, Prevalence, Systematic, Review, Protocol, Adolescent

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

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ABSTRACT

Introduction

Almost a third of the world population has latent TB infection [LTBI], approximately 10 million of whom develop TB disease annually, despite existence of effective, but lengthy, preventive and curative drug regimens. Although adolescents appear to have a very high force of LTBI, their reported incidence of TB disease is less than that of their corresponding general population. The few available studies on adolescent TB infection and disease prevalence are not sufficient to address the apparent discordance between rates of infection and disease in high TB burden countries in Africa. Therefore, we aim to perform a systematic review to examine the relationship between adolescent LTBI and TB disease, benchmarked against national TB disease burden data.

Methods and analysis

A comprehensive literature search will be performed for cross-sectional studies and screening data in cohort studies to determine prevalence of LTBI and TB disease among adolescents in high TB burden countries in Africa in the following databases; *Pubmed*, *Scopus*, *Cochrane* library, *Web of Science, Africa Wide, CINAHL and the Africa Index Medicus*. This will be supplemented by a search of reference lists of selected articles for potentially relevant articles. We will restrict our search to articles published in English language between 1990 and 2016 among adolescents in order to obtain estimates reflective of the mature HIV epidemic in most high TB burden countries in Africa that occurred over this critical period. Primary end-points are; prevalence of LTBI and TB disease. We will use the random-effects or fixed effects modelling for our meta-analysis based on heterogeneity estimates.

Ethics and dissemination

No ethics approval is required given this is a systematic review. Findings will be disseminated in a peer-reviewed journal in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* [PRISMA].

Registration details

This protocol is registered with the *International Prospective Register of Ongoing Systematic Reviews* [PROSPERO], registration number CRD42015023495.

Key words

Prevalence; latent TB infection; TB disease; adolescents; protocol; systematic review.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review to conduct and compare adolescent LTBI and TB disease prevalence in high TB burden countries in Africa.
- By examining the relationship between adolescent LTBI and TB disease benchmarked against national TB disease burden data, our study will provide key insight on this relationship.
- Data reporting adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] guidelines for reviews [PRISMA] and protocols [PRISMA-P].
- Our choice of period for review is primarily driven by the need to provide findings reflective of the mature HIV epidemic in high TB burden countries in Africa both before and after the advent of wide ART availability, thus we appreciate that our estimates will not provide old or historical trends in TB burden.
- Our restriction of analysis to articles published in English language may introduce publication and language bias, respectively.

INTRODUCTION

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. (1) The estimated incidence rate of TB disease in Africa in 2015, of roughly 237 cases per 100,000 people, was almost double the global average of 133 cases per 100,000 people.(1) In 2015, TB caused 1.4 million deaths worldwide and was the leading cause of death by an infectious agent. A relatively small proportion [5–15%] of an estimated 2–3 billion people worldwide who are latently infected with *Mycobacterium tuberculosis* will develop TB disease in their lifetime. The probability of developing TB disease is much higher among people living with HIV (1).

The force of TB infection, defined as the proportion of susceptible individuals [i.e. individuals without latent TB infection [LTBI]] who become latently infected with *Mycobacterium tuberculosis* per annum, is a key measure of TB transmission in a defined population. Unfortunately, very few longitudinal cohort studies of child or adolescent LTBI exist across high TB burden countries in Africa. A South African longitudinal study reported a high annual force of TB infection among adolescents of 14.0%.(2) Similarly, there is paucity of data on prevalence of LTBI among adolescents in high TB burden countries in Africa, with most of the few available studies having been conducted in South Africa. A cross-sectional South African study reported an increase in prevalence of LTBI from 26% at 5-8 years to 53% at 14-17 years to 75% at 25 years.(3-7) A nationally representative Kenyan survey of children aged 6-14 years reported prevalence of LTBI of 10.2%, a figure that did not significantly change over 2 decades, between 1986 and 2006.(8) Although adolescents in Cape Town [South Africa] appear to have a very high force of TB infection [14%] (2), their reported incidence of TB disease [approximately 710/100,000] is less than the incidence in

young adults [1,400/100,000] and less than the incidence in the general population [834/100,000].(1,2,7,9)

A new TB infection in an infant or young child is a sentinel signal of active transmission from a person, usually an adult within their household, with active pulmonary TB disease. Thus, we would expect high rates of childhood LTBI to be associated with high prevalence of adult TB disease in the same community. There is little research that describes settings from which adolescents acquire TB infection (10) which makes it difficult to explain the apparent discordance between very high rates of adolescent force of TB infection and low rates of notified adolescent TB disease in the same community. In a South African township, prevalent TB infection among children aged 5 to 14 years was directly and significantly associated with residential [i.e. within their residential plot] exposure to an adult case of TB disease. However, a non-significant association was observed for individuals aged 15-22 years despite their high force of TB infection.(10) This finding suggests increasing significance of settings other than residential plot as a determinant of TB infection and subsequent disease from mid-adolescence onwards.(11,12) Glynn et al recently [2015] demonstrated via whole genome sequencing that, overall, known smear positive prior contacts accounted for less than 10% of tuberculosis cases in a Malawian community, and that even for those with a prior contact with smear positive tuberculosis in their family, there was a higher than 50% chance that they acquired their tuberculosis elsewhere, similar to our own previous finding in Cape Town, South Africa.(10,13,14) Andrews et al used statistical modeling techniques to estimate that up to a half of TB transmission among individuals aged 15-19 years occurs in the school setting, with this figure being 25% in individuals aged 0-14 years.(6) If this hypothesis were true, we would expect to observe high prevalence of TB disease in parallel with high force of TB infection among high school-aged adolescents in the same high burden communities. The fact that this apparently reasonable observation does not

appear to hold true deserves further investigation. 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 the design of this systematic review may not provide definitive reasons for this paradoxical yet persistent observation across many countries and settings. Due to lack of a systematic review on prevalence of LTBI and TB disease among adolescents, this systematic review will provide useful data for policy by consolidating and synthesising available data regarding a key sub-population with the highest force of TB infection(2) but a relatively low reported notification rate of TB disease as compared to their corresponding general population. Our findings will not only contribute to our better understanding of TB transmission among adolescents, but will also inform TB policies in high TB burden countries in Africa by providing a reference for monitoring future TB transmission trends in the wake of global efforts to end the TB epidemic whose targets are defined in sustainable development goals for 2035. (1) Our findings will also be useful in planning of novel TB vaccine research studies among adolescents who are increasingly becoming a key focus sub-population for global TB vaccine research efforts.

METHODS AND ANALYSIS

This protocol was developed in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P],(15,16) see Supplementary File 1 for a PRISMA-P checklist of the recommended bare minimum items to be included.

Objectives

Primary objectives

- 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.

- 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.

Secondary objective

- To explore the relationship between age-specific risk of LTBI and age-specific prevalence of TB disease, benchmarked against published estimates of national TB disease incidence and notification rates.

Definitions

Prevalence of LTBI is defined as the number of individuals with LTBI divided by total number of individuals in a cross-sectional, population-based study or screening database in cohort studies with a positive or negative result from a diagnostic test for LTBI. We will consider LTBI diagnosed by the Tuberculin Skin Test [TST] and/or the Interferon Gamma Release Assay.

Prevalence of TB disease is defined as the number of individuals with TB disease divided by total number of individuals in a cross-sectional, population-based study, or screening database in cohort studies. We will consider the following diagnostic modalities for TB disease: solid and liquid mycobacterial culture, Xpert MTB/RIF assay, sputum smear for acid fast bacilli and clinical diagnosis. Studies restricted to one or more forms of non-pulmonary TB disease only e.g. Koch's disease, TB lymphadenitis or disseminated TB, will not be included. Studies reporting on respiratory diseases in general and not clearly defining the prevalence of LTBI or TB disease will not be eligible.

Adolescents will be defined as individuals aged between 10 to 19 years, as defined by the WHO.(17)

In 2016, 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. 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. 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. (1) 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.

Criteria for consideration of studies for this review [Eligibility criteria]

(i) Study designs

We will consider cross-sectional or prevalence study designs and screening data in cohort studies that report primary data on prevalence of LTBI or TB disease. Statistical or mathematical modelling articles, cost-effectiveness studies, opinion pieces, narrative reviews, case studies, case series and letters to editors will not be considered. Grey/unpublished literature will also be excluded.

(ii) Participants

Adolescent participants should be representative of the general adolescent population in the setting in which the study was conducted. Studies conducted among the general school-going

population will also be considered provided that age is reported. For studies that report on age ranges that extend beyond the 10-to-19-year age bracket, data on individuals aged 10 to 19 years will be extracted, if possible. Otherwise, these data will be sought from corresponding authors. If extraction is not possible and these data are not obtainable from corresponding authors, at least 75% of participants should fall between the ages of 10 to 19 years. Studies reporting prevalence of TB infection or TB disease in sub-populations that are not representative of the general adolescent or school-going population in a specific study setting will be excluded e.g. studies reporting prevalence of TB restricted to HIV positive adolescents only.

(iii) Outcome measures

Outcome measures of interest will include: prevalence of LTBI and TB disease. Studies which do not measure any of our primary outcomes; do not clearly state the case definition of LTBI or TB disease; do not report primary data; or lack explicit description of methodology, will be excluded.

(iv) Time frame

We will consider studies reported between 1st January 1990 and 1st July 2016 because this period will also reflect the TB burden in mature or generalised Human Immunodeficiency Virus [HIV] epidemics across the high TB burden countries in Africa.

(v) Study setting

Studies should have been performed in at least one of the 25 high TB burden countries in Africa as defined above. (1) Studies not conducted in one of these countries or, for multi-country studies, if data pertaining to the listed high TB burden countries in Africa is not obtainable, they will be excluded.

(vi) Language

We will only consider articles published in English language because of limited time and financial resources available to this study.

Search strategy

We will systematically search for articles published between 1990 and 2016 using a combination of database specific medical subject headings [MeSH terms] and a range of free text or key words that will include the following, among others: adolescents, persons, latent, tuberculosis, LTBI, epidemiology, prevalence, morbidity and burden. Our draft *PubMed* search-term is provided in Supplementary File 2. The specific search strategies will be finalised with guidance from a health sciences librarian with expertise in systematic review searching with input from the project team. After the *PubMed* strategy is finalized, it will be adapted to the syntax and subject headings of the other targeted databases. We will review reference lists of selected articles to identify potentially relevant articles to our research questions that would have been missed by our search term in specified bibliographic databases. Our search will be limited to the following electronic databases due to limited time and financial resources; *PubMed, Scopus, Web of Science, Cochrane library, Africa Wide, Africa Index Medicus* and *CINAHL.* This review will not include grey/unpublished reports due to the low likelihood of peer-review and potential practical difficulties of obtaining supplementary or missing data. We appreciate that this may lead to publication bias and acknowledge this as a limitation of our planned review.

Selection of studies

The first author [EB] will perform a systematic search for articles by employing the search strategy. For duplicate articles or publications reporting the same data in multiple articles,

only the more recent and/or complete version of the publication will be considered. EB will review references of selected articles to identify articles relevant to our review which would have been missed by the search strategy. EB and BS will independently classify articles as either; [i] 'included', [ii] 'excluded' or [iii] 'pending'. A 'pending' status shall imply the reviewer is unsure on whether to include or exclude an article. This classification will be done by applying the inclusion and exclusion criteria, and will initially be based on the title and abstract, and then a quick scan, assessment or reading of the full text of the articles. Articles that both reviewers classify as 'excluded' will be excluded from further consideration whereas those that both reviewers classify as 'included' will be included in the review. We will obtain full reports for all 'included' titles and those with contradictories in classification between the two reviewers. We will seek additional information from study authors where necessary to resolve questions about eligibility. A discussion will be held between EB and BS to resolve differences or contradictories in classification of articles by reviewing full text. A third reviewer [LA] will be consulted to resolve persistent disagreements following discussion. We will present a flow chart, in keeping with PRISMA guidelines as much as practicable, to summarise the search process and selection of studies for the review and document reasons for exclusion of studies [see Supplementary File 3]. We will include a table of all selected studies in the final review and document reasons for exclusion of articles.

Data management

Data management will be done by the first author [EB] in liaison with the second author [BS]. A google drive electronic folder will be maintained for the review and will contain; the protocol, a record of obtained articles and documentation of steps in data synthesis and analysis [including records included and excluded], risk of bias and quality scoring, among

others. A back-up of the electronic records will be stored on a laptop and on a memory flash drive. '*Refworks'* bibliographic management software(18) will be used to manage references.

Data extraction

EB will read, extract and collate data from selected articles on to a standardised Data Extraction Form [see Supplementary File 4]. This form will be piloted on at least 4 randomly selected studies meeting the criteria for consideration. BS will verify abstracted data in order to reduce bias and reduce errors in data extraction. Data to be abstracted will include: study characteristics- title, year of publication, authors, study design; study setting and population- country, socio-demographics [age and gender]; study conduct- number of study participants [total in the study and those participants with TB, by diagnostic approach and number with LTBI]. Reviewers will resolve disagreements by discussion, with arbitration by LA for unresolved disagreements. We will contact study authors for data that may resolve any uncertainties.

Dealing with missing data

In the event of missing data that are key, we will attempt to contact the corresponding authors of the studies to obtain the relevant missing data via email. A second email will be sent after one week of the first email in the event of no response to the first email. A two-week wait period from the date of submission of the second email will be allowed for responses, failing which these studies will be excluded, if no communication or response would have been established.

Assessment of risk of bias of included studies

Risk of bias and assessment of quality will be evaluated using an assessment tool adapted from Hoy et al(19) by Werfalli et al who included a scoring system for evaluation of

prevalence studies.(20) The tool helps evaluate internal and external validity [see table 1]. This tool was preferred over others because it was designed via an expert consensus exercise then tested, retested, validated and thus optimised for evaluation of quality of prevalence studies via a rigorous published process that included a review of limitations of existing tools.(19,21) The tool was shown to have a high inter-rater agreement.(19) Two authors [EB and BS] will independently score the risk of bias using this tool and the mean score calculated. Agreement between the two raters will be assessed for each item in the tool and overall using proportion of agreement [P_0] and the Kappa [κ] statistic. For the Kappa statistic, its values range from -1 to +1. Values of 0 or less will be regarded as poor agreement, 0.01 to 0.20 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 0.99 almost perfect agreement.(22) Raw agreement and Kappa values [including their 95% confidence intervals] will be calculated using *STATA* version 14.0 for windows.(23) Neither of the review authors will be blinded to the journal titles or to the study authors or institutions.

Table 1: Risk of bias and quality assessment criteria for prevalence studies

Item under review	**Quality score [Points]**
External Validity	
Was the study's target population a close representation of the national population in relation to relevant variables?	1
Was the sampling frame a true or close representation of the target population?	1

Was some form of random selection used to select the sample, OR was a census undertaken?	1
Was the likelihood of non-response bias minimal?	1
Total	**4 points**
Internal validity	
Were data collected directly from the participants [as opposed to a proxy]?	1
Was an acceptable case definition used in the study?	1
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1
Was the same mode of data collection used for all subjects?	1
Was the length of the shortest prevalence period for the parameter of interest appropriate?	1
Were the numerator[s] and denominator[s] for the parameter of interest appropriate?	1
Total	**6 points**
Summary item on the overall risk of study bias [low, moderate or high]	

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10

items. This approach is consistent with the Cochrane and GRADE [GRADE=Grading of Recommendation, Assessment, Development and Evaluation] working group(24) recommendation or approaches. Furthermore, as summarized in the PRISMA [PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses] elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful,(25) hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low [1] or high risk of bias [0]. If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item.(19,26,27)

Data analysis

We hypothesise that there will be substantial statistical heterogeneity in study results because prevalence of LTBI and TB disease varies by distribution of socioeconomic determinants of health and HIV prevalence within and across settings, among other factors. *A priori*, random effects meta-analysis will be preferred due to the anticipated heterogeneity. However, choice of random-effects or fixed effects modelling will be based on observed statistical heterogeneity. For the latter, we will not pool the results but summarise findings in a narrative format. Additionally, we will derive Annual Risk of LTBI using the formulae: 1-[1-Prevalence] $^{1/[\text{mean age}]}$ for every year of adolescence. We will then describe the relationship between the annual risk of TB infection and observed TB prevalence from our review. Alternatively, for countries with insufficient data, we will describe the relationship between the Annual Risk of TB Infection and reported TB notification [or incidence rates estimates] by National TB Programs or estimates from the WHO.

In random effects modelling, effect measures are assumed to vary between studies and the summary effect is the weighted average of the effects reported in different studies.(28) This model directly adjusts for inverse of the standard error, and thus indirectly for the sample size reported in studies. Thus, studies with smaller standard error and larger sample sizes will be given more weight in the calculation of the pooled prevalence and 95% confidence intervals.

Data synthesis

Our outcome will be combined and calculated using the Cochrane Review Manager [*RevMan*] statistical software,(29) according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions.*(26) If statistical heterogeneity is observed, the random effects model will be chosen over the fixed effects model. If there is substantial statistical heterogeneity, we will not perform a meta-analysis; a narrative, qualitative summary will be done supported by a table [Supplementary File 5] and figures, where appropriate. This will be done by the first reviewer and checked by the second reviewer for accuracy.

Assessment of reporting biases

The potential for publication or reporting bias will be explored by funnel plots if we obtain at least10 articles. This will be done by visually assessing asymmetry of funnel plots. As suggested by Egger et al, asymmetry of funnel plots will indicate presence of publication bias.(30) We appreciate that our choice of considering articles reported in English only [language bias] and the fact that we are only searching in a sample of bibliographic databases may be a source of reporting bias.

Assessment and management of heterogeneity

We anticipate clinical and statistical heterogeneity in prevalence rate estimates within and across settings and countries. Statistical heterogeneity will be quantified using the I^2 test statistic to determine the extent of variation in effect estimates that is due to heterogeneity rather than chance. Statistical heterogeneity will be explored graphically by inspection of forest plots [i.e. the 'eyeball test']. Non-overlap of 95% confidence intervals will suggest remarkable heterogeneity. A formal test for statistical homogeneity, the Cochran's χ^2 Q test statistic, will be performed using an alpha cut-off level of 10% as suggested by Higgin's et al(31) and Cochrane(32), due to the test statistic's low power in detecting heterogeneity, particularly when the number of studies is low. The I^2 test statistic will be used to quantify statistical heterogeneity between studies i.e. provide percentage of observed total variation across studies that is due to real heterogeneity rather than chance. This will provide a quantitative measure of heterogeneity. Cochrane provides the following rough guide to interpretation of heterogeneity: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.(33) If substantial heterogeneity is observed, we will try to explain the source of heterogeneity by subgroup analysis and/or sensitivity analysis.

Subgroup analysis

Subgroup analysis will be done in order to obtain estimates that are reflective, and thus potentially more useful and applicable, for specific sub-population groups or settings, and will be conducted along the following strata, subject to availability of sufficient data; [1] schooling status- adolescents in school vs those not in school; [2] country of study participants; [3] age [4] gender; [5] 1990-1999, 2000-2016 and 1990-2016; and [6] diagnostic modality of LTBI and TB disease. The analysis along the strata of the periods 1990-1999 and 2000-2016 will be done in order to account for differences attributable to the advent of wide

and free availability of anti-retroviral therapy, although we appreciate that HIV prevalence is generally very low among adolescents as compared to adults.

Sensitivity analyses

Sensitivity analyses will be conducted to explore the source of heterogeneity i.e. determine impact of specific studies on pooled prevalence estimate, by exclusion of studies with low quality scores and thus higher risk of bias. We will also explore exclusion of studies with deficiency in specific items on the 10-point modified Hoy et al quality assessment tool, in order to evaluate impact of this exclusion on pooled prevalence estimates.

Ethics

Given that we will utilise published anonymised data, which is publicly available and peer-reviewed, ethical approval is not required for this study.

Dissemination [Reporting of this review]

Our review will be reported, as much as possible, in keeping with the Preferred Reporting Items for Systematic reviews and Meta-Analyses [*PRISMA*] Statement,(34) and will include the PRISMA check-list [or adapted as practicable]. Our findings will be published in a peer-reviewed journal and as part of a doctoral thesis at the University of Cape Town.

Synthesis of evidence

The *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P](15,16) recommends gauging of overall judgement of quality of evidence from obtained articles and indicates increasing support and use of *the Grading of Recommendations Assessment, Development and Evaluation* [GRADE] working group(24) methodology. We will consider methodological quality of included studies and strength of evidence and adapt the basic principles of the GRADE approach.

Competing interest statement

None. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Funding statement

All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf. The financial assistance of the National Research Foundation [NRF] towards the first author's PhD studies is hereby acknowledged. However, this funding is not specific to this review. Opinions expressed and conclusions arrived at, are those of the authors and are not necessarily attributed to the NRF. EWB initiated the research. This research is not done on behalf of or commissioned by the NRF, but is conducted as part of a PhD at the University of Cape Town. The first author [EB] would also like to appreciate supplementary departmental scholarship and support towards his PhD studies from the University of Cape Town [SATVI programme@UCT], of which this publication is a part of. No specific sponsor is associated with our review.

Author contributorship statement

Erick Wekesa Bunyasi conceptualised and designed the study. Erick Wekesa Bunyasi, Bey-Marrie Schmidt, Leila H. Abdullahi, Humphrey Mulenga, Michele Tameris, Angelique Luabeya, Justin Shenje, Thomas J. Scriba, Hennie Geldenhuys, Robin Wood and Mark Hatherill were involved in development of the study protocol. Erick Wekesa Bunyasi prepared the first draft of the manuscript with supervision from Hennie Geldenhuys, Robin

Wood and Mark Hatherill. Erick Wekesa Bunyasi, Bey-Marrie Schmidt, Leila H. Abdullahi, Humphrey Mulenga, Michele Tameris, Angelique Luabeya, Justin Shenje, Thomas J. Scriba, Hennie Geldenhuys, Robin Wood and Mark Hatherill critically reviewed, revised and approved the subsequent and final version of the protocol. EWB is the guarantor. EWB and BS will perform the study search, screening and extraction of data under the guidance of Hennie Geldenhuys, Robin Wood and Mark Hatherill.

Provenance and peer review: Not commissioned; externally peer reviewed.

Amendment procedure

In the event that amendment to this protocol is required, we will describe the change and give the rationale in the methods section of the published review. EB will ultimately be responsible for approving, documenting, and implementing any amendments.

Data sharing

The authors declare that this research protocol is an original work. Results from the study completed using this protocol will be published in a peer-reviewed journal.

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PRISM-P checklist of items to be reported in a systematic review

Domain	Line item & PRISM-P code	Page
Section 1: Administrative information		
1. Title:		
	Identification [1a]	1
	Update [1b]	NA
2. Registration	Registration [2]	4
3. Authors:		
	Contact [3a]	1
	Contributions [3b]	21
4. Amendments	Amendments [4]	21
5. Support:		
	Sources [5a]	20-21
	Sponsor [5b]	21
	Role of sponsor or funder [5c]	21
Section 2: Introduction		
6. Rationale	Rationale [6]	8
7. Objectives	Objectives [7]	8, 9
Section 3: Methods		
8. Eligibility	Eligibility criteria [8]	10, 11
9. Information	Information sources [9]	12
10. Search	Search strategy [10]	11
11. Study records:		
	Data management [11a]	13
	Selection process [11b]	12
	Data collection process [11c]	12, 13
12. Data	Data items [12]	13
13. Outcomes	Outcomes and prioritization [13]	10
14. Bias	Risk of bias in individual studies [14]	14-16
15. Data synthesis		
	Quantitative synthesis criteria [15a]	17-18
	Appropriateness of data for synthesis [15b]	17-18
	Sensitivity and subgroup analyses [15c]	19
	Qualitative synthesis? [15d]	17-18
16. Meta-bias(es)	Meta-bias(es) [16]	14
17. Confidence in cumulative evidence	Assessment of strength of cumulative evidence [17]	14

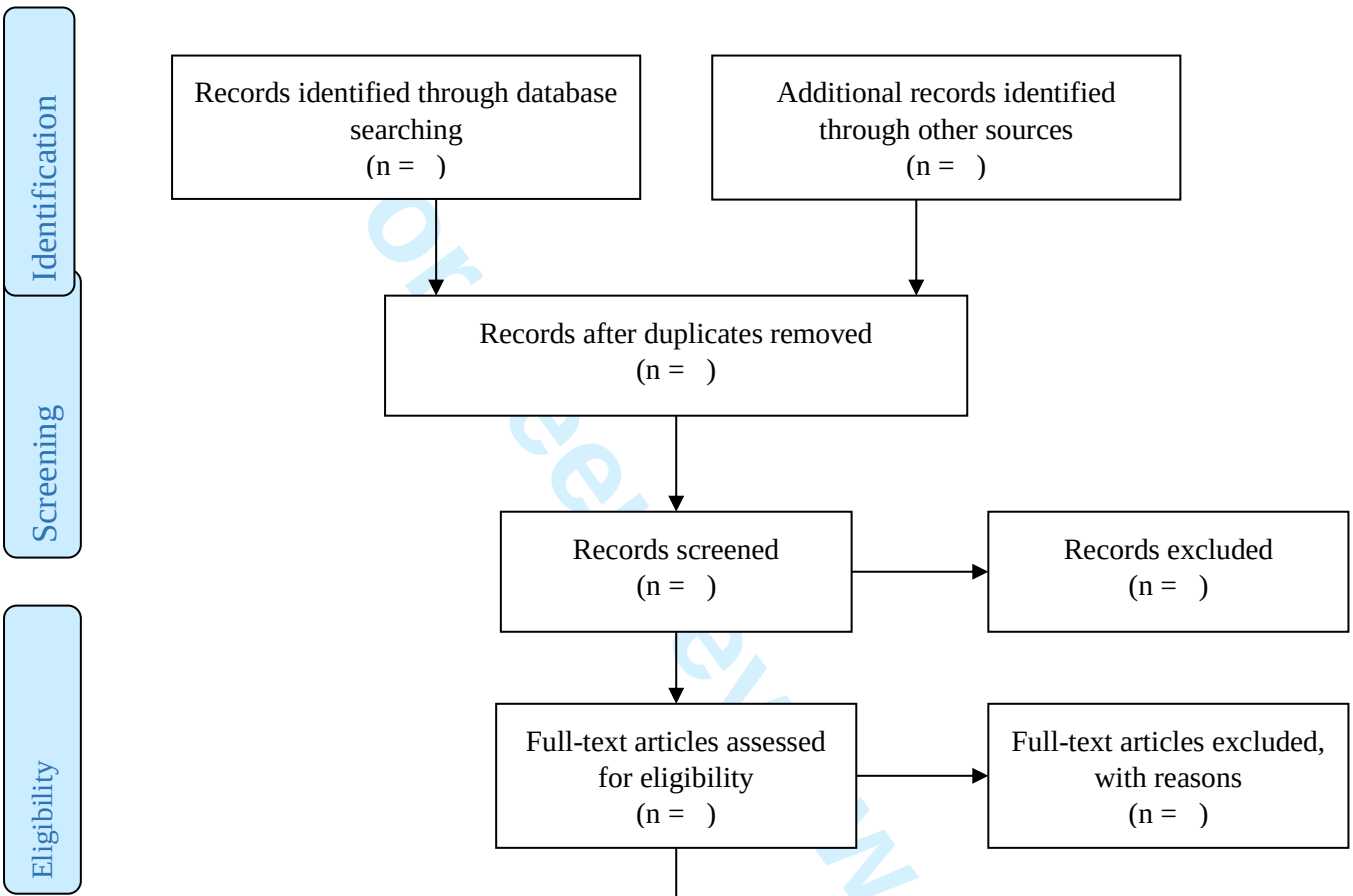
(PRISM-P=Preferred Reporting Items for Systematic Review-Protocol)

Search strategy

Item	Search term	Boolean operator
Adolescents	("adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescent" [MeSH Terms] OR "adolescence" [MeSH Terms] OR "teen*"[All Fields] OR "child" [All Fields] OR "person" [All Fields] OR "persons" [MeSH Terms] OR "people" [All Fields])	AND
Tuberculosis	("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "TB"[All Fields] OR "TB"[MeSH Terms] OR "LTBI"[MeSH Terms] OR "LTBI"[All Fields] OR "latent"[MeSH Terms] OR "latent"[All Fields])	AND
Countries	("Africa" [All Fields] OR "Africa" [MeSH Terms] OR "east*" [All Fields] OR "south*" [All Fields] OR "Congo" [All Fields] OR "Zaire" [All fields] OR "Ethiopia" [All Fields] OR "Kenya" [All Fields] OR "Uganda" [All Fields] OR "Tanzania" [All Fields] OR "Zimbabwe" [All Fields] OR "South Africa" [All Fields] OR "Mozambique" [All Fields] OR "Nigeria" [All Fields] OR "Angola" [All Fields] OR " Sierra Leone " [All Fields] OR ["Central" AND "African" AND "Republic"] [All Fields] OR "Lesotho " [All Fields] OR "Liberia " [All Fields] OR "Namibia " [All Fields] OR "Zambia " [All Fields] OR "Botswana " [All Fields] OR "Cameroon " [All Fields] OR "Chad" [All Fields] OR " Ghana " [All Fields] OR "Guinea-Bissau " [All Fields] OR "Malawi " [All Fields] OR "Swaziland " [All Fields] OR "Somalia" [All Fields])	AND
Prevalence	("epidemiology"[Subheading] OR "epidemiology"[MeSH Terms] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]	AND
Time period	Between 1st January 1990 and 1st July 2016	

*Covers both Democratic Republic of Congo and Congo

PRISMA 2009 flow diagram



Data Extraction Form

Part A: Cover sheet summary

Study ID …… Initials of eligibility assessor …….

Title of the study ……..

……..

Publication year ……..

Part B: Study characteristics

Outcome: Note: if other is selected, study is excluded. □ TB disease prevalence □ LTBI prevalence □ Other ……

Country of study Note: if non-high-TB burden country is selected, study is excluded.

□ High-TB burden country (state)…… □ Non-high-TB burden country

Study design Note: if other is selected, study is excluded.

□ Cross-sectional study

□ Cohort study

□ Other. State if other ……

Population

□ Non-students

□ Students

□ Both {(General population including students and non-students) state proportion that is students, if defined/obtainable ……..

□ Undefined ……

Diagnostic modality for TB disease or latent TB infection

TB disease	**Prevalence**
	n/N
Clinical	
Sputum smear for AFB	
Solid or liquid culture	
Xpert MTB/RIF assay	
Other microbiological. If yes, state ……. ……	
X-ray	
Latent TB infection	
Interferon Gamma Release Assay	
Tuberculin Skin Test	
Other. If yes, state & exclude …….	

Age range of study participants (Please include percentage aged 10-19 years. If disaggregated data are not obtainable and proportion of individuals aged 10-19 years is less than 75%, the study will be excluded) ……..……..……

Gender of study participants

Gender	**n/N**	**%**	**No. with LTBI**	**No. with TB disease**
Male				
Female				
Total		**100%**		

Legend: No=Number

Decision on inclusion/exclusion

□ Included

□ Excluded. Primary reason …….

□ Unsure. Reason (including need to contact authors) …….

……...

Other comments ……

……..

Part C: Quality assessment

Item under review	Score awarded (Yes=1 or No=0)
External Validity	**…**
Was the study's target population a close representation of the national population in relation to relevant variables?	…
Was the sampling frame a true or close representation of the target population?	…
Was some form of random selection used to select the sample, OR was a census undertaken?	…
Was the likelihood of non-response bias minimal?	…
Internal validity	**…**
Were data collected directly from the participants (as opposed to a proxy)?	…
Was an acceptable case definition used in the study?	…
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	…
Was the same mode of data collection used for all participants? (1 point)	…
Was the length of the shortest prevalence period for the parameter of interest appropriate?	…
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	…
Total	**…**

Summary item on the overall risk of study bias: low, moderate or high risk of bias

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10 items. This approach is consistent with the Cochrane and GRADE (GRADE=Grading of Recommendation, Assessment, Development and Evaluation) working group (26) recommendation or approaches. Furthermore, as summarized in the PRISMA (PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses) elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful (27), hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low (1) or high risk of bias (0). If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item (21,28,29).

Data Summary Table

Country	Author	TB or LTB		Sampling	Sampling	Sampling	Age range	Prevalence (%: 95% CI)			Diagnostic method	Overall quality score
		TB	LTBI	Size	Strategy	Response rate		Male	Female	Total		

Domain	Line item & PRISM-P code	Page
Section 1: Administrative information		
1. Title:		

PRISM-P checklist of items to be reported in a systematic review

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	Data collection process [11c]	12, 13
12. Data	Data items [12]	13
13. Outcomes	Outcomes and prioritization [13]	10
14. Bias	Risk of bias in individual studies [14]	14-16
15. Data synthesis		
	Quantitative synthesis criteria [15a]	17-18
	Appropriateness of data for synthesis [15b]	17-18
	Sensitivity and subgroup analyses [15c]	19
	Qualitative synthesis? [15d]	17-18
16. Meta-bias(es)	Meta-bias(es) [16]	14
17. Confidence in cumulative evidence	Assessment of strength of cumulative evidence [17]	14

(PRISM-P=Preferred Reporting Items for Systematic Review-Protocol)

BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-014609.R2
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Prevalence of latent TB infection and TB disease among adolescents in high TB burden countries in Africa: a systematic review protocol

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ABSTRACT

Introduction

Almost a third of the world population has latent TB infection [LTBI], approximately 10 million of whom develop TB disease annually, despite existence of effective, but lengthy, preventive and curative drug regimens. Although adolescents appear to have a very high force of LTBI, their reported incidence of TB disease is less than that of their corresponding general population. The few available studies on adolescent TB infection and disease prevalence are not sufficient to address the apparent discordance between rates of infection and disease in high TB burden countries in Africa. Therefore, we aim to perform a systematic review to examine the relationship between adolescent LTBI and TB disease, benchmarked against national TB disease burden data.

Methods and analysis

A comprehensive literature search will be performed for cross-sectional studies and screening data in cohort studies to determine prevalence of LTBI and TB disease among adolescents in high TB burden countries in Africa in the following databases; *Pubmed*, *Scopus*, *Cochrane* library, *Web of Science, Africa Wide, CINAHL and the Africa Index Medicus*. This will be supplemented by a search of reference lists of selected articles for potentially relevant articles. We will restrict our search to articles published in English language between 1990 and 2016 among adolescents in order to obtain estimates reflective of the mature HIV epidemic in most high TB burden countries in Africa that occurred over this critical period. Primary end-points are; prevalence of LTBI and TB disease. We will use the random-effects or fixed effects modelling for our meta-analysis based on heterogeneity estimates.

Ethics and dissemination

No ethics approval is required given this is a systematic review. Findings will be disseminated in a peer-reviewed journal in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses* [PRISMA].

Registration details

This protocol is registered with the *International Prospective Register of Ongoing Systematic Reviews* [PROSPERO], registration number CRD42015023495.

Key words

Prevalence; latent TB infection; TB disease; adolescents; protocol; systematic review.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review to conduct and compare adolescent LTBI and TB disease prevalence in high TB burden countries in Africa.
- By examining the relationship between adolescent LTBI and TB disease benchmarked against national TB disease burden data, our study will provide key insights into this relationship.
- Data reporting adheres to the Preferred Reporting Items for Systematic reviews and Meta-Analyses [PRISMA] guidelines for reviews [PRISMA] and protocols [PRISMA-P].
- Our choice of period for review is primarily driven by the need to provide findings reflective of the mature HIV epidemic in high TB burden countries in Africa both before and after the advent of wide ART availability, thus we appreciate that our estimates will not provide old or historical trends in TB burden.
- Our restriction of analysis to articles published in English language may introduce publication and language bias, respectively.

INTRODUCTION

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. (1) The estimated incidence rate of TB disease in Africa in 2015, of roughly 237 cases per 100,000 people, was almost double the global average of 133 cases per 100,000 people.(1) In 2015, TB caused 1.4 million deaths worldwide and was the leading cause of death by an infectious agent. A relatively small proportion [5–15%] of an estimated 2–3 billion people worldwide who are latently infected with *Mycobacterium tuberculosis* will develop TB disease in their lifetime. The probability of developing TB disease is much higher among people living with HIV (1).

The force of TB infection, defined as the proportion of susceptible individuals [i.e. individuals without latent TB infection [LTBI]] who become latently infected with *Mycobacterium tuberculosis* per annum, is a key measure of TB transmission in a defined population. Unfortunately, very few longitudinal cohort studies of child or adolescent LTBI exist across high TB burden countries in Africa. A South African longitudinal study reported a high annual force of TB infection among adolescents of 14.0%.(2) Similarly, there is paucity of data on prevalence of LTBI among adolescents in high TB burden countries in Africa, with most of the few available studies having been conducted in South Africa. A cross-sectional South African study reported an increase in prevalence of LTBI from 26% at 5-8 years to 53% at 14-17 years to 75% at 25 years.(3-7) A nationally representative Kenyan survey of children aged 6-14 years reported prevalence of LTBI of 10.2%, a figure that did not significantly change over 2 decades, between 1986 and 2006.(8) Although adolescents in Cape Town, South Africa, appear to have a very high force of TB infection [14%] (2), their reported incidence of TB disease [approximately 710/100,000] is less than the incidence in

young adults [1,400/100,000] and less than the incidence in the general population [834/100,000].(1,2,7,9)

A new TB infection in an infant or young child is a sentinel signal of active transmission from a person, usually an adult within their household, with active pulmonary TB disease. Thus, we would expect high rates of childhood LTBI to be associated with high prevalence of adult TB disease in the same community. There is little research that describes settings from which adolescents acquire TB infection (10) which makes it difficult to explain the apparent discordance between very high rates of adolescent force of TB infection and low rates of notified adolescent TB disease in the same community. In a South African township, prevalent TB infection among children aged 5 to 14 years was directly and significantly associated with residential [i.e. within their residential plot] exposure to an adult case of TB disease. However, a non-significant association was observed for individuals aged 15-22 years despite their high force of TB infection.(10) This finding suggests increasing significance of settings other than residential plot as a determinant of TB infection and subsequent disease from mid-adolescence onwards.(11,12) Glynn et al recently [2015] demonstrated via whole genome sequencing that, overall, known smear positive prior contacts accounted for less than 10% of tuberculosis cases in a Malawian community, and that even for those with a prior contact with smear positive tuberculosis in their family, there was a higher than 50% chance that they acquired their tuberculosis elsewhere, similar to our own previous finding in Cape Town, South Africa.(10,13,14) Andrews et al used statistical modeling techniques to estimate that up to a half of TB transmission among individuals aged 15-19 years occurs in the school setting, with this figure being 25% in individuals aged 0-14 years.(6) If this hypothesis were true, we would expect to observe high prevalence of TB disease in parallel with high force of TB infection among high school-aged adolescents in the same high burden communities. The fact that this apparently reasonable observation does not

appear to hold true deserves further investigation. 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 the design of this systematic review may not provide definitive reasons for this paradoxical yet persistent observation across many countries and settings. Due to lack of a systematic review on prevalence of LTBI and TB disease among adolescents, this systematic review will provide useful data for policy by consolidating and synthesising available data regarding a key sub-population with the highest force of TB infection(2) but a relatively low reported notification rate of TB disease as compared to their corresponding general population. Our findings will not only contribute to our better understanding of TB transmission among adolescents, but will also inform TB policies in high TB burden countries in Africa by providing a reference for monitoring future TB transmission trends in the wake of global efforts to end the TB epidemic whose targets are defined in sustainable development goals for 2035. (1) Our findings will also be useful in planning of novel TB vaccine research studies among adolescents who are increasingly becoming a key focus sub-population for global TB vaccine research efforts.

METHODS AND ANALYSIS

This protocol was developed in line with the *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P],(15,16) see Supplementary File 1 for a PRISMA-P checklist of the recommended bare minimum items to be included.

Objectives

Primary objectives

- 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.

- 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.

Secondary objective

- To explore the relationship between age-specific risk of LTBI and age-specific prevalence of TB disease, benchmarked against published estimates of national TB disease incidence and notification rates.

Definitions

Prevalence of LTBI is defined as the number of individuals with LTBI divided by total number of individuals in a cross-sectional, population-based study or screening database in cohort studies with a positive or negative result from a diagnostic test for LTBI. We will consider LTBI diagnosed by the Tuberculin Skin Test [TST] and/or the Interferon Gamma Release Assay.

Prevalence of TB disease is defined as the number of individuals with TB disease divided by total number of individuals in a cross-sectional, population-based study, or screening database in cohort studies. We will consider the following diagnostic modalities for TB disease: solid and liquid mycobacterial culture, Xpert MTB/RIF assay, sputum smear for acid fast bacilli and clinical diagnosis. Studies restricted to one or more forms of non-pulmonary TB disease only e.g. Koch's disease, TB lymphadenitis or disseminated TB, will not be included. Studies reporting on respiratory diseases in general and not clearly defining the prevalence of LTBI or TB disease will not be eligible.

Adolescents will be defined as individuals aged between 10 to 19 years, as defined by the WHO.(17)

In 2016, 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. 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. 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. (1) These include: (a) The Democratic Republic of Congo, (b) Ethiopia, (c) Kenya, (d) Uganda, (e) United Republic of Tanzania, (f) Zimbabwe, (g) South Africa, (h) Mozambique, (i) Angola, (j) Sierra Leone, (k) Central African Republic, (l) Congo, (m) Lesotho, (n) Liberia, (o) Namibia, (p) Zambia, (q) Botswana, (r) Cameroon, (s) Chad, (t) Ghana, (u) Guinea-Bissau, (v) Malawi, (w) Swaziland, (x) Somalia and (y) Nigeria.

Criteria for consideration of studies for this review [Eligibility criteria]

(i) Study designs

We will consider cross-sectional or prevalence study designs and screening data in cohort studies that report primary data on prevalence of LTBI or TB disease. Statistical or mathematical modelling articles, cost-effectiveness studies, opinion pieces, narrative reviews, case studies, case series and letters to editors will not be considered. Grey/unpublished literature will also be excluded.

(ii) Participants

Adolescent participants should be representative of the general adolescent population in the setting in which the study was conducted. Studies conducted among the general school-going population will also be considered provided that age is reported. For studies that report on age ranges that extend beyond the 10-to-19-year age bracket, data on individuals aged 10 to 19 years will be extracted, if possible. Otherwise, these data will be sought from corresponding authors. If extraction is not possible and these data are not obtainable from corresponding authors, at least 75% of participants should fall between the ages of 10 to 19 years. Studies reporting prevalence of TB infection or TB disease in sub-populations that are not representative of the general adolescent or school-going population in a specific study setting will be excluded e.g. studies reporting prevalence of TB restricted to HIV positive adolescents only.

(iii) Outcome measures

Outcome measures of interest will include: prevalence of LTBI and TB disease. Studies which do not measure any of our primary outcomes; do not clearly state the case definition of LTBI or TB disease; do not report primary data; or lack explicit description of methodology, will be excluded.

(iv) Time frame

We will consider studies reported between 1st January 1990 and 1st July 2016 because this period will also reflect the TB burden in mature or generalised Human Immunodeficiency Virus [HIV] epidemics across the high TB burden countries in Africa.

(v) Study setting

Studies should have been performed in at least one of the 25 high TB burden countries in Africa as defined above. (1) Studies not conducted in one of these countries or, for multi-

country studies, if data pertaining to the listed high TB burden countries in Africa is not obtainable, they will be excluded.

(vi) Language

We will only consider articles published in English language because of limited time and financial resources available to this study.

Search strategy

We will systematically search for articles published between 1990 and 2016 using a combination of database specific medical subject headings [MeSH terms] and a range of free text or key words that will include the following, among others: adolescents, persons, latent, tuberculosis, LTBI, epidemiology, prevalence, morbidity and burden. Our draft *PubMed* search-term is provided in Supplementary File 2. The specific search strategies will be finalised with guidance from a health sciences librarian with expertise in systematic review searching with input from the project team. After the *PubMed* strategy is finalized, it will be adapted to the syntax and subject headings of the other targeted databases. We will review reference lists of selected articles to identify potentially relevant articles to our research questions that would have been missed by our search term in specified bibliographic databases. Our search will be limited to the following electronic databases due to limited time and financial resources; *PubMed, Scopus, Web of Science, Cochrane library, Africa Wide, Africa Index Medicus* and *CINAHL.* This review will not include grey/unpublished reports due to the low likelihood of peer-review and potential practical difficulties of obtaining supplementary or missing data. We appreciate that this may lead to publication bias and acknowledge this as a limitation of our planned review.

Selection of studies

The first author [EB] will perform a systematic search for articles by employing the search strategy. For duplicate articles or publications reporting the same data in multiple articles, only the more recent and/or complete version of the publication will be considered. EB will review references of selected articles to identify articles relevant to our review which would have been missed by the search strategy. EB and BS will independently classify articles as either; [i] 'included', [ii] 'excluded' or [iii] 'pending'. A 'pending' status shall imply the reviewer is unsure on whether to include or exclude an article. This classification will be done by applying the inclusion and exclusion criteria, and will initially be based on the title and abstract, and then a quick scan, assessment or reading of the full text of the articles. Articles that both reviewers classify as 'excluded' will be excluded from further consideration whereas those that both reviewers classify as 'included' will be included in the review. We will obtain full reports for all 'included' titles and those with contradictories in classification between the two reviewers. We will seek additional information from study authors where necessary to resolve questions about eligibility. A discussion will be held between EB and BS to resolve differences or contradictories in classification of articles by reviewing full text. A third reviewer [LA] will be consulted to resolve persistent disagreements following discussion. We will present a flow chart, in keeping with PRISMA guidelines as much as practicable, to summarise the search process and selection of studies for the review and document reasons for exclusion of studies [see Supplementary File 3]. We will include a table of all selected studies in the final review and document reasons for exclusion of articles.

Data management

Data management will be done by the first author [EB] in liaison with the second author [BS]. A google drive electronic folder will be maintained for the review and will contain; the

protocol, a record of obtained articles and documentation of steps in data synthesis and analysis [including records included and excluded], risk of bias and quality scoring, among others. A back-up of the electronic records will be stored on a laptop and on a memory flash drive. '*Refworks'* bibliographic management software(18) will be used to manage references.

Data extraction

EB will read, extract and collate data from selected articles on to a standardised Data Extraction Form [see Supplementary File 4]. This form will be piloted on at least 4 randomly selected studies meeting the criteria for consideration. BS will verify abstracted data in order to reduce bias and reduce errors in data extraction. Data to be abstracted will include: study characteristics- title, year of publication, authors, study design; study setting and population- country, socio-demographics [age and gender]; study conduct- number of study participants [total in the study and those participants with TB, by diagnostic approach and number with LTBI]. Reviewers will resolve disagreements by discussion, with arbitration by LA for unresolved disagreements. We will contact study authors for data that may resolve any uncertainties.

Approach to missing data

In the event of missing data that are key, we will attempt to contact the corresponding authors of the studies to obtain the relevant missing data via email. A second email will be sent after one week of the first email in the event of no response to the first email. A two-week wait period from the date of submission of the second email will be allowed for responses, failing which these studies will be excluded, if no communication or response is established.

Assessment of risk of bias of included studies

Risk of bias and assessment of quality will be evaluated using an assessment tool adapted from Hoy et al(19) by Werfalli et al who included a scoring system for evaluation of prevalence studies.(20) The tool helps evaluate internal and external validity [see table 1]. This tool was preferred over others because it was designed via an expert consensus exercise then tested, retested, validated and thus optimised for evaluation of quality of prevalence studies via a rigorous published process that included a review of limitations of existing tools.(19,21) The tool was shown to have a high inter-rater agreement.(19) Two authors [EB and BS] will independently score the risk of bias using this tool and the mean score calculated. Agreement between the two raters will be assessed for each item in the tool and overall using proportion of agreement [P_0] and the Kappa [κ] statistic. For the Kappa statistic, its values range from -1 to +1. Values of 0 or less will be regarded as poor agreement, 0.01 to 0.20 slight, 0.21 to 0.40 fair, 0.41 to 0.60 moderate, 0.61 to 0.80 substantial, and 0.81 to 0.99 almost perfect agreement.(22) Raw agreement and Kappa values [including their 95% confidence intervals] will be calculated using *STATA* version 14.0 for windows.(23) Neither of the review authors will be blinded to the journal titles or to the study authors or institutions.

Table 1: Risk of bias and quality assessment criteria for prevalence studies

Item under review	**Quality score [Points]**
External Validity	
Was the study's target population a close representation of the national population in relation to relevant variables?	1

Was the sampling frame a true or close representation of the target population?	1
Was some form of random selection used to select the sample, OR was a census undertaken?	1
Was the likelihood of non-response bias minimal?	1
Total	**4 points**
Internal validity	
Were data collected directly from the participants [as opposed to a proxy]?	1
Was an acceptable case definition used in the study?	1
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	1
Was the same mode of data collection used for all subjects?	1
Was the length of the shortest prevalence period for the parameter of interest appropriate?	1
Were the numerator[s] and denominator[s] for the parameter of interest appropriate?	1
Total	**6 points**
Summary item on the overall risk of study bias [low, moderate or	

high]	

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10 items. This approach is consistent with the Cochrane and GRADE [GRADE=Grading of Recommendation, Assessment, Development and Evaluation] working group(24) recommendation or approaches. Furthermore, as summarized in the PRISMA [PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses] elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful,(25) hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low [1] or high risk of bias [0]. If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item.(19,26,27)

Data analysis

We hypothesise that there will be substantial statistical heterogeneity in study results because prevalence of LTBI and TB disease varies by distribution of socioeconomic determinants of health and HIV prevalence within and across settings, among other factors. *A priori*, random effects meta-analysis will be preferred due to the anticipated heterogeneity. However, choice of random-effects or fixed effects modelling will be based on observed statistical heterogeneity. For the latter, we will not pool the results but summarise findings in a narrative format. Additionally, we will derive Annual Risk of LTBI using the formulae: 1-[1-Prevalence] $^{1/[\text{mean age}]}$ for every year of adolescence. We will then describe the relationship between the annual risk of TB infection and observed TB prevalence from our review. Alternatively, for countries with insufficient data, we will describe the relationship between

the Annual Risk of TB Infection and reported TB notification [or incidence rates estimates] by National TB Programs or estimates from the WHO.

In random effects modelling, effect measures are assumed to vary between studies and the summary effect is the weighted average of the effects reported in different studies.(28) This model directly adjusts for inverse of the standard error, and thus indirectly for the sample size reported in studies. Thus, studies with smaller standard error and larger sample sizes will be given more weight in the calculation of the pooled prevalence and 95% confidence intervals.

Data synthesis

Our outcome will be combined and calculated using the Cochrane Review Manager [*RevMan*] statistical software,(29) according to the statistical guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions.*(26) If statistical heterogeneity is observed, the random effects model will be chosen over the fixed effects model. If there is substantial statistical heterogeneity, we will not perform a meta-analysis; a narrative, qualitative summary will be done supported by a table [Supplementary File 5] and figures, where appropriate. This will be done by the first reviewer and checked by the second reviewer for accuracy.

Assessment of reporting biases

The potential for publication or reporting bias will be explored by funnel plots if we obtain at least 10 articles. This will be done by visually assessing asymmetry of funnel plots. As suggested by Egger et al, asymmetry of funnel plots will indicate presence of publication bias.(30) We appreciate that our choice of considering articles reported in English only [language bias] and the fact that we are only searching in a sample of bibliographic databases may be a source of reporting bias.

Assessment and management of heterogeneity

We anticipate clinical and statistical heterogeneity in prevalence rate estimates within and across settings and countries. Statistical heterogeneity will be quantified using the I^2 test statistic to determine the extent of variation in effect estimates that is due to heterogeneity rather than chance. Statistical heterogeneity will be explored graphically by inspection of forest plots [i.e. the 'eyeball test']. Non-overlap of 95% confidence intervals will suggest remarkable heterogeneity. A formal test for statistical homogeneity, the Cochran's χ^2 Q test statistic, will be performed using an alpha cut-off level of 10% as suggested by Higgin's et al(31) and Cochrane(32), due to the test statistic's low power in detecting heterogeneity, particularly when the number of studies is low. The I^2 test statistic will be used to quantify statistical heterogeneity between studies i.e. provide percentage of observed total variation across studies that is due to real heterogeneity rather than chance. This will provide a quantitative measure of heterogeneity. Cochrane provides the following rough guide to interpretation of heterogeneity: 0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; 75% to 100%: considerable heterogeneity.(33) If substantial heterogeneity is observed, we will try to explain the source of heterogeneity by subgroup analysis and/or sensitivity analysis.

Subgroup analysis

Subgroup analysis will be done in order to obtain estimates that are reflective, and thus potentially more useful and applicable, for specific sub-population groups or settings, and will be conducted along the following strata, subject to availability of sufficient data; [1] schooling status- adolescents in school vs those not in school; [2] country of study participants; [3] age [4] gender; [5] years of data collection, i.e. 1990-1999, 2000-2016 and 1990-2016; and [6] diagnostic modality of LTBI and TB disease. The analysis along the

strata of years of data collection i.e. 1990-1999 and 2000-2016 will be done in order to account for differences attributable to the advent of wide and free availability of anti-retroviral therapy, although we appreciate that HIV prevalence is generally very low among adolescents as compared to adults.

Sensitivity analyses

Sensitivity analyses will be conducted to explore the source of heterogeneity i.e. determine impact of specific studies on pooled prevalence estimate, by exclusion of studies with low quality scores and thus higher risk of bias. We will also explore exclusion of studies with deficiency in specific items on the 10-point modified Hoy et al quality assessment tool, in order to evaluate impact of this exclusion on pooled prevalence estimates.

Ethics

Given that we will utilise published anonymised data, which is publicly available and peer-reviewed, ethical approval is not required for this study.

Dissemination [Reporting of this review]

Our review will be reported, as much as possible, in keeping with the Preferred Reporting Items for Systematic reviews and Meta-Analyses [*PRISMA*] Statement,(34) and will include the PRISMA check-list [or adapted as practicable]. Our findings will be published in a peer-reviewed journal and as part of a doctoral thesis at the University of Cape Town.

Synthesis of evidence

The *Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for protocols* [PRISMA-P](15,16) recommends gauging of overall judgement of quality of evidence from obtained articles and indicates increasing support and use of *the Grading of Recommendations Assessment, Development and Evaluation* [GRADE] working group(24)

methodology. We will consider methodological quality of included studies and strength of evidence and adapt the basic principles of the GRADE approach.

Competing interest statement

None. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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All authors have completed the ICMJE uniform disclosure at www.icmje.org/coi_disclosure.pdf. The financial assistance of the National Research Foundation [NRF] towards the first author's PhD studies is hereby acknowledged. However, this funding is not specific to this review. Opinions expressed and conclusions arrived at, are those of the authors and are not necessarily attributed to the NRF. EWB initiated the research. This research is not done on behalf of or commissioned by the NRF, but is conducted as part of a PhD at the University of Cape Town. The first author [EB] would also like to appreciate supplementary departmental scholarship and support towards his PhD studies from the University of Cape Town [SATVI programme@UCT], of which this publication is a part of. No specific sponsor is associated with our review.

Author contributorship statement

Erick Wekesa Bunyasi conceptualised and designed the study. 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 were involved in development of the study protocol. Erick Wekesa Bunyasi prepared the first draft of the manuscript with supervision from Hennie Geldenhuys, Robin

Wood and Mark Hatherill. 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 critically reviewed, revised and approved the subsequent and final version of the protocol. Erick Wekesa Bunyasi is the guarantor. Erick Wekesa Bunyasi and Bey-Marrie Schmidt will perform the study search, screening and extraction of data under the guidance of Hennie Geldenhuys, Robin Wood and Mark Hatherill.

Provenance and peer review: Not commissioned; externally peer reviewed.

Amendment procedure

In the event that amendment to this protocol is required, we will describe the change and give the rationale in the methods section of the published review. EB will ultimately be responsible for approving, documenting, and implementing any amendments.

Data sharing

The authors declare that this research protocol is an original work. Results from the study completed using this protocol will be published in a peer-reviewed journal.

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PRISM-P checklist of items to be reported in a systematic review

Domain	Line item & PRISM-P code	Page
Section 1: Administrative information		
1. Title:		
	Identification [1a]	1
	Update [1b]	NA
2. Registration	Registration [2]	4
3. Authors:		
	Contact [3a]	1
	Contributions [3b]	21
4. Amendments	Amendments [4]	21
5. Support:		
	Sources [5a]	20-21
	Sponsor [5b]	21
	Role of sponsor or funder [5c]	21
Section 2: Introduction		
6. Rationale	Rationale [6]	8
7. Objectives	Objectives [7]	8, 9
Section 3: Methods		
8. Eligibility	Eligibility criteria [8]	10, 11
9. Information	Information sources [9]	12
10. Search	Search strategy [10]	11
11. Study records:		
	Data management [11a]	13
	Selection process [11b]	12
	Data collection process [11c]	12, 13
12. Data	Data items [12]	13
13. Outcomes	Outcomes and prioritization [13]	10
14. Bias	Risk of bias in individual studies [14]	14-16
15. Data synthesis		
	Quantitative synthesis criteria [15a]	17-18
	Appropriateness of data for synthesis [15b]	17-18
	Sensitivity and subgroup analyses [15c]	19
	Qualitative synthesis? [15d]	17-18
16. Meta-bias(es)	Meta-bias(es) [16]	14
17. Confidence in cumulative evidence	Assessment of strength of cumulative evidence [17]	14

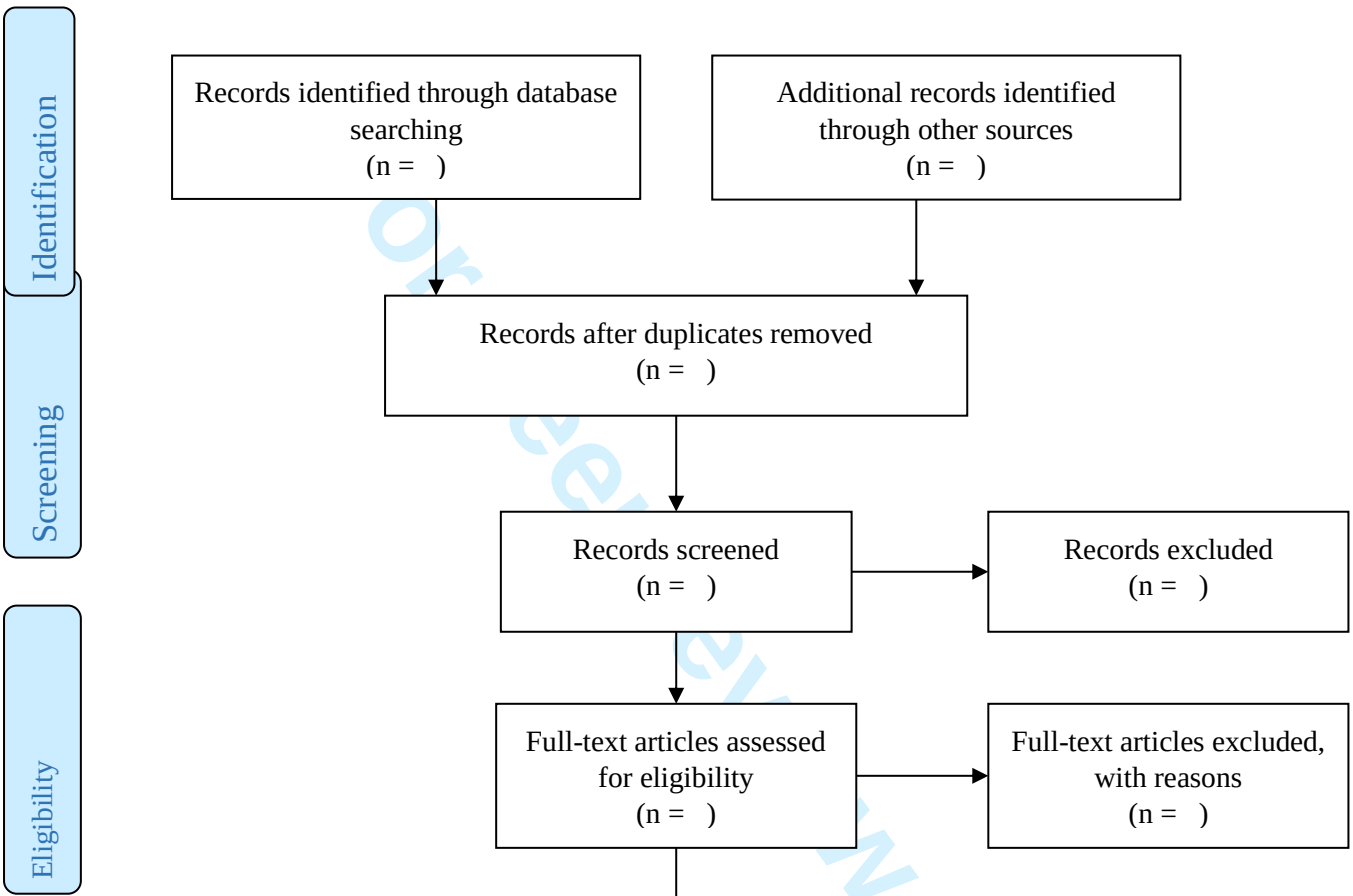
(PRISM-P=Preferred Reporting Items for Systematic Review-Protocol)

Search strategy

Item	Search term	Boolean operator
Adolescents	("adolescent"[All Fields] OR "adolescence"[All Fields] OR "adolescent" [MeSH Terms] OR "adolescence" [MeSH Terms] OR "teen*"[All Fields] OR "child" [All Fields] OR "person" [All Fields] OR "persons" [MeSH Terms] OR "people" [All Fields])	AND
Tuberculosis	("tuberculosis"[All Fields] OR "tuberculosis"[MeSH Terms] OR "TB"[All Fields] OR "TB"[MeSH Terms] OR "LTBI"[MeSH Terms] OR "LTBI"[All Fields] OR "latent"[MeSH Terms] OR "latent"[All Fields])	AND
Countries	("Africa" [All Fields] OR "Africa" [MeSH Terms] OR "east*" [All Fields] OR "south*" [All Fields] OR "Congo" [All Fields] OR "Zaire" [All fields] OR "Ethiopia" [All Fields] OR "Kenya" [All Fields] OR "Uganda" [All Fields] OR "Tanzania" [All Fields] OR "Zimbabwe" [All Fields] OR "South Africa" [All Fields] OR "Mozambique" [All Fields] OR "Nigeria" [All Fields] OR "Angola" [All Fields] OR " Sierra Leone " [All Fields] OR ["Central" AND "African" AND "Republic"] [All Fields] OR "Lesotho " [All Fields] OR "Liberia " [All Fields] OR "Namibia " [All Fields] OR "Zambia " [All Fields] OR "Botswana " [All Fields] OR "Cameroon " [All Fields] OR "Chad" [All Fields] OR " Ghana " [All Fields] OR "Guinea-Bissau " [All Fields] OR "Malawi " [All Fields] OR "Swaziland " [All Fields] OR "Somalia" [All Fields])	AND
Prevalence	("epidemiology"[Subheading] OR "epidemiology"[MeSH Terms] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms]	AND
Time period	Between 1st January 1990 and 1st July 2016	

*Covers both Democratic Republic of Congo and Congo

PRISMA 2009 flow diagram



Data Extraction Form

Part A: Cover sheet summary

Study ID …… Initials of eligibility assessor …….

Title of the study ……..

……..

Publication year ……..

Part B: Study characteristics

Outcome: Note: if other is selected, study is excluded. □ TB disease prevalence □ LTBI prevalence □ Other ……

Country of study Note: if non-high-TB burden country is selected, study is excluded.

□ High-TB burden country (state)…… □ Non-high-TB burden country

Study design Note: if other is selected, study is excluded.

□ Cross-sectional study

□ Cohort study

□ Other. State if other …….

Population

□ Non-students

□ Students

□ Both {(General population including students and non-students) state proportion that is students, if defined/obtainable ……..

□ Undefined …….

Diagnostic modality for TB disease or latent TB infection

TB disease	**Prevalence**
	n/N
Clinical	
Sputum smear for AFB	
Solid or liquid culture	
Xpert MTB/RIF assay	
Other microbiological. If yes, state ……. ……	
X-ray	
Latent TB infection	
Interferon Gamma Release Assay	
Tuberculin Skin Test	
Other. If yes, state & exclude …….	

Age range of study participants (Please include percentage aged 10-19 years. If disaggregated data are not obtainable and proportion of individuals aged 10-19 years is less than 75%, the study will be excluded) ……..……..……

Gender of study participants

Gender	**n/N**	**%**	**No. with LTBI**	**No. with TB disease**
Male				
Female				
Total		**100%**		

Legend: No=Number

Decision on inclusion/exclusion

□ Included

□ Excluded. Primary reason …….

□ Unsure. Reason (including need to contact authors) …….

……...

Other comments ……

……..

Part C: Quality assessment

Item under review	Score awarded (Yes=1 or No=0)
External Validity	**…**
Was the study's target population a close representation of the national population in relation to relevant variables?	…
Was the sampling frame a true or close representation of the target population?	…
Was some form of random selection used to select the sample, OR was a census undertaken?	…
Was the likelihood of non-response bias minimal?	…
Internal validity	**…**
Were data collected directly from the participants (as opposed to a proxy)?	…
Was an acceptable case definition used in the study?	…
Was the study instrument that measured the parameter of interest shown to have validity and reliability?	…
Was the same mode of data collection used for all participants? (1 point)	…
Was the length of the shortest prevalence period for the parameter of interest appropriate?	…
Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	…
Total	**…**

Summary item on the overall risk of study bias: low, moderate or high risk of bias

Legend: As described by Hoy et al, the summary assessment evaluates the overall risk of study bias and is based on the rater's subjective judgment given responses to the preceding 10 items. This approach is consistent with the Cochrane and GRADE (GRADE=Grading of Recommendation, Assessment, Development and Evaluation) working group (26) recommendation or approaches. Furthermore, as summarized in the PRISMA (PRISMA= The Preferred Reporting Items for Systematic reviews and Meta-Analyses) elaboration document, summative scales that numerically summarize multiple components into a single number are misleading and unhelpful (27), hence our choice of an overall ordinal scale for risk of bias. Response options for individual items are either low (1) or high risk of bias (0). If there is insufficient information in the article to permit judgment of a particular item, then the article is deemed to be at high risk of bias with respect to that item (21,28,29).

Data Summary Table

Country	Author	TB or LTB		Sampling	Sampling	Sampling	Age range	Prevalence (%: 95% CI)			Diagnostic method	Overall quality score
		TB	LTBI	Size	Strategy	Response rate		Male	Female	Total		

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