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Keywords:	Bacille Calmette-Guerin (BCG), Revaccination, Tuberculosis < INFECTIOUS DISEASES

A systematic review protocol on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis.

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ABSTRACT

Introduction

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis*. Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. Since 1921, the bacille Calmette-Guerin (BCG) vaccine derived from a live, attenuated strain of *Mycobacterium bovis* has been used for the prevention of TB in humans worldwide. Evidence from previous randomized trials show that the efficacy of primary BCG vaccination against pulmonary TB ranged from no protection to very high protection. In addition, some studies suggest a benefit of BCG revaccination. For example, a recent trial conducted in South Africa showed that BCG revaccination of adolescents could reduce the risk of TB infection by half. However, we are not aware of any recent systematic reviews of the effects of BCG revaccination. Thus the need for this systematic review of the effects of BCG revaccination on protection against TB infection and disease.

Method and analysis

We will search PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, WHO International Clinical Trials Registry Platform, and reference lists of relevant publications for potentially eligible studies. We will screen search outputs, select eligible studies, extract data, and assess risk of bias in duplicate. Discrepancies will be resolved by discussion and consensus or arbitration. We will use the Grading of Recommendations Assessment, Development and Evaluation method to assess the certainty of the evidence. The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.

Ethics and dissemination

Publicly available data will be used, hence no formal ethical approval will be required for this review. The findings of the review will be disseminated through conference presentations and publication in an open-access peer reviewed journal.

PROSPERO registration number is: CRD42018105916

Strengths and limitations of this study:

- ✓ A comprehensive search will be conducted to ensure that we obtain an unbiased summary of intervention effects for potentially eligible trials.
- ✓ During the systematic review, selection of records, data collection, assessment of the risk of bias, and judgement of the strength of evidence will be performed in duplicate.
- ✓ This review will include non-randomized trials which are more prone to bias than randomized trials. However, to minimize the effect of the bias, we will perform subgroup analyses by study design.
- ✓ The protocols of industry trials may be more likely to be confidential due to commercially sensitive information, hence we may miss ongoing industry-funded trials which are not available from the WHO International Clinical Trials Registry Platform.

INTRODUCTION

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis* (*MTB*). Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. More than 1.7 billion people are estimated to be infected with *MTB*, of these only between 5-15% will develop TB disease in their lifetime.[1] In 2016, an estimated 10.4 million people were recorded to have fell ill with TB globally. Adults contributed 90%, with male contributing 65% and 10% TB incident cases were people living with the human immunodeficiency virus (HIV). The latter have a higher risk of developing TB disease, estimated to be between 16-27 times greater than HIV negative people.[2] An estimated 1.3 million TB deaths were recorded in 2016, among HIV negative people with an additional 374 000 deaths among people living with HIV.[1]

Among healthy adults with immunological evidence of pre-exposure to *MTB*, the overall lifetime risk of progressing to active disease is between 5-10% if not treated, and this will happen when the body ‘s immune system is weakened, months or years after the primary infection.[3] The most vulnerable populations with higher probability of developing active TB

disease are young children, diabetic patients, and people living with HIV.[4-6] A study by Marais *et al,* showed that 50% of infants with evidence of latent TB infection if untreated will progress to active TB disease.[7] To reduce the pool of active TB cases an early diagnosis and treatment is required for those people with latent TB infection, particularly in high risk groups such as those co-infected with HIV.[8]

Over the years it has been shown that using long courses of multiple antibiotics TB can be treated, but the spread of multi-drug resistant tuberculosis (MDR-TB) and the rise of HIV makes TB one of the largest threats to public health globally.[1] In a study conducted by Daftary *et al*, it was shown that biological factors such as HIV and the spread of MDR-TB, alongside social determinants such as poor housing and poverty as well as structural determinants such as economic inequalities and rapid urbanization of populations plays a very important role in the spread of TB through vulnerable populations.[9]

Since 1921, the bacille Calmette-Guerin (BCG) vaccine derived from a live, attenuated strain of *Mycobacterium bovis* has been used for the prevention of TB in humans. Annually, with approximately 100 million vaccinations given to newborn children, BCG vaccine is the most widely used vaccine around the world.[10] In children under 5 years, immunization with BCG is thought to reduce hematogenous spread of *MTB* from the site of primary infection which may result in severe disease, such as milliary TB and TB meningitis.[11] Studies conducted in the past showed that its efficacy varies ranging from zero to 80% against pulmonary TB,[12-15] and over 70% against TB meningitis.[16-18] Other systematic reviews in the past found substantial variation between trials on the protective efficacy of BCG against pulmonary TB,[19 20] and in one review 50% average protective efficacy was estimated.[19]

There are several regimens for BCG vaccination such as: i) routine administration of all newborns, ii) administration to selected newborns at risk, iii) to all adolescents, iv) only to selected high risk groups or when tuberculin negative, or v) it may be given later in life to those without immunity.[21] Revaccination with two or more doses was proposed to boost immunity. However, the tuberculin response is not associated with protective benefit derived from BCG vaccination and there is no evidence that a waning of tuberculin sensitivity with time equates to a loss of TB immunity. However, currently there is no vaccine which is effective for the

prevention of TB disease in adults either before or after exposure to TB infection. Currently there are 13 TB vaccines in Phase 1, Phase II or Phase III trials around the world and a new TB vaccine remains an important global research priority.[1]

BCG revaccination is still used in some TB endemic countries around the world. In February 2018, WHO recommended that for persons who have received BCG vaccination, repeat vaccination is not recommended as scientific evidence does not support this practice.[1] Evidence from a systematic review published in 2013 suggested that BCG revaccination conferred no additional protection from TB.[22] However, at least one new study published since then suggests a benefit of BCG revaccination.[23]

OBJECTIVE

The aim is to assess the effects of BCG revaccination against tuberculosis infection and active tuberculosis disease.

METHODS

Patient and public involvement

The review uses already published data, hence patients were not involved in the design of this study. However, patient's experiences, preference, and priorities informed the development of the research question and outcome measures as reported in the literature in support of this review. The findings of this review will provide governments, policy makers, patients, and the scientific community in the field of vaccinology with the evidence of the efficacy of BCG revaccination.

Criteria for considering studies for this review

Types of studies

We will include randomized trials, non-randomized trials, case-control studies, and cohort studies.

Types of participants

Any person regardless of age.

Types of intervention

BCG revaccination compared to no revaccination, placebo, or another vaccine.

Types of outcome measures

Primary outcomes measures

(i) The incidence of TB disease (pulmonary tuberculosis and extra-pulmonary tuberculosis),

(ii) TB infection (i.e. latent tuberculosis), diagnosed by interferon gamma release assay (IGRA) or tuberculin skin test (Mantoux) without clinical or radiological evidence of active tuberculosis disease.

Secondary outcomes

(i) Adverse reactions (mild or severe),

(ii) Deaths (due to tuberculosis and from any causes),

(iii) Immunogenicity (i.e. the ability of BCG vaccine to induce an immune response including antibody- and/or cell-mediated immunity in a vaccinated individual), as defined by the primary study authors.

Search methods for identification of eligible studies

We have developed a comprehensive search strategy for peer-reviewed and grey literature to identify all potential studies regardless of language or publication status (i.e. published, unpublished, in press, and in progress). Eligible studies must report at least one of our primary or secondary outcomes of interest.

Electronic searches

We will conduct our search to build a comprehensive search strategy that will be used to search the following databases: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, WHO International Clinical Trials Registry Platform (ICTRP) and reference lists of

relevant publications for potentially eligible studies. The proposed search strategy for PubMed is provided in **Table 1**.

Searching other resources

We will search reference lists of relevant publications, including eligible studies, related reviews, and relevant WHO vaccine position papers.

Data collection and analysis

Selection of studies

Two review authors (PWM and EJM) will independently screen the titles and abstracts of all records retrieved by the search strategy above, for potentially eligible studies. We will obtain full-texts for all the potentially eligible studies. Two authors (PWM and EJM) will assess and compare these full-text publications for eligibility. We plan to translate full-texts of potentially eligible studies which are not written in English before assessing for eligibility. Any disagreements between the two review authors regarding study eligibility, will be resolved by discussion and consensus. A third author will arbitrate any unresolved disagreements. We will provide a table with the characteristics of the included studies, and another of excluded studies with reasons for their exclusion. We will seek additional information, for studies with missing information, to assist us in our decision-making process. The study selection process will be illustrated in a PRISMA diagram.

Data extraction and management

One author (PWM) will design the data extraction form in agreement with the review team, two review authors (PWM and EJM) will pilot the form, discuss, and resolve any differences by consensus; failing which a third author (DN) will arbitrate. For each included study, the two authors will independently extract information using the piloted data extraction form. Data extracted will include study details (number of participants, and geographical locations);

intervention details (number of participants, number of doses, and type of vaccine); comparator details (number of participants and type of comparator used); outcome details and funding sources. Any differences in data extraction between the two review authors will be resolved through discussion and consensus. The third author will be consulted to arbitrate if disagreements persist between the two authors. We will contact the authors and request for more information, if any selected study has incomplete or missing data. We will include the study in the review, if the authors provide no additional information. However, we will not synthesize the findings that are unavailable with findings from other included studies addressing the relevant outcome.

Assessment of risk of bias in included studies

Two authors (CSW and MS) will assess the risk of bias independently using the Cochrane Risk of Bias tool for trials,[24] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[25] resolving discrepancies by discussion and consensus. If disagreements persist a third author will arbitrate (PWM).

The Cochrane Risk of Bias tool for trials includes information for assessment of the risk of selection bias (adequacy of the generation of the allocation sequence and allocation concealment), detection bias (blinding of outcome assessors), attrition bias (completeness of outcome data), and reporting bias (completeness of outcome reporting).[24]

The ROBINS-I tool includes information for assessment of the risk of bias at three different stages (i.e. pre-intervention, intervention, and post-intervention). For the pre-intervention stage we will assess selection bias (due to selection of participants into the study and confounding); at the intervention stage we will assess "classification of interventions" bias (introduced either by differential or non-differential misclassification of intervention status); and at the post-intervention stage we will assess performance bias (due to deviations from intended interventions), attrition bias (due to missing data), detection bias (in the measurement of outcomes) and outcome reporting bias (in selection of the reported result).[25]

Dealing with missing data

We will assess missing data to see if it is related to the outcome. If there is missing or unclear information or restrictions to use the study, we will contact study investigators and request the missing information. For older publications it is anticipated that it may not be possible to reach the authors. Only the available data will be analyzed if there is missing data. We may use imputation and perform sensitivity analyses to investigate the impact of missing data, if the amount of incomplete outcome data is such that the trial is thought to be at a high risk of bias.

An intention to treat (ITT) analysis will be used for all outcomes where a treatment received analysis will be done, except with adverse effects. We will further assess whether the published endpoints match those specified and whether outcome measures are specified *a priori* in study protocols. To determine the proportion of missing results and whether the missing data affects the results or not in terms of effect size and event risk, each included trial will be assessed for incomplete outcome data.

We will also assess if reasons for missing data are related to adverse events or death from BCG revaccination. In order to have an overall decision on risk associated with incomplete outcome we will assess if the missing data was balanced in the different studies. High risks of bias will include extreme differences in baseline characteristics, stopping the trial before completion without clear reasons and influence by funders.

To determine adverse effects and adverse events methods used previously in systematic reviews will be used. All trials included will be assessed for risk of bias by examining whether all participants were included; whether participants and outcome assessors were blinded; whether data analysis was independent of pharmaceutical companies; whether the outcome data reporting was complete; and if monitoring was active or passive.[26] To adequately assess the risk of bias where there is insufficient information to assess the risk of bias, authors will be contacted to obtain needed information.

Assessment of reporting biases

We will use a funnel plot to assess for publication bias, if we have more than 10 studies are included for meta-analysis.

Data synthesis

For all included studies, data will be analyzed using RevMan 5.[27] We will use the risk ratio (RR) and its corresponding 95% confidence interval (CI) to summarize binary data. For studies with similar participants, interventions, outcomes, and study designs, we will combine study data using the random-effect method of meta-analysis. The level of heterogeneity will be determined by inspecting forest plots for overlapping CIs and by examining the Chi² P value. The degree of heterogeneity will be quantified using the I^2 test. An I^2 statistic value of > 40% and a Chi² P value significance level of ≤ 0.1 will be regarded as showing important heterogeneity. In case of heterogeneity we will investigate the causes using subgroup analyses. We will define subgroups based on age of the participants (children versus adults), the timing of the first dose of BCG vaccination (immediately versus four or more weeks after birth), age of revaccination, the level of immune response and country income status. Data from studies that are similar enough will be quantitatively synthesized using a meta-analysis with random-effects. In the event of significant heterogeneity, a Meta-analysis will not be performed. Instead, the data will be synthesized using a narrative synthesis. We will perform sensitivity analysis, by assessing results after excluding trials that have unclear or high risk of bias.

Reporting review findings

The strength or certainty of the evidence will be assessed using the Grade of Recommendations Assessment, Development and Evaluation (GRADE) approach,[28] which rates the certainty of evidence for each outcome by taking into consideration the directness of evidence, risk of bias, risk of publication bias, precision and heterogeneity. A table for 'Summary of findings', will be constructed which will review findings for outcomes listed under the 'Types of outcome measures' section.

Timeline for the systematic review

The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.[29] The search strategy will be finalized in February 2019, we plan to conduct the searches and studies eligibility selection between

February and April 2019; and to collect data, conduct statistical analyses, and prepare and submit the manuscript to a peer-reviewed journal between May and August 2019.

Ethics and dissemination

No formal ethical approval is required for this review, because we will use already published data. The findings of this review will provide donors, health workers, policy makers, patients, and the scientific community in the field of vaccinology with the evidence for decision making with regards to the benefits of BCG revaccination in adolescents and adults populations. In the face of no MTB vaccine currently available for adult populations, this might improve the immediate and long-term measures to eradicate TB. The findings of this review will be presented at relevant conferences and published in a peer-reviewed journal. This protocol has been written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines,[30] and the findings of this review and any amendments will be reported according to the PRISMA statement.[31]

Contributors

PWM led the development of the protocol, wrote the first draft, coordinated and integrated comments from co-authors, approved the final version for publication and is the guarantor of the manuscript. DN, EM and MS critically revised successive drafts of the manuscript, provided important intellectual input and approved the final version of the manuscript. CSW conceived the study, provided supervision and mentorship to PWM, critically revised successive drafts of the manuscript, provided important intellectual input and approved the final version of the manuscript.

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Competing interests

None declared.

Patients consent

Not required

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Table 1. Search strategy

Search	Query
#1	Search BCG OR "bacille calmette guerin" OR "Bacille calmette-guerin" OR BCG VACCINE [MH]
#2	Search REVACCINATION OR REVACCINATE OR ((secondary immuni*[TW]) OR (booster immuni*[TW]) OR (revaccin*[TW]) OR ("booster" [TW]) OR ("Immunization, Secondary"[Mesh])))
#3	Search #1 AND #2
#4	Search NOT (animals[mh] NOT humans[mh]))
#5	Search #4 AND TUBERCULOSIS[MH:EXP]

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	2
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes	11
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	11
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	11
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	11
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	5-6
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	Yes	Table 1.

		it could be repeated		supplementary material
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	Yes	7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	8-9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	9-10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	9
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	10

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Key words:

Bacille Calmette-Guerin (BCG), Revaccination, Tuberculosis

ABSTRACT

Introduction:

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis* (M.TB) and other species of the Mycobacterium tuberculosis complex. Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. Since 1921, the bacille Calmette-Guerin (BCG) vaccine derived from a live, attenuated strain of *Mycobacterium bovis* has been used for the prevention of TB in humans worldwide. Evidence from previous randomized trials show that the efficacy of primary BCG vaccination against pulmonary TB ranged from no protection to very high protection. In addition, some studies suggest a benefit of BCG revaccination. For example, a recent trial conducted in South Africa showed that BCG revaccination of adolescents could reduce the risk of TB infection by half. However, we are not aware of any recent systematic reviews of the effects of BCG revaccination. Thus, the need for this systematic review of the effects of BCG revaccination on protection against TB infection and disease.

Method and analysis

We will search PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, WHO International Clinical Trials Registry Platform, and reference lists of relevant publications for potentially eligible studies. We will screen search outputs, select eligible studies, extract data, and assess risk of bias in duplicate. Discrepancies will be resolved by discussion and consensus or arbitration. We will use the Grading of Recommendations Assessment, Development and Evaluation method to assess the certainty of the evidence. The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.

Ethics and dissemination

Publicly available data will be used, hence no formal ethical approval will be required for this review. The findings of the review will be disseminated through conference presentations and publication in an open-access peer reviewed journal.

PROSPERO registration number is: CRD42018105916

Strengths and limitations of this study:

- ✓ A comprehensive search will be conducted to ensure that we obtain an unbiased summary of intervention effects for potentially eligible trials.
- ✓ During the systematic review, selection of records, data collection, assessment of the risk of bias, and judgement of the strength of evidence will be performed in duplicate.
- ✓ This review will include non-randomized trials which are more prone to bias than randomized trials. However, to minimize the effect of the bias, we will perform subgroup analyses by study design.
- ✓ Diagnosing latent TB infection (LTBI) using the tuberculin skin test (TST) has several limitations due to its sensitivity and specificity. A positive result may be observed in people with prior BCG vaccination or exposure to nontuberculous mycobacteria. Based on these limitations TST results will be interpreted with caution considering the pretest risk of reactivation or M.TB infection. Therefore, given these limitations a subgroup analysis based on the QuantiFERON-TB Gold tests alone will be performed.

INTRODUCTION

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis* (M.TB) and other species of the Mycobacterium TB complex. Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. More than 1.7 billion people are estimated to be infected with TB, of these only between 5-15% will develop TB disease in their lifetime.[1] In 2016, an estimated 10.4 million people were recorded to have fallen ill with TB globally. Adults contributed 90%, with male contributing 64%; and 9% TB incident cases were people living with the human immunodeficiency virus (HIV)[1]. The latter have a higher risk of developing TB disease, estimated to be between 16-27 times greater than HIV negative people.[2] An estimated 1.3 million TB deaths were recorded in 2017 among HIV negative people, with an additional 300 000 deaths among people living with HIV.[1]

Among healthy adults with immunological evidence of pre-exposure to M.TB, the overall lifetime risk of progressing to active disease is between 5-10% if not treated, and this will happen when

the body 's immune system is weakened, months or years after the primary infection.[3] The most vulnerable populations with higher probability of developing active TB disease are young children, diabetic patients, and people living with HIV.[4-6] A study by Marais *et al,* showed that 50% of infants with evidence of latent TB infection (LTBI) if untreated will progress to active TB disease.[7] To reduce the pool of active TB cases an early diagnosis and treatment is required for those people with LTBI, particularly in high risk groups such as those co-infected with HIV.[8]

Over the years it has been shown that using long courses of multiple antibiotics, TB can be treated, but the spread of multi-drug resistant TB (MDR-TB) and the rise of HIV makes TB one of the largest threats to public health globally.[1] In a study conducted by Daftary *et al*, it was shown that biological factors such as HIV and the spread of MDR-TB, alongside social determinants such as poor housing and poverty as well as structural determinants such as economic inequalities and rapid urbanization of populations play a very important role in the spread of TB through vulnerable populations.[9]

Since 1921, the bacille Calmette-Guerin (BCG) vaccine derived from a live, attenuated strain of *Mycobacterium bovis* has been used for the prevention of TB in humans. Annually, with approximately 100 million vaccinations given to newborn children, BCG vaccine is the most widely used vaccine around the world.[10] In children under 5 years, immunization with BCG is thought to reduce hematogenous spread of M.TB from the site of primary infection which may result in severe disease, such as milliary TB and TB meningitis.[11] Studies conducted in the past showed that its efficacy varies ranging from zero to 80% against pulmonary TB,[12-15] and over 70% against TB meningitis.[16-18] Other systematic reviews in the past found substantial variation between trials on the protective efficacy of BCG against pulmonary TB,[19,20] and in one review 50% average protective efficacy was estimated.[19]

There are several regimens for BCG vaccination such as: i) routine administration of all newborns, ii) administration to selected newborns at risk, iii) to all adolescents, iv) only to selected high risk groups or when tuberculin negative, or v) it may be given later in life to those without immunity.[21] Revaccination with two or more doses was proposed to boost immunity. However, the tuberculin response is not associated with protective benefit derived from BCG vaccination and there is no evidence that a waning of tuberculin sensitivity with time equates to a loss of TB immunity.

However, currently there is no vaccine which is effective for the prevention of TB disease in adults either before or after M.TB infection. Currently there are 13 TB vaccines in Phase 1, Phase II or Phase III trials around the world and a new TB vaccine remains an important global research priority.[22] A study conducted in Kenya, Zambia, South Africa and Tanzania by Van Der Meeren *et al*, assessed the safety and efficacy of M72/AS01$_E$ tuberculosis vaccine and showed a 54% protection against pulmonary TB disease in individuals infected with M.TB. The results from this study represent a positive step forward in the fight against TB.[23]

BCG revaccination is still used in some TB endemic countries around the world. In February 2018, WHO recommended that for persons who have received BCG vaccination, repeat vaccination is not recommended as scientific evidence does not support this practice.[22] Evidence from a systematic review published in 2013 suggested that BCG revaccination conferred no additional protection from TB.[24] However, at least one new study published since then suggests a benefit of BCG revaccination.[25]

OBJECTIVE

The aim is to assess the effects of BCG revaccination against M.TB infection and active TB disease.

METHODS

Patient and public involvement

The review uses already published data, hence patients were not involved in the design of this study. However, patient's experiences, preference, and priorities informed the development of the research question and outcome measures as reported in the literature in support of this review. The findings of this review will provide governments, policy makers, patients, and the scientific community in the field of vaccinology with the evidence of the efficacy of BCG revaccination.

Criteria for considering studies for this review

Types of studies

We will include randomized trials, non-randomized trials, case-control studies, and cohort studies.

Types of participants

Any person regardless of age.

Types of intervention

BCG revaccination compared to no revaccination, placebo, or another vaccine.

Types of outcome measures

Primary outcomes measures

(i) TB disease (pulmonary TB and extra-pulmonary TB),

(ii) M.TB infection (i.e. latent TB), diagnosed by interferon gamma release assay (IGRA) or tuberculin skin test (Mantoux) without clinical or radiological evidence of active TB disease.

Secondary outcomes

(i) Adverse reactions (mild or severe),

(ii) Deaths (due to TB and from any causes),

(iii) Immunogenicity (i.e. the ability of BCG vaccine to induce an immune response including antibody- and/or cell-mediated immunity in a vaccinated individual), as defined by the primary study authors. It should be noted that we do not have an immune correlate of protection, so we do not know which immune response is protective.

Search methods for identification of eligible studies

We have developed a comprehensive search strategy for peer-reviewed and grey literature to identify all potential studies regardless of language or publication status (i.e. published, unpublished, in press, and in progress). Eligible studies must report at least one of our primary or secondary outcomes of interest.

Electronic searches

We will conduct our search to build a comprehensive search strategy that will be used to search the following databases: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, WHO International Clinical Trials Registry Platform (ICTRP) and reference lists of relevant publications for potentially eligible studies. The proposed search strategy for PubMed is provided in **Table 1**.

Table 1. Search strategy

Search	Query
#1	Search BCG OR "bacille calmette guerin" OR "Bacille calmette-guerin" OR BCG VACCINE [MH]
#2	Search REVACCINATION OR REVACCINATE OR ((secondary immuni*[TW]) OR (booster immuni* [TW]) OR (revaccin*[TW]) OR ("booster" [TW]) OR ("Immunization, Secondary"[Mesh]))
#3	Search #1 AND #2
#4	Search #3 not NOT (animals[mh] NOT humans[mh]))
#5	Search #4 AND Tuberculosis[MH:EXP]

Searching other resources

We will search reference lists of relevant publications, including eligible studies, related reviews, and relevant WHO vaccine position papers.

Data collection and analysis

Selection of studies

Two review authors (PWM and EJM) will independently screen the titles and abstracts of all records retrieved by the search strategy above, for potentially eligible studies. All studies which are not eligible after screening of titles and abstracts will be excluded. We will obtain full-texts for all the potentially eligible studies. Two authors (PWM and EJM) will assess and compare these full-text publications for eligibility. We plan to translate full-texts of potentially eligible studies which are not written in English before assessing for eligibility. Any disagreements between the two review authors regarding study eligibility, will be resolved by discussion and consensus. A

third author will arbitrate any unresolved disagreements. We will provide a table with the characteristics of the included studies, and another of excluded studies with reasons for their exclusion. We will seek additional information, for studies with missing information, to assist us in our decision-making process. The study selection process will be illustrated in a PRISMA diagram.

Data extraction and management

One author (PWM) will design the data extraction form in agreement with the review team, two review authors (PWM and EJM) will pilot the form, discuss, and resolve any differences by consensus; failing which a third author (DN) will arbitrate. For each included study, the two authors will independently extract information using the piloted data extraction form. Data extracted will include some of the following: study details (study design, number of participants, study duration, methods used to measure outcomes and geographical locations); intervention details [number of participants, age of participants at time of administration, number of doses, and type of vaccine strain used (either BCG revaccination or another vaccine, co-interventions)]; comparator details (number of participants and type of comparator used); outcome details and funding sources. Any differences in data extraction between the two review authors will be resolved through discussion and consensus. The third author will be consulted to arbitrate if disagreements persist between the two authors. We will contact the authors and request for more information, if any selected study has incomplete or missing data. We will include the study in the review, if the authors provide no additional information. However, we will not synthesize the findings that are unavailable with findings from other included studies addressing the relevant outcome.

Assessment of risk of bias in included studies

Two authors (CSW and MS) will assess the risk of bias independently using the Cochrane Risk of Bias tool for trials,[26] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[27] resolving discrepancies by discussion and consensus. If disagreements persist a third author will arbitrate (PWM).

The Cochrane Risk of Bias tool for trials includes information for assessment of the risk of selection bias (adequacy of the generation of the allocation sequence and allocation concealment), detection bias (blinding of outcome assessors), attrition bias (completeness of outcome data), and reporting bias (completeness of outcome reporting).[26]

The ROBINS-I tool includes information for assessment of the risk of bias at three different stages (i.e. pre-intervention, intervention, and post-intervention). For the pre-intervention stage we will assess selection bias (due to selection of participants into the study and confounding); at the intervention stage we will assess "classification of interventions" bias (introduced either by differential or non-differential misclassification of intervention status); and at the post-intervention stage we will assess performance bias (due to deviations from intended interventions), attrition bias (due to missing data), detection bias (in the measurement of outcomes) and outcome reporting bias (in selection of the reported result).[27]

Dealing with missing data

We will assess missing data to see if it is related to the outcome. If there is missing or unclear information or restrictions to use the study, we will contact study investigators and request the missing information. For older publications it is anticipated that it may not be possible to reach the authors. Only the available data will be analyzed if there is missing data. We may use imputation and perform sensitivity analyses to investigate the impact of missing data, if the amount of incomplete outcome data is such that the trial is thought to be at a high risk of bias.

An intention to treat (ITT) analysis will be used for all outcomes where a treatment received analysis will be done, except with adverse effects. We will further assess whether the published endpoints match those specified and whether outcome measures are specified *a priori* in study protocols. To determine the proportion of missing results and whether the missing data affects the results or not in terms of effect size and event risk, each included trial will be assessed for incomplete outcome data.

We will also assess if reasons for missing data are related to adverse events or death from BCG revaccination. In order to have an overall decision on risk associated with incomplete outcome we will assess if the missing data was balanced in the different studies. High risks of bias will

include extreme differences in baseline characteristics, stopping the trial before completion without clear reasons and influence by funders.

To determine adverse effects and adverse events methods used previously in systematic reviews will be used. All trials included will be assessed for risk of bias by examining whether all participants were included; whether participants and outcome assessors were blinded; whether data analysis was independent of pharmaceutical companies; whether the outcome data reporting was complete; and if monitoring was active or passive.[28] To adequately assess the risk of bias where there is insufficient information to assess the risk of bias, authors will be contacted to obtain needed information.

Assessment of reporting biases

If more than ten studies are included for meta-analysis, we will use a funnel plot to assess for publication bias.

Data synthesis

For all included studies, data will be analyzed using RevMan 5.[29] We will use the risk ratio (RR) and its corresponding 95% confidence interval (CI) to summarize binary data. For studies with similar participants, interventions, outcomes, and study designs, we will combine study data using the random-effect method of meta-analysis. The level of heterogeneity will be determined by inspecting forest plots for overlapping CIs and by examining the Chi^2 P value. The degree of heterogeneity will be quantified using the I^2 test. An I^2 statistic value of > 40% and a Chi^2 P value significance level of ≤ 0.1 will be regarded as showing important heterogeneity. In case of heterogeneity we will investigate the causes using subgroup analyses. We will define subgroups based on age of the participants (children versus adults), the timing of the first dose of BCG vaccination (immediately versus four or more weeks after birth), age of revaccination, the level of immune response and country income status. Data from studies that are similar enough will be quantitatively synthesized using a meta-analysis with random-effects. In the event of significant heterogeneity, a Meta-analysis will not be performed. Instead, the data will be synthesized using a narrative synthesis. We will perform sensitivity analysis, by assessing results after excluding trials that have unclear or high risk of bias.

Reporting review findings

The strength or certainty of the evidence will be assessed using the Grade of Recommendations Assessment, Development and Evaluation (GRADE) approach,[30] which rates the certainty of evidence for each outcome by taking into consideration the directness of evidence, risk of bias, risk of publication bias, precision and heterogeneity. A table for 'Summary of findings', will be constructed which will review findings for outcomes listed under the 'Types of outcome measures' section.

Timeline for the systematic review

The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.[31] The search strategy will be finalized in February 2019, we plan to conduct the searches and studies eligibility selection between February and April 2019; and to collect data, conduct statistical analyses, and prepare and submit the manuscript to a peer-reviewed journal between May and August 2019.

Ethics and dissemination

No formal ethical approval is required for this review, because we will use already published data. The findings of this review will provide donors, health workers, policy makers, patients, and the scientific community in the field of vaccinology with the evidence for decision making with regards to the benefits of BCG revaccination in adolescents and adults populations. In the face of no M.TB vaccine currently available for adult populations, this might improve the immediate and long-term measures to eradicate TB. The findings of this review will be presented at relevant conferences and published in a peer-reviewed journal. This protocol has been written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines,[32] and the findings of this review and any amendments will be reported according to the PRISMA statement.[33]

Contributors

PWM led the development of the protocol, wrote the first draft, coordinated and integrated comments from co-authors, approved the final version for publication and is the guarantor of the manuscript. DN,

EM and MS critically revised successive drafts of the manuscript, provided important intellectual input and approved the final version of the manuscript. CSW conceived the study, provided supervision and mentorship to PWM, critically revised successive drafts of the manuscript, provided important intellectual input and all authors approved the final version of the manuscript.

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Competing interests

None declared.

Patients consent

Not required

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	11-12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes	11
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	12
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	12
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	5-6
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	Yes	Table 1. pg 7

		it could be repeated		
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	7-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	Yes	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	8,12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	11

BMJ Open

A systematic review protocol on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis.

Journal:	*BMJ Open*
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Primary Subject Heading:	Public health
Secondary Subject Heading:	Evidence based practice, Global health, Health policy, Health services research
Keywords:	Bacille Calmette-Guerin (BCG), Revaccination, Tuberculosis < INFECTIOUS DISEASES

A systematic review protocol on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis.

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Key words:

Bacille Calmette-Guerin (BCG), Revaccination, Tuberculosis

ABSTRACT

Introduction:

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis* (M.TB) and other species of the Mycobacterium tuberculosis complex. Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. The bacille Calmette-Guerin (BCG) vaccine has been used globally since 1921 for the prevention of TB in humans, and was derived from an attenuated strain of *Mycobacterium bovis*. Evidence from previous randomized trials show that the efficacy of primary BCG vaccination against pulmonary TB ranged from no protection to very high protection. In addition, some studies suggest a benefit of BCG revaccination. For example, a recent trial conducted in South Africa showed that BCG revaccination of adolescents could reduce the risk of TB infection by half. However, we are not aware of any recent systematic reviews of the effects of BCG revaccination. Thus, the need for this systematic review of the effects of BCG revaccination on protection against TB infection and disease.

Method and analysis

We will search PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, WHO International Clinical Trials Registry Platform, and reference lists of relevant publications for potentially eligible studies. We will screen search outputs, select eligible studies, extract data, and assess risk of bias in duplicate. Discrepancies will be resolved by discussion and consensus or arbitration. We will use the Grading of Recommendations Assessment, Development and Evaluation method to assess the certainty of the evidence. The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.

Ethics and dissemination

Publicly available data will be used, hence no formal ethical approval will be required for this review. The findings of the review will be disseminated through conference presentations and publication in an open-access peer reviewed journal.

PROSPERO registration number is: CRD42018105916

Strengths and limitations of this study:

- ✓ A comprehensive search will be conducted to ensure that we obtain an unbiased summary of intervention effects for potentially eligible trials.
- ✓ During the systematic review, selection of records, data collection, assessment of the risk of bias, and judgement of the strength of evidence will be performed in duplicate.
- ✓ This review will include non-randomized trials which are more prone to bias than randomized trials; however, to minimize the effect of the bias, we will perform subgroup analyses by study design.
- ✓ Diagnosing latent TB infection (LTBI) using the tuberculin skin test (TST) has several limitations due to its sensitivity and specificity, and based on these a positive result may be observed in people with prior BCG vaccination or exposure to nontuberculous mycobacteria; therefore, given these limitations TST results will be interpreted with caution considering the pretest risk of reactivation or M.TB infection and a subgroup analysis based on the QuantiFERON-TB Gold tests alone will be performed.

INTRODUCTION

Tuberculosis (TB) is the disease caused by *Mycobacterium tuberculosis* (M.TB) and other species of the Mycobacterium TB complex. Globally, TB is ranked as the ninth leading cause of death and the leading cause of death from a single infectious agent. More than 1.7 billion people are estimated to be infected with TB, of these only between 5-15% will develop TB disease in their lifetime.[1] In 2016, an estimated 10.4 million people were recorded to have fallen ill with TB globally. Adults contributed 90%, with male contributing 64%; and 9% TB incident cases were people living with the human immunodeficiency virus (HIV)[1]. The latter have a higher risk of developing TB disease, estimated to be between 16-27 times greater than HIV negative people.[2] An estimated 1.3 million TB deaths were recorded in 2017 among HIV negative people, with an additional 300 000 deaths among people living with HIV.[1]

Among healthy adults with immunological evidence of pre-exposure to M.TB, the overall lifetime risk of progressing to active disease is between 5-10% if not treated, and this will happen when

the body 's immune system is weakened, months or years after the primary infection.[3] The most vulnerable populations with higher probability of developing active TB disease are young children, diabetic patients, and people living with HIV.[4-6] A study by Marais *et al,* showed that 50% of infants with evidence of latent TB infection (LTBI) if untreated will progress to active TB disease.[7] To reduce the pool of active TB cases an early diagnosis and treatment is required for those people with LTBI, particularly in high risk groups such as those co-infected with HIV.[8]

Over the years it has been shown that using long courses of multiple antibiotics, TB can be treated, but the spread of multi-drug resistant TB (MDR-TB) and the rise of HIV makes TB one of the largest threats to public health globally.[1] In a study conducted by Daftary *et al*, it was shown that biological factors such as HIV and the spread of MDR-TB, alongside social determinants such as poor housing and poverty as well as structural determinants such as economic inequalities and rapid urbanization of populations play a very important role in the spread of TB through vulnerable populations.[9]

The bacille Calmette-Guerin (BCG) vaccine has been used globally since 1921 for the prevention of TB in humans, and was derived from an attenuated strain of *Mycobacterium bovis*.[2] Worldwide, BCG is the most widely used vaccine with approximately 100 million vaccinations given to newborn children per annum.[10] In children under 5 years, immunization with BCG is thought to reduce hematogenous spread of M.TB from the site of primary infection which may result in severe disease, such as milliary TB and TB meningitis.[11] Studies conducted in the past showed that its efficacy varies ranging from zero to 80% against pulmonary TB,[12-15] and over 70% against TB meningitis.[16-18] Other systematic reviews in the past found substantial variation between trials on the protective efficacy of BCG against pulmonary TB,[19,20] and in one review 50% average protective efficacy was estimated.[19]

There are various BCG vaccination regimes which can be administered as follows: to those without immunity later on in life, to at risk selected newborns, routinely to all newborns, to all adolescents, to those tuberculin negative and/or high risk selected groups.[21] Immunity can be boosted when revaccinated with two or more doses of the BCG vaccine. However, the tuberculin response is not associated with protective benefit derived from BCG vaccination and there is no evidence that a waning of tuberculin sensitivity with time equates to a loss of TB immunity.

However, currently there is no vaccine which is effective for the prevention of TB disease in adults either before or after M.TB infection. Currently there are 13 TB vaccines in Phase 1, Phase II or Phase III trials around the world and a new TB vaccine remains an important global research priority.[22] A study conducted in Kenya, Zambia, South Africa and Tanzania by Van Der Meeren *et al*, assessed the safety and efficacy of M72/AS01$_E$ tuberculosis vaccine and showed a 54% protection against pulmonary TB disease in individuals infected with M.TB. The results from this study represent a positive step forward in the fight against TB.[23]

BCG revaccination is still used in some TB endemic countries around the world. In February 2018, WHO recommended that for persons who have received BCG vaccination, repeat vaccination is not recommended as scientific evidence does not support this practice.[22] Evidence from a systematic review published in 2013 suggested that BCG revaccination conferred no additional protection from TB.[24] However, at least one new study published since then suggests a benefit of BCG revaccination.[25]

OBJECTIVE

The aim is to assess the effects of BCG revaccination against M.TB infection and active TB disease.

METHODS

Patient and public involvement

The review uses already published data, hence patients were not involved in the design of this study. However, patient's experiences, preference, and priorities informed the development of the research question and outcome measures as reported in the literature in support of this review. The findings of this review will provide governments, policy makers, patients, and the scientific community in the field of vaccinology with the evidence of the efficacy of BCG revaccination.

Criteria for considering studies for this review

Types of studies

We will include randomized trials, non-randomized trials, case-control studies, and cohort studies.

Types of participants

Any person regardless of age.

Types of intervention

BCG revaccination compared to no revaccination, placebo, or another vaccine.

Types of outcome measures

Primary outcomes measures

(i) TB disease (pulmonary TB and extra-pulmonary TB),

(ii) M.TB infection (i.e. latent TB), diagnosed by interferon gamma release assay (IGRA) or tuberculin skin test (Mantoux) without clinical or radiological evidence of active TB disease.

Secondary outcomes

(i) Adverse reactions (mild or severe),

(ii) Deaths (due to TB and from any causes),

(iii) Immunogenicity (i.e. the ability of BCG vaccine to induce an immune response including antibody- and/or cell-mediated immunity in a vaccinated individual), as defined by the primary study authors. It should be noted that we do not have an immune correlate of protection, so we do not know which immune response is protective.

Search methods for identification of eligible studies

We have developed a comprehensive search strategy for peer-reviewed and grey literature to identify all potential studies regardless of language or publication status (i.e. published, unpublished, in press, and in progress). Eligible studies must report at least one of our primary or secondary outcomes of interest.

Electronic searches

We will conduct our search to build a comprehensive search strategy that will be used to search the following databases: PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, WHO International Clinical Trials Registry Platform (ICTRP) and reference lists of relevant publications for potentially eligible studies. The proposed search strategy for PubMed is provided in **Table 1**.

Table 1. Search strategy

Search	Query
#1	Search BCG OR "bacille calmette guerin" OR "Bacille calmette-guerin" OR BCG VACCINE [MH]
#2	Search REVACCINATION OR REVACCINATE OR ((secondary immuni*[TW]) OR (booster immuni* [TW]) OR (revaccin*[TW]) OR ("booster" [TW]) OR ("Immunization, Secondary"[Mesh]))
#3	Search #1 AND #2
#4	Search #3 not NOT (animals[mh] NOT humans[mh]))
#5	Search #4 AND Tuberculosis[MH:EXP]

Searching other resources

We will search reference lists of relevant publications, including eligible studies, related reviews, and relevant WHO vaccine position papers.

Data collection and analysis

Selection of studies

Two review authors (PWM and EJM) will independently screen the titles and abstracts of all records retrieved by the search strategy above, for potentially eligible studies. All studies which are not eligible after screening of titles and abstracts will be excluded. We will obtain full-texts for all the potentially eligible studies. Two authors (PWM and EJM) will assess and compare these full-text publications for eligibility. We plan to translate full-texts of potentially eligible studies which are not written in English before assessing for eligibility. Any disagreements between the two review authors regarding study eligibility, will be resolved by discussion and consensus. A

third author will arbitrate any unresolved disagreements. We will provide a table with the characteristics of the included studies, and another of excluded studies with reasons for their exclusion. We will seek additional information, for studies with missing information, to assist us in our decision-making process. The study selection process will be illustrated in a PRISMA diagram.

Data extraction and management

One author (PWM) will design the data extraction form in agreement with the review team, two review authors (PWM and EJM) will pilot the form, discuss, and resolve any differences by consensus; failing which a third author (DN) will arbitrate. For each included study, the two authors will independently extract information using the piloted data extraction form. Data extracted will include some of the following: study details (study design, number of participants, study duration, methods used to measure outcomes and geographical locations); intervention details [number of participants, age of participants at time of administration, number of doses, and type of vaccine strain used (either BCG revaccination or another vaccine, co-interventions)]; comparator details (number of participants and type of comparator used); outcome details and funding sources. Any differences in data extraction between the two review authors will be resolved through discussion and consensus. The third author will be consulted to arbitrate if disagreements persist between the two authors. We will contact the authors and request for more information, if any selected study has incomplete or missing data. We will include the study in the review, if the authors provide no additional information. However, we will not synthesize the findings that are unavailable with findings from other included studies addressing the relevant outcome.

Assessment of risk of bias in included studies

Two authors (CSW and MS) will assess the risk of bias independently using the Cochrane Risk of Bias tool for trials,[26] and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool,[27] resolving discrepancies by discussion and consensus. If disagreements persist a third author will arbitrate (PWM).

The Cochrane Risk of Bias tool for trials includes information for assessment of the risk of selection bias (adequacy of the generation of the allocation sequence and allocation concealment), detection bias (blinding of outcome assessors), attrition bias (completeness of outcome data), and reporting bias (completeness of outcome reporting).[26]

The ROBINS-I tool includes information for assessment of the risk of bias at three different stages (i.e. pre-intervention, intervention, and post-intervention). For the pre-intervention stage we will assess selection bias (due to selection of participants into the study and confounding); at the intervention stage we will assess "classification of interventions" bias (introduced either by differential or non-differential misclassification of intervention status); and at the post-intervention stage we will assess performance bias (due to deviations from intended interventions), attrition bias (due to missing data), detection bias (in the measurement of outcomes) and outcome reporting bias (in selection of the reported result).[27]

Dealing with missing data

We will assess missing data to see if it is related to the outcome. If there is missing or unclear information or restrictions to use the study, we will contact study investigators and request the missing information. For older publications it is anticipated that it may not be possible to reach the authors. Only the available data will be analyzed if there is missing data. We may use imputation and perform sensitivity analyses to investigate the impact of missing data, if the amount of incomplete outcome data is such that the trial is thought to be at a high risk of bias.

An intention to treat (ITT) analysis will be used for all outcomes where a treatment received analysis will be done, except with adverse effects. We will further assess whether the published endpoints match those specified and whether outcome measures are specified *a priori* in study protocols. To determine the proportion of missing results and whether the missing data affects the results or not in terms of effect size and event risk, each included trial will be assessed for incomplete outcome data.

We will also assess if reasons for missing data are related to adverse events or death from BCG revaccination. In order to have an overall decision on risk associated with incomplete outcome we will assess if the missing data was balanced in the different studies. High risks of bias will

include extreme differences in baseline characteristics, stopping the trial before completion without clear reasons and influence by funders.

To determine adverse effects and adverse events methods used previously in systematic reviews will be used. All trials included will be assessed for risk of bias by examining whether all participants were included; whether participants and outcome assessors were blinded; whether data analysis was independent of pharmaceutical companies; whether the outcome data reporting was complete; and if monitoring was active or passive.[28] To adequately assess the risk of bias where there is insufficient information to assess the risk of bias, authors will be contacted to obtain needed information.

Assessment of reporting biases

If more than ten studies are included for meta-analysis, we will use a funnel plot to assess for publication bias.

Data synthesis

For all included studies, data will be analyzed using RevMan 5.[29] We will use the risk ratio (RR) and its corresponding 95% confidence interval (CI) to summarize binary data. For studies with similar participants, interventions, outcomes, and study designs, we will combine study data using the random-effect method of meta-analysis. The level of heterogeneity will be determined by inspecting forest plots for overlapping CIs and by examining the Chi^2 P value. The degree of heterogeneity will be quantified using the I^2 test. An I^2 statistic value of > 40% and a Chi^2 P value significance level of ≤ 0.1 will be regarded as showing important heterogeneity. In case of heterogeneity we will investigate the causes using subgroup analyses. We will define subgroups based on age of the participants (children versus adults), the timing of the first dose of BCG vaccination (immediately versus four or more weeks after birth), age of revaccination, the level of immune response and country income status. Data from studies that are similar enough will be quantitatively synthesized using a meta-analysis with random-effects. In the event of significant heterogeneity, a Meta-analysis will not be performed. Instead, the data will be synthesized using a narrative synthesis. We will perform sensitivity analysis, by assessing results after excluding trials that have unclear or high risk of bias.

Reporting review findings

The strength or certainty of the evidence will be assessed using the Grade of Recommendations Assessment, Development and Evaluation (GRADE) approach,[30] which rates the certainty of evidence for each outcome by taking into consideration the directness of evidence, risk of bias, risk of publication bias, precision and heterogeneity. A table for 'Summary of findings', will be constructed which will review findings for outcomes listed under the 'Types of outcome measures' section.

Timeline for the systematic review

The planned systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO) in August 2018.[31] The search strategy will be finalized in February 2019, we plan to conduct the searches and studies eligibility selection between February and April 2019; and to collect data, conduct statistical analyses, and prepare and submit the manuscript to a peer-reviewed journal between May and August 2019.

Ethics and dissemination

No formal ethical approval is required for this review, because we will use already published data. The findings of this review will provide donors, health workers, policy makers, patients, and the scientific community in the field of vaccinology with the evidence for decision making with regards to the benefits of BCG revaccination in adolescents and adults populations. In the face of no M.TB vaccine currently available for adult populations, this might improve the immediate and long-term measures to eradicate TB. The findings of this review will be presented at relevant conferences and published in a peer-reviewed journal. This protocol has been written following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols guidelines,[32] and the findings of this review and any amendments will be reported according to the PRISMA statement.[33]

Contributors

PWM led the development of the protocol, wrote the first draft, coordinated and integrated comments from co-authors, approved the final version for publication and is the guarantor of the manuscript. DN,

EM and MS critically revised successive drafts of the manuscript, provided important intellectual input and approved the final version of the manuscript. CSW conceived the study, provided supervision and mentorship to PWM, critically revised successive drafts of the manuscript, provided important intellectual input and all authors approved the final version of the manuscript.

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Competing interests

None declared.

Patients consent

Not required

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Information reported	Page number
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	Identify the report as a protocol of a systematic review	Yes	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA	
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Yes	3
Authors:				
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Yes	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Yes	11-12
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Yes	11
Support:				
Sources	5a	Indicate sources of financial or other support for the review	Yes	12
Sponsor	5b	Provide name for the review funder and/or sponsor	Yes	12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Yes	12
INTRODUCTION				
Rationale	6	Describe the rationale for the review in the context of what is already known	Yes	3-5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Yes	5-6
METHODS				
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Yes	5-6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Yes	6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that	Yes	Table 1. pg 7

		it could be repeated		
Study records:				
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Yes	7-7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility, and inclusion in meta-analysis)	Yes	7-8
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Yes	7-8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Yes	8,12
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Yes	6
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Yes	8-10
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Yes	10
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Yes	10
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Yes	10
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Yes	10
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Yes	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Yes	11