BMJ Open

Systematic review protocol on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis

Phetole Walter Mahasha 1, Duduzile Edith Ndwandwe, 1 Edison Johannes Mavundza 2, Muki Shey, 2 Charles Shey Wiysonge 1,3,4

ABSTRACT

Introduction Tuberculosis (TB) is a 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. Evidence from previous randomised 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 CRD42018105916

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% and 15% will develop TB disease in their lifetime.

In 2016, an estimated 10.4 million people were recorded to have fallen ill with TB globally. Adults contributed 90%, with men contributing 64%; and 9% TB incident cases were people living with the HIV.1 The latter have a higher risk of developing TB disease, estimated to be between 16 and 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.

Among healthy adults with immunological evidence of pre-exposure to M.TB, the overall lifetime risk of progressing to active disease is between 5% and 10% if not treated, and this will happen when the body’s immune system is weakened, months or years after the

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-randomised trials which are more prone to bias than randomised trials; however, to minimise the effect of the bias, we will perform subgroup analyses by study design.

► Diagnosing latent TB infection (LTB) using the tuberculin skin test (TST) has several limitations due to its sensitivity and specificity, and 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.


Received 02 October 2018
Revised 04 September 2019
Accepted 17 September 2019

© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

1 Cochrane South Africa, South African Medical Research Council, Cape Town, South Africa
2 Welcome Centre for Infectious Disease Research in Africa (CIDRI-Africa) & Department of Medicine, University of Cape Town, Cape Town, South Africa
3 Centre for Evidence-based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa
4 Division of Epidemiology and Biostatistics, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa

Correspondence to Dr Phetole Walter Mahasha; Phetole.Mahasha@mrc.ac.za

Protocol
primary infection. The most vulnerable populations with higher probability of developing active TB disease are young children, diabetic patients and people living with HIV. 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. 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 coinfected with HIV.

Over the years, it has been shown that using long courses of multiple antibiotics, TB can be treated, but the spread of multidrug resistant TB (MDR-TB) and the rise of HIV makes TB one of the largest threats to public health globally. 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 urbanisation of populations, play a very important role in the spread of TB through vulnerable populations.

The bacille Calmette-Guérin (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. Worldwide, BCG is the most widely used vaccine with approximately 100 million vaccinations given to newborn children per annum. In children under 5 years, immunisation 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 miliary TB and TB meningitis. Studies conducted in the past showed that its efficacy varies from 0 to 80% against pulmonary TB, and over 70% against TB meningitis. Other systematic reviews in the past found substantial variation between trials on the protective efficacy of BCG against pulmonary TB, and in one review 50% average protective efficacy was estimated.

There are various BCG vaccination regimes which can be administered as follows: to all newborns, to all adolescents, to those tuberculin negative and/or high-risk selected groups. 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 I, Phase II or Phase III trials 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. Evidence from a systematic review published in 2013 suggested that BCG revaccination conferred no additional protection from TB. However, at least one new study published since then suggests a benefit of BCG revaccination.

**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 randomised trials, non-randomised trials, case-control studies and cohort studies.

**Types of participants**

Any person regardless of age.

**Types of intervention**

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

**Types of outcome measures**

**Primary outcomes measures**

1. TB disease (pulmonary TB and extrapulmonary TB).
2. M.TB infection (ie, 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**

1. Adverse reactions (mild or severe),
2. Deaths (due to TB and from any causes),
3. Immunogenicity (ie, the ability of BCG vaccine to induce an immune response including antibody-mediated 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 (ie, 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>
<thead>
<tr>
<th>Search</th>
<th>Query</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>Search BCG OR “bacille calmette guerin” OR “Bacille calmette-guerin” OR BCG VACCINE (MH)</td>
</tr>
<tr>
<td>#2</td>
<td>Search REVACCINATION OR REVACCINATE OR ((secondary immuni*(TW)) OR (booster immuni* (TW)) OR (revaccin*(TW)) OR (“booster” (TW)) OR (“Immunisation, Secondary”(Mesh)))</td>
</tr>
<tr>
<td>#3</td>
<td>Search #1 AND #2</td>
</tr>
<tr>
<td>#4</td>
<td>Search #3 not NOT (animals(mh) NOT humans(mh))</td>
</tr>
<tr>
<td>#5</td>
<td>Search #4 AND Tuberculosis(MH:EXP)</td>
</tr>
</tbody>
</table>

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 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 synthesise 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, and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool, 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). The ROBINS-I tool includes information for assessment of the risk of bias at three different stages (ie,
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 analysed 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. 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 10 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 analysed using RevMan V.5.29 We will use the risk ratio (RR) and its corresponding 95% CI to summarise 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 vs adults), the timing of the first dose of BCG vaccination (immediately vs 4 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 synthesised 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 synthesised 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 outcomes 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 finalised 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,\textsuperscript{32} and the findings of this review and any amendments will be reported according to the PRISMA statement.\textsuperscript{33}

Twitter Phetole Walter Mahasha @PhetoleMahasha and Charles Shey Wiysonge @CharlesShey

Acknowledgements The authors would like to thank Elizabeth Pienaar for her assistance in developing the search strategy. We would also like to acknowledge the South Africa Medical Research Council for funding this review.

Contributors PWM led the development of the protocol, wrote the first draft, coordinated and integrated comments from coauthors, approved the final version for publication and is the guarantor of the manuscript. DEN, EJM 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 and provided important intellectual input. All authors approved the final version of the manuscript.

Funding This review will be supported by the South African Medical Research Council and the National Research Foundation of South Africa (grant number: 106035).

Disclaimer The sponsors played no role in the design of the protocol, writing of the report and in the decision to submit the protocol for publication.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval No formal ethical approval is required for this review, because we will use already published data.

Provenance and peer review

Data availability statement There are no data in this work. No data are available.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs

Phetole Walter Mahasha http://orcid.org/0000-0002-5750-3595
Edison Johannes Mavundza http://orcid.org/0000-0002-0890-0164
Charles Shey Wiysonge http://orcid.org/0000-0002-1273-4779

REFERENCES

8 Sharma SK, Mohanan S, Sharma A. Relevance of latent TB infection in areas of high TB prevalence. Chest 2012;142:761–73.
30 Mahasha P, Ndawandwe D, Wiysonge C. An updated systematic review on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis. . PROSPERO 2018:CRD42016105916 http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42016105916