Objectives

This review and meta-analysis will examine the changes in bacillus Calmette–Guérin (BCG) efficacy over time by a) age at vaccination, b) gender, c) site of disease, and d) country tuberculosis (TB) epidemiology (high, medium, low prevalence) with a focused discussion on how this information relates to use of BCG in the UK.

Research methods

The review will include a broad and comprehensive search for, and a critical assessment of, studies on the duration of protection of BCG. It will include all the studies in the previous review (Sterne and Rodrigues, *Int J Tuberculosis Lung Dis* 1998;**2**:200–7) and other relevant studies, including newer studies and observational studies.

Outcome measures

For trials and cohort studies we will extract rate ratios comparing unvaccinated with vaccinated individuals, with appropriate measures of precision, for successive time periods since vaccination.

For case–control and cross-sectional studies we will extract odds ratios, with appropriate measures of precision, where these can be related to time since vaccination. For example, in a population vaccinated in the first year of life, odds ratios in different age groups correspond to time since vaccination.

The precise time periods presented will depend on the detail with which the primary studies were reported.

When results are reported in sufficient detail, we will stratify by site of disease (e.g., miliary, meningitis, pulmonary, all TB), gender, and age at vaccination.

We will extract study characteristics that may relate to the extent or duration of protection, including geographic region and latitude, vaccine strain, and risk of bias in the results.

Search strategy

Search terms:

We will combine search terms of the disease (TB, tuberculosis, tubercle bacill*, *Mycobacterium tuberculosis*, *M. bovis*, *M. africanum*, *M. canetti*, *M. microti* and 'M.TB') with terms for the vaccination (BCG Vaccine, BCG, BCG Vacc*, BCG Imm*, bacillus calmette) to extract all possible studies on BCG efficacy from 1920 until present. For the time period of 1920 to 1965 we will also search on the term BCG to identify studies that are indexed differently from more modern studies, as such searches have revealed additional papers on the efficacy of BCG for protecting against TB.

Databases:

The following search databases/engines will be used to find relevant papers: 1) MEDLINE (PreMEDLINE, Old MEDLINE), 2) Google scholar, 3) Embase, 4) Web of Science, 5) BIOSIS, 6) CINHAL, 7) Dissertation abstracts online database, 8) DARE, 9) SIGLE, 10) Scopus, 11) CAB Abstracts 12) British National Bibliography for Report Literature, 13) LILACS, 14) Global Health and Global Health Archives, 15) Index to Theses, 16) African healthline, and 17) ELDIS. Current trials/data will be searched using the: Cochran library, National Research Register, Health technologies assessment database and National guideline clearing house, clinicaltrials.gov, and control-trials.com. Search engines may be added, or redundant engines removed, following our consolation with a reference librarian and literature search specialist.

Additionally, all relevant manuscripts referenced in each reviewed manuscript will be searched for further articles. All BCG Reviews will be used to further gather references (from their reference lists).

Nominated experts in the area of TB and BCG will be contacted to determine if we are missing key references after our primary list is constructed.

We will include articles in all languages and studies carried out in humans.

Review strategy

Study eligibility and application of inclusion and exclusion criteria:

The titles and abstracts of papers identified will be screened by two reviewers. Given the unexpectedly large number of references on this topic, approximately 22,000, the initial title and abstract review will be split between the two reviewers by author surname alphabetically. The first 5% of titles and abstracts in each reviewer's section, total 10%, will be reviewed in duplicate and checked for agreement to ensure consistency in nominating papers for full review by both reviewers. All articles that are considered to potentially meet the eligibility criteria outlined below by either of the reviewers will be selected. The assessment of study eligibility of this initial selection will not be blinded to publication details such as journal or author names.

Once the title an abstract screening is complete, all papers that were identified as potentially meeting eligibility will be obtained and reviewed completely. Pertinent data for the review and meta-analysis will be extracted in duplicate by both reviewers and reviewer consistency will be monitored periodically to ensure consistency in data extraction. Any necessary adjustments to ensure consistency will be made as a result of this monitoring. Any inconsistencies will be reviewed and resolved by one of the study investigators. Consistency on key items will be evaluated and reported at completion of data extraction.

The criteria for inclusion and exclusion of studies in the review are:

A. Inclusion

Case–control, cohort (longitudinal), cross-sectional, research letters that present new data and controlled trial studies (regardless of randomization) on the efficacy of BCG on TB disease/mortality will be included regardless of follow-up time, population, or level or type of bias (this information will be collected and assessed as part of the review/meta-analysis)

Studies examining re-vaccination with BCG for protection against TB.

Full, peer-reviewed articles, non-peer reviewed articles (e.g., PNAS), conference abstracts, and dissertations should be included if focusing on the efficacy of BCG protection.

Studies examining vaccinated people in any age group (infants, school aged children, adults including occupational), gender, or region.

All languages.

All studies previously included in Sterne & Rodrigues. 1998. Does the efficacy of BCG decline with time since vaccination? *International Journal of Tuberculosis and Lung Disease*. 2(3): 200-207.

Studies without efficacy measures, but containing information sufficient to calculate these.

All human studies.

B. Exclusion

Studies that do not present new data, recent trials of modified or boosted BCG, studies on animals, and ecological studies will not be included in the review.

Data extraction

Two reviewers will independently use standard forms to extract data from all identified papers. Key data items will include study characteristics (authors, date, location, journal, sources of funding, study design), participant characteristics, inclusion criteria, organism (s), test used, BCG vaccine (strain, location, reported outcome measures).

Assessment of methodological quality

For RCTs, we will assess the risk of bias in results according to the methods described in Chapter 8 of the recently-published 5th edition of the Cochrane Handbook (Higgins JPT *et al.* 2008 see www.cochrane-handbook.org). For each domain, trial results will be assessed at high, unclear or low risk of bias.

Standardised tools for assessing the risk of bias in results from observational studies are not available.

For cohort studies, we will record whether assessments of vaccination status were made prospectively and whether outcomes were ascertained blind to vaccination status.

For case-control studies, we will record whether cases and control subjects were recruited blind to vaccination status, and whether the control subjects were sampled from the population that gave rise to the cases.

Statistical analysis

We will derive summary estimates of rate ratios (odds ratios for case-control studies), separately according to time period since vaccination, using both fixed and random-effects meta-analysis.

Because substantial between-study heterogeneity is a well-known feature of studies of BCG vaccination, we will report analyses stratified by geographic region and latitude, and report any potential biases identified when interpreting the results.

Due to the high frequency of adverse effects in HIV infected individuals, we will conduct separate analysis for studies involving HIV infected populations.

We will use fixed- and random-effects Poisson regression models to quantify rates of change in the duration of protection with time, allowing for between-study heterogeneity.

We will conduct separate analyses for each type of study (trials, cohort studies, case–control studies, and cross-sectional), for different geographical areas, age at vaccination, site of TB disease, and gender. However, due to heterogeneity between studies, we may not be able to combine results from all studies of the same type, nor stratify on all variables of interest.

We will use random-effects Poisson regression models, and random-effects meta-regression models, to examine associations of study characteristics (including summary assessments of risk of bias) with the extent and duration of protection.

Ethics

This study will not require a review by a research ethics committee as it does not involve any patient or health care staff contact.

Output of the research

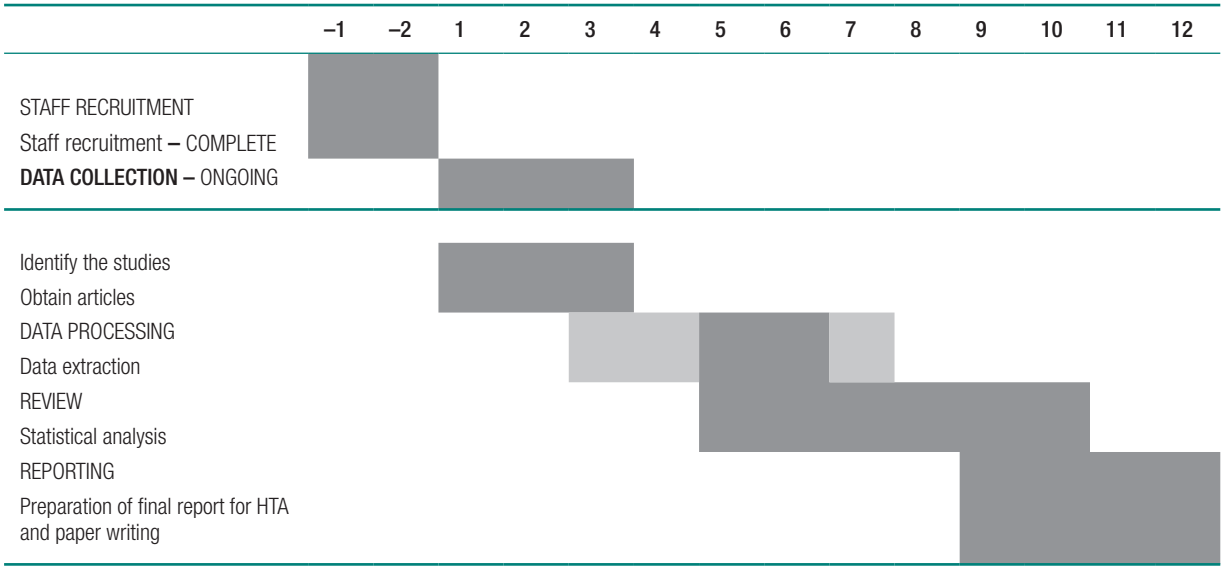
A comprehensive report of the findings with recommendations to the NIHR HTA including evidence for the duration of BCG protection by age at vaccination, gender, site of disease, and geographical area will be prepared.

This report will summarise findings particularly relevant to UK vaccination policy.

We will also identify the need for further research and the best way to answer questions arising from the review using primary research.

In addition to a formal report to the HTA, the research will be disseminated through peer reviewed publications, conference presentations and engagement with policy makers (Joint Vaccination and Immunisation Committee, Department of Health and the Health Protection Agency).

Project timetable



Milestones (1–5 linked to study objectives).