Systematic review and meta-analysis of the current evidence on the duration of protection by bacillus Calmette–Guérin vaccination against tuberculosis

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Scientific summary

Protection by BCG vaccination against tuberculosis

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Scientific summary

Background

Recent evidence suggests that the duration of protection by bacillus Calmette–Guérin (BCG) vaccination may exceed previous estimates. Such information is essential for estimating both the impact of BCG vaccination programmes and their cost-efficacy. This systematic review was commissioned by the National Institute for Health Research (NIHR) Health Technology Assessment programme in order to assess the duration of protection by BCG vaccine.

Objectives

To assess and quantify changes in protection by BCG vaccination against tuberculosis over time, against all tuberculosis, tuberculosis mortality, pulmonary tuberculosis and extrapulmonary tuberculosis (meningeal/miliary and other extrapulmonary sites separately and together), based on controlled trials and observational studies. To estimate, if data are available, overall clinical efficacy for the above tuberculosis disease categories and variations in clinical efficacy according to location (latitude/geographic region), time since vaccination and age at vaccination (neonatal, school age, occupational), stringency of tuberculin testing before vaccination, risk of bias in the different study designs, vaccine strain, gender and human immunodeficiency virus (HIV) status.

Methods

Search strategy

Electronic databases were searched from inception to October 2009, including MEDLINE, Excerpta Medica Database (EMBASE), Cochrane Databases, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment database and NHS Economic Evaluation Database (NHS EED), Web of Knowledge, Bioscience Information Service (BIOSIS), Latin American and Caribbean Health Sciences Literature (LILACs), MEDCARIB, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Index to Theses, System for Information on Grey Literature in Europe (SIGLE), Centre for Agricultural Bioscience International (CABI) Abstracts, Scopus, Article First, Academic Complete, Africa-Wide Information, Google Scholar, Global Health, British National Bibliography for Report Literature, and clinical trials and controlled trials websites.

Inclusion/exclusion criteria

All studies, observational or trial, which assessed the efficacy of BCG vaccines in any human population compared with another vaccine or a placebo that provided sufficient outcome on tuberculosis disease or mortality were included. Case series and ecological studies, those assessing efficacy of oral BCG vaccination or clinical efficacy of BCG vaccination against infection rather than disease, and cohort studies that did not use stringent tuberculin testing before vaccination were all excluded. For each study design, further criteria were developed to determine which studies had all necessary data and were therefore suitable for data extraction.

Data extraction

Data extraction of English-language papers was carried out by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus. A baseline data extraction form was used to collect information on study design, participants' characteristics, years of recruitment and follow-up, characteristics of BCG vaccination, including strain and whether preceded by tuberculin testing, characteristics of tuberculin testing, *Mycobacterium tuberculosis* Koch infection, regional vaccination

policies, BCG vaccination procedures and properties, and tuberculosis outcomes. The Cochrane Risk of Bias tool was used to assess bias in randomised controlled trials (RCTs). Bias assessment forms were developed in order to assess the observational study designs.

Analysis

Estimates of BCG vaccination efficacy were derived for each study and displayed in forest plots together with both fixed- and random-effects summary effect estimates categorised by site of disease and study design. Variation in efficacy according to latitude of study location, age at vaccination (and tuberculin testing stringency for trials), BCG strain (for trials), and diagnostic detection bias whether prospective or retrospective design for cohort studies were examined. Meta-regression analyses were conducted, when sufficient studies were available, for each outcome and heterogeneity was quantified by estimating the between-study variance, tau-squared, using restricted maximum likelihood, using the metareg command in Stata 11 (StataCorp LP, College Station, TX, USA). The analyses of the duration of protection by BCG vaccination focused on changes in efficacy with time since vaccination (or age as proxy for time since vaccination, for infant vaccination) and was estimated within studies.

Results

Study selection

A total of 21,030 references were identified through the literature search. The titles, and abstracts if available, were screened for eligibility. Full-text copies of 800 articles selected for potential inclusions were retrieved. In total, 211 articles met the inclusion criteria for this review (of which 60 were published in non-English languages), providing data on 132 studies.

Efficacy

The results of trials and observational studies are consistent with previous observations that protection against pulmonary tuberculosis in adults is variable and greater away from the equator. One finding is that BCG vaccination efficacy was usually high, and varied little by form of disease (although magnitude of protection appeared to still be higher against meningeal and miliary tuberculosis) or study design when BCG vaccination was given only to infants or to children after strict screening for tuberculin sensitivity. There were not enough studies to determine the individual impact of prior tuberculin sensitivity, age at vaccination and latitude. High levels of protection against death were observed from both trials and observational studies. Our analysis found that the protective effect of BCG vaccination did not differ by the strain of BCG vaccine used in trials.

Duration

We found good evidence from trials and observational studies that BCG vaccination protects against pulmonary and extrapulmonary tuberculosis for up to 10 years. Most studies either did not follow up participants for long enough or had very few cases after 15 years. The meagre evidence from the majority of trials should not be taken to indicate an absence of effect: five studies (one trial and four observational studies) provided evidence of measurable protection at least 15 years after vaccination. Clinical efficacy declined with time. The rate of decline differed between studies and, although the number of studies was limited, the pattern of decline was consistent with faster decline in latitudes further from the equator and in situations where BCG vaccination was given only to either infants or to children after strict screening for tuberculin sensitivity.

Conclusions

This review of clinical trials and observational studies confirmed that BCG vaccination provides protection against tuberculosis, and that effectiveness of BCG vaccines in protecting against tuberculosis varies considerably between populations, to an extent that cannot be attributed to chance alone. BCG

vaccination provided good protection when given to naive individuals. Age at which the vaccine was given, pre-vaccination tuberculin sensitivity status and latitude were the factors that explained most of the observed variation. There was no evidence that other factors such as BCG vaccine strain explain the observed variation.

The strength of protection appeared to decline with time. There was evidence of protection beyond 15 years; however, data were limited. Most studies either did not follow up participants for long enough or had very few cases after 10 years. The absence of evidence from the majority of trials should, therefore, not be taken as an absence of effect.

Recommendations for research

For bacillus Calmette–Guérin research

1. Further research into the duration of protection conferred by BCG vaccination would be useful to inform future vaccination policy. We would recommend a case–control study taking into account the purified protein derivative status of participants at vaccination, as this approach is likely to be cheaper and provide results in the shortest amount of time.
2. Replication of the REVAC study (Brazilian revaccination study) (Rodrigues LC, Pereira SM, Cunha SS, Genser B, Ichihara MY, de Brito SC, *et al*. Effect of BCG revaccination on incidence of tuberculosis in school-aged children in Brazil: the BCG–REVAC cluster-randomised trial. *Lancet* 2005;**366**:1290–5) in other settings to see whether similar or different results would be obtained in different environments may also be beneficial.
3. Further research into the efficacy of BCG vaccination in those > 35 years should be carried out.
4. Studies should investigate the role of stringent tuberculin skin testing in the protective effect of BCG vaccination.

For new vaccines

1. Given the limited protection conferred by BCG vaccination against post-primary adult pulmonary disease, new tuberculosis vaccines against these forms of the disease are of high priority.
2. BCG vaccination appears to offer little or no protection to those previously infected with *M. tuberculosis*. Vaccines that are effective in this group ('post-exposure vaccines') should be a priority for research. This will require better animal models of tuberculosis that allow the assessment of the efficacy of BCG vaccination against reactivation disease.
3. Future studies need to take into account the observation from this review that prior tuberculin sensitivity is a key determinant of whether or not a trial shows significant evidence of protection by BCG vaccination. This is particularly pertinent, as most trials of new vaccines will be undertaken in high tuberculosis incidence countries that also have a high burden of non-tuberculous mycobacterial infection.
4. Investigating the mechanism behind the failure of BCG vaccination to protect previously sensitised individuals will provide useful information for the development of new vaccines against tuberculosis. This should be assessed for different non-tuberculous mycobacteria, prior BCG vaccination and tuberculosis exposure.
5. Future research should also investigate whether the clinical efficacy of new vaccines differs depending on the predominant strain of *M. tuberculosis* circulating in the population, as well as the interaction between the predominant circulating strains of *M. tuberculosis* and human genetic polymorphisms that affect susceptibility to tuberculosis. There is also a need for studies in HIV-infected individuals.

Implications for practice

1. The economic analysis to inform the tuberculosis incidence threshold at which universal BCG vaccination becomes cost-effective should be re-examined if further evidence emerges that BCG vaccination protects for longer than 15 years.
2. There is a need to consider whether or not all individuals should be tested to identify those likely to benefit from BCG vaccination, especially with the increased used of interferon-gamma release assays for contact investigation.

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