BCG vaccination and allergy: a systematic review and meta-analysis
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CRD summary
The review found that pre-school BCG vaccination was unlikely to protect against allergic sensitisation, atopic eczema and allergic rhinoconjunctivitis. A possible benefit in relation to asthma was unlikely to be due to allergic sensitisation. In view of the reported poor quality of the included studies and heterogeneity between them, these conclusions should be interpreted with caution.

Authors' objectives
To assess the relationship between BCG vaccination in infancy and allergy.

Searching
Major databases and electronic sources that included MEDLINE, EMBASE, Web of Science, BIOSIS, Index to Theses, ClinicalTrials.gov, Digital Dissertations Online and OpenSIGLE database and Google Scholar were searched. Search terms were reported. Reference lists of included studies were checked. Manufacturers of BCG vaccine and international experts were contacted to identify published and unpublished studies. The search was not limited by date or language.

Study selection
Randomised controlled trials (RCTs), non-randomised controlled trials, cohort studies, case-control and cross-sectional studies of BCG vaccination administered in childhood (up to the age of five) were eligible for inclusion. Participants were required to be aged under 17 years. Outcomes of interest were sensitisation to common allergens and potentially relevant diseases.

Participants in the included studies were children from a wide range of countries and settings that included primary and secondary schools, health care centres and national population groups. At least two studies were set in UK. Some participants were at high risk of allergy (such as those with a family history of allergy) and others were without known risk factors. Age at BCG vaccination ranged from a few days after birth to any time up to two years (where stated). Outcomes reported by the included studies were sensitisation (measured by specific immunoglobulin E (IgE) level or skin prick test), atopic dermatitis or eczema, asthma, allergic rhinoconjunctivitis, overall risk of atopic allergic disease, urticaria and food allergy. Studies used a range of tools to measure outcomes. In the review, lifetime asthma, lifetime wheezing and 12-month prevalence of wheezing were preferred measures for asthma (in order of preference). Lifetime prevalence was the preferred measure for rhinoconjunctivitis. None of the studies reported angio-oedema and anaphylaxis. In more than half of the studies effect sizes were adjusted for confounders.

Two reviewers independently selected the studies. Disagreements were resolved by discussion or by a third reviewer.

Assessment of study quality
Study validity was assessed using methods recommended by the Cochrane Collaboration (Higgins 2009) for experimental studies and a checklist based on Strengthening the Reporting of Observational Studies in Epidemiology criteria (Vandenbroucke 2007) for epidemiological studies. Studies were assessed as high, moderate or low quality according to their risk of bias.

Two reviewers independently assessed study validity. Disagreements were resolved by discussion or a third reviewer.

Data extraction
Odds ratios (ORs), with 95% confidence intervals (CIs), were extracted or calculated.

Two reviewers independently extracted data. Disagreements were resolved by discussion or by a third reviewer.
Methods of synthesis
Studies were combined to calculate pooled odds ratios and 95% CIs. Fixed-effect models were used except where there was significant heterogeneity, in which case random-effects models were used. Heterogeneity was assessed using the $I^2$ statistic and assumed heterogeneity where $I^2$ was over 40%. Where heterogeneity was detected, it was explored by subgroup analyses based on family history of allergy and/or region of birth. Risk of publication bias was assessed using funnel plots. Sensitivity analyses excluded low-quality studies.

Results of the review
Seventeen studies were included (n=85,593 participants, range 121 to 38,808): one RCT (n=121), seven cohort studies (six retrospective and one prospective, n=53,305), two case-control studies (n=14,768) and seven cross-sectional studies (n=17,399). Overall study quality was weak: eight studies were rated as moderate quality and nine as low quality. Not all studies included analysable data.

Vaccination was associated with a significantly higher risk of sensitisation than non-vaccination, when measured by specific IgE level (OR 1.31, 95% CI 1.07 to 1.60, $I^2$=0%; five studies). Sensitisation rates did not differ significantly when measured by skin prick tests (five studies, $I^2$=57%). There was no significant difference between vaccinated and non-vaccinated participants in rates of eczema or atopic dermatitis (nine studies, $I^2$=89%), rhinoconjunctivitis (nine studies, $I^2$=67%), atopic allergic disease (two studies), urticaria (one study) and food allergy (two studies). Vaccination was associated with a significantly lower risk of asthma than non-vaccination (OR 0.73, 95% CI 0.56 to 0.95, $I^2$=91%; 12 studies).

There was substantial heterogeneity for several outcomes. Results of subgroup and sensitivity analyses were reported in the review. Funnel plots showed evidence of publication bias in the analyses of asthma, eczema/atopic dermatitis and rhinoconjunctivitis, but not for other outcomes.

Authors' conclusions
Pre-school BCG vaccination was unlikely to protect against allergic sensitisation, atopic eczema and allergic rhinoconjunctivitis. A possible benefit in relation to asthma was unlikely to be due to allergic sensitisation.

CRD commentary
The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies without restriction by language or publication status. The search date was not stated. Steps were taken to minimise the risk of reviewer bias and error by having more than one reviewer independently select studies, undertake validity assessment and extract data. Use of summary indicators made it unclear which specific validity criteria were met or unmet by each study. It was questionable whether pooling of the data was justified, in view of marked differences between the studies in design, sample size and participant characteristics and high levels of statistical heterogeneity for most outcomes. Heterogeneity was explored in subgroup and sensitivity analyses, but no clear explanation for the heterogeneity was suggested. The authors noted that study quality was poor, with only one RCT, no high-quality trials and high potential for confounding. There was possible publication bias for some outcomes. The authors did not comment on the significant link found between vaccination and specific IgE level.

In view of the reported poor quality of the included studies and heterogeneity between the studies, the authors’ conclusions should be interpreted with caution.

Implications of the review for practice and research
Practice: The authors stated that there was insufficient evidence to recommend that BCG vaccination be incorporated into national vaccination programmes for prevention of asthma.

Research: The authors stated that researchers should consider conducting a large RCT to investigate the role of BCG vaccination in the first few months of life for preventing asthma. It should include participants with and without family history of allergy, continue until at least five years of age and include mechanistic outcomes, cost-effectiveness and safety.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.