Authors' objectives
To quantify the efficacy of BCG vaccine against tuberculosis (TB).

Searching
MEDLINE was searched using the terms 'BCG vaccine', 'tuberculosis' and 'human'. Bibliographies of retrieved studies and review papers were examined for additional material, and the World Health Organization (WHO) and the Centre for Disease Control and Prevention (CDC) were contacted for unpublished trials. Studies and trials in any language were considered.

Study selection
Study designs of evaluations included in the review
Prospective trials and case-control studies measuring the efficacy of BCG vaccination in preventing TB cases and death. Prospective trials had to include a randomly-established concurrent control group, employ equivalent surveillance procedures for treatment and control groups, and have similar lengths of follow-up. Case-control studies had to define the criteria for selecting cases and controls, and the method for determining their BCG vaccination status.

Specific interventions included in the review
BCG vaccine.

Participants included in the review
Details of included participants are unclear. Eight trials involved patients vaccinated as infants.

Outcomes assessed in the review
The outcomes assessed were cases of TB, deaths from TB and meningitis.

How were decisions on the relevance of primary studies made?
Two readers independently evaluated study validity and any discrepancies were resolved by a third reviewer.

Assessment of study quality
Two readers evaluated study validity. The readers recorded study design, age range of population, number of patients enrolled, location of study, strain and dose of BCG used, route of administration, years of follow-up or time since immunisation, outcomes measured, efficacy of design, and items for assessing potential bias in study design and diagnosis. Potential bias was assessed using a scoring system, which for trials, assessed the method of vaccine assignment to study population, equality of surveillance among control and treatment arm, criteria used to diagnose TB, and preparation of BCG vaccine. In the case-control studies, potential bias was examined in data collection, and the criteria used to collect information. Two readers independently evaluated study validity and any discrepancies were resolved by a third reviewer.

Data extraction
Two readers extracted the data independently and any differences were resolved by a third reviewer.

Methods of synthesis
How were the studies combined?
The data from trials and case-control studies were combined separately using random-effects models. Summary tables of the individual studies were also presented.

How were differences between studies investigated?
Differences between the studies were examined by a random-effects regression model using 7 single-covariate, 2 two-covariate and 1 three-covariate regression models.

Results of the review
Of the 70 studies reviewed, 26 were included: 14 prospective trials (n=360,000; 7 RCTs, 2 trials with alternate allocation and 4 trials with systematic allocation; details were only provided for 13 studies) and 12 case-controls (n=1,414; details were only provided for 10 studies).

In the 13 prospective trials, the relative risk (RR) of TB was 0.49 (95% confidence interval, CI: 0.34, 0.70) for vaccine recipients, compared with nonrecipients (protective effect of 51%). In the 10 case-control studies, the odds ratio (OR) for TB was 0.50 (95% CI: 0.39, 0.64), or a 50% protective effect. Seven trials reporting deaths from TB showed a protective effect from BCG vaccine of 71% (RR 0.29, 95% CI: 0.16, 0.53), and 5 studies reporting on meningitis showed a protective effect from BCG vaccine of 64% (OR 0.36, 95% CI: 0.18, 0.70). Geographic latitude of the study site and study validity score explained 66% of the heterogeneity among trials in a random-effects regression model.

Authors’ conclusions
On average, BCG vaccine significantly reduces the risk of TB by 50%. Protection is observed across many populations, study designs and forms of TB. Age at vaccination did not enhance predictiveness of BCG efficacy. Protection against death from TB, meningitis and disseminated disease is higher than for total TB cases, although this result may reflect reduced error in disease classification rather than greater BCG efficacy.

CRD commentary
There are some inconsistencies in the reporting of the number of included studies: the abstract reports 14 trials, Table 1 describes 15 (maybe 3 Comstock papers are linked), but design details are provided for only 13; similarly, the abstract reports 12 case studies but presents data on 10. The study failed to provide adequate details of the scoring system applied in the validity assessment. The paper does not provide enough detail of the study population or the geographic location of the studies. Geographic latitude of the study site and study validity explained 66% of the heterogeneity in the random-effects regression model. Apart from the presentation inconsistencies noted above, this is a well-conducted meta-analysis.

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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.