The efficacy of Bacillus Calmette-Guerin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature

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Authors' objectives
To quantify the efficacy of vaccination of infants with bacillus Calmette-Guerin (BCG) against tuberculosis.

Searching
MEDLINE was searched (search years unclear) using the index terms 'BCG vaccine', 'tuberculosis' and 'human', and the references of all retrieved articles were reviewed. Unpublished studies were identified by examining previously compiled lists of BCG studies and articles providing an overview of these studies, and by contacting experts on BCG vaccination and knowledgeable individuals (World Health Organization and the Centers for Disease Control and Prevention). The search was not limited to English language articles.

Study selection

Study designs of evaluations included in the review
Randomised controlled trials (RCTs) and case-control studies were included. Groups within RCTs had to be concurrent, have equivalent surveillance and similar length of follow-up. Case-control studies had to define the criteria for the selection of cases and controls, and the method for the determination of the BCG vaccination status of the cases and controls. If controls were identified from a tuberculin-screened population but cases were not, the study was excluded.

Specific interventions included in the review
BCG vaccine against tuberculosis.

Participants included in the review
Mainly infants aged 1 year or less at vaccination, although 2 case-control studies included an unknown number of children who were vaccinated at more than 1 year of age.

Outcomes assessed in the review
The outcomes were tuberculosis deaths, tuberculosis cases (laboratory confirmed and non-laboratory confirmed), tuberculous meningitis cases and disseminated tuberculosis cases.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection. Titles and abstracts were examined.

Assessment of study quality
For RCTs the criteria included: method of assignment to vaccination or control arms, loss to follow-up, equality of surveillance between control and vaccination arms, diagnostic criteria and preparation of BCG. For case-control studies, diagnostic criteria and potential bias in the collection of information, such as vaccine status, were examined. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
At least two readers independently extracted the data, with adjudication by a third reader if disagreements arose. The categories of data extracted are listed in the paper. Relative risks (RRs) were calculated for each trial and odds ratios (ORs) were calculated for the case-control studies.
Methods of synthesis
How were the studies combined?
Results from the RCTS are presented as RRs and, from the case-control studies, as ORs using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.1). Tuberculosis cases, tuberculous meningitis cases, disseminated tuberculosis cases, laboratory confirmed tuberculosis cases and tuberculosis deaths were combined separately and the 95% confidence interval (95% CI) reported.

Three RCTs and 3 case-control studies provided sufficient information to enable year-since-vaccination specific RRs and ORs to be computed.

How were differences between studies investigated?
Regression analysis was undertaken using a random-effects model and 2 covariates: distance of the trial or study from the equator and data validity score. These 2 covariates were chosen because they had 'shown promise' in an earlier analysis (see Other Publications of Related Interest no.2).

Results of the review
Five RCTs and 11 case-control studies were included. The numbers of participants in each trial were not given.

Tuberculosis cases: RCTs (n=4), combined RR 0.258 (95% CI: 0.174, 0.384, p<0.05); case-control studies (n=9), combined OR 0.476 (95% CI: 0.365, 0.621, p<0.05).

Tuberculosis deaths: RCTs (n=5), combined RR 0.352 (95% CI: 0.140, 0.882, p<0.05).

Laboratory confirmed cases: case-control studies (n=3), combined OR 0.174 (95% CI: 0.072, 0.418, p<0.05).

Tuberculous meningitis: case-control studies (n=3), combined OR 0.356 (95% CI: 0.18, 0.70, p<0.05).

Disseminated tuberculosis: case-control studies (n=3), combined OR 0.22 (95% CI: 0.117, 0.419, p<0.05).

Heterogeneity in the case-control studies was not explained by data validity score or distance from the equator. The RCTs were homogeneous.

Most of the duration-specific evidence suggests that BCG efficacy may persist through 10 years after infant vaccination.

Authors’ conclusions
BCG vaccination of newborns and infants significantly reduces the risk of tuberculosis by over 50% on average. Protection has been observed across many populations, study designs and forms of tuberculosis. Rates of protection against cases that are confirmed by laboratory tests, reflecting reduced error in disease classification and consequently more accurate estimates of BCG efficacy, are highest at 83%.

CRD commentary
The authors use a well-defined specific question and make a good search for unpublished literature, although it would have been useful to search more than one electronic database for published studies. Inclusion criteria are clear, an assessment of validity is undertaken and the data from different study designs are kept appropriately separate. The review could have been improved with more details of primary studies, especially numbers of participants in each study and validity scores, although validity scores were not found to affect the results in a regression model for case-control studies. The authors’ conclusions follow from the results presented.

Implications of the review for practice and research
The authors state that future studies might consider whether the administration of a booster dose of vaccine in childhood would further enhance BCG efficacy and extend its duration.
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