Mycobacterium vaccae vaccine to prevent tuberculosis in high risk people: a meta-analysis

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CRD summary
The review concluded that the available evidence showed that *Mycobacterium vaccae* vaccine was effective in preventing tuberculosis in high-risk patients, but that better quality research was urgently needed. These conclusions should be interpreted with caution since they were based on very small numbers of cases of tuberculosis.

Authors' objectives
To evaluate the effectiveness and safety of *Mycobacterium vaccae* vaccine in preventing tuberculosis in high-risk people.

Searching
MEDLINE, EMBASE, BIOSIS Previews, Science Citation Index, Cochrane Central Register of Controlled Trials, and the Chinese databases CBM (Chinese Biological Medicine), CNKI (China National Knowledge Infrastructure) and VIP were searched to July 2009; the keywords used were *M. vaccae* and tuberculosis.

Study selection
Controlled trials that compared *Mycobacterium vaccae* (applied as an intervention) with either no intervention or pharmacotherapy to prevent tuberculosis in high-risk individuals (who had no evidence of active tuberculosis) were eligible for inclusion. The positive stimulation index, the protection index (calculated as the number of patients without onset of tuberculosis divided by the total number of patients in the trial arm of interest, expressed as a percentage), lymphocyte counts and HIV viral load were the outcomes of interest.

Included participants had tested positive for either HIV, purified protein derivative, diabetes mellitus, or had clinically cured pulmonary tuberculosis. More than half the included studies were conducted in China. Intradermal or intramuscular vaccines were administered using between three and 24 doses, over a range of time periods. In most trials, control groups were unvaccinated.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
Two reviewers independently evaluated trial quality (a third reviewer checked the results) by assessing the adequacy of methods relating to the following criteria: randomisation, allocation concealment, blinding, and completeness of outcome data.

Data extraction
Data were extracted in order to calculate risk differences (RD) or risk ratios (RR) with 95% confidence intervals (CI).

Two reviewers independently extracted data; a third reviewer checked the results.

Methods of synthesis
Meta-analyses were performed to calculate pooled risk ratios or risk differences, using a fixed-effect model. Heterogeneity was assessed using I².

Results of the review
Thirteen trials were included in the review (n=6,101 relevant participants, range 16 to 5,115). None of the trials had adequate methods of randomisation or allocation concealment. Only two trials were blinded.

*Mycobacterium vaccae* vaccine was no different to isoniazid in preventing tuberculosis (measured using the protection index) in purified protein derivative positive patients (three trials, I²=0%), but was significantly protective compared
with no vaccination in purified protein derivative positive soldiers (RD 0.04, 95% CI 0.00 to 0.08; I²=0%; two trials) and patients with diabetes mellitus (RD 0.08, 95% CI 0.01 to 0.14; I²=0%; two trials). *Mycobacterium vaccae* vaccination was also associated with a greater chance of positive stimulation index compared with control vaccine in patients with HIV (RR 2.39, 95% CI 1.56 to 3.66; I²=0%; three trials). The most common adverse effects of the vaccine were induration and a sore arm. Further (non-significant) results were reported.

Authors’ conclusions
The available evidence showed that *Mycobacterium vaccae* was effective in preventing tuberculosis in purified protein derivative strong positive/type 2 diabetes mellitus/aged people of clinical cured pulmonary tuberculosis; it was safe, well-tolerated and effective in inducing biologically-relevant immune response against tuberculosis in HIV-infected patients. However, further (high-quality) trials are urgently needed.

CRD commentary
The review addressed a clear question and was supported by appropriate inclusion criteria. Although numerous databases were searched to identify studies, it was unclear whether there were any language restrictions or whether searches were made specifically for unpublished trials, so some relevant studies may have been missed. Suitable methods were used to reduce the risks of reviewer error and bias for the processes of data extraction and study quality assessment, although the authors did not report on whether such methods were used to select studies for inclusion.

Appropriate methods were used to pool data and assess heterogeneity. The authors qualified their conclusions by noting that the quality assessment results indicated the trials were at risk of bias, and that further research was needed. However, their conclusions should be interpreted with caution since they were based on very small numbers of cases of tuberculosis.

Implications of the review for practice and research
**Practice:** The authors stated that *Mycobacterium vaccae* was a good alternative option to orally administered drugs (like isoniazid) for tuberculosis prevention in high risk people.

**Research:** The authors stated that further study is needed to test whether *Mycobacterium vaccae* is superior to isoniazid. They added that high quality studies among different populations, targeting different risk groups, are urgently need.

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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.