

Mycobacterium vaccae immunotherapy for treating tuberculosis (Review)

de Bruyn G, Garner P



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 1

<http://www.thecochranelibrary.com>



TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	2
METHODS	2
RESULTS	3
DISCUSSION	5
AUTHORS' CONCLUSIONS	6
ACKNOWLEDGEMENTS	6
REFERENCES	6
CHARACTERISTICS OF STUDIES	8
DATA AND ANALYSES	15
Analysis 1.1. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 1 Death.	16
Analysis 1.2. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 2 Sputum smear negative by 2 months.	17
Analysis 1.3. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 3 Sputum culture negative at 2 months.	18
Analysis 1.4. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 4 Sputum culture negative at completion of chemotherapy.	19
Analysis 1.5. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 5 Number with cavities present.	20
Analysis 1.6. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 6 Change in x-ray score.	21
Analysis 1.7. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 7 Erythrocyte sedimentation rate (mm/h) at completion of chemotherapy.	22
Analysis 1.8. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 8 Weight change (kg).	22
Analysis 1.9. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 9 Weight (kg) at completion of chemotherapy.	23
Analysis 1.10. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 10 Tuberculin skin test reaction: mean size (mm).	23
Analysis 1.11. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 11 Number requiring retreatment.	24
Analysis 1.12. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 12 Adverse events (local).	24
Analysis 1.13. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 13 Adverse events (any systemic).	25
WHAT'S NEW	26
HISTORY	26
CONTRIBUTIONS OF AUTHORS	26
DECLARATIONS OF INTEREST	27
SOURCES OF SUPPORT	27
INDEX TERMS	27

[Intervention Review]

Mycobacterium vaccae immunotherapy for treating tuberculosis

Guy de Bruyn¹, Paul Garner²

¹Perinatal HIV Research Unit, Wits Health Consortium, Johannesburg, South Africa. ²International Health Group, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Guy de Bruyn, Perinatal HIV Research Unit, Wits Health Consortium, PO Box 114, Diepkloof, Johannesburg, Gauteng, 1864, South Africa. debruyng@phru.co.za.

Editorial group: Cochrane Infectious Diseases Group.

Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 1, 2010.

Review content assessed as up-to-date: 4 October 2002.

Citation: de Bruyn G, Garner P. *Mycobacterium vaccae* immunotherapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2003, Issue 1. Art. No.: CD001166. DOI: 10.1002/14651858.CD001166.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

A B S T R A C T

Background

Some authorities have advocated *Mycobacterium vaccae* immunotherapy for treating tuberculosis and other infections caused by mycobacteria.

Objectives

To evaluate *M. vaccae* immunotherapy as an adjunct to chemotherapy in people with tuberculosis.

Search strategy

In October 2002, we searched the Cochrane Infectious Diseases Group Specialized Register, Cochrane Controlled Trials Register (*The Cochrane Library* 2002, Issue 3), MEDLINE, EMBASE, LILACS, and reference lists of articles. We also contacted organizations and individuals working in the field.

Selection criteria

Randomized and quasi-randomized controlled trials of inoculation with whole killed *M. vaccae* versus placebo for people with tuberculosis.

Data collection and analysis

Both authors assessed trial quality and extracted data. Dichotomous outcomes were analysed with risk ratio (RR) and 95% confidence intervals (CI).

Main results

Eight trials involving 2140 adults met the inclusion criteria. *M. vaccae* immunotherapy had no significant effect on the number of deaths (RR 1.09, 95% CI 0.83 to 1.42; 1741 participants, 4 trials). Meta-analysis suggested small effects on the number of people who were sputum smear negative and sputum culture negative at two months, but these apparent effects were not present in sensitivity analyses that only included adequately concealed trials. Most immunotherapy recipients experienced local adverse reactions (RR 18.82, 95% CI 5.47 to 64.77; 131 participants, 2 trials), some of which progressed to ulceration and scarring.

Mycobacterium vaccae immunotherapy for treating tuberculosis (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

1

Authors' conclusions

M. vaccae immunotherapy does not benefit people with tuberculosis. No further trials are warranted and, as a result, the authors do not intend to update this review.

PLAIN LANGUAGE SUMMARY

No benefit from immunotherapy with *Mycobacterium vaccae* in people with tuberculosis

Injections that aim to influence a person's immune system have been used by doctors to lessen the chance of a person developing a disease, or sometimes to reduce the damage the disease does to the body. *M. vaccae* is a type of bacterium related to the one that causes tuberculosis. Scientists have wondered if injections of this could reduce the damage done to someone when they are infected with tuberculosis, and some early trials suggested this might be true. However, this overview involving eight trials identified that the research does not show any consistent effect of this injection on death or the course of tuberculosis illness. It may be that the early trials had methodological problems that led to false optimism about this intervention.

BACKGROUND

Immunotherapy aims to alter a person's immune response with the intention of reducing illness either by protecting against it or reducing the severity of the condition (Weber 1997). Allergen immunotherapy, for example, aims to reduce a person's sensitivity to an allergen that causes allergic symptoms, such as asthma (Abramson 2000) or allergic rhinitis (Bousquet 1998). Venom immunotherapy is used to modify the response to venoms, such as those of bees or wasps, for people who have severe reactions following prior exposure (Ewan 1998). Immunotherapy for a wide range of infectious agents has been tested, including chronic viral infections, chronic bacterial infections, and parasitic diseases (Convit 1989; Straus 1997; Kahn 2000).

In tuberculosis, the host immune response influences the damage caused by the infection (Rook 1996). Experiments in animals suggest that a type 1 lymphocyte response is less likely to be associated with death of local tissues than a mixed lymphocyte response that includes both type 1 and type 2 responses (Grange 1998). A person's immunity to tuberculosis is thought in part to be related to a type 1 response, characterized by production of interferon-gamma (Barnes 2000).

Mycobacterium vaccae is a rapid-growing mycobacterium species found in the environment. The use of this bacterium as a whole-cell killed vaccine has been advocated as immunotherapy for tuberculosis (Stanford 1990a; Stanford 1994). Although the mechanisms of its potential effect are unknown, it has been proposed that immunotherapy allows immune recognition of antigens com-

mon to all mycobacteria or that immunotherapy directs T-lymphocyte responses towards a type 1 pattern. There is some indirect experimental evidence that this occurs in humans (Rook 1994). More recently, the reduction of allergic responses through induction of regulatory T cells by immunization with *M. vaccae* has been demonstrated (Zuany-Amorim 2002). Immunotherapy is thought to enable the host to destroy organisms and achieve a more rapid cure of infection.

OBJECTIVES

To evaluate *M. vaccae* immunotherapy as an adjunct to chemotherapy in people with tuberculosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized and quasi-randomized controlled trials. We excluded trials with high losses of follow up for the main outcome (> 25%).

Types of participants

People with tuberculosis infection as diagnosed by direct sputum smear microscopy, culture of sputum, or culture of material from a clinically affected anatomical site.

Types of interventions

Intervention

Inoculation with preparations of whole killed *M. vaccae*.

Control

Placebo.

Other treatments, including chemotherapy for tuberculosis, when used, must be the same regimen in both intervention and control groups.

Types of outcome measures

Primary

- Death.
- Sputum smear conversion to negative at two months.
- Sputum culture negative at two months and at the end of chemotherapy.

Secondary

- Changes in chest x-ray appearance, assessed using scoring systems.
 - Erythrocyte sedimentation rate.
 - Weight gain.
 - Tuberculin skin test reaction.
 - Delayed hypersensitivity responses.
 - Need for retreatment.

Adverse events

- Local (eg vaccine site ulceration and induration).
- Systemic (eg fever).
- Immunological (eg increase in HIV viral load, as measured by polymerase chain reaction).

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress). We used the following search terms for all trial registers and databases: tuberculosis and vaccae.

We searched the Cochrane Infectious Diseases Group Specialized Register (October 2002), Cochrane Controlled Trials Register (published in *The Cochrane Library* 2002, Issue 3), MEDLINE (1966 to October 2002), EMBASE (1980 to September 2002), and LILACS (September 2002).

We contacted organizations and individuals working in the field for information regarding unpublished data and work in progress. We also drew on existing reviews of this topic ([Stanford 1990a](#); [Stanford 1994](#)) and checked the citations of all the trials identified by the above methods.

Data collection and analysis

The first author screened the full articles of potentially relevant studies for eligibility. In cases of doubt, both authors reviewed the papers and reached a consensus decision. Both authors assessed the risk of bias in the trials, and the second author checked data extraction. We assessed the risk of bias in relation to the method of generation of allocation sequence and allocation concealment (adequate, inadequate, or unclear as defined by [Jüni 2001](#)), the use of blinding, and losses to follow up.

Data were extracted for outcome variables and entered and analysed in [Review Manager 5](#). We expressed dichotomous outcomes as risk ratio (RR) with 95% confidence intervals (CI), and continuous outcomes as mean difference (MD) with the same CI. Sensitivity analysis of effect estimates were performed on the adequacy of allocation concealment.

In trials that recruited people infected with human immunodeficiency virus (HIV-positive) and people not infected (HIV-negative), we would have stratified the analyses by HIV status had the data been available. This is because the number of deaths in the HIV-positive group would be likely to be higher than in the HIV-negative group and imbalance in numbers could confound the results. We combined the results if no difference was evident visibly in the analyses or statistically.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Eight trials met the inclusion criteria (see 'Characteristics of included studies') and 11 trials were excluded for reasons including that they were of poor quality, abstracts with little information, or trials that had been carried out and no data were available (see 'Characteristics of excluded studies'). The included trials were conducted in China (Wang 1999), Kuwait (Stanford 1990a), Romania (Corlan 1997a; Corlan 1997b), South Africa (DITG 1999), Uganda (Johnson 2000), and the United Kingdom (Kon 1998). Mwinga 2002 was conducted in Malawi and Zambia. The trials enrolled 2140 adults, of whom slightly more than 60% were males. Participants ranged from 15 to 80 years in age. Two trials enrolled HIV-positive participants (DITG 1999; Mwinga 2002). In all but two of the trials the participants were undergoing treatment for a first episode of pulmonary tuberculosis. The exceptions were one trial that enrolled people with recurrent disease (Corlan 1997b) and another that did not state whether participants were receiving retreatment (Mwinga 2002). BCG scars were present in 49% and 83% of patients from Uganda and South Africa, respectively, and in 38% of control patients from the trial in Kuwait. The participants were all on standard chemotherapeutic regimens, as routinely prescribed in the country where the trial was being conducted. Mwinga 2002 used an eight-month regimen, Stanford 1990 used a nine-month regimen, and the other six trials used six-month regimens. All but Mwinga 2002 used rifampicin and isoniazid in the continuation phase, which lasted four to seven months. Differences between the trials mainly involved the drugs used for the initial eight weeks.

Chemotherapy was given on an inpatient basis for two to four months in two trials (Stanford 1990; DITG 1999) and in the Malawian participants in another (Mwinga 2002). Otherwise, drug therapy was self-administered (Corlan 1997a; Corlan 1997b), or self-administered with monitoring of dispensing records and monthly urine testing for metabolites of isoniazid (Johnson 2000; Mwinga 2002). One trial reported that participants received 25 mg of pyridoxine daily (DITG 1999).

Immunotherapy was generally a single dose of 10^9 heat-killed organisms. Five trials reported the strain used (NCTC 11659). Immunotherapy was given on day eight of chemotherapy (DITG 1999, Johnson 2000), between days seven and 14 (Kon 1998), in the first two weeks of antituberculous chemotherapy (Mwinga 2002), or day 28/one month in three trials (Stanford 1990a; Corlan 1997a; Corlan 1997b). One trial administered 0.1 mg of the vaccine product (equivalent number of organisms not stated) in sterile water at the end of week two of chemotherapy, and at week four increased to 0.5 mg every two weeks for an unstated duration (Wang 1999).

Risk of bias in included studies

The allocation sequence was generated using computer-generated randomization in two trials (Corlan 1997a; Corlan 1997b), computer-generated block randomization in two trials (Johnson 2000;

Mwinga 2002), and by means of random, permuted blocks in one trial (DITG 1999). The other three trials did not report the method used.

Three trials described adequate allocation concealment (DITG 1999; Johnson 2000; Mwinga 2002). The method was not described in the other trial reports.

Five trials were described as double blind (Stanford 1990; Kon 1998; DITG 1999; Johnson 2000; Mwinga 2002). Two trials blinded participants (Corlan 1997a; Corlan 1997b). No details were given for blinding in Wang 1999.

Adverse reactions were evaluated by the person who gave the injections or separate assessors. The two trials conducted in Romania blinded only the participants (Corlan 1997a; Corlan 1997b); Corlan 1997b reports on an apparent corruption of randomization: "rather fewer women (9/56) received immunotherapy than received placebo (14/46) probably because the most severely ill patients tended to be directed towards immunotherapy".

In relation to reporting of participants enrolled, the two Romanian trials lost fewer than 10% of randomized participants at 11 months of follow up (Corlan 1997a; Corlan 1997b). All of the participants in the China, South Africa, and Ugandan trials were accounted for at conclusion of the trial (Wang 1999; DITG 1999; Johnson 2000). In Mwinga 2002, approximately 12% of 1145 participants were lost to follow up or had moved from the district by 12 months after the start of chemotherapy. The Kuwaiti trial did not disclose losses to follow up (Stanford 1990); and no participants were reported as lost to follow up in Kon 1998.

Effects of interventions

Primary outcomes

Four trials assessed the number of deaths to the completion of chemotherapy (Corlan 1997b; DITG 1999; Johnson 2000; Mwinga 2002) and, when combined, did not demonstrate a difference between the immunotherapy and placebo groups (RR 1.09, 95% CI 0.83 to 1.42; 1741 participants, Analysis 1.1). A sensitivity analysis that only included trials with adequate allocation concealment did not change this finding (analysis not shown).

Three trials measured the number of participants whose sputum smear converted to negative at two months (Corlan 1997a; Corlan 1997b; Wang 1999). More conversions occurred in the immunotherapy group (RR 1.26, 95% CI 1.11 to 1.43; 356 participants, Analysis 1.2). No sensitivity analysis was possible as these trials all had unclear allocation concealment.

The number of participants who were sputum culture negative at two months was examined in five trials (Corlan 1997a; Corlan 1997b; DITG 1999; Johnson 2000; Mwinga 2002). The forest plot suggests heterogeneity (chi-square 10.55, $P = 0.03$, 1441 participants, Analysis 1.3). The analysis of trials with adequate allocation concealment was not statistically significant (1136 par-

participants, 3 trials, [Analysis 1.3](#)). When measured at completion of chemotherapy, no statistically significant difference was apparent (RR 1.01, 95% CI 0.97 to 1.06; 1490 participants, 5 trials, [Analysis 1.4](#)).

Secondary outcomes

Three trials reported the number of people with chest cavities ([Corlan 1997a](#); [Corlan 1997b](#); [Johnson 2000](#)); see [Analysis 1.5](#). There were fewer with cavities at trial entry in the placebo group (RR 1.15, 95% CI 1.05 to 1.27; 447 participants, 3 trials), but no significant difference was detected between the groups for the number of cavities seen at completion of chemotherapy (240 participants, 2 trials) or at six months after completing chemotherapy (226 participants, 2 trials).

The combined results of two trials, [Corlan 1997a](#) and [Corlan 1997b](#), also found no significant differences in x-ray scores at entry to the trial ([Analysis 1.6](#)), as defined by the trial authors (307 participants, 2 trials). The scores tended to improve in the treatment group at completion of treatment and at six months after treatment had ended, and were significant in [Corlan 1997b](#). Neither trial reported on methods to blind the radiographic assessors to the treatment group.

The *M. vaccae* immunotherapy group was associated with a lower erythrocyte sedimentation rate at the end of chemotherapy compared with the placebo group (WMD 8.96 mm/h, 95% CI 12.95 to 4.97; 299 participants, 2 trials, [Analysis 1.7](#)).

Weight gain was measured in five trials. [Stanford 1990a](#) reported a mean difference of 1.60 kg in weight from the start to end of treatment in the *M. vaccae* group (95% CI 0.41 to 2.79; 112 participants, [Analysis 1.8](#)). [DITG 1999](#) and reported no difference, but no standard deviation was given. [Corlan 1997b](#) and [Corlan 1997a](#) reported greater weight gain in the intervention group, but no statistical test or standard deviation was given; however, in these two trials, weight at the completion of treatment did suggest higher mean weight in the *M. vaccae* group (WMD 2.63, 95% CI 0.51 to 4.78; 299 participants, [Analysis 1.9](#)).

The mean size of tuberculin skin test reactions showed no difference between immunotherapy and placebo groups when measured at entry (106 participants) and three months after starting chemotherapy (90 participants, [Stanford 1990](#)); see [Analysis 1.10](#). There was a trend towards immunotherapy being associated with fewer participants requiring retreatment, but the difference was not statistically significant (308 participants, 3 trials, [Analysis 1.11](#)).

Adverse events

Local adverse reactions were reported in four trials ([Kon 1998](#); [DITG 1999](#); [Johnson 2000](#); [Mwinga 2002](#)); see [Analysis 1.12](#). They were more common overall in immunotherapy recipients (RR 18.82, 95% CI 5.47 to 64.77; 131 participants, 2 trials).

Swelling and redness were significantly more common in recipients of immunotherapy (RR 10.71, 95% CI 6.81 to 16.85; 374 participants, 1 trial), as was ulceration (RR 17.79, 95% CI 5.05 to 62.70; 505 participants, 3 trials). Immunotherapy also resulted in more reports of scarring in the two trials that contained events (RR 10.33, 95% CI 6.61 to 16.13; 706 participants).

One trial, [DITG 1999](#), systematically monitored serious adverse events and did not demonstrate a statistically significant difference between the groups for any systemic adverse events (RR 1.07, 95% CI 0.70 to 1.62; 385 participants, [Analysis 1.13](#)).

DISCUSSION

Three of the eight included trials had adequate concealment of allocation ([DITG 1999](#); [Johnson 2000](#); [Mwinga 2002](#)). Of these three trials, no impact was demonstrated on death, sputum culture at three months, and sputum culture at completion of treatment; nor was there any trend with these outcomes. Overall, the analysis showed no consistent evidence of a benefit of immunotherapy over placebo for people with pulmonary tuberculosis receiving antituberculous chemotherapy, nor has an effect of immunotherapy on mortality been demonstrated.

Two of the trials, [Corlan 1997a](#) and [Corlan 1997b](#), did not assess adherence to prescribed chemotherapy. Also, participants found to have resistance to prescribed agents may not have received a second-line drug because of the lack of availability of these agents in Romania at the time the trials were conducted. The number of participants in each group requiring a change in therapy because of resistance to prescribed agents was not disclosed. These factors may have influenced the effect of drug therapy on the course of the illness, making drug treatment a source of potential bias in the outcome of these trials.

Overall, the earlier trials were small and had methodological weaknesses around allocation concealment, blinding, and accuracy of reporting losses to follow up. In these trials, some benefits with some outcomes were apparent. The recent rigorous trials from South Africa ([DITG 1999](#)), Uganda ([Johnson 2000](#)), and Malawi and Zambia ([Mwinga 2002](#)) have consistently shown no effect of this intervention.

There is no evidence that immunotherapy recipients, including those with HIV infection, had a greater rate of serious adverse events recorded in the same trial. No trials have as yet reported on important outcomes such as the effect of immunotherapy on HIV disease progression, although the impact of tuberculosis itself on survival was clearly demonstrated in the Zambian trial by the 10-fold difference in mortality rate over the trial period between those infected with HIV and those without.

AUTHORS' CONCLUSIONS

Implications for practice

M. vaccae immunotherapy does not benefit people with tuberculosis.

Implications for research

The results of this systematic review underline the importance of carefully planned and executed randomized controlled trials, with strict adherence to concealment of allocation.

No further trials are warranted and, as a result, the authors do not intend to update this review.

ACKNOWLEDGEMENTS

This document is an output from a project funded by the UK Department for International Development (DFID) for the benefit of developing countries. The views expressed are not necessarily those of DFID.

REFERENCES

References to studies included in this review

Corlan 1997a {published data only}

Corlan E, Marica C, Macavei C, Stanford JL, Stanford CA. Immunotherapy with *Mycobacterium vaccae* in the treatment of tuberculosis in Romania. 1. Newly-diagnosed pulmonary disease. *Respiratory Medicine* 1997;**91**(1):13–9.

Corlan 1997b {published data only}

Corlan E, Marica C, Macavei C, Stanford JL, Stanford CA. Immunotherapy with *Mycobacterium vaccae* in the treatment of tuberculosis in Romania. 2. Chronic or relapsed disease. *Respiratory Medicine* 1997;**91**(1):21–9.

DITG 1999 {published data only}

Durban Immunotherapy Trial Group. Immunotherapy with *Mycobacterium vaccae* in patients with newly diagnosed pulmonary tuberculosis: a randomised controlled trial. *Lancet* 1999;**354**(9173):116–9.

Johnson 2000 {published data only}

Johnson JL, Kanya RM, Okwera A, Loughlin AM, Nyole S, Hom SL, et al. Randomized controlled trial of *Mycobacterium vaccae* immunotherapy in non-human immunodeficiency virus-infected Ugandan adults with newly diagnosed pulmonary tuberculosis. The Uganda-Case Western Reserve University Research Collaboration. *Journal of Infectious Diseases* 2000;**181**(4):1304–12.

Kon 1998 {published data only}

Kon OM, Goyal M, Filley E, Gleissberg G, Cunningham D, Rook GA, et al. *Mycobacterium vaccae*: a study of safety and outcome measures. *Respiratory Medicine* 1998;**92**(3):597–8.

Mwinga 2002 {published data only}

Mwinga A, Nunn A, Ngwira B, Chintu C, Warndorff D, Fine P, et al. *Mycobacterium vaccae* (SRL172) immunotherapy as an adjunct to standard antituberculosis treatment in HIV-infected adults with pulmonary tuberculosis: a randomised placebo-controlled trial. *Lancet* 2002;**360**(9339):1050–5.

Stanford 1990 {published data only}

Bahr GM, Stanford JL, Chugh TD, Shaaban MA, Gabriel M, Al-Shimali B, et al. An investigation of patients with pulmonary tuberculosis in Kuwait in preparation for studies of immunotherapy with *Mycobacterium vaccae*. *Tubercle* 1990;**71**(2):77–86.
Stanford JL, Bahr GM, Rook GA, Shaaban MA, Chugh TD, Gabriel M, et al. Immunotherapy with *Mycobacterium vaccae* as an adjunct to chemotherapy in the treatment of pulmonary tuberculosis. *Tubercle* 1990;**71**(2):87–93.

Wang 1999 {published data only}

Wang W, Jin G, Ye Y, Xia X, Wang A, Zhang Y, et al. A clinical study on vaccine of *Mycobacterium vaccae* in treating pulmonary tuberculosis. *Zhonghua Jiehe He Huxi Zazhi [Chinese Journal of Tuberculosis and Respiratory Diseases]* 1999;**22**(2):108–10.

References to studies excluded from this review

Bahr 1990 {published data only}

Bahr GM, Shaaban MA, Gabriel M, al-Shimali B, Siddiqui Z, Chugh TD, et al. Improved immunotherapy for pulmonary tuberculosis with *Mycobacterium vaccae*. *Tubercle* 1990;**71**(4):259–66.

Bottasso 1995 *{published data only}*

Bottasso OA, Vacirca A, Dominino J, Valentini E, Hartopp R. Immunotherapy applied [a pilot study of immunotherapy with M.vaccae against tuberculosis]. *Tubercle and Lung Disease* 1995;**76** Suppl 2:9.

Corrah unpublished *{unpublished data only}*

Corrah T. Trial of M. vaccae from the Medical Research Council Unit in The Gambia. Unpublished.

Dlugovitzky 1999 *{published data only}*

Dlugovitzky D, Bottasso O, Dominino JC, Valentini E, Hartopp R, Singh M, et al. Clinical and serological studies of tuberculosis patients in Argentina receiving immunotherapy with Mycobacterium vaccae (SRL 172). *Respiratory Medicine* 1999;**93** (8):557–62.

Huong unpublished *{unpublished data only}*

Professors Huong, Linh. Trial of M. vaccae. Unpublished.

Luo 2000 *{published data only}*

Luo Y, Lu S, Guo S. Immunotherapeutic effect of Mycobacterium vaccae on multi-drug resistant pulmonary tuberculosis. *Zhonghua Jiehe He Huxi Zazhi [Chinese Journal of Tuberculosis and Respiratory Diseases]* 2000;**23**(2):85–8.

Luo 2001 *{published data only}*

Luo Y, National Cooperation Group on Clinical Study of Mycobacterium Vaccae Vaccine. The immunotherapeutic effect of Mycobacterium vaccae vaccine on initially treated pulmonary tuberculosis. *Zhonghua Jiehe He Huxi Zazhi [Chinese Journal of Tuberculosis and Respiratory Diseases]* 2001;**24**(1):43–7.

Mayo 2000a *{published data only}*

Mayo RE, Stanford JL. Double-blind placebo-controlled trial of Mycobacterium vaccae immunotherapy for tuberculosis in KwaZulu, South Africa, 1991-97. *Transactions of the Royal Society of Tropical Medicine and Hygiene* 2000;**94**(5):563–8.

Onyebujoh 1995 *{published data only}*

Onyebujoh PC, Abdulumini T, Robinson S, Rook GA, Stanford JL. Immunotherapy with Mycobacterium vaccae as an addition to chemotherapy for the treatment of pulmonary tuberculosis under difficult conditions in Africa. *Respiratory Medicine* 1995;**89**(3): 199–207.

Vacirca 1994 *{published data only}*

Vacirca A, Dominino J, Valentini E, Hartopp R, Bottasso OA. A pilot study of immunotherapy with M. vaccae against tuberculosis. *Tubercle and Lung Disease* 1994;**75** Suppl 1:47–8.

Waddell 2000b *{published data only}*

Waddell RD, Chintu C, Lein AD, Zumla A, Karagas MR, Baboo KS, et al. Safety and immunogenicity of a five-dose series of inactivated Mycobacterium vaccae vaccination for the prevention of HIV-associated tuberculosis. *Clinical Infectious Diseases* 2000;**30** Suppl 3:309–15.

Additional references**Abramson 2000**

Abramson MJ, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [DOI: 10.1002/14651858.CD001186]

Barnes 2000

Barnes PF, Wize B. Type 1 cytokines and the pathogenesis of tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2000; Vol. 161, issue 6:1773–4.

Bousquet 1998

Bousquet J, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. *Journal of Allergy and Clinical Immunology* 1998;**102**(4):558–62.

Convit 1989

Convit J, Castellanos PL, Ulrich M, Castes M, Rondon A, Pinaroli ME, et al. Immunotherapy of localized, intermediate, and diffuse forms of American cutaneous leishmaniasis. *Journal of Infectious Diseases* 1989;**160**(1):104–15.

Ewan 1998

Ewan PW. Venom allergy. *BMJ* 1998;**316**(7141):1365–8.

Grange 1998

Grange JM. Pathogenesis of mycobacterial disease. In: Gangadharam PRJ, Jenkins PA editor(s). *Mycobacteria*. Vol. 1: **Basic Aspects**, New York: Chapman-Hall, 1998:145–77.

Jüni 2001

Jüni P, Altman DG, Egger M. Systematic reviews in health care: Assessing the quality of controlled clinical trials. *BMJ* 2001;**323** (7303):42–6.

Kahn 2000

Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. *JAMA* 2000;**284**(17): 2193–202.

Review Manager 5

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Rook 1994

Rook GA, Onyebujoh P, Wilkins E, Ly HM, al Attiyah R, Bahr G, et al. A longitudinal study of per cent agalotonyl IgG in tuberculosis patients receiving chemotherapy, with or without immunotherapy. *Immunology* 1994;**81**(1):149–54.

Rook 1996

Rook GA, Stanford JL. The Koch phenomenon and the immunopathology of tuberculosis. In: Shinnick TM editor(s). *Current Topics in Microbiology and Immunology*. Vol. 215, Berlin: Springer-Verlag, 1996:239–62.

Stanford 1990a

Stanford JL, Rook GA, Bahr GM, Dowlati Y, Ganapati R, Ghazi Saidi K, et al. Mycobacterium vaccae in immunoprophylaxis and immunotherapy of leprosy and tuberculosis. *Vaccine* 1990;**8**(6): 525–30.

Stanford 1994

Stanford JL, Stanford CA. Immunotherapy of tuberculosis with Mycobacterium vaccae NCTC 11659. *Immunobiology* 1994;**191** (4-5):555–63.

Straus 1997

Straus SE, Wald A, Kost RG, McKenzie R, Langenberg AG, Hohman P, et al. Immunotherapy of recurrent genital herpes with

recombinant herpes simplex virus type 2 glycoproteins D and B: results of a placebo-controlled vaccine trial. *Journal of Infectious Diseases* 1997;**176**(5):1129–34.

Weber 1997

Weber RW. Immunotherapy with allergens. *JAMA* 1997;**278**(22): 1881–7.

Zuany-Amorim 2002

Zuany-Amorim C, Sawicka E, Manlius C, Le Moine A, Brunet LR, Kemeny DM, et al. Suppression of airway eosinophilia by killed Mycobacterium vaccae-induced allergen-specific regulatory T-cells. *Nature Medicine* 2002;**8**(6):625–9.

References to other published versions of this review

de Bruyn 1998

de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for TB. *Cochrane Database of Systematic Reviews* 1998, Issue 3.

de Bruyn 1999

de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 1999, Issue 4. [Art. No.: CD001166. DOI: 10.1002/14651858.CD001166]

de Bruyn 2000

de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2000, Issue 2. [Art. No.: CD001166. DOI: 10.1002/14651858.CD001166]

de Bruyn 2003

de Bruyn G, Garner P. Mycobacterium vaccae immunotherapy for treating tuberculosis. *Cochrane Database of Systematic Reviews* 2003, Issue 1. [DOI: 10.1002/14651858.CD001166]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Corlan 1997a

Methods	Generation of allocation sequence: computer-generated randomization Allocation concealment: no information Blinding: participants blinded; provider aware of allocation Losses to follow up at 11 months after entry: <i>Mycobacterium vaccae</i> 6/97 (6.2%); placebo 8/109 (7.3%)
Participants	Number: 206 Description: adult male and female patients with newly diagnosed, sputum culture positive pulmonary tuberculosis Exclusion criteria: no indication of number of exclusions
Interventions	1. <i>M. vaccae</i> strain NCTC 11659, batch A5 (0.1 mL, 10 mg/mL; approximately 10 ⁹ bacilli) given as intradermal injection; given over the deltoid region 1 month after starting chemotherapy 2. Placebo: saline Both groups: 2 months of isoniazid, rifampicin, pyrazinamide, and streptomycin twice weekly (usually in hospital); followed by 4 months of isoniazid and rifampicin taken twice weekly
Outcomes	No primary outcome specified 1. Death 2. Sputum positivity and culture at 6 months 3. Body weight 4. Erythrocyte sedimentation rate 5. X-ray cavities
Notes	Location: Bucharest and Brasov, Romania Adherence: "treatment not strictly supervised" Second-line drugs not generally available in Romania at the time of the study Number of participants requiring changes in prescribed drugs during the trial not disclosed

Corlan 1997b

Methods	Generation of allocation sequence: computer-generated randomization Allocation concealment: no information Blinding: participants blinded; provider aware of allocation Losses to follow up at 11 months after entry: <i>Mycobacterium vaccae</i> = 2/56 (3.6%) placebo = 2/46 (4.3%) Ascertainment bias present: "...the most severely ill patients tended to be directed to the immunotherapy group" (pg 23)
Participants	Number: 102 Description: adult patients with pulmonary tuberculosis who attended for therapy for chronic treatment failure or multiply relapsed disease Exclusion criteria: none; no disclosure of the number of people refusing entry to the trial
Interventions	1. <i>M. vaccae</i> strain NCTC 11659 batch A5: 0.1 mL given as intradermal injection (10 mg/mL; approximately 10 ⁹ bacilli); given over the deltoid muscle 1 month after starting chemotherapy

Corlan 1997b (Continued)

	<p>2. Placebo: saline</p> <p>Both groups: 2 months of rifampicin, isoniazid, streptomycin, and pyrazinamide taken twice weekly (usually in hospital); followed by 4 months of rifampicin and isoniazid taken twice weekly</p>
Outcomes	<p>No primary outcome specified</p> <ol style="list-style-type: none"> 1. Death 2. Sputum positivity and culture at 6 months 3. Body weight 4. Erythrocyte sedimentation rate 5. X-ray cavities
Notes	<p>Location: Bucharest and Bresov, Romania</p> <p>Adherence: "treatment not strictly supervised"</p> <p>Second-line drugs not generally available in Romania at the time of the study</p> <p>Number of participants requiring changes in prescribed drugs during the trial not disclosed</p> <p>Fewer women received immunotherapy than received placebo; <i>M. vaccae</i> = 9/56 (16.1%), placebo = 14/46 (30.4%).</p>

DITG 1999

Methods	<p>Generation of allocation sequence: "random, permuted blocks of size 20"</p> <p>Allocation concealment: "A person independent of the study labelled and packaged the supplies. Sealed disclosure envelopes were supplied for each vial and were stored in the hospital pharmacy." (pg 117)</p> <p>Blinding: double blind; the injection site covered with a bandage to avoid unblinding other patients and staff; local adverse effects monitored by independent assessors</p> <p>Losses to follow up: all participants accounted for at trial's conclusion</p>
Participants	<p>Number: 374</p> <p>Descriptions: patients with newly diagnosed, sputum smear positive pulmonary tuberculosis; tuberculosis bacilli were susceptible to chemotherapy; included HIV-positive people</p> <p>Exclusion criteria: persons with AIDS, leukopenia, signs of liver disease, diabetes, or malignancy</p>
Interventions	<ol style="list-style-type: none"> 1. Heat-killed <i>Mycobacterium vaccae</i> given as intradermal injection (0.1 mL 10⁹) on day 8 of treatment 2. Placebo: intradermal saline injection given on day 8 of treatment <p>Both groups: daily rifampicin 450 mg (600 mg if > 50 kg), isoniazid 300 mg (400 mg if > 50 kg), pyrazinamide 1.5 g (2.0 g if > 50 kg), and ethambutol (1200 mg) for the first 8 weeks. Followed by 4 months of continuation therapy; rifampicin and isoniazid at same doses 3 times a week; pyridoxine 25 mg daily. Treatment given in hospital for the first 8 weeks and if still sputum positive at 8 weeks, a further 4 weeks. Monthly review to completion of 6 months of treatment</p> <p>Participants received 25 mg pyridoxine daily</p>
Outcomes	<ol style="list-style-type: none"> 1. Time to sputum culture conversion in first 8 weeks (primary outcome) 2. Culture status at 6 months 3. Radiographic score at day 56 4. Change in erythrocyte sedimentation rate from day 1 to day 56 5. Change in weight from day 8 to day 56
Notes	<p>Location: South Africa</p> <p>BCG scar present in 83% of participants</p>

Johnson 2000

Methods	<p>Generation of allocation sequence: “computer-generated randomization sequence with a permuted fixed block size of 8”</p> <p>Allocation concealment: “concealed by assigning a dedicated nurse-injector, who made no other subject assessments, to administer the test article. The nurse-injector administered the contents of the next consecutively numbered vial to the subject by intradermal injection (Mantoux method) into the skin over the upper arm.” (pg 1305)</p> <p>Blinding: double blind; injection site covered with an opaque bandage to avoid unblinding; separate clinical assessors used for local and systemic responses</p> <p>Losses to follow up: all participants accounted for at trial’s conclusion</p>
Participants	<p>Number: 120</p> <p>Description: HIV-negative ambulatory adults with first episode of sputum-smear positive pulmonary tuberculosis; radiographically, patients had moderate to severe disease</p>
Interventions	<p>1. Heat-killed <i>Mycobacterium vaccae</i> (0.1 mL) given as intradermal injection on 8th day of antituberculous chemotherapy</p> <p>2. Placebo: sterile borate- buffered saline (0.1 mL), given on 8th day of treatment</p> <p>Both groups: 2 months of daily self-administered isoniazid, rifampicin, pyrazinamide, and ethambutol. Followed by 4 months of daily isoniazid and rifampicin</p>
Outcomes	<p>1. Rates of local and systemic adverse events (primary)</p> <p>2. Rate of sputum culture conversion (primary)</p> <p>3. Other immunological measures (primary)</p> <p>4. Improvement in self-reported fever, cough</p>
Notes	<p>Location: Uganda</p> <p>Adherence monitored through self reporting, review of dispensing records, and testing of urine for isoniazid metabolites</p> <p>BCG scar present in 49% of participants</p>

Kon 1998

Methods	<p>Generation of allocation sequence: randomization method not described</p> <p>Allocation concealment: method not described</p> <p>Blinding: double blind; outcomes assessors blinded to allocation</p> <p>Loss to follow up: none reported</p>
Participants	<p>Number: 11</p> <p>Description: adults (10 male, 1 female) with fully drug-sensitive pulmonary tuberculosis</p>
Interventions	<p>1. <i>Mycobacterium vaccae</i> given as intradermal injection (0.1 mL) given 1 to 2 weeks after diagnosis</p> <p>2. Placebo: saline (0.1 mL) injected intradermally</p> <p>Dosing interval (daily/3 times a week/twice weekly) not reported</p> <p>Both groups: 2 months of rifampicin, isoniazid, and pyrazinamide, followed by 4 months of rifampicin and isoniazid</p>
Outcomes	<p>No primary outcome stated</p> <p>1. Adverse events (local and systemic)</p> <p>2. Change in body weight</p> <p>3. Change in chest radiographic appearance (score)</p>

Kon 1998 (Continued)

	4. Erythrocyte sedimentation rate 5. C-reactive protein 6. Immunological measures
Notes	Location: UK Adherence: not reported

Mwinga 2002

Methods	Generation of allocation sequence: “randomisation schedule was prepared by the MRC HIV Clinical Trials Unit, London, UK, by means of computer-generated balanced randomised blocks” (pg 1051) Allocation concealment: “name of an eligible patient was entered on the next available line of the study register to obtain a study number, which identified the prelabelled treatment vial” (pg 1051); “Treatment assignment was concealed from all clinical staff involved in the management of the patient.” (pg 1051) Blinding: double blind Losses to follow up: approximately 12% of 1145 lost to follow up or had moved from the district by 12 months after the start of chemotherapy
Participants	Number: 1145 adults (642 male, 503 female) Description: with smear positive pulmonary tuberculosis; included HIV-positive people
Interventions	1. <i>Mycobacterium vaccae</i> strain NCTC 11659 (0.1 mL of SRL172 containing 10 ⁹ heat-killed organisms in sterile borate-buffered saline) given as 1 injection within the first 2 weeks of initiating antituberculous chemotherapy 2. Placebo: sterile borate-buffered saline (0.1 mL) Both groups’ antituberculous chemotherapy varied by trial site: <ul style="list-style-type: none"> • Lusaka: self-administered outpatient therapy with daily doses of rifampicin (450 mg if < 50 kg, 600 mg if 50 kg or more), pyrazinamide (1.5 g or 2.0 g), isoniazid (300 mg), ethambutol (800 mg or 1200 mg) for weeks 1 to 8, followed by isoniazid (300 mg) and ethambutol (600 mg or 800 mg) for weeks 9 to 32 • Karonga: participants admitted to hospital for the first 8 weeks of therapy, which consisted of daily doses of streptomycin (0.75 g if < 33 kg, 0.75 g if 33 to 49 kg, or 1 g if > 50 kg), isoniazid (200 mg, 300 mg, 300 mg), rifampicin (300 mg, 450 mg, 600 mg), and pyrazinamide (1 g, 1.5 g, 2 g). During weeks 9 to 32, participants were discharged to self-administer isoniazid (200 mg, 300 mg, 300 mg), and ethambutol (400 mg, 600 mg, 800 mg) daily
Outcomes	1. Death (primary outcome) 2. Time to death in HIV-infected participants 3. Sputum culture status at 2 months 4. Bacteriologic status at 12 months 4. Safety
Notes	Locations: Lusaka, Zambia and Karonga, Malawi Adherence was assessed by self-reporting, review of dispensing records, and urine tests for isoniazid metabolites

Stanford 1990

Methods	Generation of allocation sequence: randomization method not described Allocation concealment: no information Blinding: double blind; participants covered their shoulders in the presence of physicians recording data about them, other than data regarding local reactions, which were evaluated by the person who gave the injections Loss to follow up: not disclosed Length of follow up: 4 months from entry
Participants	Number: 112 Description: adult male and female adults admitted to the Kuwait Chest Diseases Hospital with pulmonary tuberculosis
Interventions	1. <i>Mycobacterium vaccae</i> strain NCTC 11659 given as intradermal injection (0.1 mL; 10 mg/mL; approximately 10 ⁹ bacilli) and given 28 days after starting chemotherapy 2. Placebo: saline Both groups: 2 months of isoniazid, rifampicin, and streptomycin given in hospital; followed by 7 months of isoniazid and rifampicin
Outcomes	No primary outcome stated 1. Body weight 2. Erythrocyte sedimentation rate 3. X-ray cavities
Notes	Location: Kuwait Results only reported for data showing differences between groups. Some participants were given ethambutol and pyrazinamide based on drug sensitivity testing 38% of placebo participants had a BCG scar (data for immunotherapy group not reported)

Wang 1999

Methods	Generation of allocation sequence: randomization method not described Allocation concealment: no comment Blinding: no details Loss to follow up: all participants accounted for at trial's conclusion
Participants	Number: 70 Description: previously untreated adults with 3 successive sputum smears positive for acid-fast bacilli
Interventions	1. <i>Mycobacterium vaccae</i> given as intramuscular injection (0.1 mg, reconstituted in 2 mL sterile water) at end of week 2 of chemotherapy; further <i>M. vaccae</i> intramuscular injections (0.5 mg of diluted in 2 mL sterile water) given at 2-weekly intervals 2. Both arms: 2 months of rifampicin, isoniazid, pyrazinamide, plus ethambutol or streptomycin as initial therapy, followed by 6 months of isoniazid and ethambutol
Outcomes	No primary outcome stated 1. Improvement in clinical symptoms 2. X-ray appearance after 2 and 4 months of chemotherapy 3. Sputum smear conversion 4. Skin test conversion

Wang 1999 (Continued)

	5. Immunological responses at 4 months
Notes	Location: China

Characteristics of excluded studies [ordered by study ID]

Bahr 1990	This trial of improved immunotherapy in Kuwait was excluded because it did not report pooled data for all patients receiving immunotherapy. It selectively reported specific secondary outcomes for specific immunotherapy subgroups
Bottasso 1995	Abstract only; insufficient detail for full assessment
Corrah unpublished	We were unable to obtain further information about this unpublished trial from the Medical Research Council Unit in The Gambia
Dlugovitzky 1999	This study of 40 patients reported data from 2 separate trials with different timing of the immunotherapeutic intervention; trial excluded because data from each trial were not presently separately in the published report
Huong unpublished	We were unable to obtain further information about this unpublished trial
Luo 2000	“Random pair” design: methods indicate use of matched controls, rather than a clear description of random allocation
Luo 2001	“Random pair” design: methods indicate use of matched controls, rather than a clear description of random allocation
Mayo 2000a	This trial of 204 participants randomized to immunotherapy and control (intradermal tetanus toxoid) was excluded as more than 30% of participants had been lost to follow up by the completion of treatment, which meant that a significant change in primary study outcomes was possible had a more complete follow up been achieved
Onyebujoh 1995	This trial of 90 participants randomized to immunotherapy and control was excluded because of significant losses at follow up (52% of control group and 62% of the immunotherapy group), which puts the trial at a high risk of bias
Vacirca 1994	Abstract only; insufficient detail for full assessment
Waddell 2000b	Immunological outcomes only; no comparison group

DATA AND ANALYSES

Comparison 1. *Mycobacterium vaccae* immunotherapy versus placebo

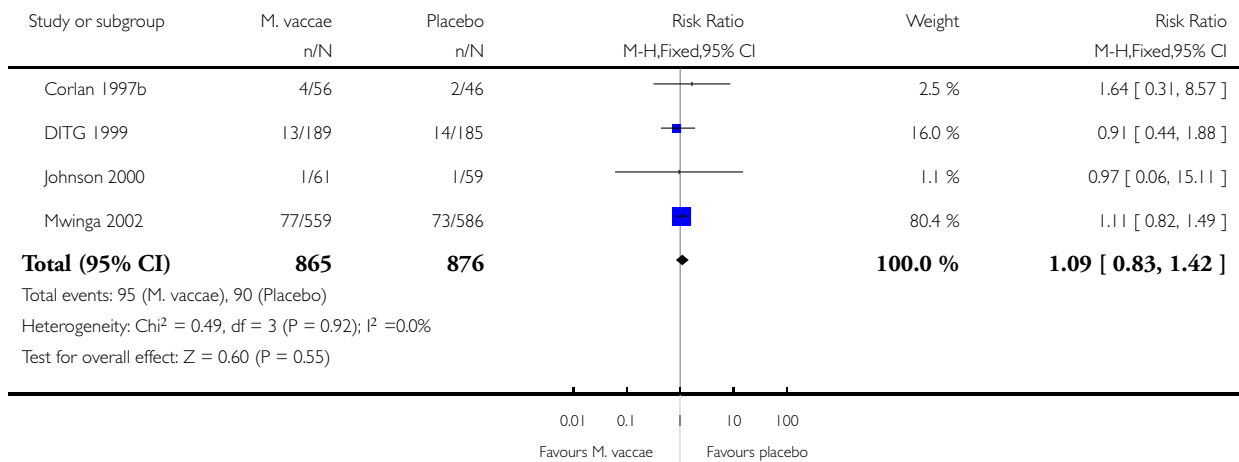
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	4	1741	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.83, 1.42]
2 Sputum smear negative by 2 months	3	356	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [1.11, 1.43]
3 Sputum culture negative at 2 months	5	1441	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.01, 1.16]
3.1 Adequate allocation concealment	3	1136	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.97, 1.12]
3.2 Unclear allocation concealment	2	305	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.08, 1.45]
4 Sputum culture negative at completion of chemotherapy	5	1490	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.97, 1.06]
5 Number with cavities present	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At entry	3	447	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.05, 1.27]
5.2 At completion of chemotherapy	2	240	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
5.3 At 6 months after completing chemotherapy	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.01]
6 Change in x-ray score	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 At entry	2	307	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.18, 0.10]
6.2 At completion of chemotherapy	2	289	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.39, -0.11]
6.3 At 6 months after completing chemotherapy	2	259	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.35, -0.07]
7 Erythrocyte sedimentation rate (mm/h) at completion of chemotherapy	2	299	Mean Difference (IV, Fixed, 95% CI)	-8.96 [-12.95, -4.97]
8 Weight change (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Weight (kg) at completion of chemotherapy	2	299	Mean Difference (IV, Fixed, 95% CI)	2.63 [0.51, 4.76]
10 Tuberculin skin test reaction: mean size (mm)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 At entry	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
10.2 At 3 months	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
11 Number requiring retreatment	2	308	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.37, 1.14]
12 Adverse events (local)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Any	2	131	Risk Ratio (M-H, Fixed, 95% CI)	18.82 [5.47, 64.77]
12.2 Swelling and redness	1	374	Risk Ratio (M-H, Fixed, 95% CI)	10.71 [6.81, 16.85]
12.3 Ulceration	3	505	Risk Ratio (M-H, Fixed, 95% CI)	17.79 [5.05, 62.70]
12.4 Scarring	3	717	Risk Ratio (M-H, Fixed, 95% CI)	10.33 [6.61, 16.13]

Analysis 1.1. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 1 Death.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 1 Death

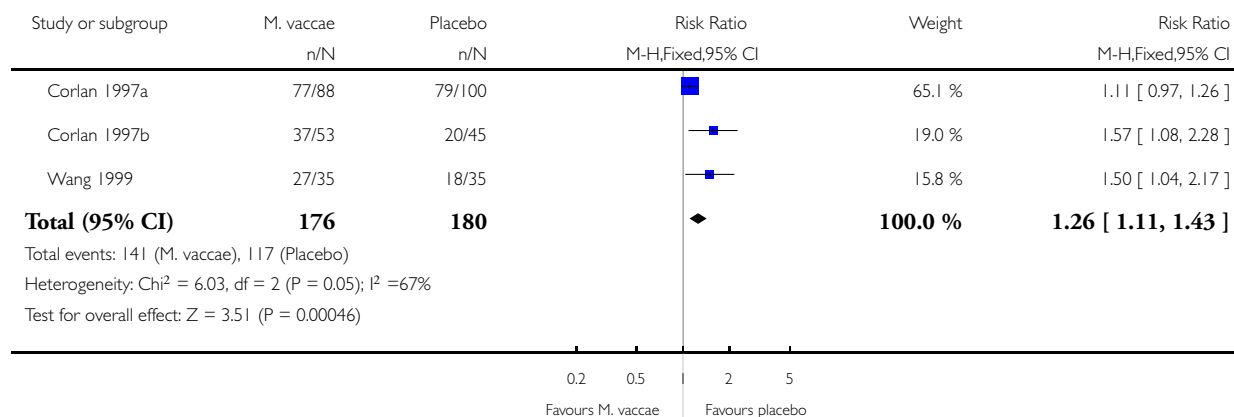


Analysis 1.2. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 2 Sputum smear negative by 2 months.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 2 Sputum smear negative by 2 months

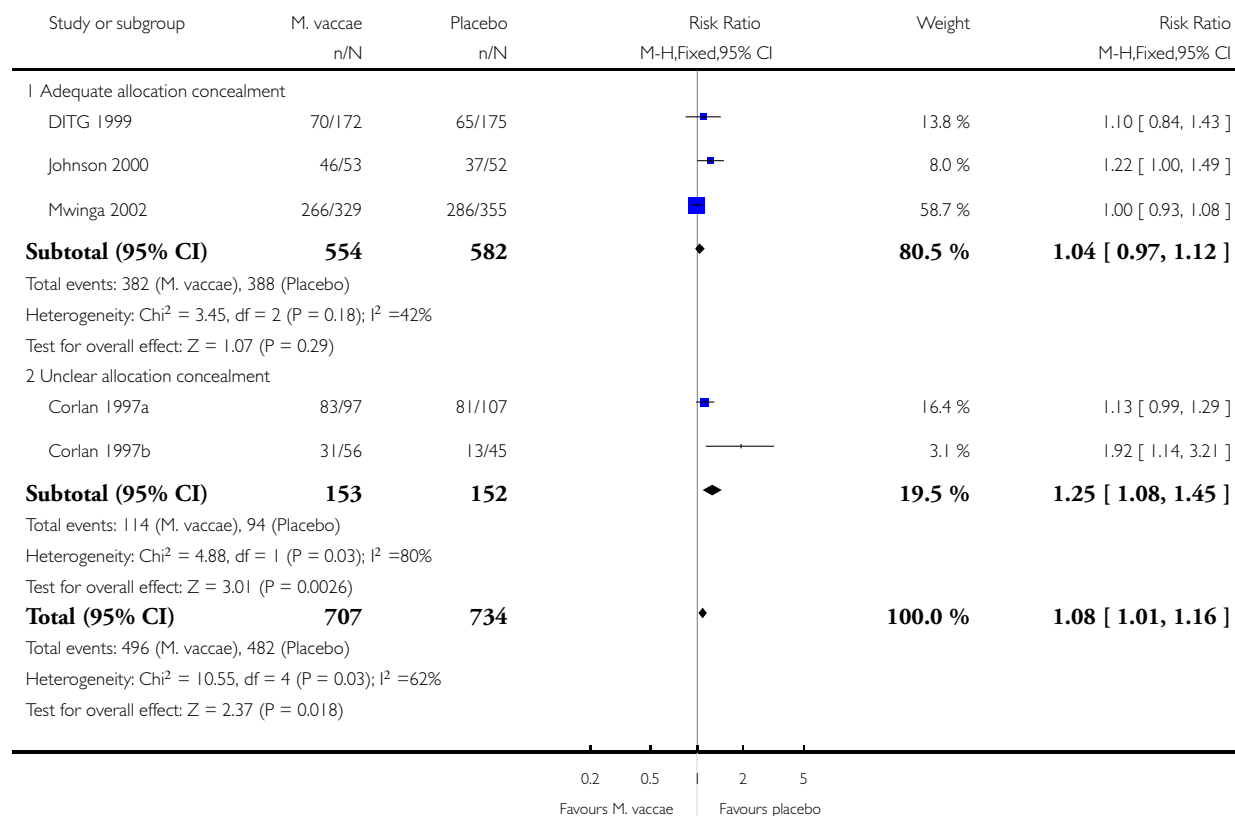


Analysis 1.3. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 3 Sputum culture negative at 2 months.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 3 Sputum culture negative at 2 months

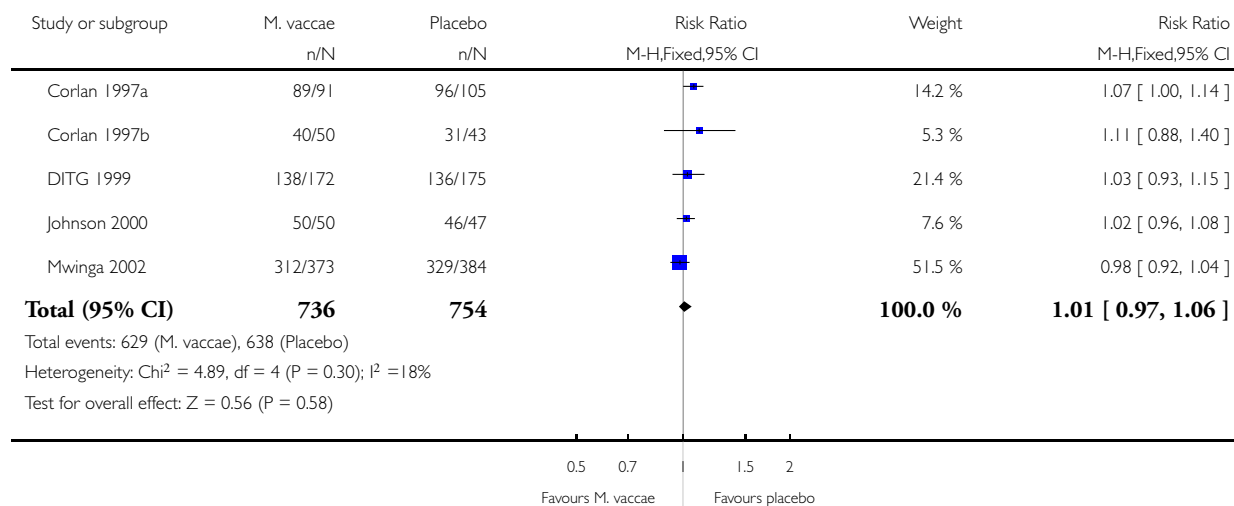


Analysis 1.4. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 4 Sputum culture negative at completion of chemotherapy.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 4 Sputum culture negative at completion of chemotherapy

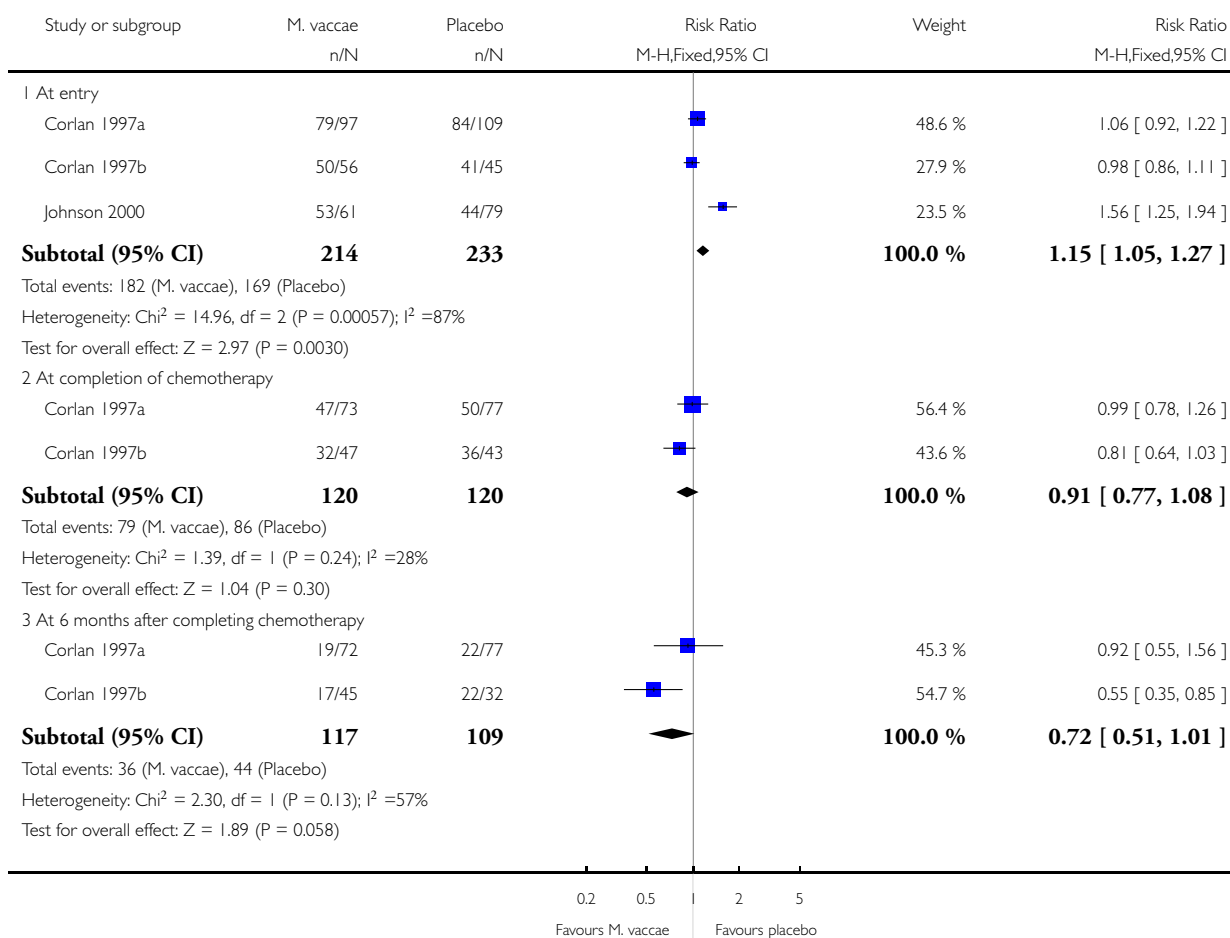


Analysis 1.5. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 5 Number with cavities present.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 5 Number with cavities present

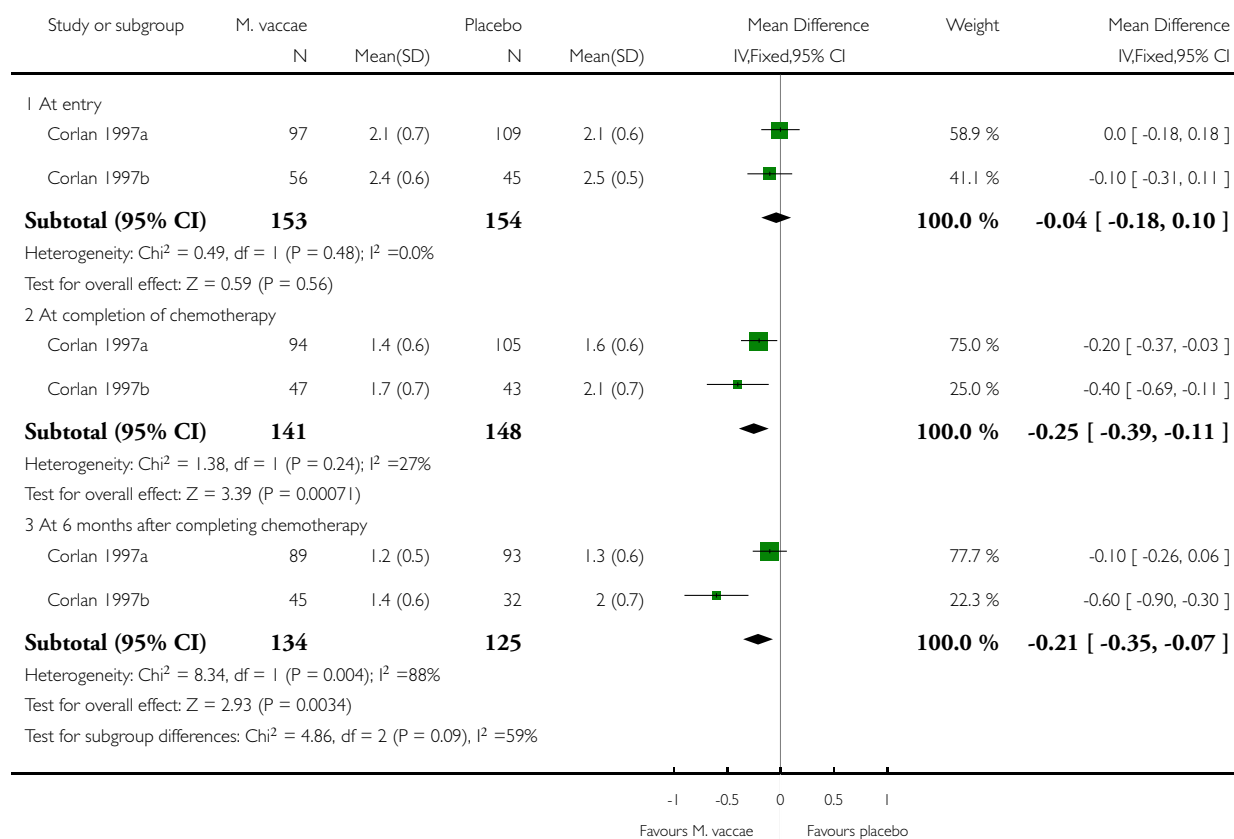


Analysis 1.6. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 6 Change in x-ray score.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 6 Change in x-ray score

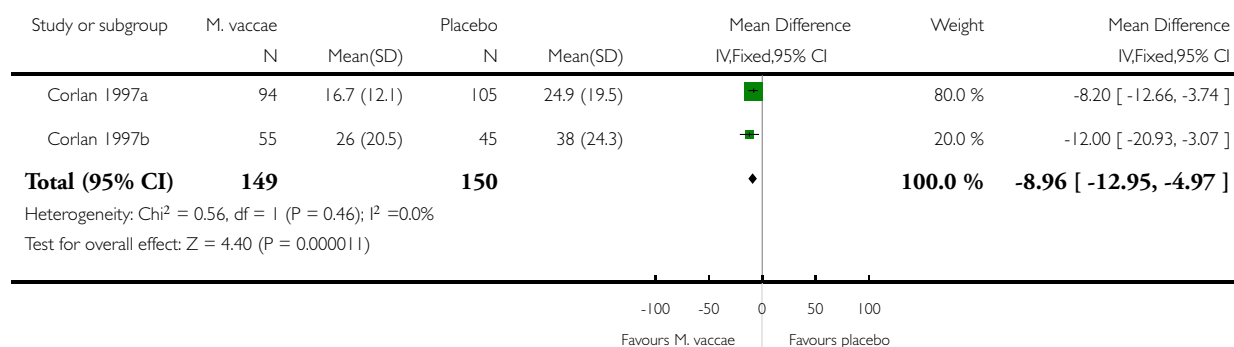


Analysis 1.7. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 7 Erythrocyte sedimentation rate (mm/h) at completion of chemotherapy.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 7 Erythrocyte sedimentation rate (mm/h) at completion of chemotherapy

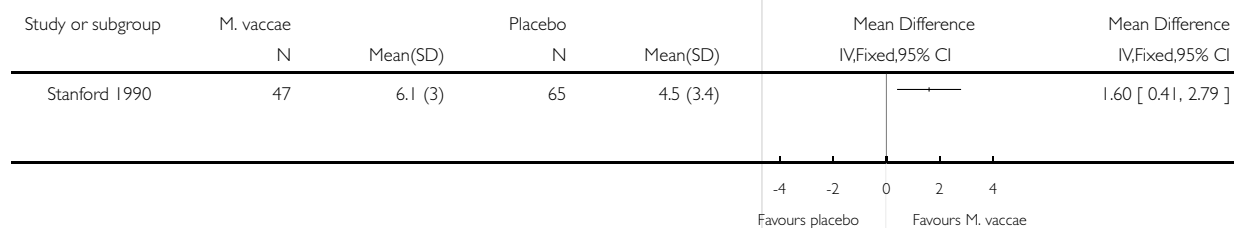


Analysis 1.8. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 8 Weight change (kg).

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 8 Weight change (kg)

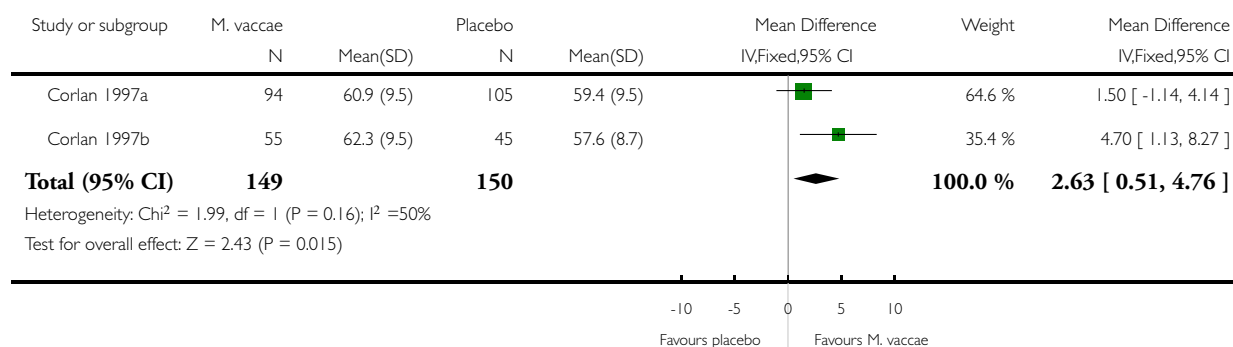


Analysis 1.9. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 9 Weight (kg) at completion of chemotherapy.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 9 Weight (kg) at completion of chemotherapy

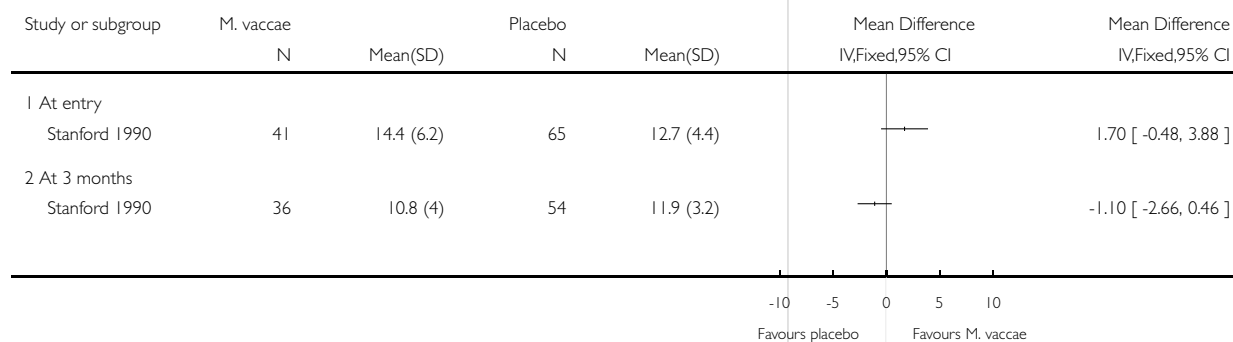


Analysis 1.10. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 10 Tuberculin skin test reaction: mean size (mm).

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 10 Tuberculin skin test reaction: mean size (mm)

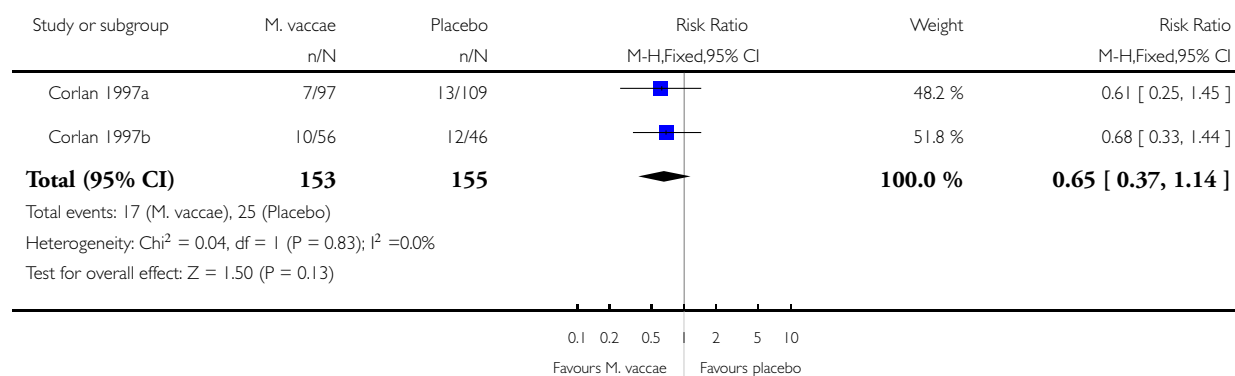


Analysis 1.11. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 11 Number requiring retreatment.

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 11 Number requiring retreatment

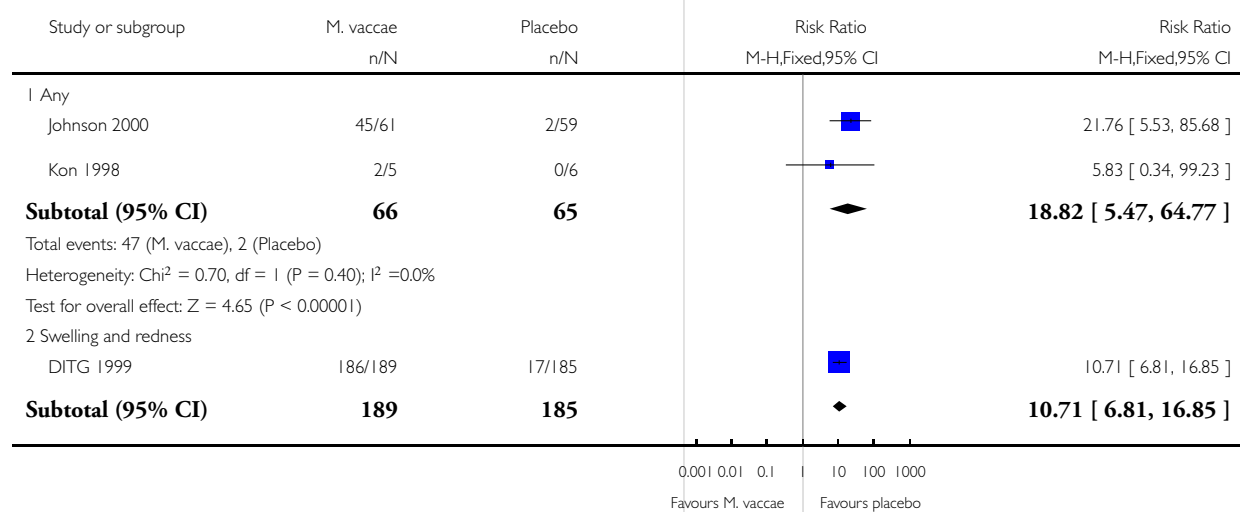


Analysis 1.12. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 12 Adverse events (local).

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

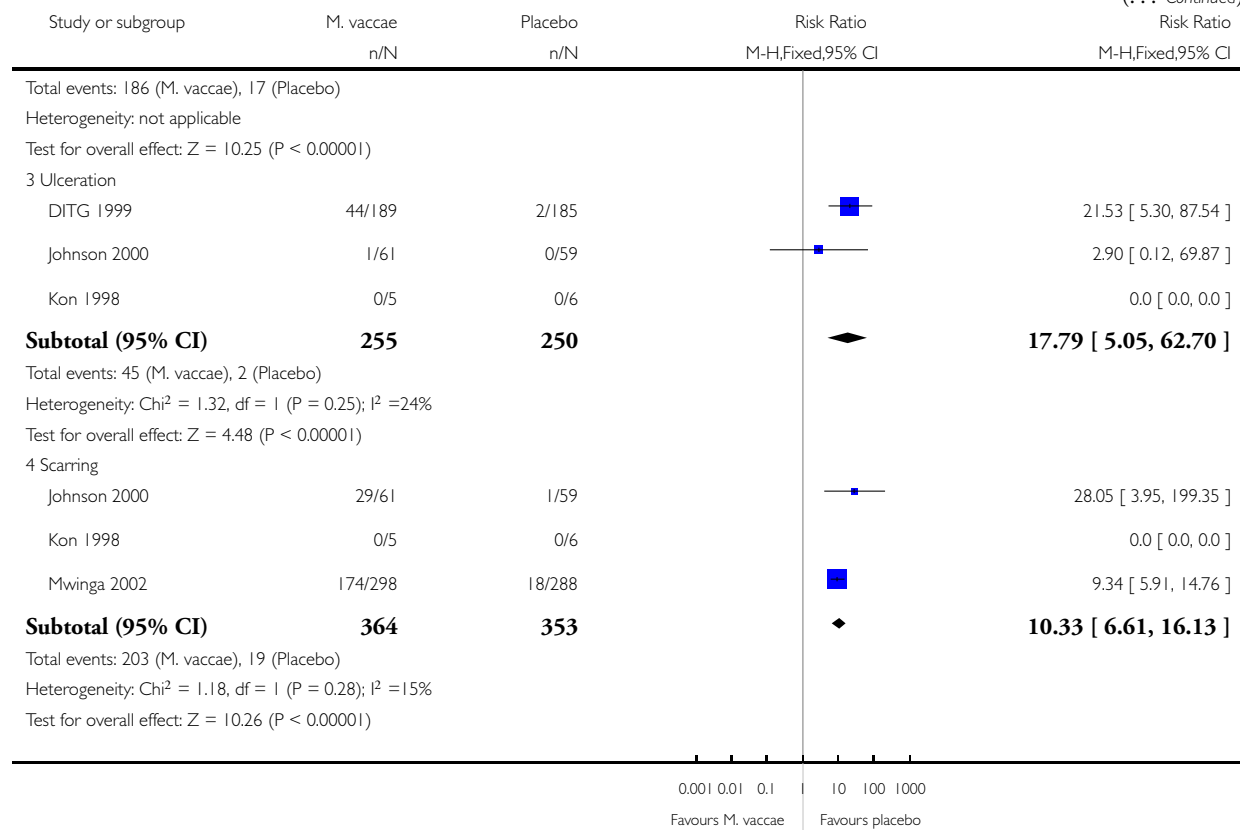
Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 12 Adverse events (local)



(Continued ...)

(... Continued)

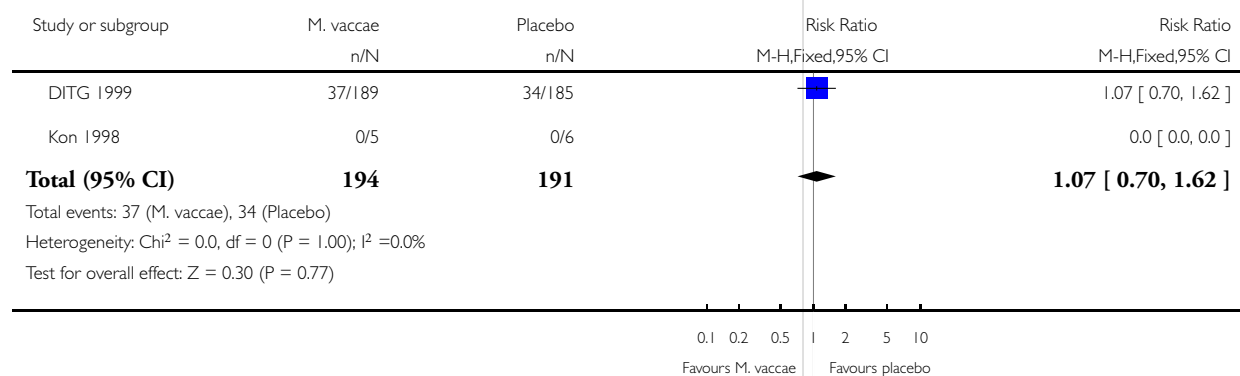


Analysis 1.13. Comparison 1 Mycobacterium vaccae immunotherapy versus placebo, Outcome 13 Adverse events (any systemic).

Review: Mycobacterium vaccae immunotherapy for treating tuberculosis

Comparison: 1 Mycobacterium vaccae immunotherapy versus placebo

Outcome: 13 Adverse events (any systemic)



WHAT'S NEW

Last assessed as up-to-date: 4 October 2002.

10 November 2009	Review declared as stable	<i>M. vaccae</i> immunotherapy does not benefit people with tuberculosis. No further trials are warranted and, as a result, the authors do not intend to update this review. This decision was taken in August 2008, prior to the introduction of a formal Cochrane policy, hence the necessity to republish now.
------------------	---------------------------	---

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 3, 1998

29 July 2008	New citation required but conclusions have not changed	2000, Issue 3: (substantive update): One new trial added; title changed from "Mycobacterium vaccae immunotherapy for TB" to Mycobacterium vaccae immunotherapy for treating tuberculosis"; and time points specified for sputum smear conversion and sputum culture negative.
21 July 2008	Amended	Converted to new review format with minor editing.
20 February 2008	New search has been performed	2008, Issue 1 (minor update): Of the five studies awaiting assessment in the de Bruyn 2003 version, we included one (Wang 1999), and excluded two because they did not meet the inclusion criteria (Luo 2000; Luo 2001) and two because we could not obtain additional information on these unpublished reports (Corrah unpublished; Linh unpublished). We changed the odds ratios to risk ratios, which are thought to be more accessible to readers. The review has also had a substantive edit.
7 October 2002	New citation required and conclusions have changed	2003, Issue 1 (substantive update): Mwinga 2002 added; conclusions altered in the light of this.

CONTRIBUTIONS OF AUTHORS

Guy de Bruyn drafted the protocol, data extraction forms, applied the inclusion criteria, assessed quality, extracted data, and prepared the review. Paul Garner helped develop the protocol, checked inclusion criteria, assessed quality, checked data extraction, and contributed to writing the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development (DFID), UK.
- European Commission (Directorate General XII), Belgium.

INDEX TERMS

Medical Subject Headings (MeSH)

Immunotherapy [*methods]; Mycobacterium [*immunology]; Randomized Controlled Trials as Topic; Tuberculosis, Pulmonary [immunology; *therapy]

MeSH check words

Humans