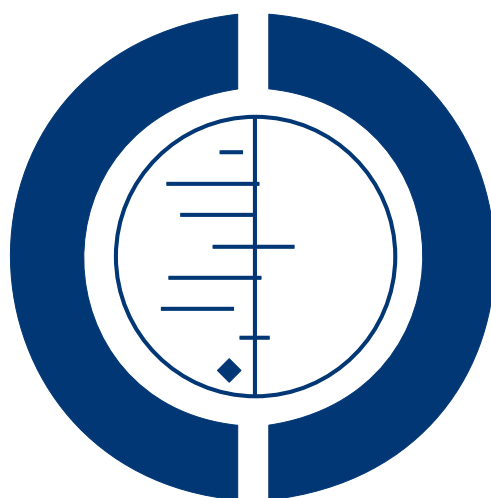


# Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis (Review)

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Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis (Review)  
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[Intervention Review]

# Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis

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## ABSTRACT

### Background

The emergence and spread of multiple-drug-resistant tuberculosis (MDR-TB), caused by strains of *Mycobacterium tuberculosis* resistant to at least isoniazid and rifampicin, is a potential threat to global tuberculosis control. Treatment is prolonged, expensive, more toxic than treatment of susceptible tuberculosis, and often unsuccessful. Experts are still undecided on the management of people exposed to MDR-TB.

### Objectives

To evaluate antituberculous drugs given to people exposed to MDR-TB in preventing active tuberculosis.

### Search strategy

We searched the Cochrane Infectious Diseases Group Specialized Register (March 2009), CENTRAL (*The Cochrane Library* 2009, Issue 1), MEDLINE (1966 to March 2009); EMBASE (1974 to March 2009), LILACS (1982 to March 2009), conference proceedings, and reference lists. We also contacted researchers and organizations.

### Selection criteria

Randomized controlled trials comparing antituberculous drug regimens with an alternative antituberculous drug regimen, placebo, or no intervention given to people exposed to MDR-TB for preventing active tuberculosis.

### Data collection and analysis

Two authors independently inspected titles and abstracts identified by the search in order to identify potentially relevant publications for inclusion and analysis.

### Main results

No randomized controlled trials met the inclusion criteria.

## Authors' conclusions

The balance of benefits and harms associated with treatment for latent tuberculosis infection in people exposed to MDR-TB is far from clear. Antituberculous drugs should only be offered within the context of a well-designed randomized controlled trial, or when people are given the details of the current evidence on benefits and harms, along with the uncertainties.

## PLAIN LANGUAGE SUMMARY

### No trials on effectiveness of treatments to prevent latent tuberculosis from developing into active disease in people exposed to multiple-drug-resistant tuberculosis (MDR-TB)

The emergence and spread of MDR-TB, caused by strains of *Mycobacterium tuberculosis* resistant to at least the common drugs used for TB (isoniazid and rifampicin), is a threat to people worldwide. Treatment of latent tuberculosis (infection without active disease) has been a key component in tuberculosis control for several decades. However, MDR-TB is spreading and people are dying. This review of evidence found no randomized controlled trials that have assessed the effectiveness of treatments of latent tuberculosis infection in people exposed to MDR-TB. Currently the balance of benefits and harms associated with treatment for latent tuberculosis infection in people exposed to MDR-TB is far from clear. Drug treatments should only be offered within the context of a well-designed randomized controlled trial, or where people are given the details of the current evidence on benefits or harms, along with the uncertainties.

## BACKGROUND

The term tuberculosis describes a broad range of clinical illnesses caused by *Mycobacterium tuberculosis*. Although *M. tuberculosis* may affect any organ, pulmonary tuberculosis is the most common and communicable form, and the focus of this review. Approximately 1.7 billion people, nearly one third of the world's population, are thought to be infected with *M. tuberculosis*, with an estimated two million deaths each year (Jasmer 2002).

Tuberculosis is transmitted through inhalation of droplet nuclei from infected people. The pathogenesis of tuberculosis involves three phases, transmission and acquisition of infection, latency, and progression of latent infection into active disease. In most instances, the infection is asymptomatic and the only evidence of infection is a positive skin hypersensitivity test, also known as a Mantoux or tuberculin test. Tuberculin testing is performed by injecting a standard dose of tuberculin into the skin of the forearm and measuring the subsequent skin reaction (an induration or palpable raised hardened area). A person who has been exposed to the bacteria is expected to mount an immune response in the skin containing the bacterial proteins. The reaction is read by measuring the diameter of induration in millimetres. Calcific foci in the lung are seen only in a minority of cases, with viable bacilli in an even smaller minority. Approximately 3% to 4% of people with latent infection progress to active tuberculosis during the first year after tuberculin conversion (converting from a negative to

positive skin reaction to a tuberculin test), and an additional 5% to 15% of people with latent infection develop active disease during their lifetime (Mandell 2000).

People who have been received a Bacille Calmette-Guérin vaccine (BCG), a live-attenuated mycobacterial strain derived from *M. bovis*, may have a reaction to a tuberculin test. No reliable method has been developed to distinguish tuberculin reactions caused by vaccination with BCG from those caused by natural mycobacterial infections, although reactions of greater than 20 mm of induration are not likely caused by BCG. Therefore, a positive reaction to tuberculin in BCG-vaccinated persons indicates infection with *M. tuberculosis* when the person tested is at increased risk for recent infection or has medical conditions that increase the risk for disease (ATS 2000). People with increased risk for developing active tuberculosis due to exposure to *M. tuberculosis* include people with recent skin test conversion, children under the age of five, and people with particular clinical conditions such as immunosuppression (ATS 2000).

Symptoms of tuberculosis include cough (sometimes with haemoptysis or blood in the sputum), chest pain, breathlessness, night sweats, and signs of pneumonia. In advanced disease, there may be extreme weight loss. About a quarter of sufferers from the disease die, most of them young adults (Dye 1999).

The emergence and spread of multiple-drug-resistant tuberculosis (MDR-TB), caused by strains of *M. tuberculosis* resistant to at least isoniazid and rifampicin, is a threat to global tuberculosis control. Treatment of MDR-TB is prolonged, expensive, more toxic than treatment of susceptible tuberculosis, and often unsuccessful (Pablos-Mendez 2002).

MDR-TB is essentially a man-made disease. Exposure to a single drug, whether as a result of poor adherence to treatment, inappropriate prescribing (including inappropriate multiple-drug therapy), irregular drug supply, or poor drug quality, suppresses the growth of bacilli susceptible to that drug but permits the multiplication of pre-existing drug-resistant mutants. The patient then develops acquired resistance. Subsequent transmission of such bacilli to other people may lead to disease that is drug resistant from the outset, an occurrence known as primary resistance (WHO 2004).

According to the World Health Organization (WHO), the prevalence of MDR-TB among new cases between 1999 and 2002 ranged from 0% to 14.2% (1.1% median). Among previously treated cases, the prevalence ranged between 0% and 60% (7% median). When all cases were combined, the prevalence ranged between 0% and 26.8% (1.7% median), and rates of over 10% were documented in 11 countries (WHO 2004).

Treatment of latent tuberculosis infection has been a key component in tuberculosis control for several decades. The American Thoracic Society recommends using isoniazid and rifampicin as chemoprophylactic agents for treating latent tuberculosis in groups at high risk for susceptible tuberculosis (ATS 2000). A Cochrane Review demonstrated that treating HIV-negative people at increased risk of developing active tuberculosis with isoniazid resulted in a reduced risk of developing active tuberculosis when compared with placebo (relative risk 0.40, 95% confidence intervals (CI) 0.31 to 0.52) (Smieja 2000). According to another Cochrane Review of HIV-positive people, any treatment regimen of latent tuberculosis results in a reduced risk of active tuberculosis (relative risk 0.64, 95% CI 0.51 to 0.81) (Woldehanna 2004). Treatment of MDR-TB contacts is complicated by resistance of the source isolates to recommended drugs and unproven cost-effectiveness of alternative treatment.

While the level of evidence regarding the effectiveness of treatment of latent tuberculosis for people at risk of susceptible tuberculosis is high, experts are still undecided on the management of people exposed to MDR-TB (Passannante 1994). According to a statement issued by the American Thoracic Society and adopted by the Centers for Disease Control and Prevention (CDC), immunocompetent people exposed to MDR-TB should be followed up for six months whether treated or not. In cases where they are treated, the American Thoracic Society recommends pyrazinamide and ethambutol *or* pyrazinamide and a quinolone (levofloxacin or ofloxacin) for six to 12 months if the organisms from the index case patient are known to be susceptible to these agents (

ATS 2000). However, frequent adverse effects, including hepatitis, hyperuricaemia, rash (pyrazinamide) and optic neuritis (ethambutol) (Yee 2003), have been documented in people who have been prescribed these drugs for latent tuberculosis.

## OBJECTIVES

To evaluate antituberculous drugs given to people exposed to MDR-TB in preventing active tuberculosis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials.

#### Types of participants

People exposed to patients with active MDR-TB. We excluded people with active tuberculosis at study enrolment, and trials involving people with active tuberculosis disease, as this would be considered treatment of disease rather than prevention of active disease.

#### Types of interventions

##### Intervention

Any antituberculous drug regimen.

##### Control

Any alternative antituberculous drug regimen, placebo, or no intervention.

#### Types of outcome measures

##### Primary

Active pulmonary tuberculosis.

##### Secondary

- Death from any cause.
- Extra-pulmonary tuberculosis.

### Adverse events

- Serious adverse events (leading to hospitalization or continuation of hospitalization, life-threatening, or persistent or significant disability).
- Adverse events requiring discontinuation of treatment.
- Other adverse events.

### 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).

### Databases

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (March 2009); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2009, Issue 1); MEDLINE (1966 to March 2009); EMBASE (1974 to March 2009); and LILACS (1982 to March 2009).

### Conference proceedings

We searched the following proceedings of the following conferences: European Congress of Clinical Microbiology and Infectious Diseases, 2001 to 2004; Annual Meeting of the Infectious Diseases Society of America (IDSA), 2001 to 2004; and the Inter-science Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 1995 to 2003.

### Researchers and organizations

We contacted researchers in the field, the World Health Organization, and the International Union Against Tuberculosis and Lung Disease for unpublished and ongoing trials.

### Reference lists

We also checked the reference lists of all studies identified by the above methods.

### Data collection and analysis

Two authors (A Fraser and M Paul) independently inspected titles and abstracts identified by the search to identify potentially relevant publications. No randomized controlled trials met the inclusion criteria. Should any trials meet these criteria in the future, we will use the plan described in the protocol ([Fraser 2005](#)) to assess their methodological quality, and extract and analyse data.

## RESULTS

### Description of studies

No randomized controlled trials met the inclusion criteria.

### Risk of bias in included studies

No randomized controlled trials met the inclusion criteria.

### Effects of interventions

No randomized controlled trials met the inclusion criteria.

## DISCUSSION

The increasing global spread of MDR-TB and the difficulties in treating it emphasize the need for effective preventive measures. Ideally this issue should be addressed in a randomized controlled trial. Treatment should include a combination of pyrazinamide and ethambutol *or* pyrazinamide and a quinolone (levofloxacin or ofloxacin), according to existing recommendations ([ATS 2000](#)) and assuming that the *M. tuberculosis* strain isolated from the index case is susceptible to these drugs. As no standard treatment exists, we believe that such a trial comparing treatment to placebo is ethical ([WMA](#)).

Such a trial should be conducted in a setting in which MDR-TB is prevalent and a tuberculosis control programme is in place. All close contacts of incident MDR-TB cases would be included. Contacts or households would be randomized to receive treatment or placebo when the drug susceptibility profile of the index case becomes available and followed up for at least 12 months, as it has been demonstrated that over 90% of active tuberculosis cases were diagnosed up to one year after the diagnosis of the index case ([Schaaf 2002](#)). Important outcomes are the development of active disease (primary outcome), all-cause death, tuberculosis-related death, and adverse events. Demographic data, data on comorbidities, history of tuberculosis disease, BCG vaccination status, previous treatment for prior exposure or disease, exposure to other people with tuberculosis, compliance to prescribed treatment, and other known confounders should be recorded. Assuming that 8% of untreated contacts develop active disease ([Kritski 1996](#)), and a 60% reduction of risk of active tuberculosis in treated contacts ([Smieja 2000](#)), a trial with 80% power and 5% chance of a type I error would require a sample size of 800 people exposed to MDR-TB. Randomization by household (cluster randomization) would increase the required sample size.

Observational data on the effectiveness of treatment of latent tuberculosis infection after exposure to MDR-TB are also scarce. We identified only two such studies in a systematic search for any study (including cohort studies, comparisons with historical controls, and case-control studies) that compared treatment of latent tuberculosis with no such treatment in people at risk of developing active MDR-TB (Fraser 2006).

Schaaf and colleagues conducted a prospective cohort study of childhood contacts of people with MDR-TB (Schaaf 1999; Schaaf 2002). Treatment was tailored to the susceptibility profile of the index case and included isoniazid (15 to 20 mg/kg/day), pyrazinamide (25 to 35 mg/kg/day), and ethionamide (10 to 15 mg/kg/day). Ethambutol (15 to 20 mg/kg/day) and/or ofloxacin (15 mg/kg/day) were added depending on the susceptibility pattern of the strain isolated from the index case. Active disease developed in two of the 41 contacts that received treatment and in 13 of 64 contacts that did not receive chemoprophylaxis (odds ratio 0.20, 95%CI 0.04 to 0.94). Therefore results of this study suggest that treatment of latent tuberculosis infection using a drug regimen tailored to the susceptibility profile of the index case may be effective in preventing active disease. Kritski and colleagues conducted a retrospective cohort study of household contacts of people with drug-resistant tuberculosis (Kritski 1996). Active disease developed in two of 45 Mantoux-positive contacts treated with isoniazid (400 mg/day) compared with 13 of 145 that did not receive isoniazid (odds ratio 0.46, 95%CI 0.07 to 2.32). The treatment effect was not statistically significant in this study. Furthermore, it is important to note that neither of the above mentioned studies addressed the issue of possible confounding as a source of bias in their analyses.

Despite the lack of evidence, the CDC, the American Thoracic Society, and the Infectious Diseases Society of America have issued suggestions for the treatment of latent infection in people exposed to MDR-TB. They recommend a two-drug regimen of pyrazinamide and ethambutol *or* pyrazinamide and a quinolone (levofloxacin or ofloxacin) (ATS 2000).

Adverse effects and limited tolerance to combination therapy including pyrazinamide have been documented in case series of people with latent tuberculosis infection (Papastavros 2002; Ijaz 2006). In 2003, the CDC withdrew its former recommendation to use a regimen of rifampicin with pyrazinamide for the treatment of latent tuberculosis infection due to an increased incidence of

severe liver injury. In a survey conducted by the CDC, the rate liver dysfunction was 26.4 per 1000 treatment initiations, clinical hepatitis occurred in 18.9, leading to hospitalization in 3.0, and death in 0.9 (CDC 2003). Serious adverse effects can affect compliance causing prolonged treatment, further development of resistance, and relapse.

Currently the balance of benefits and detriments associated with treatment for latent tuberculosis infection in people exposed to MDR-TB is far from clear, with no randomized controlled trials assessing its effectiveness.

## AUTHORS' CONCLUSIONS

### Implications for practice

Currently the balance of benefits and detriments associated with treatment for latent tuberculosis infection in people exposed to MDR-TB is far from clear. Treatment with drugs that have potentially serious adverse effects needs very careful consideration. People should be given the details of the current evidence on benefits and adverse effects, along with the uncertainties, to try to help them to decide for themselves whether they want to have drug treatment.

### Implications for research

Due to the lack of evidence, a trial evaluating the effectiveness of individualized treatment — treatment tailored to the individual susceptibility profile of the *M. tuberculosis* strain isolated from the index case compared with placebo — is warranted. Such trials should evaluate treatment among both HIV positive and negative contacts. Analysis of routine data and data from observational studies could provide some insight on efficacy and adverse events related to treatment of latent tuberculosis infection in people exposed to MDR-TB. These data could serve for better defining a provisional policy, and for designing randomized controlled trials.

## ACKNOWLEDGEMENTS

We thank the Cochrane Infectious Diseases Group for their support and help.

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#### WMA

The World Medical Association. Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. [www.wma.net/ef/policy/b3.htm](http://www.wma.net/ef/policy/b3.htm) (accessed 15 May 2005).

#### Woldehanna 2004

Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database of Systematic Reviews* 2004, Issue 1. [DOI: DOI: 10.1002/14651858.CD000171.pub2]

#### Yee 2003

Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory and Critical Care Medicine* 2003;**167**(11):1472–7.

### References to other published versions of this review

#### Fraser 2005

Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD005435]

\* Indicates the major publication for the study

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix I. Search methods: detailed search strategies

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>
1	multi-drug resistant tuberculosis	TUBERCULOSIS MULTIDRUG-RESISTANT	TUBERCULOSIS MULTIDRUG-RESISTANT	TUBERCULOSIS	tuberculosis
2	MDR-TB	multidrug resistant tuberculosis	multidrug-resistant tuberculosis	MULTIDRUG-RESISTANCE	drug resistance
3	-	multiple drug resistant tuberculosis	MDR tuberculosis	1 and 2	1 and 2
4	-	drug resistant tuberculosis	MDR-TB	multidrug resistant tuberculosis	TUBERCULOSIS FARMACO-RESISTENTE
5	-	MDR-TB	multi-drug resistant tuberculosis	multiple drug resistant tuberculosis	TUBERCULOSIS RESISTENTE A DROGAS
6	-	1 or 2 or 3 or 4 or 5 or 6	drug-resistant tuberculosis	drug resistant tuberculosis	3 or 4 or 5
7	-	-	multiple drug resistant tuberculosis	MDR tuberculosis	-
8	-	-	1 or 2 or 3 or 4 or 5 or 6 or 7	MDR TB	-
9	-	-	-	3 or 4 or 5 or 6 or 7 or 8	-

<sup>a</sup>Cochrane Infectious Diseases Group Specialized Register.

<sup>b</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2005](#)); upper case: MeSH or EMTREE heading; lower case: free text term.

## WHAT'S NEW

Last assessed as up-to-date: 4 March 2009.

5 March 2009	New search has been performed	Search updated. No new studies found
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## HISTORY

Protocol first published: Issue 3, 2005

Review first published: Issue 2, 2006

19 August 2008	Amended	Converted to new review format with minor editing.
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## CONTRIBUTIONS OF AUTHORS

Abigail Fraser collected data, and managed and wrote the review. Mical Paul searched for references, assessed studies for inclusion, and helped write the review. Ahmed Attamna conceived the review and provided general advice. Leonard Leibovici conceived and proofread the review.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### **Internal sources**

- Rabin Medical Center, Israel.

### **External sources**

- Department for International Development, UK.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Antitubercular Agents [\*therapeutic use]; Mycobacterium tuberculosis [drug effects]; Tuberculosis, Multidrug-Resistant [\*prevention & control]; Tuberculosis, Pulmonary [\*drug therapy]

### **MeSH check words**

Humans