

Regimens of less than six months for treating tuberculosis (Review)

Gelband H



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[Intervention Review]

Regimens of less than six months for treating tuberculosis

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ABSTRACT

Background

WHO recommends 6 months of treatment in TB programmes.

Objectives

The purpose of this review is to assess the effects of regimens lasting less than 6 months compared with longer regimens in the treatment of active TB.

Search strategy

Search strategy: MEDLINE 1955 to October 2005, Cochrane Infectious Diseases Specialized Register, existing reviews, and researchers in the field. Date of the most recent search: May 2004.

Selection criteria

Randomized trials comparing two or more TB drug regimens, in which at least one regimen was <6 months and it was compared with at least one regimen that lasted longer, in any patients with active TB.

Data collection and analysis

One reviewer extracted data and assessed trial quality.

Main results

Seven trials with a total of 9 comparisons of <6 months (range: 2-5 months) versus longer treatment were included. About 2200 patients were in the shorter regimens and about 1900 in the longer regimens (the same comparison groups were used for more than one shorter regimen, in two studies).

Relapse rates were consistently higher after shorter duration treatment regimens, regardless of the comparison made, though they were all relatively low. Results were significantly better in the longer groups in the meta-analyses of 2, 3, and 4 months of treatment vs longer treatment (Peto OR = 6.1 [95%CI 2.19,17.01], 3.67 [2.42,5.58], 3.64 [1.71,7.75] but not in the single trial of 5 vs. 7 months (Peto OR = 2.24 [0.90,5.59]).

Relapse rates after longer (comparison) regimens ranged from 0-7% at one year (or more), and in the shorter treatment arms, they ranged from 1-9% in 8 trials, and 18% relapsed in the one remaining.

There was little or no difference in the rates of adverse reactions or toxicity requiring a change of regimen or discontinuation of treatment. The "sterilizing efficacy" at the end of treatment varied little among treatments, providing no predictive value for relapse

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rates. Few or no deaths were reported in the individual trials, and in no case did enough deaths occur for a comparison of short vs. long regimens.

Authors' conclusions

Longer periods of treatment (at least up to 6 months) result in higher success rates in patients with active TB, but the differences are small. Under field conditions, where adherence to treatment is a big problem, and shorter regimens might improve adherence, these differences may not be evident. A comparison of <6 months vs. 6 months of treatment under programme conditions would be needed to determine this.

PLAIN LANGUAGE SUMMARY

Regimens of less than six months for treating tuberculosis

Plain language summary pending

BACKGROUND

Treatment for active pulmonary tuberculosis (TB) is a very long process compared with treatments for most other bacterial diseases, with "short-course" treatment recommended by WHO lasting 6 months. The success of short-course chemotherapy in randomized trials in the 1970s and 1980s led to randomized trials of even shorter regimens—from 3 to 5 months—which are the subject of this review. On completion of these trials in the late 1980s, the general consensus was of disappointment, because relapse rates were significantly higher than with 6 months of treatment. As a result, shorter courses were rejected and are not the norm anywhere today.

A key reason for the failure of 6-month regimens is that it is difficult for people to complete such a long course of treatment. In most cases, people feel quite well after the first month or two of treatment, when most of the tubercle bacilli have been killed, and there is a natural tendency for patients to stop taking drugs, and programs in many parts of the world are short of resources to provide them. A great deal of effort has been made worldwide to improve adherence to 6-month regimens (including the WHO-recommended approach of "directly-observed therapy"), but incomplete therapy is still an enormous problem, both in terms of leaving individuals still infected and in fostering the development of drug-resistant bacilli.

If shorter regimens can be used with better adherence than 6-month regimens, and if drug resistance is not enhanced, there may still be a practical reason to use regimens shorter than 6 months in some places.

The purpose of this review is to reexamine these trials with 2 main aims: first, to determine whether the consensus view is supported by the totality of the data; and second, to gain insight into whether further trials under program conditions might be useful to determine if adherence is enhanced with shorter regimens enough to offset the higher relapse rates. This is important because success rates in TB control programs fall far short of what can be achieved in trials under ideal conditions because it is so difficult to maintain adherence to 6-month (or longer) regimens.

OBJECTIVES

To determine the effectiveness of any TB treatment regimen lasting <6 months.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized trials comparing two or more TB regimens, in which at least one regimen was <6 months and it was compared with at least one regimen that lasted longer. The comparator did not

have to be 6 months, as long as there was a longer vs. shorter comparison (i.e., a trial could compare a 3-month regimen with a 4-month regimen, or a 5-month vs. a 7-month regimen).

Types of participants

Any patients with active TB, including those with drug-resistant bacilli and any previous treatment. Active TB is defined as having at least one of the following positive: sputum smear; sputum culture; radiographic evidence of active disease.

Types of interventions

All regimens that would have been considered appropriate at the time the trial was carried out were acceptable. All the shorter regimens contain the following 4 drugs, with their accepted abbreviations:

S: Streptomycin

H: Isoniazid

R: Rifampicin

Z: Pyrazinamide

A form of standard notation for TB regimens is used in the table and figures. The initial number denotes the number of months for that regimen or phase. The letter "I" after the letters (which stand for each drug in the regimen) denotes intermittent treatment (which was twice or thrice weekly in the trials reviewed). If no "I" is present, the regimen or phase is daily. The number of days per week drugs are given also may be denoted by a subscript after the regimen

As an example, 2SHRZ/2HRI denotes a regimen of streptomycin, isoniazid, rifampicin, and pyrazinamide given daily in the 2-month initial phase, followed by isoniazid and rifampicin given intermittently in the 2-month continuation phase.

Types of outcome measures

Primary

1. Relapse: Single positive sputum culture, single positive sputum smear with symptoms, within 12 months of completion of successful treatment (i.e., cure), when reported. In some trials, results are given only for periods other than 1 year.
2. Toxicity: Adverse drug reactions that require interruption, alteration, or complete cessation of treatment.

Other

1. Sterilizing efficacy at end of treatment (defined as sputum culture negative immediately after completion of treatment).
2. Death: Deaths recorded during and up to 12 months following completion of treatment.

Search methods for identification of studies

Search strategy: MEDLINE 1955 to May 2004; Cochrane Central Register of Controlled Trials (CENTRAL); Cochrane Infectious Diseases Specialized Register; existing reviews, and researchers who had been involved in identified trials.

Data collection and analysis

The inclusion criteria were applied to all identified trials by the author. Each included trial was assessed in terms of adequacy of concealment of allocation, generation of allocation sequence and follow up of subjects, using the protocol of the Cochrane Infectious Diseases Group.

RESULTS

Description of studies

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

Seven trials, published between 1979 and 1989, are included in the review. They were carried out in the following countries: 3 trials in India; 2 trials in Hong Kong; 1 trial in Singapore; and 1 trial in Germany.

In all trials, drug taking was fully supervised in outpatient departments or clinics. A few patients in some of the trials were hospitalized during all or part of the course of treatment, but the vast majority (more than 95% in all trials reporting this figure) were treated as outpatients.

Five of the trials had 3 or more treatment arms. In three of these (South India 1986, South India 1989, Singapore 1991), two or more arms were of the same duration, but differed either in the specific drugs used or in having daily vs. intermittent dosages. In these cases, the arms of identical length are combined into a single group for comparison. In the other two trials with multiple comparisons (Hong Kong 1979, Hong Kong 1989), the arms are of different lengths and are included as separate comparisons. The trials are all relatively small by today's standards, with between 50 and 250 individuals in most treatment arms. In all the trials, individuals who did not complete a large percentage of the treatment were excluded from the analysis, others were excluded for other reasons, and still others lost to follow-up (see "Methodological quality").

The patients in all except the two Hong Kong trials were sputum smear positive. In the Hong Kong trials, patients were sputum smear negative. Some were culture positive and some culture negative, but all had radiologic evidence of active disease.

In the trials in which it was reported, about 10-15% of patients had bacilli resistant to isoniazid or at least one other drug (see [Appendix](#)

1). Only one trial (Germany) reported excluding patients with drug-resistant bacilli.

A number of drug regimens were used, most but not all containing rifampin and pyrazinamide (see table of included studies).

France 1976 and East Africa 1978 (see table of excluded studies) are excluded because they compared regimens of equal length. The French trial was the first published report of shorter regimens, and provided the impetus for the later trials. It compared 3 months of daily streptomycin, isoniazid, and rifampicin with the same drugs given 3 times per week for 3 months. These 3-drug regimens are less effective than the 4-drug regimens used in the other trials, so the results are of less interest to the subject of this report, in any case. The East Africa study compared 4-month regimens with and without rifampicin in the continuation phase, with the result clearly favoring the inclusion of rifampicin.

Risk of bias in included studies

All studies used some form of random allocation, but only one (Singapore 1981) specified the method used (sealed envelopes provided by the Medical Research Council in London). One trial (Agra 1981) mentioned that a placebo was given to the shorter-duration treatment group to make the total lengths of treatment equal. No other mention or suggestion of blinding was mentioned in any study.

About 10% of all eligible patients (after exclusions for pre-randomization ineligibility were already taken into account) entered in 5 of the trials were not included in relapse analyses for a variety of reasons, by far the most important being “defaulting” on treatment (patients either completely lost to follow-up or who took less than a pre-specified proportion of scheduled treatments). Adverse reactions were the second most important reason. The overall proportions not included in relapse analyses were much higher in two trials: Germany 1986 (18%) and Singapore 1981 (23% not seen at 30-month follow-up). There was no evidence of higher default rates (or other losses) in longer compared with shorter treatment arms in the trials. The small trials sizes and the sometimes large number of exclusions lead to less confidence in the results than the reported precision suggests.

No trial presented an intention-to-treat analysis, nor were the data reported in sufficient detail to be able to conduct such an analysis. The trials are of similar quality. Failure to analyze the data according to intention-to-treat (or provide the data in a form that such an analysis could be conducted) is, by today's standards, a major failing, but at the time the trials were done, this would not have been a major criticism. Except for the German trial, all the trials were done with involvement of the British or Indian Medical Research Councils, both of which were using state-of-the-art methodology at the time the trials were initiated, which was in a relatively short span of years. There is no apparent reason to exclude any trials from the analyses on the basis of quality, but the lack of intention-

to-treat analyses must temper any conclusions drawn from these trials.

Effects of interventions

Relapse rates at one year (or more, depending on reporting) are consistently higher after shorter duration treatment regimens, regardless of the specific comparison made in terms of the details of the regimens or the types of patients randomized in individual trials. There appears to be no threshold for regimens of less than 6 months, i.e., the longer the regimen, the lower the relapse rate. These trials do not provide information about a possible threshold after treatment for 6 months or longer.

Nonetheless, the relapse rates were all quite low. Relapse rates after longer (comparison) regimens were all less than 10% at 1 year (or more) (ranging from 0% to 7%), and in the shorter treatment arms, they were 10% or less for eight comparisons (ranging from 1% to 9%) and 18% in the one remaining comparison (S. India 1986). It must be borne in mind that these relapse rates are based only on study participants who complied fully with the treatment protocol (in most cases meaning having taken at least 75-90% of scheduled treatments), and that failure rates based on intention-to-treat analyses (which cannot be carried out based on published data) could be higher, taking into account lack of adherence to the regimen as well as drug failure.

There was little or no difference in the rates of adverse reactions or toxicity requiring a change of regimen or discontinuation of treatment, with the exception of one trial (Hong Kong 1979) in which significantly fewer changed or discontinued treatment in the 2-month regimen than in the 12-month regimen, but these were small numbers (6/299 vs 17/299).

The regimens were all very good in terms of sterilizing efficacy after completion of treatment. The reported sterilizing efficacy for each arm of each trial is:

Agra

3-month regimen: 99%

4.5 month regimens (combined): 100%

Germany (all results at 3 months only)

3-month regimen: 94%

6-month regimens (combined): 99%

Hong Kong 1979

2- and 3-month regimens: 100%

Hong Kong 1989

2-, 3-, and 4-month regimens: 100%

S. India 1983

Initially drug sensitive infections:

5-month regimen: 97%

7-month regimens (combined): 98%

Initially drug resistant infections:

combined 5- and 7-month regimens with R: 85%

7-month regimen without R: 57%

S. India 1986

3-month regimen: 96%
5-month regimen with R: 99%
5-month regimen without R: 97%

DISCUSSION

The trials reviewed here were begun 15 to 20 years ago and their results convinced tuberculosis control researchers that regimens shorter than 6 months produced results inferior to the then-standard 6-month regimens. This systematic review supports that conclusion, at least for treatment under the best conditions that could be devised, and including in the analyses only individuals who received all or most of the prescribed regimens. That said, the failure rates at one year for shorter regimens under these ideal conditions were still very low by field standards: less than 10% in all trials except one (which had an 18% relapse rate) compared with relapse rates from 0-7% in the longer arms. Although the numbers were small, nearly all relapses were with drug-sensitive strains which could be retreated with the same drugs.

Nearly all study participants with initially drug-sensitive bacilli were sputum culture negative at the end of treatment, regardless of the length of treatment. This was not true of all those with initially drug-resistant bacilli, but this was not reported separately in most papers. These data demonstrate, however, that sterilizing efficacy at the end of treatment is not a sensitive indicator of the risk of relapse.

Few deaths were reported in any trial (and overall, more due to other causes than to TB), so no analysis of the effect on death of different lengths of treatment would be useful.

The results of this review cannot be applied directly to decide on appropriate regimens for TB control programs. They do indicate that the longer patients take anti-TB drugs, the lower the relapse rates, at least up to 6 months. The variety of comparisons, ranging from the shortest, 2 vs. 3 months; to the longest 5 vs. 7 months are consistent in showing that longer is better. Because the short regimens are not all compared with the currently recommended 6-month short course regimen, it is not possible to know how much better the 6-month regimen is. However, there seemed to be two good reasons to include all the trials, rather than to limit them to those that used a standard 6-month regimen as comparison. First, it is useful to look at a range of shorter vs. longer comparisons to determine whether the effect seen is consistent (which it was in this case). The second reason may be less compelling for some: it is of historical interest to gather these similar trials together so that

the world's literature (which is somewhat old in terms of clinical trials) on shorter treatments is reviewed and available for current researchers to know what has been done.

The patients in these trials were supervised much more closely than is possible under programme conditions, so the trials cannot answer the important question of whether adherence to treatment would be better with shorter regimens. One of the main reasons to revisit these trials was to determine whether regimens shorter than 6 months worked well enough to consider using them in the field, where, in fact, adherence might be better.

AUTHORS' CONCLUSIONS

Implications for practice

These data confirm that longer periods of treatment are likely to result in lower relapse rates in a variety of patients with active TB, but that shorter regimens (as short as 3 months for patients with initially sputum smear positive active disease) are almost as effective.

The trade off between potentially better adherence to a shorter regimen (which has not been demonstrated) and a slightly higher relapse rate may still result in an overall better (or equal) result in the program setting. However, evidence on this question is currently lacking.

Implications for research

This review has demonstrated that TB treatment regimens shorter than the current standard of 6 months are not as good as longer regimens at preventing relapse. However, because of the serious problem of adherence to treatment over long periods of time, what is achieved in programmes is usually less than the optimal. It may be that a larger proportion of the scheduled doses may be taken if the overall treatment period is shorter. This could result in success rates that are equivalent or even higher than those currently achieved with a nominal 6-month regimen.

This review provides support for a trial of shorter vs. 6-month treatment regimens under the conditions of an actual TB control programme.

ACKNOWLEDGEMENTS

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Agra 1981

Methods	Randomized trial of 2 4.5-month and one 3-month regimens, each with SHRZ. A regimen adding ethionamide as a 5th drug was discontinued because of high side effect rates and is not included in this review.
Participants	266 adults with smear- and culture-positive TB, and <15 days of previous TB treatment entered Excluded from relapse analysis: Pretreatment ineligibility: 34/266 (13%) Continued drug after trial: 4/266 (2%) Defaulted: 3RSZH: 7/62 (11.3%) 3SHRZ/1.5RH: 4/34 (11.7%) 3SHRZ/1.5SHZI: 5/54 (9.3%)
Interventions	1. 3SHRZ followed by 1.5 month placebo tablets 2. 3SHRZ/1.5RH 3. 3SHRZ/1.5SHZI Daily dosages for first 3 months (all regimens): S: 0.75 g H: 58 mg/kg R: 10 mg/kg Z: 35 mg/kg Regimen 2 daily dosage final 1.5 months: H: 5-8 mg/kg R: 10 mg/kg Regimen 3 twice weekly dosage final 1.5 months: S: 0.75 g H: 14 mg/kg Z: 60 mg/kg All participants made monthly visits to the clinic and were given supplies of daily placebo tablets through 2 years after the start of the study.
Outcomes	Sputum conversion during and immediately following treatment Radiologic assessment at various points in time Relapse at 1 year (defined as a positive sputum culture in 2 consecutive months)
Notes	More than 10% of the patients entered "defaulted" in treatment, and were not included in the analysis. The two 4.5-month regimens are combined in the box and line diagram.

Germany 1986

Methods	Randomized trial of 1 3-month and 2 6-month regimens
Participants	363 patients with sputum positive TB entered Excluded from relapse analysis: Prerandomization ineligibility: 23/363 (6%)

Germany 1986 (Continued)

	Side effects: 21/363 (6%) Protocol violations, lack of cooperation, other: 19/363 (5%)
Interventions	3SHRZ 6SHRZI 3SHRZ/3SHZI Dosages: not given
Outcomes	Bacteriologic relapse at 36-48 months after starting treatment.
Notes	3-month regimen stopped enrollment early because of poor results, leading to imbalance among treatment groups. 17% of enrolled patients excluded from analysis.

Hong Kong 1979a

Methods	Randomized trial of 2-, 3-, and 12-month regimens, with shorter regimens containing 4 drugs.
Participants	1212 adults with sputum smear negative, radiographically active TB. 691 culture negative, 381 culture positive, analyzed separately. Excluded from relapse analysis: Pretreatment ineligibility: 9/1212 (1%) Side effects: 32/691 (5%) (culture negative patients only) Other reasons: 91/691 (13%) (culture negative patients only)
Interventions	2SHRZ 3SHRZ 3SPH/9SHI Daily dosages: S: 0.75 g H: 300 mg R: 450 mg Z: 1.5 g (<50 kg), 2.0 (>50 kg) PAS: 10 g Intermittent (2X/week): S: 1.0 g H: 15 mg/kg
Outcomes	Bacteriologic relapse 12 months after starting treatment.
Notes	Follow-up period is shorter than other studies.

Hong Kong 1979b

Methods	-
Participants	-

Hong Kong 1979b (Continued)

Interventions	-
Outcomes	-
Notes	-

Hong Kong 1989a

Methods	Randomized trial of 4-month and 6-month regimens of 4 drugs each in sputum culture positive patients. Randomized trial of 3-month and 4-month regimens of 4 drugs each in sputum culture negative patients.
Participants	2020 adults with sputum smear negative radiologically active TB. 592 sputum culture positive, 1118 sputum culture negative in analysis. Excluded from relapse analysis: Preadmission ineligibility: 61/2020 (3%) Side effects: 119/2020 (6%) Defaulted: 104/2020 (5%)
Interventions	Patients with positive culture - 4 v 6 month; 4-month regimens were either daily (D) or intermittent (I) 4SHRZ 4SHRZI 6SHRZI Patients with negative culture - 3 v 4 month SHRZ3D SHRZ3I SHRZ4I Daily dosages: S: 0.75 g H: 300 mg R: 450 mg (<50 kg), 600 mg (>50 kg) Z: 1.5 g (<50 kg), 2.0 g (>50 kg) Intermittent dose (3X/week): S: 0.75 g H: 15 mg/kg R: 600 mg Z: 2.0 g (>50 kg), 2.5 g (>50 kg)
Outcomes	Bacteriologic relapse up to 5 years after starting treatment
Notes	For boxes and lines, the daily and intermittent regimens are combined, as the results did not differ significantly. Therefore, those groups have about twice as many individuals as the comparison.

Hong Kong 1989b

Methods	-
Participants	-

Hong Kong 1989b (Continued)

Interventions	-
Outcomes	-
Notes	-

S. India 1983

Methods	Randomized trial of 1 5-month and 2 7-month regimens. Initial phase included 4 drugs in the 5-month and 1 7-month regimen (no R in 2nd 7-month regimen).
Participants	509 adults with active, sputum positive TB, including 103 with drug-resistant bacilli. Excluded from relapse analysis (drug sensitive group): Pretreatment ineligibility: 17/509 (3%) Died in 1st week: 4/509 (1%) Defaulted: 13/509 (3%) (5, 4, and 4 in groups 1, 2, 3, respectively) Excluded from relapse analysis (drug resistant group): Pretreatment ineligibility: 0 Died of TB: 1/103 (1%) Died other causes: 2/103 (2%)
Interventions	1. 2SHRZ/3SHZI 2. 2SHRZ/5SHZI 3. 2SHZ/5SHZI In addition, patients in all 3 groups were randomized again to receive prednisolone or no prednisolone for the first two months of treatment.
Outcomes	Bacteriological relapse at 24 months after finishing treatment (relapse after 12 months was reported only for relapses that resulted in retreatment). Results are reported by treatment group only for patients with initially drug susceptible strains. The results for a total of 52 patients in groups 1 and 2 are lumped together, compared with results in 46 patients (including "phase 1" and "phase 2" combined) in group 3. Toxicity outcomes were not reported by treatment group, but according to whether or not rifampin was included in the regimen.
Notes	

S. India 1986

Methods	Randomized trial of 1 3- and 2 5-month regimens. The 3-month and 1 5-month regimen included 4 drugs, and the other 5-month regimen included 3 drugs (no R).
Participants	919 adults with sputum-positive TB. 805 in final analysis: 694 with drug-sensitive strains, 111 with resistance to 1 or more drugs. Excluded from relapse analysis: Pretreatment ineligibility: 43/919 (5%) Deaths or adverse reactions: 7/919 (1%) Defaulted: 64/919 (7%)

S. India 1986 (Continued)

Interventions	<p>3SHRZ 3SHRZ/2SHZ 3SHZ/2SHZ Dosages: 1st 3 months, daily: S: 0.75 g H: 400 mg R: 12 mg/kg in 3 graded doses Z: 35 mg/kg in 5 graded doses For 5-month regimens, last 2 months drugs 2X/week S: 0.75 g H: 15 mg/kg in 3 graded doses Z: 70 mg/kg in 5 graded doses Patient who missed doses were given added days of treatment at end of regimen to make up for loss.</p>
Outcomes	Bacteriologic relapse requiring treatment up to 24 months after stopping treatment.
Notes	5-year follow-up is reported only for Madras patients.

Singapore 1979a

Methods	Randomized trial of 2 4-month and 2 6-month regimens, each with 4 drugs in initial 2-month phase.
Participants	<p>400 sputum-positive pulmonary TB patients, age 15 or more, with no previous anti-TB treatment entered. Excluded from relapse analysis: Pretreatment ineligibility: 12/400 (3%) Adverse reactions: 19/400 (5%) Given wrong drugs: 2/400 (1%) Died: 1/400 (0%) Defaulted: 3/400 (1%) 37 excluded for pre-treatment ineligibility. 345 assessed at 30 months (314 with initially drug-susceptible strains and 31 resistant to at least one drug initially)</p>
Interventions	<p>Daily treatment (70% of participants were outpatients), under direct observation, with the following 4 regimens: 2SHRZ/4HRZ 2SHRZ/4HR 2SHRZ/2HRZ 2SHRZ/2HR Daily dosage: S: 0.75g H: 300 mg R: 450 mg (<50 kg), 600 mg (>50 kg) Z: 1.5 g (<50 kg), 2.0 g (>50 kg)</p>
Outcomes	<p>Sputum conversion during and immediately after treatment Bacteriologic relapse (culture positive) at 6 and 30 months and 5-8 years after start of treatment Adverse reactions</p>

Singapore 1979a *(Continued)*

Notes	Includes a small number of patients in each group with bacilli resistant to H, R, or both. All patients with sensitive bacilli were culture-negative by the end of month 3 of treatment.
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Singapore 1979b

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Characteristics of excluded studies *[ordered by study ID]*

East Africa 1978	Randomized trial comparing 5 different 4-month (17-week) regimens.
France 1976	Randomized trial comparing two 3-month regimens: daily (HRS) vs partially intermittent (H and R 3 times/week, daily S) treatment.

Characteristics of studies awaiting assessment *[ordered by study ID]***Bock 2001**

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Borisova 2003

Methods	-
Participants	-

Borisova 2003 (Continued)

Interventions	-
Outcomes	-
Notes	-

Gravendeel 2003

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Hernandez 1993

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Jasmer 2002

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Lwilla 2003

Methods	-
Participants	-

Lwilla 2003 (Continued)

Interventions	-
Outcomes	-
Notes	-

Matteelli 1999

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Mawer 2001

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Sanchez 2004

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Teo 2002

Methods	-
Participants	-

Teo 2002 (Continued)

Interventions	-
Outcomes	-
Notes	-

Yu 2001

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

DATA AND ANALYSES

Comparison 1. 2 months vs longer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse within 12 months of finishing treatment	1	529	Peto Odds Ratio (Peto, Fixed, 95% CI)	6.10 [2.19, 17.01]
2 Toxicity requiring interruption, alteration, or cessation	1	598	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.37 [0.16, 0.85]

Comparison 2. 3 months vs longer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse within 12 months of finishing treatment	5	2588	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.67 [2.42, 5.58]
2 Toxicity requiring interruption, alteration, or cessation	4	2918	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.87, 1.38]

Comparison 3. 4 months vs longer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse within 12 months of finishing treatment	2	887	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.64 [1.71, 7.75]
2 Toxicity requiring interruption, alteration, or cessation	1	1114	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.63, 1.49]

Comparison 4. 5 months vs longer

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse within 12 months of finishing treatment	1	390	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.24 [0.90, 5.59]
2 Toxicity requiring interruption, alteration, or cessation	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

Analysis 1.1. Comparison 1 2 months vs longer, Outcome 1 Relapse within 12 months of finishing treatment.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 1 2 months vs longer

Outcome: 1 Relapse within 12 months of finishing treatment

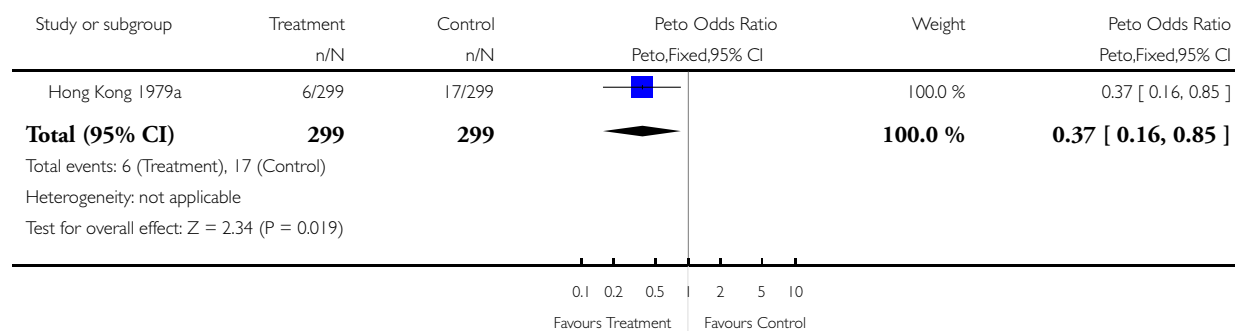
Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Hong Kong 1979a	14/261	1/268		100.0 %	6.10 [2.19, 17.01]
Total (95% CI)	261	268		100.0 %	6.10 [2.19, 17.01]
Total events: 14 (Treatment), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.45 (P = 0.00055)					
			0.01 0.1 10 100		
			Favours Treatment Favours Control		

Analysis 1.2. Comparison 1 2 months vs longer, Outcome 2 Toxicity requiring interruption, alteration, or cessation.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 1 2 months vs longer

Outcome: 2 Toxicity requiring interruption, alteration, or cessation

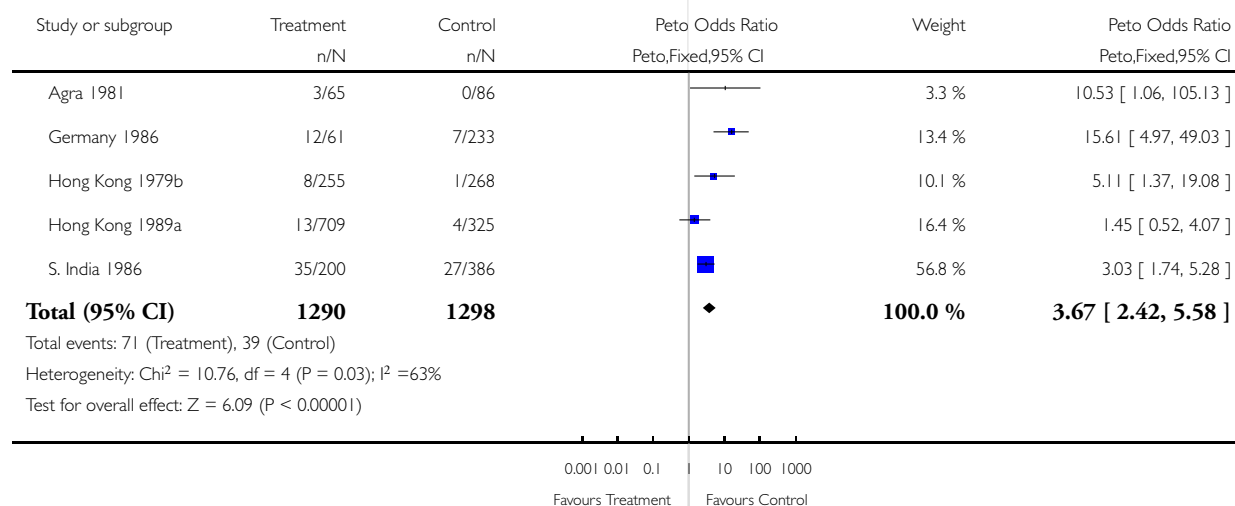


Analysis 2.1. Comparison 2 3 months vs longer, Outcome 1 Relapse within 12 months of finishing treatment.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 2 3 months vs longer

Outcome: 1 Relapse within 12 months of finishing treatment

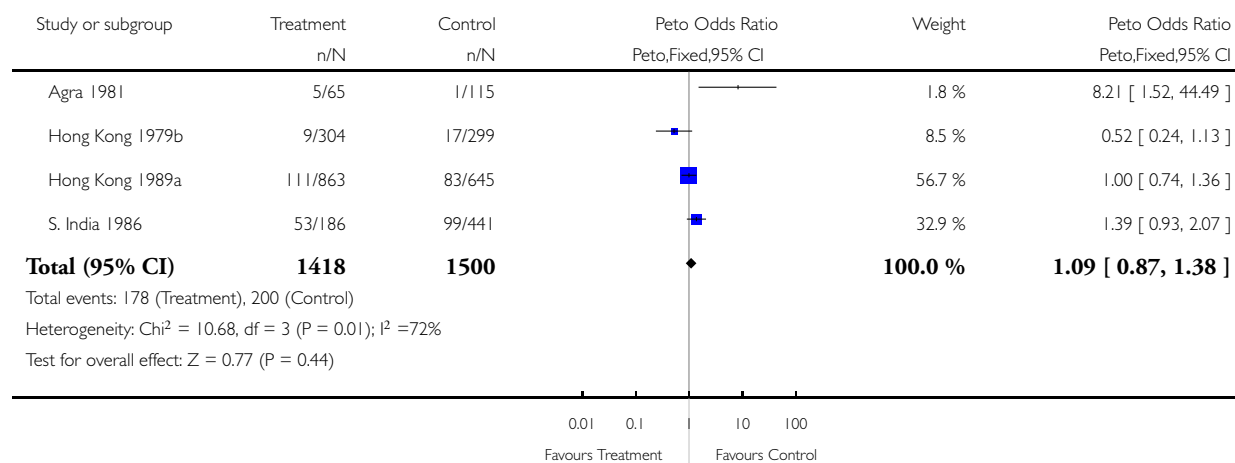


Analysis 2.2. Comparison 2 3 months vs longer, Outcome 2 Toxicity requiring interruption, alteration, or cessation.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 2 3 months vs longer

Outcome: 2 Toxicity requiring interruption, alteration, or cessation

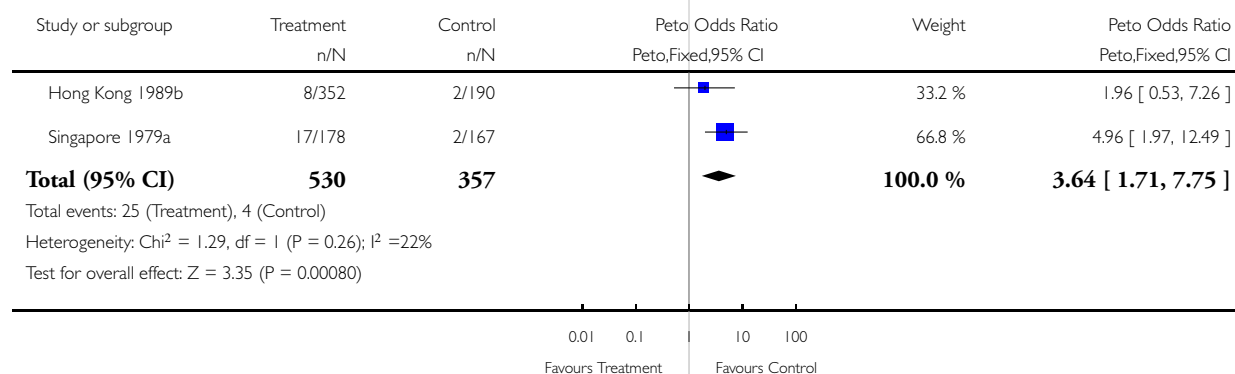


Analysis 3.1. Comparison 3 4 months vs longer, Outcome 1 Relapse within 12 months of finishing treatment.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 3 4 months vs longer

Outcome: 1 Relapse within 12 months of finishing treatment

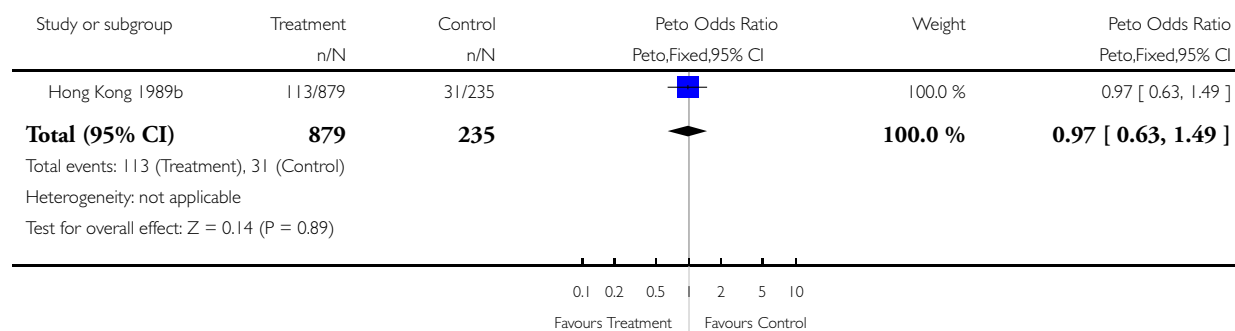


Analysis 3.2. Comparison 3 4 months vs longer, Outcome 2 Toxicity requiring interruption, alteration, or cessation.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 3 4 months vs longer

Outcome: 2 Toxicity requiring interruption, alteration, or cessation

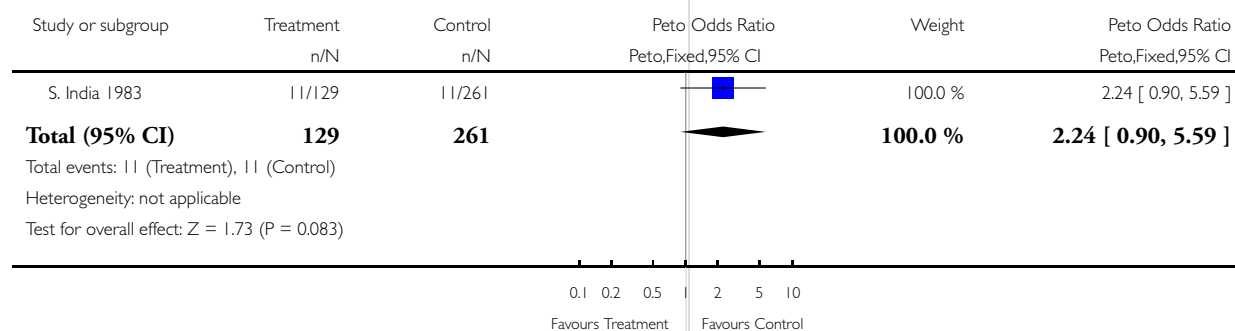


Analysis 4.1. Comparison 4 5 months vs longer, Outcome 1 Relapse within 12 months of finishing treatment.

Review: Regimens of less than six months for treating tuberculosis

Comparison: 4 5 months vs longer

Outcome: 1 Relapse within 12 months of finishing treatment



APPENDICES

Appendix I. Patients with drug-resistant bacilli at start of trial (%)

Trial	No. patients (%)
Agra 1981	Not available
East Africa 1978	64/619 (10.3)
Germany 1986	None (excluded)
Hong Kong 1989	83/542 (15.3)
Hong Kong 1979	44/274 (16.1)
Singapore	33/363 (9.1)
S. India 1986	64/469 (13.6)
S. India 1983	98/628 (15.6)

WHAT'S NEW

Last assessed as up-to-date: 15 June 1999.

13 October 2008	Amended	Converted to new review format with minor editing.
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HISTORY

Protocol first published: Issue 1, 1999

Review first published: Issue 4, 1999

31 October 2005	Amended	New studies found but not yet included/excluded.
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DECLARATIONS OF INTEREST

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of the review (e.g. employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Department for International Development, UK.
- World Health Organization, Switzerland.

INDEX TERMS

Medical Subject Headings (MeSH)

Antitubercular Agents [administration & dosage; *therapeutic use]; Drug Administration Schedule; Recurrence [prevention & control]; Tuberculosis, Pulmonary [*drug therapy]

MeSH check words

Humans