

Fully intermittent dosing with drugs for treating tuberculosis in adults (Review)

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[Intervention Review]

Fully intermittent dosing with drugs for treating tuberculosis in adults

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ABSTRACT

Background

The number of people infected with tuberculosis continues to rise worldwide. Rifampicin-containing treatment regimens can achieve high cure rates. Intermittent drug treatment delivered in the community has the potential to improve adherence to treatment.

Objectives

The objective of this review was to compare the effectiveness of rifampicin-containing short-course chemotherapy regimens, given two or three times a week, with similar regimens given daily in adult patients with pulmonary tuberculosis.

Search strategy

We searched the Cochrane Infectious Diseases Group specialized trials register (January 2003), The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2002), MEDLINE (1966 to January 2003), EMBASE (1980 to December 2002), and reference lists of articles. We contacted experts in the field.

Selection criteria

Randomized and quasi-randomized trials of any multiple drug regimen containing rifampicin in patients with confirmed pulmonary tuberculosis. Treatment had to be given up to three times a week for up to nine months, with any initial daily dosing period not more than one month, and was compared to daily dosing throughout for the same period.

Data collection and analysis

Two reviewers independently assessed trial eligibility and quality.

Main results

One trial involving 399 patients was included. The trial compared treatment three times per week with daily treatment for six months. There was no difference in cure rate (198 out of 199 people in the intermittent group compared to all 200 in the daily group), but 5 patients relapsed in the group receiving intermittent therapy compared to one in the group receiving the daily regimen.

Authors' conclusions

There is not enough evidence to assess the equivalence of effect between fully intermittent, rifampicin-containing short-course chemotherapy and similar daily therapy in patients with pulmonary tuberculosis. Larger randomized studies are required to establish the equivalence of fully intermittent, short-course chemotherapy, with daily regimens.

PLAIN LANGUAGE SUMMARY

There is insufficient evidence to compare equivalence of effect between fully intermittent and daily treatment in adult patients with pulmonary tuberculosis.

Rifampicin-containing drug combinations can achieve high cure rates in patients with pulmonary tuberculosis when given for six months. Such treatment can be given either daily or intermittently (eg three times a week) from the beginning. This review compared the equivalence of effect between such treatments but did not find enough evidence to be able to assess this.

BACKGROUND

The number of people infected with *Mycobacterium tuberculosis* is increasing globally (WHO 1996). Most people infected and ill with tuberculosis (TB) are in developing countries (Dolin 1994). Human immunodeficiency virus (HIV) has contributed to the increase in TB (Harries 1996). Pulmonary TB is the predominant clinical presentation of this disease and sputum positive cases are the most important sources of infection in the community (Grzybowski 1975).

Historically, effective drug treatment for TB lasted between 18 and 24 months. Adding rifampicin to TB treatment in 1967 helped establish short-course chemotherapy regimens lasting 6 to 9 months. Today, most of these shorter regimens contain rifampicin, are given daily (7 days a week) for the duration, and result in cure rates approaching 100% providing the disease is sensitive to the drugs and the patients adhere to treatment (Singapore 1981, E&C Africa 1983, BTS 1984). Several cohort studies conducted in Africa, East Asia, the Indian subcontinent, and Poland have suggested that equally high cure rates can be achieved with rifampicin-containing regimens which comprise an initial phase of daily treatment (usually two months) followed by intermittent treatment for a further four to six months (referred to as 'partial intermittent short-course chemotherapy').

When short-course chemotherapy is prescribed daily, direct supervision appears important for good adherence (Anonymous 1993, Weis 1994, Chaulk 1995). In the past, health providers have hospitalized patients to maintain supervision (Enarson 1996). How-

ever, this option is not sustainable where limited hospital resources are further stretched by the HIV epidemic (Wilkinson 1997a).

In these circumstances, drug regimens that are 'fully intermittent', that is, where patients are only required to take drugs on three occasions or less within a week could help in ensuring delivery with direct observation (Wilkinson 1997b). Such fully intermittent short-course chemotherapy has the potential to reduce the requirement for prolonged hospitalization, which carries significant negative social consequences for patients. It also has the potential to improve adherence to treatment and, consequently, cure rates. It may be that such regimens commence with a daily regimen for a variable period while the patient is carefully stabilized as an inpatient on treatment. Thus this review defines fully intermittent short course chemotherapy as: (1) regimens lasting no longer than nine months, and (2) regimens in which an initial daily dosing phase does not exceed one month.

Data from several cohort studies suggest that fully intermittent drug administration (as defined in this review) is well tolerated and effective, with cure rates of 80 to 100% in populations where treatment is given under direct supervision for 6 to 9 months (Roumania 1977, Dutt 1979, Cohn 1990, Manalo 1990, Hong Kong 1991a, Hong Kong 1991b, Sedlaczek 1995, Caminero 1996, China 1996, Neher 1996, Bechan 1997, Wilkinson 1997c). However, we are not aware of any formal comparison with daily drug administration, and therefore decided to summarize evidence evaluating the effects of fully intermittent regimens (or regimens with an initial daily phase of not more than one month) compared

with daily regimens.

OBJECTIVES

To compare twice or thrice weekly (with or without daily therapy for the first month) with daily short-course chemotherapy (containing rifampicin) in adult patients with pulmonary tuberculosis in relation to cure, mortality, sterilizing sputum, recurrence of disease, emergence of drug resistance, adherence to treatment, and drug toxicity.

It was intended to explore these hypotheses if data allowed:

Comparative cure rates between fully intermittent and daily short course chemotherapy are independent of:

1. adherence to treatment;
2. the patient's HIV status;
3. previous treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Any trial in which a form of random allocation was attempted, including alternate allocation.

Types of participants

Previously treated and untreated adult patients aged 16 or above, with a positive growth on culture of *Mycobacterium tuberculosis*, or one or more sputum smears positive for mycobacteria by direct or indirect microscopy.

Previously untreated patients were defined as those with less than 4 months of previous chemotherapy, including not more than 2 weeks during the 12 months immediately preceding the diagnosis. Patients with more than 4 months of previous chemotherapy including more than 2 weeks during the preceding 12 months were considered as having had previous treatment.

Standard laboratory definitions of positive growth of *M. tuberculosis* in laboratory culture systems (using Lowenstein-Jensen or equivalent media) were used (Crowle 1986). A minimum of one sputum sample was taken as adequate for these definitions.

For smear microscopy, at least one sputum sample in which at least 10 acid fast bacilli were identified in 100 high power fields was taken as indicating sputum smear positivity. Smear negativity required at least 2 separate sputum samples in which no acid fast

bacilli were identified following examination of 100 high power fields. Smears which had been prepared directly from the samples or following sputum concentration with a recognised technique were accepted.

HIV status of participants determined by a recognised testing strategy. For the purpose of this review HIV status was assumed to be negative if the trial was conducted in a community with an HIV prevalence among tuberculosis patients of <5%.

Types of interventions

Both regimens should contain rifampicin for at least the initial two months of therapy, and continue for a maximum of nine months.

Experimental

Intermittent short course therapy: any rifampicin-containing multiple drug regimen, administered up to three times a week for a maximum of nine months; initial daily dosing phase does not exceed one month.

Comparator

Daily short course chemotherapy: any rifampicin-containing regimen given daily throughout for a maximum of nine months.

Types of outcome measures

Primary outcome

- Cure
- Proportion of participants with a negative sputum culture (or two negative sputum smears) within one month of completion of treatment.

Secondary outcomes

- Death
- Death while on treatment and up to 12 months after treatment.

Sterilizing efficacy

- Proportion of participants with a negative sputum culture (or two negative smears) two months after start of treatment.

Recurrence of disease

- Proportion of participants with a single positive sputum culture (or 1 positive smear if symptomatic) within 12 months of cure (as defined above). The 12 month cut-off was chosen because a significant proportion of recurrent disease within this time frame may reasonably be attributed to relapse (ie therapeutic failure). Beyond 12 months, recurrent disease is increasingly likely to be due to reinfection, depending on the country prevalence of infection.

Drug resistance

- Proportion of participants developing in vitro drug resistance while on treatment. It is recognised that the interpretation of the laboratory methods used in assessing in vitro drug resistance (such as ID₅₀ [infective dose for 50% of the population] versus MIC [minimum inhibitory concentration]) is complicated. For this reason, details of laboratory methodology were scrutinized before assessing the validity of in vitro resistance data, if present.

Drug toxicity

- Proportion of participants experiencing adverse drug reactions requiring interruption or alteration of the drug regimen.

Non-adherence

- The proportion of participants who discontinue therapy of their own accord for at least one month.

Search methods for identification of studies

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

The Cochrane Infectious Diseases Group specialized trials register was searched for relevant trials up to January 2003 using the search terms: 'tuberculosis', 'rifampin', and 'rifampicin'. As our definition of short-course chemotherapy is "any rifampicin-containing regimen lasting 9 months or less". The terms rifampin (USA terminology) or rifampicin (European terminology) were used, and this was more sensitive than the term 'treatment'. Full details of the Cochrane Infectious Disease Group methods and the journals hand searched are published in *The Cochrane Library* in the section on Collaborative Review Groups.

We searched The Cochrane Controlled Trials Register, published in *The Cochrane Library* (Issue 4, 2002) using the search terms: 'tuberculosis', 'rifampin', and 'rifampicin'. This contains mainly reference information to randomized controlled trials and controlled clinical trials in health care.

The following databases were also searched using the search terms in combination with the search strategy developed by The Cochrane Collaboration and detailed in the Cochrane Reviewers' Handbook (Clarke 2002): MEDLINE (1966 to January 2003); and EMBASE (1980 to December 2002). The search terms used were: tuberculosis (textword or MESH heading), rifampin or rifampicin (textword), and rifampin (MESH heading).

Organizations and individual researchers working in the field were contacted for unpublished data, confidential reports, and raw data of published trials. These included the World Health Organization, the International Union Against Tuberculosis and Lung Disease, and the British Medical Research Council.

External referees were asked to check the completeness of the search strategy, and the efforts made to identify unpublished, ongoing, and planned trials.

We also checked the citations of existing reviews and of all trials identified by the above methods.

Data collection and analysis

The inclusion criteria were applied by the two reviewers independently and differences resolved by discussion. Data on study methods, participants, interventions, and outcomes were collected for each study. Quality of allocation concealment, allocation sequence generation, and follow-up of participants were assessed in each trial, using the guidelines of the Cochrane Infectious Diseases Group. Data on outcomes after the interventions were compared using the risk ratio (RR) and 95% confidence intervals (CI).

Subgroup analysis was conducted between fully intermittent and daily short course chemotherapy in order to explore potential heterogeneity:

1. adherent and non-adherent patients (patients judged to have completed the full course of therapy without missing more than 28 consecutive days of treatment were defined as adherent. Patients who did not fulfil this definition were defined as non-adherent);
2. HIV positive and HIV negative patients;
3. previously treated and untreated patients.

RESULTS

Description of studies

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

One study by the Hong Kong Chest Service / British Medical Research Council ([Hong Kong 1981](#)) included a concurrent comparison of fully intermittent with daily short course chemotherapy and met the inclusion criteria (see 'Characteristics of included studies'). The study randomized 1207 adults with smear positive, culture confirmed pulmonary tuberculosis to 5 different short course regimens.

One comparison was between daily isoniazid, rifampicin, pyrazinamide, and ethambutol for six months and the same drugs administered three times a week from the start for six months. All drugs were administered by clinic staff under direct supervision. Patients with a history of antituberculous chemotherapy (more than 4 months in total or more than 2 weeks in the preceding 12 months) were excluded. Outcomes were stratified for patients with pretreatment strains showing resistance to at least one drug (there were no true multiple drug resistant cases) and patients with pretreatment strains that were fully sensitive. No HIV serology was carried out as the study took place before international recognition of the HIV pandemic.

Risk of bias in included studies

The [Hong Kong 1981](#) study was described as randomized but the method of allocation concealment and randomization was not given. Trial participants were not blinded to the therapy allocated and blinding of assessors was not described.

The paper does not report whether all the participants meeting the entry criteria were enrolled but exclusions after randomization and losses to follow-up are detailed. Exclusions were for reasons present before treatment (such as pretreatment sputum cultures were negative or prolonged duration of previous chemotherapy) or arising during treatment (eg missed at least six weeks of treatment because of drug toxicity).

In the fully intermittent comparison, 242 participants were randomized, and in the daily treatment group, 239 were randomized. This includes participants with both pretreatment drug sensitive and drug resistant strains. 29 (12%) were excluded and 14 (6%) lost to follow-up from the fully intermittent arm, while 33 (14%) were excluded, and 6 (3%) were lost to follow-up from the daily treatment arm.

An 'intention-to-treat' analysis was not employed.

Effects of interventions

In the [Hong Kong 1981](#) study, bacteriological cure rates were reported as 99.5% (198/199) in the fully intermittent arm and 100% (200/200) in the daily arm (95% CI 0.90 to 1.10; [Analysis 1.1](#)). One patient was not cured in the fully intermittent arm and died during the fifth month of chemotherapy giving a mortality of 0.5% in this arm compared with 0% in the daily treatment arm (see [Analysis 1.2](#)).

There were more recurrences in the fully intermittent arm compared with the daily treatment, but this was not statistically significant (5/186 (3%) compared to the 1/192 (0.5%) (RR 4.00, 95% CI 0.66 to 24.10; [Analysis 1.3](#)). The development of in vitro drug resistance was not identified in either arm despite monthly sputum cultures for 18 months from the start of chemotherapy (see [Analysis 1.4](#)).

Adherence was reported as 100% in both arms and verified by urine testing for isoniazid (see [Analysis 1.5](#)). Adverse events led to the interruption of drug therapy or the termination of 1 or more drugs in 12% (30/241) of participants while on fully intermittent compared to 13% (30/239) on the daily regimen (see [Analysis 1.6](#)). This comparison includes patients who were randomized, but excluded from the bacteriological analyses because drug therapy was interrupted for more than 6 weeks.

When participants with pretreatment drug sensitive strains were compared with those with pretreatment drug resistant strains, no differences with respect to cure, adherence to treatment, drug toxicity, and emergence of drug resistance were detected. Only one patient in the fully intermittent arm with pretreatment drug resistance died during the fifth month of chemotherapy. Five patients with drug sensitive strains pretreatment had recurrent disease (4/164 in the fully intermittent arm, 1/161 in the daily arm). Only one patient in the fully intermittent arm with pretreatment drug resistance had recurrent disease and there were no recurrences in the daily treatment arm.

Sterilizing capacity could not be compared because data on sputum smear and culture rates two months following the start of chemotherapy were not presented for the whole study population.

DISCUSSION

The [Hong Kong 1981](#) study shows equally high bacteriological cure rates in the two regimens (around 100%). More patients relapsed in the fully intermittent regimen compared with the daily regimen, but the size of the study was insufficient to be clear if this was a true effect or had arisen by chance.

There was no indication of differential adverse reactions or the development of in vitro drug resistance during chemotherapy. The cure rate appeared to be as high in participants with pretreatment drug resistant strains of *Mycobacterium tuberculosis* as in those with pretreatment drug sensitive strains although the power of the study to detect a difference in these two subgroups was low. No pretreatment multiple drug resistant strains were identified.

These conclusions can, however, only be tentative because only one study with significant methodological deficiencies was identified. These consisted mainly in the lack of an intention-to-treat analysis and a lack of detail on the randomization and concealment process.

Further studies in larger groups of patients are warranted to firmly establish the apparent equivalent effectiveness of fully intermittent

short course chemotherapy with respect to bacteriological cure. It is, however, difficult to assess how urgent such studies are in the light of the accumulated evidence from cohort studies that fully intermittent drug administration (as defined in this review) is well tolerated and effective, with cure rates of 80 to 100% in studies which have included HIV negative patients (Roumania 1977, Dutt 1979, Cohn 1990, Manalo 1990, Hong Kong 1991a, Hong Kong 1991b, Sedlaczek 1995, China 1996, Neher 1996, Bechan 1997), predominantly HIV negative patients (Caminero 1996, Wilkinson 1997c) and significant numbers of HIV positive patients (Alwood 1994, Davies 1999). Nonetheless it will be important to include HIV positive participants in such studies as the effectiveness of intermittent therapy for these individuals should not automatically be extrapolated from evidence from those who are HIV negative.

AUTHORS' CONCLUSIONS

Implications for practice

Reviewers' opinion

Fully intermittent regimens have been advocated on the basis of several uncontrolled cohort studies with good outcomes. However, from this review, only one study has directly compared outcomes between daily and intermittent regimens. The number of patients randomized in this one comparison are too small to prove either that one form of dosing is superior or that they are equivalent.

Implications for research

Reviewers' opinion

Research with HIV positive participants is required to be sure of the effectiveness of regimens in these groups, as extrapolation of the evidence from HIV negative patients may not be valid.

Large studies comparing fully intermittent regimens directly with daily regimens are required with adequate follow-up to at least 12 months post chemotherapy to establish equivalence between these two forms of drug administration.

ACKNOWLEDGEMENTS

To the referees of this review for their rapid and constructive comments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Hong Kong 1981

Methods	Randomized controlled trial, allocation method not stated
Participants	Adult attenders at chest clinic with smear positive pulmonary tuberculosis
Interventions	Randomized to 5 regimens Only one comparison relevant to this review: Group 1: Daily isoniazid, rifampicin, pyrazinamide, and ethambutol for 6 months Group 2: Same drugs as in group 1 but given 3 times a week for 6 months
Outcomes	Microbiological cure, mortality, sterility, recurrence, resistance, adherence, and toxicity
Notes	No human immunodeficiency virus (HIV) positive participants (pre-HIV epidemic)

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

Brazil 1989	Long duration of initial daily therapy for the intermittent group (2 months).
Hong Kong 1974	Long duration of treatment (more than 9 months).
Hong Kong 1982	This is the same study as the one included (Hong Kong 1981) but details a longer follow-up period (18 months after stopping treatment). In our review relapse of disease has been defined within the context of a 12 month follow-up period after stopping treatment, so further episodes of recurrent disease beyond 12 months do not add to the analysis.
Hong Kong 1987	This is the same study as the one included (Hong Kong 1981) but detailing longer follow-up to 5 years. Once again it is difficult to classify episodes of disease in this time period as arising because of reinfection or relapse.
India 1990	Conducted in children aged 1 to 15 years. Included participants with pulmonary, lymph node, and disseminated tuberculosis. Daily treatment was for 2 months followed by 4 months of twice weekly therapy.
Korea 1988	Long duration of treatment (more than 9 months).
South Africa 2000	Study conducted in children with all forms of intrathoracic tuberculosis. Tuberculosis was confirmed in 4%, was probable in 94%, and was suspected in 2% of the patients.

DATA AND ANALYSES

Comparison 1. Thrice weekly tuberculosis treatment versus daily treatment

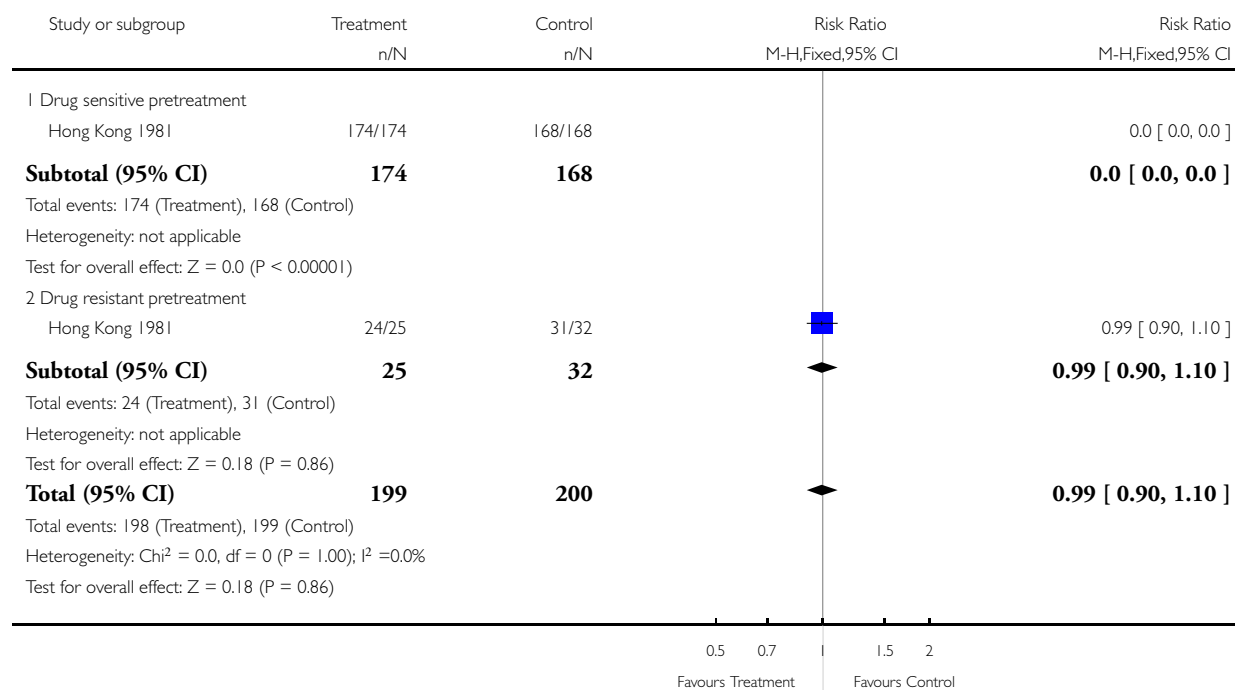
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cure	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.10]
1.1 Drug sensitive pretreatment	1	342	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Drug resistant pretreatment	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.10]
2 Death	1	399	Risk Ratio (M-H, Fixed, 95% CI)	3.81 [0.16, 89.67]
2.1 Drug sensitive pretreatment	1	342	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Drug resistant pretreatment	1	57	Risk Ratio (M-H, Fixed, 95% CI)	3.81 [0.16, 89.67]
3 Recurrence	1	378	Risk Ratio (M-H, Fixed, 95% CI)	4.00 [0.66, 24.10]
3.1 Drug sensitive pretreatment	1	325	Risk Ratio (M-H, Fixed, 95% CI)	3.93 [0.44, 34.75]
3.2 Drug resistant pretreatment	1	53	Risk Ratio (M-H, Fixed, 95% CI)	4.17 [0.18, 97.93]
4 Resistance	1	399	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.1 Drug sensitive pretreatment	1	342	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Drug resistant pretreatment	1	57	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 Adherence	1	399	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.10]
5.1 Drug sensitive pretreatment	1	342	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.2 Drug resistant pretreatment	1	57	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.10]
6 Toxicity	1	480	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.62, 1.59]

Analysis 1.1. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 1 Cure.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 1 Cure

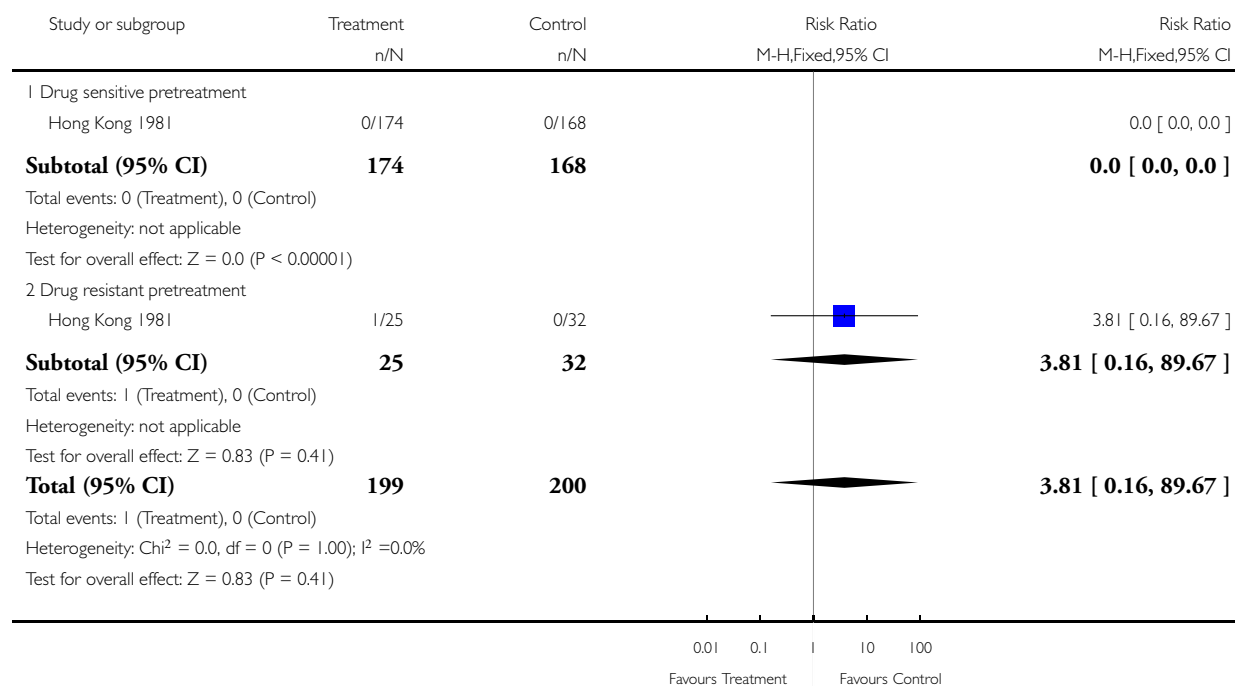


Analysis 1.2. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 2 Death.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 2 Death

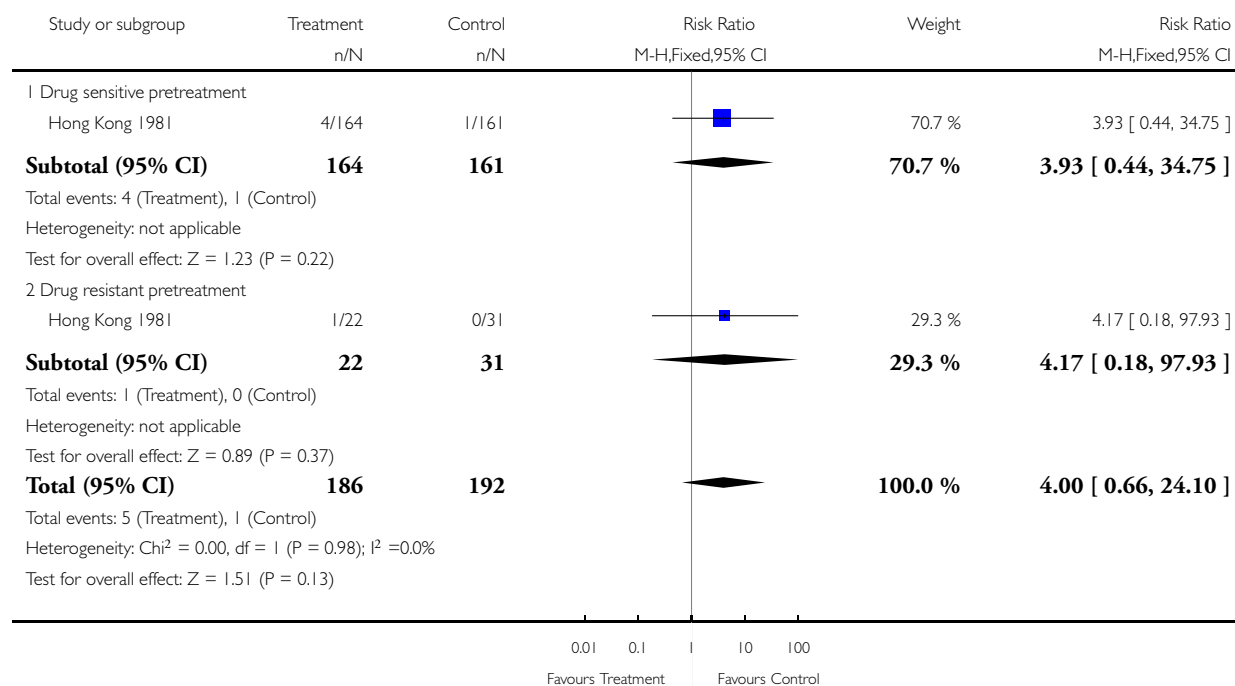


Analysis 1.3. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 3 Recurrence.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 3 Recurrence



Analysis 1.4. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 4 Resistance.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 4 Resistance

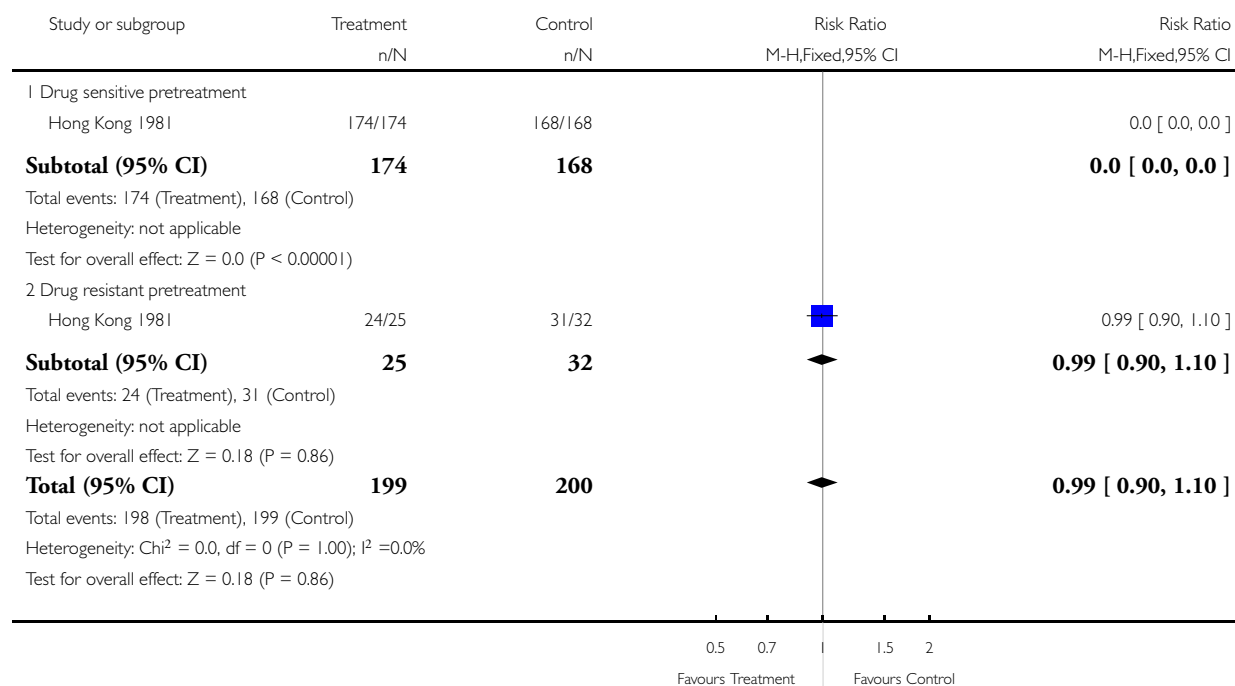
Study or subgroup	Treatment	Control	Risk Ratio	
	n/N	n/N	M-H,Fixed,95% CI	
1 Drug sensitive pretreatment				
Hong Kong 1981	0/174	0/168	0.0 [0.0, 0.0]	
Subtotal (95% CI)	174	168	0.0 [0.0, 0.0]	
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Drug resistant pretreatment				
Hong Kong 1981	0/25	0/32	0.0 [0.0, 0.0]	
Subtotal (95% CI)	25	32	0.0 [0.0, 0.0]	
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	199	200	0.0 [0.0, 0.0]	
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Chi ² = 0.0, df = 0 (P<0.00001); I ² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				

Analysis 1.5. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 5 Adherence.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 5 Adherence

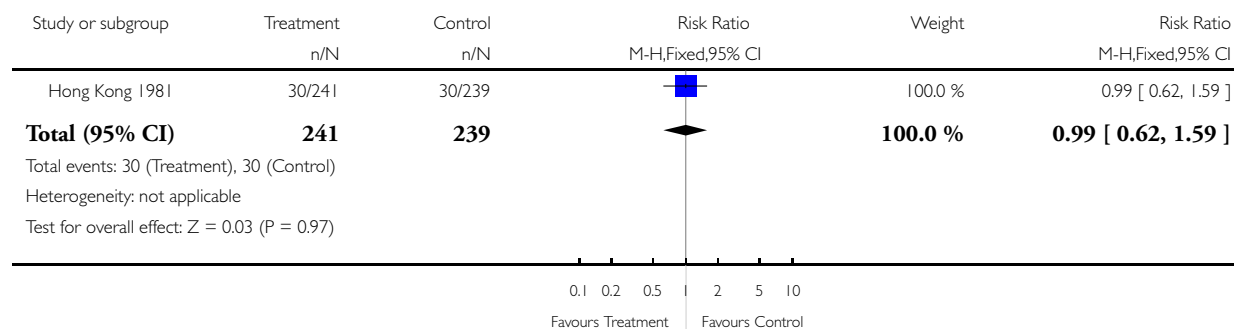


Analysis 1.6. Comparison 1 Thrice weekly tuberculosis treatment versus daily treatment, Outcome 6 Toxicity.

Review: Fully intermittent dosing with drugs for treating tuberculosis in adults

Comparison: 1 Thrice weekly tuberculosis treatment versus daily treatment

Outcome: 6 Toxicity



WHAT'S NEW

Last assessed as up-to-date: 5 September 2005.

18 August 2008	Amended	Converted to new review format with minor editing.
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HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 1, 1999

15 November 2005	Amended	The world 'adult' has been added to the title, synopsis, and the abstract to emphasize the fact that the review's focus is on adults with smear positive tuberculosis. The text in the 'Search strategy for identification of studies' has been revised to reflect the extent and completeness of our search for relevant studies.
6 September 2005	New search has been performed	New studies sought but none found.

DECLARATIONS OF INTEREST

We certify that we have no affiliations with or involvement in any organization or entity with a direct financial interest in the subject matter of the review (eg employment, consultancy, stock ownership, honoraria, expert testimony).

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK.

External sources

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

INDEX TERMS

Medical Subject Headings (MeSH)

Antitubercular Agents [*administration & dosage; therapeutic use]; Drug Administration Schedule; Drug Therapy, Combination; Randomized Controlled Trials as Topic; Rifampin [*administration & dosage; therapeutic use]; Tuberculosis, Pulmonary [*drug therapy; prevention & control]

MeSH check words

Humans