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[Intervention Review]

Adjunctive steroid therapy for managing pulmonary tuberculosis

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ABSTRACT

Background

Tuberculosis causes approximately 8.6 million disease episodes and 1.3 million deaths worldwide per year. Although curable with standardized treatment, outcomes for some forms of tuberculosis are improved with adjunctive corticosteroid therapy. Whether corticosteroid therapy would be beneficial in treating people with pulmonary tuberculosis is unclear.

Objectives

To evaluate whether adjunctive corticosteroid therapy reduces mortality, accelerates clinical recovery or accelerates microbiological recovery in people with pulmonary tuberculosis.

Search methods

We identified studies indexed from 1966 up to May 2014 by searching: Cochrane Infectious Diseases Group's trials register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and LILACS using comparative search terms. We handsearched reference lists of all identified studies and previous reviews and contacted relevant researchers, organizations and companies to identify grey literature.

Selection criteria

Randomized controlled trials and quasi-randomized control trials of recognized antimicrobial combination regimens and corticosteroid therapy of any dose or duration compared with either no corticosteroid therapy or placebo in people with pulmonary tuberculosis were included.

Data collection and analysis

At least two investigators independently assessed trial quality and collected data using pre-specified data extraction forms. Findings were reported as narrative or within tables. If appropriate, Mantel-Haenszel meta-analyses models were used to calculate risk ratios.

Main results

We identified 18 trials, including 3816 participants, that met inclusion criteria. When compared to taking placebo or no steroid, corticosteroid use was not shown to reduce all-cause mortality, or result in higher sputum conversion at 2 months or at 6 months (mortality: RR 0.77, 95%CI 0.51 to 1.15, 3815 participants, 18 studies, *low quality evidence*; sputum conversion at 2 months RR 1.03,

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95%CI 0.97 to 1.09, 2750 participants, 12 studies; at 6 months; RR1.01, 95%CI 1.01, 95%CI 0.98 to 1.04, 2150 participants, 9 studies, both *low quality evidence*). However, corticosteroid use was found to increase weight gain (data not pooled, eight trials, 1203 participants, *low quality evidence*), decrease length of hospital stay (data not pooled, three trials, participants 379, very low quality of evidence) and increase clinical improvement within one month (RR 1.16, 95% CI 1.09 to 1.24; five trials, 497 participants, *low quality evidence*).

Authors' conclusions

It is unlikely that adjunctive corticosteroid treatment provides major benefits for people with pulmonary tuberculosis. Short term clinical benefits found did not appear to be maintained in the long term. However, evidence available to date is of low quality. In order to evaluate whether adjunctive corticosteroids reduce mortality, or accelerate clinical or microbiological recovery in people with pulmonary tuberculosis further large randomized control trials sufficiently powered to detect changes in such outcomes are needed.

PLAIN LANGUAGE SUMMARY

Adjunctive steroid therapy for managing pulmonary tuberculosis

Pulmonary tuberculosis is a common infectious disease. Although curable with standard anti-pulmonary tuberculosis drugs, it has been reported that an individuals recovery could be improved by adding corticosteroids to their treatment. Current clinical guidelines advise the use of corticosteroids for treatment of other types of tuberculosis; tuberculosis meningitis and tuberculosis pericarditis. Whether corticosteroids would be beneficial in the treatment of pulmonary tuberculosis remains unclear. After reviewing the evidence available to date we found that there was not enough high quality data to support or reject corticosteroid use alongside anti-pulmonary tuberculosis drugs.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Steroid therapy comparative to either no therapy or placebo for managing pulmonary tuberculosis						
Patient or population: patients with managing pulmonary tuberculosis						
Settings:						
Intervention: Steroid therapy comparative to either no therapy or placebo						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Steroid therapy comparative to either no therapy or placebo				
All-cause mortality	27 per 1000	21 per 1000 (14 to 31)	RR 0.77 (0.51 to 1.15)	3815 (18 studies)	⊕⊕○○ low ^{1,2,3,4,5}	
Sputum Conversion by 2 months	656 per 1000	722 per 1000 (676 to 768)	RR 1.1 (1.03 to 1.17)	1475 (11 studies)	⊕⊕○○ low ^{1,3,4,6,7}	
Sputum conversion at 6 months	Study population		RR 1.01 (0.97 to 1.05)	875 (8 studies)	⊕⊕⊕○ moderate ^{1,3,4,5,6}	
	911 per 1000	920 per 1000 (883 to 956)				
Clinical Improvement at 1 month	Study population		RR 1.16 (1.09 to 1.24)	497 (5 studies)	⊕○○○ very low ^{1,2,4,8,9}	
	794 per 1000	921 per 1000 (865 to 985)				
*The assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio;						

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

¹ Not downgraded for risk of bias: Most of these studies were conducted in the 1960s and provided minimal detail on trial methods. However, the most recent trial from 2005 was well conducted and showed no evidence of clinical benefit with steroids.

² Downgraded by 1 for inconsistency: The overall effect estimate is unduly influenced by two small trials from the 1960s with unusually high mortality rates. One of these trials enrolled severely sick patients who were expected to die within the next few days and found a strong effect in favour of steroids. None of the remaining 16 trials suggest benefit with steroids.

³ Downgraded by 1 for serious indirectness: The majority of these studies are from the 1960s and the result may no longer be applicable to current TB treatment.

⁴ Not downgraded for imprecision: The 95% CI around the absolute effect estimate is sufficiently narrow to exclude clinically important effects.

⁵ Funnel plot symmetry suggests limited risk of publication bias

⁶ Not downgraded for inconsistency: Inconsistency across study results is negligible

⁷ Publication bias is suspected due to the asymmetry in the funnel plot for this outcome.

⁸ Downgraded by 1 for inconsistency: The overall effect estimate is unduly influenced by a single very small trial from the 1960's with extremely polarised rates of clinical improvement in each study arm.

⁹ Publication bias is suspected due to asymmetry identified within the funnel plot for this outcome. Relatively few of the trials identified report upon this outcome and in those which do findings are positive.

BACKGROUND

Tuberculosis (TB) is a chronic infectious disease which causes a high mortality and morbidity burden worldwide. In 2012, approximately 1.3 million deaths and 8.6 million disease episodes were due to TB (WHO 2013). It spreads, most commonly, via horizontal transmission when an individual inhales respiratory droplets containing *Mycobacterium tuberculosis* which have been expelled by someone with active TB. TB is broadly classified as being pulmonary or extra-pulmonary dependent upon the site of infection. Pulmonary tuberculosis (PTB) affects the lung or lymph nodes at the site of primary infection (usually the lung and upper respiratory tract) while extra-pulmonary TB describes TB disease which affects other areas of the body (WHO NOV 2010).

Although effective treatments are available, TB remains the seventh largest cause of mortality worldwide. Within the UK incident case numbers have increased by approximately one fifth over the past decade (PHE 2013). Standard TB treatment regimens are comprised of a combination of drugs which most often includes rifampicin. They are usually given daily, sometimes intermittently (for example three days per week), for at least six months (Garner 2003).

TB infection initiates an inflammatory immune response that itself causes considerable tissue damage. Adjunctive steroid therapy may be used to counteract this, especially where inflammatory disease complicates recovery. Clinical guidance advises the use of adjunctive steroid therapy for treatment of TB meningitis and TB pericarditis (NICE 2006; WHO 2009). However, when given without anti-TB treatment, steroids can actually promote the activation of TB disease (Cisneros 1996). There is also evidence that concurrent administration of anti-TB drugs and steroids causes pharmacokinetic interactions that hinder efficacy of both drugs thus impairing clinical outcomes (Edwards 1974; Sarma 1980; Bergrem 1983; Wagay 1990; Kaojarern 1991).

Three Cochrane reviews have examined the use of steroids as an adjunctive therapy in relieving the complications of TB: pleurisy (Engel 2007), pericarditis (Mayosi 2002) and meningitis (Prasad 2008). Most of the trials included in these reviews were small, and although some benefits were observed, results were often inconclusive.

Approximately 79% of global TB cases are pulmonary, as such it is important to know whether or not there is a benefit from using steroids in treatment of PTB. An earlier systematic review (Smeego 2003) examined the use of steroids as an adjunctive therapy for PTB identifying eleven studies, all of which showed significant improvement in at least one PTB outcome amongst steroid users. This review updates the former review (Smeego 2003), with searches up until May 2014, and refines the outcomes assessed to further evaluate the benefit of adjunctive corticosteroid therapy for the management of PTB.

OBJECTIVES

To evaluate whether adjunctive corticosteroids reduce mortality, improve quality of life or accelerate clinical or microbiological recovery in people with PTB.

METHODS

Criteria for considering studies for this review

Types of studies

Both Randomized Control Trials (RCTs) and quasi-RCTs were included in this review regardless of setting and publication language.

Types of participants

Participants with PTB, defined either clinically or microbiologically, were included. There were no exclusion criteria for studies regarding participants age group or co-morbidities.

Types of interventions

In each study participants were treated with the same antimicrobial regimen for PTB and given the same care other than as follows:

Intervention group

Also given a corticosteroid of any dose, duration or mode of administration as an adjunct to standard PTB treatment.

Control group

Given either standard PTB treatment alone or in combination with a placebo.

Types of outcome measures

Primary

All-cause mortality

Deaths due to any cause during treatment and trial follow-up.

Secondary

Microbiological Outcomes

Microbiological outcomes are assessed, when possible, using numbers reaching WHO defined TB outcomes within each trial arm.

Conversion

Number of participants whose sputum smear or culture became negative by specified time-points (only data for monthly time-point intervals, not weekly, is presented).

Cure

Number of participants whose sputum smear or culture was positive at the beginning of the treatment but who had become smear or culture negative in the last month of treatment and on at least one prior occasion.

Treatment failure

Number of participants whose sputum smear or culture is positive after 5 months or more of treatment.

Relapse

Number of patients newly diagnosed with bacteriologically positive TB who have previously been treated for TB and declared cured or treatment completed.

Where available microbiological data on study specific indicators were also extracted.

Clinical improvement

Mean change in clinician defined symptom scores or study specific indicators of clinical improvement.

Fever

Change in average temperature since baseline or number of participants becoming afebrile since baseline.

Weight change

Mean weight change from baseline and where available indicators of variation.

Length of hospital stay

Mean time spent as an inpatient and where available indicators of variation.

Functional disability

Mean change from baseline in trial specific measures of pulmonary function and where available indicators of variation.

Adverse events

Counts of each adverse event as specified within each trial. Where possible presented as numbers occurring in each trial arm, when only reported for steroid arm presented separately.

Search methods for identification of studies

Databases

The following databases were searched using the search terms and strategy described in [Appendix 1](#)

- Cochrane Infectious Diseases Group's trials register (1993 to May 2014)
- Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (Issue 5, May 2014)
- MEDLINE (1966 to May 2014)
- EMBASE (1974 to May 2014) and
- LILACS (1982 to May 2014)

Reference lists

The reference lists of all studies identified by the above methods and of the previously published reviews were hand searched for further relevant non-indexed publications.

Researchers, organizations and pharmaceutical companies

Individual researchers working in the field and those within pertinent organizations including the International Union Against Tuberculosis and Lung Disease, World Health Organization (WHO), Centers for Disease Control and Prevention (CDC), National Institutes of Health, European and Developing Countries Clinical Trials Directive, Research Institute of Tuberculosis (Kiyose, Japan), National Tuberculosis Institute (Bangalore, India) and the Tuberculosis Research Centre (Chennai, India) were contacted.

All relevant studies were included regardless of language.

Data collection and analysis

Selection of studies

Three authors (JC, LO and FP) scanned the citations retrieved by the search strategy. For non-English language papers, the assistance of translators was used. Study eligibility was assessed using a pre-specified eligibility form based on the review inclusion criteria. The reasons for excluding potentially relevant trials are given in the '[Characteristics of excluded studies](#)' section. Any disagreements on study inclusion were resolved by discussion between JC, LO

and FP. Where necessary authors of studies were contacted for clarification.

Data extraction and management

JC obtained full text articles published on potentially relevant studies. At least two investigators (JC, LO or FP) extracted relevant data from included papers using a pre-agreed extraction form. Any disagreements in data extraction were resolved by discussion, consultation of a Cochrane Infectious Disease Group editor or by contacting authors for further clarification of specific points.

Assessment of risk of bias in included studies

At least two investigators assessed the methodological quality of each trial in terms of generation of allocation sequence, allocation concealment and blinding. The risk that methods of allocation sequence, allocation concealment and blinding were introducing bias into each study were assessed as either low risk, high risk or unclear (if inadequate, detail was given). The decisions made on the risk methods were introducing bias and the reasoning for them is recorded within the '[Characteristics of included studies](#)' section and within [Figure 1](#). Funnel plots were generated for outcomes for which data were pooled and used to assess the risk of publication bias.

Figure 1. Risk of bias summary: review authors' judgements regarding each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)
Angel 1960	+	+	-
Bell 1960	?	?	-
Bilaceroglu 1999	?	?	+
BTA 1961	+	+	+
BTA - Corticotrophin data	+	+	+
BTA - Prednisone data	+	+	+
De Alemquer 1955	?	?	+
Horne 1960	+	+	+
Johnson 1965	?	+	+
Keidan 1961	+	?	+
Malik 1969	+	?	-
Marcus 1962	+	+	-
Mayanja-Kizza 2005	+	+	+
McLean 1963	?	?	?
Nemir 1967	?	+	+
Park 1997	?	?	?
TBRC 1983	?	?	-
TBRC 1983 - No Rif	?	?	-
TBRC 1983 - Rif 5/7months	?	?	-
Toppett 1990	?	-	-
USPHS 1965	+	+	+
USPHS 1965 - 5 week data	+	+	+
USPHS 1965 - 9 week data	+	+	+
Weinstein 1959	?	?	+

Data synthesis

Extracted data was analysed using [Review Manager \(RevMan\)](#). Heterogeneity amongst trials was assessed using the Chi^2 test with a 10% level of statistical significance and the I^2 statistic. Since heterogeneity was, in general, modest for most comparisons we used the Mantel-Haenszel fixed-effect risk ratio with 95% confidence intervals (CI) to pool and summarise dichotomous outcomes reported in trials. In sensitivity analyses, trials were excluded in which the assessed methodological items were judged as creating a high risk of bias. Since many of the included trials were carried out some time ago, where feasible we also carried out sensitivity analyses including only trials utilising a more effective rifampicin-containing anti-TB chemotherapy. Sensitivity analyses were also completed excluding trials where bias assessment criteria were judged to be at high risk of introducing bias.

All data available on the secondary outcomes assessed by this review are presented in the additional tables ([Table 1](#); [Table 2](#); [Table 3](#); [Table 4](#); [Table 5](#); [Table 6](#); [Table 7](#); [Table 8](#); [Table 9](#); [Table 10](#)). Of the secondary outcomes assessed, it was only appropriate to pool data on clinical improvement at 1 month and microbiological outcomes. Data for all other secondary outcomes were not pooled as there was great heterogeneity in study specific indicators recorded for each trial. A narrative summary of all findings is given (for further details see '[Effects of interventions](#)' section)

RESULTS

Description of studies

Please also refer to the following sections: '[Characteristics of included studies](#)' and '[Characteristics of excluded studies](#)'.

We identified 123 papers following searches. Eighteen of these studies met the inclusion criteria and 105 studies were excluded (refer to '[Characteristics of excluded studies](#)' for further details). The 18 included studies were conducted between 1955 and 2005 with the majority undertaken over 20 years ago before TB regimens as used today were implemented. The trials included 3816 participants in total, with three trials having over 100 participants ([USPHS 1965](#); [BTA 1961](#); [TBRC 1983](#)). Only five of these trials (1087 participants) were completed during a time period when more effective rifampicin-containing multi-drug treatment regimens were being used ([TBRC 1983](#); [Toppett 1990](#); [Park 1997](#); [Bilaceroglu 1999](#); [Mayanja-Kizza 2005](#)). One of these five stud-

ies enrolled only patients who were HIV positive ([Mayanja-Kizza 2005](#)).

Trials were conducted in a variety of geographical settings including the USA ([Weinstein 1959](#); [Angel 1960](#); [USPHS 1965](#); [Marcus 1962](#); [McLean 1963](#); [Johnson 1965](#); [Nemir 1967](#); [Malik 1969](#)), UK ([Horne 1960](#); [Keidan 1961](#); [BTA 1961](#)), Belgium ([Toppett 1990](#)), Italy ([De Alemquer 1955](#)), Turkey ([Bilaceroglu 1999](#)), South India ([TBRC 1983](#)), South Korea ([Park 1997](#)), Uganda ([Mayanja-Kizza 2005](#)) and Ghana ([Bell 1960](#)). As such, trial participants when grouped became a very diverse population.

We summarized the specific steroid interventions the trials utilised and reported upon in the '[Characteristics of included studies](#)' table. There was large heterogeneity not only in the adjunctive steroid therapy trials used but also in the chemotherapeutic regimens used especially amongst trials conducted before the 1980's when more effective short-course, rifampicin containing therapy became treatment main-stay.

All trials reported on all-cause mortality, 13 studies reported on indicators of microbiological resolution, eight studies on clinical improvement, six on fever, eight on weight change, three on length of time spent in hospital, five studies on functional disability, and 12 studies on adverse events.

Risk of bias in included studies

Methods of allocation generation, allocation concealment and blinding within trials were used as indicators of methodological quality. Although methodological quality of included trials is shown to have differed substantially, it is unlikely that it caused inherent bias within any of the trials (for details on individual trials see '[Characteristics of included studies](#)' section). Often descriptions of allocation generation, allocation concealment and blinding were missing from publications meaning that a judgement of unclear was given to the trial for its methodological quality rather than this judgement being made as an unsuitable method had been used. Six trials ([Angel 1960](#); [Bell 1960](#); [Malik 1969](#); [Marcus 1962](#); [TBRC 1983](#); [Toppett 1990](#)) had a single indicator judged as being at high risk of causing bias, a summary of methodological assessments is given in [Figure 1](#).

Funnel plots were constructed for each meta-analysis, most showed no inherent risk of publication bias within the trials included in meta-analyses. However, asymmetry was seen in funnel plots for the following outcomes; sputum conversion at two months ([Figure 2](#)) and clinical improvement at 1 month ([Figure 3](#)) indicating a potential risk of publication bias.

Figure 2. Funnel plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: 1.2 Sputum conversion by 2 months.

Figure 3. Funnel plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: I.6 Clinical Improvement at 1 month.

Effects of interventions

See: [Summary of findings for the main comparison Steroid therapy comparative to either no therapy or placebo for managing pulmonary tuberculosis](#)

All-cause mortality

All 18 trials identified, including 3816 participants, reported on all-cause mortality. Pooled results showed a 23% non significant decrease in all-cause mortality amongst the intervention group (RR 0.77, 95% CI 0.51 to 1.15; 18 trials, 3816 participants, *low quality evidence*; [Analysis 1.1](#), [Figure 4](#)).

Figure 4. Forest plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: I.I All-cause mortality.

Of the included trials, only five trials were carried out after the introduction of rifampicin containing regimens (TBRC 1983; Toppett 1990; Park 1997; Bilaceroglu 1999; Mayanja-Kizza 2005) and of these five trials only one trial amongst HIV positive PTB participants reported any deaths (Mayanja-Kizza 2005). The risk ratio of mortality from this trial was RR 1.23, 95% CI 0.64 to 2.34; one trial, 187 participants. A sensitivity analysis pooling only data from these five trials found no difference in mortality amongst individuals taking steroids compared to those taking no steroid or placebo (RR 1.23, 95% CI 0.64 to 2.34; five trials, 957 participants, *very low quality evidence*). However, pooling the older trials which used non-rifampicin containing regimens showed a statistically significant 43% decrease in all-cause mortality amongst the intervention group (RR 0.57, 95% CI 0.34 to 0.97; 13 trials, 2858 participants, *very low quality evidence*).

We undertook a sensitivity analysis, only pooling studies where bias assessment criteria were judged not to be at high risk of introducing bias (Figure 1). A negligible difference in RR was found (RR 0.76, 95% CI 0.50 to 1.14; 12 trials, 2794 participants).

Secondary outcomes

Microbiological improvement

The WHO lists the following as standardised microbiological outcomes for TB:

- Cure - a patient initially smear-positive who becomes smear-negative by the last month of treatment and was smear negative on at least one previous occasion.
- Failure - a patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.
- Completed treatment - a patient who completed treatment but did not meet the criteria for cure or failure.
- Successfully treated - a patient who was cured or who completed treatment.
- Relapse - a patient previously declared cured but with a new episode of bacteriologically positive (sputum smear or culture) tuberculosis.

Data was available amongst the 18 identified trials on sputum conversion, failure and relapse but not on cure, numbers completing treatment, or successfully treated.

Sputum conversion

Thirteen trials reported upon study-specific indicators of sputum and culture clearance (Weinstein 1959; Angel 1960; Bell 1960; Horne 1960; BTA 1961; USPHS 1965; Marcus 1962; McLean 1963; Johnson 1965; Malik 1969; TBRC 1983; Bilaceroglu 1999; Mayanja-Kizza 2005), just two of which were undertaken after the introduction of rifampicin-containing TB regimens (TBRC 1983; Mayanja-Kizza 2005) (Table 1).

Pooled results showed no difference in sputum conversion both at two months after treatment initiation (RR 1.03, 95% CI 0.97 to 1.09; 12 trials, 2750 participants, [Analysis 1.2, Figure 5](#), *low quality evidence*) and in the longer term (at six months after treatment initiation) (nine trials, 2150 participants, [Analysis 1.3, Figure 6](#), *low quality evidence*).

Figure 5. Forest plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: 1.2 Sputum conversion by 2 months.

Figure 6. Forest plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: 1.3 Sputum conversion at 6 months.

In sensitivity analysis only data from studies where bias assessment criteria were judged not to be at high risk of introducing bias were pooled, a negligible difference in RR was found at both 2 months (RR 1.15, 95% CI 1.05 to 1.24; seven trials, 1232 participants) and 6 months (Figure 1).

Treatment Failure

The WHO defines TB patients as 'failed' if they were initially smear positive and remained so beyond their 5th month of treatment. Nine trials (Weinstein 1959; Angel 1960; Horne 1960; BTA 1961; Marcus 1962; McLean 1963; Johnson 1965; Malik 1969; TBRC 1983) reported on treatment failure, only one of which was completed after the introduction of rifampicin-containing treat-

ments.

Amongst the nine trials study-specific definitions of treatment failure differed substantially (for example 'failure to clear susceptible AFB after five consecutive months of anti-tuberculous therapy' and 'those needing re-treatment up to two years after first regimen of anti-tuberculous therapy', see Table 2) and, as such, it was not appropriate to pool these results. However, it was possible to pool results extracted using the WHO definition as a guide, no difference in failure rate was found between those taking steroids comparative to those taking no steroid or placebo (9 trials, participants 1124, Analysis 1.4, Figure 7, *very low quality evidence*).

Figure 7. Forest plot of comparison: 1 Steroid therapy comparative to either no therapy or placebo, outcome: 1.4 Treatment Failure.

Sensitivity analyses only including studies where bias assessment criteria were judged not to be at high risk of introducing bias made negligible difference (five trials, 558 participants) (Figure 1).

Treatment Relapse

Four trials (Johnson 1965; TBRC 1983; Bilaceroglu 1999; Mayanja-Kizza 2005) reported on study specific indicators of treatment relapse (see Characteristics of included studies), no trials reported on relapse as defined by the WHO (see Table 3). Three of the four studies were completed after the introduction of rifampicin-containing treatments (TBRC 1983; Bilaceroglu 1999; Mayanja-Kizza 2005). No difference in relapse rates were found between those taking steroids comparative to those taking no steroid or placebo (four trials, 995 participants, Analysis 1.5, Figure 8, *very low quality evidence*).

Figure 8. Forest plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: I.5 Relapse.

In sensitivity analyses removing the single study that did not utilise rifampicin made little difference to the results (three trials, 634 participants) as did only including studies where bias assessment criteria were judged not to be at high risk of introducing bias (three trials, 178 participants) (Figure 1).

Clinical improvement

We identified seven trials (Bell 1960; BTA 1961; Marcus 1962; McLean 1963; Johnson 1965; Keidan 1961; Nemir 1967) which reported numeric data for study specific indicators of clinical progress and a single study (Angel 1960) which commented nar-

ratively upon this outcome (Table 4). None of these trials were carried out after the introduction of rifampicin-containing TB regimens (Table 4). Four trials reported upon clinical improvement at one month following treatment (Marcus 1962; BTA 1961; McLean 1963; Nemir 1967; Table 4) with pooled results showing a statistically significant 16% increase in clinical improvement amongst those taking steroids comparative to those taking no steroids or taking placebo (RR 1.16, 95% CI 1.09 to 1.24; four trials, 497 participants, Analysis 1.6, Figure 9, *low quality of evidence*).

Figure 9. Forest plot of comparison: I Steroid therapy comparative to either no therapy or placebo, outcome: I.6 Clinical Improvement at 1 month.

In sensitivity analyses including only studies where bias assessment criteria were judged to be at low risk of introducing bias (three trials, 178 participants, *low quality evidence*) the difference in RR was negligible.

Fever

Six trials (Angel 1960; BTA 1961; Marcus 1962; McLean 1963; Johnson 1965; Bilaceroglu 1999) reported upon study specific in-

dicators of fever. Only one of the trials was carried out after the introduction of rifampicin-containing TB regimens (Bilaceroglu 1999) (Table 5). Five of the six studies (Angel 1960; Marcus 1962; McLean 1963; Johnson 1965; Bilaceroglu 1999) saw an improvement in fever reduction or time to fever reduction amongst the intervention group. Study-specific indicators of fever abatement differed substantially so it was not appropriate to pool results. For two of the trials (Angel 1960; Marcus 1962) a single indicator of

bias assessment is deemed to be at high risk of causing bias (Figure 1).

Weight change

Seven trials (Angel 1960; Bell 1960; Horne 1960; BTA 1961; Marcus 1962; Johnson 1965; Malik 1969; Bilaceroglu 1999) reported upon weight change at different time-points since baseline (Table 6). Only one of these trials was carried out after the introduction of rifampicin-containing TB regimens (Bilaceroglu 1999) (Table 6).

In seven of the eight trials reporting upon weight change it is significantly increased (during at least one time-point) amongst individuals taking steroids compared to those taking no steroid or placebo (data not pooled, seven trials, 1203 participants, *low quality evidence*). For four of the trials (Angel 1960; Bell 1960; Malik 1969; Marcus 1962) an indicator of bias assessment is deemed to be at high risk of causing bias (Figure 1).

Length of hospital stay

Three trials reported study-specific indicators of hospital stay length, all demonstrating statistically significant and potentially important reductions in length of stay (ranging from an average of 18 to 30 days) in the steroid group (Weinstein 1959; Johnson 1965; Bilaceroglu 1999), (data not pooled, three trials, participants 379, *very low quality evidence*). However the relevance of this finding is limited as most TB patients no longer remain inpatients whilst on treatment. Study-specific indicators for length of stay differed substantially so it was not appropriate to pool results (Table 7).

Only one of these trials was carried out after the introduction of rifampicin-containing TB regimens (Bilaceroglu 1999) (Table 7). For all three trials, bias assessment criteria were judged to be at low risk of introducing bias (Figure 1).

Functional disability

Five studies (Angel 1960; Marcus 1962; McLean 1963; Malik 1969; Park 1997) reported upon changes in specific indicators of lung function, only one of which was carried out after the introduction of rifampicin-containing TB regimens (Park 1997). No differences were found between the control and steroid groups for any indicator of lung function in three of the five trials (Marcus 1962; McLean 1963; Park 1997). Two studies (Angel 1960; Malik 1969) reported a significant difference in one of the three recorded indicators of lung function (Table 8). Amongst all five trials the majority of multiple measures of functional disability are unaffected by steroid use (data not pooled, five trials, participants 363, *very low quality evidence*).

For three of the five trials, bias assessment criteria were judged to be at high risk of introducing bias (Figure 1).

Adverse Events

There was considerable variation in the way adverse events were reported (Table 9; Table 10). Some studies reported adverse events only amongst the intervention group. It appeared that there was no increase in the number of adverse events amongst the intervention group excluding side effects that would be associated with steroid usage, the majority of which were minor (Table 10, *very low quality evidence*). However, reporting of adverse events was not consistent and it seems unlikely that all such events were captured by the trials.

DISCUSSION

We identified 18 trials which met review inclusion criteria, published between 1955 and 2005, with a total of 3816 participants.

Corticosteroids did not reduce mortality from pulmonary tuberculosis (18 trials, 3816 participants, *low quality evidence*). We attempted to stratify all-cause mortality results according to whether or not more effective rifampicin-containing regimens had been used. However, in practice this was inconclusive as these more recent trials were generally very small and reported no deaths, apart from one single trial among people who were HIV positive (Mayanja-Kizza 2005). For other outcomes, sensitivity analyses also made negligible differences to findings as trials excluded were again few and small.

Compared to placebo or no steroid adjunctive steroid therapy was associated with a significant 16% increase in clinical improvement at one month (RR 1.16, 95% CI 1.09 to 1.24; four trials, 497 participants, Analysis 1.6, Figure 9 *low quality evidence*). However, there was no difference in sputum conversion at two months (RR 1.03, 95% CI 0.97 to 1.09; 12 trials, 2170 participants). Significant, short term clinical benefits of corticosteroid use were not maintained in the long term. Neither sputum conversion at 6 months (RR 1.01, CI 0.98 to 1.04; nine trials, 2150 participants), failure rate (RR 1.02, CI 0.98 to 1.05; 10 trials, 1124 participants) or relapse rate (RR 0.61, CI 0.35 to 1.07; four trials, 995 participants) were found to differ amongst those taking corticosteroid compared to those taking no steroid or placebo.

Corticosteroid use was also found to: reduce the duration of fever (data not pooled, six trials, 851 participants, *very low quality evidence*), increase weight gain during differing study specific time points (data not pooled, eight trials, 1203 participants, *low quality evidence*), and to decrease length of hospital stay (data not pooled, three trials, participants 379, *very low quality evidence*) when compared with no steroid treatment or placebo. No differences in functional disability were found (data not pooled, five trials, participants 363, *low quality evidence*) between those taking corticosteroids and those taking no steroids or placebo. The reporting of adverse events amongst both the intervention and control groups

was poor in the majority of studies reviewed. However, amongst those treated with adjunctive steroid therapy in the most recent study (completed amongst HIV patients) hyperglycaemia, fluid retention, and hypertension were all reported as being significantly more common.

Although improvement of symptoms, signs, clinical and microbiological outcomes amongst those taking corticosteroid are continually reported within publication text and narrative reviews and our findings support such comment, they should be interpreted with caution as the evidence behind these findings is of poor quality. Findings are often based upon few trials with low participant numbers. In this review, three trials included were completed amongst children (Keidan 1961; Nemir 1967; Toppett 1990) who are known to react differently to TB infection and treatment. There is also great heterogeneity within intervention and control treatment regimens utilised in included trials, as well as in methodology of included trials. How findings from trials utilising historic treatment regimens can be extrapolated to modern short-course rifampicin including treatment regimens is unknown. As such, we were unable to draw any robust conclusions upon whether adjunctive corticosteroids reduce mortality or accelerate microbiological or clinical recovery in people with PTB based upon current evidence.

There is limited evidence from older trials (not using modern multi-drug rifampicin-containing treatment regimens) that steroids could improve clinical symptoms, particularly in the short term. Corticosteroids may have some clinical benefits for those with PTB, but the trials published to date are too few, too small and too old to demonstrate any statistically significant and clinically relevant effects (Critchley 2013).

TB incidence has remained high in some parts of the world. One

of the key drivers of TB rates over recent decades has been the HIV epidemic, yet only one trial identified was carried out amongst HIV positive PTB patients. Corticosteroids are a very cheap intervention, and might have the potential to improve TB treatment outcomes amongst those with advanced disease especially in resource poor settings, where PTB case-fatality remains high. However, it should also be noted that corticosteroids can cause severe adverse effects, and the benefit to risk ratio of their use for PTB remains unclear. Further adequately powered, well-designed RCTs for adjunctive steroid use in HIV positive, immuno-compromised and immuno-competent patients are needed before robust conclusions upon the potential benefits of this intervention can be made. Such trials should report on patient quality of life and cost-effectiveness, as well as more standard TB treatment outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

No implications for the current treatment guidelines for pulmonary TB were found from this review.

Implications for research

In order to evaluate further whether adjunctive corticosteroids reduce mortality or accelerate clinical or microbiological recovery in people with PTB, a large, sufficiently powered, triple blind RCT is needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Angel 1960

Methods	<p>RCT</p> <p>Generation of allocation sequence: Random sampling numbers, stratified for ethnicity</p> <p>Allocation concealment: Stated concealed, method not described</p> <p>Blinding: Partial blinding (one outcome). Radiographic changes fully blinded, three independent observers examined each X-ray film</p> <p>Inclusion of enrolled/randomized participants: 104 analysed of 134 enrolled (22% excluded or withdrawn)</p>
Participants	<p>Number of participants: 134 enrolled</p> <p>Inclusion criteria: Males and females aged 14-70 years with acute, progressive PTB of moderately or far advanced extent, recent origin and bacteriologically proven</p> <p>Exclusion criteria: History of or presenting with evidence of hypertension, cardiac failure, renal disease, peptic ulceration, mental disease, HIV, Addison's disease or any other bacterial infection, prior anti-TB therapy for >3 weeks</p>
Interventions	<p>(1) Chemotherapy: Streptomycin sulphate (1 g/day) IM, sodium aminosalicylic acid (16 g daily, 12 g for females), isoniazid (100 mg 3 times/day). In patients over 50 years, combostep, a mixture of streptomycin and dihydro-streptomycin was substituted for streptomycin. Para-aminosalicylic acid only used in patients with fluid retention causing difficulties</p> <p>(2) Steroid: Chemotherapy and corticotrophin gel 60 units for four days (30 units every twelve hours), 50 units for four days (25 units every twelve hours), 40 units for three weeks (20 units every twelve hours). Then, a maintenance dose of 30 units once daily for six weeks gradually reduced over three weeks. Total duration 13 weeks</p>
Outcomes	<p>Included in review:</p> <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Fever 5. Weight change 6. Functional disability 7. Adverse events <p>Not included in review:</p> <ol style="list-style-type: none"> 1. Tuberculin sensitivity 2. Radiological outcomes 3. Surgical intervention
Notes	<p>Study location: New York, USA</p> <p>Study dates: February 1957 to January 1958</p>

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling numbers utilised
Allocation concealment (selection bias)	Low risk	Allocation concealed (although method undescribed)
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding

Bell 1960

Methods	RCT Generation of allocation sequence: not described Allocation concealment: not described Blinding: Partial blinding, sputum conversion blinded. Inclusion of enrolled/randomized participants: 91 of 100 (9% excluded or withdrawn)
Participants	Number of participants: 100 enrolled and randomized Inclusion criteria: West African (Ashanti) males aged 16 to 40, radiographic evidence of acute extensive pulmonary disease of recent origin and previously untreated, excreting tubercle bacilli in sputum and fully sensitive to anti-TB drugs employed Exclusion criteria: Concomitant disease known to be adversely affected by corticosteroids (hypertension, cardiac failure, diabetes)
Interventions	(1) Chemotherapy: Streptomycin sulphate (1 g/day), sodium para-aminosalicylic acid (4 g, three times daily), isoniazid (100 mg three times daily), potassium citrate 20 g (three times daily) Duration: 12 weeks (2) Steroid: Chemotherapy + prednisolone, 5 mg four times per day. Started after one week of chemotherapy, continued for eight weeks. In 10th to 11th week dose gradually dropped and none given after 12th week (last week in hospital)
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Weight change Not included in review: <ol style="list-style-type: none"> 1. Volume and character of sputum 2. Radiographic picture 3. White Blood Cell counts 4. Tuberculin sensitivity

Bell 1960 (Continued)

Notes	Study location: Kumasi, Ghana Study dates: not clear	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding

Bilaceroglu 1999

Methods	RCT Generation of allocation sequence: not described Allocation concealment: not described Blinding: Only outcome assessors blinded (except for temperature and weight) Inclusion of enrolled/randomized participants: Unclear. 178 randomized/selected over study period but not sure how identified from the 4379 confirmed PTB cases
Participants	Number of participants: 4379 with 178 randomized Inclusion criteria: Inpatients with advanced PTB that is smear or culture positive or accompanied by granulomatous inflammation with caseous necrosis causing persistent high-grade fever ($\geq 38^{\circ}\text{C}$), weight loss (≥ 2 kg/week) and/or low serum albumin levels (< 3 g/dL) Exclusion criteria: Patients with HIV, uncontrolled hypertension, recalcitrant diabetes, active or recent peptic ulcer, or gastrointestinal bleeding, resistant hypokalaemia or florid sepsis
Interventions	(1) Chemotherapy: Isoniazid, rifampicin, pyrazinamide and streptomycin and/or ethambutol for first three months. Isoniazid, rifampicin and ethambutol for following 6 months (2) Steroid: Chemotherapy + 20 mg Prednisilone twice per day IV/IM for 10 days, then orally for 30 days reduced by 10 mg every 10 days. Duration of use: 40 days in total (from days 18-57 of admission)
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Fever 4. Weight change 5. Length of hospital stay 6. Adverse events

	Not included in review: 1. Serum cortisol 2. Serum albumin 3. Liver function 4. Radiographic improvement	
Notes	Study location: Izmir, Turkey Study dates: January 1992 to December 1997	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Partial blinding

BTA - Corticotrophin data

Methods	*RCT with two treatment arms* Generation of allocation sequence: random sampling numbers Allocation concealment: randomization schedule held confidentially at the co-ordinating centre Blinding: Unblinded except for outcome assessors Inclusion of enrolled/randomized participants: 346 (85%) randomized
Participants	Number of participants: 408 enrolled Inclusion criteria: Men and women aged 15-60 years with acute PTB, newly diagnosed and of recent origin, more than one lung zone involved, treated for ≤ 3 weeks and with tubercle bacilli in sputum Exclusion criteria: Empysema or spontaneous pneumothorax, gross active TB outside the thorax, evidence of other bacterial infection, diabetes, CVD including considerable hypertension, history of radiographically confirmed peptic ulcer, Addison's disease, history of mental disorder, pregnant females
Interventions	(1) Chemotherapy group: Streptomycin 1 g/day, sodium para-aminosalicylic acid 16 g/day in three or four divided doses, M and isoniazid 300mg daily in two equal doses for first six months In month two to six, chemotherapy continued according to choice of each hospital or clinic, most (about 90%) received a combination of para-aminosalicylic acid or isoniazid, about 10% also continued with streptomycin (2) Corticotrophin Arm: Chemotherapy + corticotrophin for three months. ACTH (corticotrophin ZN) 60 iu for four days, 40 iu for four days, 30 iu for 10 weeks (all daily

BTA - Corticotrophin data (Continued)

	in two equal doses). 20 iu for seven days, 10 iu for seven days (daily as single dose) and KCl with food (3) Prednisone Arm: Described in BTA - Prednisone data	
Outcomes	Included in review: 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Fever 5. Weight change 6. Adverse events Not included in review: 1. Erythrocyte sedimentation rates 2. Tuberculin tests 3. Radiographic improvement 4. Surgical intervention	
Notes	Study location: England and Wales Study dates: 27th September 1957 to 27th July 1961	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling numbers utilised
Allocation concealment (selection bias)	Low risk	Randomization schedule held confidentially at co-ordinating centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and patient blinded

BTA - Prednisone data

Methods	*RCT with two treatment arms* Generation of allocation sequence: random sampling numbers Allocation concealment: randomization schedule held confidentially at the co-ordinating centre Blinding: Unblinded except for outcome assessors Inclusion of enrolled/randomized participants: 346 (85%) randomized	
Participants	Number of participants: 408 enrolled Inclusion criteria: Men and women aged 15-60 years with acute PTB, newly diagnosed and of recent origin, more than one lung zone involved, treated for <= 3 weeks and with tubercle bacilli in sputum Exclusion criteria: Empysema or spontaneous pneumothorax, gross active TB outside	

BTA - Prednisone data (Continued)

	the thorax, evidence of other bacterial infection, diabetes, CVD including considerable hypertension, history of radiographically confirmed peptic ulcer, Addison’s disease, history of mental disorder, pregnant females	
Interventions	<p>(1) Chemotherapy group: Streptomycin 1 g/day, sodium para-aminosalicylic acid 16 g/day in three or four divided doses, M and isoniazid 300 mg daily in two equal doses for first six months</p> <p>In month two to six, chemotherapy continued according to choice of each hospital or clinic, most (about 90%) received a combination of para-aminosalicylic acid or isoniazid, about 10% also continued with streptomycin</p> <p>(2) Corticotrophin Arm: Described in BTA - Corticotrophin data</p> <p>(3) Prednisone Arm: Chemotherapy + prednisone for three months. 50 mg for four days, 37.5 mg for four days, 30 mg for 10 weeks (given every four hours excluding the night dose), ACTH 20 iu daily as single dose for seven days plus daily reduction of prednisolone to 20, 15, 10, 5 and 0 mg. ACTH 10 iu daily as a single dose for seven days and KCl with food</p>	
Outcomes	<p>Included in review:</p> <ol style="list-style-type: none">1. All-cause mortality2. Microbiological outcomes3. Clinical improvement4. Fever5. Weight change6. Adverse events <p>Not included in review:</p> <ol style="list-style-type: none">1. Erythrocyte sedimentation rates2. Tuberculin tests3. Radiographic improvement4. Surgical intervention	
Notes	<p>Study location: England and Wales</p> <p>Study dates: September 1957 to July 1961</p>	
<i>Risk of bias</i>		
Bias	Authors’ judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling numbers utilised
Allocation concealment (selection bias)	Low risk	Randomization schedule held confidentially at co-ordinating centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and patient blinded

Methods	<p>*RCT with two treatment arms*</p> <p>Generation of allocation sequence: random sampling numbers</p> <p>Allocation concealment: randomization schedule held confidentially at the co-ordinating centre</p> <p>Blinding: Unblinded except for outcome assessors</p> <p>Inclusion of enrolled/randomized participants: 346 (85%) randomized</p>
Participants	<p>Number of participants: 408 enrolled</p> <p>Inclusion criteria: Men and women aged 15-60 years with acute PTB, newly diagnosed and of recent origin, more than one lung zone involved, treated for <= 3 weeks and with tubercle bacilli in sputum</p> <p>Exclusion criteria: Empysema or spontaneous pneumothorax, gross active TB outside the thorax, evidence of other bacterial infection, diabetes, CVD including considerable hypertension, history of radiographically confirmed peptic ulcer, Addison's disease, history of mental disorder, pregnant females</p>
Interventions	<p>(1) Chemotherapy group: Streptomycin 1 g/day, sodium para-aminosalicylic acid 16 g/day in three or four divided doses, M and isoniazid 300 mg daily in two equal doses for first six months</p> <p>In month two to six, chemotherapy continued according to choice of each hospital or clinic, most (about 90%) received a combination of para-aminosalicylic acid or isoniazid, about 10% also continued with streptomycin</p> <p>(2) Corticotrophin Arm: Chemotherapy + corticotrophin for three months. ACTH (corticotrophin ZN) 60 iu for four days, 40 iu for four days, 30 iu for 10 weeks (all daily in two equal doses). 20 iu for seven days, 10 iu for seven days (daily as single dose) and KCl with food</p> <p>(3) Prednisone Arm: Chemotherapy + prednisone for three months. 50 mg for four days, 37.5 mg for four days, 30 mg for 10 weeks (given every four hours excluding the night dose), ACTH 20 iu daily as single dose for seven days plus daily reduction of prednisolone to 20, 15, 10, 5 and 0 mg. ACTH 10 iu daily as a single dose for seven days and KCl with food</p>
Outcomes	<p>Included in review:</p> <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Fever 5. Weight change 6. Adverse events <p>Not included in review:</p> <ol style="list-style-type: none"> 1. Erythrocyte sedimentation rates 2. Tuberculin tests 3. Radiographic improvement 4. Surgical intervention
Notes	<p>Study location: England and Wales</p> <p>Study dates: September 1957 to July 1961</p>
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling numbers utilised
Allocation concealment (selection bias)	Low risk	Randomization schedule held confidentially at co-ordinating centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and patient blinded

De Alemquer 1955

Methods	RCT Generation of allocation sequence: not described Allocation concealment: not described Blinding: not blinded, but only outcome reported is mortality Inclusion of enrolled/randomized participants: 33 (85%) six excluded as died 'before hormone had time to work'
Participants	Number of participants: 39 randomized Inclusion criteria: male and female 21-70 years with pulmonary TB, "serious disease" (death envisaged in next few days) Exclusion criteria: "certain complications", not specified
Interventions	(1) Chemotherapy: 1 g streptomycin, 200 mg isoniazid, 500,000 u penicillin by IV every 12 hours (penicillin only to prevent and treat infections associated with cortisone, and also in case on diagnostic error eg pneumonia) (2) Steroid: chemotherapy + IV cortisone for 15 days, 1st to 3rd day 300 mg/day, 4-6 days 200 mg, 7-9 days 100 mg, 10-15 days 50 mg (total 2100 mg)
Outcomes	Included in review: 1. All-cause mortality
Notes	Study location: Lisbon, Italy Study dates: 1955

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

De Alemquer 1955 (Continued)

Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding however measures of mortality are unlikely to be affected by this
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Horne 1960

Methods	RCT Generation of allocation sequence: random sampling numbers Allocation concealment: allocated centrally from pre-arranged lists by a study manager Blinding: Triple blind (patients, physicians and radiographers unaware of allocation) Inclusion of enrolled/randomized participants: 178 (84%)
Participants	Number of Participants: 213 randomized Inclusion criteria: Men and women, expected to remain in hospital for six months, no surgical treatment or collapse therapy envisaged for six months Exclusion criteria: Received collapse therapy at any time, chemotherapy previously given (protocol allowed patients to be admitted to trial who had been started on chemotherapy <one month prior to acceptance (n = 4)), bacilli known to be resistant to streptomycin, para-aminosalicylic acid or isoniazid, active extra-pulmonary disease, pregnant or within three months of parturition, other condition known to be adversely affected by steroids eg peptic ulcer, hypertension, cardiac failure, etc
Interventions	(1) Chemotherapy: If aged <40 years 1 g streptomycin sulphate and 100 mg isoniazid 2 times/day for 6 months If aged >40 years 5 g sodium para-aminosalicylic acid and 100 mg isoniazid 2 times/day, 1 g streptomycin sulphate 3 times/week for 6 months (2) Steroid: Chemotherapy and 5 mg Prednisone 4 times/day, 2 g Potassium citrate 2 times/day and 30 units ACTH gel intra-muscularly two days every fortnight for three months
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Weight 4. Adverse events Not included in review: <ol style="list-style-type: none"> 1. Erythrocyte sedimentation rate 2. Blood pressure 3. Urine for albumin and sugars 4. Serum electrolytes 5. Radiological improvement 6. Need for surgical intervention
Notes	Study location: Scotland Study dates: 1956 to 1957
Risk of bias	

Horne 1960 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sampling numbers utilised
Allocation concealment (selection bias)	Low risk	Allocation by co-ordinating centre from pre-arranged lists
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, physicians and radiographer blinded

Johnson 1965

Methods	Quasi-RCT Generation of allocation sequence: alternate Allocation concealment: N/A Blinding: Triple blind (patients doctors and radiographers) Inclusion of enrolled/randomized: 102 (86%)
Participants	Number of participants: 118 enrolled but 11 excluded and 7 lost to follow up Inclusion criteria: previously untreated cavitary PTB, admitted to pulmonary disease services of the Madison and Minneapolis Veterans Administration hospitals Exclusion criteria: Steroid contraindications such as diabetes, ulcers or any other serious complicating condition
Interventions	(1) Chemotherapy: Isoniazid 300 mg, para-aminosalicylic acid 12 mg, streptomycin sulphate 1 gm/day for one month, three times weekly after. Total duration not stated (2) Steroid: Chemotherapy + prednisolone. 4 mg daily in four equal doses for 10 weeks, then dose reduced by 4 mg every four days for 12 days
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Length of hospital stay 5. Fever 6. Weight gain 7. Adverse events Not included in review: <ol style="list-style-type: none"> 1. Anaemia 2. Tuberculin hypersensitivity 3. Radiographic improvement 4. Surgical intervention
Notes	Study location: Madison & Minneapolis, USA Study dates: Dec 1958 to Jul 1961

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No described
Allocation concealment (selection bias)	Low risk	Allocated via 'random assignment'
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, physicians and radiographers blinded

Keidan 1961

Methods	Quasi-RCT Method of allocation: Alternate Blinding: Triple blind (including radiographer) Inclusion of enrolled/randomized: unclear	
Participants	Number of participants: 16 Inclusion criteria: Children aged six months to 15 years with PTB, infection seemed to be of recent onset, clearly defined radiological lesions and a Mantoux test positive at a dilution of 1 in 10,000 Exclusion criteria: not stated	
Interventions	(1) Chemotherapy: Streptomycin 20 mg/lb body weight/day intra-muscularly in a single daily dose & oral isoniazid total daily dose of 5 mg/lb body weight/day in divided doses three times daily for 12 weeks (2) Steroid: Chemotherapy + triamcinolone 0.25 mg/lb body weight/day for four weeks, then 0.125 mg for four weeks then dose gradually reduced and stopped after a further two weeks	
Outcomes	Included in review: 1. All-cause mortality 2. Clinical improvement Not included in review: 1. ESR 2. Tuberculin sensitivity 3. Ability to isolate bacilli 4. Radiographic improvement	
Notes	Study location: Liverpool, UK Study dates: May 1958 - Nov 1959	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement

Keidan 1961 (Continued)

Random sequence generation (selection bias)	Low risk	Quasi-RCT, alternately allocated
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician, patient and radiographer blinded

Malik 1969

Methods	Quasi-RCT Generation of sequence: Alternate Allocation concealment: not described Blinding: Outcome assessors only Inclusion of enrolled/randomized: 104 (88%)	
Participants	Number of participants: 118 Inclusion criteria: not described Exclusion criteria: not described	
Interventions	(1) Chemotherapy: "standard anti-TB drugs" - no further details (2) Steroid: prednisone, 40 mg every other day for six weeks, then reduced to 25 mg every other day; continued for total of six months	
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Weight 4. Functional disability 5. Adverse events Not included in review: <ol style="list-style-type: none"> 1. Radiographic improvement 	
Notes	Study location: USA Study dates: unclear	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quasi-randomized, alternately allocated
Allocation concealment (selection bias)	Unclear risk	Not described

Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding
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Marcus 1962

Methods	<p>RCT</p> <p>Generation of allocation sequence: stratification into one of 12 subgroups by duration of illness (> or < three months by history), total area of lung involvement on roentograph (> or < one lung) and cavitation (cavity, 0 to 2 cm, at least one cavity with larger than 4 cm diameter). Each of 12 subgroups randomized separately using sealed envelopes</p> <p>Allocation concealment: One envelope for each strata containing equal numbers of slips with steroid or control</p> <p>Blinding: Unblinded</p> <p>Inclusion of enrolled/randomized patients: 100 (92%)</p>
Participants	<p>Number of participants: 109</p> <p>Inclusion criteria: active previously untreated TB (<two weeks conventional anti-TB therapy at study onset)</p> <p>Exclusion criteria: Major illnesses other than TB as judged by history, physical exam, roentgenograms; psychosis; any patients judged so ill that they required steroid therapy and could not be randomized (estimated at 6 or less); Haematocrit <30 (except for two patients in early course of study)</p>
Interventions	<p>1) Chemotherapy: 300 mg isoniazid, 12 g para-aminosalicylic acid and 1 g streptomycin sulphate daily for one month then three times per week</p> <p>2) Steroid: Chemotherapy + prednisolone 40 mg/day reduced by 2.5 mg every five days, distributed as equally as possible in four doses. Reduction continued until daily total of 20 mg reached. Continued on 20 mg until two roentographs taken two weeks apart showed little further change. Then reduction of 2.5 mg again made every five days until total discontinuation. Total dose averaged 1040 mg in first month, overall dosage averaged 2372 mg over an average of three months and 16 days</p>
Outcomes	<p>Included in review:</p> <ol style="list-style-type: none"> 1. All-cause mortality 2. Clinical improvement 3. Microbiological outcomes 4. Fever 5. Weight Change 6. Functional disability 7. Adverse events <p>Not included in review:</p> <ol style="list-style-type: none"> 1. Erythrocyte sedimentation rates 2. Radiographic improvement 3. Cavitation closure 4. Surgical intervention

Marcus 1962 (Continued)

Notes	Study location: New York, USA Study dates: not known	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing of a sealed envelope
Allocation concealment (selection bias)	Low risk	Allocation using concealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding

Mayanja-Kizza 2005

Methods	RCT Generation of allocation sequence: Randomly drawn blocks of 6 by computer generated random numbers Allocation concealment: Allocated blindly using sequentially drawn lots Blinding: Double-blind Inclusion of enrolled/randomized participants: 187 (93%)
Participants	Participants: 202 Inclusion criteria: >18 years of age, with an initial episode of acid fast smear positive PTB Exclusion criteria: Smear negative, previous TB treatment, advanced HIV infection, Karnofsky score <80, Kaposi sarcoma, active herpes zoster, glucose level of >160 mg/dL, DM history, serum aminotransferase >65 IU/L, potassium >5.5 mmol/L, a positive beta urinary human chorionic gonadotrophin test, history of immunomodulator use, history of hypertension, psychiatric disease, peptic ulcer or pancreatitis
Interventions	1) Chemotherapy: Standard HIV associated TB regimen (weight adjusted doses of isoniazid, rifampin, pyrazinamide and ethambutol) 2) Steroid: Chemotherapy and Prednisilone 2.75 mg/kg daily for four weeks then tapered over the next four weeks (8 weeks total)
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Adverse events Not included in review: <ol style="list-style-type: none"> 1. CD4+ T cell counts 2. Immune activation 3. HIV RNA levels

Notes	Study location: Uganda Study dates: October 1998 to August 2000	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized utilising computer generated random numbers
Allocation concealment (selection bias)	Low risk	Allocated blindly using sequentially drawn lots
Blinding (performance bias and detection bias) All outcomes	Low risk	Physician and patients blinded

McLean 1963

Methods	RCT Generation of allocation sequence: not described Allocation concealment: not described Blinding: not described Inclusion of enrolled/randomized participants: 21 (78%)
Participants	Number of participants: 27 enrolled Inclusion criteria: endobronchial lesions suggestive of endobronchial TB (such as cheese like material, stenosis, granular, ulceration or inflammatory changes) observed by bronchoscopy with either caseating necrosis on tissue biopsy, positive stains or cultures of acid-fast bacilli on the sputum, bronchial washing or brushing Exclusion criteria: Other systematic disease or infection, history of previous TB, patients who stopped anti-TB medications or corticosteroid due to severe side-effects, patients who were pregnant
Interventions	(1) Chemotherapy: Isoniazid 10 mg/kg/day, pyridoxine at 50-100mg/day, para-aminosalicylic acid 12 g/day* (2) Steroid: Prednisolone 48 mg/day for 2 weeks, then dosage was decreased by 50% every 3-4 days to reach discontinuation* *First 6 patients in each arm received 100 IU of ACTH this was given as 40 IU/day per day for the last 3 days of therapy
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Clinical improvement 4. Fever 5. Functional disability Not included in review

McLean 1963 (Continued)

	1. Radiographic improvement	
Notes	Study location: Baltimore, USA Study dates: 1959	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described

Nemir 1967

Methods	RCT Generation of allocation sequence: Not described Allocation concealment: Codes sealed from view Blinding: Triple blind, placebo controlled (patients, doctors and outcome assessors) Inclusion of randomized/enrolled participants: not clear
Participants	Number of participants: 118 enrolled Inclusion criteria: children (>four months) with primary TB of not >six months duration Exclusion criteria: known Varicella-susceptible children excluded during epidemics, patients with TB meningitis, pleurisy or miliary disease
Interventions	(1) Chemotherapy: Isoniazid 20 mg/kg/day and 200 mg/kg/day para-aminosalicylic acid, usually for one year (2) Steroid: prednisone 5 mg/kg for two days, 3 mg/kg for two days, 2 mg/kg for two days, then 1 mg/kg to end fourth week (28 days), 0.5 mg/kg fifth week, 0.25 mg/kg sixth week, total duration of use: 37 days
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Clinical improvement 3. Adverse events
Notes	Study location: New York, USA Study dates: 1960 to 1966
<i>Risk of bias</i>	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Low risk	Codes sealed from view
Blinding (performance bias and detection bias) All outcomes	Low risk	Physicians and patients blinded

Park 1997

Methods	RCT Generation of allocation sequence: Not described Allocation concealment: Not described Blinding: Not described Inclusion of all randomized patients: 34
Participants	Number of participants: 34 Inclusion criteria: 15 to 60 years old, males and females Exclusion criteria: Patients with other systemic disease or infection, history of previous TB, patients who stopped anti-TB medications or corticosteroid due to severe side-effects, or patients who were pregnant
Interventions	1) Chemotherapy: Isoniazid, rifampin, pyrazinamide, streptomycin or ethambutol or both 2) Steroid: Chemotherapy + Prednisolone 0.5 mg doses, approximately 1.0 mg/kg per day for four or eight weeks and then tapered followed up with bronchoscopy
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Functional disability Not included in review: <ol style="list-style-type: none"> 1. Radiographic improvement
Notes	Study location: South Korea Study dates: 1991 to 1995

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not sufficiently described

Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not described
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TBRC 1983

Methods	RCT *3 control arms* Generation of allocation sequence: Not described Allocation concealment: Not described Blinding: Outcome assessors only Inclusion of enrolled/randomized participants: Not clear	
Participants	Participants: 530 Inclusion criteria: over 12 years of age, newly diagnose PTB, at least two positive sputum cultures Exclusion criteria: Prior TB treatment for 2 weeks or more	
Interventions	1) Chemotherapy: either Rifampicin 7 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine) , and 70 mg/kg pyrazinamide twice weekly for five months Rifampicin 5 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine) , and 70 mg/kg pyrazinamide twice weekly for three months No rifampicin - 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine), and 70 mg/kg pyrazinamide twice weekly for five monthsIn phase 2 patients were only enrolled onto this chemotherapeutic regimen 2) Steroid: Chemotherapy (a, b or c) and Prednisilone 20 mg 3 times daily for one week, then 10 mg once and 5 mg twice a day for five weeks, then 5 mg twice a day for one week and then 5 mg daily for a final week (8 weeks in total)	
Outcomes	Published and included in review: 1. All cause mortality 2. Microbiological improvement 3. Adverse events Not included in review: 1. Radiographic improvements	
Notes	Study location: South India, Madras Study dates: Not stated	
Risk of bias		
Bias	Authors' judgement	Support for judgement

TBRC 1983 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding

TBRC 1983 - No Rif

Methods	<p>RCT *3 control arms*</p> <p>Generation of allocation sequence: Not described</p> <p>Allocation concealment: Not described</p> <p>Blinding: Outcome assessors only</p> <p>Inclusion of enrolled/randomized participants: Not clear</p>
Participants	<p>Participants: 530</p> <p>Inclusion criteria: over 12 years of age, newly diagnose PTB, at least two positive sputum cultures</p> <p>Exclusion criteria: Prior TB treatment for 2 weeks or more</p>
Interventions	<p>1) Chemotherapy: either</p> <p>Rifampicin 7 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine) , and 70 mg/kg pyrazinamide twice weekly for five months</p> <p>Rifampicin 5 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine) , and 70 mg/kg pyrazinamide twice weekly for three months</p> <p>No rifampicin - 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine), and 70 mg/kg pyrazinamide twice weekly for five monthsIn phase 2 patients were only enrolled onto this chemotherapeutic regimen</p> <p>2) Steroid: Chemotherapy (a, b or c) and Prednisilone 20 mg 3 times daily for one week, then 10 mg once and 5 mg twice a day for five weeks, then 5 mg twice a day for one week and then 5 mg daily for a final week (8 weeks in total)</p>
Outcomes	<p>Published and included in review:</p> <ol style="list-style-type: none"> 1. All cause mortality 2. Microbiological improvement 3. Adverse events <p>Not included in review:</p> <ol style="list-style-type: none"> 1. Radiographic improvements

Notes	Study location: South India, Madras Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding

TBRC 1983 - Rif 5/7months

Methods	RCT Generation of allocation sequence: Not described Allocation concealment: Not described Blinding: Outcome assessors only Inclusion of enrolled/randomized participants: Not clear
Participants	Participants: 530 Inclusion criteria: over 12 years of age, newly diagnose PTB, at least two positive sputum cultures Exclusion criteria: Prior TB treatment for 2 weeks or more
Interventions	1) Chemotherapy: either Rifampicin 7 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine), and 70 mg/kg pyrazinamide twice weekly for five months Rifampicin 5 months - 12 mg/kg rifampicin, 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine), and 70 mg/kg pyrazinamide twice weekly for three months No rifampicin - 400 mg of isoniazid (incorporating 6 mg pyridoxine), 40 mg/kg pyrazinamide, 0.75 g streptomycin sulphate daily for two months. Then 0.75 g streptomycin, 15 mg/kg isoniazid (incorporating 6 mg pyridoxine), and 70 mg/kg pyrazinamide twice weekly for five months In phase 2 patients were only enrolled onto this chemotherapeutic regimen 2) Steroid: Chemotherapy (a, b or c) and Prednisilone 20 mg 3 times daily for one week, then 10 mg once and 5 mg twice a day for five weeks, then 5 mg twice a day for one week and then 5 mg daily for a final week (8 weeks in total)

Outcomes	Published and included in review: 1. All cause mortality 2. Microbiological improvement 3. Adverse events Not included in review: 1. Radiographic improvements	
Notes	Study location: South India, Madras Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	High risk	Incomplete blinding

Toppett 1990

Methods	Open RCT Generation of allocation sequence: Not described Allocation concealment: Not described Blinding: Open trial (but radiography and bronchoscopy blind) Inclusion of randomized/enrolled patients: 23 (79%)	
Participants	Number of participants: 29 Inclusion criteria: Individuals with primary TB and bronchial obstruction without fistulisation confirmed by bronchoscopy. Age range of participants was four months to 15 years and the male:female ratio was 10:19 Exclusion criteria: None stated	
Interventions	1) Chemotherapy: Isoniazid 10 mg/kg to a maximum dose of 300 mg/kg, rifampicin 15 mg/kg to a maximum dose of 600 mg/kg for a year with ethambutol 20 mg/kg for two months. When cultures were positive or sensitivity tests showed choice of treatment unsuitable, treatment regimen was adjusted 2) Steroid: Chemotherapy + daily dose of prednisolone 2 mg/kg for 15 days tapered and stopped between 1.5 and three months	
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality Not included in review: <ol style="list-style-type: none"> 1. Radiographic Improvement 	

Notes	Study location: Belgium Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described sufficiently “children were divided at random”
Allocation concealment (selection bias)	High risk	Open trial
Blinding (performance bias and detection bias) All outcomes	High risk	Open trial

USPHS 1965

Methods	*RCT with 2 treatment arms* Generation of allocation sequence: Random assignment of centrally labelled medication sets Allocation concealment: Carried out at central office, medication put into opaque bottles and randomly sent to participating centres Blinding: Triple blind, placebo controlled (patients, doctors and outcome assessors) Inclusion of enrolled/randomized patients: 424 (75%)
Participants	Number of participants: 566 Inclusion criteria: 14+ with roentographic and bacteriologic proof of active TB, treated for less than two weeks Exclusion criteria: Organic CNS disease, abnormal mental or emotional signs or history of, heart disease with sodium retention. A physicians discretion: DM, chronic renal disease
Interventions	1) Chemotherapy: Daily 1 gm streptomycin, 35-45 g/kg body weight pyrazinamide, isoniazid 4-6 mg/kg body weight and 10-12 g para-aminosalicylic acid for 12 weeks 2) Steroid for 5 weeks: Chemotherapy + prednisolone 20 mg for three days, 15 mg for the next four days, 10 mg each day for 3 weeks 5 mg for four days and 2.5 mg for next three days 3) Steroid for 9 weeks: Chemotherapy + prednisolone 20 mg for three days, 15 mg for the next four days, 10 mg each day for 7 weeks 5 mg for four days and 2.5 mg for next three days
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Adverse events Not included in review

USPHS 1965 (Continued)

	1. Radiographic improvement	
Notes	Study location: USA Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally controlled randomization
Allocation concealment (selection bias)	Low risk	Randomly assigned by central centre, opaque bottles sent to treatment centres
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, physicians and outcome assessors blinded

USPHS 1965 - 5 week data

Methods	*RCT with 2 treatment arms* Generation of allocation sequence: Random assignment of centrally labelled medication sets Allocation concealment: Carried out at central office, medication put into opaque bottles and randomly sent to participating centres Blinding: Triple blind, placebo controlled (patients, doctors and outcome assessors) Inclusion of enrolled/randomized patients: 424 (75%)
Participants	Number of participants: 566 Inclusion criteria: 14+ with roentographic and bacteriologic proof of active TB, treated for less than two weeks Exclusion criteria: Organic CNS disease, abnormal mental or emotional signs or history of, heart disease with sodium retention. At physicians discretion: DM, chronic renal disease
Interventions	1) Chemotherapy: Daily 1 gm streptomycin, 35-45 g/kg body weight pyrazinamide, isoniazid 4-6 mg/kg body weight and 10-12 g para-aminosalicylic acid for 12 weeks 2) Steroid for 5 weeks: Chemotherapy + prednisolone 20 mg for three days, 15 mg for the next four days, 10 mg each day for 3 weeks 5 mg for four days and 2.5 mg for next three days 3) Steroid for 9 weeks: see USPHS 1965 - 9 week data
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Adverse events Not included in review

USPHS 1965 - 5 week data (Continued)

	1. Radiographic improvement	
Notes	Study location: USA Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally controlled randomization
Allocation concealment (selection bias)	Low risk	Randomly assigned by central centre, opaque bottles sent to treatment centres
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, physicians and outcome assessors blinded

USPHS 1965 - 9 week data

Methods	*RCT with 2 treatment arms* Generation of allocation sequence: Random assignment of centrally labelled medication sets Allocation concealment: Carried out at central office, medication put into opaque bottles and randomly sent to participating centres Blinding: Triple blind, placebo controlled (patients, doctors and outcome assessors) Inclusion of enrolled/randomized patients: 424 (75%)
Participants	Number of participants: 566 Inclusion criteria: 14+ with roentographic and bacteriologic proof of active TB, treated for less than two weeks Exclusion criteria: Organic CNS disease, abnormal mental or emotional signs or history of, heart disease with sodium retention. A physicians discretion: DM, chronic renal disease
Interventions	1) Chemotherapy: Daily 1 g streptomycin, 35-45 g/kg body weight pyrazinamide, isoniazid 4-6 mg/kg body weight and 10-12 g para-aminosalicylic acid for 12 weeks 2) Steroid for 5 weeks: see USPHS 1965 - 5 week data 3) Steroid for 9 weeks: Chemotherapy + prednisolone 20 mg for three days, 15 mg for the next four days, 10 mg each day for 7 weeks 5 mg for four days and 2.5 mg for next three days
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All-cause mortality 2. Microbiological outcomes 3. Adverse events Not included in review

USPHS 1965 - 9 week data (Continued)

	1. Radiographic improvement	
Notes	Study location: USA Study dates: Not stated	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally controlled randomization
Allocation concealment (selection bias)	Low risk	Randomly assigned by central centre, opaque bottles sent to treatment centres
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, physicians and outcome assessors blinded

Weinstein 1959

Methods	RCT Generation of allocation sequence: Not described Allocation concealment: Not described Blinding: Triple blinded Inclusion of enrolled/randomized patients: 100
Participants	Number of participants: 100 Inclusion criteria: None described Exclusion criteria: Non-tuberculous diagnostic problems, those previously treated with anti-TB chemotherapy, those with contraindications; pregnancy, renal disease, hypertension, peptic ulcerative disease and diabetes
Interventions	1) Chemotherapy: 300 mg isoniazid daily and 9 to 12 gm of aminosalicylic acid daily 2) Steroid: Chemotherapy plus 5 mg of prednisolone every six hours for 10 days, every eight hours for 10 days, every 12 hours for 40 days, every day for four days, then 2.5 mg every day for four days
Outcomes	Included in review: <ol style="list-style-type: none"> 1. All cause mortality 2. Microbiological outcomes 3. Length of hospital stay Not included in review: <ol style="list-style-type: none"> 1. Radiographic improvement 2. Surgical intervention
Notes	Study location: USA Study dates: 1954 to 1956

<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Patient, physician and outcome assessors blinded

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Alrajhi 1998	Retrospective case control, peritoneal TB not PTB.
Ashby 1955	All received steroids, no control group.
Aspin 1958	Control group not concurrent.
Bergin 1989	A case series.
Bergrem 1983	Did not examine steroid efficacy as an adjunctive TB therapy
Bhan 1980	Did not examine steroid efficacy as an adjunctive TB therapy
Chakrabarti 2006	A review.
Chan 1989	A case report.
Chan 1990	All receive steroids, no control group.
Cherednikova 1973	A set of case reviews.
Chotmongkol 1996	Meningeal TB not PTB.
Cisneros 1996	A review.
Cochran 1954	All receive steroids, no control group.
Dooley 1997	A review.

(Continued)

Edwards 1974	Didn't examine steroid efficacy as an adjunctive TB therapy.
Elliot 2004	TB pleurisy not PTB.
Escobar 1975	Meningeal TB not PTB.
Fairall 2005	Non-steroidal intervention.
Fleishman 1960	Not TB patients.
Freiman 1970	Didn't examine steroid efficacy as an adjunctive TB therapy.
Galarza 1995	Pleural TB not PTB.
Girgis 1991	Meningeal TB not PTB.
Gopi 2007	A review.
Green 2009	Didn't examine steroid efficacy as an adjunctive TB therapy.
Grewal 1969	TB pleurisy not PTB.
Gusmao Filho 2001	Central nervous system TB not PTB.
Hakim 2000	Pericardial TB not PTB.
Hockaday 1966	A case series.
Hoheisel 2004	Didn't examine steroid efficacy as an adjunctive therapy.
Humphries 1992	A review.
Hussey 1991	Didn't examine steroid efficacy as an adjunctive TB therapy.
Iareshko 1989	Contacted authors regarding eligibility criteria, no reply.
Ip 1986	A case series.
Ivanova 1991	Looking at efficacy of tuberculin and steroid (not chemotherapy and steroids)
Ivanova 1994	Didn't examine steroid efficacy as an adjunctive TB therapy, looked at immunotherapy
Johnson 1954	A review.
Johnson 1967	Part of a review series.
Kaojaren 1991	Didn't examine steroid efficacy as an adjunctive TB therapy.

(Continued)

Karak 1998	Commentary on Schoeman 1997 .
Khomenko 1990	Contacted authors regarding eligibility criteria, no reply.
Kumarvelu 1994	Meningeal TB not PTB.
Kwon 2007	Non-TB haemoptysis, not PTB.
Lardizibal 1998	Meningeal TB not PTB.
Lee 1993	Didn't examine steroid efficacy as an adjunctive PTB therapy
Lee 1998	TB pleurisy not PTB.
Lepper 1963	Meningeal TB not PTB.
Lorin 1983	A review.
Malhorta 2009	Meningeal TB not PTB.
Manresa 1997	Letter referring to Galarza 1995 .
Mansour 2006	Control group not concurrent.
Marras 2005	Letter to editor, not novel data.
Mathur 1960	Pleural TB not PTB.
Mayosi 2008	Didn't examine steroid efficacy as an adjunctive PTB therapy, looked at prednisolone with immunotherapy
McAllister 1983	Didn't examine steroid efficacy as an adjunctive TB therapy.
Meintjes 2010	TB IRIS not PTB.
Meintjes 2012	TB IRIS not PTB.
Menon 1964	Severe cases favourably allocated to steroid treatment group
Misra 2010	Didn't examine steroid efficacy as an adjunctive TB therapy, role of aspirin
Ntsekhe 2003	Systematic review of pericarditis.
O'Toole 1969	Meningeal TB not PTB.
Paheco 1973	No control group. Didn't examine efficacy of steroid and chemotherapy compared to lone chemotherapy, compared efficacy of two types of steroid

(Continued)

Paley 1959	A review.
Pavlova 1994	No control group, did not compare steroid use to 'placebo or no treatment'
Pavlova et al 1994	No control group, does not compare steroid use to 'placebo or no treatment'
Porsio 1966	Participants did not have pleurisy - cases of pulmonary TB.
Quagliarello 2004	An editorial.
Reuter 2006	A review.
Reuter 2007	A review of 233 pericardial TB cases, not PTB cases.
Rikimaru 1999	Didn't examine steroid efficacy as an adjunctive PTB therapy
Rikimaru 2001	Didn't examine steroid efficacy as an adjunctive PTB therapy
Rikimaru 2004	Didn't examine steroid efficacy as an adjunctive PTB therapy
Rooney 1970	Tuberculous Pericarditis, not PTB
Sarma 1980	Pharmacokinetic study of Isoniazid
Schoeman 1997	Meningeal TB not PTB.
Schoeman 2001	Meningeal TB not PTB (not novel data same information as Schoeman 1997).
Schoeman 2004	Not looking at steroid efficacy as an adjunctive TB therapy, adjunctive thalidomide therapy
Schrire 1959	TB pericarditis, not PTB.
Sergeev 1969	Contacted authors regarding eligibility criteria, no reply.
Simmons 2005	Meningeal TB, not PTB.
Singh 1965	Pleural effusion, not PTB.
Singh 1969	A review.
Spodick 1994	A letter.
Starostenko 1989	Contacted authors regarding eligibility criteria, no reply.
Strang 1987	Pericardial TB, not PTB.

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Strang 1988	Pericardial TB, not PTB.
Strang 2004	Pericardial TB, not PTB.
Sun 1981	Milliary TB, no distinction between organ type.
Sushkin 1992	Didn't examine steroid efficacy as an adjunctive TB therapy, looked at metabolic rate in patients who have TB and pneumonia
Tani 1964	Tuberculous pleurisy, not PTB.
Tanzj 1965	Tuberculous pleurisy, not PTB.
TBSSRC 1957	Updated by Horne 1960 .
Thwaites 2004	Meningeal TB, not PTB
Thwaites 2007	Looked at the pathway through which steroids improve meningeal TB outcomes, not PTB
Torok 2011	TB meningitis, not PTB
USPHS 1959	Didn't examine steroid efficacy as an adjunctive TB therapy.
USPHS 1960	Preliminary results from USPHS 1965 - 5 week data .
Voljavec 1960	Controls not concurrent.
Wagay 1990	Didn't examine steroid efficacy as an adjunctive TB therapy.
Wasz-Hokert 1956	Controls not concurrent.
Wasz-Hokert 1963	Controls not concurrent.
Wiysonge 2008	Didn't examine steroid efficacy as an adjunctive TB therapy, looked at risk factors for not taking corticosteroid for TB pericarditis
Wyser 1996	Pleural TB, not PTB.
Yang 2005	Didn't examine steroid efficacy as an adjunctive TB therapy, looked at TB diagnostic techniques
Yew 1999	Didn't examine steroid efficacy as an adjunctive TB therapy, steroids as therapy for tuberculous pyrexia

DATA AND ANALYSES

Comparison 1. Steroid therapy comparative to either no therapy or placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	18	3815	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.15]
2 Sputum conversion by 2 months	13	2750	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.97, 1.09]
3 Sputum conversion at 6 months	10	2150	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]
4 Treatment Failure	10	1124	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
5 Relapse	5	995	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.35, 1.07]
6 Clinical Improvement at 1 month	5	497	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.09, 1.24]

Analysis 1.1. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 1 All-cause mortality.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 1 All-cause mortality

(Continued ...)

Analysis 1.2. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 2 Sputum conversion by 2 months.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 2 Sputum conversion by 2 months

Analysis 1.3. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 3 Sputum conversion at 6 months.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 3 Sputum conversion at 6 months

Analysis 1.4. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 4 Treatment Failure.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 4 Treatment Failure

Analysis 1.5. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 5 Relapse.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 5 Relapse

Analysis 1.6. Comparison 1 Steroid therapy comparative to either no therapy or placebo, Outcome 6 Clinical Improvement at 1 month.

Review: Adjunctive steroid therapy for managing pulmonary tuberculosis

Comparison: 1 Steroid therapy comparative to either no therapy or placebo

Outcome: 6 Clinical Improvement at 1 month

ADDITIONAL TABLES

Table 1. Microbiological resolution: conversion

Study ID	Outcome Definition	Culture or Smear (if culture not reported) Negative			
		Time point (month)	Steroid	Control	Reported Statistical Significance
Angel 1960	Culture negative; three samples of sputum or gastric washings were sent for culture at start of treatment then at monthly intervals	Baseline	0/54	0/50	No significant difference
		1	7/34	12/38	
		2	25/42	32/47	
		3	29/46	39/42	P < 0.001 significantly greater among controls
		4	39/45	41/45	No significant difference

Table 1. Microbiological resolution: conversion (Continued)

			5	40/44	38/40	
			6	45/47	43/46	
Bell 1960		Culture negative; 24 hour specimens of sputum were collected until treatment started, then collected monthly. Concentrates prepared by tri-sodium phosphate method and incubated for 12 weeks	Baseline	0/45	0/46	No significant difference
	1		16/44	11/45		
	2		27/42	25/46		
	3		31/41	35/43		
Bilaceroglu 1999		Culture conversion rate (Sputum taken twice weekly)	Reported as 'comparable'			P = 0.0794
BTA 1961	BTA - Corticotrophin data	Culture negative; direct smear and culture exam taken monthly and analysed using local lab facilities	Baseline	9/111	5/118	Not reported
			1	36/100	31/109	
			3	70/89	77/104	
			6	86/87	91/95	
			9	67/67	74/74	
			12	40/40	39/40	
			BTA - Prednisone data	Culture negative; direct smear and culture exam taken monthly and analysed using local lab facilities	Baseline	
	1	36/109			31/109	
	3	80/104			77/104	
	6	93/95			91/95	
	9	80/80			74/74	
	12	45/45			39/40	

Table 1. Microbiological resolution: conversion (Continued)

Horne 1960		Culture negative; direct sputum smear, gastric lavage or laryngeal swabs	1	40/87	28/91	No significant difference
			2	64/87	45/91	P < 0.01
			3	67/87	62/91	No significant difference
			4	75/87	75/91	
			5	80/87	82/91	
			6	86/87	91/91	
			9	75/77	80/80	
			12	77/77	80/80	
Johnson 1965		Specimens of sputum were collected every two weeks for four months and then every month thereafter. Reversal of infectiousness; the first of three consecutive monthly specimens negative for tubercle bacilli on microscopy and culture	2	18/52	11/50	No significant difference
			4	30/52	31/50	
			6	38/52	37/50	
			8	46/52	42/50	
			10	49/52	44/50	
			12	48/52	46/50	
Malik 1969		Sputum negative; disappearance of sputum in bacilli was monitored for monthly	1	11/46	14/58	No significant difference
			2	26/46	20/58	P < 0.05
			3	28/46	28/58	P < 0.05
			6	35/46	46/58	No significant difference
Marcus 1962		Culture negative; specimens of sputum were collected every two weeks until 2 months then at 3 months and 6 months	1	35/49	31/51	Not reported

Table 1. Microbiological resolution: conversion (Continued)

			2	40/49	45/51	
			3	45/49	45/51	
			6	48/49	48/51	
Mayanja-Kizza 2005		Culture negative; sputum cultures obtained at month 1 and 2 and examined for AFB	1	58/93	35/94	P = 0.001
			2	80/93	80/94	No significant difference
McLean 1963		Smear or sputum negative; Smear or culture of sputum or gastric aspirate	1	0/13	0/14	No significant difference
			2	3/12	4/14	
			3	5/11	8/14	
			4	8/12	11/14	
			5	8/11	13/13	
			6	9/9	10/11	
Nemir 1967		Culture from bronchial aspiration and gastric washings on 3 successive morning on admission; culture positive after therapy	During therapy	4/58	2/59	Not reported
			After therapy	2/58	2/59	Not reported
TBRC 1983	TBRC 1983 - Rif 5/7months	Culture negative; Sputum smears examined by fluorescence microscopy and cultured using a modification of	1	59/132	70/129	No significant difference
			2	121/132	120/129	
			3	1284/132	123/129	
	TBRC 1983 - No Rif	Culture negative; Sputum smears examined by fluorescence microscopy and cultured using a modification of	1	46/129	36/140	No significant difference

Table 1. Microbiological resolution: conversion (Continued)

		Petroffs method. TB chemothera-				
			2	97/129	104/140	
			3	116/129	123/140	
USPHS 1965 - 5 week data	USPHS 1965	Culture negative	1	121/426	101/424	Not reported
			2	208/426	220/424	Not reported
			3	316/426	308/424	Not reported
			4	365/426	342/424	Not reported
			5	387/426	374/424	Not reported
			6	389/426	372/424	Not reported
			8	410/426	392/424	Not reported
	USPHS 1965 - 9 week data	Culture negative	1	107/425	101/424	Not reported
			2	202/425	220/424	Not reported
			3	263/425	308/424	Not reported
			4	330/425	342/424	Not reported
			5	368/425	374/424	Not reported
			6	395/425	372/424	Not reported
			8	389/425	392/424	Not reported
Weinstein 1959		Sputum nega- tive; Cumulative sputum conver- sion	Baseline	16/38	6/33	Not reported
			2	20/38	8/33	
			8	33/38	25/33	

Table 2. Microbiological outcomes: treatment failure

Study ID		Outcome Definition	Steroid	Control	Reported Statistical Significance
Angel 1960		Culture positive at 5 months	4/44	2/40	Not reported
BTA 1961	BTA - Corticotrophin data	Culture positive at 6 months	1/87	4/95	
	BTA - Prednisone data	Culture positive at 6 months	2/95	4/95	
Horne 1960		Culture positive at 5 months	7/87	9/91	
Johnson 1965		Culture or smear positive at 6 months	8/50	8/52	
		Study specific indicator, failure to convert by 12 months	2/50	4/52	No significant difference
Malik 1969		Culture or smear positive at 6 months	11/46	12/58	
Marcus 1962		Culture or smear positive at 6 months	1/49	3/51	
Mayanja-Kizza 2005		Study specific indicator, not described further	1/93	1/94	Not reported
McLean 1963		Culture positive at 6 months	0/9	1/11	
Weinstein 1959		Sputum positive at end of study (6 to 16 months)	2/38	6/33	

Table 3. Microbiological outcomes: relapse

Study ID	Method	Steroid	Control	Reported Statistical Significance
Bilaceroglu 1999	Smear or culture positive TB within 3 years follow up	0/91	0/87	Not reported
Johnson 1965	Number readmitted for TB during up to	3/50	10/50	P < 0.05

Table 3. Microbiological outcomes: relapse (Continued)

		five years of follow up			
Mayanja-Kizza 2005		Those needing re-treatment up to two years after first regimen of anti-tuberculous therapy	8/93	11/94	No difference
TBRC 1983	TBRC 1983 - Rif 5/7months	Two or more of six cultures positive in any three consecutive monthly exams	4/132	3/129	No difference
	TBRC 1983 - No Rif		3/129	6/140	

Table 4. Clinical improvement

Study ID	Outcome Definition	Time Point (months)	Steroid Group	Control Group	Reported Statistical Significance
Angel 1960	Immediate and pronounced non-specific improvement in general condition reported by nurses and patients	N/A, described as being immeasurable numerically			
Bell 1960	Number of participants judged by treating physician to be in 'fair' or 'good' condition as opposed to 'severely ill' or 'poor' condition	1	44/44	39/46	Improvement from baseline greater in steroid group $P < 0.01$
		2	42/42	46/46	No difference
BTA 1961	BTA - Corticotrophin data	1	96/99	100/114	Not reported
		3	91/92	102/107	
		6	85/86	94/95	
	BTA - Prednisone data	1	113/116	100/114	

Table 4. Clinical improvement (Continued)

			3	107/108	102/107	
			6	98/98	94/95	
Johnson 1965	Par- ticipants initially with; any degree of cough or spu- tum, or moderate to severe symp- toms, who saw moderate to marked improve- ment in condition	10 weeks	39/48	28/46	P < 0.05	
Keidan 1961	Participants showing definite- striking improve- ment	1	8/8	0/8	Not reported	
Marcus 1962	Improvement in 'well-being and strength'	7 weeks	49/49	48/51	Not reported	
McLean 1963	'Rapid symptom response'; method of assess- ment unclear	Not reported	13/13	1/14	P < 0.0001	
Nemir 1967	'Improved'; Method of assess- ment unclear.	1	23/31	14/31	No difference	
		2	10/16	9/18		
		3	5/6	3/4		
		6	0/1	0/2		
		7	0/1	0/1		
		time point un- clear	39/58	27/59	P < 0.05	

Table 5. Fever

Author		Outcome Definition	Steroid Group	Control Group	Reported Statistical Significance
Angel 1960		Mean time till patients afebrile, temperature not specified	5 days	19.4 days	Not reported
Bilaceroglu 1999		Mean time till patients afebrile (<37.5°C)	25 days	47 days	Not reported
		Mean temperature change 72 hours after treatment initiation	-1.2 °C	+ 0.2°C	P = 0.003
BTA 1961	BTA - Corticotrophin data	Patients with an average temperature of 99°F or more (1 month)	23/100	52/113	Not reported
	BTA - Prednisone data		17/113	52/113	
	BTA - Corticotrophin data	Patients with an average temperature of 99°F or more (3 months)	12/92	24/104	
	BTA - Prednisone data		36/106	24/104	
	BTA - Corticotrophin data	Patients with an average temperature of 99°F or more (6 months)	7/92	10/104	
	BTA - Prednisone data		7/106	10/104	
Johnson 1965		Median fever duration	1 day	6 days	Not reported
		Mean fever duration	1 day	13 days	
Marcus 1962		Mean number of days for temperature to permanently drop below 100°F	1 day	26 day	Not reported
McLean 1963		Mean number of febrile days	2.9 days	10.2 days	Not reported

Table 6. Weight

Study ID		Outcome	Time Point	Steroid Group	Control Group	Reported Statistical Significance
Angel 1960		Mean gain in weight from base-line (lbs)*	1 months	13	4	Not reported
			2 months	19	8	
			3 months	24	11	P < 0.001
			4 months	25	13	Not reported
			5 months	26	15	
			6 months	27	17	P < 0.001
Bell 1960		Mean gain in weight from base-line (lbs)	1 month	2.75	2.13	No statistically significant differences in mean weight of trial arms at any time point
			2 months	7.56	4.93	
			3 months	8.05	8.09	
Bilaceroglu 1999		Mean gain in weight (kg)	from day 18 to 70	7.2	4.2	P = 0.0022
BTA 1961	BTA - Corticotrophin data	Mean gain in weight from base-line (lbs)	1 month	12	6	Not reported
			3 months	21	11	
			6 months	24	17	P = 0.1
			12 months	23	21	
	BTA - Prednisone data	Mean gain in weight from base-line (lbs)	1 month	9	6	P = 0.1
			3 months	26	11	
			6 months	24	17	No statistically significant difference
			12 months	21	21	
Horne 1960		Mean gain in weight from base-line(lbs)	1 month	8	6	Not reported
			2 months	17	11	
			3 months	21	15	
			4 months	21	15	
			5 months	21	16	
			6 months	21	16	

Table 6. Weight (Continued)

Johnson 1965	Pa- tients initially un- der 130 lbs who gained 15 lbs or more (n)	2 months	8/23	0/17	P<0.025
	Number of pa- tients initially 15 lbs or more under ideal weight who gained 15 lbs or more by	2 months	9/24	2/21	P<0.05
	Num- ber of patients ini- tially more than 20 lbs under ideal weight who gained 15 lbs or more by	2 months	9/24	2/19	
Malik 1969	Mean gain in weight from base- line (lbs)	1 month	8.6	4.4	Not significant
		2 months	12.3	5.1	P<0.05
		3 months	13.3	7.2	
		6 months	16.51	11.74	Not significant
Marcus 1962	Mean gain in weight from base- line (lbs)	6 months	25	16	P<0.01

*Read from graph,

Table 7. Length of hospital stay

Author	Outcome definition	Steroid Group	Control Group	Statistical Significance
Bilaceroglu 1999	Average length of stay for those discharged	53.4 +/- 3.1 days	71.3 +/- 5.6 days	P=0.0284
Johnson 1965	Average length of stay for those discharged	10 months	11 months	Not reported
Weinstein 1959	Average length of stay for those discharged	188.7 days	207.4 days	Not reported

Table 8. Functional disability

Study ID	Outcome definition	Time point (months)	Steroid	Control	Statistical Significance Reported
Angel 1960	Max expiratory flow rate (body temperature and pressure saturated; litres/minute)	Baseline	189.8 (SD 101.7)	205.1 (SD 114.4)	Significantly higher in the corticotrophin group, no value given
		3	241.1 (SD 137.7)	227.3 (SD 115.4)	
		6	238.7 (SD 125.2)	228.4 (SD 100.2)	
	Mean vital capacity (maximal inhalation; standard temperature and pressure dry)	Baseline	2,649 (SD 751)	2,523 (SD 838)	Increased to the same extent in both groups, no value given
		3	2,940 (SD 757)	2,728 (SD 790)	
		6	2,995 (SD 817)	2,874 (SD 786)	
	Max breathing capacity (body temperature and pressure saturated; litres/minute)	Baseline	88.6 (SD 36.3)	82.0 (SD 26.5)	Increased to the same extent in both groups, no value given
		3	102.6 (SD 25.6)	97.8 (SD 32.3)	
		6	100.4 (SD 28.7)	99.1 (SD 31.2)	
Malik 1969	Abnormal maximal	6	12/46	20/58	P < 0.05
	Abnormal vital capacity	6	14/46	12/58	
		12	19/46	24/58	
	Abnormal maximal expiratory flow	6	17/46	21/58	
		12	19/46	24/58	
Marcus 1962	Diffusion capacity normal	1	34/49	35/51	No significant difference
		2	34/49	35/51	
		3	34/49	36/51	
		6	34/49	37/51	
	Maximal Mid expiratory flow rate (1/sec)	1	2	2	No significant difference
		2	2.1	2.1	
		3	2.1	2.3	
		6	2.2	2.3	
	Vital capacity normal	1	35/49	36/51	No significant difference
		2	36/49	37/51	

Table 8. Functional disability (Continued)

		3	36/49	37/51	
		6	39/49	40/51	
McLean 1963	Lung volumes (6 variables measured)	Not reported	Data not extracted		No significant difference in any of the measures
	Ventilation Effects (6 variables measured)				
	Perfusion Effects (6 variables measured)				
	Diffusion Effects (3 variables measured)				
Park 1997	Mean improvement in forced vital capacity (%)	2	9.2	10.4	No significant difference
	Mean improvement in forced expiratory capacity (%)		13.1	9.4	No significant difference

Table 9. Adverse events

Author	Outcome definition	Steroid	Control	Statistical significance
Angel 1960	Sepsis, venous thrombosis, mental changes, and partial deafness	Numbers not given, stated equal in each treatment arm.		Not reported
	Hypersensitivity reactions	4/54	8/54	
Bell 1960	Hypertension	1/45	0/46	
	Toxicity	0/45	0/46	
Bilaceroglu 1999	Drug resistance	18/91	Not reported	
BTA 1961; BTA - Corticotrophin data & BTA - Prednisone data	Developed co-morbidities	28/275	13/133	
	Chemotherapy regimen changed due to PAS intolerance	3/275	0/133	

Table 9. Adverse events (Continued)

	Chemotherapy regimen changed due to streptomycin toxicity	6/275	6/133	
	Chemotherapy regimen changed due to hypersensitivity reactions	7/275	9/133	
Horne 1960	Vestibular disturbance	2/87	5/91	
	Hypersensitivity	5/87	4/91	
Johnson 1965	Hypertension, diabetes, peptic ulcer, psychosis and infections	Incidence equal in each treatment arm (6%, 4%, 0%, 0%, and 4% respectively)		
	Changes to chemo regimen due to hypersensitivity, intolerance, drug resistance and ineffectiveness	29/52	24/50	P < 0.05
	Related respiratory illness (5 years follow up)	11/52	15/50	Not reported
	Acne	23/52	9/50	
	Mooning of the face	34/52	8.5/50	
	Bronchitis, pneumonia or respiratory insufficiency	4/52	11/50	Not reported
	Hypersensitivity reactions	19/52	7/50	P < 0.025
Marcus 1962	Hypersensitivity reactions	1/49	4/51	Not reported
Mayanja-Kizza 2005	≥ 1 adverse event	87/93	82/94	P = 0.38
	≥ 1 severe or life threatening event within 3 years	22/93	18/94	P = 0.19
	Candidiasis	32/93	36/94	Not reported
	Hyperglycemia	9/93	3/94	P = 0.036

Table 9. Adverse events (Continued)

	Abdominal pain	17/93	13/94	P = 0.47
	Hepatitis	12/93	6/94	P = 0.09
	Fluid retention	28/93	4/94	P < 0.001
	Pruritis	33/93	33/94	P = 0.95
	Herpes simplex	10/93	4/94	Not reported
	Herpes Zoster	16/93	17/94	P = 0.99
	Kaposi sarcoma	0/93	2/94	P = 0.49
	Pneumonia	16/93	16/94	P = 0.93
	Urinary tract infection	14/93	7/94	P = 0.19
	Hypertension	12/93	4/94	P = 0.039
McLean 1963	Number of complications	1/14	5/13	Not reported
	Number of side effects	3/14	13/13	
	Rebound phenomena - fever	8/13	0/14	
Nemir 1967	Infectious disease	1/19	5/29	
	Viral disease	2/19	9/29	
	bacterial disease	2/19	3/29	
TBRC 1983	Incidence of adverse events	Figures not reported, stated no difference between groups		
	Athralgia	Figures not reported, stated no difference between groups		
	Swelling of feet or face	62/344	3/339	P = 0.00001
	GI disturbances	21/344	1/339	P = 0.00001
	Induced hyperglycaemia	2/344	0/339	Not reported
USPHS 1965	Severe adverse event requiring discontinuation	2/851	1/424	Not reported

Table 9. Adverse events (Continued)

	Hepatitis	4/851	2/424	Not reported
	Sensitivity to Streptomycin-Pyrazinamide	68/851	22/424	More patients showed intolerance in steroid groups
	Sensitivity to Isoniazid-PAS	38/851	26/424	Not reported
	Blood pressure	No differences in mean SBP or DBP at any time point		
	Fasting plasma glucose	No differences at any time points		
USPHS 1965 - 5 week data	Acne	14/426	11/424	Not reported
	Moonface	10/426	3/424	Not reported
	Euphoria	6/426	4/424	Not reported
	Oedema	3/426	9/424	Not reported
USPHS 1965 - 9 week data	Acne	17/425	11/424	Not reported
	Moonface	11/425	3/424	Not reported
	Euphoria	11/425	4/424	Not reported
	Oedema	8/425	9/424	Not reported

Table 10. Adverse events only reported for steroid group

Author	Outcome definition	Steroid
Angel 1960	Acne	11/54
	Mooning of face	22/54
	Fluid retention	7/54
	Transient diabetes mellitus	6/54
	DBP over 100 mm	2/54
	Paroxysmal nocturnal dyspnoea	1/54
Bell 1960	Withdrawal phenomena	None
	Mooning of face	None

Table 10. Adverse events only reported for steroid group (Continued)

Bilaceroglu 1999		Steroid side effects	None
BTA 1961	BTA - Corticotrophin data	Steroid therapy changed or stopped	15/111
		Mooning of the face	7/72
		Rebound Phenomena	6/111
		Hypertension	7/111
		Pyschiatric disturbance	6/111
	BTA - Prednisone data	Steroid therapy changed or stopped	7/116
		Mooning of the face	30/116
		Rebound Phenomena	34/116
		Hypertension	6/116
		Glycosuria	10/116
		Pyschiatric problems	2/116
Horne 1960		Marked obesity	3/87
		Hypertension	11/87
		Mooning of the face	18/87
		Hirsutism	1/87
		Transient glycosuria	6/87
		Transient rash on prednisolone withdrawal	17/87
		Withdrawn from prednisolone therapy	2/87
Marcus 1962		Acute thrombophlebitis	1
		Herpes Zoster	1
		Diabetes	1
		Marked weight gain (23lb)	1
		Moderate Acne	1

Table 10. Adverse events only reported for steroid group (Continued)

Nemir 1967	Temporary elevation of blood pressure	3
	Abdominal distension	7
	Steroid therapy suspended	2
Park 1997	Adverse events	None
	Increased infection rate	None

APPENDICES

Appendix I. Search methods: detailed search strategies

Search set	CIDG ^a	CENTRAL	MEDLINE ^b	EMBASE ^b	LILACS ^b
1	tuberculosis	tuberculosis	TUBERCULOSIS	TUBERCULOSIS	tuberculosis
2	TB	steroids	tuberculosis	tuberculosis	TB
3	steroids	corticosteroids	TB	TB	1 or 2
4	corticosteroids	glucocorticoids	1 or 2 or 3	1 or 2 or 3	steroids
5	dexamethasone	hydrocortisone	Steroid*	Steroids	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroids	corticosteroids	prednisolone
8	-	2 or 3 or 4 or 5 or 6 or 7	glucocorticoids	glucocorticoids	4 or 5 or 6 or 7
9	-	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	-	-	dexamethasone	dexamethasone	-
11	-	-	prednisolone	prednisolone	-
12	-	-	prednisone	methylprednisone	-

(Continued)

13	-	-	methylprednisone	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	-
14	-	-	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13	4 and 13	-
15	-	-	4 and 14	Limit 13 to human	-
16	-	-	Limit 15 to human	-	-

^aCIDG Specialized Register.

^bSearch terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration (([Lefebvre 2011](#)); upper case: MeSH or EMTREE heading; lower case: textword.

CONTRIBUTIONS OF AUTHORS

JC drafted the protocol. JC, LO and FP assessed possible studies for inclusion. JC requested full papers then JC, LO and FP acted as data extractors. JC, LO and FP drafted and edited the final draft.

DECLARATIONS OF INTEREST

No known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine (LSTM), UK.

External sources

- Department for International Development (DFID), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Some changes made to outcomes and timing of reporting of outcomes between protocol and review. This was to make reported outcomes as consistent as possible with current WHO definitions, although often, mainly due to the age of included trials, reporting of such outcomes was unfeasible.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [adverse effects; *therapeutic use]; Cause of Death; Chemotherapy, Adjuvant; Fever [drug therapy]; Length of Stay; Randomized Controlled Trials as Topic; Steroids [adverse effects; therapeutic use]; Tuberculosis, Pulmonary [*drug therapy; mortality]; Weight Gain

MeSH check words

Humans