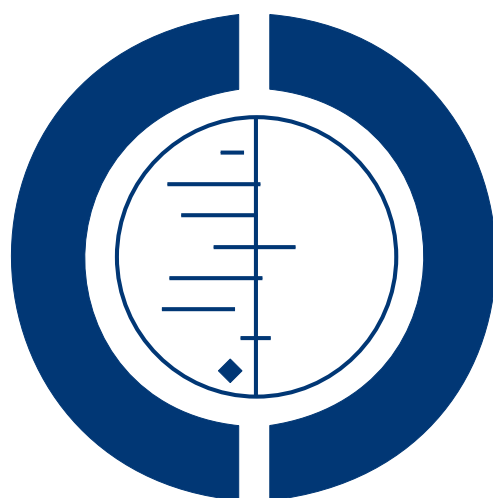


# Corticosteroids for managing tuberculous meningitis (Review)

Prasad K, Singh MB



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[Intervention Review]

# Corticosteroids for managing tuberculous meningitis

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## ABSTRACT

### Background

Tuberculous meningitis, a serious form of tuberculosis that affects the meninges covering the brain and spinal cord, is associated with high mortality and disability among survivors. Corticosteroids have been used as an adjunct to antituberculous drugs to improve the outcome, but their role is controversial.

### Objectives

To evaluate the effects of corticosteroids as an adjunct to antituberculous treatment on death and severe disability in people with tuberculous meningitis.

### Search strategy

In September 2007, we searched the Cochrane Infectious Diseases Group Specialized Register; CENTRAL (*The Cochrane Library* 2007, Issue 3); MEDLINE; EMBASE; LILACS and Current Controlled Trials. We also contacted researchers and organizations working in the field, and checked reference lists.

### Selection criteria

Randomized controlled trials comparing a corticosteroid *plus* antituberculous treatment with antituberculous treatment alone in people with clinically diagnosed tuberculosis meningitis and which include death and/or disability as outcome measures.

### Data collection and analysis

We independently assessed search results and methodological quality, and independently extracted data. We analysed the data using risk ratios (RR) with 95% confidence intervals (CI) and the fixed-effect model. We also conducted complete-case and best-worst case analyses.

### Main results

Seven trials involving 1140 participants (with 411 deaths) met the inclusion criteria. All used dexamethasone or prednisolone. Overall, corticosteroids reduced the risk of death (RR 0.78, 95% CI 0.67 to 0.91; 1140 participants, 7 trials). Data on disabling residual neurological deficit from three trials showed that corticosteroids reduce the risk of death or disabling residual neurological deficit (RR 0.82, 95% CI 0.70 to 0.97; 720 participants, 3 trials). Adverse events included gastrointestinal bleeding, bacterial and fungal infections and hyperglycaemia, but they were mild and treatable.

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**Corticosteroids for managing tuberculous meningitis (Review)**

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## Authors' conclusions

Corticosteroids should be routinely used in HIV-negative people with tuberculous meningitis to reduce death and disabling residual neurological deficit amongst survivors. However, there is not enough evidence to support or refute a similar conclusion for those who are HIV positive.

## PLAIN LANGUAGE SUMMARY

### Corticosteroids for managing tuberculous meningitis

Tuberculous meningitis is a serious form of tuberculosis affecting the meninges covering the brain and spinal cord. The clinical outcome is poor even when treated with conventional antituberculous drugs. Corticosteroids are commonly used in addition to antituberculous drugs for treating the condition. They help reduce swelling and congestion of the meninges, and thus decrease pressure inside the brain and the attendant risk of death or disabling residual neurological deficit among survivors. This review identified seven trials involving 1140 people that evaluated either dexamethasone or prednisolone given in addition to antituberculous drugs; only one trial was of high quality. Overall, the trials showed that corticosteroids help reduce the risk of death or a risk of death or disabling residual neurological deficit. Only one trial evaluated the effects of corticosteroids in HIV-positive people, but the effects were unclear. Given the results of the review, all HIV-negative people with tuberculous meningitis should receive corticosteroids, but more trials are needed in HIV-positive people.

## BACKGROUND

Tuberculous meningitis is an inflammation of the meninges, which envelope the brain and the spinal cord. It is caused by infection with *Mycobacterium tuberculosis*, the bacterium responsible for tuberculosis. Tuberculous meningitis is a severe form of tuberculosis and accounts for many deaths (Tandon 1988). In some countries it accounts for 5% to 7% of all admissions to neurology and paediatric wards in specialist hospitals (Tandon 1988). Extrapulmonary involvement (ie tuberculosis occurring outside the lungs) can be seen in more than 50% people who also have HIV/AIDS (Rieder 1990; Shafer 1991). It appears also that the higher risk of tuberculosis in HIV-infected people means that tuberculous meningitis is also more common in this group (Berenguer 1992; Berger 1994).

Tuberculous meningitis usually presents with headache, fever, vomiting, altered sensorium, and sometimes convulsions. It is diagnosed clinically with confirmation by microscopy, culture of cerebral spinal fluid, or the polymerase chain reaction test. Disability in tuberculous meningitis is multifactorial. Some of the important causes of disability are persistent or progressive hydrocephalus, involvement of the optic nerves or optic chiasm in the supracellar region, vasculitis leading to cerebral infarcts and stroke, multiple cranial neuropathies, and arachnoiditis. Disability related to antituberculous treatment most often occurs as ethambutol-in-

duced toxic optic neuritis, which may be irreversible, or isoniazid-related peripheral neuropathy.

Tuberculous meningitis can be classified according to its severity. The British Medical Research Council (MRC) use three stages (MRC 1948): stage I (mild cases) is for those without altered consciousness or focal neurological signs; stage II (moderately advanced cases) is for those with altered consciousness who are not comatose and those with moderate neurological deficits (eg single cranial nerve palsies, paraparesis, and hemiparesis); and stage III (severe cases) is for comatose patients and those with multiple cranial nerve palsies, and hemiplegia or paraplegia, or both.

### Treatment options

Without treatment, people with tuberculous meningitis die. Streptomycin, one of the earliest antituberculous drugs to be introduced, reduced the case-fatality rate to 63% (Parsons 1988). Newer antituberculous drugs – isoniazid, rifampicin, pyrazinamide, and ethambutol – are associated with better survival, but mortality remains comparatively high. Recent reports of mortality rates vary from 20% to 32%, and permanent neurological deficits in an additional 5% to 40% of survivors (Ramchandran 1986; Alarcon 1990; Jacobs 1990; Jacobs 1992).

The role of corticosteroids in the treatment of tuberculous meningitis as an adjunct to antituberculous treatment remains controversial despite being in use since early 1950s. Some authors have reported them as being effective (Ramchandran 1986; Alarcon 1990; Chotmongkol 1996), while others have reported that their use is not supported by the evidence (Holdiness 1990; Prasad 1997; Schoeman 1997). Indirect evidence from animal studies provides a biological basis to how the drug could be effective (Feldman 1958) – they may: decrease inflammation, especially in the subarachnoid space; reduce cerebral and spinal cord oedema and intracranial pressure (Feldman 1958; Parsons 1988); and reduce inflammation of small blood vessels and therefore reduce damage from blood flow slowing to the underlying brain tissue. However, corticosteroids can also cause harm by suppressing the immune mechanism – they may: suppress the symptoms of tuberculosis infection but promote an unchecked growth of the bacteria and an increased bacterial load; reduce inflammation of the meninges, which will then reduce the ability of drugs to seep into the subarachnoid space; and cause gastrointestinal haemorrhage, electrolyte imbalance, hyperglycaemia, and infections from fungi or bacteria. Corticosteroids are also known to have certain adverse effects, such as gastrointestinal bleeding, invasive bacterial or fungal infections, hyperglycaemia, and electrolyte disturbances. Adjunctive corticosteroids are not known to result in disability, especially when used for short durations as is the case in most clinical trials of this intervention. However, there is a concern that although corticosteroids may save lives of some very sick patients, they may not necessarily improve their quality of life as they are often left bed-bound due to sequelae. In other words, if the survival rate is increased with corticosteroids but not disability-free survival, then corticosteroids actually increase the financial and disease burden on the family and society.

### Why it is important to do this review?

Several randomized controlled trials have been conducted on the effect of corticosteroids in managing tuberculous meningitis. The conclusions from these trials, seen individually, appear inconsistent. One trial, Thwaites 2004, showed that dexamethasone increases survival rate, but it also raised two questions – do patients who survive because of dexamethasone therapy tend to be left with severe disability, and are there differential effects among subgroups of patients with different degrees of disease severity? The editorial that accompanied the trial (Quagliarello 2004) and several letters to the editor in response to this trial (Marras 2005; Seligman 2005) have commented that the trial did not have enough statistical power to answer these questions. We have prepared a meta-analysis that synthesizes the results from all the trials to try and provide the necessary power to address these questions.

## OBJECTIVES

To evaluate the effects of corticosteroids as an adjunct to antituberculous treatment on death and severe disability in people with tuberculous meningitis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomized controlled trials.

#### Types of participants

People of any age with clinically diagnosed tuberculous meningitis.

#### Types of interventions

##### Intervention

Corticosteroid (hydrocortisone, prednisolone, or dexamethasone) given orally, intramuscularly, or intravenously *plus* antituberculous treatment.

##### Control

Antituberculous treatment (same as intervention) with or without placebo.

#### Types of outcome measures

##### Primary

- Death.
- Death or disabling residual neurological deficit at the end of follow up.

##### Adverse events

Adverse events, including upper gastrointestinal bleeding, invasive bacterial or fungal infections, and hyperglycaemia.

## Search methods for identification of studies

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

## Databases

We searched the following databases using the search terms and strategy described in [Appendix 1](#): Cochrane Infectious Diseases Group Specialized Register (September 2007); Cochrane Central Register of Controlled Trials (CENTRAL), published in *The Cochrane Library* (2007, Issue 3); MEDLINE (1966 to September 2007); EMBASE (1974 to September 2007); and LILACS (1982 to September 2007). We also searched Current Controlled Trials ([www.controlled-trials.com](http://www.controlled-trials.com); accessed September 2007) using 'tuberculosis' and 'meningitis' as search terms.

## Researchers

We contacted the following organizations and individuals working in the field: delegates at the V<sup>th</sup> Annual Conference of Indian Academy of Neurology, Madras, India, 1997; and the XIII<sup>th</sup> Global Joint Meeting of the International Clinical Epidemiology Network and Field Epidemiology Training Program, Victoria Falls, Zimbabwe, 1994.

## Reference lists

We also drew on existing reviews of this topic ([Ramchandran 1986](#); [Jacobs 1990](#); [Geiman 1992](#)), and checked the citations of all the trials identified by the above methods.

## Data collection and analysis

### Heterogeneity

We assessed heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of confidence intervals. We used the chi-square test with a P value of 0.10 to indicate statistical significance and the  $I^2$  statistic to assess heterogeneity with a value of 50% taken to indicate statistical heterogeneity. We planned to investigate heterogeneity through the following subgroup analyses: drug resistance (susceptible versus resistant *M. tuberculosis*); severity of illness (MRC stages I, II, and III); and HIV status (seropositive versus seronegative).

## Sensitivity analyses

For trials with missing data, we conducted two analyses: an available-case analysis and then a 'worst-case scenario' analysis for trials with missing data. All participants who had dropped out of the corticosteroid group were considered to have an unfavourable outcome whereas those who had dropped out of the control group were considered to have a favourable outcome. We conducted a sensitivity analysis imputing the missing data in this way to determine whether the overall results were sensitive to this assumption.

## Assessment of reporting biases

We also conducted visual inspection of the funnel plot of the studies for any obvious asymmetry that could be evidence of publication bias.

## Selection of studies

We independently screened the search results and retrieved the full articles of all potentially relevant trials. Each trial report was scrutinized to ensure that multiple publications from the same trial were included only once. Trial investigators were contacted for clarification if a trial's eligibility was unclear. We resolved disagreements through discussion and listed the excluded studies and the reasons for their exclusion.

## Data extraction and management

We independently extracted data using a pre-piloted data extraction form. Data extracted included participant characteristics, diagnostic criteria, disease severity, HIV status, antituberculous drug regimen, corticosteroid regimen, and outcome measures. We resolved disagreements through discussion and contacted the corresponding publication author in the case of unclear or missing data. We contacted the authors of [Lardizabal 1998](#) to determine the number of deaths in participants with stage II and III disease. For dichotomous outcomes, we recorded the number of participants experiencing the event and the number randomized in each treatment group. To allow an available-case analysis, we recorded the numbers of participants analysed in each treatment group and used them in the analyses. However, the number of participants randomized into the treatment arms was also recorded and the discrepancy between the figures used to calculate the loss to follow up. Also, these figures allowed a worst-case scenario analysis to be carried out to investigate the effect of missing data.

## Assessment of risk of bias in included studies

We independently assessed methodological quality and reported the results in a table. We classified generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear according to [Jüni 2001](#). We reported who was blinded in

each trial. We classified inclusion of all randomized participants as adequate if at least 90% of participants were followed up to the trial's completion; otherwise we classified inclusion as inadequate. We attempted to contact the authors if this information was not specified or if it was unclear. We resolved any disagreements by discussion between review authors.

### Data synthesis

We analysed the data using [Review Manager 5](#). A decision to perform meta-analysis was made in view of absence of significant heterogeneity. We used risk ratios (RR) with 95% confidence intervals (CI) and the fixed-effect model. We determined the number needed to treat (NNT) for various control-event rates (CER) by calculating experimental event rate (EER = CER\*RR) and taking inverse of the difference between the CER and EER ([Table 1](#)).

**Table 1. Effect of different control group experimental event rates on the number needed to treat**

Control event rate	Risk ratio	Experimental event rates	Number needed to treat
20%	0.8	16%	25
30%	0.8	24%	17
40%	0.8	32%	13
50%	0.8	40%	10
60%	0.8	48%	9
80%	0.8	64%	7

We summarized the adverse event data in tables and did not perform a meta-analysis since some events were reported in only one trial and others were rare events in which the same participant could have contributed more than one event. We were unable to calculate rate ratios or summary rate ratios because person-time over which these events were observed was not available.

## RESULTS

### Description of studies

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

### Search results

The [Prasad 2000](#) version of this Cochrane Review included six trials with 595 participants (574 with follow up, 215 deaths). This update includes one new trial with 545 participants (535 with follow up, 199 deaths). All these studies were identified after scanning the search results (titles and abstracts), selecting 23 abstracts for detailed appraisal, and assessing eligibility based on the full articles. The seven trials (with 1140 participants) from eight articles are described in the '[Characteristics of included studies](#)' and summarized below. The reasons for excluding the other 15 studies are given in the '[Characteristics of excluded studies](#)'. We also identified one trial that started in 1996 with a planned 10-year follow-up period and are awaiting the results (see '[Characteristics of ongoing studies](#)').

## Geographical location and time period

The trials were conducted in different time periods (two in the 1960s, four in the 1990s, and one in 2004) and in different geographical regions: Thailand (Chotmongkol 1996); Egypt (Girgis 1991); India (O'Toole 1969; Kumarvelu 1994); Philippines (Lardizabal 1998); South Africa (Schoeman 1997); and Vietnam (Thwaites 2004).

## Participants

All participants were entered on the basis of clinical diagnosis, which was subsequently proven by cerebrospinal fluid culture or autopsy in varying proportions: 70% (O'Toole 1969); 57% (Girgis 1991); 16% (Schoeman 1997); 10% (Chotmongkol 1996); percentage not mentioned (Kumarvelu 1994); and culture from cerebrospinal fluid or other sites in Thwaites 2004 (31%). In Schoeman 1997, 60% of participants had a chest x-ray suggestive of tuberculosis, 65% had strongly positive Mantoux test, and 24% (besides 16% cerebrospinal fluid positive culture) had a *M. tuberculosis* positive culture from gastric aspirate. Chotmongkol 1996 and Kumarvelu 1994 excluded non-tuberculosis chronic lymphocytic meningitis by negative fungal and bacterial culture, cytology for malignant cells, and HIV serology. However, only Girgis 1991 reported the outcome in culture-positive cases separately.

The trials included young children (Schoeman 1997) or adults (Kumarvelu 1994; Chotmongkol 1996; Lardizabal 1998; Thwaites 2004), or both (O'Toole 1969, Girgis 1991), and both sexes. All trials used the MRC system (MRC 1948) to assess baseline severity; two trials included only those with stage II and III tuberculous

meningitis (Schoeman 1997; Lardizabal 1998), while the other trials included all stages of severity. Thwaites 2004 specifically reported the inclusion of HIV-positive and HIV-negative patients.

## Interventions

Five of the trials used the corticosteroid dexamethasone; the other two trials used prednisolone (Chotmongkol 1996; Schoeman 1997). Six of the trials used a three- or four-drug antituberculous regimen. O'Toole 1969, the earliest trial, used a two-drug regimen.

## Follow up

The follow-up period was clearly described in six trials: two months (Lardizabal 1998); three months (Kumarvelu 1994); six months (Schoeman 1997); nine months (Thwaites 2004); two years (Girgis 1991); and 16 to 45 months (Chotmongkol 1996). It was unclear in O'Toole 1969.

## Outcome measures

Death was reported in all seven trials and residual neurological deficit in all but two (O'Toole 1969; Lardizabal 1998); Lardizabal 1998 assessed "functional independence". We accepted the definition of disability as presented by the trial authors, and, for the purpose of analysis, classified residual deficits into disabling or non-disabling as shown in Table 2. Only three of trials quantified disability and each used a different scale or method:

**Table 2. Classification of residual neurological deficits**

Trial	Disabling	Non-disabling
Kumarvelu 1994	Major sequelae	Minor sequelae
Schoeman 1997	Severe disability	Healthy and mild disability
Thwaites 2004	Severe disability	Intermediate and good outcome

- Kumarvelu 1994 described "major sequelae" (totally dependent for activities of daily living) at three months and "minor sequelae" (activities of daily living with no or minimal assistance) at three months.

- Schoeman 1997 classified this as "healthy" (IQ(DQ) > 90 and no motor or sensory deficit); "mild disability" (= 1 of IQ(DQ) 75 to 90, hemiparesis, and decreased vision or hearing); or "severe disability" (= 1 of IQ(DQ) < 75, quadriaparesis, and blindness or deafness).

- Thwaites 2004 quantified disability into "severe disability",

"intermediate outcome", and "good outcome" using the Rankin scale and a "simple questions" score.

Four trials mentioned adverse events. The trials reported on a number of other immediate outcome measures not considered in the review (see 'Characteristics of included studies').

## Drug resistance

Only Thwaites 2004 reported on drug resistance. In this study, *M. tuberculosis* was cultured from the cerebrospinal fluid or another

site in 170 participants (31.2%), 85 from each group. *M. tuberculosis* isolates were tested for susceptibility to isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. Of 170 isolates, 99 (58.2%) were susceptible to all first-line drugs (51 in the placebo group and 48 in the dexamethasone group), 60 (35.3%) were resistant to streptomycin, isoniazid, or both (29 in the placebo group and 31 in the dexamethasone group), one was monoresistant to rifampicin (in the dexamethasone group), and 10 (5.9%) were resistant to at least isoniazid and rifampicin (3 in the placebo group and 7 in the dexamethasone group).

### Risk of bias in included studies

See [Table 3](#) for a summary and 'Characteristics of included studies' for details of methods.

[Thwaites 2004](#) was the only trial that we assessed as adequate for the generation of allocation sequence and allocation concealment. This trial used a computer-generated sequence of random numbers to generate the allocation sequence and numbered individual treatment packs containing the study drug to conceal allocation. The methods used in the other trials were unclear.

**Table 3. Risk of bias assessment**

Trial	Allocation generation	Allocation sequence	Allocation concealment	Blinding	Inclusion <sup>a</sup>
<a href="#">Chotmongkol 1996</a>	Unclear		Unclear	Participants, enrolling physicians, and assessors	Adequate
<a href="#">Girgis 1991</a>	Unclear		Unclear	None	Unclear
<a href="#">Kumarvelu 1994</a>	Unclear		Unclear	None	Inadequate
<a href="#">Lardizabal 1998</a>	Unclear		Unclear	None	Adequate
<a href="#">O'Toole 1969</a>	Unclear		Unclear	Participants and enrolling physicians	Unclear
<a href="#">Schoeman 1997</a>	Unclear		Unclear	Assessors	Adequate
<a href="#">Thwaites 2004</a>	Adequate		Adequate	Participants, enrolling physicians, and investigators	Adequate

<sup>a</sup>Inclusion of all randomized participants in the analysis.

Chotmongkol 1996 and Thwaites 2004 used blinding for the participants, enrolling physicians, and assessors or investigators, O'Toole 1969 used blinding for the participants and enrolling physicians, and Schoeman 1997 used blinding only for the assessors. The other three trials did not use blinding.

Four trials included 90% or more of the randomized participants in the analysis (Chotmongkol 1996; Lardizabal 1998; Schoeman 1997; Thwaites 2004); Chotmongkol 1996 and Lardizabal 1998 had no losses to follow up. Kumarvelu 1994 included 87.24% of the participants after six participants were lost to follow up (4/24 in the corticosteroid group and 2/23 in the control group), which we considered inadequate. The number of participants lost to follow up was unclear for O'Toole 1969 and Girgis 1991.

## Effects of interventions

### Death

All seven trials reported on death. The two larger trials, Girgis 1991 and Thwaites 2004, had more than 150 deaths in each, but the rest were small trials with fewer deaths. Overall, the direction of effect in each of the trials favoured a benefit for corticosteroids except for Chotmongkol 1996, which had a prognostic imbalance at baseline that favoured the control group. Overall the pooled results showed statistically significant fewer deaths with corticosteroids (RR 0.78, 95% CI 0.67 to 0.91; 1140 participants, 7 trials, Analysis 1.1). This translates to a 22% risk ratio reduction for death, and, with about 40% case-fatality without corticosteroids, a 10% absolute risk reduction and NNT of 10. The benefit of corticosteroids seems to be independent of the length of follow up (Table 4).

**Table 4. Length of follow up vs number of deaths**

Trial	Follow up (months)	Corticosteroids: n/N	Corticosteroids: %	Control: n/N	Control: %	Overall: %
Chotmongkol 1996	16 to 45	5/29	17%	2/30	7%	12%
Girgis 1991	24	72/145	50%	79/135	59%	54%
Kumarvelu 1994	3	5/20	25%	7/21	33%	29%
Lardizabal 1998	2	4/29	14%	6/29	21%	17%
O'Toole 1969	-	6/11	55%	9/12	75%	65%
Schoeman 1997	6	4/67	6%	13/67	19%	13%
Thwaites 2004	9	87/274	32%	112/271	41%	36%

n/N: number of deaths/number of participants.

### Death or disabling residual neurological deficit

The disabling sequelae could be extracted separately from only three trials. With respect to death or disabling residual neurological deficit, the overall estimate showed a significant reduction in the risk of death or disabling residual neurological deficit with corticosteroids (RR 0.82, 95% CI 0.70 to 0.97; 720 participants, 3 trials, [Analysis 1.2](#)). This refers to a risk ratio reduction of 17%, which translates to an absolute risk reduction of 10% and NNT of 10, taking 50% event rate without corticosteroid use.

### Adverse events

Of the five trials that mentioned adverse events ([O'Toole 1969](#); [Kumarvelu 1994](#); [Chotmongkol 1996](#); [Schoeman 1997](#); [Thwaites 2004](#)), two reported on incidence ([O'Toole 1969](#); [Thwaites 2004](#)). [O'Toole 1969](#) reported four different adverse events (gastrointestinal bleeding, glycosuria, infections, and hypothermia), which occurred in both groups ([Table 5](#)). [Thwaites 2004](#) reported on several adverse events, which were divided into "severe" and other events ([Table 5](#)). [Schoeman 1997](#) had "serious side effects" as an outcome measure and reported "no serious side effects of corticosteroid therapy".

**Table 5. Adverse events reported in O'Toole 1969 and Thwaites 2004**

Trial	Event	Corticosteroid: n/N <sup>a</sup>	Control: n/N <sup>b</sup>
<a href="#">O'Toole 1969</a>	Gastrointestinal bleeding	5	5
-	Glycosuria	1	0
-	Infections	2	5
-	Hypothermia	5	1
<a href="#">Thwaites 2004</a> : "severe"	Hepatitis (severe)	0	8
-	Gastrointestinal bleeding (severe)	2	3
-	Bacterial sepsis (severe)	3	4
-	Hyperglycaemia (severe)	0	0
<a href="#">Thwaites 2004</a> : other	Subclinical hepatitis	0	0
-	Septic shock	3	0
-	Brain herniation syndrome	1	4
-	Decrease in visual acuity	6	8

**Table 5. Adverse events reported in O’Toole 1969 and Thwaites 2004** (Continued)

-	Hyponatraemia	1	6
-	Hypertension	0	0
-	Vertigo	0	0
-	Deafness	3	3
-	Cushing’s features	0	0
-	Pruritis	0	0
-	Polyarthralgia	0	0
-	Streptomycin reaction	0	0
-	Rifampicin flu	0	0
-	Rash	1	0

<sup>a</sup>O’Toole 1969: episodes/11 participants in arm; Thwaites 2004: no. with event/274 participants in study.

<sup>b</sup>O’Toole 1969: no. with event/274 participants in study arm; Thwaites 2004: no. with event/271 participants in study arm.

### Exploring subgroup effects

#### Drug resistance

No data were available for this subgroup analysis.

#### Severity of illness

We stratified the results on death by the severity of illness (MRC stages I, II, and III) in [Analysis 2.1](#). Corticosteroids statistically significantly reduced the risk of death across all stages of the disease: stage I (RR 0.52, 95% CI 0.30 to 0.89; 197 participants, 4 trials); stage II (RR 0.73, 95% CI 0.56 to 0.97; 441 participants, 5 trials); and stage III (RR 0.70, 95% CI 0.54 to 0.90; 330 participants, 3 trials). As the trials did not stratify randomization for severity stage, these results should be interpreted with caution.

#### HIV status

[Thwaites 2004](#) specifically mentioned that 98 of the included participants were HIV-positive. We stratified the results for death

([Analysis 3.1](#)) and death or disabling residual neurological deficit by HIV status ([Analysis 03.02](#)). The results for each group and the overall results did not reach statistical significance. However, as this trial did not stratify randomization for HIV status, these results should be interpreted with caution.

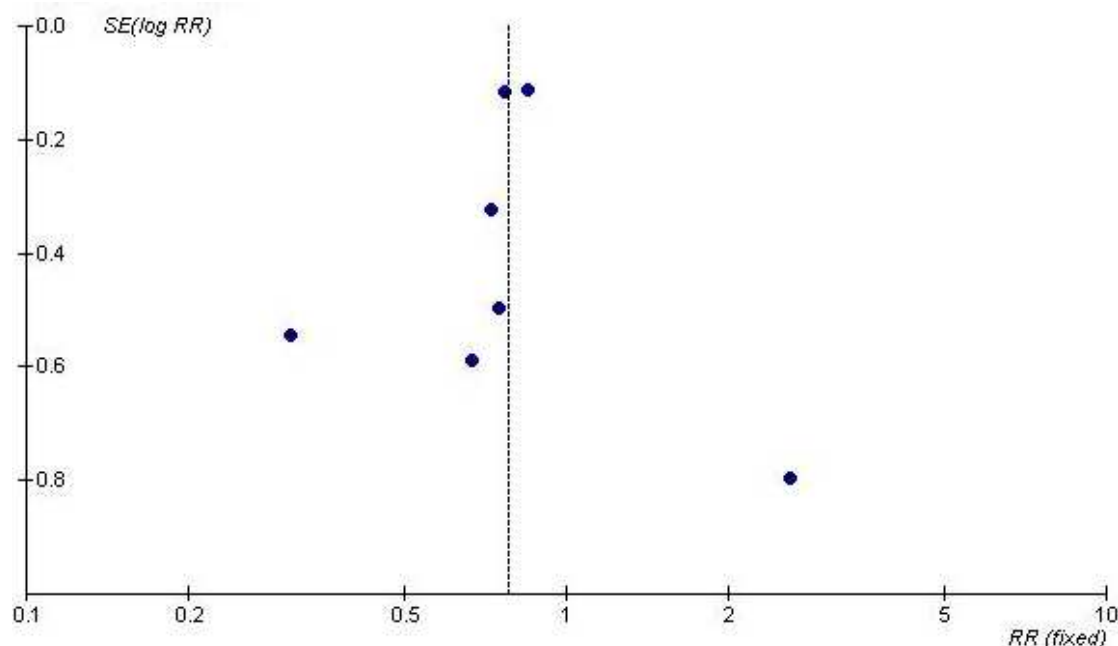
#### Sensitivity analysis

As three trials had losses to follow up ([Kumarvelu 1994](#); [Schoeman 1997](#); [Thwaites 2004](#)), we performed sensitivity analysis using the worst-case scenario, that is, assuming that all those lost to follow up in the corticosteroid group had unfavourable outcomes while those in the control group had favourable outcomes. The point estimates of the results remained in favour of corticosteroids for death (RR 0.80, 95% CI 0.65 to 0.98) and also death or disabling residual neurological deficit (RR 0.88, 95% CI 0.75 to 1.04), but only the result for death remained statistically significant.

#### Assessment of reporting biases

The funnel plot of the included trials is shown in Figure 1. It refers to mortality and values below one favour corticosteroids. The plot does not show a definite inference with regard to publication bias.

**Figure 1. Funnel plot of risk ratio (RR) from the included trials with the log of their standard error (SE)**



## DISCUSSION

### Summary of main results

Overall, the results of this review favour routine use of corticosteroids in tuberculous meningitis for reducing death and death or disabling residual neurological deficit. In comparison to the benefits, adverse effects were poorly reported, but those recorded in the trials were infrequent and often mild and treatable. There is no direct evidence to guide selection of the specific corticosteroid to be used in tuberculous meningitis; most trials used dexamethasone or prednisolone, and we therefore favour either of these two drugs in clinical practice or for future studies.

### Quality of evidence

This review because included only randomized controlled trials. One trial, [Thwaites 2004](#), had adequate concealment of random-

ization, good follow up, and blinded outcome assessment. While the other trials did not provide clear information about the generation of the allocation sequence or allocation concealment, they have reasonable internal validity for the outcome of death because the lack of blinding is unlikely to influence the measurement of death.

### Overall completeness and applicability of evidence

The trials included male and female children and adults, most of whom were HIV negative. [Thwaites 2004](#) reported that 98 HIV-positive participants were included, but they did not stratify the randomization for this subgroup; the results for this subgroup therefore should be interpreted with caution. The effect of corticosteroids was not significantly different between HIV-positive and HIV-negative participants, but due to the small number of HIV-positive participants the trial lacked the power to detect such a difference even if one did exist.

Though the trials varied in their use of bacteriological confirmation of diagnosis, there is reasonable evidence to suggest that the trial participants had tuberculous meningitis. Moreover, the intention-to-treat analysis in clinically diagnosed participants provides assurance that use of corticosteroids on the basis of clinical diagnosis does more good than harm. This is important because the decision to use corticosteroids is often taken on a purely clinical basis when culture reports are not available and it is the balance of benefit and risk of such a decision that needs to be determined to set a clinical policy. The proportion of confirmed cases is mentioned only to provide confidence in the clinical diagnosis made by the investigators. Separate analysis of culture-positive cases is probably less relevant for clinical decision making and was reported by the trial authors of only one included trial.

### Potential biases in the review process

We have attempted to limit bias in the review process. The literature search was conducted by the Cochrane Infectious Diseases Group Information Specialist, and it is unlikely that any major trials were missed; however, we cannot rule out the possibility that missing some small unpublished trials were missed. The funnel plot did not assist with this because there were too few trials. To limit bias in the trial selection process and data extraction, we independently examined the search results and determined study selection, and extracted data.

### Agreements and disagreements with other studies or reviews

A question with regard to use of corticosteroids in tuberculous meningitis, which has been repeatedly raised, is whether corticosteroids save patients' lives only to leave them disabled. Apparently, it emerged from statistically non-significant reduction of combined outcome of death or disability within individual studies with inadequate power to address the question. This is apparent from the fact that two of the three trials reporting this outcome showed a trend of risk reduction for this outcome but could not reach statistical significance. When all the three trials are combined, there is statistically significant as well as clinically important reduction in the combined endpoint of death or disabling residual neurological deficit, which means corticosteroids in tuberculous meningitis save lives without increasing the number of individuals with disabling residual neurological deficit. The worst-case scenario analysis for losses to follow up is somewhat unsettling, but it is known that this scenario is a rather stringent test unlikely to be true. The overall interpretation of evidence remains in favour of corticosteroids.

## AUTHORS' CONCLUSIONS

### Implications for practice

Corticosteroids should be routinely used in HIV-negative people with tuberculous meningitis to reduce death and disabling residual neurological deficit amongst survivors. The drug and dose as used in most trials may be dexamethasone (for adults 12 to 16 mg/day for three weeks, tapered over the next three weeks; for children 0.3 to 0.4 mg/kg/day for one to two weeks and tapered over the next two weeks; given intravenously until the patient starts accepting orally when tablets can be used) or prednisolone (for adults 60 mg/day for three weeks and tapered over the next three weeks; for children 2 mg/kg/day for three weeks and tapered over the next three weeks), and either of the two may be used in clinical practice. However, there is not enough evidence to support or refute a similar conclusion for those who are HIV positive.

### Implications for research

New randomized controlled trials should address the following research questions.

- Is there a difference in effectiveness of various corticosteroids such as dexamethasone, prednisolone, or pulse methylprednisolone?
- What is the optimum duration of corticosteroid therapy (eg six weeks versus 12 weeks)?
- Do corticosteroids reduce mortality and morbidity in HIV-positive people with tuberculous meningitis? (Such trials could restrict inclusion to only HIV-positive people, or, if they include both HIV-positive and HIV-negative people, investigators could stratify randomization based on HIV status.)

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\* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Chotmongkol 1996

Methods	<p>Generation of allocation sequence: unclear, but randomization in blocks of 4</p> <p>Allocation concealment: unclear</p> <p>Blinding: participants, enrolling physicians, and assessors; using identical appearing placebo</p> <p>Inclusion of all randomized participants in analysis: 100% (no loss to follow up)</p> <p>Length of follow up: 6 months but post-study follow up continued for 16 to 45 months (mean = 30 months)</p>
Participants	<p>Number: 59 randomized</p> <p>Description: age &gt; 15 years; both sexes; clinically diagnosed tuberculous meningitis (characteristic clinical features, typical cerebrospinal fluid profile consisting of lymphocytic meningitis with low glucose level and elevated protein, negative cerebrospinal fluid culture for bacteria and fungus, cerebrospinal fluid negative for bacterial and cryptococcal antigen and malignant cells, negative serologic tests for syphilis and HIV); all stages of severity and all duration of disease (range 1 to 60 days); HIV-negative</p>
Interventions	<p>1. Antituberculous treatment plus prednisolone</p> <p>2. Antituberculous treatment alone</p> <p>Antituberculous treatment: isoniazid oral (300 mg), rifampicin oral (600 mg, 450 mg for those weighing &lt; 50 kg), pyrazinamide oral (1500 mg), and streptomycin intramuscular (750 mg) for the first 2 months; followed by isoniazid and rifampicin in above dosage for 4 months; prednisolone oral on tapering dosage for 5 weeks (week 1 = 60 mg, week 2 = 45 mg, week 3 = 30 mg; week 4 = 20 mg, week 5 = 10 mg)</p>
Outcomes	<p>1. Death at the end of 6 months</p> <p>2. Residual deficits at the end of 6 months</p> <p>3. Time until normal body temperature</p> <p>4. Adverse events recorded were gastrointestinal bleeding and hyperglycaemia</p> <p>Not included in review:</p> <p>5. Time until disappearance of headache</p>
Notes	<p>Location: Thailand</p> <p>Date: July 1990 to December 1992</p> <p>Trialists: Department of Medicine, Khon Kaen University, Thailand; no collaborators</p>

#### Girgis 1991

Methods	<p>Generation of allocation sequence: pre-designed chart</p> <p>Allocation concealment: unclear</p> <p>Blinding: none</p> <p>Inclusion of all randomized participants in analysis: unclear</p> <p>Length of follow up: 24 months</p>
Participants	<p>Number: 280 randomized</p> <p>Description: all ages; both sexes; clinically diagnosed tuberculous meningitis based on history/findings (duration of illness &gt; 30 days, consisting of fever, headache, vomiting, altered sensorium, generalized weakness or cranial nerve deficits); comparison of first and second cerebrospinal fluid findings; and a poor response to antibacterial therapy for</p>

**Girgis 1991** (Continued)

	48 h; unclear whether either or both the duration of illness criteria and poor response to antibacterial therapy had to be satisfied Exclusion criteria: not mentioned Unclear whether those participants already receiving a corticosteroid were also included
Interventions	1. Antituberculous treatment plus dexamethasone (Group I of the study) 2. Antituberculous treatment alone (Group II of the study) Antituberculous treatment: isoniazid intramuscular (10 mg/kg/day, maximum 600 mg), streptomycin intramuscular (25 mg/kg/day, maximum 1000 mg), and ethambutol oral (25 mg/kg/day, maximum 1200 mg); dexamethasone given intramuscularly (12 mg/day to adults and 8 mg/day to children weighing < 25 kg) for 3 weeks and then tapered during the next 3 weeks)
Outcomes	1. Death during 2-year follow up 2. Residual neurological sequelae 3. Neurological complications developing during therapy 4. Cerebrospinal fluid leucocytes, glucose, and protein on day 15 and day 30 after initiation of treatment Trial authors reported case-fatality rate, which by definition includes all deaths caused by tuberculous meningitis, but not the ones attributed to other causes. Not reported whether any death during the follow-up period was considered to be due to any cause other than tuberculous meningitis
Notes	Location: Egypt Date: 1982 to 1987 Trialists: United States Naval Medical Research Unit No. 3, Cairo, Egypt; no collaborators 160/280 cerebrospinal fluid culture positive for <i>M. tuberculosis</i>

**Kumarvelu 1994**

Methods	Generation of allocation sequence: pre-designed chart Allocation concealment: unclear Blinding: none Inclusion of all randomized participants in analysis: 87.24% (6/47 lost to follow up) Length of follow up: 3 months
Participants	Number: 47 randomized Description: age > 12 years; both sexes; clinically diagnosed tuberculous meningitis (meeting any 3 of the following 4 criteria: (1) fever, headache, neck stiffness for 2 weeks; (2) cerebrospinal fluid profile of > 20 cells/mm <sup>3</sup> predominantly lymphocytes, protein > 1 g/L, and sugar < 2/3 of corresponding blood sugar with no malignant cells on cytological examination and bacteria/fungi on culture; (3) head contrast-enhanced CT showing basal exudates or hydrocephalus; and (4) clinical, radiological, or histological evidence of extracranial tuberculosis); all stages of severity and all duration of disease included
Interventions	1. Antituberculous treatment plus dexamethasone 2. Antituberculous treatment alone Antituberculous treatment: rifampicin (450 mg), isoniazid (300 mg), and pyrazinamide (1500 mg) all oral daily; for those weighing < 30 kg 15 mg/kg, 10 mg/kg, and 30 mg/kg respectively Duration of treatment: 1 year Dexamethasone: intravenous 16 mg/day in 4 divided doses for 7 days, then oral tablet 8 mg/day for 21 doses

**Kumarvelu 1994** (Continued)

Outcomes	<ol style="list-style-type: none"> <li>1. Death at 3 months</li> <li>2. Major sequelae (totally dependent for activities of daily living) at 3 months</li> <li>3. Minor sequelae (activities of daily living with no or minimal assistance) at 3 months</li> <li>4. Adverse effects</li> </ol> <p>Not included in review:</p> <ol style="list-style-type: none"> <li>5. Time to recover from altered sensorium, from fever, and from headache</li> </ol>
Notes	<p>Location: India</p> <p>Date: March 1991 to March 1992</p> <p>Trialists: Department of Neurology, All India Institute of Medical Sciences, New Delhi, India; no collaborators</p> <p>Number cerebrospinal fluid culture positive for <i>M. tuberculosis</i> not stated</p>

**Lardizabal 1998**

Methods	<p>Generation of allocation sequence: unclear, but randomization in blocks of 8</p> <p>Allocation concealment: unclear</p> <p>Blinding: none</p> <p>Inclusion of all randomized participants in analysis: 100%</p> <p>Length of follow up: 2 months</p>
Participants	<p>Number: 58 randomized</p> <p>Description: ages 18 years and above; both sexes; probable tuberculous meningitis diagnosed using ASEAN Neurological Association criteria based on: (1) fever, headache, vomiting followed by altered consciousness, cranial nerve palsies, or long tract signs; (2) cerebrospinal fluid profile of lymphocyte predominance, elevated protein and reduced glucose; (3) cerebrospinal fluid negative for cryptococcal antigen plus 1 or more of the following: basilar/meningeal enhancement on contrast CT scanning, active pulmonary disease, positive purified protein derivative (PPD), history of contact with tuberculosis; confirmed tuberculous meningitis based on positive cerebrospinal fluid culture and/or microscopy; only patients with British MRC stages II and III disease included; HIV testing not mentioned</p>
Interventions	<ol style="list-style-type: none"> <li>1. Antituberculous treatment plus dexamethasone</li> <li>2. Antituberculous treatment alone</li> </ol> <p>Antituberculous treatment: rifampicin (10 to 15 mg/kg/day), isoniazid (5 to 10 mg/kg/day), pyrazinamide (15 to 30 mg/kg/day), and ethambutol (15 to 20 mg/kg/day) for the first 2 months; thereafter, rifampicin and isoniazid only for 10 months; total treatment duration 12 months; route of administration not stated</p> <p>Dexamethasone: 16 mg/day for 3 weeks (first 5 days intravenous thereafter orally or via nasogastric tube); after 3 weeks corticosteroid was tapered by 4 mg decrements every 5 days</p> <p>An H2-antagonist (famotidine or ranitidine) was given during the period of corticosteroid administration</p>
Outcomes	<ol style="list-style-type: none"> <li>1. Death on days 15, 30, and 60 post-randomization</li> <li>2. Functional independence assessed by attending doctor on admission and 60 days after randomization: Functional Independence Measure (FIM) used assesses self care, sphincter control, mobility, locomotion, and social cognition on a 7-point scale</li> <li>3. Potential adverse reactions to corticosteroids including weakness, oedema, hypertension, euphoria, psychosis, epigastric discomfort, cushingoid facies, hirsutism, acne, insomnia, and increased appetite</li> </ol>
Notes	<p>Location: Philippines</p> <p>Date: November 1996 to July 1997</p> <p>Trialists: University of Philippines, College of Medicine; no collaborators</p>

**Lardizabal 1998** (Continued)

We contacted the trial authors to determine the number of deaths in participants with stage II and III disease  
Number cerebrospinal fluid culture positive for *M. tuberculosis* not stated

**O'Toole 1969**

Methods	Generation of allocation sequence: random allocation Allocation concealment: unclear Blinding: double, using placebo injections and tablets Inclusion of all randomized participants in analysis: no mention of losses to follow up Length of follow up: unclear
Participants	Number: 23 randomized Description: all ages; both sexes; eligibility criteria not mentioned, but 16/23 participants had either smear (2) or culture (9), or both smear and culture (5) positive for tubercle bacillus; remaining 7 participants had clinical features consistent with the diagnosis of tuberculous meningitis and cerebrospinal fluid profile consisting of elevated white cell count and protein, decreased glucose, and negative India ink smear for cryptococcus; authors intended to include only moderately advanced (stage II) and severe (stage III) cases, but 1 case of stage I was entered in the treatment group
Interventions	1. Antituberculous treatment plus dexamethasone 2. Antituberculous treatment alone Antituberculous treatment: isoniazid intramuscular or oral (10 mg/kg/day, except in children < 2 years of age who received 20 mg/kg/day) and streptomycin (20 mg/kg/day, maximum 1 g) Dexamethasone: given for up to 4 weeks in an adult dose of 9 mg/day during the first week, 6 mg/day during the second week, 3 mg/day during the third week, and 1.5 mg/day during the fourth week; dose for children was calculated according to their body surface area (no more details available)
Outcomes	1. Death at the end of follow up (duration not clear) 2. Number with elevated cerebrospinal fluid opening pressure on days 1, 4, 7, 14 3. Cerebrospinal fluid sugar, protein, and cell count on days 1, 4, 7, 14, 21, and 28 in decreasing number of participants, depending apparently on the surviving number. Number with residual deficits not given. Surviving participants all been described as "significantly improved" 4. Adverse events recorded: upper gastrointestinal bleed, invasive bacterial infection, hypoglycaemia, and hypothermia Not included in the review: 5. Resolution of cerebrospinal fluid findings
Notes	Location: Calcutta, India Date: February 1966 to March 1967 Trialists: Calcutta School of Tropical Medicine and the Infectious Disease Hospital, Calcutta, India, in collaboration with Johns Hopkins University, Baltimore, USA

**Schoeman 1997**

Methods	Generation of allocation sequence: random allocation Allocation concealment: unclear Blinding: assessors only; blinded disability assessment Inclusion of all randomized participants in analysis: 95.04% (apparently, the losses to follow up were 3/70 in the treatment group and 4/71 in the control group as evident from table 4 of the report) Length of follow up: 6 months
Participants	Number: 141 randomized Description: children; both sexes; clinically diagnosed tuberculous meningitis fulfilling the following criteria of history and cerebrospinal fluid suggestive of tuberculous meningitis with any 2 or more of a strongly positive (> 15 mm) Mantoux test, chest x-ray suggesting tuberculosis or CT of head showing basal enhancement and acute hydrocephalus; only stage II and III included
Interventions	1. Antituberculous treatment plus prednisolone 2. Antituberculous treatment alone Antituberculous treatment: isoniazid (20 mg/kg/day), rifampicin (20 mg/kg/day), ethionamide (20 mg/kg/day), and pyrazinamide (40 mg/kg/day) for 6 months Prednisolone: given to first 16 participants in a dose of 2 mg/kg/day and to the remaining 54 participants in a dose of 4 mg/kg/day (once in the morning); decision to double the dose after the first 16 participants was taken when the authors became aware of a study that showed that rifampicin decreased the bioavailability of prednisolone by 66% and increased the plasma clearance of the drug by 45%; trial authors reported the outcome of both the dose groups together and mentioned that the mortality or morbidity between the 2 prednisolone dosage groups did not differ significantly
Outcomes	1. Deaths at 6 months 2. Disability (mild and severe) at 6 months 3. Serious side effects Not included in review: 4. Baseline and pulse pressure of lumbar cerebrospinal fluid 5. Changes in ventricular size in CT 6. Proportion of participants with successful treatment of raised intracranial pressure 7. Proportion of participants with basal ganglia infarcts, tuberculomas, meningeal enhancement, and enlarged sub-arachnoid spaces
Notes	Location: South Africa Date: not mentioned Trialists: Department of Paediatrics and Child Health, Faculty of Medicine, University of Stellenbosch and Tygerberg, South Africa, in collaboration with CERSA, Division of Biostatistics, Medical Research Council, Parow-Valley, South Africa 23/141 cerebrospinal fluid culture positive for <i>M. tuberculosis</i>

**Thwaites 2004**

Methods	<p>Generation of allocation sequence: computer-generated sequence of random numbers used to allocate treatment in blocks of 30</p> <p>Allocation concealment: numbered individual treatment packs containing the study drug prepared for duration of treatment and distributed for sequential use once a patient fulfilled the entry criteria</p> <p>Blinding: using matching placebo; blinded disability assessment; participants, enrolling physicians, and investigators</p> <p>Inclusion of all randomized participants in analysis: 98.17% (5/271 lost to follow up)</p> <p>Length of follow up: 9 months; post-randomization follow up of 28 to 442 days (median 274 days)</p>
Participants	<p>Number: 545 randomized</p> <p>Description: age &gt; 14 years; both sexes; clinically diagnosed meningitis (defined as combination of nuchal rigidity and cerebrospinal fluid abnormalities); tuberculous meningitis defined as “definite” if acid-fast bacilli were seen in cerebrospinal fluid, “probable” if &gt;/-1 of following present: suspected active pulmonary tuberculosis on chest radiography, acid-fast bacilli in any specimen other than cerebrospinal fluid, clinical evidence of extrapulmonary tuberculosis, and “possible” if at least 4 of the following were present: history of tuberculosis, predominance of lymphocytes in cerebrospinal fluid, duration of illness &gt; 5 days, ratio of cerebrospinal fluid to plasma glucose &lt; 0.5, altered consciousness, yellow cerebrospinal fluid, or focal neurological signs</p> <p>Exclusion criteria: contraindication to corticosteroids; received &gt; 1 dose of any corticosteroid or &gt; 30 days of antituberculous chemotherapy immediately before study</p>
Interventions	<p>1. Antituberculous treatment plus dexamethasone</p> <p>2. Antituberculous treatment plus placebo</p> <p>Antituberculous treatment:</p> <p>1. For previously untreated patients: oral isoniazid (5 mg/kg), rifampicin (10 mg/kg), pyrazinamide (25 mg/kg, maximum, 2 g/day), and intramuscular streptomycin (20 mg/kg, maximum 1 g/day) for 3 months followed by 6 months of isoniazid, rifampicin, and pyrazinamide at the same daily doses; ethambutol (20 mg/kg; maximum 1.2/day) substituted for streptomycin in HIV-positive participants and was added to the regimen for 3 months for participants previously treated for tuberculosis</p> <p>2. Grade II and III disease: intravenous dexamethasone sodium phosphate given 0.4 mg/kg/day for week 1, 0.3 mg/kg/d for week 2, 0.2 mg/kg/d for week 3, and 0.1 mg/kg/day for week 4, and then oral dexamethasone for 4 weeks decreasing by 1 mg each week</p> <p>3. Grade I disease: intravenous dexamethasone sodium phosphate 0.3 mg/kg/day for week 1 and 0.2 mg/kg/day for week 2 followed by 4 weeks of oral dexamethasone (0.1 mg/kg/day for week 3 then a total of 3 mg/day, decreasing by 1 mg each week)</p>
Outcomes	<p>Assessed at 9 months post-randomization</p> <p>1. Death or severe disability</p> <p>2. Adverse events: hepatitis; gastrointestinal bleeding, bacterial sepsis, septic shock, brain herniation, syndrome, decreased visual acuity, hyponatraemia, hyperglycaemia, hypertension, vertigo, deafness, cushingoid features, pruritis, polyarthralgia, streptomycin, reaction, rifampicin flu, rash, and others</p> <p>Not included in review:</p> <p>3. Coma clearance time</p> <p>4. Fever clearance time</p> <p>5. Time to discharge</p> <p>6. Time to relapse</p> <p>7. Presence of focal neurological deficit (9 months post-randomization)</p>
Notes	<p>Location: Vietnam</p> <p>Date: April 2001 to March 2003</p> <p>Trialists: Oxford University Clinical Research Unit at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam,</p>

**Thwaites 2004** (Continued)

and Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease, Ho Chi Minh City, Vietnam, in collaboration with Centre for Tropical Medicine, Nuffield, and Department of Clinical Medicine, John Radcliffe Hospital, Oxford, UK  
187/545 acid-fast stain/culture positive for *M. tuberculosis*

CT: computerized tomography; HIV: human immunodeficiency virus; MRC: Medical Research Council; *M. tuberculosis*: Mycobacterium tuberculosis.

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

Donald 2004	Perspective article with no original data
Escobar 1975	Not a randomized study. The report says that a pair of participants matched for age and neurological status was administered differential therapy in a double-blind fashion. However, it is unclear if this differential administration was random
Freiman 1970	Case series
Girgis 1983	Patients allocated to steroid or non-steroid group on alternate basis; unclear why there is a difference of 4 in the number of participants in the 2 groups (non-steroid 70 and steroid 66)
Hockaday 1966	Case series
Kalita 2001	Study with historical controls, not a randomized study
Kapur 1969	Case series
Karak 1998	Commentary on an included trial (Schoeman 1997)
Lepper 1963	Not truly randomized: the first half of the study was an alternate patient design, whereas in the last half, patients were randomized by using random numbers
Marras 2005	Letter to editor with no original data
Quagliarello 2004	Editorial
Seligman 2005	Letter to the editor with no original data
Vagenakis 2005	Letter to the editor with no original data
Voljavec 1960	Comparison cohort with historical controls

(Continued)

Wasz-Hockert 1963	Control trial using historical controls
Weiss 1965	Retrospective case series of 102 cases

### Characteristics of ongoing studies [ordered by study ID]

#### Prasad 2006

Trial name or title	A randomized controlled trial to study the effectiveness of dexamethasone as an adjunct to standard antituberculous treatment in patients with clinically presumed tuberculous meningitis: 10-year follow-up study
Methods	Randomized controlled trial
Participants	Adults, both sexes, clinically presumed tubercular meningitis based on validated criteria
Interventions	1. Antituberculous treatment plus dexamethasone 2. Antituberculous treatment plus placebo Antituberculous treatment (for previously untreated patients): oral isoniazid (5 mg/kg bodyweight), rifampicin (10 mg/kg bodyweight), pyrazinamide (25 mg/kg bodyweight, maximum, 1.5 g/day), and ethambutol (20 mg/kg; maximum 1 g/day) for 12 months
Outcomes	Treatment success defined as resolution of meningitic symptoms and category 1 or 2 of modified Glasgow Outcome Scale
Starting date	February 1996
Contact information	Prof K Prasad Room 704, Neurosciences Centre AIIMS, New Delhi-110029
Notes	-

## DATA AND ANALYSES

### Comparison 1. Any corticosteroid vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	7	1140	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.91]
2 Death or disabling residual neurological deficit	3	720	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.70, 0.97]

### Comparison 2. Any corticosteroid vs control: stratified by severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Stage I (mild)	4	197	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.30, 0.89]
1.2 Stage II (moderately severe)	5	441	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.97]
1.3 Stage III (severe)	6	330	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.54, 0.90]

### Comparison 3. Any corticosteroid vs control: stratified by HIV status

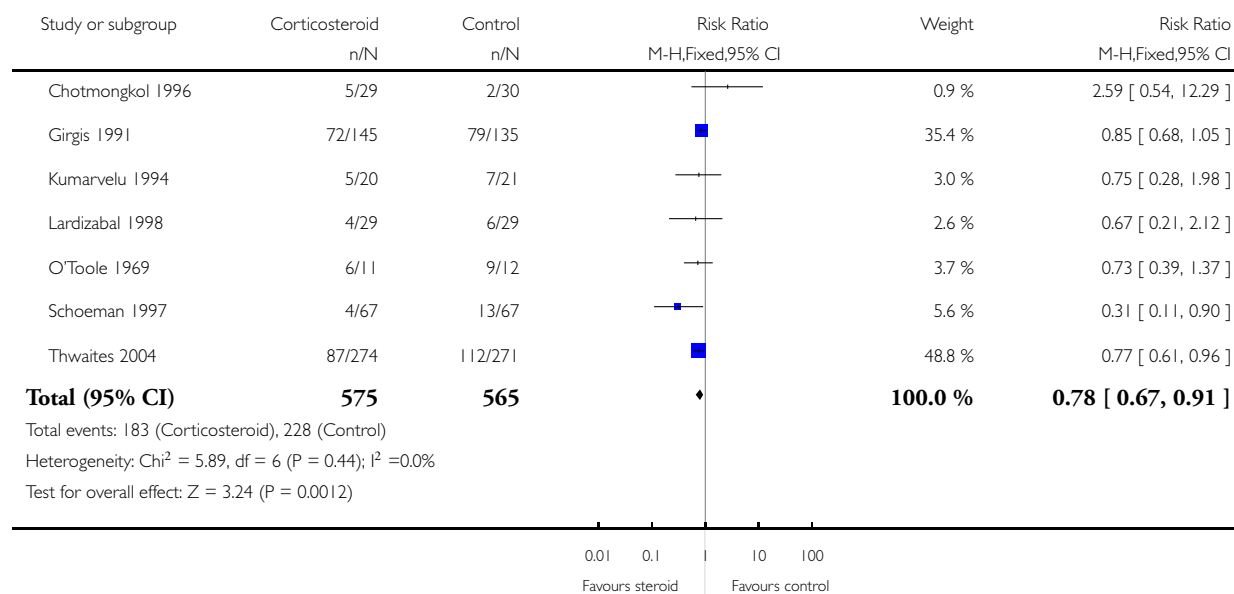
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	534	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
1.1 HIV positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.20]
1.2 HIV negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
2 Death or disabling residual neurological deficit	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
2.1 HIV positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.20]
2.2 HIV negative	1	447	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]

### Analysis 1.1. Comparison 1 Any corticosteroid vs control, Outcome 1 Death.

Review: Corticosteroids for managing tuberculous meningitis

Comparison: 1 Any corticosteroid vs control

Outcome: 1 Death

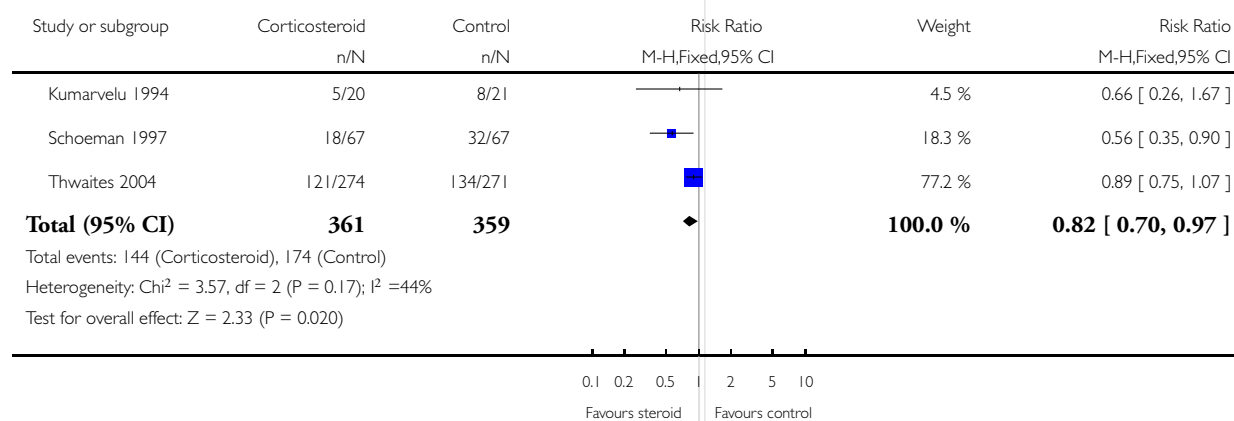


### Analysis 1.2. Comparison 1 Any corticosteroid vs control, Outcome 2 Death or disabling residual neurological deficit.

Review: Corticosteroids for managing tuberculous meningitis

Comparison: 1 Any corticosteroid vs control

Outcome: 2 Death or disabling residual neurological deficit

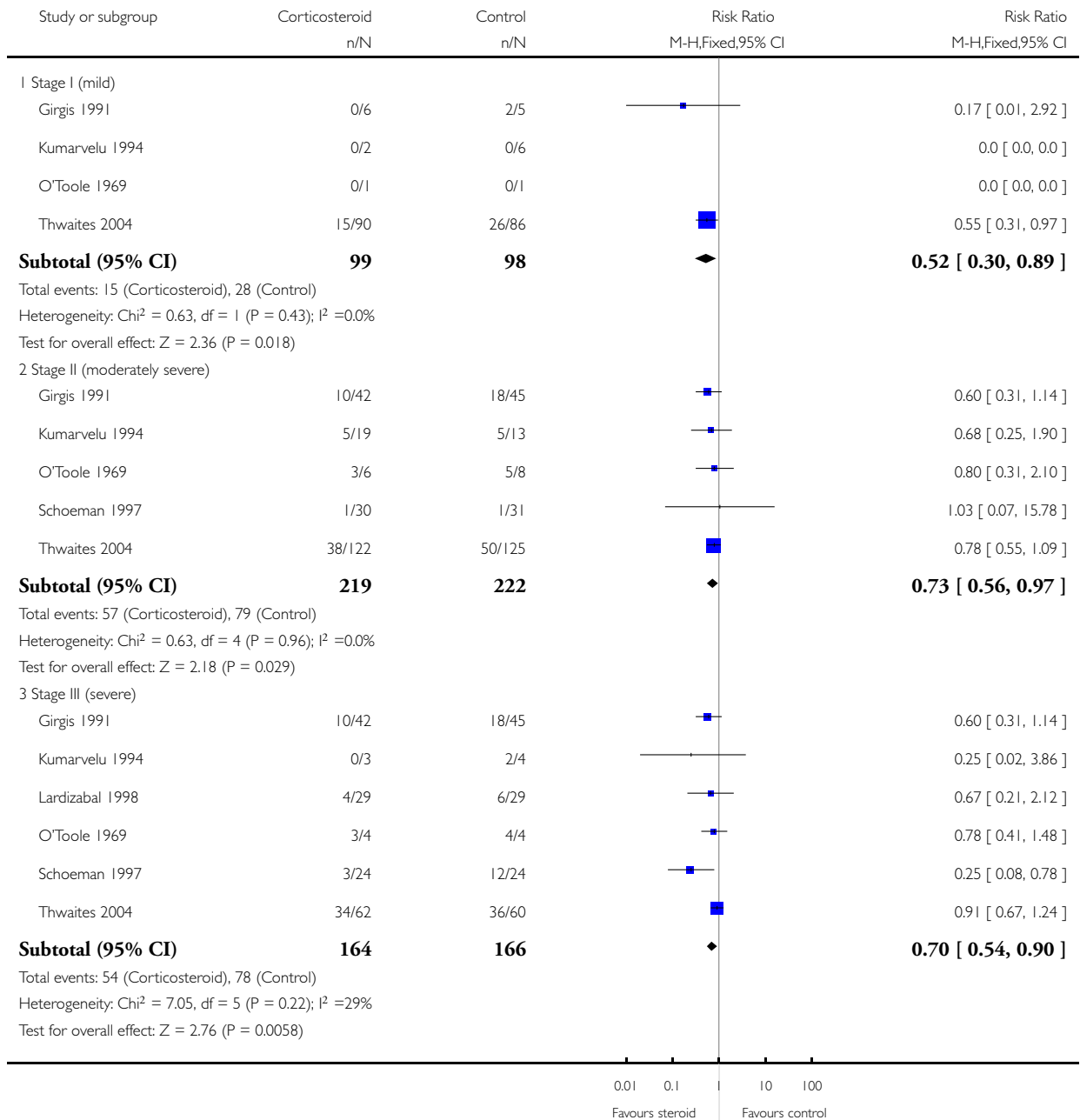


## Analysis 2.1. Comparison 2 Any corticosteroid vs control: stratified by severity, Outcome 1 Death.

Review: Corticosteroids for managing tuberculous meningitis

Comparison: 2 Any corticosteroid vs control: stratified by severity

Outcome: 1 Death

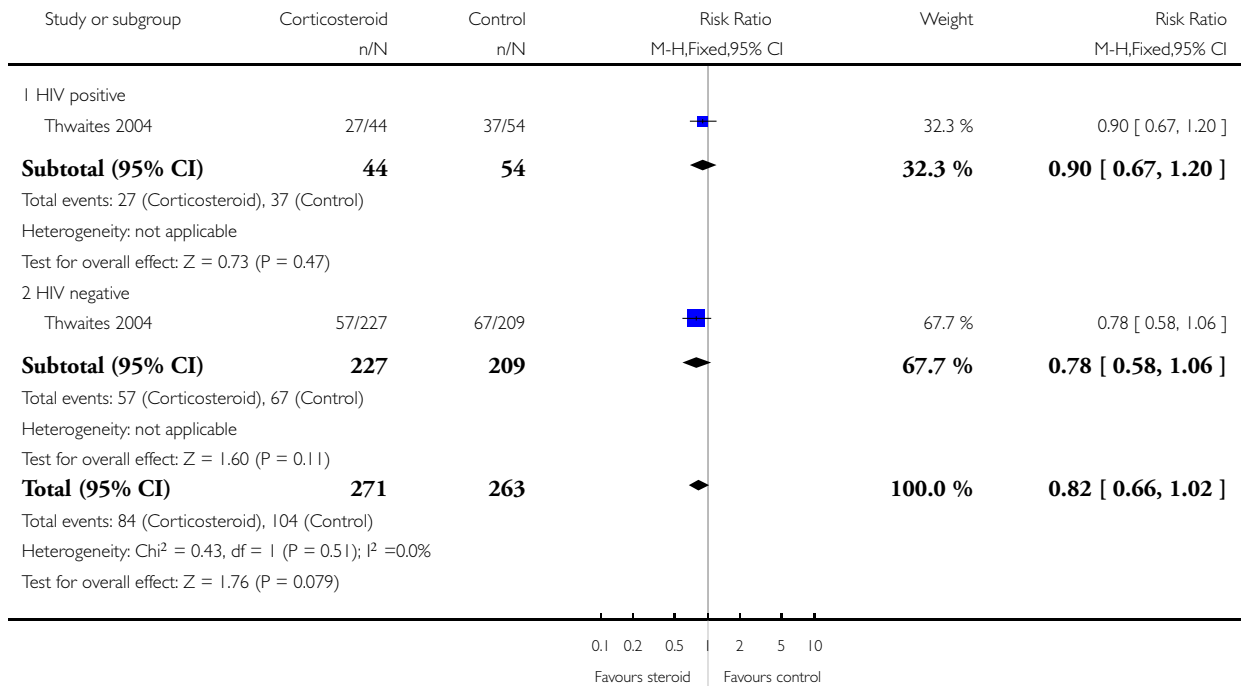


### Analysis 3.1. Comparison 3 Any corticosteroid vs control: stratified by HIV status, Outcome 1 Death.

Review: Corticosteroids for managing tuberculous meningitis

Comparison: 3 Any corticosteroid vs control: stratified by HIV status

Outcome: 1 Death

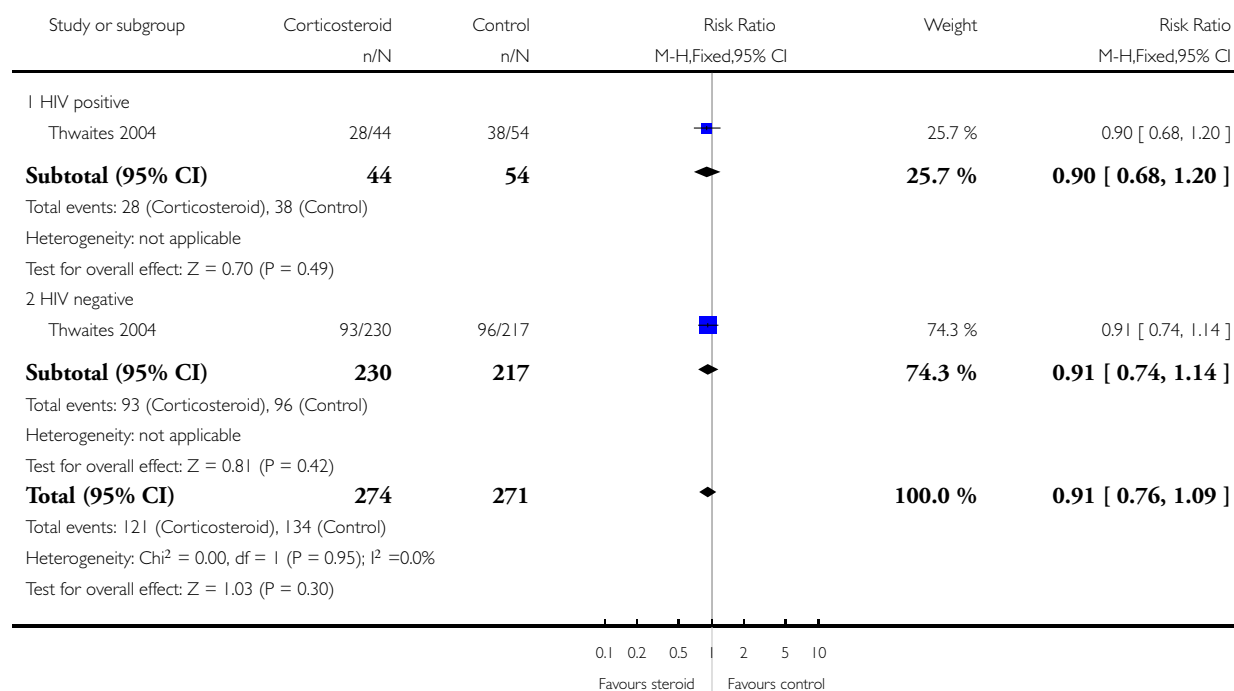


### Analysis 3.2. Comparison 3 Any corticosteroid vs control: stratified by HIV status, Outcome 2 Death or disabling residual neurological deficit.

Review: Corticosteroids for managing tuberculous meningitis

Comparison: 3 Any corticosteroid vs control: stratified by HIV status

Outcome: 2 Death or disabling residual neurological deficit



## APPENDICES

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

Search set	CIDG SR <sup>a</sup>	CENTRAL	MEDLINE <sup>b</sup>	EMBASE <sup>b</sup>	LILACS <sup>b</sup>
1	tuberculosis	tuberculosis	tuberculosis	TUBERCULOSIS-MENINGITIS	tuberculosis
2	TB	steroid*	tuberculosis	tuberculosis	TB
3	steroids	corticosteroid*	TB	TB	1 or 2
4	corticosteroids	glucocorticoid*	1 or 2 or 3	1 or 2 or 3	steroid*

(Continued)

5	dexamethasone	hydrocortisone	steroid*	steroid\$	hydrocortisone
6	hydrocortisone	prednisolone	STEROIDS	STEROIDS	dexamethasone
7	prednisolone	dexamethasone	corticosteroid*	corticosteroid\$	prednisolone
8	1 or 2	2 or 3 or 4 or 5 or 6 or 7	glucocorticoid*	glucocorticoid\$	4 or 5 or 6 or 7
9	3 or 4 or 5 or 6 or 7	1 and 8	hydrocortisone	hydrocortisone	3 and 8
10	8 and 9	-	dexamethasone	dexamethasone	-
11	-	-	prednisolone	prednisolone	-
12	-	-	prednisone	methylprednisone	-
13	-	-	methylprednisone	5-12/or	-
14	-	-	5-13/or	4 and 13	-
15	-	-	4 and 14	Limit 14 to human	-
16	-	-	Limit 15 to human	-	-

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

<sup>b</sup>Search terms used in combination with the search strategy for retrieving trials developed by The Cochrane Collaboration ([Higgins 2006](#)); upper case: MeSH or EMTREE heading; lower case: free text term.

## WHAT'S NEW

Last assessed as up-to-date: 13 November 2007.

2 September 2008	Amended	Converted to new review format with minor editing.
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## HISTORY

Protocol first published: Issue 1, 1998

Review first published: Issue 3, 2000

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14 November 2007	New citation required but conclusions have not changed	2008, Issue 1: New trial added ( <a href="#">Thwaites 2004</a> ); review text and title updated; MB Singh joined the review team, and J Volmink and GR Menon stepped down.
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## CONTRIBUTIONS OF AUTHORS

K Prasad conceptualized and developed the first review. During this update he screened the search results, assessed methodological quality, extracted and analysed data, interpreted the results, and rewrote several sections of the review. MB Singh also screened the search results, assessed methodological quality, extracted data, and entered data into Review Manager. She added some parts to the review text and participated in data interpretation.

## DECLARATIONS OF INTEREST

K Prasad is involved in one ongoing study ([Prasad 2006](#)) and is a co-author of one of the included trials ([Kumarvelu 1994](#)).

## SOURCES OF SUPPORT

### Internal sources

- All India Institute of Medical Sciences, India.

### External sources

- No sources of support supplied

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Antitubercular Agents [\* therapeutic use]; Chemotherapy, Adjuvant; Dexamethasone [therapeutic use]; Glucocorticoids [\* therapeutic use]; Hydrocortisone [therapeutic use]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic; Tuberculosis, Meningeal [\* drug therapy; mortality]

**MeSH check words**

Adult; Child; Humans