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Corticosteroids for managing tuberculous meningitis (Review)

Prasad K, Singh MB, Ryan H

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[Intervention Review]

Corticosteroids for managing tuberculous meningitis

Kameshwar Prasad[1], Mamta B Singh[1], Hannah Ryan[2]

[1]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India. [2]Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Kameshwar Prasad, Department of Neurology, All India Institute of Medical Sciences, Ansarinagar, New Delhi, 110029, India. drkameshwarprasad@gmail.com.

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ABSTRACT

Background

Tuberculous meningitis is a serious form of tuberculosis (TB) that affects the meninges that cover a person's brain and spinal cord. It is associated with high death rates and with disability in people who survive. Corticosteroids have been used as an adjunct to antituberculous drugs to treat people with tuberculous meningitis, but their role has been 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 methods

We searched the Cochrane Infectious Diseases Group Specialized Register up to the 18 March 2016; CENTRAL; 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 that compared corticosteroid plus antituberculous treatment with antituberculous treatment alone in people with clinically diagnosed tuberculous meningitis and included death or disability as outcome measures.

Data collection and analysis

We independently assessed search results and methodological quality, and extracted data from the included trials. We analysed the data using risk ratios (RR) with 95% confidence intervals (CIs) and used a fixed-effect model. We performed an intention-to-treat analysis, where we included all participants randomized to treatment in the denominator. This analysis assumes that all participants who were lost to follow-up have good outcomes. We carried out a sensitivity analysis to explore the impact of the missing data.

Main results

Nine trials that included 1337 participants (with 469 deaths) met the inclusion criteria.

At follow-up from three to 18 months, steroids reduce deaths by almost one quarter (RR 0.75, 95% CI 0.65 to 0.87; nine trials, 1337 participants, *high quality evidence*). Disabling neurological deficit is not common in survivors, and steroids may have little or no effect on this outcome (RR 0.92, 95% CI 0.71 to 1.20; eight trials, 1314 participants, *low quality evidence*). There was no difference between groups in the incidence of adverse events, which included gastrointestinal bleeding, invasive bacterial infections, hyperglycaemia, and liver dysfunction.

One trial followed up participants for five years. The effect on death was no longer apparent at this time-point (RR 0.93, 95% CI 0.78 to 1.12; one trial, 545 participants, *moderate quality evidence);* and there was no difference in disabling neurological deficit detected (RR 0.91, 95% CI 0.49 to 1.69; one trial, 545 participants, *low quality evidence*).

One trial included human immunodeficiency virus (HIV)-positive people. The stratified analysis by HIV status in this trial showed no heterogeneity, with point estimates for death (RR 0.90, 95% CI 0.67 to 1.20; one trial, 98 participants) and disability (RR 1.23, 95% CI 0.08 to 19.07; one trial, 98 participants) similar to HIV-negative participants in the same trial.

Authors' conclusions

Corticosteroids reduce mortality from tuberculous meningitis, at least in the short term.

Corticosteroids may have no effect on the number of people who survive tuberculous meningitis with disabling neurological deficit, but this outcome is less common than death, and the CI for the relative effect includes possible harm. However, this small possible harm is unlikely to be quantitatively important when compared to the reduction in mortality.

The number of HIV-positive people included in the review is small, so we are not sure if the benefits in terms of reduced mortality are preserved in this group of patients.

PLAIN LANGUAGE SUMMARY

Corticosteroids for managing people with tuberculous meningitis

What is tuberculous meningitis and how might corticosteroids work?

Tuberculous meningitis is a serious form of tuberculosis that affects the meninges that cover the brain and spinal cord, causing headache, coma and death. The clinical outcome is often poor even when people with tuberculous meningitis are treated with antituberculous drugs.

Corticosteroids are commonly used in addition to antituberculous drugs for treating people with the condition. These drugs help reduce inflammation of the surface of the brain and associated blood vessels, and are thought to decrease pressure inside the brain, and thus reduce the risk of death. Some clinicians are concerned that corticosteroids may improve survival, but result in more severely disabled survivors.

What the evidence shows

We examined the evidence published up to 18 March 2016 and included nine trials with 1337 people that evaluated either dexamethasone, methylprednisolone, or prednisolone given in addition to antituberculous drugs; one trial was of high quality, while the other trials had uncertainties over study quality due to incomplete reporting.

The analysis shows that corticosteroids reduce the risk of death by a quarter at two months to two years after treatment was started (*high quality evidence*). Corticosteroids make little or no difference to the number of people who survive TB meningitis with brain damage causing disability (*low quality evidence*); because this event is uncommon, even taking the most pessimistic estimate from the analysis of a slight increased risk with corticosteroids means this would not be quantitatively important when compared to the reduction in deaths.

One trial followed up participants for five years, by which time there was no difference in the effect on death between the two groups, although the reason for this change over time is unknown.

Only one trial evaluated the effects of corticosteroids in human immunodeficiency virus (HIV)-positive people but the number is small so we are not sure if the benefits in terms of fewer deaths are preserved in this group of patients.

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

Any corticosteroid compared to control for tuberculous meningitis

Participant or population: adults or children with tuberculous meningitis on tuberculosis (TB) chemotherapy
Settings: hospital care
Intervention: any corticosteroid
Comparison: placebo or no corticosteroid

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Quality of the evidence (GRADE)
	Assumed risk*	Corresponding risk			
	Control	Corticosteroid			
Follow-up to 2 to 24 months					
Death	**41 per 100**	**31 per 100** (27 to 36)	**RR 0.75** (0.65 to 0.87)	1337 (9 trials)	⊕⊕⊕⊕ **high**[1,2,3,4,5]
Disabling neurological deficit	**8 per 100**	**7 per 100** (6 to 10)	**RR** 0.92 (0.71 to 1.20)	1314 (8 trials)	⊕⊕◯◯[6,7,8] **low**
Follow-up to 5 years					
Death	**47 per 100**	**44 per 100** (37 to 53)	**RR 0.93** (0.78 to 1.12)	545 participants (1 trial)	⊕⊕⊕◯[9,10] **moderate**
Disabling neurological deficit	**15 per 100**	**14 per 100** (7 to 25)	**RR 0.91** (0.49 to 1.69)	244 (1 trial)	⊕◯◯◯[10,11,12] **very low**

*The **assumed risk** is from the median control group risk across studies. The **corresponding risk** (and its 95% CI) 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; **TB:** tuberculosis.

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. There are few uncertainties regarding allocation concealment or sequence generation in one of the two largest studies, but the largest trial was high quality and effects between these two trials were consistent.
[2]Not downgraded for inconsistency: low statistical heterogeneity, and the forest plot shows a consistent benefit.
[3]Not downgraded for indirectness in relation to age: all the participants in Schoeman 1997 and 59% of the participants in Girgis 1991 were children, and the effect is consistent with the other large trial, Thwaites 2004, which included participants aged 14 and over.
[4]Not downgraded for indirectness for HIV status: one trial included 98 HIV-positive participants, with no obvious qualitative heterogeneity when compared to HIV-negative participants (Thwaites 2004). If making recommendations for HIV-positive participants only, a guidelines panel may wish to downgrade on indirectness.
[5]Not downgraded for serious imprecision: the overall meta-analysis is adequately powered to detect this effect, but is only adequately powered when the trials at unclear or high risk of bias are included. The effect is clinically important.
[6]Downgraded by one for risk of bias: four of the eight trials were at high risk of bias due to lack of blinding of outcome assessors, which could impact on the interpretation of assessments of disability.
[7]Not downgraded for indirectness: trials included children, adults, some HIV-positive people, and people from different continents.
[8]Downgraded by one for imprecision: effects range from clinically important benefits of 29% reduction to 20% increase in disability.
[9]Not downgraded on risk of bias or imprecision: number of participants followed up was high: 91% at five years.
[10]Downgraded by one for indirectness. This was a single trial conducted in a high quality health care unit in a population with high levels of infectious diseases endemicity and poverty. The attenuation of the effect may be less marked in populations with lower exposure to infectious diseases and other causes of reduced life expectancy associated with poverty. The authors were not able to establish the cause of death in most of the people who died after 9 months follow-up, and so it is not possible to assess whether these deaths were related to tuberculous meningitis or to other causes.
[11]Not downgraded on risk of bias. Although the assessors were not blind to the allocation, and some assessments were conducted by telephone, the numbers of disabled participants in the two groups were the same, and it is unlikely that systematic bias in the observers is present.
[12]Downgraded by two for imprecision. There were few events, and the confidence interval ranges from substantive harms to substantive benefits.

BACKGROUND

Description of the condition

Tuberculous meningitis is an inflammation of the meninges, which are membranes that envelope a person's brain and the spinal cord. It is caused by infection with one of several mycobacterial species that belong to the *Mycobacterium tuberculosis* complex, which are responsible for tuberculosis (TB) disease. Tuberculous meningitis is a severe form of TB and accounts for many deaths (Tandon 1988). It is a form of extrapulmonary TB (that is, TB that occurs outside the lungs). The World Health Organization (WHO) reported that 0.8 million of the 5.4 million new TB cases reported worldwide in 2013 were extrapulmonary cases (WHO 2014). There is an association between extrapulmonary TB and human immunodeficiency virus (HIV) infection, particularly in people with low CD4 cell counts (Naing 2013). It appears that the higher risk of TB infection in HIV-positive people means that tuberculous meningitis is also more common in this group (Berenguer 1992; Berger 1994).

People with tuberculous meningitis usually present with headache, fever, vomiting, altered conscious level, and sometimes convulsions. It is diagnosed clinically, with confirmation by microscopy and culture of cerebral spinal fluid (CSF) or a polymerase chain reaction (PCR) test. The low sensitivity of the diagnostic tests currently available presents a particular challenge for clinicians, especially when treating children and HIV-positive people. Early diagnosis and prompt treatment are the main determinants of a good outcome in people with tuberculous meningitis (Thwaites 2013).

The causes of death and disability in tuberculous meningitis are multifactorial. The main pathological mechanisms are persistent or progressive raised intracranial pressure with or without hydrocephalus, involvement of the optic nerves or optic chiasm leading to visual deficit, cranial neuropathies, arachnoiditis, and vasculitis of the cerebral blood vessels leading to stroke. Neurological disability related to antituberculous treatment may occur due to optic neuritis related to ethambutol or isoniazid, which sometimes causes permanent loss of vision, or isoniazid-related peripheral neuropathy.

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

Description of the intervention

Without anti-tuberculous treatment, people with tuberculous meningitis die (Tandon 1988; Thwaites 2002). Streptomycin, one of the earliest antituberculous drugs to be introduced, reportedly 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. Reports of mortality rates vary from 20% to 32%, and permanent neurological deficits in an additional 5% to 40% of people who survive tuberculous meningitis (Ramchandran 1986; Alarcón 1990; Jacobs 1990; Jacobs 1992).

Indirect evidence from animal studies provides a biological basis for how corticosteroids 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 damage due to blood flow slowing to the underlying brain tissue. However, corticosteroids could also cause harm by suppressing the person's immune system. They may suppress the symptoms of TB infection but promote an unchecked growth of the bacteria and an increased bacterial load, and reduce inflammation of the meninges, which will then reduce the ability of drugs to cross the blood-brain barrier and enter the subarachnoid space. Other adverse effects of corticosteroids include gastrointestinal haemorrhage, electrolyte imbalance, hyperglycaemia, hypertension, and increased risk of infections from other pathogens (D'Arcy-Hart 1950).

The use of adjunctive corticosteroids is not known to result in disability in tuberculous meningitis, especially when used for short periods of time as is the case in most clinical trials of this intervention. However, there is concern that although corticosteroids may save the lives of some people who have severe tuberculous meningitis, they may not necessarily improve their quality of life, as some people may survive but be left with a severe disability, rendering them bed-bound and highly dependent. In other words, if corticosteroids increase the survival rate but not disability-free survival, then corticosteroids might actually increase a person's suffering.

Why it is important to do this review

Several randomized controlled trials (RCTs) have been conducted on the effect of corticosteroids in managing people with tuberculous meningitis. The conclusions from these trials, seen individually, appear inconsistent. One trial, Thwaites 2004, showed that dexamethasone increases survival rate. However, it also raised two questions: do people who survive because of dexamethasone therapy tend to be left with severe disability, and are there differential effects among subgroups of people 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) commented that the trial did not

have sufficient statistical power to answer these questions. We have prepared a meta-analysis that synthesizes the results from all available RCTs 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 (RCTs).

Types of participants

People of any age with clinically diagnosed tuberculous meningitis.

Types of interventions

Intervention

Corticosteroid (hydrocortisone, prednisolone, methylprednisolone, 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 outcomes

1. Death.
2. Persisting disabling neurological deficit at the end of follow-up.

Adverse events

Adverse events as reported by the authors, 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).

Electronic searches

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (18 March 2016); Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library, up to Issue 2, February 2016; MEDLINE (1966 to 18 March 2016); EMBASE (1974 to 18 March 2016); and LILACS (1982 to 18 March 2016). We also searched Current Controlled Trials (www.controlled-trials.com; accessed 18 March 2016) using 'tuberculosis' and 'meningitis' as search terms.

Searching other resources

Researchers

We contacted the following organizations and individuals working in the field: delegates at the V^{th} Annual Conference of Indian Academy of Neurology, Madras, India, 1997; delegates at the XIII th Global Joint Meeting of the International Clinical Epidemiology Network and Field Epidemiology Training Program, Victoria Falls, Zimbabwe, 1994; and members of the INDEX-TB Guidelines technical advisory committee, New Delhi, India, 2015.

Reference lists

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

Data collection and analysis

For selection of studies and data extraction, we independently conducted each step, and examined agreement between the review authors. We resolved any disagreements through discussion.

Selection of studies

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

One of the review authors, KP, conducted one of the included trials (Prasad 2006), which was started at the same time as Prasad 2000 (the first edition of this Cochrane Review). As of March 2016, this trial had not been published, but the unpublished data is included in this review. KP is also a co-author on Kumarvelu 1994. For both of these studies, HR performed the description of studies, 'Risk of bias' assessments, data extraction, and interpretation in consultation with the CIDG Co-ordinating Editor, Paul Garner.

Data extraction and management

We independently extracted data on participant characteristics, diagnostic criteria, disease severity, HIV status, antituberculous drug regimen, corticosteroid regimen, and outcome measures using a pre-piloted data extraction form. We resolved disagreements through discussion and contacted the corresponding trial 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, and also the authors of Thwaites 2004 to determine the number of deaths in the five-year follow-up study (Török 2011).

For dichotomous outcomes, we recorded the number of participants that experienced the event and the number of participants randomized to each treatment group, and used them in the analysis. We also recorded number of participants analysed in each treatment arm, and used the discrepancy between the figures to calculate the number of participants lost to follow-up. These figures allowed us to perform a worst-case scenario analysis to investigate the effect of missing data.

Assessment of risk of bias in included studies

We independently assessed methodological quality using the Cochrane 'Risk of bias' tool and reported the results in a 'Risk of bias' table (Higgins 2011). Regarding generation of allocation sequence and allocation concealment, we classified each of these as either adequate, inadequate, or unclear according to Jüni 2001. We reported who was blinded in each trial, and assessed the risk of bias associated with blinding separately for the two primary outcomes. If at least 90% of participants were followed up to the trial's completion we classified inclusion of all randomized participants as adequate; otherwise we classified inclusion as inadequate. We attempted to contact the trial authors if this information was not specified or if it was unclear. We resolved any disagreements by discussion between the review authors.

Measures of treatment effect

We used relative risk as the measure of treatment effect for analysis.

Unit of analysis issues

There were no cluster RCTs.

Dealing with missing data

The primary analysis is an intention-to-treat analysis where all participants randomized to treatment are included in the denominator. This analysis assumes that all losses to follow-up have good outcomes. We carried out a sensitivity analysis to explore the impact of the missing data on the summary effect estimate for death.

Assessment of heterogeneity

We assessed heterogeneity by visually inspecting the forest plots to determine closeness of point estimates with each other and overlap of confidence intervals (CIs). We used the Chi² 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).

Assessment of reporting biases

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

Data synthesis

We analysed the data using Review Manager (RevMan) (RevMan 2014). In view of the absence of significant heterogeneity we decided to perform a meta-analysis. We used risk ratios (RR) with 95% CIs and the fixed-effect model. We summarized the adverse event data in tables and performed meta-analysis for four types of treatment-related adverse event: gastrointestinal bleeding, hyperglycaemia/glycosuria, invasive bacterial infection (all of which could be related to corticosteroid use), and hepatitis (related to antituberculous treatment). We were unable to calculate rate ratios or summary rate ratios because the person-time over which these events were observed was unavailable.

Subgroup analysis and investigation of heterogeneity

There was no significant heterogeneity to indicate investigation of its potential sources.

Sensitivity analysis

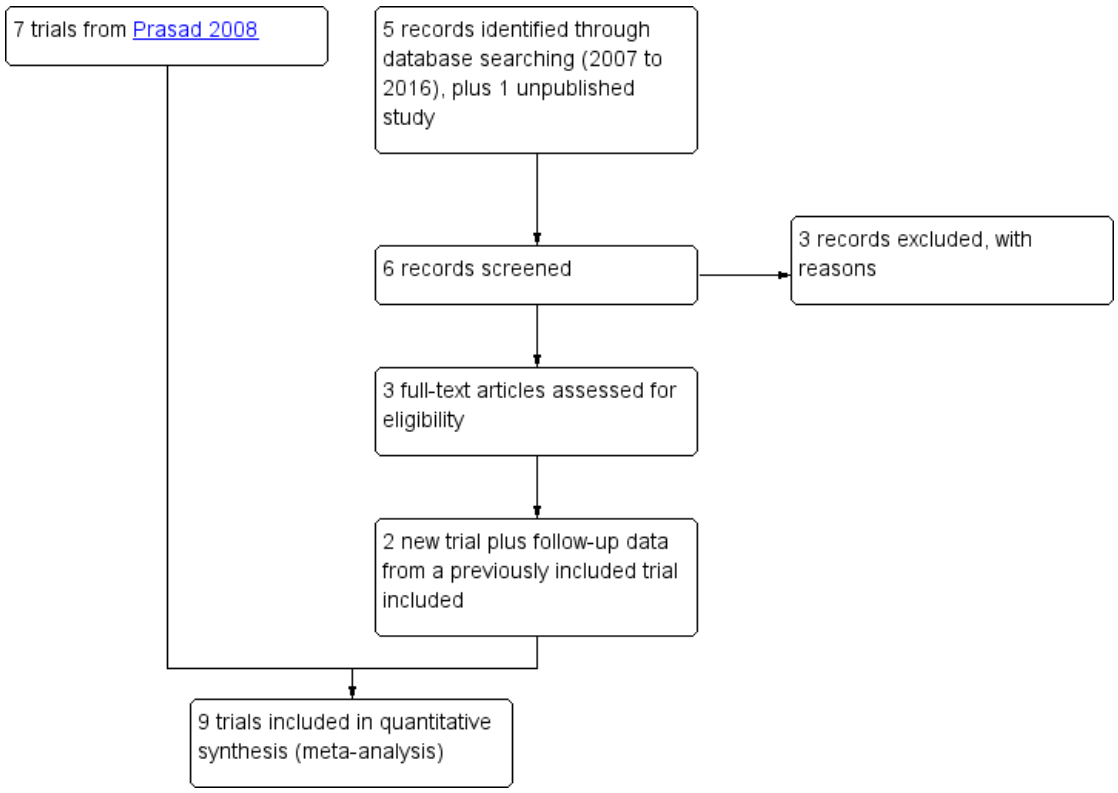
To explore the possible effect of losses to follow-up on the effect estimate for the outcome death, we performed a worst case scenario analysis and compared it with an available case analysis. We assumed all participants who had dropped out of the corticosteroid group had an unfavourable outcome whereas those who had dropped out of the control group had a favourable outcome, and compared these results to an available case analysis.

RESULTS

Description of studies

We included nine trials and excluded 18 trials (Figure 1; Characteristics of included studies; Characteristics of excluded studies).

Figure 1. Study flow diagram.



Results of the search

The original version of this Cochrane Review, Prasad 2000, included six trials with 595 participants (574 with follow-up, 215 deaths).

The 2008 update, Prasad 2008, added one new trial with 545 participants (535 with follow-up, 199 deaths).

In this update, we included two additional trials: Malhotra 2009 with 97 participants and Prasad 2006 with 87 participants, as well as follow-up data from a previously included trial (Thwaites 2004).

Included studies

We have provided a description of the included RCTs in Table 1.

Geographical location and time period

The included trials were conducted in different time periods (one in the 1960s, one in the 1980s, four in the 1990s, and two between 2001 and 2007) and in different geographical regions: Thailand (Chotmongkol 1996); Egypt (Girgis 1991); India (O'Toole

1969; Kumarvelu 1994; Prasad 2006; Malhotra 2009); Philippines (Lardizabal 1998); South Africa (Schoeman 1997); and Vietnam (Thwaites 2004).

Participants

All participants were enrolled on the basis of clinical diagnosis of probable tuberculous meningitis. All included trials attempted to confirm the diagnosis by microbiological tests, but only Girgis 1991 reported the outcomes for culture-confirmed cases separately. We have described the diagnostic criteria used in each included trial in Table 2.

The trials included young children (Schoeman 1997) or adults (Kumarvelu 1994; Chotmongkol 1996; Lardizabal 1998; Thwaites 2004; Prasad 2006), or both (O'Toole 1969; Girgis 1991), and both sexes. All trials used the British Medical Research Council (MRC) system, MRC 1948, to assess baseline severity; two trials included only participants with stage II and III tuberculous meningitis (Schoeman 1997; Lardizabal 1998), while the other trials included participants with all stages of severity. Thwaites 2004 specifically reported the inclusion of HIV-positive and HIV-negative people, while Chotmongkol 1996 and Malhotra 2009 specifically reported excluding HIV-positive people.

Only Thwaites 2004 reported on drug resistance. In this trial, *M. tuberculosis* was cultured from the cerebrospinal fluid (CSF) 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 resistant to rifampicin alone (in the dexamethasone group); and 10 (5.9%) were resistant to at least isoniazid and rifampicin (three in the placebo group and seven in the dexamethasone group).

Interventions

Six included trials used the corticosteroid dexamethasone and two trials used prednisolone (Chotmongkol 1996; Schoeman 1997). One trial, Malhotra 2009, compared both dexamethasone and methylprednisolone with placebo. We have described the dose regimens of corticosteroids used in Table 3.

Eight trials used three- or four-drug antituberculous regimens. O'Toole 1969, the earliest trial, used a two-drug regimen consisting of isoniazid and streptomycin.

Duration of antituberculous treatment varied from six months (Chotmongkol 1996; Schoeman 1997), nine months (Thwaites 2004; Prasad 2006; Malhotra 2009), 12 months (Kumarvelu 1994; Lardizabal 1998), to 24 months (Girgis 1991). In one trial, O'Toole 1969, the duration of antituberculous treatment was unclear.

Follow-up

Seven trials clearly described the follow-up period: two months (Lardizabal 1998); three months (Kumarvelu 1994); six months (Schoeman 1997); nine months (Thwaites 2004); 10 months (Malhotra 2009); two years (Girgis 1991); and 16 to 45 months (Chotmongkol 1996). It was unclear in O'Toole 1969 and Prasad 2006.

Thwaites 2004 followed up participants over a five-year period, and reported the results separately in Török 2011.

Outcome measures

All nine trials reported death.

All but one trial reported on disabling neurological deficit in some way, although there was substantial variation in methods of assessment of this outcome between the trials (O'Toole 1969). We accepted the trial authors' definition of disability and, for the purpose of analysis, classified residual deficits into disabling or non-disabling (as shown in Table 4).

Five trials mentioned adverse events. The trials reported on a number of other immediate outcome measures we had not considered in this Cochrane review (see 'Characteristics of included studies' section).

Excluded studies

We have listed the reasons for excluding 18 studies in the 'Characteristics of excluded studies' section.

Risk of bias in included studies

See the 'Characteristics of included studies' section, which includes a 'Risk of bias' table for each included trial. We have summarized the results of the 'Risk of bias' assessments across all included trials in Figure 2 and Figure 3.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included trials.

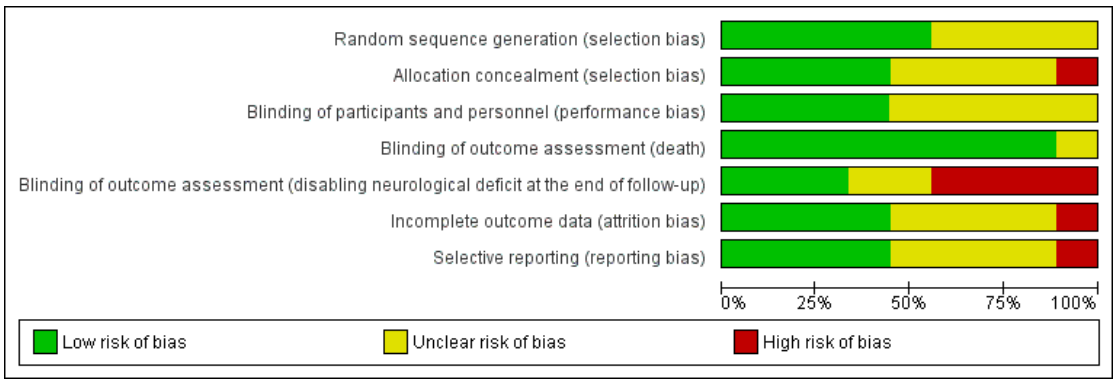
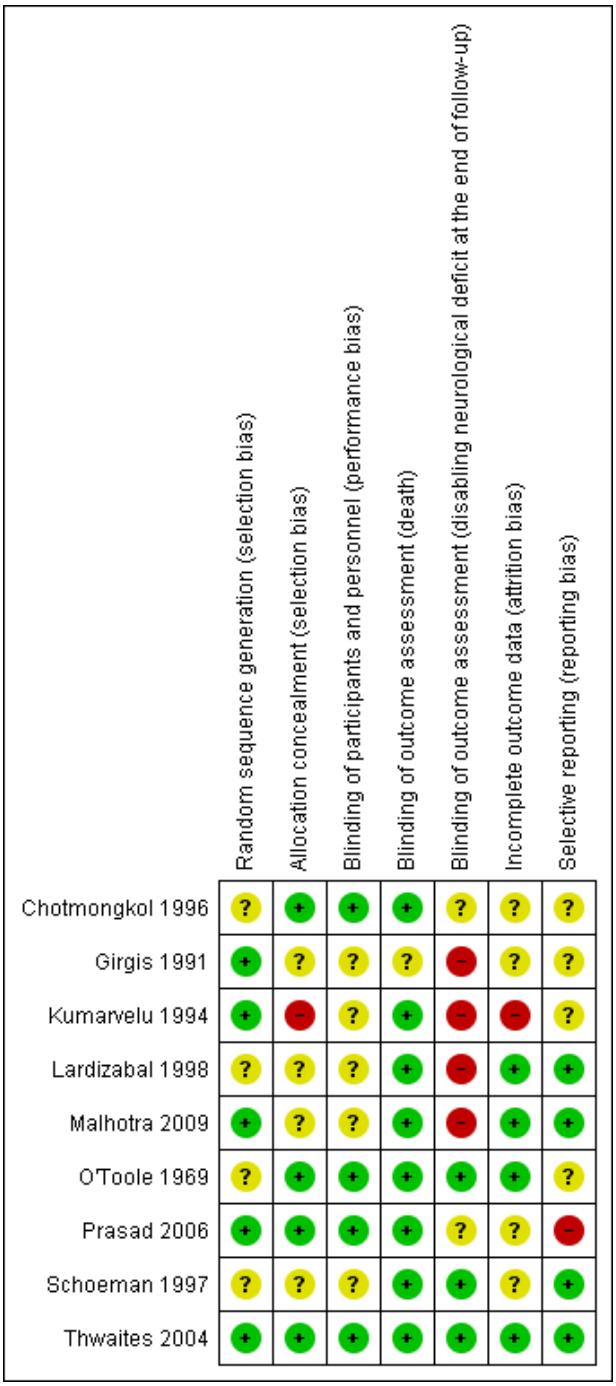


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial.



Allocation

Five included trials reported adequate methods of randomization using either computer generated sequences of random numbers or random number tables (Girgis 1991; Kumarvelu 1994; Thwaites 2004; Prasad 2006; Malhotra 2009). The remaining included trials did not clearly report the method of randomization.

We assessed four trials (O'Toole 1969; Chotmongkol 1996; Thwaites 2004; Prasad 2006) as having adequate allocation concealment, with participants allocated coded treatment packs. The remaining trials did not clearly describe allocation concealment.

Chotmongkol 1996 reported an imbalance in the severity of disease between the two groups, with the placebo group having a greater number of cases with Grade I disease and the steroid group having a greater number with Grade III disease. MRC stage 3 disease was present in 6/29 participants (20.7%) in the prednisolone group, but 4/30 participants (13.3%) in the placebo group. Conversely, stage 1 disease was present in 3/29 participants (10.3%) in the prednisolone group, but 6/30 participants (20%) in the placebo group. Both favoured the placebo group.

Blinding

Four included trials had adequate blinding of participants and personnel (O'Toole 1969; Chotmongkol 1996; Thwaites 2004; Prasad 2006). Participants and personnel were not blinded in the remaining trials.

We evaluated the blinding of outcome assessors separately for the two primary outcome measures.

For death, we assessed all included trials as at low risk of bias, apart from Girgis 1991. We considered that all-cause death was unlikely to be affected by risk of bias relating to outcome assessment, and therefore we assessed included trials as at low risk of bias regardless of blinding of outcome assessors for this outcome. We assessed Girgis 1991 as having unclear risk of bias because this trial reported death as a case fatality rate, meaning that death was attributed specifically to tuberculous meningitis. The effect of misclassification of deaths as being due to tuberculous meningitis when they were in fact due to another cause on the overall estimate of mortality is unknown.

For disabling neurological deficit, we categorized unblinded outcome assessments as high risk, given the subjectivity of such assessments. Two trials blinded assessors of neurological disability and were assessed as low risk of bias (Schoeman 1997; Thwaites 2004); and two trials had unblinded outcome assessors and were assessed as high risk of bias (Kumarvelu 1994; Malhotra 2009).

Incomplete outcome data

Four trials included over 90% of their randomized participants in the analysis (Lardizabal 1998; Malhotra 2009; O'Toole 1969; Thwaites 2004), and we assessed these trials as at low risk of bias. 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), and did not report on the reasons participants were lost to follow-up. We therefore assessed this trial as high risk of bias.

Four trials did not report losses to follow-up (Girgis 1991; Chotmongkol 1996; Schoeman 1997; Prasad 2006). We assessed these trials as at unclear risk of bias.

Selective reporting

For two included trials we had access to a trial protocol (Thwaites 2004; Prasad 2006). We assessed Thwaites 2004 as at low risk of bias as the trial authors reported on all outcomes stated in the protocol in full. We assessed Prasad 2006 as at high risk of bias, as the definitions of the main outcomes were altered in the available (unpublished) data set, and adverse events were not reported.

Lardizabal 1998; Malhotra 2009 and Schoeman 1997 reported all outcomes stated in the methods section in the results, so we assessed them as having low risk of bias. Chotmongkol 1996; Girgis 1991; Kumarvelu 1994 and O'Toole 1969 did not state the outcome measures in the results, so we assessed them as having unclear risk of reporting bias.

Other potential sources of bias

All included trials based the inclusion of participants on a clinical diagnosis of tuberculous meningitis, due to the limitations of microbiological tests to confirm the diagnosis. This means that the trials may have included some non-tuberculous meningitis cases. The direction of bias caused by such inclusions is not likely to favour corticosteroids.

Effects of interventions

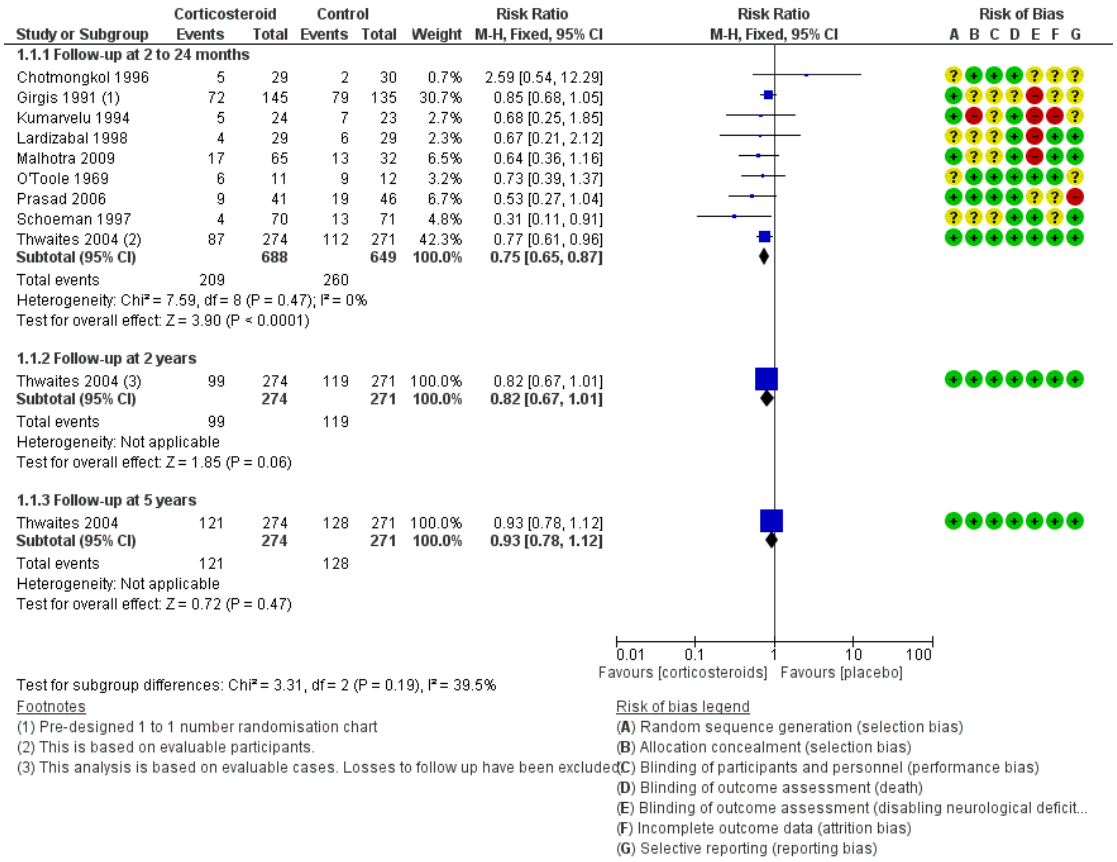
See: **Summary of findings for the main comparison** Any corticosteroid compared to control for tuberculous meningitis

Comparison: any corticosteroid versus control

Death

All nine included trials reported on death (Figure 4). The two largest trials, Girgis 1991 and Thwaites 2004, had more than 150 deaths in each, and the remaining trials were small trials with fewer deaths. Overall, the direction of effect indicated a benefit of steroids, with no statistical heterogeneity: the I^2 statistic was 0%.

Figure 4. Forest plot of comparison: 1 Any corticosteroid versus control, outcome: 1.1 Death.

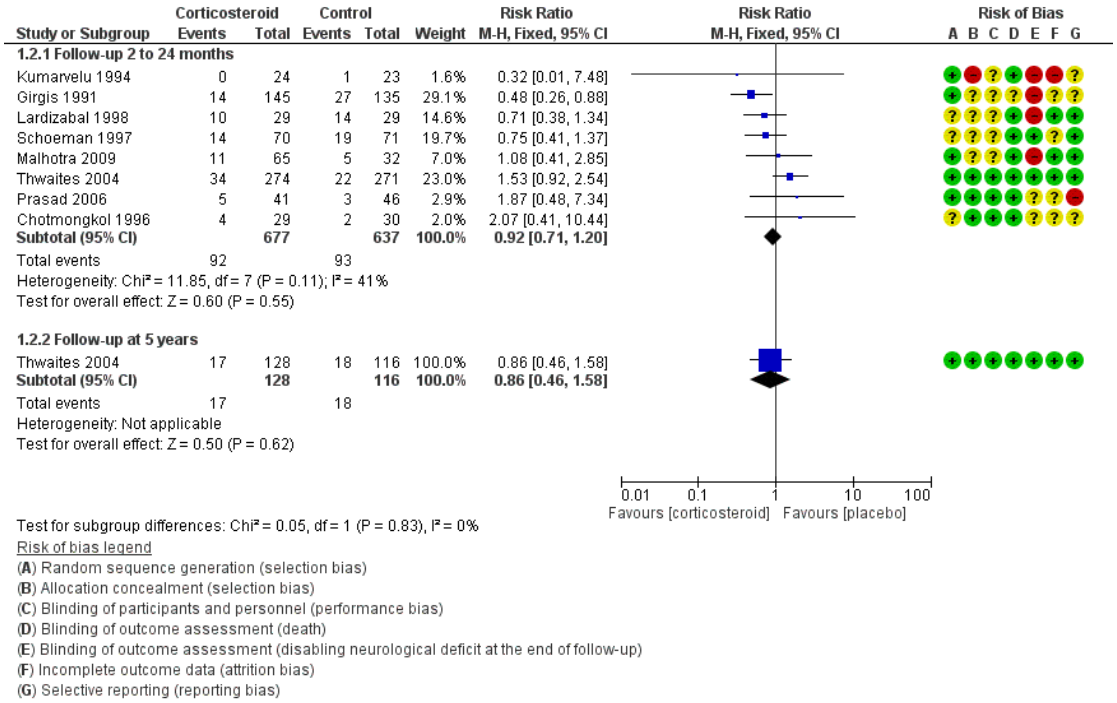


The pooled analysis found that there were 25% fewer deaths with corticosteroids (RR 0.75, 95% CI 0.65 to 0.87; nine trials, 1337 participants, Analysis 1.1). The median death rate across trials was 41% without corticosteroids, which translates to a 10% absolute risk reduction with corticosteroids when applying this relative risk. This summary estimate of effect was deemed to be high quality evidence using the GRADE approach (see Summary of findings for the main comparison).

Disabling neurological deficit

Eight trials reported on disabling neurological deficit (Figure 5). In both the intervention and control groups there were fewer events compared with death, and there was no difference between the two groups detected at two to 24 months follow-up (RR 0.92, 95% CI 0.71 to 1.20; eight trials, 1314 participants, Analysis 1.2). This summary estimate of effect was deemed to be low quality using the GRADE approach, because half the trials were at high risk of bias due to lack of blinding of outcome assessors and the estimate was imprecise.

Figure 5. Forest plot of comparison: 1 Any corticosteroid versus control, outcome: 1.2 Disabling neurological deficit.



Death or disabling neurological deficit - combined outcome

Eight trials reported data from which we could derive a combined outcome incorporating death and disabling neurological deficit (Chotmongkol 1996; Girgis 1991; Kumarvelu 1994; Lardizabal 1998; Malhotra 2009; Prasad 2006; Schoeman 1997; Thwaites 2004). For this outcome, the overall estimate showed a reduction in the risk of death or disabling residual neurological deficit with corticosteroids (RR 0.80, 95% CI 0.72 to 0.89; eight trials, 1314 participants, Analysis 1.3). This effect mirrors the results of the mortality analysis which is the main contributor of events.

Outcome at five years

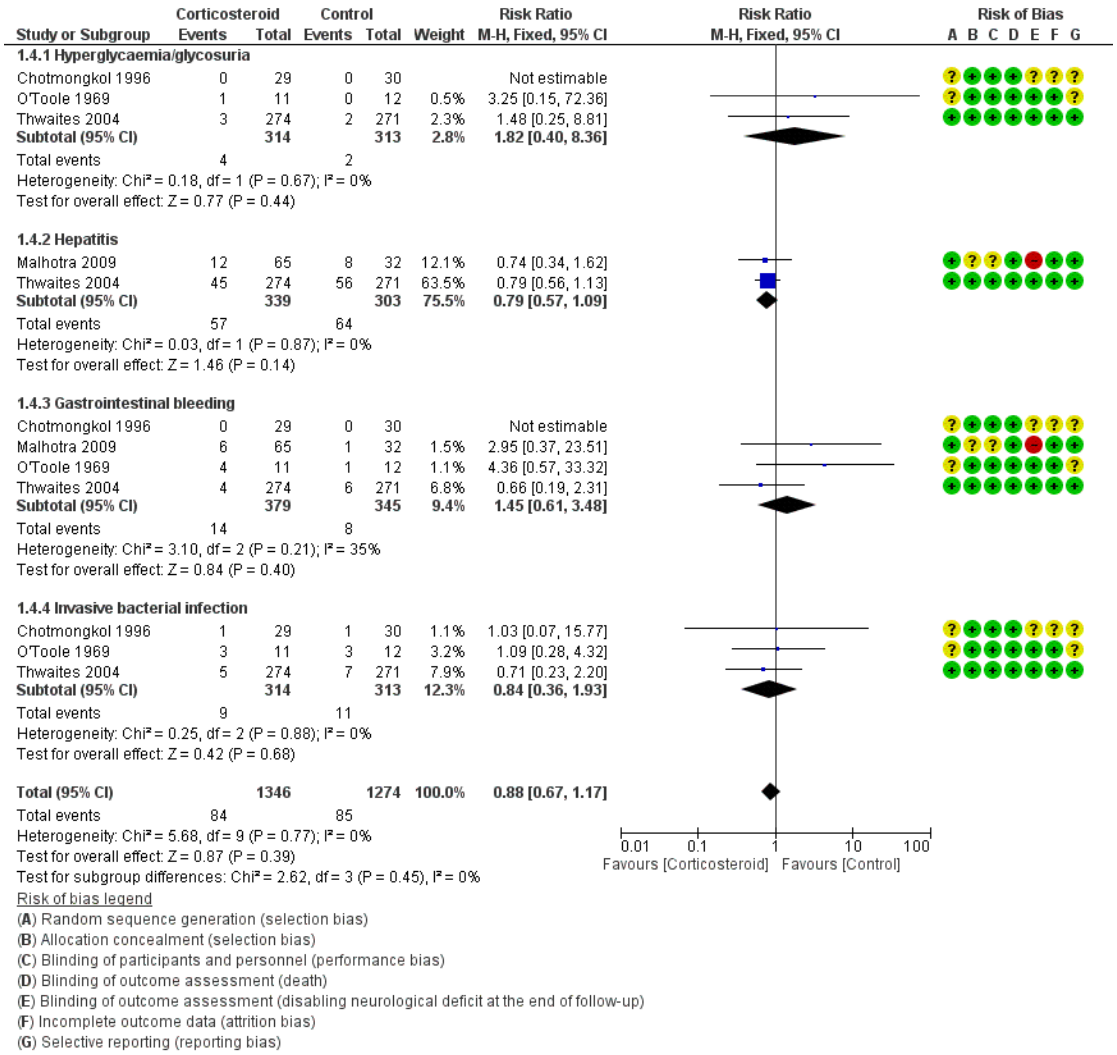
Only one recently published trial, Thwaites 2004, reported the long-term outcome of people with tuberculous meningitis randomized to receive either dexamethasone or placebo. The primary long-term outcome was survival during the five years follow-up, while secondary outcomes were status of disability and TB relapse. Fifty participants (9.4%) were lost to follow-up by the end of the follow-up period. The participants in the dexamethasone arm fared better on two-year survival rate (0.63 versus 0.55; risk difference 0.8, 95% CI 0.00 to 0.16; P = 0.07), but this advantage was lost at five years (0.54 versus 0.51; risk difference 0.03, 95% CI −0.06 to 0.12; P = 0.51). Analysis of hazard ratios by stage of disease at presentation suggested that benefit of dexamethasone in MRC stage I disease tended to persist longer with five-year probability of survival being 0.69 versus 0.55 (risk difference 0.14, 95% CI −0.01 to 0.29; P = 0.07). However, the test of interaction between disease severity and effect size was not statistically significant (P = 0.46 for zero to three months and P = 0.18 after three months). For disability, the follow-up study reported similar numbers with severe persistent neurological disability in both the steroid and non-steroid groups.

Adverse events

Of the six included trials that mentioned adverse events (O'Toole 1969; Kumarvelu 1994; Chotmongkol 1996; Schoeman 1997; Thwaites 2004; Malhotra 2009), three trials reported on incidence (O'Toole 1969; Thwaites 2004; Malhotra 2009; Figure 6). 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). Malhotra 2009 reported incidences of hepatitis,

anti-epileptic toxicity, gastrointestinal bleeding, and paradoxical tuberculoma in both groups. Schoeman 1997 had "serious side effects" as an outcome measure and reported "no serious side effects of corticosteroid therapy".

Figure 6. Forest plot of comparison: 1 Any corticosteroid versus control, outcome: 1.4 Adverse events.



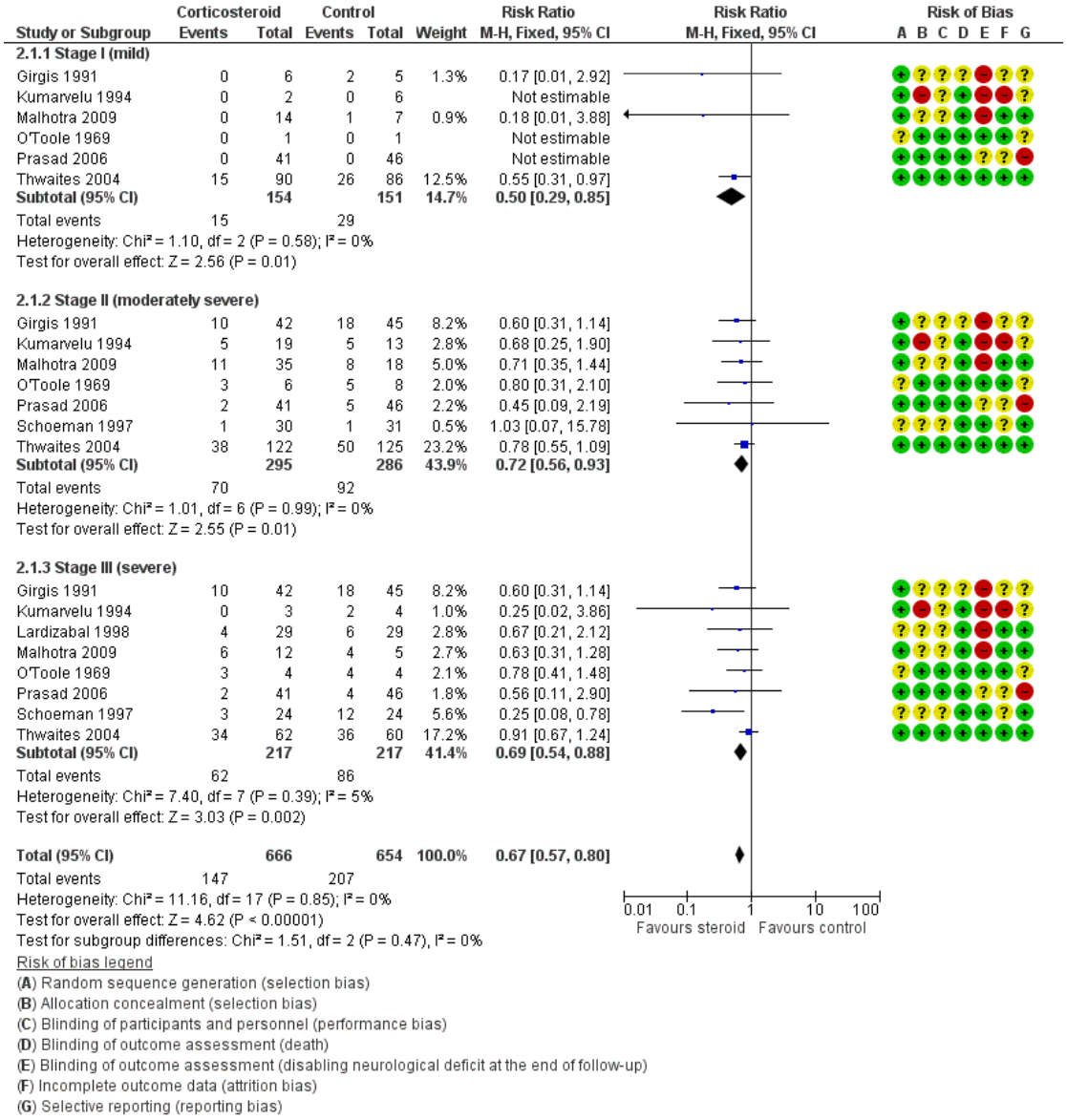
Meta-analyses examining gastrointestinal bleeding, hepatitis, hyperglycaemia, and invasive bacterial infection did not demonstrate a difference in the incidence of these events between the corticosteroid and placebo groups (Analysis 1.4). However, the meta-analysis is not sufficiently powered to detect a significant difference in adverse events between groups, so the results should be interpreted with caution.

Subgroup analysis

We explored whether heterogeneity was explained within two main pre-specified subgroups.

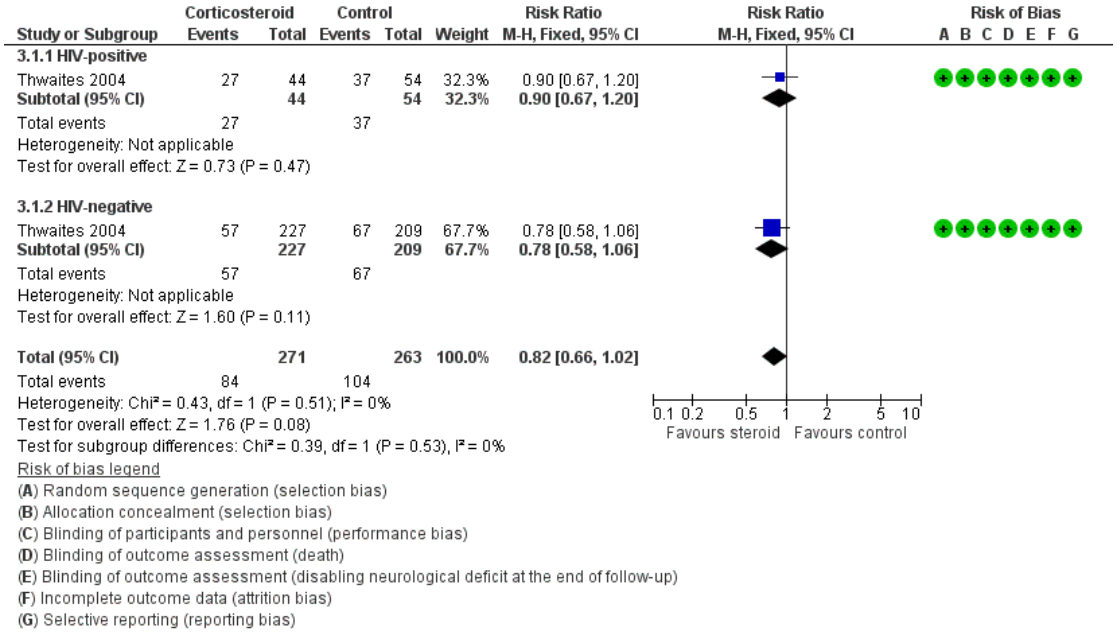
For severity of illness, we stratified the results on death by the severity of illness (MRC stages I, II, and III) in Figure 7. The effect of corticosteroids appeared to be consistent across all stages of the disease although the analysis is relatively underpowered (stage I RR 0.50, 95% CI 0.29 to 0.85; six trials, 305 participants); stage II (RR 0.72, 95% CI 0.56 to 0.93; seven trials, 581 participants); and stage III (RR 0.69, 95% CI 0.54 to 0.88; eight trials, 651 participants, Analysis 2.1).

Figure 7. Forest plot of comparison: 2 Any corticosteroid versus control: stratified by severity of illness, outcome: 2.1 Death.



For HIV status, one trial specifically mentioned that 98 of the included participants were HIV-positive (Thwaites 2004). Analyses stratifying the outcomes of death and disabling neurological deficit did not detect any large differences, and so showed no apparent effect of HIV status on the effect estimates, but the analysis is underpowered (Analysis 3.1; Analysis 3.2; Figure 8).

Figure 8. Forest plot of comparison: 3 Any corticosteroid versus control: stratified by HIV status, outcome: 3.1 Death.



Sensitivity analysis

Six trials reported on losses to follow-up (Kumarvelu 1994; Lardizabal 1998; Malhotra 2009; O'Toole 1969; Schoeman 1997; Thwaites 2004), with two trials reporting no losses to follow-up (Lardizabal 1998; O'Toole 1969). We performed a worst case scenario analysis, assuming that all participants lost to follow-up in the corticosteroid group died while those in the control group survived (Analysis 4.1). Under this extreme assumption, there was still a reduction in deaths with corticosteroids (RR 0.80, 95% CI 0.66 to 0.96), and the estimate was similar to the available case analysis (RR 0.71, 95% CI 0.59 to 0.86). Thus, losses to follow-up are unlikely to have introduced bias in favour of corticosteroids.

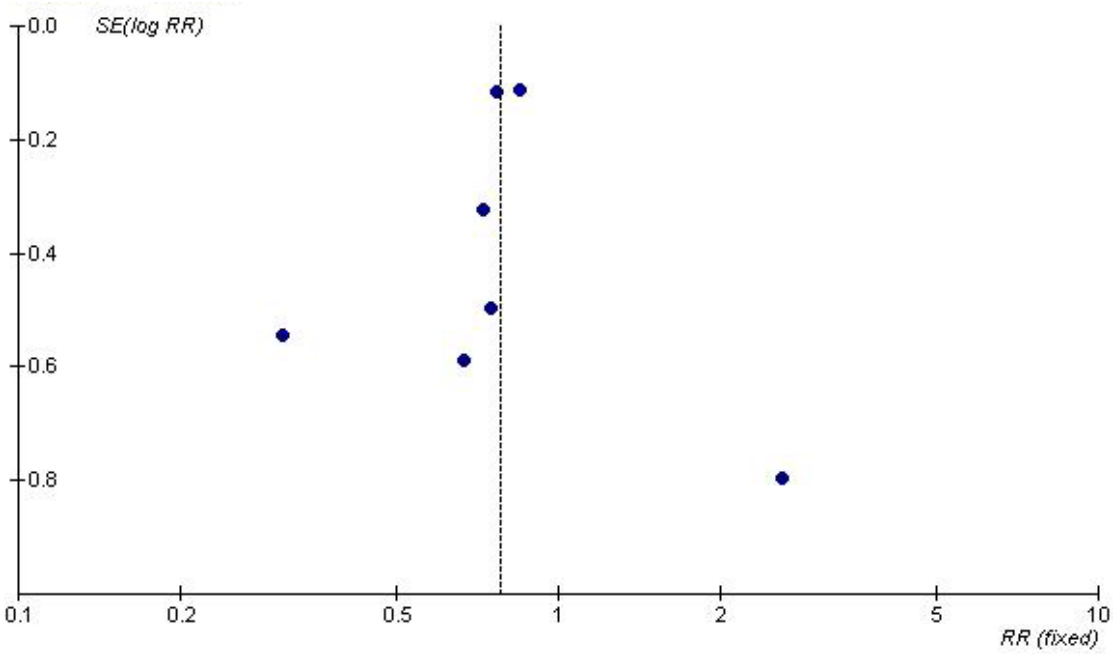
Assessment of reporting biases

Six included trials date to the period when registry of clinical trials was not mandatory or routine. Protocols of the included trials were unavailable except for two trials (Prasad 2006; Thwaites 2004). For five trials where the outcomes were not clearly specified in the methods section, we assessed the risk of reporting bias as unclear. We assessed three trials as at low risk of reporting bias as all outcomes specified in the protocol or methods were reported (Schoeman 1997; Thwaites 2004; Malhotra 2009). We assessed one trial as at high risk of bias, as outcome definitions were changed in the reported data (unpublished), and adverse events were not reported (Prasad 2006). Overall, the main analysis is unlikely to have been affected by reporting bias.

Publication bias

We have presented a funnel plot of the included trials in Figure 9. It refers to the outcome death and values below one favour corticosteroids. There is no obvious evidence of publication bias, but the number of included trials was low.

Figure 9. Funnel plot of risk ratio (RR) from the included trials with the log of their standard error (SE) values.



DISCUSSION

Summary of main results

See 'Summary of findings' table 1 (Summary of findings for the main comparison).

Nine trials met the inclusion criteria. At follow-up from 2 to 24 months, steroids reduce deaths by one quarter. Disabling neurological deficit is less common in survivors, and steroids may have little or no effect on this outcome; even taking the upper confidence limit of 20% increased risk, this is probably not quantitatively important when compared to the reduced mortality. There was no difference between groups in the incidence of adverse events, which included gastrointestinal bleeding, invasive bacterial infections, hyperglycaemia and hepatitis, although adverse events were not reported in all studies.

One trial followed up participants for five years. The effect on death and was no longer apparent at this time-point, and there was no difference in disabling neurological deficit detected.

One trial included human immunodeficiency virus (HIV)-positive people. The stratified analysis by HIV status in this trial showed no heterogeneity, with point estimates for death similar to HIV-negative participants in the same trial.

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 they included 98 HIV-positive participants, but they did not stratify the randomization for this subgroup; therefore the results for this

subgroup should be interpreted with caution. The effect of corticosteroids was not significantly different between HIV-positive and HIV-negative participants, but the trial lacked the power to detect such a difference if one did exist due to the low number of HIV-positive participants.

Though the included 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 usually taken on a purely clinical basis when culture reports are unavailable 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.

All included trials were conducted in high TB burden settings, in specialist referral hospitals.

Quality of the evidence

We used the GRADE approach to assess the quality of the evidence for the two primary outcomes at two to 24 months follow-up, and at five years follow-up (Summary of findings for the main comparison).

We graded the quality of the estimate of effect for the outcome death at two to 24 months follow-up as high. We assessed the estimate of effect as being at low risk of bias, as while there are some included trials that did not clearly report on the randomization method or allocation concealment, or both, the two largest included trials had few concerns and showed a consistent effect. The trials provided evidence of benefit for all age groups. Although only one trial reported on outcomes for people living with HIV, there was no obvious qualitative heterogeneity. We did not find any serious imprecision. We graded the estimate of effect for death at five years follow-up as moderate, and downgraded by one for indirectness as the data came from a single trial conducted in a high quality healthcare unit in a setting with high levels of endemic infectious diseases and poverty.

We assessed the quality of the estimate of effect for the outcome disabling neurological deficit as low quality. The lack of blinding of outcome assessors of disabling neurological deficit in four of the eight trials reporting this outcome led us to downgrade the quality of evidence by one for risk of bias. There was imprecision of this estimate relating to the small number of events, which led us to downgrade by one. We graded the estimate of effect for disabling neurological deficit at five years follow-up as very low quality, and downgraded by one for indirectness as the data was from a single trial (as for the outcome death, see above) and by two for imprecision as there were few events and the CI ranged from substantive harms to substantive benefits of corticosteroids.

Potential biases in the review process

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

Agreements and disagreements with other studies or reviews

Several TB guidelines recommend the use of corticosteroids as an adjunct to treatment of TB meningitis internationally (CDC 2003; BSI 2009; SNHS 2010; NICE 2011).

Questions remain about the mechanism by which corticosteroids improve clinical outcomes, and advances in understanding of these mechanisms have led to a suggestion that some people may benefit from corticosteroids while others do not, and some may even be adversely affected by steroids (Thwaites 2013). Leukotriene A4 hydrolase (LTA4H) has been implicated in the pathogenesis of mycobacterial infection through its effect on the equilibrium between pro- and anti-inflammatory eicosanoids. Tobin et al. showed that both low- and high-LTA4H expression zebrafish morphants show increased mycobacterial bacterial burden compared with wildtype controls (Tobin 2010; Tobin 2012). Low-LTA4H expression led to increased lipoxin A4 production and dampening of the early tissue necrosis factor-alpha (TNF-α) response, and high-LTA4H morphants showed increased macrophage lysis despite early control of intracellular mycobacterial replication by TNF-α, with subsequent extracellular mycobacterial growth. Both of these states led to uncontrolled mycobacterial replication. Thus, hypersusceptibility to mycobacterial infection is associated with both inadequate and excessive inflammatory responses.

The use of dexamethasone in the zebrafish morphants rescued high-LTA4H animals but led to increased susceptibility in low-LTA4H animals (Tobin 2012). In people, the LTA4H transcription level is regulated by a polymorphism in the gene promoter at SNP rs17525495, with rs17525495 TT associated with high LTA4H protein expression, rs17525495 CC associated with low expression, and rs17525495 CT intermediate expression. Genotyping performed on 182 participants from a series of clinical studies in Vietnam demonstrated that people with the TT genotype (high LTA4H, hyperinflammatory) had the highest mortality amongst participants who did not receive dexamethasone, but the lowest in the dexamethasone group; the people with the CC genotype (low LTA4H, hypoinflammatory) had the highest mor-

tality in the dexamethasone group (Tobin 2012). These results suggest that LTA4H genotype may have an important influence on whether or not steroids are effective in tuberculous meningitis, at least in this population.

Further investigation into the relationship between LTA4H expression in people, dexamethasone use, and outcomes in people with TB meningitis is needed to determine whether dexamethasone use is associated with harm in the subset of people with LTA4H deficiency, and whether genotyping people for LTA4H at diagnosis is useful to guide treatment with corticosteroids. Other drugs that target parts of this inflammatory pathway, such as thalidomide, adulimumab and infliximab, have been used as rescue therapy in people with severe inflammatory complications of TB meningitis, but few clinical trials have been conducted on the use of these agents, and all these potent immunosuppressive drugs have the potential to cause harm as well as benefit (Schoeman 2001; Schoeman 2004; Schoeman 2010; Jorge 2012; Lee 2012; Molton 2015).

AUTHORS' CONCLUSIONS

Implications for practice

There is high quality evidence of the benefit of corticosteroids in preventing death in people with tuberculous meningitis. This effect is probably attenuated over time, as five-year follow-up data from one trial suggests this, but there may be confounding factors leading to this observation. Corticosteroids appear to reduce mortality in people with TB meningitis, regardless of the British Medical Research Council (MRC) stage at presentation. Corticosteroids may have no effect on rates of disabling neurological deficit in people who survive TB meningitis, but the confidence interval around this estimate includes increased risk of this outcome. However, given the benefit associated with reduced risk of death, this is unlikely to be quantitatively important when considering whether or not to use corticosteroids in patients with TB meningitis. There is uncertainty about whether or not corticosteroids are beneficial for HIV-positive people with TB meningitis due to the lack of direct evidence in this group. Corticosteroids may not be associated with increased risk of adverse events, but there is uncertainty related to the limited reporting of adverse events in the included trials.

Implications for research

Further research is unlikely to add to certainty about the effect of corticosteroids in people with tuberculous meningitis who are HIV-negative in preventing death.

In people that are immunosuppressed, such as people living with HIV, it is unclear whether corticosteroids are of benefit. As corticosteroids could lead to greater risk of harm in these people, further research would be useful to provide clear guidance for treatment.

Another question that remains unanswered is the optimum choice of corticosteroid drug and dosing regimen. Given the fact that use of corticosteroids carries the risk of adverse events, and that many of these are dose-dependent, further research examining this question would be beneficial.

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CHARACTERISTICS OF STUDIES

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

Chotmongkol 1996

Methods	Randomized parallel group study. Length of follow-up: 6 months but post-study follow-up continued for 16 to 45 months (mean = 30 months)
Participants	Setting: Sringarind Hospital, Khon Kaen, Thailand - tertiary referral centre Number of participants: 59 participants; 27 females, 32 males; 29 received prednisolone, 30 received no steroid Inclusion criteria: age > 15 years; clinically diagnosed tuberculous meningitis (characteristic clinical features with typical CSF profile consisting of lymphocytic meningitis with low glucose level and elevated protein), all stages of disease included Exclusion criteria: children <15 years old, HIV-positive, VDRL positive for syphilis, cryptococcal antigen positive, CSF positive for bacterial or fungal infection on latex agglutination or culture, malignant cells in CSF HIV status: HIV-positive participants excluded.
Interventions	1. Antituberculous treatment (ATT) plus prednisolone orally 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). 2. ATT alone. ATT: isoniazid oral (300 mg), rifampicin oral (600 mg, 450 mg for those weighing < 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
Outcomes	1. Death at the end of 6 months. 2. Residual neurological deficits at the end of 6 months. 3. Time until resolution of fever. 4. Time until disappearance of headache. Adverse events recorded were gastrointestinal bleeding and hyperglycaemia
Notes	Date: July 1990 to December 1992. Trialists: Department of Medicine, Khon Kaen University, Thailand; no collaborators There was baseline prognostic imbalance in favour of placebo group: MRC stage 3 disease was present in 6/29 (20.7%) in prednisolone group, but 4/30 (13.3%) in placebo group. Conversely, stage 1 disease was present in 3/29 (10.3%) in prednisolone group, whereas 6/30 (20%) in placebo group. Both favoured the placebo group Ziehl-Nielsen staining of CSF for AFBs or culture positive for *M. tuberculosis*, or both, in 4/29 in the prednisolone group and 1/30 in the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomization by a block size of 4, but insufficient information on sequence

Chotmongkol 1996 (*Continued*)

		generation
Allocation concealment (selection bias)	Low risk	"Patients were randomised to receive prednisolone or placebo by a block size of four using coded treatment A and B."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding with use of placebo.
Blinding of outcome assessment (death)	Low risk	Blinding of outcome assessors was not specified, but this is unlikely to introduce bias for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Unclear risk	Blinding of outcome assessors was not specified, so impact on assessment of neurological deficits during follow-up was unclear
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up were not reported.
Selective reporting (reporting bias)	Unclear risk	The protocol was unavailable, and outcomes were not clearly specified in the methods

Girgis 1991

Methods	Randomized parallel group, 2-arm study with allocation ratio: 1:1 Length of follow-up: 24 months.
Participants	Setting: Abbassia Fever Hospital, Cairo, Egypt - tertiary referral centre Number of participants: 280 participants; 158 males, 122 females; 145 received dexamethasone, 135 received no steroid Age: all ages included, 37% aged 0 to 5 years, 22% aged 5 to 16 years Inclusion criteria: clinically diagnosed tuberculous meningitis based on history and examination (duration of illness > 30 days, consisting of fever, headache, vomiting, altered sensorium, generalized weakness or cranial nerve deficits); comparison of first and second CSF findings; and a poor response to antibacterial therapy for 48 hrs Exclusion criteria: not reported. HIV status: not reported.
Interventions	1. ATT plus 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). 2. ATT alone. ATT: isoniazid (10 mg/kg/day, maximum 600 mg) intramuscularly for 2 weeks then orally for 2 years, streptomycin intramuscular (25 mg/kg/day, maximum 1000 mg) for 6 weeks, and ethambutol oral (25 mg/kg/day, maximum 1200 mg) for 6 weeks, then 15

Girgis 1991 (*Continued*)

	mg/kg/day for 2 years
Outcomes	1. Death during 2-year follow-up. 2. Residual neurological sequelae. 3. Neurological complications developing during therapy. 4. CSF 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 deaths attributed to other causes. They did not report whether any death during the follow-up period was considered to be due to any cause other than tuberculous meningitis
Notes	Date: 1982 to 1987. Trialists: United States Naval Medical Research Unit No. 3, Cairo, Egypt; no collaborators 160/280 CSF culture positive for *M. tuberculosis.*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Pre-designed 1-to-1 number randomization chart.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No attempt at blinding, but the impact on mortality is unclear
Blinding of outcome assessment (death)	Unclear risk	Outcome assessors were not blinded, and impact on risk of bias for case fatality rate is unclear as this is a measure of death attributed to tuberculous meningitis only
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	High risk	Outcome assessors were not blinded, so risk of bias in assessment of neurological deficit during follow-up is high
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up were not reported.
Selective reporting (reporting bias)	Unclear risk	The protocol was unavailable and outcomes were not clearly specified in the methods

Kumarvelu 1994

Methods	Randomized parallel group 2-arm study with allocation ratio 1:1 Length of follow-up: 3 months.
Participants	Setting: all India Institute of Medical Sciences (AIIMS), New Delhi, India - tertiary referral centre Number of participants: 47 participants; 22 females, 25 males; 24 received dexamethasone, 23 received no steroid Inclusion criteria: aged over 10 years; clinically diagnosed tuberculous meningitis (meeting any 3 of the following criteria) 1. Fever, headache, neck stiffness for 2 weeks. 2. CSF profile of > 20 cells/mm³ 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. 4. Clinical, radiological, or histological evidence of extracranial TB). All stages of severity and any duration of disease included. Exclusion criteria: aged < 10 years, received ATT for more than 4 weeks prior to admission, received corticosteroids before admission HIV status: not reported.
Interventions	1. ATT plus dexamethasone (intravenous 16 mg/day in 4 divided doses for 7 days, then oral tablet 8 mg/day for 21 doses, and in children 0.6 mg/kg/day for 7 days, reducing to 0.3 mg/kg/day for 21 days). 2. ATT alone. ATT: 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.
Outcomes	1. Death at 3 months. 2. Major sequelae (totally dependent for activities of daily living) at 3 months. 3. Minor sequelae (activities of daily living with no or minimal assistance) at 3 months. 4. Adverse effects. 5. Time to recover from altered sensorium, from fever, and from headache.
Notes	Location: India. Date: March 1991 to March 1992. Trialists: Department of Neurology, All India Institute of Medical Sciences, New Delhi, India; no collaborators Number of participants that were CSF culture positive for *M. tuberculosis* was not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used random numbers from Fisher's table.
Allocation concealment (selection bias)	High risk	Not done.

Kumarvelu 1994 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding but its impact on mortality remains unclear.
Blinding of outcome assessment (death)	Low risk	Outcome assessors were not blinded, but this is unlikely to introduce bias for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	High risk	Outcome assessors were not blinded, so the risk of bias in assessment of neurological deficit during follow-up is high
Incomplete outcome data (attrition bias) All outcomes	High risk	Six out of 47 participants were lost to follow-up (4 in the treatment arm and 2 in the control arm)
Selective reporting (reporting bias)	Unclear risk	Protocol unavailable and outcomes not clearly specified in the methods

Lardizabal 1998

Methods	Randomized parallel group, 2-arm study with allocation ratio 1:1 Length of follow-up: 2 months
Participants	Setting: University of the Phillipines College of Medicine, tertiary care facility, single centre Number of participants: 58 participants; 31 males and 27 females; 29 received dexamethasone, 29 received no steroid Inclusion criteria: aged 18 years and above; probable tuberculous meningitis diagnosed using ASEAN Neurological Association criteria based on the following 1. Insidious onset fever for at least 1 week, headache and vomiting, with or without nuchal rigidity followed by altered consciousness, cranial nerve palsies, or long tract signs. 2. CSF profile of lymphocyte predominance, elevated protein and reduced glucose. 3. CSF 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 TB; confirmed tuberculous meningitis based on positive CSF culture or microscopy, or both. 4. British MRC stages II and III disease. Exclusion criteria 1. Aged under 18. 2. British MRC stage I TB meningitis, or bacterial or fungal meningitis diagnosed on CSF culture. 3. Pregnancy or lactation. 4. History of diabetes mellitus or hypertension. 5. Upper gastrointestinal bleeding, or history of peptic ulcer disease in the previous month. 6. Raised bilirubin, SGPT or serum creatinine.

Lardizabal 1998 (*Continued*)

Interventions	1. Antituberculous treatment plus 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). 2. Antituberculous treatment alone. 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 was not stated An H2-antagonist (famotidine or ranitidine) was given during the period of corticosteroid administration
Outcomes	1. Death on days 15, 30, and 60 post-randomization. 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. 3. Potential adverse reactions to corticosteroids including weakness, oedema, hypertension, euphoria, psychosis, epigastric discomfort, Cushingoid facies, hirsutism, acne, insomnia, and increased appetite.
Notes	Location: Philippines. Date: November 1996 to July 1997. Trialists: University of Philippines, College of Medicine; no collaborators We contacted the trial authors to determine the number of deaths in participants with stage II and III disease Number of participants that were CSF culture positive for *M. tuberculosis* was not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Generation of allocation sequence was unclear.
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding but its impact on mortality remains unclear.
Blinding of outcome assessment (death)	Low risk	Outcome assessors were not blinded, but unlikely to introduce bias for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	High risk	Outcome assessors were not blinded, so risk of bias in assessment of neurological deficit during follow-up is high

Lardizabal 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up, changes of treatment arm, or withdrawals. Outcomes were reported for all randomized participants
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but all outcomes specified in the methods section are reported on in the results

Malhotra 2009

Methods	Randomized parallel group 3-arm study with allocation ratio 1:1:1 Length of follow-up: 10 months.
Participants	Setting: Chhatrapati Shahuji Maharaj Medical University (CSMMU), Lucknow, India - tertiary referral centre Number of participants: 91 participants; 48 males, 43 females (6 participants randomized but lost to follow-up); 32 randomized to dexamethasone (1 lost to follow-up), 33 randomized to methylprednisolone (3 lost to follow-up), 32 randomized to no steroid (2 lost to follow-up) Inclusion criteria: age > 14 years; meningitic syndrome; tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if one or more than one of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness > 5 days, radio of CSF to plasma glucose < 0.5, altered consciousness, yellow CSF, or focal neurological signs Exclusion criteria: age < 14 years; HIV-positive; contraindication to corticosteroids; received corticosteroid or antituberculous drugs before presentation at the CSMMU, evidence of space occupying lesion on CT brain, refused consent
Interventions	1. ATT + dexamethasone (intravenous for 4 weeks as (at 0.4, 0.3, 0.2 and 0.1 mg/kg.day during weeks 1, 2, 3, 4 respectively); daily oral dose for following 4 weeks as 4, 3, 2, 1 mg/day on weeks 5, 6, 7, 8 respectively). 2. ATT + methylprednisolone (intravenous for 5 days (1 g/day for participants weighing > 50kg and 20 mg/kg/day for participant weighing < 50 kg). 3. ATT alone. ATT: rifampicin (15 mg/kg/day), isoniazid (10 mg/kg/day), pyrazinamide (30 mg/kg/day) and either ethambutol (20 mg/kg/day) or streptomycin (15 mg/kg/day) for 2 months and isoniazid (10 mg/kg/day) for 7 months
Outcomes	Assessed at 6 months post-randomization. 1. Death or severe disability. 2. Adverse events: hepatitis; anti-epileptic toxicity, gastro-intestinal bleeding, paradoxical tuberculoma. 3. Deterioration in vision, development of new focal neurological deficit and new-onset seizures.

Malhotra 2009 (*Continued*)

Notes	Date: January 2006 to July 2007. Trialists: CSMMU, Lucknow, Department of Neurology, Uttar Pradesh, India 97/126 acid-fast stain/culture positive for*M. tuberculosis.*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation using computer-generated randomization sheet
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but the impact on mortality is unclear.
Blinding of outcome assessment (death)	Low risk	Outcome assessors were not blinded, but this is unlikely to introduce bias for all cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	High risk	Outcome assessors were not blinded, so the risk of bias in assessment of neurological deficit during follow-up is high
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six out of 97 participants were lost to follow-up (1 in dexamethasone, 3 in methylprednisolone, and 2 in the control arm)
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but all outcomes specified in the methods were reported

O'Toole 1969

Methods	Randomized parallel group 2-arm study with allocation ratio 1:1 Length of follow-up: unclear.
Participants	Setting: Infectious Diseases Hospital, Calcutta, India - tertiary referral centre Number of participants: 23 participants in total, 11 females, 12 males; 11 received dexamethasone, 12 received no steroid Inclusion criteria: not explicitly specified, but the trial authors state that due to the trial institution's admissions policy only participants with a short history or acute signs and symptoms of meningitis were selected; due to limited bed availability only moderate to severely unwell participants were included (MRC Stage II and III). All age groups were included. Treatment allocation was stratified for age and disease severity HIV status: not reported.

O'Toole 1969 (*Continued*)

Interventions	1. ATT plus 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 4th week; dose for children was calculated according to their body surface area (no more details available). 2. ATT alone. ATT: 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), duration not specified
Outcomes	1. Death at the end of follow-up (duration unclear). 2. Number with elevated CSF opening pressure on days 1, 4, 7, and 14. 3. CSF 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. 5. Resolution of CSF findings.
Notes	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 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 CSF profile consisting of elevated white cell count and protein, decreased glucose, and negative India ink smear for *Cryptococcus*; the trial 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information.
Allocation concealment (selection bias)	Low risk	"New admissions to the study were assigned their drug by matching age and stage of disease then selecting the next unused coded preparation in that prognostic category."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding unlikely to have been broken.
Blinding of outcome assessment (death)	Low risk	Blinding of outcome assessors was not specified, but this was unlikely to introduce bias

O'Toole 1969 (*Continued*)

		for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Low risk	Neurological deficit was not reported on in this trial.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported in 23/23 participants.
Selective reporting (reporting bias)	Unclear risk	The protocol was unavailable and outcomes not clearly specified in the methods

Prasad 2006

Methods	Double-blind, randomized, concurrent placebo-controlled parallel group trial Length of follow-up: 18 months. A 10-year follow-up was planned, but not completed
Participants	Setting: All India Institute of Medical Sciences, New Delhi, India - tertiary referral centre Number of participants: 87 participants; 39 females, 48 males; 41 received dexamethasone, 46 received placebo Inclusion criteria: clinically diagnosed tuberculous meningitis based on meeting these 3 criteria 1. Gradual onset of any 2 of fever, progressive headache, or impaired consciousness with at least 1 symptom of 3 weeks duration. 2. At least 1 sign of meningeal irritation for example, neck stiffness, Kernig's sign, Brudzinski's sign (except in deeply comatose cases). 3. CSF profile characteristic of tuberculous meningitis (containing more than 0.02 × 10^9 cells per litre with predominant lymphocytes , protein more than 1 g/Pl, sugar less than two-thirds of simultaneous blood sugar). Exclusion criteria 1. Alternative diagnosis (including non-tubercular infection, malignancy) made on CSF testing or imaging. 2. Treatment with steroids regularly for more than 10 days used during the current illness. 3. Liver disease or gout. 4. History of gastric or duodenal ulcer, gastrointestinal haemorrhage, malignant hypertension. 5. Pregnant women. HIV status: not specified.
Interventions	1. ATT plus dexamethasone 0.15 mg per kg body weight (up to a maximum of 4 mg) every 6 hours for 3 weeks then tapered gradually. 2. ATT plus placebo (0.9% saline). ATT: oral (through nasogastric tube in unconscious participants) administration of isoniazid 10 mg/kg up to 300 mg, rifampicin 15 mg/kg up to 450 mg, and pyrazinamide 30 mg/kg for participants less than 30 kg and 1500 mg for participants over 30 kg daily, plus pyridoxine 50 mg daily. Total duration was 9 months

Prasad 2006 (*Continued*)

Outcomes	Outcomes identified in trial protocol 1. Treatment success, defined as resolution of meningitic symptoms and achievement of good neurologic function and stability of this state for 3 consecutive months. 2. All-cause death in the first 3 months. 3. Secondary treatment failure. 4. Adverse events related to ATT or dexamethasone, for example deranged liver function tests, hypertension, hyperglycaemia, secondary infection, rash, gastrointestinal bleeding. Outcomes reported in results 1. Death. 2. Non-disabling neurological deficit. 3. Disabling neurological deficit. 4. Bad outcome (death plus disabling neurological deficit). 5. Any deficit (non-disabling neurological deficit plus disabling neurological deficit.
Notes	Date: recruitment started February 1996. Trialists: Department of Neurology, All India Institute of Medical Sciences, New Delhi, India We based this trial description and our 'Risk of bias' assessment on the trial protocol and unpublished outcome data, including baseline characteristics of participants. As the final report was unavailable, we could not assess variations between the protocol and the trial itself There were 6 losses to follow-up at 18 months follow-up, 3 in each group Number of participants that were CSF culture positive for *M. tuberculosis* was not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Eligible consenting subjects will be randomised using block randomisation method. A varying block size of 4 and 6 will be used to avoid possible bias in selection of subjects if preceding ones had noticeable adverse effects. Patients will be randomised to either group in 1:1 ratio by statistician in the biostatistics department."
Allocation concealment (selection bias)	Low risk	"Each patient will be assigned a unique identification number which remained with him throughout the study and had a drug code incorporated into it. All the care givers, outcome evaluators and patients will be masked to treatment allocation. Vials containing indistinguishable solutions of either dexamethasone or placebo (0.9% NaCl) will be prepared, labelled and distributed by the pharmacist at AIIMS.

Prasad 2006 (*Continued*)

		Vials will be boxed in sets of thirty (more than one patient's requirement) and each vial will have the same code number as the box and were identically labelled as containing 5mg dexamethasone sodium phosphate per ml. Coding will be done by assigning a random set of numbers to the active drug and a different set to the placebo. "
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"each vial will have the same code number as the box and were identically labelled as containing 5mg dexamethasone sodium phosphate per ml"
Blinding of outcome assessment (death)	Low risk	Blinding of outcome assessors was not specified, but this was unlikely to introduce bias for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Unclear risk	Outcome assessors and methods of assessment were not clearly described in the protocol
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial profile was not reported, including number of participants eligible, and number of participants excluded. Reasons for losses to follow-up were not described
Selective reporting (reporting bias)	High risk	Outcome measures are re-defined in the reported results. Adverse events and secondary treatment failure were not reported

Schoeman 1997

Methods	Randomized parallel group 2-arm study with allocation ratio 1:1 Length of follow-up: 6 months.
Participants	Setting: Tygerberg Hospital, Tygerberg, South Africa. Number of participants: 141 randomized (gender balance not specified); 70 received prednisolone and 71 received no steroid Inclusion criteria: children (age limit not specified); diagnosis of tuberculous meningitis based on history and "typical CSF changes" with at least 2 of the following: strongly positive (> 15 mm) Mantoux test, chest x-ray suggesting TB or CT head showing basal enhancement and acute hydrocephalus. Only MRC Stage II and III included HIV status: not reported.
Interventions	1. ATT plus 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).

	2. ATT alone. ATT: isoniazid (20 mg/kg/day), rifampicin (20 mg/kg/day), ethionamide (20 mg/kg/day), and pyrazinamide (40 mg/kg/day) for 6 months
Outcomes	1. Deaths at 6 months. 2. Disability (mild and severe) at 6 months. 3. Serious side effects. 4. Baseline and pulse pressure of lumbar CSF. 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 subarachnoid spaces.
Notes	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 The decision to double the prednisolone dose 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 23/141 CSF culture positive for *M. tuberculosis.*

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"patients whose parents gave informed written consent were randomly allocated to a steroid or nonsteroid treatment group"
Allocation concealment (selection bias)	Unclear risk	Insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No blinding, but the impact on mortality is unclear.
Blinding of outcome assessment (death)	Low risk	Blinding of outcome assessors not specified, but unlikely to introduce bias for all cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Low risk	Blinding of assessors. "All these individuals were blinded to the treatment status of the patients at admission."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Three participants in the steroid group and 4 participants in the nonsteroid group were not accounted for in the results section.

Schoeman 1997 (*Continued*)

		Losses to follow-up were not reported, so the impact on results is unclear
Selective reporting (reporting bias)	Low risk	The protocol was unavailable, but all pre-specified outcomes stated in the methods were reported

Thwaites 2004

Methods	Randomized parallel group 2-arm study with allocation ratio 1:1 Length of follow-up: 9 months (initial report), followed by a 5-year follow-up trial
Participants	Setting: Pham Ngoc Thach Hospital for Tuberculosis and Lung Disease and the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam - two tertiary referral centres Number of participants: 545 randomized, 331 males, 214 females; 274 received dexamethasone, 271 received placebo Inclusion criteria: aged over 14 years, clinical meningitis (defined as combination of nuchal rigidity and CSF abnormalities). Tuberculous meningitis defined as "definite" if acid-fast bacilli were seen in CSF, "probable" if at least 1 of the following present: suspected active pulmonary TB on chest radiography, acid-fast bacilli in any specimen other than CSF, clinical evidence of extrapulmonary TB, and "possible" if at least 4 of the following were present: history of TB, predominance of lymphocytes in CSF, duration of illness more than 5 days, ratio of CSF to plasma glucose less than 0.5, altered consciousness, yellow CSF, focal neurological signs Exclusion criteria: contraindication to corticosteroids; received more than 1 dose of any corticosteroid, or more than 30 days of ATT immediately before the trial HIV status: 98/545 HIV-positive, 44/274 (16.1%) in dexamethasone group, 54/271 (19.9%) in placebo group. Three participants in the dexamethasone group, and eight participants in the placebo group were not tested for HIV
Interventions	1. ATT plus dexamethasone, dose stratified by disease severity*. 2. ATT plus placebo. ATT: For previously untreated participants: 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 TB *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. 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)
Outcomes	Assessed at 9 months post-randomization. 1. Death or severe disability. 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. 3. Coma clearance time. 4. Fever clearance time. 5. Time to discharge. 6. Time to relapse. 7. Presence of focal neurological deficit (9 months post-randomization). Assessed during 5-year follow-up study (9 months to 5 years post-randomization) 1. Death. 2. Disability status. 3. TB relapse.
Notes	Date: April 2001 to March 2003 (randomization period). Trialists: Oxford University Clinical Research Unit at the Hospital for Tropical Diseases, Ho Chi Minh City, Vietnam, 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 In this trial, 187/545 participants were acid-fast stain/culture positive for *M. tuberculosis* in CSF. Participants were reclassified to "definite" tuberculous meningitis if participant CSF was culture positive for *M. tuberculosis*, or to "not TBM" if an alternative diagnosis was made.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated sequence of random numbers was used to allocate treatment in blocks of 30."
Allocation concealment (selection bias)	Low risk	"Numbered individual treatment packs containing the study drug were prepared for the duration of treatment and were distributed for sequential use once a patient fulfilled the entry criteria. Parenteral placebo and dexamethasone were identical in appearance, as were oral placebo and dexamethasone."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up." In five-year follow-up study: no blinding.

Thwaites 2004 (*Continued*)

Blinding of outcome assessment (death)	Low risk	"All participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up." In five-year follow-up study: no blinding, unlikely to introduce risk of bias for all-cause mortality
Blinding of outcome assessment (disabling neurological deficit at the end of follow-up)	Low risk	"All participants, enrolling physicians, and investigators remained blinded to the treatment allocation until the last patient completed follow-up." In five-year follow-up study: no blinding, risk of bias was unclear for neurological disability
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up (initial study): 5/274 in dexamethasone arm and 5/271 in placebo arm Lost to follow-up (5-year follow-up study): 18/274 in dexamethasone arm and 22/271 in placebo arm
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported as per protocol.

Abbreviations: CT: computerized tomography; HIV: human immunodeficiency virus; MRC: Medical Research Council; *M. tuberculosis*: *Mycobacterium tuberculosis* complex; CSF: cerebrospinal fluid; ATT: antituberculous treatment; TBM: tuberculous meningitis; TB: tuberculosis.

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

Study	Reason for exclusion
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	Participants 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)

(*Continued*)

Heemskerk 2016	RCT comparing standard ATT regimen with an intensified ATT regimen, all participants received dexamethasone
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	Allocation was not truly randomized: the first half of the study was an alternate participant design, whereas in the last half, participants were randomized by using random numbers
Marras 2005	Letter to the editor with no original data.
Quagliarello 2004	Editorial.
Seligman 2005	Letter to the editor with no original data.
Shah 2014	RCT comparing three different doses of prednisolone; no placebo arm
Vagenakis 2005	Letter to the editor with no original data.
Voljavec 1960	Comparison cohort with historical controls.
Wasz-Höckert 1963	Control trial using historical controls.
Weiss 1965	Retrospective case series of 102 cases.

DATA AND ANALYSES

Comparison 1. Any corticosteroid versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Follow-up at 2 to 24 months	9	1337	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.65, 0.87]
1.2 Follow-up at 2 years	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.67, 1.01]
1.3 Follow-up at 5 years	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.78, 1.12]
2 Disabling neurological deficit	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Follow-up 2 to 24 months	8	1314	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.20]
2.2 Follow-up at 5 years	1	244	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.46, 1.58]
3 Death or disabling neurological deficit	8	1314	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.72, 0.89]
4 Adverse events	4	2620	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.67, 1.17]
4.1 Hyperglycaemia/ glycosuria	3	627	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [0.40, 8.36]
4.2 Hepatitis	2	642	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.57, 1.09]
4.3 Gastrointestinal bleeding	4	724	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.61, 3.48]
4.4 Invasive bacterial infection	3	627	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.36, 1.93]

Comparison 2. Any corticosteroid versus control: stratified by severity of illness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	8	1320	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.57, 0.80]
1.1 Stage I (mild)	6	305	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.29, 0.85]
1.2 Stage II (moderately severe)	7	581	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.56, 0.93]
1.3 Stage III (severe)	8	434	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.88]

Comparison 3. Any corticosteroid versus 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 Disabling neurological deficit	1	534	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.79]
2.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.08, 19.07]

2.2 HIV-negative	1	436	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.73, 1.80]
3 Death or disabling residual neurological deficit	1	545	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
3.1 HIV-positive	1	98	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.20]
3.2 HIV-negative	1	447	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]

Comparison 4. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Worst case scenario analysis	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Worst case: death	6	911	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.96]
1.2 Available case: death	6	882	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.59, 0.86]

ADDITIONAL TABLES

Table 1. Summary of characteristics of included trials

Trial ID	Country	Year	Setting	Age	TB meningitis MRC Grade[a]	HIV status reported	TB treatment regimen[b]	Steroid	Route	Starting dose	Duration
O'Toole 1969	India	1966 to 1967	Tertiary	All	II and III	No	HS (duration not specified)	Dexamethasone	IM/IV	Adults: 9 mg/day Children: unclear	4 weeks
Girgis 1991	Egypt	1982 to 1987	Research	All	All	No	24HE1.5S	Dexamethasone	IM	Adults: 12 mg/day Children: 8 mg/day	6 weeks
Kumarvelu 1994	India	1991 to 1992	Tertiary	> 12 years	All	No	12HRZ	Dexamethasone	IV	16 mg/day	4 weeks
Chotmongkol 1996	Thailand	1990 to 1992	Tertiary	> 15 years	All	Yes, HIV-positive participants	2HRZS+4	Prednisolone	Oral	60 mg/day	5 weeks

Table 1. Summary of characteristics of included trials (*Continued*)

						excluded					
Schoeman 1997	South Africa	Unclear	Tertiary	Children	II and III	No	6HRZE	Prednisolone	Oral	2 to 4 mg/kg/day	4 weeks
Lardizabal 1998	Phillipines	1996 to 1997	Tertiary	> 18 years	II and III	No	2HRZE+1	Dexamethasone	IV/oral	16 mg/day	7 weeks
Thwaites 2004	Vietnam	2001 to 2003	Tertiary	> 14 years	All	Yes, HIV participants included	3HRZE (or S) +6HRZ	Dexamethasone	IV	Grade II & III: 0.4 mg/kg/day Grade I: 0.3 mg/kg/day	8 weeks
Prasad 2006	India	1996 onwards	Tertiary	> 16 years	All	No	9RHZ	Dexamethasone	IV	0.6 to 12 mg/day	3 weeks then tapered
Malhotra 2009	India	2006 to 2007	Tertiary	> 14 years	All	Yes, HIV-positive participants excluded	2HRZE (or S) +7HR	Dexamethasone	IV	0.4 mg/kg/day	8 weeks
								Methylprednisolone	IV	20 mg/kg/day	5 days

[a] TB meningitis MRC Grade: I = mild cases with no altered consciousness or focal neurological signs; II = moderately advanced cases with reduced conscious level but not comatose or with moderate neurological deficits, or both (for example, single cranial nerve palsies, paraparesis, and hemiparesis); III = severe cases including comatose participants, or participants with multiple cranial nerve palsies, hemiplegia or paraplegia, or both.

[b] TB treatment regimen: H = isoniazid; R = rifampicin; Z = pyrazinamide; S = streptomycin; E = Ethambutol; the number = number of months of treatment.

Abbreviations: TB: tuberculosis; IM: intramuscular; IV: intravenous

Table 2. Diagnostic criteria used in the included trials

Trial ID	Number of participants with microbiologically-confirmed tuberculous meningitis[a] (percentage)		Other diagnostic criteria
	Steroid group	Control group	
O'Toole 1969	8/11 (72.7)	6/12 (50)	Not described.
Girgis 1991	75/145 (51.7)	85/135 (63.0)	Characteristic clinical features and CSF findings, plus poor response to broad spectrum antibiotics

Table 2. Diagnostic criteria used in the included trials (*Continued*)

Kumarvelu 1994	Not reported	Not reported	Characteristic clinical, CSF and CT findings. Pyogenic meningitis and malignancy excluded
Chotmongkol 1996	4/29 (13.8)	1/30 (3.3)	Characteristic clinical and CSF findings, negative latex agglutination tests on CSF for bacterial and cryptococcal antigens, negative CSF cytology for malignant cells, negative serology for syphilis and HIV
Schoeman 1997	56/141 (39.7) had culture-positive gastric aspirate 23/141 (16.3) had culture-positive CSF		Characteristic clinical and CSF findings, plus two or more of: positive Mantoux test, chest X-ray suggestive of TB, CT brain with acute hydrocephalus and basal enhancement
Lardizabal 1998	Not reported	Not reported	"Probable TBM" if characteristic clinical and CSF findings, negative latex agglutination test on CSF for cryptococcal antigen plus one or more of meningeal/basilar enhancement on contrast CT brain, positive PPD, history of contact with TB participant, evidence of active pulmonary TB "Confirmed TBM" if CSF microscopy positive for AFBs on Ziehl-Nielsen staining, or culture positive for MTB, or both
Thwaites 2004	98/274 (35.8)	89/271 (32.8)	"Probable" TBM if one or more of chest X-ray suggestive of TB, AFB in non-CSF specimen, clinical evidence of other EPTB "Possible" TBM if 4 of history of TB, lymphocytic CSF, ill for more than 5 days, CSF:plasma glucose ratio less than 0.5, altered consciousness, yellow CSF, focal neurological signs
Prasad 2006	Not reported	Not reported	Characteristic clinical and CSF findings. Pyogenic meningitis and malignancy excluded
Malhotra 2009	4/30 (13.3)	15/61 (24.6)	"Probable" TBM if one or more of chest X-ray suggestive of TB, AFB in non-CSF specimen, clinical evidence of other EPTB "Possible" TBM if 4 of history of TB, lymphocytic CSF, ill for more than 5 days, CSF:plasma glucose ratio less than 0.5, altered consciousness, yellow CSF, focal neurological signs

[a] Referring to positive microbiological test on CSF, including microscopy for acid-fast bacilli, mycobacterial culture and PCR-based methods.

Abbreviations: TBM: tuberculous meningitis; CSF: cerebrospinal fluid; CT: computer tomography; HIV: human immunodeficiency virus; EPTB: extrapulmonary tuberculosis; AFB: MTB.

Table 3. Corticosteroid dose regimens used in the included trials

Trial	Steroid	Dose regimen	
		Adults	**Children**
O'Toole 1969	Dexamethasone IV	9 mg daily for 7 days 6 mg daily for 7days 3 mg daily for 7 days 1.5 mg daily for 7 days	Derived from a standard table based on surface area.
Girgis 1991	Dexamethasone IM	12 mg daily for 21 days, then tapered over 21 days	8 mg daily if weight less than 25 kg, then tapered over 21 days
Kumarvelu 1994	Dexamethasone	16 mg IV daily for 7 days 8 mg PO daily for 21 days	0.6 mg per kg daily for 7 days 0.3 mg per kg daily for 21 days
Chotmongkol 1996	Prednisolone	60 mg daily for 7 days 45 mg daily for 7 days 30 mg daily for 7 days 20 mg daily for 7 days 10 mg daily for 7 days	--
Schoeman 1997	Prednisolone	n/a	2 mg/kg daily (first 16 participants) 4 mg/kg daily (remaining 54 participants)
Lardizabal 1998	Dexamethasone	16 mg daily for 21 days (IV for first 5 days, PO/NG thereafter) 12 mg daily for 5 days 8 mg daily for 5 days 4 mg daily for 5 days	--
Thwaites 2004	Dexamethasone	Grade II and III disease: IV therapy 0.4 mg per kg daily for 7 days 0.3 mg per kg daily for 7 days 0.2 mg per kg daily for 7 days 0.1 mg per kg daily for 7 days Then oral therapy starting at 4 mg per day and decreasing by 1 mg every 7 days Grade I disease: IV therapy 0.3 mg per kg daily for 7 days 0.2 mg per kg daily for 7 days Then oral therapy 0.1 mg per kg daily for 7 days 3 mg per day decreasing by 1 mg every 7 days	--

Table 3. Corticosteroid dose regimens used in the included trials (*Continued*)

Prasad 2006	Dexamethasone	0.15 mg per kg (up to a maximum of 4mg) every 6 hours for 21 days then tapered gradually	--
Malhotra 2009	Dexamethasone IV	0.4 mg per kg daily for 7 days 0.3 mg per kg daily for 7 days 0.2 mg per kg daily for 7 days 0.1 mg per kg daily for 7 days	--
	Methylprednisolone IV	1 g per day for 5 days (if weight over 50 kg)	20 mg/kg (if weight under 50 kg)

Abbreviations: IV: intravenous; IM: intramuscular; n/a: not applicable.

Table 4. Disabling/non-disabling terms used in this review: mapped onto terms in primary trials

Trial	"Disabling" as defined in this Cochrane Review	"Non-disabling" as defined in this Cochrane Review
Girgis 1991	Permanent residual neurological sequelae, including hydrocephalus, hemiparesis and fundus abnormalities	Not described.
Kumarvelu 1994	Major sequelae: persistent vegetative state, blind, symptomatic hydrocephalus, moderate-severe intellectual impairment, severe functional disability (totally dependent)	Minor sequelae: mild intellectual impairment, mild to moderate functional disability (activities of daily living with no/minimal assistance) or no sequelae
Chotmongkol 1996	Persisting neurological abnormalities, including decreased vision, spastic paraparesis and hemiparesis	Not described.
Schoeman 1997	Severe disability: "One or more of the following present: IQ (DQ) less than 75, quadriparesis, and blindness or deafness"	Healthy: "IQ (DQ) greater than 90; no motor or sensory deficit" Mild disability: "One or more of the following present: IQ (DQ) 75 to 90, hemiparesis, and decreased vision or hearing"
Lardizabal 1998	Functional Independence Measure: Score 18 to 36: severely disabled, requiring maximal to total assistance. The subject can carry out less than 25% of the activities for self-care, sphincter control, mobility, locomotion, communication and cognition Score 37 to 54: moderate to severe disability, requiring moderate to maximal assistance. The subject can carry out more than 25 to 50 % of the activities for self-care, sphincter control, mobility, locomotion, communication and cognition	Functional Independence Measure: Score 55 to 90: minimal to moderate disability, requiring only minimal assistance. The subject can carry out more than 50% of the activities of self-care, sphincter control, mobility, locomotion, communication and cognition Score 91-126: minimal disability to functionally independent. The subject requires no assistance in self-care, sphincter control, mobility, Iocomotion, communication, cognition

Table 4. Disabling/non-disabling terms used in this review: mapped onto terms in primary trials (*Continued*)

Thwaites 2004	Severe disability: "Severe disability: assessed on Rankin scale (assessor reported outcome) AND "simple questions" (patient reported outcome) Rankin scale - "3 indicated symptoms that restricted lifestyle and prevented independent living; 4 indicated symptoms that prevented independent living, although constant care and attention were not required; and 5 indicated total dependence on others, requiring help day and night" Scores of 3, 4 or 5 indicated severe disability. "simple questions" - 2 simple questions on recovery (question 1: do you feel that you have made a complete recovery?) and dependency (question 2: do you require help from another person for everyday activities?) "yes" to either indicates severe disability	Good outcome: Rankin score 0 indicating no symptoms. 'No' to all simple questions Intermediate outcome: Rankin score 1 or 2. "1 indicated minor symptoms not interfering with lifestyle; 2 indicated symptoms that might restrict lifestyle, but patients could look after themselves" 'No' to simple questions, but 'yes' to follow-up question asking about "any other problems"
Prasad 2006	"Bad outcome: If the patient has neither recovered nor is independent in activities of daily living"	"Functionally independent: If the patient is independent in activities of daily living. He may or may not have got minimal residual neurological deficit"
Malhotra 2009	Severe disability: Rankin score of 3, 4 or 5. "A subject with moderate disability (requiring some help, but able to walk without assistance) is scored 3, one with moderately severe disability (unable to walk without assistance and unable to attend to own bodily needs without assistance) is scored 4, while a patient who is bedridden, incontinent and requiring constant nursing care and attention is scored 5"	Good outcome: Rankin score 0. "A score of 0 indicates that there are no symptoms at all" Intermediate outcome: Rankin score of 1 to 2. "A score of 1 indicates no significant disability despite the presence of symptoms (with the subject able to carry out all their usual duties and activities) and a score of 2 indicates slight disability (with the subject unable to carry out all their previous activities, but able to look after their own affairs without assistance)"

Abbreviations: IQ: intelligence quotient; DQ: development quotient

Table 5. Adverse events

Trial	Severity	Event	Corticosteroid n out of total in group	Control n out of total in group
O'Toole 1969[a]	-	Gastrointestinal bleeding	5	5
		Glycosuria	1	0
		Infections	2	5
		Hypothermia	5	1

Table 5. Adverse events (*Continued*)

Schoeman 1997[b]	-	"Serious side effects"	0	0
Thwaites 2004[c]	Severe	Hepatitis (severe)	0	8
		Gastrointestinal bleeding (severe)	2	3
		Bacterial sepsis (severe)	3	4
		Hyperglycaemia (severe)	0	0
	Other	Subclinical hepatitis	0	0
		Septic shock	3	0
		Brain herniation syndrome	1	4
		Decrease in visual acuity	6	8
		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
Malhotra 2009[d]	-	Hepatitis	12	8
		Anti-epileptic toxicity	4	3
		Gastrointestinal bleeding	6	1
		Paradoxical tuberculoma	3	5

Abbreviations; n: number of participants with event.

[a] O'Toole 1969: n/11 participants in corticosteroid arm; n/12 participants in control arm.
[b] Schoeman 1997: n/67 participants in corticosteroid arm; n/67 participants in control arm.
[c] Thwaites 2004: n/274 participants in corticosteroid arm; n/271 participants in control arm.
[d] Malhotra 2009: n/61 participants in corticosteroid arm; n/30 participants in control arm.

WHAT'S NEW

Date	Event	Description
13 April 2016	New citation required but conclusions have not changed	We included nine trials in total, and the review's conclusions remain unchanged
13 April 2016	New search has been performed	Hannah Ryan joined the review author team. We included two new trials (one published and one unpublished), added published follow-up data from Thwaites 2004, and constructed 'Risk of bias' tables and a 'Summary of findings' table. We presented outcomes for disabling neurological deficit separately following feedback, reviewed all included studies, and re-extracted data. We rewrote the Results and Discussion sections, and revised the plain language summary.

HISTORY

Date	Event	Description
14 November 2007	New citation required but conclusions have not changed	2008, Issue 1: we added one new trial, Thwaites 2004. We updated the review text and title. MB Singh joined the author team, and J Volmink and GR Menon stepped down from the author team

CONTRIBUTIONS OF AUTHORS

Kameshwar Prasad (KP) developed the first published version of this Cochrane Review (Prasad 2000). During the 2008 update, KP 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 RevMan (RevMan 2014). For the 2015 update, Hannah Ryan (HR) re-extracted and analysed the data, revised the 'Risk of bias' assessment, constructed a 'Summary of findings' table with GRADE assessment, and revised the Background, Results, and Discussion sections.

DECLARATIONS OF INTEREST

KP is a co-author of two of the included trials (Kumarvelu 1994; Prasad 2006). HR independently conducted 'Risk of bias' assessments and data entry and interpretation with the CIDG Co-ordinating Editor, Paul Garner.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans