Corticosteroids for acute bacterial meningitis (Review)

Brouwer MC, McIntyre P, Prasad K, van de Beek D

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 6

http://www.thecochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Corticosteroids for acute bacterial meningitis

Matthijs C Brouwer[1], Peter McIntyre[2], Kameshwar Prasad[3], Diederik van de Beek[1]

[1]Department of Neurology, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center University of Amsterdam, Amsterdam, Netherlands. [2]National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases, Children's Hospital at Westmead and University of Sydney, Sydney, Australia. [3]Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Contact address: Diederik van de Beek, Department of Neurology, Center for Infection and Immunity Amsterdam (CINIMA), Academic Medical Center University of Amsterdam, P.O. Box 22660, Amsterdam, 1100 DE, Netherlands. D.vandeBeek@amc.uva.nl.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 6, 2013.
Review content assessed as up-to-date: 18 January 2013.

Citation: Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No.: CD004405. DOI: 10.1002/14651858.CD004405.pub4.

ABSTRACT

Background

In experimental studies, the outcome of bacterial meningitis has been related to the severity of inflammation in the subarachnoid space. Corticosteroids reduce this inflammatory response.

Objectives

To examine the effect of adjuvant corticosteroid therapy versus placebo on mortality, hearing loss and neurological sequelae in people of all ages with acute bacterial meningitis.

Search methods

We searched CENTRAL 2012, Issue 12, MEDLINE (1966 to January week 2, 2013), EMBASE (1974 to January 2013), Web of Science (2010 to January 2013), CINAHL (2010 to January 2013) and LILACS (2010 to January 2013).

Selection criteria

Randomised controlled trials (RCTs) of corticosteroids for acute bacterial meningitis.

Data collection and analysis

We scored RCTs for methodological quality. We collected outcomes and adverse effects. We performed subgroup analyses for children and adults, causative organisms, low-income versus high-income countries, time of steroid administration and study quality.

Main results

Twenty-five studies involving 4121 participants were included. Corticosteroids were associated with a non-significant reduction in mortality (17.8% versus 19.9%; risk ratio (RR) 0.90, 95% confidence interval (CI) 0.80 to 1.01, P = 0.07). A similar non-significant reduction in mortality was observed in adults receiving corticosteroids (RR 0.74, 95% CI 0.53 to 1.05, P = 0.09). Corticosteroids were associated with lower rates of severe hearing loss (RR 0.67, 95% CI 0.51 to 0.88), any hearing loss (RR 0.74, 95% CI 0.63 to 0.87) and neurological sequelae (RR 0.83, 95% CI 0.69 to 1.00).

Subgroup analyses for causative organisms showed that corticosteroids reduced mortality in *Streptococcus pneumoniae* (*S. pneumoniae*) meningitis (RR 0.84, 95% CI 0.72 to 0.98), but not in *Haemophilus influenzae* (*H. influenzae*) or*Neisseria meningitidis* (*N. meningitidis*) meningitis. Corticosteroids reduced severe hearing loss in children with *H. influenzae* meningitis (RR 0.34, 95% CI 0.20 to 0.59) but not in children with meningitis due to non-*Haemophilus* species.

In high-income countries, corticosteroids reduced severe hearing loss (RR 0.51, 95% CI 0.35 to 0.73), any hearing loss (RR 0.58, 95% CI 0.45 to 0.73) and short-term neurological sequelae (RR 0.64, 95% CI 0.48 to 0.85). There was no beneficial effect of corticosteroid therapy in low-income countries.

Subgroup analysis for study quality showed no effect of corticosteroids on severe hearing loss in high-quality studies.

Corticosteroid treatment was associated with an increase in recurrent fever (RR 1.27, 95% CI 1.09 to 1.47), but not with other adverse events.

Authors' conclusions

Corticosteroids significantly reduced hearing loss and neurological sequelae, but did not reduce overall mortality. Data support the use of corticosteroids in patients with bacterial meningitis in high-income countries. We found no beneficial effect in low-income countries.

PLAIN LANGUAGE SUMMARY

Corticosteroids for bacterial meningitis

Acute bacterial meningitis is an infection of the meninges (the system of membranes which envelops the brain and spinal cord) that often causes hearing loss. Bacterial meningitis is fatal in 5% to 40% of children and 20% to 50% of adults despite treatment with adequate antibiotics. It is caused by bacteria that usually spread from an ear or respiratory infection and is treated with antibiotics. Corticosteroids are drugs that can reduce the inflammation caused by infection. This inflammation has been shown to aggravate damage to the nervous system in experimental meningitis studies in animals. Research on the use of corticosteroids in addition to antibiotics has had conflicting results. This review of 25 trials, including 4121 participants, found that the corticosteroid dexamethasone leads to a reduction in hearing loss and other neurological sequelae in participants in high-income countries who have bacterial meningitis, but is not effective in low-income countries. An analysis for different bacteria causing meningitis showed that patients with meningitis due to *Streptococcus pneumoniae* (*S. pneumoniae*) treated with corticosteroids had a lower death rate, while no effect on mortality was seen in patients with *Haemophilus influenzae* (*H. influenzae*) and *Neisseria meningitidis* (*N. meningitidis*) meningitis. Corticosteroids decreased the rate of hearing loss in children with meningitis due to *H. influenzae*, but not in children with meningitis due to other bacteria. Dexamethasone increased the rate of recurrent fever but was not associated with other adverse events.

BACKGROUND

Description of the condition

Bacterial meningitis is a severe infection of the meninges (the membrane lining of the brain and spinal cord) that is associated with high mortality and morbidity rates despite optimal antibiotic therapy and advances in critical care (Baraff 1993; Bohr 1983; Brouwer 2010c; van de Beek 2002; van de Beek 2004b; van de Beek 2006b). Late sequelae such as cranial nerve impairment, especially hearing loss, occur in 5% to 40% of patients (Baraff 1993; Bohr 1983; Brouwer 2010b; Heckenberg 2012a; van de Beek 2002; van de Beek 2004b; van de Beek 2006b).

Description of the intervention

Intravenously or orally administered corticosteroids, such as prednisolone, hydrocortisone and dexamethasone, are given before, with or after antibiotic treatment for suspected or proven bacterial meningitis.

How the intervention might work

In experimental animal studies, the outcome of meningitis worsens with increasing severity of the inflammatory process in the subarachnoidal space (Scheld 1980; Tauber 1985). Treatment with corticosteroids was shown to result in a reduction of the inflammatory response in the cerebrospinal fluid (CSF), reversal of brain oedema and improved outcome (Scheld 1980; Tauber 1985). These pathophysiological insights prompted investigators to evaluate corticosteroids as an adjuvant therapy in acute bacterial meningitis.

Why it is important to do this review

In the 1960s two randomised controlled trials (RCTs) evaluated the effect of corticosteroids in patients with bacterial meningitis (Bennett 1963; DeLemos 1969). New randomised clinical trials were performed in the late 1980s and 1990s (Lebel 1988a; Lebel 1988b; Lebel 1989; Odio 1991), with conflicting results. Two meta-analyses of RCTs were published showing a reduction in bilateral hearing loss in dexamethasone-treated children with *Haemophilus influenzae* (*H. influenzae*) meningitis (Geiman 1992; Havens 1989).

In the early 1990s the epidemiology of bacterial meningitis changed due to introduction of the *H. influenzae* type B conjugate vaccine that resulted in near elimination of this bacterium as cause of meningitis in high-income countries (Peltola 2000). New trials were performed in children with bacterial meningitis, most commonly caused by *Streptococcus pneumoniae* (*S. pneumoniae*). In 1997, a new meta-analysis was published showing adjunctive corticosteroid therapy to prevent hearing loss in patients with *H. influenzae* meningitis (McIntyre 1997). This meta-analysis also showed a beneficial trend of dexamethasone on neurological sequelae and hearing loss in patients with meningitis due to *S. pneumoniae.*

In the 2000s, five large randomised clinical trials have been performed. Two trials in children were performed in Malawi and South America and three trials in adults were performed in Europe, Vietnam and Malawi (de Gans 2002; Molyneux 2002; Nguyen 2007; Peltola 2007; Scarborough 2007). The European trial showed a beneficial effect in all patients, with the most apparent effect on mortality and unfavourable outcomes in pneumococcal meningitis (de Gans 2002). The Vietnamese trial showed a beneficial effect only in patients with proven bacterial meningitis (Nguyen 2007). The other trials did not show a beneficial effect. In 2010 an individual patient data meta-analysis was performed with patients from these five trials to determine in which subgroups of patients adjunctive dexamethasone was effective (van de Beek 2010). In this meta-analysis no benefit of adjunctive dexamethasone was found in any of the pre-specified subgroups. However, a post hoc analysis did show a reduction in any hearing loss in surviving patients treated with dexamethasone.

The results of many trials have been inconclusive and most studies have been relatively small. Trials have varied greatly in study population, study design, timing and dosage of corticosteroids. Furthermore, mortality was substantially higher in studies in low-income countries, primarily related to access to care and co-morbidities. This Cochrane systematic review and meta-analysis facilitates an interpretation of these varying results and might identify subgroups that benefit from adjunctive corticosteroid therapy. See Appendix 1 for a glossary of terms.

OBJECTIVES

To examine the effect of adjuvant corticosteroid therapy versus placebo on mortality, hearing loss and neurological sequelae in people of all ages with acute bacterial meningitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Participants of any age and in any clinical condition.

Types of interventions

Participants with community-acquired bacterial meningitis treated with antibacterial agents and randomised to adjuvant corticosteroid therapy of any type.

Types of outcome measures

At least case-fatality rate or hearing loss had to be recorded for studies to be included.

Primary outcomes

1. Mortality
2. Hearing loss
3. Neurological sequelae

Hearing loss was defined as severe when there was bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. We analysed any hearing loss and severe hearing loss separately. Neurological sequelae were defined as focal neurological deficits other than hearing loss, epilepsy (not present before meningitis onset), severe ataxia and severe memory or concentration disturbance. We did not count children with isolated speech or language disturbances as having non-hearing deficits if these problems were associated with severe hearing loss. We analysed both short- and long-term neurological sequelae, other than hearing loss. Short-term neurological sequelae were defined as sequelae assessed between discharge and six weeks after hospital discharge. Long-term neurological sequelae were defined as sequelae assessed between six weeks and 12 months after discharge. Whenever possible, we extracted data for both these outcomes.

Secondary outcomes

1. Adverse events

Adverse events were defined as clinically evident gastrointestinal tract bleeding, reactive arthritis, pericarditis, herpes zoster or herpes simplex virus infection, fungal infection, recurrent fever (defined as a temperature of 38 °C or above occurring after at least one afebrile day during the course of hospitalisation) and persistent fever (defined as fever continuing longer than five consecutive days after initiation of appropriate antibiotic therapy).

Search methods for identification of studies

Electronic searches

For this 2013 update we searched, as in previous years, the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 12, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 18 January 2013), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (January 2010 to January Week 2, 2013), EMBASE (February 2010 to January 2013) and Web of Science (2010 to January 2013). In addition, in order to cover more of the published literature, we broadened our search to include CINAHL (2010 to January 2013) and LILACS (2010 to January 2013). Details of earlier searches are in Appendix 2.

We used the following search strategy to search CENTRAL and MEDLINE. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search EMBASE (Appendix 3), Web of Science (Appendix 4), CINAHL (Appendix 5) and LILACS (Appendix 6). We did not apply any language or publication restrictions.

MEDLINE (Ovid)

1 exp Meningitis/
2 meningit*.tw.
3 exp Neisseria meningitidis/
4 exp Haemophilus influenzae/
5 Streptococcus pneumoniae/
6 (“N. meningitidis” or “H. influenzae” or “S. pneumoniae”).tw.
7 (“neisseria meningitidis” or “haemophilus influenzae” or “streptococcus pneumoniae”).tw.
8 or/1-7
9 exp Adrenal Cortex Hormones/
10 corticosteroid*.tw,nm.
11 glucocorticoid*.tw,nm.
12 exp Steroids/
13 steroid*.tw,nm.
14 exp Dexamethasone/
15 (dexamethasone* or hydrocortisone* or prednisolone* or methylprednisolone*).tw,nm.
16 or/9-15
17 8 and 16

Searching other resources

Besides the electronic search we identified relevant trials by searching references listed in published studies, handsearching congress abstracts, personal communication with researchers and experts in the field and from literature lists of pharmaceutical companies.

Data collection and analysis

Selection of studies

Two review authors (MD, DvdB) independently screened the search results and retrieved the full articles of all potentially relevant trials. We scrutinised each trial report to ensure that multiple publications from the same trial were included only once. We resolved disagreements through discussion and listed the excluded studies and the reasons for their exclusion.

Data extraction and management

Two review authors (MB, DvdB) independently extracted data according to a pre-specified protocol. Data extracted included study design, inclusion criteria, patients’ characteristics, country in which the study was performed, intervention characteristics and outcome measures. Scored intervention characteristics were corticosteroid type, daily corticosteroid dose, duration of steroid therapy and timing of corticosteroid therapy initiation (before/with the first dose of antibiotic therapy, or after first dose of antibiotic therapy). We resolved disagreements through discussion and contacted the corresponding publication author in the case of unclear or missing data.

For dichotomous outcomes, we recorded the number of participants experiencing the event and the number randomised in each treatment group. To allow an available-case analysis, we recorded the numbers of participants analysed in each treatment group and used them in the analyses. However, the number of participants randomised into the treatment arms was also recorded and the discrepancy between the figures used to calculate the loss to follow-up. Also, these figures allowed a worst-case scenario analysis to be carried out to investigate the effect of missing data.

Assessment of risk of bias in included studies

For each study we completed a 'Risk of bias' table, scoring for adequacy of sequence generation, allocation concealment, blinding, if incomplete data were addressed, selective reporting and other sources of bias (Higgins 2011). We excluded studies without adequate sequence generation from the meta-analyses.

Measures of treatment effect

All outcome measures were dichotomous. We used risk ratios (RR) with 95% confidence intervals (CI) as measures of treatment effect.

Unit of analysis issues

For studies using multiple treatment groups, we included only groups receiving corticosteroids or placebo in the meta-analysis.

Dealing with missing data

We contacted the corresponding publication author in the case of unclear or missing data. If details were not provided, results used in the analysis were as provided in the publication.
We scored missing data in the outcome measures severe hearing loss and neurological sequelae for each study if reported. We assessed whether missing data were equally distributed between treatment and control groups using the Chi^2 test. These tests were two-tailed and a P value of < 0.05 was considered significant.

Assessment of heterogeneity

We assessed heterogeneity in all analysis with the I^2 statistic with a value of >= 50% taken to indicate statistical heterogeneity.

Assessment of reporting biases

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

Data synthesis

We analysed the data using Review Manager 5.1 (RevMan 2011).
We performed meta-analyses using the Mantel-Haenszel method with a fixed-effect model when heterogeneity was absent. When significant heterogeneity was established we used a random-effects model.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analyses for children and adults, causative organisms, low-income versus high-income countries, time of administration of steroids and quality of studies. Two age groups were defined: patients younger than 16 years and those aged 16 years and older. Three categories of causative organisms were defined: *H. influenzae*,*Neisseria meningitidis* (*N. meningitidis*) and*S. pneumoniae*. We analysed studies in two subsets divided into low-income and high-income countries. Low-income countries had a United Nations Human Development Index of less than 0.7 and high-income countries had an index of 0.7 or higher (UNHDI 2009). Studies were divided into three categories of methodological quality: high, medium and low according to the score in the 'Risk of bias' table. If all questions in the 'Risk of bias' table were answered positively the study was categorised as high quality, three through five as medium and if less than three questions were answered positively as low.
In the subgroup analysis the inverse variance method was used with a fixed-effect model to detect significant heterogeneity between subgroups, using a P value of < 0.05 and I^2 statistic => 50%.

Sensitivity analysis

For trials with missing data, we conducted two analyses: an available-case analysis and a worst-case scenario analysis for trials with missing data. All participants who had dropped out of the corticosteroid group were considered to have an unfavourable outcome whereas those who had dropped out of the control group were considered to have a favourable outcome. We conducted a sensitivity analysis imputing the missing data in this way to determine whether the overall results were sensitive to this assumption.
We performed additional random-effects model analyses for all studies without significant heterogeneity determined by the I^2 statistic (I^2 statistic < 50%) to see if results were valid with this method as well.
Finally we performed the analyses for the primary outcome measures without studies with unclear or unknown sequence generation.

R E S U L T S

Description of studies

Results of the search

We identified 40 potentially eligible trials, of which two were described in one paper (Lebel 1988a; Lebel 1988b). Two papers presented data from one study (Sankar 2007; Singhi 2008).

Included studies

A total of 25 studies were eligible for inclusion in the meta-analysis (Characteristics of included studies). These studies included 4121 patients (2064 dexamethasone, 2057 placebo). Participants over 16 years were included in seven studies (1517 patients: 756 dexamethasone, 761 placebo) (Bhaumik 1998; de Gans 2002; Girgis 1989; Nguyen 2007; Scarborough 2007; Thomas 1999). In two studies, participants older than 12 years were considered adults (Bhaumik 1998; Girgis 1989). The study intervention consisted of dexamethasone in 22 out of 25 studies; dosages ranged from 0.4 to 1.5 mg/kg/d and duration ranged from two to four days. In the other studies hydrocortisone, prednisolone or a combination of both were given and duration ranged from three to 14 days (Bademosi 1979; Bennett 1963; DeLemos 1969).

Study medication was administered before or with the first dose of antibiotics in 13 studies, and after the first dose in eight studies. In four studies the time of administration was not stated.

A sample size calculation was given in eight studies (de Gans 2002; Mathur 2013; Molyneux 2002; Nguyen 2007; Peltola 2007; Qazi 1996; Scarborough 2007; Thomas 1999).

Mortality rates ranged from 0% to 54%. In one study participants who died during the first 18 hours of admission were excluded (Belsey 1969); nevertheless, these participants were included in the meta-analysis. Hearing was assessed by audiometry in seven studies in children and four studies in adults; other studies used brainstem evoked potentials (10) or age-specific behavioural measures (eight). Four studies assessed both short-term and long-term neurological sequelae (Lebel 1988a; Lebel 1988b; Lebel 1989; Wald 1995). Definitions of adverse events were heterogeneous and the number of events were recalculated for each study.

Ethical review by hospital committees was described in 18 (72%) studies. Eighteen (72%) studies described informed consent procedures. There were no disagreements on inclusion or exclusion of studies between the review authors extracting study data. No study authors needed to be contacted to provide additional information for this updated version of the review.

Excluded studies

Sixteen trials were excluded (Characteristics of excluded studies). Three studies did not randomise between treatment and control groups (Marguet 1993; Ozen 2006; Tolaj 2010). Nine trials did not adequately generate a randomisation sequence and in most of these alternate allocation schemes were used (Ayaz 2008; Baldy 1986; Daoud 1999; Gijwani 2002; Gupta 1996; Jensen 1969; Lepper 1959; Passos 1979; Shembesh 1997). One study compared two dexamethasone regimens (Syrogiannopoulos 1994), one was a duplicate study (Singhi 2008) and one study provided insufficient data (communications during scientific meetings only) (Farina 1995).

Risk of bias in included studies

Allocation

The sequence generation for participant allocation was adequate in 20 studies. In five studies the method of sequence generation was unclear or not specified (Bademosi 1979; Belsey 1969; Bennett 1963; Ciana 1995; King 1994) (Figure 1; Figure 2). In five studies the treatment allocation was not concealed (Bademosi 1979; Bhaumik 1998; Ciana 1995; Girgis 1989; Kilpi 1995) and in one study treatment allocation concealment was unclear as participants were paired for placebo or dexamethasone (Belsey 1969). A multicentre study performed in several South American countries compared two treatments in a 2 x 2 design, dexamethasone and glycerol with placebo, in four randomisation arms (glycerol-dexamethasone, glycerol-placebo, dexamethasone-placebo, placebo-placebo). However, some centres did not include participants in the double placebo group, thereby disturbing the allocation concealment (Peltola 2007; van de Beek 2010). Data were extracted as derived from one study, comparing the dexamethasone-placebo versus placebo-placebo groups.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

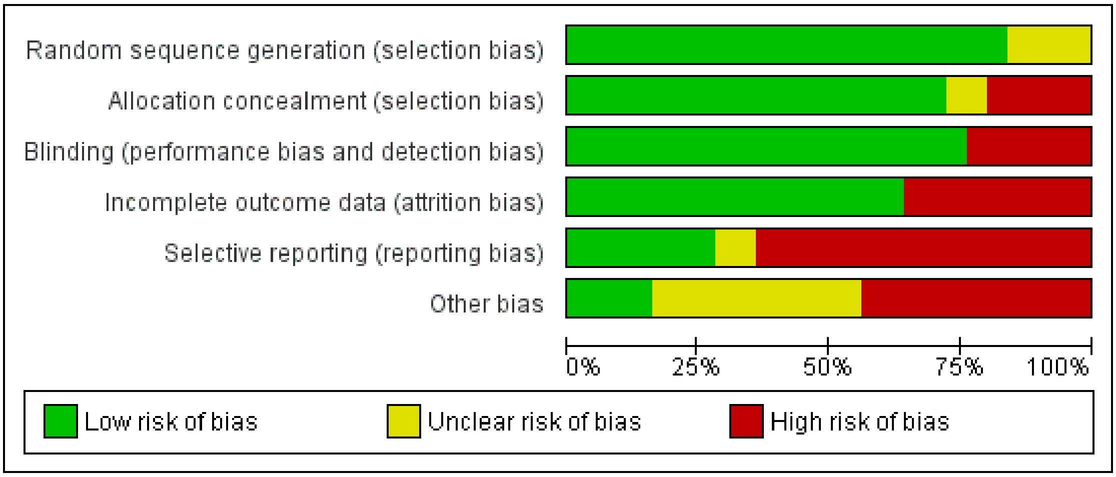
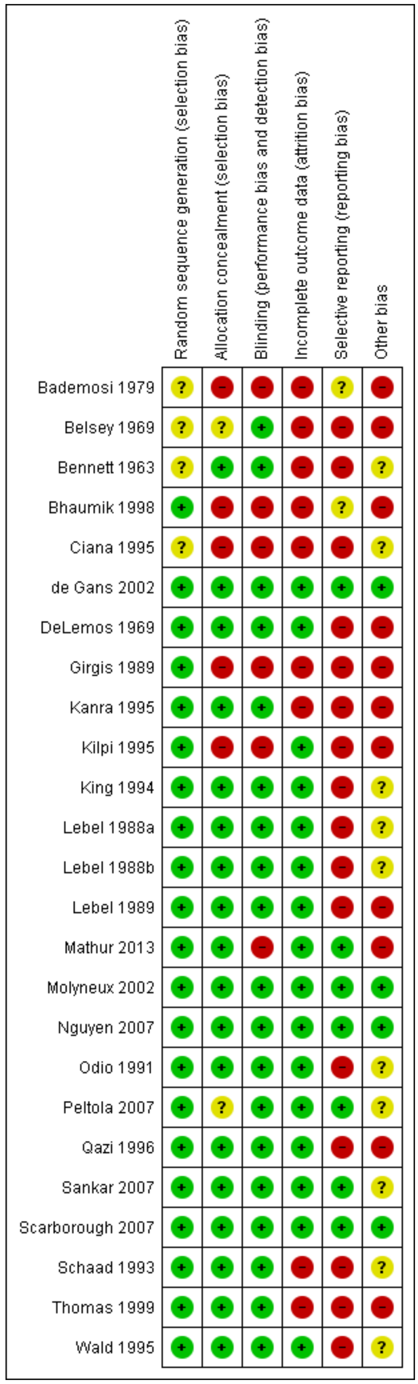


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Blinding

Nineteen studies had a double-blind design and broke the treatment code after follow-up for the last participant was complete. Six studies did not use blinding (Bademosi 1979; Bhaumik 1998; Ciana 1995; Girgis 1989; Kilpi 1995; Mathur 2013).

Incomplete outcome data

Missing data were addressed in 16 studies and were not addressed in eight (Bademosi 1979; Belsey 1969; Bennett 1963; Bhaumik 1998; Girgis 1989; Kanra 1995; Schaad 1993; Thomas 1999). One study reported to have complete data for all included participants (Mathur 2013). Out of 2694 survivors who were included in studies that analysed severe hearing loss, 216 (8.0%) were not tested or had inconclusive test results. Data on any hearing loss were missing in 223 of 3029 (7.4%) surviving participants included in studies that assessed hearing loss. Short-term neurological sequelae were assessed in 1695 of 1850 survivors included in studies that scored short-term sequelae; data on 155 (8.3%) were missing. Data on long-term sequelae were missing in 157 of 1705 participants (9.2%). The number of missing data was equally distributed between treatment and control group (P value for differences in missing data > 0.10 for all analyses with missing data).

Selective reporting

An intention-to-treat (ITT) analysis was performed in six studies (de Gans 2002; Molyneux 2002; Nguyen 2007; Peltola 2007; Sankar 2007; Scarborough 2007), comprising 2147 out of 4041 participants (53%). One study that reported no loss to follow-up or discontinuing treatment was analysed as ITT (Mathur 2013). In the other 18 studies only per-protocol data were available to be ascertained. The final analysis for mortality is equally based upon per-protocol figures (46% of included participants) and ITT figures (56%).

Funnel plots of outcomes (mortality, any hearing loss, short-term neurological sequelae and long-term neurological sequelae and adverse events) did not show obvious asymmetry, except for severe hearing loss (Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6).

Other potential sources of bias

In 12 studies differences in baseline and clinical characteristics between treatment and control groups influenced comparability of groups (Bademosi 1979; Belsey 1969; Bhaumik 1998; DeLemos 1969; Kanra 1995; Kilpi 1995; Lebel 1989; Mathur 2013; Peltola 2007; Sankar 2007; Thomas 1999) indicating either insufficient sample size to equal out the random differences between randomisation arms or a selection bias. Other indications of a selection bias were found in studies with high numbers of comatose participants or low numbers of culture-positive participants (Girgis 1989; Mathur 2013; Qazi 1996; Sankar 2007). Nine studies did not present sufficient participant characteristics to determine whether the participants in each randomisation arm were comparable.

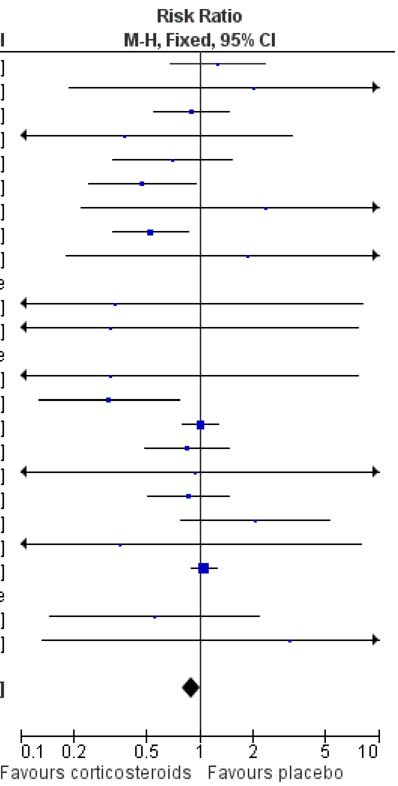
Effects of interventions

A lower overall number of deaths in the corticosteroid-treated group was observed compared to the placebo group (367 of 2064 (17.8%) versus 408 out of 2057 (19.8%), risk ratio (RR) 0.90, 95% confidence interval (CI) 0.80 to 1.01, P = 0.07), although the difference did not reach statistical significance (Bademosi 1979; Belsey 1969; Bennett 1963; Bhaumik 1998; Ciana 1995; de Gans 2002; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Molyneux 2002; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Scarborough 2007; Schaad 1993; Thomas 1999; Wald 1995) (Figure 3).

Figure 3. Forest plot of comparison: 1 All patients, outcome: 1.1 Mortality.

Study or Subgroup	Corticosteroids Events	Corticosteroids Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bademosi 1979	12	24	11	28	2.5%	1.27 [0.69, 2.34]
Belsey 1969	2	43	1	43	0.2%	2.00 [0.19, 21.24]
Bennett 1963	16	38	22	47	4.8%	0.90 [0.56, 1.46]
Bhaumik 1998	1	14	3	16	0.7%	0.38 [0.04, 3.26]
Ciana 1995	8	34	12	36	2.8%	0.71 [0.33, 1.51]
de Gans 2002	11	157	21	144	5.3%	0.48 [0.24, 0.96]
DeLemos 1969	2	54	1	63	0.2%	2.33 [0.22, 25.03]
Girgis 1989	21	225	43	245	10.0%	0.53 [0.33, 0.87]
Kanra 1995	2	29	1	27	0.3%	1.86 [0.18, 19.38]
Kilpi 1995	0	32	0	26		Not estimable
King 1994	0	50	1	51	0.4%	0.34 [0.01, 8.15]
Lebel 1988a	0	51	1	49	0.4%	0.32 [0.01, 7.68]
Lebel 1988b	0	51	0	49		Not estimable
Lebel 1989	0	31	1	30	0.4%	0.32 [0.01, 7.63]
Mathur 2013	5	40	16	40	3.9%	0.31 [0.13, 0.77]
Molyneux 2002	96	305	91	293	22.6%	1.01 [0.80, 1.29]
Nguyen 2007	22	217	26	218	6.3%	0.85 [0.50, 1.45]
Odio 1991	1	52	1	49	0.3%	0.94 [0.06, 14.65]
Peltola 2007	23	166	26	163	6.4%	0.87 [0.52, 1.46]
Qazi 1996	12	48	5	41	1.3%	2.05 [0.79, 5.33]
Sankar 2007	0	12	1	13	0.4%	0.36 [0.02, 8.05]
Scarborough 2007	129	231	120	228	29.4%	1.06 [0.90, 1.26]
Schaad 1993	0	60	0	55		Not estimable
Thomas 1999	3	31	5	29	1.3%	0.56 [0.15, 2.14]
Wald 1995	1	69	0	74	0.1%	3.21 [0.13, 77.60]
Total (95% CI)		**2064**		**2057**	**100.0%**	**0.90 [0.80, 1.01]**
Total events	367		409			

Heterogeneity: Chi² = 26.68, df = 21 (P = 0.18); I² = 21%
Test for overall effect: Z = 1.80 (P = 0.07)



The number of participants with hearing loss was significantly smaller in the corticosteroid-treated group than in the placebo group (any hearing loss: 197 of 1424 (14%) versus 259 of 1361 (19%), RR 0.74, 95% CI 0.63 to 0.87; severe hearing loss: 75 of 1234 (6%) versus 112 of 1203 (9%), RR 0.67, 95% CI 0.51 to 0.88) (Belsey 1969; Bhaumik 1998; de Gans 2002; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Molyneux 2002; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Scarborough 2007; Schaad 1993; Wald 1995) (Figure 4; Figure 5).

Figure 4. Forest plot of comparison: 1 All patients, outcome: 1.3 Any hearing loss.

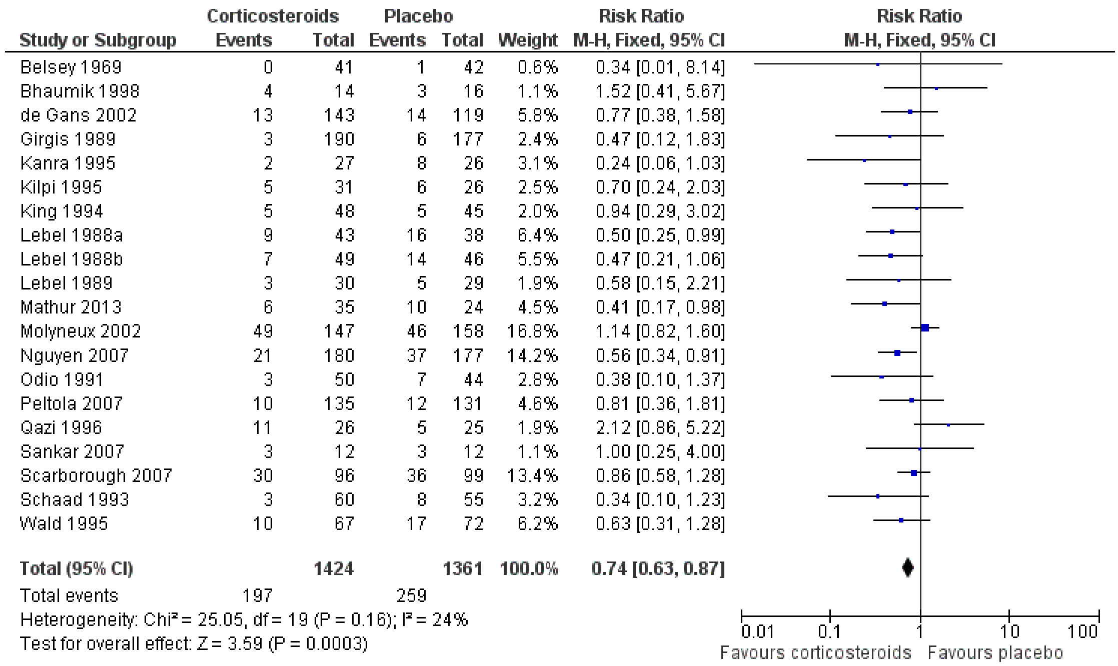
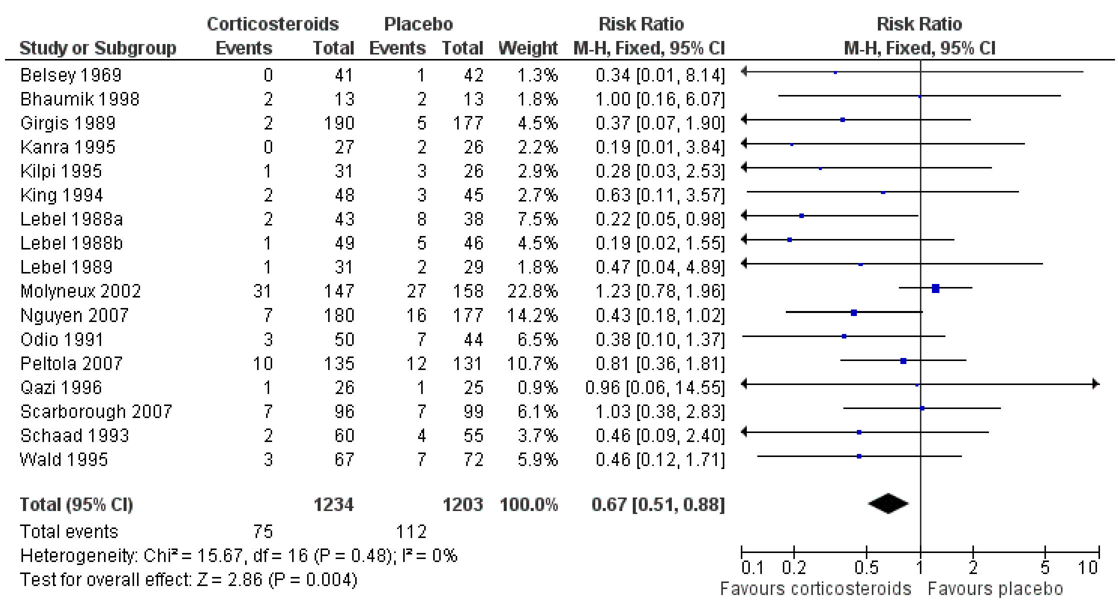


Figure 5. Forest plot of comparison: 1 All patients, outcome: 1.2 Severe hearing loss.

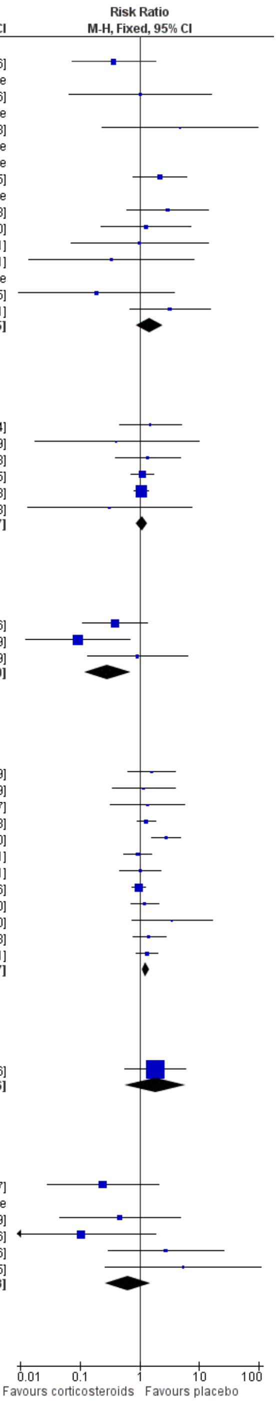


Short-term neurologic sequelae (excluding hearing loss) were assessed in 13 studies including 1756 participants (Bhaumik 1998; Ciana 1995; de Gans 2002; Kanra 1995; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Peltola 2007; Sankar 2007; Scarborough 2007; Thomas 1999; Wald 1995) (Analysis 1.4). Fewer sequelae were observed in the corticosteroid-treated group (161 of 900 (17.9%) versus 185 of 856 (21.6%), RR 0.83, 95% CI 0.69 to 1.00, P = 0.05). Long-term neurological sequelae were assessed in 12 studies including 1652 participants (DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Nguyen 2007; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995) (Analysis 1.5). The occurrence of long-term sequelae was not significantly different between corticosteroid-treated participants and the controls (125 of 836 (15.3%) versus 136 of 816 (16.7%), RR 0.90, 95% CI 0.74 to 1.10).

Adverse events were recorded in 20 studies: 16 evaluated gastrointestinal haemorrhage, 12 recurrent fever, six reactive arthritis, five herpes zoster, three persistent fever and one fungal infections (Belsey 1969; Bennett 1963; Bhaumik 1998; de Gans 2002; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Scarborough 2007; Schaad 1993; Thomas 1999; Wald 1995) (Figure 6). Participants treated with corticosteroids had an increase in recurrent fever (RR 1.27, 95% CI 1.09 to 1.47). The rate of persistent fever was lower in the corticosteroid-treated patients (RR 0.29, 95% CI 0.12 to 0.70). Other complications occurred in similar proportions of the treatment and control groups.

Figure 6. Forest plot of comparison: 1 All patients, outcome: 1.6 Adverse events.

Study or Subgroup	Corticosteroids Events	Corticosteroids Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 Gastrointestinal bleeding						
de Gans 2002	2	157	5	144	22.8%	0.37 [0.07, 1.86]
Kilpi 1995	0	32	0	26		Not estimable
King 1994	1	50	1	51	4.3%	1.02 [0.07, 15.86]
Lebel 1988a	0	51	0	49		Not estimable
Lebel 1988b	2	51	0	49	2.2%	4.81 [0.24, 97.68]
Lebel 1989	0	31	0	29		Not estimable
Mathur 2013	0	40	0	40		Not estimable
Nguyen 2007	11	217	5	218	21.8%	2.21 [0.78, 6.25]
Odio 1991	0	52	0	48		Not estimable
Peltola 2007	6	166	2	163	8.8%	2.95 [0.60, 14.38]
Qazi 1996	3	48	2	41	9.4%	1.28 [0.22, 7.30]
Sankar 2007	1	12	1	12	4.4%	1.00 [0.07, 14.21]
Scarborough 2007	0	233	1	232	6.6%	0.33 [0.01, 8.11]
Schaad 1993	0	60	0	55		Not estimable
Thomas 1999	0	31	2	29	11.3%	0.19 [0.01, 3.75]
Wald 1995	6	69	2	74	8.4%	3.22 [0.67, 15.41]
Subtotal (95% CI)		**1300**		**1260**	**100.0%**	**1.45 [0.86, 2.45]**
Total events	32		21			
Heterogeneity: Chi² = 8.52, df = 9 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
1.6.2 Herpes zoster infection						
Belsey 1969	6	43	4	43	3.8%	1.50 [0.46, 4.94]
Bennett 1963	0	38	1	47	1.3%	0.41 [0.02, 9.79]
de Gans 2002	6	157	4	144	3.9%	1.38 [0.40, 4.78]
Nguyen 2007	33	217	30	218	28.2%	1.11 [0.70, 1.75]
Scarborough 2007	70	233	65	232	61.4%	1.07 [0.81, 1.43]
Thomas 1999	0	31	1	29	1.5%	0.31 [0.01, 7.38]
Subtotal (95% CI)		**719**		**713**	**100.0%**	**1.09 [0.86, 1.37]**
Total events	115		105			
Heterogeneity: Chi² = 1.39, df = 5 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.47)						
1.6.3 Persistent fever						
King 1994	3	50	8	51	38.8%	0.38 [0.11, 1.36]
Odio 1991	1	52	10	48	51.0%	0.09 [0.01, 0.69]
Schaad 1993	2	60	2	55	10.2%	0.92 [0.13, 6.29]
Subtotal (95% CI)		**162**		**154**	**100.0%**	**0.29 [0.12, 0.70]**
Total events	6		20			
Heterogeneity: Chi² = 2.80, df = 2 (P = 0.25); I² = 28%						
Test for overall effect: Z = 2.75 (P = 0.006)						
1.6.4 Recurrent fever						
Ciana 1995	9	34	6	36	3.0%	1.59 [0.63, 3.99]
Kanra 1995	5	29	4	27	2.2%	1.16 [0.35, 3.89]
Kilpi 1995	4	50	3	51	1.6%	1.36 [0.32, 5.77]
Lebel 1988a	31	51	23	49	12.3%	1.29 [0.89, 1.88]
Lebel 1988b	32	51	11	49	5.9%	2.80 [1.59, 4.90]
Lebel 1989	14	31	14	29	7.6%	0.94 [0.54, 1.61]
Odio 1991	10	52	9	48	4.9%	1.03 [0.46, 2.31]
Peltola 2007	65	166	66	163	34.8%	0.97 [0.74, 1.26]
Qazi 1996	20	48	14	41	7.9%	1.22 [0.71, 2.10]
Scarborough 2007	7	233	2	232	1.0%	3.48 [0.73, 16.60]
Schaad 1993	19	60	11	50	6.3%	1.44 [0.76, 2.73]
Wald 1995	31	69	25	74	12.6%	1.33 [0.88, 2.01]
Subtotal (95% CI)		**874**		**849**	**100.0%**	**1.27 [1.09, 1.47]**
Total events	247		188			
Heterogeneity: Chi² = 15.16, df = 11 (P = 0.18); I² = 27%						
Test for overall effect: Z = 3.06 (P = 0.002)						
1.6.5 Fungal infection						
de Gans 2002	8	157	4	144	100.0%	1.83 [0.56, 5.96]
Subtotal (95% CI)		**157**		**144**	**100.0%**	**1.83 [0.56, 5.96]**
Total events	8		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.6.6 Arthritis						
Lebel 1988a	1	51	4	49	33.0%	0.24 [0.03, 2.07]
Lebel 1988b	0	51	0	49		Not estimable
Lebel 1989	1	31	2	29	16.7%	0.47 [0.04, 4.89]
Odio 1991	0	52	4	48	37.9%	0.10 [0.01, 1.86]
Schaad 1993	3	60	1	55	8.4%	2.75 [0.29, 25.66]
Wald 1995	2	69	0	74	3.9%	5.36 [0.26, 109.65]
Subtotal (95% CI)		**314**		**304**	**100.0%**	**0.64 [0.27, 1.53]**
Total events	7		11			
Heterogeneity: Chi² = 5.94, df = 4 (P = 0.20); I² = 33%						
Test for overall effect: Z = 1.00 (P = 0.32)						



Subgroup analysis

One hundred and sixty-seven children out of 1269 (13.1%) in the corticosteroid-treated group died, compared to 182 of 1242 (14.7%) in the placebo group (RR 0.89, 95% CI 0.74 to 1.07) (Belsey 1969; Ciana 1995; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Molyneux 2002; Peltola 2007; Qazi 1996; Sankar 2007; Schaad 1993; Mathur 2013) (Analysis 2.1).

Corticosteroids prevented hearing loss in children: any hearing loss was found in 146 of 1001 (14.6%) corticosteroid-treated participants, compared to 196 of 960 (20.4%) in the control group (RR 0.73, 95% CI 0.61 to 0.86); severe hearing loss was found in 57 of 772 (7.3%) corticosteroid-treated participants, compared to 86 of 752 (11.2%) in the control group (RR 0.67, 95% CI 0.49 to 0.91) (Analysis 2.3; Analysis 2.2).

For adults, study results on mortality were significantly heterogeneous (I^2 statistic = 54%). Using the random-effects model there was a non-significant reduction in mortality rate: 187 of 756 (24.7%) died in the corticosteroid-treated group versus 215 of 761 (28.3%; RR 0.74, 95% CI 0.53 to 1.05, P = 0.09) (Bennett 1963; Bhaumik 1998; de Gans 2002; Girgis 1989; Nguyen 2007; Scarborough 2007; Thomas 1999) (Analysis 3.1). The rate of hearing loss in adults was lower in corticosteroid-treated participants as compared to controls (68 of 433 (15.7%) versus 90 of 411 (21.9%), RR 0.74, 95% CI 0.56 to 0.98; Analysis 3.2). There was a non-significant reduction in short-term neurologic sequelae in the corticosteroid-treated group (RR 0.72, 95% CI 0.51 to 1.01, P = 0.06; Analysis 3.3).

Case-fatality rate varied according to causative micro-organism (Analysis 4.1). Out of 825 participants with *H. influenzae* meningitis, 87 died (10.5%); compared to 371 of 1132 (32.8%) participants with pneumococcal meningitis and 27 of 620 (4.3%) participants with meningococcal meningitis. Corticosteroids protected against death in pneumococcal meningitis (RR 0.84, 95% CI 0.72 to 0.98) (Bademosi 1979; Bennett 1963; de Gans 2002; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; Lebel 1988a; Lebel 1988b; Molyneux 2002; Nguyen 2007; Odio 1991; Peltola 2007; Scarborough 2007; Schaad 1993; Thomas 1999; Wald 1995). In meningococcal meningitis, corticosteroids were associated with a non-significant reduction in mortality (RR 0.71, 95% CI 0.35 to 1.46). For children with meningitis caused by *H. influenzae*, hearing loss was significantly reduced by corticosteroids (RR 0.34, 95% CI 0.20 to 0.59; Analysis 4.3). For children with meningitis caused by bacteria other than *H. influenzae*, no significant beneficial effect was seen (RR 0.95, 95% CI 0.65 to 1.39) (Analysis 4.2).

We analysed studies in two subsets divided into high-income (Belsey 1969; Bennett 1963; DeLemos 1969; de Gans 2002; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Nguyen 2007; Odio 1991; Peltola 2007; Schaad 1993; Thomas 1999; Wald 1995) and low-income countries (Bademosi 1979; Bhaumik 1998; Ciana 1995; Girgis 1989; Mathur 2013; Molyneux 2002; Qazi 1996; Scarborough 2007; Sankar 2007). The risk ratio for mortality in high-income countries was 0.81 (95% CI 0.63 to 1.05, P = 0.10) in corticosteroid-treated participants and 0.87 (95% CI 0.67 to 1.15, random-effects model, I^2 statistic 55%) (Analysis 5.1) in low-income countries, with no heterogeneity between subgroups.

In high-income countries the rates of severe hearing loss (RR 0.51, 95% CI 0.35 to 0.73) (Analysis 5.2), any hearing loss (RR 0.58, 95% CI 0.45 to 0.73) (Analysis 5.3) and short-term neurologic sequelae (RR 0.64, 95% CI 0.48 to 0.85) (Analysis 5.4) were lower in corticosteroid-treated participants and showed significant heterogeneity with rates in the low-income subgroup (severe hearing loss RR 0.99, 95% CI 0.72 to 1.38, I^2 statistic for subgroups 86%; any hearing loss RR 0.89, 95% CI 0.76 to 1.04, I^2 statistic 89%; short-term neurological sequelae RR 1.03, 95% CI 0.81 to 1.31, I^2 statistic 84%). Subgroup analysis for children in high-income countries showed a decrease in risk of severe hearing loss and neurologic sequelae in the corticosteroid group (severe hearing loss, RR 0.52, 95% CI 0.35 to 0.78; short-term sequelae, RR 0.67, 95% CI 0.46 to 0.97), whereas no difference was seen in low-income countries (severe hearing loss, RR 1.00, 95% CI 0.69 to 1.47, I^2 statistic for subgroups 81%; short-term sequelae, RR 1.08, 95% CI 0.81 to 1.43, I^2 statistic for subgroups 75%) (Analysis 5.5; Analysis 5.6; Analysis 5.7; Analysis 5.8). For adults in high-income countries, no significant heterogeneity between subgroups was found (Analysis 5.9; Analysis 5.10).

Subgroup analysis on timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotics) showed similar results for mortality (RR 0.87 95% CI 0.69 to 1.09 (I^2 statistic 52%, random-effects model); RR 0.83, 95% CI 0.55 to 1.26) (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4). For subgroup analyses of severe hearing loss and short-term neurological sequelae, administration after the first dose of antibiotics had slightly more favourable point estimates than studies with early administration of corticosteroids, but there was no significant heterogeneity between subgroups.

We analysed studies in three categories of study quality according to the studies' 'Risk of bias' score (Figure 2). Four studies including 1793 participants were categorised as high quality (de Gans 2002; Molyneux 2002; Nguyen 2007; Scarborough 2007), 14 studies with 1477 participants as medium quality (DeLemos 1969; Kanra 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Mathur 2013; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Sankar 2007; Schaad 1993; Thomas 1999; Wald 1995) and seven studies including 851 participants as low quality (Bademosi 1979; Belsey 1969; Bennett 1963; Bhaumik 1998; Ciana 1995; Girgis 1989;

Kilpi 1995). No significant heterogeneity was found between subgroups of study quality for mortality, any hearing loss and short-term neurological sequelae (Analysis 7.1; Analysis 7.3; Analysis 7.4). Severe hearing loss was reduced in studies of medium quality (RR 0.47, 95% 0.29 to 0.75; Analysis 7.2), but not in studies of high and low quality, with significant heterogeneity between subgroups (I^2 statistic for subgroups 70%).

Sensitivity analysis

In the worst-case scenario analyses where participants with missing data on severe hearing loss or any hearing loss in the corticosteroid groups were considered to have an unfavourable outcome, corticosteroids had no effect on severe or any hearing loss (Analysis 8.1; Analysis 8.2). In these analyses, studies were significantly heterogeneous and therefore we used the random-effects model. One study provided 46% of missing values in the severe hearing loss analysis and 45% of missing values in the analysis on any hearing loss (Molyneux 2002). The worst-case scenario for short-term and long-term neurological sequelae showed no beneficial effect of corticosteroids (Analysis 8.3; Analysis 8.4). None of the worst-case scenarios showed evidence of harm with corticosteroid therapy.
Using the random-effects model in analyses with no significant heterogeneity, the beneficial effect effects of corticosteroids remained significant in Analysis 1.2, Analysis 1.3, Analysis 1.6, Analysis 2.2, Analysis 2.3, Analysis 3.2, Analysis 4.3, Analysis 5.2, Analysis 5.3, Analysis 5.4, Analysis 5.6, Analysis 5.7, Analysis 6.3 and Analysis 7.2. The decrease in short-term neurological sequelae did not remain significant with the random-effects model, but did show a trend towards benefit (RR 0.83, 95% CI 0.69 to 1.00; P = 0.05). The beneficial effect of corticosteroids on mortality in pneumococcal meningitis found with the fixed-effect model did not remain significant in the random-effects model (Analysis 4.1, RR 0.81, 95% CI 0.61 to 1.08, P = 0.16).
The sensitivity analyses of studies with adequate sequence generation only showed that the decrease in short-term neurological sequelae did not remain significant (RR 0.83, 95% CI 0.69 to 1.01). Results for other primary outcome measures did not differ from the initial analyses.

DISCUSSION

Summary of main results

This meta-analysis showed a beneficial effect of adjunctive corticosteroids in acute bacterial meningitis. Overall, corticosteroids significantly reduced the rate of hearing loss (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.63 to 0.87), severe hearing loss (RR 0.67, 95% CI 0.51 to 0.88) and short-term neurological sequelae (RR 0.83, 95% CI 0.69 to 1.00). The use of adjunctive corticosteroids was associated with a non-significant decrease in mortality (RR 0.90, 95% CI 0.80 to 1.01). Use of adjunctive corticosteroids was not associated with a decrease in long-term neurological sequelae (RR 0.90, 95% CI 0.74 to 1.10). Recurrent fever occurred more often in corticosteroid-treated participants (RR 1.27, 95% CI 1.09 to 1.47), but other adverse events were found in similar proportions of the treatment and control group.
Subgroup analyses for age showed that in children with bacterial meningitis, corticosteroids prevented severe hearing loss (RR 0.67, 95% CI 0.49 to 0.91) and any hearing loss (RR 0.73, 95% CI 0.61 to 0.86). In adults, the rate of any hearing loss was lower in the corticosteroid-treated group (RR 0.74, 95% CI 0.56 to 0.98); there was a non-significant reduction in mortality in adults receiving corticosteroids (RR 0.74, 95% CI 0.53 to 1.05, P = 0.09).
Subgroup analysis for causative organism showed that corticosteroids reduce severe hearing loss in children with meningitis due to *H. influenzae* (RR 0.34, 95% CI 0.20 to 0.59), while no effect of corticosteroids on hearing loss was observed in children with non-*Haemophilus* meningitis. Subgroup analysis on *S. pneumoniae* showed a favourable effect of corticosteroids on mortality (RR 0.84, 95% CI 0.72 to 0.98). A non-significant reduction in mortality was found in the *N. meningitidis* meningitis subgroup (RR 0.71, 95% CI 0.35 to 1.46). No effect on mortality was shown in *H. influenzae* meningitis.
Subgroup analysis for high-income and low-income countries showed no significant effect on mortality for corticosteroid-treated participants in high-income and low-income countries overall. Corticosteroids were protective against severe hearing loss (RR 0.51, 95% CI 0.35 to 0.73), any hearing loss (RR 0.58, 95% CI 0.45 to 0.73) and short-term neurological sequelae (RR 0.64, 95% CI 0.48 to 0.85) in high-income countries, with significant heterogeneity between subgroups. For children in high-income countries, corticosteroids showed a protective effect against severe hearing loss (RR 0.52, 95% CI 0.35 to 0.78) and short-term neurological sequelae (RR 0.67, 95% CI 0.46 to 0.97). No effect was observed in low-income countries.
The sensitivity analyses showed that corticosteroids would have no effect on severe or any hearing loss and short- or long-term neurological sequelae if all missing data were imputed as unfavourable events in the corticosteroid-treated participants. Corticosteroids were not associated with harm in this worst-case scenario. Further sensitivity analyses showed that the effect of corticosteroids on overall short-term neurological sequelae and mortality in pneumococcal meningitis would not be significant if the random-effects model was used. The beneficial effect on short-term neurological sequelae changed to a trend towards benefit if only studies with adequate sequence generation were included.

Overall completeness and applicability of evidence

Overall completeness

The available studies do not address four important issues - the minimum duration of corticosteroid therapy, type of corticosteroids, the maximum length of time after parenteral antibiotic therapy for commencement of corticosteroid therapy and long-term effect of corticosteroid therapy. In most studies, a four-day regimen of dexamethasone (0.4 or 0.6 mg/kg/day) divided into four daily doses was used. One randomised, prospective study involving 118 children with bacterial meningitis showed a two-day and four-day regimen of dexamethasone to be similarly effective (Syrogiannopoulos 1994). In this study physicians were not blinded to the treatment groups. Long-term neurological sequelae, or moderate hearing impairment (or both), were found in 1.8% and 3.8% of patients treated with dexamethasone for two and four days, respectively. It is unlikely that a randomised controlled trial (RCT) will be performed to answer the question of whether a two-day or four-day regimen should be used in bacterial meningitis; such a clinical trial would need a very large number of patients enrolled to detect significant differences between groups. Since most studies used a four-day regimen (without increase of side effects) we advise the use of the four-day corticosteroid therapy.

Three studies used hydrocortisone and/or prednisolone; all others used dexamethasone. Clinical efficacy depends on glucocorticoid pharmacokinetics and pharmacodynamics; of glucocorticoids, dexamethasone has superior penetration in the cerebrospinal fluid (CSF) and a longer half life (Balis 1987). Therefore, dexamethasone is considered to be the corticosteroid of choice in bacterial meningitis.

Subgroup analyses for timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotic) showed no differences in efficacy of corticosteroids. In previous reports, administration of corticosteroids before or with the first dose of parenteral antibiotics seemed to be more effective than administration after the first dose of antibiotics (King 1994; McIntyre 1997). A RCT involving 301 adults with bacterial meningitis in European countries showed a beneficial effect of the corticosteroid dexamethasone on unfavourable outcome and mortality (de Gans 2002). In this European study, dexamethasone or placebo was administered before or with the first dose of antibiotic (de Gans 2002). The beneficial effect of dexamethasone on mortality was most apparent in patients with pneumococcal meningitis. In a post hoc analysis of this study, the beneficial effect of dexamethasone on mortality in patients with pneumococcal meningitis was attributable to a reduction in systemic complications (van de Beek 2004a). Although speculative and not supported by clinical data, one implication of this finding might be that the effect of dexamethasone is not restricted to the first hours after administration (van de Beek 2006b).

A meta-analysis of individual patient data (van de Beek 2010) was performed of five recent large RCTs on adjunctive dexamethasone therapy in bacterial meningitis in (de Gans 2002; Molyneux 2002; Nguyen 2007; Peltola 2007; Scarborough 2007). Data from 2029 patients from five trials were included and the aim of this analysis was to establish whether any subgroups of patients with acute bacterial meningitis might benefit from adjunctive dexamethasone. Extensive exploration of 15 pre-specified subgroups did not show robust evidence that a particular subgroup would benefit; although there was a benefit in adults aged over 55 years (McIntyre 2010; van de Beek 2010). There were no differences in efficacy of adjunctive dexamethasone with regard to the timing of corticosteroids.

In experimental pneumococcal meningitis, CSF bacterial concentrations appeared to be more important than the timing of dexamethasone therapy in influencing the antibacterial-induced inflammatory response (Lutsar 2003). Hence, there is a time period beyond which corticosteroid loses its effectiveness after the first (parenteral) administration of an antibiotic agent but this time interval has not been clearly defined. On the basis of the available evidence, dexamethasone should be preferably started before or with the first dose of antibiotic therapy.

A long-term follow-up study on adjunctive dexamethasone treatment in tuberculous meningitis showed the initial beneficial effect of adjunctive dexamethasone was abolished because of delayed mortality within five years (Török 2011). To assess the long-term effects of adjunctive corticosteroid treatment in bacterial meningitis and determine whether a similar phenomenon could be identified, a long-term follow-up study was performed in participants included in the European Dexamethasone Study (de Gans 2002; Fritz 2012). The study included 228 of 246 evaluable participants surviving the initial trial period. After a median follow-up of 13 years, mortality in the dexamethasone group was 22% compared to 33% in the placebo group (P = 0.029) (Fritz 2012). The authors conclude the beneficial effect of dexamethasone that is obtained in the acute phase of the disease remains for years. This provides another reason to administer adjunctive corticosteroids in adult bacterial meningitis patients in high-income countries.

However, long-term follow-up studies of patients included in other RCTs are needed to confirm the persistence of benefit from adjunctive dexamethasone.

Applicability of evidence

In children with acute bacterial meningitis, corticosteroids reduced hearing loss from 20.4% to 14.6% and severe hearing loss from 11.2% to 7.3%. A large proportion of included children had meningitis due to *H. influenzae* type B, which has been virtually eliminated in high-income countries since routine vaccination of children against this bacterium started (McIntyre 2012; Peltola 2000; van de Beek 2006b). Nevertheless, subgroup analysis in children in high-income countries showed a protective effect of adjunctive corticosteroids on severe hearing loss overall and a favourable point estimate for severe hearing loss due to non-*Haemophilus* meningitis. The results of this review support the use of adjunctive corticosteroids in children in high-income countries with meningitis due to all micro-organisms based on the lack of evidence of adverse events (in general and micro-organism specific) of dexamethasone in the corticosteroid-treated group. However, as conclusive evidence is lacking for this subgroup, administration of corticosteroids to children with meningitis due to bacteria other than *H. influenzae* remains controversial.

Only one study in this analysis involved children with neonatal meningitis and showed a beneficial effect of corticosteroids on outcomes (Mathur 2013). However, the study was relatively small and treatment groups were not well balanced with regards to patient age, culture positivity and causative micro-organisms. Additional RCTs evaluating corticosteroids in neonatal meningitis need to be performed before definitive conclusions can be drawn on the role of dexamethasone treatment in neonatal meningitis.

On the basis of the benefits of corticosteroid therapy in the adult population in high-income countries, dexamethasone should be commenced in adults with suspected or proven community-acquired bacterial meningitis in high-income countries (van de Beek 2006a). For adults in low-income countries, the use of corticosteroids is neither beneficial nor harmful.

The use of steroids was associated with fewer cases of persistent fever and more cases of recurrent fever, but not with serious adverse events. However, definitions of adverse events used in the studies were heterogeneous and most studies had no specified criteria in advance, so under-ascertainment is likely.

Concerns have been raised over the interference by corticosteroids on CSF eradication of meningeal pathogens by reducing the blood-brain barrier permeability and thereby the penetration of antibiotics in the subarachnoid space. Therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive dexamethasone (Viladrich 1991). However, two studies showed with repeated lumbar punctures that in both adults and children, treatment of dexamethasone did not reduce vancomycin levels in the CSF (Klugman 1995; Ricard 2007). Although these results are reassuring, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should still be carefully observed throughout therapy (van de Beek 2006a).

In adults who survive acute bacterial meningitis, cognitive impairment occurs frequently (van de Beek 2002; van de Beek 2006a). As corticosteroids may potentiate ischaemic injury to neurons (Sapolsky 1985), it is important to know whether corticosteroids have beneficial effects on hearing loss and mortality but worsen cerebral cortical functioning (van de Beek 2006b). Neuropsychological outcome was evaluated in patients included in the European Dexamethasone Study who survived pneumococcal or meningococcal meningitis (Weisfelt 2006). In 87 out of 99 eligible patients, 46 (53%) of whom were treated with dexamethasone and 41 (47%) of whom received placebo, no significant differences in outcome were found between patients in the dexamethasone and placebo groups (medium time between meningitis and testing was eight years). In another recent study on long-term neuropsychological outcomes and dexamethasone in children, children who contracted pneumococcal meningitis and were treated with corticosteroids showed better academic achievements compared with children with pneumococcal meningitis who were not treated with adjunctive corticosteroids (Ozen 2006).

Quality of the evidence

Of the 25 randomised clinical trials included in the meta-analysis four were of high quality, 14 of medium quality and seven of low quality. Although the number of high-quality studies was low, the number of participants in these studies accounted for 45% of participants included in the meta-analysis. Studies were mostly categorised as medium or low quality due to a lack of addressing missing data or because no intention-to-treat analysis was performed. For the analysis on severe hearing loss, significant heterogeneity between trials of high, medium and low quality was found. As studies of high quality showed no effect the results of this meta-analysis should interpreted with caution.

The sensitivity analysis showed that in a worst-case scenario dexamethasone would have no beneficial or harmful effect on hearing loss or neurological sequelae. However, this analysis was heavily influenced by a single study accounting for 46% of missing values. When this study was left out a trend towards benefit of dexamethasone on any hearing loss was found (Molyneux 2002). Further sensitivity analyses showed that the effect of corticosteroids on overall short-term neurological sequelae and mortality in pneumococcal meningitis would not be significant if the random-effects model was used.

Potential biases in the review process

Several biases may have diminished the reliability of our results. The first confounding factor is selection bias. Several studies on childhood meningitis had exceptionally low mortality rates; nine studies had mortality rates of 3% or less. Mortality rates of childhood bacterial meningitis in previous reported studies ranged from 8% to 20% (Baraff 1993; Bohr 1983). Inclusion of studies in the meta-analysis with less severe illness, as reflected in the very low case-fatality rates, will probably underestimate the protective effect of corticosteroids (Glasziou 1995). Five studies had very high mortality rates (over 25%). For patients admitted in a late state of disease, adjuvant corticosteroids are less protective and might even be harmful (Prasad 1995). Inclusion of such patients might again lead to an underestimation of the treatment effect.

A second bias is introduced when participants are withdrawn (Prasad 1995; Qazi 1996). The analysis was based upon per-protocol figures, as intention-to-treat (ITT) figures were only available for six studies (24%). A total of 211 participants were withdrawn after the randomisation process, often for unknown reasons. Reasons for withdrawal include ineligibility according to the trial criteria or inability to complete the treatment protocol (Prasad

1995). Withdrawals on the grounds on ineligibility may have been influenced by knowledge of outcome; if so, this would advantage the corticosteroid regimen. Excluding participants because of an inability to complete the course of corticosteroids due to side effects (for example, upper gastrointestinal bleeding) clearly introduces bias in favour of the study medication, whereas withdrawals due to loss to follow-up might favour the placebo group. In the Egyptian study, which was not placebo-controlled and not double-blinded, only three pathogens were cultured from the cerebral spinal fluid of enrolled participants, suggesting withdrawal of participants with other bacteria culture from CSF and those with negative CSF cultures (Girgis 1989).

A third bias is introduced by competing risks. The comparisons of hearing loss and neurologic sequelae (other than hearing loss) were made excluding all participants who died. Since mortality is possibly a treatment-related outcome, the treatment groups that exclude fatality cases may not be comparable. Competing risks in this analysis will lead to an underestimation of the treatment effect of corticosteroids.

Finally, the included studies were heterogeneous with respect to the study protocols. The first study was published in 1963 (Bennett 1963), the last in 2012 (Mathur 2013). Several different study interventions were used. Therefore, study population effect sizes were calculated as risk ratios.

Agreements and disagreements with other studies or reviews

Four meta-analyses on the use of adjunctive dexamethasone in adults were published, two in 2009 (Assiri 2009; Vardakas 2009) and two in 2012 (Borchorst 2012; Bernardo 2012). The first meta-analysis (Vardakas 2009) concluded that dexamethasone was associated with a non-significant decrease in mortality, but when the trial from Malawi was left out the decrease in mortality did reach significance. The reasons for excluding the Malawian trial were a HIV-positive population, high mortality, poor general status and low human development index (HDI) (< 0.5). However, other countries that were included had only slightly higher HDIs at the time of inclusion (Girgis 1989, Egypt 0.53; Bhaumik 1998 India 0.53, Scarborough 2007 Malawi 0.49). Several subgroup analyses showed that dexamethasone was most beneficial in patients with definite meningitis, in high- and medium-income countries and patients with a short duration of symptoms. Out of four analyses eight subgroups consisted of only one or two studies, limiting the value of the meta-analysis. Analyses on mortality and hearing loss in high- and medium-income countries were similar to our results. The study by Bennett 1963 was not included in this meta-analysis for unknown reasons. The second meta-analysis included four recent trials in adults (de Gans 2002; Nguyen 2007; Scarborough 2007; Thomas 1999) and concluded that dexamethasone reduced mortality in high-income countries (Assiri 2009). The third meta-analysis (Borchorst 2012) included 29 randomised studies and had similar conclusions as the Cochrane 2010 meta-analysis (Brouwer 2010a), which were that adjunctive dexamethasone was beneficial in adults in high-income countries, especially in patients with pneumococcal meningitis. The fourth meta-analysis (Bernardo 2012) included only paediatric studies and concluded that adjunctive dexamethasone was not associated with a reduction in mortality, hearing loss or sequelae (Bernardo 2012). The reason why seven studies included in the current Cochrane 2012 updated meta-analysis were not included in the meta-analysis of paediatric studies was not specified. According to the classification of study quality used, most of these studies were of similar quality to those that were included.

The difference in efficacy of corticosteroids between high- and low-income countries was mainly driven by two large studies from Malawi (Molyneux 2002; Scarborough 2007), together representing 60% of included participants from low-income countries. Participants included in these studies were often HIV-positive, presented late in the disease course or received inappropriate antibiotic therapy (Molyneux 2002; Scarborough 2007). There may be several reasons for the difference in efficacy of corticosteroids such as delayed presentation, clinical severity, underlying anaemia, malnutrition, the antibiotics used, HIV infection or other unidentified differences between populations. Recently, genetic factors were suggested to influence the patient's response to corticosteroids (Brouwer 2012). A study compared characteristics of children with culture-positive community-acquired bacterial meningitis in the Children's Unit, Queen Elizabeth Central Hospital, Blantyre, Malawi and in the Royal Liverpool Children's Hospital, UK from time periods before the introduction of vaccines (Molyneux 2006). Children in Malawi presented later and were more often comatose and malnourished, compared to children in Britain. Mortality from bacterial meningitis in children in Malawi was much higher than in children in Britain (41% versus 7%), even when infected with the same organism. Several studies have shown that a delay in initiation of antibiotic treatment is associated with worse outcome in bacterial meningitis (McMillan 2001; Køster-Rasmussen 2008; Proulx 2005). A meta-analysis on timing of steroids with respect to initial symptoms could not be performed because outcome data were not specified for patients presenting early or late during clinical course in any of the studies. Nevertheless, we stress the need for early diagnosis and treatment.

A meta-analysis of individual patient data was performed with five large RCTs (de Gans 2002; Molyneux 2002; Nguyen 2007; Peltola 2007; Scarborough 2007; van de Beek 2010). Data from 2029 patients from five trials were included in the analysis (833 (41.0%) aged < 15 years). HIV infection was confirmed or likely in 580 (28.6%) patients and bacterial meningitis was confirmed in 1639 (80.8%). Dexamethasone was not associated with a significant reduction in death (270 of 1019 (26.5%) on dexamethasone versus 275 of 1010 (27.2%) on placebo; odds ratio (OR) 0.97, 95% CI 0.79 to 1.19), death or severe neurological sequelae or bilateral severe deafness (42.3% versus 44.3%; OR 0.92, 95% CI 0.76

to 1.11), death or any neurological sequelae or any hearing loss (54.2% versus 57.4%; OR 0.89, 95% CI 0.74 to 1.07), or death or severe bilateral hearing loss (36.4% versus 38.9%; OR 0.89, 95% CI 0.73 to 1.69). However, dexamethasone reduced hearing loss among survivors (24.1% versus 29.5%; OR 0.77, 95% CI 0.60 to 0.99, P = 0.04). Dexamethasone had no effect in any of the pre-specified subgroups, including specific causative organisms, pre-dexamethasone antibiotic treatment, HIV status or age. The differences between Malawi and the other clinical settings call into question the appropriateness of summary measures that combine the results, even if statistical tests of heterogeneity are deemed acceptable. Mortality rates in the two studies from Malawi were three to five-fold higher than in the studies from Europe, South America and Vietnam (de Gans 2002; Molyneux 2002; Nguyen 2007; Peltola 2007; Scarborough 2007). In subgroups of the individual patient data meta-analysis, there were several instances in which the I^2 statistic was more than 50%, which indicates at least moderate heterogeneity (McIntyre 2010). This current Cochrane review confirms the beneficial effect of corticosteroids on hearing loss that was found in the subgroups of the individual meta-analysis (van de Beek 2010). Treatment with adjunctive corticosteroids was not associated with harm. In order to establish with certainty whether or not dexamethasone has a place in the treatment of bacterial meningitis, a large multinational RCT in that subgroup would be necessary. Such a trial would need to include approximately 13,500 participants to show an odds ratio (OR) of 0.9 with a power of 90% in a population with 27% risk of death in the placebo group, and is therefore unlikely to be performed or finished in the next decade. Meanwhile, results of our analysis support the use of corticosteroids in children and adults with community-acquired bacterial meningitis in high-income countries.

Four studies evaluated the implementation of adjunctive dexamethasone treatment and its effect on the outcome of bacterial meningitis (Brouwer 2010b; Cornelis 2011; Heckenberg 2012b; Peterković 2012). Two studies compared the prognosis of adult pneumococcal and meningococcal meningitis between two nation-wide prospective cohort studies; one was performed before and the other after the implementation of adjunctive dexamethasone (Brouwer 2010b; Heckenberg 2012b). The studies showed that after the introduction of adjunctive dexamethasone, 84% of patients with pneumococcal meningitis and 89% of adults with meningococcal meningitis received the recommended four-day regimen (40 mg/day in four doses). The mortality from pneumococcal meningitis decreased from 30% to 20% after the introduction of dexamethasone (P = 0.001) and the rate of hearing loss decreased from 22% to 12% (P = 0.001) (Brouwer 2010b). Meningococcal disease mortality declined from 7% to 4% and hearing loss from 8% to 3%, but these differences did not reach statistical significance (Heckenberg 2012b). No evidence of harm from dexamethasone was identified in either study. The beneficial effect of dexamethasone on pneumococcal meningitis was similar to that identified in the European Dexamethasone Study (de Gans 2002). These studies provide additional (class III) evidence that adjunctive dexamethasone is beneficial in adults with bacterial meningitis in high-income countries. Retrospective studies in Belgium and Croatia evaluated whether the use of dexamethasone improved prognosis in adults (Peterković 2012), or both adults and children (Cornelis 2011). Both studies showed no effect of dexamethasone. However, in both studies the rationale to give or withhold dexamethasone was unclear and therefore confounding by indication (patients with severe sickness get more medication, i.e. dexamethasone, but still have a worse prognosis) is a major problem in these studies, as is the retrospective design.

AUTHORS' CONCLUSIONS

Implications for practice

In summary, the consistency and degree of benefit identified in this analysis merits the use of corticosteroids in adults and children with acute bacterial meningitis in high-income countries, although the strength of the evidence is not optimal. We recommend a four-day regimen of dexamethasone (0.6 mg/kg daily) given before or with the first dose of antibiotics.

Implications for research

1. Although additional evidence from well-designed randomised controlled trials (RCTs) would be optimal, this is impractical for reasons of cost and logistics.

2. Follow-up studies in countries where dexamethasone has been implemented may provide additional circumstantial evidence on the effectiveness of adjunctive dexamethasone.

3. The role of corticosteroids in neonatal meningitis is currently unclear due to the different spectrum of causative micro-organisms and the lack of applicable RCT data. Additional RCTs in neonatal meningitis are needed.

4. Case series are needed to determine the effect of adjunctive dexamethasone therapy in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.

ACKNOWLEDGEMENTS

Diederik van de Beek is supported by grants from the Netherlands Organization for Health Research and Development (ZonMw; NWO Veni grant 2006 (916·76·023); NWO Vidi grant 2010 (016.116.358)), the Academic Medical Center (AMC Fellowship 2008) and European Research Council (ERC Starting Grant (281156)). Matthijs Brouwer is supported by a grant from the

Netherlands Organization for Health Research and Development (ZonMw; NWO Veni grant 2012 (916.13.078)).

We wish to thank the following people for commenting on the 2010 updated review: Amy Zelmer, Andrew Herxheimer, Mark Coulthard, Mark Jones and Inge Axelsson. We also thank the following people for commenting on this 2013 updated review: Marilyn Bamford, Ram Yogev, Elaind Beller and Inge Axelsson.

REFERENCES

References to studies included in this review

Bademosi 1979 ***{published data only}***
Bademosi O, Osuntokun BO. Prednisolone in the treatment of pneumococcal meningitis. *Tropical and Geographical Medicine* 1979;**31**(1):53–6.

Belsey 1969 ***{published data only}***
Belsey MA, Hoffpauir CW, Smith MH. Dexamethasone in the treatment of acute bacterial meningitis: the effect of study design on the interpretation of results. *Pediatrics* 1969;**44**(4):503–13.

Bennett 1963 ***{published data only}***
Bennett IL, Finland M, Hamburger M, Kass EH, Lepper M, Waisbren BA. The effectiveness of hydrocortisone in the management of severe infections. *JAMA* 1963;**183**(6):462–5.

Bhaumik 1998 ***{published data only}***
Bhaumik S, Behari M. Role of dexamethasone as adjunctive therapy in acute bacterial meningitis in adults. *Neurology India* 1998;**46**:225–8.

Ciana 1995 ***{published data only}***
Ciana G, Parmar N, Antonio C, Pivetta S, Tamburlini G, Cuttini M. Effectiveness of adjunctive treatment with steroids in reducing short-term mortality in a high-risk population of children with bacterial meningitis. *Journal of Tropical Pediatrics* 1995;**41**(3):164–8.

de Gans 2002 ***{published data only}***
de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *New England Journal of Medicine* 2002;**347**(20):1549–56.

DeLemos 1969 ***{published data only}***
DeLemos RA, Haggerty RJ. Corticosteroids as an adjunct to treatment in bacterial meningitis. A controlled clinical trial. *Pediatrics* 1969;**44**(1):30–4.

Girgis 1989 ***{published data only}***
Girgis NI, Farid Z, Mikhail IA, Farrag I, Sultan Y, Kilpatrick ME. Dexamethasone treatment for bacterial meningitis in children and adults. *Pediatric Infectious Disease Journal* 1989;**8**(12):848–51.

Kanra 1995 ***{published data only}***
Kanra GY, Ozen H, Secmeer G, Ceyhan M, Ecevit Z, Belgin E. Beneficial effects of dexamethasone in children with pneumococcal meningitis. *Pediatric Infectious Disease Journal* 1995;**14**(6):490–4.

Kilpi 1995 ***{published data only}***
Kilpi T, Peltola H, Jauhiainen T, Kallio MJ. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. The Finnish Study Group. *Pediatric Infectious Disease Journal* 1995;**14**(4):270–8.

King 1994 ***{published data only}***
King SM, Law B, Langley JM, Heurter H, Bremner D, Wang EE, et al.Dexamethasone therapy for bacterial meningitis: better never than late?. *Canadian Journal of Infectious Diseases* 1994;**5**:210–5.

Lebel 1988a ***{published data only}***
Lebel MH, Freij BJ, Syrogiannopoulos GA, Chrane DF, Hoyt MJ, Stewart SM, et al.Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. *New England Journal of Medicine* 1988;**319**(15):964–71.

Lebel 1988b ***{published data only}***
Lebel MH, Freij BJ, Syrogiannopoulos GA, Chrane DF, Hoyt MJ, Stewart SM, et al.Dexamethasone therapy for bacterial meningitis. Results of two double-blind, placebo-controlled trials. *New England Journal of Medicine* 1988;**319**(15):964–71.

Lebel 1989 ***{published data only}***
Lebel MH, Hoyt MJ, Waagner DC, Rollins NK, Finitzo T, McCracken GH Jr, et al.Magnetic resonance imaging and dexamethasone therapy for bacterial meningitis. *American Journal of Diseases of Children* 1989;**143**(3):301–6.

Mathur 2013 ***{published data only}***
* Mathur NB, Garg A, Mishra TK. Role of dexamethasone in neonatal meningitis: a randomized controlled trial. *Indian Journal of Pediatrics* 2013;**80**(2):102–7.

Molyneux 2002 ***{published data only}***
Molyneux EM, Walsh AL, Forsyth H, Tembo M, Mwenechanya J, Kayira K, et al.Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomised controlled trial. *Lancet* 2002;**360**(9328):211–8.

Nguyen 2007 ***{published data only}***
Nguyen TH, Tran TH, Thwaites G, Ly VC, Dinh XS, Ho Dang TN, et al.Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *New England Journal of Medicine* 2007;**357**:2431–40.

Odio 1991 *{published data only}*
Odio CM, Faingezicht I, Paris M, Nassar M, Baltodano A, Rogers J, et al.The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. *New England Journal of Medicine* 1991;**324**(22):1525–31.

Peltola 2007 *{published data only}*
Peltola H, Roine I, Fernández J, Zavala I, Ayala SG, Mata AG, et al.Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clinical Infectious Diseases* 2007;**45**:1277–86.

Qazi 1996 *{published data only}*
Qazi SA, Khan MA, Mughal N, Ahmad M, Joomro B, Sakata Y, et al.Dexamethasone and bacterial meningitis in Pakistan. *Archives of Disease in Childhood* 1996;**75**(6):482–8.

Sankar 2007 *{published data only}*
Sankar J, Singhi P, Bansal A, Ray P, Singhi S. Role of dexamethasone and oral glycerol in reducing hearing and neurological sequelae in children with bacterial meningitis. *Indian Pediatrics* 2007;**44**:649–56.

Scarborough 2007 *{published data only}*
Scarborough M, Gordon SB, Whitty CJ, French N, Njalale Y, Chitani A, et al.Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *New England Journal of Medicine* 2007;**357**:2441–50.

Schaad 1993 *{published data only}*
Schaad UB, Lips U, Gnehm HE, Blumberg A, Heinzer I, Wedgwood J. Dexamethasone therapy for bacterial meningitis in children. Swiss Meningitis Study Group. *Lancet* 1993;**342**(8869):457–61.

Thomas 1999 *{published data only}*
Thomas R, Le Tulzo Y, Bouget J, Camus C, Michelet C, Le Corre P, et al.Trial of dexamethasone treatment for severe bacterial meningitis in adults. Adult Meningitis Steroid Group. *Intensive Care Medicine* 1999;**25**(5):475–80.

Wald 1995 *{published data only}*
Wald ER, Kaplan SL, Mason EOJ, Sabo D, Ross L, Arditi M, et al.Dexamethasone therapy for children with bacterial meningitis. Meningitis Study Group. *Pediatrics* 1995;**95**(1):21–8.

References to studies excluded from this review

Ayaz 2008 *{published data only}*
Ayaz C, Celen MK, Geyik MF, Ulug M. The efficacy of dexamethasone treatment in adult patients with acute bacterial meningitis. *Neurosciences* 2008;**13**:146–50.

Baldy 1986 *{published data only}*
Baldy JL, Passos JN. Dexamethasone in the treatment of meningococcal meningitis. *Revista Paulista de Medicina* 1986;**104**(2):61–5.

Daoud 1999 *{published data only}*
Daoud AS, Batieha A, Al-Sheyyab M, Abuekteish F, Obeidat A, Mahafza T. Lack of effectiveness of dexamethasone in neonatal bacterial meningitis. *European Journal of Pediatrics* 1999;**158**(3):230–3.

Farina 1995 *{published data only}*
Farina JSL, Alencastro R, Dalligna C, Rotta NT. Dexamethasone and bacterial meningitis: a randomised controlled trial in Brazilian children and a meta-analysis study. Neurology 1995; Vol. 45, issue A349:45.

Gijwani 2002 *{published data only}*
Gijwani D, Kumhar MR, Singh VB, Chadda VS, Soni PK, Nayak KC, et al.Dexamethasone therapy for bacterial meningitis in adults: a double blind placebo control study. *Neurology India* 2002;**50**(1):63–7.

Gupta 1996 *{published data only}*
Gupta A, Singh NK. Dexamethasone in adults with bacterial meningitis. *Journal of the Association of Physicians of India* 1996;**44**(2):90–2.

Jensen 1969 *{published data only}*
Jensen K, Ranek L, Rosdahl N. Bacterial meningitis; a review of 356 cases with special reference to corticosteroid and antiserum treatment. *Scandinavian Journal of Infectious Diseases* 1969;**1**(1):21–30.

Lepper 1959 *{published data only}*
Lepper M, Spies HW. Treatment of pneumococcic meningitis. *Archives of Internal Medicine* 1959;**104**(3):253–9.

Marguet 1993 *{published data only}*
Marguet C, Mallet E. Value of dexamethasone in purulent meningitis in children. Apropos of a comparative study of 85 children. *Archives Français Pediatrie* 1993;**50**(2):111–7.

Ozen 2006 *{published data only}*
Ozen M, Kanra G, Kara A, Bakar EE, Ceyhan M, Secmeer G, et al.Long-term beneficial effects of dexamethasone on intellectual and neuropsychological outcome of children with pneumococcal meningitis. *Scandinavian Journal of Infectious Diseases* 2006;**38**(2):104–9.

Passos 1979 *{published data only}*
Passos JN, Baldy JL. Evaluation of the use of dexamethasone in the therapeutic schedule for purulent meningitis. *Revista do Instituto de Medicina Tropical de São Paulo* 1979;**21**(2):90–8.

Peltola 2004 *{unpublished data only}*
Peltola H. Childhood bacterial meningitis relieved better by glycerol than dexamethasone. 44th ICAAC, Chicago. Chicago, 2004.

Shembesh 1997 *{published data only}*
Shembesh NM, Elbargathy SM, Kashbur IM, Rao BN, Mahmoud KS. Dexamethasone as an adjunctive treatment of bacterial meningitis. *Indian Journal of Pediatrics* 1997;**64**(4):517–22.

Singhi 2008 *{published data only}*
Singhi S, Järvinen A, Peltola H. Increase in serum osmolality is possible mechanism for the beneficial effects of glycerol in childhood bacterial meningitis. *Pediatric Infectious Disease Journal* 2008;**27**:892–6.

Syrogiannopoulos 1994 *{published data only}*
Syrogiannopoulos GA, Lourida AN, Theodoridou MC, Pappas IG, Babilis, GC, Economidis JJ, et al.Dexamethasone therapy for bacterial meningitis in children: 2- versus 4-day regimen. *Journal of Infectious Diseases* 1994;**169**(4):853–8.

Tolaj 2010 *{published data only}*
Tolaj I, Dreshaj S, Qehaja E, Tolaj J, Doda-Ejupi T, Mehmeti M. Dexamethasone as adjuvant therapy in the treatment of invasive meningococcal diseases. *Medicinski Arhiv* 2010;**64**(4):228–30.

Additional references

Assiri 2009
Assiri AM, Alasmari FA, Zimmerman VA, Baddour LM, Erwin PJ, Tleyjeh IM. Corticosteroid administration and outcome of adolescents and adults with acute bacterial meningitis: a meta-analysis. *Mayo Clinic Proceedings* 2009; **84**(5):403–9.

Balis 1987
Balis FM, Lester CM, Chrousos GP, Heideman RL, Poplack DG. Differences in cerebrospinal fluid penetration of corticosteroids: possible relationship to the prevention of meningeal leukemia. *Journal of Clinical Oncology* 1987;**5**: 202–7.

Baraff 1993
Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatric Infectious Disease Journal* 1993;**12**(5):389–94.

Bernardo 2012
Bernardo WM, Aires FT, Sá FP. Effectiveness of the association of dexamethasone with antibiotic therapy in pediatric patients with bacterial meningitis. *Revista da Associação Médica Brasileira* 2012;**58**(3):319–22.

Bohr 1983
Bohr V, Hansen B, Jessen O, Johnsen N, Kjersem H, Kristensen HS, et al.Eight hundred and seventy-five cases of bacterial meningitis. Part I of a three-part series: clinical data, prognosis, and the role of specialised hospital departments. *Journal of Infection* 1983;**7**(1):21–30.

Borchorst 2012
Borchorst S, Moller K. The role of dexamethasone in the treatment of bacterial meningitis - a systematic review. *Acta Anaesthesiologica Scandinavica* 2012;**56**:1210–21.

Brouwer 2010b
Brouwer MC, Heckenberg SG, de Gans J, Spanjaard L, Reitsma JB, van de Beek D. Nationwide implementation of adjunctive dexamethasone therapy for pneumococcal meningitis. *Neurology* 2010;**75**(17):1533–9.

Brouwer 2010c
Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clinical Microbiology Reviews* 2010;**23**(3): 467–92.

Brouwer 2012
Brouwer MC, van der Ende A, Baas F, van de Beek D. Genetic variation in GLCCI1 and dexamethasone in bacterial meningitis. *Journal of Infection* 2012;**65**(5):465–7.

Cornelis 2011
Cornelis AS, Hachimi-Idrissi S. The use of dexamethasone in bacterial meningitis in children and adults: a retrospective analysis. *ISRN Pediatrics* 2011;**2011**:380283.

Fritz 2012
Fritz D, Brouwer MC, van de Beek D. Dexamethasone and long-term survival in bacterial meningitis. *Neurology* 2012; **79**(22):2177–9.

Geiman 1992
Geiman BJ, Smith AL. Dexamethasone and bacterial meningitis. A meta-analysis of randomized clinical trials. *Western Journal of Medicine* 1992;**157**:27–31.

Glasziou 1995
Glasziou PP, Irwig LM. An evidence based approach to individualising treatment. *BMJ* 1995;**311**(7016):1356–9.

Havens 1989
Havens PL, Wendelberger KJ, Hoffman GM, Lee MB, Chusid MJ. Corticosteroids as adjunctive therapy in bacterial meningitis. A meta-analysis of clinical trials. *American Journal of Diseases of Children* 1989;**143**:1051–5.

Heckenberg 2012a
Heckenberg SG, Brouwer MC, van der Ende A, Hensen EF, van de Beek D. Hearing loss in adults surviving pneumococcal meningitis is associated with otitis and pneumococcal serotype. *Clinical Microbiology and Infection* 2012;**18**(9):849–55.

Heckenberg 2012b
Heckenberg SG, Brouwer MC, van der Ende A, van de Beek D. Adjunctive dexamethasone in adults with meningococcal meningitis. *Neurology* 2012;**79**(15):1563–9.

Higgins 2011
Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org. Chichester, UK: Wiley–Blackwell.

Klugman 1995
Klugman KP, Friedland IR, Bradley JS. Bactericidal activity against cephalosporin-resistant Streptococcus pneumoniae in cerebrospinal fluid of children with acute bacterial meningitis. *Antimicrobial Agents and Chemotherapy* 1995; **39**(9):1988–92.

Køster-Rasmussen 2008
Køster-Rasmussen R, Korshin A, Meyer CN. Antibiotic treatment delay and outcome in acute bacterial meningitis. *Journal of Infection* 2008;**57**:449–54.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). *Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration,*

2011. Available from www.cochrane-handbook.org. Chichester, UK: Wiley-Blackwell, 2011.

Lutsar 2003
Lutsar I, Friedland IR, Jafri HS, Wubbel L, Ahmed A, Trujillo M, et al.Factors influencing the anti-inflammatory effect of dexamethasone therapy in experimental pneumococcal meningitis. *Journal of Antimicrobial Chemotherapy* 2003;**52**(4):651–5.

McIntyre 1997
McIntyre PB, Berkey CS, King SM, Schaad UB, Kilpi T, Kanra GY, et al.Dexamethasone as adjunctive therapy in bacterial meningitis. A meta-analysis of randomized clinical trials since 1988. *JAMA* 1997;**278**(11):925–31.

McIntyre 2010
McIntyre P. Adjunctive dexamethasone in meningitis: does value depend on clinical setting?. *Lancet Neurology* 2010;**9**: 229–31.

McIntyre 2012
McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis world-wide. *Lancet* 2012;**380**(9854):1703–11.

McMillan 2001
McMillan DA, Lin CY, Aronin SI, Quagliarello VJ. Community-acquired bacterial meningitis in adults: categorization of causes and timing of death. *Clinical Infectious Diseases* 2001;**33**:969–75.

Molyneux 2006
Molyneux E, Riordan FA, Walsh A. Acute bacterial meningitis in children presenting to the Royal Liverpool Children's Hospital, Liverpool, UK and the Queen Elizabeth Central Hospital in Blantyre, Malawi: a world of difference. *Annals of Tropical Paediatrics* 2006;**26**(1):29–37.

Peltola 2000
Peltola H. Worldwide Haemophilus influenzae type B disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clinical Microbiology Reviews* 2000;**13**(2): 302–17.

Peterković 2012
Peterković V, Trkulja V, Kutleša M, Krajinović V, Lepur D. Dexamethasone for adult community-acquired bacterial meningitis: 20 years of experience in daily practice. *Journal of Neurology* 2012;**259**(2):225–36.

Prasad 1995
Prasad K, Haines T. Dexamethasone treatment for acute bacterial meningitis: how strong is the evidence for routine use?. *Journal of Neurology, Neurosurgery and Psychiatry* 1995; **59**(1):31–7.

Proulx 2005
Proulx N, Fréchette D, Toye B, Chan J, Kravcik S. Delays in the administration of antibiotics are associated with mortality from adult acute bacterial meningitis. *QJM* 2005; **94**:291–8.

RevMan 2011
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Ricard 2007
Ricard JD, Wolff M, Lacherade JC, Mourvillier B, Hidri N, Barnaud G, et al.Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. *Clinical Infectious Diseases* 2007;**44**: 250–5.

Sapolsky 1985
Sapolsky RM, Pulsinelli WA. Glucocorticoids potentiate ischemic injury to neurons: therapeutic implications. *Science* 1985;**229**(4720):1397–400.

Scheld 1980
Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis. Alterations with penicillin and methylprednisolone. *Journal of Clinical Investigation* 1980;**66**(2):243–53.

Tauber 1985
Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *Journal of Infectious Diseases* 1985;**151**(3):528–34.

Török 2011
Török ME, Nguyen DB, Tran TH, Nguyen TB, Thwaites GE, Hoang TQ, et al. Dexamethasone and long-term outcome of tuberculous meningitis in Vietnamese adults and adolescents. *PLoS One* 2011;**6**(12):e27821.

UNHDI 2009
United Nations Human Development Index. Human Development Index. http://hdr.undp.org/en/statistics/ 2009 (accessed 25 November 2009).

van de Beek 2002
van de Beek D, Schmand B, De Gans J, Weisfelt M, Vaessen H, Dankert J, et al.Cognitive impairment in adults with good recovery after bacterial meningitis. *Journal of Infectious Diseases* 2002;**186**(7):1047–52.

van de Beek 2004a
van de Beek D, de Gans J. Dexamethasone and pneumococcal meningitis. *Annals of Internal Medicine* 2004;**141**(4):327.

van de Beek 2004b
van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *New England Journal of Medicine* 2004;**351**(18):1849–59.

van de Beek 2006a
van de Beek D, de Gans J, Tunkel AR, Wijdicks EFM. Community-acquired bacterial meningitis in adults. *New England Journal of Medicine* 2006;**354**(1):44–53. [MEDLINE: 16394301]

van de Beek 2006b
van de Beek D, de Gans J. Dexamethasone in adults with community-acquired bacterial meningitis. *Drugs* 2006;**66** (4):415–27.

van de Beek 2010
van de Beek D, Farrar JJ, de Gans J, Mai NT, Molyneux EM, Peltola H, et al.Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurology* 2010;**9**:254–63.

Vardakas 2009
Vardakas KZ, Matthaiou DK, Falagas ME. Adjunctive dexamethasone therapy for bacterial meningitis in adults: a meta-analysis of randomized controlled trials. *European Journal of Neurology* 2009;**16**:662–73.

Viladrich 1991
Viladrich PF, Gudiol F, Linares J, Pallares R, Sabate I, Rufi G, et al.Evaluation of vancomycin for therapy of adult pneumococcal meningitis. *Antimicrobial Agents and Chemotherapy* 1991;**35**(12):2467–72.

Weisfelt 2006
Weisfelt M, Hoogman M, van de Beek D, de Gans J, Dresschler WA, Schmand B. Dexamethasone and long-term outcome in adults with bacterial meningitis. *Annals of Neurology* 2006;**60**(4):456–68.

References to other published versions of this review

Brouwer 2010a
Brouwer MC, McIntyre P, de Gans J, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2010, Issue 9. [DOI: 10.1002/14651858.CD004405.pub3]

van de Beek 2003
van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids in acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD004405.pub2]

van de Beek 2007
van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD004405.pub2]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bademosi 1979

Methods	Randomised, unblinded
Participants	10 to 59 years; bacteriologically proven pneumococcal meningitis
Interventions	Hydrocortisone, 100 mg; followed by prednisolone 60 mg/d, 14 d; before or with antibiotics (AB)
Outcomes	Mortality
Notes	AB - Sulf/pen, mortality 44%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure is not specified
Allocation concealment (selection bias)	High risk	The treatment allocation is not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The study is not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	Unclear risk	No information provided
Other bias	High risk	Limited data presented; unevenly distributed severity of disease

Belsey 1969

Methods	Randomised, double-blind
Participants	0 to 17 years; purulent meningitis
Interventions	DXM 1.2 mg/m^2/d, 4 d; timing unclear
Outcomes	Mortality, hearing loss, adverse events (herpes zoster infections)

Notes	AB - Chlor/sulf/pen, mortality 3% Other - matching of patients and controls in 48 categories	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	Unclear risk	No information on allocation concealment is provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	16 randomised patients that could not be matched were not included; patients dying < 18 hours of hospitalisation were excluded from the analysis. No intention-to-treat analysis
Other bias	High risk	Unevenly distributed severity of disease at admission (control group worse)

Bennett 1963

Methods	Randomised, double-blind
Participants	All ages; life-threatening infectious diseases, subgroup meningitis
Interventions	Hydrocortisone scheme, 7 d; after AB
Outcomes	Mortality
Notes	AB - not specified, mortality 45%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	Low risk	Allocation was concealed

Bennett 1963 (*Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis for suspected bacterial meningitis patients. Selection of culture-proven bacterial meningitis patients from a large cohort of severely ill patients
Other bias	Unclear risk	Baseline characteristics and treatment specifications of DXM and control groups are not reported

Bhaumik 1998

Methods	Randomised, unblinded
Participants	12 to 75 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 16 mg/day, 4 d, plus 3 d scheme; after AB
Outcomes	Mortality, neurological sequelae, adverse events (not specified)
Notes	AB - pen/chlor or ceph, mortality 13%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised table chart
Allocation concealment (selection bias)	High risk	The treatment allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The study is not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	Unclear risk	No intention-to-treat analysis
Other bias	High risk	Unevenly distributed baseline and clinical characteristics

Ciana 1995

Methods	Randomised, unblinded
Participants	2 months to 6 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.4 mg/kg, 3 d; timing unclear
Outcomes	Mortality, neurological sequelae, adverse events (recurrent fever)
Notes	AB - ampi/chlor, mortality 28%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation procedure not specified
Allocation concealment (selection bias)	High risk	The treatment allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	The study is not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	Patient retrospectively excluded because of different diagnosis; high number of comatose patients compared to other trials. No intention-to-treat analysis
Other bias	Unclear risk	Limited clinical data available

de Gans 2002

Methods	Randomised, double-blind
Participants	Older than 16 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 4 d; before or with AB
Outcomes	Mortality, neurological sequelae, adverse events (herpes zoster/fungal infections, gastrointestinal bleeding, hyperglycaemia)
Notes	AB - various, mortality 11%

Risk of bias

Bias	Authors' judgement	Support for judgement

de Gans 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, block size 6
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	Inclusion chart provided. Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

DeLemos 1969

Methods	Randomised, double-blind
Participants	1 month to 17 years; diagnosis bacterial meningitis
Interventions	Methylprednisolone 120 mg/d, 3 d; after AB
Outcomes	Mortality
Notes	AB - chlor/sulf/pen, mortality 3%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised, block size 12
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis

Other bias	High risk	Antibiotic pretreatment unevenly distributed between randomisation arms

Girgis 1989

Methods	Randomised, unblinded
Participants	3 months to 70 years; diagnosis bacterial meningitis
Interventions	DXM 16 to 24 mg/d, 4 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae
Notes	AB - chlor/ampi, mortality 15%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pre-designed randomisation chart
Allocation concealment (selection bias)	High risk	The treatment allocation was not concealed
Blinding (performance bias and detection bias) All outcomes	High risk	Study was not blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	The very high number of comatose patients compared to other studies suggests a selection bias

Kanra 1995

Methods	Randomised, double-blind
Participants	2 to 6 years; bacteriologically proven pneumococcal meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (recurrent fever)

Kanra 1995 *(Continued)*

Notes	AB - sulf/ampi, mortality 5%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	Study was double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis; selection of pneumococcal meningitis patients
Other bias	High risk	Unevenly distributed severity of disease (Glasgow Coma Scale) at admission (control group better)

Kilpi 1995

Methods	Randomised, unblinded
Participants	3 months to 15 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 1.5 mg/kg/d, 3 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding)
Notes	AB - ceph, mortality 2% Other - trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated list of random therapy assignments
Allocation concealment (selection bias)	High risk	The treatment allocation was not concealed

Blinding (performance bias and detection bias) All outcomes	High risk	Study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	High number of pre-treated patients compared to other studies. Unevenly distributed between randomisation arms

King 1994

Methods	Randomised, double-blind
Participants	1 month to 13 years; suspected bacterial meningitis with CSF or blood criterion; also patients with suspected bacterial meningitis who were too unstable for lumbar puncture
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, persistent fever, recurrent fever)
Notes	AB - various, mortality 1%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis; more patients were excluded in the dexamethasone group because of final diagnosis other than bacterial meningitis
Other bias	Unclear risk	Insufficient information to determine other bias

Lebel 1988a

Methods	Randomised, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurrent fever, arthritis)
Notes	AB - ceph, mortality 2%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

Lebel 1988b

Methods	Randomised, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurrent fever, arthritis)
Notes	AB - ceph, mortality 2%

Risk of bias

Bias	Authors' judgement	Support for judgement

Lebel 1988b *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

Lebel 1989

Methods	Randomised, double-blind	
Participants	2 months to 16 years; suspected or proven bacterial meningitis	
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurrent fever, arthritis)	
Notes	AB - ceph, mortality 2%	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis

Lebel 1989 *(Continued)*

Other bias	High risk	Unevenly distributed number of antimicrobial resistance rates between treatment groups (control group worse)

Mathur 2013

Methods	Randomised, unblinded
Participants	Neonates (not defined)
Interventions	DXM 0.6 mg/kg/d, 2 days, with AB
Outcomes	Mortality, hearing loss, CSF parameters of inflammation at 24 h, disease severity
Notes	AB - ceph/amikacine + meropenem in severe cases, mortality 26%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Web-based randomisation
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data complete, no patients lost to follow-up or discontinued treatment
Selective reporting (reporting bias)	Low risk	Data complete, no patients lost to follow-up or discontinued treatment
Other bias	High risk	Differences in causative bacteria and culture-positive cases between treatment groups

Molyneux 2002

Methods	Randomised, double-blind
Participants	2 months to 13 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.8 mg/kg/d, 2 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae

Molyneux 2002 (*Continued)*

Notes	AB - pen/chlor, mortality 31%	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

Nguyen 2007

Methods	Randomised, double-blind	
Participants	Older than 14 years; culture-proven bacterial meningitis or suspected bacterial meningitis with CSF criteria	
Interventions	DXM 0.8 mg/kg/d, 4 d; before or with AB	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (herpes zoster infection, gastrointestinal bleeding)	
Notes	AB - various; mortality 11%	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, block size 100
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind

Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

Odio 1991

Methods	Randomised, double-blind
Participants	6 weeks to 16 years; culture-proven bacterial meningitis or suspected bacterial meningitis with CSF inflammation
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, persistent fever, recurrent fever, arthritis)
Notes	AB - ceph, mortality - 2%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

Peltola 2007

Methods	Randomised, double-blind
Participants	2 months to 16 years; proven or suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB
Outcomes	Mortality, neurological sequelae, hearing loss, adverse events (gastrointestinal bleeding, recurrent fever)
Notes	AB - ceph, mortality 15% Other - trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list, block size 24
Allocation concealment (selection bias)	Unclear risk	Partial allocation concealment: 2 hospitals did not allow double placebo treatment
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis
Other bias	Unclear risk	Unevenly distributed antibiotic pretreatment between randomisation arms

Qazi 1996

Methods	Randomised, double-blind
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding)
Notes	AB - ampi/chlor, mortality 19%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	High rate of culture-negative patients. High mortality but low rate of hearing loss. More changes in antibiotic therapy in control population

Sankar 2007

Methods	Randomised, double-blind
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.9 mg/kg, 2 d; timing unclear
Outcomes	Mortality, neurological sequelae, adverse events (gastrointestinal bleeding)
Notes	AB - ceph, mortality 4% Other - trial also evaluated adjunctive glycerol and combined adjunctive glycerol and DXM therapy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind

Sankar 2007 (*Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis
Other bias	Unclear risk	Only 1 patient with positive culture in DXM randomisation arm. Unevenly distributed numbers in randomisation arms. Large differences in baseline characteristics between randomisation arms

Scarborough 2007

Methods	Randomised, double-blind
Participants	Older than 15 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 32 mg/day, 4 d; before or with AB
Outcomes	Mortality, neurological sequelae, hearing loss, adverse events (herpes zoster infection, gastrointestinal bleeding, recurrent fever)
Notes	AB - ceph, mortality 54%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, block size 8
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	Low risk	Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

Schaad 1993

Methods	Randomised, double-blind
Participants	3 months to 16 years; suspected or proven bacterial
Interventions	DXM 0.8 mg/kg/d, 2 d; before or with AB
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurrent fever, persistent fever, arthritis)
Notes	AB - ceph, mortality 0%

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

Thomas 1999

Methods	Randomised, double-blind
Participants	17 to 99 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 3 d; after AB
Outcomes	Mortality, neurological sequelae, adverse events (herpes zoster infection, gastrointestinal bleeding)
Notes	AB - amox, mortality 13%

Risk of bias

Bias	Authors' judgement	Support for judgement

Thomas 1999 (*Continued)*

Random sequence generation (selection bias)	Low risk	Stratified, equilibrated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	Limited baseline and clinical characteristics. Age of participants unevenly distributed between randomisation arms

Wald 1995

Methods	Randomised, double-blind	
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria	
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurrent fever, arthritis)	
Notes	AB - cephalosporin, mortality - 1%	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list, block size 10
Allocation concealment (selection bias)	Low risk	Allocation was concealed
Blinding (performance bias and detection bias) All outcomes	Low risk	The study was double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (reporting bias)	High risk	No intention-to-treat analysis

Other bias	Unclear risk	Distribution of resistant bacterial strains (23 out of 143 strains) between randomisation arms is not reported

AB: antibiotics
Amox: amoxicillin
Ampi: ampicillin
Ceph: cephalosporin
Chlor: chloramphenicol
CSF: cerebrospinal fluid
d: days
DXM: dexamethasone
m^2: square metre
Pen: penicillin
Sulf: sulfadiazine

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

Study	Reason for exclusion
Ayaz 2008	Inadequate sequence generation
Baldy 1986	Inadequate sequence generation
Daoud 1999	Inadequate sequence generation
Farina 1995	Not enough data for inclusion (abstract only)
Gijwani 2002	Inadequate sequence generation
Gupta 1996	Inadequate sequence generation
Jensen 1969	Inadequate sequence generation
Lepper 1959	Inadequate sequence generation
Marguet 1993	No randomisation
Ozen 2006	No randomisation
Passos 1979	Inadequate sequence generation
Peltola 2004	Not enough data for inclusion

(*Continued*)

Shembesh 1997	Inadequate sequence generation
Singhi 2008	Data previously published (Sankar 2007)
Syrogiannopoulos 1994	No placebo group, compared 2-day 4-day regimen of dexamethasone
Tolaj 2010	No randomisation

DATA AND ANALYSES

Comparison 1. All patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	25	4121	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.80, 1.01]
2 Severe hearing loss	17	2437	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.51, 0.88]
3 Any hearing loss	20	2785	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.63, 0.87]
4 Short-term neurological sequelae	13	1756	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 1.00]
5 Long-term neurological sequelae	13	1706	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.10]
6 Adverse events	20		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 Gastrointestinal bleeding	16	2560	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.86, 2.45]
6.2 Herpes zoster infection	6	1432	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.86, 1.37]
6.3 Persistent fever	3	316	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.70]
6.4 Recurrent fever	12	1723	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [1.09, 1.47]
6.5 Fungal infection	1	301	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.56, 5.96]
6.6 Arthritis	6	618	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.27, 1.53]

Comparison 2. Children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	18	2511	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.07]
2 Severe hearing loss	14	1524	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.49, 0.91]
3 Any hearing loss	16	1961	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.86]

Comparison 3. Adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7	1517	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.53, 1.05]
2 Any hearing loss	4	844	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.56, 0.98]
3 Short-term neurological sequelae	4	542	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.01]

Comparison 4. Causative species

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	18		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 *Haemophilus influenzae*	11	825	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.53, 1.09]
1.2 *Streptococcus pneumoniae*	17	1132	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
1.3 *Neisseria meningitidis*	13	618	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.35, 1.46]
2 Severe hearing loss in children - non-*Haemophilus influenzae* species	13	860	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.65, 1.39]
3 Severe hearing loss in children - *Haemophilus influenzae*	10	756	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.20, 0.59]

Comparison 5. Income of countries

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality - all patients	25	4121	Risk Ratio (IV, Random, 95% CI)	0.88 [0.75, 1.03]
1.1 Low-income countries	9	1873	Risk Ratio (IV, Random, 95% CI)	0.87 [0.67, 1.15]
1.2 High-income countries	16	2248	Risk Ratio (IV, Random, 95% CI)	0.81 [0.63, 1.05]
2 Severe hearing loss - all patients	17	2445	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.58, 0.94]
2.1 Low-income countries	5	944	Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.72, 1.38]
2.2 High-income countries	12	1501	Risk Ratio (IV, Fixed, 95% CI)	0.51 [0.35, 0.73]
3 Any hearing loss	20	2805	Risk Ratio (IV, Fixed, 95% CI)	0.79 [0.69, 0.89]
3.1 Low-income countries	7	1051	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.76, 1.04]
3.2 High-income countries	13	1754	Risk Ratio (IV, Fixed, 95% CI)	0.58 [0.45, 0.73]
4 Short-term neurological sequelae - all patients	14	1814	Risk Ratio (IV, Fixed, 95% CI)	0.84 [0.70, 1.02]
4.1 Low-income countries	5	735	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.81, 1.31]
4.2 High-income countries	9	1079	Risk Ratio (IV, Fixed, 95% CI)	0.64 [0.48, 0.85]
5 Mortality - children	17	2486	Risk Ratio (IV, Fixed, 95% CI)	0.92 [0.77, 1.11]
5.1 Low-income countries	5	1119	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.75, 1.12]
5.2 High-income countries	12	1367	Risk Ratio (IV, Fixed, 95% CI)	0.96 [0.61, 1.50]
6 Severe hearing loss - children	14	1531	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.56, 0.98]
6.1 Low-income countries	3	387	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.69, 1.47]
6.2 High-income countries	11	1144	Risk Ratio (IV, Fixed, 95% CI)	0.52 [0.35, 0.78]
7 Short-term neurological sequelae - children	10	1271	Risk Ratio (IV, Fixed, 95% CI)	0.90 [0.72, 1.13]
7.1 Low-income countries	3	506	Risk Ratio (IV, Fixed, 95% CI)	1.08 [0.81, 1.43]
7.2 High-income countries	7	765	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.46, 0.97]
8 Severe hearing loss in children due to non-*Haemophilus influenzae* species	13	862	Risk Ratio (IV, Fixed, 95% CI)	0.97 [0.66, 1.42]
8.1 Low-income countries	2	297	Risk Ratio (IV, Fixed, 95% CI)	1.20 [0.72, 2.00]
8.2 High-income countries	11	565	Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.41, 1.31]
9 Mortality - adults	7	1517	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.82, 1.10]

9.1 Low-income countries	3	636	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.86, 1.20]
9.2 High-income countries	4	881	Risk Ratio (IV, Fixed, 95% CI)	0.76 [0.56, 1.04]
10 Any hearing loss adults	4	844	Risk Ratio (IV, Fixed, 95% CI)	0.76 [0.57, 1.00]
10.1 Low-income countries	1	195	Risk Ratio (IV, Fixed, 95% CI)	0.86 [0.58, 1.28]
10.2 High-income countries	3	649	Risk Ratio (IV, Fixed, 95% CI)	0.67 [0.45, 0.99]

Comparison 6. Timing of steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	22	3940	Risk Ratio (IV, Random, 95% CI)	0.87 [0.73, 1.05]
1.1 Before or with first dose antibiotic	13	3143	Risk Ratio (IV, Random, 95% CI)	0.87 [0.69, 1.09]
1.2 After first dose antibiotic	9	797	Risk Ratio (IV, Random, 95% CI)	0.83 [0.55, 1.26]
2 Severe hearing loss	16	2300	Risk Ratio (IV, Fixed, 95% CI)	0.82 [0.64, 1.06]
2.1 Before or with first dose antibiotic	10	1866	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.62, 1.07]
2.2 After first dose antibiotic	6	434	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.47, 1.68]
3 Any hearing loss	18	2754	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.68, 0.88]
3.1 Before or with antibiotics	12	2257	Risk Ratio (IV, Fixed, 95% CI)	0.80 [0.70, 0.92]
3.2 After first dose of antibiotics	6	497	Risk Ratio (IV, Fixed, 95% CI)	0.62 [0.43, 0.89]
4 Short-term neurologic sequelae	12	1739	Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.71, 1.03]
4.1 Before or with first dose antibiotic	6	1282	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.73, 1.13]
4.2 After first dose antibiotic	6	457	Risk Ratio (IV, Fixed, 95% CI)	0.70 [0.47, 1.04]

Comparison 7. Study quality

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	25	4121	Risk Ratio (IV, Fixed, 95% CI)	0.95 [0.85, 1.06]
1.1 High quality	4	1793	Risk Ratio (IV, Fixed, 95% CI)	1.00 [0.88, 1.14]
1.2 Medium quality	14	1477	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.57, 1.17]
1.3 Low quality	7	851	Risk Ratio (IV, Fixed, 95% CI)	0.79 [0.60, 1.04]
2 Severe hearing loss	17	2442	Risk Ratio (IV, Fixed, 95% CI)	0.72 [0.55, 0.95]
2.1 High quality	3	857	Risk Ratio (IV, Fixed, 95% CI)	0.99 [0.69, 1.41]
2.2 Medium quality	10	1051	Risk Ratio (IV, Fixed, 95% CI)	0.47 [0.29, 0.75]
2.3 Low quality	4	534	Risk Ratio (IV, Fixed, 95% CI)	0.50 [0.20, 1.29]
3 Any hearing loss	20	2806	Risk Ratio (IV, Fixed, 95% CI)	0.79 [0.69, 0.90]
3.1 High quality	4	1119	Risk Ratio (IV, Fixed, 95% CI)	0.90 [0.73, 1.12]
3.2 Medium quality	12	1150	Risk Ratio (IV, Fixed, 95% CI)	0.73 [0.62, 0.87]
3.3 Low quality	4	537	Risk Ratio (IV, Fixed, 95% CI)	0.76 [0.38, 1.51]
4 Short-term neurological sequelae	13	1756	Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.70, 1.03]
4.1 High quality	3	896	Risk Ratio (IV, Fixed, 95% CI)	0.97 [0.77, 1.23]

4.2 Medium quality	8	784	Risk Ratio (IV, Fixed, 95% CI)	0.63 [0.45, 0.89]
4.3 Low quality	2	76	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.35, 1.95]

Comparison 8. Sensitivity analysis - worst-case scenario

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Severe hearing loss	17	2694	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.81, 1.93]
2 Any hearing loss	20	3029	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.71, 1.35]
3 Short-term neurological sequelae	13	1850	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
4 Long-term neurological sequelae	13	1758	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.78, 1.78]

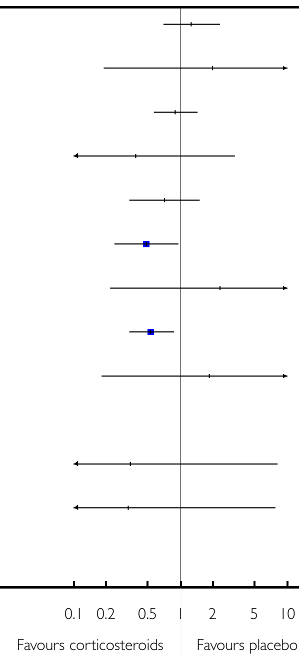
Analysis 1.1. Comparison 1 All patients, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 1 Mortality

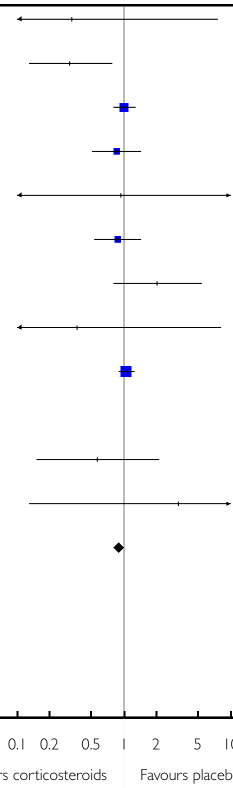
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bademosi 1979	12/24	11/28		2.5 %	1.27 [0.69, 2.34]
Belsey 1969	2/43	1/43		0.2 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		4.8 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		0.7 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		2.8 %	0.71 [0.33, 1.51]
de Gans 2002	11/157	21/144		5.3 %	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.2 %	2.33 [0.22, 25.03]
Girgis 1989	21/225	43/245		10.0 %	0.53 [0.33, 0.87]
Kanra 1995	2/29	1/27		0.3 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51		0.4 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.4 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49			Not estimable



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1989	0/31	1/30		0.4 %	0.32 [0.01, 7.63]
Mathur 2013	5/40	16/40		3.9 %	0.31 [0.13, 0.77]
Molyneux 2002	96/305	91/293		22.6 %	1.01 [0.80, 1.29]
Nguyen 2007	22/217	26/218		6.3 %	0.85 [0.50, 1.45]
Odio 1991	1/52	1/49		0.3 %	0.94 [0.06, 14.65]
Peltola 2007	23/166	26/163		6.4 %	0.87 [0.52, 1.46]
Qazi 1996	12/48	5/41		1.3 %	2.05 [0.79, 5.33]
Sankar 2007	0/12	1/13		0.4 %	0.36 [0.02, 8.05]
Scarborough 2007	129/231	120/228		29.4 %	1.06 [0.90, 1.26]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	3/31	5/29		1.3 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.1 %	3.21 [0.13, 77.60]
Total (95% CI)	**2064**	**2057**		**100.0 %**	**0.90 [0.80, 1.01]**



Total events: 367 (Corticosteroids), 409 (Placebo)

Heterogeneity: Chi^2 = 26.68, df = 21 (P = 0.18); I^2 =21%

Test for overall effect: Z = 1.80 (P = 0.072)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 All patients, Outcome 2 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 2 Severe hearing loss

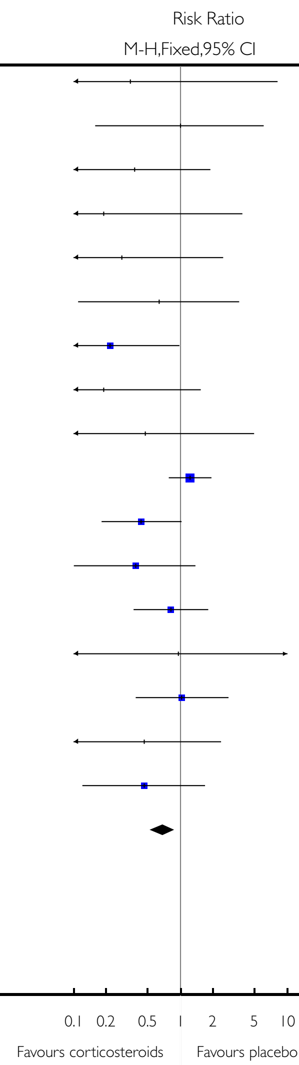
Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42	1.3 %	0.34 [0.01, 8.14]
Bhaumik 1998	2/13	2/13	1.8 %	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177	4.5 %	0.37 [0.07, 1.90]
Kanra 1995	0/27	2/26	2.2 %	0.19 [0.01, 3.84]
Kilpi 1995	1/31	3/26	2.9 %	0.28 [0.03, 2.53]
King 1994	2/48	3/45	2.7 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38	7.5 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46	4.5 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29	1.8 %	0.47 [0.04, 4.89]
Molyneux 2002	31/147	27/158	22.8 %	1.23 [0.78, 1.96]
Nguyen 2007	7/180	16/177	14.2 %	0.43 [0.18, 1.02]
Odio 1991	3/50	7/44	6.5 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131	10.7 %	0.81 [0.36, 1.81]
Qazi 1996	1/26	1/25	0.9 %	0.96 [0.06, 14.55]
Scarborough 2007	7/96	7/99	6.1 %	1.03 [0.38, 2.83]
Schaad 1993	2/60	4/55	3.7 %	0.46 [0.09, 2.40]
Wald 1995	3/67	7/72	5.9 %	0.46 [0.12, 1.71]
Total (95% CI)	**1234**	**1203**	**100.0 %**	**0.67 [0.51, 0.88]**

Total events: 75 (Corticosteroids), 112 (Placebo)

Heterogeneity: Chi^2 = 15.67, df = 16 (P = 0.48); I^2 =0.0%

Test for overall effect: Z = 2.86 (P = 0.0042)

Test for subgroup differences: Not applicable



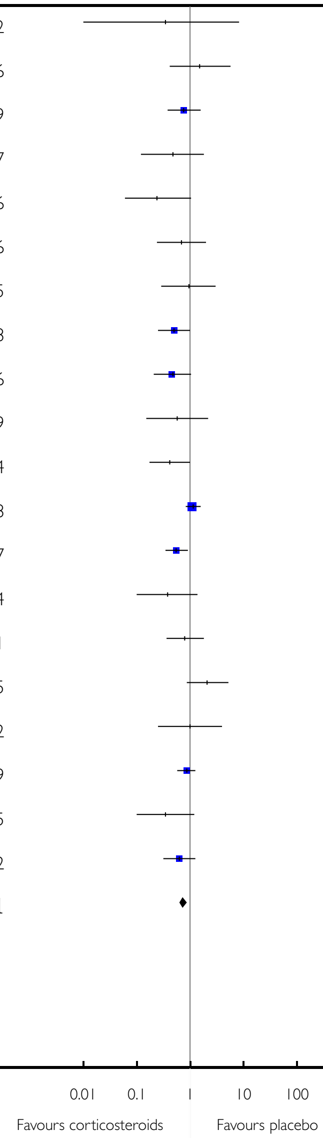
Analysis 1.3. Comparison 1 All patients, Outcome 3 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 3 Any hearing loss

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		0.6 %	0.34 [0.01, 8.14]
Bhaumik 1998	4/14	3/16		1.1 %	1.52 [0.41, 5.67]
de Gans 2002	13/143	14/119		5.8 %	0.77 [0.38, 1.58]
Girgis 1989	3/190	6/177		2.4 %	0.47 [0.12, 1.83]
Kanra 1995	2/27	8/26		3.1 %	0.24 [0.06, 1.03]
Kilpi 1995	5/31	6/26		2.5 %	0.70 [0.24, 2.03]
King 1994	5/48	5/45		2.0 %	0.94 [0.29, 3.02]
Lebel 1988a	9/43	16/38		6.4 %	0.50 [0.25, 0.99]
Lebel 1988b	7/49	14/46		5.5 %	0.47 [0.21, 1.06]
Lebel 1989	3/30	5/29		1.9 %	0.58 [0.15, 2.21]
Mathur 2013	6/35	10/24		4.5 %	0.41 [0.17, 0.98]
Molyneux 2002	49/147	46/158		16.8 %	1.14 [0.82, 1.60]
Nguyen 2007	21/180	37/177		14.2 %	0.56 [0.34, 0.91]
Odio 1991	3/50	7/44		2.8 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131		4.6 %	0.81 [0.36, 1.81]
Qazi 1996	11/26	5/25		1.9 %	2.12 [0.86, 5.22]
Sankar 2007	3/12	3/12		1.1 %	1.00 [0.25, 4.00]
Scarborough 2007	30/96	36/99		13.4 %	0.86 [0.58, 1.28]
Schaad 1993	3/60	8/55		3.2 %	0.34 [0.10, 1.23]
Wald 1995	10/67	17/72		6.2 %	0.63 [0.31, 1.28]
Total (95% CI)	**1424**	**1361**		**100.0 %**	**0.74 [0.63, 0.87]**



Total events: 197 (Corticosteroids), 259 (Placebo)

Heterogeneity: Chi^2 = 25.05, df = 19 (P = 0.16); I^2 =24%

Test for overall effect: Z = 3.59 (P = 0.00033)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 All patients, Outcome 4 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 4 Short-term neurological sequelae

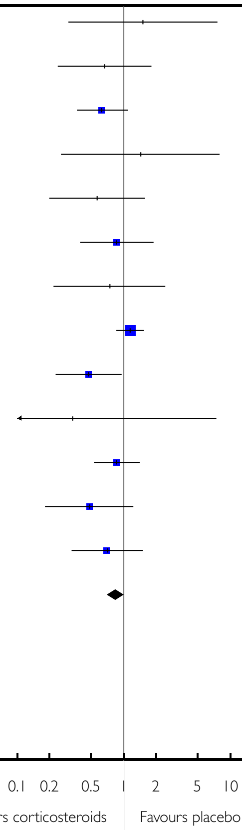
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	3/13	2/13		1.1 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		3.8 %	0.66 [0.24, 1.80]
de Gans 2002	18/143	24/119		13.8 %	0.62 [0.36, 1.09]
Kanra 1995	3/27	2/26		1.1 %	1.44 [0.26, 7.96]
Lebel 1988a	5/48	8/43		4.4 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		5.4 %	0.86 [0.39, 1.92]
Lebel 1989	4/28	5/26		2.7 %	0.74 [0.22, 2.47]
Molyneux 2002	69/223	56/209		30.4 %	1.15 [0.86, 1.56]
Peltola 2007	10/139	21/137		11.1 %	0.47 [0.23, 0.96]
Sankar 2007	0/12	1/12		0.8 %	0.33 [0.01, 7.45]
Scarborough 2007	21/98	26/104		13.3 %	0.86 [0.52, 1.42]
Thomas 1999	5/28	9/24		5.1 %	0.48 [0.18, 1.23]
Wald 1995	9/68	14/74		7.1 %	0.70 [0.32, 1.51]
Total (95% CI)	**900**	**856**		**100.0 %**	**0.83 [0.69, 1.00]**

Total events: 161 (Corticosteroids), 185 (Placebo)

Heterogeneity: Chi^2 = 11.75, df = 12 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 1.99 (P = 0.046)

Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1 All patients, Outcome 5 Long-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 5 Long-term neurological sequelae

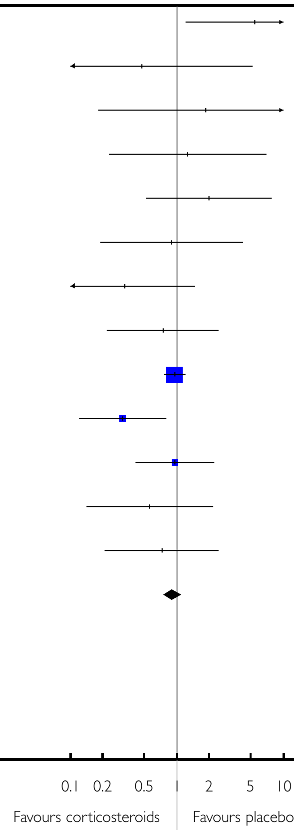
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
DeLemos 1969	9/48	2/57		1.3 %	5.34 [1.21, 23.55]
Girgis 1989	1/190	2/177		1.5 %	0.47 [0.04, 5.09]
Kanra 1995	2/29	1/27		0.7 %	1.86 [0.18, 19.38]
Kilpi 1995	3/31	2/26		1.5 %	1.26 [0.23, 6.97]
King 1994	5/37	3/44		1.9 %	1.98 [0.51, 7.75]
Lebel 1988a	3/38	3/34		2.2 %	0.89 [0.19, 4.14]
Lebel 1988b	2/43	6/41		4.3 %	0.32 [0.07, 1.49]
Lebel 1989	4/28	5/26		3.6 %	0.74 [0.22, 2.47]
Nguyen 2007	79/193	83/192		58.4 %	0.95 [0.75, 1.20]
Odio 1991	5/51	15/48		10.8 %	0.31 [0.12, 0.80]
Qazi 1996	9/48	8/41		6.1 %	0.96 [0.41, 2.26]
Schaad 1993	3/60	5/55		3.7 %	0.55 [0.14, 2.19]
Wald 1995	4/68	6/74		4.0 %	0.73 [0.21, 2.46]
Total (95% CI)	**864**	**842**		**100.0 %**	**0.90 [0.74, 1.10]**

Total events: 129 (Corticosteroids), 141 (Placebo)

Heterogeneity: $Chi^2 = 15.20$, df = 12 (P = 0.23); I^2 =21%

Test for overall effect: Z = 1.03 (P = 0.30)

Test for subgroup differences: Not applicable



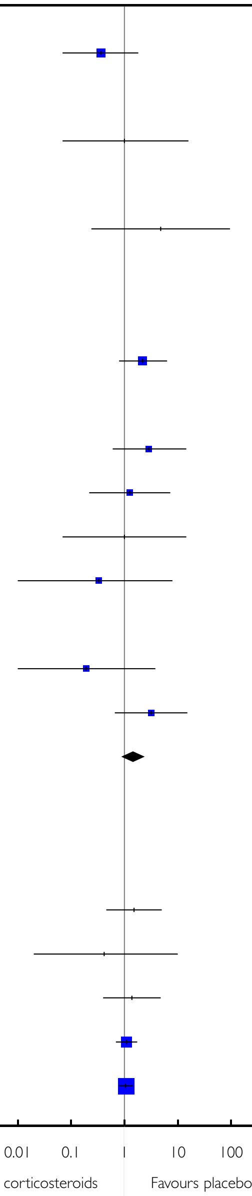
Analysis 1.6. Comparison 1 All patients, Outcome 6 Adverse events.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 6 Adverse events

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Gastrointestinal bleeding					
de Gans 2002	2/157	5/144		22.8 %	0.37 [0.07, 1.86]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	1/50	1/51		4.3 %	1.02 [0.07, 15.86]
Lebel 1988a	0/51	0/49			Not estimable
Lebel 1988b	2/51	0/49		2.2 %	4.81 [0.24, 97.68]
Lebel 1989	0/31	0/29			Not estimable
Mathur 2013	0/40	0/40			Not estimable
Nguyen 2007	11/217	5/218		21.8 %	2.21 [0.78, 6.25]
Odio 1991	0/52	0/48			Not estimable
Peltola 2007	6/166	2/163		8.8 %	2.95 [0.60, 14.38]
Qazi 1996	3/48	2/41		9.4 %	1.28 [0.22, 7.30]
Sankar 2007	1/12	1/12		4.4 %	1.00 [0.07, 14.21]
Scarborough 2007	0/233	1/232		6.6 %	0.33 [0.01, 8.11]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	0/31	2/29		11.3 %	0.19 [0.01, 3.75]
Wald 1995	6/69	2/74		8.4 %	3.22 [0.67, 15.41]
Subtotal (95% CI)	**1300**	**1260**		**100.0 %**	**1.45 [0.86, 2.45]**
Total events: 32 (Corticosteroids), 21 (Placebo)					
Heterogeneity: Chi^2 = 8.52, df = 9 (P = 0.48); I^2 =0.0%					
Test for overall effect: Z = 1.41 (P = 0.16)					
2 Herpes zoster infection					
Belsey 1969	6/43	4/43		3.8 %	1.50 [0.46, 4.94]
Bennett 1963	0/38	1/47		1.3 %	0.41 [0.02, 9.79]
de Gans 2002	6/157	4/144		3.9 %	1.38 [0.40, 4.78]
Nguyen 2007	33/217	30/218		28.2 %	1.11 [0.70, 1.75]
Scarborough 2007	70/233	65/232		61.4 %	1.07 [0.81, 1.43]



(Continued . . .)

(... *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thomas 1999	0/31	1/29		1.5 %	0.31 [0.01, 7.38]
Subtotal (95% CI)	**719**	**713**		**100.0 %**	**1.09 [0.86, 1.37]**
Total events: 115 (Corticosteroids), 105 (Placebo)					
Heterogeneity: Chi^2 = 1.39, df = 5 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.73 (P = 0.47)					
3 Persistent fever					
King 1994	3/50	8/51		38.8 %	0.38 [0.11, 1.36]
Odio 1991	1/52	10/48		51.0 %	0.09 [0.01, 0.69]
Schaad 1993	2/60	2/55		10.2 %	0.92 [0.13, 6.29]
Subtotal (95% CI)	**162**	**154**		**100.0 %**	**0.29 [0.12, 0.70]**
Total events: 6 (Corticosteroids), 20 (Placebo)					
Heterogeneity: Chi^2 = 2.80, df = 2 (P = 0.25); I^2 =28%					
Test for overall effect: Z = 2.75 (P = 0.0059)					
4 Recurrent fever					
Ciana 1995	9/34	6/36		3.0 %	1.59 [0.63, 3.99]
Kanra 1995	5/29	4/27		2.2 %	1.16 [0.35, 3.89]
Kilpi 1995	4/50	3/51		1.6 %	1.36 [0.32, 5.77]
Lebel 1988a	31/51	23/49		12.3 %	1.29 [0.89, 1.88]
Lebel 1988b	32/51	11/49		5.9 %	2.80 [1.59, 4.90]
Lebel 1989	14/31	14/29		7.6 %	0.94 [0.54, 1.61]
Odio 1991	10/52	9/48		4.9 %	1.03 [0.46, 2.31]
Peltola 2007	65/166	66/163		34.8 %	0.97 [0.74, 1.26]
Qazi 1996	20/48	14/41		7.9 %	1.22 [0.71, 2.10]
Scarborough 2007	7/233	2/232		1.0 %	3.48 [0.73, 16.60]
Schaad 1993	19/60	11/50		6.3 %	1.44 [0.76, 2.73]
Wald 1995	31/69	25/74		12.6 %	1.33 [0.88, 2.01]
Subtotal (95% CI)	**874**	**849**		**100.0 %**	**1.27 [1.09, 1.47]**
Total events: 247 (Corticosteroids), 188 (Placebo)					
Heterogeneity: Chi^2 = 15.16, df = 11 (P = 0.18); I^2 =27%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
5 Fungal infection					
de Gans 2002	8/157	4/144		100.0 %	1.83 [0.56, 5.96]
Subtotal (95% CI)	**157**	**144**		**100.0 %**	**1.83 [0.56, 5.96]**
Total events: 8 (Corticosteroids), 4 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.01 (P = 0.31)					
6 Arthritis					
Lebel 1988a	1/51	4/49		33.0 %	0.24 [0.03, 2.07]

0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

(*Continued* ...)

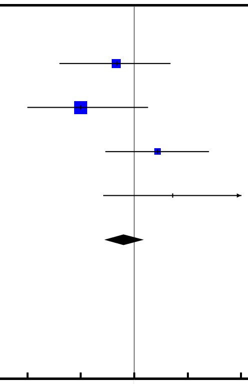
(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	1/31	2/29		16.7 %	0.47 [0.04, 4.89]
Odio 1991	0/52	4/48		37.9 %	0.10 [0.01, 1.86]
Schaad 1993	3/60	1/55		8.4 %	2.75 [0.29, 25.66]
Wald 1995	2/69	0/74		3.9 %	5.36 [0.26, 109.65]
Subtotal (95% CI)	**314**	**304**		**100.0 %**	**0.64 [0.27, 1.53]**

Total events: 7 (Corticosteroids), 11 (Placebo)

Heterogeneity: Chi^2 = 5.94, df = 4 (P = 0.20); I^2 =33%

Test for overall effect: Z = 1.00 (P = 0.32)



0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

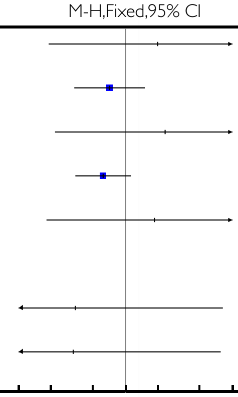
Analysis 2.1. Comparison 2 Children, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 2 Children

Outcome: 1 Mortality

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	2/43	1/43		0.5 %	2.00 [0.19, 21.24]
Ciana 1995	8/34	12/36		6.2 %	0.71 [0.33, 1.51]
DeLemos 1969	2/54	1/63		0.5 %	2.33 [0.22, 25.03]
Girgis 1989	15/142	24/140		12.9 %	0.62 [0.34, 1.12]
Kanra 1995	2/29	1/27		0.6 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51		0.8 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.8 %	0.32 [0.01, 7.68]



0.1 0.2 0.5 1 2 5 10

Favours corticosteroids Favours placebo

(*Continued* . . .)

(... *Continued*)

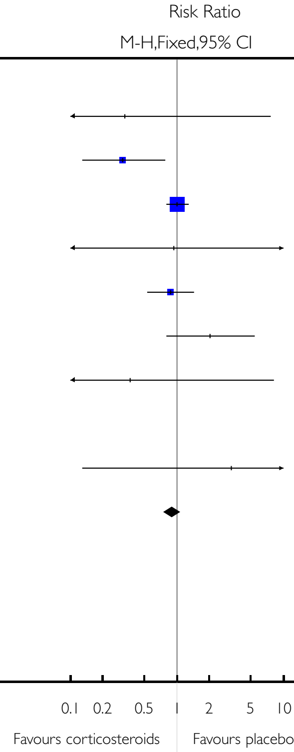
Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1988b	0/51	0/49		Not estimable
Lebel 1989	0/31	1/30	0.8 %	0.32 [0.01, 7.63]
Mathur 2013	5/40	16/40	8.6 %	0.31 [0.13, 0.77]
Molyneux 2002	96/305	91/293	49.7 %	1.01 [0.80, 1.29]
Odio 1991	1/52	1/49	0.6 %	0.94 [0.06, 14.65]
Peltola 2007	23/166	26/163	14.1 %	0.87 [0.52, 1.46]
Qazi 1996	12/48	5/41	2.9 %	2.05 [0.79, 5.33]
Sankar 2007	0/12	1/13	0.8 %	0.36 [0.02, 8.05]
Schaad 1993	0/60	0/55		Not estimable
Wald 1995	1/69	0/74	0.3 %	3.21 [0.13, 77.60]
Total (95% CI)	**1269**	**1242**	**100.0 %**	**0.89 [0.74, 1.07]**

Total events: 167 (Corticosteroids), 182 (Placebo)

Heterogeneity: $Chi^2 = 14.58$, df = 14 (P = 0.41); $I^2 = 4\%$

Test for overall effect: Z = 1.22 (P = 0.22)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Children, Outcome 2 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 2 Children

Outcome: 2 Severe hearing loss

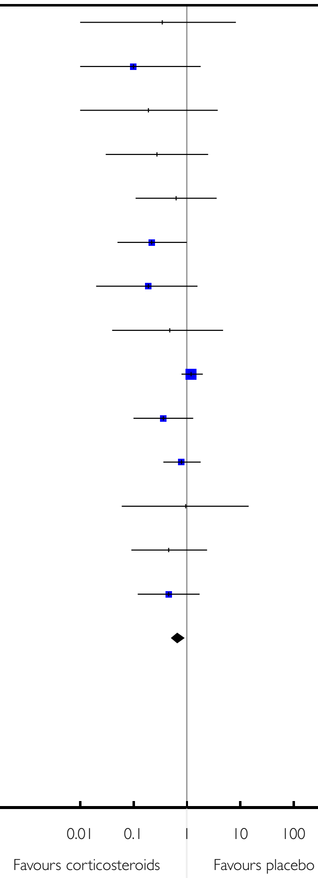
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		1.7 %	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		5.2 %	0.10 [0.01, 1.79]
Kanra 1995	0/27	2/26		2.9 %	0.19 [0.01, 3.84]
Kilpi 1995	1/31	3/26		3.7 %	0.28 [0.03, 2.53]
King 1994	2/48	3/45		3.5 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38		9.6 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46		5.8 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29		2.3 %	0.47 [0.04, 4.89]
Molyneux 2002	31/147	27/158		29.4 %	1.23 [0.78, 1.96]
Odio 1991	3/51	7/44		8.5 %	0.37 [0.10, 1.34]
Peltola 2007	10/135	12/131		13.8 %	0.81 [0.36, 1.81]
Qazi 1996	1/26	1/25		1.2 %	0.96 [0.06, 14.55]
Schaad 1993	2/60	4/55		4.7 %	0.46 [0.09, 2.40]
Wald 1995	3/67	7/72		7.6 %	0.46 [0.12, 1.71]
Total (95% CI)	**772**	**752**		**100.0 %**	**0.67 [0.49, 0.91]**

Total events: 57 (Corticosteroids), 86 (Placebo)

Heterogeneity: Chi^2 = 15.02, df = 13 (P = 0.31); I^2 =13%

Test for overall effect: Z = 2.58 (P = 0.0099)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Children, Outcome 3 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 2 Children

Outcome: 3 Any hearing loss

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		0.7 %	0.34 [0.01, 8.14]
Girgis 1989	3/190	6/177		3.1 %	0.47 [0.12, 1.83]
Kanra 1995	2/27	8/26		4.1 %	0.24 [0.06, 1.03]
Kilpi 1995	5/31	6/26		3.3 %	0.70 [0.24, 2.03]
King 1994	5/48	5/45		2.6 %	0.94 [0.29, 3.02]
Lebel 1988a	9/43	16/38		8.5 %	0.50 [0.25, 0.99]
Lebel 1988b	7/49	14/46		7.2 %	0.47 [0.21, 1.06]
Lebel 1989	3/30	5/29		2.5 %	0.58 [0.15, 2.21]
Mathur 2013	6/35	10/24		5.9 %	0.41 [0.17, 0.98]
Molyneux 2002	49/147	46/158		22.2 %	1.14 [0.82, 1.60]
Odio 1991	3/50	7/44		3.7 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131		6.1 %	0.81 [0.36, 1.81]
Qazi 1996	28/36	32/35		16.2 %	0.85 [0.70, 1.04]
Sankar 2007	3/12	3/12		1.5 %	1.00 [0.25, 4.00]
Schaad 1993	3/60	8/55		4.2 %	0.34 [0.10, 1.23]
Wald 1995	10/67	17/72		8.2 %	0.63 [0.31, 1.28]
Total (95% CI)	**1001**	**960**		**100.0 %**	**0.73 [0.61, 0.86]**

Total events: 146 (Corticosteroids), 196 (Placebo)

Heterogeneity: $Chi^2 = 19.33$, df = 15 (P = 0.20); $I^2 = 22\%$

Test for overall effect: Z = 3.60 (P = 0.00032)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

Analysis 3.1. Comparison 3 Adults, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 3 Adults

Outcome: 1 Mortality

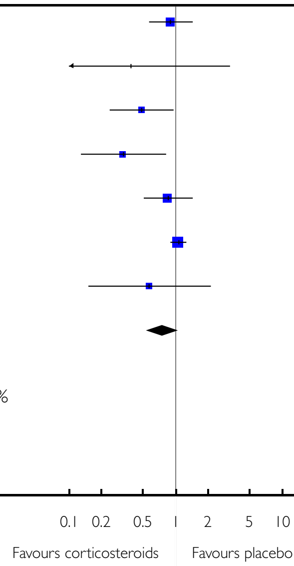
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bennett 1963	16/38	22/47		19.9 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		2.4 %	0.38 [0.04, 3.26]
de Gans 2002	11/157	21/144		14.0 %	0.48 [0.24, 0.96]
Girgis 1989	5/68	18/79		9.5 %	0.32 [0.13, 0.82]
Nguyen 2007	22/217	26/218		18.2 %	0.85 [0.50, 1.45]
Scarborough 2007	129/231	120/228		30.5 %	1.06 [0.90, 1.26]
Thomas 1999	3/31	5/29		5.5 %	0.56 [0.15, 2.14]
Total (95% CI)	**756**	**761**		**100.0 %**	**0.74 [0.53, 1.05]**

Total events: 187 (Corticosteroids), 215 (Placebo)

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 13.07$, df = 6 (P = 0.04); $I^2 = 54\%$

Test for overall effect: Z = 1.70 (P = 0.089)

Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3 Adults, Outcome 2 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 3 Adults

Outcome: 2 Any hearing loss

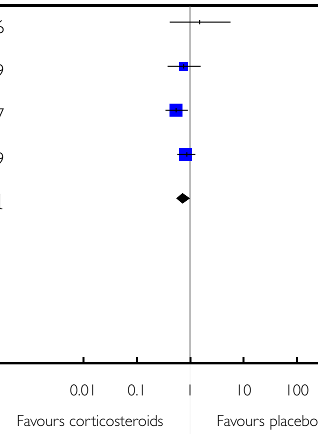
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	4/14	3/16		3.1 %	1.52 [0.41, 5.67]
de Gans 2002	13/143	14/119		16.8 %	0.77 [0.38, 1.58]
Scarborough 2007	21/180	37/177		41.1 %	0.56 [0.34, 0.91]
Thomas 1999	30/96	36/99		39.0 %	0.86 [0.58, 1.28]
Total (95% CI)	**433**	**411**		**100.0 %**	**0.74 [0.56, 0.98]**

Total events: 68 (Corticosteroids), 90 (Placebo)

Heterogeneity: $Chi^2 = 2.98$, df = 3 (P = 0.40); $I^2 = 0.0\%$

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3 Adults, Outcome 3 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 3 Adults

Outcome: 3 Short-term neurological sequelae

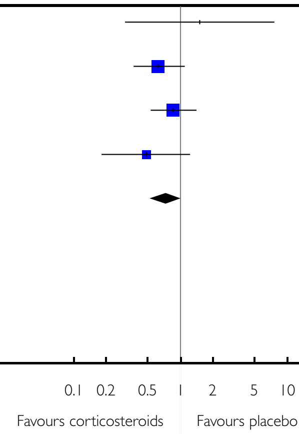
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	3/13	2/13		3.2 %	1.50 [0.30, 7.55]
de Gans 2002	18/143	24/119		41.5 %	0.62 [0.36, 1.09]
Scarborough 2007	21/98	26/104		40.0 %	0.86 [0.52, 1.42]
Thomas 1999	5/28	9/24		15.4 %	0.48 [0.18, 1.23]
Total (95% CI)	**282**	**260**		**100.0 %**	**0.72 [0.51, 1.01]**

Total events: 47 (Corticosteroids), 61 (Placebo)

Heterogeneity: $Chi^2 = 2.23$, $df = 3$ ($P = 0.53$); $I^2 = 0.0\%$

Test for overall effect: $Z = 1.88$ ($P = 0.059$)

Test for subgroup differences: Not applicable



Analysis 4.1. Comparison 4 Causative species, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 *Haemophilus influenzae*					
de Gans 2002	0/2	0/2			Not estimable
DeLemos 1969	1/32	0/37		0.9 %	3.45 [0.15, 81.95]
Girgis 1989	7/26	10/30		17.4 %	0.81 [0.36, 1.82]
Kilpi 1995	0/16	0/14			Not estimable
Lebel 1988a	0/40	1/37		2.9 %	0.31 [0.01, 7.36]
Lebel 1988b	0/39	0/38			Not estimable
Molyneux 2002	21/81	27/89		48.3 %	0.85 [0.53, 1.39]
Odio 1991	1/39	1/40		1.9 %	1.03 [0.07, 15.83]
Peltola 2007	7/54	10/60		17.8 %	0.78 [0.32, 1.90]
Schaad 1993	0/37	0/30			Not estimable
Wald 1995	0/43	5/39		10.8 %	0.08 [0.00, 1.45]
Subtotal (95% CI)	**409**	**416**		**100.0 %**	**0.76 [0.53, 1.09]**
Total events: 37 (Corticosteroids), 54 (Placebo)					
Heterogeneity: $Chi^2 = 3.79$, df = 6 (P = 0.70); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.50 (P = 0.13)					
2 *Streptococcus pneumoniae*					
Bademosi 1979	12/24	11/28		5.0 %	1.27 [0.69, 2.34]
Bennett 1963	12/26	15/30		6.9 %	0.92 [0.53, 1.60]
de Gans 2002	8/58	17/50		9.0 %	0.41 [0.19, 0.86]
DeLemos 1969	1/5	1/8		0.4 %	1.60 [0.13, 20.22]
Girgis 1989	7/52	22/54		10.7 %	0.33 [0.15, 0.71]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/1	0/5			Not estimable
Lebel 1988a	0/4	0/4			Not estimable
Lebel 1988b	0/4	0/4			Not estimable
Molyneux 2002	46/132	42/106		23.1 %	0.88 [0.63, 1.22]

0.02 0.1 1 10 50

Favours treatment Favours control

(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Nguyen 2007	0/26	5/29		2.6 %	0.10 [0.01, 1.74]
Odio 1991	0/4	0/4			Not estimable
Peltola 2007	8/35	10/36		4.9 %	0.82 [0.37, 1.84]
Scarborough 2007	68/129	72/143		33.8 %	1.05 [0.83, 1.32]
Schaad 1993	0/5	0/6			Not estimable
Thomas 1999	1/14	5/17		2.2 %	0.24 [0.03, 1.84]
Wald 1995	3/13	2/20		0.8 %	2.31 [0.44, 11.98]
Subtotal (95% CI)	**561**	**571**		**100.0 %**	**0.84 [0.72, 0.98]**
Total events: 168 (Corticosteroids), 203 (Placebo)					
Heterogeneity: Chi^2 = 20.60, df = 11 (P = 0.04); I^2 =47%					
Test for overall effect: Z = 2.16 (P = 0.031)					
3 *Neisseria meningitidis*					
Bennett 1963	1/4	2/5		10.6 %	0.63 [0.08, 4.66]
Ciana 1995	0/1	0/1			Not estimable
de Gans 2002	2/50	1/47		6.2 %	1.88 [0.18, 20.05]
DeLemos 1969	0/9	0/7			Not estimable
Girgis 1989	6/132	10/135		59.2 %	0.61 [0.23, 1.64]
Kilpi 1995	0/14	0/7			Not estimable
Lebel 1988a	0/3	0/4			Not estimable
Lebel 1988b	0/6	0/4			Not estimable
Molyneux 2002	1/32	2/35		11.4 %	0.55 [0.05, 5.75]
Peltola 2007	0/26	1/26		9.0 %	0.33 [0.01, 7.82]
Schaad 1993	0/12	0/16			Not estimable
Thomas 1999	1/11	0/7		3.6 %	2.00 [0.09, 43.22]
Wald 1995	0/11	0/13			Not estimable
Subtotal (95% CI)	**311**	**307**		**100.0 %**	**0.71 [0.35, 1.46]**
Total events: 11 (Corticosteroids), 16 (Placebo)					
Heterogeneity: Chi^2 = 1.45, df = 5 (P = 0.92); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					

0.02 0.1 1 10 50

Favours treatment Favours control

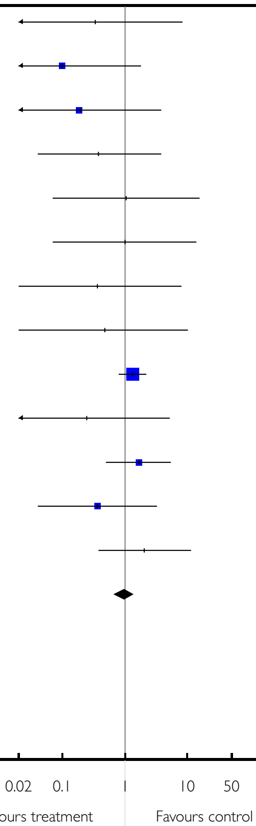
Analysis 4.2. Comparison 4 Causative species, Outcome 2 Severe hearing loss in children - non-Haemophilus influenzae species.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 2 Severe hearing loss in children - non-*Haemophilus influenzae* species

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		3.2 %	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		9.9 %	0.10 [0.01, 1.79]
Kanra 1995	0/27	2/26		5.4 %	0.19 [0.01, 3.84]
Kilpi 1995	1/17	2/13		4.8 %	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.1 %	1.05 [0.07, 15.69]
Lebel 1988a	1/9	1/9		2.1 %	1.00 [0.07, 13.64]
Lebel 1988b	0/10	1/11		3.1 %	0.36 [0.02, 8.03]
Lebel 1989	0/6	1/9		2.6 %	0.48 [0.02, 10.07]
Molyneux 2002	27/132	21/134		44.5 %	1.31 [0.78, 2.19]
Odio 1991	0/13	1/9		3.7 %	0.24 [0.01, 5.26]
Peltola 2007	7/89	4/84		8.8 %	1.65 [0.50, 5.44]
Schaad 1993	1/23	3/25		6.1 %	0.36 [0.04, 3.24]
Wald 1995	3/24	2/33		3.6 %	2.06 [0.37, 11.41]
Total (95% CI)	**428**	**432**		**100.0 %**	**0.95 [0.65, 1.39]**



Total events: 41 (Corticosteroids), 44 (Placebo)

Heterogeneity: $Chi^2 = 9.58$, df = 12 (P = 0.65); I^2 =0.0%

Test for overall effect: Z = 0.27 (P = 0.79)

Test for subgroup differences: Not applicable

Analysis 4.3. Comparison 4 Causative species, Outcome 3 Severe hearing loss in children - Haemophilus influenzae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 3 Severe hearing loss in children - *Haemophilus influenzae*

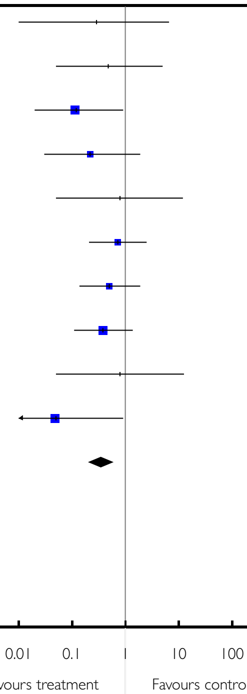
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kilpi 1995	0/15	1/13		3.5 %	0.29 [0.01, 6.60]
King 1994	1/29	2/28		4.4 %	0.48 [0.05, 5.03]
Lebel 1988a	1/34	7/29		16.4 %	0.12 [0.02, 0.93]
Lebel 1988b	1/39	4/35		9.1 %	0.22 [0.03, 1.91]
Lebel 1989	1/25	1/20		2.4 %	0.80 [0.05, 12.01]
Molyneux 2002	4/81	6/89		12.4 %	0.73 [0.21, 2.50]
Odio 1991	3/38	6/39		12.9 %	0.51 [0.14, 1.91]
Peltola 2007	3/46	8/47		17.2 %	0.38 [0.11, 1.35]
Schaad 1993	1/37	1/30		2.4 %	0.81 [0.05, 12.43]
Wald 1995	0/43	8/39		19.3 %	0.05 [0.00, 0.90]
Total (95% CI)	**387**	**369**		**100.0 %**	**0.34 [0.20, 0.59]**

Total events: 15 (Corticosteroids), 44 (Placebo)

Heterogeneity: $Chi^2 = 5.51$, df = 9 (P = 0.79); $I^2 = 0.0\%$

Test for overall effect: Z = 3.82 (P = 0.00013)

Test for subgroup differences: Not applicable



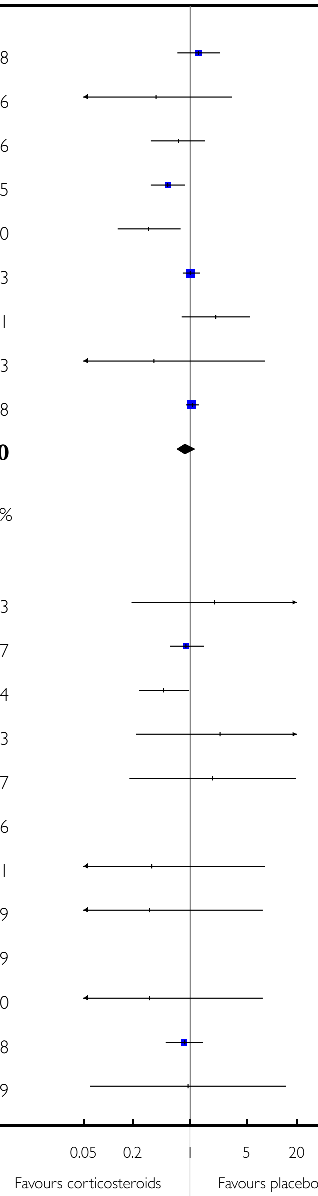
Analysis 5.1. Comparison 5 Income of countries, Outcome 1 Mortality - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 1 Mortality - all patients

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Low-income countries					
Bademosi 1979	12/24	11/28		5.9 %	1.27 [0.69, 2.34]
Bhaumik 1998	1/14	3/16		0.6 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		4.0 %	0.71 [0.33, 1.51]
Girgis 1989	21/225	43/245		8.3 %	0.53 [0.33, 0.87]
Mathur 2013	5/40	16/40		3.0 %	0.31 [0.13, 0.77]
Molyneux 2002	96/305	91/293		19.1 %	1.01 [0.80, 1.29]
Qazi 1996	12/48	5/41		2.7 %	2.05 [0.79, 5.33]
Sankar 2007	0/12	1/13		0.3 %	0.36 [0.02, 8.05]
Scarborough 2007	129/231	120/228		23.9 %	1.06 [0.90, 1.26]
Subtotal (95% CI)	**933**	**940**		**67.7 %**	**0.87 [0.67, 1.15]**
Total events: 284 (Corticosteroids), 302 (Placebo)					
Heterogeneity: Tau² = 0.07; Chi² = 17.92, df = 8 (P = 0.02); I² =55%					
Test for overall effect: Z = 0.97 (P = 0.33)					
2 High-income countries					
Belsey 1969	2/43	1/43		0.5 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.5 %	0.90 [0.56, 1.46]
de Gans 2002	11/157	21/144		4.7 %	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.5 %	2.33 [0.22, 25.03]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51		0.3 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.3 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30		0.3 %	0.32 [0.01, 7.63]
Nguyen 2007	22/217	26/218		7.2 %	0.85 [0.50, 1.45]
Odio 1991	1/52	1/49		0.4 %	0.94 [0.06, 14.65]



(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Peltola 2007	23/166	26/163		7.6 %	0.87 [0.52, 1.46]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	3/31	5/29		1.4 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**1131**	**1117**		**32.3 %**	**0.81 [0.63, 1.05]**

Total events: 83 (Corticosteroids), 107 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.23$, df = 12 (P = 0.90); I^2 =0.0%

Test for overall effect: Z = 1.62 (P = 0.10)

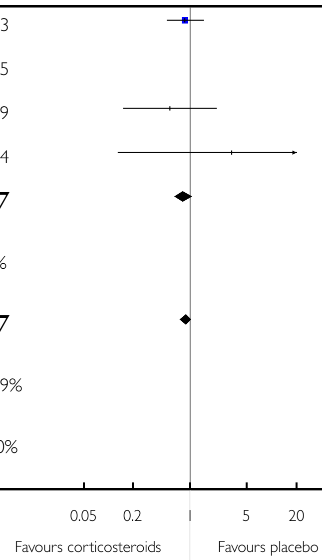
Total (95% CI)	**2064**	**2057**		**100.0 %**	**0.88 [0.75, 1.03]**

Total events: 367 (Corticosteroids), 409 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 25.92$, df = 21 (P = 0.21); I^2 =19%

Test for overall effect: Z = 1.55 (P = 0.12)

Test for subgroup differences: $Chi^2 = 0.17$, df = 1 (P = 0.68), I^2 =0.0%



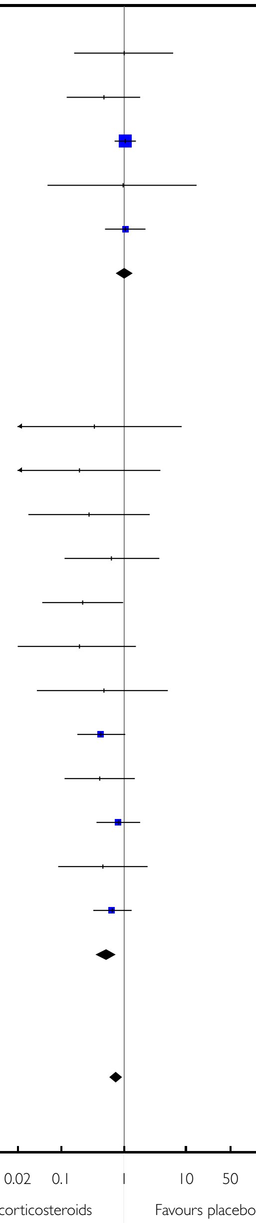
Analysis 5.2. Comparison 5 Income of countries, Outcome 2 Severe hearing loss - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 2 Severe hearing loss - all patients

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	2/13	2/13		1.8 %	1.00 [0.16, 6.07]
Girgis 1989	3/190	6/177		3.1 %	0.47 [0.12, 1.83]
Molyneux 2002	38/147	39/158		39.7 %	1.05 [0.71, 1.54]
Qazi 1996	1/26	1/25		0.8 %	0.96 [0.06, 14.55]
Scarborough 2007	12/96	12/99		10.5 %	1.03 [0.49, 2.18]
Subtotal (95% CI)	**472**	**472**		**56.0 %**	**0.99 [0.72, 1.38]**
Total events: 56 (Corticosteroids), 60 (Placebo)					
Heterogeneity: $Chi^2 = 1.25$, df = 4 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.03 (P = 0.98)					
2 High-income countries					
Belsey 1969	0/41	1/42		0.6 %	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/26		0.7 %	0.19 [0.01, 3.84]
Kilpi 1995	1/31	3/26		1.2 %	0.28 [0.03, 2.53]
King 1994	2/48	3/45		1.9 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38		2.7 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46		1.3 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29		1.1 %	0.47 [0.04, 4.89]
Nguyen 2007	7/180	16/177		7.9 %	0.43 [0.18, 1.02]
Odio 1991	3/51	7/48		3.5 %	0.40 [0.11, 1.47]
Peltola 2007	10/135	12/131		9.1 %	0.81 [0.36, 1.81]
Schaad 1993	2/60	4/55		2.2 %	0.46 [0.09, 2.40]
Wald 1995	10/68	17/74		11.8 %	0.64 [0.32, 1.30]
Subtotal (95% CI)	**764**	**737**		**44.0 %**	**0.51 [0.35, 0.73]**
Total events: 39 (Corticosteroids), 80 (Placebo)					
Heterogeneity: $Chi^2 = 4.84$, df = 11 (P = 0.94); I^2 =0.0%					
Test for overall effect: Z = 3.65 (P = 0.00026)					
Total (95% CI)	**1236**	**1209**		**100.0 %**	**0.74 [0.58, 0.94]**
Total events: 95 (Corticosteroids), 140 (Placebo)					



(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Heterogeneity: $Chi^2 = 13.43$, df = 16 (P = 0.64); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.44 (P = 0.015)					
Test for subgroup differences: $Chi^2 = 7.34$, df = 1 (P = 0.01), $I^2 = 86\%$					

0.02 0.1 1 10 50

Favours corticosteroids Favours placebo

Analysis 5.3. Comparison 5 Income of countries, Outcome 3 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 3 Any hearing loss

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	4/14	3/16		1.0 %	1.52 [0.41, 5.67]
Girgis 1989	3/190	6/177		0.9 %	0.47 [0.12, 1.83]
Mathur 2013	6/35	10/24		2.2 %	0.41 [0.17, 0.98]
Molyneux 2002	49/147	46/158		14.9 %	1.14 [0.82, 1.60]
Qazi 1996	28/36	32/35		40.8 %	0.85 [0.70, 1.04]
Sankar 2007	3/12	3/12		0.9 %	1.00 [0.25, 4.00]
Scarborough 2007	30/96	36/99		10.7 %	0.86 [0.58, 1.28]
Subtotal (95% CI)	**530**	**521**		**71.4 %**	**0.89 [0.76, 1.04]**
Total events: 123 (Corticosteroids), 136 (Placebo)					
Heterogeneity: $Chi^2 = 6.97$, df = 6 (P = 0.32); $I^2 = 14\%$					
Test for overall effect: Z = 1.52 (P = 0.13)					
2 High-income countries					
Belsey 1969	0/41	1/42		0.2 %	0.34 [0.01, 8.14]
de Gans 2002	13/143	14/119		3.3 %	0.77 [0.38, 1.58]
Kanra 1995	2/27	8/26		0.8 %	0.24 [0.06, 1.03]

0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

(*Continued* . . .)

(... *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio IV,Fixed,95% CI
Kilpi 1995	5/31	6/26	1.5 %	0.70 [0.24, 2.03]
King 1994	5/48	5/45	1.2 %	0.94 [0.29, 3.02]
Lebel 1988a	9/43	16/38	3.5 %	0.50 [0.25, 0.99]
Lebel 1988b	7/49	14/46	2.5 %	0.47 [0.21, 1.06]
Lebel 1989	3/30	5/29	0.9 %	0.58 [0.15, 2.21]
Nguyen 2007	21/180	37/177	6.8 %	0.56 [0.34, 0.91]
Odio 1991	3/50	7/44	1.0 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131	2.6 %	0.81 [0.36, 1.81]
Schaad 1993	3/60	8/55	1.0 %	0.34 [0.10, 1.23]
Wald 1995	10/67	17/72	3.3 %	0.63 [0.31, 1.28]
Subtotal (95% CI)	**904**	**850**	**28.6 %**	**0.58 [0.45, 0.73]**
Total (95% CI)	**1434**	**1371**	**100.0 %**	**0.79 [0.69, 0.89]**

Subtotal: Total events: 91 (Corticosteroids), 150 (Placebo)

Heterogeneity: $Chi^2 = 5.16$, df = 12 (P = 0.95); I^2 =0.0%

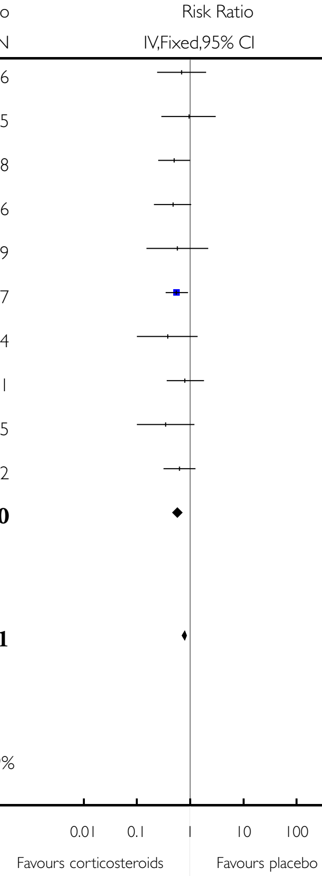
Test for overall effect: Z = 4.47 (P < 0.00001)

Total: Total events: 214 (Corticosteroids), 286 (Placebo)

Heterogeneity: $Chi^2 = 20.91$, df = 19 (P = 0.34); I^2 =9%

Test for overall effect: Z = 3.67 (P = 0.00024)

Test for subgroup differences: $Chi^2 = 8.78$, df = 1 (P = 0.00), I^2 =89%



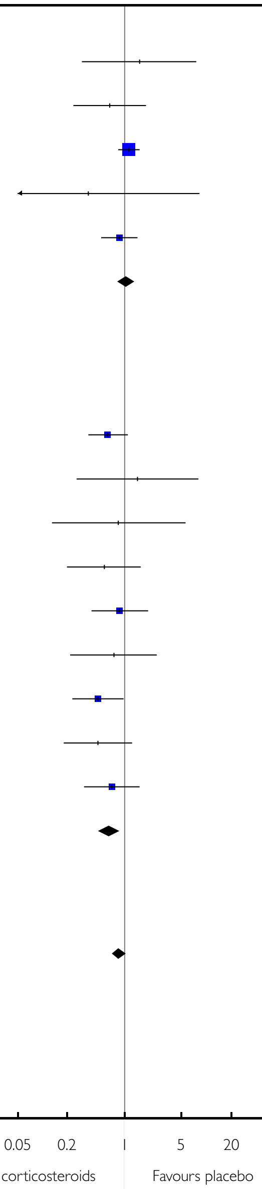
Analysis 5.4. Comparison 5 Income of countries, Outcome 4 Short-term neurological sequelae - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 4 Short-term neurological sequelae - all patients

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	3/13	2/13		1.3 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		3.5 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		40.0 %	1.13 [0.84, 1.52]
Sankar 2007	0/12	1/13		0.4 %	0.36 [0.02, 8.05]
Scarborough 2007	21/98	26/104		13.7 %	0.86 [0.52, 1.42]
Subtotal (95% CI)	**372**	**363**		**58.9 %**	**1.03 [0.81, 1.31]**
Total events: 98 (Corticosteroids), 93 (Placebo)					
Heterogeneity: $Chi^2 = 2.33$, df = 4 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
2 High-income countries					
de Gans 2002	18/143	24/119		11.1 %	0.62 [0.36, 1.09]
Kanra 1995	3/27	2/26		1.2 %	1.44 [0.26, 7.96]
Kilpi 1995	2/31	2/26		1.0 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		3.2 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		5.4 %	0.86 [0.39, 1.92]
Lebel 1989	4/28	5/26		2.4 %	0.74 [0.22, 2.47]
Peltola 2007	10/139	21/137		6.8 %	0.47 [0.23, 0.96]
Thomas 1999	5/28	9/24		3.9 %	0.48 [0.18, 1.23]
Wald 1995	9/68	14/74		5.9 %	0.70 [0.32, 1.51]
Subtotal (95% CI)	**559**	**520**		**41.1 %**	**0.64 [0.48, 0.85]**
Total events: 65 (Corticosteroids), 95 (Placebo)					
Heterogeneity: $Chi^2 = 2.76$, df = 8 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 3.04 (P = 0.0024)					
Total (95% CI)	**931**	**883**		**100.0 %**	**0.84 [0.70, 1.02]**
Total events: 163 (Corticosteroids), 188 (Placebo)					
Heterogeneity: $Chi^2 = 11.21$, df = 13 (P = 0.59); I^2 =0.0%					
Test for overall effect: Z = 1.77 (P = 0.076)					
Test for subgroup differences: $Chi^2 = 6.13$, df = 1 (P = 0.01), I^2 =84%					



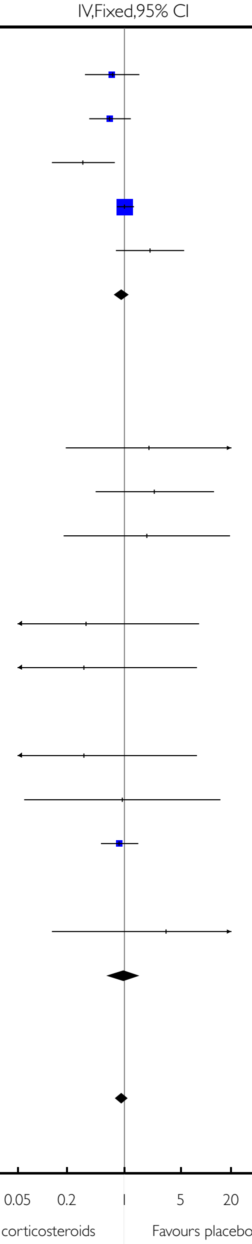
Analysis 5.5. Comparison 5 Income of countries, Outcome 5 Mortality - children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 5 Mortality - children

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Ciana 1995	8/34	12/36		5.8 %	0.71 [0.33, 1.51]
Girgis 1989	16/142	24/140		9.8 %	0.66 [0.37, 1.18]
Mathur 2013	5/40	16/40		4.1 %	0.31 [0.13, 0.77]
Molyneux 2002	96/305	91/293		59.7 %	1.01 [0.80, 1.29]
Qazi 1996	12/48	5/41		3.7 %	2.05 [0.79, 5.33]
Subtotal (95% CI)	**569**	**550**		**83.2 %**	**0.91 [0.75, 1.12]**
Total events: 137 (Corticosteroids), 148 (Placebo)					
Heterogeneity: $Chi^2 = 10.54$, df = 4 (P = 0.03); $I^2 = 62\%$					
Test for overall effect: Z = 0.88 (P = 0.38)					
2 High-income countries					
Belsey 1969	2/43	1/43		0.6 %	2.00 [0.19, 21.24]
DeLemos 1969	4/54	2/63		1.2 %	2.33 [0.44, 12.25]
Kanra 1995	2/29	1/27		0.6 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51		0.3 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.3 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30		0.3 %	0.32 [0.01, 7.63]
Odio 1991	1/52	1/49		0.4 %	0.94 [0.06, 14.65]
Peltola 2007	23/166	26/163		12.6 %	0.87 [0.52, 1.46]
Schaad 1993	0/60	0/55			Not estimable
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**688**	**679**		**16.8 %**	**0.96 [0.61, 1.50]**
Total events: 33 (Corticosteroids), 34 (Placebo)					
Heterogeneity: $Chi^2 = 3.80$, df = 8 (P = 0.87); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.18 (P = 0.86)					
Total (95% CI)	**1257**	**1229**		**100.0 %**	**0.92 [0.77, 1.11]**
Total events: 170 (Corticosteroids), 182 (Placebo)					



(Continued . . .)

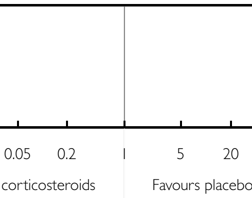
(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI

Heterogeneity: $Chi^2 = 14.37$, df = 13 (P = 0.35); I^2 =10%

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85), I^2 =0.0%



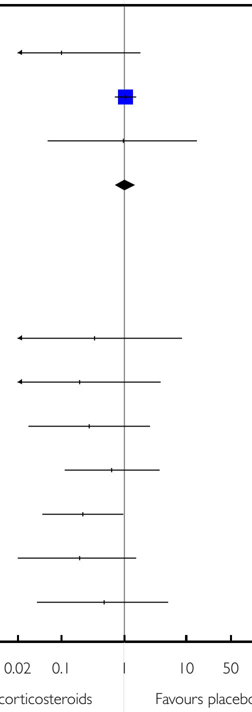
Analysis 5.6. Comparison 5 Income of countries, Outcome 6 Severe hearing loss - children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 6 Severe hearing loss - children

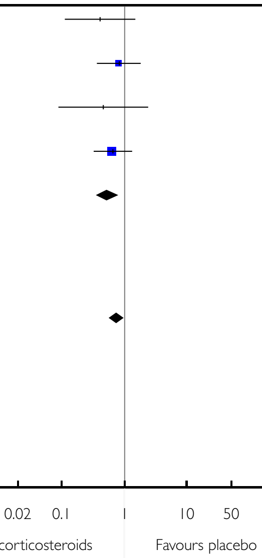
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		0.9 %	0.10 [0.01, 1.79]
Molyneux 2002	38/147	39/158		51.3 %	1.05 [0.71, 1.54]
Qazi 1996	1/26	1/25		1.0 %	0.96 [0.06, 14.55]
Subtotal (95% CI)	**189**	**198**		**53.3 %**	**1.00 [0.69, 1.47]**
Total events: 39 (Corticosteroids), 44 (Placebo)					
Heterogeneity: $Chi^2 = 2.48$, df = 2 (P = 0.29); I^2 =19%					
Test for overall effect: Z = 0.02 (P = 0.99)					
2 High-income countries					
Belsey 1969	0/41	1/42		0.8 %	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/26		0.9 %	0.19 [0.01, 3.84]
Kilpi 1995	1/31	3/26		1.6 %	0.28 [0.03, 2.53]
King 1994	2/48	3/45		2.5 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38		3.5 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46		1.7 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29		1.4 %	0.47 [0.04, 4.89]



(*Continued* . . .)

(. . . Continued)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Odio 1991	3/51	7/48		4.6 %	0.40 [0.11, 1.47]
Peltola 2007	10/135	12/131		11.8 %	0.81 [0.36, 1.81]
Schaad 1993	2/60	4/55		2.8 %	0.46 [0.09, 2.40]
Wald 1995	10/68	17/74		15.2 %	0.64 [0.32, 1.30]
Subtotal (95% CI)	**584**	**560**		**46.7 %**	**0.52 [0.35, 0.78]**
Total events: 32 (Corticosteroids), 64 (Placebo)					
Heterogeneity: $Chi^2 = 4.67$, df = 10 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 3.13 (P = 0.0017)					
Total (95% CI)	**773**	**758**		**100.0 %**	**0.74 [0.56, 0.98]**
Total events: 71 (Corticosteroids), 108 (Placebo)					
Heterogeneity: $Chi^2 = 12.44$, df = 13 (P = 0.49); I^2 =0.0%					
Test for overall effect: Z = 2.13 (P = 0.033)					
Test for subgroup differences: $Chi^2 = 5.29$, df = 1 (P = 0.02), I^2 =81%					



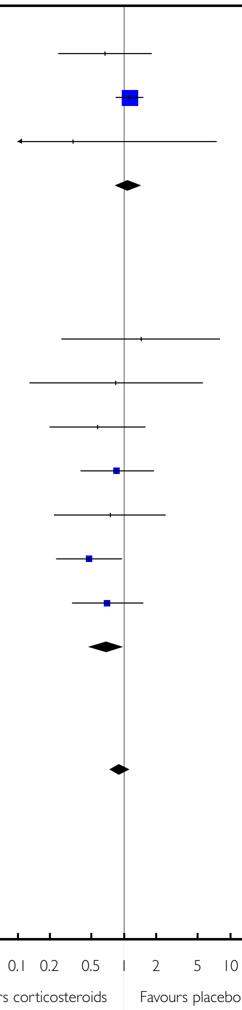
Analysis 5.7. Comparison 5 Income of countries, Outcome 7 Short-term neurological sequelae - children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 7 Short-term neurological sequelae - children

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Ciana 1995	5/26	7/24		5.0 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		57.3 %	1.13 [0.84, 1.52]
Sankar 2007	0/12	1/12		0.5 %	0.33 [0.01, 7.45]
Subtotal (95% CI)	**261**	**245**		**62.7 %**	**1.08 [0.81, 1.43]**
Total events: 74 (Corticosteroids), 65 (Placebo)					
Heterogeneity: Chi^2 = 1.58, df = 2 (P = 0.45); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					
2 High-income countries					
Kanra 1995	3/27	2/26		1.7 %	1.44 [0.26, 7.96]
Kilpi 1995	2/31	2/26		1.4 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		4.6 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		7.8 %	0.86 [0.39, 1.92]
Lebel 1989	4/28	5/26		3.5 %	0.74 [0.22, 2.47]
Peltola 2007	10/139	21/137		9.8 %	0.47 [0.23, 0.96]
Wald 1995	9/68	14/74		8.4 %	0.70 [0.32, 1.51]
Subtotal (95% CI)	**388**	**377**		**37.3 %**	**0.67 [0.46, 0.97]**
Total events: 42 (Corticosteroids), 62 (Placebo)					
Heterogeneity: Chi^2 = 2.32, df = 6 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 2.14 (P = 0.032)					
Total (95% CI)	**649**	**622**		**100.0 %**	**0.90 [0.72, 1.13]**
Total events: 116 (Corticosteroids), 127 (Placebo)					
Heterogeneity: Chi^2 = 7.92, df = 9 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 0.90 (P = 0.37)					
Test for subgroup differences: Chi^2 = 4.02, df = 1 (P = 0.04), I^2 =75%					



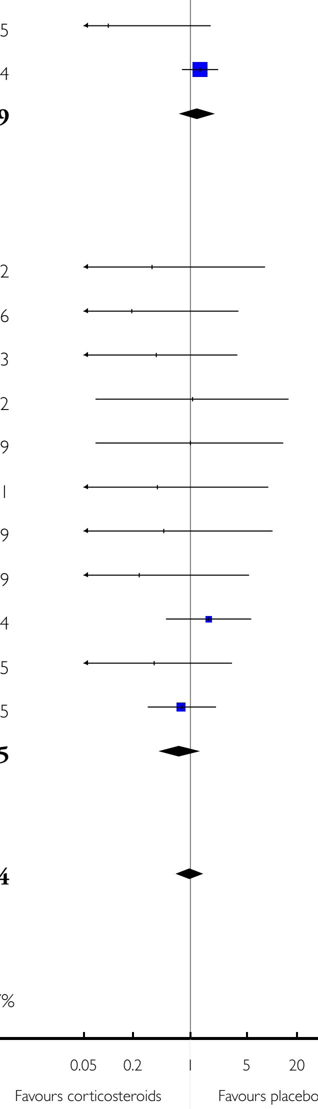
Analysis 5.8. Comparison 5 Income of countries, Outcome 8 Severe hearing loss in children due to non-Haemophilus influenzae species.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 8 Severe hearing loss in children due to non-*Haemophilus influenzae* species

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		1.8 %	0.10 [0.01, 1.79]
Molyneux 2002	27/132	21/134		54.6 %	1.31 [0.78, 2.19]
Subtotal (95% CI)	**148**	**149**		**56.4 %**	**1.20 [0.72, 2.00]**
Total events: 27 (Corticosteroids), 25 (Placebo)					
Heterogeneity: $Chi^2 = 2.94$, df = 1 (P = 0.09); $I^2 = 66\%$					
Test for overall effect: Z = 0.71 (P = 0.48)					
2 High-income countries					
Belsey 1969	0/41	1/42		1.5 %	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/26		1.6 %	0.19 [0.01, 3.84]
Kilpi 1995	1/17	2/13		2.8 %	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.0 %	1.05 [0.07, 15.69]
Lebel 1988a	1/9	1/9		2.1 %	1.00 [0.07, 13.64]
Lebel 1988b	0/9	1/11		1.5 %	0.40 [0.02, 8.78]
Lebel 1989	0/6	1/9		1.6 %	0.48 [0.02, 10.07]
Odio 1991	0/13	1/9		1.5 %	0.24 [0.01, 5.26]
Peltola 2007	7/89	4/84		10.3 %	1.65 [0.50, 5.44]
Schaad 1993	1/23	3/25		3.0 %	0.36 [0.04, 3.24]
Wald 1995	5/25	9/35		15.7 %	0.78 [0.30, 2.04]
Subtotal (95% CI)	**280**	**285**		**43.6 %**	**0.73 [0.41, 1.31]**
Total events: 16 (Corticosteroids), 26 (Placebo)					
Heterogeneity: $Chi^2 = 4.35$, df = 10 (P = 0.93); $I^2 = 0.0\%$					
Test for overall effect: Z = 1.04 (P = 0.30)					
Total (95% CI)	**428**	**434**		**100.0 %**	**0.97 [0.66, 1.42]**
Total events: 43 (Corticosteroids), 51 (Placebo)					
Heterogeneity: $Chi^2 = 8.86$, df = 12 (P = 0.71); $I^2 = 0.0\%$					
Test for overall effect: Z = 0.15 (P = 0.88)					
Test for subgroup differences: $Chi^2 = 1.58$, df = 1 (P = 0.21), $I^2 = 37\%$					



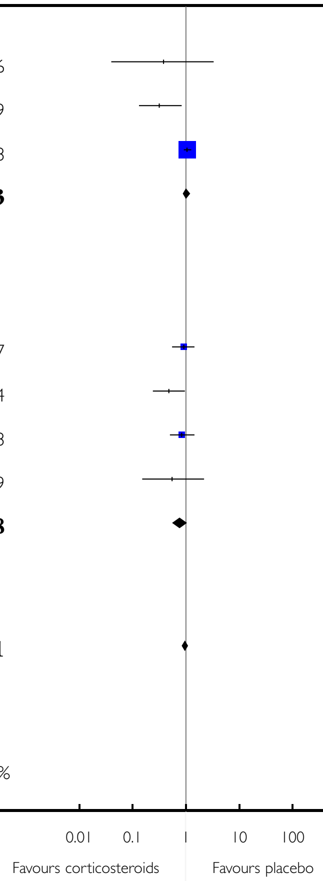
Analysis 5.9. Comparison 5 Income of countries, Outcome 9 Mortality - adults.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 9 Mortality - adults

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	1/14	3/16		0.5 %	0.38 [0.04, 3.26]
Girgis 1989	5/68	18/79		2.4 %	0.32 [0.13, 0.82]
Scarborough 2007	129/231	120/228		75.0 %	1.06 [0.90, 1.26]
Subtotal (95% CI)	**313**	**323**		**77.9 %**	**1.02 [0.86, 1.20]**
Total events: 135 (Corticosteroids), 141 (Placebo)					
Heterogeneity: $Chi^2 = 6.82$, df = 2 (P = 0.03); I^2 =71%					
Test for overall effect: Z = 0.19 (P = 0.85)					
2 High-income countries					
Bennett 1963	16/38	22/47		9.2 %	0.90 [0.56, 1.46]
de Gans 2002	11/157	21/144		4.4 %	0.48 [0.24, 0.96]
Nguyen 2007	22/217	26/218		7.4 %	0.85 [0.50, 1.45]
Thomas 1999	3/31	5/29		1.2 %	0.56 [0.15, 2.14]
Subtotal (95% CI)	**443**	**438**		**22.1 %**	**0.76 [0.56, 1.04]**
Total events: 52 (Corticosteroids), 74 (Placebo)					
Heterogeneity: $Chi^2 = 2.52$, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 1.74 (P = 0.082)					
Total (95% CI)	**756**	**761**		**100.0 %**	**0.95 [0.82, 1.10]**
Total events: 187 (Corticosteroids), 215 (Placebo)					
Heterogeneity: $Chi^2 = 11.98$, df = 6 (P = 0.06); I^2 =50%					
Test for overall effect: Z = 0.65 (P = 0.52)					
Test for subgroup differences: $Chi^2 = 2.64$, df = 1 (P = 0.10), I^2 =62%					



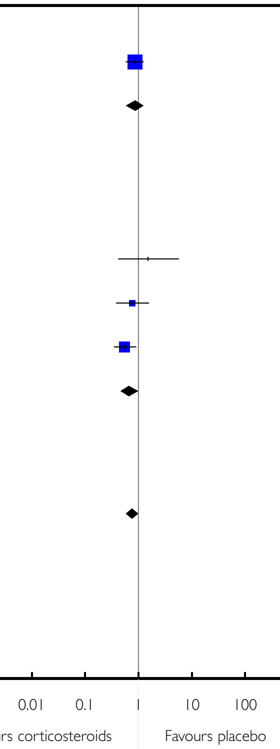
Analysis 5.10. Comparison 5 Income of countries, Outcome 10 Any hearing loss adults.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 10 Any hearing loss adults

Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio IV,Fixed,95% CI
1 Low-income countries				
Scarborough 2007	30/96	36/99	49.1 %	0.86 [0.58, 1.28]
Subtotal (95% CI)	**96**	**99**	**49.1 %**	**0.86 [0.58, 1.28]**
Total events: 30 (Corticosteroids), 36 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.75 (P = 0.45)				
2 High-income countries				
Bhaumik 1998	4/14	3/16	4.4 %	1.52 [0.41, 5.67]
de Gans 2002	13/143	14/119	15.0 %	0.77 [0.38, 1.58]
Nguyen 2007	21/180	37/177	31.4 %	0.56 [0.34, 0.91]
Subtotal (95% CI)	**337**	**312**	**50.9 %**	**0.67 [0.45, 0.99]**
Total events: 38 (Corticosteroids), 54 (Placebo)				
Heterogeneity: $Chi^2 = 2.18$, df = 2 (P = 0.34); I^2 =8%				
Test for overall effect: Z = 2.02 (P = 0.044)				
Total (95% CI)	**433**	**411**	**100.0 %**	**0.76 [0.57, 1.00]**
Total events: 68 (Corticosteroids), 90 (Placebo)				
Heterogeneity: $Chi^2 = 2.95$, df = 3 (P = 0.40); I^2 =0.0%				
Test for overall effect: Z = 1.97 (P = 0.049)				
Test for subgroup differences: $Chi^2 = 0.77$, df = 1 (P = 0.38), I^2 =0.0%				



Analysis 6.1. Comparison 6 Timing of steroids, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 1 Mortality

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
1 Before or with first dose antibiotic					
Bademosi 1979	12/24	11/28		6.6 %	1.27 [0.69, 2.34]
de Gans 2002	11/157	21/144		5.4 %	0.48 [0.24, 0.96]
Girgis 1989	21/225	43/245		9.1 %	0.53 [0.33, 0.87]
Kanra 1995	2/29	1/27		0.6 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26			Not estimable
Mathur 2013	5/40	16/40		3.5 %	0.31 [0.13, 0.77]
Molyneux 2002	96/305	91/293		18.7 %	1.01 [0.80, 1.29]
Nguyen 2007	22/217	26/218		8.0 %	0.85 [0.50, 1.45]
Odio 1991	1/52	1/49		0.4 %	0.94 [0.06, 14.65]
Peltola 2007	23/166	26/163		8.4 %	0.87 [0.52, 1.46]
Qazi 1996	12/48	5/41		3.2 %	2.05 [0.79, 5.33]
Scarborough 2007	129/231	120/228		22.4 %	1.06 [0.90, 1.26]
Schaad 1993	0/60	0/55			Not estimable
Subtotal (95% CI)	**1586**	**1557**		**86.4 %**	**0.87 [0.69, 1.09]**
Total events: 334 (Corticosteroids), 361 (Placebo)					
Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 20.80$, df = 10 (P = 0.02); $I^2 = 52\%$					
Test for overall effect: Z = 1.22 (P = 0.22)					
2 After first dose antibiotic					
Bennett 1963	16/38	22/47		9.3 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		0.7 %	0.38 [0.04, 3.26]
DeLemos 1969	2/54	1/63		0.6 %	2.33 [0.22, 25.03]
King 1994	0/50	1/51		0.3 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.3 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30		0.3 %	0.32 [0.01, 7.63]
Thomas 1999	3/31	5/29		1.7 %	0.56 [0.15, 2.14]

0.05 0.2 1 5 20

Favours corticosteroids Favours placebo

(Continued . . .)

(. . . Continued)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Random,95% CI	Weight	Risk Ratio IV,Random,95% CI
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**389**	**408**		**13.6 %**	**0.83 [0.55, 1.26]**
Total events: 23 (Corticosteroids), 34 (Placebo)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.35$, df = 7 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 0.87 (P = 0.38)					
Total (95% CI)	**1975**	**1965**		**100.0 %**	**0.87 [0.73, 1.05]**
Total events: 357 (Corticosteroids), 395 (Placebo)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 24.59$, df = 18 (P = 0.14); I^2 =27%					
Test for overall effect: Z = 1.45 (P = 0.15)					
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.86), I^2 =0.0%					

0.05 0.2 1 5 20

Favours corticosteroids Favours placebo

Analysis 6.2. Comparison 6 Timing of steroids, Outcome 2 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 2 Severe hearing loss

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Before or with first dose antibiotic					
Girgis 1989	3/190	6/177		3.4 %	0.47 [0.12, 1.83]
Kanra 1995	0/27	2/26		0.7 %	0.19 [0.01, 3.84]
Kilpi 1995	1/32	3/26		1.3 %	0.27 [0.03, 2.45]
Molyneux 2002	38/147	39/158		42.5 %	1.05 [0.71, 1.54]
Nguyen 2007	7/180	16/177		8.5 %	0.43 [0.18, 1.02]
Odio 1991	3/51	7/48		3.8 %	0.40 [0.11, 1.47]
Peltola 2007	10/135	12/131		9.8 %	0.81 [0.36, 1.81]
Qazi 1996	1/26	1/25		0.9 %	0.96 [0.06, 14.55]

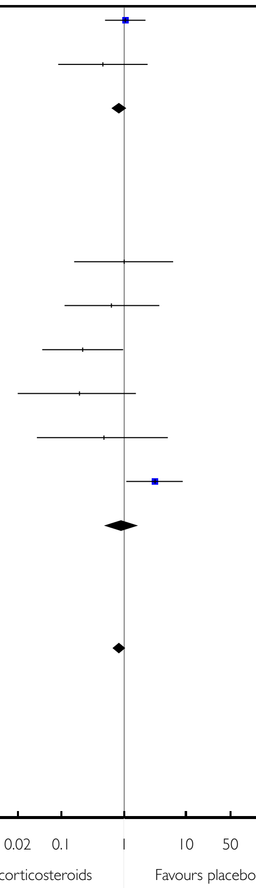
0.02 0.1 1 10 50

Favours corticosteroids Favours placebo

(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Scarborough 2007	12/96	12/99		11.3 %	1.03 [0.49, 2.18]
Schaad 1993	2/60	4/55		2.3 %	0.46 [0.09, 2.40]
Subtotal (95% CI)	**944**	**922**		**84.5 %**	**0.81 [0.62, 1.07]**
Total events: 77 (Corticosteroids), 102 (Placebo)					
Heterogeneity: $Chi^2 = 8.21$, df = 9 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 1.50 (P = 0.13)					
2 After first dose antibiotic					
Bhaumik 1998	2/13	2/13		2.0 %	1.00 [0.16, 6.07]
King 1994	2/48	3/45		2.1 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38		2.9 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46		1.4 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29		1.2 %	0.47 [0.04, 4.89]
Wald 1995	3/7	10/72		6.0 %	3.09 [1.10, 8.65]
Subtotal (95% CI)	**191**	**243**		**15.5 %**	**0.89 [0.47, 1.68]**
Total events: 11 (Corticosteroids), 30 (Placebo)					
Heterogeneity: $Chi^2 = 11.52$, df = 5 (P = 0.04); I^2 =57%					
Test for overall effect: Z = 0.37 (P = 0.71)					
Total (95% CI)	**1135**	**1165**		**100.0 %**	**0.82 [0.64, 1.06]**
Total events: 88 (Corticosteroids), 132 (Placebo)					
Heterogeneity: $Chi^2 = 19.79$, df = 15 (P = 0.18); I^2 =24%					
Test for overall effect: Z = 1.52 (P = 0.13)					
Test for subgroup differences: $Chi^2 = 0.06$, df = 1 (P = 0.80), I^2 =0.0%					



Analysis 6.3. Comparison 6 Timing of steroids, Outcome 3 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 3 Any hearing loss

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Before or with antibiotics					
de Gans 2002	13/143	14/119		3.3 %	0.77 [0.38, 1.58]
Girgis 1989	3/190	6/177		0.9 %	0.47 [0.12, 1.83]
Kanra 1995	2/27	8/26		0.8 %	0.24 [0.06, 1.03]
Kilpi 1995	5/59	16/54		1.9 %	0.29 [0.11, 0.73]
Mathur 2013	6/35	10/24		2.2 %	0.41 [0.17, 0.98]
Molyneux 2002	49/147	46/158		14.9 %	1.14 [0.82, 1.60]
Nguyen 2007	24/180	37/177		7.5 %	0.64 [0.40, 1.02]
Odio 1991	3/50	7/44		1.0 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131		2.6 %	0.81 [0.36, 1.81]
Qazi 1996	28/36	32/35		40.8 %	0.85 [0.70, 1.04]
Scarborough 2007	30/96	36/99		10.7 %	0.86 [0.58, 1.28]
Schaad 1993	3/60	8/55		1.0 %	0.34 [0.10, 1.23]
Subtotal (95% CI)	**1158**	**1099**		**87.6 %**	**0.80 [0.70, 0.92]**
Total events: 176 (Corticosteroids), 232 (Placebo)					
Heterogeneity: Chi^2 = 18.93, df = 11 (P = 0.06); I^2 =42%					
Test for overall effect: Z = 3.11 (P = 0.0018)					
2 After first dose of antibiotics					
Bhaumik 1998	4/14	3/16		1.0 %	1.52 [0.41, 5.67]
King 1994	5/48	5/45		1.2 %	0.94 [0.29, 3.02]
Lebel 1988a	9/43	16/38		3.5 %	0.50 [0.25, 0.99]
Lebel 1988b	7/49	14/46		2.5 %	0.47 [0.21, 1.06]
Lebel 1989	3/30	5/29		0.9 %	0.58 [0.15, 2.21]
Wald 1995	10/67	17/72		3.3 %	0.63 [0.31, 1.28]
Subtotal (95% CI)	**251**	**246**		**12.4 %**	**0.62 [0.43, 0.89]**
Total events: 38 (Corticosteroids), 60 (Placebo)					
Heterogeneity: Chi^2 = 3.13, df = 5 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 2.61 (P = 0.0092)					

0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Total (95% CI)	**1409**	**1345**		**100.0 %**	**0.78 [0.68, 0.88]**
Total events: 214 (Corticosteroids), 292 (Placebo)					
Heterogeneity: Chi^2 = 23.86, df = 17 (P = 0.12); I^2 =29%					
Test for overall effect: Z = 3.83 (P = 0.00013)					
Test for subgroup differences: Chi^2 = 1.80, df = 1 (P = 0.18), I^2 =44%					

0.01 0.1 1 10 100

Favours corticosteroids Favours placebo

Analysis 6.4. Comparison 6 Timing of steroids, Outcome 4 Short-term neurologic sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 4 Short-term neurologic sequelae

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 Before or with first dose antibiotic					
de Gans 2002	18/143	24/119		11.6 %	0.62 [0.36, 1.09]
Kanra 1995	3/27	2/26		1.3 %	1.44 [0.26, 7.96]
Kilpi 1995	2/31	2/26		1.0 %	0.84 [0.13, 5.55]
Molyneux 2002	69/223	57/209		41.6 %	1.13 [0.84, 1.52]
Peltola 2007	10/139	21/137		7.1 %	0.47 [0.23, 0.96]
Scarborough 2007	21/98	26/104		14.3 %	0.86 [0.52, 1.42]
Subtotal (95% CI)	**661**	**621**		**76.9 %**	**0.91 [0.73, 1.13]**
Total events: 123 (Corticosteroids), 132 (Placebo)					
Heterogeneity: Chi^2 = 7.51, df = 5 (P = 0.19); I^2 =33%					
Test for overall effect: Z = 0.88 (P = 0.38)					
2 After first dose antibiotic					
Bhaumik 1998	3/13	2/13		1.4 %	1.50 [0.30, 7.55]
Lebel 1988a	5/48	8/43		3.4 %	0.56 [0.20, 1.58]

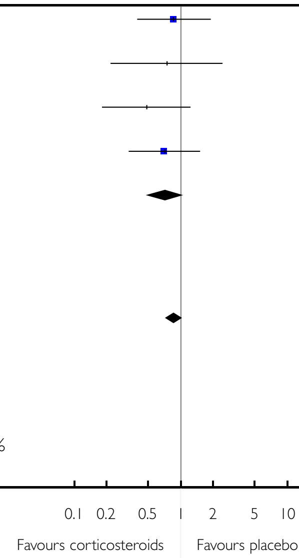
0.1 0.2 0.5 1 2 5 10

Favours corticosteroids Favours placebo

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Lebel 1988b	9/47	10/45		5.7 %	0.86 [0.39, 1.92]
Lebel 1989	4/28	5/26		2.5 %	0.74 [0.22, 2.47]
Thomas 1999	5/28	9/24		4.1 %	0.48 [0.18, 1.23]
Wald 1995	9/68	14/74		6.1 %	0.70 [0.32, 1.51]
Subtotal (95% CI)	**232**	**225**		**23.1 %**	**0.70 [0.47, 1.04]**
Total events: 35 (Corticosteroids), 48 (Placebo)					
Heterogeneity: Chi^2 = 1.93, df = 5 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.75 (P = 0.080)					
Total (95% CI)	**893**	**846**		**100.0 %**	**0.85 [0.71, 1.03]**
Total events: 158 (Corticosteroids), 180 (Placebo)					
Heterogeneity: Chi^2 = 10.67, df = 11 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 1.61 (P = 0.11)					
Test for subgroup differences: Chi^2 = 1.23, df = 1 (P = 0.27), I^2 =19%					



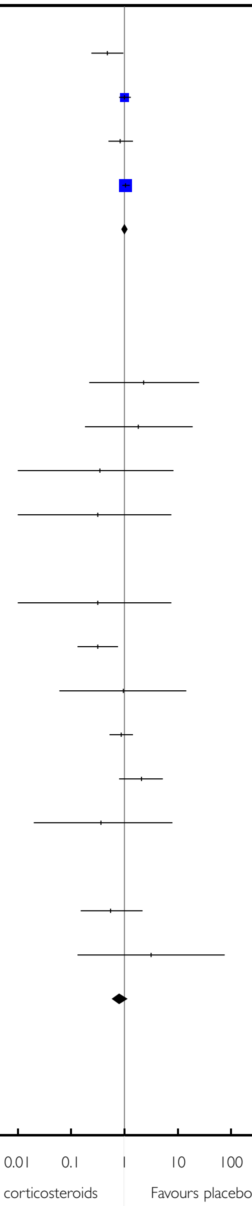
Analysis 7.1. Comparison 7 Study quality, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 7 Study quality

Outcome: 1 Mortality

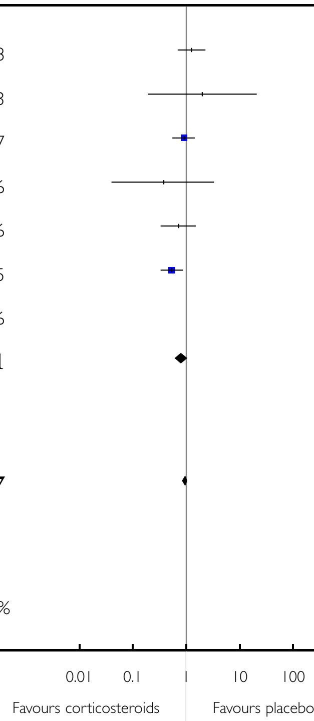
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 High quality					
de Gans 2002	11/157	21/144		2.6 %	0.48 [0.24, 0.96]
Molyneux 2002	96/305	91/293		22.3 %	1.01 [0.80, 1.29]
Nguyen 2007	22/217	26/218		4.4 %	0.85 [0.50, 1.45]
Scarborough 2007	129/231	120/228		44.4 %	1.06 [0.90, 1.26]
Subtotal (95% CI)	**910**	**883**		**73.7 %**	**1.00 [0.88, 1.14]**
Total events: 258 (Corticosteroids), 258 (Placebo)					
Heterogeneity: Chi^2 = 5.13, df = 3 (P = 0.16); I^2 =42%					
Test for overall effect: Z = 0.06 (P = 0.95)					
2 Medium quality					
DeLemos 1969	2/54	1/63		0.2 %	2.33 [0.22, 25.03]
Kanra 1995	2/29	1/27		0.2 %	1.86 [0.18, 19.38]
King 1994	0/50	1/51		0.1 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.1 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30		0.1 %	0.32 [0.01, 7.63]
Mathur 2013	5/40	16/40		1.5 %	0.31 [0.13, 0.77]
Odio 1991	1/52	1/49		0.2 %	0.94 [0.06, 14.65]
Peltola 2007	23/166	26/163		4.7 %	0.87 [0.52, 1.46]
Qazi 1996	12/48	5/41		1.4 %	2.05 [0.79, 5.33]
Sankar 2007	0/12	1/13		0.1 %	0.36 [0.02, 8.05]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	3/31	5/29		0.7 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.1 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**744**	**733**		**9.6 %**	**0.81 [0.57, 1.17]**
Total events: 49 (Corticosteroids), 59 (Placebo)					
Heterogeneity: Chi^2 = 11.43, df = 11 (P = 0.41); I^2 =4%					
Test for overall effect: Z = 1.11 (P = 0.27)					



(Continued . . .)

(... *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
3 Low quality					
Bademosi 1979	12/24	11/28		3.4 %	1.27 [0.69, 2.34]
Belsey 1969	2/43	1/43		0.2 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		5.4 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		0.3 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		2.2 %	0.71 [0.33, 1.51]
Girgis 1989	21/225	43/245		5.3 %	0.53 [0.33, 0.87]
Kilpi 1995	0/32	0/26			Not estimable
Subtotal (95% CI)	**410**	**441**		**16.7 %**	**0.79 [0.60, 1.04]**
Total events: 60 (Corticosteroids), 92 (Placebo)					
Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² =20%					
Test for overall effect: Z = 1.68 (P = 0.092)					
Total (95% CI)	**2064**	**2057**		**100.0 %**	**0.95 [0.85, 1.06]**
Total events: 367 (Corticosteroids), 409 (Placebo)					
Heterogeneity: Chi² = 25.92, df = 21 (P = 0.21); I² =19%					
Test for overall effect: Z = 0.98 (P = 0.33)					
Test for subgroup differences: Chi² = 3.10, df = 2 (P = 0.21), I² =36%					



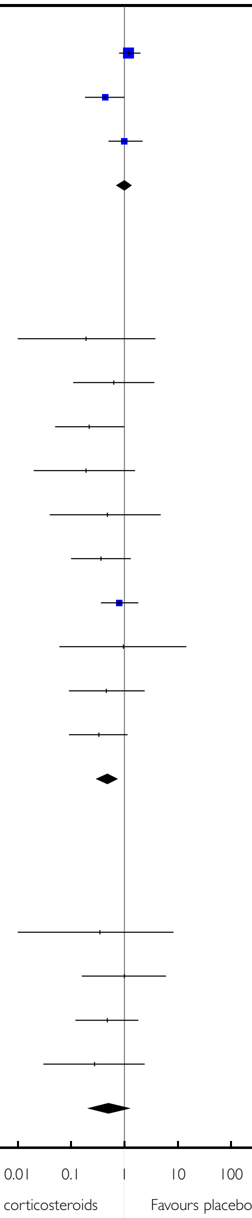
Analysis 7.2. Comparison 7 Study quality, Outcome 2 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 7 Study quality

Outcome: 2 Severe hearing loss

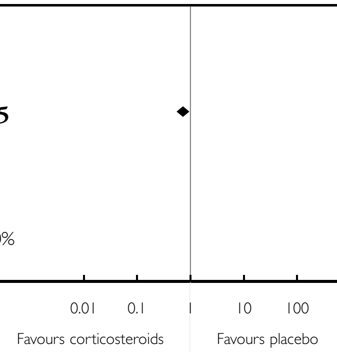
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 High quality					
Molyneux 2002	31/147	27/158		34.4 %	1.23 [0.78, 1.96]
Nguyen 2007	7/180	16/177		9.9 %	0.43 [0.18, 1.02]
Scarborough 2007	12/96	12/99		13.2 %	1.03 [0.49, 2.18]
Subtotal (95% CI)	**423**	**434**		**57.5 %**	**0.99 [0.69, 1.41]**
Total events: 50 (Corticosteroids), 55 (Placebo)					
Heterogeneity: Chi² = 4.45, df = 2 (P = 0.11); I² =55%					
Test for overall effect: Z = 0.07 (P = 0.94)					
2 Medium quality					
Kanra 1995	0/27	2/26		0.8 %	0.19 [0.01, 3.84]
King 1994	2/48	3/45		2.4 %	0.63 [0.11, 3.57]
Lebel 1988a	2/43	8/38		3.4 %	0.22 [0.05, 0.98]
Lebel 1988b	1/49	5/46		1.7 %	0.19 [0.02, 1.55]
Lebel 1989	1/31	2/29		1.3 %	0.47 [0.04, 4.89]
Odio 1991	3/51	7/44		4.4 %	0.37 [0.10, 1.34]
Peltola 2007	10/135	12/131		11.5 %	0.81 [0.36, 1.81]
Qazi 1996	1/26	1/25		1.0 %	0.96 [0.06, 14.55]
Schaad 1993	2/60	4/55		2.7 %	0.46 [0.09, 2.40]
Wald 1995	3/68	10/74		4.8 %	0.33 [0.09, 1.14]
Subtotal (95% CI)	**538**	**513**		**34.0 %**	**0.47 [0.29, 0.75]**
Total events: 25 (Corticosteroids), 54 (Placebo)					
Heterogeneity: Chi² = 4.64, df = 9 (P = 0.86); I² =0.0%					
Test for overall effect: Z = 3.17 (P = 0.0015)					
3 Low quality					
Belsey 1969	0/41	1/42		0.7 %	0.34 [0.01, 8.14]
Bhaumik 1998	2/13	2/13		2.3 %	1.00 [0.16, 6.07]
Girgis 1989	3/190	6/177		3.9 %	0.47 [0.12, 1.83]
Kilpi 1995	1/32	3/26		1.5 %	0.27 [0.03, 2.45]
Subtotal (95% CI)	**276**	**258**		**8.5 %**	**0.50 [0.20, 1.29]**



(Continued . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Total events: 6 (Corticosteroids), 12 (Placebo)					
Heterogeneity: Chi^2 = 0.93, df = 3 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.43 (P = 0.15)					
Total (95% CI)	**1237**	**1205**		**100.0 %**	**0.72 [0.55, 0.95]**
Total events: 81 (Corticosteroids), 121 (Placebo)					
Heterogeneity: Chi^2 = 16.76, df = 16 (P = 0.40); I^2 =5%					
Test for overall effect: Z = 2.32 (P = 0.020)					
Test for subgroup differences: Chi^2 = 6.74, df = 2 (P = 0.03), I^2 =70%					



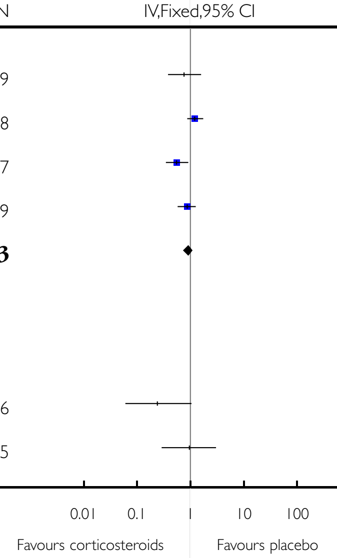
Analysis 7.3. Comparison 7 Study quality, Outcome 3 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 7 Study quality

Outcome: 3 Any hearing loss

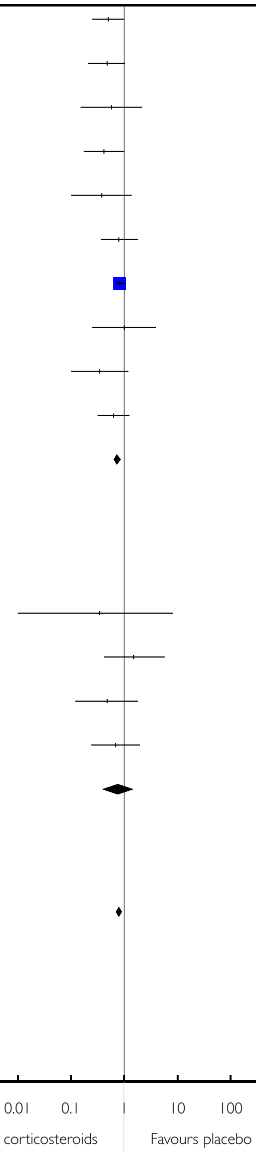
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
1 High quality					
de Gans 2002	13/143	14/119		3.3 %	0.77 [0.38, 1.58]
Molyneux 2002	49/147	43/158		14.3 %	1.22 [0.87, 1.73]
Nguyen 2007	21/180	37/177		6.9 %	0.56 [0.34, 0.91]
Scarborough 2007	30/96	36/99		10.8 %	0.86 [0.58, 1.28]
Subtotal (95% CI)	**566**	**553**		**35.2 %**	**0.90 [0.73, 1.12]**
Total events: 113 (Corticosteroids), 130 (Placebo)					
Heterogeneity: Chi^2 = 6.94, df = 3 (P = 0.07); I^2 =57%					
Test for overall effect: Z = 0.92 (P = 0.36)					
2 Medium quality					
Kanra 1995	2/27	8/26		0.8 %	0.24 [0.06, 1.03]
King 1994	5/48	5/45		1.2 %	0.94 [0.29, 3.02]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
Lebel 1988a	9/43	16/38		3.5 %	0.50 [0.25, 0.99]
Lebel 1988b	7/49	14/46		2.5 %	0.47 [0.21, 1.06]
Lebel 1989	3/30	5/29		0.9 %	0.58 [0.15, 2.21]
Mathur 2013	6/35	10/24		2.2 %	0.41 [0.17, 0.98]
Odio 1991	3/50	7/44		1.0 %	0.38 [0.10, 1.37]
Peltola 2007	10/135	12/131		2.6 %	0.81 [0.36, 1.81]
Qazi 1996	28/36	32/35		41.2 %	0.85 [0.70, 1.04]
Sankar 2007	3/12	3/12		0.9 %	1.00 [0.25, 4.00]
Schaad 1993	3/60	8/55		1.0 %	0.34 [0.10, 1.23]
Wald 1995	10/68	17/72		3.4 %	0.62 [0.31, 1.26]
Subtotal (95% CI)	**593**	**557**		**61.3 %**	**0.73 [0.62, 0.87]**
Total events: 89 (Corticosteroids), 137 (Placebo)					
Heterogeneity: Chi^2 = 11.53, df = 11 (P = 0.40); I^2 =5%					
Test for overall effect: Z = 3.66 (P = 0.00025)					
3 Low quality					
Belsey 1969	0/41	1/42		0.2 %	0.34 [0.01, 8.14]
Bhaumik 1998	4/14	3/16		1.0 %	1.52 [0.41, 5.67]
Girgis 1989	3/190	6/177		0.9 %	0.47 [0.12, 1.83]
Kilpi 1995	5/31	6/26		1.5 %	0.70 [0.24, 2.03]
Subtotal (95% CI)	**276**	**261**		**3.5 %**	**0.76 [0.38, 1.51]**
Total events: 12 (Corticosteroids), 16 (Placebo)					
Heterogeneity: Chi^2 = 1.84, df = 3 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 0.79 (P = 0.43)					
Total (95% CI)	**1435**	**1371**		**100.0 %**	**0.79 [0.69, 0.90]**
Total events: 214 (Corticosteroids), 283 (Placebo)					
Heterogeneity: Chi^2 = 22.52, df = 19 (P = 0.26); I^2 =16%					
Test for overall effect: Z = 3.56 (P = 0.00037)					
Test for subgroup differences: Chi^2 = 2.22, df = 2 (P = 0.33), I^2 =10%					



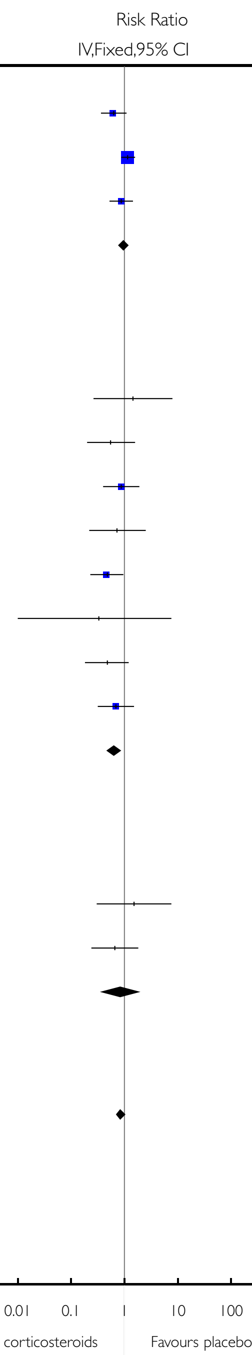
Analysis 7.4. Comparison 7 Study quality, Outcome 4 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 7 Study quality

Outcome: 4 Short-term neurological sequelae

Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio IV,Fixed,95% CI
1 High quality				
de Gans 2002	18/143	24/119	11.3 %	0.62 [0.36, 1.09]
Molyneux 2002	69/223	56/209	40.1 %	1.15 [0.86, 1.56]
Scarborough 2007	21/98	26/104	14.0 %	0.86 [0.52, 1.42]
Subtotal (95% CI)	**464**	**432**	**65.4 %**	**0.97 [0.77, 1.23]**
Total events: 108 (Corticosteroids), 106 (Placebo)				
Heterogeneity: Chi^2 = 3.92, df = 2 (P = 0.14); I^2 =49%				
Test for overall effect: Z = 0.22 (P = 0.83)				
2 Medium quality				
Kanra 1995	3/27	2/26	1.2 %	1.44 [0.26, 7.96]
Lebel 1988a	5/48	8/43	3.3 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45	5.5 %	0.86 [0.39, 1.92]
Lebel 1989	4/28	5/26	2.5 %	0.74 [0.22, 2.47]
Peltola 2007	10/139	21/137	6.9 %	0.47 [0.23, 0.96]
Sankar 2007	0/12	1/12	0.4 %	0.33 [0.01, 7.45]
Thomas 1999	5/28	9/24	4.0 %	0.48 [0.18, 1.23]
Wald 1995	9/68	14/74	6.0 %	0.70 [0.32, 1.51]
Subtotal (95% CI)	**397**	**387**	**29.8 %**	**0.63 [0.45, 0.89]**
Total events: 45 (Corticosteroids), 70 (Placebo)				
Heterogeneity: Chi^2 = 2.83, df = 7 (P = 0.90); I^2 =0.0%				
Test for overall effect: Z = 2.62 (P = 0.0088)				
3 Low quality				
Bhaumik 1998	3/13	2/13	1.4 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24	3.5 %	0.66 [0.24, 1.80]
Subtotal (95% CI)	**39**	**37**	**4.9 %**	**0.83 [0.35, 1.95]**
Total events: 8 (Corticosteroids), 9 (Placebo)				
Heterogeneity: Chi^2 = 0.72, df = 1 (P = 0.40); I^2 =0.0%				
Test for overall effect: Z = 0.43 (P = 0.67)				
Total (95% CI)	**900**	**856**	**100.0 %**	**0.85 [0.70, 1.03]**
Total events: 161 (Corticosteroids), 185 (Placebo)				
Heterogeneity: Chi^2 = 11.68, df = 12 (P = 0.47); I^2 =0.0%				
Test for overall effect: Z = 1.70 (P = 0.089)				
Test for subgroup differences: Chi^2 = 4.20, df = 2 (P = 0.12), I^2 =52%				



Analysis 8.1. Comparison 8 Sensitivity analysis - worst-case scenario, Outcome 1 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 8 Sensitivity analysis - worst-case scenario

Outcome: 1 Severe hearing loss

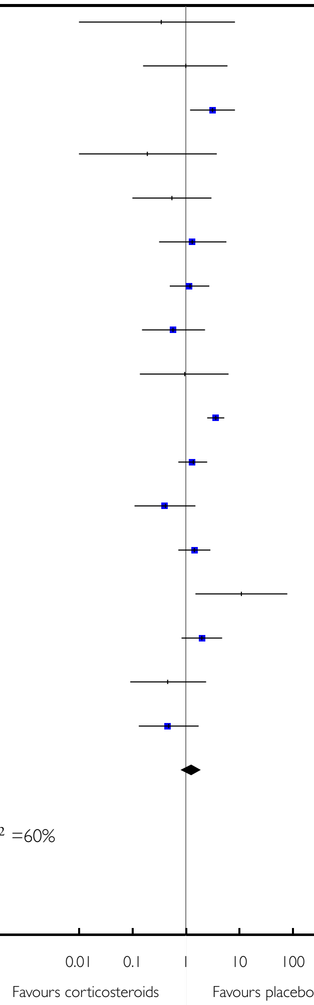
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Belsey 1969	0/41	1/42		1.6 %	0.34 [0.01, 8.14]
Bhaumik 1998	2/13	2/13		3.9 %	1.00 [0.16, 6.07]
Girgis 1989	16/204	5/202		7.5 %	3.17 [1.18, 8.49]
Kanra 1995	0/27	2/26		1.8 %	0.19 [0.01, 3.84]
Kilpi 1995	2/32	3/26		4.2 %	0.54 [0.10, 3.00]
King 1994	4/50	3/50		5.2 %	1.33 [0.31, 5.65]
Lebel 1988a	10/51	8/48		8.4 %	1.18 [0.51, 2.73]
Lebel 1988b	3/51	5/49		5.5 %	0.58 [0.15, 2.28]
Lebel 1989	2/31	2/29		3.7 %	0.94 [0.14, 6.21]
Molyneux 2002	100/206	27/200		11.3 %	3.60 [2.46, 5.25]
Nguyen 2007	22/195	16/191		9.9 %	1.35 [0.73, 2.48]
Odio 1991	3/50	7/48		5.9 %	0.41 [0.11, 1.50]
Peltola 2007	18/143	12/137		9.4 %	1.44 [0.72, 2.87]
Qazi 1996	11/36	1/36		3.4 %	11.00 [1.50, 80.82]
Scarborough 2007	13/102	7/108		8.2 %	1.97 [0.82, 4.73]
Schaad 1993	2/60	4/55		4.4 %	0.46 [0.09, 2.40]
Wald 1995	3/68	7/74		5.8 %	0.47 [0.13, 1.73]
Total (95% CI)	**1360**	**1334**		**100.0 %**	**1.25 [0.81, 1.93]**

Total events: 211 (Corticosteroids), 112 (Placebo)

Heterogeneity: $Tau^2 = 0.39$; $Chi^2 = 40.05$, df = 16 (P = 0.00077); $I^2 = 60\%$

Test for overall effect: Z = 1.02 (P = 0.31)

Test for subgroup differences: Not applicable



Analysis 8.2. Comparison 8 Sensitivity analysis - worst-case scenario, Outcome 2 Any hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 8 Sensitivity analysis - worst-case scenario

Outcome: 2 Any hearing loss

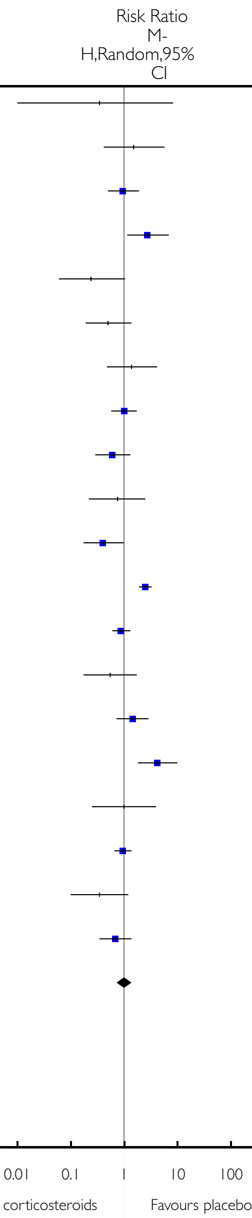
Study or subgroup	Corticosteroids n/N	Placebo n/N	Weight	Risk Ratio M-H,Random,95% CI
Belsey 1969	0/41	1/42	0.9 %	0.34 [0.01, 8.14]
Bhaumik 1998	4/14	3/16	3.5 %	1.52 [0.41, 5.67]
de Gans 2002	16/146	14/123	6.1 %	0.96 [0.49, 1.89]
Girgis 1989	17/204	6/202	5.0 %	2.81 [1.13, 6.97]
Kanra 1995	2/27	8/26	3.1 %	0.24 [0.06, 1.03]
Kilpi 1995	5/32	8/26	4.7 %	0.51 [0.19, 1.37]
King 1994	7/50	5/50	4.3 %	1.40 [0.48, 4.12]
Lebel 1988a	17/51	16/48	6.7 %	1.00 [0.57, 1.75]
Lebel 1988b	9/51	14/49	5.8 %	0.62 [0.29, 1.29]
Lebel 1989	4/31	5/29	3.8 %	0.75 [0.22, 2.52]
Mathur 2013	6/35	10/24	5.2 %	0.41 [0.17, 0.98]
Molyneux 2002	120/206	46/200	7.9 %	2.53 [1.92, 3.35]
Nguyen 2007	36/195	37/177	7.4 %	0.88 [0.59, 1.33]
Odio 1991	4/51	7/48	4.0 %	0.54 [0.17, 1.72]
Peltola 2007	18/143	12/137	6.0 %	1.44 [0.72, 2.87]
Qazi 1996	21/36	5/36	5.2 %	4.20 [1.78, 9.91]
Sankar 2007	3/12	3/12	3.3 %	1.00 [0.25, 4.00]
Scarborough 2007	36/102	36/99	7.5 %	0.97 [0.67, 1.41]
Schaad 1993	3/60	8/55	3.6 %	0.34 [0.10, 1.23]
Wald 1995	11/69	17/74	6.1 %	0.69 [0.35, 1.38]
Total (95% CI)	**1556**	**1473**	**100.0 %**	**0.98 [0.71, 1.35]**

Total events: 339 (Corticosteroids), 261 (Placebo)

Heterogeneity: Tau^2 = 0.32; Chi^2 = 69.43, df = 19 (P<0.00001); I^2 =73%

Test for overall effect: Z = 0.11 (P = 0.91)

Test for subgroup differences: Not applicable



Analysis 8.3. Comparison 8 Sensitivity analysis - worst-case scenario, Outcome 3 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 8 Sensitivity analysis - worst-case scenario

Outcome: 3 Short-term neurological sequelae

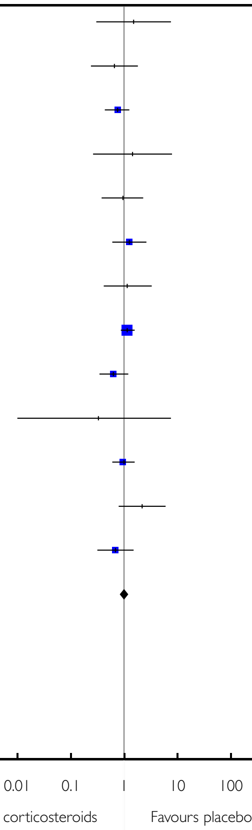
Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	3/13	2/13		1.1 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		4.0 %	0.66 [0.24, 1.80]
de Gans 2002	21/143	24/123		14.0 %	0.75 [0.44, 1.28]
Kanra 1995	3/27	2/26		1.1 %	1.44 [0.26, 7.96]
Lebel 1988a	8/51	8/48		4.5 %	0.94 [0.38, 2.31]
Lebel 1988b	13/51	10/49		5.6 %	1.25 [0.60, 2.58]
Lebel 1989	7/31	5/26		3.0 %	1.17 [0.42, 3.26]
Molyneux 2002	68/209	56/202		31.0 %	1.17 [0.87, 1.58]
Peltola 2007	14/143	21/137		11.7 %	0.64 [0.34, 1.20]
Sankar 2007	0/12	1/12		0.8 %	0.33 [0.01, 7.45]
Scarborough 2007	25/102	26/104		14.0 %	0.98 [0.61, 1.58]
Thomas 1999	5/28	9/108		2.0 %	2.14 [0.78, 5.89]
Wald 1995	9/68	14/74		7.3 %	0.70 [0.32, 1.51]
Total (95% CI)	**904**	**946**		**100.0 %**	**0.98 [0.82, 1.18]**

Total events: 181 (Corticosteroids), 185 (Placebo)

Heterogeneity: $Chi^2 = 9.22$, df = 12 (P = 0.68); I^2 =0.0%

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable



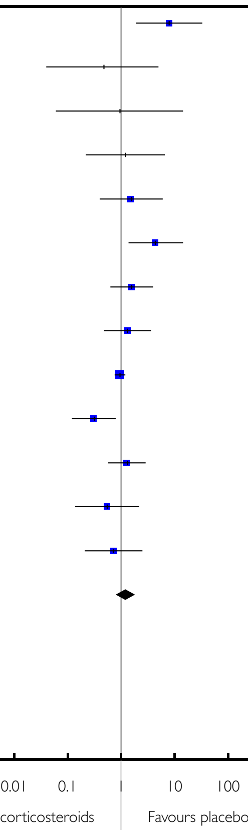
Analysis 8.4. Comparison 8 Sensitivity analysis - worst-case scenario, Outcome 4 Long-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 8 Sensitivity analysis - worst-case scenario

Outcome: 4 Long-term neurological sequelae

Study or subgroup	Corticosteroids n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
DeLemos 1969	14/53	2/61		5.8 %	8.06 [1.92, 33.84]
Girgis 1989	1/190	2/177		2.6 %	0.47 [0.04, 5.09]
Kanra 1995	1/27	1/26		2.1 %	0.96 [0.06, 14.60]
Kilpi 1995	3/32	2/26		4.5 %	1.22 [0.22, 6.76]
King 1994	5/48	3/45		6.2 %	1.56 [0.40, 6.16]
Lebel 1988a	14/51	3/48		7.5 %	4.39 [1.35, 14.34]
Lebel 1988b	10/51	6/49		9.8 %	1.60 [0.63, 4.07]
Lebel 1989	7/31	5/29		8.8 %	1.31 [0.47, 3.67]
Nguyen 2007	81/195	83/192		18.5 %	0.96 [0.76, 1.21]
Odio 1991	5/51	15/48		9.8 %	0.31 [0.12, 0.80]
Qazi 1996	10/35	8/36		11.2 %	1.29 [0.57, 2.88]
Schaad 1993	3/60	5/55		6.1 %	0.55 [0.14, 2.19]
Wald 1995	4/68	6/74		7.2 %	0.73 [0.21, 2.46]
Total (95% CI)	**892**	**866**		**100.0 %**	**1.18 [0.78, 1.78]**



Total events: 158 (Corticosteroids), 141 (Placebo)

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 23.98$, df = 12 (P = 0.02); I^2 =50%

Test for overall effect: Z = 0.79 (P = 0.43)

Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. Glossary of terms

Adjuvant therapy - medication given in addition to primary therapy (for bacterial meningitis primary therapy consist of antibiotics).
Low-income countries - countries with a UN human development index below 0.7 (58 of 182 countries in 2009).
High-income countries - countries with a UN human development index over 0.7.

Appendix 2. Details of previous searches

In the first publication of this review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2003, issue 1), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (1966 to April 2002), EMBASE (1974 to April 2002), HEALTHLINE (1988 to April 2002), Current Contents for trials published before 1 April 2002 and reference lists of all articles. We also contacted manufacturers and researchers in the field (DvdB).
In a 2006 update, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2006, issue 2), MEDLINE (1966 to July 2006), EMBASE (1974 to June 2006) and Current Contents (2001 to June 2006).
In a 2010 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, issue 1), MEDLINE (1966 to February 2010), EMBASE (1974 to February 2010), Current Contents (2001 to February 2010) and Web of Science, restricting search results to years published 2006 to 2009.
In this 2012 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, issue 11), MEDLINE (1966 to July 2012), EMBASE (1974 to July 2012), Current Contents (2001 to July 2012) and Web of Science, restricting search results to years published 2009 to 2012.
MEDLINE was searched using keywords and MeSH terms below in conjunction with the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs (Higgins 2011). The same strategy was used to search CENTRAL and adapted to search EMBASE (WebSpirs) and Current Contents (OVID).
We performed the search without any language or publication restrictions.
1 exp Meningitis/
2 meningit*:ab,ti
3 or/1-2
4 exp 'corticosteroid'/
5 'adrenal cortex hormones':ab,ti
6 'adrenal cortex hormone':ab,ti
7 corticosteroid*:ab,ti
8 dexameth*:ab,ti
9 exp 'dexamethasone'/
10 steroid*:ab,ti
11 exp 'steroid'
12 or/ 4-11
13 3 and 11

Appendix 3. EMBASE.com search strategy

#21 #6 AND #12 AND #20
#20 #19 NOT #18
#19 #13 OR #14
#18 #15 NOT #17
#17 #15 AND #16
#16 'human'/de
#15 'nonhuman'/de OR 'animal'/de OR 'animal experiment'/de
#14 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR allocat*:ab,ti OR trial:ti OR (doubl* NEXT/1 blind*):ab,ti
#13 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp

#12 #7 OR #8 OR #9 OR #10 OR #11
#11 dexamethasone*:ab,ti OR hydrocortisone*:ab,ti OR prednisolone*:ab,ti OR methylprednisolone*:ab,ti
#10 steroid*:ab,ti
#9 'steroid'/exp
#8 corticosteroid*:ab,ti OR glucocorticoid*:ab,ti
#7 'corticosteroid'/exp
#6 #1 OR #2 OR #3 OR #4 OR #5
#5 'neisseria meningitidis':ab,ti OR 'haemophilus influenzae':ab,ti OR 'streptococcus pneumoniae':ab,ti
#4 'n. meningitidis':ab,ti OR 'h. influenzae':ab,ti OR 's. pneumoniae':ab,ti
#3 'neisseria meningitidis'/de OR 'haemophilus influenzae'/exp OR 'streptococcus pneumoniae'/de
#2 meningit*:ab,ti
#1 'meningitis'/exp

Appendix 4. Web of Science (Thomson Reuters) search strategy

# 3	**32**	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=2010-2012* *Lemmatization=Off*
# 2	**217,233**	Title=(trial) OR Topic=(random* or placebo* or allocat* or ((double or single) NEAR/1 blind*)) *Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=2010-2012* *Lemmatization=Off*
# 1	**263**	Topic=(meningit* or "N. meningitidis" or "H. influenzae" or "S. pneumoniae" or "neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae") AND Topic=(corticosteroid* or glucocorticoid* or steroid* or dexamethasone* or hydrocortisone* or prednisolone* or methylprednisolone*) *Databases=SCI-EXPANDED, CPCI-S, CCR-EXPANDED, IC Timespan=2010-2012* *Lemmatization=Off*

Appendix 5. CINAHL (Ebsco) search strategy

S25 S14 and S24
S24 S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
S23 (MH "Random Assignment")
S22 (MH "Quantitative Studies")
S21 TI placebo* OR AB placebo*
S20 (MH "Placebos")
S19 TI random* OR AB random*
S18 TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S17 TI clinic* trial* OR AB clinic* trial*
S16 PT clinical trial
S15 (MH "Clinical Trials+")
S14 S6 and S13
S13 S7 or S8 or S9 or S10 or S11 or S12

S12 TI (dexamethasone* or hydrocortisone* or prednisolone* or methylprednisolone*) OR AB (dexamethasone* or hydrocortisone* or prednisolone* or methylprednisolone*)
S11 TI steroid* OR AB steroid*
S10 (MH "Steroids+")
S9 TI glucocorticoid* OR AB glucocorticoid*
S8 TI corticosteroid* OR AB corticosteroid*
S7 (MH "Adrenal Cortex Hormones+")
S6 S1 or S2 or S3 or S4 or S5
S5 TI ("neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae") OR AB ("neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae")
S4 TI ("N. meningitidis" or "H. influenzae" or "S. pneumoniae") OR AB ("N. meningitidis" or "H. influenzae" or "S. pneumoniae")
S3 (MH "Haemophilus Influenzae")
S2 TI meningit* OR AB meningit*
S1 (MH "Meningitis+")

Appendix 6. LILACS (Bireme) search strategy

> Search > (MH:meningitis OR meningit$ MH:C10.228.228.507$ OR MH:C10.228.566$ OR MH:"Neisseria meningitidis" OR MH:B03.440.400.425.550.550.641$ OR B03.660.075.525.520.500$ OR MH:"Haemophilus influenzae" OR MH: B03.440.450.600.450.330$ OR MH:B03.660.250.550.290.330$ OR MH:"Streptococcus pneumoniae" OR "N. meningitidis" OR "H. influenzae" OR "S. pneumoniae" OR "neisseria meningitidis" or "haemophilus influenzae" or "streptococcus pneumoniae") AND (MH:"Adrenal Cortex Hormones" OR corticosteroid$ OR Corticoesteroides OR Corticosteróides OR Corticoids OR MH: D06.472.040$ OR MH:glucocorticoids OR glucocorticoid$ OR Glucocorticoides OR Glucocorticóides OR Glicocorticoides OR MH:steroids OR Esteroides OR Esteróides OR MH:D04.808$ OR MH:Dexamethasone OR Dexametasona OR Hexadecadrol OR Hydrocortisone OR Hidrocortisona OR Cortisol OR MH:methylprednisolone OR Metilprednisolona OR MH:prednisolone OR prednisolon$) > clinical˙trials

WHAT'S NEW

Last assessed as up-to-date: 18 January 2013.

Date	Event	Description
18 January 2013	New search has been performed	Searches conducted. One new trial was included in this updated review (Mathur 2013) and one new trial was excluded (Tolaj 2010).
18 January 2013	New citation required but conclusions have not changed	Our conclusions remain unchanged.

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 2003

Date	Event	Description
19 June 2008	New search has been performed	Converted to new review format.
10 November 2004	Feedback has been incorporated	Comment and reply added to review.
13 April 2002	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Matthijs Brouwer (MB) was responsible for co-designing and writing the review, selecting studies, extracting and analysing data.

Peter McIntyre (PM) was responsible for co-writing the protocol, co-writing the review and extracting data.

Kameshwar Prasad (KP) was responsible for co-designing and co-writing the review.

Diederik van de Beek (DvdB) was responsible for co-designing and writing the review, selecting studies, extracting and analysing data.

DECLARATIONS OF INTEREST

The review authors have no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Academic Medical Center, Netherlands.

AMC Fellowship 2008 (D. van de Beek)

External sources

- Netherlands Organization for Health Research and Development, Netherlands.

NWO Veni grant 2012 (916.13.078) to M.C. Brouwer; NWO Veni grant 2006 (916.76.023), NWO Vidi grant (016.116.358) to D. van de Beek

- European Research Council, Not specified.

ERC Starting Grant to D. van de Beek

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Inflammatory Agents [adverse effects; *therapeutic use]; Dexamethasone [therapeutic use]; Glucocorticoids [adverse effects; *therapeutic use]; Hearing Loss [etiology; prevention & control]; Meningitis, Bacterial [complications; *drug therapy]; Prednisolone [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Child; Humans