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Corticosteroids for acute bacterial meningitis (Review)

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

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[Intervention Review]

Corticosteroids for acute bacterial meningitis

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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 (2015, Issue 1), MEDLINE (1966 to January week 4, 2015), Emabse (1974 to February 2015), Web of Science (2010 to February 2015), CINAHL (2010 to February 2015) and LILACS (2010 to February 2015).

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

We included 25 studies involving 4121 participants (2511 children and 1517 adults; 93 mixed population). Four studies were of high quality with no risk of bias, 14 of medium quality and seven of low quality, indicating a moderate risk of bias for the total analysis. Nine studies were performed in low-income countries and 16 in high-income countries.

There was insufficient evidence that corticosteroids caused a reduction in mortality overall (17.8% versus 19.9%; risk ratio (RR) 0.90, 95% confidence interval (CI) 0.80 to 1.01; P = 0.07), or for adults (RR 0.74, 95% CI 0.53 to 1.05; P = 0.09). However they caused 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).

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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% Cl 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

Review question

We reviewed the evidence about the effect of corticosteroids on mortality, hearing loss and/or neurological sequelae (such as hearing loss, neurologic deficits) in adults and children with acute bacterial meningitis.

Background

Acute bacterial meningitis is an infection of the meninges (the system of membranes that envelops the brain and spinal cord), which 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.

We wanted to discover whether use of corticosteroids was better of worse than placebo.

Study characteristics

The evidence is current to February 2015. We identified 25 trials, including 4121 participants with acute bacterial meningitis of which seven were performed in adults (over 16 years old), two included both children and adults and the other were performed in children. In 22 studies the corticosteroid used was dexamethasone, in three others hydrocortisone or prednisone were used. Nine studies were performed in low-income countries and 16 in high-income countries.

Key results

This review found that the corticosteroid dexamethasone did not significantly reduce the death rate (17.8% versus 19.9%). Patients treated with corticosteroids had significantly lower rates of severe hearing loss (6.0% versus 9.3%), any hearing loss (13.8% versus 19.0%) and neurological sequelae (17.9% versus 21.6%).

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 (29.9% versus 36.0%), while no effect on mortality was seen in patients with *Haemophilus influenzae* (*H influenzae*) and *Neisseria meningitidis* (*N meningitidis*) meningitis.

In high-income countries, corticosteroids reduced severe hearing loss, any hearing loss and short-term neurological sequelae. There was no beneficial effect of corticosteroid therapy in low-income countries.

Corticosteroids decreased the rate of hearing loss in children with meningitis due to *H influenzae* (4% versus 12%), but not in children with meningitis due to other bacteria.

Dexamethasone increased the rate of recurrent fever (28% versus 22%) but was not associated with other adverse events.

Quality of the evidence

Out of 25 studies, four were of high quality, 14 of medium quality and seven of low quality, leading to a moderate overall quality of evidence.

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Corticosteroids for acute bacterial meningitis (Review) Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table

Comparison of corticosteroids against placebo in patients with acute bacterial meningitis

Patient or population: acute bacterial meningitis

Setting: hospitals, low- and high-income countries

Intervention: corticosteroids

Comparison: placebo

Outcomes	Anticipated absolute ef	ffects [*] (95% CI)	Relative effect (95% CI)	No of partici- pants	Quality of the evidence	Comments
	Risk with placebo	Risk with corticosteroids		(studies)	(GRADE)	
Mortality	Study population		RR 0.90 (0.80 to 1.01)	4121 (25 RCTs)	\$\$\$	_
	199 per 1000	179 per 1000 (159 to 201)	(0.00 to 1.01)	(25 ((615)	MODERATE ¹	
	Moderate					
	188 per 1000	169 per 1000 (150 to 189)				
Severe hearing loss	e hearing Study population		RR 0.67 (0.51 to 0.88)	$\oplus \oplus \oplus \ominus$	_	
1055	93 per 1000	62 per 1000 (47 to 82)	(0.51 (0 0.00)	(17 RCTs)	HIGH	
	Moderate					
	40 per 1000	27 per 1000 (20 to 35)				
Any hearing loss	Study population		RR 0.74 (0.63 to 0.87)	2785 (20 RCTs)	$\oplus \oplus \oplus \ominus$	_
1035	190 per 1000	141 per 1000 (120 to 166)	(0.03 10 0.87)	(20 KC13)	HIGH	
	Moderate					
	233 per 1000	173 per 1000				

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Cort			(147 to 203)						
coster	Short-term neu- rological seque-	Study population		RR 0.83 - (0.69 to 1.00)	1756 (13 RCTs)	$\Phi\Phi\Phi\Theta$ —			
oids for ac	lae	216 per 1000	179 per 1000 (149 to 216)	- (0.03 to 1.00)	(13 ((13)	HIGH			
ute ba		Moderate							
cterial me		222 per 1000	184 per 1000 (153 to 222)						
ningit	Adverse events - recurrent fever	Study population		RR 1.27 - (1.09 to 1.47)	1723 (12 RCTs)	⊕⊕⊖⊖ MODERATE ²	-		
is (Review		221 per 1000	281 per 1000 (241 to 326)	(100 to 111)	(12 ((013)	MODEIXTE			
2		Moderate							
		281 per 1000	357 per 1000 (307 to 413)						

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio; OR: odds ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

 ${}^1\!Variable\ mortality\ between\ studies,\ consistent\ with\ differences\ across\ the\ world\ in\ meningitis\ prognosis.$

²Different definitions used for recurrent fever makes this imprecise.

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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 200

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 the 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 metaanalysis 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 lowincome countries, primarily related to access to care and comorbidities. 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

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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 2015 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2015, Issue 1), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (January 2013 to January Week 4, 2015), Embase (January 2013 to February 2015), Web of Science (January 2013 to February 2015), CINAHL (January 2013 to February 2015) and LILACS (January 2013 to February 2015). Details of earlier searches are in Appendix 2.

We used the search strategy described in Appendix 3 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 4), Web of Science (Appendix 5), CINAHL (Appendix 6) and LILACS (Appendix 7). We did not apply any language or publication restrictions.

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. We also searched the trials registries World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov for completed and ongoing trials (June 2015).

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, we also recorded the number of participants randomised into the treatment arms and used the discrepancy between the figures 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 Chi² test. These tests were two-tailed and we considered a P value of < 0.05 significant.

Assessment of heterogeneity

We assessed heterogeneity in all analysis with the l^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.

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Data synthesis

We analysed the data using Review Manager 5.3 (RevMan 2014). 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 randomeffects 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 lowincome 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 we categorised the study as high quality, three through five as medium quality and less than three questions answered positively as low quality.

In the subgroup analysis we used the inverse variance method 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. We considered all participants who had dropped out of the corticosteroid group to have an unfavourable outcome whereas we considered those who had dropped out of the control group to have a favourable outcome. We conducted a sensitivity analysis by 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 I² statistic (I² 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.

RESULTS

Description of studies

Results of the search

Since the first publication of this review we have retrieved a total of 4421 records. After removing duplicates we identified 3559 records in the electronic databases.

In the previous publications of this review, Brouwer 2013, 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). In this 2015 search we did not identify any new trials for inclusion.

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, we included these participants 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 we recalculated the number of events 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.

Ten studies were funded in part by pharmaceutical companies, which were often only providing study medication. Five studies were funded by charities, four by government funding organisations, and funding was not reported for nine studies.

Excluded studies

We excluded 16 trials (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).

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Risk of bias in included studies

Summary of general risk of bias

Four of 25 studies were free of bias, whereas the other 21 had one or more biases. Attrition, reporting and potential selection bias were most common, occurring in eight, 18 and 12 studies (Figure 1).

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Figure 1. 'Risk of bias' summary: review authors' judgements about each methodological quality item for each included study.



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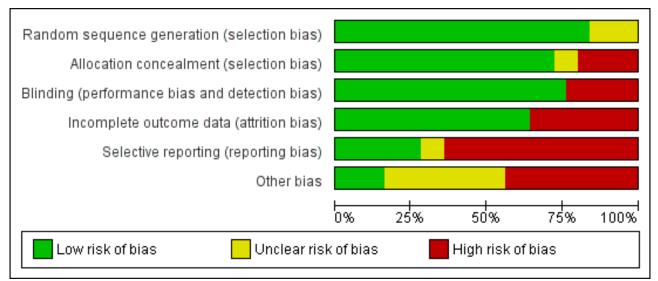
Figure 1. (Continued)

Scarborough 2007	•	•	•	•	•	•
Schaad 1993	•	•	÷			?
Thomas 1999	•	•	•		•	•
Wald 1995	•	+	+	•		?

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 2; Figure 1). 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, dexamethasoneplacebo, 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.





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 having 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

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per-protocol figures (46% of included participants) and ITT figures (56%).

A study protocol with pre-specification of the analyses had not been published prior to publication of the complete study results for any of the included studies. None of the trials registered a study protocol in a trial registry.

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. We found other indications of a selection bias in studies with high numbers of comatose participants or low

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

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

See: Summary of findings for the main comparison Summary of findings table

Primary outcomes

1. Mortality

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 value = 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) (Analysis 1.1; Figure 3).

	Corticoste	roids	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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 = Test for overall effect		`	l.18); I²=	21%			0.1 0.2 0.5 1 2 5 Favours corticosteroids Favours placebo

2. Hearing loss

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;

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Sankar 2007; Scarborough 2007; Schaad 1993; Wald 1995) (Analysis 1.2; Analysis 1.3; Figure 4; Figure 5).

Figure 4. Forest plot of comparison: 1 All patients, outcome: 1.2 Severe hearing loss.

	Corticoste	roids	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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]	← → <u>+</u>
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		112				
Heterogeneity: Chi ² =	15.67, df = 1	6 (P = 0	.48); I ² =	0%			0.1 0.2 0.5 1 2 5 10
Test for overall effect	Z = 2.86 (P =	0.004)					0.1 0.2 0.5 1 2 5 10 Favours corticosteroids Favours placebo

Figure 5. Forest plot of comparison: 1 All patients, outcome: 1.3 Any hearing loss.

	Corticoste	roids	Place	bo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
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		259				
Heterogeneity: Chi ² =	25.05, df = 1	19 (P = 0	.16); I ² =	24%			0.01 0.1 1 10 100
Test for overall effect	: Z = 3.59 (P =	= 0.0003)				0.01 0.1 1 10 100 Favours corticosteroids Favours placebo

3. Neurological sequelae

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% Cl 0.69 to 1.00, P value = 0.05). Long-term neurological sequelae were assessed in 12 studies

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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 the 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) (Analysis 1.5).

Secondary outcome

1. Adverse events

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 1988; Lebel 1989; Mathur 2013; Nguyen 2007; Odio 1991; Peltola 2007; Qazi 1996; Sankar 2007; Scarborough 2007; Schaad 1993; Thomas 1999; Wald 1995) (Analysis 1.6; 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	Corticoste Events		Placel Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
1.6.1 Gastrointestina		TUTAL	Lvents	rotar	weight	m-n, rixeu, 95% Cl	m-n, rikeu, 95% Ci
		157	5	1 4 4	22.8%	0.07/0.07/4.061	
de Gans 2002	2 0	157	5 0	144	22.070	0.37 [0.07, 1.86]	
Kilpi 1995 King 1994		32	-	26	4.000	Not estimable	
King 1994	1	50	1	51	4.3%	1.02 [0.07, 15.86]	
Lebel 1988a	0	51	0	49	0.000	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:	•	` '					
		r					
1.6.2 Herpes zoster i	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]	<u> </u>
	Ŭ	719		713			•
Subtotal (95% CI)	-					1.09 [0.86, 1.37]	•
Subtotal (95% CI) Total events	115	719	105	713			•
Subtotal (95% Cl) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (719 (P = 0.93)	105	713			•
Subtotal (95% CI) Total events	115 1.39, df = 5 (719 (P = 0.93)	105	713			•
Subtotal (95% Cl) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (Z = 0.73 (P =	719 (P = 0.93)	105	713			•
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve	115 1.39, df = 5 (Z = 0.73 (P =	719 (P = 0.93) = 0.47)	105 i; i² = 0%	713	100.0%	1.09 (0.86, 1.37)	▲
Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: I.6.3 Persistent feve King 1994	115 1.39, df = 5 (Z = 0.73 (P = r 3	719 (P = 0.93) = 0.47) 50	105 ;; I ^z = 0% 8	51	100.0% 38.8%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991	115 :1.39, df = 5 (:Z = 0.73 (P = er 3 1	719 (P = 0.93) = 0.47) 50 52	105 ;; I² = 0% 8 10	713 51 48	100.0% 38.8% 51.0%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: I.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993	115 1.39, df = 5 (Z = 0.73 (P = r 3	719 (P = 0.93) = 0.47) 50 52 60	105 ;; I ^z = 0% 8	713 51 48 55	100.0% 38.8% 51.0% 10.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI)	115 1.39, df = 5 (Z = 0.73 (P = 9r 3 1 2	719 (P = 0.93) = 0.47) 50 52	105 ; I ^z = 0% 8 10 2	713 51 48	100.0% 38.8% 51.0%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: I.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events	115 1.39, df = 5 (Z = 0.73 (P = 97 3 1 2 6	719 (P = 0.93) = 0.47) 50 52 60 162	105 ;; ² = 0% 8 10 2 20	51 48 55 154	100.0% 38.8% 51.0% 10.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: I.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (Z = 0.73 (P = or 3 1 2 6 2.80, df = 2 (719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25)	105 ;; ² = 0% 8 10 2 20	51 48 55 154	100.0% 38.8% 51.0% 10.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: I.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events	115 1.39, df = 5 (Z = 0.73 (P = or 3 1 2 6 2.80, df = 2 (719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25)	105 ;; ² = 0% 8 10 2 20	51 48 55 154	100.0% 38.8% 51.0% 10.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: I.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (Z = 0.73 (P = 3 1 2 6 2.80, df = 2 (Z = 2.75 (P =	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25)	105 ;; ² = 0% 8 10 2 20	51 48 55 154	100.0% 38.8% 51.0% 10.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fevent	115 1.39, df = 5 (Z = 0.73 (P = r 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = r	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006)	105 ;; ² = 0% 10 2 ;; ² = 28 ;	51 48 55 154 %	100.0% 38.8% 51.0% 10.2% 100.0%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995	115 1.39, df = 5 (Z = 0.73 (P = r 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = r 9	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34	105 ;; ² = 0% 10 2 ;; ² = 28 6	713 51 48 55 154 %	100.0% 38.8% 51.0% 10.2% 100.0% 3.0%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.59 (0.63, 3.99)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Kanra 1995	115 1.39, df = 5 (Z = 0.73 (P = r 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = r 9 5	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29	105 ; ² = 0% 10 2 ; ² = 28 ; 6 4	713 51 48 55 154 % 36 27	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.59 (0.63, 3.99) 1.16 (0.35, 3.89)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Kilpi 1995	115 1.39, df = 5 (Z = 0.73 (P = r 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = r 9 5 4	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50	105 ; ² = 0% 10 2 ; ² = 28 6 4 3	713 51 48 55 154 % 36 27 51	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fevel Ciana 1995 Kanra 1995 Kanra 1995 Lebel 1988a	115 1.39, df = 5 (Z = 0.73 (P = r 3 2.80, df = 2 (Z = 2.75 (P = r 9 5 4 31	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51	105 ; ² = 0% 10 2 20 ; ² = 28 6 4 3 23	713 51 48 55 154 % 36 27 51 49	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.59 (0.63, 3.99) 1.16 (0.35, 3.89) 1.36 (0.32, 5.77) 1.29 (0.89, 1.88)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fevel Ciana 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b	115 1.39, df = 5 (Z = 0.73 (P = r 2.80, df = 2 (Z = 2.75 (P = r 9 5 4 31 32	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 23 11	713 51 48 55 154 % 36 27 51 49 49	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988b Lebel 1989	115 1.39, df = 5 (Z = 0.73 (P = 9 2.80, df = 2 (2.80, df = 2 (2.2 = 2.75 (P = 7 9 5 4 31 32 14	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14	713 51 48 55 154 % 36 27 51 49 49 29	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.16 (0.35, 3.89) 1.36 (0.32, 5.77) 1.29 (0.89, 1.88) 2.80 (1.59, 4.90) 0.94 (0.54, 1.61)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 1991	115 1.39, df = 5 (Z = 0.73 (P = ar 2.80, df = 2 (Z = 2.75 (P = r 9 5 4 31 32 14 10	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) (P = 0.25) = 0.006) 34 29 50 51 51 31 51 31 52	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9	713 51 48 55 154 % 36 27 51 49 49 29 48	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.16 (0.35, 3.89) 1.36 (0.32, 5.77) 1.29 (0.89, 1.88) 2.80 (1.59, 4.90) 0.94 (0.54, 1.61) 1.03 (0.46, 2.31)	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007	115 1.39, df = 5 (Z = 0.73 (P = 1 2.80, df = 2 (Z = 2.75 (P = 7 9 5 4 31 32 14 10 65	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66	713 51 48 55 154 % 36 27 51 49 49 29 48 163	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988 Dioio 1991 Peltola 2007 Qazi 1996	115 1.39, df = 5 (Z = 0.73 (P = m 2.80, df = 2 (Z = 2.75 (P = 9 5 4 31 32 14 10 65 20	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 162 (P = 0.25) = 0.006) 162 51 51 51 51 51 31 52 166 48	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14	713 51 48 55 154 % 36 27 51 49 49 29 48 163 41	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent feven Ciana 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b Lebel 1988b Lebel 1988b Ddio 1991 Peltola 2007 Qazi 1996 Scarborough 2007	115 1.39, df = 5 (Z = 0.73 (P = 7 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = 7 9 5 4 31 32 14 10 65 20 7	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233	105 ; ² = 0% 8 10 2 20 ; ² = 28' 6 4 3 23 11 14 9 66 14 2	713 51 48 55 154 % 36 27 51 49 29 49 29 48 163 41 232	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 34.8% 7.9% 1.0%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b Lebel 1988b Lebel 1988b Ddio 1991 Peltola 2007 Qazi 1996 Scarborough 2007 Schaad 1993	115 1.39, df = 5 (Z = 0.73 (P = 1 2 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = 9 5 4 31 32 14 10 65 20 7 19	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 51 51 51 51 51 51 52 166 48 233 60	105 ; ² = 0% 8 10 2 20 ; ² = 28' 6 4 3 23 11 14 9 66 14 2 11	713 51 48 55 154 % 36 27 51 49 49 29 49 29 48 163 41 232 50	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73]	
Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.4 Recurrent fevel Ciana 1995 Kanra 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 2007 Qazi 1996 Scarborough 2007 Schaad 1993	115 1.39, df = 5 (Z = 0.73 (P = 7 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = 7 9 5 4 31 32 14 10 65 20 7	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 51 31 51 66 48 233 60 69	105 ; ² = 0% 8 10 2 20 ; ² = 28' 6 4 3 23 11 14 9 66 14 2	713 51 48 55 154 % 36 27 51 49 49 29 49 29 49 29 48 163 41 232 50 74	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 (0.86, 1.37) 0.38 (0.11, 1.36) 0.09 (0.01, 0.69) 0.92 (0.13, 6.29) 0.29 (0.12, 0.70) 1.59 (0.63, 3.99) 1.16 (0.35, 3.89) 1.36 (0.32, 5.77) 1.29 (0.89, 1.88) 2.80 (1.59, 4.90) 0.94 (0.54, 1.61) 1.03 (0.46, 2.31) 0.97 (0.74, 1.26) 1.22 (0.71, 2.10) 3.48 (0.73, 16.60) 1.44 (0.76, 2.73) 1.33 (0.88, 2.01)	
Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.4 Recurrent fevel Ciana 1995 Kilpi 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 2007 Qazi 1996 Scarborough 2007 Schaad 1993 Wald 1995 Subtotal (95% CI)	115 1.39, df = 5 (Z = 0.73 (P = 1 2 6 2.80, df = 2 (Z = 2.75 (P = 9 5 4 31 32 14 10 65 20 7 19 31	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 51 51 51 51 51 51 52 166 48 233 60	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 6 6 14 9 6 14 2 5	713 51 48 55 154 % 36 27 51 49 49 29 49 29 48 163 41 232 50	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73]	
Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007 Qazi 1996 Scarborough 2007 Schaad 1993 Wald 1995 Subtotal (95% CI) Total events	115 1.39, df = 5 (Z = 0.73 (P = 1 2 6 2.80, df = 2 (Z = 2.75 (P = 9 5 4 31 32 14 10 65 20 7 19 31 247	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233 60 69 874	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14 2 11 25 188	713 51 48 55 154 % 36 27 51 49 49 29 48 163 49 29 48 163 41 232 50 74 849	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73] 1.33 [0.88, 2.01]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007 Qazi 1996 Scarborough 2007 Schaad 1993 Wald 1995 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (Z = 0.73 (P = T 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = T 9 5 4 31 32 14 10 65 20 7 19 31 247 15.16, df = 1	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233 60 69 874 1 (P = 0.25)	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14 2 11 25 188	713 51 48 55 154 % 36 27 51 49 49 29 48 163 49 29 48 163 41 232 50 74 849	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73] 1.33 [0.88, 2.01]	
Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Lebel 1988a Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007 Qazi 1996 Scarborough 2007 Schaad 1993 Wald 1995 Subtotal (95% CI) Total events	115 1.39, df = 5 (Z = 0.73 (P = T 3 1 2 6 2.80, df = 2 (Z = 2.75 (P = T 9 5 4 31 32 14 10 65 20 7 19 31 247 15.16, df = 1	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233 60 69 874 1 (P = 0.25)	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14 2 11 25 188	713 51 48 55 154 % 36 27 51 49 49 29 48 163 49 29 48 163 41 232 50 74 849	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73] 1.33 [0.88, 2.01]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fevel Ciana 1995 Kanra 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007 Gazi 1996 Scarborough 2007 Schaad 1993 Avald 1995 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	115 1.39, df = 5 (Z = 0.73 (P = 9 2.80, df = 2 (2.2 = 2.75 (P = 7 9 5 4 31 32 14 10 65 20 7 19 31 247 15.16, df = 1 Z = 3.06 (P =	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233 60 69 874 1 (P = 0.25)	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14 2 11 25 188	713 51 48 55 154 % 36 27 51 49 49 29 48 163 49 29 48 163 41 232 50 74 849	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73] 1.33 [0.88, 2.01]	
Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.3 Persistent feve King 1994 Odio 1991 Schaad 1993 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: 1.6.4 Recurrent fever Ciana 1995 Kanra 1995 Lebel 1988a Lebel 1988a Lebel 1988b Lebel 1988b Lebel 1989 Odio 1991 Peltola 2007 Qazi 1996 Scarborough 2007 Schaad 1993 Wald 1995 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	115 1.39, df = 5 (Z = 0.73 (P = 9 2.80, df = 2 (2.2 = 2.75 (P = 7 9 5 4 31 32 14 10 65 20 7 19 31 247 15.16, df = 1 Z = 3.06 (P =	719 (P = 0.93) = 0.47) 50 52 60 162 (P = 0.25) = 0.006) 34 29 50 51 51 31 52 166 48 233 60 69 874 1 (P = 0.25)	105 ; ² = 0% 8 10 2 20 ; ² = 28 6 4 3 23 11 14 9 66 14 2 11 25 188	713 51 48 55 154 % 36 27 51 49 49 29 48 163 41 232 50 74 849 227%	100.0% 38.8% 51.0% 10.2% 100.0% 3.0% 2.2% 1.6% 12.3% 5.9% 7.6% 4.9% 34.8% 7.9% 1.0% 6.3% 12.6%	1.09 [0.86, 1.37] 0.38 [0.11, 1.36] 0.09 [0.01, 0.69] 0.92 [0.13, 6.29] 0.29 [0.12, 0.70] 1.59 [0.63, 3.99] 1.16 [0.35, 3.89] 1.36 [0.32, 5.77] 1.29 [0.89, 1.88] 2.80 [1.59, 4.90] 0.94 [0.54, 1.61] 1.03 [0.46, 2.31] 0.97 [0.74, 1.26] 1.22 [0.71, 2.10] 3.48 [0.73, 16.60] 1.44 [0.76, 2.73] 1.33 [0.88, 2.01]	

Corticosteroids for acute bacterial meningitis (Review)



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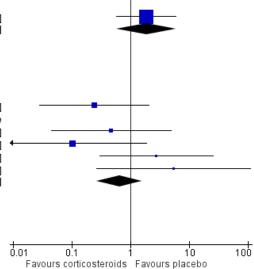
Figure 6. (Continued)

1.6.5 Fungal infection de Gans 2002 Subtotal (95% CI) Total events Heterogeneity: Not applica	8 8 hle	157 157	4 4	144 144	100.0% 100.0 %	1.83 [0.56, 5.96] 1.83 [0.56, 5.96]	
Test for overall effect: Z = 1		= 0.31)					
1.6.6 Arthritis		,					
Lebel 1988a	1	51	4	49	33.0%	0.24 [0.03, 2.07]	
Lebel 1988b	Ó	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]	

Subtotal (95% CI) Total events

Heterogeneity: Chi² = 5.94, df = 4 (P = 0.20); l² = 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 (I² 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 corticosteroidtreated 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 Hinfluenzae, 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; I² 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 corticosteroidtreated 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, I² statistic for subgroups 86%; any hearing loss RR 0.89, 95% CI 0.76 to 1.04, I² statistic 89%; short-term neurological sequelae RR 1.03, 95% CI 0.81 to 1.31, I² 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, I² statistic for subgroups 81%; short-term sequelae, RR 1.08, 95% CI 0.81 to 1.43, I² statistic for subgroups 75%) (Analysis 5.5; Analysis 5.6; Analysis

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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 (I² 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 1). 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 (I² 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 (RR 0.81, 95% CI 0.61 to 1.08; P = 0.16; Analysis 4.1).

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 value = 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 longterm 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

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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 shortterm 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 with five recent large RCTs on adjunctive dexamethasone therapy in bacterial meningitis (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 prespecified 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 followup 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 that 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 microorganism 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.

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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 in 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 with 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 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.

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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 metaanalysis (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 metaanalysis 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 Cochrane 2013 updated meta-analysis were not included in the meta-analysis of paediatric studies was not specified (Brouwer 2013). 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 highand 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 communityacquired 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 I² 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 communityacquired bacterial meningitis in high-income countries.

Implementation studies

Seven studies evaluated the implementation of adjunctive dexamethasone treatment and its effect on the outcome of bacterial meningitis (Bodilsen 2014; Brouwer 2010b; Castelblanco

Corticosteroids for acute bacterial meningitis (Review)

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2014; Cornelis 2011; Heckenberg 2012b; Koopmans 2013; Peterković 2012). Three studies compared the prognosis of adult pneumococcal, meningococcal and Listeria monocytogenes meningitis between two nationwide prospective cohort studies; one was performed before and the other after the implementation of adjunctive dexamethasone (Brouwer 2010b; Heckenberg 2012b; Koopmans 2013). The studies showed that after the introduction of adjunctive dexamethasone, 84% of patients with pneumococcal meningitis, 89% of adults with meningococcal meningitis and 53% of L monocytogenes 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 value = 0.001) and the rate of hearing loss decreased from 22% to 12% (P value = 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 studies on pneumococcal and meningococcal meningitis. The beneficial effect of dexamethasone on pneumococcal meningitis was similar to that identified in the European Dexamethasone Study (de Gans 2002). For listerial meningitis, an increase in unfavourable outcome from 27% to 61% was observed between the first and second cohort study (Koopmans 2013). In a multivariate analysis bacterial genotype was found to be the main cause of the poorer prognosis. Dexamethasone was not associated with a change in mortality, hearing loss or sequelae in listerial meningitis. However, as adjunctive dexamethasone treatment was another major change between cohorts, it was suggested to discontinue dexamethasone when L monocytogenes is identified. A nationwide retrospective study from Denmark showed dexamethasone was administered to 60% of meningitis cases between 2008 and 2012 compared to 37% between 2003 and 2007 (Bodilsen 2014). Dexamethasone treatment was associated with a significant decrease in the risk of an unfavourable outcome (33% versus 53%) and mortality (15% versus 24%). The implementation studies provide additional (class III) evidence that adjunctive dexamethasone is beneficial in adults with bacterial meningitis in high-income countries.

In a population-based observational study from the USA, incidence and mortality of bacterial meningitis due to the five most common pathogens between 1997 and 2010 were studied in a network database (Castelblanco 2014). The study showed that over time mortality declined. This was attributed to the publication of the IDSA guideline of 2004, which advised adjunctive dexamethasone for all suspected bacterial meningitis cases (Castelblanco 2014). However, data on dexamethasone use were not available and therefore a causal relation could not be established.

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. Further follow-up studies in countries where dexamethasone has been implemented may provide additional circumstantial evidence on the effectiveness of adjunctive dexamethasone.
- The role of corticosteroids in neonatal meningitis is currently unclear due to the different spectrum of causative microorganisms and the lack of applicable RCT data. Additional RCTs in neonatal meningitis are needed.
- Case series are needed to determine the effect of adjunctive dexamethasone therapy in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporinresistant strains.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

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* Indicates the major publication for the study

Bademosi 1979

Bademosi 1979	
Methods	Randomised, unblinded
Participants	10 to 59 years; bacteriologically proven pneumococcal meningitis; 52 participants (27 male, 25 female; 24 received steroids, 28 placebo); Nigeria
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%
	Funding - not reported
Risk of bias	

NISK OF BIUS

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Bademosi 1979 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting 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; 86 participants (40 male, 46 female; 43 DXM, 43 placebo; USA
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
	Funding - not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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

Corticosteroids for acute bacterial meningitis (Review)



Belsey 1969 (Continued)

Selective reporting (re- porting 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 inten- tion-to-treat analysis
Other bias	High risk	Unevenly distributed severity of disease at admission (control group worse)

Methods	Randomised, double-blind		
Participants	All ages; life-threatening infectious diseases, subgroup meningitis; 85 participants (gender not reported for meningitis subgroup; 38 hydrocortisone/47 placebo); USA		
Interventions	Hydrocortisone schem	e, 7 d; after AB	
Outcomes	Mortality		
Notes	AB - not specified, mortality 45%		
	Funding - not reported	Funding - not reported	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (selection bias)	Unclear risk	Randomisation procedure not specified	
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 (re- porting 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

bildulink 1990	
Methods	Randomised, unblinded
Participants	12 to 75 years; suspected bacterial meningitis with CSF criteria; 30 participants (26 male, 4 female; 14 DXM, 16 placebo); India

Corticosteroids for acute bacterial meningitis (Review)



Bhaumik 1998 (Continued) DXM 16 mg/day, 4 d, plus 3 d scheme; after AB Interventions Outcomes Mortality, neurological sequelae, adverse events (not specified) Notes AB - pen/chlor or ceph, mortality 13% Funding - not reported **Risk of bias** Bias **Authors' judgement** Support for judgement Randomised table chart Random sequence genera-Low risk tion (selection bias) Allocation concealment High risk The treatment allocation was not concealed (selection bias) The study is not blinded Blinding (performance High risk bias and detection bias) All outcomes Incomplete outcome data High risk Incomplete outcome data not addressed (attrition bias) All outcomes Unclear risk Selective reporting (re-No intention-to-treat analysis porting bias) Other bias High risk Unevenly distributed baseline and clinical characteristics

Ciana 1995

Randomised, unblinded		
2 months to 6 years; suspected bacterial meningitis with CSF criteria; 70 participants (gender not re- ported; 34 DXM, 36 placebo); Mozambique		
DXM 0.4 mg/kg, 3 d; timing unclear		
Mortality, neurological sequelae, adverse events (recurrent fever)		
AB - ampi/chlor, mortality 28%		
Funding - not reported		
Authors' judgement	Support for judgement	
Unclear risk	Randomisation procedure not specified	
High risk	The treatment allocation was not concealed	
	2 months to 6 years; su ported; 34 DXM, 36 plac DXM 0.4 mg/kg, 3 d; tin Mortality, neurological AB - ampi/chlor, morta Funding - not reported Authors' judgement Unclear risk	

Corticosteroids for acute bacterial meningitis (Review)



Ciana 1995 (Continued)

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 (re- porting 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; 301 participants (169 male, 132 female; 157 DXM and 144 placebo); Netherlands, Belgium, Denmark, Austria, Germany		
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%		
	Funding - NV Organon provided study medication (pharmaceutical company)		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	Low risk	Inclusion chart provided. Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

Corticosteroids for acute bacterial meningitis (Review)



DeLemos 1969

Methods	Randomised, double-blind	
Participants	1 month to 17 years; diagnosis bacterial meningitis; 117 participants (gender not reported; 54 methyl- prednisolone, 63 placebo); USA	
Interventions	Methylprednisolone 120 mg/d, 3 d; after AB	
Outcomes	Mortality	
Notes	AB - chlor/sulf/pen, mortality 3%	
	Funding - not reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	Antibiotic pretreatment unevenly distributed between randomisation arms

Girgis 1989

Bias	Authors' judgement Support for judgement		
Risk of bias			
	Funding - United States naval medical research and development command (government funding body)		
Notes	AB - chlor/ampi, mortality 15%		
Outcomes	Mortality, hearing loss, neurological sequelae		
Interventions	DXM 16 to 24 mg/d, 4 d; before or with AB		
Participants	3 months to 70 years; diagnosis bacterial meningitis; 470 participants (gender specified 429 - 278 ma 151 female; 225 DXM, 245 placebo); Egypt		
Methods	Randomised, unblinded		

Corticosteroids for acute bacterial meningitis (Review)

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Girgis 1989 (Continued)

Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	The very high number of comatose patients compared to other studies sug- gests a selection bias

Kanra 1995

Methods	Randomised, double-blind	
Participants	2 to 6 years; bacteriologically proven pneumococcal meningitis; 53 participants (32 male, 21 female; 27 DXM, 26 no dexamethasone); Turkey	
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (recurrent fever)	
Notes	AB - sulf/ampi, mortality 5%	
	Funding - not reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis; selection of pneumococcal meningitis patients

Corticosteroids for acute bacterial meningitis (Review)



Kanra 1995 (Continued)

Other bias

High risk

Unevenly distributed severity of disease (Glasgow Coma Scale) at admission (control group better)

Kilpi 1995			
Methods	Randomised, unblinde	d	
Participants	3 months to 15 years; suspected bacterial meningitis with CSF criteria; 58 participants (gender not re- ported; 32 DXM, 26 placebo); Finland		
Interventions	DXM 1.5 mg/kg/d, 3 d; l	before or with AB	
Outcomes	Mortality, hearing loss,	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		
	Funding - Arvo and Leo Ylppö foundation (charity)		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis	
Other bias	High risk	High number of pre-treated patients compared to other studies. Unevenly dis- tributed 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 sus- pected bacterial meningitis who were too unstable for lumbar puncture; 101 participants (gender not reported; 50 DXM, 51 placebo); Canada
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB

Corticosteroids for acute bacterial meningitis (Review)



King 1994 (Continued)

Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, persistent fever, recurrent fever)		
Notes	AB - various, mortality	B - various, mortality 1%	
	Funding - Physicians' Services Incorporated Foundation (charity)		
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis; more patients were excluded in the dexametha- sone 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; 100 participants (50 male, 50 female; 51 DXM, 49 placebo); USA	
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%	
	Funding - Glaxo and Roche Laboratories (pharmaceutical company)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation was concealed

Corticosteroids for acute bacterial meningitis (Review)



Lebel 1988a (Continued)

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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

Lebel 1988b

Methods	Randomised, double-blind	
Participants2 months to 16 years; suspected or proven bacterial meningitis; 100 participants (551 DXM, 49 placebo); USA		
Interventions	DXM 0.6 mg/kg/d, 4 d; after AB	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, recurre fever, arthritis)	
Notes	AB - ceph, mortality 2%	
	Funding - Glaxo and Roche Laboratories (pharmaceutical company)	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Insufficient information to determine other bias

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Methods	Randomised, double-blind			
Participants	2 months to 16 years; suspected or proven bacterial meningitis; 61 participants (38 male, 23 female; 30 DXM, 31 placebo); USA			
Interventions	DXM 0.6 mg/kg/d, 4 d; a	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% Funding - in part by Glaxo (pharmaceutical company)			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis		
Other bias	High risk	Unevenly distributed number of antimicrobial resistance rates between treat- ment groups (control group worse)		

Mathur 2013

Methods	Randomised, unblinded		
Participants	Neonates (not defined); suspected meningitis with CSF criteria; 80 participants (51 male, 39 female; 40 DXM, 40 placebo); India		
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%		
	Funding - none reported		
Risk of bias			

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Mathur 2013 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting 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 treat- ment groups

Molyneux 2002

Methods	Randomised, double-blind	
Participants	2 months to 13 years; suspected bacterial meningitis with CSF criteria; 598 participants (337 male, 261 female; 307 DXM, 295 placebo); Malawi	
Interventions	DXM 0.8 mg/kg/d, 2 d; before or with AB	
Outcomes	Mortality, hearing loss, neurological sequelae	
Notes	AB - pen/chlor, mortality 31%	
	Funding - Child and Adolescent Health and Development Division of WHO	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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

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Molyneux 2002 (Continued)

Selective reporting (re- porting 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 cri- teria; 435 participants (317 male, 118 female; 217 DXM, 218 placebo); Vietnam			
Interventions	DXM 0.8 mg/kg/d, 4 d;	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%			
	Funding - Wellcome Tr	ust (charity)		
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence genera- tion (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 (re- porting 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 in- flammation; 101 participants (59 male, 42 female; 52 DXM, 49 placebo); USA		
Interventions	DXM 0.6 mg/kg/d, 4 d; before or with AB		

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Odio 1991 (Continued)

Outcomes	Mortality, hearing loss, neurological sequelae, adverse events (gastrointestinal bleeding, persistent fever, recurrent fever, arthritis)		
Notes	AB - ceph, mortality - 2%		
	Funding - Hoechst-Rou	issel Pharmaceuticals (pharmaceutical company)	
Risk of bias			
Bias	Authors' judgement	Support for judgement	
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis	
Other bias	Unclear risk	Insufficient information to determine other bias	

Peltola 2007

ettola 2007		
Methods	Randomised, double-blind	
Participants	2 months to 16 years; proven or suspected bacterial meningitis with CSF criteria; 329 participants (191 male, 138 female; 166 DXM, 163 placebo); Argentina, Ecuador,Venezuela, Dominican Republic, Paraguay, Brazil	
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 evalua	ated adjunctive glycerol and combined adjunctive glycerol and DXM therapy
	Funding - Alfred Kordelin, Paivikki and Sakari Sohlberg, and Sigfrid Juselius Funds (charities). G oSmithKline, Farmacia Ahumada, Laboratorio de Chile (pharmaceutical companies)	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence genera-	Low risk	Randomisation list, block size 24

tion (selection bias)

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Peltola 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Partial allocation concealment: 2 hospitals did not allow double placebo treat- ment
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 (re- porting 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; 89 participants (54 male, 35 fe- male; 48 DXM, 41 placebo); Pakistan		
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%		
	Funding - Department of Paediatrics and Child Health, Kurume University, Kurume, Japan and the Japanese International Cooperation Agency (government funding body)		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting 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

Corticosteroids for acute bacterial meningitis (Review)



Sankar 2007

Methods	Randomised, double-blind	
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria; 25 participants (22 male, 3 fe- male; 12 DXM, 13 placebo); India	
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	
	Funding - none reported	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data addressed
Selective reporting (re- porting bias)	Low risk	Intention-to-treat analysis
Other bias	Unclear risk	Only 1 patient with positive culture in DXM randomisation arm. Unevenly dis- tributed numbers in randomisation arms. Large differences in baseline charac- teristics between randomisation arms

Scarborough 2007	
Methods	Randomised, double-blind
Participants	Older than 15 years; suspected bacterial meningitis with CSF criteria; 465 participants (230 male, 236 female; 233 DXM, 232placebo); Malawi
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%

Corticosteroids for acute bacterial meningitis (Review)



Scarborough 2007 (Continued)

Funding - Meningitis Research Foundation (charity), Emcure Pharmaceuticals and Cipla (pharmaceutical companies)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	Low risk	Intention-to-treat analysis
Other bias	Low risk	No indication of other bias

Schaad 1993

5011880 1555				
Methods	Randomised, double-blind			
Participants	3 months to 16 years; suspected or proven bacterial; 115 participants (69 male, 46 female; 60 DXM, 55 placebo); Switzerland			
Interventions	DXM 0.8 mg/kg/d, 2 d; l	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%			
	Funding - Merck Sharp & Dohme-Chibret Ltd (pharmaceutical company)			
Risk of bias				
Bias	Authors' judgement	Support for judgement		
Random sequence genera- tion (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

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Schaad 1993 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	Incomplete outcome data not addressed
Selective reporting (re- porting 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; 60 participants (34 male, 26 female; 31 DXM, 29 placebo); France and Switzerland		
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%		
	Funding - Institut National de la Sante et de la Recherche Medicale (government funding body), the Beecham Institute and the Merck Sharp & Dohme Chibret laboratory (pharmaceutical company)		

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	High risk	Limited baseline and clinical characteristics. Age of participants unevenly dis- tributed between randomisation arms

Wald 1995

Methods

Randomised, double-blind

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Wald 1995 (Continued)

Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria; 143 participants (79 male, 64 fe- male; 69 DXM, 74 placebo); USA
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%
	Funding - Hoffman-LaRoche (pharmaceutical company)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (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 (re- porting bias)	High risk	No intention-to-treat analysis
Other bias	Unclear risk	Distribution of resistant bacterial strains (23 out of 143 strains) between ran- domisation arms is not reported

AB: antibiotics Amox: amoxicillin Ampi: ampicillin Ceph: cephalosporin Chlor: chloramphenicol CSF: cerebrospinal fluid d: days DXM: dexamethasone m²: 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

Corticosteroids for acute bacterial meningitis (Review)



Study	Reason for exclusion
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
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 ti- tle	No. of studies	No. of partici- pants	•	
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 bleed- ing	16	2560	Risk Ratio (M-H, Fixed, 95% CI)	1.45 [0.86, 2.45]

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Outcome or subgroup ti- tle	No. of studies	No. of partici- pants	Statistical method	Effect size
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]

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Bademosi 1979	12/24	11/28	— 1	2.48%	1.27[0.69,2.34]
Belsey 1969	2/43	1/43	+	0.24%	2[0.19,21.24]
Bennett 1963	16/38	22/47		4.8%	0.9[0.56,1.46]
Bhaumik 1998	1/14	3/16	•	0.68%	0.38[0.04,3.26]
Ciana 1995	8/34	12/36		2.84%	0.71[0.33,1.51]
de Gans 2002	11/157	21/144	+	5.34%	0.48[0.24,0.96]
DeLemos 1969	2/54	1/63		0.23%	2.33[0.22,25.03]
Girgis 1989	21/225	43/245	+	10.04%	0.53[0.33,0.87]
Kanra 1995	2/29	1/27		0.25%	1.86[0.18,19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51		- 0.36%	0.34[0.01,8.15]
Lebel 1988a	0/51	1/49	•	0.37%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30	•	0.37%	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	-	22.63%	1.01[0.8,1.29]
Nguyen 2007	22/217	26/218	+	6.32%	0.85[0.5,1.45]
Odio 1991	1/52	1/49		0.25%	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		1.31%	2.05[0.79,5.33]
Sankar 2007	0/12	1/13	•	- 0.35%	0.36[0.02,8.05]
Scarborough 2007	129/231	120/228		29.45%	1.06[0.9,1.26]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	3/31	5/29		1.26%	0.56[0.15,2.14]
Wald 1995	1/69	0/74		0.12%	3.21[0.13,77.6]
Total (95% CI)	2064	2057	•	100%	0.9[0.8,1.01]
Total events: 367 (Corticosteroids),	409 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =26.68,	df=21(P=0.18); I ² =21.29	9%			
Test for overall effect: Z=1.8(P=0.07))				

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI		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		1.76%	1[0.16,6.07]	
Girgis 1989	2/190	5/177	+	4.55%	0.37[0.07,1.9]	
Kanra 1995	0/27	2/26	↓	2.23%	0.19[0.01,3.84]	
Kilpi 1995	1/31	3/26	+	2.86%	0.28[0.03,2.53]	
King 1994	2/48	3/45		2.72%	0.63[0.11,3.57]	
Lebel 1988a	2/43	8/38	↓	7.46%	0.22[0.05,0.98]	
Lebel 1988b	1/49	5/46	↓	4.53%	0.19[0.02,1.55]	
Lebel 1989	1/31	2/29	+ +	1.81%	0.47[0.04,4.89]	
Molyneux 2002	31/147	27/158	- +•	22.85%	1.23[0.78,1.96]	
Nguyen 2007	7/180	16/177	+	14.16%	0.43[0.18,1.02]	
Odio 1991	3/50	7/44	+	6.54%	0.38[0.1,1.37]	
Peltola 2007	10/135	12/131		10.69%	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		6.05%	1.03[0.38,2.83]	
Schaad 1993	2/60	4/55	+	3.66%	0.46[0.09,2.4]	
Wald 1995	3/67	7/72		5.92%	0.46[0.12,1.71]	
Total (95% CI)	1234	1203	•	100%	0.67[0.51,0.88]	
Total events: 75 (Corticosteroids), 112 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =15.6	67, df=16(P=0.48); l ² =0%					
Test for overall effect: Z=2.86(P=0	D)					
	Favours	s corticosteroids	0.1 0.2 0.5 1 2 5 1	⁰ Favours placebo		

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

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
Belsey 1969	0/41	1/42 -	+	0.56%	0.34[0.01,8.14]	
Bhaumik 1998	4/14	3/16	++	1.06%	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		2.36%	0.47[0.12,1.83]	
Kanra 1995	2/27	8/26	+	3.09%	0.24[0.06,1.03]	
Kilpi 1995	5/31	6/26		2.48%	0.7[0.24,2.03]	
King 1994	5/48	5/45		1.96%	0.94[0.29,3.02]	
Lebel 1988a	9/43	16/38	-+	6.45%	0.5[0.25,0.99]	
Lebel 1988b	7/49	14/46	-+	5.48%	0.47[0.21,1.06]	
Lebel 1989	3/30	5/29		1.93%	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	-+	16.82%	1.14[0.82,1.6]	
Nguyen 2007	21/180	37/177	-+	14.16%	0.56[0.34,0.91]	
Odio 1991	3/50	7/44		2.83%	0.38[0.1,1.37]	
Peltola 2007	10/135	12/131	+	4.62%	0.81[0.36,1.81]	
Qazi 1996	11/26	5/25	+-+	1.93%	2.12[0.86,5.22]	
Sankar 2007	3/12	3/12		1.14%	1[0.25,4]	
Scarborough 2007	30/96	36/99	-+-	13.45%	0.86[0.58,1.28]	
Schaad 1993	3/60	8/55		3.17%	0.34[0.1,1.23]	
Wald 1995	10/67	17/72	_+	6.22%	0.63[0.31,1.28]	
	Favou	rs corticosteroids 0.0	1 0.1 1 10	¹⁰⁰ Favours placebo		

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Study or subgroup	Corticosteroids n/N	Placebo n/N		M-H	Risk Ratio I, Fixed, 9	-		Weight	Risk Ratio M-H, Fixed, 95% Cl
Total (95% CI)	1424	1361			•			100%	0.74[0.63,0.87]
Total events: 197 (Corticoste	roids), 259 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =	25.05, df=19(P=0.16); l ² =24.16	%							
Test for overall effect: Z=3.59)(P=0)								
	Favours	s corticosteroids	0.01	0.1	1	10	100	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo		Risk Ratio	۱	Neight	Risk Ratio	
	n/N	n/N	n/N M-H, Fixed, 9		6 CI		M-H, Fixed, 95% Cl	
Bhaumik 1998	3/13	2/13				1.05%	1.5[0.3,7.55]	
Ciana 1995	5/26	7/24		+		3.83%	0.66[0.24,1.8]	
de Gans 2002	18/143	24/119		+		13.78%	0.62[0.36,1.09]	
Kanra 1995	3/27	2/26				1.07%	1.44[0.26,7.96]	
Lebel 1988a	5/48	8/43	-			4.44%	0.56[0.2,1.58]	
Lebel 1988b	9/47	10/45		+		5.37%	0.86[0.39,1.92]	
Lebel 1989	4/28	5/26				2.73%	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		+		11.12%	0.47[0.23,0.96]	
Sankar 2007	0/12	1/12	←			0.79%	0.33[0.01,7.45]	
Scarborough 2007	21/98	26/104		+		13.27%	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		+		7.05%	0.7[0.32,1.51]	
Total (95% CI)	900	856		•		100%	0.83[0.69,1]	
Total events: 161 (Corticosteroic	ds), 185 (Placebo)							
Heterogeneity: Tau ² =0; Chi ² =11.	75, df=12(P=0.47); l ² =0%							
Test for overall effect: Z=1.99(P=	0.05)							

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

Study or subgroup	Corticosteroids	Placebo		Risk	Ratio		Weight	Risk Ratio
	n/N	n/N	N M-H, Fixed, 95% CI					M-H, Fixed, 95% CI
DeLemos 1969	9/48	2/57			·		1.28%	5.34[1.21,23.55]
Girgis 1989	1/190	2/177	◀—				1.45%	0.47[0.04,5.09]
Kanra 1995	2/29	1/27	_			\rightarrow	0.73%	1.86[0.18,19.38]
Kilpi 1995	3/31	2/26			+		1.53%	1.26[0.23,6.97]
King 1994	5/37	3/44					1.92%	1.98[0.51,7.75]
Lebel 1988a	3/38	3/34	-	+		-	2.22%	0.89[0.19,4.14]
Lebel 1988b	2/43	6/41	◀	+			4.31%	0.32[0.07,1.49]
Lebel 1989	4/28	5/26		++-			3.64%	0.74[0.22,2.47]
Nguyen 2007	79/193	83/192			-		58.35%	0.95[0.75,1.2]
Odio 1991	5/51	15/48					10.84%	0.31[0.12,0.8]
Qazi 1996	9/48	8/41		+			6.05%	0.96[0.41,2.26]
Schaad 1993	3/60	5/55		+			3.66%	0.55[0.14,2.19]
	Favour	s corticosteroids	0.1 0.2	2 0.5 1	1 2	5 10	Favours placebo	

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Study or subgroup	Corticosteroids	Placebo		Risk Ratio				Weight		Risk Ratio	
	n/N	n/N		I	M-H, Fi	ixed, 9	5% CI				M-H, Fixed, 95% CI
Wald 1995	4/68	6/74			+					4.03%	0.73[0.21,2.46]
Total (95% CI)	864	842				•				100%	0.9[0.74,1.1]
Total events: 129 (Corticoste	roids), 141 (Placebo)										
Heterogeneity: Tau ² =0; Chi ² =	=15.2, df=12(P=0.23); I ² =21.07%)									
Test for overall effect: Z=1.03	B(P=0.3)				- 1						
	Favours	s corticosteroids	0.1	0.2	0.5	1	2	5	10	Favours placebo	

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

	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
1.6.1 Gastrointestinal bleed	ing				
de Gans 2002	2/157	5/144		22.78%	0.37[0.07,1.86]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	1/50	1/51		4.32%	1.02[0.07,15.86]
Lebel 1988a	0/51	0/49			Not estimable
Lebel 1988b	2/51	0/49		- 2.23%	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		21.79%	2.21[0.78,6.25]
Odio 1991	0/52	0/48			Not estimable
Peltola 2007	6/166	2/163		8.82%	2.95[0.6,14.38]
Qazi 1996	3/48	2/41		9.42%	1.28[0.22,7.3]
Sankar 2007	1/12	1/12		4.37%	1[0.07,14.21]
Scarborough 2007	0/233	1/232 -		6.57%	0.33[0.01,8.11]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	0/31	2/29 —	+	11.27%	0.19[0.01,3.75]
Wald 1995	6/69	2/74	+	8.43%	3.22[0.67,15.41]
Subtotal (95% CI)	1300	1260	◆	100%	1.45[0.86,2.45]
Total events: 32 (Corticostero	ids), 21 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =8	3.52, df=9(P=0.48); I ² =0%				
Test for overall effect: Z=1.41(P=0.16)				
1.6.2 Herpes zoster infectior	n				
Belsey 1969	6/43	4/43		3.77%	1.5[0.46,4.94]
Bennett 1963	0/38	1/47		1.27%	0.41[0.02,9.79]
de Gans 2002	6/157	4/144		3.93%	1.38[0.4,4.78]
Nguyen 2007	33/217	30/218		28.2%	1.11[0.7,1.75]
Scarborough 2007	70/233	65/232	÷	61.37%	1.07[0.81,1.43]
Thomas 1999	0/31	1/29 -		1.46%	0.31[0.01,7.38]
Subtotal (95% CI)	719	713	•	100%	1.09[0.86,1.37]
Total events: 115 (Corticoster	oids), 105 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1	L.39, df=5(P=0.93); I ² =0%				
Test for overall effect: Z=0.73(P=0.47)				
1.6.3 Persistent fever					
King 1994	3/50	8/51		38.81%	0.38[0.11,1.36]
Odio 1991	1/52	10/48 -	_	50.96%	0.09[0.01,0.69]
	Favou	rs corticosteroids 0.0	1 0.1 1 10 1	⁰⁰ Favours placebo	

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
Study of Subgroup	n/N	n/N	M-H, Fixed, 95% Cl	weight	M-H, Fixed, 95% Cl
Schaad 1993	2/60	2/55		10.23%	0.92[0.13,6.29]
Subtotal (95% CI)	162	154		100%	0.29[0.12,0.7]
Total events: 6 (Corticosteroid			-		
Heterogeneity: Tau ² =0; Chi ² =2					
Test for overall effect: Z=2.75(
1.6.4 Recurrent fever	0 /0 /	c / c c		0.050/	
Ciana 1995	9/34	6/36		3.05%	1.59[0.63,3.99]
Kanra 1995	5/29	4/27		2.17%	1.16[0.35,3.89]
Kilpi 1995	4/50	3/51		1.55%	1.36[0.32,5.77]
Lebel 1988a	31/51	23/49	T•	12.26%	1.29[0.89,1.88]
Lebel 1988b	32/51	11/49] —	5.87%	2.8[1.59,4.9]
Lebel 1989	14/31	14/29		7.56%	0.94[0.54,1.61]
Odio 1991	10/52	9/48		4.89%	1.03[0.46,2.31]
Peltola 2007	65/166	66/163		34.82%	0.97[0.74,1.26]
Qazi 1996	20/48	14/41		7.89%	1.22[0.71,2.1]
Scarborough 2007	7/233	2/232		1.05%	3.48[0.73,16.6]
Schaad 1993	19/60	11/50		6.27%	1.44[0.76,2.73]
Wald 1995	31/69	25/74		12.61%	1.33[0.88,2.01]
Subtotal (95% CI)	874	849		100%	1.27[1.09,1.47]
Total events: 247 (Corticoster		20/			
Heterogeneity: Tau ² =0; Chi ² =1		5%0			
Test for overall effect: Z=3.06(P=0)				
1.6.5 Fungal infection					
de Gans 2002	8/157	4/144		100%	1.83[0.56,5.96]
Subtotal (95% CI)	157	144		100%	1.83[0.56,5.96]
Total events: 8 (Corticosteroio	ds), 4 (Placebo)				
Heterogeneity: Not applicable	2				
Test for overall effect: Z=1.01(P=0.31)				
1.6.6 Arthritis					
Lebel 1988a	1/51	4/49		33.04%	0.24[0.03,2.07]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	1/31	2/29	•	16.73%	0.47[0.04,4.89]
Odio 1991	0/52	4/48		37.87%	0.1[0.01,1.86]
Schaad 1993	3/60	1/55		8.45%	2.75[0.29,25.66]
Wald 1995	2/69	0/74		- 3.91%	5.36[0.26,109.65]
Subtotal (95% CI)	314	304	-	100%	0.64[0.27,1.53]
Total events: 7 (Corticosteroid					
Heterogeneity: Tau ² =0; Chi ² =5					
Test for overall effect: Z=1(P=0					
Test for overall effect: Z=1(P=0		rs corticosteroids 0.0	1 0.1 1 10 10	⁰⁰ Favours placebo	

Comparison 2. Children

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Mortality	18	2511	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.07]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
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]

Analysis 2.1. Comparison 2 Children, Outcome 1 Mortality.

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI
Belsey 1969	2/43	1/43		0.54%	2[0.19,21.24]
Ciana 1995	8/34	12/36	+	6.24%	0.71[0.33,1.51]
DeLemos 1969	2/54	1/63		0.49%	2.33[0.22,25.03]
Girgis 1989	15/142	24/140	+	12.94%	0.62[0.34,1.12]
Kanra 1995	2/29	1/27		0.55%	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	•	0.82%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30	•	0.82%	0.32[0.01,7.63]
Mathur 2013	5/40	16/40		8.57%	0.31[0.13,0.77]
Molyneux 2002	96/305	91/293		49.71%	1.01[0.8,1.29]
Odio 1991	1/52	1/49	+	0.55%	0.94[0.06,14.65]
Peltola 2007	23/166	26/163	+	14.05%	0.87[0.52,1.46]
Qazi 1996	12/48	5/41	+	2.89%	2.05[0.79,5.33]
Sankar 2007	0/12	1/13	•	0.77%	0.36[0.02,8.05]
Schaad 1993	0/60	0/55			Not estimable
Wald 1995	1/69	0/74	+	0.26%	3.21[0.13,77.6]
Total (95% CI)	1269	1242	•	100%	0.89[0.74,1.07]
Total events: 167 (Corticosteroi	ds), 182 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =14	.58, df=14(P=0.41); l ² =3.969	6			
Test for overall effect: Z=1.22(P=	=0.22)				

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl	
Belsey 1969	0/41	1/42		1.68%	0.34[0.01,8.14]	
Girgis 1989	0/16	4/15	< → →	5.24%	0.1[0.01,1.79]	
Kanra 1995	0/27	2/26		2.88%	0.19[0.01,3.84]	
Kilpi 1995	1/31	3/26	+	3.69%	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		9.61%	0.22[0.05,0.98]	
Lebel 1988b	1/49	5/46	+	5.83%	0.19[0.02,1.55]	
Lebel 1989	1/31	2/29		2.34%	0.47[0.04,4.89]	
Molyneux 2002	31/147	27/158		29.44%	1.23[0.78,1.96]	
	Favou	rs corticosteroids	0.01 0.1 1 10	¹⁰⁰ Favours placebo		

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Study or subgroup	Corticosteroids	Placebo		Risk Ratio		Weight	Risk Ratio
	n/N	n/N	M-H	l, Fixed, 95% Cl			M-H, Fixed, 95% CI
Odio 1991	3/51	7/44		+		8.5%	0.37[0.1,1.34]
Peltola 2007	10/135	12/131		-+		13.78%	0.81[0.36,1.81]
Qazi 1996	1/26	1/25				1.15%	0.96[0.06,14.55]
Schaad 1993	2/60	4/55		- -		4.72%	0.46[0.09,2.4]
Wald 1995	3/67	7/72		•		7.63%	0.46[0.12,1.71]
Total (95% CI)	772	752		•		100%	0.67[0.49,0.91]
Total events: 57 (Corticoster	oids), 86 (Placebo)						
Heterogeneity: Tau ² =0; Chi ² =	=15.02, df=13(P=0.31); l ² =13.42	2%					
Test for overall effect: Z=2.58	B(P=0.01)						
	Favou	rs corticosteroids	0.01 0.1	1 10	100	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Belsey 1969	0/41	1/42 —		0.74%	0.34[0.01,8.14]
Girgis 1989	3/190	6/177		3.11%	0.47[0.12,1.83]
Kanra 1995	2/27	8/26		4.07%	0.24[0.06,1.03]
Kilpi 1995	5/31	6/26		3.26%	0.7[0.24,2.03]
King 1994	5/48	5/45		2.58%	0.94[0.29,3.02]
Lebel 1988a	9/43	16/38		8.49%	0.5[0.25,0.99]
Lebel 1988b	7/49	14/46	-+	7.22%	0.47[0.21,1.06]
Lebel 1989	3/30	5/29		2.54%	0.58[0.15,2.21]
Mathur 2013	6/35	10/24		5.93%	0.41[0.17,0.98]
Molyneux 2002	49/147	46/158		22.16%	1.14[0.82,1.6]
Odio 1991	3/50	7/44		3.72%	0.38[0.1,1.37]
Peltola 2007	10/135	12/131	+	6.09%	0.81[0.36,1.81]
Qazi 1996	28/36	32/35	+	16.22%	0.85[0.7,1.04]
Sankar 2007	3/12	3/12		1.5%	1[0.25,4]
Schaad 1993	3/60	8/55		4.17%	0.34[0.1,1.23]
Wald 1995	10/67	17/72	-++	8.19%	0.63[0.31,1.28]
Total (95% CI)	1001	960	•	100%	0.73[0.61,0.86]
Total events: 146 (Corticosterc	oids), 196 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1	9.33, df=15(P=0.2); l ² =22.38 ⁰	%			
Test for overall effect: Z=3.6(P=	=0)				

Comparison 3. Adults

Outcome or subgroup title	No. of studies	No. of partici- pants	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]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
3 Short-term neurological sequelae	4	542	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.01]

Analysis 3.1. Comparison 3 Adults, Outcome 1 Mortality.

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI
Bennett 1963	16/38	22/47		19.94%	0.9[0.56,1.46]
Bhaumik 1998	1/14	3/16	<	2.36%	0.38[0.04,3.26]
de Gans 2002	11/157	21/144	+	14%	0.48[0.24,0.96]
Girgis 1989	5/68	18/79		9.51%	0.32[0.13,0.82]
Nguyen 2007	22/217	26/218	+	18.23%	0.85[0.5,1.45]
Scarborough 2007	129/231	120/228		30.5%	1.06[0.9,1.26]
Thomas 1999	3/31	5/29		5.46%	0.56[0.15,2.14]
Total (95% CI)	756	761	•	100%	0.74[0.53,1.05]
Total events: 187 (Corticoste	roids), 215 (Placebo)				
Heterogeneity: Tau ² =0.09; Ch	ni²=13.07, df=6(P=0.04); l²=54.	08%			
Test for overall effect: Z=1.7(P=0.09)				
	Favour	rs corticosteroids	0.1 0.2 0.5 1 2 5	¹⁰ Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo		I	Risk Ratio	D		Weight	Risk Ratio
	n/N	n/N		М-Н,	Fixed, 9	5% CI			M-H, Fixed, 95% Cl
Bhaumik 1998	4/14	3/16			-++-			3.08%	1.52[0.41,5.67]
de Gans 2002	13/143	14/119			-+-			16.82%	0.77[0.38,1.58]
Nguyen 2007	21/180	37/177						41.07%	0.56[0.34,0.91]
Scarborough 2007	30/96	36/99			-			39.02%	0.86[0.58,1.28]
Total (95% CI)	433	411			•			100%	0.74[0.56,0.98]
Total events: 68 (Corticostero	ids), 90 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =2	2.98, df=3(P=0.4); I ² =0%								
Test for overall effect: Z=2.11((P=0.03)		1	1		1			
	Favour	rs corticosteroids	0.005	0.1	1	10	200	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo		Ris	sk Rat	io			Weight	Risk Ratio
	n/N	n/N		M-H, F	ixed, 9	95% CI				M-H, Fixed, 95% CI
Bhaumik 1998	3/13	2/13				+		-	3.17%	1.5[0.3,7.55]
de Gans 2002	18/143	24/119		<mark></mark>	+				41.51%	0.62[0.36,1.09]
Scarborough 2007	21/98	26/104							39.97%	0.86[0.52,1.42]
	Favour	s corticosteroids	0.1 0.2	0.5	1	2	5	10	Favours placebo	

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Study or subgroup	Corticosteroids	Placebo			Ri	sk Rat	tio			Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI							M-H, Fixed, 95% CI	
Thomas 1999	5/28	9/24			+	+				15.36%	0.48[0.18,1.23]
Total (95% CI)	282	260								100%	0.72[0.51,1.01]
Total events: 47 (Corticoster	oids), 61 (Placebo)										
Heterogeneity: Tau ² =0; Chi ² =	=2.23, df=3(P=0.53); I ² =0%										
Test for overall effect: Z=1.88	8(P=0.06)										
	Favour	s corticosteroids	0.1	0.2	0.5	1	2	5	10	Favours placebo	

Comparison 4. Causative species

Outcome or subgroup title	No. of studies	No. of partici- pants	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]

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

Study or subgroup	Corticosteroids	Placebo		Risk Ratio	Weight	Risk Ratio
	n/N	n/N		M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl
4.1.1 Haemophilus influenzae						
de Gans 2002	0/2	0/2				Not estimable
DeLemos 1969	1/32	0/37			0.87%	3.45[0.15,81.95]
Girgis 1989	7/26	10/30		+	17.43%	0.81[0.36,1.82]
Kilpi 1995	0/16	0/14				Not estimable
Lebel 1988a	0/40	1/37	-		2.92%	0.31[0.01,7.36]
Lebel 1988b	0/39	0/38				Not estimable
Molyneux 2002	21/81	27/89			48.31%	0.85[0.53,1.39]
Odio 1991	1/39	1/40			1.85%	1.03[0.07,15.83]
Peltola 2007	7/54	10/60			17.79%	0.78[0.32,1.9]
Schaad 1993	0/37	0/30				Not estimable
Wald 1995	0/43	5/39	-	+	10.82%	0.08[0,1.45]
Subtotal (95% CI)	409	416		•	100%	0.76[0.53,1.09]
Total events: 37 (Corticosteroids), 5	4 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =3.79, d	f=6(P=0.7); I ² =0%					
Test for overall effect: Z=1.5(P=0.13)						
	Favou	rs corticosteroids	0.02	0.1 1 10	⁵⁰ Favours placebo	

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	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% Cl		M-H, Fixed, 95% CI
4 1 2 Streptococcus prove					
4.1.2 Streptococcus pneum Bademosi 1979		11/20		5.03%	1 27[0 00 2 2/
	12/24	11/28		6.9%	1.27[0.69,2.34
Bennett 1963	12/26	15/30			0.92[0.53,1.
de Gans 2002	8/58	17/50		9.05%	0.41[0.19,0.8
DeLemos 1969	1/5	1/8		0.38%	1.6[0.13,20.2]
Girgis 1989	7/52	22/54		10.7%	0.33[0.15,0.7
Kanra 1995	2/29	1/27		0.51%	1.86[0.18,19.3
Kilpi 1995	0/1	0/5			Not estimab
Lebel 1988a	0/4	0/4			Not estimab
Lebel 1988b	0/4	0/4			Not estimab
Molyneux 2002	46/132	42/106		23.09%	0.88[0.63,1.2]
Nguyen 2007	0/26	5/29		2.58%	0.1[0.01,1.7
Odio 1991	0/4	0/4			Not estimab
Peltola 2007	8/35	10/36	+	4.89%	0.82[0.37,1.8
Scarborough 2007	68/129	72/143	+	33.85%	1.05[0.83,1.3
Schaad 1993	0/5	0/6			Not estimab
Thomas 1999	1/14	5/17		2.24%	0.24[0.03,1.8
Wald 1995	3/13	2/20		0.78%	2.31[0.44,11.9
Subtotal (95% CI)	561	571	•	100%	0.84[0.72,0.9
	5(P=0.03)				
	5(P=0.03)				
4.1.3 Neisseria meningitidi					
4.1.3 Neisseria meningitidi Bennett 1963		2/5		10.64%	0.63[0.08,4.6
Bennett 1963	s	2/5 0/1		10.64%	0.63[0.08,4.6 Not estimab
Bennett 1963 Ciana 1995	s 1/4			10.64% 6.17%	Not estimab
Bennett 1963 Ciana 1995 de Gans 2002	s 1/4 0/1	0/1			Not estimab 1.88[0.18,20.0
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969	s 1/4 0/1 2/50	0/1 1/47			Not estimab 1.88[0.18,20.0 Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989	s 1/4 0/1 2/50 0/9	0/1 1/47 0/7		6.17%	
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995	s 1/4 0/1 2/50 0/9 6/132	0/1 1/47 0/7 10/135		6.17%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a	s 1/4 0/1 2/50 0/9 6/132 0/14	0/1 1/47 0/7 10/135 0/7	 	6.17%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3	0/1 1/47 0/7 10/135 0/7 0/4		6.17%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6	0/1 1/47 0/7 10/135 0/7 0/4 0/4		6.17% 59.18%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002 Peltola 2007	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6 1/32	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35		6.17% 59.18% 11.44%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7 0.33[0.01,7.8
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002 Peltola 2007 Schaad 1993	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6 1/32 0/26	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35 1/26		6.17% 59.18% 11.44%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002 Peltola 2007 Schaad 1993 Thomas 1999	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6 1/32 0/26 0/12	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35 1/26 0/16		6.17% 59.18% 11.44% 8.98%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7 0.33[0.01,7.8 Not estimab 2[0.09,43.2
-	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6 1/32 0/26 0/12 1/11	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35 1/26 0/16 0/7		6.17% 59.18% 11.44% 8.98%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7 0.33[0.01,7.8 Not estimab 2[0.09,43.2 Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002 Peltola 2007 Schaad 1993 Thomas 1999 Wald 1995	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/6 1/32 0/26 0/12 1/11 0/11 311	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35 1/26 0/16 0/7 0/13		6.17% 59.18% 11.44% 8.98% - 3.59%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7 0.33[0.01,7.8 Not estimab
Bennett 1963 Ciana 1995 de Gans 2002 DeLemos 1969 Girgis 1989 Kilpi 1995 Lebel 1988a Lebel 1988b Molyneux 2002 Peltola 2007 Schaad 1993 Thomas 1999 Wald 1995 Subtotal (95% CI)	s 1/4 0/1 2/50 0/9 6/132 0/14 0/3 0/14 0/3 0/6 1/32 0/26 0/12 1/11 0/11 311 oids), 16 (Placebo)	0/1 1/47 0/7 10/135 0/7 0/4 0/4 2/35 1/26 0/16 0/7 0/13		6.17% 59.18% 11.44% 8.98% - 3.59%	Not estimab 1.88[0.18,20.0 Not estimab 0.61[0.23,1.6 Not estimab Not estimab 0.55[0.05,5.7 0.33[0.01,7.8 Not estimab 2[0.09,43.2 Not estimab

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

Study or subgroup	Corticosteroids	Placebo		Risk Ratio	Weight	Risk Ratio	
	n/N	n/N		M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Belsey 1969	0/41	1/42		+	3.16%	0.34[0.01,8.14]	
Girgis 1989	0/16	4/15	-		9.9%	0.1[0.01,1.79]	
Kanra 1995	0/27	2/26	-		5.43%	0.19[0.01,3.84]	
Kilpi 1995	1/17	2/13	-	+	4.84%	0.38[0.04,3.77]	
King 1994	1/21	1/22			2.09%	1.05[0.07,15.69]	
Lebel 1988a	1/9	1/9			2.13%	1[0.07,13.64]	
Lebel 1988b	0/10	1/11			3.06%	0.36[0.02,8.03]	
Lebel 1989	0/6	1/9			2.64%	0.48[0.02,10.07]	
Molyneux 2002	27/132	21/134			44.49%	1.31[0.78,2.19]	
Odio 1991	0/13	1/9	-		3.74%	0.24[0.01,5.26]	
Peltola 2007	7/89	4/84		++	8.79%	1.65[0.5,5.44]	
Schaad 1993	1/23	3/25	-	+	6.14%	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%	0.95[0.65,1.39]	
Total events: 41 (Corticoster	oids), 44 (Placebo)						
Heterogeneity: Tau ² =0; Chi ² =	=9.58, df=12(P=0.65); l ² =0%						
Test for overall effect: Z=0.27	7(P=0.79)						
	Favour	s corticosteroids	0.02	0.1 1 10	⁵⁰ Favours placebo		

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Kilpi 1995	0/15	1/13		3.47%	0.29[0.01,6.6]
King 1994	1/29	2/28		4.42%	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	+	9.15%	0.22[0.03,1.91]
Lebel 1989	1/25	1/20		2.41%	0.8[0.05,12.01]
Molyneux 2002	4/81	6/89	+	12.41%	0.73[0.21,2.5]
Odio 1991	3/38	6/39	+	12.85%	0.51[0.14,1.91]
Peltola 2007	3/46	8/47	+	17.17%	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		19.32%	0.05[0,0.9]
Total (95% CI)	387	369	•	100%	0.34[0.2,0.59]
Total events: 15 (Corticosteroids),	44 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =5.51,	df=9(P=0.79); I ² =0%				
Test for overall effect: Z=3.82(P=0)					
	Favour	rs corticosteroids	0.01 0.1 1 10 1	¹⁰⁰ Favours placebo	

Comparison 5. Income of countries

Outcome or subgroup title	No. of studies	No. of partici- pants	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 pa- tients	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 se- quelae - 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 se- quelae - 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 chil- dren due to non- <i>Haemophilus</i> <i>influenzae</i> 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]

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Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
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	Odds Ratio (IV, Fixed, 95% CI)	0.68 [0.47, 0.98]
10.1 Low-income countries	2	225	Odds Ratio (IV, Fixed, 95% CI)	0.87 [0.49, 1.52]
10.2 High-income countries	2	619	Odds Ratio (IV, Fixed, 95% CI)	0.58 [0.36, 0.92]

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Random, 95% CI		IV, Random, 95% CI
5.1.1 Low-income countries					
Bademosi 1979	12/24	11/28		5.87%	1.27[0.69,2.34]
Bhaumik 1998	1/14	3/16	• • · · · ·	0.57%	0.38[0.04,3.26]
Ciana 1995	8/34	12/36	+ <u>-</u>	4.03%	0.71[0.33,1.51]
Girgis 1989	21/225	43/245		8.28%	0.53[0.33,0.87]
Mathur 2013	5/40	16/40		2.97%	0.31[0.13,0.77]
Molyneux 2002	96/305	91/293	- - -	19.1%	1.01[0.8,1.29]
Qazi 1996	12/48	5/41		2.68%	2.05[0.79,5.33]
Sankar 2007	0/12	1/13	+ +	0.27%	0.36[0.02,8.05]
Scarborough 2007	129/231	120/228	-	23.91%	1.06[0.9,1.26]
Subtotal (95% CI)	933	940	◆	67.69%	0.87[0.67,1.15]
Total events: 284 (Corticostero	ids), 302 (Placebo)				
Heterogeneity: Tau ² =0.07; Chi ²	=17.92, df=8(P=0.02); l ² =55.	37%			
Test for overall effect: Z=0.97(P	=0.33)				
5.1.2 High-income countries					
Belsey 1969	2/43	1/43		0.47%	2[0.19,21.24]
Bennett 1963	16/38	22/47		8.48%	0.9[0.56,1.46]
de Gans 2002	11/157	21/144		4.74%	0.48[0.24,0.96]
DeLemos 1969	2/54	1/63		- 0.47%	2.33[0.22,25.03]
Kanra 1995	2/29	1/27		0.48%	1.86[0.18,19.38]
Kilpi 1995	0/32	0/26			Not estimable
King 1994	0/50	1/51	+ +	0.26%	0.34[0.01,8.15]
Lebel 1988a	0/51	1/49	+ +	0.26%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30	+ +	0.27%	0.32[0.01,7.63]
Nguyen 2007	22/217	26/218	+	7.22%	0.85[0.5,1.45]
Odio 1991	1/52	1/49		0.35%	0.94[0.06,14.65]
Peltola 2007	23/166	26/163	-+	7.61%	0.87[0.52,1.46]
Schaad 1993	0/60	0/55			Not estimable
Thomas 1999	3/31	5/29		1.43%	0.56[0.15,2.14]
Wald 1995	1/69	0/74	+	0.26%	3.21[0.13,77.6]
	1131	1117		32.31%	0.81[0.63,1.05]

Corticosteroids for acute bacterial meningitis (Review)



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Study or subgroup	Corticosteroids	Placebo			Risk Ratio)		Weight	Risk Ratio
	n/N	n/N		IV, Random, 95% CI					IV, Random, 95% CI
Total events: 83 (Corticoster	oids), 107 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =	=6.23, df=12(P=0.9); I ² =0%								
Test for overall effect: Z=1.62	2(P=0.1)								
Total (95% CI)	2064	2057			•			100%	0.88[0.75,1.03]
Total events: 367 (Corticoste	roids), 409 (Placebo)								
Heterogeneity: Tau ² =0.02; Cl	ni²=25.92, df=21(P=0.21); l²=18	8.99%							
Test for overall effect: Z=1.55	5(P=0.12)								
Test for subgroup difference	s: Chi ² =0.17, df=1 (P=0.68), I ² =	0%							
	Favou	s corticosteroids	0.05	0.2	1	5	20	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.2.1 Low-income countries					
Bhaumik 1998	2/13	2/13		1.82%	1[0.16,6.07]
Girgis 1989	3/190	6/177		3.15%	0.47[0.12,1.83]
Molyneux 2002	38/147	39/158	-	39.65%	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	<u> </u>	10.53%	1.03[0.49,2.18]
Subtotal (95% CI)	472	472	•	55.95%	0.99[0.72,1.38]
Total events: 56 (Corticosteroid	s), 60 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1.2	25, df=4(P=0.87); I ² =0%				
Test for overall effect: Z=0.03(P=	=0.98)				
5.2.2 High-income countries					
Belsey 1969	0/41	1/42	•	0.59%	0.34[0.01,8.14]
Kanra 1995	0/27	2/26		0.66%	0.19[0.01,3.84]
Kilpi 1995	1/31	3/26		1.22%	0.28[0.03,2.53]
King 1994	2/48	3/45		1.95%	0.63[0.11,3.57]
Lebel 1988a	2/43	8/38		2.68%	0.22[0.05,0.98]
Lebel 1988b	1/49	5/46 -		1.33%	0.19[0.02,1.55]
Lebel 1989	1/31	2/29		1.07%	0.47[0.04,4.89]
Nguyen 2007	7/180	16/177		7.93%	0.43[0.18,1.02]
Odio 1991	3/51	7/48	+	3.53%	0.4[0.11,1.47]
Peltola 2007	10/135	12/131	+	9.15%	0.81[0.36,1.81]
Schaad 1993	2/60	4/55		2.15%	0.46[0.09,2.4]
Wald 1995	10/68	17/74	-+	11.79%	0.64[0.32,1.3]
Subtotal (95% CI)	764	737	•	44.05%	0.51[0.35,0.73]
Total events: 39 (Corticosteroid	s), 80 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =4.8	84, df=11(P=0.94); I ² =0%				
Test for overall effect: Z=3.65(P=	=0)				
Total (95% CI)	1236	1209	•	100%	0.74[0.58,0.94]
Total events: 95 (Corticosteroid	s), 140 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =13.	.43, df=16(P=0.64); l ² =0%				
Test for overall effect: Z=2.44(P=	=0.01)				
Test for subgroup differences: C	hi²=7.34, df=1 (P=0.01), I²=	86.38%			
	Favou	rs corticosteroids 0.	02 0.1 1 10 5	⁰ Favours placebo	

Corticosteroids for acute bacterial meningitis (Review)



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

n/N N/Excl. 59% CI W/Excl. 59% CI W/Excl. 59% CI 5.3.1 Low-income countries 4/14 3/15 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.95% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05% 0.05	Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
Bhaumik 1996 4/14 3/16 0.96% 1.52[0.41,5.67] Girgi 1995 3/190 6/177 0.89% 0.47[0.21,0.8] Mahur 2013 6/35 10/24 2.21% 0.41[0.17,0.96] Moyneux 2002 49/14/1 46/158 1.494% 1.14(0.82,1.08] Sankar 2007 3/12 0.87% 11(0.25,4] Sankar 2007 3/12 0.87% 11(0.25,4] Schforough 2007 30/96 3/99 0.68(0.58,1.26] Subtol (95% CI) 530 521 71.39% 0.89[0.76,1.04] Total events: 123 (Corticosteroids), 136 (Placebo) 1 1/42 0.17% 0.34[0.01,8,1.6] King 1995 5/31 6/26 1.46% 0.7[0.24,2.03] 1/42 0.17% 0.34[0.01,8,1.6] King 1995 5/31 6/26 1.46% 0.7[0.24,2.03] 1/42 0.17% 0.34[0.01,8,1.6] King 1994 5/48 5/51 6/26 1.46% 0.7[0.24,2.03] 1/22.1% 0.47[0.21,1.66] 1/22.1% 0.47[0.21,1.66] 1/21.1% 0.47[0.21,1.66] 1/21.1% 0.47[0.21,1.66] 1/21.1% <td< th=""><th></th><th>n/N</th><th>n/N</th><th>IV, Fixed, 95% CI</th><th></th><th>IV, Fixed, 95% CI</th></td<>		n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Girgis 1989 3/190 6/177 0.89% 0.47[0.12.13] Mathur 2013 6/35 10/24 2.11% 0.41[0.17,0.8] Mathur 2013 6/35 10/24 2.11% 0.41[0.17,0.8] Mathur 2013 6/35 32/35 40.84% 0.85[0.7,1,04] Sankar 2007 3/12 3/12 0.37% 1[0.25,4] Scarborough 2007 30/96 36/99 0.86[0.58,1,28] 0.86[0.58,1,28] Stotbat (15% C1) 330 521 71.13% 0.86[0.76,1,04] tecrogenelity: Tau ¹ or, Chi ² =6.97, df=6[P=0.32]; i*13.88% Tail events: 123 (Corticosteroids), 136 (Placebo) 1.86% 0.76[0.48,1.8] tecrogenelity: Tau ¹ or, Chi ² =6.97, df=6[P=0.32]; i*13.88% Tail events: 213 (Corticosteroids), 137[4 1.01% 0.34[0.01, 6.14] de Ganz 2002 13/143 14/119 3.26% 0.77[0.38, 1.58] King 1994 5/48 5/45 1.21% 0.94[0.29, 2.02] Lebel 1988 3/30 5/29 0.33% 0.56[0.25, 0.9] Bioley 195 13/3 1.21% 0.34[0.01, 1.31] 0.56[0.34, 0.3] Lebel 1988 3/30 5/2	5.3.1 Low-income countries					
Mathur 2013 6/35 10/24 221% 0.41[0.17,0.96] Molyneux 2002 49/147 46/158 14.49% 1.14(0.82,1.6] Qazi 1996 28/36 32/35 40.84% 0.85[0.71,1.04] Scahorough 2007 30/96 36/99 10.66% 0.86[0.58,1.26] Subtatel (95% CI) 530 521 71.39% 0.89[0.76,1.04] Total events: 123 (Corticosteroids), 136 (Placebo) 11.44% 1.14% 0.86[0.58,1.26] State 123 (Sorticosteroids), 136 (Placebo) 11.49% 1.14% 0.89[0.76,1.04] State 123 (Sorticosteroids), 136 (Placebo) 11.49% 0.17% 0.34[0.01,8,16] Kipi 1995 5/31 6/25 0.77(0.34,16] 0.44[0.06,1.03] Kipi 1995 5/31 6/25 0.79% 0.24[0.06,1.03] Kipi 1995 5/31 6/26 0.79% 0.24[0.06,1.03] Lebel 1988 9/43 16/38 1.25% 0.67[0.24,0.25,0.99] Lebel 1988 7/49 14/46 2.52% 0.47[0.21,0.6] Lebel 1988 7/49 14/46 2.52% 0.47[0.21,0.6] Lebel 1988 </td <td>Bhaumik 1998</td> <td>4/14</td> <td>3/16</td> <td></td> <td>0.96%</td> <td>1.52[0.41,5.67]</td>	Bhaumik 1998	4/14	3/16		0.96%	1.52[0.41,5.67]
Molyneux 2002 49/147 46/158 11.4[0.82,1.6] Qai 1996 28/36 32/35 40.84% 0.85[0.7,1.04] Sankar 2007 3/12 3/12 0.87% 11.025,4 Scarborugh 2007 30/96 36/99 0.666% 0.6610.83,1.28] Subtal (95% CI) 530 521 71.39% 0.89[0.76,1.04] Total events: 123 (Corticosteroids), 136 (Placebo) Heterogeneity: Trub-°, Chi®=27, 164(ePle-32,1); 1=13.83% 71.39% 0.34[0.01,6.14] de Gans 2002 13/143 14/119 0.17% 0.34[0.01,6.14] de Gans 2002 13/143 14/119 3.26% 0.77[0.38,1.58] King 1994 5/48 5/45 0.79% 0.24[0.06,0.3] King 1994 5/48 5/45 1.21% 0.94[0.29,3.02] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.9] Lebel 1988b 7/49 14/46 2.52% 0.47[0.21,1.66] Lebel 1989 3/30 5/29 0.93% 0.58[0.25,0.2] Nguyen 2007 10/135 12/13 4.038[0.1,1.2] 1.02% 0.38[0.1,3.1,2]	Girgis 1989	3/190	6/177		0.89%	0.47[0.12,1.83]
Qari 1996 28/36 32/35 40.44% 0.85[0.7,1.04] Sankar 2007 31/12 31/12 0.87% 110.25.4 Scarborough 2007 30/96 36/99 10.68% 0.86[0.58,1.28] Subtotal (95% CI) 530 521 71.39% 0.86[0.76,1.04] Total events: 123 (conticosteroids), 136 (Placebo) Heterogeneity: Tau ⁻⁰ ; Chi ⁻⁰ =6.37, df=6(P=0.32); l ⁺ =13.89% Test for overall effect: 2-1.52 (P=0.13) 5.3.2 High-income countries Selsey 1969 0.41 1/42 0.17% 0.34 (0.01, 8.14) de Gans 2002 13/143 14/119 3.26% 0.77 (0.38, 1.58) King 1995 5/31 6/26 1.46% 0.6 (0.23, 0.2) Lebel 1988a 9/43 16/38 3.5% 0.5 (0.25, 0.9) Lebel 1988a 9/43 16/38 3.5% 0.5 (0.25, 0.9) Lebel 1988a 9/43 16/38 4.52% 0.47 (0.21, 0.6) Nguyen 2007 21/180 37/177 6.83% 0.5 (0.34, 0.91) Odio 1991 3/50 7/44 1.02% 0.33((0	Mathur 2013	6/35	10/24		2.21%	0.41[0.17,0.98]
Sankar 2007 3/12 3/12	Molyneux 2002	49/147	46/158	+-	14.94%	1.14[0.82,1.6]
Scarborough 2007 30/96 36/99	Qazi 1996	28/36	32/35	•	40.84%	0.85[0.7,1.04]
Subtota (95% Ci) 530 521 71.39% 0.89[0.76,1.04] Total events: 123 (Corticosteroids), 136 (Placebo) Heterogeneity: Tau ² =0, Chi ² =6.97, df=6[P=0.32]; l ² =13.88% State	Sankar 2007	3/12	3/12	_	0.87%	1[0.25,4]
Total events: 123 (Corticosteroids), 136 (Placebo) Heterogeneity: Tau ² =0; Ch ² =6.37, df=6(P=0.32); l ² =13.88% 5.3.2 High-income countries Belsey 1369 0/41 1/42 6.3.2002 13/143 14/119 3.26% 0.79% 0.24(0.06,1.03) Kinra 1995 2/27 8/26 101% 0.4(% 0.70% 0.24(0.06,1.03) King 1994 5/48 5/45 1.21% 0.94(0.22,3.02) Lebel 1988a 9/43 16/38 3.5% 0.5(0.25,0.99) Lebel 1988b 7/49 1/46 2.52% 0.47(0.21,1.06) Lebel 1988b 7/49 1/46 2.52% 0.47(0.21,1.06) Lebel 1989 3/30 5/29 0.39% 0.58(0.15,2.21) Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.33(0.1,1.37] Naudu 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (55% Cl) 904 850 28.61% 0.58[0.45,0.73] Total events: 214 (Corticosteroids), 266 (Placebo)	Scarborough 2007	30/96	36/99	-+	10.68%	0.86[0.58,1.28]
Heterogeneity: Tau ² -0; Chi ² =6.97, df=6(P=0.32); l ² =1.3.88% Test for overall effect: Z=1.52(P=0.13) 5.3.2 High-income countries Belsey 1969 0/41 1/42 6 Gans 2002 13/143 14/119 3.26% 0.77% 0.38,1.58] Kanra 1995 2/27 8/26 11/195 5/31 6/66 11/195 5/31 6/67 11/195 5/31 6/67 11/195 5/31 6/68 11/195 5/31 6/67 11/195 5/31 16/38 11/195 5/48 5/45 12/196 0.94(0.23,02) 1.46% 12/198 0.94(0.23,02) 1.46% 12/198 0.94(0.23,02) 1.46% 12/198 3/30 5/29 0.93% 12/198 3/30 5/29 0.93% 12/199 3/50 7/44 1% 12/199 10/67 1/177 3.33% 13/107 10/67 1/17/2 3.33% 10/195 10/67 1/17/12 3.33% <t< td=""><td>Subtotal (95% CI)</td><td>530</td><td>521</td><td>•</td><td>71.39%</td><td>0.89[0.76,1.04]</td></t<>	Subtotal (95% CI)	530	521	•	71.39%	0.89[0.76,1.04]
Test for overall effect: Z=1.52(P=0.13) 5.3.2 High-income countries Belsey 1969 0/41 1/42 6 Gans 2002 13/143 14/119 King 1995 2/27 8/26 King 1995 5/31 6/26 Lebel 1980 9/43 16/38 Lebel 1980 7/49 14/46 Lebel 1980 7/49 14/46 Lebel 1989 3/30 5/29 Pettola 2007 21/180 37/177 Pettola 2007 10/135 12/11 Odi 1991 3/50 7/44 1995 10/67 17/72 Subtcal (95% CI) 904 850 Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² -0; Ch ² -20.91; 1 ² -9.12% Test for subgroup differences: Ch ² -8.78, di=1 (P=0), 1 ² -88.61% 100% 0.79[0.690.89]	Total events: 123 (Corticosteroi	ds), 136 (Placebo)				
5.3.2 High-income countries Belsey 1969 0/41 1/42 0.17% 0.34[0.01,8.14] de Gans 2002 13/143 14/119 3.26% 0.77[0.38,158] Kanra 1995 2/27 8/26 0.79% 0.24[0.06,1.03] Klipl 1995 5/31 6/26 1.46% 0.70/24,20.32] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1989b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989 3/30 5/29 0.93% 0.5[0.15,2.1] Nguyen 2007 21/180 37/17 6.83% 0.56[0.34,0.31] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Petlola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Subtotal (95% cl) 904 850 2.8.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 4.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0.0	Heterogeneity: Tau ² =0; Chi ² =6.9	97, df=6(P=0.32); I ² =13.88%				
Belsey 1969 0/41 1/42 0.17% 0.34[0.01,8.14] de Gans 2002 13/143 14/19 3.26% 0.77[0.38,1.58] Kana 1995 2/27 8/26 0.79% 0.24[0.06,1.03] Kilp 1995 5/31 6/26 1.46% 0.7[0.24,2.03] King 1994 5/48 5/45 1.21% 0.94[0.29,0.02] Lebel 1980a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1980b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1980 3/30 5/29 0.93% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 195 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 100%	Test for overall effect: Z=1.52(P=	=0.13)				
Belsey 1969 0/41 1/42 0.17% 0.34[0.01,8.14] de Gans 2002 13/143 14/19 3.26% 0.77[0.38,1.58] Kana 1995 2/27 8/26 0.79% 0.24[0.06,1.03] Kilp 1995 5/31 6/26 1.46% 0.7[0.24,2.03] King 1994 5/48 5/45 1.21% 0.94[0.29,0.02] Lebel 1980a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1980b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1980 3/30 5/29 0.93% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 195 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 100%						
de Gans 2002 13/143 14/19 3.26% 0.77[0.38,158] Kana 1995 2/27 8/26 0.79% 0.24[0.06,1.03] Kilpi 1995 5/31 6/26 1.46% 0.7[0.24,2.03] King 1994 5/48 5/45 1.21% 0.94[0.29,3.02] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.92] Lebel 1988b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1980 3/30 5/29 0.93% 0.58[0.52,21] Nguyen 2007 21/180 37/17 6.83% 0.56[0.25,0.9] Odio 1991 3/50 7/44 1% 0.38[0.4],1.37] Pettola 2007 10/135 12/131 2.58% 0.88[0.4],1.28] Subtotal (95% Cl) 94 850 0 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 1067 17/72 3.33% 0.63[0.31,1.28] Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.35); l ² =0.9% Test for overall effect: Z=4.47(P<0.0001)	5.3.2 High-income countries					
Kara 1995 2/27 8/26 ● 0.79% 0.24[0.6,1.03] Kilp 1995 5/31 6/26 1.46% 0.7[0.24,2.03] King 1994 5/48 5/45 1.21% 0.94[0.29,3.02] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1989b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989 3/30 5/29 0.93% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 ● 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Pettola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% <	Belsey 1969	0/41	1/42	+	0.17%	0.34[0.01,8.14]
Kilpi 1995 5/31 6/26 1.46% 0.7[0.24,2.03] King 1994 5/48 5/45 1.21% 0.94[0.29,3.02] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1988b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989 3/30 5/29 0.93% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² -0; Chi ² =5.16, df=12(P=0.95); l ² =0% 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] 1.54 Heterogeneity: Tau ² -0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89]	de Gans 2002	13/143	14/119	-+	3.26%	0.77[0.38,1.58]
King 1994 5/48 5/45 1.21% 0.94[0.29,3.02] Lebel 1988a 9/43 16/38 3.5% 0.5[0.25,0.99] Lebel 1988b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989 3/30 5/29 0.93% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² -0; Chi ² =5.16, df=12(P=0.95); i ² =0% Test for overall effect: Z=4.47(P<0.0001)	Kanra 1995	2/27	8/26		0.79%	0.24[0.06,1.03]
Lebel 1988a 9/43 16/38	Kilpi 1995	5/31	6/26	+	1.46%	0.7[0.24,2.03]
Lebel 1988b 7/49 14/46 2.52% 0.47[0.21,1.06] Lebel 1989 3/30 5/29 0.33% 0.58[0.15,2.21] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Pettola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); i ² =9.12% 100% 0.79[0.69,0.89] Test for overall effect: Z=3.67(P=0) Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61%	King 1994	5/48	5/45	<u> </u>	1.21%	0.94[0.29,3.02]
Lebel 1989 3/30 5/29 0.58[0.5,2.1] Nguyen 2007 21/180 37/177 6.83% 0.56[0.34,0.91] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtoal (95% CI) 904 850 • 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% Test for overall effect: Z=4.47(P<0.0001) Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =2.091, df=19(P=0.34); l ² =9.12% Test for overall effect: Z=3.67(P=0) Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61%	Lebel 1988a	9/43	16/38	-+	3.5%	0.5[0.25,0.99]
Nguyen 2007 21/180 37/177 → 6.83% 0.56[0.34,0.9] Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 ◆ 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); 1 ² =0% Test for overall effect: Z=4.47(P<0.0001)	Lebel 1988b	7/49	14/46	-+	2.52%	0.47[0.21,1.06]
Odio 1991 3/50 7/44 1% 0.38[0.1,1.37] Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% Cl) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 434 1371 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 1371 100% 0.79[0.69,0.89] 100% Heterogeneity: Tau ² =0; Chi ² =2.0.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =2.0.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61% 100% 0.79[0.69,0.89]	Lebel 1989	3/30	5/29		0.93%	0.58[0.15,2.21]
Peltola 2007 10/135 12/131 2.58% 0.81[0.36,1.81] Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 € 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% 5 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 ● 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61% 100% 0.79[0.69,0.89]	Nguyen 2007	21/180	37/177	-+	6.83%	0.56[0.34,0.91]
Schaad 1993 3/60 8/55 1.02% 0.34[0.1,1.23] Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 1434 1371 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] 100% Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] 100% Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61% 100% 100% 100% 10%	Odio 1991	3/50	7/44	+	1%	0.38[0.1,1.37]
Wald 1995 10/67 17/72 3.33% 0.63[0.31,1.28] Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) 100% 0.58[0.45,0.73] Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 100% 100% Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61% 100% 100% 100%	Peltola 2007	10/135	12/131	-+	2.58%	0.81[0.36,1.81]
Subtotal (95% CI) 904 850 28.61% 0.58[0.45,0.73] Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% Feature Feature Feature Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total (95% CI) 1434 1371 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% 100% 0.79[0.69,0.89] Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61% 100% 0.79[0.69,0.89]	Schaad 1993	3/60	8/55		1.02%	0.34[0.1,1.23]
Total events: 91 (Corticosteroids), 150 (Placebo) Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% Test for overall effect: Z=4.47(P<0.0001) Total (95% CI) 1434 1371 ♦ 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61%	Wald 1995	10/67	17/72	-+	3.33%	0.63[0.31,1.28]
Heterogeneity: Tau ² =0; Chi ² =5.16, df=12(P=0.95); l ² =0% Test for overall effect: Z=4.47(P<0.0001)	Subtotal (95% CI)	904	850	•	28.61%	0.58[0.45,0.73]
Test for overall effect: Z=4.47(P<0.0001)	Total events: 91 (Corticosteroid	s), 150 (Placebo)				
Total (95% CI) 1434 1371 ♦ 100% 0.79[0.69,0.89] Total events: 214 (Corticosteroids), 286 (Placebo) 100% 0.79[0.69,0.89] Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% Test for overall effect: Z=3.67(P=0) </td <td>Heterogeneity: Tau²=0; Chi²=5.1</td> <td>.6, df=12(P=0.95); I²=0%</td> <td></td> <td></td> <td></td> <td></td>	Heterogeneity: Tau ² =0; Chi ² =5.1	.6, df=12(P=0.95); I ² =0%				
Total events: 214 (Corticosteroids), 286 (Placebo) Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); l ² =9.12% Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61%	Test for overall effect: Z=4.47(P<	<0.0001)				
Heterogeneity: Tau ² =0; Chi ² =20.91, df=19(P=0.34); I ² =9.12% Test for overall effect: Z=3.67(P=0) Test for subgroup differences: Chi ² =8.78, df=1 (P=0), I ² =88.61%	Total (95% CI)	1434	1371	•	100%	0.79[0.69,0.89]
Test for subgroup differences: Chi ² =8.78, df=1 (P=0), I ² =88.61%	Total events: 214 (Corticosteroi	ds), 286 (Placebo)				
Test for subgroup differences: Chi ² =8.78, df=1 (P=0), l ² =88.61%	Heterogeneity: Tau ² =0; Chi ² =20.	.91, df=19(P=0.34); I ² =9.12%	6			
	Test for overall effect: Z=3.67(P=	=0)				
Eavours corticosteroids 0.01 0.1 1 10 100 Eavours placebo	Test for subgroup differences: C	hi²=8.78, df=1 (P=0), I²=88.	61%			
		Favour	s corticosteroids 0.01	0.1 1 10	¹⁰⁰ Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N n/N		IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.4.1 Low-income countries					
Bhaumik 1998	3/13	2/13		1.34%	1.5[0.3,7.55]
Ciana 1995	5/26	7/24		3.47%	0.66[0.24,1.8]
	Favou	rs corticosteroids	0.05 0.2 1 5 2	⁰ Favours placebo	

Corticosteroids for acute bacterial meningitis (Review)



Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI	-	IV, Fixed, 95% CI
Molyneux 2002	69/223	57/209	-	40.02%	1.13[0.84,1.52]
Sankar 2007	0/12	1/13	+	0.36%	0.36[0.02,8.05]
Scarborough 2007	21/98	26/104	-+	13.75%	0.86[0.52,1.42]
Subtotal (95% CI)	372	363	+	58.94%	1.03[0.81,1.31]
Total events: 98 (Corticosteroi	ds), 93 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2	.33, df=4(P=0.68); I ² =0%				
Test for overall effect: Z=0.23(P=0.82)				
5.4.2 High-income countries					
de Gans 2002	18/143	24/119		11.13%	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		0.98%	0.84[0.13,5.55]
Lebel 1988a	5/48	8/43		3.24%	0.56[0.2,1.58]
Lebel 1988b	9/47	10/45	+	5.44%	0.86[0.39,1.92]
Lebel 1989	4/28	5/26		2.42%	0.74[0.22,2.47]
Peltola 2007	10/139	21/137	+	6.84%	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%	0.7[0.32,1.51]
Subtotal (95% CI)	559	520	◆	41.06%	0.64[0.48,0.85]
Total events: 65 (Corticosteroi	ids), 95 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2	.76, df=8(P=0.95); I ² =0%				
Test for overall effect: Z=3.04(I	P=0)				
Total (95% CI)	931	883	•	100%	0.84[0.7,1.02]
Total events: 163 (Corticostero	oids), 188 (Placebo)				- / -
Heterogeneity: Tau ² =0; Chi ² =1					
Test for overall effect: Z=1.77(
Test for subgroup differences:		83.68%			
		rs corticosteroids	0.05 0.2 1 5 20	Favours placebo	
	Favou	s conticosteroids		Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.5.1 Low-income countries					
Ciana 1995	8/34	12/36		5.82%	0.71[0.33,1.51]
Girgis 1989	16/142	24/140		9.77%	0.66[0.37,1.18]
Mathur 2013	5/40	16/40		4.14%	0.31[0.13,0.77]
Molyneux 2002	96/305	91/293	<u>+</u>	59.75%	1.01[0.8,1.29]
Qazi 1996	12/48	5/41	+ +	3.69%	2.05[0.79,5.33]
Subtotal (95% CI)	569	550	•	83.16%	0.91[0.75,1.12]
Total events: 137 (Corticostero	oids), 148 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =1	0.54, df=4(P=0.03); l ² =62.03 ⁰	%			
Test for overall effect: Z=0.88(F	P=0.38)				
5.5.2 High-income countries					
Belsey 1969	2/43	1/43	+	0.6%	2[0.19,21.24]
DeLemos 1969	4/54	2/63		1.23%	2.33[0.44,12.25]
Kanra 1995	2/29	1/27		0.62%	1.86[0.18,19.38]
	Favou	rs corticosteroids	0.05 0.2 1 5 20	Favours placebo	

Corticosteroids for acute bacterial meningitis (Review)



Study or subgroup	Corticosteroids	Placebo		Risk Ratio		Weight	Risk Ratio
	n/N	n/N		IV, Fixed, 95% CI			IV, Fixed, 95% CI
Kilpi 1995	0/32	0/26					Not estimable
King 1994	0/50	1/51	◀	•		0.33%	0.34[0.01,8.15]
Lebel 1988a	0/51	1/49	◀	•		0.33%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49					Not estimable
Lebel 1989	0/31	1/30	◀──	•		0.34%	0.32[0.01,7.63]
Odio 1991	1/52	1/49				0.45%	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				0.33%	3.21[0.13,77.6]
Subtotal (95% CI)	688	679		+		16.84%	0.96[0.61,1.5]
Total events: 33 (Corticosteroids), 3	34 (Placebo)						
Heterogeneity: Tau ² =0; Chi ² =3.8, df	f=8(P=0.87); l ² =0%						
Test for overall effect: Z=0.18(P=0.8	36)						
Total (95% CI)	1257	1229		•		100%	0.92[0.77,1.11]
Total events: 170 (Corticosteroids),	, 182 (Placebo)						
Heterogeneity: Tau ² =0; Chi ² =14.37,	df=13(P=0.35); I ² =9.56%						
Test for overall effect: Z=0.87(P=0.3	38)						
Test for subgroup differences: Chi ²	=0.04, df=1 (P=0.85), I ² =0	%					
	Favours	corticosteroids	0.05	0.2 1	5 20	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.6.1 Low-income countries					
Girgis 1989	0/16	4/15		0.95%	0.1[0.01,1.79]
Molyneux 2002	38/147	39/158	+	51.29%	1.05[0.71,1.54]
Qazi 1996	1/26	1/25		1.04%	0.96[0.06,14.55]
Subtotal (95% CI)	189	198	+	53.28%	1[0.69,1.47]
Total events: 39 (Corticosteroids	s), 44 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2.4	8, df=2(P=0.29); l ² =19.42%				
Test for overall effect: Z=0.02(P=	0.99)				
5.6.2 High-income countries					
Belsey 1969	0/41	1/42		0.76%	0.34[0.01,8.14]
Kanra 1995	0/27	2/26		0.86%	0.19[0.01,3.84]
Kilpi 1995	1/31	3/26		1.58%	0.28[0.03,2.53]
King 1994	2/48	3/45	+	2.52%	0.63[0.11,3.57]
Lebel 1988a	2/43	8/38		3.46%	0.22[0.05,0.98]
Lebel 1988b	1/49	5/46		1.72%	0.19[0.02,1.55]
Lebel 1989	1/31	2/29		1.39%	0.47[0.04,4.89]
Odio 1991	3/51	7/48	+	4.57%	0.4[0.11,1.47]
Peltola 2007	10/135	12/131	+	11.83%	0.81[0.36,1.81]
Schaad 1993	2/60	4/55		2.78%	0.46[0.09,2.4]
Wald 1995	10/68	17/74	-+-	15.25%	0.64[0.32,1.3]
Subtotal (95% CI)	584	560	◆	46.72%	0.52[0.35,0.78]
Total events: 32 (Corticosteroids	s), 64 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =4.6	7, df=10(P=0.91); l ² =0%				
	Favour	rs corticosteroids	0.02 0.1 1 10	⁵⁰ Favours placebo	

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Study or subgroup	Corticosteroids	Corticosteroids Placebo			Risk Ratio			Weight	Risk Ratio
	n/N	n/N	_	IV	, Fixed, 95%	CI			IV, Fixed, 95% CI
Test for overall effect: Z=3.13	3(P=0)								
Total (95% CI)	773	758			•			100%	0.74[0.56,0.98]
Total events: 71 (Corticoster	roids), 108 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =	=12.44, df=13(P=0.49); l ² =0%								
Test for overall effect: Z=2.13	3(P=0.03)								
Test for subgroup difference	es: Chi ² =5.29, df=1 (P=0.02), I ² =8	31.08%					1		
	Favour	s corticosteroids	0.02	0.1	1	10	50	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.7.1 Low-income countries	5				
Ciana 1995	5/26	7/24	+	4.96%	0.66[0.24,1.8]
Molyneux 2002	69/223	57/209	- <mark></mark>	57.26%	1.13[0.84,1.52]
Sankar 2007	0/12	1/12	+	- 0.52%	0.33[0.01,7.45]
Subtotal (95% CI)	261	245	•	62.75%	1.08[0.81,1.43]
Total events: 74 (Corticostero	oids), 65 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	1.58, df=2(P=0.45); I ² =0%				
Test for overall effect: Z=0.51	(P=0.61)				
5.7.2 High-income countrie	s				
Kanra 1995	3/27	2/26		- 1.72%	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		4.64%	0.56[0.2,1.58
Lebel 1988b	9/47	10/45	+	7.78%	0.86[0.39,1.92
Lebel 1989	4/28	5/26	+	3.47%	0.74[0.22,2.47
Peltola 2007	10/139	21/137		9.79%	0.47[0.23,0.96
Wald 1995	9/68	14/74	+	8.45%	0.7[0.32,1.51]
Subtotal (95% CI)	388	377	•	37.25%	0.67[0.46,0.97
Total events: 42 (Corticostero	oids), 62 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	2.32, df=6(P=0.89); I ² =0%				
Test for overall effect: Z=2.14	(P=0.03)				
Total (95% CI)	649	622	•	100%	0.9[0.72,1.13
Total events: 116 (Corticoste	roids), 127 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	7.92, df=9(P=0.54); I ² =0%				
Test for overall effect: Z=0.9(F	P=0.37)				
Test for subgroup differences	s: Chi ² =4.02, df=1 (P=0.04), I ² =	75.14%			

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% Cl		IV, Fixed, 95% CI
5.8.1 Low-income countries					
Girgis 1989	0/16	4/15	┥──┤──	1.81%	0.1[0.01,1.79]
Molyneux 2002	27/132	21/134		54.58%	1.31[0.78,2.19]
Subtotal (95% CI)	148	149	*	56.39%	1.2[0.72,2]
Total events: 27 (Corticosteroid	s), 25 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2.9	94, df=1(P=0.09); l ² =65.93%				
Test for overall effect: Z=0.71(P=	=0.48)				
5.8.2 High-income countries					
Belsey 1969	0/41	1/42	↓	1.45%	0.34[0.01,8.14]
Kanra 1995	0/27	2/26	↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓	1.63%	0.19[0.01,3.84]
Kilpi 1995	1/17	2/13		2.79%	0.38[0.04,3.77]
King 1994	1/21	1/22		1.99%	1.05[0.07,15.69]
Lebel 1988a	1/9	1/9		2.14%	1[0.07,13.64]
Lebel 1988b	0/9	1/11	+	1.53%	0.4[0.02,8.78]
Lebel 1989	0/6	1/9	+	1.57%	0.48[0.02,10.07]
Odio 1991	0/13	1/9	+	1.52%	0.24[0.01,5.26]
Peltola 2007	7/89	4/84		10.28%	1.65[0.5,5.44]
Schaad 1993	1/23	3/25		3.04%	0.36[0.04,3.24]
Wald 1995	5/25	9/35		15.67%	0.78[0.3,2.04]
Subtotal (95% CI)	280	285	-	43.61%	0.73[0.41,1.31]
Total events: 16 (Corticosteroid	s), 26 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =4.3	5, df=10(P=0.93); l ² =0%				
Test for overall effect: Z=1.04(P=	=0.3)				
Total (95% CI)	428	434	\checkmark	100%	0.97[0.66,1.42]
Total events: 43 (Corticosteroid	s), 51 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =8.8	36, df=12(P=0.71); l ² =0%				
Test for overall effect: Z=0.15(P=	=0.88)				
Test for subgroup differences: C	hi²=1.58, df=1 (P=0.21), I²=	36.63%			
	Favour	s corticosteroids	0.05 0.2 1 5 20	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo		Ri	sk Ratio			Weight	Risk Ratio IV, Fixed, 95% Cl	
	n/N	n/N		IV, Fiz	xed, 95%	b CI				
5.9.1 Low-income countries	i i i i i i i i i i i i i i i i i i i									
Bhaumik 1998	1/14	3/16				-		0.46%	0.38[0.04,3.26]	
Girgis 1989	5/68	18/79			-			2.42%	0.32[0.13,0.82]	
Scarborough 2007	129/231	120/228			+			74.97%	1.06[0.9,1.26]	
Subtotal (95% CI)	313	323			•			77.85%	1.02[0.86,1.2]	
Total events: 135 (Corticoster	oids), 141 (Placebo)									
Heterogeneity: Tau ² =0; Chi ² =6	6.82, df=2(P=0.03); l ² =70.68%									
Test for overall effect: Z=0.19((P=0.85)									
5.9.2 High-income countries	s									
Bennett 1963	16/38	22/47		I	+			9.15%	0.9[0.56,1.46]	
	Favour	rs corticosteroids	0.01	0.1	1	10	100	Favours placebo		

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Study or subgroup	Corticosteroids	Placebo			Risk Ratio			Weight	Risk Ratio
	n/N	n/N		IV,	IV, Fixed, 95% CI				IV, Fixed, 95% CI
de Gans 2002	11/157	21/144		-	-+			4.41%	0.48[0.24,0.96]
Nguyen 2007	22/217	26/218			-+-			7.4%	0.85[0.5,1.45]
Thomas 1999	3/31	5/29						1.18%	0.56[0.15,2.14]
Subtotal (95% CI)	443	438			•			22.15%	0.76[0.56,1.04]
Total events: 52 (Corticoster	oids), 74 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =	2.52, df=3(P=0.47); I ² =0%								
Test for overall effect: Z=1.74	(P=0.08)								
Total (95% CI)	756	761			•			100%	0.95[0.82,1.1]
Total events: 187 (Corticoste	roids), 215 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² =	11.98, df=6(P=0.06); l ² =49.929	6							
Test for overall effect: Z=0.65	(P=0.52)								
Test for subgroup differences	s: Chi ² =2.64, df=1 (P=0.1), I ² =6	2.19%							
	Favour	s corticosteroids	0.01	0.1	1	10	100	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
5.10.1 Low-income countries	i				
Bhaumik 1998	4/14	3/16		4.45%	1.73[0.31,9.57]
Scarborough 2007	30/96	36/99		36.71%	0.8[0.44,1.44]
Subtotal (95% CI)	110	115	•	41.16%	0.87[0.49,1.52]
Total events: 34 (Corticosteroi	ds), 39 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =0.	71, df=1(P=0.4); l ² =0%				
Test for overall effect: Z=0.5(P=	=0.61)				
5.10.2 High-income countries	5				
de Gans 2002	13/143	14/119		20.43%	0.75[0.34,1.67]
Nguyen 2007	21/180	37/177		38.41%	0.5[0.28,0.89]
Subtotal (95% CI)	323	296	•	58.84%	0.58[0.36,0.92]
Total events: 34 (Corticosteroid	ds), 51 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =0.	65, df=1(P=0.42); I ² =0%				
Test for overall effect: Z=2.3(P=	=0.02)				
Total (95% CI)	433	411	◆	100%	0.68[0.47,0.98]
Total events: 68 (Corticosteroio	ds), 90 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2.	55, df=3(P=0.47); I ² =0%				
Test for overall effect: Z=2.09(P	P=0.04)				
Test for subgroup differences:	Chi ² =1.19, df=1 (P=0.27), I ² =	16.11%			
	Favou	rs corticosteroids 0.0	1 0.1 1 10	¹⁰⁰ Favours placebo	

Comparison 6. Timing of steroids

Outcome or subgroup title	No. of studies	No. of partici- pants	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 antibi- otic	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 antibi- otic	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 antibi- otic	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]

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Random, 95% CI		IV, Random, 95% CI
6.1.1 Before or with first do	ose antibiotic				
Bademosi 1979	12/24	11/28		6.65%	1.27[0.69,2.34]
de Gans 2002	11/157	21/144		5.44%	0.48[0.24,0.96]
Girgis 1989	21/225	43/245	+	9.12%	0.53[0.33,0.87]
Kanra 1995	2/29	1/27		0.58%	1.86[0.18,19.38]
Kilpi 1995	0/32	0/26			Not estimable
Mathur 2013	5/40	16/40	+	3.48%	0.31[0.13,0.77]
Molyneux 2002	96/305	91/293	-	18.74%	1.01[0.8,1.29]
Nguyen 2007	22/217	26/218	+	8.05%	0.85[0.5,1.45]
Odio 1991	1/52	1/49		0.43%	0.94[0.06,14.65]
Peltola 2007	23/166	26/163	+	8.44%	0.87[0.52,1.46]
Qazi 1996	12/48	5/41		3.15%	2.05[0.79,5.33]
Scarborough 2007	129/231	120/228	-	22.38%	1.06[0.9,1.26]
Schaad 1993	0/60	0/55			Not estimable
Subtotal (95% CI)	1586	1557	•	86.45%	0.87[0.69,1.09]
	Favou	rs corticosteroids	0.05 0.2 1 5 20	Favours placebo	

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Random, 95% CI		IV, Random, 95% CI
Total events: 334 (Corticosteroids)	, 361 (Placebo)				
Heterogeneity: Tau ² =0.06; Chi ² =20.	.8, df=10(P=0.02); l ² =51.	91%			
Test for overall effect: Z=1.22(P=0.2	22)				
6.1.2 After first dose antibiotic					
Bennett 1963	16/38	22/47	_ _	9.32%	0.9[0.56,1.46]
Bhaumik 1998	1/14	3/16		0.69%	0.38[0.04,3.26]
DeLemos 1969	2/54	1/63		0.57%	2.33[0.22,25.03]
King 1994	0/50	1/51	•	0.32%	0.34[0.01,8.15]
Lebel 1988a	0/51	1/49	•	0.32%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30	├───	0.32%	0.32[0.01,7.63]
Thomas 1999	3/31	5/29	t	1.7%	0.56[0.15,2.14]
Wald 1995	1/69	0/74		0.32%	3.21[0.13,77.6]
Subtotal (95% CI)	389	408	•	13.55%	0.83[0.55,1.26]
Total events: 23 (Corticosteroids),	34 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =3.35, o	df=7(P=0.85); I ² =0%				
Test for overall effect: Z=0.87(P=0.3	38)				
Total (95% CI)	1975	1965	•	100%	0.87[0.73,1.05]
Total events: 357 (Corticosteroids)					
Heterogeneity: Tau ² =0.03; Chi ² =24.		6.79%			
Test for overall effect: Z=1.45(P=0.1					
Test for subgroup differences: Chi ²		0%			
			0.05 0.2 1 5 20	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
6.2.1 Before or with first dose	antibiotic				
Girgis 1989	3/190	6/177	+	3.38%	0.47[0.12,1.83]
Kanra 1995	0/27	2/26		0.71%	0.19[0.01,3.84]
Kilpi 1995	1/32	3/26		1.31%	0.27[0.03,2.45]
Molyneux 2002	38/147	39/158	-	42.55%	1.05[0.71,1.54]
Nguyen 2007	7/180	16/177		8.51%	0.43[0.18,1.02]
Odio 1991	3/51	7/48		3.79%	0.4[0.11,1.47]
Peltola 2007	10/135	12/131	+	9.82%	0.81[0.36,1.81]
Qazi 1996	1/26	1/25		0.86%	0.96[0.06,14.55]
Scarborough 2007	12/96	12/99	_	11.3%	1.03[0.49,2.18]
Schaad 1993	2/60	4/55		2.31%	0.46[0.09,2.4]
Subtotal (95% CI)	944	922	•	84.53%	0.81[0.62,1.07]
Total events: 77 (Corticosteroids	s), 102 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =8.2	1, df=9(P=0.51); I ² =0%				
Test for overall effect: Z=1.5(P=0	0.13)				
6.2.2 After first dose antibiotic	:				
Bhaumik 1998	2/13	2/13		1.95%	1[0.16,6.07]
King 1994	2/48	3/45		2.09%	0.63[0.11,3.57]
	Favou	rs corticosteroids 0.0	02 0.1 1 10	⁵⁰ Favours placebo	

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Study or subgroup	Corticosteroids	Placebo	R	sk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fi	xed, 95% CI		IV, Fixed, 95% CI
Lebel 1988a	2/43	8/38		_	2.87%	0.22[0.05,0.98]
Lebel 1988b	1/49	5/46		<u> </u>	1.43%	0.19[0.02,1.55]
Lebel 1989	1/31	2/29	+		1.15%	0.47[0.04,4.89]
Wald 1995	3/7	10/72			5.97%	3.09[1.1,8.65]
Subtotal (95% CI)	191	243		•	15.47%	0.89[0.47,1.68]
Total events: 11 (Corticosteroids	s), 30 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =11.	52, df=5(P=0.04); l ² =56.59%	6				
Test for overall effect: Z=0.37(P=	0.71)					
Total (95% CI)	1135	1165		•	100%	0.82[0.64,1.06]
Total events: 88 (Corticosteroids	s), 132 (Placebo)					
Heterogeneity: Tau ² =0; Chi ² =19.	79, df=15(P=0.18); I ² =24.19	%				
Test for overall effect: Z=1.52(P=	0.13)					
Test for subgroup differences: Cl	hi ² =0.06, df=1 (P=0.8), I ² =0 ⁰	%				
	Favour	s corticosteroids	0.02 0.1	1 10	⁵⁰ Favours placebo	

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

6.3.1 Before or with antibiotics de Gans 2002 Girgis 1989 Kanra 1995	n/N 13/143 3/190 2/27 5/59	n/N 14/119 6/177 8/26	IV, Fixed, 95% Cl	3.26%	IV, Fixed, 95% Cl 0.77[0.38,1.58]
de Gans 2002 Girgis 1989	3/190 2/27	6/177			0.77[0.38,1.58]
Girgis 1989	3/190 2/27	6/177			0.77[0.38,1.58]
-	2/27				
Kanra 1995		8/26		0.89%	0.47[0.12,1.83]
	5/59			0.79%	0.24[0.06,1.03]
Kilpi 1995		16/54	—+—	1.91%	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	-+-	14.92%	1.14[0.82,1.6]
Nguyen 2007	24/180	37/177	-+	7.53%	0.64[0.4,1.02]
Odio 1991	3/50	7/44		1%	0.38[0.1,1.37]
Peltola 2007	10/135	12/131	<u> </u>	2.57%	0.81[0.36,1.81]
Qazi 1996	28/36	32/35	-	40.79%	0.85[0.7,1.04]
Scarborough 2007	30/96	36/99	+	10.67%	0.86[0.58,1.28]
Schaad 1993	3/60	8/55		1.02%	0.34[0.1,1.23]
Subtotal (95% CI)	1158	1099	•	87.56%	0.8[0.7,0.92]
Total events: 176 (Corticosteroids), 232	l (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =18.93, df=	11(P=0.06); l ² =41.99	6			
Test for overall effect: Z=3.11(P=0)					
6.3.2 After first dose of antibiotics					
Bhaumik 1998	4/14	3/16		0.96%	1.52[0.41,5.67]
King 1994	5/48	5/45		1.21%	0.94[0.29,3.02]
Lebel 1988a	9/43	16/38	-+	3.49%	0.5[0.25,0.99]
Lebel 1988b	7/49	14/46		2.52%	0.47[0.21,1.06]
Lebel 1989	3/30	5/29		0.93%	0.58[0.15,2.21]
Wald 1995	10/67	17/72	-+	3.33%	0.63[0.31,1.28]
Subtotal (95% CI)	251	246	•	12.44%	0.62[0.43,0.89]
Total events: 38 (Corticosteroids), 60 (F	Placebo)				
Heterogeneity: Tau ² =0; Chi ² =3.13, df=5	(P=0.68); I ² =0%				
Test for overall effect: Z=2.61(P=0.01)					
	Favour	s corticosteroids 0.01	0.1 1 10	¹⁰⁰ Favours placebo	

Corticosteroids for acute bacterial meningitis (Review)



Study or subgroup	Corticosteroids	Placebo			Risk Ratio	D		Weight	Risk Ratio
	n/N	n/N		IV, Fixed, 95% CI					IV, Fixed, 95% CI
Total (95% CI)	1409	1345			•			100%	0.78[0.68,0.88]
Total events: 214 (Corticoste	eroids), 292 (Placebo)								
Heterogeneity: Tau ² =0; Chi ² :	=23.86, df=17(P=0.12); l ² =28.75	%							
Test for overall effect: Z=3.83	3(P=0)								
Test for subgroup difference	es: Chi²=1.8, df=1 (P=0.18), I²=44	1.3%							
	Favours	s corticosteroids	0.01	0.1	1	10	100	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
6.4.1 Before or with first do	se antibiotic				
de Gans 2002	18/143	24/119		11.58%	0.62[0.36,1.09]
Kanra 1995	3/27	2/26		- 1.25%	1.44[0.26,7.96]
Kilpi 1995	2/31	2/26 -		1.02%	0.84[0.13,5.55]
Molyneux 2002	69/223	57/209	<mark></mark>	41.61%	1.13[0.84,1.52]
Peltola 2007	10/139	21/137		7.12%	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	•	76.87%	0.91[0.73,1.13]
Total events: 123 (Corticoste	roids), 132 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	7.51, df=5(P=0.19); I ² =33.41%				
Test for overall effect: Z=0.88	(P=0.38)				
6.4.2 After first dose antibio	otic				
Bhaumik 1998	3/13	2/13		- 1.39%	1.5[0.3,7.55]
Lebel 1988a	5/48	8/43	t	3.37%	0.56[0.2,1.58]
Lebel 1988b	9/47	10/45		5.65%	0.86[0.39,1.92]
Lebel 1989	4/28	5/26		2.52%	0.74[0.22,2.47]
Thomas 1999	5/28	9/24	i	4.05%	0.48[0.18,1.23]
Wald 1995	9/68	14/74	_	6.14%	0.7[0.32,1.51]
Subtotal (95% CI)	232	225		23.13%	0.7[0.47,1.04]
Total events: 35 (Corticoster			-		
Heterogeneity: Tau ² =0; Chi ² =					
Test for overall effect: Z=1.75					
Total (95% CI)	893	846	•	100%	0.85[0.71,1.03]
Total events: 158 (Corticoste					
Heterogeneity: Tau ² =0; Chi ² =					
Test for overall effect: Z=1.61					
Test for subgroup differences	s: Chi ² =1.23, df=1 (P=0.27), I ² =	18.69%			
	Favou	rs corticosteroids 0.1	0.2 0.5 1 2 5	¹⁰ Favours placebo	

Comparison 7. Study quality

Outcome or subgroup title	No. of studies	No. of partici- pants	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 neurologi- cal 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]

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

Study or subgroup	Corticosteroids	Placebo			Risk Ratio			Weight	Risk Ratio	
	n/N	n/N		IV, Fixed, 95% CI					IV, Fixed, 95% CI	
7.1.1 High quality										
de Gans 2002	11/157	21/144		_				2.62%	0.48[0.24,0.96]	
Molyneux 2002	96/305	91/293			+			22.26%	1.01[0.8,1.29]	
Nguyen 2007	22/217	26/218			-+-			4.38%	0.85[0.5,1.45]	
Scarborough 2007	129/231	120/228			÷			44.45%	1.06[0.9,1.26]	
Subtotal (95% CI)	910	883			•			73.71%	1[0.88,1.14]	
Total events: 258 (Corticoste	eroids), 258 (Placebo)									
Heterogeneity: Tau ² =0; Chi ² =	=5.13, df=3(P=0.16); I ² =41.52%									
Test for overall effect: Z=0.06	6(P=0.95)									
7.1.2 Medium quality										
	Favou	s corticosteroids	0.01	0.1	1	10	100	Favours placebo		

Corticosteroids for acute bacterial meningitis (Review)



Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
DeLemos 1969	2/54	1/63	+	0.22%	2.33[0.22,25.03]
Kanra 1995	2/29	1/27	+	0.23%	1.86[0.18,19.38]
King 1994	0/50	1/51		0.12%	0.34[0.01,8.15]
Lebel 1988a	0/51	1/49		0.12%	0.32[0.01,7.68]
Lebel 1988b	0/51	0/49			Not estimable
Lebel 1989	0/31	1/30	+	0.13%	0.32[0.01,7.63]
Mathur 2013	5/40	16/40		1.54%	0.31[0.13,0.77]
Odio 1991	1/52	1/49		0.17%	0.94[0.06,14.65]
Peltola 2007	23/166	26/163	-+-	4.69%	0.87[0.52,1.46]
Qazi 1996	12/48	5/41		1.38%	2.05[0.79,5.33]
Sankar 2007	0/12	1/13 —	+	0.13%	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		0.12%	3.21[0.13,77.6
Subtotal (95% CI)	744	733	•	9.56%	0.81[0.57,1.17
Total events: 49 (Corticoster	oids), 59 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	=11.43, df=11(P=0.41); l ² =3.76%	6			
Test for overall effect: Z=1.11	L(P=0.27)				
7.1.3 Low quality					
Bademosi 1979	12/24	11/28	_ + _	3.38%	1.27[0.69,2.34
Belsey 1969	2/43	1/43		0.23%	2[0.19,21.24
Bennett 1963	16/38	22/47	_+_	5.43%	0.9[0.56,1.46]
Bhaumik 1998	1/14	3/16		0.27%	0.38[0.04,3.26
Ciana 1995	8/34	12/36	+	2.17%	0.71[0.33,1.51
Girgis 1989	21/225	43/245		5.25%	0.53[0.33,0.87
Kilpi 1995	0/32	0/26			Not estimable
Subtotal (95% CI)	410	441	•	16.73%	0.79[0.6,1.04
Total events: 60 (Corticoster	oids), 92 (Placebo)				- /
	=6.26, df=5(P=0.28); l ² =20.14%				
Test for overall effect: Z=1.68					
	()				
	2064	2057	•	100%	0.95[0.85,1.06
Total (95% CI)					
Total (95% CI) Total events: 367 (Corticoste	eroids), 409 (Placebo)				
Total events: 367 (Corticoste	eroids), 409 (Placebo) =25.92, df=21(P=0.21); l²=18.99	%			
Total events: 367 (Corticoste	=25.92, df=21(P=0.21); l ² =18.99	%			

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

Study or subgroup	Corticosteroids	s Placebo Risk Ratio		io	Weight	Risk Ratio	
	n/N	n/N	IV, Fixed, 95	5% CI		IV, Fixed, 95% CI	
7.2.1 High quality							
Molyneux 2002	31/147	27/158			34.36%	1.23[0.78,1.96]	
Nguyen 2007	7/180	16/177			9.94%	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 (Corticoster	oids), 55 (Placebo)						
	Favour	s corticosteroids	0.01 0.1 1	10	¹⁰⁰ Favours placebo		

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Heterogeneity: Tau ² =0; Chi ² =	4.45, df=2(P=0.11); I ² =55.09%				
Test for overall effect: Z=0.07	(P=0.94)				
7.2.2 Medium quality					
Kanra 1995	0/27	2/26		0.83%	0.19[0.01,3.84]
King 1994	2/48	3/45		2.44%	0.63[0.11,3.57]
Lebel 1988a	2/43	8/38	+	3.35%	0.22[0.05,0.98]
Lebel 1988b	1/49	5/46		1.67%	0.19[0.02,1.55]
Lebel 1989	1/31	2/29		1.35%	0.47[0.04,4.89]
Odio 1991	3/51	7/44		4.45%	0.37[0.1,1.34]
Peltola 2007	10/135	12/131	+	11.47%	0.81[0.36,1.81]
Qazi 1996	1/26	1/25		1%	0.96[0.06,14.55]
Schaad 1993	2/60	4/55		2.7%	0.46[0.09,2.4]
Wald 1995	3/68	10/74		4.76%	0.33[0.09,1.14]
Subtotal (95% CI)	538	513	•	34.01%	0.47[0.29,0.75]
Total events: 25 (Corticostero	oids), 54 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =	4.64, df=9(P=0.86); I ² =0%				
Test for overall effect: Z=3.17	(P=0)				
7.2.3 Low quality					
Belsey 1969	0/41	1/42 —		0.74%	0.34[0.01,8.14]
Bhaumik 1998	2/13	2/13		2.28%	1[0.16,6.07]
Girgis 1989	3/190	6/177		3.95%	0.47[0.12,1.83]
Kilpi 1995	1/32	3/26	ł	1.53%	0.27[0.03,2.45]
Subtotal (95% CI)	276	258		8.49%	0.5[0.2,1.29]
Total events: 6 (Corticosteroi	ds), 12 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =					
Test for overall effect: Z=1.43					
Total (95% CI)	1237	1205	•	100%	0.72[0.55,0.95]
Total events: 81 (Corticostero	oids), 121 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =					
Test for overall effect: Z=2.32					
	:: Chi ² =6.74, df=1 (P=0.03), I ² =				

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

Study or subgroup	Corticosteroids	Placebo		Risk Ratio		Weight	Risk Ratio	
	n/N	n/N		IV, Fixed, 95%	CI		IV, Fixed, 95% CI	
7.3.1 High quality								
de Gans 2002	13/143	14/119		+		3.29%	0.77[0.38,1.58]	
Molyneux 2002	49/147	43/158		+-		14.31%	1.22[0.87,1.73]	
Nguyen 2007	21/180	37/177		-+-		6.89%	0.56[0.34,0.91]	
Scarborough 2007	30/96	36/99		-+-		10.76%	0.86[0.58,1.28]	
Subtotal (95% CI)	566	553		•		35.24%	0.9[0.73,1.12]	
Total events: 113 (Corticoste	eroids), 130 (Placebo)							
Heterogeneity: Tau ² =0; Chi ² =	=6.94, df=3(P=0.07); I ² =56.74%							
Test for overall effect: Z=0.92	2(P=0.36)							
	Favou	rs corticosteroids	0.01 0.1	. 1	10 1	⁰⁰ Favours placebo		

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI		IV, Fixed, 95% CI
7.3.2 Medium quality					
Kanra 1995	2/27	8/26		0.79%	0.24[0.06,1.03
King 1994	5/48	5/45	<u> </u>	1.22%	0.94[0.29,3.02
Lebel 1988a	9/43	16/38	+	3.52%	0.5[0.25,0.99
Lebel 1988b	7/49	14/46	— I	2.54%	0.47[0.21,1.06
Lebel 1989	3/30	5/29		0.94%	0.58[0.15,2.21
Mathur 2013	6/35	10/24		2.22%	0.41[0.17,0.98
Odio 1991	3/50	7/44		1.01%	0.38[0.1,1.37
Peltola 2007	10/135	12/131	<u> </u>	2.6%	0.81[0.36,1.81
Qazi 1996	28/36	32/35	-	41.15%	0.85[0.7,1.04
Sankar 2007	3/12	3/12	_	0.87%	1[0.25,4
Schaad 1993	3/60	8/55		1.03%	0.34[0.1,1.23
Wald 1995	10/68	17/72	+ _	3.35%	0.62[0.31,1.26
Subtotal (95% CI)	593	557	◆	61.25%	0.73[0.62,0.87
Total events: 89 (Corticosteroids),	137 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =11.53,)			
Test for overall effect: Z=3.66(P=0)					
7.3.3 Low quality					
Belsey 1969	0/41	1/42	+	0.17%	0.34[0.01,8.14
Bhaumik 1998	4/14	3/16		0.97%	1.52[0.41,5.67
Girgis 1989	3/190	6/177	_	0.89%	0.47[0.12,1.83
Kilpi 1995	5/31	6/26	—— —	1.48%	0.7[0.24,2.03
Subtotal (95% CI)	276	261	•	3.51%	0.76[0.38,1.51
Total events: 12 (Corticosteroids),	16 (Placebo)		•		
Heterogeneity: Tau ² =0; Chi ² =1.84, o					
Test for overall effect: Z=0.79(P=0.4					
Total (95% CI)	1435	1371	▲	100%	0 70[0 60 0 6
Total events: 214 (Corticosteroids)		13/1	V	100%	0.79[0.69,0.9
		204			
Heterogeneity: Tau ² =0; Chi ² =22.52,	, ai=19(P=0.26); i=15.63	5%0			
Test for overall effect: Z=3.56(P=0)		0.000/			
Test for subgroup differences: Chi ²		9.98%	0.1 1 10	100 Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo			Risk Ratio			Weight	Risk Ratio	
	n/N	n/N		IV, Fixed, 95% CI					IV, Fixed, 95% CI	
7.4.1 High quality										
de Gans 2002	18/143	24/119			-+			11.31%	0.62[0.36,1.09]	
Molyneux 2002	69/223	56/209			-			40.08%	1.15[0.86,1.56]	
Scarborough 2007	21/98	26/104			-+-			13.96%	0.86[0.52,1.42]	
Subtotal (95% CI)	464	432			•			65.35%	0.97[0.77,1.23]	
Total events: 108 (Corticoste	roids), 106 (Placebo)									
Heterogeneity: Tau ² =0; Chi ² =	3.92, df=2(P=0.14); l ² =49.02%									
Test for overall effect: Z=0.22	(P=0.83)									
	Favour	s corticosteroids	0.01	0.1	1	10	100	Favours placebo		

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Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV, Fixed, 95% CI	-	IV, Fixed, 95% CI
7.4.2 Medium quality					
Kanra 1995	3/27	2/26		1.22%	1.44[0.26,7.96]
Lebel 1988a	5/48	8/43	+	3.29%	0.56[0.2,1.58]
Lebel 1988b	9/47	10/45		5.52%	0.86[0.39,1.92]
Lebel 1989	4/28	5/26		2.46%	0.74[0.22,2.47]
Peltola 2007	10/139	21/137	_ -	6.95%	0.47[0.23,0.96]
Sankar 2007	0/12	1/12 -		0.37%	0.33[0.01,7.45]
Thomas 1999	5/28	9/24	+	3.96%	0.48[0.18,1.23]
Wald 1995	9/68	14/74	-+	5.99%	0.7[0.32,1.51]
Subtotal (95% CI)	397	387	•	29.77%	0.63[0.45,0.89]
Total events: 45 (Corticosteroids	i), 70 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =2.83	3, df=7(P=0.9); l ² =0%				
Test for overall effect: Z=2.62(P=	0.01)				
7.4.3 Low quality					
Bhaumik 1998	3/13	2/13	++	1.36%	1.5[0.3,7.55]
Ciana 1995	5/26	7/24	+	3.52%	0.66[0.24,1.8]
Subtotal (95% CI)	39	37	-	4.88%	0.83[0.35,1.95]
Total events: 8 (Corticosteroids),	, 9 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =0.72	2, df=1(P=0.4); I ² =0%				
Test for overall effect: Z=0.43(P=	0.67)				
Total (95% CI)	900	856	•	100%	0.85[0.7,1.03]
Total events: 161 (Corticosteroid	ls), 185 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =11.6	68, df=12(P=0.47); l ² =0%				
Test for overall effect: Z=1.7(P=0.	.09)				
Test for subgroup differences: Ch	ni²=4.2, df=1 (P=0.12), I²=5	2.41%			
	Favou	s corticosteroids 0.01	0.1 1 10	¹⁰⁰ Favours placebo	

Comparison 8. Sensitivity analysis - worst-case scenario

Outcome or subgroup title	No. of studies	No. of partici- pants	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 se- quelae	13	1850	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.82, 1.18]
4 Long-term neurological se- quelae	13	1758	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.78, 1.78]

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% Cl
Belsey 1969	0/41	1/42 —		1.61%	0.34[0.01,8.14]
Bhaumik 1998	2/13	2/13		3.92%	1[0.16,6.07]
Girgis 1989	16/204	5/202		7.53%	3.17[1.18,8.49]
Kanra 1995	0/27	2/26		1.78%	0.19[0.01,3.84]
Kilpi 1995	2/32	3/26		4.2%	0.54[0.1,3]
King 1994	4/50	3/50		5.19%	1.33[0.31,5.65]
Lebel 1988a	10/51	8/48		8.42%	1.18[0.51,2.73]
Lebel 1988b	3/51	5/49		5.48%	0.58[0.15,2.28]
Lebel 1989	2/31	2/29		3.66%	0.94[0.14,6.21]
Molyneux 2002	100/206	27/200	-+-	11.31%	3.6[2.46,5.25]
Nguyen 2007	22/195	16/191		9.91%	1.35[0.73,2.48]
Odio 1991	3/50	7/48	+	5.86%	0.41[0.11,1.5]
Peltola 2007	18/143	12/137	- + •	9.39%	1.44[0.72,2.87]
Qazi 1996	11/36	1/36	+	- 3.4%	11[1.5,80.82]
Scarborough 2007	13/102	7/108		8.19%	1.97[0.82,4.73]
Schaad 1993	2/60	4/55		4.38%	0.46[0.09,2.4]
Wald 1995	3/68	7/74		5.78%	0.47[0.13,1.73]
Total (95% CI)	1360	1334	•	100%	1.25[0.81,1.93]
Total events: 211 (Corticostero	ids), 112 (Placebo)				
Heterogeneity: Tau ² =0.39; Chi ²	=40.05, df=16(P=0); l ² =60.05	5%			
Test for overall effect: Z=1.02(P	=0.31)				

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

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio	
	n/N	n/N	M-H, Random, 95% Cl		M-H, Random, 95% CI	
Belsey 1969	0/41	1/42 —		0.91%	0.34[0.01,8.14]	
Bhaumik 1998	4/14	3/16		3.49%	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	+	5.01%	2.81[1.13,6.97]	
Kanra 1995	2/27	8/26		3.09%	0.24[0.06,1.03]	
Kilpi 1995	5/32	8/26	+	4.66%	0.51[0.19,1.37]	
King 1994	7/50	5/50		4.31%	1.4[0.48,4.12]	
Lebel 1988a	17/51	16/48	_ + _	6.68%	1[0.57,1.75]	
Lebel 1988b	9/51	14/49	+	5.79%	0.62[0.29,1.29]	
Lebel 1989	4/31	5/29		3.81%	0.75[0.22,2.52]	
Mathur 2013	6/35	10/24	+	5.19%	0.41[0.17,0.98]	
Molyneux 2002	120/206	46/200	-	7.87%	2.53[1.92,3.35]	
Nguyen 2007	36/195	37/177	-+-	7.36%	0.88[0.59,1.33]	
Odio 1991	4/51	7/48		3.99%	0.54[0.17,1.72]	
Peltola 2007	18/143	12/137		6.03%	1.44[0.72,2.87]	
Qazi 1996	21/36	5/36	│ <u> </u> +	5.24%	4.2[1.78,9.91]	
Sankar 2007	3/12	3/12		3.27%	1[0.25,4]	
Scarborough 2007	36/102	36/99	-+-	7.53%	0.97[0.67,1.41]	
Schaad 1993	3/60	8/55		3.61%	0.34[0.1,1.23]	
Wald 1995	11/69	17/74	+	6.07%	0.69[0.35,1.38]	

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Study or subgroup	Corticosteroids	Placebo Risk Ratio			Weight	Risk Ratio			
	n/N	n/N		м-н,	Random, 95	% CI			M-H, Random, 95% CI
Total (95% CI)	1556	1473			•			100%	0.98[0.71,1.35]
Total events: 339 (Corticoster	roids), 261 (Placebo)								
Heterogeneity: Tau ² =0.32; Ch	i ² =69.43, df=19(P<0.0001); I ² =	72.63%							
Test for overall effect: Z=0.11	(P=0.91)								
	Favour	s corticosteroids	0.01	0.1	1	10	100	Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Bhaumik 1998	3/13	2/13		1.09%	1.5[0.3,7.55]
Ciana 1995	5/26	7/24	+ <u>-</u>	3.96%	0.66[0.24,1.8]
de Gans 2002	21/143	24/123	-+-	14.04%	0.75[0.44,1.28]
Kanra 1995	3/27	2/26		1.11%	1.44[0.26,7.96]
Lebel 1988a	8/51	8/48	<u> </u>	4.49%	0.94[0.38,2.31]
Lebel 1988b	13/51	10/49		5.55%	1.25[0.6,2.58]
Lebel 1989	7/31	5/26	<u> </u>	2.96%	1.17[0.42,3.26]
Molyneux 2002	68/209	56/202		30.99%	1.17[0.87,1.58]
Peltola 2007	14/143	21/137	-+	11.67%	0.64[0.34,1.2]
Sankar 2007	0/12	1/12		0.82%	0.33[0.01,7.45]
Scarborough 2007	25/102	26/104	_ + _	14.01%	0.98[0.61,1.58]
Thomas 1999	5/28	9/108		2.02%	2.14[0.78,5.89]
Wald 1995	9/68	14/74	-+-	7.3%	0.7[0.32,1.51]
Total (95% CI)	904	946	•	100%	0.98[0.82,1.18]
Total events: 181 (Corticosteroid	ls), 185 (Placebo)				
Heterogeneity: Tau ² =0; Chi ² =9.22	2, df=12(P=0.68); I ² =0%				
Test for overall effect: Z=0.19(P=0	0.85)				
· · ·	Fourier	rs corticosteroids	0.01 0.1 1 10	¹⁰⁰ Favours placebo	

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

Study or subgroup	Corticosteroids	Placebo		Risk Ratio			Weight	Risk Ratio
	n/N	n/N		M-H, Random, 9	5% CI			M-H, Random, 95% CI
DeLemos 1969	14/53	2/61			+	_	5.81%	8.06[1.92,33.84]
Girgis 1989	1/190	2/177			_		2.58%	0.47[0.04,5.09]
Kanra 1995	1/27	1/26					2.06%	0.96[0.06,14.6]
Kilpi 1995	3/32	2/26		+			4.47%	1.22[0.22,6.76]
King 1994	5/48	3/45		+			6.18%	1.56[0.4,6.16]
Lebel 1988a	14/51	3/48			•		7.5%	4.39[1.35,14.34]
Lebel 1988b	10/51	6/49			-		9.78%	1.6[0.63,4.07]
Lebel 1989	7/31	5/29			-		8.82%	1.31[0.47,3.67]
Nguyen 2007	81/195	83/192		+			18.46%	0.96[0.76,1.21]
Odio 1991	5/51	15/48		•			9.79%	0.31[0.12,0.8]
Qazi 1996	10/35	8/36		-+			11.22%	1.29[0.57,2.88]
Schaad 1993	3/60	5/55		·	1		6.11%	0.55[0.14,2.19]
	Favou	rs corticosteroids	0.01	0.1 1	10	100	Favours placebo	

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Study or subgroup	Corticosteroids	Placebo			Risk Ratio			Weight	Risk Ratio
	n/N	n/N		М-Н, Р	Random, 95	% CI			M-H, Random, 95% CI
Wald 1995	4/68	6/74			+			7.21%	0.73[0.21,2.46]
Total (95% CI)	892	866			•			100%	1.18[0.78,1.78]
Total events: 158 (Corticoste	eroids), 141 (Placebo)								
Heterogeneity: Tau ² =0.23; C	hi ² =23.98, df=12(P=0.02); l ² =49	.97%							
Test for overall effect: Z=0.79	9(P=0.43)					1	1		
	Favour	s corticosteroids	0.01	0.1	1	10	100	Favours placebo	

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 the 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 the 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 the 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

For the 2013 update we searched, as in previous years, the Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 12) (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).

Appendix 3. MEDLINE (Ovid) search strategy

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/9-15 178 and 16 Appendix 4. 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 5. Web of Science (Thomson Reuters) search strategy

# 3	32
# 2	217,233
#1	263

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Appendix 6. 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 7. 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 Corticosteroides OR Corticoids OR MH:D06.472.040\$ OR MH:glucocorticoids OR glucocorticoid \$ OR Glucocorticoides OR Glicocorticoides OR MH:steroids OR Esteroides OR Esteroides OR MH:D04.808\$ OR MH:Dexamethasone OR Dexametasona OR Hexadecadrol OR Hydrocortisone OR Hidrocortisona OR Cortisol OR MH:methylprednisolone OR MH:prednisolone OR prednisolone \$ clinical_trials

FEEDBACK

Corticosteroids for acute bacterial meningitis, 3 October 2015

Summary

We have read with interest the updated Review on Corticosteroids for acute bacterial meningitis. We would specifically like to comment on the subject of 'any hearing loss in adults'.

The figure for Analysis 3.2 contains some typographical errors. The figures quoted for the Scarborough (2007) paper for any hearing loss in adults (21/180 on corticosteroids and 37/177 on placebo) are in fact from the paper by Nguyen (2007). The figures quoted for the Thomas (1999) paper (30/96 on corticosteroids and 36/99 on placebo) are in fact the figures from the paper by Scarborough (2007). These errors are not present in other figures for the quoted papers. The Thomas (1999) paper is misplaced in Analysis 3.2.

Analysis 5.10 regroups four studies on any hearing loss in adults according to country income, be it high or low-income. The Scarborough (2007) paper is from Malawi and correctly categorised as from a low income country. The Bhaumik (1998) paper is categorised as from a high income country, but is in fact from India. The earlier text and all other analyses all place the Bhaumik paper in a low income country category. The Nguyen (2007) paper is categorised as from a high income country, but is in fact from Viet Nam. The World Bank defines Viet Nam as a low middle income country. In fact the World Bank now defines India as a low middle income country. The only study clearly from high income countries is that by de Gans (2002) from Europe.

Corticosteroids for acute bacterial meningitis (Review)

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The study which appears to demonstrate the greatest benefit from steroids on any hearing loss in adults is that by Nguyen (2007) in Viet Nam. In that paper the authors comment on the high proportion of cases of meningitis due to Streptococcus suis, and in Asia this is a recognised cause of deafness. However S.suis is not a cause of meningitis in high income countries. This is another reason why placing the Nguyen study in the high income category is inappropriate. The distinction between adults and children varies by study and the Nguyen paper included individuals over 14 years of age. There is clear evidence for benefit from steroids in reducing deafness from Haemophilus influenzae meningitis in children (Analysis 4.3), but in high income countries the incidence of H.influenzae infection has declined considerably with immunisation (Okike et al, 2014).

Reference

Okike IO et al. Trends in bacterial, mycobacterial, and fungal meningitis in England and Wales 2004-11: an observational study. Lancet Infectious Diseases 2014;14:301-7.

Yours sincerely,

Rebacca Wong, Medical Student, Medical Student Cameron Goodwin, Medical Student Dr P Venkatesan, Consultant in Infectious Diseases Affiliation: Nottingham University Hospitals NHS Trust, City Campus, Nottingham. NG5 1PB. United Kingdom.

I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Analysis 3.2 on any hearing loss have been updated to display the correct names with the figures.

Analysis 5.10 has been updated with Bhaumik 1998 in the low-income countries, which did not change the results. 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). We used the UNHDI score that was given to the country at the time the study was performed.

We agree there are differences in epidemiology between studies, therefore we also performed a subgroup analysis for the major pathogens (Analysis 4.1; Analysis 4.2; Analysis 4.3). For all other analyses we pooled all available data irrespective of epidemiology to find an overall effect. We agree that changes in epidemiology over time have occurred, which however, does not influence the results of the meta-analysis. In the applicability of the results it is good to realize the RCTs were performed in different time periods and multiple countries with variable epidemiology.

Contributors

Matthijs Brouwer Diederik van de Beek

Corticosteroids for acute bacterial meningitis, 16 October 2015

Summary

In their review titled, "Corticosteroids for acute bacterial meningitis", Brouwer et al. conclude that corticosteroids should be given to patients with acute bacterial meningitis in high-income countries, citing a significant reduction in hearing loss and neurological sequelae with corticosteroids.1 In addition, Brouwer et al. state that corticosteroids provide no mortality benefit in treatment of acute bacterial meningitis. We feel that the results of this systematic review and meta-analysis require further context.

Our assessment of trials included in the review that reported mortality and were deemed to be free of bias reveals an issue that we would like to highlight. Pooling the data for effect of corticosteroids on mortality resulted in a non-statistically significant difference (RR 0.90, 95% CI 0.80, 1.01). A surprising inclusion in the meta-analysis was the trial by Scarborough et al., since the population in the trial were primarily patients who were HIV positive (89.7%) with a mean CD4 count of 102/mm3 (IQR 51 to 169).2 The inclusion of this trial adds significant clinical heterogeneity, since HIV positive patients would be expected to respond in a manner different from their immunocompetent counterparts. A sensitivity analysis that excludes the Scarborough et al. trial from the pooled data results in a statistically significant difference in mortality (RR 0.83, 95% CI 0.72, 0.97). While one may argue that the upper bound of the confidence interval is close to the line of no difference, it is important to present the data this way as it is more reflective of the results of a pooling of less heterogeneous data and suggests that there may be benefit in an immunocompetent population.

Four trials included in this review and meta-analysis were deemed to be free of bias (Scarborough 2007, Molyneux 2002, de Gans 2002, Nguyen 2007).2-5 Our assessment is that bias is present in all of these studies that would affect interpretation of the final results. In all four trials, selective outcome reporting is present. Specifically, none of the trials reported all adverse events (AE). In addition, serious adverse events (SAE) data was not included in any of the trials. In two trials, AE were reported only if they were deemed by the investigator to be



due to the study drug: the Scarborough et al. trial reported that, "[n]ineteen patients had adverse events that were more likely to be due to antibiotics than corticosteroids", while the Molyneux et al. trial reported, "[w]e recorded no deleterious side-effects attributable to use of dexamethasone.".2,3 Another issue with AE reporting in all four trials is the absence of details on how AE were recorded, specifically whether all AE were recorded or if only the first AE reported was recorded. The selective reporting present in these trials impacts the interpretation of the results of the meta-analysis, since a lack of AE data prevents clinicians from determining the net clinical benefit of adjunctive corticosteroids in acute bacterial meningitis.

We respectfully suggest the authors of this review revisit the inclusion of the Scarborough et al. trial in the pooling of mortality data and provide context for interpretation of subsequent results. In addition, a revision of the risk of bias table should be considered to provide readers with appropriate context with which to interpret the results, namely that AE were likely underreported in trials.

References:

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I agree with the conflict of interest statement below:

I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Based on the chosen inclusion criteria we did not exclude studies from countries with high HIV positivity rates. To identify differences between areas of inclusion, which include HIV positivity but also e.g. malnourishment and access to health care, we performed the subgroup analysis by income status.

We agree there is lack of detail in the adverse events reporting in the included studies and thereby selective reporting. However, we feel this does not merit a full update of the review.

Contributors

Matthijs Brouwer Diederik van de Beek

Corticosteroids for acute bacterial meningitis, 11 September 2017

Summary

May I comment on the statistical significance of the mortality benefit of corticosteroids when used for patients with *Streptococcus pneumoniae* (pneumococcal) meningitis as shown in Analysis 4.1.

As a simple rule we consider P values < 0.05 as indicating statistical significance. On this measure Analysis 4.1 clearly shows that there is statistical significance in the effect of corticosteroids in reducing mortality in pneumococcal meningitis. On this basis numerous guidelines around the world advocate the use of corticosteroids for meningitis in adults, particularly with *St. pneumoniae*. We need to appreciate more about what underpins this calculation and I would make four points.

1) The study by Girgis *et al* (1999) is regarded as having a high risk of selection bias. Exclusion of this single study results in loss of statistical significance.

2) The study de Gans *et al* (2002) on the other hand was an excellent individual study. The overall P value being <0.05 is dependent on this study as its exclusion results in loss of statistical significance. This study included patients with suspected meningitis and any of three features : cloudy CSF, CSF leucocyte counts > 1,000 / ml and Gram stain positive CSF.

3) A further analysis of patients in the latter study by de Beek *et al* (2004) reviewed deaths within 14 days and found no difference between corticosteroid and placebo groups in those who suffered a neurological death (including brain herniation, cerebrovascular complications

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and withdrawal of care because of poor neurological process). However there was a difference, with benefit in the corticosteroid group, in those who had a 'systemic cause' of death (due to septic shock, respiratory failure, multiple-organ dysfunction and cardiac ischaemia).

4) From data in Analysis 4.1 I calculate the relative risk of mortality between the corticosteroid group (168 deaths / 561) vs placebo (203 deaths / 571) as 0.8423 (95%CI 0.7121 – 0.9964) with P = 0.0453.

Having only one less death in the placebo group (202 / 571) changes the relative risk to 0.8465 (95% CI 0.7154-1.0016) with P = 0.0522, or only one more death in the corticosteroid group (169/561) changes the relative risk to 0.8474 (95% CI 0.7166-1.0019) with P = 0.0527.

Thus is there sufficient power to reach a clinically significant conclusion and do corticosteroids benefit the brain or protect against systemic complications?

We need to be aware that corticosteroids used to be used after head injuries to reduce intra-cerebral inflammation on the basis of a number of small studies, until the large MRC CRASH study actually showed that corticosteroids increased mortality (Edwards *et al*, 2005).

References

de Beek D, de Gans J. Dexamethasone and pneumococcal meningitis. *Ann Int Med* 2004;141:327. Edwards P, Arango M, Balica L *et al.* Final results of MRC CRASH, a randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury-outcomes at 6 months. *Lancet* 2005;365:1957-9.

Dr Pradhib Venkatesan Consultant in Infectious Diseases

Reply

Indeed, exclusion of the studies by Girgis would lead to a non-significant p-value for mortality in pneumococcal meningitis. It is also correct that one less death would change the p-value towards non-significance. We would like to stress that we have included all results as they were from the studies at hand, of which the selection was based on the criteria described in the methods. In our opinion the margin by which the significance is established does not influence the conclusion of the meta-analysis.

Furthermore, in our opinion the sole focus on mortality in pneumococcal meningitis to decide to advise to for or against dexamethasone in bacterial meningitis patients is not justified. The other analyses on hearing loss, severe hearing loss and neurological sequelae also show a consistent beneficial effect of corticosteroids without harm identified in any of the RCTs.

Additional evidence of the beneficial effect of corticosteroids on mortality is presented in the section "implementation studies" which have shown a reduction in mortality in different countries following introduction of adjunctive dexamethasone as routine therapy. The identified reduction in mortality was similar as described in the European Dexamethasone trial (absolute risk reduction of 10% for mortality). The comparison to the MRC Crash study does not hold.

Contributors

Matthijs Brouwer Diederik van der Beek

Corticosteroids for acute bacterial meningitis, 9 July 2018

Summary

In this review abstract, authors report that "corticosteroids were associated with a non-significant reduction in mortality". This may be misleading, and the use of term "non-significant" does not follow Handbook recommendations.

In addition, the summary of findings table grades evidence as moderate and high quality. The methods section does not explain the application of the GRADE process. The discussion section "quality of evidence" does not clearly discuss the rationale for downgrading the quality of the body of evidence. This section also appears to confuse quality with the risk of bias assessments. We would suggest that the authors reassess using the most up-to-date GRADE methods and consider whether the certainty of evidence should be downgraded for risk of bias, inconsistency, and indirectness.

Within their conclusion the authors state: "We recommend a four day regimen of dexamethasone (0.6mg/kg daily) given before or with the first dose of antibiotics". Authors should not make recommendations. Also, this recommendation goes beyond the evidence for two reasons: the subgroup analyses (Analysis 6.1; Analysis 6.2; Analysis 6.3; Analysis 6.4) indicate little or no difference in relation to timing for primary outcomes of mortality and severe hearing loss; there are lower point estimates for the primary outcomes of any hearing loss or short-term neurologic sequelae in the subgroup receiving steroids after first dose of antibiotics.

We note that Prof Diederik van de Beek (senior author of this review) is also senior author of one of the included trials, which contributes a weight of 10% to the meta-analysis (De Gans 2002). This should be declared as a conflict of interest, and assurance given that the data extraction and quality assessment of this study was independent.



We would suggest that this review is updated to ensure transparency.

Dr Paul Hine, Clinical Research Assistant

Prof Paul Garner, Co-ordinating Editor, Cochrane Infectious Diseases Group

Reply

We did not identify the Cochrane Handbook recommendation referred to by Dr. Hine and Prof. Garner after checking the sections 11.7.1 (general methods for Cochrane reviews > 11 Presenting results > presenting results in the text > results of meta-analyses) and 11.5 (summary of findings table).

The GRADE assessment was conducted in 2014. This may not have been with the most up-to-date version that is currently available. Although we agree this may change the certainty of evidence, we do not think it justifies revision of the meta-analysis, especially since no new RCTs have been published.

We agree that the recommendation of the regimen goes beyond the results of the meta-analysis as Cochrane meta-analyses are not intended to provide recommendations. As the recommendation complies with the international guidelines on treatment for bacterial meningitis by the IDSA, ESCMID and NICE, we feel revising the meta-analysis for this purpose is not warranted.

We agree this should have been mentioned as a conflict of interest and we have now changed the statement. However, all data extracted from the de Gans 2002 study that were included in the meta-analysis can be verified in the original publication and quality assessment was based on objective criteria. Matthijs C Brouwer independently extracted data and assessed quality.

Although valid points are raised in the comments, the lack of new RCTs and thereby similar conclusions of an updated meta-analysis in our opinion argues against an update.

Contributors

Matthijs Brouwer Diederik van der Beek

WHAT'S NEW

Date	Event	Description
8 November 2018	Feedback has been incorporated	Authors responded to feedback comments

HISTORY

Protocol first published: Issue 3, 1998 Review first published: Issue 3, 2003

Date	Event	Description
20 August 2018	Feedback has been incorporated	Feedback comment added to the review.
11 March 2016	Feedback has been incorporated	Feedback comments added to the review
3 February 2015	New citation required but conclusions have not changed	Three new implementation trials included in the Discussion. Our conclusions remain unchanged.
3 February 2015	New search has been performed	Searches updated. We did not identify any new trials for inclu- sion.
18 January 2013	New search has been performed	New citation required but conclusions have not changed.
19 June 2008	New search has been performed	Converted to new review format.

Corticosteroids for acute bacterial meningitis (Review)

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Date	Event	Description
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

Matthijs C Brouwer: none known. Peter McIntyre: none known. Kameshwar Prasad: none known. Diederik van de Beek is a primary author of one of the included trials (de Gans 2002). Matthijs C Brouwer independently extracted data and assessed quality.

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Internal sources

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

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INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adolescent; Adult; Child; Humans