Corticosteroids for acute bacterial meningitis (Review)

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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 1

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[Intervention Review]

Corticosteroids for acute bacterial meningitis

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Cochrane Database of Systematic Reviews, Issue 1, 2009 (Status in this issue: *Unchanged, commented*)
Copyright © 2009 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
DOI: 10.1002/14651858.CD004405.pub2
This version first published online: 24 January 2007 in Issue 1, 2007.
Last assessed as up-to-date: 9 November 2006. (Help document - Dates and Statuses explained)

This record should be cited as: van de Beek D, de Gans J, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No.: CD004405. DOI: 10.1002/14651858.CD004405.pub2.

ABSTRACT

Background

In experimental studies, the clinical outcome of acute bacterial meningitis has been related to the severity of the inflammatory process in the subarachnoidal space. Treatment with corticosteroids can reduce this inflammatory response and thereby may improve outcome. We conducted a meta-analysis of randomised controlled trials (RCTs) of adjuvant corticosteroids in the treatment of acute bacterial meningitis.

Objectives

We conducted a systematic review examining the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.

Search strategy

In this updated review, 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); Current Contents (2001 to June 2006); and reference lists of all articles. We also contacted manufacturers and researchers in the field.

Selection criteria

Eligible published and non-published RCTs on corticosteroids as adjuvant therapy in acute bacterial meningitis. Patients of any age and in any clinical condition, treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type, could be included. At least case fatality rate or hearing loss had to be recorded for inclusion.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Adverse effects were collected from the trials. Additional analyses were performed for children and adults, causative organisms, and low-income and developed countries.

Main results

Eighteen studies involving 2750 people were included. Overall, adjuvant corticosteroids were associated with lower case fatality (relative risk (RR) 0.83, 95% CI 0.71 to 0.99), lower rates of severe hearing loss (RR 0.65, 95% CI 0.47 to 0.91) and long-term neurological

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sequelae (RR 0.67, 95% CI 0.45 to 1.00). In children, corticosteroids reduced severe hearing loss (RR 0.61, 95% CI 0.44 to 0.86). In adults, corticosteroids gave significant protection against death (RR 0.57, 95% CI 0.40 to 0.81) and short-term neurological sequelae (RR 0.42, 95% CI 0.22 to 0.87). Subgroup analysis for causative organisms showed that corticosteroids reduced mortality in patients with meningitis due to *Streptococcus pneumoniae* (RR 0.59, 95% CI 0.45 to 0.77) and reduced severe hearing loss in children with meningitis due to *Haemophilus influenzae* (RR 0.37, 95% CI 0.20 to 0.68); subgroup analysis for patients with meningococcal showed a nonsignificant favourable trend in mortality (RR 0.71, 95% CI 0.31 to 1.62). Sub analyses for high-income and low-income countries of the effect of corticosteroids on mortality showed RRs of 0.83 (95% CI 0.52 to 1.05) and 0.87 (95% CI 0.72 to 1.05), respectively. Corticosteroids were protective against short-term neurological sequelae in patients with bacterial meningitis in high-income countries (RR 0.56, 95% CI 0.3 to 0.84); in low-income countries this RR was 1.09 (95% CI 0.83 to 1.45). For children with bacterial meningitis admitted in high-income countries, corticosteroids showed a protective effect against severe hearing loss (RR 0.61, 95% CI 0.41 to 0.90) and favourable point estimates for severe hearing loss associated with non-*Haemophilus influenzae* meningitis (RR 0.51, 95% CI 0.23 to 1.13) and short-term neurological sequelae (RR 0.72, 95% CI 0.39 to 1.33). For children in low-income countries, the use of corticosteroids was neither associated with benefit nor with harmful effects. Overall, adverse events were not increased significantly with the use of corticosteroids.

Authors' conclusions

Overall, corticosteroids significantly reduced rates of mortality, severe hearing loss and neurological sequelae. In adults with community-acquired bacterial meningitis, corticosteroid therapy should be administered in conjunction with the first antibiotic dose. In children, data support the use of adjunctive corticosteroids in children in high-income countries. We found no beneficial effect of corticosteroids for children in low-income countries.

PLAIN LANGUAGE SUMMARY

The corticosteroid dexamethasone can reduce hearing loss and death after meningitis for both children and adults

Acute bacterial meningitis is an infection of the membrane lining the brain that often causes hearing loss and is frequently fatal. It is usually caused by bacteria spreading from an ear or throat infection. Corticosteroids are drugs that can reduce inflammation caused by infection. Research on the use of corticosteroids for meningitis has had conflicting results. This review of trials found that the corticosteroid dexamethasone leads to a major reduction in hearing loss and death in both children and adults, without major adverse effects.

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BACKGROUND

Acute bacterial meningitis remains a disease with a high mortality rate, ranging from 10 to 30% despite advances in critical care (Bohr 1983; Baraff 1993; van de Beek 2004b; van de Beek 2006a). Late sequelae such as cranial nerve impairment, especially hearing loss, occur in 5 to 40% of patients (Bohr 1983; Baraff 1993; van de Beek 2002; van de Beek 2004b; van de Beek 2006a). In experimental studies, the outcome has been related to the severity of the inflammatory process in the subarachnoidal space (Scheld 1980; Tauber 1985). Treatment with corticosteroids results in a reduction of the inflammatory response in the cerebrospinal fluid (CSF) (Scheld 1980; Tauber 1985). These pathophysiological insights prompted investigators to evaluate corticosteroids as an adjuvant therapy in acute bacterial meningitis. We conducted a meta-analysis of randomised controlled trials (RCTs) of adjuvant corticosteroids in the treatment of acute bacterial meningitis.

OBJECTIVES

To examine the efficacy and safety of adjuvant corticosteroid therapy in acute bacterial meningitis.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible randomised controlled trials (RCTs) of corticosteroids as an adjuvant therapy in acute bacterial meningitis.

Types of participants

Participants of any age and in any clinical condition.

Types of interventions

Participants treated with antibacterial agents and randomised to corticosteroid therapy (or placebo) of any type.

Types of outcome measures

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

Search methods for identification of studies

In the first publication of this review, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2003, issue 1); MEDLINE (1966 to April 2002); EMBASE (1974 to April 2002); HEALTHLINE (1988 to April 2002); Current Contents for trials published before April 1st 2002, and reference lists of all articles. We also contacted manufacturers and researchers in the field (DvdB).

In this 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).

MEDLINE was searched using the following keywords and MeSH terms in conjunction with the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs (Higgins 2005). The same strategy was used to search CENTRAL and adapted to search EMBASE (WebSpirs) and Current Contents (OVID).

MEDLINE (OVID)

1 exp Meningitis/
2 meningit$.mp.
3 or/1-2
4 exp Adrenal Cortex Hormones/
5 corticosteroid$.mp.
6 exp Steroids/
7 steroid$.mp.
8 exp Dexamethasone/
9 dexameth$.mp.
10 or/4-9
11 3 and 10

We performed the search without any language restrictions. In addition, 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. Two review authors did the assessment for inclusion in the methodological appraisal (DvdB, JdG).

Data collection and analysis

Methodological appraisal

We performed the study appraisal using the Jadad scale (Jadad 1996). This is a validated 5-point scale evaluating randomisation (0 to 2 points), double blinding (0 to 2 points), and withdrawals and dropouts (0 to 1 point). Two experienced researchers, not working in the field of infectious diseases, performed a blinded appraisal. We resolved disagreements by consensus. All trials with 1 or 2 points for randomisation in the Jadad score were included in the analysis. In addition, allocation concealment was assessed as adequate, inadequate, unclear, or not used (by DvdB; 'Characteristics of included studies' table; Schulz 1995).

Extraction of data

Two review authors (DvdB, JdG) independently extracted the data, using a pre-determined protocol. We included all patients who were randomised or who started therapy in the intention-to-treat analysis. We included all patients who complied with the study protocol in the per-protocol analysis. Data were cross checked and differences were resolved by discussion.

Efficacy

Primary outcome measures were mortality, severe hearing loss and neurological sequelae. Hearing loss was defined as severe when

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there was bilateral hearing loss greater than 60 dB or requiring bilateral hearing aids. 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. Children whose only non hearing deficit(s) were speech or language disturbances were not counted as having non-hearing deficits if these problems were associated with severe hearing loss. We analysed both short- and long-term neurological sequelae, other than hearing loss. Short-term neurological sequelae were defined as sequelae assessed between discharge and six weeks after hospital discharge. Long-term neurological sequelae were defined as sequelae assessed between 6 and 12 months after discharge. Whenever possible, we extracted data for both these outcomes.

We performed subgroup analyses regarding age, causative organism and time of administration of steroids. Two age groups were defined: patients younger than 16 years and those of 16 years and older. Four categories of causative organisms were defined: *Haemophilus influenzae (H. influenzae), Neisseria meningitidis (N. meningitidis), Streptococcus pneumoniae (S. pneumoniae)* and other pathogens (including patients with negative CSF culture).

Studies were analysed 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 2003).

Safety

Adverse events were defined as clinically evident gastrointestinal tract bleeding, reactive arthritis, pericarditis, herpes zoster or herpes simplex virus infection, fungal infection, secondary 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 that continued longer than five consecutive days after initiation of appropriate antibiotic therapy). The total number of adverse events in each treatment group was calculated. The frequency of clinically evident gastrointestinal tract bleeding was evaluated separately.

Statistical analysis

Statistical analysis was performed using Review Manager 4.2 software. Chi-squared tests were used to test for heterogeneity on the basis of DerSimonian and Laird Q statistics; P values for heterogeneity among studies ranged from 0.6 to 1, so a fixed-effect model was chosen (Mantel-Haenszel visu-ratio method); these P values for sub analyses of high-income and low-income countries were sometimes lower than 0.6 (noted in-text). The effect of steroids was expressed as relative risks (RR), where a value below 1.0 indicates a beneficial effect of steroids. Statistical uncertainty was expressed with 95% confidence intervals (CI).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Selection of studies

We identified 32 potential eligible trials, of which two were described in one paper (Lebel 1988a; Lebel 1988b). Nine trials which did not obtain the necessary points for randomisation on the Jadad score were excluded - see Additional Table 1(Baldy 1986; Daoud 1999; Gijwani 2002; Jensen 1969; Lepper 1959; Marguet 1993; Ozen 2006; Passos 1979; Shembesh 1997). Subsequently, one study which compared two dexamethasone regimens (Syrogiannopoulos1994) and two studies presenting insufficient data (communications during scientific meetings only) (Farina 1995; Peltola 2004) were excluded, leaving 20 eligible trials.

Table 1. Quality assessment and characteristics of excluded studies

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	DXM before/with AB	Death %
1959 (Lepper)	0	0	0	0	All ages	Pen or pen/strep	NS	13
1969 (Jensen)	0	0	0	0	All ages	Sulf/pen	NS	19

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Table 1. Quality assessment and characteristics of excluded studies *(Continued)*

1979 (Passos)	0	0	0	0	All ages	Pen	NS	0
1986 (Baldy)	0	0	0	0	All ages	Amp or pen	NS	0
1993 (Marguet)	0	0	0	0	1 month to 14 years	Ceph	No	5
1994 (Syrogian)	2	0	0	2	2 months to 15 years	Various	No	0
1995 (Farina)	1	1	0	2	NG	NG	No	NG
1996 (Gupta)	0	0	0	0	12 to 70 years	Pen/chlor/gen	NS	23
1997 (Shembesh)	0	0	0	0	> 1month	Ceph	NS	13
1999 (Daoud)	0	0	0	0	Neonates	Amp+ceph	Yes	25
2002 (Gijwani)	0	0	0	0	Adults	Ceph	Yes	15
2004 (Peltola)	1	0	0	1	Children	NG	NS	NS
2006 (Ozen)	0	0	0	0	Children	NG	NS	NA

Characteristics of studies

Subjects over the age of 16 years were included in five studies (Bennett 1963; Bhaumik 1998; de Gans 2002; Girgis 1989; Thomas 1999). In two other studies, patients older than 12 years were considered adults (Bhaumik 1998; Girgis 1989). The study intervention consisted of dexamethasone in 17 of 20 studies; dosages ranged from 0.4 to 0.9 mg/kg and the duration ranged from two to four days (Additional Table 2). In the other studies hydrocortisone, prednisolone or a combination of both was given (Bademosi 1979; Bennett 1963; DeLemos 1969).

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Table 2. Quality assessment and characteristics of included studies

Year (author)	1. Randomisation (0-	2. Blinding (0-2)	3. Withdrawals (0-1)	Total Jadad (0-5)	Age of patients	Antibiotics (AB)	Intervention	DXM before/with AB	Deaths %
1963 (Bennet)	2	2	0	4	All ages	NS	Hydrocortison scheme, 7 d	No	45
1969 (deLemos)	1	1	0	2	1 month to 17 years	Chlor/sulf/p	Methylprednisolone 120 mg/d , 3d	No	3
1969 (Belsey)	1	1	0	2	0 to 17 years	Clor/sulf/pe	DXM 1.2 mg/M2/d, 4 d	NS	3
1979 (Bademosi)	1	0	0	1	10 to 59 years	Sulf/pen	Hydrocortisone, 100 mg; followed by prednisolone 60 mg/d, 14 d	Yes	44
1988 (Lebel)	2	2	1	5	2 months to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	2
1989 (Lebel)	2	2	1	5	3 months to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	2
1989 (Girgis)	1	0	0	1	3 months to 70 years	Ampi/chlor	DXM 16-24 mg/d, 4 d	Yes	15
1991 (Odio)	2	2	0	4	6 weeks to 16 years	Ceph	DXM 0.6 mg/kg/d, 4 d	Yes	2

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Table 2. Quality assessment and characteristics of included studies *(Continued)*

1993 (Schaad)	2	2	1	5	3 months to 16 years	Ceph	DXM 0.8 mg/kg/d, 2 d	Yes	0
1994 (King)	1	2	0	3	1 month to 13 years	Various	DXM 0.6 mg/kg/d, 4 d	No	1
1995 (Kilpi)	2	0	0	2	3 months to 15 years	Ceph	DXM 1.5 mg/kg/d, 3 d	Yes	2
1995 (Ciana)	1	0	1	2	2 months to 6 years	Ampi/chlor	DXM 0.4mg/kg, 3 d	NG	28
1995 (Wald)	2	2	1	5	2 months to 12 years	Ceph	DXM 0.6 mg/kg/d, 4 d	No	1
1995 (Kanra)	2	2	1	5	2 to 6 years	Sulf/amp	DXM 0.6 mg/kg/d, 4 d	Yes	5
1996 (Qazi)	2	2	1	5	2 months to 12 years	Ampi/chlor	DXM 0.6 mg/kg/d, 4 d	Yes	19
1998 (Baumik)	1	0	0	1	12 to 75 years	Pen/chlor or ceph	DXM 16 mg/d, 4 d; plus 3 d scheme	No	13
1999 (Thomas)	1	2	1	4	17 to 99 years	Amox	DXM 40 mg/d, 3 d	No	13
2002 (de Gans)	2	2	1	5	Older than 16 years	Various	DXM 40 mg/d, 4 d	Yes	11
2002 (Molyneux)	2	2	1	5	2 months to 13 years	Pen/chlor	DXM 0.8 mg/kg/d, 2 d	Yes	31

Third generation cephalosporins were most frequently prescribed.

Study medication was administered with or before the first dose of antibiotic in nine studies (Bademosi 1979; de Gans 2002; Girgis 1989; Kanra 1995; Kilpi 1995; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993) and in seven studies after the first doses. In four studies, the time of administration was not stated. Various antibiotic regimens were used and are listed in Additional Table 2.

A sample size calculation was given in four studies (de Gans 2002; Molyneux 2002; Qazi 1996; Thomas 1999). An intention-to-treat analysis was available from three studies (Bennett 1963; de Gans 2002; Molyneux 2002). In the other studies only per-protocol data were available to be ascertained. Therefore, the final analysis was based mostly upon per-protocol figures, including 2750 of

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2961 (93%) randomised patients; in two studies, intention-to-treat figures were used (de Gans 2002; Molyneux 2002).

Mortality rates ranged between 0 and 45% (Table 2). In one study, patients who died during the first 18 hours of admission were excluded (Belsey 1969). Nevertheless these results were included in the analysis. Hearing was adequately assessed (by audiometry and/or brainstem auditory evoked potentials) in 1383 children. Definitions of adverse events were heterogeneous and the numbers of events were recalculated for each study.

Risk of bias in included studies

The quality of included studies was high, with a median Jadad score of 4 (Additional Table 2).

Effects of interventions

Primary outcomes

The overall number of participants who died was significantly smaller in the corticosteroid group than in the placebo group (186 out of 1387 (13.4%) versus 220 out of 1363 (16.1%), RR 0.83, 95% CI 0.71 to 0.99) (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; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Thomas 1999; Wald 1995). The number of participants with severe hearing loss was significantly smaller in the corticosteroid group than in the placebo group (50 out of 884 (5.7%) versus 77 out of 863 (9.8%), RR 0.65, 95% CI 0.44 to 0.91) (Belsey 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b;Girgis 1989;Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995; Bhaumik 1998). Short-term neurological sequelae (other than hearing loss) were assessed in ten studies including 1175 participants (Bhaumik 1998; Ciana 1995; de Gans 2002; Kanra 1995; Kilpi 1995; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Thomas 1999); although the point estimate was favourable, there was no significant beneficial effect of corticosteroids (95% CI 0.68 to 1.08). The number of participants with long-term neurological sequelae was significantly less in the corticosteroid group than in the placebo group (36 out of 596 (6.0%) versus 51 out of 567 (9.0%), RR 0.67, 95% CI 0.45 to 1.00) (Girgis 1989; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Kanra 1995; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995). Adverse events were equally divided between the treatment and placebo group (RR 1.08, 95% CI 0.90 to 1.29) (Bennett 1963; Belsey 1969; Bhaumik 1998; de Gans 2002; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Thomas 1999; Wald 1995). The risk for gastrointestinal tract bleeding was not increased in patients treated with corticosteroids (data not shown).

Subgroup analyses

One hundred and forty-two out of 1051 (13.5%) children in the placebo group died, compared to 139 out of 1023 (13.6%) who received corticosteroids (RR 0.99, 95% CI 0.81 to 1.20) (Belsey 1969; Ciana 1995; DeLemos 1969; Girgis 1989; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Molyneux 2002; Odio 1991; Qazi 1996; Schaad 1993; Wald 1995). Corticosteroids prevented hearing loss in children: 76 of the 688 (11.0%) children in the control group had severe hearing loss, compared to 46 out of 695 (6.6%) who received corticosteroids (RR 0.61, 95% CI 0.44 to 0.86). Sub-analysis of children gave a favourable point estimate for risk reduction of long-term sequelae by corticosteroids (which did not reach statistical significance). For adult participants, corticosteroids gave significant protection against death: 69 out of 315 (21.9%) adults in the placebo group died, compared to 36 out of 308 (11.7%) who received corticosteroids (RR 0.57, 95% CI 0.40 to 0.81) (Bhaumik 1998; Bennett 1963; de Gans 2002; Girgis 1989; Thomas 1999). In addition, there was protective effect of corticosteroids on short-term sequelae in adults (RR 0.42, 95% CI 0.22 to 0.78).

Case-fatality rates varied according to the bacteria. Of the 709 participants with meningitis due to *H. influenzae*, 70 died (9.9%); compared with 22 out of 517 participants with meningococcal meningitis (4.3%) and 160 out of 641 participants with pneumococcal meningitis (25.0%). Corticosteroids protected against death in pneumococcal meningitis (RR 0.59, 95% CI 0.45 to 0.77), as well as in meningitis caused by bacteria other than *H. influenzae* (including participants with negative CSF culture; RR 0.77, 95% CI 0.62 to 0.96); there was considerable heterogeneity among included studies in these analyses (P = 0.01 and 0.04, respectively). In patients with meningococcal meningitis, corticosteroids were associated with a non-significant reduction in mortality (RR 0.71, 95% CI 0.31 to 1.62). For children with meningitis caused by *H. influenzae*, hearing loss was significantly reduced by steroids (RR 0.37, 95% CI 0.20 to 0.68). For children with meningitis caused by bacteria other than *H. influenzae,* no significant beneficial effect was seen (RR 0.86, 95% CI 0.57 to 1.30). If data from the Malawi study were excluded, the RR was 0.42 (95% CI 0.20 to 0.89) (Molyneux 2002). There were too few participants with specified neurological sequelae (other than hearing loss) and a known causative organism to assess pathogen-specific effects.

Studies were analysed in two subsets divided into low-income (Bademosi 1979; Bhaumik 1998; Ciana 1995; Girgis 1989; Molyneux 2002; Qazi 1996) and high-income countries (Belsey 1969; Bennett 1963; de Gans 2002; DeLemos 1969; Kanra 1995; Kilpi 1995; King 1994; Lebel 1988a; Lebel 1988b; Lebel 1989; Odio 1991; Schaad 1993; Thomas 1999; Wald 1995). On mortality, point estimates were 0.87 (95% CI 0.72 to 1.05) for low-income countries and 0.74 (95% CI 0.52 to 1.05) for high-income countries. The P value for heterogeneity among studies included in the analysis on mortality in low-income countries was 0.06, indicating considerable heterogeneity. Sub-analyses for children

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in high-income countries showed a protective effect of corticosteroids on severe hearing loss (RR 0.32, 95% CI 0.18 to 0.57); a favourable point estimate for severe hearing loss in meningitis caused by bacteria other than *H. influenzae* (6 of 175 (3.4%) versus 15 of 188 (8.0%); RR 0.48, 95% CI 0.20 to 1.15); and a favourable point estimate for short-term neurological sequelae (RR 0.76, 95% CI 0.45 to 1.27). For children in low-income countries, corticosteroids had no beneficial effect on mortality (RR 0.96, 95% CI 0.78 to 1.18), severe hearing loss (RR 1.04, 95% CI 0.66 to 1.63), and short-term neurological sequelae (RR 1.08, 95% CI 0.82 to 1.44).

Sub-analyses for timing of corticosteroids (before or with the first dose of antibiotics versus after the first dose of antibiotics) showed similar results for mortality (RR 0.84, 95% CI 0.70 to 1.02 and RR 0.80, 95% CI 0.70 1.02). Within the analysis of studies with administration before or with the first dose of antibiotics there was significant heterogeneity between studies (P = 0.05). For sub-analyses of severe hearing loss and short-term neurological sequelae, pooled studies with administration after the first dose of antibiotics had slightly more favourable point estimates than studies with early administration of corticosteroids.

DISCUSSION

This meta-analysis showed a beneficial effect of adjunctive corticosteroids in acute bacterial meningitis. Overall, corticosteroids significantly reduced rates of mortality, severe hearing loss and neurological sequelae.

In children with acute bacterial meningitis, corticosteroids reduced the rate of severe hearing loss from 11.0 to 6.6%. A large proportion of included children had meningitis due to *H. influenzae*, and Hib meningitis has virtually been eliminated in high-income countries since routine vaccination of children against this bacterium was started (Peltola 2000; van de Beek 2006b). Sub-analyses for children in high-income countries showed a protective effect of corticosteroids on severe hearing loss overall, and favourable point estimates for severe hearing loss in non-*Haemophilus* meningitis and for short-term neurological sequelae. Therefore, we recommend the use of adjunctive corticosteroids in children in high-income countries. For children in low-income countries, the use of corticosteroids was neither associated with benefit nor with harmful effects.

None of the studies in this analysis involved children younger than one month (neonatal meningitis). Since this is a specific group of patients with specific causative agents (Saez-Llorens 2003), the use of adjunctive corticosteroids is not recommended in neonates with acute bacterial meningitis. A RCT evaluating corticosteroids in neonatal meningitis should be performed.

In adults with acute bacterial meningitis, corticosteroids reduced mortality rate from 21.7 to 11.7%; so, 10 adult patients with acute bacterial meningitis would need to be treated with corticosteroids to save one additional life. On the basis of overall benefit, corticosteroid therapy should be commenced in adults with suspected or proven community-acquired bacterial meningitis (van de Beek 2006a).

There was a difference in efficacy of corticosteroids between high and low-income countries. This difference was mainly caused by inclusion of the Malawian study, which included children in whom treatment began late, HIV-1 positive children, and children receiving inappropriate antibiotic therapy (Molyneux 2002). There may be several reasons for the difference in efficacy of corticosteroids, such as delayed presentation, clinical severity, underlying anemia, malnutrition, the antibiotic used and HIV-1 positive children. A recent study compared characteristics of children with culture-positive bacterial meningitis treated in the Royal Liverpool Children's Hospital and in the Children's Unit, Queen Elizabeth Central Hospital, Blantyre, Malawi (Molyneux 2006); the two cohort studies were derived from time-periods before the introduction of vaccines. Children in Malawi presented later and were more often comatose and malnourished, compared with 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 organisms. A meta-analysis of individual patient data should try to define the reasons for differing outcomes in high versus low income countries and identify those children in low-income countries who could benefit from corticosteroids.

Several biases may have diminished the reliability of our results. The first confounding factor is selection bias. Several included studies on childhood bacterial meningitis had exceptional low mortality rates; nine studies had mortality rates of 3% or less. Mortality rates of childhood bacterial meningitis in previously reported studies ranged from 8 to 20% (Baraff 1993; Bohr 1983). Inclusion of patients in the meta-analysis with a less severe illness, as reflected in very low case fatality rates, will probably underestimate the protective effect of corticosteroids (Glasziou 1995). Few included studies had high mortality rates but in three studies, mortality rates were over 30%. For patients admitted in a late stage of disease, adjuvant corticosteroids are less protective and might even be harmful (Prasad 1995). Inclusion of such patients will again lead to an underestimate 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 figures were available for only three studies. In total, 211 participants were withdrawn after the randomisation process, often for unknown reasons. Reasons for withdrawal include ineligibility according to 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

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example, upper gastro-intestinal 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 patients with other bacteria culture form CSF and those with negative CSF cultures (Girgis 1989).

A third bias might be introduced by including only RCTs as assessed by the previous validated Jadad scale (Jadad 1996). Studies that used quasi-randomisation, such as alternate allocation, were excluded (Gijwani 2002). Although the quality of included studies was high, reflected in a high median Jadad score, several included studies suffered from methodological flaws and drawbacks. Quality assessment and methods of its incorporation into systemic reviews remain controversial; nevertheless, its importance is clearly accepted (Moher 1998).

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

Finally, the included studies were heterogeneous with respect to study protocol. The first study was published in 1963 (Bennett 1963), the last two in 2002 (de Gans 2002; Molyneux 2002). Several different study interventions were used. Therefore, study population effect-sizes were calculated as relative risks.

The use of steroids was associated with only few side effects. However, definitions of adverse events used in the studies were heterogeneous and most studies had no specified criteria in advance, so under ascertainment is possible. The relative risk for gastro-intestinal bleeding did not reach statistical significance. Concerns have been raised over the interference by corticosteroids on CSF eradication of meningeal pathogens by reducing the blood brain barrier permeability and thereby the penetration of antibiotics in the subarachnoid space. Although in children with acute bacterial meningitis, treatment of dexamethasone did not reduce vancomycin levels in the CSF (Klugman 1995), therapeutic failures have been described in adults treated with standard doses of vancomycin and adjunctive dexamethasone (Viladrich 1991). Therefore, patients with pneumococcal meningitis who are treated with vancomycin and dexamethasone should 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 recently 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 (median time between meningitis and testing was eight years). In another recent study on long-term neuropsychological outcome and dexamethasone in children, children after pneumococcal meningitis who were treated with corticosteroids showed better academic achievements compared with children with pneumococcal meningitis who were not treated with adjunctive corticosteroids (Ozen 2006).

The available studies do not address two important other issues - the minimum duration of corticosteroid therapy or the maximum length of time after parenteral antibiotic therapy for commencement 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 (Syrogiannopoulos1994). In this study, physicians were not blinded for 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 RCT will be performed to answer the question of whether a two-day or four-day 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 advice the use of the four-days of corticosteroid therapy.

Subanalyses 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 3301 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

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dexamethasone is not restricted to the first hours after administration (van de Beek 2006b). 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 agents but this time interval has not clearly been defined. Upcoming RCTs and a meta-analysis of individual patient data might provide an answer about pretreatment with (parenteral) antibiotic therapy and the effect of adjunctive corticosteroid therapy. On basis of available evidence, dexamethasone should be preferably started before of with the first dose of antibiotic therapy.

The beneficial effect of corticosteroids was most apparent in meningitis due to *H. influenzae* and *S. pneumoniae*. Subgroup analysis for patients with meningococcal showed a favourable trend in mortality. In clinical practice, the causative organisms in many cases will not be known when treatment is started. On basis of the overall benefit and absence of excess of adverse events, if corticosteroids are indicated, a four-day regimen of dexamethasone therapy should be given, regardless of bacterial aetiology.

Despite these encouraging results, the use of adjunctive corticosteroids in acute bacterial meningitis remains controversial in certain other patient subgroups. The role of corticosteroids for patients who present with both evidence of acute bacterial meningitis and septic shock remains unclear. Lower doses of corticosteroids have shown to be beneficial in septic shock (Annane 2002), while higher doses have shown to be either of no benefit or have a trend towards increased mortality (Cronin 1995; Lefering 1995).

Results of one study in children comparing placebo, adjunctive corticosteroids, glycerol and the combination of corticosteroids and glycerol, were presented during a scientific meeting in 2004 (Peltola 2004); however, results are not yet published. Two other RCTs on the effect of adjunctive corticosteroids in lower-income countries studies were recently performed. Peer-reviewed results of these three RCT are eagerly awaited.

AUTHORS' CONCLUSIONS

Implications for practice

In summary, the consistency and degree of benefit identified in this analysis merits the use of corticosteroids in adults with acute bacterial meningitis and in children with acute bacterial meningitis in high-income countries with good access to services. 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. Trials of adjuvant dexamethasone in adults with acute bacterial meningitis in low-income countries with non-optimal access to medical services are needed. Results of upcoming RCTs are eagerly awaited.
2. RCTs are required to assess the use of corticosteroids in neonatal meningitis.
3. A meta-analysis of individual patient data should try to define the reasons for differing outcomes in high- versus low-income countries and identify those children in low-income countries who could benefit from corticosteroids.
4. This individual meta-analysis may further define patient groups in whom the effect of adjunctive corticosteroids is uncertain; international RCTs should be performed in these patient groups.
5. Case series are needed to determine the effect of adjunctive dexamethasone therapy in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the following people for commenting on the draft of this updated review: Alex Hakuzimana, Paul Heath, Ram Yogev, Terry Neeman and Juan Lozano.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bademosi 1979

Methods	Randomized, unblinded
Participants	10 to 59 years; bacteriologically proven pneumococcal meningitis
Interventions	Hydrocortisone, 100 mg; followed by prednisolone 60 mg/d, 14 d
Outcomes	Mortality

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Bademosi 1979 (*Continued*)

Notes	Jadad score and additional study characteristics in Additional Table 2	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Belsey 1969

Methods	Randomized, double-blind	
Participants	0 to 17 years; purulent meningitis	
Interventions	DXM 1.2 mg/M2/d, 4 d	
Outcomes	Mortality, hearing loss, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Bennett 1963

Methods	Randomized, double-blind	
Participants	All ages; life-threatening infectious diseases, subgroup meningitis	
Interventions	Hydrocortisone scheme, 7 d	
Outcomes	Mortality, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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Bhaumik 1998

Methods	Randomized, unblinded	
Participants	12 to 75 years; suspected bacterial meningitis with CSF criteria	
Interventions	DXM 16 mg/day, 4 d; plus 3 d scheme	
Outcomes	Mortality, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

Ciana 1995

Methods	Randomized, unblinded	
Participants	2 months to 6 years; suspected bacterial meningitis with CSF criteria	
Interventions	DXM 0.4 mg/kg, 3 d	
Outcomes	Mortality, neurological sequelae	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

de Gans 2002

Methods	Randomized, double-blind
Participants	Older than 16 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 4 d
Outcomes	Mortality, neurological sequelae, adverse events

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de Gans 2002 (*Continued*)

Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

DeLemos 1969

Methods	Randomized, double-blind	
Participants	1 month to 17 years; diagnosis bacterial meningitis	
Interventions	Methylprednisolone 120 mg/d, 3 d	
Outcomes	Mortality	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Girgis 1989

Methods	Randomized, unblinded	
Participants	3 months to 70 years; diagnosis bacterial meningitis	
Interventions	DXM 16 -24 mg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

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Kanra 1995

Methods	Randomized, double-blind	
Participants	2 to 6 years; bacteriologically proven pneumococcal meningitis	
Interventions	DXM 0.6 mg/kg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Kilpi 1995

Methods	Randomized, unblinded	
Participants	3 months to 15 years; suspected bacterial meningitis with CSF criteria	
Interventions	DXM 1.5 mg/kg/d, 3 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	D - Not used

King 1994

Methods	Randomized, double-blind
Participants	1 month to 13 years; suspected bacterial meningitis with CSF or blood criterion; also patients with suspected bacterial meningitis who were too unstable for a LP
Interventions	DXM 0.6 mg/kg/d, 4 d

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King 1994 (*Continued*)

Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Lebel 1988a

Methods	Randomized, double-blind	
Participants	2 months to 16 years; suspected or proven bacterial meningitis	
Interventions	DXM 0.6 mg/kg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Lebel 1988b

Methods	Randomized, double-blind	
Participants	2 months to 16 years; suspected or proven bacterial meningitis	
Interventions	DXM 0.6 mg/kg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**

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Lebel 1988b (*Continued*)

Allocation concealment?	Yes	A - Adequate

Lebel 1989

Methods	Randomized, double-blind
Participants	2 months to 16 years; suspected or proven bacterial meningitis
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Molyneux 2002

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

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Odio 1991

Methods	Randomized, double-blind

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Odio 1991 (*Continued*)

Participants	6 weeks to 16 years; culture proved bacterial meningitis or suspected bacterial meningitis with CSF inflammation	
Interventions	DXM 0.6 mg/kg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Qazi 1996

Methods	Randomized, double-blind	
Participants	2 months to 12 years;suspected bacterial meningitis with CSF criteria	
Interventions	DXM 0.6 mg/kg/d, 4 d	
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Schaad 1993

Methods	Randomized, double-blind
Participants	3 months to 16 years; suspected or proven bacterial
Interventions	DXM 0.8 mg/kg/d, 2 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	

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Schaad 1993 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Thomas 1999

Methods	Randomized, double-blind
Participants	17 to 99 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 40 mg/d, 3 d
Outcomes	Mortality, neurological sequelae, adverse events
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Wald 1995

Methods	Randomized, double-blind
Participants	2 months to 12 years; suspected bacterial meningitis with CSF criteria
Interventions	DXM 0.6 mg/kg/d, 4 d
Outcomes	Mortality, hearing loss, neurological sequelae, adverse events
Notes	

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

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

Baldy 1986	Score on Jadad-scale of 0 for randomisation Jadad score and additional study characteristics in the additional Table 1
Daoud 1999	Score on Jadad-scale of 0 for randomisation
Farina 1995	Not enough data for inclusion (abstract only)
Gijwani 2002	Score on Jadad-scale of 0 for randomisation
Gupta 1996	Score on Jadad-scale of 0 for randomisation
Jensen 1969	Score on Jadad-scale of 0 for randomisation
Lepper 1959	Score on Jadad-scale of 0 for randomisation
Marguet 1993	Score on Jadad-scale of 0 for randomisation
Ozen 2006	Score on Jadad-scale of 0 for randomisation
Passos 1979	Score on Jadad-scale of 0 for randomisation
Peltola 2004	Not enough data for inclusion
Shembesh 1997	Score on Jadad-scale of 0 for randomisation
Syrogiannopoulos1994	Compared 2-day 4-day regimen of dexamethasone

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DATA AND ANALYSES

Comparison 1. All patients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	20	2750	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.99]
2 Severe hearing loss	14	1747	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.47, 0.91]
3 Short-term neurological sequelae	10	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.08]
4 Long-term neurological sequelae	10	1163	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.45, 1.00]
5 Adverse events	15	1484	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.90, 1.29]

Comparison 2. Children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	15	2074	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.20]
2 Severe hearing loss	13	1383	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.86]

Comparison 3. Adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	5	623	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.40, 0.81]
2 Short-term neurological sequelae	3	339	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.22, 0.78]

Comparison 4. Causative species

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	14		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Haemophilus influenzae	10	709	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.59, 1.31]
1.2 Neisseria meningitidis	10	517	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.31, 1.62]
1.3 Streptococcus pneumoniae	12	641	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.45, 0.77]
1.4 All other species than H. influenzae	11	1416	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
2 Severe hearing loss in children - non-Haemophilus influenzae species	11	660	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]

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3 Severe hearing loss in children - Haemophilus influenzae species	9	663	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.20, 0.68]

Comparison 5. Income of countries

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality - all patients	20	2750	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.71, 0.99]
1.1 Low-income countries	6	1266	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.05]
1.2 High-income countries	14	1484	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.52, 1.05]
2 Severe hearing loss - all patients	14	1747	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.47, 0.91]
2.1 Low-income countries	4	835	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.69, 1.63]
2.2 High-income countries	10	912	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.18, 0.58]
3 Short-term neurological sequelae - all patients	10	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.08]
3.1 Low-income countries	3	508	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.83, 1.45]
3.2 High-income countries	7	667	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.37, 0.84]
4 Mortality - children	15	2074	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.20]
4.1 Low-income countries	4	1037	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.18]
4.2 High-income countries	11	1037	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.59, 3.33]
5 Severe hearing loss - children	12	1311	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.43, 0.86]
5.1 Low-income countries	2	401	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.66, 1.63]
5.2 High-income countries	10	910	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.18, 0.57]
6 Short-term neurological sequelae -children	7	836	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.26]
6.1 Low-income countries	2	482	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.44]
6.2 High-income countries	5	354	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.45, 1.27]
7 Severe hearing loss in children due to non-Heamophilus influenzae species	11	660	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.57, 1.30]
7.1 Low-income countries	2	297	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.67, 1.77]
7.2 High-income countries	9	363	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.23, 1.13]

Comparison 6. Timing of steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	18	2594	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.70, 0.99]
1.1 Before or with first dose antibiotic	9	1797	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.70, 1.02]
1.2 After first dose antibiotic	9	797	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.52, 1.22]
2 Severe hearing loss	13	1664	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.47, 0.92]
2.1 Before or with first dose antibiotic	7	1137	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.58, 1.26]

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2.2 After first dose antibiotic	6	527	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.17, 0.69]
3 Short-term neurologic sequelae	9	1125	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.10]
3.1 Before or with first dose antibiotic	4	804	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.73, 1.26]
3.2 After first dose antibiotic	5	321	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.43, 1.08]

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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bademosi 1979	11/28	12/24		5.8 %	0.79 [0.43, 1.45]
Belsey 1969	2/43	1/43		0.4 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.8 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		1.3 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		5.2 %	0.71 [0.33, 1.51]
de Gans 2002	11/157	21/144		9.8 %	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.4 %	2.33 [0.22, 25.03]
Girgis 1989	20/210	42/219		18.5 %	0.50 [0.30, 0.82]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		0.7 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1989	0/31	1/30		0.7 %	0.32 [0.01, 7.63]
Molyneux 2002	96/305	91/291		41.8 %	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.5 %	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		2.4 %	2.05 [0.79, 5.33]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Thomas 1999	3/31	5/29		2.3 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2 %	3.21 [0.13, 77.60]

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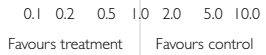
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	**1387**	**1363**		**100.0 %**	**0.83 [0.71, 0.99]**

Total events: 186 (Treatment), 220 (Control)

Heterogeneity: Chi^2 = 16.96, df = 16 (P = 0.39); I^2 =6%

Test for overall effect: Z = 2.12 (P = 0.034)



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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

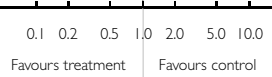
Outcome: 2 Severe hearing loss

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Bhaumik 1998	2/13	2/13		2.6 %	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177		6.6 %	0.37 [0.07, 1.90]
Kanra 1995	0/29	0/27		0.0 %	0.0 [0.0, 0.0]
Kilpi 1995	1/32	3/26		4.2 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.8 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Molyneux 2002	31/181	27/189		33.9 %	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.3 %	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6 %	0.31 [0.07, 1.45]
Total (95% CI)	**884**	**863**		**100.0 %**	**0.65 [0.47, 0.91]**

Total events: 50 (Treatment), 77 (Control)

Heterogeneity: Chi^2 = 13.57, df = 12 (P = 0.33); I^2 =12%

Test for overall effect: Z = 2.51 (P = 0.012)



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Analysis 1.3. Comparison 1 All patients, Outcome 3 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

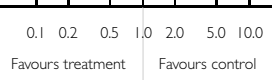
Outcome: 3 Short-term neurological sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	3/13	2/13		1.7 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		6.0 %	0.66 [0.24, 1.80]
de Gans 2002	4/143	14/118		12.7 %	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.8 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.8 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		7.0 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		8.4 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.1 %	0.62 [0.20, 1.99]
Molyneux 2002	69/223	57/209		48.6 %	1.13 [0.84, 1.52]
Thomas 1999	5/28	9/24		8.0 %	0.48 [0.18, 1.23]
Total (95% CI)	**617**	**558**		**100.0 %**	**0.86 [0.68, 1.08]**

Total events: 108 (Treatment), 116 (Control)

Heterogeneity: Chi^2 = 12.53, df = 9 (P = 0.19); I^2 =28%

Test for overall effect: Z = 1.31 (P = 0.19)



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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

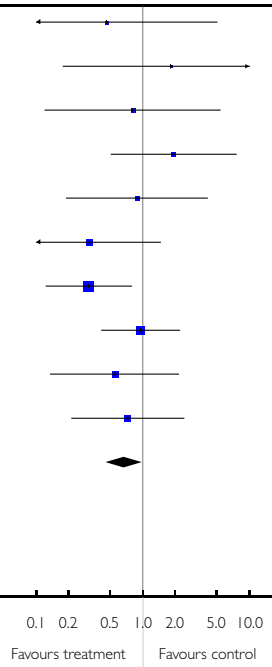
Outcome: 4 Long-term neurological sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Girgis 1989	1/190	2/177		4.0 %	0.47 [0.04, 5.09]
Kanra 1995	2/29	1/27		2.0 %	1.86 [0.18, 19.38]
Kilpi 1995	2/32	2/26		4.2 %	0.81 [0.12, 5.38]
King 1994	5/37	3/44		5.2 %	1.98 [0.51, 7.75]
Lebel 1988a	3/38	3/34		6.0 %	0.89 [0.19, 4.14]
Lebel 1988b	2/43	6/41		11.7 %	0.32 [0.07, 1.49]
Odio 1991	5/51	15/48		29.5 %	0.31 [0.12, 0.80]
Qazi 1996	9/48	8/41		16.5 %	0.96 [0.41, 2.26]
Schaad 1993	3/60	5/55		10.0 %	0.55 [0.14, 2.19]
Wald 1995	4/68	6/74		11.0 %	0.73 [0.21, 2.46]
Total (95% CI)	**596**	**567**		**100.0 %**	**0.67 [0.45, 1.00]**

Total events: 36 (Treatment), 51 (Control)

Heterogeneity: $Chi^2 = 7.65$, df = 9 (P = 0.57); $I^2 = 0.0\%$

Test for overall effect: Z = 1.96 (P = 0.050)



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Analysis 1.5. Comparison 1 All patients, Outcome 5 Adverse events.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 1 All patients

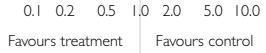
Outcome: 5 Adverse events

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	6/43	4/43		2.7 %	1.50 [0.46, 4.94]
Bennett 1963	5/38	2/47		1.2 %	3.09 [0.63, 15.06]
Bhaumik 1998	0/14	0/16		0.0 %	0.0 [0.0, 0.0]
de Gans 2002	16/144	13/157		8.4 %	1.34 [0.67, 2.69]
Kanra 1995	5/29	4/27		2.8 %	1.16 [0.35, 3.89]
Kilpi 1995	21/32	16/26		12.0 %	1.07 [0.72, 1.58]
King 1994	8/50	12/50		8.1 %	0.67 [0.30, 1.49]
Lebel 1988a	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	2/51	0/49		0.3 %	4.81 [0.24, 97.68]
Lebel 1989	0/31	0/29		0.0 %	0.0 [0.0, 0.0]
Odio 1991	13/52	30/49		20.9 %	0.41 [0.24, 0.69]
Qazi 1996	23/48	16/41		11.7 %	1.23 [0.76, 1.99]
Schaad 1993	22/60	17/55		12.0 %	1.19 [0.71, 1.99]
Thomas 1999	2/31	3/29		2.1 %	0.62 [0.11, 3.47]
Wald 1995	39/69	27/74		17.7 %	1.55 [1.08, 2.23]
Total (95% CI)	**743**	**741**		**100.0 %**	**1.08 [0.90, 1.29]**

Total events: 162 (Treatment), 144 (Control)

Heterogeneity: Chi^2 = 22.65, df = 11 (P = 0.02); I^2 =51%

Test for overall effect: Z = 0.84 (P = 0.40)



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Analysis 2.1. Comparison 2 Children, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 2 Children

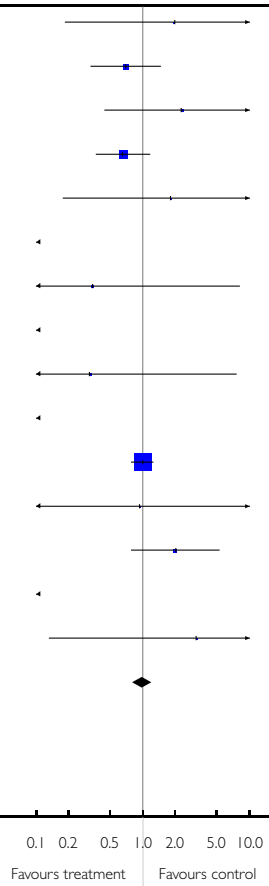
Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	2/43	1/43		0.7 %	2.00 [0.19, 21.24]
Ciana 1995	8/34	12/36		8.2 %	0.71 [0.33, 1.51]
DeLemos 1969	4/54	2/63		1.3 %	2.33 [0.44, 12.25]
Girgis 1989	16/142	24/140		16.9 %	0.66 [0.37, 1.18]
Kanra 1995	2/29	1/27		0.7 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		1.0 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/51	1/49		1.1 %	0.32 [0.01, 7.68]
Lebel 1989	0/31	0/29		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	96/305	91/291		65.2 %	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.7 %	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		3.8 %	2.05 [0.79, 5.33]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Total (95% CI)	**1051**	**1023**		**100.0 %**	**0.99 [0.81, 1.20]**

Total events: 142 (Treatment), 139 (Control)

Heterogeneity: Chi^2 = 7.95, df = 10 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.14 (P = 0.89)



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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 2 Children

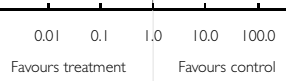
Outcome: 2 Severe hearing loss

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		6.0 %	0.10 [0.01, 1.79]
Kanra 1995	0/27	2/27		3.2 %	0.20 [0.01, 3.98]
Kilpi 1995	1/32	3/26		4.2 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.9 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Molyneux 2002	31/181	27/189		33.9 %	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.3 %	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6 %	0.31 [0.07, 1.45]
Total (95% CI)	**695**	**688**		**100.0 %**	**0.61 [0.44, 0.86]**

Total events: 46 (Treatment), 76 (Control)

Heterogeneity: Chi^2 = 15.44, df = 12 (P = 0.22); I^2 =22%

Test for overall effect: Z = 2.81 (P = 0.0050)



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Analysis 3.1. Comparison 3 Adults, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 3 Adults

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bennett 1963	16/38	22/47		29.7 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		4.2 %	0.38 [0.04, 3.26]
de Gans 2002	11/157	21/144		33.1 %	0.48 [0.24, 0.96]
Girgis 1989	5/68	18/79		25.2 %	0.32 [0.13, 0.82]
Thomas 1999	3/31	5/29		7.8 %	0.56 [0.15, 2.14]
Total (95% CI)	**308**	**315**		**100.0 %**	**0.57 [0.40, 0.81]**

Total events: 36 (Treatment), 69 (Control)

Heterogeneity: $Chi^2 = 5.27$, df = 4 (P = 0.26); $I^2 = 24\%$

Test for overall effect: Z = 3.14 (P = 0.0017)

Analysis 3.2. Comparison 3 Adults, Outcome 2 Short-term neurological sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 3 Adults

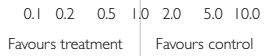
Outcome: 2 Short-term neurological sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bhaumik 1998	3/13	2/13		7.4 %	1.50 [0.30, 7.55]
de Gans 2002	4/143	14/118		56.7 %	0.24 [0.08, 0.70]
Thomas 1999	5/28	9/24		35.9 %	0.48 [0.18, 1.23]
Total (95% CI)	**184**	**155**		**100.0 %**	**0.42 [0.22, 0.78]**

Total events: 12 (Treatment), 25 (Control)

Heterogeneity: $Chi^2 = 3.55$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 2.73 (P = 0.0064)



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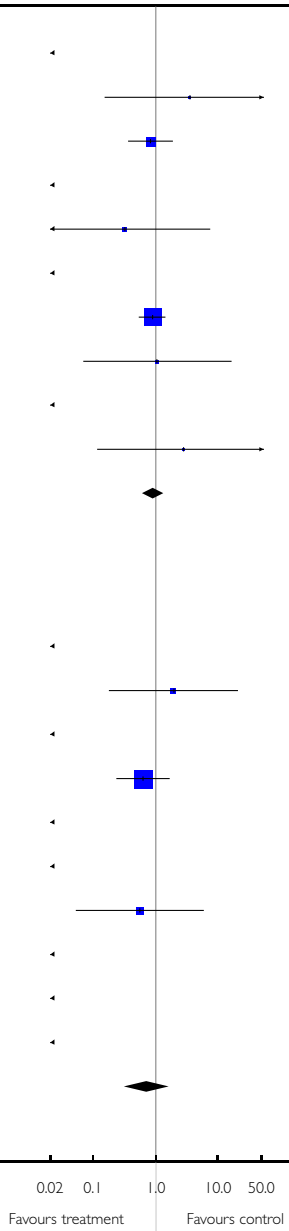
Analysis 4.1. Comparison 4 Causative species, Outcome 1 Mortality.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Haemophilus influenzae					
de Gans 2002	0/2	0/2		0.0 %	0.0 [0.0, 0.0]
DeLemos 1969	1/32	0/37		1.2 %	3.45 [0.15, 81.95]
Girgis 1989	7/26	10/30		24.1 %	0.81 [0.36, 1.82]
Kilpi 1995	0/15	0/13		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/40	1/37		4.0 %	0.31 [0.01, 7.36]
Lebel 1988b	0/39	0/38		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	21/81	27/89		66.7 %	0.85 [0.53, 1.39]
Odio 1991	1/39	1/40		2.6 %	1.03 [0.07, 15.83]
Schaad 1993	0/37	0/30		0.0 %	0.0 [0.0, 0.0]
Wald 1995	1/43	0/39		1.4 %	2.73 [0.11, 65.05]
Subtotal (95% CI)	**354**	**355**		**100.0 %**	**0.88 [0.59, 1.31]**
Total events: 31 (Treatment), 39 (Control)					
Heterogeneity: Chi^2 = 1.70, df = 5 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 Neisseria meningitidis					
Ciana 1995	0/1	0/1		0.0 %	0.0 [0.0, 0.0]
de Gans 2002	2/50	1/47		8.0 %	1.88 [0.18, 20.05]
DeLemos 1969	0/9	0/7		0.0 %	0.0 [0.0, 0.0]
Girgis 1989	6/132	10/135		77.1 %	0.61 [0.23, 1.64]
Lebel 1988a	0/3	0/4		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/3	0/4		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	1/32	2/35		14.9 %	0.55 [0.05, 5.75]
Schaad 1993	0/1	0/1		0.0 %	0.0 [0.0, 0.0]
Thomas 1999	0/16	0/12		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/11	0/13		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**258**	**259**		**100.0 %**	**0.71 [0.31, 1.62]**
Total events: 9 (Treatment), 13 (Control)					



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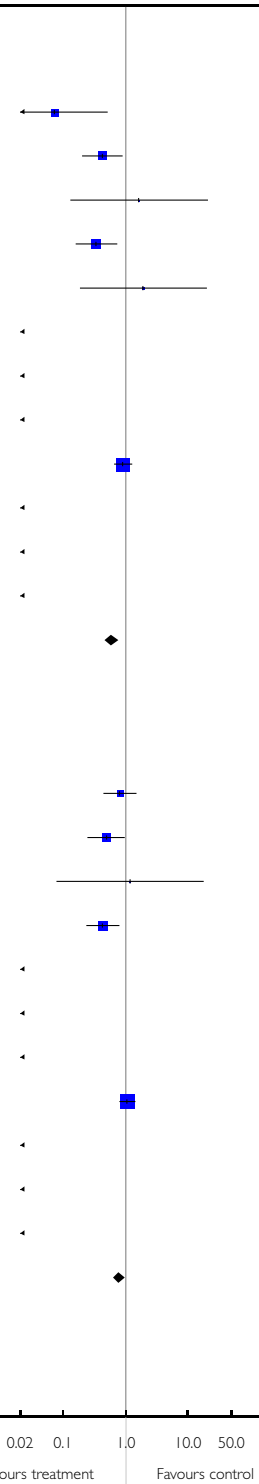
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 0.78, df = 2 (P = 0.68); I² =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					
3 Streptococcus pneumoniae					
Bademosi 1979	1/28	12/24		12.8 %	0.07 [0.01, 0.51]
de Gans 2002	8/58	17/50		18.0 %	0.41 [0.19, 0.86]
DeLemos 1969	1/5	1/8		0.8 %	1.60 [0.13, 20.22]
Girgis 1989	7/52	22/54		21.3 %	0.33 [0.15, 0.71]
Kanra 1995	2/29	1/27		1.0 %	1.86 [0.18, 19.38]
Kilpi 1995	0/1	0/5		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/4	0/6		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/4	0/3		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	46/132	42/106		46.1 %	0.88 [0.63, 1.22]
Odio 1991	0/4	0/4		0.0 %	0.0 [0.0, 0.0]
Schaad 1993	0/5	0/6		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/13	0/13		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**335**	**306**		**100.0 %**	**0.59 [0.45, 0.77]**
Total events: 65 (Treatment), 95 (Control)					
Heterogeneity: Chi² = 14.75, df = 5 (P = 0.01); I² =66%					
Test for overall effect: Z = 3.85 (P = 0.00012)					
4 All other species than H. influenzae					
Bademosi 1979	11/28	12/24		9.8 %	0.79 [0.43, 1.45]
de Gans 2002	11/155	21/142		16.5 %	0.48 [0.24, 0.96]
DeLemos 1969	1/22	1/25		0.7 %	1.14 [0.08, 17.11]
Girgis 1989	13/184	32/189		23.8 %	0.42 [0.23, 0.77]
Kilpi 1995	0/17	0/13		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/11	0/12		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/12	0/11		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	71/226	62/204		49.2 %	1.03 [0.78, 1.37]
Odio 1991	0/13	0/19		0.0 %	0.0 [0.0, 0.0]
Schaad 1993	0/23	0/25		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/26	0/35		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**717**	**699**		**100.0 %**	**0.77 [0.62, 0.96]**
Total events: 107 (Treatment), 128 (Control)					
Heterogeneity: Chi² = 9.85, df = 4 (P = 0.04); I² =59%					
Test for overall effect: Z = 2.28 (P = 0.023)					



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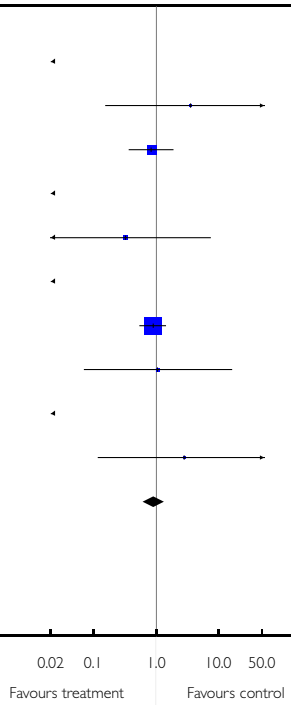
Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Haemophilus influenzae					
de Gans 2002	0/2	0/2		0.0 %	0.0 [0.0, 0.0]
DeLemos 1969	1/32	0/37		1.2 %	3.45 [0.15, 81.95]
Girgis 1989	7/26	10/30		24.1 %	0.81 [0.36, 1.82]
Kilpi 1995	0/15	0/13		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/40	1/37		4.0 %	0.31 [0.01, 7.36]
Lebel 1988b	0/39	0/38		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	21/81	27/89		66.7 %	0.85 [0.53, 1.39]
Odio 1991	1/39	1/40		2.6 %	1.03 [0.07, 15.83]
Schaad 1993	0/37	0/30		0.0 %	0.0 [0.0, 0.0]
Wald 1995	1/43	0/39		1.4 %	2.73 [0.11, 65.05]
Subtotal (95% CI)	**354**	**355**		**100.0 %**	**0.88 [0.59, 1.31]**
Total events: 31 (Treatment), 39 (Control)					
Heterogeneity: Chi^2 = 1.70, df = 5 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 Neisseria meningitidis					
Ciana 1995	0/1	0/1		0.0 %	0.0 [0.0, 0.0]
de Gans 2002	2/50	1/47		8.0 %	1.88 [0.18, 20.05]
DeLemos 1969	0/9	0/7		0.0 %	0.0 [0.0, 0.0]
Girgis 1989	6/132	10/135		77.1 %	0.61 [0.23, 1.64]
Lebel 1988a	0/3	0/4		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/3	0/4		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	1/32	2/35		14.9 %	0.55 [0.05, 5.75]
Schaad 1993	0/1	0/1		0.0 %	0.0 [0.0, 0.0]
Thomas 1999	0/16	0/12		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/11	0/13		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**258**	**259**		**100.0 %**	**0.71 [0.31, 1.62]**

Total events: 9 (Treatment), 13 (Control)

Heterogeneity: $Chi^2 = 0.78$, df = 2 (P = 0.68); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
3 Streptococcus pneumoniae					
Bademosi 1979	1/28	12/24		12.8 %	0.07 [0.01, 0.51]
de Gans 2002	8/58	17/50		18.0 %	0.41 [0.19, 0.86]
DeLemos 1969	1/5	1/8		0.8 %	1.60 [0.13, 20.22]
Girgis 1989	7/52	22/54		21.3 %	0.33 [0.15, 0.71]
Kanra 1995	2/29	1/27		1.0 %	1.86 [0.18, 19.38]
Kilpi 1995	0/1	0/5		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/4	0/6		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/4	0/3		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	46/132	42/106		46.1 %	0.88 [0.63, 1.22]
Odio 1991	0/4	0/4		0.0 %	0.0 [0.0, 0.0]
Schaad 1993	0/5	0/6		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/13	0/13		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**335**	**306**		**100.0 %**	**0.59 [0.45, 0.77]**
Total events: 65 (Treatment), 95 (Control)					
Heterogeneity: Chi^2 = 14.75, df = 5 (P = 0.01); I^2 =66%					
Test for overall effect: Z = 3.85 (P = 0.00012)					

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
4 All other species than H. influenzae					
Bademosi 1979	11/28	12/24		9.8 %	0.79 [0.43, 1.45]
de Gans 2002	11/155	21/142		16.5 %	0.48 [0.24, 0.96]
DeLemos 1969	1/22	1/25		0.7 %	1.14 [0.08, 17.11]
Girgis 1989	13/184	32/189		23.8 %	0.42 [0.23, 0.77]
Kilpi 1995	0/17	0/13		0.0 %	0.0 [0.0, 0.0]
Lebel 1988a	0/11	0/12		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/12	0/11		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	71/226	62/204		49.2 %	1.03 [0.78, 1.37]
Odio 1991	0/13	0/19		0.0 %	0.0 [0.0, 0.0]
Schaad 1993	0/23	0/25		0.0 %	0.0 [0.0, 0.0]
Wald 1995	0/26	0/35		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**717**	**699**		**100.0 %**	**0.77 [0.62, 0.96]**
Total events: 107 (Treatment), 128 (Control)					
Heterogeneity: Chi^2 = 9.85, df = 4 (P = 0.04); I^2 =59%					
Test for overall effect: Z = 2.28 (P = 0.023)					

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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

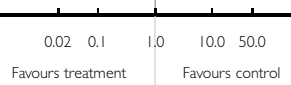
Outcome: 2 Severe hearing loss in children - non-Haemophilus influenzae species

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Belsey 1969	0/41	1/42		3.5 %	0.34 [0.01, 8.14]
Girgis 1989	0/16	4/15		11.1 %	0.10 [0.01, 1.79]
Kilpi 1995	1/17	2/13		5.4 %	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.3 %	1.05 [0.07, 15.69]
Lebel 1988a	1/17	2/19		4.5 %	0.56 [0.06, 5.63]
Lebel 1988b	0/12	2/14		5.5 %	0.23 [0.01, 4.38]
Lebel 1989	0/6	1/9		2.9 %	0.48 [0.02, 10.07]
Molyneux 2002	27/132	21/134		49.7 %	1.31 [0.78, 2.19]
Odio 1991	0/13	1/9		4.2 %	0.24 [0.01, 5.26]
Schaad 1993	1/23	3/25		6.9 %	0.36 [0.04, 3.24]
Wald 1995	2/25	2/35		4.0 %	1.40 [0.21, 9.28]
Total (95% CI)	**323**	**337**		**100.0 %**	**0.86 [0.57, 1.30]**

Total events: 33 (Treatment), 40 (Control)

Heterogeneity: Chi^2 = 8.00, df = 10 (P = 0.63); I^2 =0.0%

Test for overall effect: Z = 0.72 (P = 0.47)



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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 4 Causative species

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

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1988a	1/34	7/29		21.6 %	0.12 [0.02, 0.93]
Lebel 1988b	1/39	4/35		12.0 %	0.22 [0.03, 1.91]
Lebel 1989	1/25	1/20		3.2 %	0.80 [0.05, 12.01]
Odio 1991	3/38	6/39		16.9 %	0.51 [0.14, 1.91]
Schaad 1993	1/37	1/30		3.2 %	0.81 [0.05, 12.43]
King 1994	1/29	2/28		5.8 %	0.48 [0.05, 5.03]
Kilpi 1995	0/15	1/13		4.6 %	0.29 [0.01, 6.60]
Wald 1995	0/43	5/39		16.5 %	0.08 [0.00, 1.45]
Molyneux 2002	4/81	6/89		16.3 %	0.73 [0.21, 2.50]
Total (95% CI)	**341**	**322**		**100.0 %**	**0.37 [0.20, 0.68]**

Total events: 12 (Treatment), 33 (Control)

Heterogeneity: $Chi^2 = 4.56$, df = 8 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 3.21 (P = 0.0013)

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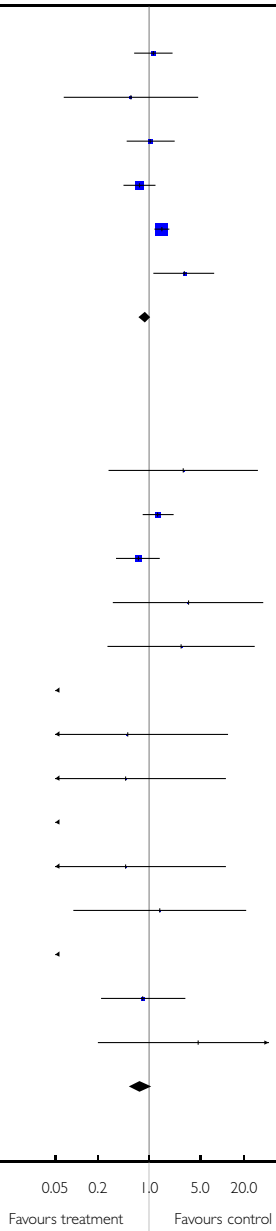
Analysis 5.1. Comparison 5 Income of countries, Outcome 1 Mortality - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 1 Mortality - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bademosi 1979	11/28	12/24		5.8 %	0.79 [0.43, 1.45]
Bhaumik 1998	1/14	3/16		1.3 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		5.2 %	0.71 [0.33, 1.51]
Girgis 1989	20/210	42/219		18.5 %	0.50 [0.30, 0.82]
Molyneux 2002	96/305	91/291		41.8 %	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		2.4 %	2.05 [0.79, 5.33]
Subtotal (95% CI)	**639**	**627**		**75.0 %**	**0.87 [0.72, 1.05]**
Total events: 148 (Treatment), 165 (Control)					
Heterogeneity: Chi² = 10.39, df = 5 (P = 0.06); I² =52%					
Test for overall effect: Z = 1.48 (P = 0.14)					
2 High-income countries					
Belsey 1969	2/43	1/43		0.4 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.8 %	0.90 [0.56, 1.46]
de Gans 2002	11/157	21/144		9.8 %	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.4 %	2.33 [0.22, 25.03]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		0.7 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1989	0/31	1/30		0.7 %	0.32 [0.01, 7.63]
Odio 1991	1/52	1/49		0.5 %	0.94 [0.06, 14.65]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Thomas 1999	3/31	5/29		2.3 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**748**	**736**		**25.0 %**	**0.74 [0.52, 1.05]**
Total events: 38 (Treatment), 55 (Control)					



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi^2 = 6.07, df = 10 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.095)					
Total (95% CI)	**1387**	**1363**		**100.0 %**	**0.83 [0.71, 0.99]**
Total events: 186 (Treatment), 220 (Control)					
Heterogeneity: Chi^2 = 16.96, df = 16 (P = 0.39); I^2 =6%					
Test for overall effect: Z = 2.12 (P = 0.034)					

0.05 0.2 1.0 5.0 20.0

Favours treatment Favours control

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 1 Mortality - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bademosi 1979	11/28	12/24		5.8 %	0.79 [0.43, 1.45]
Bhaumik 1998	1/14	3/16		1.3 %	0.38 [0.04, 3.26]
Ciana 1995	8/34	12/36		5.2 %	0.71 [0.33, 1.51]
Girgis 1989	20/210	42/219		18.5 %	0.50 [0.30, 0.82]
Molyneux 2002	96/305	91/291		41.8 %	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		2.4 %	2.05 [0.79, 5.33]
Subtotal (95% CI)	**639**	**627**		**75.0 %**	**0.87 [0.72, 1.05]**
Total events: 148 (Treatment), 165 (Control)					
Heterogeneity: Chi^2 = 10.39, df = 5 (P = 0.06); I^2 =52%					
Test for overall effect: Z = 1.48 (P = 0.14)					

0.05 0.2 1.0 5.0 20.0

Favours treatment Favours control

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 1 Mortality - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Belsey 1969	2/43	1/43		0.4 %	2.00 [0.19, 21.24]
Bennett 1963	16/38	22/47		8.8 %	0.90 [0.56, 1.46]
de Gans 2002	11/157	21/144		9.8 %	0.48 [0.24, 0.96]
DeLemos 1969	2/54	1/63		0.4 %	2.33 [0.22, 25.03]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		0.7 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1989	0/31	1/30		0.7 %	0.32 [0.01, 7.63]
Odio 1991	1/52	1/49		0.5 %	0.94 [0.06, 14.65]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Thomas 1999	3/31	5/29		2.3 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**748**	**736**		**25.0 %**	**0.74 [0.52, 1.05]**
Total events: 38 (Treatment), 55 (Control)					
Heterogeneity: Chi^2 = 6.07, df = 10 (P = 0.81); I^2 =0.0%					
Test for overall effect: Z = 1.67 (P = 0.095)					

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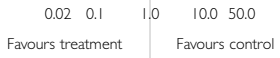
Analysis 5.2. Comparison 5 Income of countries, Outcome 2 Severe hearing loss - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 2 Severe hearing loss - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	2/13	2/13		2.6 %	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177		6.6 %	0.37 [0.07, 1.90]
Molyneux 2002	31/181	27/189		33.9 %	1.20 [0.75, 1.93]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Subtotal (95% CI)	**420**	**415**		**44.4 %**	**1.06 [0.69, 1.63]**
Total events: 36 (Treatment), 35 (Control)					
Heterogeneity: Chi^2 = 1.85, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					
2 High-income countries					
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Kanra 1995	0/29	0/27		0.0 %	0.0 [0.0, 0.0]
Kilpi 1995	1/32	3/26		4.2 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.8 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Odio 1991	3/51	7/48		9.3 %	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**464**	**448**		**55.6 %**	**0.33 [0.18, 0.58]**
Total events: 14 (Treatment), 42 (Control)					
Heterogeneity: Chi^2 = 1.82, df = 8 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 3.77 (P = 0.00016)					
Total (95% CI)	**884**	**863**		**100.0 %**	**0.65 [0.47, 0.91]**
Total events: 50 (Treatment), 77 (Control)					
Heterogeneity: Chi^2 = 13.57, df = 12 (P = 0.33); I^2 =12%					
Test for overall effect: Z = 2.51 (P = 0.012)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 2 Severe hearing loss - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	2/13	2/13		2.6 %	1.00 [0.16, 6.07]
Girgis 1989	2/190	5/177		6.6 %	0.37 [0.07, 1.90]
Molyneux 2002	31/181	27/189		33.9 %	1.20 [0.75, 1.93]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Subtotal (95% CI)	**420**	**415**		**44.4 %**	**1.06 [0.69, 1.63]**
Total events: 36 (Treatment), 35 (Control)					
Heterogeneity: Chi^2 = 1.85, df = 3 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.26 (P = 0.80)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 2 Severe hearing loss - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Kanra 1995	0/29	0/27		0.0 %	0.0 [0.0, 0.0]
Kilpi 1995	1/32	3/26		4.2 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.8 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		11.9 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		7.9 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Odio 1991	3/51	7/48		9.3 %	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.6 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**464**	**448**		**55.6 %**	**0.33 [0.18, 0.58]**
Total events: 14 (Treatment), 42 (Control)					
Heterogeneity: Chi^2 = 1.82, df = 8 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 3.77 (P = 0.00016)					

0.02 0.1 1.0 10.0 50.0

Favours treatment Favours control

Analysis 5.3. Comparison 5 Income of countries, Outcome 3 Short-term neurological sequelae - all patients.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 3 Short-term neurological sequelae - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	3/13	2/13		1.7 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		6.0 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		48.6 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**262**	**246**		**56.2 %**	**1.09 [0.83, 1.45]**
Total events: 77 (Treatment), 66 (Control)					
Heterogeneity: Chi^2 = 1.18, df = 2 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					
2 High-income countries					
de Gans 2002	4/143	14/118		12.7 %	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.8 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.8 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		7.0 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		8.4 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.1 %	0.62 [0.20, 1.99]

0.05 0.2 1.0 5.0 20.0

Favours treatment Favours control

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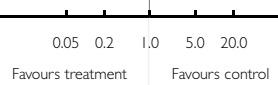
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Thomas 1999	5/28	9/24		8.0 %	0.48 [0.18, 1.23]
Subtotal (95% CI)	**355**	**312**		**43.8 %**	**0.56 [0.37, 0.84]**
Total events: 31 (Treatment), 50 (Control)					
Heterogeneity: Chi^2 = 5.03, df = 6 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 2.81 (P = 0.0050)					
Total (95% CI)	**617**	**558**		**100.0 %**	**0.86 [0.68, 1.08]**
Total events: 108 (Treatment), 116 (Control)					
Heterogeneity: Chi^2 = 12.53, df = 9 (P = 0.19); I^2 =28%					
Test for overall effect: Z = 1.31 (P = 0.19)					



Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 3 Short-term neurological sequelae - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Bhaumik 1998	3/13	2/13		1.7 %	1.50 [0.30, 7.55]
Ciana 1995	5/26	7/24		6.0 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		48.6 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**262**	**246**		**56.2 %**	**1.09 [0.83, 1.45]**
Total events: 77 (Treatment), 66 (Control)					
Heterogeneity: Chi^2 = 1.18, df = 2 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.63 (P = 0.53)					

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 3 Short-term neurological sequelae - all patients

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
de Gans 2002	4/143	14/118		12.7 %	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.8 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.8 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		7.0 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		8.4 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.1 %	0.62 [0.20, 1.99]
Thomas 1999	5/28	9/24		8.0 %	0.48 [0.18, 1.23]
Subtotal (95% CI)	**355**	**312**		**43.8 %**	**0.56 [0.37, 0.84]**

Total events: 31 (Treatment), 50 (Control)

Heterogeneity: $Chi^2 = 5.03$, df = 6 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 2.81 (P = 0.0050)

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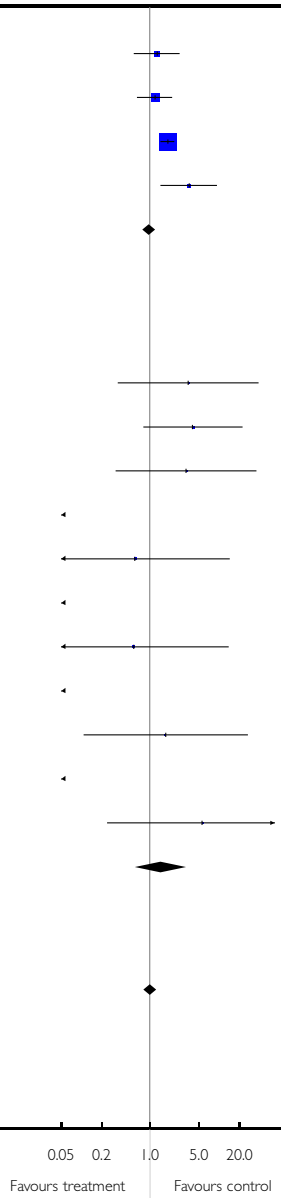
Analysis 5.4. Comparison 5 Income of countries, Outcome 4 Mortality - children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 4 Mortality - children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Ciana 1995	8/34	12/36		8.2 %	0.71 [0.33, 1.51]
Girgis 1989	16/142	24/140		16.9 %	0.66 [0.37, 1.18]
Molyneux 2002	96/305	91/291		65.2 %	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		3.8 %	2.05 [0.79, 5.33]
Subtotal (95% CI)	**529**	**508**		**94.1 %**	**0.96 [0.78, 1.18]**
Total events: 132 (Treatment), 132 (Control)					
Heterogeneity: Chi^2 = 4.79, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 0.39 (P = 0.69)					
2 High-income countries					
Belsey 1969	2/43	1/43		0.7 %	2.00 [0.19, 21.24]
DeLemos 1969	4/54	2/63		1.3 %	2.33 [0.44, 12.25]
Kanra 1995	2/29	1/27		0.7 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		1.0 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/51	1/49		1.1 %	0.32 [0.01, 7.68]
Lebel 1989	0/31	0/29		0.0 %	0.0 [0.0, 0.0]
Odio 1991	1/52	1/49		0.7 %	0.94 [0.06, 14.65]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**522**	**515**		**5.9 %**	**1.40 [0.59, 3.33]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: Chi^2 = 2.44, df = 6 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Total (95% CI)	**1051**	**1023**		**100.0 %**	**0.99 [0.81, 1.20]**
Total events: 142 (Treatment), 139 (Control)					
Heterogeneity: Chi^2 = 7.95, df = 10 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 4 Mortality - children

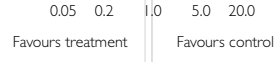
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Ciana 1995	8/34	12/36		8.2 %	0.71 [0.33, 1.51]
Girgis 1989	16/142	24/140		16.9 %	0.66 [0.37, 1.18]
Molyneux 2002	96/305	91/291		65.2 %	1.01 [0.79, 1.28]
Qazi 1996	12/48	5/41		3.8 %	2.05 [0.79, 5.33]
Subtotal (95% CI)	**529**	**508**		**94.1 %**	**0.96 [0.78, 1.18]**
Total events: 132 (Treatment), 132 (Control)					
Heterogeneity: Chi^2 = 4.79, df = 3 (P = 0.19); I^2 =37%					
Test for overall effect: Z = 0.39 (P = 0.69)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 4 Mortality - children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Belsey 1969	2/43	1/43		0.7 %	2.00 [0.19, 21.24]
DeLemos 1969	4/54	2/63		1.3 %	2.33 [0.44, 12.25]
Kanra 1995	2/29	1/27		0.7 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
King 1994	0/50	1/51		1.0 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1988b	0/51	1/49		1.1 %	0.32 [0.01, 7.68]



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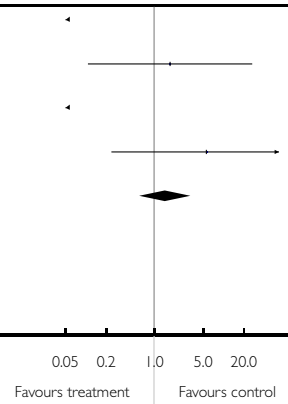
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1989	0/31	0/29		0.0 %	0.0 [0.0, 0.0]
Odio 1991	1/52	1/49		0.7 %	0.94 [0.06, 14.65]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Wald 1995	1/69	0/74		0.3 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**522**	**515**		**5.9 %**	**1.40 [0.59, 3.33]**
Total events: 10 (Treatment), 7 (Control)					
Heterogeneity: Chi^2 = 2.44, df = 6 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					



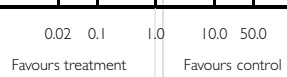
Analysis 5.5. Comparison 5 Income of countries, Outcome 5 Severe hearing loss - children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 5 Severe hearing loss - children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		6.0 %	0.10 [0.01, 1.79]
Molyneux 2002	31/181	27/189		34.4 %	1.20 [0.75, 1.93]
Subtotal (95% CI)	**197**	**204**		**40.4 %**	**1.04 [0.66, 1.63]**
Total events: 31 (Treatment), 31 (Control)					
Heterogeneity: Chi^2 = 2.87, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 0.15 (P = 0.88)					
2 High-income countries					
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/27		3.3 %	0.20 [0.01, 3.98]
Kilpi 1995	1/32	3/26		4.3 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.9 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		12.1 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		8.0 %	0.16 [0.02, 1.28]



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Odio 1991	3/51	7/48		9.4 %	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.7 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**462**	**448**		**59.6 %**	**0.32 [0.18, 0.57]**
Total events: 14 (Treatment), 44 (Control)					
Heterogeneity: Chi^2 = 1.94, df = 9 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 3.92 (P = 0.000088)					
Total (95% CI)	**659**	**652**		**100.0 %**	**0.61 [0.43, 0.86]**
Total events: 45 (Treatment), 75 (Control)					
Heterogeneity: Chi^2 = 15.38, df = 11 (P = 0.17); I^2 =28%					
Test for overall effect: Z = 2.83 (P = 0.0046)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 5 Severe hearing loss - children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		6.0 %	0.10 [0.01, 1.79]
Molyneux 2002	31/181	27/189		34.4 %	1.20 [0.75, 1.93]
Subtotal (95% CI)	**197**	**204**		**40.4 %**	**1.04 [0.66, 1.63]**
Total events: 31 (Treatment), 31 (Control)					
Heterogeneity: Chi^2 = 2.87, df = 1 (P = 0.09); I^2 =65%					
Test for overall effect: Z = 0.15 (P = 0.88)					

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 5 Severe hearing loss - children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Belsey 1969	0/41	1/42		1.9 %	0.34 [0.01, 8.14]
Kanra 1995	0/27	2/27		3.3 %	0.20 [0.01, 3.98]
Kilpi 1995	1/32	3/26		4.3 %	0.27 [0.03, 2.45]
King 1994	2/50	3/50		3.9 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		12.1 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		8.0 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Odio 1991	3/51	7/48		9.4 %	0.40 [0.11, 1.47]
Schaad 1993	2/60	4/55		5.4 %	0.46 [0.09, 2.40]
Wald 1995	2/68	7/74		8.7 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**462**	**448**		**59.6 %**	**0.32 [0.18, 0.57]**

Total events: 14 (Treatment), 44 (Control)

Heterogeneity: Chi^2 = 1.94, df = 9 (P = 0.99); I^2 =0.0%

Test for overall effect: Z = 3.92 (P = 0.000088)

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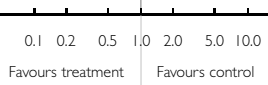
Analysis 5.6. Comparison 5 Income of countries, Outcome 6 Short-term neurological sequelae -children.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 6 Short-term neurological sequelae -children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Ciana 1995	5/26	7/24		7.7 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		62.5 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**249**	**233**		**70.2 %**	**1.08 [0.82, 1.44]**
Total events: 74 (Treatment), 64 (Control)					
Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%					
Test for overall effect: Z = 0.55 (P = 0.58)					
2 High-income countries					
Kanra 1995	2/27	1/27		1.1 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		2.3 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		9.0 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		10.9 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		6.6 %	0.62 [0.20, 1.99]
Subtotal (95% CI)	**184**	**170**		**29.8 %**	**0.76 [0.45, 1.27]**
Total events: 22 (Treatment), 27 (Control)					
Heterogeneity: Chi^2 = 1.20, df = 4 (P = 0.88); I^2 =0.0%					
Test for overall effect: Z = 1.06 (P = 0.29)					
Total (95% CI)	**433**	**403**		**100.0 %**	**0.99 [0.77, 1.26]**
Total events: 96 (Treatment), 91 (Control)					
Heterogeneity: Chi^2 = 3.71, df = 6 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.12 (P = 0.91)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 6 Short-term neurological sequelae -children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Ciana 1995	5/26	7/24		7.7 %	0.66 [0.24, 1.80]
Molyneux 2002	69/223	57/209		62.5 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**249**	**233**		**70.2 %**	**1.08 [0.82, 1.44]**

Total events: 74 (Treatment), 64 (Control)

Heterogeneity: Chi^2 = 1.03, df = 1 (P = 0.31); I^2 =3%

Test for overall effect: Z = 0.55 (P = 0.58)

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

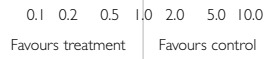
Outcome: 6 Short-term neurological sequelae -children

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Kanra 1995	2/27	1/27		1.1 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		2.3 %	0.84 [0.13, 5.55]
Lebel 1988a	5/48	8/43		9.0 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		10.9 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		6.6 %	0.62 [0.20, 1.99]
Subtotal (95% CI)	**184**	**170**		**29.8 %**	**0.76 [0.45, 1.27]**

Total events: 22 (Treatment), 27 (Control)

Heterogeneity: Chi^2 = 1.20, df = 4 (P = 0.88); I^2 =0.0%

Test for overall effect: Z = 1.06 (P = 0.29)



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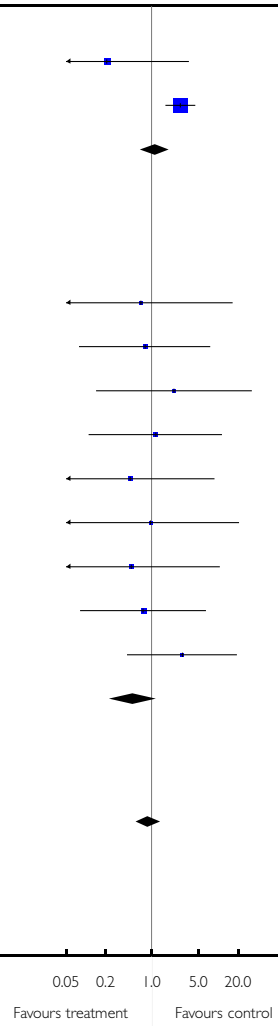
Analysis 5.7. Comparison 5 Income of countries, Outcome 7 Severe hearing loss in children due to non-Heamophilus influenzae species.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 7 Severe hearing loss in children due to non-Heamophilus influenzae species

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		11.1 %	0.10 [0.01, 1.79]
Molyneux 2002	27/132	21/134		49.7 %	1.31 [0.78, 2.19]
Subtotal (95% CI)	**148**	**149**		**60.7 %**	**1.09 [0.67, 1.77]**
Total events: 27 (Treatment), 25 (Control)					
Heterogeneity: Chi^2 = 3.09, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 0.33 (P = 0.74)					
2 High-income countries					
Belsey 1969	0/41	1/42		3.5 %	0.34 [0.01, 8.14]
Kilpi 1995	1/17	2/13		5.4 %	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.3 %	1.05 [0.07, 15.69]
Lebel 1988a	1/17	2/19		4.5 %	0.56 [0.06, 5.63]
Lebel 1988b	0/12	2/14		5.5 %	0.23 [0.01, 4.38]
Lebel 1989	0/6	1/9		2.9 %	0.48 [0.02, 10.07]
Odio 1991	0/13	1/9		4.2 %	0.24 [0.01, 5.26]
Schaad 1993	1/23	3/25		6.9 %	0.36 [0.04, 3.24]
Wald 1995	2/25	2/35		4.0 %	1.40 [0.21, 9.28]
Subtotal (95% CI)	**175**	**188**		**39.3 %**	**0.51 [0.23, 1.13]**
Total events: 6 (Treatment), 15 (Control)					
Heterogeneity: Chi^2 = 2.10, df = 8 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 1.65 (P = 0.098)					
Total (95% CI)	**323**	**337**		**100.0 %**	**0.86 [0.57, 1.30]**
Total events: 33 (Treatment), 40 (Control)					
Heterogeneity: Chi^2 = 8.00, df = 10 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 0.72 (P = 0.47)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 7 Severe hearing loss in children due to non-Heamophilus influenzae species

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Low-income countries					
Girgis 1989	0/16	4/15		11.1 %	0.10 [0.01, 1.79]
Molyneux 2002	27/132	21/134		49.7 %	1.31 [0.78, 2.19]
Subtotal (95% CI)	**148**	**149**		**60.7 %**	**1.09 [0.67, 1.77]**
Total events: 27 (Treatment), 25 (Control)					
Heterogeneity: Chi^2 = 3.09, df = 1 (P = 0.08); I^2 =68%					
Test for overall effect: Z = 0.33 (P = 0.74)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 5 Income of countries

Outcome: 7 Severe hearing loss in children due to non-Heamophilus influenzae species

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 High-income countries					
Belsey 1969	0/41	1/42		3.5 %	0.34 [0.01, 8.14]
Kilpi 1995	1/17	2/13		5.4 %	0.38 [0.04, 3.77]
King 1994	1/21	1/22		2.3 %	1.05 [0.07, 15.69]
Lebel 1988a	1/17	2/19		4.5 %	0.56 [0.06, 5.63]
Lebel 1988b	0/12	2/14		5.5 %	0.23 [0.01, 4.38]
Lebel 1989	0/6	1/9		2.9 %	0.48 [0.02, 10.07]
Odio 1991	0/13	1/9		4.2 %	0.24 [0.01, 5.26]
Schaad 1993	1/23	3/25		6.9 %	0.36 [0.04, 3.24]
Wald 1995	2/25	2/35		4.0 %	1.40 [0.21, 9.28]

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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**175**	**188**		**39.3 %**	**0.51 [0.23, 1.13]**
Total events: 6 (Treatment), 15 (Control)					
Heterogeneity: Chi^2 = 2.10, df = 8 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 1.65 (P = 0.098)					

0.05 0.2 1.0 5.0 20.0

Favours treatment Favours control

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

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
Bademosi 1979	11/28	12/24		6.2 %	0.79 [0.43, 1.45]
de Gans 2002	11/157	21/144		10.4 %	0.48 [0.24, 0.96]
Girgis 1989	20/210	42/219		19.6 %	0.50 [0.30, 0.82]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	96/305	91/291		44.3 %	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.5 %	0.94 [0.06, 14.65]
Qazi 1996	12/48	5/41		2.6 %	2.05 [0.79, 5.33]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**921**	**876**		**84.0 %**	**0.84 [0.70, 1.02]**
Total events: 153 (Treatment), 173 (Control)					
Heterogeneity: Chi^2 = 12.82, df = 6 (P = 0.05); I^2 =53%					
Test for overall effect: Z = 1.78 (P = 0.075)					
2 After first dose antibiotic					
Bennett 1963	16/38	22/47		9.4 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		1.3 %	0.38 [0.04, 3.26]
DeLemos 1969	2/54	1/63		0.4 %	2.33 [0.22, 25.03]

0.05 0.2 1.0 5.0 20.0

Favours treatment Favours control

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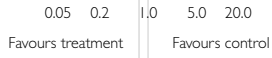
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
King 1994	0/50	1/51		0.7 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1989	0/31	1/30		0.7 %	0.32 [0.01, 7.63]
Thomas 1999	3/31	5/29		2.5 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**389**	**408**		**16.0 %**	**0.80 [0.52, 1.22]**
Total events: 23 (Treatment), 34 (Control)					
Heterogeneity: Chi^2 = 3.38, df = 7 (P = 0.85); I^2 =0.0%					
Test for overall effect: Z = 1.03 (P = 0.30)					
Total (95% CI)	**1310**	**1284**		**100.0 %**	**0.84 [0.70, 0.99]**
Total events: 176 (Treatment), 207 (Control)					
Heterogeneity: Chi^2 = 16.23, df = 14 (P = 0.30); I^2 =14%					
Test for overall effect: Z = 2.04 (P = 0.042)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
Bademosi 1979	11/28	12/24		6.2 %	0.79 [0.43, 1.45]
de Gans 2002	11/157	21/144		10.4 %	0.48 [0.24, 0.96]
Girgis 1989	20/210	42/219		19.6 %	0.50 [0.30, 0.82]
Kanra 1995	2/29	1/27		0.5 %	1.86 [0.18, 19.38]
Kilpi 1995	0/32	0/26		0.0 %	0.0 [0.0, 0.0]
Molyneux 2002	96/305	91/291		44.3 %	1.01 [0.79, 1.28]
Odio 1991	1/52	1/49		0.5 %	0.94 [0.06, 14.65]



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Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Qazi 1996	12/48	5/41		2.6 %	2.05 [0.79, 5.33]
Schaad 1993	0/60	0/55		0.0 %	0.0 [0.0, 0.0]
Subtotal (95% CI)	**921**	**876**		**84.0 %**	**0.84 [0.70, 1.02]**

Total events: 153 (Treatment), 173 (Control)

Heterogeneity: Chi^2 = 12.82, df = 6 (P = 0.05); I^2 =53%

Test for overall effect: Z = 1.78 (P = 0.075)

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

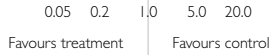
Outcome: 1 Mortality

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 After first dose antibiotic					
Bennett 1963	16/38	22/47		9.4 %	0.90 [0.56, 1.46]
Bhaumik 1998	1/14	3/16		1.3 %	0.38 [0.04, 3.26]
DeLemos 1969	2/54	1/63		0.4 %	2.33 [0.22, 25.03]
King 1994	0/50	1/51		0.7 %	0.34 [0.01, 8.15]
Lebel 1988a	0/51	1/49		0.7 %	0.32 [0.01, 7.68]
Lebel 1988b	0/51	0/49		0.0 %	0.0 [0.0, 0.0]
Lebel 1989	0/31	1/30		0.7 %	0.32 [0.01, 7.63]
Thomas 1999	3/31	5/29		2.5 %	0.56 [0.15, 2.14]
Wald 1995	1/69	0/74		0.2 %	3.21 [0.13, 77.60]
Subtotal (95% CI)	**389**	**408**		**16.0 %**	**0.80 [0.52, 1.22]**

Total events: 23 (Treatment), 34 (Control)

Heterogeneity: Chi^2 = 3.38, df = 7 (P = 0.85); I^2 =0.0%

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



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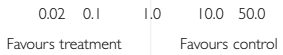
Analysis 6.2. Comparison 6 Timing of steroids, Outcome 2 Severe hearing loss.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 2 Severe hearing loss

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
Girgis 1989	2/190	5/177		6.8 %	0.37 [0.07, 1.90]
Kanra 1995	0/29	0/27		0.0 %	0.0 [0.0, 0.0]
Kilpi 1995	1/32	3/26		4.3 %	0.27 [0.03, 2.45]
Molyneux 2002	31/181	27/189		34.6 %	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.4 %	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.5 %	0.46 [0.09, 2.40]
Subtotal (95% CI)	**579**	**558**		**61.9 %**	**0.85 [0.58, 1.26]**
Total events: 40 (Treatment), 47 (Control)					
Heterogeneity: Chi^2 = 5.86, df = 5 (P = 0.32); I^2 =15%					
Test for overall effect: Z = 0.80 (P = 0.43)					
2 After first dose antibiotic					
Bhaumik 1998	2/13	2/13		2.6 %	1.00 [0.16, 6.07]
King 1994	2/50	3/50		3.9 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		12.1 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		8.0 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Wald 1995	2/68	7/74		8.8 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**264**	**263**		**38.1 %**	**0.34 [0.17, 0.69]**
Total events: 10 (Treatment), 29 (Control)					
Heterogeneity: Chi^2 = 2.94, df = 5 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 3.02 (P = 0.0025)					
Total (95% CI)	**843**	**821**		**100.0 %**	**0.66 [0.47, 0.92]**
Total events: 50 (Treatment), 76 (Control)					
Heterogeneity: Chi^2 = 13.35, df = 11 (P = 0.27); I^2 =18%					
Test for overall effect: Z = 2.44 (P = 0.015)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 2 Severe hearing loss

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
Girgis 1989	2/190	5/177		6.8 %	0.37 [0.07, 1.90]
Kanra 1995	0/29	0/27		0.0 %	0.0 [0.0, 0.0]
Kilpi 1995	1/32	3/26		4.3 %	0.27 [0.03, 2.45]
Molyneux 2002	31/181	27/189		34.6 %	1.20 [0.75, 1.93]
Odio 1991	3/51	7/48		9.4 %	0.40 [0.11, 1.47]
Qazi 1996	1/36	1/36		1.3 %	1.00 [0.07, 15.38]
Schaad 1993	2/60	4/55		5.5 %	0.46 [0.09, 2.40]
Subtotal (95% CI)	**579**	**558**		**61.9 %**	**0.85 [0.58, 1.26]**
Total events: 40 (Treatment), 47 (Control)					
Heterogeneity: Chi^2 = 5.86, df = 5 (P = 0.32); I^2 =15%					
Test for overall effect: Z = 0.80 (P = 0.43)					

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Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 2 Severe hearing loss

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 After first dose antibiotic					
Bhaumik 1998	2/13	2/13		2.6 %	1.00 [0.16, 6.07]
King 1994	2/50	3/50		3.9 %	0.67 [0.12, 3.82]
Lebel 1988a	2/51	9/48		12.1 %	0.21 [0.05, 0.92]
Lebel 1988b	1/51	6/49		8.0 %	0.16 [0.02, 1.28]
Lebel 1989	1/31	2/29		2.7 %	0.47 [0.04, 4.89]
Wald 1995	2/68	7/74		8.8 %	0.31 [0.07, 1.45]
Subtotal (95% CI)	**264**	**263**		**38.1 %**	**0.34 [0.17, 0.69]**
Total events: 10 (Treatment), 29 (Control)					
Heterogeneity: Chi^2 = 2.94, df = 5 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 3.02 (P = 0.0025)					

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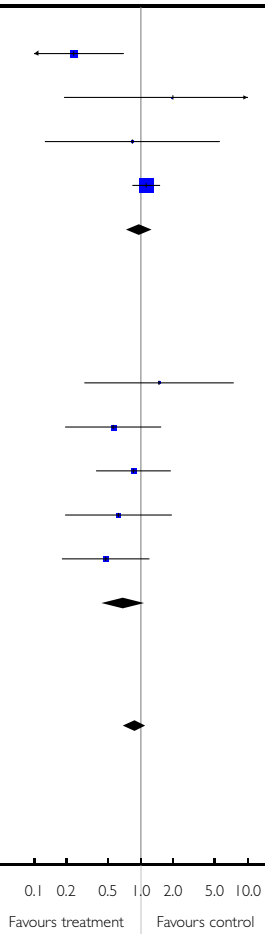
Analysis 6.3. Comparison 6 Timing of steroids, Outcome 3 Short-term neurologic sequelae.

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 3 Short-term neurologic sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
de Gans 2002	4/143	14/118		13.5 %	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.9 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.9 %	0.84 [0.13, 5.55]
Molyneux 2002	69/223	57/209		51.7 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**424**	**380**		**67.9 %**	**0.96 [0.73, 1.26]**
Total events: 77 (Treatment), 74 (Control)					
Heterogeneity: Chi^2 = 8.07, df = 3 (P = 0.04); I^2 =63%					
Test for overall effect: Z = 0.30 (P = 0.77)					
2 After first dose antibiotic					
Bhaumik 1998	3/13	2/13		1.8 %	1.50 [0.30, 7.55]
Lebel 1988a	5/48	8/43		7.4 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		9.0 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.4 %	0.62 [0.20, 1.99]
Thomas 1999	5/28	9/24		8.5 %	0.48 [0.18, 1.23]
Subtotal (95% CI)	**167**	**154**		**32.1 %**	**0.68 [0.43, 1.08]**
Total events: 26 (Treatment), 35 (Control)					
Heterogeneity: Chi^2 = 1.95, df = 4 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					
Total (95% CI)	**591**	**534**		**100.0 %**	**0.87 [0.69, 1.10]**
Total events: 103 (Treatment), 109 (Control)					
Heterogeneity: Chi^2 = 12.15, df = 8 (P = 0.14); I^2 =34%					
Test for overall effect: Z = 1.15 (P = 0.25)					



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Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 3 Short-term neurologic sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Before or with first dose antibiotic					
de Gans 2002	4/143	14/118		13.5 %	0.24 [0.08, 0.70]
Kanra 1995	2/27	1/27		0.9 %	2.00 [0.19, 20.77]
Kilpi 1995	2/31	2/26		1.9 %	0.84 [0.13, 5.55]
Molyneux 2002	69/223	57/209		51.7 %	1.13 [0.84, 1.52]
Subtotal (95% CI)	**424**	**380**		**67.9 %**	**0.96 [0.73, 1.26]**
Total events: 77 (Treatment), 74 (Control)					
Heterogeneity: Chi^2 = 8.07, df = 3 (P = 0.04); I^2 =63%					
Test for overall effect: Z = 0.30 (P = 0.77)					

Review: Corticosteroids for acute bacterial meningitis

Comparison: 6 Timing of steroids

Outcome: 3 Short-term neurologic sequelae

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
2 After first dose antibiotic					
Bhaumik 1998	3/13	2/13		1.8 %	1.50 [0.30, 7.55]
Lebel 1988a	5/48	8/43		7.4 %	0.56 [0.20, 1.58]
Lebel 1988b	9/47	10/45		9.0 %	0.86 [0.39, 1.92]
Lebel 1989	4/31	6/29		5.4 %	0.62 [0.20, 1.99]
Thomas 1999	5/28	9/24		8.5 %	0.48 [0.18, 1.23]
Subtotal (95% CI)	**167**	**154**		**32.1 %**	**0.68 [0.43, 1.08]**
Total events: 26 (Treatment), 35 (Control)					
Heterogeneity: Chi^2 = 1.95, df = 4 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 1.64 (P = 0.10)					

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FEEDBACK

Progress

Summary

Is the review due for publication in the near future? I note it was submitted over 12 months ago.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

It will be published 07-21-2003.
Contact address D.vandeBeek@amc.uva.nl

Contributors

Dr Anna Holdgate
Feedback added 25/07/04
Reply added 11/11/04

Paper by Shembesh et al

Summary

I have not seen the full text article, but in the medline abstract it states ages 1 month to 10 years are included. Table 01 states all ages were included.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Patients of any age could be included in our review (as stated in the Pubmed abstract). In the study of Shembesh et al, patients aged 1 month to 10 years were included. However, this is only one of the 29 potential eligible trials evalutated in our review.
Diederik van der Beek

Contributors

Andrew Webster
Feedback added 25/07/04
Reply added 11/11/04

WHAT'S NEW

Last assessed as up-to-date: 9 November 2006.

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14 May 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 1998

Review first published: Issue 3, 2003

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

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

Jan de Gans (JdG) was responsible for co-designing, co-writing the review, selecting studies, extracting 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-writing the protocol and co-writing the review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Dept. of Neurology, Academic Medical Center, University of Amsterdam, Netherlands.

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External sources

- Netherlands Organisation for Health Research and Development (NWO-Veni and Rubicon Grants 2006), Netherlands.

NOTES

2006 updated review: two large new clinical trials were included.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Child; Humans

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