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Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants (Review)

Onland W, Offringa M, van Kaam A

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Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants.
Cochrane Database of Systematic Reviews 2017, Issue 8. Art. No.: CD002311.
DOI: 10.1002/14651858.CD002311.pub4.

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[Intervention Review]

Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants

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Editorial group: Cochrane Neonatal Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2017.

Citation: Onland W, Offringa M, van Kaam A. Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. *Cochrane Database of Systematic Reviews* 2017, Issue 8. Art. No.: CD002311. DOI: 10.1002/14651858.CD002311.pub4.

ABSTRACT

Background

Bronchopulmonary dysplasia (BPD), defined as oxygen dependence at 36 weeks postmenstrual age (PMA), remains an important complication of prematurity. Pulmonary inflammation plays a central role in the pathogenesis of BPD. Attenuating pulmonary inflammation with postnatal systemic corticosteroids reduces the incidence of BPD in preterm infants but may be associated with an increased risk of adverse neurodevelopmental outcomes. Local administration of corticosteroids via inhalation might be an effective and safe alternative.

Objectives

To determine if administration of inhalation corticosteroids after the first week of life until 36 weeks PMA to preterm infants at high risk of developing BPD is effective and safe in reducing the incidence of death and BPD as separate or combined outcomes.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 4), MEDLINE via PubMed (1966 to 19 May 2017), Embase (1980 to 19 May 2017), and CINAHL (1982 to 19 May 2017). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials**.**

Selection criteria

We included randomised controlled trials comparing inhalation corticosteroids, started ≥ 7 days postnatal age (PNA) but before 36 weeks PMA, to placebo in ventilated and non-ventilated infants at risk of BPD. We excluded trials investigating systemic corticosteroids versus inhalation corticosteroids.

Data collection and analysis

We collected data on participant characteristics, trial methodology, and inhalation regimens. The primary outcome was death or BPD at 36 weeks PMA. Secondary outcomes were the combined outcome death or BPD at 28 days PNA, the seperate outcomes of death and BPD at both 28 days PNA, and at 36 weeks PMA, and short-term respiratory outcomes, such as failure to extubate; total days of mechanical ventilation and oxygen use; and the need for systemic corticosteroids. We contacted the original trialists to verify the validity of extracted data and to provide missing data. We analysed all data using Review Manager 5. When possible, we performed meta-analysis using typical risk ratio (RR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes along with their 95% confidence intervals (CI). We analysed ventilated and non-ventilated participants separately.

We used the GRADE approach to assess the quality of the evidence.

Main results

We included eight trials randomising 232 preterm infants in this review. Inhalation corticosteroids did not reduce the separate or combined outcomes of death or BPD. The meta-analyses of the studies showed a reduced risk in favor of inhalation steroids regarding failure to extubate at seven days (typical RR (TRR) 0.80, 95% CI 0.66 to 0.98; 5 studies, 79 infants) and at the latest reported time point after treatment onset (TRR 0.60, 95% CI 0.45 to 0.80; 6 studies, 90 infants). However, both analyses showed increased statistical heterogeneity (I^2 statistic 73% and 86%, respectively). Furthermore, inhalation steroids did not impact total duration of mechanical ventilation or oxygen dependency. There was a trend toward a reduction in the use of systemic corticosteroids in infants receiving inhalation corticosteroids (TRR 0.51, 95% CI 0.26 to 1.00; 4 studies, 74 infants; very low-quality evidence). There was a paucity of data on short- and long-term adverse effects. Our results should be interpreted with caution because the total number of randomised participants is relatively small, and most trials differed considerably in participant characteristics, inhalation therapy, and outcome definitions.

Authors' conclusions

Based on the results of the currently available evidence, inhalation corticosteroids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time. More and larger randomised, placebo-controlled trials are needed to establish the efficacy and safety of inhalation corticosteroids.

PLAIN LANGUAGE SUMMARY

Inhalation corticosteroids for bronchopulmonary dysplasia

Review question

Does inhalation of corticosteroids after the first week of life reduce the risk of developing bronchopulmonary dysplasia (BPD) in preterm infants? This review looked at studies comparing preterm infants at risk of developing BPD after the first week of life treated with inhalation corticosteroids to those treated with inhalation placebo.

Background

Preterm infants have an increased risk of developing chronic lung disease or bronchopulmonary dysplasia. Inflammation in the lung seems to play a central role in the development of BPD. Administration of anti-inflammatory drugs known as corticosteroids into the bloodstream (systemically) reduces the risk of BPD but can also cause serious side effects. Administering corticosteroids via inhalation directly into the lungs may reduce these side effects.

Study characteristics

We identified eight studies investigating this therapy in 232 infants. Although we deemed the risk of bias as low, very few studies reported our outcomes of interest.

Key results

The included trials did not show a beneficial effect of inhalation corticosteroids on death or BPD. In addition, the safety of inhalation corticosteroids was assessed in only a small number of trials. Based on these results, inhalation corticosteroids initiated after the first week of life cannot be recommended for preterm infants at risk of BPD. More studies are needed.

Quality of evidence

The quality of the evidence was low to very low for the main outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants

Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants

Patient or population: preterm infants
Setting: neonatal intensive care units
Intervention: inhaled corticosteroids
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with inhaled corticosteroids				
Combined outcome mortality or bronchopulmonary dysplasia at 36 weeks postmenstrual age	Study population		RR 1.10 (0.74 to 1.63)	30 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3 4 5]	
	533 per 1000	587 per 1000 (395 to 869)				
Mortality at 36 weeks postmenstrual age	Study population		RR 3.00 (0.35 to 25.78)	61 (3 RCTs)	⊕⊕⊖⊖ LOW [1 2 5 6 7]	
	0 per 1000	0 per 1000 (0 to 0)				
Bronchopulmonary dysplasia at 36 weeks postmenstrual age	Study population		RR 1.00 (0.59 to 1.70)	30 (1 RCT)	⊕⊖⊖⊖ VERY LOW [1 2 3 4 5]	
	600 per 1000	600 per 1000 (354 to 1000)				
Open-label intravenous corticosteroids	Study population		RR 0.51 (0.26 to 1.00)	74 (4 RCTs)	⊕⊖⊖⊖ VERY LOW [1 5 8 9 10]	
	432 per 1000	320 per 1000 (216 to 476)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[1]Risk of bias: No serious limitations. No downgrade.
[2]Indirectness: Head-to-head comparison. No downgrade.
[3]Publication bias: Only one trial was able to provide data for this outcome for ventilated and non-ventilated infants separately. Downgraded one level.
[4]Inconsistency: Difference in effect estimates might be explained by inclusion of both ventilated and non-ventilated infants. Downgraded one level.
[5]Imprecision: Total number of included infants less than optimal information size calculation. Downgraded one level.
[6]Inconsistency: No inconsistency detected. No downgrade.
[7]Publication bias: Only two of the eight included studies reported this outcome. Downgraded one level.
[8]Inconsistency: Included trials investigated different inhalation drugs. Downgraded one level.
[9]Indirectness: No serious limitations. No downgrade.
[10]Publication bias: Funnel plot is asymmetrical. Downgraded one level.

BACKGROUND

Description of the condition

Bronchopulmonary dysplasia (BPD), defined as oxygen dependency at 36 weeks postmenstrual age (PMA), is the most important complication of prematurity, with a reported incidence of 23% in infants born at 28 weeks and increasing to 73% in infants born at 23 weeks (Stoll 2010). Bronchopulmonary dysplasia is characterised by prolonged respiratory support, compromised lung function, and recurrent respiratory infections during the first years of life (Bolton 2015; Doyle 2006). Furthermore, BPD is considered an independent risk factor for neurodevelopmental impairment (Short 2007; Walsh 2005). Bronchopulmonary dysplasia is a multifactorial disease with mechanical ventilation, oxygen toxicity, and pre- and postnatal infection as the most important risk factors, and pulmonary inflammation playing a central mediating role.

Description of the intervention

The intervention of interest was inhaled corticosteroids administered to either ventilated or non-ventilated newborn infants at risk of developing BPD. Budesonide, beclomethasone, and fluticasone are the most frequently used inhaled corticosteroids in newborn infants, and these drugs are almost exclusively delivered using a pressurised metered dose inhaler or a nebuliser. Studies in preterm infants have revealed that metered-dose inhalation results in a far better deposition than nebulisation. In addition, inhalation via an endotracheal tube provides better deposition than inhalation via a face mask (Fok 1996).

How the intervention might work

Pulmonary inflammation plays a central modulating role in the pathogenesis of BPD (Jobe 2001; McEvoy 2014; Pierce 1995). Corticosteroids have a strong anti-inflammatory effect, making them an ideal candidate to attenuate the inflammatory response associated with BPD. Randomised controlled trials (RCTs) have shown that systemic administration of corticosteroids reduces the incidence of BPD and the combined outcome of death or BPD in ventilated preterm infants (Doyle 2014; Doyle 2014a). However, systemic corticosteroids are also associated with short-term (e.g. hyperglycaemia, hypertension, infection) and long-term (neurodevelopmental impairment) adverse effects. This balance between beneficial and adverse effects of corticosteroids may be more favourable when using the inhalation route because, ideally, inhaled corticosteroids should demonstrate high pulmonary deposition in addition to a low systemic bioavailability and rapid systemic clearance.

Why it is important to do this review

The association between early (< 7 days of life) systemic corticosteroids use and adverse neurodevelopmental outcomes has resulted in a reduction in the overall use of corticosteroids in ventilated preterm infants (Cheong 2013; Walsh 2006; Yoder 2009). Administering corticosteroids by inhalation might be a safe and effective alternative, and this method of administering corticosteroids to infants at risk for BPD is already frequently being used in every part of the world (Job 2015; Maas 2010; Ogawa 2015; Slaughter 2014). A systematic review of the randomised evidence on inhaled corticosteroids in preterm infants was first published in the Cochrane Library in 1999, followed by an update in 2002 (Lister 2000). The second update of this systematic review included those RCTs published after 2002 and extended the inclusion criteria by including all RCTs initiating inhalation corticosteroids after the first week of life, in line with the Cochrane Reviews on systemic corticosteroids (Doyle 2014; Doyle 2014a). The conclusions of that review were that in ventilated infants, administration of inhalation corticosteroids resulted in an improved rate of extubation without any apparent adverse effects. No firm conclusions could be drawn for non-ventilated infants (Onland 2012).

Other Cochrane Neonatal reviews of corticosteroids in the Cochrane Library

Additional neonatal reviews in the Cochrane Library that address the use of corticosteroids in the prevention or treatment of bronchopulmonary dysplasia include the following.

- Use of systemic steroids:
  - early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants (Doyle 2014a);
  - late (> 7 days) postnatal corticosteroids for chronic lung disease in preterm infants (Doyle 2014);
  - systemic corticosteroid regimens for the prevention of bronchopulmonary dysplasia in preterm infants (Onland 2017).
- Inhaled steroids:
  - early administration of inhaled corticosteroids for preventing chronic lung disease in ventilated very low birthweight preterm neonates (Shah 2017).
- Comparison trials (inhaled versus systemic corticosteroids):
  - inhaled versus systemic corticosteroids for preventing chronic lung disease in ventilated very low birthweight preterm neonates (Shah 2012);
  - inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birthweight preterm infants (Shah 2012a).
- Other studies of corticosteroids in neonates:
  - intravenous dexamethasone for extubation of newborn infants (Davis 2001);
  - corticosteroids for treating hypotension in preterm infants (Ibrahim 2011);
  - steroid therapy for meconium aspiration syndrome in newborn infants (Ward 2003).

OBJECTIVES

To determine if administration of inhalation corticosteroids after the first week of life until 36 weeks PMA to preterm infants at high risk of developing BPD is effective and safe in reducing the incidence of death and BPD as separate or combined outcomes.

The secondary objective was to compare the effectiveness of inhaled corticosteroids versus placebo on respiratory support, the need for systemic corticosteroids, and adverse effects during hospitalisation and long-term follow-up. Furthermore, we performed subgroup analyses on the timing of therapy onset and the difference in effect estimates for ventilated and non-ventilated infants.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised placebo-controlled trials.

Types of participants

Preterm infants ≥ 7 days postnatal age (PNA) but before 36 weeks PMA needing mechanical ventilation or supplemental oxygen, or both.

Types of interventions

We included trials if infants were randomised to treatment with inhalation corticosteroid or placebo. The intervention had to be a standardised (non-individualised) dosage regimen of inhalation corticosteroids, initiated between seven days of life and 36 weeks PMA. We excluded studies investigating inhalation corticosteroids compared to, or in addition to, systemic corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone).

Types of outcome measures

To be included in the review, the trials had to report on one or more of the following outcome parameters.

- The combined outcome death or BPD at 28 days PNA and 36 weeks PMA
- Death at 28 days PNA, 36 weeks PMA, and hospital discharge
- BPD (defined as the need for supplemental oxygen) at 28 days PNA and 36 weeks PMA
- Failure to extubate at day 7 and 14 after initiating therapy and at the latest reported time point
- Days of mechanical ventilation
- Days of supplemental oxygen
- Days of hospitalisation
- The use of systemic corticosteroids
- Sepsis, defined as clinical suspected or culture proven
- Hypertension
- Hyperglycaemia
- Gastrointestinal bleeding or perforation (spontaneous intestinal perforation)
- Necrotising enterocolitis
- Patent ductus arteriosus (PDA)
- Intraventricular haemorrhage, any grade
- Periventricular leukomalacia
- Retinopathy of prematurity, any grade
- Long-term neurodevelopmental sequelae, assessed after at least one year corrected gestational age (CGA) and before a CGA of four years, including cerebral palsy and Bayley Scales of Infant Development (Mental Development Index)
- Blindness
- Deafness

Primary outcomes

1. Combined outcome of death or BPD at 36 weeks PMA (BPD defined as oxygen dependency at 36 weeks PMA).

Secondary outcomes

Secondary outcomes in the ventilated infants were total duration of mechanical ventilation, failure to extubate at day 7 and day 14 after initiating therapy and, in the non-ventilated infants, the supplemental fractional concentration of inspired oxygen (FiO_2).

In both groups further secondary outcomes were mortality at hospital discharge, at 28 days PNA, and 36 weeks PMA, BPD at 28 days PNA and at 36 weeks PMA, the airway resistance, dynamic lung compliance, the use of systemic corticosteroids; incidence of PDA, necrotising enterocolitis, hypertension, sepsis, or hyperglycaemia during hospitalisation; long-term neurodevelopmental sequelae, assessed after at least one-year corrected gestational age (CGA) and before a CGA of four years including cerebral palsy and Bayley Scales of Infant Development (Mental Development Index).

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialized register).

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 4) in the Cochrane Library; MEDLINE via PubMed (1966 to 19 May 2017); Embase (1980 to 19 May 2017); and CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1982 to 19 May 2017) using the following search terms: (Adrenal cortex hormones[MeSH] OR steroids[MeSH] OR glucocorticoid OR dexamethasone OR flixotide OR fluticasone OR becotide OR beclomethasone OR pulmicort OR budesonide OR (anti-inflammatory Agents[MeSH] NOT anti-inflammatory Agents, non-steroidal[MeSH])) AND (inhal* OR nebulis* OR nebuliz* OR aerolis* OR aeroliz*), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We applied no language restrictions.

See Appendix 2 for the search methodology used in previous versions of this review.

We searched clinical trials registries (19 May 2017) for ongoing or recently completed trials (ClinicalTrials.gov (www.clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform (www.whoint/ictrp/search/en/), and the ISRCTN registry (www.isrctn.com/)).

Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles.

Data collection and analysis

Selection of studies

Two review authors (WO and AvK) further classified the relevant citations found following the database searches into three groups, namely 'clearly an RCT', 'clearly not an RCT', and 'possibly an RCT'. We performed full-text review on all studies except those 'clearly not an RCT'. We resolved any disagreements by consensus.

Data extraction and management

In addition to the predefined outcome parameters, two review authors (WO and AvK) independently extracted the following clinical data using a preset data extraction form: participant characteristics (birthweight, gestational age, gender), number of participants randomised, treatment with antenatal glucocorticoids, postnatal surfactant. We resolved any disagreement by consensus.

We asked the original investigators of the included RCTs to confirm whether the data extraction was accurate and, where necessary, to provide additional (unpublished) data.

Assessment of risk of bias in included studies

Two review authors (WO and AvK) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains (Higgins 2011).

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

Any disagreements were resolved by discussion or by a third assessor. See Appendix 3 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We performed meta-analysis of the extracted data using the standard methods of the Cochrane Neonatal Review Group. We processed the extracted data using the Cochrane statistical package, RevMan 5. Treatment effect estimates for all trials were calculated, expressed as typical risk ratio (typical RR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes, all with a 95% confidence interval (CI).

Unit of analysis issues

This review did not include trials with non-standard designs, and no effect measures for counts and rates were necessary.

Dealing with missing data

All trials were performed with an intention-to-treat analysis. We asked the original investigators of the included RCTs to provide additional (unpublished) data.

Assessment of heterogeneity

We assessed heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity employing the I^2 statistic, using the following categories as defined by the Cochrane Neonatal Review Group.

- Less than 25%: no heterogeneity
- 25% to 49%: low heterogeneity
- 50% to 74%: moderate heterogeneity
- 75% or greater: high heterogeneity

We explored possible causes of statistical heterogeneity using prespecified subgroup analysis (e.g. differences in inclusions of ventilated and non-ventilated infants). We used fixed-effect models for the meta-analyses.

Assessment of reporting biases

We planned funnel plots to assess possible reporting biases. We used no language restriction in the search strategy.

Data synthesis

We performed meta-analysis of the extracted data using standard Cochrane methods and Review Manager 5. Treatment effects for dichotomous outcomes were expressed as typical RR with a 95% CI, typical risk difference (TRD), and number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH) in case of significance. We used mean differences (MD) for continuous outcomes. In case of variance of outcome measures (with different standard deviation) measuring the same outcome, we calculated standardised mean differences (SMD) in the meta-analysis. We used fixed-effect models.

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: the combined outcome of BPD or death at 36 weeks PMA, as well as the combined outcomes of death or cerebral palsy, and death or abnormal neurodevelopmental outcome, and open-label rescue therapy of systemic corticosteroids during study medication or after study medication was stopped.

Two review authors (WO and AvK) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used GRADEpro to create a 'Summary of findings' table to report the quality of the evidence (GRADEpro GDT).

The GRADE approach results in an assessment of the quality of a body of evidence in one of the following four grades.

1. High: We are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We handled data on outcomes of ventilated and non-ventilated participants at trial entry as two separate subgroups.

Sensitivity analysis

We planned sensitivity analyses to examine the potential influence of treatment variation (type and dose of inhalation corticosteroid, duration of treatment, and delivery system).

RESULTS

Description of studies

See Characteristics of included studies.

Results of the search

The original search strategy in 2011 identified 46 relevant manuscripts (27 published in MEDLINE and 19 by handsearching) (Figure 1). Electronic searches of Embase, CINAHL, and CENTRAL in 2011 revealed no new relevant manuscripts. Two review authors (WO and AvK) independently reviewed the abstracts of these studies for inclusion in this review. There was consensus between the review authors. The electronic search of the different registries from 2011 to 2017 revealed one potentially eligible abstract (Figure 2). However, after reading the full-text manuscript, we excluded this RCT because it included only infants > 36 weeks PMA (Kugelman 2017).

Figure 1. Flow of inclusion of randomised controlled trials in different phases of search.

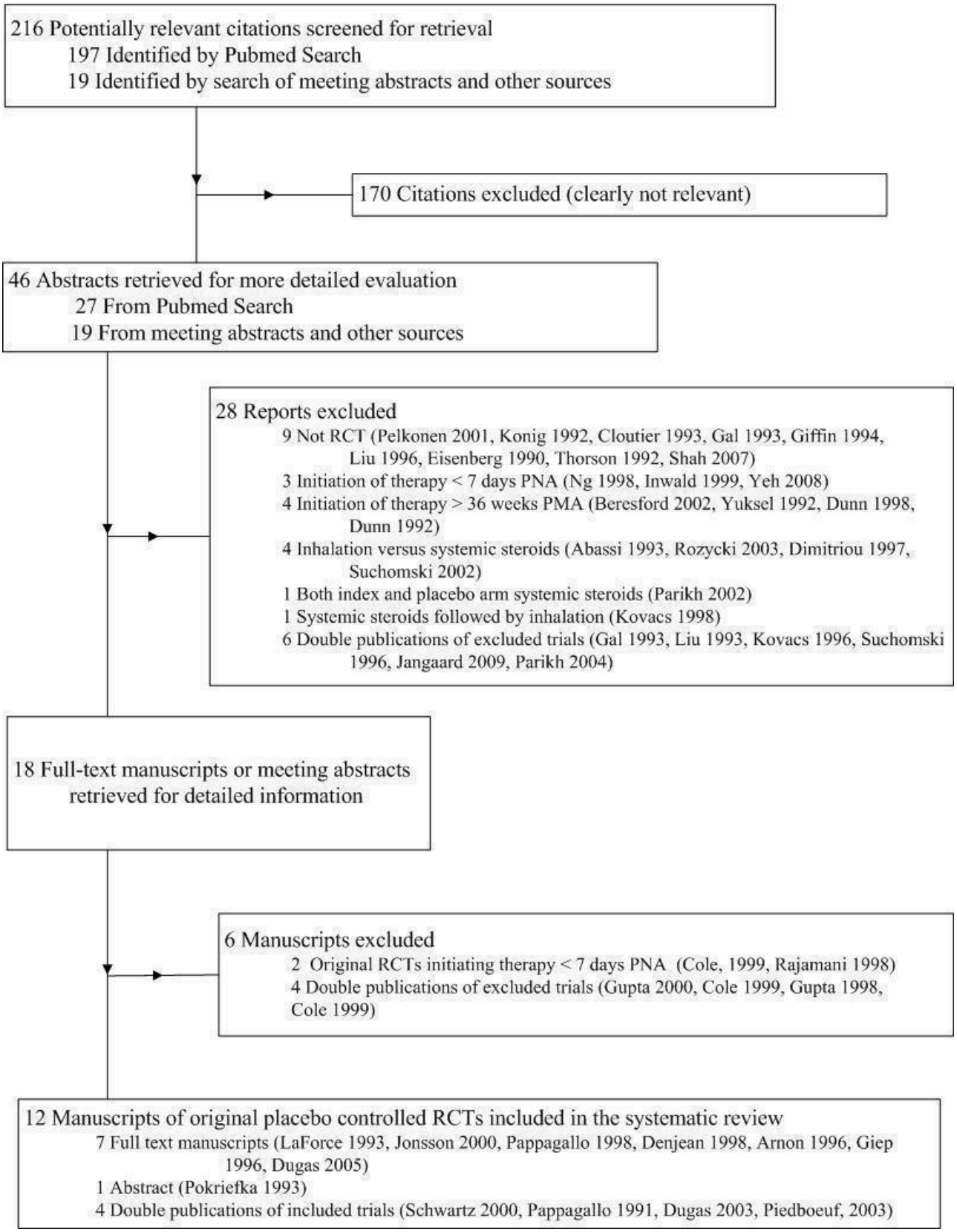
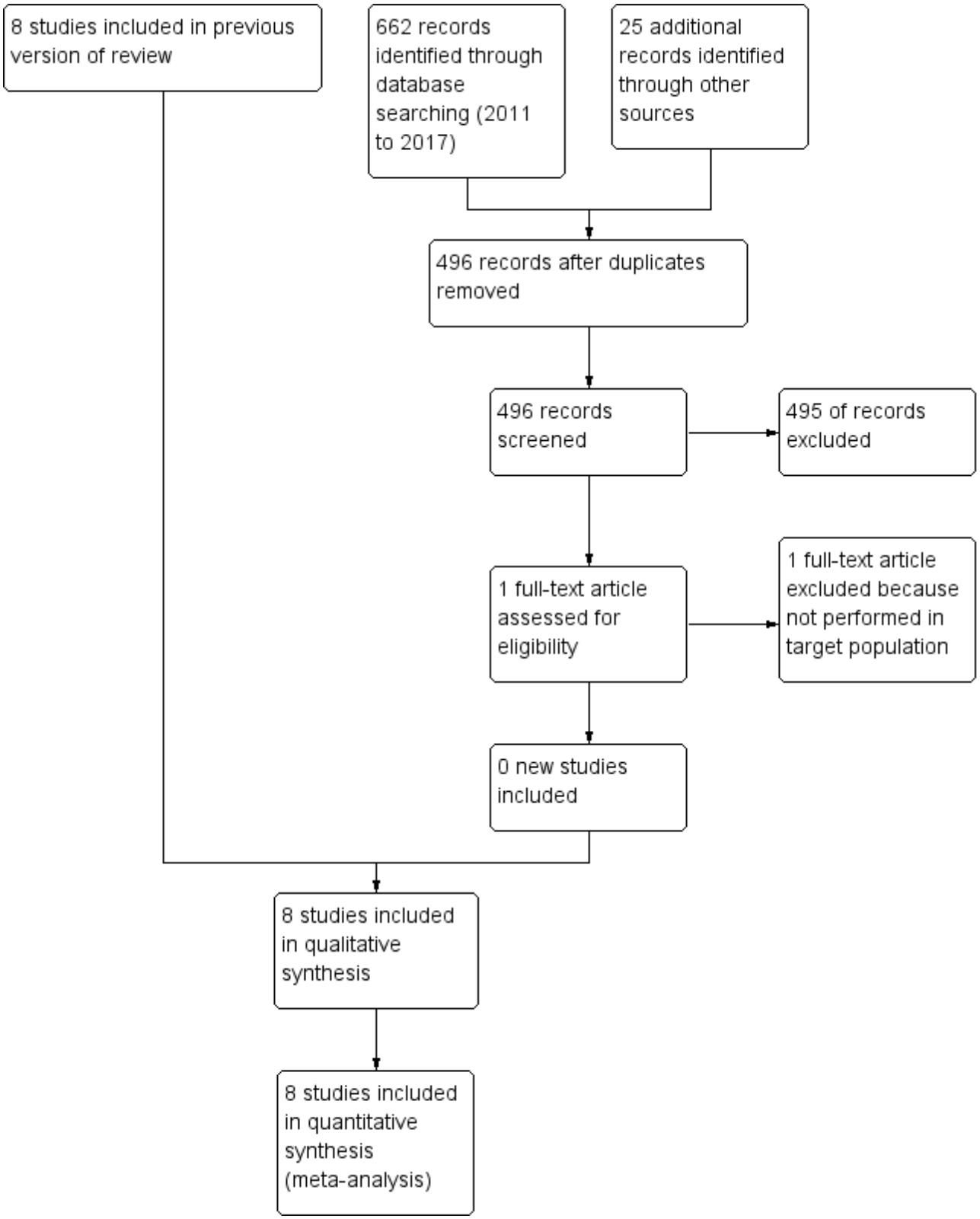


Figure 2. Study flow diagram: review update.



Included studies

Eight RCTs, reported in a total of 12 manuscripts, met the inclusion criteria for this review. Seven trials were available as full-text publications (Arnon 1996; Denjean 1998; Dugas 2005; Giep 1996; Jonsson 2000; LaForce 1993; Pappagallo 1998), and one as an abstract (Pokriefka 1993).

Description of separate trials

Arnon 1996: This double-blind trial included 20 preterm infants with a birthweight < 2000 grams and a gestational age < 33 weeks that were still in need of mechanical ventilation at 14 days PNA with a FiO_2 ≥ 0.30. Participants with PDA, sepsis, air leak, or congenital malformation were not included. Eligible participants were randomly assigned to budesonide 600 µg twice daily or placebo given by metered-dose inhalation (MDI), inserted into small volume spacer, for seven days or until extubation, whichever came first. From the reported outcome parameters, only the rate of PDA and sepsis rate during the study period could be used for this review. The authors provided additional data on extubation rate.

Denjean 1998: This was a double-blind, placebo-controlled, multicentre trial conducted in six centres in France over a two-year period. A total of 86 preterm infants with gestational age < 31 weeks, respiratory distress syndrome (RDS), and in need of mechanical ventilation, nasal ventilation, or continuous positive airway pressure at 10 days PNA were included in this study. Infants with PDA, sepsis, pulmonary infections, major malformation, or prior treatment with corticosteroids or bronchodilators were excluded. Although this study consisted of four treatment arms, only those infants treated with beclomethasone 250 µg/puff delivered by a MDI (inserted into a small volume spacer) four times a day or placebo were included in this review. Therapy was started on the 10th or 11th day and given for 28 days with a tapering dose for the last eight days. The primary outcome was BPD, defined as oxygen dependency at 28 days PNA in combination with radiographic abnormalities consistent with BPD. However, except for the total duration of supplemental oxygen, all outcomes of interest for this review were presented for the combined group of ventilated and non-ventilated infants and were therefore excluded from the final analysis. The author provided additional data on the randomisation process.

Dugas 2005: This was a double-blind, randomised trial of 32 infants with a gestational age ≤ 32 weeks, postnatal age between 28 and 60 days, and a diagnosis of BPD, which was defined as FiO_2 ≥ 0.25 to maintain oxygen saturation between 88% and 92%, partial pressure of carbon dioxide (pCO_2) ≥ 45 mmHg, and chest radiography consistent with BPD. Reasons for exclusion were hypertension, hyperglycaemia, sepsis, pneumonia, renal failure, treatment with corticosteroids five days prior to inclusion, a FiO_2 ≥ 0.30 in ventilated or FiO_2 ≥ 0.40 in non-ventilated infants, and congenital heart disease. The infants were treated with placebo or fluticasone propionate 125 µg/puff given by MDI inserted into a small volume spacer and interposed between an anaesthesia bag and the tube or a face mask. Infants with a birthweight between 500 and 1200 grams received one puff twice daily for three weeks and once daily in the fourth week. The number of puffs was double if the infant's weight was ≥ 1200 grams. The primary outcome was the total duration of supplemental oxygen. Other outcomes, such as total duration of hospitalisation or duration of mechanical ventilation, were only reported for the combined group of ventilated and non-ventilated infants and therefore could not be used for this review. From the reported outcome parameters, only mortality at 36 weeks PMA, mortality at hospital discharge, open-label intravenous glucocorticoids, and hyperglycaemia during the study period in the ventilated subgroup could be used for this review. The original authors did not provide additional data.

Giep 1996: A total of 19 infants were included in this feasibility and safety study with a randomised design. Infants were eligible if their birthweight was between 500 and 1500 grams, the X-ray showed signs of RDS or BPD, the postnatal age was at least 14 days, and the infant was still mechanically ventilated with a FiO_2 > 0.40 and a peak inspiratory pressure > 14 cm H_2O after failing an extubation attempt. Infants with PDA, sepsis, congenital heart disease, congenital malformations, or previous postnatal or concurrent administration of corticosteroids were not included. The participating infants were randomised to be treated with beclomethasone (1 mg/kg/day) or placebo delivered by MDI and an AeroChamber. Infants weighing 500 to 799 grams, 800 to 1000 grams, 1001 to 1300 grams, and above 1300 grams were treated with three, four, five, and six puffs every eight hours, respectively, for a total duration of seven days. We included the reported outcomes failure to extubate, use of systemic corticosteroids, sepsis rate, and intraventricular haemorrhage in this review. Although data on blood pressure and blood glucose were reported on a daily basis, the number of infants with hypertension and hyperglycaemia was not reported. Attempts to contact the original authors failed.

Jonsson 2000: In this double-blind, placebo-controlled study, 30 very low birthweight infants, either mechanically ventilated or supported by continuous positive airway pressure with FiO_2 ≥ 0.3, were randomised to budesonide or placebo, delivered by an electronic dosimetric jet nebuliser. Infants with malformations, congenital heart disease, intraventricular haemorrhage grades III-IV, deteriorating ventilator settings, or on high frequency ventilation were excluded. Starting on day seven of life, infants were treated with a dose of 500 µg twice a day for a total duration of 14 days. Reported outcomes of interest for this review were use of open-label corticosteroids, failure to extubate on day 14 in the ventilated subgroup, and mortality at hospital discharge and at 36 weeks PMA. The authors provided separate data for the ventilated and non-ventilated subgroups for the outcomes oxygen requirements at 28 days of age and at 36 weeks PMA, duration of supplemental oxygen, duration of mechanical ventilation, failure to extubate, and the adverse outcomes hyperglycaemia, hypertension, and sepsis.

LaForce 1993: This prospective, randomised, paired analysis study included infants with a birthweight < 1500 grams and RDS who were ventilator dependent at 14 days with X-ray abnormalities indicative of BPD. Infants with PDA, pneumonia, sepsis, congenital heart disease, or an air leak were not included. Those allocated to the intervention group were treated with nebulised beclomethasone dipropionate 50 µg three times a day for 28 days. Medication was delivered via a Whisper Jet nebuliser system in the ventilator circuit or a blow-by with 8 litre of humidified gas per minute in ventilated and non-ventilated infants, respectively. The reported outcome of interest for this review was mortality at hospital discharge.The original authors provided data on randomisation and sepsis rates.

Pappagallo 1998: This single-centre study included preterm infants with a birthweight < 1500 grams of more than seven days PNA with a high probability of developing BPD based on a prediction model or ventilator dependency. This study had two phases, with only the second phase having a randomised, placebo-controlled design. We used data on the 18 infants included in this second phase for this review. Infants with sepsis, pulmonary hypoplasia, congenital anomalies, or heart disease were excluded. Infants were randomly assigned to dexamethasone inhalation 1 mg/kg 8-hourly

for seven days followed by 0.5 mg/kg for three days or placebo using a jet nebuliser. The reported outcomes of interest for this review were the use of intravenous corticosteroids, duration of mechanical ventilation, days on supplemental oxygen, and total duration of hospitalisation. We found the rate of failure to extubate in an abstract identified by handsearching, which reported on the preliminary outcomes of 10 infants. The original authors could not provide additional data.

Pokriefka 1993: In this RCT, 14 ventilator-dependent preterm infants with moderate to severe BPD were enrolled and treated with flunisolide or placebo for 28 days, followed by a weaning schedule. No inclusion or exclusion criteria were described. This study was available only as an abstract, reporting clinical and respiratory outcomes without dichotomous or continuous data. Continuous data on the mean number of intubation days were reported with neither standard deviations nor standard errors, therefore these data could not be used. The rates of extubation were stated, although not on which day after initiating therapy. We used these data in the outcome failure to extubate at the latest reported time point. All attempts to contact the original authors failed.

Description of aggregated participant characteristics and intervention

Five trials included only ventilated infants at trial entry (Arnon 1996; Giep 1996; LaForce 1993; Pappagallo 1998; Pokriefka 1993), whereas three trials included both ventilated and non-ventilated preterm infants (Denjean 1998; Dugas 2005; Jonsson 2000). Criteria for including participants were comparable between trials, that is ventilator or oxygen dependency, or both, at ≥ 7 days PNA. The exclusion criteria were the presence of a PDA, signs of sepsis, congenital malformations, and treatment with postnatal corticosteroids prior to inclusion. Most trials started therapy moderately early (seven to 21 days PNA), whereas one study started therapy > 21 days PNA (delayed onset) (Dugas 2005). The gestational age and birthweight of the included infants were comparable between trials.

Three trials did not report on the use of antenatal corticosteroids or postnatal surfactant (LaForce 1993; Pappagallo 1998; Pokriefka 1993). In the remaining trials the use of antenatal corticosteroids and postnatal surfactant varied from 25% to 80% and 69% to 100%, respectively. Within the trials, participants in the treatment and placebo groups were similar with regard to clinical characteristics such as birthweight, gestational age, gender, use of antenatal corticosteroids and surfactant, Apgar scores, FiO_2 and ventilator settings or respiratory support at trial entry.

Interventions differed in every trial with regard to the type of corticosteroid, dosage, delivery system, and duration of treatment. The corticosteroids used included beclomethasone, flunisolide, budesonide, and dexamethasone. Delivery systems included MDI with a spacer device and nebulisation. Total duration of study medication ranged from seven to 28 days.

Description of aggregated outcome parameters

Three trials reported or provided data on mortality in the ventilated infants at the different points in hospitalisation (mortality at 28 days PNA, 36 weeks PMA, and at hospital discharge) (Dugas 2005; Jonsson 2000; LaForce 1993), whereas Jonsson 2000 provided us with additional data on non-ventilated infants.

None of the manuscripts reported the incidence of BPD at 28 days PNA or 36 weeks PMA for the ventilated and non-ventilated infants separately; however, we obtained these data for the study of Jonsson 2000 by personal communication.

Five trials reported failure to extubate seven days after initiating therapy (Arnon 1996; Dugas 2005; Giep 1996; Jonsson 2000; Pappagallo 1998), whereas Pokriefka 1993 reported failure to extubate at an unknown date. Three trials reported on the duration of mechanical ventilation for the subgroup of ventilated infants at trial entry (Dugas 2005; Jonsson 2000; Pappagallo 1998). Four trials reported data on the total days of supplemental oxygen in the subgroup of ventilated infants (Denjean 1998; Dugas 2005; Jonsson 2000; Pappagallo 1998), and two in the subgroup of non-ventilated infants (Denjean 1998; Jonsson 2000). Pappagallo 1998 reported total days of hospitalisation in the intervention and placebo arms.

Five trials reported the incidence of open-label corticosteroid use outside the study protocol in both arms (Denjean 1998; Dugas 2005; Giep 1996; Jonsson 2000; Pappagallo 1998). Four studies reported or provided additional data on the outcome of sepsis (Arnon 1996; Giep 1996; Jonsson 2000; LaForce 1993). The studies of Arnon 1996, Giep 1996, Jonsson 2000, and LaForce 1993 also reported or provided additional data on one of the following outcomes in both arms: PDA, hypertension, necrotising enterocolitis, and intraventricular haemorrhage.

Three studies reported no increase in adverse side effects, such as impaired glucose homeostasis and hypertension, but did not provide the actual data in the manuscripts (Arnon 1996; Giep 1996; Pokriefka 1993).

None of the included trials reported on gastrointestinal bleeding or perforation, periventricular leukomalacia, retinopathy of prematurity, and long-term neurodevelopmental sequelae. None of the original authors were able to provide data on these outcomes.

Excluded studies

See Characteristics of excluded studies table.

We excluded 29 trials (17 full-text publications and 12 abstracts) for the following reasons (Figure 1; Figure 2): non-randomised design or without placebo (N = 9) (Cloutier 1993; Eisenberg 1990; Giffin 1994; Konig 1992; Liu 1996; Pappagallo 1990; Pelkonen 2001; Shah 2007; Thorson 1992), initiation of therapy before seven days PNA or after 36 weeks PMA (N = 8) (Beresford 2002; Dunn 1989; Dunn 1992; Inwald 1999; Kugelman 2017; Ng 1998; Yeh 2008; Yuksel 1992), administration of systemic steroids as co-intervention or as control intervention (N = 6) (Abbasi 1993; Kovacs 1998; Parikh 2002; Rozycki 2003; Suchomski 1996), and double publications of excluded trials (N = 6) (Kovacs 1998; Liu 1996; Parikh 2002; Shah 2007; Suchomski 1996; Thorson 1992).

Two trials might have included participants within the inclusion criteria of this review (Cole 1999a; Rajamani 1998), however all attempts at contacting the original trialist to request subgroup data failed, therefore these trials were excluded.

Risk of bias in included studies

All of the included trials were randomised and double-blinded with placebo controls. LaForce 1993, Arnon 1996, Giep 1996, and

Jonsson 2000 provided us with additional information. The quality of the trials ranged from moderate to high, with some trials failing to provide sufficient details on the randomisation process, method of blinding, the management of withdrawals, and reporting bias (Figure 3; Figure 4).

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

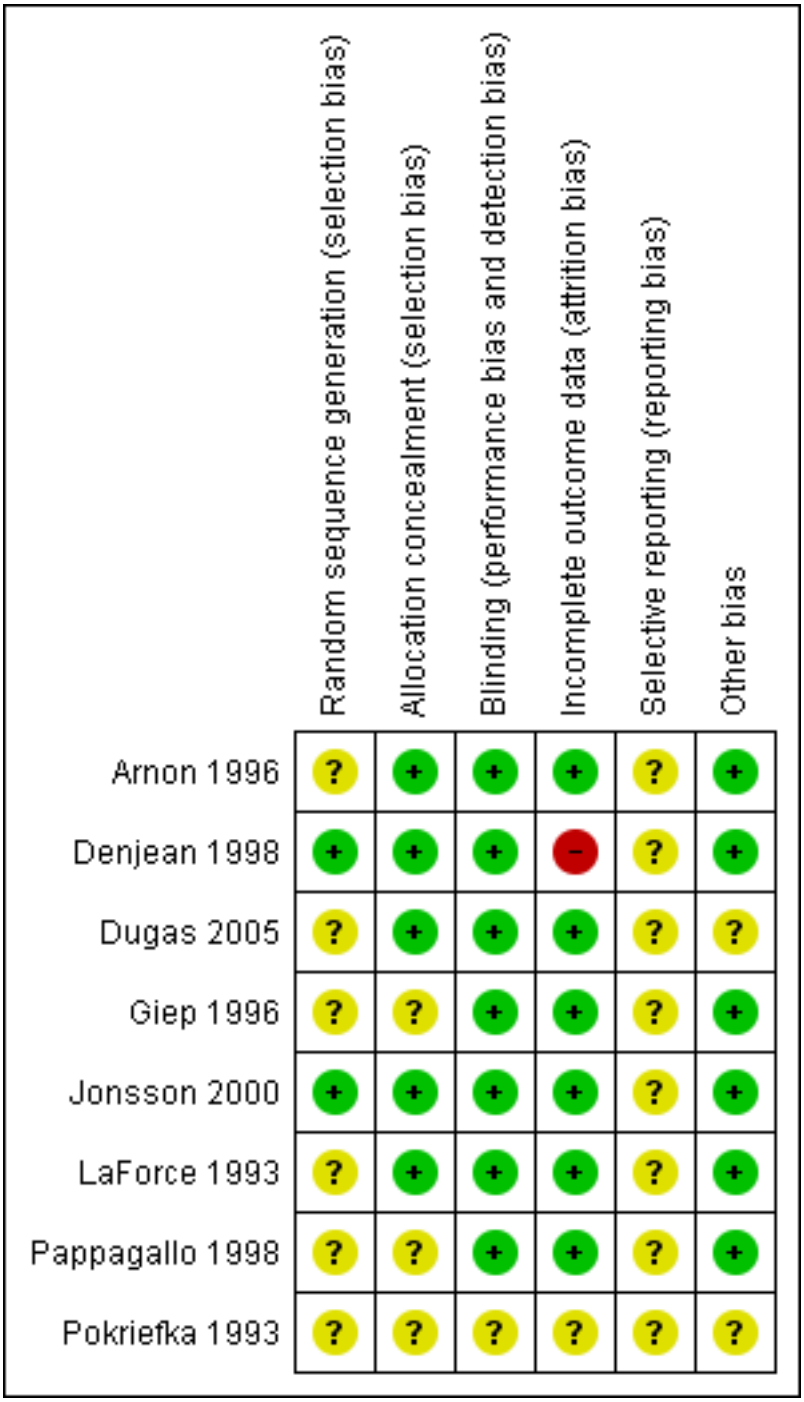
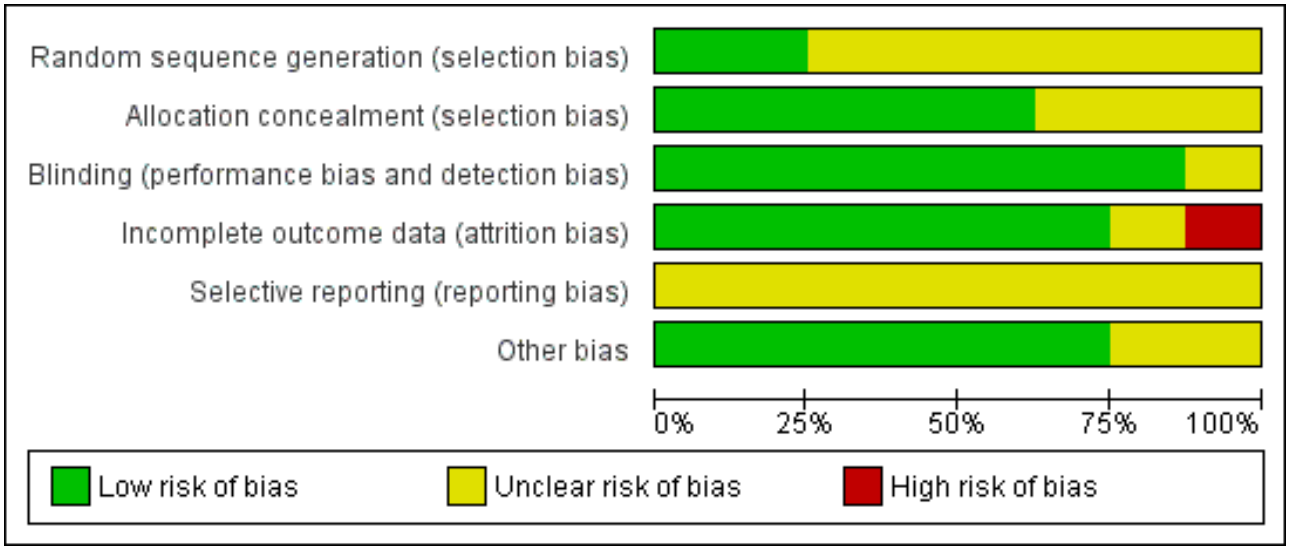


Figure 4. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Risk of bias in individual studies

Arnon 1996: The method of randomisation was not mentioned in the manuscript. Personal communication revealed that randomisation was performed by the pharmacy. The code and drugs were kept until the end of the trial and released from the hospital pharmacy in sealed envelopes. Blinding was established by using identical MDIs for corticosteroids and placebo administration. Ten infants were withdrawn and did not complete the study: five because of sepsis (three placebo, two treatment group), four because of PDA (two in each group), and one because of an air leak (treatment group). These infants were excluded from the analysis in the original manuscript but were included in this review. It was unclear whether the study was free of selective reporting.

Denjean 1998: The methods of allocation concealment or randomisation process were not mentioned in the manuscript, however accuracy was confirmed by personal communication. Randomisation by pre-established tables was stratified by centre, gestational age, and type of ventilator support. The method of blinding was not clearly stated in the manuscript, but again we ensured it to be genuine by personal communication. Due to severe clinical deterioration, the code for three infants was broken. Furthermore, it was stated that of the 178 infants randomised, informed consent was either not obtained or withdrawn for five infants for unclear reasons. It was unclear whether the study was free of selective reporting.

Dugas 2005: The method of concealment was not mentioned in the manuscripts. Infants were assigned to the treatment or placebo arm by block randomisation with stratification of intubated and extubated infants. Blinding was ensured by identical MDIs supplied by the drug manufacturer. The pharmacist in charge of the medication, the treating physician, and the investigators were unaware of treatment allocation. Three infants in the placebo group did not complete the study protocol (two because of clinical pulmonary deterioration and one because of central line sepsis). All infants were analysed on an intention-to-treat basis. Mean supplemental oxygen at study enrolment differed between the treatment and placebo arms, being significantly lower in the treatment group. The predefined outcomes were reported accurately.

Giep 1996: The methods of allocation concealment or randomisation of the infants were not described in the manuscript. Observers were blinded to treatment allocation, however the method ensuring this was not reported. Three infants in the placebo group and two in the treatment group received systemic corticosteroids after study entry, and continuous data that were not of interest for this review were excluded from the analysis thereafter.

Jonsson 2000: Randomisation was computer generated, and sealed envelopes were consecutively numbered. Clinical staff were blinded to group assignment, and the code was broken after the last infant finished the treatment. Blinding of the intervention was ensured by supplying the study drug in identical opaque, unmarked plastic vials. Outcome assessments were also blinded. Two infants were withdrawn by attending clinician due to deterioration and received systemic corticosteroids, and one died on ninth day of life. Outcomes for all enrolled infants were provided. The predefined outcomes were reported accurately.

LaForce 1993: The attending neonatologist was unaware of the treatment regimen. However, the method of allocation concealment or blinding was unclear. Nine infants were withdrawn from the analysis due to technical problems with equipment (two in each group), lost to referring hospital (two in each group), and one because of sudden death before start of the study (in treatment group). These infants were not included in the analyses of the original manuscript but were used for the dichotomous outcomes during the study period in this review. It was unclear whether the study was free of selective reporting.

Pappagallo 1998: The manuscript revealed no information regarding the method of sequence generation, allocation concealment, or randomisation. Clinical staff were unaware of the intervention since the vials were prepared by the pharmacist, labelled with a code, and both the study and placebo medications

were clear solutions and the dosage was calculated on the basis of volume. Outcomes were given for all infants enrolled.

Pokriefka 1993: The authors stated in the abstract that this was a double-blind, randomised trial, but no information was available regarding the method of randomisation, blinding of intervention, or outcome assessments. Outcomes for all enrolled infants were provided.

Summarised risk of bias

Allocation

Allocation concealment was blinded in five trials (Arnon 1996; Denjean 1998; Dugas 2005; Jonsson 2000; LaForce 1993), and unclear in the remaining trials. However, adequate sequence generation was only clear in two trials (Denjean 1998; Jonsson 2000).

Blinding

Based on the reported data and personal communications, we judged all studies as having a double-blind design. The double-blind design was not clearly stated in the abstract of Pokriefka 1993.

Incomplete outcome data

Five trials reported the outcomes of all included infants (Dugas 2005; Giep 1996; Jonsson 2000; Pappagallo 1998; Pokriefka 1993), whereas in two trials infants were not included due to not obtaining informed consent or excluded for the outcomes (Arnon 1996; Denjean 1998), and in one trial this was unclear (LaForce 1993).

Selective reporting

Five trials reported the predefined outcome data completely. In three trials it was unclear whether all predefined outcome data had been reported (Arnon 1996; Denjean 1998; LaForce 1993). None of the studies published a study protocol.

Other potential sources of bias

With the exception of three trials (Arnon 1996; Giep 1996; Jonsson 2000), we could not exclude other potential sources of bias based on the available information.

Effects of interventions

See: **Summary of findings for the main comparison** Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants

Inhaled corticosteroids versus placebo, administered after the first week of life until 36 weeks PMA in preterm infants at high risk of developing BPD (Comparison 1)

Primary outcome

Combined outcome death or BPD at 36 weeks PMA:

Meta-analysis of combined outcomes mortality and BPD at 36 weeks PMA did not show a significant difference between the treatment and placebo arms in either the ventilated or non-ventilated subgroup (RR 1.10, 95% CI 0.74 to 1.63) (Analysis 1.1).

Secondary outcomes

Other respiratory outcomes

Meta-analysis of separate outcomes death at 28 days PNA and at 36 weeks PMA, the seperate outcomes BPD at 28 days PNA and at 36 weeks PMA, as well as the combined outcome death or BPD at 28 days PNA did not show a significant difference between the treatment and placebo arms in either the ventilated or non-ventilated subgroup.

Compared to the infants allocated to the placebo group, the infants treated with inhalation corticosteroids had a lower risk of failure to extubate at seven days (typical RR 0.80, 95% CI 0.66 to 0.98; NNTB 5, 95% CI 3 to 19; 5 studies, 79 infants) (Analysis 1.8) and at the latest reported time point after treatment onset (typical RR 0.60, 95% CI 0.45 to 0.80; NNTB 3, 95% CI 2 to 5; 6 studies, 90 infants) (Analysis 1.10), respectively. However, both analyses showed increased statistical heterogeneity (I^2 statistic 73% and 86%, respectively).

Failure to extubate at 14 days showed no difference between the two groups (typical RR 0.36, 95% CI 0.10 to 1.33; 2 studies, 27 infants) (Analysis 1.9).

The meta-analysis of the outcome duration of mechanical ventilation in the ventilated infants showed no significant statistical difference between the treatment arms. Meta-analysis showed no significant difference between the treatment and placebo arms regarding duration of supplemental oxygen for the ventilated (MD 5.53, 95% CI -3.99 to 15.05) and non-ventilated infants (MD -3.74, 95% CI -12.63 to 5.14) (Analysis 1.12).

Adverse effects during hospitalisation

Meta-analysis showed that open-label intravenous corticosteroids were used less often in ventilated infants treated with inhaled corticosteroids, but this difference only approached statistical significance (typical RR 0.51, 95% CI 0.26 to 1.00; 4 studies, 74 infants) (Analysis 1.13). Only one trial reported on the use of open-label intravenous corticosteroids in non-ventilated infants (Jonsson 2000), stating that this intervention was not used in any of the included infants.

Five trials reported either suspected, in Giep 1996, or documented sepsis rates (Arnon 1996; Dugas 2005; Jonsson 2000; LaForce 1993), and the meta-analysis of these results failed to show a significant difference between the inhaled corticosteroids and placebo groups (typical RR 0.90, 95% CI 0.50 to 1.64; 5 studies, 107 infants) (Analysis 1.14). Subgroup analysis did not change this finding.

We were unable to perform meta-analysis on the outcomes of PDA, hypertension, necrotising enterocolitis, intraventricular haemorrhage, and total days of hospitalisation because these outcomes were only reported in single trials. None of these trials reported a significant difference in these outcomes, except for total days of hospitalisation; Pappagallo 1998 showed a significant decrease in the total days of hospitalisation in favour of the inhaled corticosteroids group (MD -24.70, 95% CI -41.75 to -7.65) (Analysis 1.19). Two trials assessed the airway resistance and dynamic lung compliance, but we were unable to perform a meta-analyses including both studies, because LaForce 1993 did not report the standard deviations or absolute numbers of the measurement. Compared to the placebo group, Pappagallo 1998 did show a significant decreased lung compliance in the patient

group allocated to inhalation steroids (Analysis 1.21), but not in airway resistance. None of the studies reported the outcomes hyperglycaemia and long-term neurodevelopmental sequelae, assessed between one-year and four years of CGA, including cerebral palsy and Bayley Scales of infant Development.

DISCUSSION

Summary of main results

Based on the predefined inclusion criteria, this systematic review identified eight relatively small RCTs comparing inhalation corticosteroids to placebo in a total of 232 ventilated and non-ventilated preterm infants. These trials differed considerably in participant characteristics, intervention (medication, dose, duration, and delivery), reported outcomes, and the definitions of these outcomes. This heterogeneity and the small number of randomised infants should be taken into account when interpreting the results of this review.

As the aim of this review was to examine the use of inhalation corticosteroids to prevent BPD, we chose the endpoint of inclusion to exclude those trials investigating inhaled corticosteroids in preterms with established BPD after 36 weeks PMA. It is, to our knowledge, unknown how much time before the primary endpoint BPD the inhaled corticosteroids might be effective. It could be argued that therapy would need to be initiated two weeks before that endpoint, or even four weeks before, as there needs to be an exposure for some time to reduce inflammation. The only trial that could have theoretically included infants around the corrected gestation of 36 weeks PMA could not provide us with data on the primary outcome BPD at 36 weeks PMA (Dugas 2005). All of the other included trials treated infants for an average of eight weeks. Consequently, we feel that the inclusion criteria fulfilled the purpose of this review.

Meta-analysis of reported and provided data showed that inhalation corticosteroids do not improve the separate or combined outcomes mortality or BPD at any time point during hospitalisation. In addition, there were no significant differences in the short-term respiratory outcomes such as failure to extubate at 14 days, total days of mechanical ventilation, or days of supplemental oxygen. This is despite the fact that several studies reported that inhalation corticosteroids improved resistance and compliance of the respiratory system, sometimes resulting in a reduction in FiO_2 or respiratory rate. However, the heterogeneity in how lung function was measured and the data were reported prevented a valid meta-analysis of these outcomes (Arnon 1996; Giep 1996; LaForce 1993; Pappagallo 1998; Pokriefka 1993). This review showed a significant reduction in failure to extubate at day seven, and at the latest reported time point, but these analyses were seriously hampered by moderate to high statistical heterogeneity (I^2 statistic 73% and 86%, respectively). No firm conclusions can therefore be drawn from these analyses. One possible explanation for this heterogeneity might be that the trials reporting these outcomes used different drugs and methods of delivery.

Our meta-analysis did show a trend to a reduced use of systemic corticosteroids for the reduction of BPD in the inhaled corticosteroids group. In light of the growing concerns about the adverse effects of systemic corticosteroids, this might prove to be an important and clinically relevant finding. However, the lack of data on short- and long-term adverse effects in most trials precludes any firm conclusions at this time.

Overall completeness and applicability of evidence

The overall completeness and applicability of this review are low for several reasons. First, most of the manuscripts identified by the search strategy had either an observational study design or were not placebo controlled, instead comparing systemic versus inhalation corticosteroids, and were therefore not eligible for inclusion. The numbers of participants within each of these included trials were small, which limits their power to detect small but clinically important effects of treatment. Second, most placebo-controlled trials investigating inhalation corticosteroids differed considerably in terms of participant characteristics and study design, including differences in type of inhalation medication, dose, duration of therapy, and delivery systems. It is unknown if and how these factors modify the treatment effect of inhalation corticosteroids on the outcome parameters reported in this review since we were unable to perform sensitivity analysis to assess the potential impact of different drugs, dosages, delivery systems, and treatment duration on the magnitude of the expected benefit. Third, not all trials reported the primary and secondary outcome parameters. Various definitions were used, and outcomes were assessed at different time points. Our extended attempts to retrieve unpublished data did not change this shortcoming.

Quality of the evidence

Three out of the eight included studies did not report allocation concealment, and the majority of included studies did not report adequacy of allocation sequence (Figure 3). However, all but one included trial reported adequate blinding of the intervention, therefore we judged the quality of these RCTs as moderate to high. Nevertheless, the overall quality of the evidence provided by the meta-analyses using the GRADE approach for each outcome was assessed as low to very low due to inconsistency, imprecision of the effect estimates, and risk of publication bias (Summary of findings for the main comparison). The sample size of the reported outcomes was small, resulting in inadequate power to detect clinically relevant differences in all of the important outcomes. Even if all the trials were to have reported on the same outcomes, the meta-analyses are at high risk of inconsistency due to the considerable diversity between the different trials in design, choice of drugs, dosage, and delivery systems.

Potential biases in the review process

Due to the lack of possible aggregation data reported in the eligible trials, we were unable to create funnel plots, therefore we cannot exclude the potential risk of publication bias.

AUTHORS' CONCLUSIONS

Implications for practice

Inhalation corticosteroids administered after the first week of life to preterm infants do not improve the separate or combined outcomes of mortality or bronchopulmonary dysplasia (BPD) at any time point during hospitalisation. Although inhalation corticosteroids might improve short-term lung function as shown by a reduced incidence of failure to extubate in the corticosteroid group, this does not seem to impact the duration of mechanical ventilation. The meta-analyses of the outcomes failure to extubate

at seven days after initiation and at latest reported time point were hampered by statistical heterogeneity. We can only speculate about the source of this heterogeneity, but one possible explanation may be that the trials used different drugs, dosages, and delivery systems. Furthermore, inhalation corticosteroids may reduce the use of systemic corticosteroids, but the clinical relevance of this treatment effect is unclear, as short- and long-term adverse effects of inhalation corticosteroids are under-reported. The results of this meta-analysis are compromised by the fact that most of the included trials were underpowered and were heterogeneous in design. Based on these results, the use of inhalation corticosteroids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended.

Implications for research

Studies are needed to determine the optimal inhaled corticosteroid drug, dose, duration, and device using short-term markers of lung function and inflammation. The optimal treatment regimen should be tested in a randomised, placebo-controlled trial including a large number of preterm infants at high risk of developing BPD. The trial design should avoid bias by using adequate allocation concealment and a double-blinded intervention and outcome assessment. Outcomes should be reported using predefined, modern definitions and timing and using accepted diagnostic tests for these outcomes. Data should be collected for the primary outcome parameters BPD at 36 weeks postmenstrual age, and mortality at 36 weeks postmenstrual age and at discharge, and a complete assessment made of major neurosensory impairment using predefined definitions. Short-term benefits (i.e. time of extubation, duration of ventilation) and adverse effects (i.e. hypertension, infection, hyperglycaemia, and the use of open-label intravenous corticosteroids) can be reported as secondary outcomes.

ACKNOWLEDGEMENTS

Dr P Lister, Dr R Iles, Dr B Shaw, Dr F Ducharme for writing the previous version of this review, 'Inhaled steroids for neonatal chronic lung disease'.

Dr DSchwartz, Dr T Giep, Prof M Silverman, and Dr S Brudno provided additional information for the previous version of this review.

Prof Silverman and Dr Jonsson provided precious additional data for this updated version of the review.

Ms D Haughton, Ms Y Montagne, Ms C Ovelman, Ms J Spano, and Prof R Soll of Cochrane Neonatal.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Arnon 1996

Methods	Single-centre, double-blind, placebo-controlled trial Blinding of randomisation: yes (sealed envelopes) Blinding of intervention: yes (identical MDIs for placebo and corticosteroid administration) Complete follow-up: no, withdrawals n = 10 Blinding of outcome measurements: yes
Participants	Ventilated infants Eligible: preterm infants with birthweight < 2000 grams and gestational age < 33 weeks, still in need of mechanical ventilation at 14 days PNA with $FiO_2 \geq 0.30$ and no significant changes in respiratory support 3 days prior to study Excluded if: PDA, sepsis, air leak, or congenital malformation Budesonide group n = 9 versus placebo group n = 11 Trial entry budesonide group 15 (±0.6) versus placebo group 14 (±0.5) days No significant statistical differences found between groups with regard to birthweight, gestational age, postnatal age, sex, Apgar scores, rates of maternal infection, or the use of antenatal steroids
Interventions	Budesonide (Astra Draco, UK 200 µg/puff) 600 µg twice daily or placebo given by MDI for 7 days or until extubation, whichever came earlier. MDI was inserted into small volume spacer (AeroChamber MV15, Trudell Medical, Ontario, Canada), and filled with oxygen without a rubber flap valve. Distal end of spacer was directly connected onto the endotracheal tube.
Outcomes	Primary outcome: extubation for 24 hours within the 7-day period Secondary outcomes: ventilatory efficiency index, FiO_2 Alveolar-arterial oxygen difference calculated on 1st daily arterial blood gas measurement, serum cortisol, sepsis rates, bronchoalveolar lavage. Ventilator efficiency index (VEI) = k/f x (PIP - PEEP) x $PaCO_2$ (where k is a constant, f is the respiratory rate, PIP is the peak inspiratory pressure, and PEEP is the positive end-expiratory pressure. $PaCO_2$ denotes the arterial partial pressure of carbon dioxide.)
Notes	Authors provided data on extubation rate.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation
Allocation concealment (selection bias)	Low risk	Randomisation by pharmacy. Code and drugs released from hospital pharmacy in sealed envelopes, and code was concealed until end of trial. Investigators unaware of treatment group assignment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical MDI of placebo and steroid, pharmacy randomised and issued drugs ensuring double-blinding

Arnon 1996 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	10 infants were withdrawn and did not complete the study, 5 due to sepsis (3 placebo, 2 treatment group), 4 had a PDA (2 in each group), 1 air leak (treatment group). No intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of other bias.

Denjean 1998

Methods	Multicentre (n = 6), double-blind, placebo-controlled trial Blinding of randomisation: yes, method unknown Blinding of intervention: yes Complete follow-up: no, withdrawals n = 5 Blinding of outcome measurements: yes Infants were randomised into 1 of 4 groups: placebo + placebo, placebo + beclomethasone, placebo + salbutamol, and beclomethasone + salbutamol. Only infants treated with placebo + placebo (as the control group) and placebo + beclomethasone (as the treatment group) were included in this review. Stratification by centre, gestational age ≤ 28 weeks versus 29 to 30 weeks and type of ventilator support
Participants	Ventilated and non-ventilated infants Eligible: preterm infants with gestational age < 31 weeks, respiratory distress syndrome, and in need of mechanical ventilation or nasal ventilation or continuous positive airway pressure at 10 days PNA and no significant changes in respiratory support 3 days prior to study Excluded if: PDA, sepsis, pulmonary infections, major malformation, or prior treatment with corticosteroids or bronchodilators Beclomethasone group n = 43 versus placebo group n = 43 Trial entry beclomethasone group 10 (±1.5) versus placebo group 10.1 (±1.6) days No significant statistical differences found between groups with regard to birthweight, gestational age, mode of delivery, multiple pregnancy, or the use of antenatal steroids. No significant differences in outcome criteria at start of study
Interventions	Beclomethasone or corresponding placebo (Glaxo France) 250 µg/puff 4 times a day given by MDI inserted into small volume spacer (AeroChamber MV15, Trudell Medical, Ontario, Canada). Therapy started on the 10th to 11th day for 1 month with a tapering course for the last 8 days.
Outcomes	Primary outcome: BPD, based on oxygen dependency at 28 days PNA and radiographic criteria, and BPD severity, defined as severe when ventilation > 3 months or oxygen supplementation > 4 months; moderate as ventilation > 1 month or oxygen > 2 months; mild as ventilation < 1 month and oxygen < 2 months Secondary outcomes: ventilatory index (FiO_2 x main airway pressure), pneumothorax, interstitial emphysema, need for intravenous corticosteroid treatment, infections, hypertension, blood glucoses, and plasma electrolytes
Notes	Author provided additional information on randomisation process.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By personal communication

Denjean 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	Method of allocation concealment unknown. Stratification by centre, gestational age ≤ 28 weeks versus 29 to 30 weeks, and type of ventilator support
Blinding (performance bias and detection bias) All outcomes	Low risk	However, in 3 infants the code was broken due to severe clinical deterioration.
Incomplete outcome data (attrition bias) All outcomes	High risk	It was stated that of 178 infants randomised, 5 were withdrawn or informed consent not obtained, without explanation.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of bias.

Dugas 2005

Methods	Multicentre (n = 2), double-blind, placebo-controlled trial Blinding of randomisation: yes, by block randomisation, method unknown Blinding of intervention: yes. Pharmacist in charge of the medication, the treating physician, and the investigators were unaware of treatment allocation. Complete follow-up: yes Blinding of outcome measurements: yes Intubated and extubated infants were stratified separately at randomisation.
Participants	Ventilated and non-ventilated infants Eligible: preterm infants with gestational age ≤ 32 weeks, postnatal age between 28 and 60 days, and diagnosis of BPD (FiO_2 ≥ 0.25 to maintain oxygen saturation between 88% and 92%, pCO_2 ≥ 45 mmHg, and chest radiography consistent with BPD) Excluded if: hypertension, hyperglycaemia, sepsis, pneumonia, renal failure, treatment with corticosteroids 5 days prior to inclusion, or mechanical ventilation with FiO_2 ≥ 0.30 or oxygen dependency FiO_2 ≥ 0.40 if non-intubated or congenital heart disease Fluticasone propionate group n = 16 versus placebo group n = 16 Trial entry fluticasone propionate group 44.8 (±11) versus placebo group 45.4 (±10) days No significant statistical differences found between groups with regard to birthweight, gestational age, multiple pregnancy, or the use of antenatal steroids and clinical diagnosis as PDA, necrotising enterocolitis, intraventricular haemorrhage, hypotension, and sepsis. No significant differences in outcome criteria at start of study, with the exception of mean FiO_2, which was significantly lower in the treatment group.
Interventions	Fluticasone propionate or corresponding placebo (Flovent; GlaxoSmithKline, St-Laurent, Quebec, Canada; 125 µg/puff) was given by MDI. MDI was inserted into small volume spacer (AeroChamber MV15, Trudell Medical, Ontario, Canada) and interposed between an anaesthesia bag and the tube or a face mask. In infants weighing 500 to 1200 grams, the medication was given as 1 puff twice daily for 3 weeks, then once daily in the 4th week. The number of puffs was double if the infant's weight was ≥ 1200 grams. Systemic corticosteroids were allowed at the discretion of the attending physician, after which the inhalation medication was stopped.
Outcomes	Primary outcome: mean difference in duration of oxygen supplementation Secondary outcomes: survival without supplemental oxygen at the end of the study protocol, duration of ventilatory support, blood glucose, hypertension, diuresis, growth, cortisol axis, chest radiography score, and duration of hospital stay
Notes	Authors did not respond to queries.

Dugas 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on sequence generation
Allocation concealment (selection bias)	Low risk	Block randomisation, stratified intubated and extubated infants separately
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical format of MDIs supplied by the drug manufacturer. Pharmacist in charge of the medication, the treating physician, and the investigators were unaware of treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 infants in the placebo group did not complete the study protocol (2 due to clinical pulmonary deterioration and 1 due to central line sepsis). All analysed on an intention-to-treat basis.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Unclear risk	Mean FiO_2 was significantly lower in the treatment group.

Giep 1996

Methods	Single-centre, double-blind, placebo-controlled trial Blinding of randomisation: yes, method unknown Blinding of intervention: yes. Respiratory therapists, nurses, medical staff, investigators, and parents all blinded Complete follow-up: yes. Withdrawals (n = 5) due to their need for systemic corticosteroids Blinding of outcome measurements: yes
Participants	Ventilated infants Eligible: preterm infants with birthweight 500 to 1500 grams, clinical and X-ray changes consistent with respiratory distress syndrome and BPD, at least 14 days old, still on mechanical ventilator with FiO_2 > 0.40 and peak inspiratory pressure > 14 cm H_2O and failing previous extubate attempt Excluded if: PDA, sepsis, congenital heart disease, congenital malformations, or previous postnatal or concurrent administration of corticosteroids Beclomethasone n = 10 and placebo group n = 9 Trial entry beclomethasone group 18 versus placebo group 20 days No statistical differences found between groups with respect to birthweight, gestational age, antenatal steroid usage, sex, race, mode of delivery, or use of surfactant. There were no significant differences in the outcome variables between groups at the start of the study.
Interventions	Beclomethasone or placebo by MDI (Allen and Hanburys, Division of Glaxo, Research Triangle Park, NC) and AeroChamber (Monaghan Medical Corp, Plattsburgh, NY) The infants were treated with approximately 1 mg/kg/day in 3 doses. Infants weighing 500 to 799 grams were treated with 3 puffs; 800 to 1000 grams 4 puffs; 1001 to 1300 grams 5 puffs; and above 1301 grams 6 puffs every 8 hours. Total duration of therapy was 7 days.
Outcomes	No primary outcomes prespecified since this was a feasibility and safety-of-administration trial. Outcomes reported were respiratory rate, FiO_2, peak inspiratory pressure, positive end-expiratory pressure, mean airway pressure, inspiration time and

Giep 1996 *(Continued)*

	time to extubation, heart rate, blood pressure, infection rate, intraventricular haemorrhage rate, retinopathy of prematurity, weight and caloric intake, cortisol and adrenocorticotropic hormone levels.
Notes	Authors did not respond to queries.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of sequence generation not provided.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Respiratory therapists, nurses, medical staff, investigators, and parents were all blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 infants in the placebo group and 2 in the treatment group received systemic corticosteroids after study entry, and continuous data were excluded from analysis thereafter.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of other bias.

Jonsson 2000

Methods	Single-centre, randomised, double-blind, placebo-controlled trial Blinding of randomisation: yes. Computer-generated randomisation, sealed envelopes were consecutively numbered Blinding of intervention: yes. Clinical staff were blinded to group assignment. Code broken after last infant finished inhalations. Vials were kept in the hospital pharmacy in consecutively numbered cartons. Complete follow-up: yes. Withdrawal (n = 3) of 2 infants by attending clinician due to deterioration and received systemic corticosteroids; 1 infant died on 9th day of life due to sepsis, disseminated intravascular coagulation, and intraventricular haemorrhage grade IV Blinding of outcome measurements: yes
Participants	Ventilated and non-ventilated infants Eligible: very low birthweight infants on mechanical ventilator postnatal day 6 or if extubated, nasal continuous positive airway pressure with $FiO_2 \geq 0.3$ Excluded if: congenital malformations, congenital heart disease, and intraventricular haemorrhage (grades III-IV), or on ventilator with increasing $FiO_2 > 60\%$ and/or $pCO_2 > 8.5$ kPa, or on high frequency oscillatory ventilation on day 7 Budesonide group n = 13 and placebo group n = 14 Trial entry budesonide group 7 (±0) versus placebo group 7 (±0) days Demographic data: values are presented as median (range) or number (%) No significant statistical differences found between groups with regard to birthweight, gestational age, postnatal age, sex, Apgar scores, rates of maternal infection, or the use of antenatal steroids. All infants except 1 received surfactant treatment. No significant differences in outcome criteria at start of study

Jonsson 2000 *(Continued)*

Interventions	Budesonide (Pulmicort) (Astra Draco Pharmaceuticals, AB, Lund, Sweden) or placebo aerosol was used. The drug was delivered using an electronic dosimetric jet nebuliser (Spira Electro 4, Respiratory Center, Hameenlinna, Finland), delivering the aerosol during the inspiration but not the expiration phase of mechanical breaths. In spontaneously breathing infants, a Laerdal mask modified to fit to the inhalator nozzle was used. The infants were treated with a dose of 500 µg twice a day, starting on day 7 of life, for the total 14-day duration of therapy.
Outcomes	Primary outcome: change in FiO_2 Secondary outcomes include: duration of supplemental oxygen, duration of mechanical ventilation, duration of nasal continuous positive airway pressure, oxygen requirements at 28 days of age and at 36 weeks PMA, adrenal cortisol response to stimulation at baseline and at the end of the study period. Information on adverse events, such as hyperglycaemia, hypertension, sepsis, PDA, intraventricular haemorrhage, and gastrointestinal problems, was collected.
Notes	Author provided additional outcome data and checked data extraction.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed envelopes were consecutively numbered.
Blinding (performance bias and detection bias) All outcomes	Low risk	Clinical staff were blinded to group assignment. Code broken after last infant finished inhalations. Vials were kept in the hospital pharmacy in consecutively numbered cartons.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal (n = 3) of 2 infants by attending clinician due to deterioration and received systemic corticosteroids; 1 infant died on 9th day of life due to sepsis, disseminated intravascular coagulation, and intraventricular haemorrhage grade IV.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of other bias.

LaForce 1993

Methods	Single-centre, randomised, double-blind, placebo-controlled trial Blinding of randomisation: yes. Random number generated, sequential card draws. Odd numbers were allocated to treatment group, and even numbers fell into the placebo group. The next infant enrolled was matched with the randomised subject. Blinding of intervention: yes. Pharmacy prepared identical single-use vials labelled with only the infant's name, hospital number, and the identity code of the study protocol. Complete follow-up: yes. Withdrawals/lost to follow-up n = 9 (4 due to technical problems with equipment (2 in each group), 4 lost after transfer to referring hospital (2 in each group), and 1 sudden death before start of study (in treatment group) Blinding of outcome measurements: yes Stratification by birthweight greater than or less than 1000 grams, and paired by birthweight
Participants	Ventilated infants

LaForce 1993 *(Continued)*

	Eligible: birthweight < 1500 grams with clinical and X-ray signs of respiratory distress syndrome, ventilated at 14 days, X-ray changes consistent with BPD Excluded if: PDA, pneumonia, sepsis, congenital heart disease, or air leak All participants were treated with Exosurf Neonatal. 6 matched pairs and 1 unmatched in the placebo group No significant statistical differences found between groups with regard to initial inspired oxygen concentration, ventilator settings, or respiratory rate.
Interventions	Nebulisation with beclomethasone dipropionate (Vancenase AQ Nasal; Schering) 50 µg or placebo, 8 hourly for 28 days. Treatments were delivered through ventilator circuit with a Whisper Jet nebuliser system (model No. 123025; Marquest Medical Products, Inc., Englewood, CO) in ventilated infants and through blow-by with 8 litre of humidified gas per minute.
Outcomes	No primary or secondary outcomes defined. Reported outcomes were weekly measurements of lung compliance and airway resistance, sepsis rate, and weekly tracheal cultures.
Notes	Author provided data on randomisation process and sepsis rates.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of random sequence generation not mentioned.
Allocation concealment (selection bias)	Low risk	Investigators unaware as to order of treatment group assignment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Attending neonatologist was unaware of treatment regimen.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals/lost to follow-up = 9 (4 due to technical problems with equipment (2 in each group), 4 lost to referring hospital (2 in each group) and 1 sudden death before start of study (in treatment group)
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of other bias.

Pappagallo 1998

Methods	Single-centre, randomised, double-blind, placebo-controlled trial Blinding of randomisation: unclear Blinding of intervention: yes. Vials were prepared by the pharmacist and labelled with a code. Since both study and placebo medications were clear solutions, and dosage was calculated on basis of volume, the clinical staff were unaware of intervention. Complete follow-up: no mention of withdrawals Blinding of outcome measurements: unclear
Participants	Ventilated infants Eligible: preterm infants with birthweight < 1500 grams, older than 7 days of age, and with a high probability of BPD based on a prediction model or being ventilator dependent Excluded if: sepsis, pulmonary hypoplasia, congenital anomalies or heart diseases Dexamethasone group n = 9 and placebo group n = 9 Trial entry dexamethasone group 22.6 (±3.0) versus placebo group 19.13 (±1.6) days

Pappagallo 1998 *(Continued)*

	No differences between groups in gestational age, birthweight, study age, or study weight
Interventions	Dexamethasone 1 mg/kg for 7 days every 8 hours followed by 0.5 mg/kg from day 8 to 10 or placebo by jet nebuliser
Outcomes	Changes in tidal volume, minute ventilation, dynamic compliance, airway resistance, work of breathing, peak oesophageal pressure, extubation rates, cortisol levels, and mucosal changes on bronchoscopy
Notes	Manuscript reports on 2 study phases, the first being a non-randomised pilot study, followed by an RCT. Only the second phase is included in this review. Authors could not provide additional data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding (performance bias and detection bias) All outcomes	Low risk	Vials were prepared by the pharmacist and labelled with a code. Since both study and placebo medications were clear solutions, and dosage was calculated on basis of volume, the clinical staff were unaware of intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No attrition bias detected.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Low risk	Appears to be free of other bias.

Pokriefka 1993

Methods	Single-centre, randomised, double-blind, placebo-controlled study Blinding of randomisation: unclear Blinding of intervention: unclear Complete follow-up: unclear. Withdrawals not mentioned. Blinding of outcome measurements: unclear
Participants	Ventilated infants Inclusion or exclusion criteria not mentioned. Participants: ventilator-dependent premature infants with moderate to severe BPD Flunisolide group n = 8 and placebo group n = 6
Interventions	Treatment with placebo or nebulised flunisolide 0.037 mg, 6 hourly for 28 days, weaned thereafter over 11 days
Outcomes	No primary or secondary outcomes were mentioned, except for failure to extubate at latest reported time point. Manuscript states that there were changes in FiO_2, dynamic compliance, airway resistance, peak inspiratory pressure, peak expiratory flow rate, power of breathing without providing data. Other outcomes were reported as not differing between study arms, such as hypertension, hyperglycaemia,

Pokriefka 1993 *(Continued)*	glycosuria, adrenal suppression, leukocytosis, sepsis, retinopathy of prematurity, weight gain, and mortality, but again without providing data. Continuous data reported without standard deviations or standard errors.
Notes	Only published abstract form. Authors did not respond to queries.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available.
Allocation concealment (selection bias)	Unclear risk	Information not available.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available.
Selective reporting (reporting bias)	Unclear risk	Study protocol was not published, therefore unclear if any protocol deviations occurred.
Other bias	Unclear risk	Information not available.

BPD: bronchopulmonary dysplasia
FiO_2: fraction of inspired oxygen
MDI: metered-dose inhaler
pCO_2: partial pressure of carbon dioxide
PDA: patent ductus arteriosus
PMA: postmenstrual age
PNA: postnatal age
RCT: randomised controlled trial

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

Study	Reason for exclusion
Abbasi 1993	Not an RCT, study compared inhalation with systemic corticosteroids, without a placebo arm
Beresford 2002	RCT investigating inhalation corticosteroids for 1 year in preterm infants with established BPD. Excluded, all infants were randomised > 36 weeks PMA.
Cloutier 1993	Cross-over trial, not a randomised trial. Participants between 7 to 18 months of age were not initially randomised to the treatment or placebo arm. All of the participants acted as their own controls during the first 3 months, then all began treatment for the second 3 months. Some participants were also treated with systemic steroids during the study.
Cole 1999a	RCT including infants between 3rd and 14th day PNA. Attempts to contact the original trialist for separate data in ventilated and non-ventilated infants failed.
Dimitriou 1997	RCT comparing inhalation with systemic corticosteroids, without a placebo arm

Study	Reason for exclusion
Dunn 1989	This was not a controlled trial but a cross-over trial after 1 week of life, without a placebo arm. Futhermore, infants were included > 36 weeks PMA.
Dunn 1992	This was not a controlled trial but a cross-over trial after 1 week of life, without a placebo arm. Futhermore, infants were included > 36 weeks PMA.
Eisenberg 1990	This was not a controlled trial with a placebo arm. Only a few of the participants would have qualified for inclusion, as 3 were treated on the basis of asthma and not BPD, and 2 had multiple congenital abnormalities. Several of the participants were treated with systemic steroids.
Giffin 1994	This was not a placebo-controlled trial.
Inwald 1999	This was a longitudinal study without randomisation, investigating early inhalation corticosteroids.
Konig 1992	This was not a controlled trial with a placebo arm. Some of the participants were treated with systemic steroids during the study. Futhermore, participants were included after 36 weeks PMA.
Kovacs 1998	RCT investigating systemic corticosteroids, followed by 18 days of nebulised budesonide in the treatment arm compared to a placebo.
Kugelman 2017	RCT investigating inhalation corticosteroids in preterm infants with established BPD. Excluded, all infants were randomised > 36 weeks PMA.
Liu 1996	This was not a controlled trial with a placebo arm.
Ng 1998	RCT starting inhalation corticosteroids within the first 24 hours of life
Pappagallo 1990	This was not a controlled trial with a placebo arm.
Parikh 2002	Both treatment and placebo arms received systemic corticosteroids for 7 days, after which the treatment arm received a tapering course of beclomethasone and the control group received placebo inhalation.
Pelkonen 2001	Not a randomised study design. Older participants (school age) were included.
Rajamani 1998	Only in abstract form. RCT including infants from day 6 PNA. Attempts to contact the original trialist for separate data in ventilated and non-ventilated infants failed.
Rozycki 2003	RCT comparing inhalation with systemic corticosteroids, without a placebo arm
Shah 2007	This was a dose effect study without a placebo arm.
Suchomski 1996	RCT comparing inhalation with systemic corticosteroids, without a placebo arm
Thorson 1992	This was not a controlled trial with a placebo arm.
Yeh 2008	RCT investigating early installation of budesonide using surfactant as a vehicle shortly after birth
Yuksel 1992	RCT investigating inhalation corticosteroids to reduce recurrent respiratory symptoms in preterms less than 2 years of age. Excluded because all infants were randomised at > 36 weeks PMA.

BPD: bronchopulmonary dysplasia
PMA: postmenstrual age
PNA: postnatal age
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants

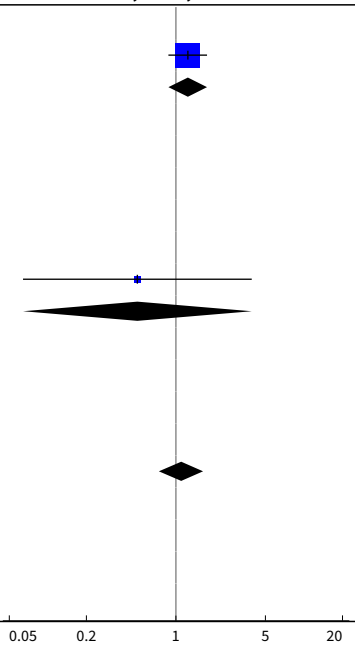
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Combined outcome mortality or bronchopulmonary dysplasia at 36 weeks PMA	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.74, 1.63]
1.1 Ventilated infants	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.87, 1.75]
1.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.06, 3.91]
2 Mortality at 28 days PNA	2	51	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 65.90]
2.1 Ventilated infants	2	41	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.14, 65.90]
2.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mortality at 36 weeks PMA	3	61	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.78]
3.1 Ventilated infants	3	51	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.78]
3.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality at hospital discharge	3	53	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.78]
4.1 Ventilated infants	3	43	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.78]
4.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Bronchopulmonary dysplasia at 28 days PNA	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.21]
5.1 Ventilated infants	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.29]
5.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.71, 1.41]
6 Bronchopulmonary dysplasia at 36 weeks PMA	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.59, 1.70]
6.1 Ventilated infants	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.69, 1.90]
6.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.06, 3.91]
7 Combined outcome mortality and bronchopulmonary dysplasia at 28 days PNA	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.85, 1.18]
7.1 Ventilated infants	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.83, 1.20]
7.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.71, 1.41]
8 Failure to extubate day 7	5	79	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Failure to extubate day 14	2	27	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.10, 1.33]
10 Failure to extubate at the latest reported moment	6	90	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.45, 0.80]
11 Days of mechanical ventilation	3	45	Mean Difference (IV, Fixed, 95% CI)	3.42 [-1.30, 8.13]
12 Days of supplemental oxygen	4	141	Mean Difference (IV, Fixed, 95% CI)	0.57 [-5.92, 7.07]
12.1 Ventilated infants	4	100	Mean Difference (IV, Fixed, 95% CI)	5.53 [-3.99, 15.05]
12.2 Non-ventilated infants	2	41	Mean Difference (IV, Fixed, 95% CI)	-3.74 [-12.63, 5.14]
13 Open-label intravenous corticosteroids	4	74	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 1.00]
13.1 Ventilated infants	4	64	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 1.00]
13.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Sepsis (clinical suspected or culture proven)	5	107	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.50, 1.64]
14.1 Ventilated infants	5	97	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.44, 1.77]
14.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.36, 2.75]
15 Patent ductus arteriosus	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
15.1 Ventilated infants	1	30	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.16, 6.20]
16 Hypertension (> 2 SD)	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.1 Ventilated infants	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Necrotising enterocolitis	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.1 Ventilated infants	1	17	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Non-ventilated infants	1	10	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Intraventricular haemorrhage (any grade)	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.13, 2.82]
18.1 Ventilated infants	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.13, 2.82]
19 Days of hospitalisation	1	18	Mean Difference (IV, Fixed, 95% CI)	-24.70 [-41.75, -7.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Ventilated infants	1	18	Mean Difference (IV, Fixed, 95% CI)	-24.70 [-41.75, -7.65]
20 Airway resistance	1	18	Mean Difference (IV, Fixed, 95% CI)	21.40 [-71.11, 113.91]
21 Dynamic lung compliance	1	18	Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.33, -0.11]

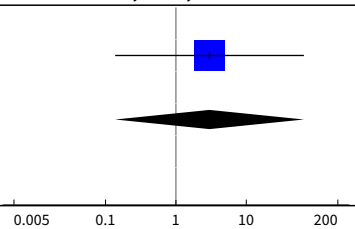
Analysis 1.1. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 1 Combined outcome mortality or bronchopulmonary dysplasia at 36 weeks PMA.

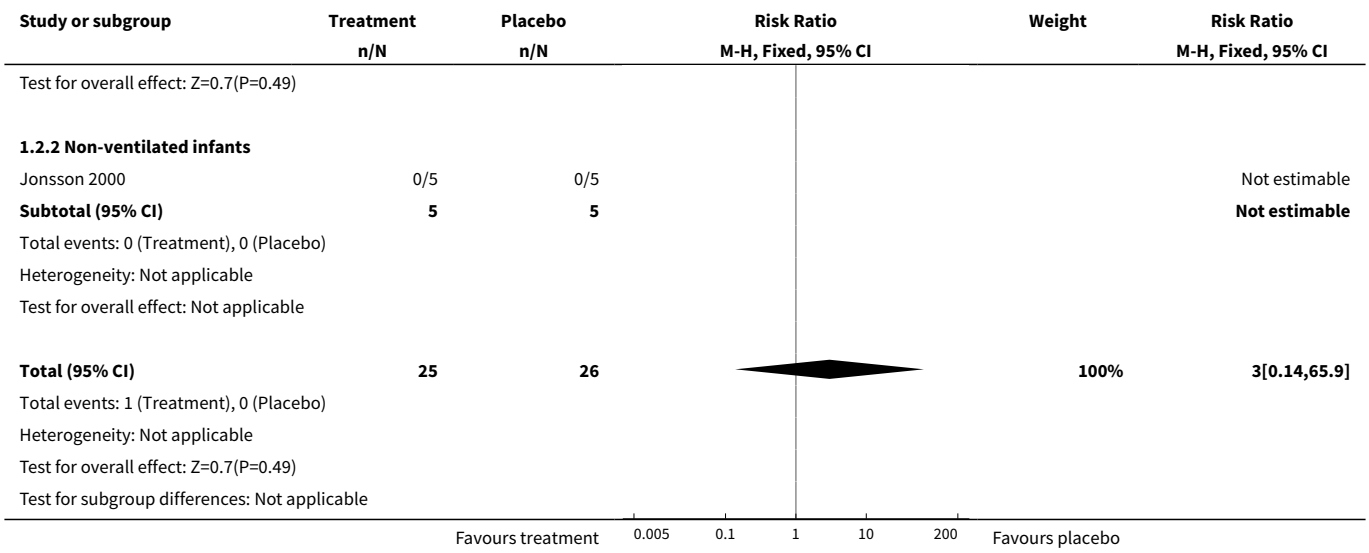
Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Ventilated infants					
Jonsson 2000	10/10	8/10		80.95%	1.24[0.87,1.75]
Subtotal (95% CI)	**10**	**10**		**80.95%**	**1.24[0.87,1.75]**
Total events: 10 (Treatment), 8 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.2(P=0.23)					
1.1.2 Non-ventilated infants					
Jonsson 2000	1/5	2/5		19.05%	0.5[0.06,3.91]
Subtotal (95% CI)	**5**	**5**		**19.05%**	**0.5[0.06,3.91]**
Total events: 1 (Treatment), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**15**	**15**		**100%**	**1.1[0.74,1.63]**
Total events: 11 (Treatment), 10 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.03, df=1(P=0.31); I^2=2.45%					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Chi^2=0.72, df=1 (P=0.4), I^2=0%					



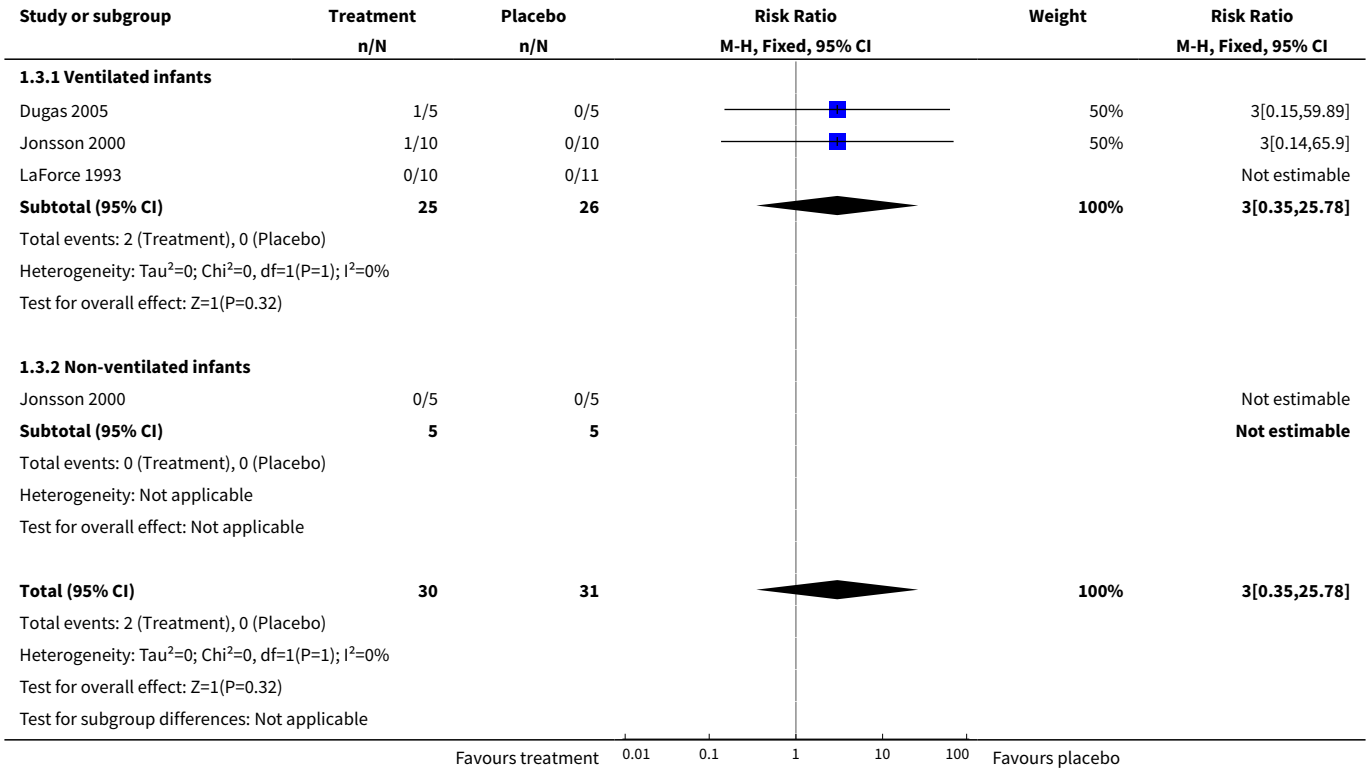
Analysis 1.2. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 2 Mortality at 28 days PNA.

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Ventilated infants					
Jonsson 2000	1/10	0/10		100%	3[0.14,65.9]
LaForce 1993	0/10	0/11			Not estimable
Subtotal (95% CI)	**20**	**21**		**100%**	**3[0.14,65.9]**
Total events: 1 (Treatment), 0 (Placebo)					
Heterogeneity: Not applicable					





Analysis 1.3. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 3 Mortality at 36 weeks PMA.



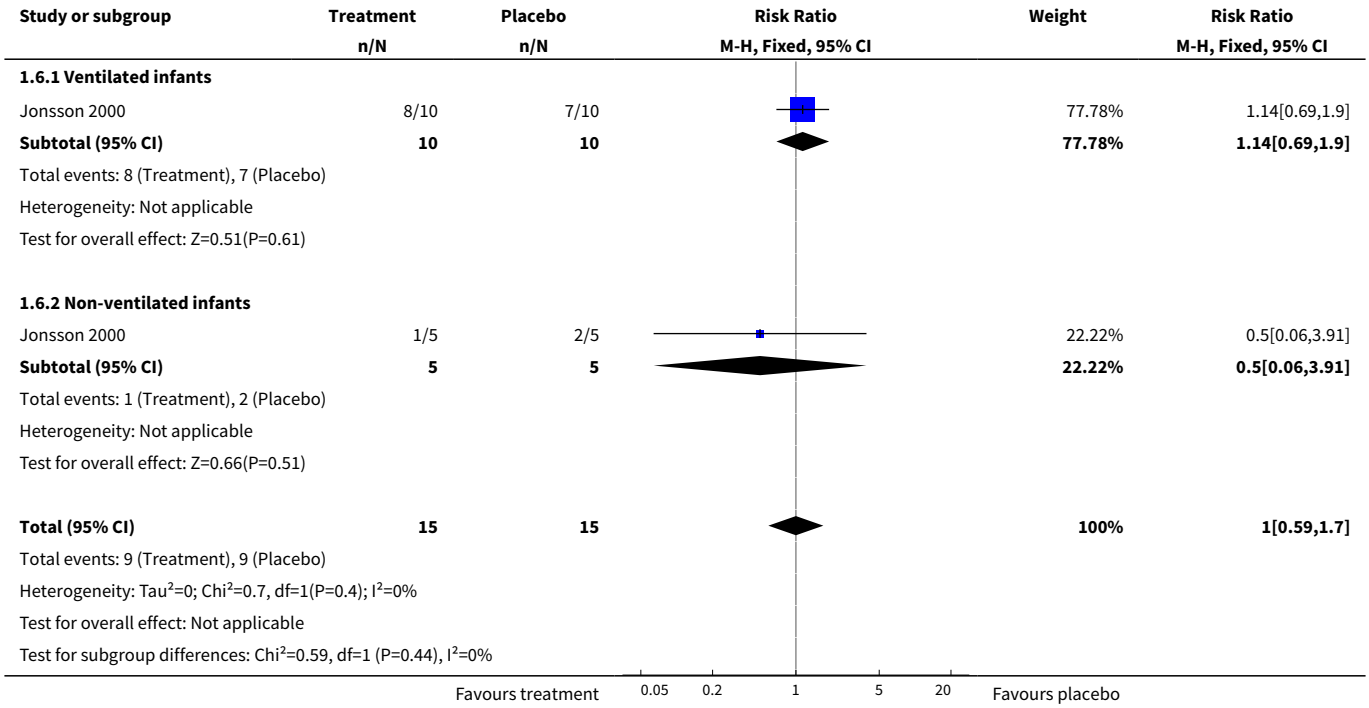
Analysis 1.4. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 4 Mortality at hospital discharge.

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.4.1 Ventilated infants					
Dugas 2005	1/5	0/5		50%	3[0.15,59.89]
Jonsson 2000	1/10	0/10		50%	3[0.14,65.9]
LaForce 1993	0/6	0/7			Not estimable
Subtotal (95% CI)	**21**	**22**		**100%**	**3[0.35,25.78]**
Total events: 2 (Treatment), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
1.4.2 Non-ventilated infants					
Jonsson 2000	0/5	0/5			Not estimable
Subtotal (95% CI)	**5**	**5**			**Not estimable**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**26**	**27**		**100%**	**3[0.35,25.78]**
Total events: 2 (Treatment), 0 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=1(P=0.32)					
Test for subgroup differences: Not applicable					

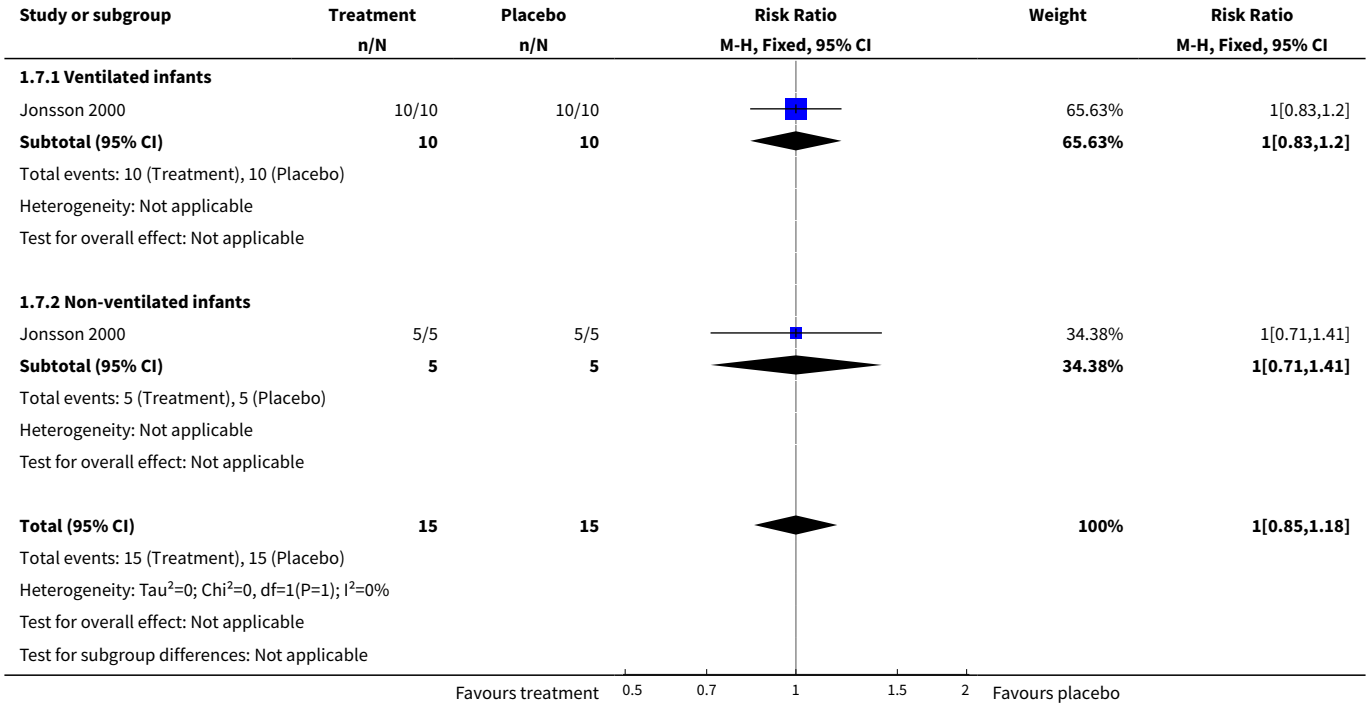
Analysis 1.5. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 5 Bronchopulmonary dysplasia at 28 days PNA.

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Ventilated infants					
Jonsson 2000	8/10	9/10		62.07%	0.89[0.61,1.29]
Subtotal (95% CI)	**10**	**10**		**62.07%**	**0.89[0.61,1.29]**
Total events: 8 (Treatment), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.62(P=0.54)					
1.5.2 Non-ventilated infants					
Jonsson 2000	5/5	5/5		37.93%	1[0.71,1.41]
Subtotal (95% CI)	**5**	**5**		**37.93%**	**1[0.71,1.41]**
Total events: 5 (Treatment), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**15**	**15**		**100%**	**0.93[0.72,1.21]**
Total events: 13 (Treatment), 14 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=1(P=0.63); I^2=0%					
Test for overall effect: Z=0.53(P=0.59)					
Test for subgroup differences: Chi^2=0.21, df=1 (P=0.65), I^2=0%					

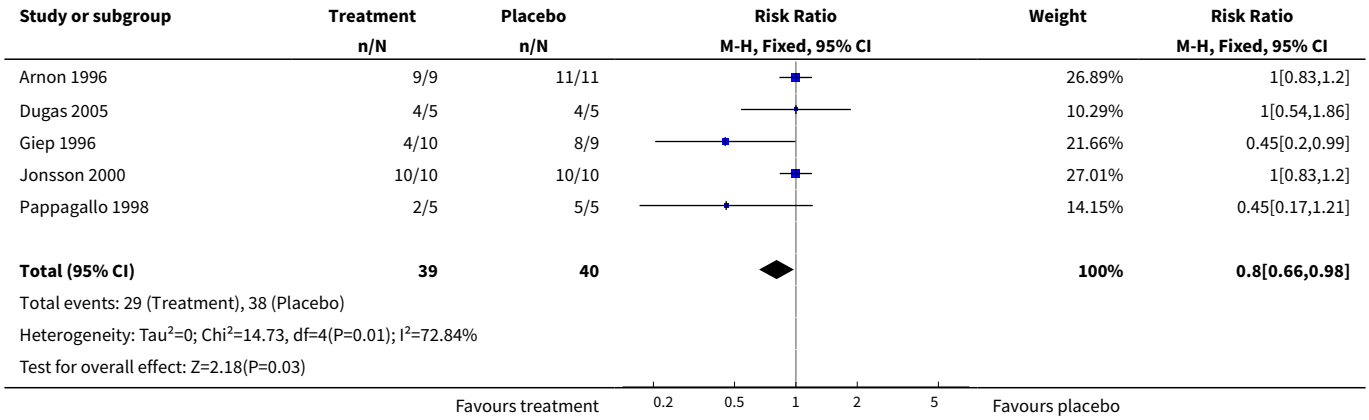
Analysis 1.6. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 6 Bronchopulmonary dysplasia at 36 weeks PMA.



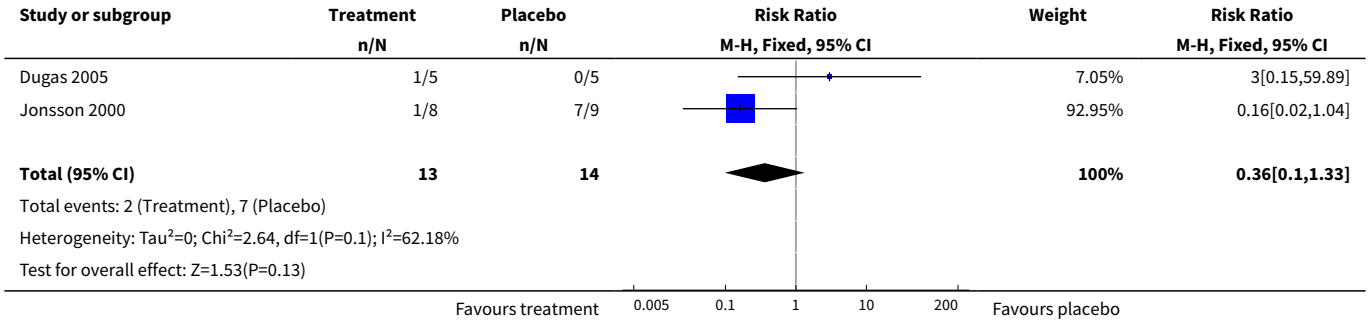
Analysis 1.7. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 7 Combined outcome mortality and bronchopulmonary dysplasia at 28 days PNA.



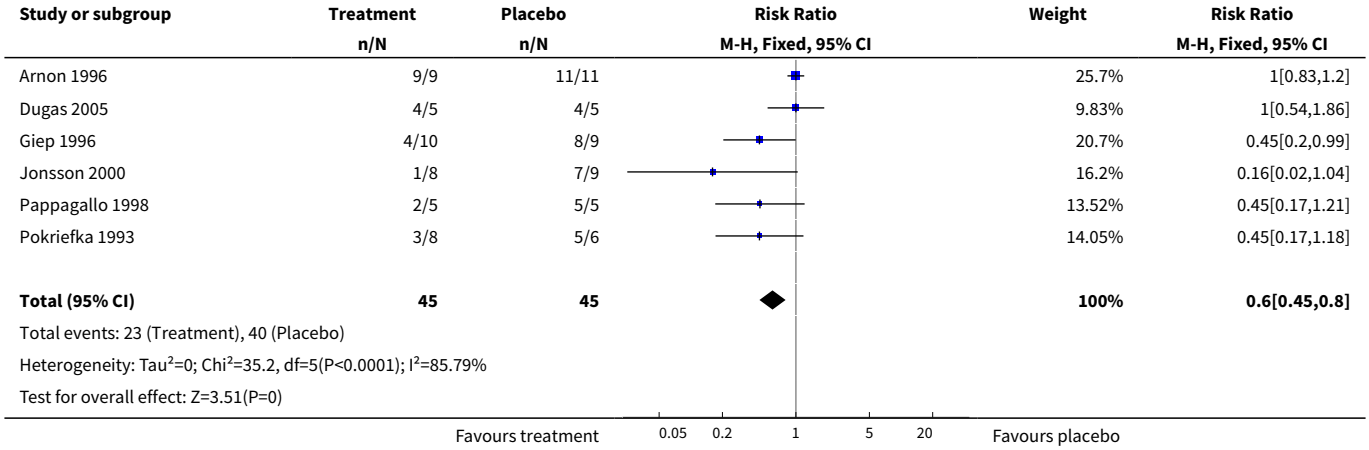
Analysis 1.8. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 8 Failure to extubate day 7.



Analysis 1.9. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 9 Failure to extubate day 14.

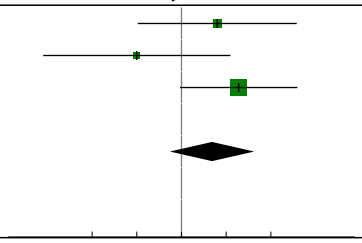


Analysis 1.10. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 10 Failure to extubate at the latest reported moment.



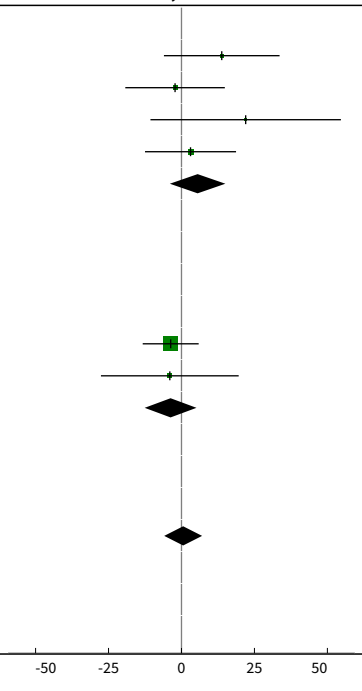
Analysis 1.11. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 11 Days of mechanical ventilation.

Study or subgroup	Treatment N	Treatment Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Pappagallo 1998	9	62.6 (10.3)	9	58.6 (8.9)		28.1%	4[-4.89,12.89]
Jonsson 2000	8	13 (11)	9	18 (11)		20.25%	-5[-15.48,5.48]
Dugas 2005	5	14.4 (6.9)	5	8 (2.9)		51.64%	6.4[-0.16,12.96]
Total ***	**22**		**23**			**100%**	**3.42[-1.3,8.13]**
Heterogeneity: Tau²=0; Chi²=3.29, df=2(P=0.19); I²=39.22%							
Test for overall effect: Z=1.42(P=0.16)							



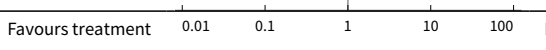
Analysis 1.12. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 12 Days of supplemental oxygen.

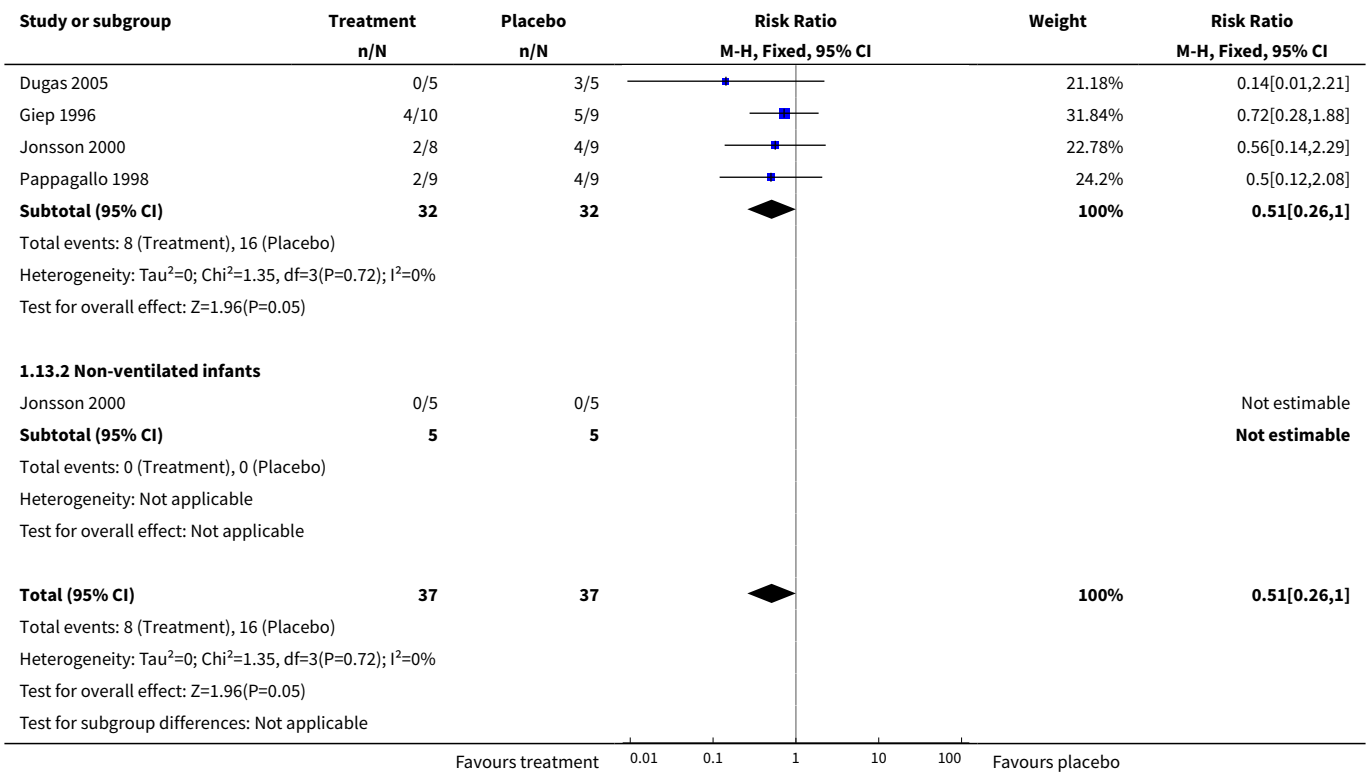
Study or subgroup	Treatment N	Treatment Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.12.1 Ventilated infants							
Denjean 1998	27	49.5 (46.7)	28	35.7 (24.5)		10.74%	13.8[-6.02,33.62]
Dugas 2005	5	64.8 (14.2)	5	67 (13.3)		14.51%	-2.2[-19.25,14.85]
Jonsson 2000	8	100 (39)	9	78 (28)		3.96%	22[-10.63,54.63]
Pappagallo 1998	9	91.4 (15.8)	9	88.3 (17.9)		17.34%	3.1[-12.5,18.7]
Subtotal ***	**49**		**51**			**46.55%**	**5.53[-3.99,15.05]**
Heterogeneity: Tau²=0; Chi²=2.53, df=3(P=0.47); I²=0%							
Test for overall effect: Z=1.14(P=0.26)							
1.12.2 Non-ventilated infants							
Denjean 1998	16	14.9 (13.3)	15	18.6 (13.9)		45.88%	-3.7[-13.29,5.89]
Jonsson 2000	5	61 (7)	5	65 (26)		7.57%	-4[-27.6,19.6]
Subtotal ***	**21**		**20**			**53.45%**	**-3.74[-12.63,5.14]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.98); I²=0%							
Test for overall effect: Z=0.83(P=0.41)							
Total ***	**70**		**71**			**100%**	**0.57[-5.92,7.07]**
Heterogeneity: Tau²=0; Chi²=4.48, df=5(P=0.48); I²=0%							
Test for overall effect: Z=0.17(P=0.86)							
Test for subgroup differences: Chi²=1.95, df=1 (P=0.16), I²=48.63%							



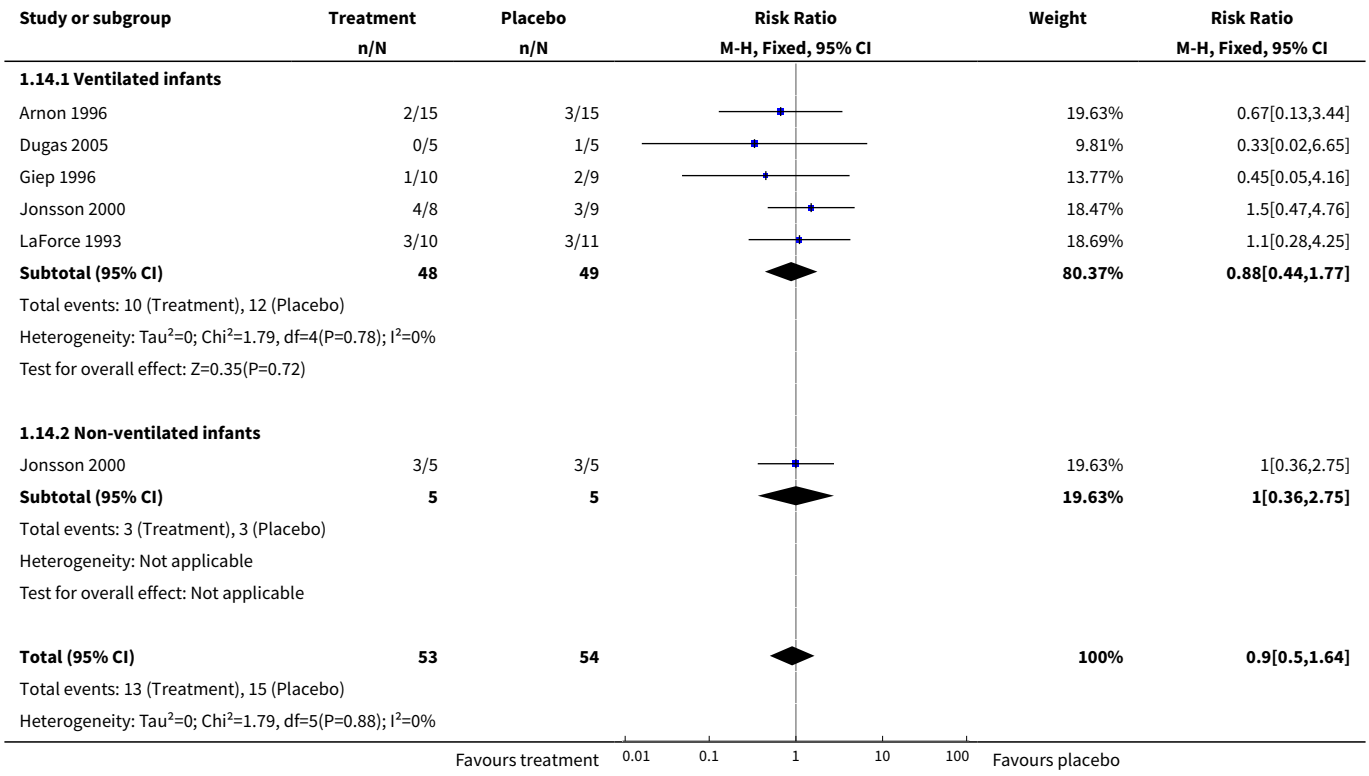
Analysis 1.13. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 13 Open-label intravenous corticosteroids.

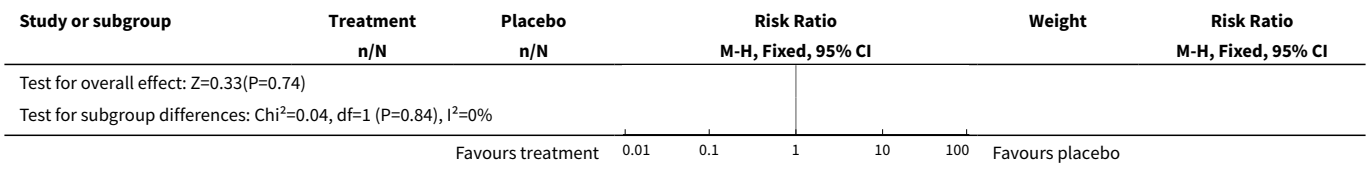
Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Ventilated infants					



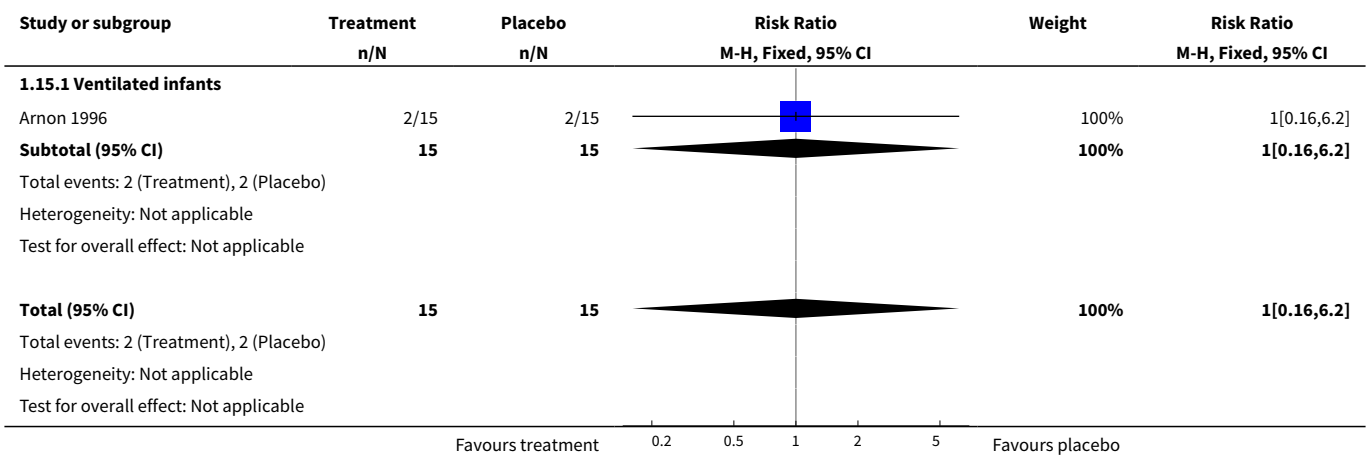


Analysis 1.14. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 14 Sepsis (clinical suspected or culture proven).

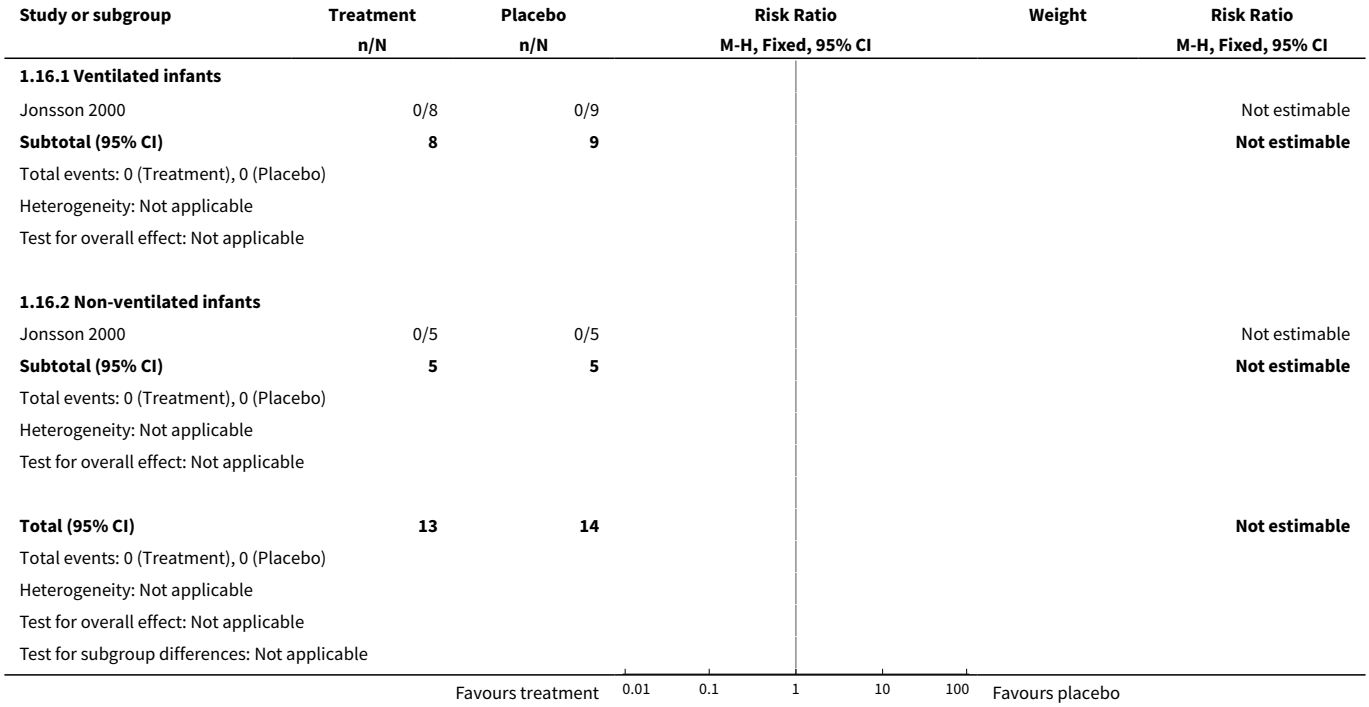




Analysis 1.15. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 15 Patent ductus arteriosus.

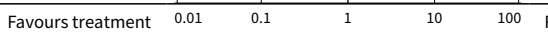


Analysis 1.16. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 16 Hypertension (> 2 SD).



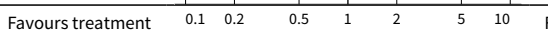
Analysis 1.17. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 17 Necrotising enterocolitis.

Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Ventilated infants					
Jonsson 2000	0/8	0/9			Not estimable
Subtotal (95% CI)	**8**	**9**			**Not estimable**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.17.2 Non-ventilated infants					
Jonsson 2000	0/5	0/5			Not estimable
Subtotal (95% CI)	**5**	**5**			**Not estimable**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**13**	**14**			**Not estimable**
Total events: 0 (Treatment), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

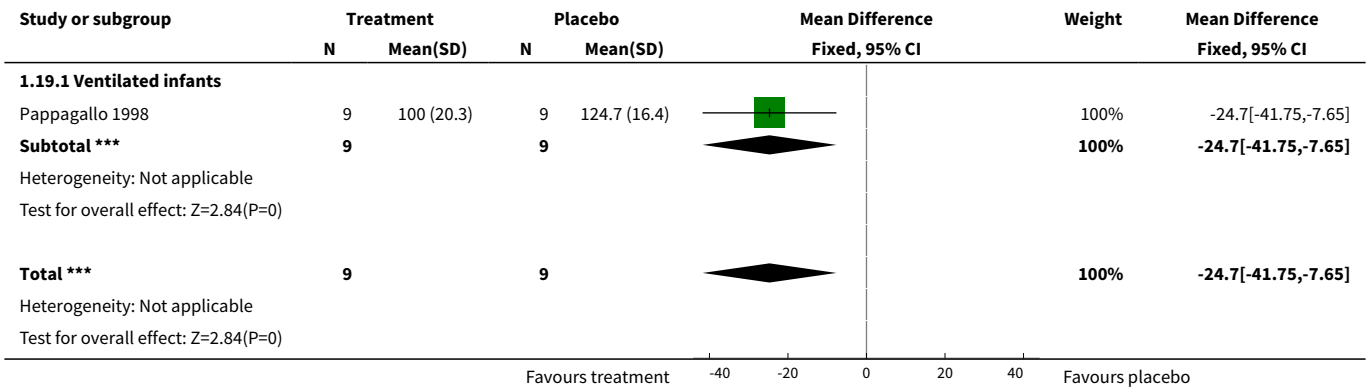


Analysis 1.18. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 18 Intraventricular haemorrhage (any grade).

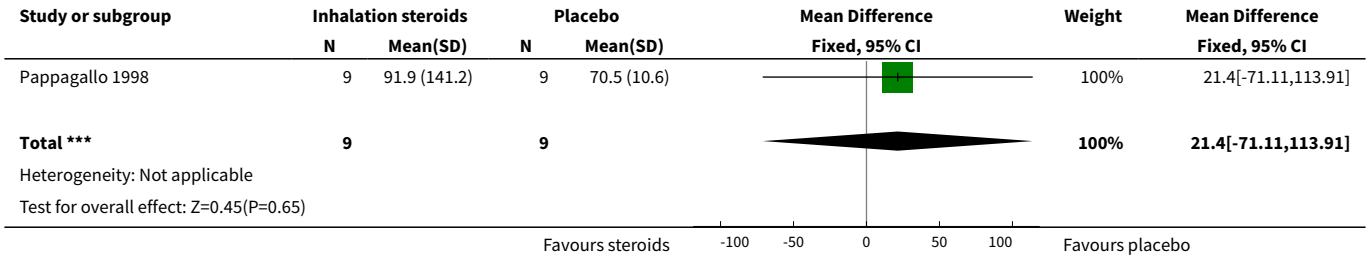
Study or subgroup	Treatment n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Ventilated infants					
Giep 1996	2/10	3/9		100%	0.6[0.13,2.82]
Subtotal (95% CI)	**10**	**9**		**100%**	**0.6[0.13,2.82]**
Total events: 2 (Treatment), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
Total (95% CI)	**10**	**9**		**100%**	**0.6[0.13,2.82]**
Total events: 2 (Treatment), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					



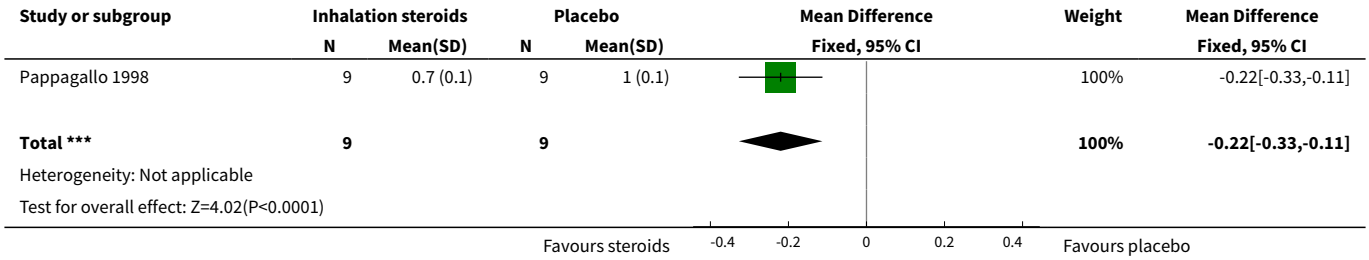
Analysis 1.19. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 19 Days of hospitalisation.



Analysis 1.20. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 20 Airway resistance.



Analysis 1.21. Comparison 1 Inhaled corticosteroids versus placebo to reduce bronchopulmonary dysplasia in preterm infants, Outcome 21 Dynamic lung compliance.



APPENDICES

Appendix 1. Standard search methodology

PubMed: ((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))

Embase: (infant, newborn or newborn or neonate or neonatal or premature or very low birth weight or low birth weight or VLBW or LBW or Newborn or infan* or neonat*) AND (human not animal) AND (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

CINAHL: (infant, newborn OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or Newborn or infan* or neonat*) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)

Cochrane Library: (infant or newborn or neonate or neonatal or premature or preterm or very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Previous search methodology

Previous versions of this review used the following Medical Subject Heading terms (MeSH) and text words:

(steroids or *glucocorticoids* or *flixotide* or *fluticasone* or *becotide* or *beclomethasone* or *pulmicort* or *budesonide* or *anti inflammatory agents)* and *(inhal** or *nebulis** or *nebuliz** or *aerolis** or *aeroliz*)* and *(neonatal chronic lung disease* or *bronchopulmonary dysplasia* or *neonatal respiratory distress syndrome* or *chronic lung disease of prematurity* or *chronic lung disease of infancy)*.

No search limits were used.

Appendix 3. 'Risk of bias' tool

We used the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality (to meet the validity criteria) of the trials. For each trial, we sought information regarding the method of randomisation and the blinding and reporting of all outcomes of all the infants enrolled in the trial. We assessed each criterion as low, high, or unclear risk. Two review authors separately assessed each study. Any disagreements were resolved by discussion. We added this information to the Characteristics of included studies table. We evaluated the following issues and entered the findings into the 'Risk of bias' table.

Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process, e.g. random number table; computer random number generator);
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk.

Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk.

Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for personnel.

Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors;
- unclear risk for outcome assessors.

Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data);
- unclear risk.

Selective reporting bias. Are reports of the study free of the suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk.

Other sources of bias. Was the study apparently free of other problems that could put it at high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (e.g. whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we explored the impact of the level of bias through the undertaking of sensitivity analyses.

WHAT'S NEW

Date	Event	Description
10 July 2017	New citation required but conclusions have not changed	Conclusions are not changed.
12 June 2017	New search has been performed	Updated search until May 2017, no new studies identified. GRADE assessment included in review.

HISTORY

Protocol first published: Issue 4, 1999
Review first published: Issue 2, 2001

Date	Event	Description
4 February 2011	New search has been performed	This updates the review 'Inhaled steroids for neonatal chronic lung disease' published in the Cochrane Database of Systematic Reviews (Lister 2000).

Date	Event	Description
		In October 2009, editorial responsibility for this review was transferred to the Neonatal Group from the Airways Group. New authorship assigned. The revised title is 'Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants'. We have changed the inclusion criteria for this review from the previous version (inclusion of studies initiating therapy ≥ 7 days postnatal age and exclusion of studies initiating therapy ≥ 36 weeks postmenstrual age).
24 January 2011	New citation required and conclusions have changed	Conclusions have changed. New authorship.
23 October 2009	Amended	October 2009, editorial responsibility for review transferred to Neonatal Group from Airways Group. New authorship assigned.
5 August 2008	Amended	Converted to new review format.
6 August 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Dr Onland and Dr van Kaam have full access to all of the data in the review and take responsibility for the integrity of the data and the accuracy of the data analysis.

- Study concept and design: Onland, van Kaam
- Acquisition of data: Onland, van Kaam
- Analysis and interpretation of data: Onland, Offringa, van Kaam
- Drafting of the manuscript: Onland, van Kaam
- Critical revision of the manuscript for important intellectual content: Onland, Offringa, van Kaam
- Stastical analysis: Onland
- Study supervision: Offringa, van Kaam

DECLARATIONS OF INTEREST

Wes Onland: No financial disclosure to be declared. No potential conflicts of interest known.
Martin Offringa: No financial disclosure to be declared. No potential conflicts of interest known.
Anton van Kaam: No financial disclosure to be declared. No potential conflicts of interest known.

SOURCES OF SUPPORT

Internal sources

- Department of Neonatology, AMC, Amsterdam, Netherlands.
- Department of Pediatric Clinical Epidemiology, AMC, Netherlands.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

  Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201600005C.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the paucity of data, we failed to perform the sensitivity analyses examining the potential influence of treatment variation (type and dose of inhalation corticosteroid, duration of treatment, and delivery system).

NOTES

Editorial responsibility for the review 'Inhaled steroids for neonatal chronic lung disease' has been transferred to the Cochrane Neonatal Review Group from the Cochrane Airways Group.

A new team of review authors has been assigned: Dr Wes Onland, Dr Martin Offringa, and Dr Anton Van Kaam.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Anti-Inflammatory Agents [*administration & dosage]; Beclomethasone [administration & dosage]; Bronchopulmonary Dysplasia [etiology] [*prevention & control]; Budesonide [administration & dosage]; Dexamethasone [administration & dosage]; Fluocinolone Acetonide [administration & dosage] [analogs & derivatives]; Fluticasone [administration & dosage]; Glucocorticoids [*administration & dosage]; Infant, Premature; Pneumonia [complications] [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn