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Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants

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Ng G, da Silva O, Ohlsson A

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[Intervention Review]

Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants

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ABSTRACT

Background

Chronic lung disease (CLD) occurs frequently in preterm infants. Bronchodilators have the potential effect of dilating small airways with muscle hypertrophy. Increased compliance and tidal volume and decreased pulmonary resistance have been documented with the use of bronchodilators in infants with CLD. Therefore, bronchodilators might have a role in the prevention and treatment of CLD.

Objectives

To determine the effect of bronchodilators given as prophylaxis or as treatment for CLD on mortality and other complications of preterm birth in infants at risk for or identified as having CLD.

Search methods

On 2016 March 7, we used the standard strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2), MEDLINE (from 1966), Embase (from 1980) and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; from 1982). We searched clinical trials databases, conference proceedings and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials. We applied no language restrictions.

Selection criteria

Randomised and quasi-randomised controlled trials involving preterm infants were eligible for inclusion. Initiation of bronchodilator therapy for prevention of CLD had to occur within two weeks of birth. Treatment of patients with CLD had to be initiated before discharge from the neonatal unit. The intervention had to include administration of a bronchodilator by nebulisation, by metered dose inhaler (with or without a spacer device) or by intravenous or oral administration versus placebo or no intervention. Eligible studies had to include at least one of the following predefined clinical outcomes: mortality, CLD, number of days on oxygen, number of days on ventilator, patent ductus arteriosus (PDA), pulmonary interstitial emphysema (PIE), pneumothorax, intraventricular haemorrhage (IVH) of any grade, necrotising enterocolitis (NEC), sepsis and adverse effects of bronchodilators.

Data collection and analysis

We used the standard method described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors extracted and assessed all data provided by each study. We reported risk ratio (RR), risk difference (RD) and number needed to

treat for an additional beneficial outcome (NNTB) with 95% confidence interval (CI) for dichotomous outcomes and mean difference (MD) for continuous data. We assessed the quality of the evidence by using the GRADE approach.

Main results

For this update, we identified one new randomised controlled trial investigating effects of bronchodilators in preterm infants. This study, which enrolled 73 infants but reported on 52 infants, examined prevention of CLD with the use of aminophylline. According to GRADE, the quality of the evidence was very low. One previously included study enrolled 173 infants to look at prevention of CLD with the use of salbutamol. According to GRADE, the quality of the evidence was moderate. We found no eligible trial that studied the use of bronchodilator therapy for treatment of individuals with CLD. Prophylaxis with salbutamol led to no statistically significant differences in mortality (RR 1.08, 95% CI 0.50 to 2.31; RD 0.01, 95% CI -0.09 to 0.11) nor in CLD (RR 1.03, 95% CI 0.78 to 1.37; RD 0.02, 95% CI -0.13 to 0.17). Results showed no statistically significant differences in other complications associated with CLD nor in preterm birth. Investigators in this study did not comment on side effects due to salbutamol. Prophylaxis with aminophylline led to a significant reduction in CLD at 28 days of life (RR 0.18, 95% CI 0.04 to 0.74; RD -0.35, 95% CI -0.56 to -0.13; NNTB 3, 95% CI 2 to 8) and no significant difference in mortality (RR 3.0, 95% CI 0.33 to 26.99; RD 0.08, 95% CI -0.07 to 0.22), along with a significantly shorter dependency on supplementary oxygen in the aminophylline group compared with the no treatment group (MD -17.75 days, 95% CI -27.56 to -7.94). Tests for heterogeneity were not applicable for any of the analyses, as each meta-analysis included only one study.

Authors' conclusions

Data are insufficient for reliable assessment of the use of salbutamol for prevention of CLD. One trial of poor quality reported a reduction in the incidence of CLD and shorter duration of supplementary oxygen with prophylactic aminophylline, but these results must be interpreted with caution. Additional clinical trials are necessary to assess the role of bronchodilator agents in prophylaxis or treatment of CLD. Researchers studying the effects of bronchodilators in preterm infants should include relevant clinical outcomes in addition to pulmonary mechanical outcomes. We identified no trials that studied the use of bronchodilator therapy for treatment of CLD.

PLAIN LANGUAGE SUMMARY

Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants

Review question: What are the effects of bronchodilators on mortality and other complications of preterm birth in infants at risk for or having chronic lung disease (CLD)?

Background: Chronic lung disease is common in babies born before 34 weeks' gestation. Bronchodilators are drugs that cause widening of the air passages in the lungs. They have been used for chronic lung disease because of their potential effect of dilating small airways in babies born preterm. Bronchodilators can be inhaled, taken by mouth (a puffer) or injection or received through a nebuliser with a pressurised aerosol.

Study characteristics: We included randomised and quasi-randomised trials. We included in the analyses two studies that reported on 225 infants.

Study funding resources: We did not identify funding by industry for any trials.

Key results: This review of trials found too little evidence to show positive or negative effects of bronchodilators for prevention of chronic lung disease. More research is needed. We found no trials that studied the use of bronchodilator therapy for treatment of CLD.

Quality of evidence: The quality of the evidence was moderate for one included trial and low for the other.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Salbutamol compared with placebo for prevention of CLD

Patient or population: preterm infants at risk of having CLD

Settings: hospital

Intervention: salbutamol

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Salbutamol				
Mortality	**High-risk population**		**RR 1.08 (95% CI 0.50 to 2.31)**	173 infants (1 study)	⊕⊕⊖⊖ **low**	Bias: no concerns about allocation concealment and performance bias in this single study (Denjean 1998) Consistency: N/A as only 1 study Precision: serious lack of precision due to small sample size Indirectness: study conducted in the target population
	138 per 1000	**128 per 1000**				
CLD at 28 days	**High-risk population**		**RR1.03 (95% CI 0.78 to 1.37)**	173 infants (1 study)	⊕⊕⊕⊖ **moderate**	Bias: no concerns about allocation concealment and performance bias in this single study (Denjean 1998) Consistency: N/A as only 1 study Precision: lack of precision due to small sample size Indirectness: study conducted in the target population
	540 per 1000	**523 per 1000**				

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

Summary of findings 2.

Aminophylline compared with no intervention for prevention of CLD

Patient or population: preterm infants at risk of developing CLD

Settings: hospital

Intervention: aminophylline

Comparison: no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Aminophylline				
Mortality	**High-risk population**		**RR 3.0 (95% CI 0.33 to 26.99)**	52 infants (1 study)	⊕⊖⊖⊖ **very low**	Bias: serious concerns about allocation concealment and performance bias in this single quasi-randomised controlled trial (Denjean 1998) Consistency: N/A as only 1 study Precision: lack of precision due to small sample size Indirectness: study conducted in the target population
	115 per 1000	**39 per 1000**				
CLD at 28 days	**High-risk population**		**RR 0.18 (95% CI 0.04 to 0.74)**	52 infants (1 study)	⊕⊖⊖⊖ **very low**	Bias: serious concerns about allocation concealment and performance bias in this single quasi-randomised controlled trial (Denjean 1998) Consistency: N/A as only 1 study Precision: lack of precision due to small sample size
	77 per 1000	**423 per 1000**				

	Indirectness: study conducted in the target population

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on assumed risk in the comparison group and **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; N/A: not applicable; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Chronic lung disease (CLD), defined as oxygen dependency at 28 days of life or at 36 weeks' postmenstrual age with compatible chest x-rays, is a pulmonary disorder that occurs frequently in preterm infants (Northway 1967; Shennan 1988). It is the consequence of unresolved or abnormally repaired lung damage, and its multi-factorial aetiology has been detailed extensively by previous authors. This includes exposure to high oxygen concentration, volume-derived trauma, barotrauma, sepsis and inflammation (Avery 1987; Paita 1991; Rojas 1995). Over past decades, the survival rate of very low birth weight infants has increased, and the prevalence of CLD remains high (Parker 1992). Incidence varies depending on the population studied, the diagnostic criteria used and variations between clinical management approaches reported at study centres (O'Brodovich 1985; Avery 1987; Shennan 1988; Hack 1991; Lee 2000). CLD may be associated with chronic respiratory difficulties, prolonged and recurrent hospitalisation, growth restriction and death (O'Brodovich 1985; Lee 2000). Administration of antenatal corticosteroids to mothers likely to give birth preterm reduces neonatal mortality and the incidence of respiratory distress syndrome (RDS) but does not reduce the incidence of CLD (Crowley 2001). Administration of prophylactic natural surfactant extract does not reduce the incidence of CLD but reduces the combined outcome of death or CLD (Soll 2001).

Description of the intervention

Bronchodilators may be delivered orally, intravenously or by nebuliser or pressurised aerosol with or without a spacer device. With nebulisation or aerosol, only 0.22% to 1.3% of the dose will reach the lungs (Grigg 1992; Fok 1996). Aerosol tends to be deposited in the central lung region rather than at the periphery (Fok 1996). Humidification of the gas reduces lower respiratory tract deposition of aerosol (Diot 1995). Addition of a spacer device between the nebuliser and the endotracheal tube (Harvey 1995) and synchronising nebulisation with inspiratory airflow (Diot 1995) increase deposition. Variability in lung deposition among individuals has been considerable (Fok 1996). All of these factors serve to modify therapeutic effects.

Numerous bronchodilators are available. Inhaled bronchodilators include non-specific beta-adrenergic agents, such as isoproterenol and isoetharine, and specific beta-adrenergic agents, such as albuterol, metaproterenol, terbutaline and isoetharine. Side effects of beta agonists include hypokalaemia, tachycardia, cardiac arrhythmia, tremor, hypertension and hyperglycaemia (Davis 1990; Farrell 1997; Sweet 2000). Inhaled anticholinergic agents include atropine and ipratropium. Atropine results in more side effects when compared with ipratropium, as the latter is poorly absorbed. Side effects of inhaled anticholinergic agents include tachycardia, decreased gastrointestinal motility, tremor and drying of respiratory secretions (Davis 1990). Systemic bronchodilators include the methylxanthines - caffeine and theophylline - which act by blockage of adenosine receptors. Reported side effects include vomiting, diarrhoea, tachycardia, hypertension and agitation (Davis 1990; Farrell 1997; Sweet 2000).

How the intervention might work

Use of bronchodilators in CLD has been justified by their potential effect of dilating small airways that have muscular hypertrophy. Increased compliance and tidal volume and decreased pulmonary resistance have been documented when bronchodilators were used in short-term studies of pulmonary mechanics in infants with CLD (Sosulski 1982; Cabal 1987; Brudno 1989; Kirpalani 1990; Pfenninger 1993; Gappa 1997; Fok 1998b).

Why it is important to do this review

This review, titled "Bronchodilators for the prevention and treatment of CLD in preterm infants", updates a previously published review in the *Cochrane Database of Systematic Reviews* (Ng 2012). We are aware of no other reviews on this topic.

OBJECTIVES

To determine the effect of bronchodilators given as prophylaxis or as treatment for CLD on mortality and other complications of preterm birth in infants at risk for or identified as having CLD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised and quasi-randomised controlled clinical trials.

Types of participants

Preterm infants (< 37 weeks' gestational age (GA)) at risk for or identified as having CLD.

Types of interventions

The intervention had to include randomised or quasi-randomised administration of a bronchodilator by nebulisation, by spacer device, intravenously or orally versus placebo or no intervention. Bronchodilators include albuterol, aminophylline, atropine, caffeine, clenbuterol, cromakalim, ephedrine, epinephrine, fenoterol, hexoprenaline, ipratropium, isoetharine, isoproterenol, orciprenaline, procaterol, terbutaline, theophylline and tretoquinol. For prevention of CLD, treatment had to be initiated during the first two weeks of life and had to be provided for more than seven days. For treatment of CLD, infants had to receive treatment for more than seven days. Treatment had to be initiated before discharge from the neonatal unit.

Types of outcome measures

Primary outcomes

For prophylaxis of CLD

Primary outcomes were mortality within the study period and CLD (defined as oxygen dependency at 28 days of life or at 36 weeks' postmenstrual age with compatible chest x-ray signs).

For treatment of CLD

Primary outcome was mortality within the study period.

Secondary outcomes

For prophylaxis of CLD

Secondary outcomes were number of days on oxygen, number of days on ventilator, patent ductus arteriosus (PDA), pulmonary interstitial emphysema (PIE), pneumothorax, intraventricular haemorrhage (IVH) of any grade, necrotising enterocolitis (NEC),

sepsis and adverse effects of bronchodilators. Adverse effects of bronchodilators included hypokalaemia, tachycardia, cardiac arrhythmia, tremor, hypertension and hyperglycaemia.

For treatment of CLD

Secondary outcomes were number of days on oxygen, number of days on ventilator, PDA, PIE, pneumothorax, IVH of any grade, NEC, sepsis and adverse effects of bronchodilators.

Search methods for identification of studies

See Cochrane Review Group search strategy. Standard search methods of the Cochrane Neonatal Review Group were employed (http://neonatal.cochrane.org/; Overview of Searching Databases for Randomised Trials in Neonatology).

Electronic searches

For the March 2016 update, we used the criteria and standard methods of Cochrane and the Cochrane Neonatal Review Group (see the Cochrane Neonatal Group search strategy for specialized register).

We conducted a comprehensive search that included the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 2) in the Cochrane Library; MEDLINE via PubMed (1996 to 7 March 2016); Embase (1980 to 2016 March 7); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to 7 March 2016) using the following search terms: (bronchodilator agents OR adrenergic agents OR anticholinergic agents OR albuterol OR aminophylline OR atropine OR clenbuterol OR cromakalim OR ephedrine OR epinephrine OR fenoterol OR hexoprenaline OR ipratropium OR isoetharine OR isoproterenol OR orciprenaline OR procaterol OR terbutaline OR theophylline OR tretoquinol) AND (bronchopulmonary dysplasia OR lung diseases OR chronic lung disease OR BPD OR CLD), plus database-specific limiters for RCTs and neonates (see Appendix 1 for the full search strategies for each database). We applied no language restrictions.

For the MEDLINE search, we used the following medical subject heading (MeSH) terms: bronchopulmonary dysplasia, chronic disease, lung diseases, bronchodilator agents, adrenergic agents, anticholinergic agents, albuterol, aminophylline, atropine, clenbuterol, cromakalim, ephedrine, epinephrine, fenoterol, hexoprenaline, ipratropium, isoetharine, isoproterenol, orciprenaline, procaterol, terbutaline, theophylline and tretoquinol. We used the following text words: chronic lung disease, caffeine, salbutamol, terbutaline, albuterol, aminophylline, atropine, ipratropium, isoetharine and theophylline. We applied the following limits: newborn infant birth to 1 month, human, clinical trial, controlled clinical trial, meta-analysis, multicenter study and randomised controlled trial.

For the Embase search, we used the following MeSH terms: bronchodilating agent, adrenergic receptor stimulating agent, albuterol, clenbuterol, fenoterol, salbutamol, terbutaline, isoetharine, isoproterenol, lung dysplasia, evidence-based medicine, clinical trial and multicenter study. We used the following text words: bronchopulmonary dysplasia, clinical trial, RCT, RCTs, random, meta-analysis, meta analysis, multicenter, newborn, neonate, neonatal. We applied the following limits: infant to one year.

For the CINAHL search, we used the following MeSH terms: bronchopulmonary dysplasia, chronic disease, lung diseases, adrenergic agents, anticholinergic agents, bronchodilator agents. We used the following text words: albuterol, aminophylline, atropine, clenbuterol, cromakalim, ephedrine, epinephrine, fenoterol, hexoprenaline, ipratropium, isoetharine, isoproterenol, orciprenaline, procaterol, terbutaline, theophylline and tretoquinol. We applied the following limits: newborn infant birth to 1 month.

We updated searches as described above in March 2016. In addition, we electronically searched abstracts from the Pediatric Academic Societies' Annual Meetings (2012 to 2015) at PAS Abstracts2View™ and Web of Science.

Searching other resources

We searched clinical trials registries for ongoing and recently completed trials (clinicaltrials.gov; controlled-trials.com; the World Health Organization International Trials Registry and Platform (www.whoint/ictrp/search/en/) and the ISRCTN Registry).

Data collection and analysis

We employed standard methods of the Cochrane Neonatal Review Group and those provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For Armanian 2014, we estimated the sample mean and standard deviation from sample size, median and interquartile range, according to the method used in Wan 2014.

Selection of studies

We included all randomised and quasi-randomised controlled trials fulfilling the selection criteria described in the previous section. Each of two review authors (GN, AO) reviewed the search results and separately selected studies for inclusion. We resolved differences by discussion.

Data extraction and management

Each of two review authors (GN, AO) extracted data separately. We resolved differences by discussion. For each included trial, we sought information regarding random sequence generation, allocation concealment and whether the trial was single centred or multi-centred. We looked for information on trial participants including birth weight, gestational age (GA) at birth, postnatal age, need for mechanical ventilation and sex; information on clinical outcomes analysed for CLD at 28 days of life, CLD at 36 weeks' postmenstrual age, overall mortality, IVH, NEC, air leaks, sepsis and adverse effects ascribed to the drug. We also sought information on length of hospital stay and days on oxygen or on mechanical ventilation.

Assessment of risk of bias in included studies

We employed the standard methods of the Cochrane Neonatal Review Group. Two review authors (GN, AO) independently assessed the methodological quality of each trial with respect to random sequence generation, masking of allocation, masking of intervention, masking of outcome assessment, completeness of follow-up, selective reporting and other sources of bias. We have provided this information in the Characteristics of included studies tables.

For this 2016 update, we independently assessed risk of bias (low, high or unclear) of all included trials by using the Cochrane 'Risk of bias' tool (Higgins 2011) for the following domains.

- Selection bias.
- Performance bias.
- Attrition bias.
- Reporting bias.
- Any other bias.

We resolved disagreements by discussion. See Appendix 2 for a detailed description of risk of bias for each domain.

Measures of treatment effect

We performed statistical analyses using Review Manager software (RevMan 2014). We analysed categorical data using risk ratio (RR), risk difference (RD) and the number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH). We analysed continuous data using mean difference (MD) and reported the 95% confidence interval (CI) for all estimates.

Assessment of heterogeneity

We planned to estimate treatment effects in individual trials and to examine heterogeneity between trials by inspecting forest plots and to quantify the impact of heterogeneity by using the I^2 statistic. We would describe heterogeneity according to the following cutoffs and labels: < 25% none, 25% to 49% low, 50% to 74% moderate, 75%+ high.

If we detected statistical heterogeneity, we planned to explore possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) by performing post hoc subgroup analyses.

Data synthesis

We used the standard methods of the Cochrane Neonatal Review Group to synthesise data reported as typical RR, RD if we included in the analysis data from more than one trial, and NNTB if we observed a statistically significant reduction in RD and NNTH or a statistically significant increase in RD. We used weighted mean difference (WMD) for continuous variables if we included in the analysis data from more than one trial. We used a fixed-effect model for meta-analysis.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the *GRADE Handbook* (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: CLD (defined as oxygen dependency at 28 days of life or at 36 weeks' postmenstrual age with compatible chest x-ray signs) and mortality within the study period. Secondary outcomes were number of days on oxygen, number of days on ventilator, patent ductus arteriosus (PDA), pulmonary interstitial emphysema (PIE), pneumothorax, intraventricular haemorrhage (IVH) of any grade, necrotising enterocolitis (NEC), sepsis and adverse effects of bronchodilators. Adverse effects of bronchodilators included hypokalaemia, tachycardia, cardiac arrhythmia, tremor, hypertension and hyperglycaemia.

Two review authors independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high quality but downgraded the evidence one level for serious (two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of evidence, precision of estimates and presence of publication bias. We used the GRADEpro 2014 Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach yields an assessment of the quality of a body of evidence and assignment to one of four grades.

- High: We are very confident that the true effect lies close to that of the estimate of effect.
- Moderate: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different.
- Low: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
- 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.

RESULTS

Description of studies

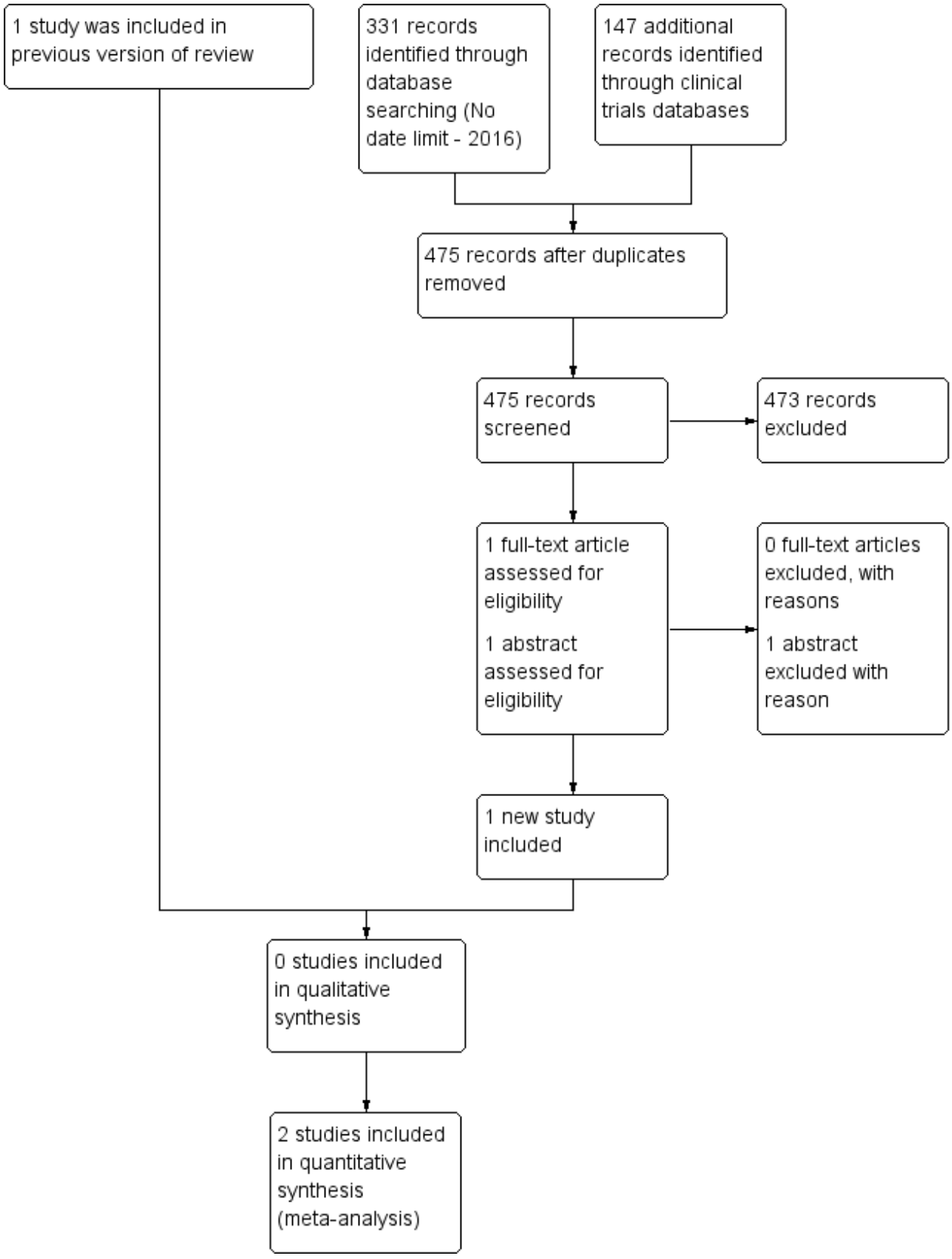
Results of the search

Previous searches revealed one study on prevention (Denjean 1998) and no studies on treatment of CLD. For the update in 2012, review authors identified four studies assessing pulmonary mechanics after the use of bronchodilators (Khalaf 2000; Fayon 2007; Ramos 2007; Costa 2009), but none qualified for inclusion in the review (see table of Characteristics of excluded studies).

For this update in 2016, the search revealed two additional studies. Armanian 2014 investigated the prophylactic effect of aminophylline on the incidence of CLD in very preterm infants. Almaraz 2012 studied effects of inhaled fluticasone 125 µg, theophylline 1 mg and fluticasone + theophylline and measured lung liquid interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α. This study did not qualify for inclusion (see Characteristics of excluded studies).

Figure 1 shows the study flow diagram for this review update.

Figure 1. Study flow diagram: review update.



Included studies

Denjean 1998, a multi-centre, randomised, double-blind trial, enrolled 173 infants needing ventilatory support from six neonatal intensive care units (NICUs) in France.

- Objective: To investigate the potential efficacy of inhaled beclomethasone, salbutamol or their combination for preventing CLD in ventilator-dependent preterm neonates.
- Population: Infants with respiratory distress syndrome and gestational age of less than 31 weeks' PMA were eligible for the study if they required ventilatory support on the 10th postnatal day (re-assessed daily between the 7th and 10th days). The study did not include babies with major malformations, sepsis or current bronchopulmonary infection and those treated with corticosteroids or bronchodilators.
- Intervention: Investigators provided interventions to four treatment groups: placebo + placebo (P + P), placebo + salbutamol (P + S), placebo + beclomethasone (P + B) and salbutamol + beclomethasone (S + B). Salbutamol was given at a dose of 200 micrograms every four hours (1200 micrograms/d) via metered dose inhaler and spacer device. Beclomethasone was given at a dose of 250 micrograms via metered dose inhaler and spacer device. Researchers initiated treatment on the 10th or 11th postnatal day and continued treatment for 28 days, tapering the dose off over eight days.
- Outcomes: Primary outcomes were mortality and CLD characterised at 28 days of life on the basis of clinical (oxygen dependency) and radiographic criteria. Secondary outcomes were duration of ventilatory support, duration of oxygen supplementation, ventilatory index (product of oxygen tension and mean airway pressure) measured every week until extubation, pulmonary complications (pneumothorax, interstitial emphysema), sepsis, mandatory intravenous corticosteroid treatment according to usual practice at each centre and episodes of bronchospasm treated with intravenous bronchodilators. Study authors did not provide data on drug deposition.

Armanian 2014 enrolled 73 infants and was conducted in the NICU at Alzahra and Shahid Beheshti Hospitals in Isfahan, Iran, between March 2012 and April 2013.

- Objective: To assess the safety and preventive effects of aminophylline in terms of the incidence of CLD in very preterm infants.
- Population: Infants were born preterm with birth weight of 1200 grams or less. The study did not include infants who had major congenital anomalies, asphyxia, occurrence of apnoea and need for mechanical ventilation in the first 24 hours after birth, congenital cyanotic heart disease, small for gestational age intrauterine growth and sepsis in the first 10 days after birth.
- Intervention: For the aminophylline group (A), after consideration of inclusion and exclusion criteria for the preterm neonate with birth weight of 1200 grams or less, investigators began treatment with 5 mg/kg of aminophylline, given as a loading dose parenterally; this was followed by 1.5 mg/kg given as a maintenance dose each eight hours for the first 10 days of life. In the control group (C), after consideration of inclusion and exclusion criteria for the premature neonate with birth weight of 1200 grams or less, investigators administered no aminophylline during the first 10 days of life.
- Outcomes: Primary and secondary outcomes included duration of dependency on oxygen and incidence of CLD. Both groups made decisions regarding CLD uniformly. Neonates were considered as having CLD/bronchopulmonary dysplasia (BPD) if they had been oxygen dependent for at least 28 days after birth, and if the severity of CLD was judged according to preset criteria. Aminophylline side effects (tachycardia,hypertension) and mortality were recorded as other secondary outcomes.
- Note: This was a quasi-randomised trial of 73 infants, 52 of whom (26 in each group) were analysed.

We identified no trials that studied use of bronchodilator therapy for treatment of individuals with CLD.

Excluded studies

We rejected the following studies because they addressed only pulmonary mechanics: Kao 1984; Kao 1987; Wilkie 1987; Kao 1988; Kao 1989; Rotschild 1989; Stefano 1991; Pfenninger 1993; Lee 1994; Gappa 1997; Nguyen 1997; Fok 1998a and Sivakumar 1999. We rejected Guimaraes 1993 because it was not a randomised controlled trial, and infants were given beclomethasone and salbutamol together. For the 2012 update, we excluded the following four studies because they addressed only pulmonary mechanics: Khalaf 2000; Fayon 2007; Ramos 2007; and Costa 2009. For this 2016 update, we rejected Almaraz 2012 because study authors presented study findings as an abstract and provided insufficient information on the study population.

Risk of bias in included studies

We presented information on risk of bias in the included trials in the Risk of bias graph (Figure 2) and in the Risk of bias summary (Figure 3).

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

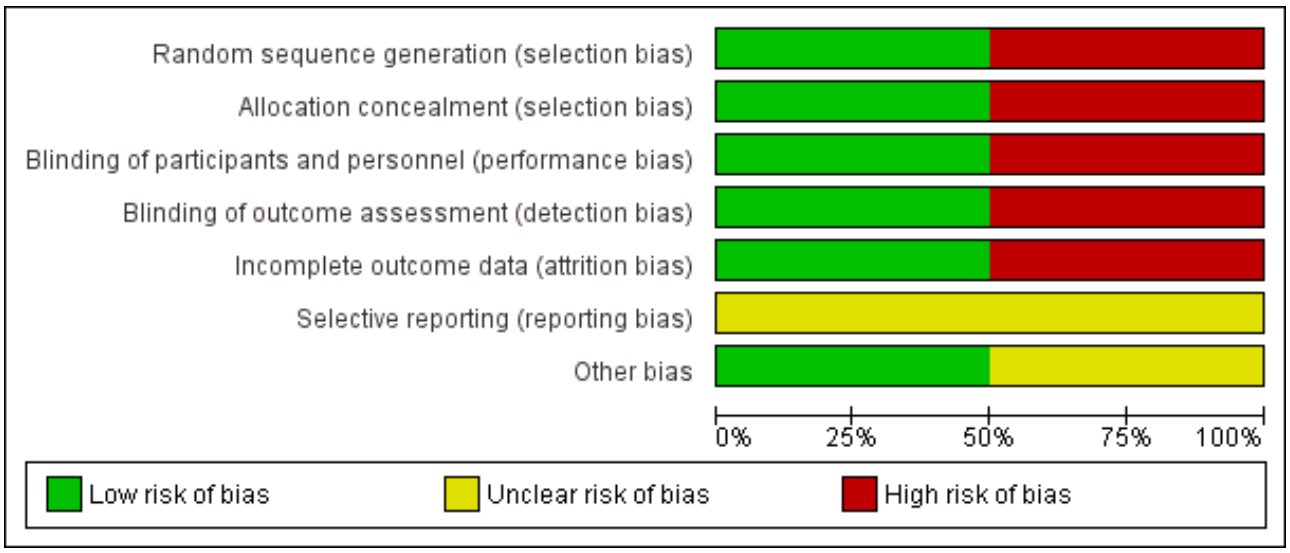
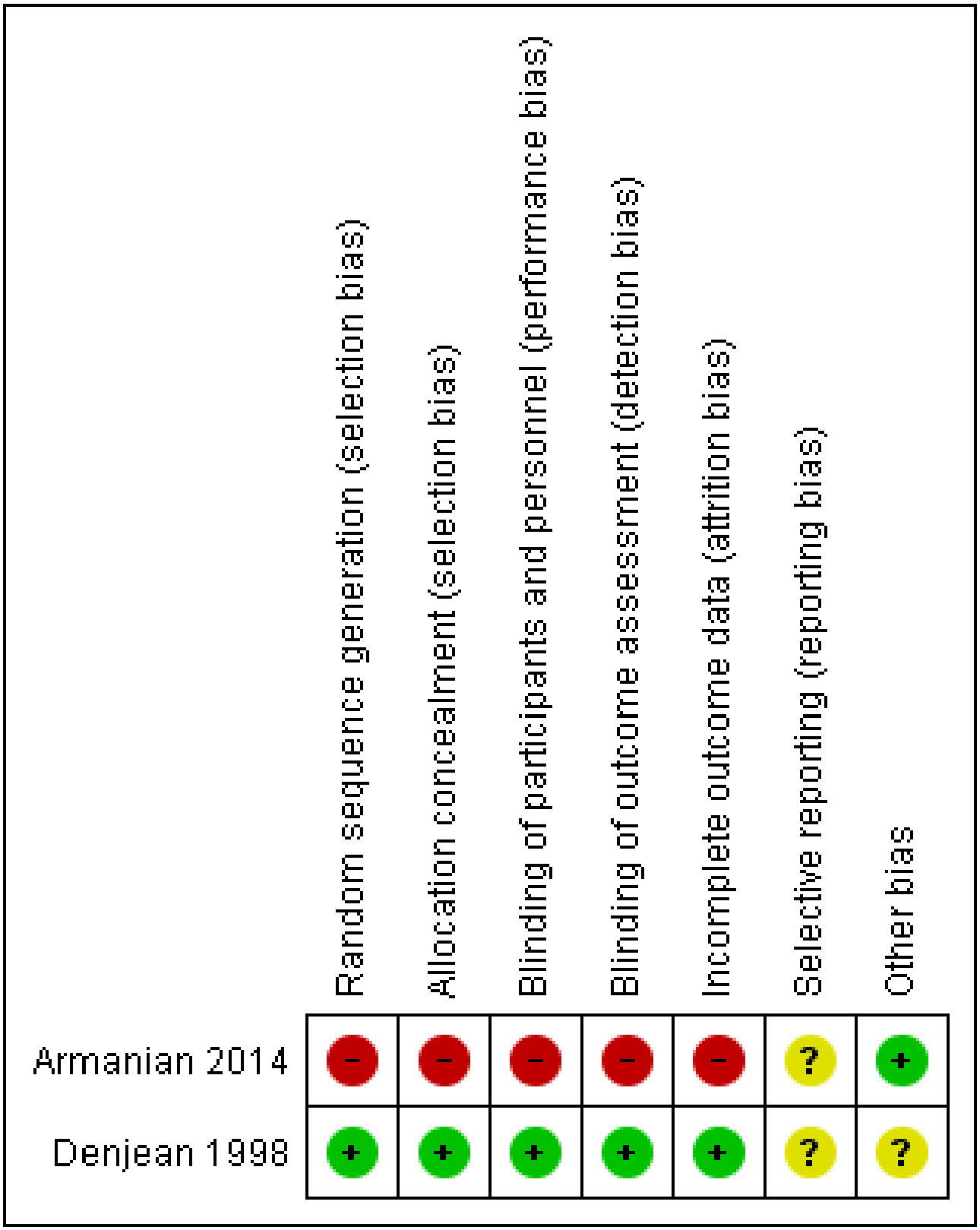


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We determined that Denjean 1998 had low risk of bias, as the randomisation process and preparation of therapeutic units were centralised. Armanian 2014 had high risk of bias regarding random sequence generation and allocation concealment because in selecting neonates randomly, investigators assigned neonates with an even digit at the end of their file numbers to the aminophylline group and those with file numbers ending in an odd digit to the control group.

Blinding

Armanian 2014 had high risk of bias as investigators used no placebo. Risk was low in Denjean 1998.

Incomplete outcome data

Denjean 1998 originally randomised 178 infants but did not obtain informed consent for or withdrew five infants, leaving 173 infants in the trial. Researchers reported results for these 173 infants. We rated the study as having low risk of attrition bias.

However, Armanian 2014 had high risk of attrition bias; of 73 infants randomised, we included only 52 in the analyses.

Selective reporting

Protocols for the included studies were not available to us, so we could not judge whether any deviations occurred.

Other potential sources of bias

We judged Denjean 1998 as having unclear risk of other bias, as some infants were randomised before consent was obtained.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**

Salbutamol *versus* placebo in the prophylaxis of CLD (Comparison 1)

In Denjean 1998, investigators compared results of salbutamol and placebo groups (n = 173) in terms of the following outcomes.

(As only one study performed these comparisons, tests for heterogeneity were not applicable.)

Primary outcomes

Mortality (Outcome 1.1)

Results showed no significant effect (RR 1.08, 95% CI 0.50 to 2.31; RD 0.01, 95% CI -0.09 to 0.11) (Analysis 1.1) (low-quality evidence).

CLD at 28 days (Outcome 1.2)

For overall (mild, moderate or severe) CLD, results revealed no significant effect (RR 1.03, 95% CI 0.78 to 1.37; RD 0.02, 95% CI -0.13 to 0.17) (Analysis 1.2) (moderate-quality evidence).

Secondary outcomes

Duration of assisted ventilation (Outcome 1.3)

Results showed no statistically significant difference in the duration of assisted ventilation (MD -1.63 days, 95% CI -5.63 to 2.37) (Analysis 1.3).

Duration of oxygen supplementation (Outcome 1.4)

Results revealed no statistically significant difference in the duration of oxygen supplementation (MD -2.82 days, 95% CI -11.91 to 6.27) (Analysis 1.4).

Mean age of weaning from ventilatory support (Outcome 1.5)

Researchers found no statistically significant difference in weaning from respiratory support (assisted ventilation or oxygen supplementation) (MD -2.87 days, 95% CI -11.28 to 5.54) (Analysis 1.5).

Need for intravenous dexamethasone (Outcome 01.6)

Investigators found no significant effect (RR 0.77, 95% CI 0.49 to 1.19; RD -0.08, 95% CI -0.22 to 0.05) (Analysis 1.6).

Infants with one or more episodes of infection (Outcomes 1.7 and 1.8)

Results showed no statistically significant effect on respiratory infection, defined as increasing ventilatory requirements associated with increased serum C-reactive protein and bacteria in tracheal aspirates (RR 0.61, 95% CI 0.27 to 1.39; RD -0.06, 95% CI -0.16 to 0.04) (Analysis 1.7), and no significant effect on sepsis, defined as a positive blood culture (RR 1.06, 95% CI 0.54 to 2.06; RD 0.01, 95% CI -0.10 to 0.12) (Analysis 1.8).

Study authors stated that they found no differences in the secondary outcomes of pulmonary complications, weekly ventilatory index until extubation, interruptions in randomised treatment for intravenous salbutamol and episodes of bronchospasm treated with intravenous bronchodilators. However, they did not present these data and did not comment on adverse effects associated with salbutamol.

Aminophylline versus no intervention in the prophylaxis of CLD (Comparison 2)

In Armanian 2014, investigators compared results of the aminophylline and placebo groups (n = 52) for the following outcomes.

(As only one study performed these comparisons, tests for heterogeneity were not applicable.)

Primary outcomes

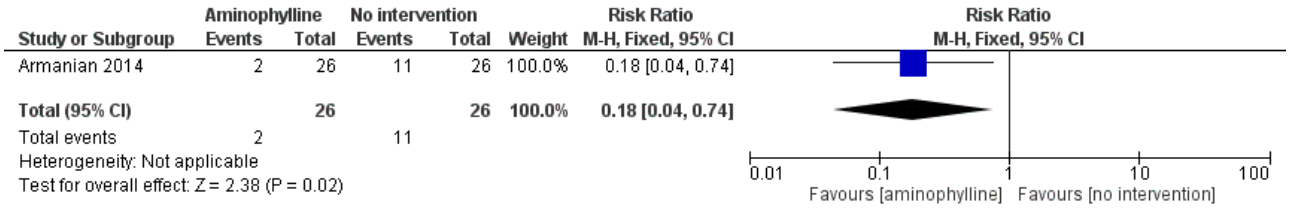
Mortality (Outcome 2.1)

Results showed no significant effect (RR 3.0, 95% CI 0.33 to 26.99; RD 0.08, 95% CI -0.07 to 0.22) (Analysis 2.1).

CLD at 28 days (Outcome 2.2)

Risk for CLD at 28 days was significantly less in the aminophylline group than in the no intervention group (RR 0.18, 95% CI 0.04 to 0.74; RD -0.35, 95% CI -0.56 to -0.13; NNTB 3, 95% CI 2 to 8) (Analysis 2.2; Figure 4).

Figure 4. Forest plot of comparison: 2 Aminophylline versus no intervention in the prophylaxis of CLD, outcome: 2.2 CLD at 28 days.

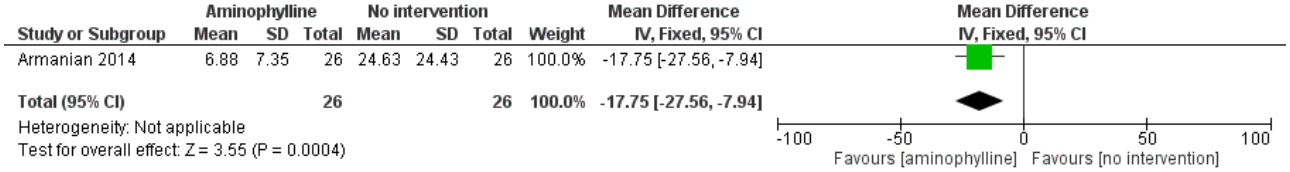


Secondary outcomes

Duration of dependency on supplementary oxygen (days) (Outcome 2.3)

The mean time of oxygen dependency was significantly shorter in the aminophylline group than in the no intervention group (MD -17.75 days, 95% CI -27.56 to -7.94) (Analysis 2.3; Figure 5).

Figure 5. Forest plot of comparison: 2 Aminophylline versus no intervention in the prophylaxis of CLD, outcome: 2.3 Duration of dependency on supplementary oxygen (days).



Side effects (tachycardia, hypertension) (Outcome 2.4)

Investigators noted no side effects among infants included in the study (RR not estimable; RD 0.08, 95% CI -0.07 to 0.07) (Analysis 2.4).

DISCUSSION

For the update conducted in March 2016, review authors identified two trials (Armanian 2014; Almaraz 2012). We excluded Almaraz 2012, as the study was published only in abstract format. Investigators did not report the age of infants at the time of treatment for severe bronchopulmonary dysplasia. They did report the following outcomes: decreased fraction of inspired oxygen (FiO_2) > 0.20; lung liquid interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF-α).

For the update conducted in April 2012, review authors identified four trials (Khalaf 2000; Fayon 2007; Ramos 2007; Costa 2009). However, they excluded these trials as all reported on pulmonary mechanical outcomes and provided no information on clinical outcomes of interest for this review. Denjean 1998 examined prevention of chronic lung disease (CLD). No studies assessed important clinical outcomes of treatment for CLD. Excluded studies (Kao 1984; Kao 1987; Wilkie 1987; Kao 1988; Kao 1989; Rotschild 1989; Stefano 1991; Guimaraes 1993; Pfenninger 1993; Lee 1994; Gappa 1997; Nguyen 1997; Fok 1998a; Sivakumar 1999) found short-term decreases in pulmonary resistance and increases in pulmonary compliance. However, they did not examine our primary and secondary clinical outcomes.

Denjean 1998 showed no evidence that salbutamol reduced mortality or CLD at 28 days of life in preterm infants at risk of developing CLD. This study did not report outcomes for CLD at 36 weeks' postmenstrual age, which is generally regarded as the more important outcome with regards to CLD. Study authors did not demonstrate earlier weaning from respiratory support with salbutamol and did not report the duration of oxygen supplementation. Researchers demonstrated that salbutamol does not affect the need for intravenous dexamethasone or sepsis compared with placebo. Use of dexamethasone may have varied between the six neonatal intensive care units (NICUs) involved in the study. Denjean 1998 did not comment on adverse effects of salbutamol.

Denjean 1998 found no significant differences in outcomes upon comparing salbutamol with placebo. Salbutamol showed no evidence of effect in Denjean 1998; several reasons may explain this. The study did not assess drug deposition, which is known to change the therapeutic effect of the drug. The amount of drug delivered to the lungs varied with the route of administration. The mode of delivery used may have led to delivery of insufficient drug to the lungs. The pathophysiology of CLD is multi-factorial. Mechanisms besides muscle hypertrophy in small airways may explain why salbutamol showed no evidence of effect for prevention of CLD.

Armanian 2014 found that aminophylline reduced CLD at 28 days in preterm infants at risk of developing CLD and reduced the duration of dependency on supplementary oxygen but found no differences in mortality. Study authors reported no side effects of aminophylline. However, this study was of overall poor methodological quality, and these outcomes should be interpreted with caution.

Review authors identified no trials that studied use of bronchodilator therapy for treatment of CLD.

Summary of main results

Review authors were surprised at the paucity of trials that assessed clinical outcomes of bronchodilators in CLD. We found no randomised controlled trials in an extensive search of the literature on use of bronchodilators in the treatment of CLD. Two trials assessed the effectiveness of two different bronchodilators (aminophylline and salbutamol); as interventions differed, we could not combine study results in meta-analyses. Aminophylline may have beneficial effects in prevention of CLD, but the poor quality of the one small included trial prevents application of findings to clinical practice.

Overall completeness and applicability of evidence

Evidence on the use of bronchodilators for prevention or treatment of CLD is currently lacking.

Quality of the evidence

According to GRADE, the quality of the evidence varied; Denjean 1998 provided high-quality evidence, and Armanian 2014 provided evidence of low quality.

Potential biases in the review process

We are aware of no bias in our review process. No review authors have published studies regarding bronchodilators for prevention and treatment of CLD.

Agreements and disagreements with other studies or reviews

We are aware of no other systematic reviews on this topic.

AUTHORS' CONCLUSIONS

Implications for practice

Results of this systematic review show no current evidence for the use of salbutamol or aminophylline for prevention of CLD. We were unable to address the question of whether bronchodilators are useful in the treatment of CLD. Future use of bronchodilators in preterm infants should occur in the scenario of placebo-controlled randomised clinical trials.

Implications for research

In light of the paucity of clinical trials available for inclusion in this systematic review, future research should be directed towards addressing the question of whether bronchodilators have a preventive role in the following: treatment of preterm infants at risk of CLD to reduce mortality, CLD at 36 weeks' postmenstrual age, duration of ventilatory support, duration of oxygen supplementation and long-term outcomes (to 18 months' corrected gestational age). Future studies should be conducted to evaluate whether bronchodilators have a role in the treatment of preterm infants with established CLD to reduce mortality, duration of ventilatory support or duration of oxygen supplementation. It is important that researchers assess whether this occurs without undue side effects, and that they assess clinical outcomes beyond short-term pulmonary function. A wide variety of bronchodilators are available, and studies included in this review assessed only salbutamol and aminophylline. Future research should examine use of different bronchodilator drugs, different drug dosages and different modes of delivery, and should assess drug deposition.

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CHARACTERISTICS OF STUDIES

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

Armanian 2014

Methods	• Blinding to randomisation - no; quasi-randomised trial • Blinding to intervention - no • Complete follow-up - no; 73 infants were randomised, but only 26 in each group (52) were included in analyses • Blinding to outcome - no
Participants	Infants born preterm with `at-birth` weight of 1200 grams or less
Interventions	In the aminophylline group (A), after consideration of inclusion and exclusion criteria for the preterm neonate with weight ≤ 1200 grams, 5 mg/kg of aminophylline was given as a loading dose; this was followed by 1.5 mg/kg, given each 8 hours as a maintenance dose, for the first 10 days of life.

Armanian 2014 *(Continued)*

Outcomes	Duration of oxygen dependency, incidence of CLD
Notes	73 infants were randomised, but only 26 in each group (52) were included in analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	To select neonates randomly, investigators assigned neonates with an even digit at the end of their file numbers to group A, and those with file numbers ending in an odd digit to group C.
Allocation concealment (selection bias)	High risk	To select neonates randomly, investigators assigned neonates with an even digit at the end of their file numbers to group A, and those with file numbers ending in an odd digit to group C.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Researchers used no placebo.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Researchers used no placebo.
Incomplete outcome data (attrition bias) All outcomes	High risk	73 infants were randomised, but only 52 were included in analyses. No intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	The protocol for this study was not available to us, so we cannot judge whether deviations from the protocol occurred.
Other bias	Low risk	Study appears free of other bias.

Denjean 1998

Methods	Randomised prospective double-blind placebo-controlled trial Study location: 6 NICUs in France. Study period: April 1993 to April 1995 • Blinding to randomisation - yes • Blinding to intervention - yes • Complete follow-up; originally investigators randomised 178 infants, but they did not obtain informed consent for or withdrew 5 infants, leaving 173 infants in the trial. They provided results for all 173 infants. • Blinding to outcome - no
Participants	Number of patients entered into the study: 87 in treatment (salbutamol) group and 86 in placebo group Mean (SD) BW: 1028 grams ± 220 grams in the salbutamol arm; 1071 grams ± 254 grams in the placebo arm Mean (SD) GA: 27.7 weeks ± 1.5 weeks in the salbutamol arm; 27.7 weeks ± 1.6 weeks in the placebo arm Age at enrolment into the study: day 10 or day 11 Other characteristics: All infants had RDS and GA < 31 weeks and needed ventilatory support on the 10th postnatal day

Denjean 1998 *(Continued)*

	Exclusion criteria: major malformations, sepsis, current bronchopulmonary infection, treatment with corticosteroids or bronchodilators
Interventions	Researchers used metered dose inhalers to administer salbutamol 200 micrograms every 4 hours or the corresponding placebo. They provided treatment on the 10th or 11th postnatal day and for 28 days, with dose tapering over a period of 8 days
Outcomes	Primary outcomes were mortality and CLD at 28 days on the basis of oxygen dependency and radiographic criteria. Secondary outcomes were duration of ventilatory support, duration of oxygen supplementation, ventilatory index measured every week until extubation, pulmonary complications (pneumothorax, interstitial emphysema), mandatory intravenous corticosteroid treatment according to usual practice at each centre and episodes of bronchospasm treated with intravenous bronchodilators. Results showed no significant differences for any outcomes.
Notes	Incidence of pulmonary complications and episodes of bronchospasm were said to be the same, but investigators did not present the data. Joseph Beyene assembled data for the 2 main groups - salbutamol and placebo - from subgroup data provided in the original report for the following outcomes: duration of assisted ventilation, duration of oxygen supplementation and age at weaning from respiratory support.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was blinded and was stratified by centre, GA and mode of ventilation used at trial entry at 10 days of age (ET IMV or IMV/CPAP) (Denjean [pers comm]).
Allocation concealment (selection bias)	Low risk	Randomisation was blinded.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Staff was blinded to which drug or placebo was given.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Staff assessed outcomes while blinded to which drug or placebo was given.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete follow-up: Originally, investigators randomised 178 infants, but they did not obtain informed consent or withdrew 5 infants, leaving 173 infants in the trial. They reported results for all 173 infants.
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available to us, so we cannot judge whether deviations from the protocol occurred.
Other bias	Unclear risk	Investigators randomised some infants before obtaining consent.

BW: birth weight; CLD: chronic lung disease; CPAP: continuous positive airway pressure; ET: endotracheal; GA: gestational age; IMV: invasive mechanical ventilation; NICU: neonatal intensive care unit; RDS: respiratory distress syndrome; SD: standard deviation.

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

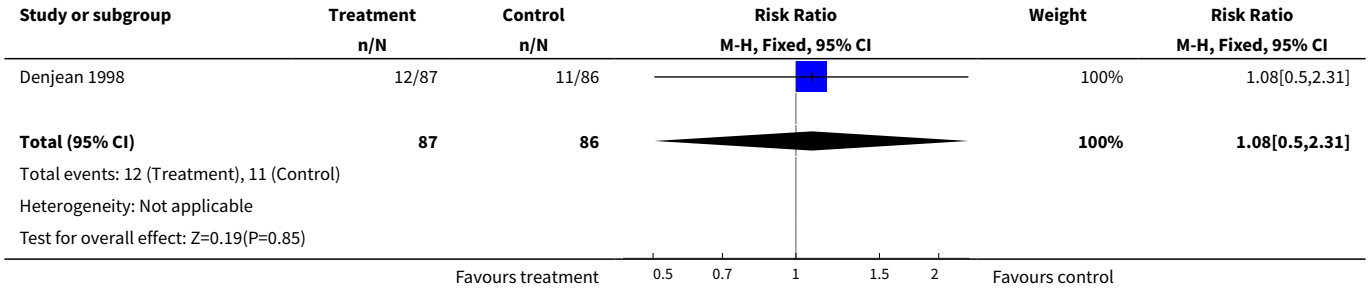
Study	Reason for exclusion
Almaraz 2012	Investigators published study findings in abstract form only. They did not report age of infants at time of treatment for severe bronchopulmonary dysplasia. They reported the following outcomes: decreased fraction of inspired oxygen (FiO_2) > 0.20; lung liquid interleukin (IL)-1β, IL-6 and tumour necrosis factor (TNF)-α.
Costa 2009	Researchers reported only pulmonary mechanics.
Fayon 2007	Researchers reported only pulmonary mechanics.
Fok 1998a	Researchers reported only pulmonary mechanics.
Gappa 1997	Researchers reported only pulmonary mechanics.
Guimaraes 1993	Not a randomised controlled trial. Investigators gave infants both beclomethasone and salbutamol but not separately.
Kao 1984	Not a randomised controlled trial
Kao 1987	Researchers reported only pulmonary mechanics.
Kao 1988	Researchers reported only pulmonary mechanics.
Kao 1989	Cross-over study; infants received placebo, metaproterenol, atropine and metaproterenol plus atropine. Researchers reported only pulmonary mechanics.
Khalaf 2000	This study compared doses of albuterol delivered by metered dose inhaler with spacer and jet nebuliser. It is not clear whether this was a randomised controlled trial or a controlled trial.
Lee 1994	Researchers reported only pulmonary mechanics.
Nguyen 1997	Researchers reported only pulmonary mechanics.
Pfenninger 1993	Researchers reported only pulmonary mechanics.
Ramos 2007	The objective of the study was to assess the effect of salbutamol on pulmonary mechanics of asymptomatic very low birth weight infants at the moment of discharge from the neonatal intensive care unit. Researchers reported only pulmonary mechanics.
Rotschild 1989	Each participant was his own control and was randomly assigned to a placebo-salbutamol or salbutamol-placebo sequence. Researchers reported only pulmonary mechanics.
Sivakumar 1999	Researchers reported only pulmonary mechanics.
Stefano 1991	Researchers reported only pulmonary mechanics.
Wilkie 1987	Researchers reported only pulmonary mechanics.

DATA AND ANALYSES

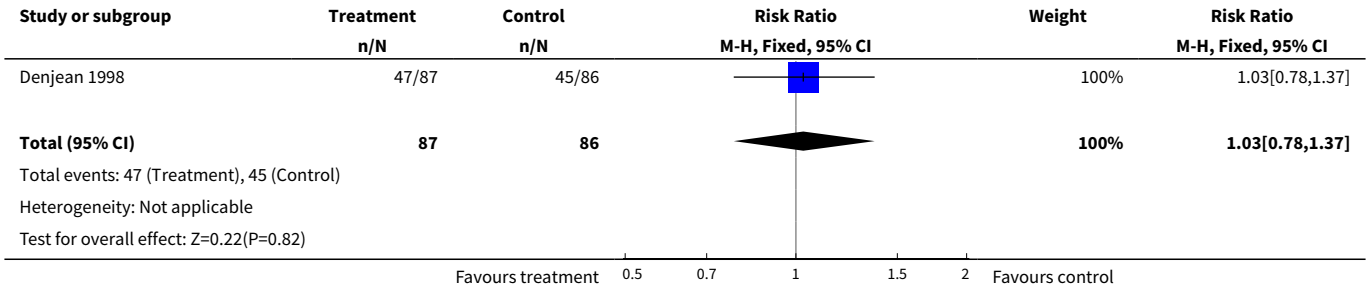
Comparison 1. Salbutamol versus placebo in the prophylaxis of CLD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	173	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.50, 2.31]
2 CLD at 28 days	1	173	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.78, 1.37]
3 Duration of assisted ventilation (days)	1	173	Mean Difference (IV, Fixed, 95% CI)	-1.63 [-5.63, 2.37]
4 Duration of oxygen supplementation (days)	1	173	Mean Difference (IV, Fixed, 95% CI)	-2.82 [-11.91, 6.27]
5 Age of weaning from ventilatory support (days)	1	173	Mean Difference (IV, Fixed, 95% CI)	-2.87 [-11.28, 5.54]
6 Need for intravenous dexamethasone	1	173	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.49, 1.19]
7 Infants with 1 or more episodes of respiratory infection	1	173	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.27, 1.39]
8 Infants with 1 or more episodes of sepsis (positive blood culture)	1	173	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.54, 2.06]

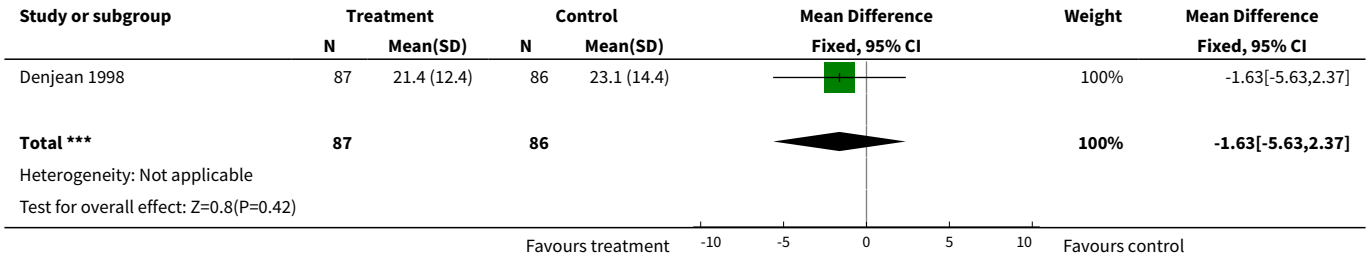
Analysis 1.1. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 1 Mortality.



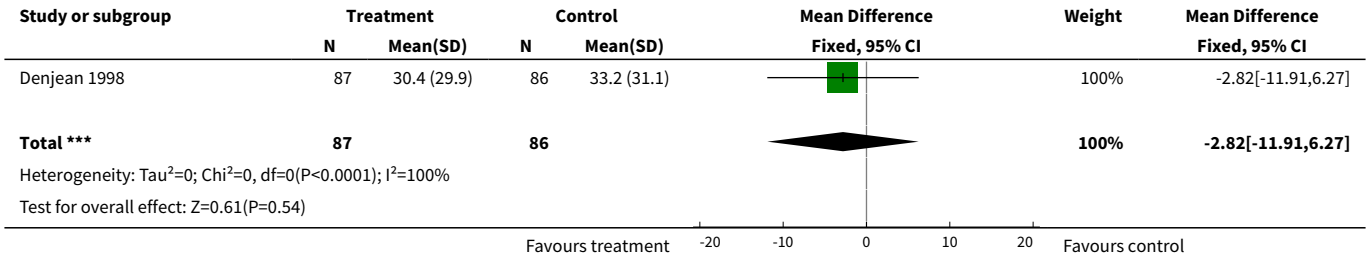
Analysis 1.2. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 2 CLD at 28 days.



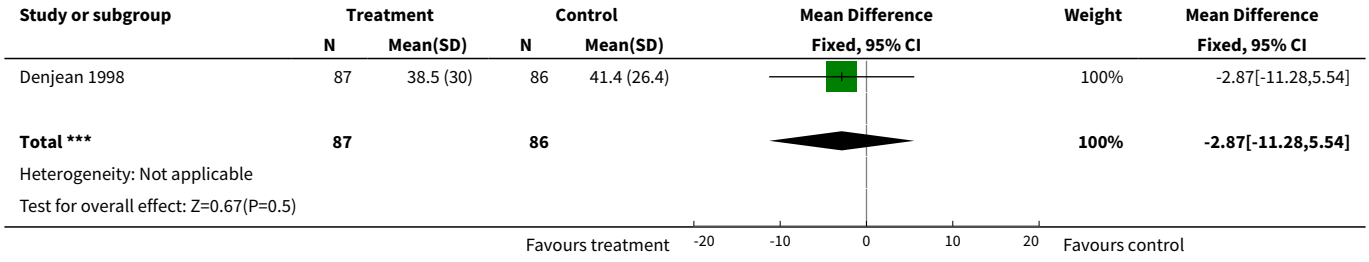
Analysis 1.3. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 3 Duration of assisted ventilation (days).



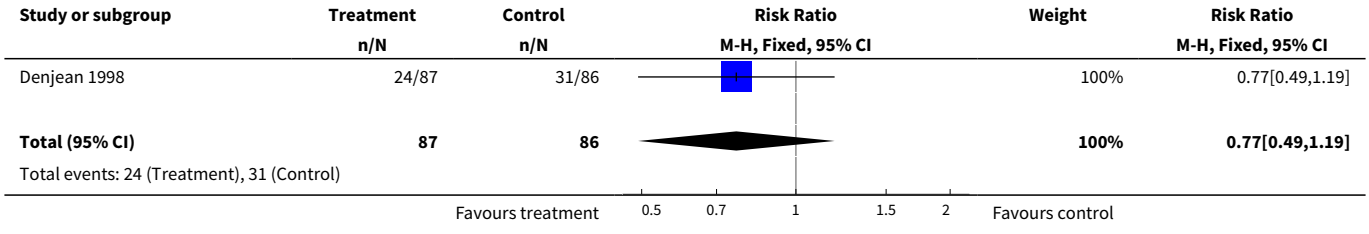
Analysis 1.4. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 4 Duration of oxygen supplementation (days).

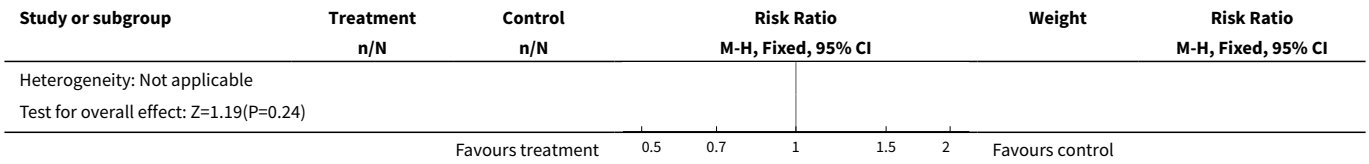


Analysis 1.5. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 5 Age of weaning from ventilatory support (days).

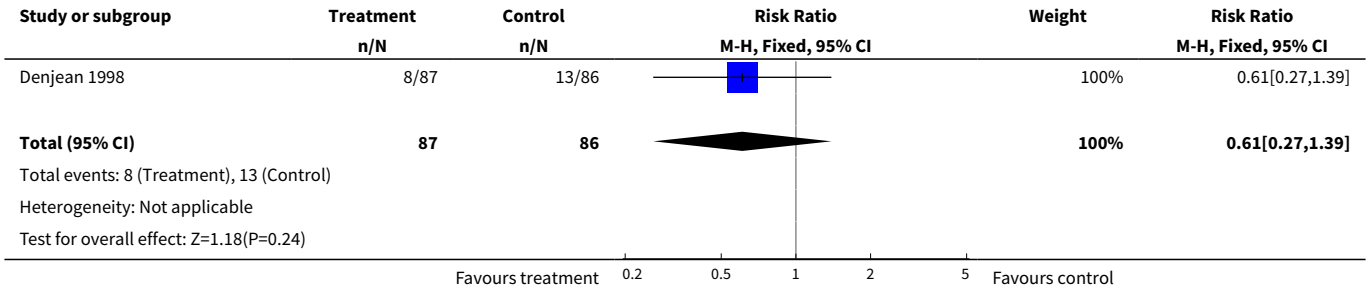


Analysis 1.6. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 6 Need for intravenous dexamethasone.

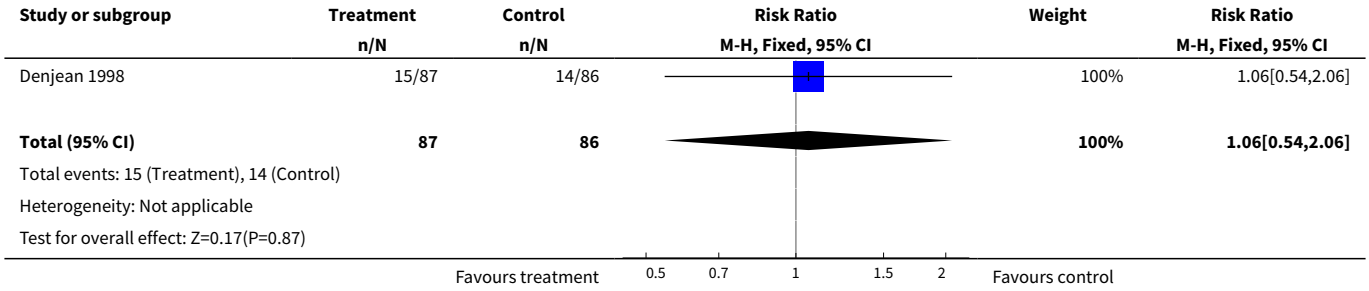




Analysis 1.7. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 7 Infants with 1 or more episodes of respiratory infection.



Analysis 1.8. Comparison 1 Salbutamol versus placebo in the prophylaxis of CLD, Outcome 8 Infants with 1 or more episodes of sepsis (positive blood culture).



Comparison 2. Aminophylline versus no intervention in the prophylaxis of CLD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	52	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.33, 26.99]
2 CLD at 28 days	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.18 [0.04, 0.74]
3 Duration of dependency of supplementary oxygen (days)	1	52	Mean Difference (IV, Fixed, 95% CI)	-17.75 [-27.56, -7.94]
4 Side effects (tachycardia, hypertension)	1	52	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

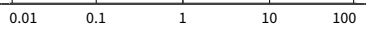
Analysis 2.1. Comparison 2 Aminophylline versus no intervention in the prophylaxis of CLD, Outcome 1 Mortality.

Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2014	3/26	1/26		100%	3[0.33,26.99]
Total (95% CI)	**26**	**26**		**100%**	**3[0.33,26.99]**
Total events: 3 (Aminophylline), 1 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.98(P=0.33)					

Favours [aminophylline] Favours [no intervention]

Analysis 2.2. Comparison 2 Aminophylline versus no intervention in the prophylaxis of CLD, Outcome 2 CLD at 28 days.

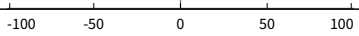
Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2014	2/26	11/26		100%	0.18[0.04,0.74]
Total (95% CI)	**26**	**26**		**100%**	**0.18[0.04,0.74]**
Total events: 2 (Aminophylline), 11 (No intervention)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.38(P=0.02)					



Favours [aminophylline] Favours [no intervention]

Analysis 2.3. Comparison 2 Aminophylline versus no intervention in the prophylaxis of CLD, Outcome 3 Duration of dependency of supplementary oxygen (days).

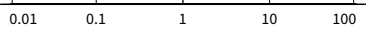
Study or subgroup	Aminophylline N	Aminophylline Mean(SD)	No intervention N	No intervention Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Armanian 2014	26	6.9 (7.4)	26	24.6 (24.4)		100%	-17.75[-27.56,-7.94]
Total ***	**26**		**26**			**100%**	**-17.75[-27.56,-7.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.55(P=0)							



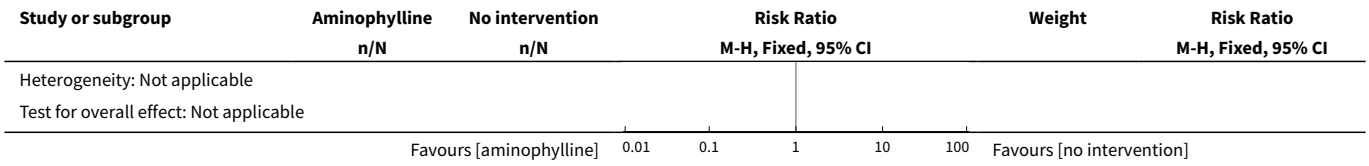
Favours [aminophylline] Favours [no intervention]

Analysis 2.4. Comparison 2 Aminophylline versus no intervention in the prophylaxis of CLD, Outcome 4 Side effects (tachycardia, hypertension).

Study or subgroup	Aminophylline n/N	No intervention n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Armanian 2014	0/26	0/26			Not estimable
Total (95% CI)	**26**	**26**			**Not estimable**
Total events: 0 (Aminophylline), 0 (No intervention)					



Favours [aminophylline] Favours [no intervention]



APPENDICES

Appendix 1. Standard search methods

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 (randomised controlled trial [pt] OR controlled clinical trial [pt] OR Clinical Trial[ptyp] OR randomised [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti]) 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 (randomised controlled trial or controlled clinical trial or randomised 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 (randomised controlled trial OR controlled clinical trial OR randomised 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 very low birth weight or low birth weight or VLBW or LBW)

Appendix 2. Risk of bias tool

The following issues were evaluated and entered into the risk of bias table.
1. 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:
a. low risk (any truly random process e.g. random number table; computer random number generator);
b. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
c. unclear risk.

2. 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:
a. low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
b. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
c. unclear risk.

3. Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

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 classes of outcomes. We categorized the methods as:
a. low risk, high risk or unclear risk for participants;
b. low risk, high risk or unclear risk for personnel; and
c. low risk, high risk or unclear risk for outcome assessors.

4. 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 when reported and whether missing data were balanced across groups or were related to outcomes. When sufficient information was reported or supplied by trial authors, we re-included missing data in the analyses. We categorised the methods as:
a. low risk (< 20% missing data);

b. high risk (≥ 20% missing data); or
c. unclear risk.

5.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:
a. low risk (when it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
b. high risk (when not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and were 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); or
c. unclear risk.

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

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

If needed, we planned to explore the impact of the level of bias by undertaking sensitivity analyses.

1. Sequence generation: Was the allocation sequence adequately generated?
2. Allocation concealment: Was allocation adequately concealed?
3. Blinding of participants, personnel and outcome assessors: Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?
4. Incomplete outcome data: Were incomplete outcome data adequately addressed?
5. Selective outcome reporting: Are reports of the study free of the suggestion of selective outcome reporting?
6. Other sources of bias: Was the study apparently free of other problems that could put it at high risk of bias?

WHAT'S NEW

Date	Event	Description
28 January 2020	Amended	Arne Ohlsson deceased.

HISTORY

Protocol first published: Issue 3, 1998
Review first published: Issue 3, 2001

Date	Event	Description
1 August 2016	New citation required but conclusions have not changed	One new study added; conclusions unchanged
28 April 2016	New search has been performed	This review updates the existing review, "Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants", which was published in the *Cochrane Database of Systematic Reviews* (Ng 2012). New searches of the literature were conducted in March 2016 and led to the inclusion of 1 additional study.

Date	Event	Description
19 April 2012	New search has been performed	This review updates the existing review, "Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants", which was published in the *Cochrane Database of Systematic Reviews* (Ng 2009).
19 April 2012	New citation required but conclusions have not changed	Updated search revealed 4 trials that did not qualify for inclusion in this review. No changes were made to review conclusions.
11 September 2008	Amended	This review updates the existing review, "Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants", which was published in the *Cochrane Database of Systematic Reviews* (Ng 2006). Updated search revealed no new trials. No changes were made to review conclusions. Review has been converted to new review format.
30 April 2006	New search has been performed	This review updates the existing review, "Bronchodilators for the prevention and treatment of chronic lung disease in preterm infants", which was published in the Cochrane Library, 2003, Issue 3 (Ng 2003). Ng 2006 An updated search conducted in April 2006 (Ng 2006) identified no new eligible studies. Review conclusions remain unchanged: Randomised trials provided no evidence for the use of salbutamol for prevention of chronic lung disease (CLD). We are unable to address the question as to whether bronchodilators are useful in the treatment of patients with CLD. Future use of salbutamol and other bronchodilators in preterm infants should occur in the scenario of a placebo-controlled randomised clinical trial.
7 February 2001	New citation required and conclusions have changed	Substantive amendments were made.

CONTRIBUTIONS OF AUTHORS

G Ng
Performing literature search and identifying trials for inclusion
Evaluating the methodological quality of included trials
Abstracting data
Verifying and entering data into RevMan
Writing text of the review

A Ohlsson
Writing the protocol
Performing literature search and identifying trials for inclusion
Evaluating the methodological quality of included trials
Abstracting data
Verifying and entering data into RevMan
Revising the final review

O Da Silva
Writing the protocol

Translating the article
Revising the final review

G Ng and A Ohlsson conducted the 2012 review update.

G Ng, O da Silva and A Ohlsson conducted this 2016 review update.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Imperial College Healthcare NHS Trust, London, UK.
- Children's Hospital at London Health Sciences Centre, London, Ontario, Canada.
- Mount Sinai Hospital, Toronto, Ontario, Canada.

External sources

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Albuterol [therapeutic use]; Aminophylline [therapeutic use]; Beclomethasone [therapeutic use]; Bronchodilator Agents [*therapeutic use]; Chronic Disease; Drug Therapy, Combination; Infant, Premature; Infant, Premature, Diseases [mortality] [*prevention & control]; Lung Diseases [mortality] [*prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant, Newborn