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Prophylactic animal derived surfactant extract for preventing morbidity and mortality in preterm infants.
Cochrane Database of Systematic Reviews 1997, Issue 4. Art. No.: CD000511.
DOI: 10.1002/14651858.CD000511.

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[Intervention Review]

Prophylactic animal derived surfactant extract for preventing morbidity and mortality in preterm infants

Roger Soll[1], Eren Özek[2]

[1]Division of Neonatal-Perinatal Medicine, University of Vermont, Burlington, Vermont, USA. [2]Pediatrics / Division of Neonatology, Maramara University Medical Center, Istanbul, Turkey

Contact address: Roger Soll, Division of Neonatal-Perinatal Medicine, University of Vermont, Fletcher Allen Health Care, Smith 552A, 111 Colchester Avenue, Burlington, Vermont, 05401, USA. Roger.Soll@vtmednet.org.

Editorial group: Cochrane Neonatal Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 4, 2010.

Citation: Soll R, Özek E. Prophylactic animal derived surfactant extract for preventing morbidity and mortality in preterm infants. *Cochrane Database of Systematic Reviews* 1997, Issue 4. Art. No.: CD000511. DOI: 10.1002/14651858.CD000511.

ABSTRACT

Background

Respiratory distress syndrome (RDS) is caused by a deficiency or dysfunction of pulmonary surfactant. A variety of animal derived surfactant extracts have been formulated and given to infants at risk of developing RDS.

Objectives

To assess the effect of prophylactic intratracheal administration of animal derived surfactant extract on mortality, bronchopulmonary dysplasia (BPD) and other morbidities in preterm newborns at risk for developing RDS. Subgroup analysis were planned according to the specific surfactant product and the degree of prematurity.

Search methods

Searches were made of MEDLINE and the Cochrane Central Register of Controlled Trials through January 2010.

Selection criteria

Randomized or quasi-randomized controlled trials that compared the effect of prophylactic animal derived surfactant extract administration (surfactant obtained from human, porcine or bovine sources, either modified with additional phospholipids or not) administered to high risk preterm newborns at or shortly after birth in order to prevent RDS, mortality and other complications of prematurity.

Data collection and analysis

Data extraction and analysis was done in accordance with the standards of the CNRG.

Main results

All nine of the included studies note an initial improvement in respiratory status and a decrease in the risk of RDS in infants who receive prophylactic animal derived surfactant extract. The meta-analysis supports a decrease in the risk of pneumothorax (typical relative risk 0.40, 95% CI 0.29, 0.54; typical risk difference -0.12, 95% CI -0.16, -0.09), a decrease in the risk pulmonary interstitial emphysema (PIE) (typical relative risk 0.46, 95% CI 0.36, 0.59; typical risk difference -0.16, 95% CI -0.21, -0.11), a decrease in the risk of neonatal mortality (typical relative risk 0.60, 95% CI 0.47, 0.77; typical risk difference -0.07, 95% CI -0.12, -0.03), and a decrease in the risk of BPD or death (typical relative risk 0.80, 95% CI 0.72, 0.88; typical risk difference -0.10, 95% CI -0.16, -0.04). No differences are reported in the risk of intraventricular hemorrhage, patent ductus arteriosus, necrotizing enterocolitis or retinopathy of prematurity. Few data are available on long-term follow-up of treated infants.

Authors' conclusions

Prophylactic intratracheal administration of animal derived surfactant extract to infants judged to be at risk of developing respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who receive prophylactic animal derived surfactant extract have a decreased risk of pneumothorax, a decreased risk of PIE, a decreased risk of mortality, and a decreased risk of BPD or death.

PLAIN LANGUAGE SUMMARY

Prophylactic animal derived surfactant extract for preventing morbidity and mortality in preterm infants

Animal derived surfactant extract improves outcomes for babies at risk of respiratory distress.

Surfactant is essential to normal lung function in babies. Respiratory distress syndrome (RDS) is caused by a lack of, or dysfunction in, surfactant, the chemicals that line the lung air spaces and help keep the lung expanded. A variety of animal derived and synthetic surfactants have been formulated and are given to babies at risk to prevent them developing RDS. The review found that animal derived surfactant given at birth lowers rates of death and many serious and disabling conditions for babies at risk of RDS.

BACKGROUND

Description of the condition

Respiratory distress syndrome (RDS) is caused by a deficiency or dysfunction of pulmonary surfactant. Surfactant lines the alveolar surface and prevents atelectasis at end expiration. Pulmonary surfactant is predominantly dipalmitoylphosphatidylcholine with lesser amounts of other phospholipids including phosphatidylglycerol (PG), phosphatidylethanolamine, and phosphatidylinositol. Pulmonary surfactant also contains neutral lipids and distinct surfactant proteins. The physiologic functions of surfactant include the ability to lower surface tension, and the ability to rapidly adsorb, spread and reform a monolayer in the dynamic conditions associated with the respiratory cycle.

Description of the intervention

Investigators in the 1960s attempted to aerosolize dipalmitoylphosphatidylcholine (DPPC) to infants with established respiratory distress syndrome. These investigators could not demonstrate any beneficial effect of surfactant replacement. The poor results were, in part, due to an incomplete understanding of what constitutes pulmonary surfactant. The first successful animal model of surfactant replacement therapy was conducted by Enhorning and coworkers (Enhorning 1972). Enhorning administered a crude animal derived surfactant extract obtained from lavage of the lungs of mature rabbits directly into the trachea of immature rabbits. Improvement in lung compliance and alveolar expansion was noted. Success in animal models led to widespread clinical trials in the newborn.

A wide variety of surfactant products have been formulated and studied in clinical trials. These include synthetic surfactants and animal derived surfactant extracts. Animal derived surfactant extracts (also known as natural surfactant extracts) are derived from animal or human sources. Animal derived surfactant extracts can be further classified as either modified or unmodified surfactant extracts; modified animal derived surfactant extract is supplemented with phospholipids or other surface active material while unmodified animal derived surfactant extract contains only the components remaining after the extraction process.

How the intervention might work

Trials of prophylactic administration of animal derived surfactant extract attempt to identify infants at high risk of developing respiratory distress syndrome. In these studies, infants were randomized to receive surfactant or control treatment immediately after delivery either prior to the onset of respiratory symptoms or within 15 minutes of birth. These investigators hoped to assure more homogeneous distribution of surfactant and decreased barotrauma which can occur with even short periods of ventilation (Jobe 1984; Nilsson 1978).

Why it is important to do this review

The following analysis is a systematic review of the randomized controlled trials that compare the prophylactic administration of animal derived surfactant extract to placebo or control treatment.

OBJECTIVES

To assess the effect of prophylactic intratracheal administration of animal derived surfactant extract in preterm newborns at risk for developing respiratory distress syndrome (RDS).

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials comparing prophylactic animal derived surfactant extract administration (surfactant given down the endotracheal tube prior to the first breath or immediately after delivery room intubation and stabilization) to control treatment.

Types of participants

Premature infants gestational age < 30 weeks with or without evidence of surfactant deficiency.

Types of interventions

Infants randomized to receive prophylactic animal derived surfactant administration (pre-ventilatory or post-ventilatory) versus control treatment (intratracheal administration of normal saline or air placebo). All included studies utilized surfactant products derived from mammalian sources (human amniotic fluid extract, calf lung surfactant extract, porcine lung surfactant extract or modified bovine surfactant extract).

Types of outcome measures

Primary outcomes

1. Neonatal mortality (mortality < 28 days of age) from any cause.
2. Mortality prior to hospital discharge (from any cause).
3. Broncholpulmonary dysplasia (oxygen requirement at 28 to 30 days of age).
4. Bronchpulmonary dysplasia or death prior to 28 days of age.
5. Chronic lung disease (use of supplemental oxygen at 36 weeks postmenstrual age).
6. Chronic lung disease (use of supplemental oxygen at 36 weeks postmenstrual age) or death prior to 36 weeks postmenstrual age.

Secondary outcomes

1. Any air leak syndromes (including pulmonary interstitial emphysema, pneumothorax, pneumomediastinum).
2. Any pneumothorax.
3. Pulmonary interstitial emphysema.
4. Any pulmonary hemorrhage.
5. Patent ductus arteriosus (PDA that has been treated with cyclo-oxygenase inhibitor or surgery).
6. Any culture proven bacterial sepsis
7. Any culture proven fungal sepsis
8. Necrotizing enterocolitis (defined as Bell Stage II or greater)
9. Periventricular leukomalacia.
10. Retinopathy of prematurity [all stages and severe (stage 3 or greater)].

11. Intraventricular hemorrhage [any grade and severe (grade 3 to 4)].
12. Cerebral palsy.
13. Neurodevelopmental outcome at approximately two years corrected age (acceptable range 18 months to 28 months) including: cerebral palsy, mental retardation (Bayley Scales of Infant Development Mental Developmental Index < 70), legal blindness (< 20/200 visual acuity), and hearing deficit (aided or < 60 dB on audiometric testing). The composite outcome "neurodevelopmental impairment" will be defined as having any one of the aforementioned deficits.

Post hoc analyses will be considered for any unexpected adverse effects reported by the studies.

Search methods for identification of studies

See: Collaborative Review Group search strategy. The standard search method of the Cochrane Neonatal Review Group was used.

Electronic searches

Search included PubMed (1966 to January 2010) and the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 2, 2009). All languages were included. Search terms: {surfactant OR pulmonary surfactant}, limited to humans and further limited to the age group of newborn infants (infant, newborn) and type of publication (clinical trial). A similar search was performed using the following text words: beractant, calfactant, poractant with similar limits noted above. From the resulting studies randomized or quasi-randomized controlled studies that fulfil the inclusion criteria were selected. To identify long-term neurodevelopmental sequelae, a search using the following keywords was performed: (outcome OR sequelae OR follow-up OR mental retardation OR cerebral palsy OR hearing OR visual OR motor OR mental OR psychological) AND (surfactant OR pulmonary surfactant) not limited to any age group or language. The bibliography cited in each publication obtained was searched in order to identify additional relevant articles.

Searching other resources

Published abstracts: The abstracts of the Society for Pediatric Research (USA) (published in Pediatric Research) for the years 1985 to 1999 were searched by hand using the following key words: {surfactant OR pulmonary surfactant} AND {respiratory distress syndrome}. Abstracts from 2000 to 2009 were searched electronically through the PAS web site (abstractsonline). For abstract books that do not include keywords, the search was limited to relevant sections such as pulmonary and neonatology.

Clinical trials registries were also searched for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp)

Data collection and analysis

The standard methods of the Cochrane Neonatal Review Group Guidelines were employed.

Selection of studies

All randomized and quasi-randomized controlled trials fulfilling the selection criteria described in the previous section were included. Both investigators reviewed the results of the search and separately selected the studies for inclusion. The review authors resolved any disagreement by discussion.

Data extraction and management

The review authors (EO, RFS) separately extracted, assessed and coded all data for each study using a form that was designed specifically for this review. Any standard error of the mean was replaced by the corresponding standard deviation. Any disagreement was resolved by discussion. For each study, final data was entered into RevMan by one review author (RFS) and then checked by a second review author (EO). Any disagreements were addressed and resolved by consensus.

Assessment of risk of bias in included studies

The standard methods of the Cochrane Neonatal Review Group were employed. The methodological quality of the studies were assessed using the following key criteria: allocation concealment (blinding of randomization), blinding of intervention, completeness of follow-up, and blinding of outcome measurement/assessment. For each criterion, assessment was yes, no, can't tell. Two review authors separately assessed each study (EO, RFS). Any disagreement was resolved by discussion. This information was added to the Characteristics of Included Studies Table.

In addition, 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 categorized the method used to generate the allocation sequence as:

- adequate (any truly random process e.g. random number table; computer random number generator);

- inadequate (any non random process e.g. odd or even date of birth; hospital or clinic record number);

- unclear.

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

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

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);

- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

- unclear.

(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 categorized 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:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;

- adequate, inadequate or unclear for outcome assessors.

In some situations there may be partial blinding e.g. where outcomes are self-reported by unblinded participants but they are recorded by blinded personnel without knowledge of group assignment. Where needed "partial" was added to the list of options for assessing quality of blinding.

(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 randomized 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 categorized the methods as:

- adequate (< 20% missing data);

- inadequate (≥ 20% missing data):

- unclear.

(5) Selective reporting bias. Are reports of the study free of 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:

- adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- inadequate (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest 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.

(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 we had about other possible sources of bias (for example, 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:

- yes; no; or unclear.

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

Measures of treatment effect

Statistical analyses were performed using Review Manager software. Categorical data were analyzed using relative risk (RR), risk difference (RD) and the number needed to treat (NNT). Continuous data were analyzed using weighted mean difference (WMD). The 95% Confidence interval (CI) was reported on all estimates.

Assessment of heterogeneity

We estimated the treatment effects of individual trials and examined heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we explored the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using *post hoc* subgroup analyses.

Data synthesis

Meta-analysis was performed using Review Manager software (RevMan 5) supplied by the Cochrane Collaboration. For estimates of typical relative risk and risk difference, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. All meta-analyses were done using the fixed effect model.

Subgroup analysis and investigation of heterogeneity

Comparison I: Studies that treated infants at risk of RDS (prophylaxis)

1. Gestational age (infants born at < 30 weeks gestation).
2. Birth weight < 1000 g.
3. Surfactant product.
4. Single or multiple doses of surfactant.

RESULTS

Description of studies

Studies included in this review: Enhorning 1985; Kwong 1985; Merritt 1986; Kendig 1988; Shennan 1989; Soll 1990; Dunn 1991; Hoekstra 1991; Bevilacqua 1996. Details of each study are given in the "Characteristics of Included Studies" table and references.

All studies attempted to include infants thought to be at risk of developing respiratory distress syndrome, though entry criteria differ between the studies. All nine studies sought to enroll infants < 30 weeks gestation, although the specific gestational age criteria differ slightly. Enhorning 1985 and Dunn 1991 include infants < 30 weeks gestation. Kwong 1985 included infants between 24 and 28 weeks gestation. Merritt 1986 included infants between 24 and 29 weeks gestational age. Kendig 1988 included infants between 25 and 29 weeks gestational age. Soll 1990 and Bevilacqua 1996 included infants between 24 and 30 weeks gestational age, and Hoekstra 1991 included infants between 23 and 29 weeks gestation. Shennan 1989 included all infants less than 29 weeks gestation. Merritt 1986; Hoekstra 1991 and Dunn 1991 excluded infants with

evidence of lung maturity. Kwong 1985 excluded infants who had received > 24 hours of antenatal steroid therapy. All studies attempted to exclude infants who were diagnosed as having major congenital anomalies.

Studies either administered the prophylactic animal derived surfactant prior to onset of the initiation of respiration (Enhorning 1985; Kwong 1985; Kendig 1988; Dunn 1991 and Shennan 1989), or administered surfactant in the delivery room immediately after intubation and stabilization (Merritt 1986; Soll 1990; Hoekstra 1991) In the study of Bevilacqua 1996, surfactant was administered within the first 10 minutes of birth, if possible before the first breath.

In all of the studies, the surfactants used were animal derived surfactant extracts. Enhorning 1985, Kwong 1985, Kendig 1988, Dunn 1991, and Shennan 1989 all utilized a calf lung surfactant extract (CLL, CLSE, or BLSE). Merritt 1986 utilized a surfactant obtained from human amniotic fluid. Soll 1990 and Hoekstra 1991 utilized a modified bovine surfactant extract (Survanta). Bevilacqua 1996 utilized porcine surfactant.

Study outcomes included initial respiratory status, the incidence of respiratory distress syndrome, and a variety of complications of prematurity including pneumothorax, pulmonary interstitial emphysema, patent ductus arteriosus, intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, and mortality.

Risk of bias in included studies

Randomized controlled trials which compare the effect of prophylactic animal derived surfactant administration (surfactant given down the endotracheal tube prior to the first breath or immediately after intubation and stabilization in the delivery room) compared to control treatment (sham air treatment or instillation of normal saline) to premature infants thought to be at risk for developing respiratory distress syndrome are included in the analysis. The nine included studies were of high methodologic quality. Specific methodologic issues are discussed below:

Randomization:
All included studies allocated assigned treatment by randomization. In eight of the studies, sealed envelopes with randomly allocated treatment assignments were provided to participating centers. In the study of Kendig 1988 coded vials were used for randomization.

Blinding of Treatment:
Investigators attempted to blind treatment. Most studies relied on a resuscitation team to administer the randomly allocated treatment. Individuals in this resuscitation team were not responsible for ongoing care of the infant or for study evaluation.

Blinding of Outcome Assessment:
Investigators who were not involved with treatment assignment or administration assessed the study outcomes.

Exclusion after Randomization:
Minimal exclusions were noted after randomization. Kwong 1985 had a high number of exclusions because infants were enrolled prior to delivery and subsequently excluded if mothers had completed 24 hours of antenatal steroid therapy. A significant number were also excluded by Kwong 1985if they were felt to be outside of the gestational age limits of the study.

Effects of interventions

Prophylactic intratracheal administration of animal derived surfactant extract in preterm infants at risk for developing RDS improves oxygenation (improved alveolar-arterial oxygen difference, improved arterial/alveolar oxygen ratio, decreased inspired oxygen concentration) and ventilation (decreased mean airway pressure, improved ventilator efficiency index) during the first 48 to 72 hours of life. Prophylactic intratracheal administration of animal derived surfactant extract in preterm infants at risk of developing RDS also had the following clinical impact:

ANIMAL DERIVED SURFACTANT EXTRACT vs CONTROL IN THE PROPHYLAXIS OF RESPIRATORY DISTRESS SYNDROME IN PRETERM INFANTS (Comparison 1)

Pneumothorax (Outcome 1.1):

All nine randomized controlled trials reported on the risk of pneumothorax. Four of the randomized controlled trials reported a decreased incidence of pneumothorax associated with prophylactic animal derived surfactant extract administration. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract will lead to a significant reduction in the risk of pneumothorax (typical relative risk 0.40, 95% CI 0.29, 0.54; typical risk difference -0.12, 95% CI -0.16, -0.09).

Subgroup analysis: Different surfactant products (Outcomes 1.1.1 - 1.1.3):

Five randomized controlled trials of calf lung lavage reported on the risk of pneumothorax (Enhorning 1985; Kwong 1985; Kendig 1988; Shennan 1989; Dunn 1991). The typical estimate from the meta-analysis suggests a decrease in the risk of pneumothorax associated with prophylactic administration of calf lung surfactant extract (typical relative risk 0.30, 95% CI 0.19, 0.49; typical risk difference -0.23, 95% CI -0.31, -0.15).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of pneumothorax (typical relative risk 0.27, 95% CI 0.06, 1.18; typical risk difference -0.18, 95% CI -0.36, 0.00). Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no statistically significant impact of porcine surfactant on the risk of pneumothorax (typical relative risk 0.81, 95% CI 0.36, 1.81; typical risk difference -0.02, 95% CI -0.08, 0.05).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of pneumothorax (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis suggests a decrease in the risk of pneumothorax associated with prophylactic administration of modified bovine surfactant extract (typical relative risk 0.42, 95% CI 0.26, 0.67; typical risk difference -0.11, 95% CI -0.16, -0.05).

Pulmonary Interstitial Emphysema (Outcome 1.2):

Six of the randomized controlled trials reported on the incidence of pulmonary interstitial emphysema. Five of these trials noted a significant reduction in the incidence of pulmonary interstitial emphysema associated with prophylactic animal

derived surfactant extract administration. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract will lead to a significant reduction in the risk of pulmonary interstitial emphysema (typical relative risk 0.46, 95% CI 0.36, 0.59; typical risk difference -0.16, 95% CI -0.21, -0.11).

Subgroup analysis: Different surfactant products (1.2.1 - 1.2.3):

Three randomized controlled trials of calf lung surfactant extract reported on the risk of pulmonary interstitial emphysema (Enhorning 1985; Kendig 1988; Dunn 1991).The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract will lead to a significant reduction in the risk of pulmonary interstitial emphysema (typical relative risk 0.25, 95% CI 0.13, 0.49; typical risk difference -0.22, 95% CI -0.31, -0.13).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of pulmonary interstitial emphysema (typical relative risk 0.07, 95% CI 0.01, 0.48; typical risk difference -0.45, 95% CI -0.64, -0.26).

Hoekstra 1991 conducted a randomized controlled trial with modified bovine surfactant extract in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of pulmonary interstitial emphysema (typical relative risk 0.63, 95% CI 0.47, 0.85 ; typical risk difference -0.14, 95% CI -0.22, -0.05). Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of pulmonary interstitial emphysema (typical relative risk 0.46 , 95% CI 0.22, 0.98; typical risk difference -0.08 95% CI -0.15, -0.00).

Patent Ductus Arteriosus (Outcome 1.3):
All nine randomized controlled trials reported on the risk of patent ductus arteriosus. None of the individual trials reported a difference in the risk of patent ductus arteriosus. The typical estimate of the meta-analysis supports no difference in the risk of patent ductus arteriosus (typical relative risk 1.05, 95% CI 0.92, 1.20; typical risk difference 0.02, 95% CI -0.03, 0.07).

Subgroup analysis: Different surfactant products (1.3.1 - 1.3.4):

Five randomized controlled trials of calf lung lavage reported on the risk of patent ductus arteriosus (Enhorning 1985; Kwong 1985; Kendig 1988; Shennan 1989; Dunn 1991). The typical estimate from the meta-analysis supports no difference in the risk of patent ductus arteriosus associated with prophylactic administration of calf lung surfactant extract (typical relative risk 0.97, 95% CI 0.77, 1.22; typical risk difference -0.01, 95% CI -0.12, 0.09).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of patent ductus arteriosus (typical relative risk 0.90, 95% CI 0.69, 1.17; typical risk difference -0.09, 95% CI -0.29, 0.12).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of patent ductus arteriosus (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis supports no difference in the risk of patent ductus arteriosus associated with prophylactic administration of modified bovine surfactant extract (typical relative risk 1.22, 95% CI 0.99, 1.49; typical risk difference 0.07, 95% CI -0.00, 0.15).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no statistically significant impact of porcine surfactant on the risk of patent ductus arteriosus (typical relative risk 0.84, 95% CI 0.52, 1.35; typical risk difference -0.04 95% CI -0.13, 0.06).

Sepsis (Outcome 1.4):

Four randomized controlled trials of animal derived surfactant extracts enrolling 914 infants reported on the incidence of sepsis (Merritt 1986; Bevilacqua 1996; Hoekstra 1991; Soll 1990). None of these trials noted a significant difference in the risk of sepsis associated with prophylactic animal derived surfactant extract administration. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract does not impact on the risk of sepsis (typical relative risk 1.06, 95% CI 0.81, 1.38; typical risk difference 0.01, 95% CI -0.04, 0.06).

Subgroup analysis: Different surfactant products (1.4.1 - 1.4.3)

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of sepsis (typical relative risk 0.65, 95% CI 0.29, 1.49; typical risk difference -0.12, 95% CI -0.35, 0.11).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of sepsis (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis demonstrates no difference in the risk of sepsis associated with prophylactic administration of modified bovine surfactant extract (typical relative risk 1.37, 95% CI 0.97, 1.94; typical risk difference 0.06, 95% CI -0.00, 0.12).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no statistically significant impact of porcine surfactant on the risk of sepsis (typical relative risk 0.68, 95% CI 0.40, 1.17; typical risk difference -0.06, 95% CI -0.16, 0.03).

Necrotizing Enterocolitis (Outcome 1.5):

Six randomized controlled trials of prophylactic administration of animal derived surfactant extracts enrolling 1003 infants reported on the incidence of necrotizing enterocolitis (Kendig 1988; Kwong 1985; Merritt 1986; Bevilacqua 1996; Hoekstra 1991; Soll 1990). None of these trials noted a significant reduction in the incidence of necrotizing enterocolitis associated with prophylactic animal derived surfactant extract administration. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract has no impact on the risk of necrotizing enterocolitis (typical relative risk 0.94, 95% CI 0.59, 1.49; typical risk difference -0.00, 95% CI -0.03, 0.03).

Subgroup analysis: Different surfactant products (1.5.1 - 1.5.4)

Two randomized controlled trials of calf lung surfactant extract reported on the risk of necrotizing enterocolitis (Kwong 1985;

Kendig 1988;). The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not impact on the risk of necrotizing enterocolitis (typical relative risk 0.89, 95% CI 0.19, 4.16; typical risk difference -0.01, 95% CI -0.11, 0.10).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and demonstrated no impact of surfactant obtained from human amniotic fluid extract on the risk of necrotizing enterocolitis (typical relative risk 0.47, 95% CI 0.09, 2.36; typical risk difference -0.07, 95% CI -0.23, 0.08).

Two randomized controlled trials of modified bovine surfactant extract reported on necrotizing enterocolitis (Hoekstra 1991, Soll 1990). These two trials of modified bovine surfactant extract in the prevention of respiratory distress syndrome demonstrated no impact on the risk of necrotizing enterocolitis (typical relative risk 0.75, 95% CI 0.29, 1.97; typical risk difference 0.01, 95% CI -0.03, 0.05).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and demonstrated no impact on the risk of necrotizing enterocolitis (typical relative risk 1.15, 95% CI 0.62, 2.13; typical risk difference -0.02, 95% CI -0.07, 0.04).

Intraventricular Hemorrhage (Outcome 1.6):

All nine randomized controlled trials reported on the risk of intraventricular hemorrhage. Enhorning 1985 noted a decrease in the incidence of intraventricular hemorrhage in infants who received prophylactic animal derived surfactant administration (relative risk 0.47, 95% CI 0.26, 0.82; risk difference -0.32, 95% CI -0.54, -0.11). The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract does not influence the risk of intraventricular hemorrhage (typical relative risk 0.92, 95% CI 0.81, 1.06; typical risk difference -0.03, 95% CI -0.08, 0.02).

Subgroup analysis: Different surfactant products (1.6.1 - 1.6.4):

Five randomized controlled trials of calf lung lavage reported on the risk of intraventricular hemorrhage (Enhorning 1985; Kwong 1985; Kendig 1988; Shennan 1989; Dunn 1991).The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not influence the risk of intraventricular hemorrhage (typical relative risk 0.93, 95% CI 0.70, 1.23; typical risk difference -0.03, 95% CI -0.13, 0.07).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of intraventricular hemorrhage (typical relative risk 0.85, 95% CI 0.59, 1.21; typical risk difference -0.11, 95% CI -0.35, 0.13).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of intraventricular hemorrhage (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis suggests that prophylactic administration of bovine surfactant extract does not influence the risk of intraventricular hemorrhage (typical relative risk 1.04, 95% CI 0.84, 1.29; typical risk difference 0.01, 95% CI -0.06, 0.09).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no significant impact of porcine surfactant on the risk of intraventricular hemorrhage (typical relative risk 0.78, 95% CI 0.60, 1.00; typical risk difference -0.12, 95% CI -0.24, 0.00).

Severe Intraventricular Hemorrhage (Outcome 1.7):

Eight randomized controlled trials reported on the risk of severe intraventricular hemorrhage. None of the individual trials support a difference in the incidence of severe intraventricular hemorrhage (Grade III or IV intraventricular hemorrhage). The typical estimate of the meta-analysis supports no difference in the risk of severe intraventricular hemorrhage (typical relative risk 1.10, 95% CI 0.85, 1.43; typical risk difference 0.01, 95% CI -0.03, 0.05).

Subgroup analysis: Different surfactant products (1.7.1 - 1.7.4):

Four randomized controlled trials of calf lung lavage reported on the risk of severe intraventricular hemorrhage (Enhorning 1985; Kendig 1988; Shennan 1989; Dunn 1991).The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not influence the risk of severe intraventricular hemorrhage (typical relative risk 1.56, 95% CI 0.75, 3.28; typical risk difference 0.04, 95% CI -0.02, 0.10).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of severe intraventricular hemorrhage (typical relative risk 0.94, 95% CI 0.48, 1.82; typical risk difference -0.02, 95% CI -0.27, 0.22).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of severe intraventricular hemorrhage (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis suggests that prophylactic administration of bovine surfactant extract does not influence the risk of severe intraventricular hemorrhage (typical relative risk 1.21, 95% CI 0.82, 1.79; typical risk difference 0.03, 95% CI -0.03, 0.09).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no statistically significant impact of porcine surfactant on the risk of severe intraventricular hemorrhage (typical relative risk 0.83, 95% CI 0.50, 1.37; typical risk difference -0.04, 95% CI -0.13, 0.06).

Bronchopulmonary Dysplasia (Outcome 1.8):

Eight randomized controlled trials reported on the risk of bronchopulmonary dysplasia. None of the individual trials support a difference in the incidence of bronchopulmonary dysplasia in all treated infants (not just survivors). For the purpose of these studies, bronchopulmonary dysplasia was defined as an oxygen requirement at 28 days of age. The typical estimate of the meta-analysis supports no difference in the risk of bronchopulmonary dysplasia (typical relative risk 0.91, 95% CI 0.79, 1.05; typical risk difference -0.03, 95% CI -0.08, 0.02).

Subgroup analysis: Different surfactant products (1.8.1 - 1.8.4):

Four randomized controlled trials of calf lung lavage reported on the risk of bronchopulmonary dysplasia (Enhorning 1985;

Kwong 1985; Kendig 1988; Dunn 1991).The typical estimate from the meta-analysis suggests a marginal decrease in the risk of bronchopulmonary dysplasia associated with prophylactic administration of calf lung surfactant extract (typical relative risk 0.80, 95% CI 0.64, 0.99; typical risk difference -0.12, 95% CI -0.23, -0.01).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed no statistically significant impact of human amniotic fluid extract on the risk of bronchopulmonary dysplasia (typical relative risk 0.52, 95% CI 0.20, 1.37; typical risk difference -0.15, 95% CI -0.36, 0.06).

Two randomized controlled trials of modified bovine surfactant extract reported (Soll 1990; Hoekstra 1991) on the risk of bronchopulmonary dysplasia. The typical estimate from the meta-analysis suggests that prophylactic administration of bovine surfactant extract does not influence the risk of bronchopulmonary dysplasia (typical relative risk 1.07, 95% CI 0.88, 1.30; typical risk difference 0.03, 95% CI -0.05, 0.10).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed no statistically significant impact of porcine surfactant on the risk of bronchopulmonary dysplasia. (typical relative risk 0.69, 95% CI 0.34,1.38; typical risk difference -0.04, 95% CI -0.11, 0.03).

Neonatal Mortality (Outcome 1.9):

Eight of the randomized controlled trials reported on the risk of neonatal mortality. The studies of Enhorning 1985, Merritt 1986, Hoekstra 1991 and Bevilacqua 1996 all support a decrease in the incidence of neonatal mortality associated with the administration of prophylactic animal derived surfactant extract. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract leads to a significant reduction in the risk of neonatal mortality (typical relative risk 0.60, 95% CI 0.47, 0.77; typical risk difference -0.09, 95% CI -0.13, -0.05).

Subgroup analysis: Different surfactant products (1.9.1 - 1.9.4):

Four randomized controlled trials of calf lung lavage reported on the risk of neonatal mortality (Enhorning 1985; Kwong 1985; Kendig 1988; Dunn 1991). The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not influence the risk of mortality (typical relative risk 0.80, 95% CI 0.46, 1.40; typical risk difference -0.03, 95% CI -0.11, 0.05).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed a statistically significant impact of human amniotic fluid extract on the risk of mortality (typical relative risk 0.31, 95% CI 0.13, 0.75; typical risk difference -0.36, 95% CI -0.58, -0.13).

Two randomized controlled trials of modified bovine surfactant extract reported on the risk of neonatal mortality (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis suggests a decrease in the risk of neonatal mortality associated with prophylactic administration of modified bovine surfactant extract (typical relative risk 0.60, 95% CI 0.39, 0.93; typical risk difference -0.06 , 95% CI -0.12, -0.01).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of neonatal mortality (typical relative risk 0.59, 95% CI 0.39, 0.89; typical risk difference -0.14, 95% CI -0.25, -0.04).

Mortality prior to hospital discharge (Outcome 1.10):

Six of the randomized controlled trials reported on mortality prior to hospital discharge. Enhorning 1985 and Merritt 1986 reported a decrease in the incidence of mortality prior to hospital discharge. The typical estimate from the meta-analysis supports no difference in the risk of dying prior to hospital discharge (typical relative risk 0.70, 95% CI 0.47, 1.06; typical risk difference -0.06, 95% CI -0.14, 0.01).

Subgroup analysis: Different surfactant products (1.10.1-1.10.2):

Five randomized controlled trials of calf lung lavage reported on the risk of mortality prior to hospital discharge (Enhorning 1985; Kwong 1985; Kendig 1988; Shennan 1989; Dunn 1991). The typical estimate from the meta-analysis supports no difference in the risk of dying prior to hospital discharge associated with prophylactic administration of calf lung surfactant extract (typical relative risk 0.92, 95% CI 0.56, 1.52; typical risk difference -0.01, 95% CI -0.09, 0.06).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of mortality prior to hospital discharge (typical relative risk 0.39, 95% CI 0.19, 0.79; typical risk difference -0.36, 95% CI -0.59, -0.13).

Bronchopulmonary Dysplasia or Death (Outcome 1.11):

Eight of the randomized controlled trials reported the combined outcome of bronchopulmonary dysplasia or death. Three of the randomized controlled trials supported a decrease in this combined outcome. The typical estimate from the meta-analysis suggests that prophylactic administration of animal derived surfactant extract will lead to a significant reduction in the risk of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.80, 95% CI 0.72, 0.88; typical risk difference -0.12, 95% CI -0.17, -0.07).

Subgroup analysis: Different surfactant products (1.11.1 - 1.11.4):

Four randomized controlled trials of calf lung lavage reported on the combined outcome of bronchopulmonary dysplasia or death (Enhorning 1985; Kwong 1985; Kendig 1988; Dunn 1991). The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract will lead to a significant reduction in the risk of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.81, 95% CI 0.69, 0.94; typical risk difference -0.15, 95% CI -0.25, -0.04).

Merritt 1986 conducted a randomized controlled trial with human amniotic fluid extract in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk

of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.39, 95% CI 0.23, 0.67; typical risk difference -0.51, 95% CI -0.72, -0.29).

Two randomized controlled trials of modified bovine surfactant extract reported on the combined outcome of bronchopulmonary dysplasia or death at 28 days (Soll 1990; Hoekstra 1991). The typical estimate from the meta-analysis suggests that prophylactic administration of bovine surfactant extract does not influence the risk of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.93, 95% CI 0.80, 1.08; typical risk difference -0.04, 95% CI -0.12, 0.04).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed a statistically significant decrease in the risk of bronchopulmonary dysplasia or death at 28 days (typical relative risk 0.62, 95% CI 0.45, 0.85; typical risk difference -0.18, 95% CI -0.30, -0.07).

Retinopathy of Prematurity (Outcomes 1.12 - 1.13):

Six of the randomized controlled trials reported on retinopathy of prematurity. Kwong 1985, Kendig 1988 and Bevilacqua 1996 reported on infants with any stage of retinopathy. Enhorning 1985, Shennan 1989, and Dunn 1991 only reported those infants with stage 2 disease or greater. No individual trial reported a difference in the incidence of retinopathy of prematurity and the meta-analysis supports no difference in the risk of retinopathy of prematurity associated with prophylactic administration of animal derived surfactant extract. The meta-analysis suggests that prophylactic administration of animal derived surfactant extract does not lead to differences in the risk of any retinopathy (typical relative risk 1.15, 95% CI 0.70, 1.88; typical risk difference 0.02, 95% CI -0.05, 0.09) or retinopathy stage 2 - 4 (typical relative risk 0.71, 95% CI 0.41, 1.23; typical risk difference -0.03, 95% CI -0.08, 0.02).

Subgroup analysis: Different surfactant products (1.12.1-1.12.2 / 1.13.1- 1.13.2):

Any retinopathy: Two randomized controlled trials of calf lung surfactant extract reported on infants with any stage of retinopathy (Kwong 1985; Kendig 1988). The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not influence the risk of retinopathy (typical relative risk 1.37, 95% CI 0.63, 2.98; typical risk difference 0.07, 95% CI -0.10, 0.23).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed that prophylactic administration of porcine surfactant does not lead to differences in the risk of any retinopathy (typical relative risk 1.03, 95% CI 0.54, 1.95; typical risk difference 0.00, 95% CI -0.07, 0.08).

Retinopathy stage 2 or greater: Three randomized controlled trials of calf lung surfactant extract reported on infants with Stage II disease or greater (Enhorning 1985; Shennan 1989; Dunn 1991).The typical estimate from the meta-analysis suggests that prophylactic administration of calf lung surfactant extract does not influence the risk of retinopathy of prematurity, stages 2 - 4 (typical relative risk 0.58, 95% CI 0.27, 1.24; typical risk difference -0.05, 95% CI -0.12, 0.02).

Bevilacqua 1996 conducted a randomized controlled trial with porcine surfactant in the prevention of respiratory distress syndrome and showed that prophylactic administration of porcine surfactant does not lead to differences in the risk of retinopathy of prematurity, stages 2 - 4 (typical relative risk 0.88, 95% CI 0.39, 2.01; typical risk difference -0.01, 95% CI -0.07, 0.05).

DISCUSSION

Nine randomized controlled trials were identified that compared prophylactic administration of animal derived surfactant extract to control treatment. Studies used either calf lung surfactant (Enhorning 1985; Kwong 1985; Kendig 1988; Dunn 1991; Shennan 1989), modified bovine surfactant extract (Soll 1990; Hoekstra 1991) human amniotic fluid extract (Merritt 1986), or porcine surfactant extract (Bevilacqua 1996). All trials enrolled high risk infants identified on the basis of gestational age. All infants studied were < 30 weeks gestation, although the specific gestational age criteria differ slightly between studies. Kwong 1985 did not include any infants exposed to more than 24 hours of antenatal steroids. Only Hoekstra 1991 and Bevilacqua 1996 allowed for multiple treatment with surfactant.

Prophylactic administration of animal derived surfactant extract in preterm infants at risk for developing RDS led to improvement in oxygenation and ventilatory requirements in the 48 to 72 hours after treatment.

The meta-analysis suggests that prophylactic administration of animal derived surfactant extract leads to a significant decrease in the incidence of pneumothorax, pulmonary interstitial emphysema, neonatal mortality, and the incidence of bronchopulmonary dysplasia or death. The meta-analysis suggests that for every 100 infants treated prophylactically there will be twelve fewer pneumothoraces, sixteen fewer cases of pulmonary interstitial emphysema, and nine fewer neonatal deaths. No impact is noted on the incidence of intraventricular hemorrhage or severe intraventricular hemorrhage.

A previous review reported a small increase in pulmonary hemorrhage associated with use of exogenous surfactants (Raju 1993). This complication may in fact be hemorrhagic pulmonary edema secondary to massive ductal shunting. This outcome was not addressed in the initial trials, so the estimate of this effect was not reported in this meta-analysis. In clinical practice, pulmonary hemorrhage may be preventable by treatment of the ductus arteriosus and appropriate ventilatory management. No other side effects of surfactant treatment have been reported.

The trials included in this review compared prophylactic animal derived surfactant with no surfactant treatment. After the demonstration of the efficacy of surfactant in preventing and/or treating RDS, trials were conducted which compared the policies of prophylactic surfactant administration in babies at risk of RDS with selective surfactant treatment of babies who develop RDS. These trials showed that prophylactic surfactant may be superior to the later, selective treatment of babies with established RDS (see review by Soll RF, Morley CJ: Prophylactic Surfactant vs. Treatment with Surfactant) (Soll 2001).

AUTHORS' CONCLUSIONS

Implications for practice

Prophylactic administration of animal derived surfactant extract to infants judged to be at risk for developing respiratory distress syndrome has been demonstrated to improve clinical outcome. Infants who received prophylactic animal derived surfactant have a decreased incidence of respiratory distress syndrome, a decreased incidence of pneumothorax, a decreased incidence of pulmonary interstitial emphysema, a decreased incidence of neonatal mortality, and a decreased incidence of bronchopulmonary dysplasia or death.

Implications for research

Prophylactic administration of animal derived surfactant extract has been proven to improve clinical outcomes. Further placebo controlled trials of prophylactic animal derived surfactant extract are no longer warranted. Trials have been conducted that compare the prophylactic administration of animal derived surfactant extract to selective treatment with animal derived surfactant extract (see review: "Prophylactic Surfactant versus Treatment with Surfactant") (Soll 2001). The impact of prophylactic synthetic surfactant administration is discussed in other reviews ("Prophylactic Administration of Synthetic Surfactant") (Soll 2010).

ACKNOWLEDGEMENTS

The Cochrane Neonatal Review Group has been funded in part 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. HHSN267200603418C.

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CHARACTERISTICS OF STUDIES

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

Bevilacqua 1996

Methods	Randomized

Bevilacqua 1996 *(Continued)*

	Multicenter Blinding of randomization: yes (sealed envelopes) Blinding of intervention : no Complete follow-up : yes Blinding of outcome measurement : attempted (Radiologist not aware of the treatment groups) Stratification based on gestational age (24-25 weeks, 26-28 weeks, 29-30 weeks)
Participants	Premature infants Gestational age 24 - 30 weeks No major congenital anomaly, congenital heart defect and congenital infection
Interventions	Single dose of prophylactic porcine surfactant extract (200 mg/kg phospholipids/kg bodyweight) versus control (no placebo was administered or intubated unless indicated) Single dose of rescue treatment is allowed (200 mg/kg phospholipids/kg bodyweight)
Outcomes	PRIMARY OUTCOME: Incidence of all grade 3-4 RDS SECONDARY OUTCOME: Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	unclear
Allocation concealment?	Low risk	Blinding of randomization: yes (sealed envelopes) Stratification based on gestational age (24-25 weeks, 26-28 weeks, 29-30 weeks)
Blinding? All outcomes	High risk	Blinding of intervention : no Blinding of outcome measurement : attempted (Radiologist not aware of the treatment groups)
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up : yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Dunn 1991

Methods	Randomized Single center

Dunn 1991 *(Continued)*

	Blinding of randomization: yes (sealed envelopes) Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: Stratification based on gestational age (24-26 weeks, 27-29 weeks) and antenatal steroid exposure
Participants	Premature infants Gestational age <30 weeks ROM <2 weeks No major congenital anomaly No evidence of lung maturity
Interventions	Prophylactic bovine lung surfactant extract (75-100 mg) vs. selective administration of bovine lung surfactant extract (100 mg/kg) in intubated infants with respiratory distress less than 6 hours of age vs. sham treatment (air) Infants receiving surfactant were eligible for 3 additional doses
Outcomes	PRIMARY OUTCOME: a/A ratio SECONDARY OUTCOME: Ventilatory requirements Duration of assisted ventilation Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Low risk	Blinding of randomization: yes (sealed envelopes) Stratification based on gestational age (24-26 weeks, 27-29 weeks) and antenatal steroid exposure
Blinding? All outcomes	High risk	Blinding of intervention: no Blinding of outcome measurement: no
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Enhorning 1985

Methods	Randomized Single center study Blinding of Randomization: yes (sealed envelopes)

Enhorning 1985 *(Continued)*

	Blinding of Intervention: attempted (staff not involved with clinical care for next 5-6 days after administered treatment) Complete Follow-up: yes Blinding of outcome measurement: attempted Stratification based on gestational age and exposure to antenatal steroids
Participants	Premature Infants Gestational age <30 weeks
Interventions	Prophylactic BLSE (75-100 mg) vs. control (sham air instillation) via endotracheal tube (Given prior to initiation of respiration)
Outcomes	PRIMARY OUTCOME: Improvement in a/A ratio Duration of oxygen Administration SECONDARY OUTCOMES: Duration of ventilation Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of Randomization: yes (sealed envelopes) Stratification based on gestational age and exposure to antenatal steroids
Blinding? All outcomes	Unclear risk	Blinding of Intervention: attempted (staff not involved with clinical care for next 5-6 days after administered treatment) Blinding of outcome measurement: attempted
Incomplete outcome data addressed? All outcomes	Low risk	Complete Follow-up: yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Hoekstra 1991

Methods	Randomized Multicenter study Blinding of randomization: yes (sealed envelopes) Blinding of intervention: attempted Complete follow-up: yes Blinding of outcome measurement: yes Stratification based on birthweight and antenatal steroid exposure
Participants	Premature infants Gestational age 23-29 weeks

Hoekstra 1991 *(Continued)*

	Birthweight 600-1250 grams Intubation and stabilization within 15 minutes after birth No major congenital anomaly No evidence of lung maturity
Interventions	Modified bovine surfactant extract (Survanta 100 mg/kg) vs. Sham treatment (air) Given via endotracheal tube within 15 minutes of intubation and stabilization Infants allowed up to 3 subsequent doses if requiring assisted ventilation and supplemental oxygen >30%
Outcomes	PRIMARY OUTCOME: Death or bronchopulmonary dysplasia at 28 days of age SECONDARY OUTCOME: Respiratory status at 72 hours Incidence of respiratory distress Syndrome Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of randomization: yes (sealed envelopes) Stratification based on birthweight and antenatal steroid exposure
Blinding? All outcomes	Unclear risk	Blinding of intervention: attempted Blinding of outcome measurement: yes
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Kendig 1988

Methods	Randomized Single center study Blinding of randomization: yes (coded vials) Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: yes
Participants	Premature infants Gestational age 25-29 weeks Required intubation at birth
Interventions	Prophylactic calf lung surfactant extract (3 ml=90 mg) vs. normal saline (3 ml) Given via endotracheal tube prior to initiation of respiration

Kendig 1988 *(Continued)*

Outcomes	PRIMARY OUTCOME: Severity of respiratory distress syndrome SECONDARY OUTCOMES: Physiologic variables including mean airway pressure, ventilatory index, supplemental oxygen, radiographic findings, complications of prematurity.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of randomization: yes (coded vials)
Blinding? All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Kwong 1985

Methods	Randomized Single center study Blinding of randomization: yes (opaque coded tubes) Blinding of intervention: yes Complete follow-up: no Blinding of outcome measurement: yes
Participants	Premature infants Gestational age 24-28 weeks Antenatal steroids <24 hours No major congenital anomaly
Interventions	Prophylactic CLSE (3 ml=90 mg) vs. normal saline (3 ml) given via endotracheal tube prior to initiation of respiration
Outcomes	PRIMARY OUTCOME: Score based on radiographic findings, requirement for supplemental oxygen, mean airway pressure, ventilatory rate (IMV), ventilator efficiency index SECONDARY OUTCOMES: Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of randomization: yes (opaque coded tubes)

Kwong 1985 *(Continued)*

Blinding? All outcomes	Low risk	Blinding of intervention: yes Blinding of outcome measurement: yes
Incomplete outcome data addressed? All outcomes	High risk	Complete follow-up: no
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

Merritt 1986

Methods	Randomized Two participating centers Blinding of randomization: yes (sealed envelopes) Blinding of intervention: attempted Complete follow-up: yes Blinding of outcome measurement: yes
Participants	Premature infants Gestational age 24-29 weeks Lecithin/Sphingomyelin ratio <2 Phosphaidyl glycerol absent No malformations known to influence fetal lulng development
Interventions	Human surfactact extract (3 ml=60 mg) vs sham treatment (air) Given via endotracheal tube immediately after intubation and auscultation to confirm appropriate endotracheal tube placement
Outcomes	PRIMARY OUTCOMES: Clinical status at 28 days (survival without bronchopulmonary dysplasia, survival with bronchopulmonary dysplasia, death) SECONDARY OUTCOMES: Physiologic variables, requirement for respiratory support, complications of prematurity.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Low risk	Blinding of randomization: yes (sealed envelopes)
Blinding? All outcomes	Unclear risk	Blinding of intervention: attempted Blinding of outcome measurement: yes
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes
Free of selective reporting?	Low risk	

Merritt 1986 *(Continued)*

Free of other bias?	Low risk

Shennan 1989

Methods	Randomized Single center Blinding of randomization: can't tell Blinding of intervention: can't tell Complete follow-up: can't tell Blinding of outcome measurement: can't tell
Participants	Premature infants Gestational age <29 weeks
Interventions	Prophylactic bovine lung surfactant extract vs. sham treatment (air)
Outcomes	Incidence of respiratory distress syndrome Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Blinding of randomization: can't tell
Blinding? All outcomes	Unclear risk	Blinding of intervention: can't tell Blinding of outcome measurement: can't tell
Incomplete outcome data addressed? All outcomes	Unclear risk	Complete follow-up: can't tell

Soll 1990

Methods	Randomized Multicenter study Blinding of randomization: yes (sealed envelopes) Blinding of intervention: attempted Complete follow-up: yes Blinding of outcome measurement: yes Stratification by birthweight and exposure to antenatal steroids
Participants	Premature infants Gestational age 24-30 weeks Birthweight 750-1250 grams Intubated and stabilized within 15 minutes of birth No major congenital anomalies Infants with proven sepsis excluded

Soll 1990 *(Continued)*

Interventions	Modified bovine surfactant extract [Beractant (Survanta), 100 mg/kg] vs. sham treatment (air) Given via endotracheal tube within 15 minutes of intubation and stabilization
Outcomes	PRIMARY OUTCOME: Average change in mean airway pressure and a/A ratio during 72 hours after treatment SECONDARY OUTCOMES: Clinical status at 7 and 28 days Radiographic finding at 24 hours Complications of prematurity
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Blinding of randomization: yes (sealed envelopes) Stratification by birthweight and exposure to antenatal steroids
Blinding? All outcomes	Unclear risk	Blinding of intervention: attempted Blinding of outcome measurement: yes
Incomplete outcome data addressed? All outcomes	Low risk	Complete follow-up: yes
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	

DATA AND ANALYSES

Comparison 1. Animal derived surfactant extract vs. control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Effect on pneumothorax	9	1256	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.29, 0.54]
1.1 calf lung lavage	5	342	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.19, 0.49]
1.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.27 [0.06, 1.18]
1.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.36, 1.81]

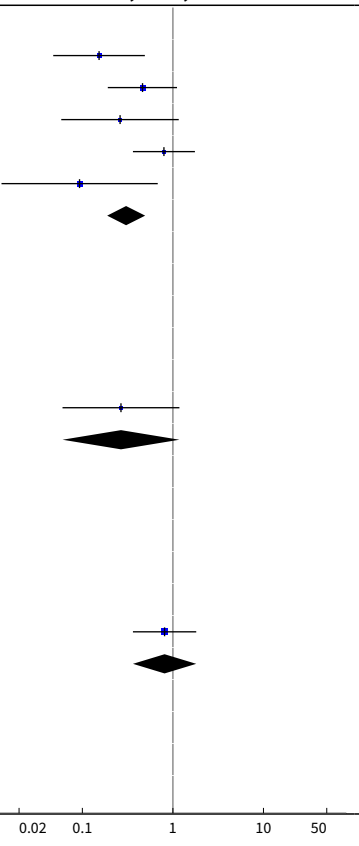
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.26, 0.67]
2 Effect on pulmonary interstitial emphysema	6	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.36, 0.59]
2.1 calf lung lavage	3	259	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.13, 0.49]
2.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.07 [0.01, 0.48]
2.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.22, 0.98]
2.4 modified bovine surfactant extract	1	430	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.47, 0.85]
3 Effect on patent ductus arteriosus	9	1256	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.92, 1.20]
3.1 calf lung lavage	5	342	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.22]
3.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.69, 1.17]
3.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.52, 1.35]
3.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.99, 1.49]
4 Effect on sepsis	4	914	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.38]
4.1 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.29, 1.49]
4.2 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.40, 1.17]
4.3 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.97, 1.94]
5 Effect on necrotizing enterocolitis	6	1003	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.59, 1.49]
5.1 calf lung lavage	2	89	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.19, 4.16]
5.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.09, 2.36]
5.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.29, 1.97]
5.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.62, 2.13]
6 Effect on intraventricular hemorrhage	9	1254	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.81, 1.06]
6.1 calf lung lavage	5	340	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.70, 1.23]
6.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.59, 1.21]

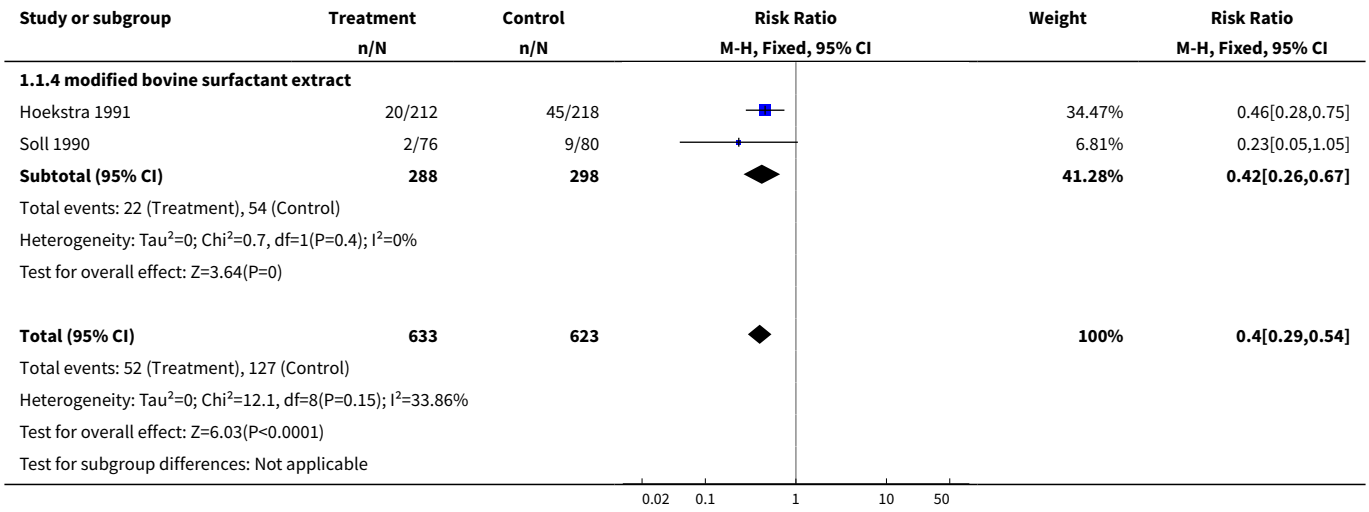
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.00]
6.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.84, 1.29]
7 Effect on severe intraventricular hemorrhage	8	1229	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.85, 1.43]
7.1 calf lung lavage	4	315	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.75, 3.28]
7.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.48, 1.82]
7.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.37]
7.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.82, 1.79]
8 Effect on bronchopulmonary dysplasia	8	1200	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.05]
8.1 calf lung lavage	4	286	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.99]
8.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.20, 1.37]
8.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.34, 1.38]
8.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.30]
9 Effect on neonatal mortality	8	1200	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.47, 0.77]
9.1 calf lung lavage	4	286	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.46, 1.40]
9.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.75]
9.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.39, 0.89]
9.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.93]
10 Effect on mortality prior to hospital discharge	6	402	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.47, 1.06]
10.1 calf lung lavage	5	342	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.56, 1.52]
10.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.19, 0.79]
11 Effect on BPD or death	8	1200	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.72, 0.88]
11.1 calf lung lavage	4	286	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.69, 0.94]
11.2 human amniotic fluid extract	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.23, 0.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.85]
11.4 modified bovine surfactant extract	2	586	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.08]
12 Effect on retinopathy of prematurity	3	360	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.70, 1.88]
12.1 calf lung lavage	2	92	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.63, 2.98]
12.2 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.54, 1.95]
13 Retinopathy of prematurity, stages 2-4	4	518	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.41, 1.23]
13.1 calf lung lavage	3	250	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.27, 1.24]
13.2 porcine surfactant extract	1	268	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.39, 2.01]

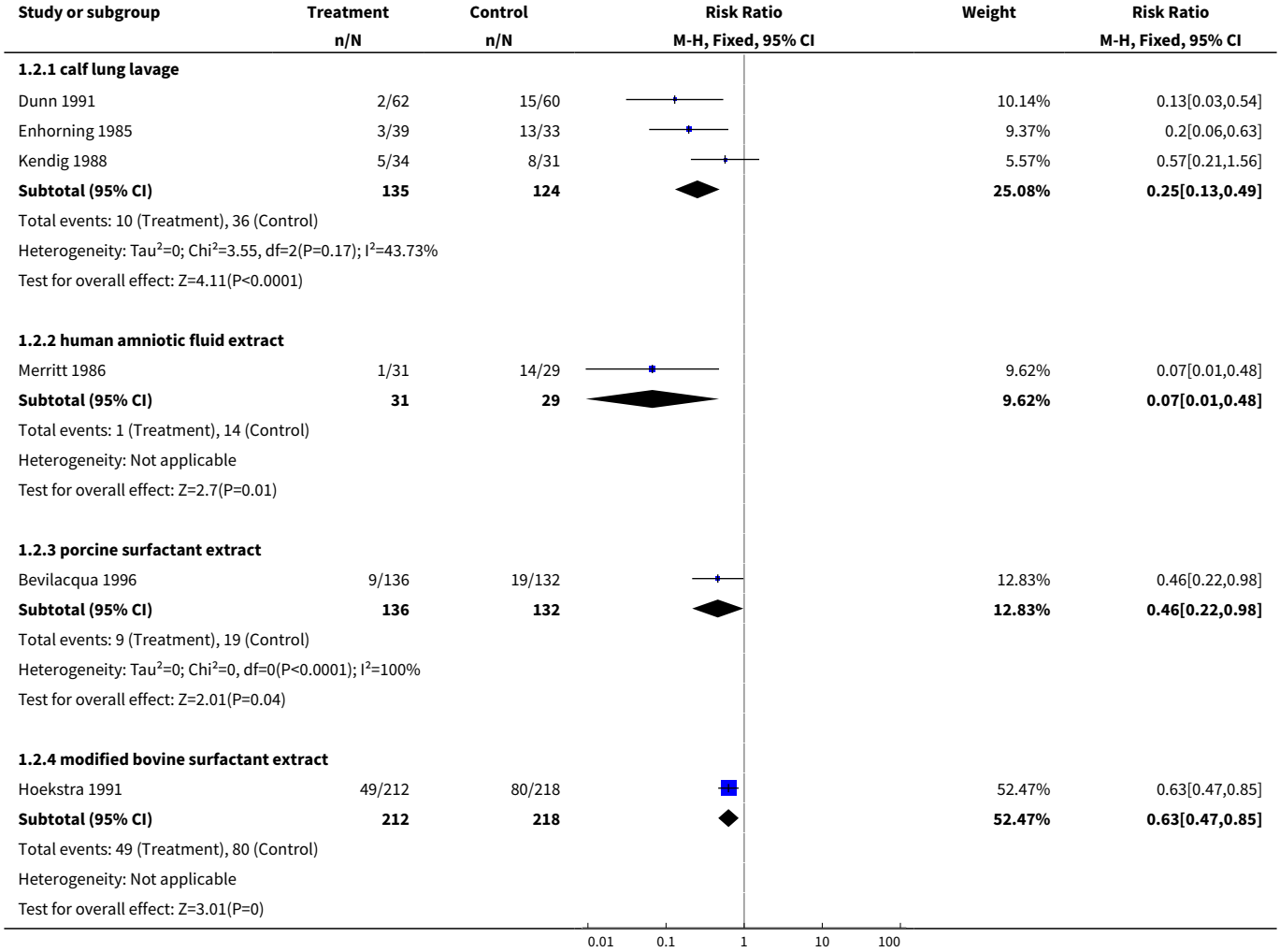
Analysis 1.1. Comparison 1 Animal derived surfactant extract vs. control, Outcome 1 Effect on pneumothorax.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 calf lung lavage					
Dunn 1991	3/62	19/60		15%	0.15[0.05,0.49]
Enhorning 1985	6/39	11/33		9.26%	0.46[0.19,1.11]
Kendig 1988	2/34	7/31		5.69%	0.26[0.06,1.16]
Kwong 1985	6/14	7/13		5.64%	0.8[0.36,1.75]
Shennan 1989	1/29	10/27		8.05%	0.09[0.01,0.68]
Subtotal (95% CI)	**178**	**164**		**43.64%**	**0.3[0.19,0.49]**
Total events: 18 (Treatment), 54 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.34, df=4(P=0.05); I^2=57.18%					
Test for overall effect: Z=4.82(P<0.0001)					
1.1.2 human amniotic fluid extract					
Merritt 1986	2/31	7/29		5.62%	0.27[0.06,1.18]
Subtotal (95% CI)	**31**	**29**		**5.62%**	**0.27[0.06,1.18]**
Total events: 2 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					
1.1.3 porcine surfactant extract					
Bevilacqua 1996	10/136	12/132		9.46%	0.81[0.36,1.81]
Subtotal (95% CI)	**136**	**132**		**9.46%**	**0.81[0.36,1.81]**
Total events: 10 (Treatment), 12 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.52(P=0.61)					





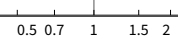
Analysis 1.2. Comparison 1 Animal derived surfactant extract vs. control, Outcome 2 Effect on pulmonary interstitial emphysema.

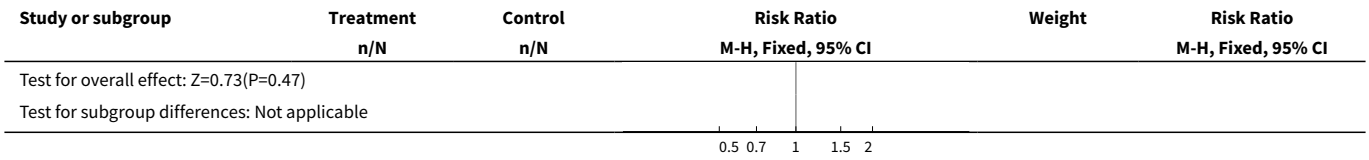


Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**514**	**503**		**100%**	**0.46[0.36,0.59]**
Total events: 69 (Treatment), 149 (Control)					
Heterogeneity: Tau^2=0; Chi^2=13.19, df=5(P=0.02); I^2=62.1%					
Test for overall effect: Z=6.04(P<0.0001)					
Test for subgroup differences: Not applicable					

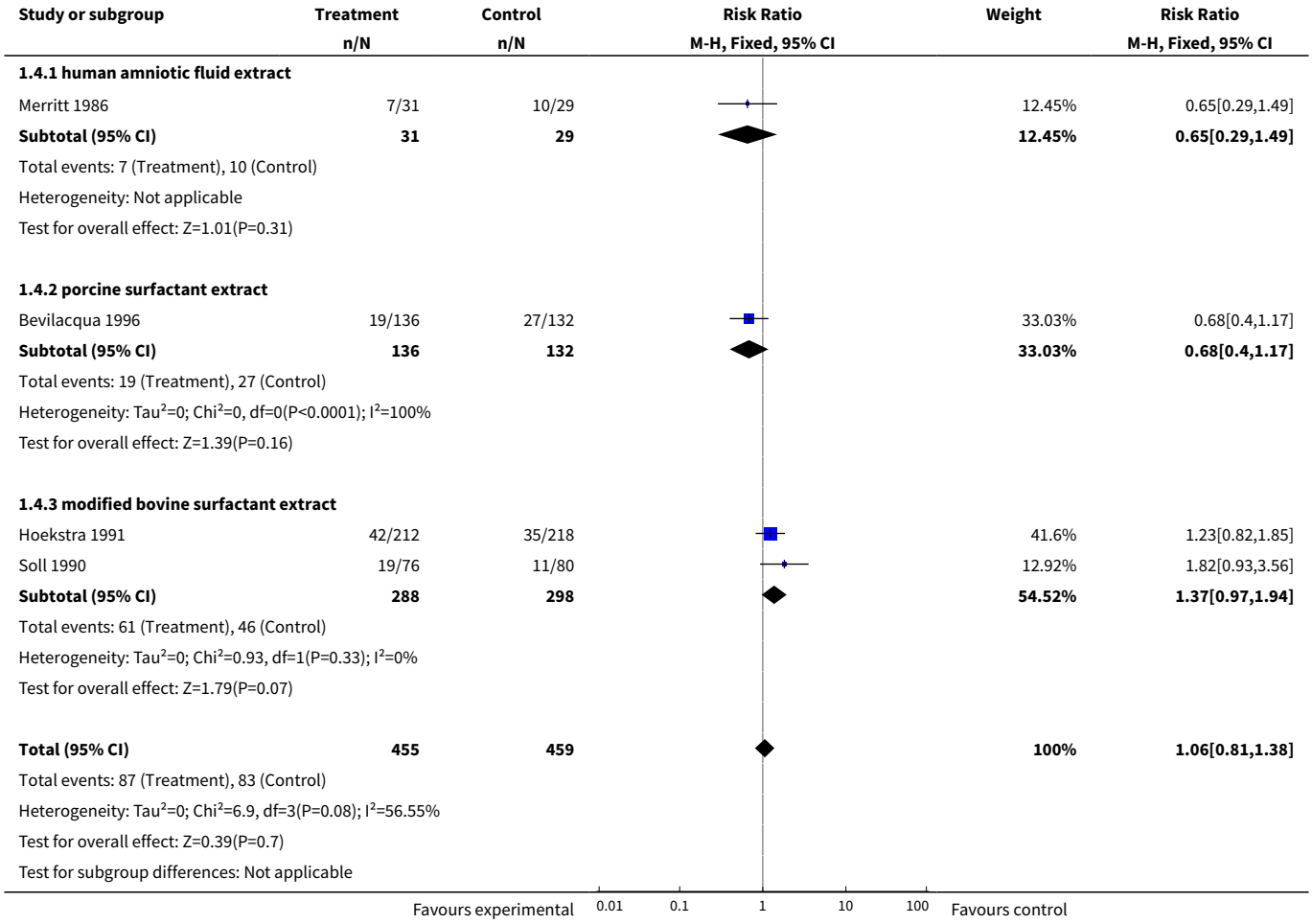
Analysis 1.3. Comparison 1 Animal derived surfactant extract vs. control, Outcome 3 Effect on patent ductus arteriosus.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 calf lung lavage					
Dunn 1991	29/62	31/60		13.55%	0.91[0.63,1.3]
Enhorning 1985	18/39	19/33		8.85%	0.8[0.51,1.25]
Kendig 1988	9/34	5/31		2.25%	1.64[0.62,4.37]
Kwong 1985	7/14	4/13		1.78%	1.63[0.62,4.28]
Shennan 1989	16/29	16/27		7.12%	0.93[0.59,1.46]
Subtotal (95% CI)	**178**	**164**		**33.55%**	**0.97[0.77,1.22]**
Total events: 79 (Treatment), 75 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.07, df=4(P=0.55); I^2=0%					
Test for overall effect: Z=0.25(P=0.8)					
1.3.2 human amniotic fluid extract					
Merritt 1986	23/31	24/29		10.66%	0.9[0.69,1.17]
Subtotal (95% CI)	**31**	**29**		**10.66%**	**0.9[0.69,1.17]**
Total events: 23 (Treatment), 24 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.81(P=0.42)					
1.3.3 porcine surfactant extract					
Bevilacqua 1996	25/136	29/132		12.65%	0.84[0.52,1.35]
Subtotal (95% CI)	**136**	**132**		**12.65%**	**0.84[0.52,1.35]**
Total events: 25 (Treatment), 29 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.73(P=0.47)					
1.3.4 modified bovine surfactant extract					
Hoekstra 1991	98/212	82/218		34.76%	1.23[0.98,1.54]
Soll 1990	22/76	20/80		8.38%	1.16[0.69,1.94]
Subtotal (95% CI)	**288**	**298**		**43.14%**	**1.22[0.99,1.49]**
Total events: 120 (Treatment), 102 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=1.85(P=0.06)					
Total (95% CI)	**633**	**623**		**100%**	**1.05[0.92,1.2]**
Total events: 247 (Treatment), 230 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.16, df=8(P=0.42); I^2=1.99%					

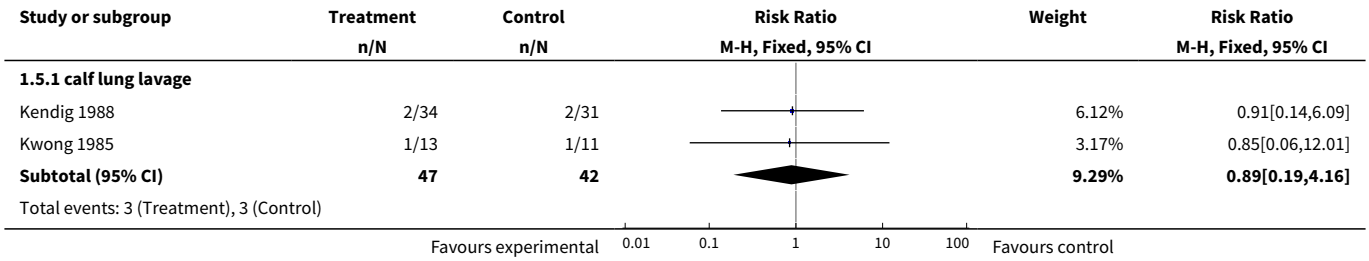


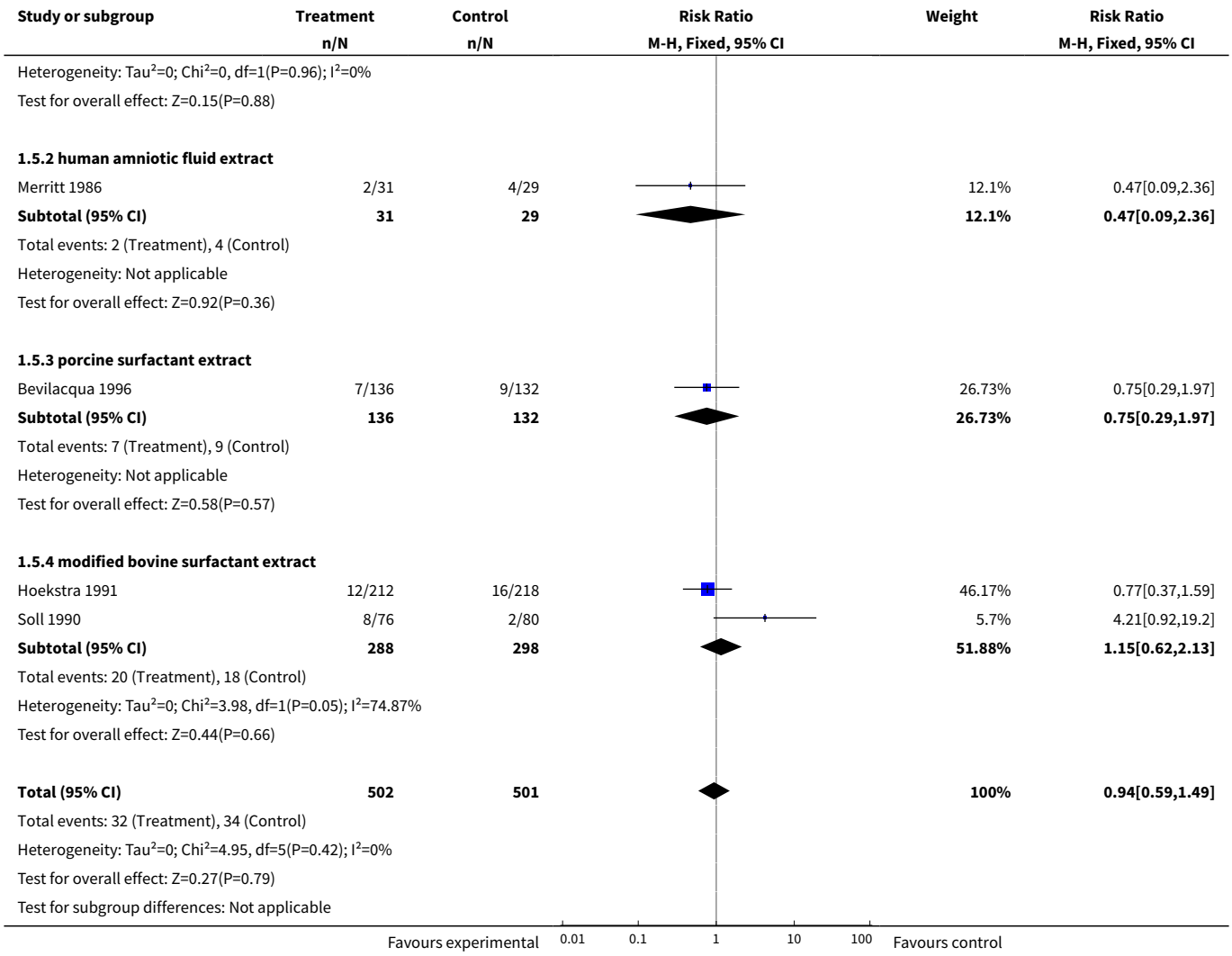


Analysis 1.4. Comparison 1 Animal derived surfactant extract vs. control, Outcome 4 Effect on sepsis.

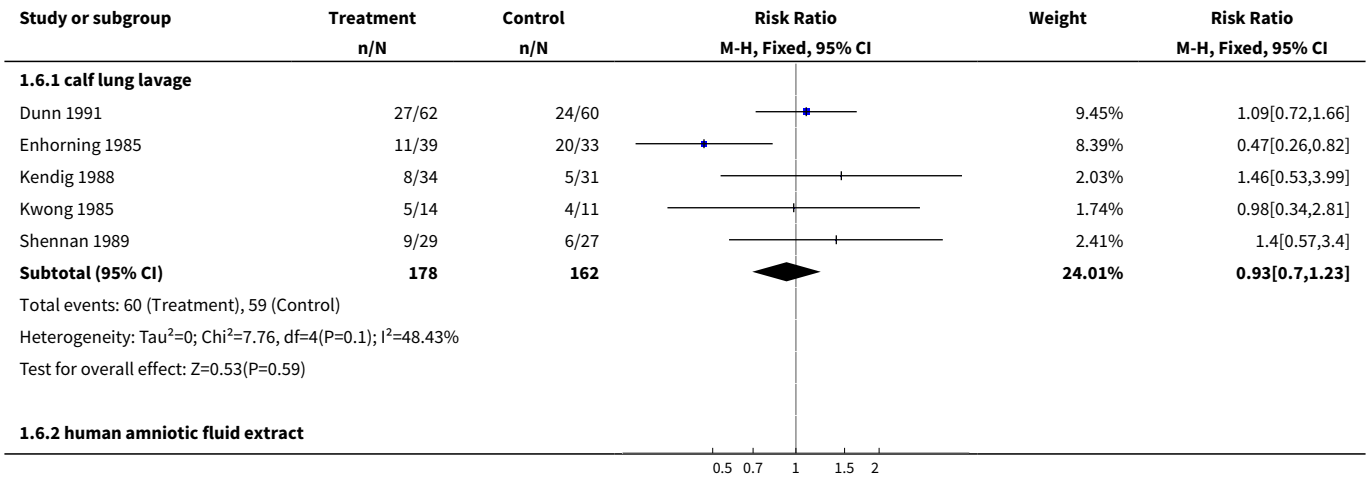


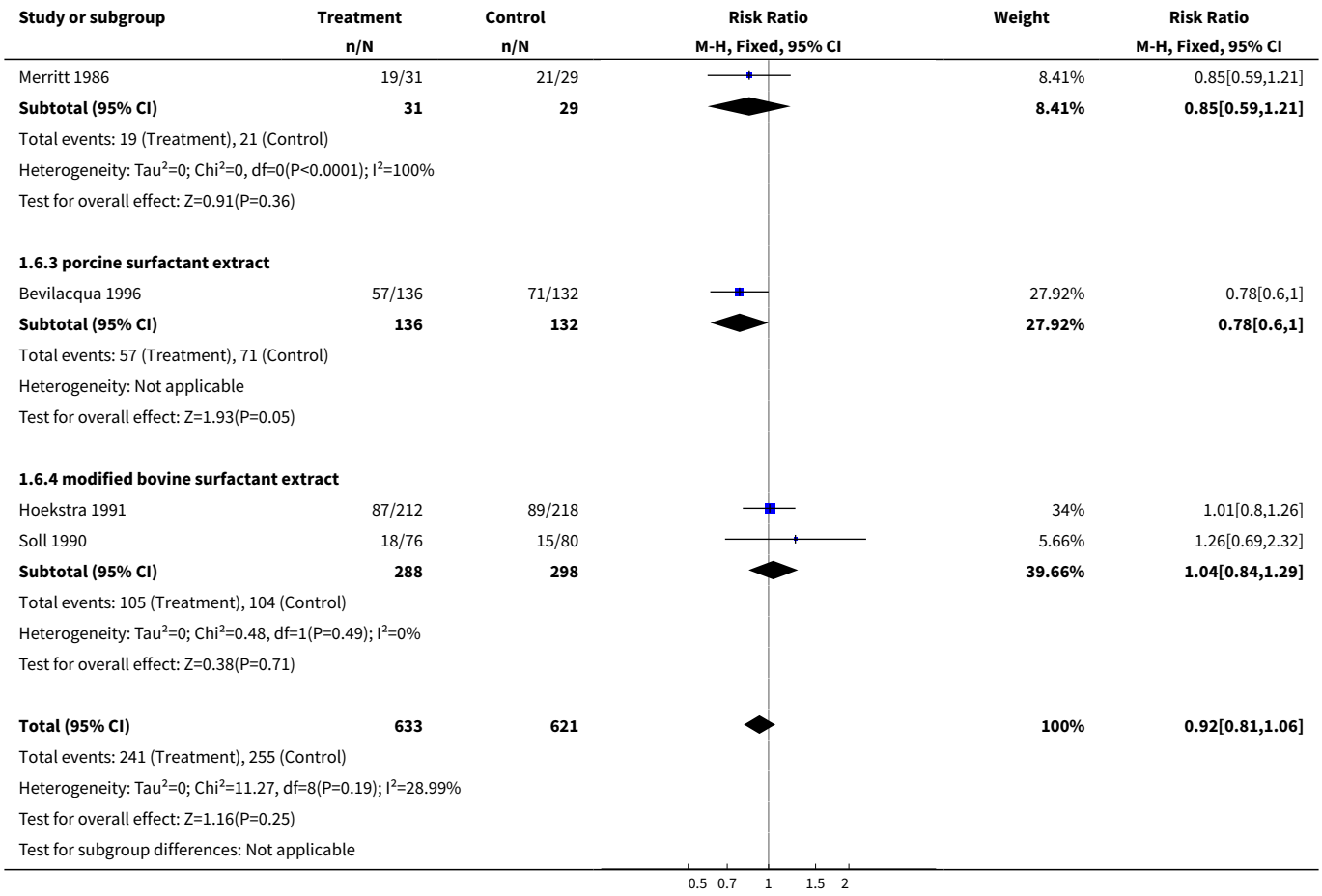
Analysis 1.5. Comparison 1 Animal derived surfactant extract vs. control, Outcome 5 Effect on necrotizing enterocolitis.



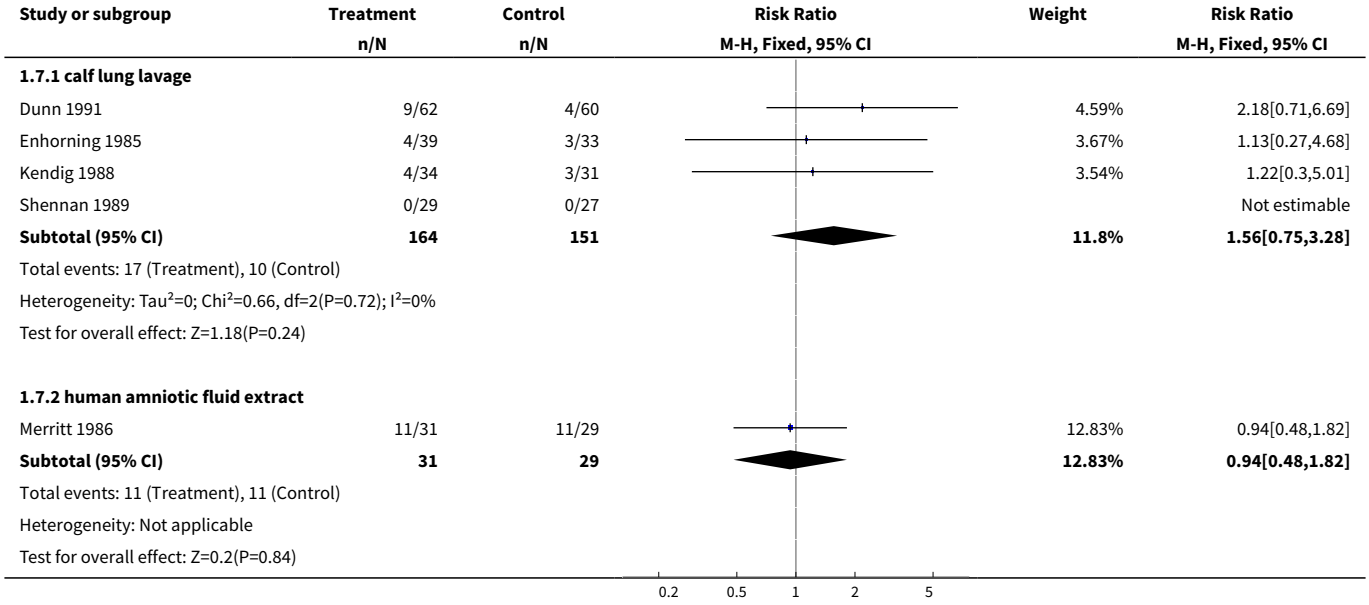


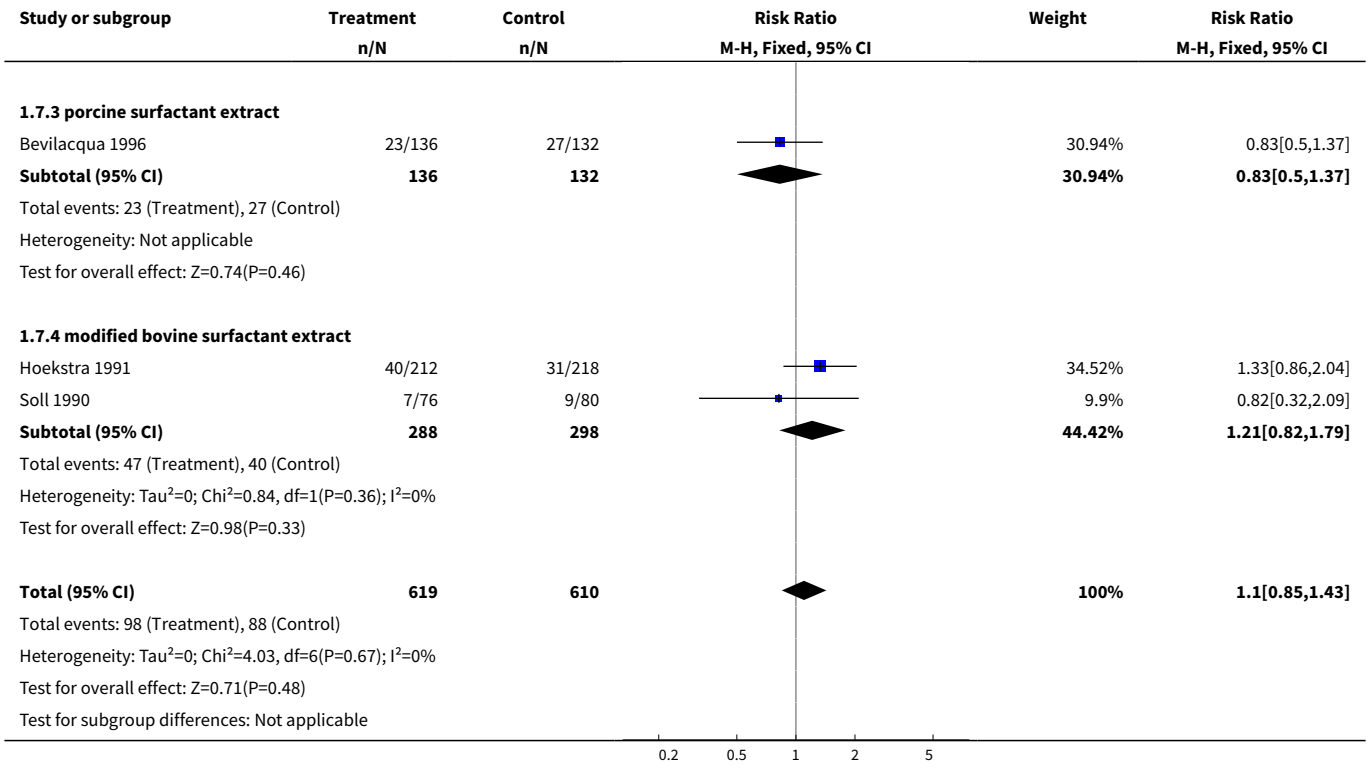
Analysis 1.6. Comparison 1 Animal derived surfactant extract vs. control, Outcome 6 Effect on intraventricular hemorrhage.



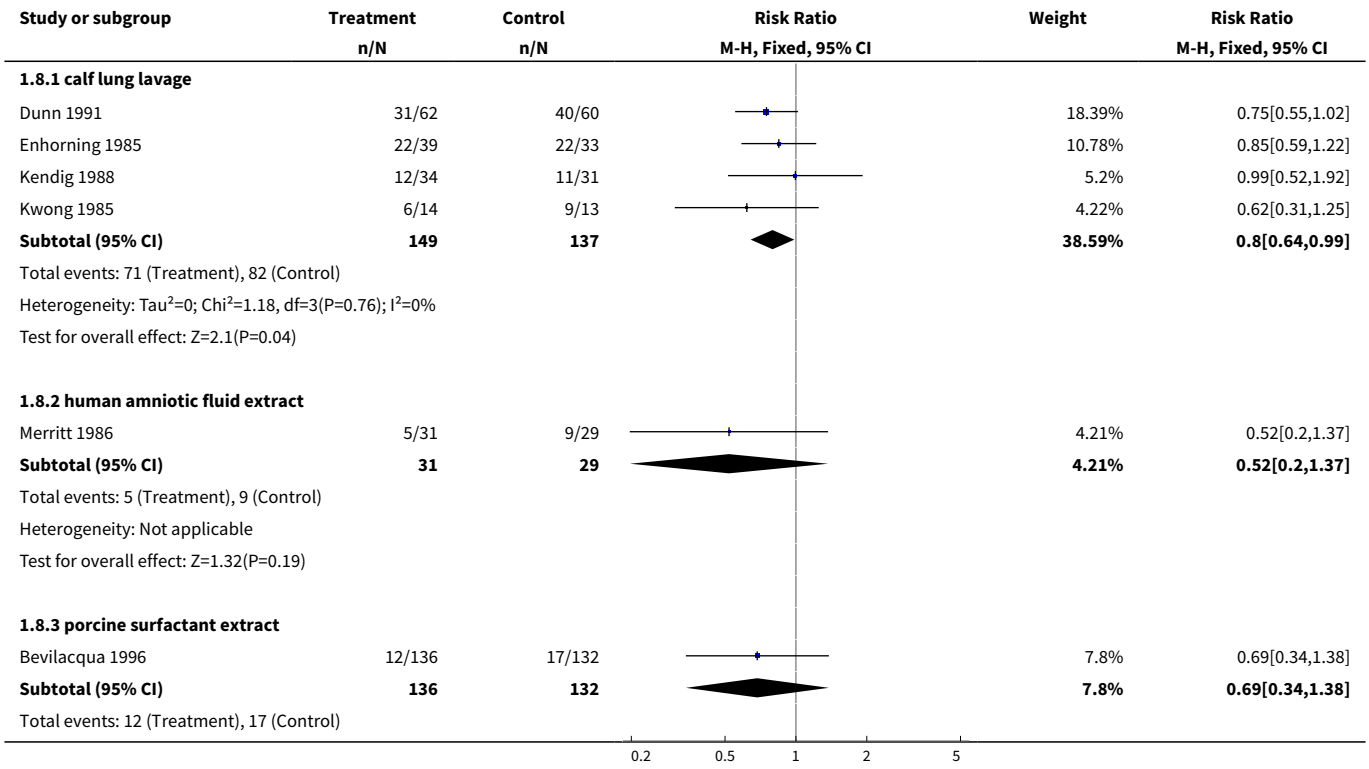


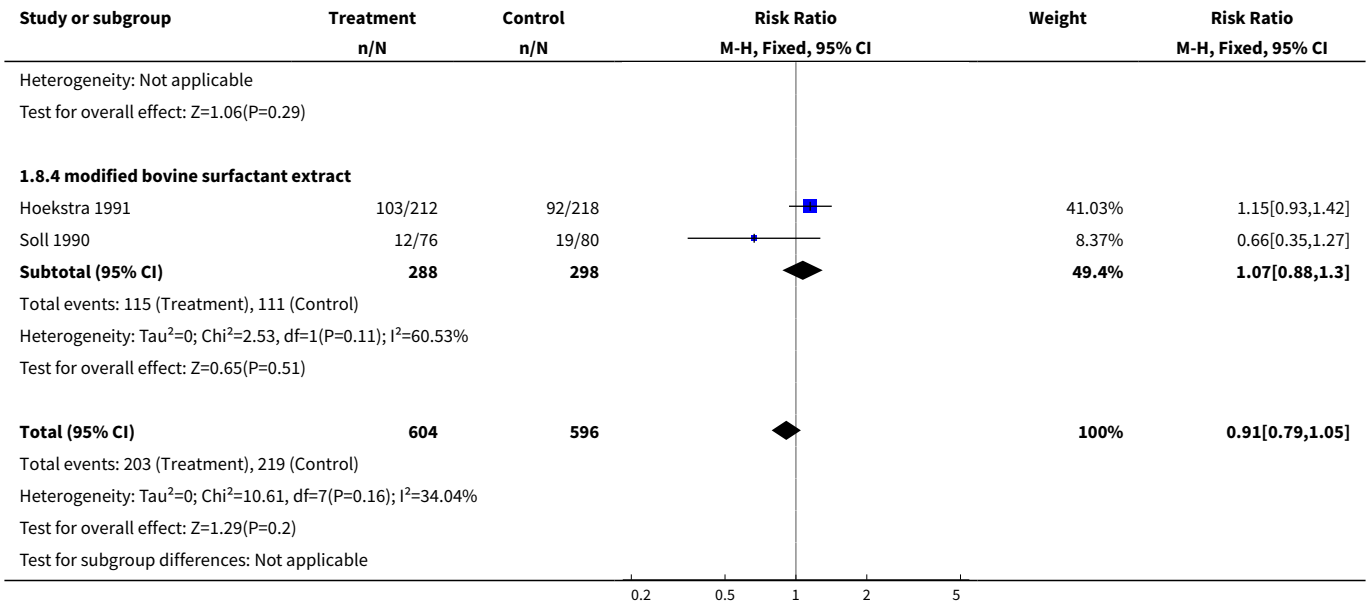
Analysis 1.7. Comparison 1 Animal derived surfactant extract vs. control, Outcome 7 Effect on severe intraventricular hemorrhage.



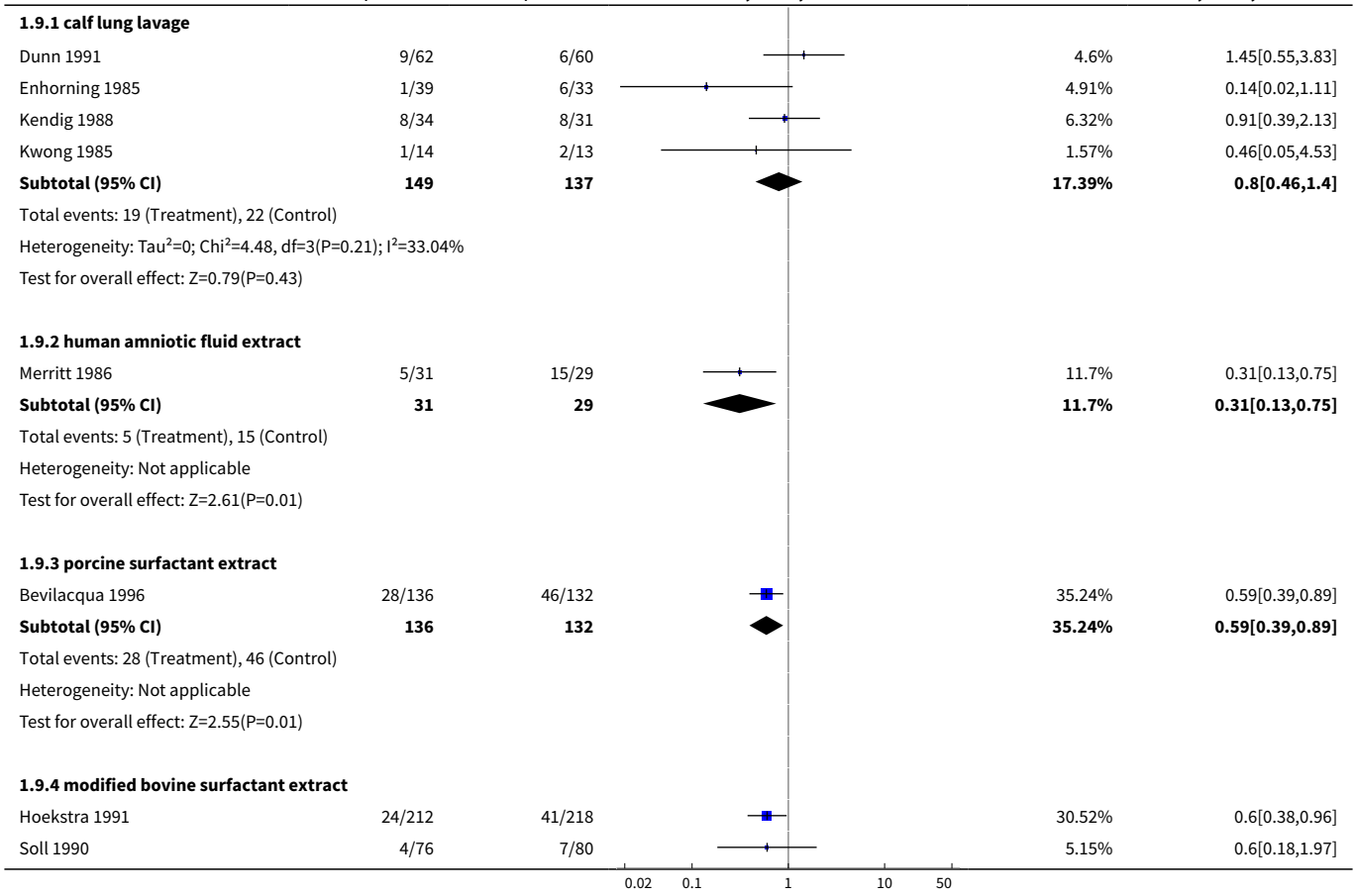


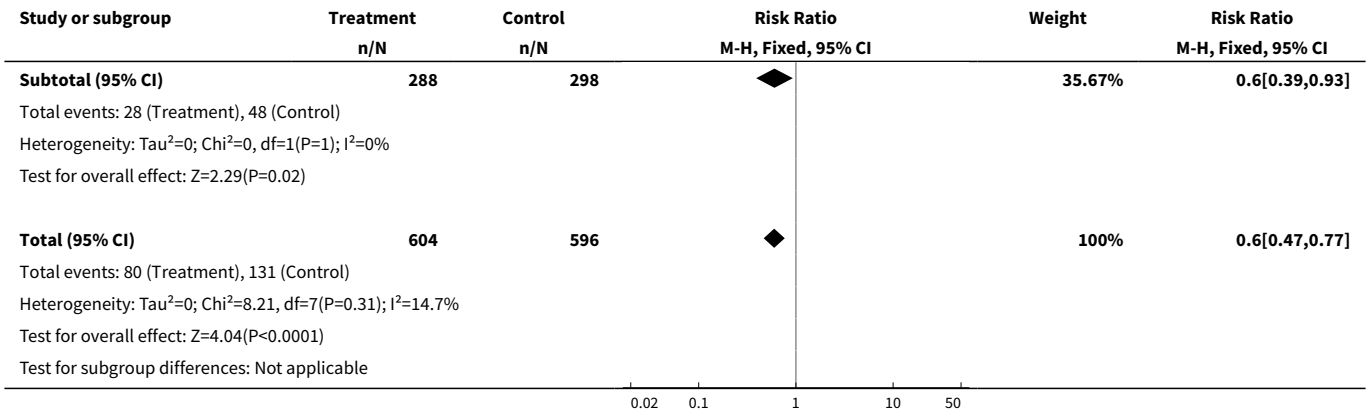
Analysis 1.8. Comparison 1 Animal derived surfactant extract vs. control, Outcome 8 Effect on bronchopulmonary dysplasia.



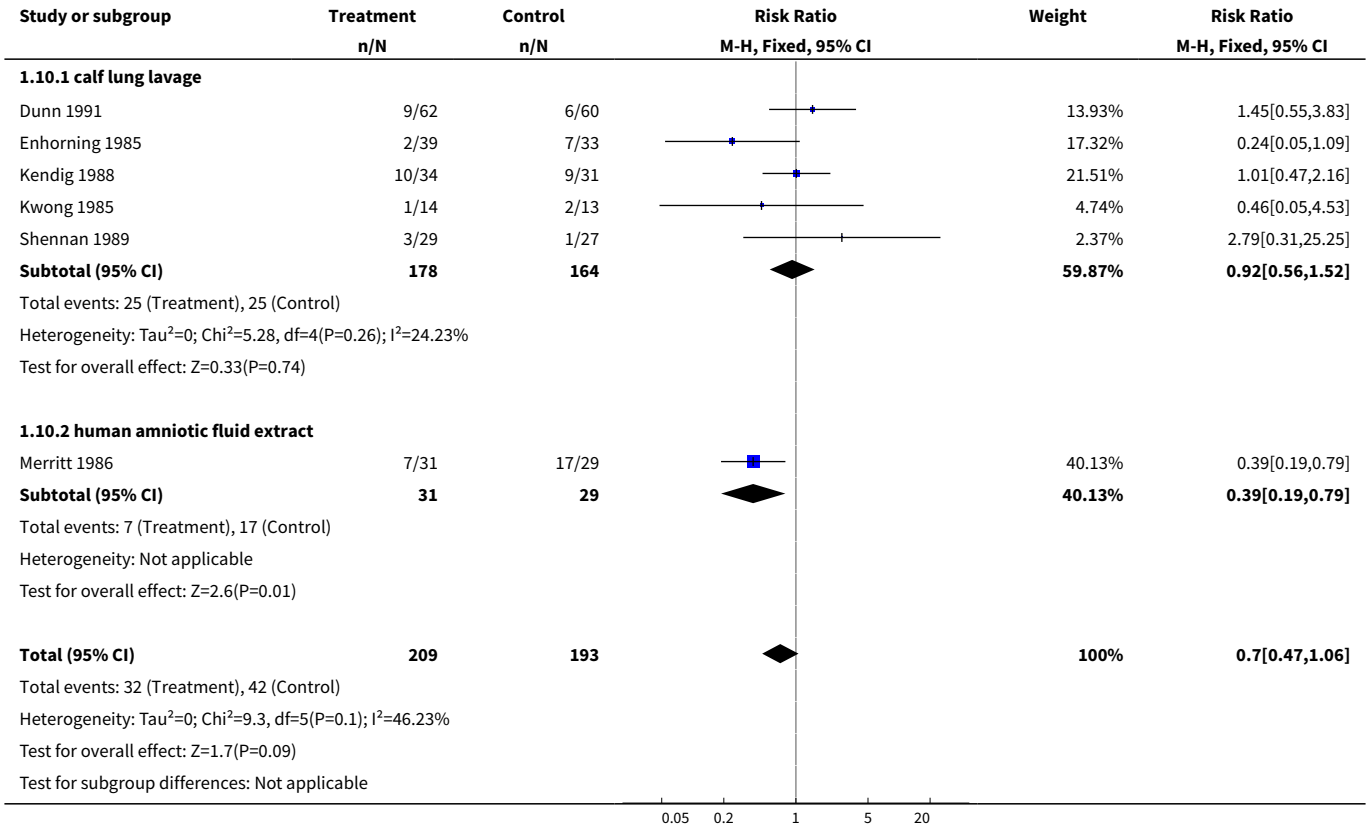


Analysis 1.9. Comparison 1 Animal derived surfactant extract vs. control, Outcome 9 Effect on neonatal mortality.

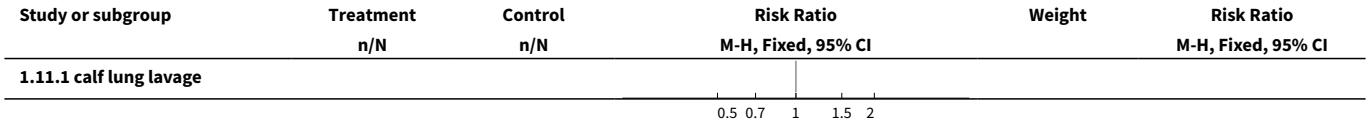


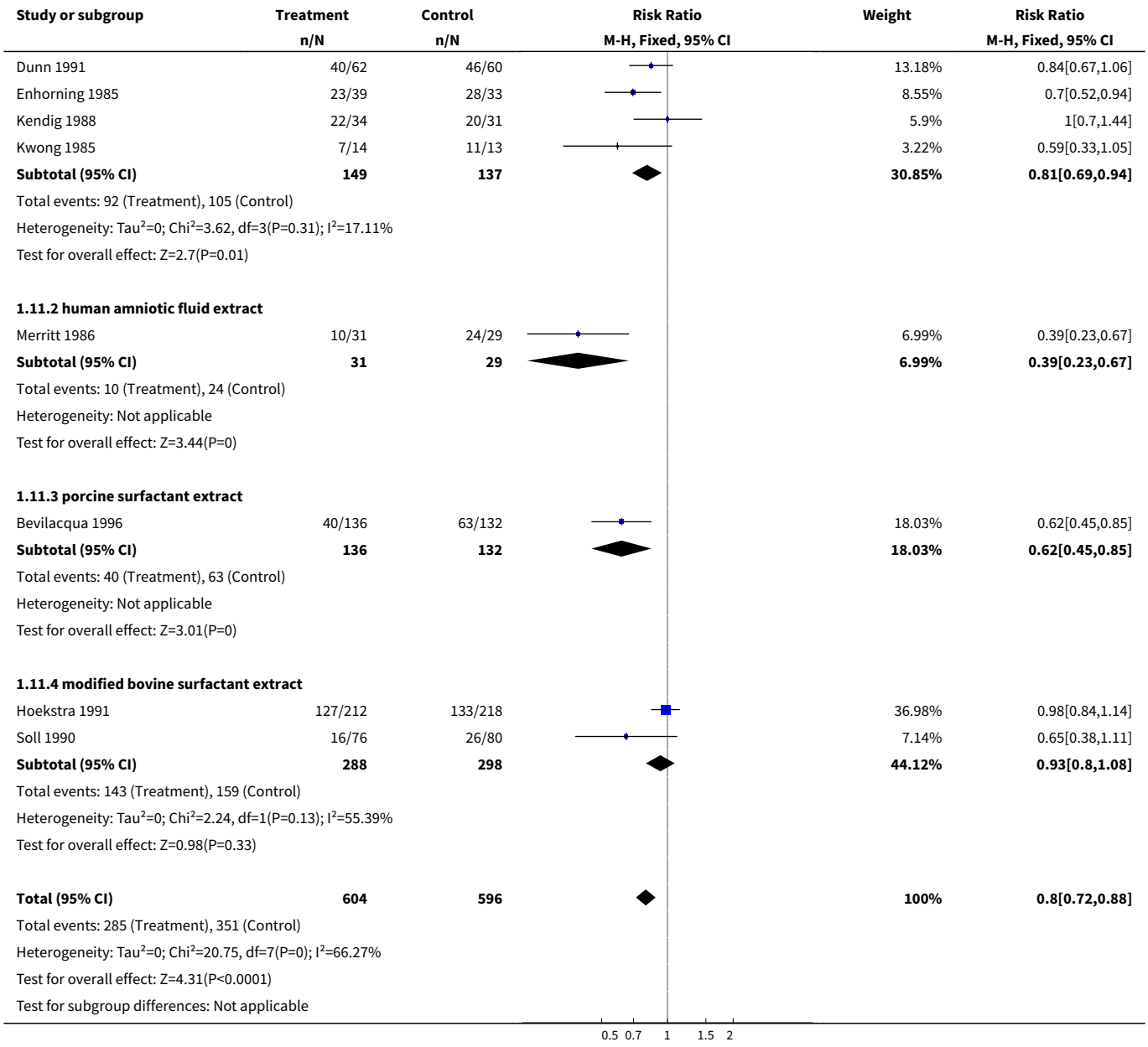


Analysis 1.10. Comparison 1 Animal derived surfactant extract vs. control, Outcome 10 Effect on mortality prior to hospital discharge.

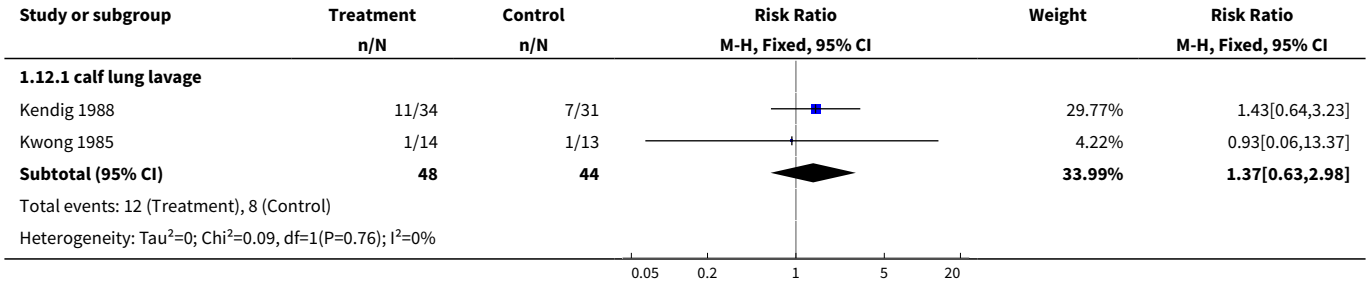


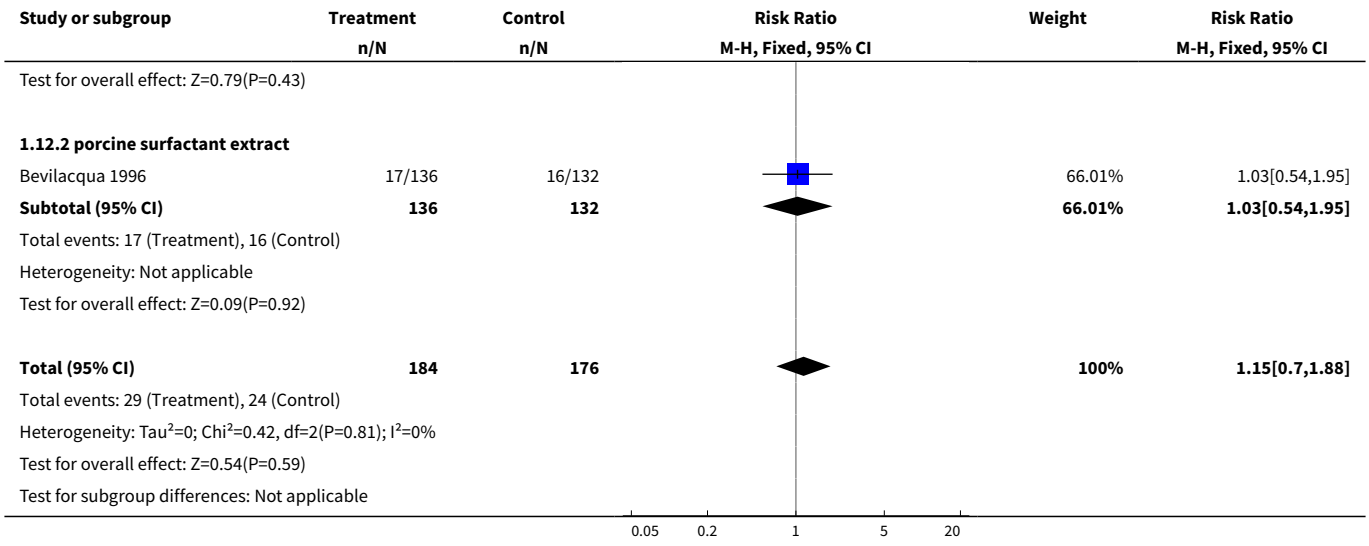
Analysis 1.11. Comparison 1 Animal derived surfactant extract vs. control, Outcome 11 Effect on BPD or death.



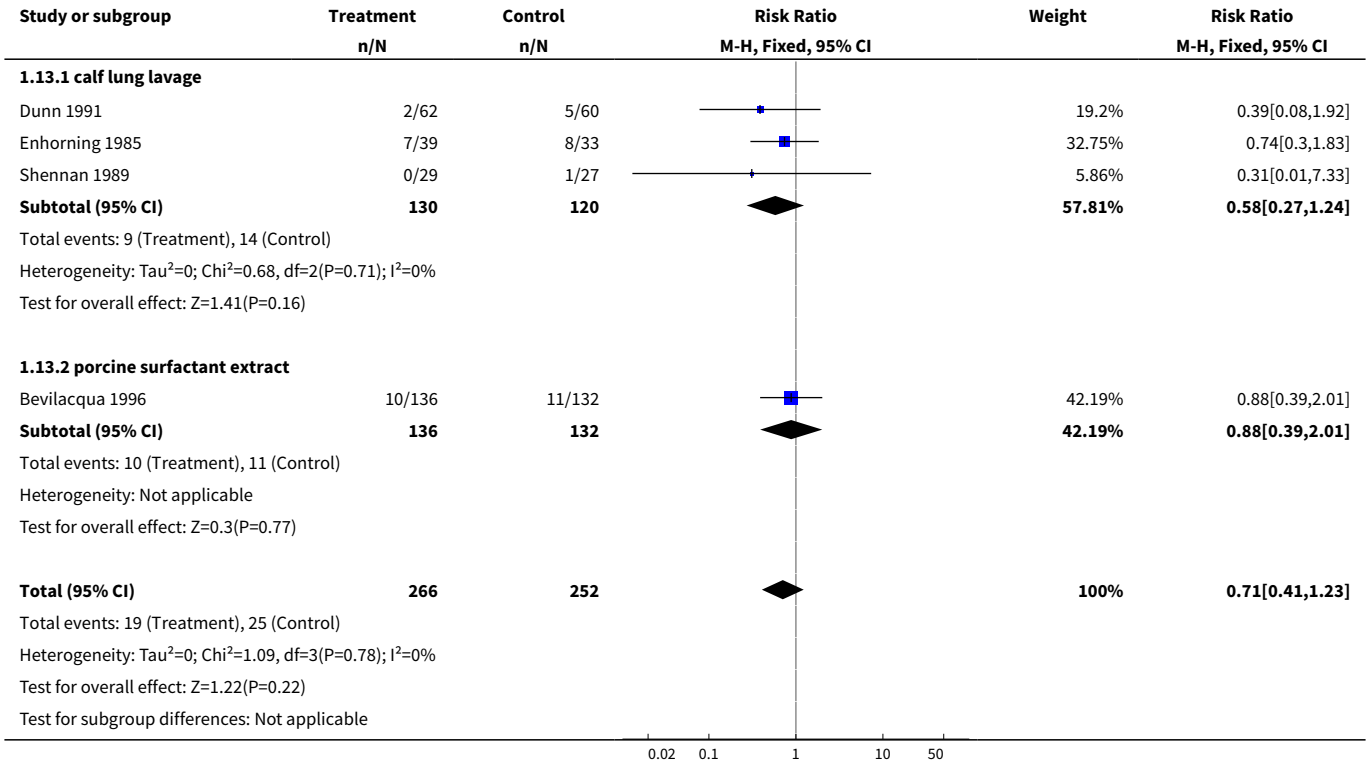


Analysis 1.12. Comparison 1 Animal derived surfactant extract vs. control, Outcome 12 Effect on retinopathy of prematurity.





Analysis 1.13. Comparison 1 Animal derived surfactant extract vs. control, Outcome 13 Retinopathy of prematurity, stages 2-4.



WHAT'S NEW

Date	Event	Description
12 March 2010	New search has been performed	For this update (February 2010), new outcomes have been added for sepsis and necrotizing enterocolitis.

HISTORY

Protocol first published: Issue 4, 1997
Review first published: Issue 4, 1997

Date	Event	Description
16 February 2010	New search has been performed	This updates the review "Prophylactic natural surfactant extract for preventing morbidity and mortality in preterm infants" published in the Cochrane Database of Systematic Reviews, Issue 4, 1997 (Soll 1997). Updated search in January 2010 revealed one additional study. Subgroup analyses based on surfactant product added. Risk of Bias tables completed. Methods section updated. No change to conclusions of the review.
27 August 1997	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

R.Soll wrote the original review. RS entered data from new studies located in the updated search and added the Risk of Bias Tables.

E. Ozek performed the search, updated the findings, updated the results section and discussion, and completed the new Characteristics of Included Studies Table.

DECLARATIONS OF INTEREST

Dr. R. Soll has acted as a consultant and invited speaker for several of the pharmaceutical companies which manufacture surfactant preparations (Abbott Laboratories, Ross Laboratories, Chiesi Pharmaceuticals, Dey Laboratories, Burroughs-Wellcome).

SOURCES OF SUPPORT

Internal sources

- Neonatal Collaborative Review Group, NIH Contract N01-MD-6-3253, USA.

External sources

- [Information not provided], Not specified.

INDEX TERMS

Medical Subject Headings (MeSH)

Infant, Premature; Pulmonary Surfactants [*therapeutic use]; Respiratory Distress Syndrome, Newborn [*prevention & control]

MeSH check words

Humans; Infant, Newborn