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Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants (Review)

Lemyre B, Laughon M, Bose C, Davis PG

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[Intervention Review]

Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants

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ABSTRACT

Background

Nasal continuous positive airway pressure (NCPAP) is a strategy for maintaining positive airway pressure throughout the respiratory cycle through the application of bias flow of respiratory gas to an apparatus attached to the nose. Treatment with NCPAP is associated with decreased risk of mechanical ventilation and might be effective in reducing chronic lung disease. Nasal intermittent positive pressure ventilation (NIPPV) is a form of noninvasive ventilation during which patients are exposed intermittently to higher levels of airway pressure, along with NCPAP through the same nasal device.

Objectives

To examine the risks and benefits of early NIPPV versus early NCPAP alone for preterm infants at risk of or in respiratory distress within the first hours after birth.

Primary endpoints are respiratory failure and the need for intubated ventilatory support during the first week of life. Secondary endpoints include chronic lung disease (CLD) (oxygen therapy at 36 weeks' postmenstrual age), air leaks, duration of respiratory support, duration of oxygen therapy, intraventricular hemorrhage, and incidence of mortality.

Search methods

We used the standard search strategy of the Cochrane Neonatal Review Group to search the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9), MEDLINE via PubMed (1966 to September 28, 2015), Embase (1980 to September 28, 2015), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to September 28, 2015). We also searched clinical trials databases, conference proceedings, and the reference lists of retrieved articles for randomized controlled trials and quasi-randomized trials. A member of the Cochrane Neonatal Review Group handsearched abstracts from the European Society of Pediatric Research (ESPR). We contacted the authors of ongoing clinical trials to ask for information.

Selection criteria

We considered all randomized and quasi-randomized controlled trials. Studies selected compared NIPPV versus NCPAP treatment, starting at birth or shortly thereafter in preterm infants (< 37 weeks' gestational age).

Data collection and analysis

We performed data collection and analysis using the recommendations of the Cochrane Neonatal Review Group.

Main results

Ten trials, enrolling a total of 1061 infants, met criteria for inclusion in this review. Meta-analyses of these studies showed significantly reduced risk of meeting respiratory failure criteria (typical risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51 to 0.82; typical risk difference (RD) -0.09, 95% CI -0.13 to -0.04) and needing intubation (typical RR 0.78, 95% CI 0.64 to 0.94; typical RD -0.07, 95% CI -0.12 to -0.02) among infants treated with early NIPPV compared with early NCPAP. The meta-analysis did not demonstrate a reduction in the risk of CLD among infants randomized to NIPPV (typical RR 0.78, 95% CI 0.58 to 1.06). Investigators observed no evidence of harm. Review authors graded the quality of the evidence as moderate (unblinded studies).

Authors' conclusions

Early NIPPV does appear to be superior to NCPAP alone for decreasing respiratory failure and the need for intubation and endotracheal tube ventilation among preterm infants with respiratory distress syndrome. Additional studies are needed to confirm these results and to assess the safety of NIPPV compared with NCPAP alone in a larger patient population.

PLAIN LANGUAGE SUMMARY

Early nasal intermittent positive pressure ventilation (NIPPV) versus early nasal continuous positive airway pressure (NCPAP) for preterm infants

Review question: Does NIPPV confer greater short-term and long-term benefits without harm to preterm infants with or at risk of respiratory distress compared with NCPAP?

Background: Some evidence suggests that nasal intermittent positive pressure ventilation (NIPPV) increases the effectiveness of nasal continuous positive airway pressure (NCPAP) in preterm babies who have respiratory difficulties or are at risk of such difficulties. Preterm babies with breathing problems often require help from a machine (ventilator) that provides regular breaths through a tube in the windpipe. Pediatricians caring for these preterm infants try to avoid use of ventilators, as they can damage the growing lung. NCPAP and NIPPV are ways of supporting babies' breathing in a less invasive way - the tubes are shorter and go only to the back of the nose, thereby causing less damage to the lungs. NCPAP and NIPPV may be used early after birth to reduce the number of babies needing to go on a ventilator. NCPAP provides steady pressure to the back of the nose that is transmitted to the lungs, helping the baby breathe more comfortably. NIPPV provides the same support but also adds some breaths through the ventilator.

Study characteristics: We searched scientific databases for studies comparing NCPAP with NIPPV in preterm infants (born before 37 completed weeks of pregnancy) who need respiratory support shortly after birth. We looked at breathing problems, the need for a breathing tube and ventilator, and side effects. The evidence is current to September 2015.

Key results: We found nine trials comparing NCPAP with NIPPV. When analyzing all trials, we found that NIPPV reduces the risk for respiratory failure and the need for a ventilator. Additional studies are needed to determine how NIPPV can be best delivered to infants.

Quality of the evidence: The overall quality of the studies included in this review was good.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. NIPPV versus NCPAP (by population)

NIPPV versus NCPAP (by population)

Patient or population: preterm infants
Setting: neonatal intensive care units
Intervention: NIPPV
Comparison: NCPAP

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with NCPAP	Risk with NIPPV				
Respiratory failure	Study population		RR 0.62 (0.47 to 0.82)	876 (9 RCTs)	Moderate[a]	Risk of bias: unblinded intervention Meets optimal information size (OIS) (N = 377)
	251 per 1000	155 per 1000 (120 to 200)				
	Moderate					
	175 per 1000	109 per 1000 (84 to 140)				
Need for intubation	Study population		RR 0.79 (0.64 to 0.97)	766 (8 RCTs)	Moderate[a]	Risk of bias: unblinded intervention Does not meet OIS (N = 838)
	300 per 1000	237 per 1000 (192 to 291)				
	Moderate					
	175 per 1000	138 per 1000 (112 to 170)				
Pneumothorax	Study population		RR 0.69 (0.35 to 1.34)	876 (9 RCTs)	Low[a,b]	Risk of bias: unblinded intervention Imprecision: wide confidence intervals
	43 per 1000	29 per 1000 (15 to 57)				
	Moderate					
	44 per 1000	30 per 1000				

		(15 to 58)				
Severe intraventricular hemorrhage (grade III/IV)	Study population		RR 1.26 (0.53 to 3.01)	430 (4 RCTs)	Very low[a,b]	Risk of bias: unblinded intervention Imprecision: extremely wide confidence intervals
	37 per 1000	46 per 1000 (19 to 110)				
	Moderate					
	49 per 1000	61 per 1000 (26 to 147)				
Chronic lung disease	Study population		RR 0.67 (0.47 to 0.94)	727 (8 RCTs)	Moderate[a]	Risk of bias: unblinded intervention Does not meet OIS (N = 1250)
	179 per 1000	120 per 1000 (84 to 168)				
	Moderate					
	170 per 1000	114 per 1000 (80 to 160)				
Mortality during study period	Study population		RR 0.77 (0.51 to 1.17)	876 (9 RCTs)	Low[a,b]	Risk of bias: unblinded intervention Imprecision: wide confidence intervals
	89 per 1000	69 per 1000 (46 to 105)				
	Low					
	0 per 1000	0 per 1000 (0 to 0)				
	Moderate					
	26 per 1000	20 per 1000 (13 to 30)				

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

CI: confidence interval; RCT: randomized controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate quality: 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 quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect.
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

[a]Unblinded intervention.
[b]Imprecision: wide confidence intervals.

BACKGROUND

Description of the condition

Chronic lung disease (CLD), also known as bronchopulmonary dysplasia (BPD), is the most common serious morbidity among preterm infants. BPD has been defined historically as the need for supplemental oxygen therapy at 28 days of life; however, over time, this definition evolved to describe the need for supplemental oxygen therapy at 36 weeks' postgestational age, and it has been further standardized to include the need for oxygen therapy at 36 weeks' postgestational age to achieve oxygen saturation of 88% for 60 minutes or longer (Bancalari 2001).

The major risk factor for chronic lung disease is prematurity necessitating treatment with oxygen and mechanical ventilation (Avery 1987; Van Marter 2000), both of which are potentially modifiable. The pathogenesis of CLD involves barotrauma or volutrauma (due to assisted ventilation) that results in airway injury, smooth muscle hypertrophy, and parenchymal lung fibrosis and emphysematous changes, often complicated by inflammation, genetic predisposition, and concomitant abnormalities such as patent ductus arteriosus (PDA). CLD is also associated with increased risk of many cardiovascular abnormalities such as progressive pulmonary hypertension (due to hypoxia and vasoconstriction in the pulmonary vasculature), systemic hypertension, and left ventricular hypertrophy. It is important to note that whereas the survival of extremely low birth weight infants has increased over the years, rates of CLD have stayed relatively constant despite improving technology. CLD remains a serious problem; the incidence of CLD may be on the rise because of increased survival among the most vulnerable infants (Stoelhorst 2005).

Neonatologists have looked for noninvasive ways to support the breathing of preterm infants to avoid the need for mechanical ventilation.

Description of the intervention

Continuous distending airway pressure with the application of nasal constant positive airway pressure (NCPAP) has been used as a strategy for avoiding endotracheal tube ventilation, thereby minimizing the risk of CLD.

Historical analyses of nasal ventilation demonstrate a decreased incidence of BPD and reduced need for intubation in infants treated with noninvasive respiratory support. A study by Avery et al in 1987 demonstrated very different rates of CLD at eight institutions in the United States. The institution with the lowest rate of CLD, Columbia University, was also the institution with the highest use of nasal prong respiratory support in preterm infants with birth weight between 700 and 1500 grams. Infants showing signs of respiratory distress received nasal positive pressure support in the delivery room or within three hours of life. These infants were less likely than infants at other institutions to need mechanical ventilation, and they were less likely to develop BPD (Avery 1987).

Unfortunately, although at some centers NCPAP is a successful therapy for preterm infants, this success is not replicated at all centers. "Failures" of NCPAP are common, and many infants born at less than 28 weeks' gestation ultimately require endotracheal intubation and mechanical ventilation (Meyer 2004). In a randomized trial by Finer et al in 2004, infants who received NCPAP in the delivery room were no less likely than infants without NCPAP to need endotracheal intubation in the delivery room or in the subsequent first week of life. This study demonstrated instead a profound effect of gestational age on the need for intubation (virtually all infants born at 23 weeks required intubation vs only 14% of infants born at 27 weeks), regardless of the cohort to which they had been randomized (Finer 2004).

Nasal intermittent positive pressure ventilation (NIPPV) is a simple, effective mode of respiratory support. NIPPV augments continuous positive airway pressure (CPAP) with superimposed inflations to a set peak pressure. NIPPV may be delivered by nasal mask or prongs, which may be short or long, single or binasal. Some devices attempt to synchronize inflations with the infant's respiratory efforts.

How the intervention might work

NIPPV reduces asynchronous thoracoabdominal motion, perhaps as a result of reduced tube resistance or better stabilization of the chest wall, or both (Kiciman 1998). NIPPV results in improved tidal and minute volumes and decreased inspiratory effort required by neonates when compared with NCPAP (Moretti 1999). NIPPV may decrease the need for intubation and endotracheal tube ventilation and their associated risks. To evaluate the efficacy of NIPPV, these potential benefits should be weighed against the risks associated with delivery of positive pressure to the upper airway, pharynx, and esophagus. Potential risks of NIPPV include nasal septal injury and gastrointestinal perforation (Garland 1985).

Why it is important to do this review

Currently, two Cochrane reviews are comparing NCPAP versus NIPPV - one for treatment of infants with apnea of prematurity (Lemyre 2002), and the other for prevention of extubation failure (Lemyre 2014).

The review by Lemyre et al titled "Nasal intermittent positive pressure ventilation (NIPPV) versus nasal continuous positive airway pressure (NCPAP) for preterm neonates after extubation" reveals a decreased need for reintubation among infants treated with NIPPV versus NCPAP. The review authors concluded that use of NIPPV may prevent extubation failure more effectively than use of NCPAP.

Thus, previous studies have shown that NIPPV may be superior to NCPAP in other clinical scenarios (eg, prevention of extubation failure, prevention of apnea), and it remains to be shown whether early NIPPV may provide similar benefit in preventing the primary need for intubation and mechanical ventilation when compared with NCPAP. This review seeks to determine whether NIPPV or NCPAP is a better primary mode of nasal ventilation for preventing respiratory failure, the need for intubation, and development of CLD, without causing harm such as air leak or intraventricular hemorrhage (IVH).

OBJECTIVES

To examine the risks and benefits of early NIPPV versus early NCPAP alone for preterm infants at risk of or in respiratory distress within the first hours after birth.

Primary endpoints are respiratory failure and the need for intubated ventilatory support during the first week of life. Secondary endpoints include chronic lung disease (oxygen therapy

at 36 weeks' postmenstrual age), air leaks, duration of respiratory support, duration of oxygen therapy, IVH, and incidence of mortality.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomized and quasi-randomized trials for inclusion. We excluded cross-over trials.

Types of participants

We included studies that enrolled newly born preterm infants. For this protocol, we defined newly born infants as infants less than six hours old, and preterm infants as those born at less than 37 weeks' gestational age. We included infants who received surfactant therapy if the duration of endotracheal intubation was short, and if application of NIPPV or NCPAP occurred before six hours of life.

Types of interventions

Intermittent positive pressure ventilation provided by a ventilator or a bilevel device and administered via the nasal route through short nasal prongs or nasopharyngeal tubes versus NCPAP delivered by the same methods. NIPPV included noninvasive support delivered by a mechanical ventilator or a bilevel device in a synchronized or nonsynchronized way.

Types of outcome measures

Primary outcomes

- Respiratory failure: defined by respiratory acidosis, increased oxygen requirement, or apnea that was frequent or severe, leading to additional ventilatory support during the first week of life
- Need for endotracheal tube (ETT) ventilation (intermittent positive pressure ventilation (IPPV) through an endotracheal tube)

Secondary outcomes

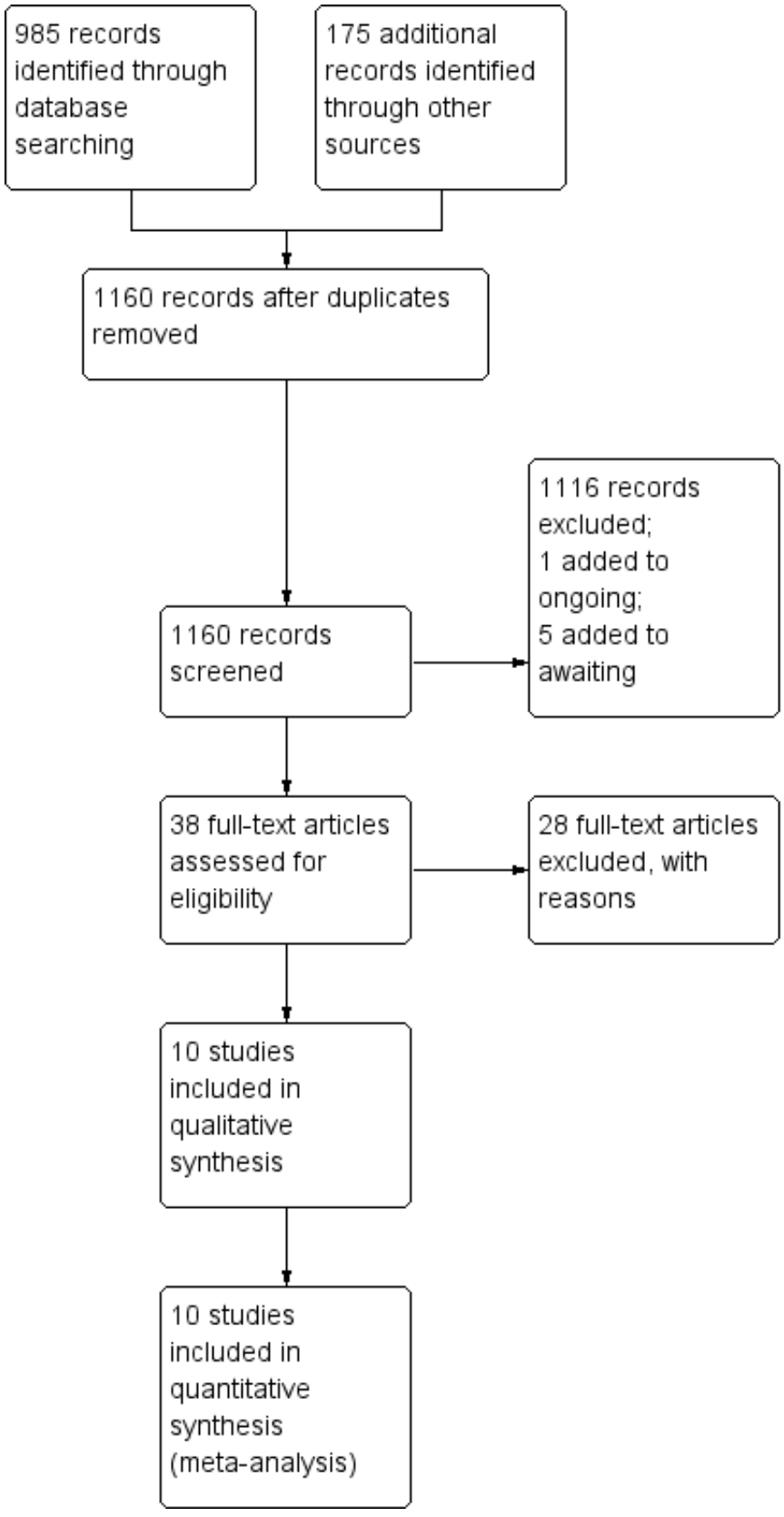
- Mortality (neonatal and before discharge)
- Major neurodevelopmental disability (cerebral palsy, developmental delay (Bayley or Griffith assessment greater than two standard deviations (SDs) below the mean) or intellectual impairment (intelligence quotient (IQ) greater than two SDs below the mean), blindness (vision < 6/60 in both eyes), sensorineural deafness requiring amplification)
- Chronic lung disease (oxygen therapy at 36 weeks' postmenstrual age)
- Pneumothorax
- Patent ductus arteriosus
- IVH (all grades) (Papile 1978)
- Severe IVH (grade III/IV) (Papile 1978)
- Necrotizing enterocolitis (Bell's ≥ stage 2) (Bell 1978)
- Sepsis
- Retinopathy of prematurity (≥ stage 3) (ICCROP 2005)
- Duration of ETT ventilation (any)
- Duration of oxygen dependence (days)
- Duration of hospital stay (days)
- Nasal septal injury
- Gastrointestinal perforation

Search methods for identification of studies

Electronic searches

Please see study flow diagram (Figure 1).

Figure 1. Study flow diagram.



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

We conducted a comprehensive search of the Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 9) in the Cochrane Library; MEDLINE via PubMed (1966 to September 28, 2015); Embase (1980 to September 28, 2015); and the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1982 to September 28, 2015) using the following search terms: (nasal continuous positive airway pressure OR NCPAP OR nasal intermittent positive pressure ventilation OR NIPPV OR nasal intermittent mandatory ventilation OR NIMV OR nasal distending pressure OR nasal positive pressure OR nasal ventilation OR non-invasive positive pressure ventilation OR synchronized intermittent mandatory ventilation OR SIMV OR nasopharyngeal synchronized intermittent mandatory ventilation OR bilevel CPAP OR BiCPAP OR BiPAP OR SiPAP), plus database-specific limiters for RCTs and neonates (see Appendix 2 for the full search strategies for each database). We applied no language restrictions.

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

Searching other resources

We searched abstracts from the Pediatric Academic Society meetings (2011 to 2014) through abstract archives on the website (www.pas-meeting.org). Members of the Cochrane Neonatal Review Group handsearched abstracts from the European Society of Pediatric Research (ESPR). We consulted experts in the field of neonatology in reference to other published articles.

Data collection and analysis

We used the standard method of conducting a systematic review, as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, which can be found online at http://www.cochrane.org/training/cochrane-handbook.

Selection of studies

Two review authors checked titles and abstracts identified through database searches. Review authors were not masked to authorship, journal, or results. Both review authors obtained the full text of all studies of possible relevance for independent assessment.

Data extraction and management

Two review authors independently extracted data. We contacted trial authors to request missing data if needed.

Assessment of risk of bias in included studies

We assessed risk of bias using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011) and presented this information in "Risk of bias tables" for the following domains.

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

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

Measures of treatment effect

For individual studies, we expressed results as risk ratios (RRs) and risk differences (RDs) with 95% confidence intervals (CIs) for dichotomous outcomes, and as mean differences (MDs and 95% CIs) for continuous outcomes.

Assessment of heterogeneity

We calculated the I^2 statistic across trials using the Cochrane statistical package (RevMan 5.1) to test for significant heterogeneity. We explored possible sources of heterogeneity if the treatment effect showed moderate to high heterogeneity between studies, as described in the *Cochrane Handbook for Systematic Reviews of Interventions,* as an I^2 statistic of > 50% heterogeneity.

Data synthesis

We synthesized data by using the standard method of the Cochrane Neonatal Review Group. We expressed results as typical risk ratios (RRs) and typical risk differences (RDs) with 95% confidence intervals (CIs) for dichotomous outcomes, and as weighted mean differences (WMDs and 95% CIs) for continuous outcomes, by using a fixed-effect "assumption free" model.

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: respiratory failure, need for endotracheal tube ventilation (IPPV through an endotracheal tube), chronic lung disease (oxygen therapy at 36 weeks' postmenstrual age), pneumothorax, severe IVH (grade III/IV), and mortality (neonatal and before discharge) (post hoc).

Two review authors independently assessed the quality of evidence for each of the outcomes above. We considered evidence from RCTs as high quality but downgraded evidence one level for serious (or two levels for very serious) limitations on the basis of the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro 2008 Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence by 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.

Subgroup analysis and investigation of heterogeneity

Planned subgroup analyses included gestational age (< 28 weeks vs ≥ 28 weeks), birth weight (< 1000 grams vs ≥ 1000 grams), whether infants received surfactant before randomization (via intubation-surfactant-extubation (INSURE) or prophylactic), whether NIPPV was delivered by a ventilator or by a bilevel device, and whether or not NIPPV was synchronized.

RESULTS

Description of studies

Please see the Characteristics of included studies table.

Results of the search

The initial literature search returned 1160 potential articles or abstracts, of which 37 were of particular interest (full-text review). See Figure 1.

Included studies

We identified 10 studies that met our inclusion criteria: Armanian 2014, Bisceglia 2007, Kirpalani 2013, Sai Sunil Kishore 2009, Kugelman 2007, Lista 2009, Meneses 2011, Ramanathan 2012, Salama 2015, and Wood 2013.

Armanian 2014 performed a quasi-randomized trial that enrolled 98 infants (< 1501 grams and/or < 35 weeks) with respiratory distress syndrome (RDS) and a compatible chest x-ray requiring noninvasive respiratory support after birth. Investigators randomized 44 infants to NIPPV and 54 to NCPAP, according to their medical chart number (odd or even number). All infants received aminophylline. A ventilator (unspecified) in the nonsynchronized mode provided NIPPV. The control group received bubble CPAP. Both groups used short binasal prongs. The primary outcome measure was respiratory failure with need for intubation within 48 hours. Secondary outcomes included need for surfactant, duration of oxygen, CLD, time to full feeds, length of hospital stay, pneumothorax, IVH, and PDA.

Bisceglia 2007 enrolled 88 preterm infants (28 to 34 weeks' gestational age) with mild to moderate RDS in the first four hours of birth. Investigators randomized 46 infants to NCPAP alone and 42 to NIPPV. They did not treat infants with aminophylline or caffeine, and they performed ventilation of both groups via nasal cannulae with the Bear Infant Ventilator CUB 750 (Ackrad Laboratories, Cranford, NJ, USA). Study authors did not synchronize NIPPV with spontaneous breathing. The primary outcome measured was number of infants needing intubation, and secondary outcomes included total duration of respiratory support, number of apneic episodes, and variation in blood gas levels. Upon receiving correspondence, study authors provided data for mortality at 28 days; presence of BPD, IVH, and necrotizing enterocolitis; and duration of hospital stay.

Kirpalani 2013 enrolled 1009 preterm infants (< 1000 grams and < 30 weeks). Researchers provided NIPPV by ventilator or bilevel device. Synchronization was allowed but was not mandatory. The primary outcome was death or moderate to severe BPD at 36 weeks. Among studied infants, 185 received noninvasive respiratory support from birth and were randomized in their first 24 hours (95 infants received NIPPV; 90 received NCPAP). We obtained data from study authors about these 185 infants for inclusion in this review.

Sai Sunil Kishore 2009 enrolled 76 infants (28 to 34 weeks' gestational age) with RDS in an RCT. Investigators randomized 37 infants to NIPPV and 39 NCPAP alone. They provided nasal respiratory support for infants by using VI P Bird-R Sterling (Viasys Health Care, Conshohocken, PA, USA) and Drager Babylog 8000 (Drager Medical Inc, Lubeck, Germany) ventilators. NIPPV was nonsynchronized. Primary outcomes measured were failure of noninvasive respiratory support and need for intubation within the first 48 hours of randomization. Secondary outcomes included failure of nasal respiratory support within the first seven days, duration of respiratory support, duration of oxygen, duration of hospitalization, time to full feeds, air leaks, septicemia, upper airway injury, feed intolerance, abdominal distention, and bowel perforation.

Kugelman 2007 performed an RCT of 84 infants (24 to 34 weeks' gestational age) with RDS. Study authors randomized 41 infants to NCPAP alone and 43 to NIPPV. They administered both modes of respiratory support using the SLE 2000 (SLE Ltd, Surrey, UK) via nasal prongs and synchronized NIPPV with spontaneous breathing and with the infants' breathing. The primary outcome measured was need for mechanical ventilation, and secondary outcomes included blood pressure, heart rate, respiratory rate, blood gases, time needed to stop respiratory support, incidence of IVH, incidence of BPD, time to full feeds, and length of hospital stay.

Lista 2009 conducted an RCT of 40 infants (28 to 34 weeks' gestational age) with RDS diagnosed in the first hour of life. Researchers randomized 20 infants to NIPPV and 20 to NCPAP. They administered both treatments using Infant Flow (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) devices, and they synchronized NIPPV. The primary outcome measured was cytokine levels, and secondary outcomes included heart rate, blood pressure, oxygen saturation, blood gas levels, length of ventilation, incidence of PDA, treatment with ibuprofen, treatment with surfactant, pneumothorax, IVH, and oxygen dependency at 28 days (or at 36 weeks' gestational age).

Meneses 2011 enrolled 200 infants (26 to 33 and 6/7 weeks' gestational age) with RDS in an RCT. Investigators randomized 100 infants to NIPPV and an equal number to NCPAP alone. They performed nasal respiratory support of infants using the InterMed continuous-flow and bubble CPAP systems (InterMed Inc, São Paulo, Brazil) via binasal prongs. NIPPV was nonsynchronized. The primary outcome measured was need for intubation in the first 72 hours of life. Secondary outcomes included total duration of ETT ventilation, total duration on NCPAP, total duration on supplemental oxygen, pneumothorax, BPD, PDA, necrotizing enterocolitis, IVH (grade III/IV), retinopathy of prematurity (ROP) (≥ stage 3), time to full feeds, and length of hospital stay.

Ramanathan 2012 performed a randomized controlled multicenter trial. Within 120 minutes of delivery, they enrolled 110 infants born between 26 + 0 and 29 + 6 weeks who required intubation for respiratory distress. They randomized infants at the time they received surfactant to NIPPV, nonsynchronized, via a ventilator or a bilevel device, or to NCPAP (bubble CPAP, synchronized inspiratory positive airway pressure (SiPAP), or ventilator). The primary outcome was the need for mechanical ventilation at seven days. Secondary outcomes included number of doses of surfactant, days on a ventilator, days on CPAP, days on oxygen, mortality, air leak, pulmonary hemorrhage, PDA, IVH grade III/IV, spontaneous intestinal perforation, ROP stage 3 or higher, length of stay, and CLD.

Salama 2015 performed a quasi-randomized trial that enrolled 60 infants (28 to 34 weeks with RDS). The population was mixed at randomization: Some infants had received prophylactic surfactant (those < 29 weeks) and others had not. Researchers randomized 30 infants to NIPPV, provided by a Neoport E100M ventilator (DRE Medical, Louisville, KY, USA) in the synchronized mode, and 30 infants to NCPAP (bubble CPAP). Randomization was based on admission numbers. The primary outcome was failure of noninvasive respiratory support with defined criteria. Secondary outcomes included duration of mechanical ventilation, nasal injury, abdominal distention, gastrointestinal perforation, pneumothorax, CLD, sepsis, and IVH.

Wood 2013 (abstract) performed a two-center RCT that enrolled 120 infants at 28 + 0 to 31 + 6 weeks and less than 6 hours of life with respiratory distress. Infants did not receive surfactant before randomization. Study authors provided NIPPV (n = 60) using a SiPAP in the synchronized mode (Trigger); the control group received CPAP (n = 60) without additional settings. The primary outcome was failure of noninvasive support.

Excluded studies

See Characteristics of excluded studies.

Studies that evaluated infants with apnea included Gizzi 2015, Lin 1998, Lin 2011, Pantalitschka 2009, and Ryan 1989.

Studies that evaluated infants after extubation included Barrington 2001, Friedlich 1999, Gao 2010, Jasani 2016, Kahramaner 2014, Khalaf 2001, Khorana 2008, Moretti 2008, and O'Brien 2012.

Studies that were not RCTs (or quasi-randomized trials) included Aghai 2006, Herber-Jonat 2006, Liu 2003, Manzar 2004, and Migliori 2005.

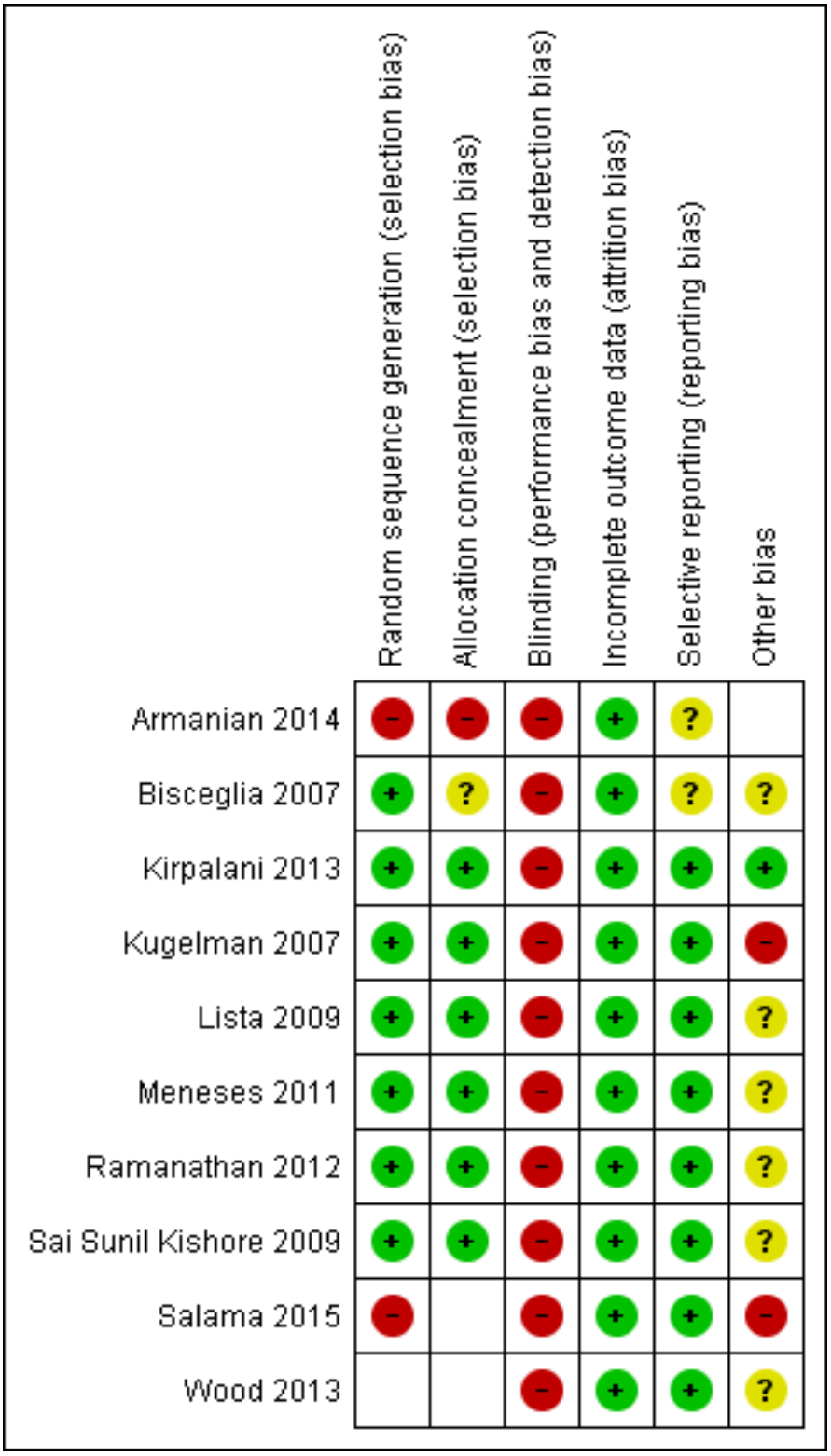
Other studies included Bhandari 2007 (compared synchronized NIPPV vs mechanical ventilation), Baneshi 2014 (no report on primary outcome), Chen 2015 (enrolled twins only), Kugelman 2014a (compared high-flow nasal cannula vs NIPPV), Salvo 2015 (compared two methods of providing NIPPV), Santin 2004 (compared NIPPV vs conventional ventilation), Shi 2010 (included term infants), Shi 2014 (included term infants), and Zhou 2015 (examined DuoPAP (Hamilton Medical, Bonaduz, Switzerland)).

Ongoing studies and studies awaiting classification included Chen 2013, Fu 2014, Gao 2014, Sasi 2013, and Silveira 2015.

Risk of bias in included studies

We assessed methodological quality using the criteria of the Cochrane Neonatal Review Group. See risk of bias descriptions in the Characteristics of included studies table and Figure 2 for details.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** NIPPV versus NCPAP (by population)

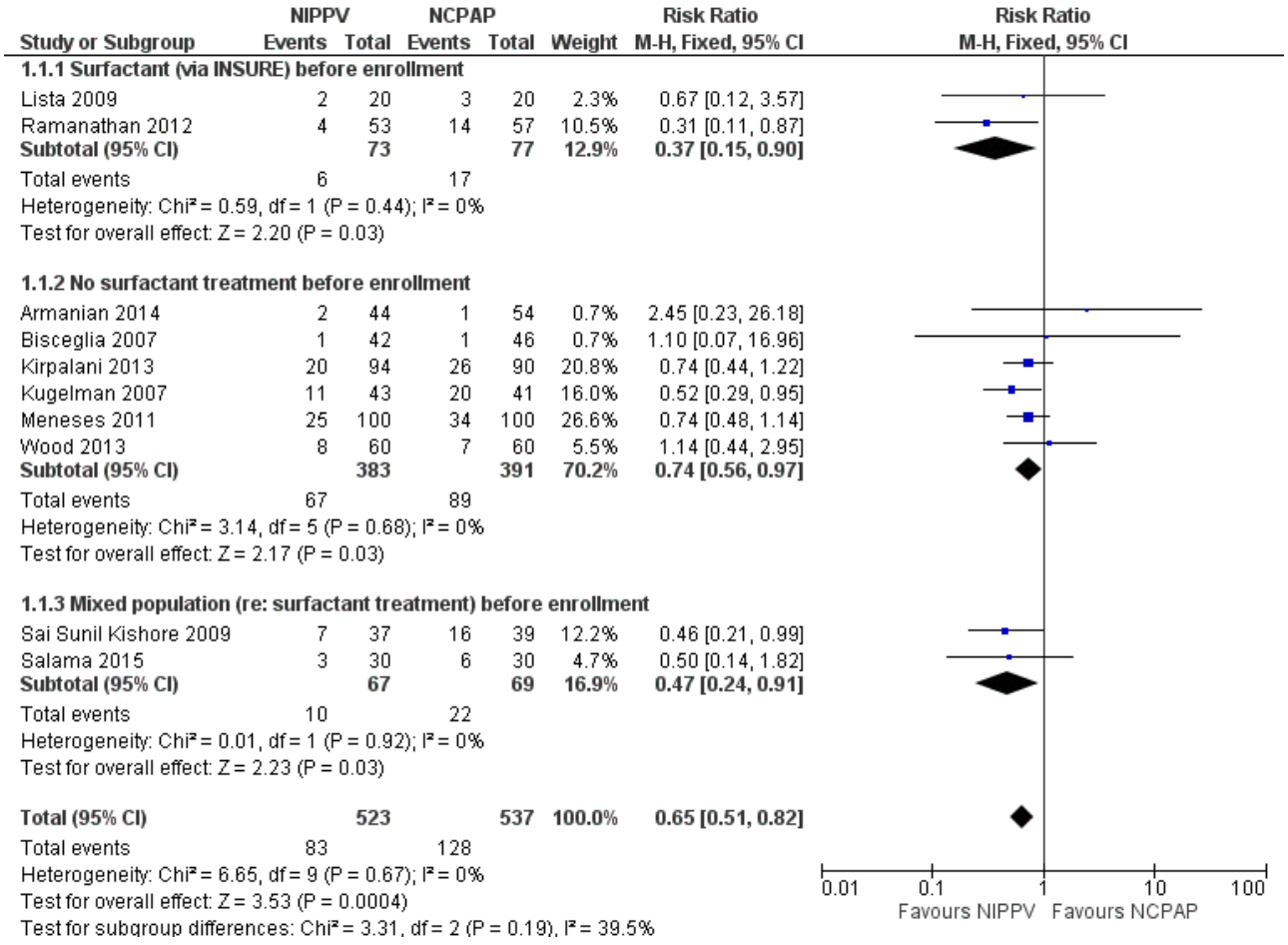
NIPPV versus NCPAP (by population) (Comparison 1)

PRIMARY OUTCOME

Respiratory failure: defined by respiratory acidosis, increased oxygen requirement, or apnea that was frequent or severe, leading to additional ventilatory support during the first week of life (Outcome 1.1)

Overall, included trials enrolled 1061 preterm infants. Three of the 10 trials (Ramanathan 2012; Kugelman 2007; Sai Sunil Kishore 2009 showed statistically significant benefit for infants initially treated with NIPPV in terms of respiratory failure in the first week of life. Meta-analysis showed that the effect was clinically important (typical risk ratio (RR) 0.65, 95% confidence interval (CI) 0.51 to 0.82; typical risk difference (RD) -0.09, 95% CI -0.13 to -0.04), with 11 infants (95% CI 8 to 25) needing to be treated with NIPPV to prevent one respiratory failure. We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.1; Figure 3). Heterogeneity was low (for all outcomes).

Figure 3. Forest plot of comparison: 1 NIPPV vs NCPAP (by population), outcome: 1.1 Respiratory failure.

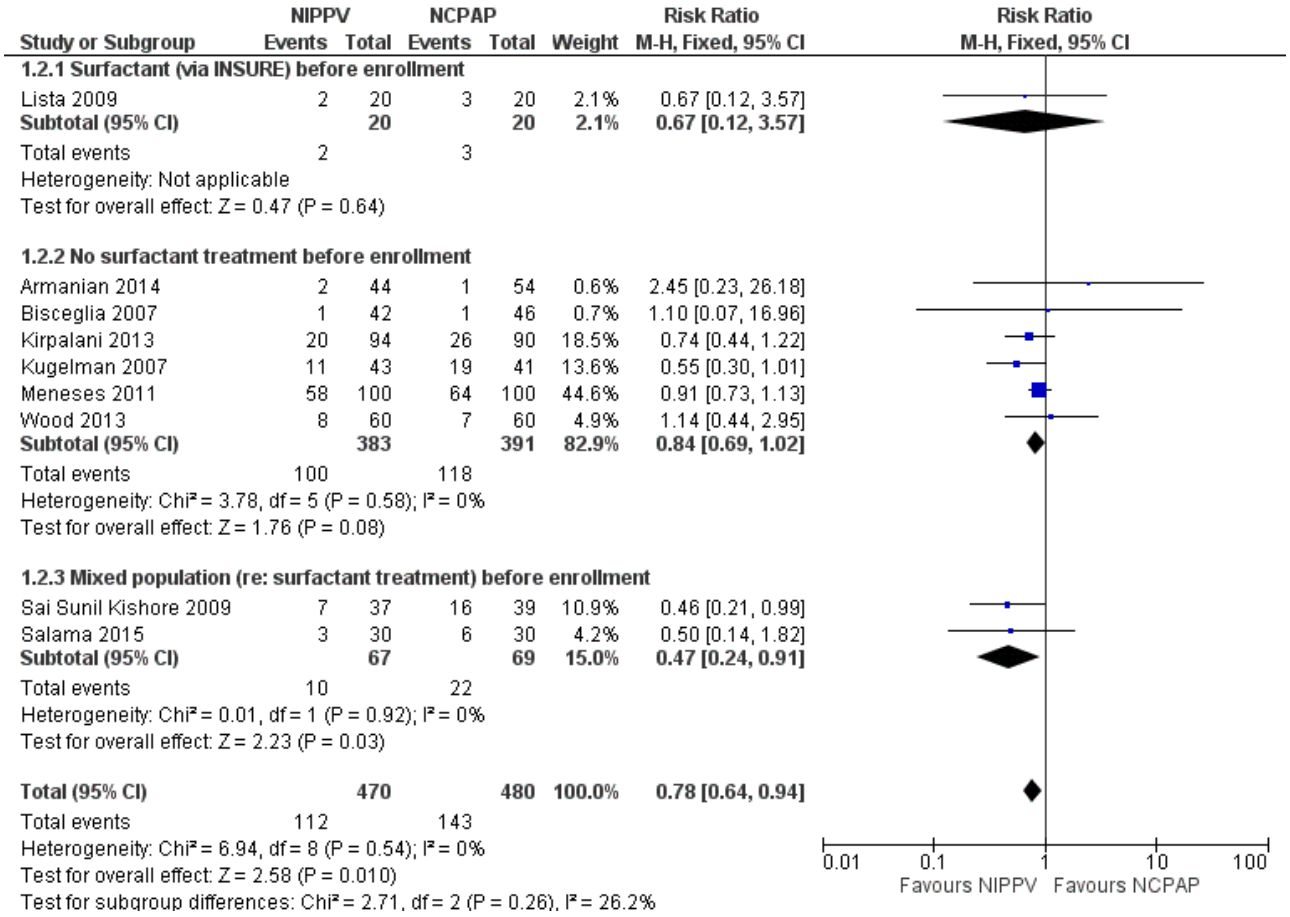


Two studies (Lista 2009; Ramanathan 2012) included infants who received surfactant before randomization via INSURE. Six studies (Armanian 2014; Bisceglia 2007; Kirpalani 2013; Kugelman 2007; Meneses 2011; Wood 2013) included infants who did not receive surfactant, and two studies (Sai Sunil Kishore 2009; Salama 2015) included a mixed population of infants. The effect on respiratory failure was statistically significant in the three populations of infants studied.

Need for endotracheal tube ventilation (Outcome 1.2)

Nine trials reported on this outcome (n = 950), which could not be ascertained in one trial (Ramanathan 2012). Meta-analysis showed statistically significant benefit for infants initially treated with NIPPV (typical RR 0.78, 95% CI 0.64 to 0.94; typical RD -0.07, 95% CI -0.12 to -0.02), with 17 infants (95% CI 8 to 50) needing to be treated with NIPPV to prevent one respiratory failure. We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.2; Figure 4).

Figure 4. Forest plot of comparison: 1 NIPPV vs NCPAP (by population), outcome: 1.2 Need for intubation.

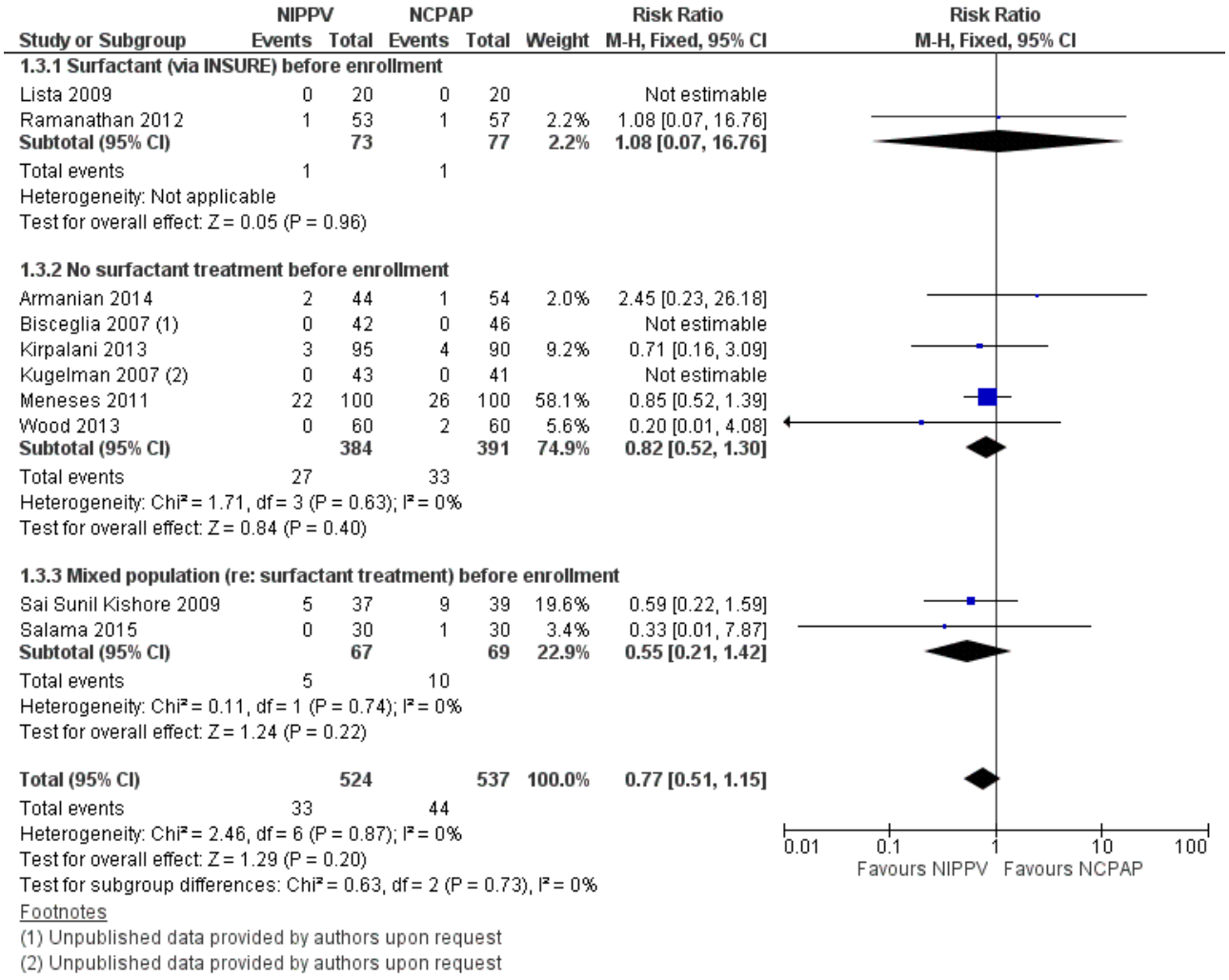


SECONDARY OUTCOMES

Mortality during study period (Outcome 1.3)

All trials reported this outcome. Overall, investigators noted no statistically significant reduction in mortality during neonatal intensive care unit (NICU) admission (typical RR 0.77, 95% CI 0.51 to 1.15). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.3; Figure 5).

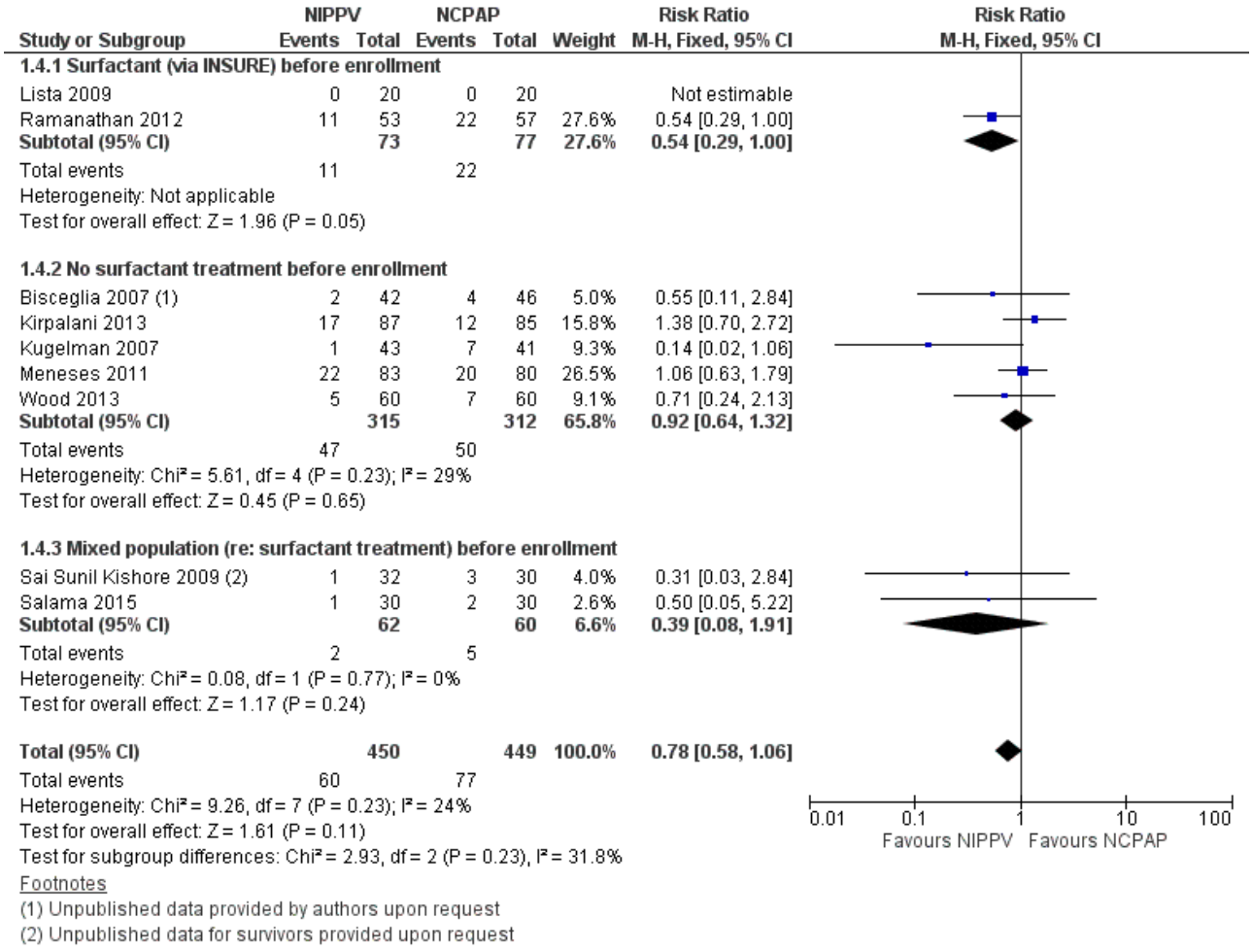
Figure 5. Forest plot of comparison: 1 NIPPV vs NCPAP (by population), outcome: 1.3 Mortality during study period.



Chronic lung disease (need for oxygen at 36 weeks in surviving infants) (Outcome 1.4)

All trials except Armanian 2014 reported oxygen need at 36 weeks' corrected gestational age (CLD). Only one trial (Ramanathan 2012), in which infants received surfactant before randomization, reported a decrease in CLD. Meta-analysis did not show a reduction in CLD (typical RR 0.78, 95% CI 0.58 to 1.06). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.4; Figure 6).

Figure 6. Forest plot of comparison: 1 NIPPV vs NCPAP (by population), outcome: 1.4 Chronic lung disease.



Pneumothorax (Outcome 1.5)

All 10 trials reported this outcome. Regardless of the population (surfactant or not before randomization), results showed no difference in the incidence of pneumothorax between infants randomized to NIPPV and those randomized to NCPAP (typical RR 0.79, 95% CI 0.42 to 1.48). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.5).

Intraventricular hemorrhage, all grades (Outcome 1.6)

Five trials (Armanian 2014; Bisceglia 2007; Kugelman 2007; Lista 2009; Salama 2015) reported on this outcome. Sai Sunil Kishore 2009 reported a combined outcome of IVH and periventricular leukomalacia. No trial showed a difference in IVH between treatment groups (typical RR 0.79, 95% CI 0.54 to 1.16; typical RD -0.05, 95% CI -0.13 to 0.03). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.6).

Severe intraventricular hemorrhage, grade III/IV (Outcome 1.7)

Only four trials (n = 430) (Bisceglia 2007 (study authors provided on request); Kugelman 2007; Meneses 2011; Ramanathan 2012) reported on this outcome. No trial showed a reduction in IVH in one treatment group compared with the other (typical RR 1.26, 95% CI 0.53 to 3.01; typical RD 0.01, 95% CI -0.03 to 0.05). We graded evidence for this outcome as low quality (unblinded intervention and wide CI) (Analysis 1.7).

Necrotizing enterocolitis ≥ Bell's stage 2 (Outcome 1.8)

Seven trials (Bisceglia 2007; Sai Sunil Kishore 2009; Kugelman 2007; Lista 2009; Meneses 2011; Ramanathan 2012; Wood 2013) reported on this outcome. No trial showed a reduction in necrotizing enterocolitis stage 2 or greater in one treatment group compared with the other (typical RR 0.67, 95% CI 0.34 to 1.31; typical RD -0.02, 95% CI -0.05 to 0.01). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.8).

Sepsis (Outcome 1.9)

Only two studies (Sai Sunil Kishore 2009; Salama 2015) (n = 136) reported on this outcome. Results of meta-analysis showed no difference between groups (typical RR 0.78, 95% CI 0.36 to 1.70; typical RD -0.04, 95% CI -0.16 to 0.08). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.9).

Retinopathy of prematurity (≥ stage 3) (Outcome 1.10)

Only two studies (Meneses 2011; Ramanathan 2012) (n = 245) reported on this outcome. Meta-analysis showed no difference between groups (typical RR 1.50, 95% CI 0.65 to 3.44; typical RD

0.03, 95% CI -0.04 to 0.10). We graded evidence for this outcome as moderate quality (unblinded intervention) (Analysis 1.10).

Duration of endotracheal tube intubation

Three studies reported on this outcome; all included infants who did not receive surfactant before randomization. Duration of intubation and mechanical ventilation varied significantly between trials, with one trial reporting mean duration of seven to 12 hours (Bisceglia 2007) and the other two trials reporting mean duration between 10 and 13 days (Kugelman 2007; Meneses 2011). This heterogeneity precludes a meaningful meta-analysis. Overall, no trial reported a clinically significant reduction in time required for mechanical ventilation in infants who received NIPPV. We graded evidence for this outcome as low quality (unblinded intervention and inconsistency).

Duration of oxygen dependence

Four studies reported this outcome (Sai Sunil Kishore 2009; Lista 2009; Meneses 2011; Ramanathan 2012) for 412 participants. These studies showed a high degree of heterogeneity, precluding meaningful meta-analysis. Only one study (Ramanathan 2012), in which all infants received surfactant before randomization, demonstrated a reduction in the number of days on oxygen among infants who received NIPPV (29 days vs 38 days). We graded evidence for this outcome as low quaity (unblinded intervention and inconsistency).

Duration of hospital stay

Five trials (Armanian 2014; Sai Sunil Kishore 2009 Kugelman 2007; Meneses 2011; Ramanathan 2012) reported this outcome (n = 554). Hospital stay ranged between 21 and 71 days with a high degree of heterogeneity between studies; therefore, we did not perform a meta-analysis. Only one study (Armanian 2014) demonstrated a reduction in duration of stay (22 days in the NIPPV group vs 29 days in the CPAP group). We graded evidence for this outcome as low quality (unblinded intervention and inconsistency).

Upper airway injury (Outcome 1.11)

Sai Sunil Kishore 2009 reported two infants in each group with local upper airway injury. Study authors did not specify the nature of the injury and did not state whether it was nasal septal injury. Salama 2015 reported 20 cases of nasal injury in the NCPAP group (out of 30 infants) and none in the NIPPV group, without further description. We graded evidence for this outcome as low quality (unblinded intervention and imprecision) (Analysis 1.11).

NIPPV versus NCPAP (by device) (Comparison 2)

Six trials used NIPPV delivered via ventilator (Bisceglia 2007; Sai Sunil Kishore 2009; Kugelman 2007; Meneses 2011; Armanian 2014; Salama 2015), two used bilevel devices (Lista 2009; Wood 2013), and two used both ventilator-driven and bilevel devices (Kirpalani 2013; Ramanathan 2012). Two of the six trials using a ventilator to generate NIPPV showed benefit of NIPPV in preventing respiratory failure post extubation. Meta-analysis of these six trials showed a reduction in rate of respiratory failure in the NIPPV group (typical RR 0.63, 95% CI 0.47 to 0.86) (Analysis 2.1). Results showed no evidence of benefit in the two trials using bilevel devices. One trial using both ventilators and bilevel devices (Ramanathan 2012) showed a reduction in respiratory failure at seven days (typical RR 0.31, 95% CI 0.11 to 0.87). Study authors provided no information on the relative proportion of infants who received NIPPV via ventilator or bilevel device (Analysis 2.1). Infants who received NIPPV via ventilator were intubated less often than those who received CPAP (typical RR 0.77, 95% CI 0.63 to 0.95; typical RD -0.08, 95% CI -0.14 to -0.02; number needed to treat for an additional beneficial outcome (NNTB) 13 (95% CI 7 to 50)) (Analysis 2.2).

When review authors examined CLD by device delivering NIPPV, we observed no reduction in CLD in any of the subgroups (Analysis 2.4). One trial using mixed devices showed a possible reduction in CLD in the NIPPV group, with the confidence interval including 1.0 (typical RR 0.54, 95% CI 0.29 to 1.0). We noted no difference in the rate of pneumothoraces between groups (Analysis 2.5) and no difference in mortality or severe IVH within subgroups (Analysis 2.3; Analysis 2.6).

Synchronized versus nonsynchronized NIPPV (Comparison 3)

Four studies used synchronized NIPPV (Kugelman 2007; Lista 2009; Salama 2015; Wood 2013), and five did not (Armanian 2014; Bisceglia 2007; Sai Sunil Kishore 2009; Meneses 2011; Ramanathan 2012). One study allowed both methods (Kirpalani 2013). Nonsynchronized studies (n = 572) showed overall benefit in reducing respiratory failure (typical RR 0.60, 95% CI 0.44 to 0.83), and synchronized studies (n = 304) did not demonstrate benefit (typical RR 0.65, 95% CI 0.41 to 1.02) (Analysis 3.1). Findings were similar when we examined the need for intubation: Nonsynchronized studies showed benefit (typical RR 0.74, 95% CI 0.60 to 0.92), and synchronized studies showed a trend toward benefit (typical RR 0.67, 95% CI 0.42 to 1.06) (Analysis 3.2). However, the subgroup difference was not statistically significant.

We noted no difference in mortality within subgroups (Analysis 3.3). When we examined CLD by synchronization, we found that no method showed statistically significant benefit (Analysis 3.4). We observed no difference in the rate of pneumothoraces between groups (Analysis 3.5). No study using synchronized NIPPV reported on severe IVH (Analysis 3.6).

Post hoc analysis

NIPPV versus NCPAP: high-quality studies (by device) (Comparison 4)

Respiratory failure: high-quality studies only (by device) (Outcome 4.1)

Overall, meta-analysis of 10 studies enrolling 1061 infants revealed a clinically important reduction in respiratory failure (defined by respiratory acidosis, increased oxygen requirement, or apnea that was frequent or severe, leading to additional ventilatory support during the first week of life) (typical RR 0.65, 95% CI 0.51 to 0.82; typical RD -0.09, 95% CI -0.13 to -0.04), with 11 infants (95% CI 8 to 25) needing to be treated with NIPPV to prevent one respiratory failure. We graded evidence for this outcome as moderate quality (unblinded intervention).

Owing to methodological limitations (risk of selection bias) in two studies (Armanian 2014; Salama 2015), we performed a post hoc analysis for the outcome respiratory failure post extubation, including only higher-quality studies in the analysis (Analysis 4.1). Results were largely unchanged (typical RR 0.64, 95% CI 0.50 to 0.82; typical RD -0.10, 95% CI -0.15 to -0.04).

DISCUSSION

The meta-analysis performed in this review showed a strong effect of nasal intermittent positive pressure ventilation (NIPPV) on prevention of respiratory failure or need for intubation the first few days after birth in infants with respiratory distress. Results showed no reduction in risk of chronic lung disease (CLD) overall but revealed a reduction in one trial, in which infants received surfactant before randomization. We identified no other short-term benefit and no harm in any trials. Most included studies were small, single-center trials. Eight of the 10 trials identified in this review had no major methodological limitations. Two trials were quasi-randomized and had potential selection bias (Armanian 2014; Salama 2015), and one was reported as an abstract with clearly presented data (Wood 2013). Because of the nature of the interventions, it has been impossible to blind caregivers, and bias may have arisen through uneven use of co-interventions. Investigators dealt with potential confounders, such as methylxanthine usage and indications for intubation, by having management protocols in place and by using objective respiratory failure criteria, enhancing confidence in study findings.

Because of the promising results of another related systematic review on NIPPV versus nasal continuous positive airway pressure (NCPAP) to aid with extubation (Lemyre 2014), it is reasonable to conclude that NIPPV might be more effective than NCPAP alone in providing respiratory support to preterm infants and in preventing the need for intubation. Results may have revealed differences in the effectiveness of different devices used to provide NIPPV (ventilator and bilevel); however, additional studies are needed to delineate this. We could not determine benefits for a subgroup of (smaller and more immature) infants included in this review. However, researchers should further assess benefits as well as relatively uncommon risks such as pneumothorax and severe intraventricular hemorrhage because occasionally large trials can disagree with the results of meta-analysis of smaller trials (Cappelleri 1996; Villar 1995).

AUTHORS' CONCLUSIONS

Implications for practice

Early NIPPV does appear to be superior to NCPAP alone for the treatment of preterm infants with respiratory distress syndrome (RDS) in decreasing respiratory failure and the need for intubation and endotracheal tube ventilation. Additional studies are needed to confirm these results and to assess the safety of NIPPV compared with NCPAP alone in a larger patient population.

Implications for research

Future research should assess the efficacy and safety of early NIPPV compared with NCPAP for treatment of preterm infants with RDS, with specific focus on devices used and on synchronization. Clinically relevant outcomes, such as long-term survival and incidence of neurodevelopmental impairment, are important to explore.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Armanian 2014

Methods	Study design: single-center RCT
	Setting: tertiary NICU
	Duration: March 2013 to January 2014

Armanian 2014 *(Continued)*

Participants	Infants with birth weight ≤ 1500 grams and/or gestational age ≤ 34 weeks with respiratory distress, including x-ray diagnosis. Infants with major congenital anomalies, asphyxia, cyanotic heart defects, cardiovascular instability, and orofacial anomalies were excluded.
Interventions	NIPPV was provided by a ventilator (exact ventilator not specified) and short binasal prongs. Settings: rate 40-50, PIP 16-20 cmH_2O, PEEP 5-6 cmH_2O; nonsynchronized CPAP was provided via bubble CPAP, 5-6 cmH_2O.
Outcomes	Primary outcomes: need for intubation due to respiratory failure (defined) within 48 hours of life, duration of noninvasive respiratory support Secondary outcomes: need for INSURE, oxygen days, chronic lung disease, length of hospital stay, air leaks
Notes	IRCT2014021410026N4; quasi-randomized trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Assigned by "file" number
Allocation concealment (selection bias)	High risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Intervention cannot be blinded. All outcomes with the exception of long-term follow-up would be potentially biased.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/98 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Stated secondary outcome of need for INSURE surfactant treatment; chronic lung disease not reported

Bisceglia 2007

Methods	Study design: prospective randomized controlled trial Setting: single-center trial at San Giovanni Di Dio Hospital in Italy Duration of study: January 2001-January 2004
Participants	Inclusion criteria: infants between 24 and 37 weeks' gestational age with mild to moderate RDS, defined as the need for FiO_2 < 0.4 to keep oxygen saturation between 90% and 96%, as well as a chest x-ray positive for early hyaline membrane disease Exlusion criteria: pneumothorax, pneumomediastinum, surgical or cardiac disease, intraventricular hemorrhage, major congenital abnormalities Infants were not treated with aminophylline or caffeine. Number randomized: 88 infants total (46 males, 42 females)

Bisceglia 2007 *(Continued)*

Interventions	Both interventions were performed with use of the Bear Infant Ventilator CUB 750 (Ackrad Laboratories, Cranford, NJ, USA) via silicone binasal prongs (Ginevri, Rome, Italy). NCPAP (n = 46) was administered at 4-6 cmH_2O. NIPPV (n = 42) was administered with PIP 14-20 cmH_2O at 40 breaths per minute and end expiratory pressure 4-6 cmH_2O. NIPPV was nonsynchronized.
Outcomes	Primary outcome: number of infants in each group who needed endotracheal intubation (i.e. failure of nasal ventilatory support) Secondary outcomes: total duration of respiratory support, number of apneic episodes, variation in blood O_2 and CO_2 partial pressures (evaluated at 4 hours after study enrollment)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors used EPISTAT, an online statistical program, to generate the sequence of interventions.
Allocation concealment (selection bias)	Unclear risk	Investigators concealed the sequence from practitioners before each participant assignment (information obtained upon personal correspondence with study authors). It is unclear, however, which method of concealment was used.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was impossible owing to the nature of the interventions used.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	Unclear from information provided
Other bias	Unclear risk	Unclear from information provided

Kirpalani 2013

Methods	Randomized controlled multicenter trial
Participants	Infants with birth weight less than 1000 grams and gestational age less than 30 weeks were assigned to 1 of 2 forms of noninvasive respiratory support - nasal intermittent positive pressure ventilation (IPPV) or nasal continuous positive airway pressure (CPAP) - at the time of first use of noninvasive respiratory support during the first 28 days of life.
Interventions	NIPPV (ventilator or bilevel, synchronized or not) vs NCPAP
Outcomes	Death or BPD at 36 weeks, air leaks and necrotizing enterocolitis, duration of respiratory support, time to full feedings
Notes	Obtained data from study authors regarding infants enrolled in the study and randomized within first 24 hours who were never on intubated respiratory support and never received surfactant (before randomization)

Kirpalani 2013 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded outcomes. BPD status determined by oxygen reduction test
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Kugelman 2007

Methods	Study design: randomized controlled prospective clinical trial Setting: single-center study at Bnai Zion Medical Center in Israel Duration of study: September 2004-April 2006
Participants	Inclusion criteria: infants between 24 and 34 6/7 weeks' gestational age with RDS, which study authors defined as clinical features such as tachypnea, grunting, nostril flaring, and retractions, as well as a positive chest x-ray Exclusion criteria: cardiac disease, congenital malformation, sepsis, anemia, severe IVH, refusal of consent, ventilatory unavailability Number randomized: 84 infants total (53 males, 31 females)
Interventions	Both modes of respiratory support were administered via nasal prongs (INCA, Ackrad Laboratories, Berlin, Germany) by the SLE 2000 Ventilator (Specialized Laboratory Equipment, Croydon, UK). NCPAP (n = 41) was administered at 6-7 cmH_2O, and NIPPV (n = 43) was given with PIP 14-22 cmH_2O (adjusted according to chest excursion and birth weight), positive end expiratory pressure 6-7 cmH_2O, and 12-30 breaths per minute. FiO_2 was adjusted to keep oxygen saturation (measured by pulse oximetry) between 88% and 92%. NIPPV was synchronized.
Outcomes	Primary outcome: failure of nasal respiratory support (i.e. need for endotracheal intubation). Criteria for failure: worsened RDS in conjunction with at least 1 of the following: pH < 7.2, PCO_2 > 60 mmHg, PO_2 < 50 mmHg, arterial oxygen saturation SpO_2 < 88% on FiO_2 > 50%, recurrent significant apnea needing stimulation or bag and mask ventilation Secondary outcomes: blood pressure, heart rate, respiratory rate, pulse oximetry saturation, respiratory status before mechanical ventilation, time to stop nasal support (stopped if FiO_2 < 30% and no clinical signs of respiratory distress), incidence of IVH, duration of mechanical ventilation, incidence of BPD, time until full feeds, and length of hospital stay

Kugelman 2007 *(Continued)*

Notes	Two infants were switched from NCPAP to NIPPV treatment group after randomization. Upon request, study authors provided raw data for outcomes of need for intubation and chronic lung disease for performance of a sensitivity analysis excluding those 2 infants. Results remained significant upon sensitivity analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study authors stated that they generated a random sequence order and performed block randomization to provide similar numbers of infants in each treatment group for the subgroup of birth weights above and below 1500 grams.
Allocation concealment (selection bias)	Low risk	Study authors placed individual cards with sequence designations in sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was impossible owing to the nature of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes listed in the protocol were published in this manuscript or in a subsequent manuscript in the journal *Acta Paediatrica*.
Other bias	High risk	Two infants were switched from NCPAP to NIPPV in violation of the study protocol.

Lista 2009

Methods	Study design: randomized controlled prospective clinical trial Setting: single-center study in Milan, Italy Duration of study: 2007-2008
Participants	Inclusion criteria: infants from 28-34 weeks' gestational age with moderate RDS, defined in the first hour of life as PO_2 ratio of 0.3-0.35 and signs on chest x-ray Exclusion criteria: infants with lethal congenital anomalies, infants requiring muscle relaxants, severe intraventricular hemorrhage, chorioamnionitis, sepsis, or suspected infection Number randomized: 40 infants total (gender not reported)
Interventions	Interventions were performed with the Infant Flow CPAP and Infant Flow SiPAP ventilators (Viasys Health Care, Conshohocken, PA, USA) via binasal prongs. NCPAP (n = 20) was administered at 6 cmH_2O, and NIPPV (n = 20) at a lower CPAP level of 4.5 cmH_2O and an upper CPAP level of 8 cmH_2O with an initial rate of 30 breaths per minute. NIPPV was synchronized.
Outcomes	Primary outcome: cytokine levels (IL-6, IL-8, and TNF-alpha) Secondary outcomes: heart rate, systemic blood pressure, oxygen saturation, arterial blood gases, length of ventilation (total duration of respiratory support), PDA, need for treatment with ibuprofen or

Lista 2009 *(Continued)*

	surfactant, incidence of air leaks, severe IVH, oxygen dependency at day 28 and/or at 36 weeks' post-conceptional age, survival
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers with stratified randomization for gestational age
Allocation concealment (selection bias)	Low risk	Random number (representing allocation) was disclosed during phone call after enrollment in the trial.
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was impossible owing to the nature of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors reported no incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the published article corresponded with outcomes listed in the original protocol. Information provided by study authors
Other bias	Unclear risk	Unclear from the information provided

Meneses 2011

Methods	Study design: randomized controlled prospective clinical trial Setting: single-center study in Brazil Duration of study: 2007-2009
Participants	Inclusion criteria: infants from 26-33 and 6/7 weeks' gestational age with clinical evidence of RDS Exclusion criteria: infants with major congenital anomalies, cardiovascular instability, intubation at admission to NICU, refusal of consent, or unavailability of ventilator Number randomized: 200 infants total (100 males, 100 females)
Interventions	Interventions were performed with the continuous-flow neonatal ventilator and Bubble CPAP systems (InterMed Inc, São Paulo, Brazil) via binasal prongs. NCPAP (n = 100) was administered at 5-6 cmH_2O, and NIPPV (n = 100) was administered at PEEP 4-6 cmH_2O and PIP 15-20 cmH_2O with initial flow rate of 8-10 L/min and rate of 20-30 breaths/min. NIPPV was nonsynchronized.
Outcomes	Primary outcome: need for intubation in the first 72 hours of life Secondary outcomes: total duration of ETT ventilation, total duration on NCPAP, total duration on supplemental oxygen, pneumothorax, BPD, PDA, necrotizing enterocolitis, IVH (grade III/IV), ROP (≥ stage 3), time to full feeds, length of hospital stay
Notes	

Meneses 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number computer-generated protocol
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes containing intervention assignments
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding was impossible owing to the nature of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors reported no incomplete outcome data.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes originally listed on ClinicalTrials.gov were the same as those reported in the published study.
Other bias	Unclear risk	Unclear from information provided

Ramanathan 2012

Methods	Study design: multicenter randomized controlled trial Setting: 2 tertiary NICUs Duration of study: October 2006-November 2008
Participants	Infants 26 + 0 to 29 + 6 weeks' gestation, intubated for respiratory distress soon after birth. Planned INSURE procedure with Curosurf and early extubation. Excluded infants at greater than 120 minutes of life, < 600 grams, those not requiring intubation and surfactant within 60 minutes of life, with Apgar of 0 at 1 minute, outborn infants and those with major congenital malformations
Interventions	NIPPV delivered via ventilator or bilevel device, by nasal prongs or nasopharyngeal prongs. Nonsynchronized mode. Settings: PIP 10-15 cmH_2O above PEEP, PEEP 5 cmH_2O, Ti 0.5 seconds, rate 30-40. NCPAP delivered via short binasal prongs, bubble CPAP, SiPAP or ventilator, PEEP of 5-8 cmH_2O
Outcomes	Need for mechanical ventilation at 7 days (primary outcome). Secondary outcomes: number of doses of surfactant, days on ventilator, days on CPAP, days on oxygen, mortality, air leaks, pulmonary hemorrhage, PDA, IVH grade 3 or worse, spontaneous intestinal perforation, ROP stage 3 or worse, length of stay, use of postnatal steroids, BPD
Notes	Infants randomized to NIPPV were extubated earlier than those randomized to NCPAP (randomization occurred after surfactant was received).

Risk of bias

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

Ramanathan 2012 *(Continued)*

Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Timing of extubation different between 2 study groups (earlier in NIPPV group)

Sai Sunil Kishore 2009

Methods	Study design: randomized controlled prospective trial Setting: single-center study at a tertiary care neonatal unit in Northern India Duration of study: January 2007-April 2008
Participants	Inclusion criteria: infants between 28 and 34 weeks' gestational age, weighting ≥ 750 grams, with Downe's score ≥ 4, and showing signs of RDS (defined as 2 or more of the following: respiratory rate > 60 breaths/min, retractions, or grunting) within 6 hours of birth Exclusion criteria: major malformations, upper airway anomalies, severe cardiovascular instability or poor respiratory efforts, ventilator unavailability, or refusal of parental consent Number randomized: 76 infants total (50 males, 26 females)
Interventions	Interventions were performed with the VIP Bird-R Sterling (Viasys Health Care, Conshohocken, PA, USA) or the Drager Babylog 8000 (Drager Medical Inc, Lubeck, Germany). NCPAP (n = 39) was administered at 5 cmH_2O with flow set at 6-7 litres/min. NIPPV (n = 37) was administered at about 50 breaths per minute, with PIP 15-16 cmH_2O, PEEP 5 cmH_2O. Settings in both groups were adjusted on the basis of arterial blood gases and clinical parameters. Maximum permissible settings were CPAP 7 cmH_2O and FiO_2 0.7. NIPPV was nonsynchronized.
Outcomes	Primary outcome: failure of noninvasive respiratory support within first 48 hours of randomization. Criteria for failure included at least 1 of the following: $PaCO_2$ ≥ 60 mmHg with pH < 7.2, more than 2 apneic episodes per hour, any episode of apnea that did not respond to tactile stimulation and needed bag and mask ventilation, episodes of desaturation (SpO_2 ≤ 85%) ≥ 3 per hour, or not responding to maximum settings for the allocated intervention. Secondary outcomes: failure of nasal respiratory support within first 7 days, duration of respiratory support, duration of oxygen, duration of hospitalization, time to full spoon feeds, air leaks, any grade IVH or periventricular leukomalacia (PVL), BPD, septicemia, upper airway injury, feed intolerance, abdominal distention, and bowel perforation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Sai Sunil Kishore 2009 *(Continued)*

Random sequence generation (selection bias)	Low risk	A study author not involved in recruitment generated a random sequence order using the online program www.randomizer.org.
Allocation concealment (selection bias)	Low risk	Treatment designations were placed in sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	A separate study author assessed outcomes, but blinding was impossible owing to the nature of the interventions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete data were noted.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported in the published article corresponded with outcomes listed in the original protocol. Information was provided by study authors.
Other bias	Unclear risk	Unclear from information provided

Salama 2015

Methods	Study design: quasi-randomised controlled trial Setting: single-center NICU in Jordania Duration of study: January 2011 to December 2011
Participants	Preterm infants born at gestational age 28-34 weeks with RDS, including positive chest x-ray (Downe's score)
Interventions	NIPPV delivered via ventilator (Neoport E100M; DRE Medical, Louisville, KY, USA) by nasal cannula. Synchronized mode. Settings: PIP 5-12 cmH_2O, PEEP 4-6 cmH_2O, Ti 0.3-0.5 seconds. Bubble CPAP delivered via nasal cannula, PEEP 6 cmH_2O
Outcomes	Primary outcome: failure of noninvasive ventilation Secondary outcomes: duration of mechanical ventilation, nasal injury, abdominal distention, GI perforation, air leak, BPD, sepsis, IVH
Notes	Mixed population: Some infants received prophylactic surfactant via INSURE (< 29 weeks) or rescue surfactant if needed, before randomization.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomized trial; allocation based on admission number (odd or even)
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias)	Low risk	

Salama 2015 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	No flow diagram

Wood 2013

Methods	Study design: randomized controlled trial Setting: 2 centers Duration of study: unspecified	
Participants	Infants with GA 28 + 0 to 31 + 6; inborn; < 6 hours old; no prior intubation; no major congenital disorders	
Interventions	SiPAP (BiPhasic Tr); settings unspecified CPAP delivered by the Infant Flow SiPAP device	
Outcomes	Primary outcome was predefined failure of noninvasive respiratory support, necessitating intubation and ventilation, in the first 72 hours of treatment.	
Notes	Abstract only. Manuscript unpublished but ongoing (communication with study author)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) All outcomes	High risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Abstract

BPD: bronchopulmonary dysplasia.
CPAP: continuous positive airway pressure.
ETT: endotracheal tube.
FiO2: fraction of inspired oxygen.
GA: gestational age.
GI: gastrointestinal.
IL: interleukin.
INSURE: intubation-surfactant-extubation.
IPPV: intermittent positive pressure ventilation.
IVH: intraventricular hemorrhage.
NCPAP: nasal continuous positive airway pressure.
NICU: neonatal intensive care unit.
NIPPV: nasal intermittent positive pressure ventilation.

PCO2: partial pressure of carbon dioxide.
PDA: patent ductus arteriosus.
PEEP: positive end expiratory pressure.
PIP: peak inspiratory pressure.
PO2: partial pressure of oxygen.
PVL: periventricular leukomalacia.
RCT: randomized controlled trial.
RDS: respiratory distress syndrome.
ROP: retinopathy of prematurity.
SiPAP: synchronized inspiratory positive airway pressure.
SNIPPV: synchronized nasal intermittent positive airway pressure.
SpO2: peripheral oxygen saturation.
TNF: tumor necrosis factor.

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

Study	Reason for exclusion
Aghai 2006	Cross-over trial design
Baneshi 2014	Did not report on primary outcome or secondary outcomes
Barrington 2001	Postextubation trial
Bhandari 2007	SNIPPV vs conventional ventilation
Chen 2015	Single-center paired design; randomized controlled trial enrolling only preterm twins with RDS. One of a pair was randomized to NIPPV, another to NCPAP.
Friedlich 1999	Postextubation trial
Gao 2010	Postextubation trial
Gizzi 2015	NIPPV for apnea of prematurity
Herber-Jonat 2006	Cross-over trial design
Jasani 2016	Postextubation trial
Kahramaner 2014	Postextubation trial
Khalaf 2001	Postextubation trial
Khorana 2008	Postextubation trial
Kugelman 2014a	RCT comparing heated, humidified high-flow nasal cannula (HHHFNC) with nasal intermittent positive pressure ventilation (NIPPV) on the requirement for endotracheal ventilation in preterm infants with respiratory distress syndrome (RDS)
Lin 1998	NIPPV vs NCPAP for apnea of prematurity
Lin 2011	NIPPV for apnea of prematurity
Liu 2003	Variable-flow nasal CPAP only
Manzar 2004	NIPPV only

Study	Reason for exclusion
Migliori 2005	Cross-over trial design; post extubation
Moretti 2008	Postextubation trial
O'Brien 2012	Postextubation trial
Pantalitschka 2009	NIPPV to reduce apnea of prematurity; cross-over design
Ramanathan 2009	Immediate extubation to NIPPV vs continued intubation followed by extubation to NCPAP
Ryan 1989	Cross-over trial design
Salvo 2015	Comparison between nonsynchronized NIPPV delivered via ventilator and NIPPV delivered by a bilevel device. No CPAP arm
Santin 2004	SNIPPV vs conventional ventilation
Shi 2010	Included term infants (outside of our age range for inclusion)
Shi 2014	Included term infants (outside of our age range for inclusion)
Zhou 2015	This study examined the usefulness of nasal Duo positive airway pressure (DuoPAP) in the treatment of very low birth weight preterm infants with neonatal respiratory distress syndrome (NRDS).

DuoPAP: Duo positive airway pressure.
HHHFNC: heated, humidified, high-flow nasal cannula.
NCPAP: nasal continuous positive airway pressure.
NIPPV: nasal intermittent positive pressure ventilation.
NRDS: neonatal respiratory distress syndrome.
RCT: randomized controlled trial.
RDS: respiratory distress syndrome.
SNIPPV: synchronized nasal intermittent positive airway pressure.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Chen 2013

Methods	Prospective randomized controlled single-center study performed on 67 preterm infants with NRDS between March 2011 and May 2012
Participants	Preterm infants were randomly assigned to receive NIPPV and NCPAP. Oxygenation index (OI), pH, $PaCO_2$, duration of respiratory support, complications, success rate, hospital mortality, and incidence of bronchopulmonary dysplasia (BPD) were compared between the 2 groups.
Interventions	Preterm infants were randomly assigned to receive NIPPV and NCPAP.
Outcomes	Preterm infants were randomly assigned to receive NIPPV and NCPAP. Oxygenation index (OI), pH, $PaCO_2$, duration of respiratory support, complications, success rate, hospital mortality, and incidence of bronchopulmonary dysplasia (BPD) were compared between the 2 groups.
Notes	Study requires translation.

Fu 2014

Methods	Randomized controlled study
Participants	One hundred neonates with neonatal RDS
Interventions	NIPPV or NCPAP
Outcomes	Reduced CO_2 retention, improved oxygenation, reduced second endotracheal intubation and second use of pulmonary surfactant (PS), reduced duration of invasive respiratory support, reduced duration of oxygen use; reduced incidence of air leak, abdominal distention, and ventilator-associated pneumonia
Notes	PMID: 24856992 (requires translation from Chinese)

Gao 2014

Methods	Randomized controlled trial
Participants	Preterm infants with RDS
Interventions	NIPPV (synchronized bilevel) vs NCPAP
Outcomes	FiO_2 at 24 hours, respiratory index (RI) at 12-24 hours post ventilation, abdominal distention, period of noninvasive ventilation, ratio of intubation for invasive ventilation if failed noninvasive ventilation, air leak syndrome, neonatal necrotizing enterocolitis, periventricular-intraventricular hemorrhage, bronchopulmonary dysplasia, retinopathy of prematurity, mortality rate after 36 hours of age, rate of abandon for discharge
Notes	PMID: 24680406 (requires translation from Chinese)

Kong 2012

Methods	Single-center randomized controlled trial
Participants	Preterm neonates (30-35 weeks) with RDS
Interventions	DuoPAP or NCPAP
Outcomes	Total invasive respiratory support rates within 48 and 72 hours after birth; BPD; OI at 1, 12, 24, 48, and 72 hours
Notes	

Sasi 2013

Methods	Randomized controlled trial

Sasi 2013 *(Continued)*

Participants	Preterm infants at 28-36 weeks with RDS
Interventions	Nonsynchronized NIMV vs NCPAP
Outcomes	Failure of allocated mode within 48 hours
Notes	PSANZ 2013 17th Annual Congress. Journal of Paediatrics and Child Health 2013;49(Suppl 2):10–58

Silveira 2015

Methods	Randomized controlled trial
Participants	Preterm infants at less than 37 weeks and weighing less than 2500 grams; with RDS and early use of noninvasive respiratory support or post extubation
Interventions	NIPPV (unspecified) vs NCPAP
Outcomes	Failure of allocated mode within 48 hours
Notes	Contact with study authors initiated to extract infants who were treated early for possible inclusion in a future update of this review

BPD: bronchopulmonary dysplasia.
DuoPAP: Duo positive airway pressure.
NCPAP: nasal continuous positive airway pressure.
NIPPV: nasal intermittent positive pressure ventilation.
NRDS: neonatal respiratory distress syndrome.
OI: oxygenation index.
PaCO2: partial pressure of carbon dioxide.
PS: pulmonary surfactant.
PSANZ: Perinatal Society of Australia and New Zealand.
RDS: respiratory distress syndrome.
RI: respiratory index.

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

Sabzehei 2015

Trial name or title	Early nasal intermittent positive pressure ventilation vs continuous positive airway pressure in preterm infants with respiratory distress syndrome
Methods	Randomized controlled trial
Participants	Infants at 28-34 weeks, single center, with respiratory distress; birth weight 1000-2000 grams
Interventions	NIPPV vs NCPAP
Outcomes	Need for mechanical ventilation, death, pneumothorax, PDA, pulmonary hemorrhage, DIC, sepsis (all within 7 days)
Starting date	
Contact information	

Sabzehei 2015 *(Continued)*

Notes	IRCT2014072618598N1

DIC: disseminated intravascular coagulation.
NCPAP: nasal continuous positive airway pressure.
NIPPV: nasal intermittent positive pressure ventilation.
PDA: patent ductus arteriosus.

DATA AND ANALYSES

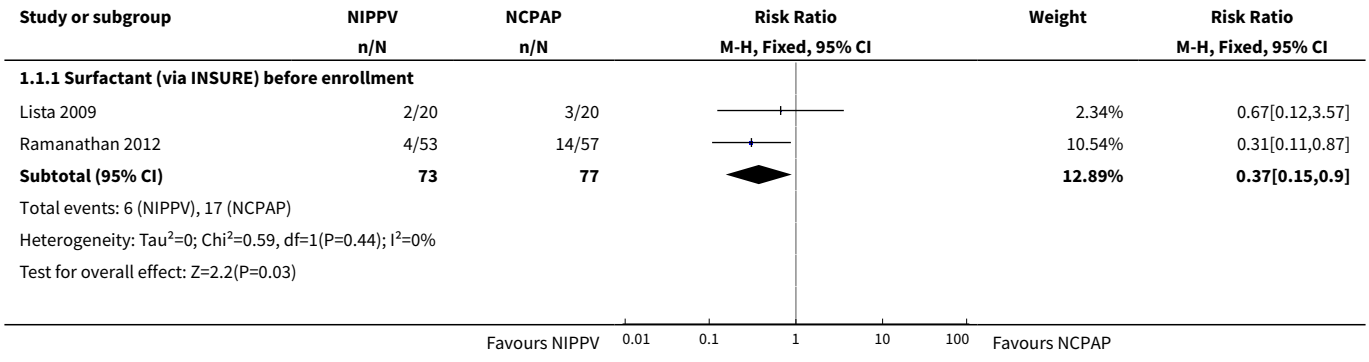
Comparison 1. NIPPV vs NCPAP (by population)

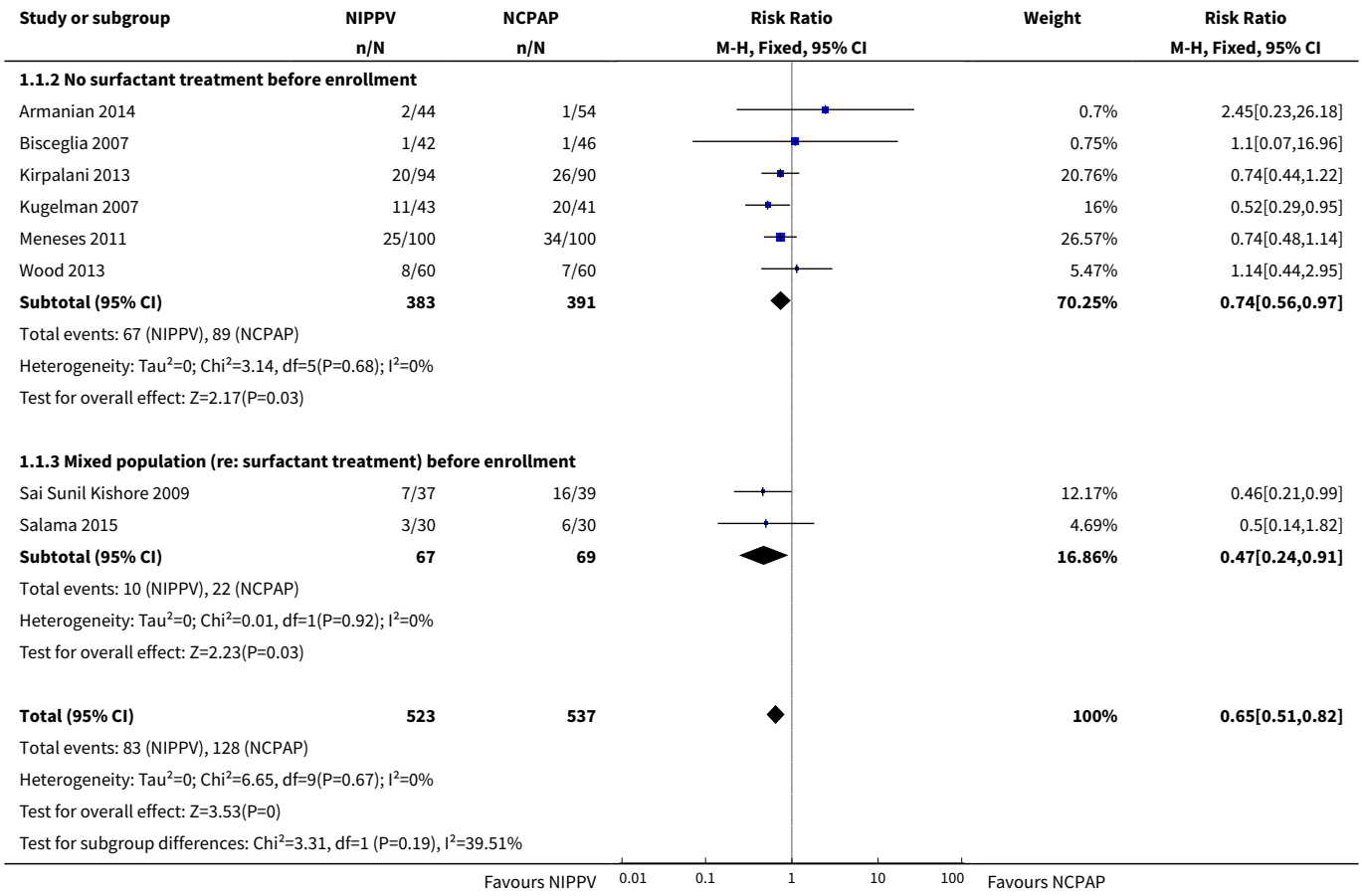
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory failure	10	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.51, 0.82]
1.1 Surfactant (via INSURE) before enrollment	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.15, 0.90]
1.2 No surfactant treatment before enrollment	6	774	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.56, 0.97]
1.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.24, 0.91]
2 Need for intubation	9	950	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.64, 0.94]
2.1 Surfactant (via INSURE) before enrollment	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.12, 3.57]
2.2 No surfactant treatment before enrollment	6	774	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.02]
2.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.24, 0.91]
3 Mortality during study period	10	1061	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.15]
3.1 Surfactant (via INSURE) before enrollment	2	150	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.07, 16.76]
3.2 No surfactant treatment before enrollment	6	775	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.52, 1.30]
3.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.21, 1.42]
4 Chronic lung disease	9	899	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Surfactant (via INSURE) before enrollment	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.29, 1.00]
4.2 No surfactant treatment before enrollment	5	627	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.64, 1.32]
4.3 Mixed population (re: surfactant treatment) before enrollment	2	122	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.08, 1.91]
5 Pneumothorax	10	1061	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.42, 1.48]
5.1 Surfactant (via INSURE) before enrollment	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.07, 2.94]
5.2 No surfactant treatment before enrollment	6	775	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.52, 2.91]
5.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.13, 1.41]
6 Intraventricular hemorrhage (all grades)	5	370	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.54, 1.16]
6.1 Surfactant (via INSURE) before enrollment	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 3.92]
6.2 No surfactant treatment before enrollment	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.56, 1.22]
6.3 Mixed population (re: surfactant treatment) before enrollment	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Severe intraventricular hemorrhage (grade III/IV)	4	430	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.53, 3.01]
7.1 Surfactant (via INSURE) before enrollment	1	110	Risk Ratio (M-H, Fixed, 95% CI)	5.37 [0.26, 109.35]
7.2 No surfactant treatment before enrollment	3	320	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.39, 2.59]
7.3 Mixed population (re: surfactant treatment) before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Necrotizing enterocolitis (≥ Bell's stage 2)	7	718	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.34, 1.31]
8.1 Surfactant (via INSURE) before enrollment	2	150	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.10, 2.82]
8.2 No surfactant treatment before enrollment	4	492	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.25, 1.33]

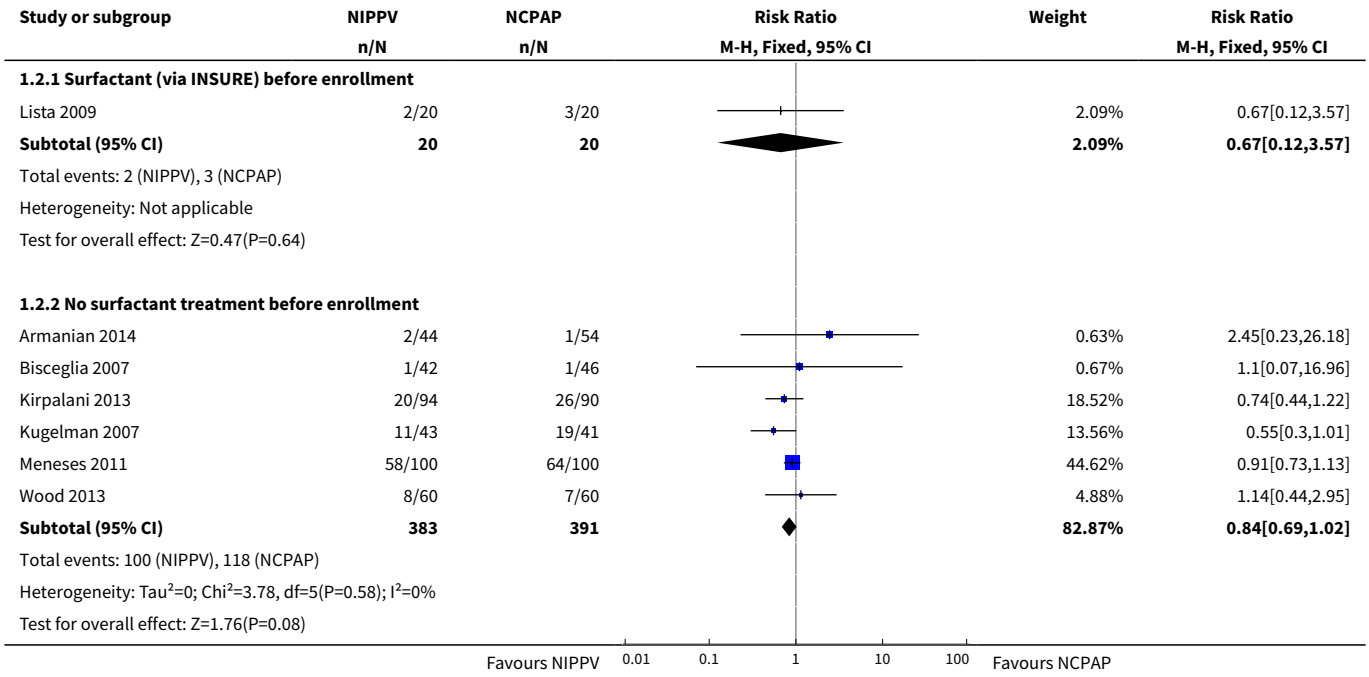
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 Mixed population (re: surfactant treatment) before enrollment	1	76	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [0.28, 8.93]
9 Sepsis	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.70]
9.1 Surfactant (via INSURE) before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 No surfactant treatment before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.36, 1.70]
10 Retinopathy of prematurity (≥ stage 3)	2	245	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.65, 3.44]
10.1 Surfactant (via INSURE) before enrollment	1	110	Risk Ratio (M-H, Fixed, 95% CI)	3.22 [0.13, 77.41]
10.2 No surfactant treatment before enrollment	1	135	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.58, 3.30]
10.3 Mixed population (re: surfactant treatment) before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Local upper airway injury	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.41]
11.1 Surfactant (via INSURE) before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 No surfactant treatment before enrollment	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Mixed population (re: surfactant treatment) before enrollment	2	136	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.03, 0.41]

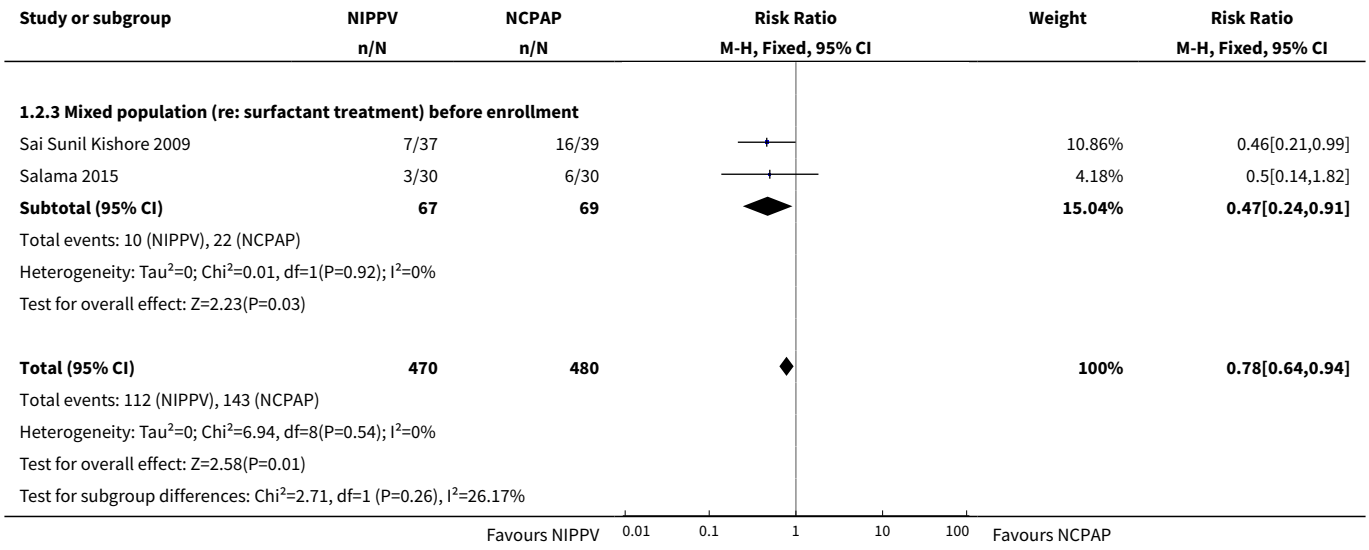
Analysis 1.1. Comparison 1 NIPPV vs NCPAP (by population), Outcome 1 Respiratory failure.



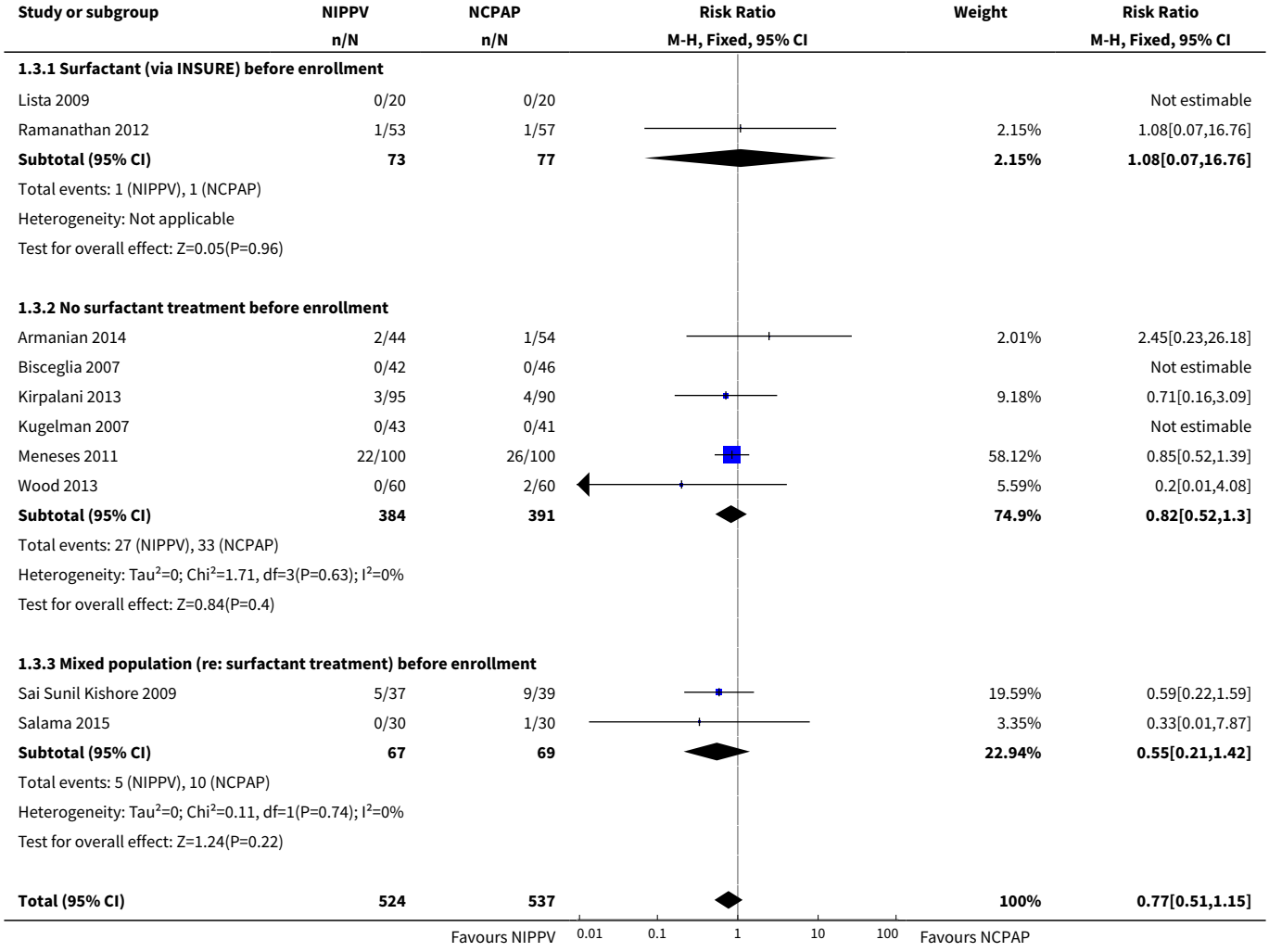


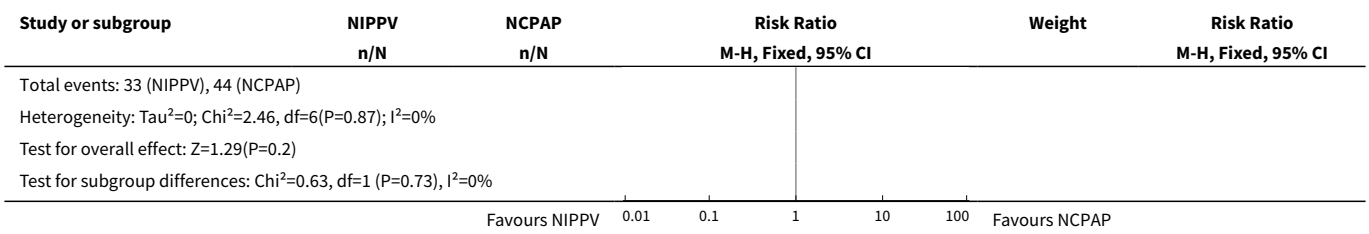
Analysis 1.2. Comparison 1 NIPPV vs NCPAP (by population), Outcome 2 Need for intubation.



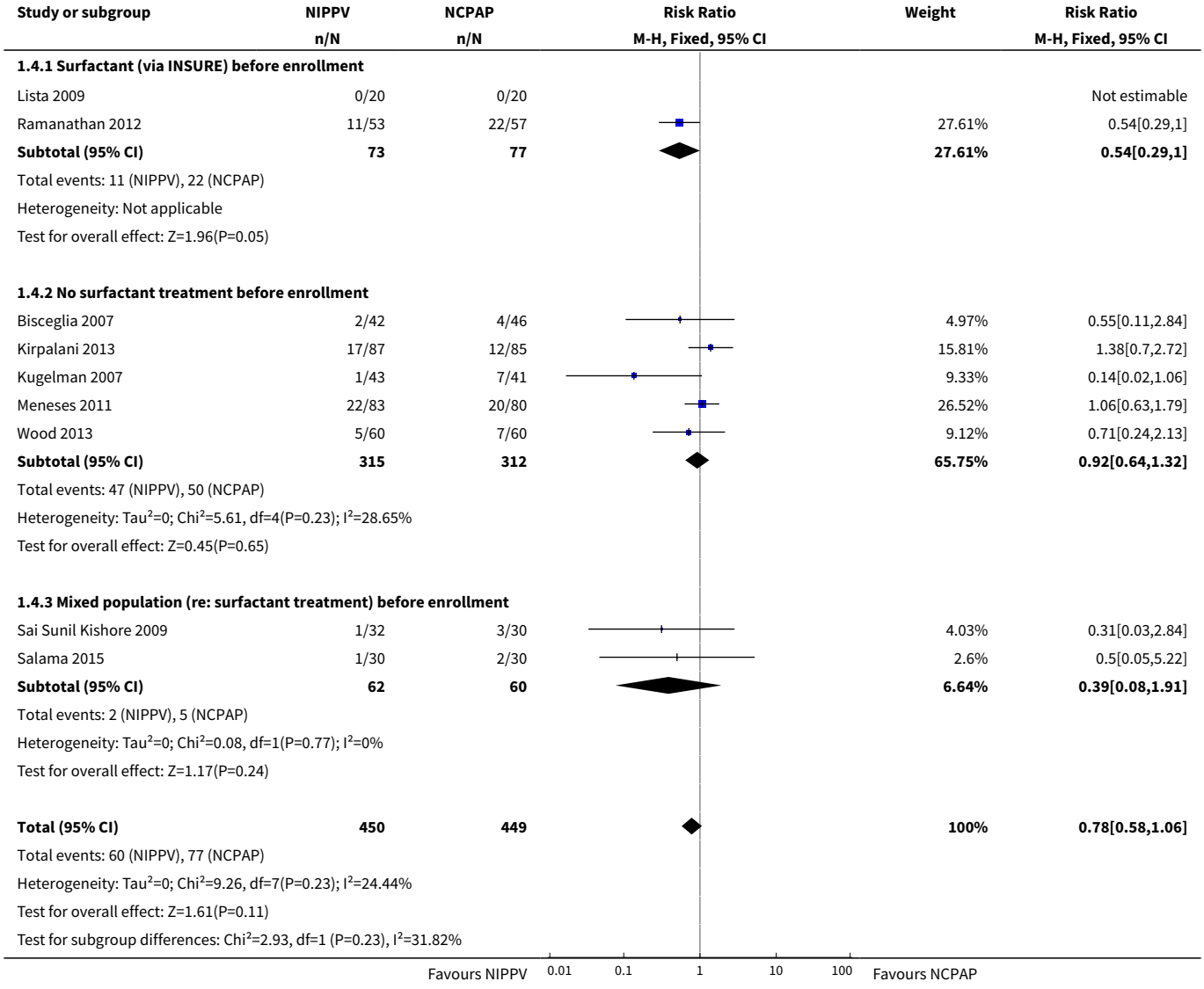


Analysis 1.3. Comparison 1 NIPPV vs NCPAP (by population), Outcome 3 Mortality during study period.

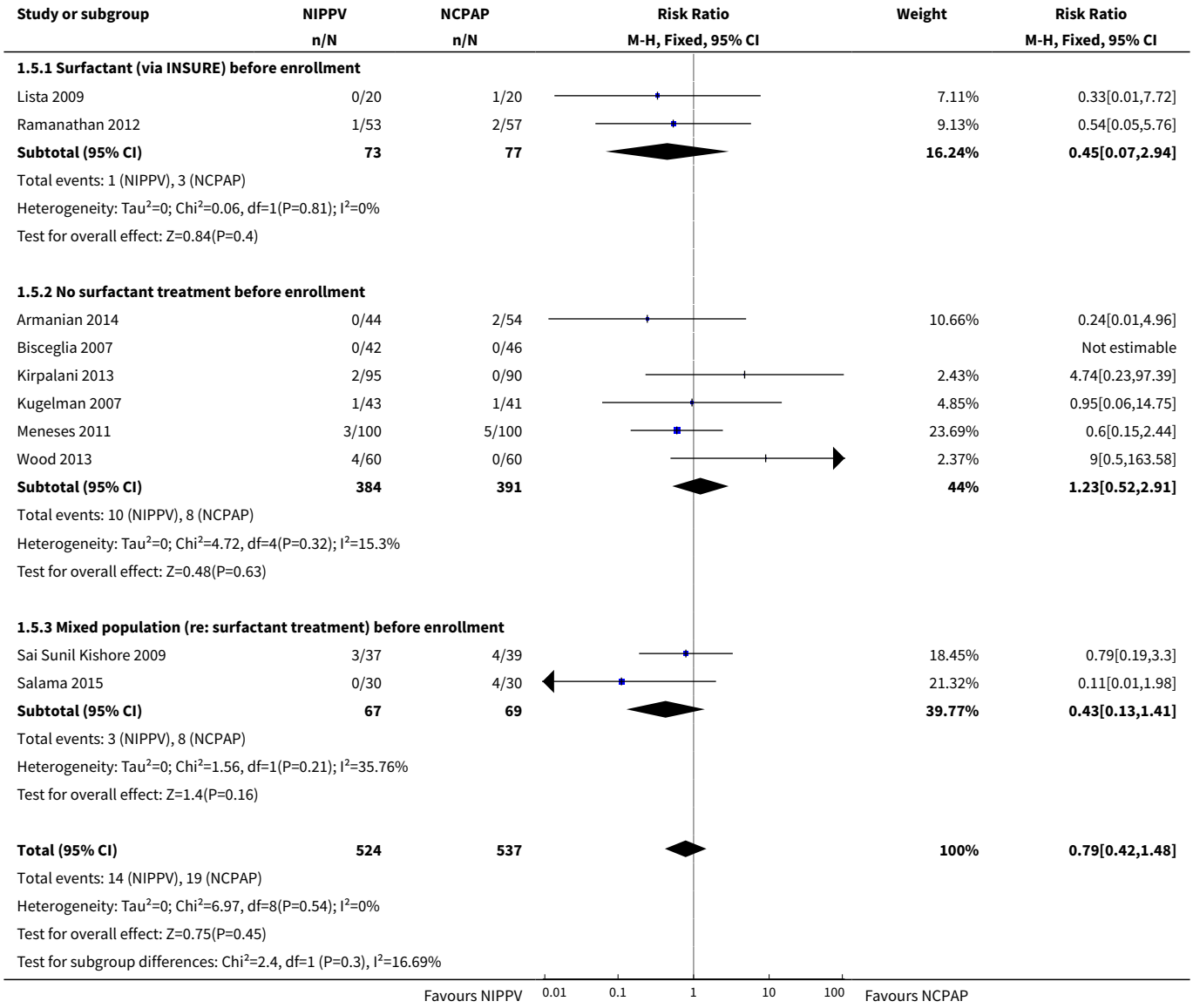




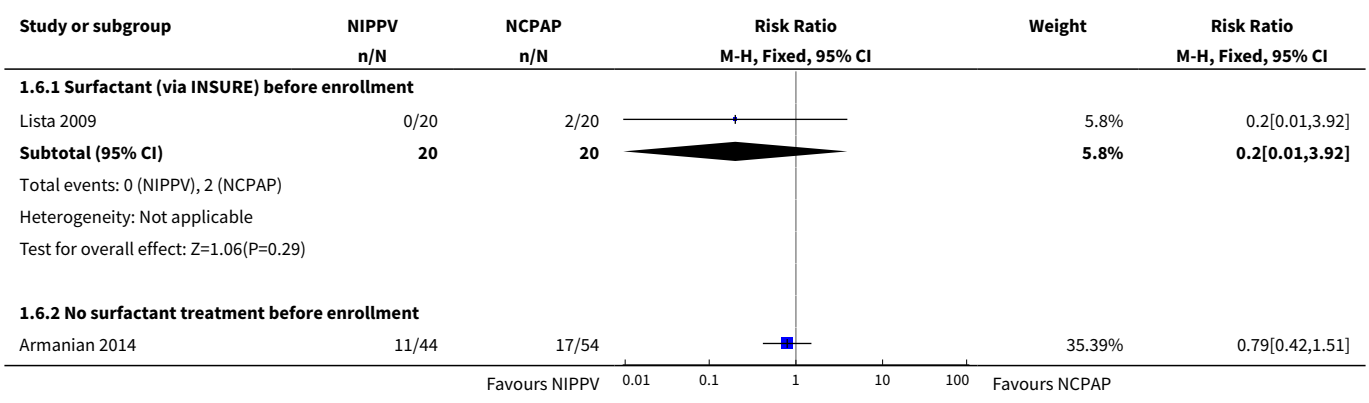
Analysis 1.4. Comparison 1 NIPPV vs NCPAP (by population), Outcome 4 Chronic lung disease.

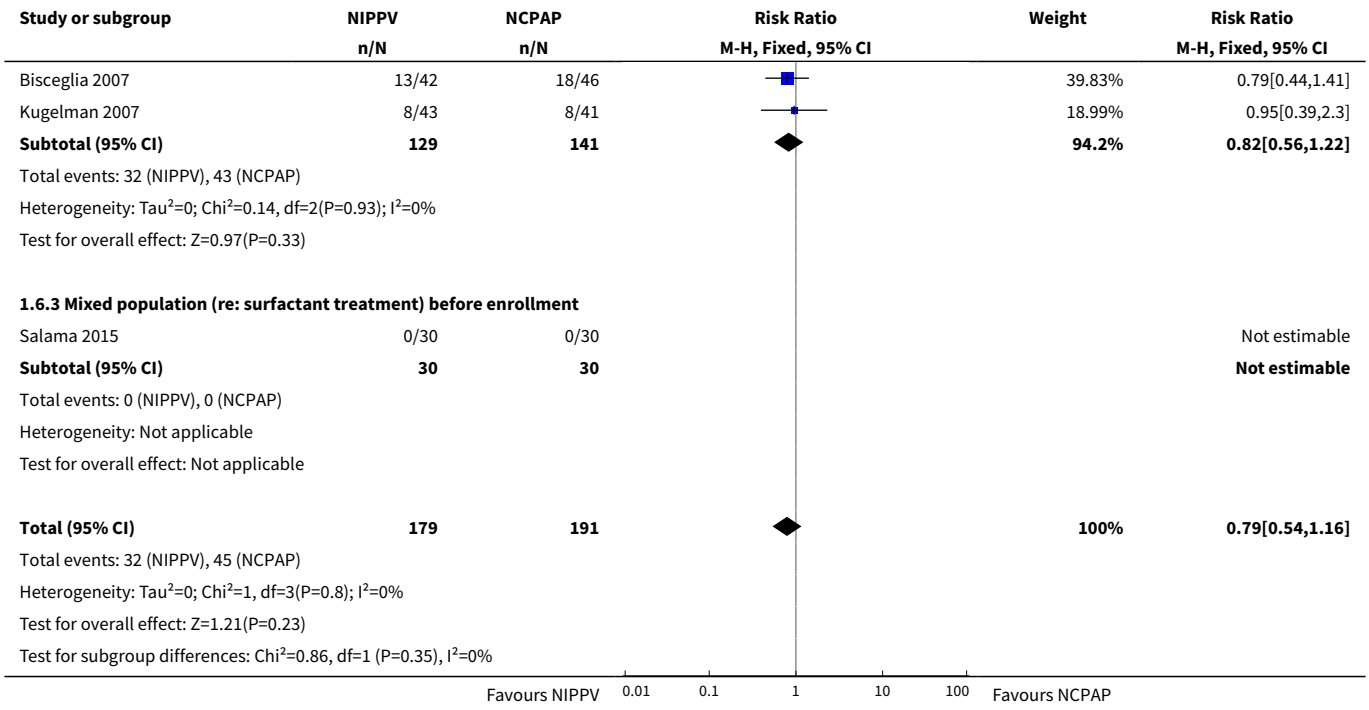


Analysis 1.5. Comparison 1 NIPPV vs NCPAP (by population), Outcome 5 Pneumothorax.

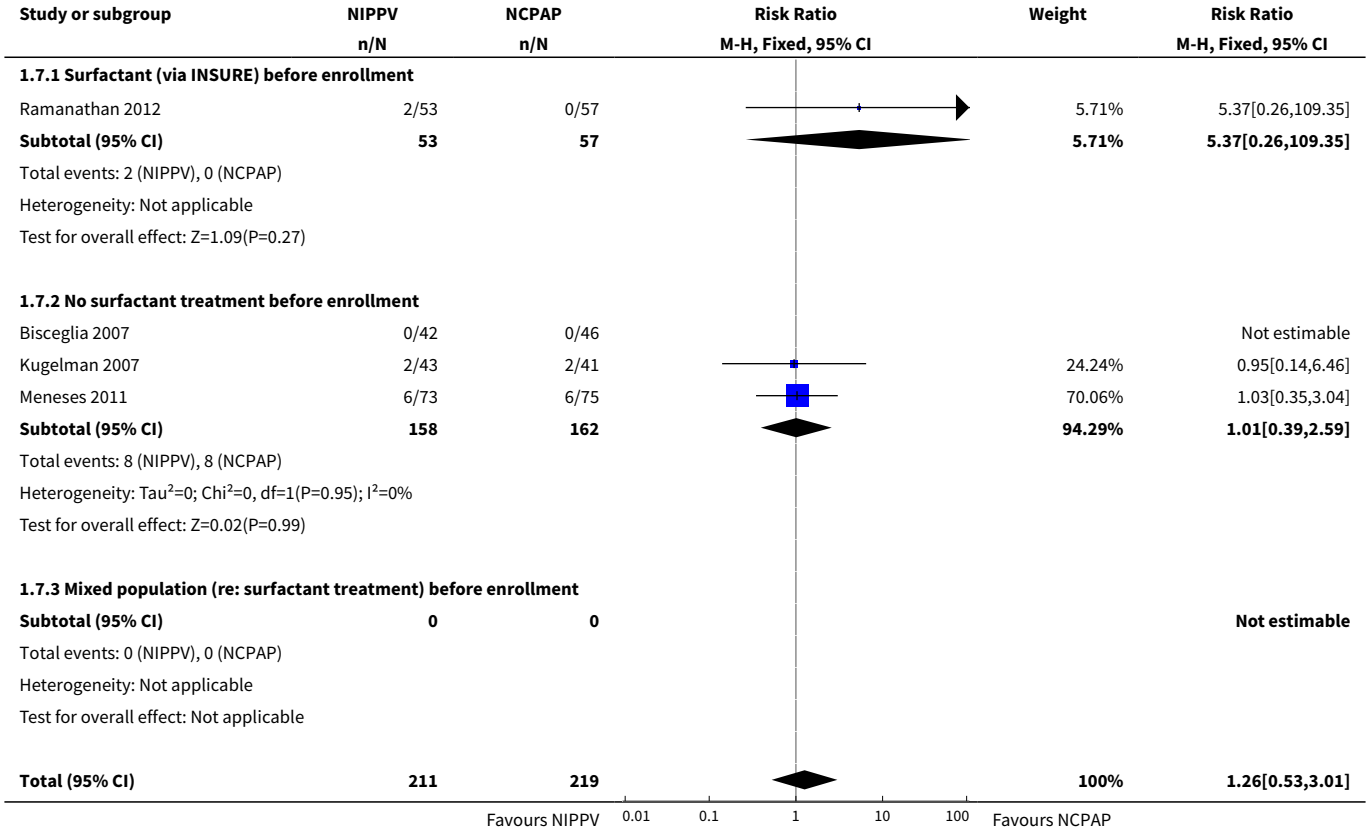


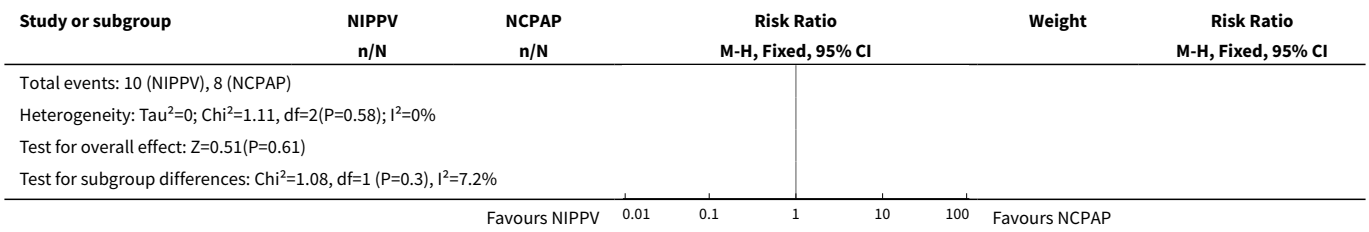
Analysis 1.6. Comparison 1 NIPPV vs NCPAP (by population), Outcome 6 Intraventricular hemorrhage (all grades).



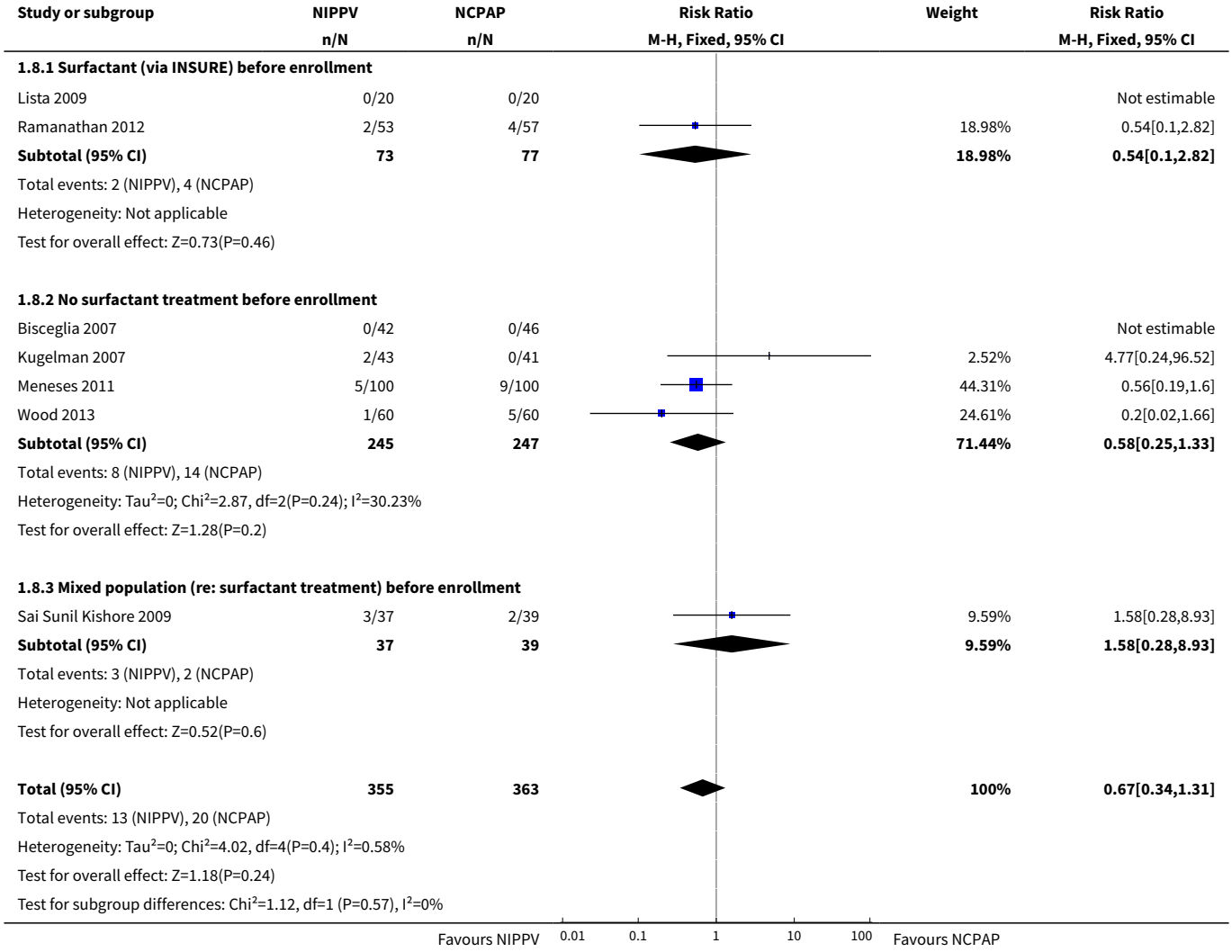


Analysis 1.7. Comparison 1 NIPPV vs NCPAP (by population), Outcome 7 Severe intraventricular hemorrhage (grade III/IV).

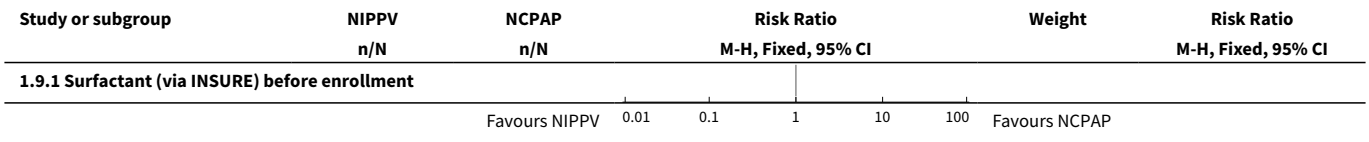


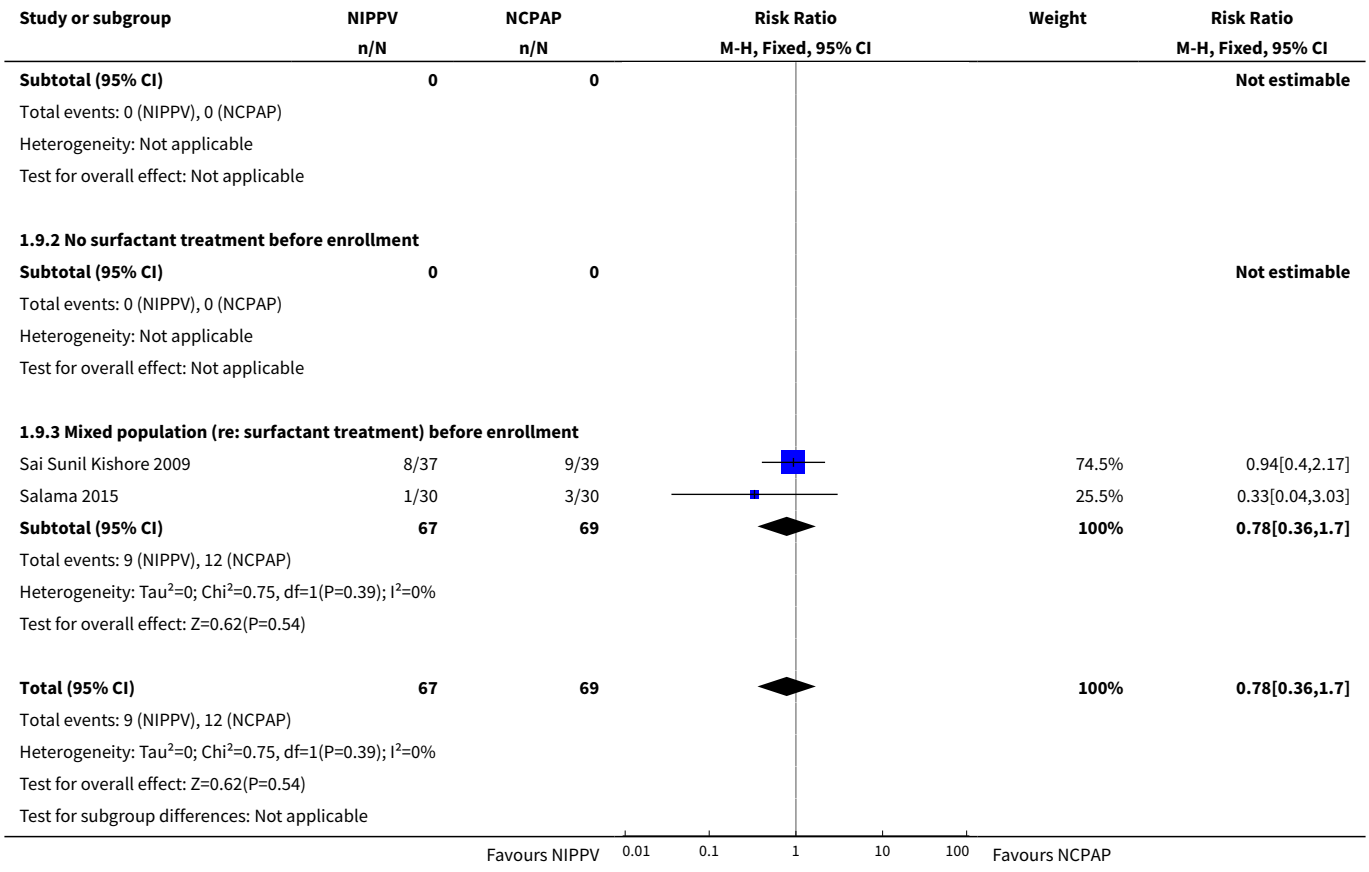


Analysis 1.8. Comparison 1 NIPPV vs NCPAP (by population), Outcome 8 Necrotizing enterocolitis (≥ Bell's stage 2).

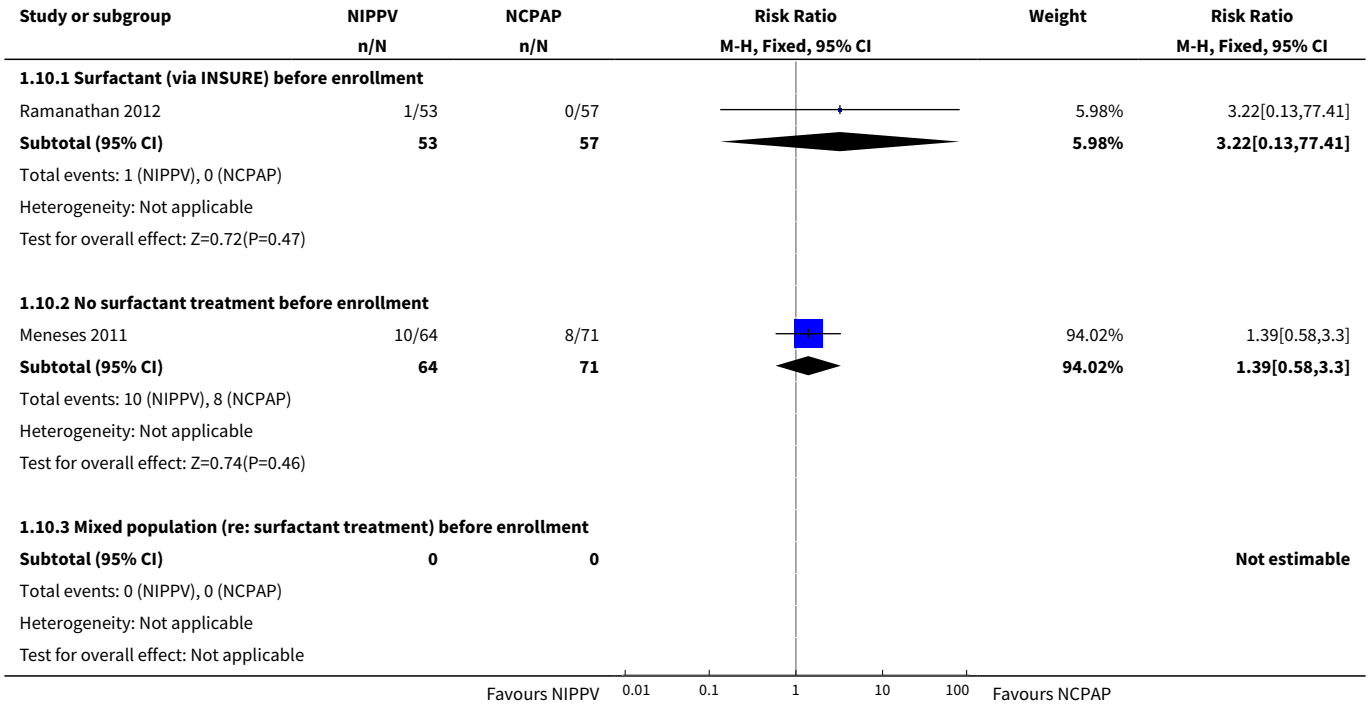


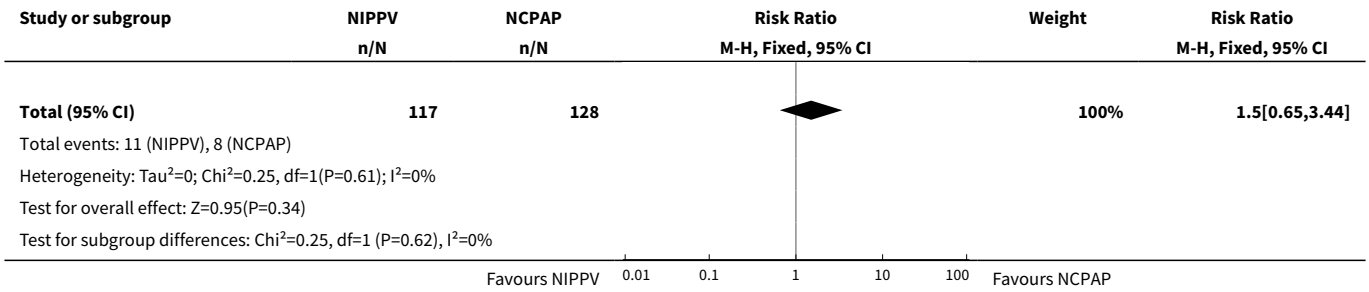
Analysis 1.9. Comparison 1 NIPPV vs NCPAP (by population), Outcome 9 Sepsis.



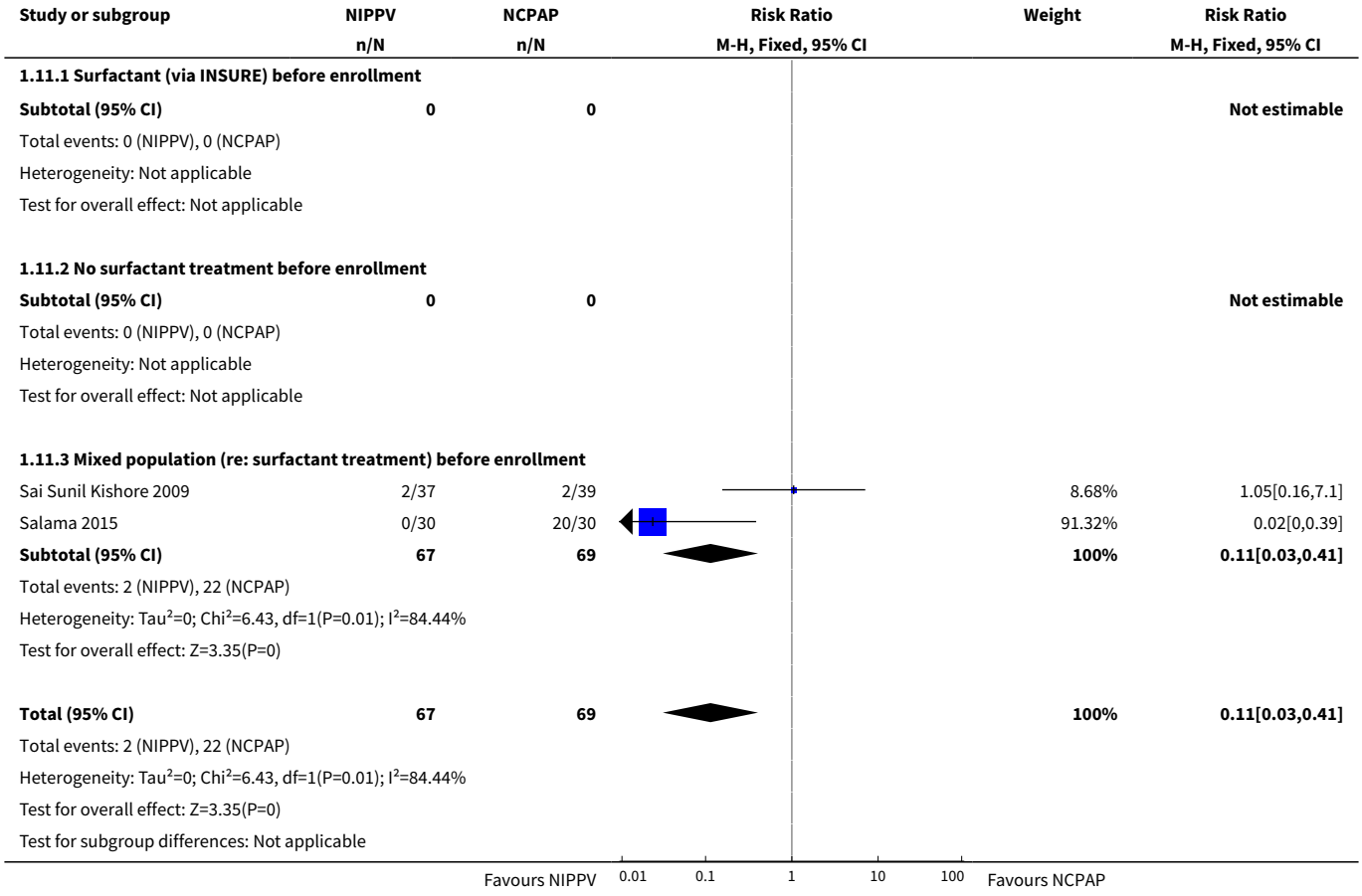


Analysis 1.10. Comparison 1 NIPPV vs NCPAP (by population), Outcome 10 Retinopathy of prematurity (≥ stage 3).





Analysis 1.11. Comparison 1 NIPPV vs NCPAP (by population), Outcome 11 Local upper airway injury.



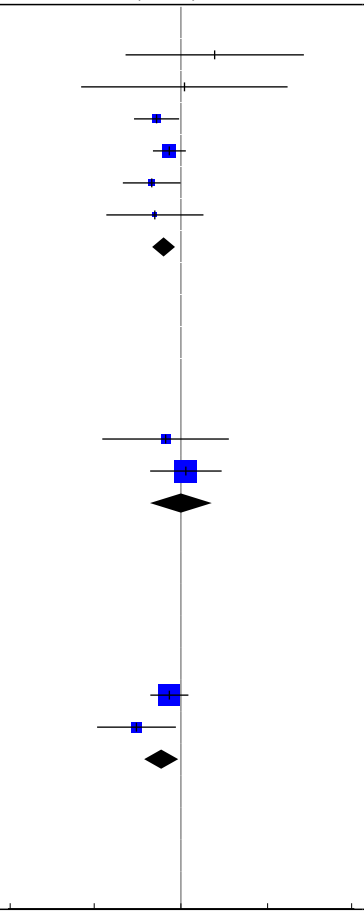
Comparison 2. NIPPV vs NCPAP (by device)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory failure	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Ventilator-generated NIPPV	6	606	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.47, 0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Bilevel NIPPV	2	160	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.44, 2.27]
1.3 Mixed devices	2	294	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.38, 0.93]
2 Need for intubation	10		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
2.1 Ventilator-generated NIPPV	6	606	Risk Difference (M-H, Fixed, 95% CI)	-0.08 [-0.14, -0.02]
2.2 Bilevel NIPPV	2	160	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.10, 0.10]
2.3 Mixed devices	2	294	Risk Difference (M-H, Fixed, 95% CI)	-0.11 [-0.20, -0.02]
3 Mortality	9	977	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.15]
3.1 Ventilator-generated NIPPV	5	522	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.52, 1.23]
3.2 Bilevel NIPPV	2	160	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.08]
3.3 Mixed devices	2	295	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.21, 2.83]
4 Chronic lung disease	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Ventilator-generated NIPPV	5	457	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.47, 1.15]
4.2 Bilevel NIPPV	2	160	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.24, 2.13]
4.3 Mixed devices	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.54, 1.32]
5 Pneumothorax	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Ventilator-generated NIPPV	6	606	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.11]
5.2 Bilevel NIPPV	2	160	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.49, 12.67]
5.3 Mixed devices	2	295	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [0.28, 7.29]
6 Severe intraventricular hemorrhage (grade III/IV)	3	346	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.51, 3.62]
6.1 Ventilator-generated NIPPV	2	236	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.35, 3.04]
6.2 Mixed devices	1	110	Risk Ratio (M-H, Fixed, 95% CI)	5.37 [0.26, 109.35]

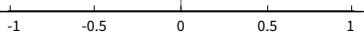
Analysis 2.1. Comparison 2 NIPPV vs NCPAP (by device), Outcome 1 Respiratory failure.

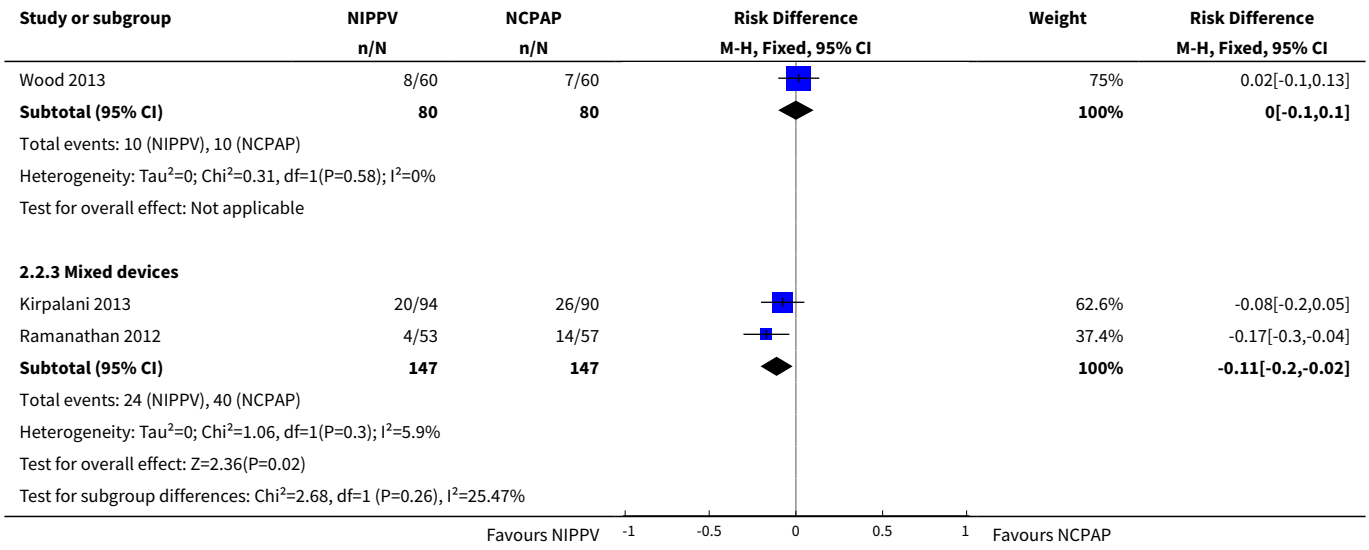
Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Ventilator-generated NIPPV					
Armanian 2014	2/44	1/54		1.15%	2.45[0.23,26.18]
Bisceglia 2007	1/42	1/46		1.23%	1.1[0.07,16.96]
Kugelman 2007	11/43	20/41		26.28%	0.52[0.29,0.95]
Meneses 2011	25/100	34/100		43.64%	0.74[0.48,1.14]
Sai Sunil Kishore 2009	7/37	16/39		20%	0.46[0.21,0.99]
Salama 2015	3/30	6/30		7.7%	0.5[0.14,1.82]
Subtotal (95% CI)	**296**	**310**		**100%**	**0.63[0.47,0.86]**
Total events: 49 (NIPPV), 78 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=3.03, df=5(P=0.7); I^2=0%					
Test for overall effect: Z=2.97(P=0)					
2.1.2 Bilevel NIPPV					
Lista 2009	2/20	3/20		30%	0.67[0.12,3.57]
Wood 2013	8/60	7/60		70%	1.14[0.44,2.95]
Subtotal (95% CI)	**80**	**80**		**100%**	**1[0.44,2.27]**
Total events: 10 (NIPPV), 10 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=0.3, df=1(P=0.58); I^2=0%					
Test for overall effect: Not applicable					
2.1.3 Mixed devices					
Kirpalani 2013	20/94	26/90		66.32%	0.74[0.44,1.22]
Ramanathan 2012	4/53	14/57		33.68%	0.31[0.11,0.87]
Subtotal (95% CI)	**147**	**147**		**100%**	**0.59[0.38,0.93]**
Total events: 24 (NIPPV), 40 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=2.22, df=1(P=0.14); I^2=55.03%					
Test for overall effect: Z=2.27(P=0.02)					
Test for subgroup differences: Chi^2=1.25, df=1 (P=0.53), I^2=0%					



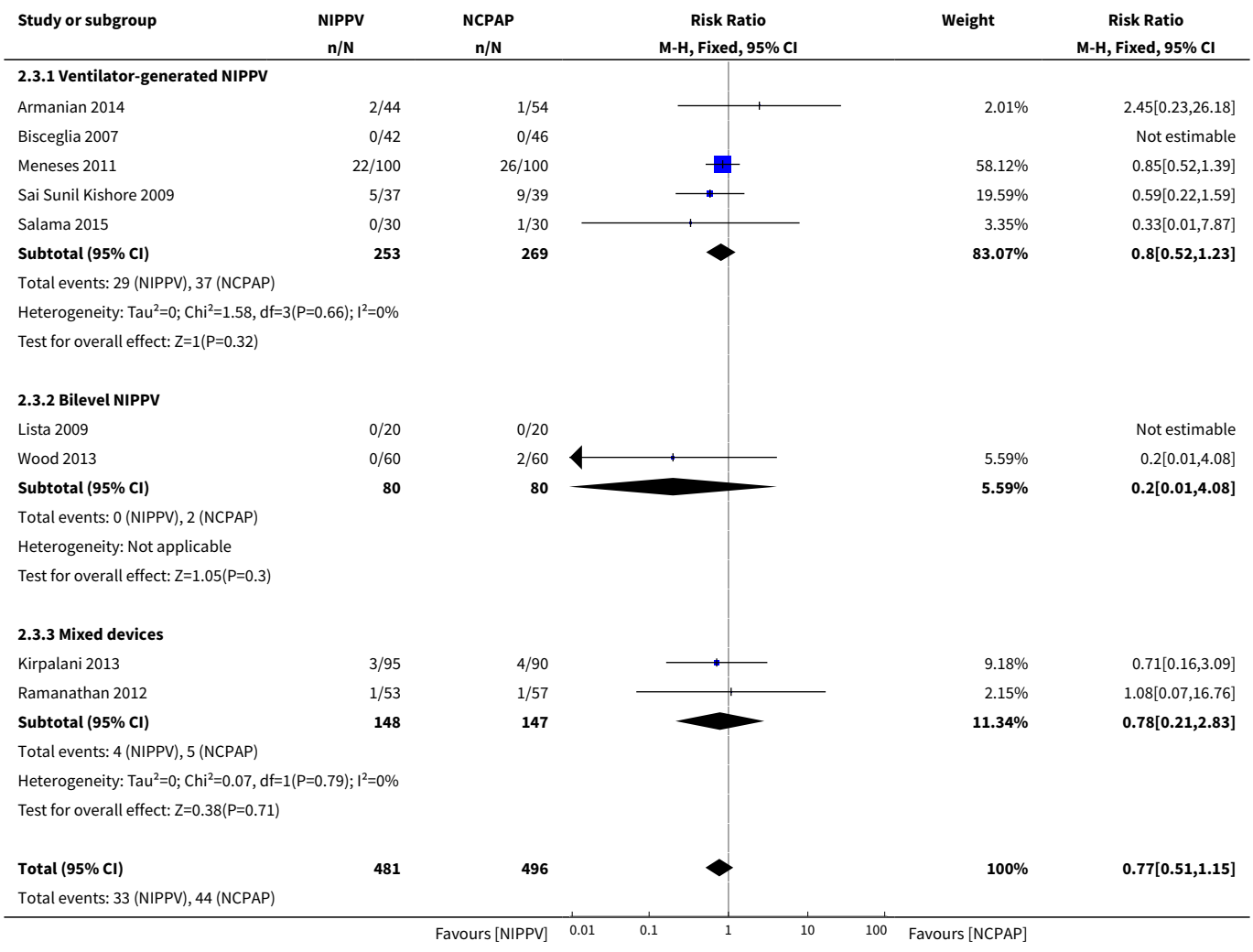
Analysis 2.2. Comparison 2 NIPPV vs NCPAP (by device), Outcome 2 Need for intubation.

Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.2.1 Ventilator-generated NIPPV					
Armanian 2014	2/44	1/54		16.04%	0.03[-0.04,0.1]
Bisceglia 2007	1/42	1/46		14.52%	0[-0.06,0.06]
Kugelman 2007	11/43	19/41		13.88%	-0.21[-0.41,-0.01]
Meneses 2011	58/100	64/100		33.07%	-0.06[-0.19,0.07]
Sai Sunil Kishore 2009	7/37	16/39		12.56%	-0.22[-0.42,-0.02]
Salama 2015	3/30	6/30		9.92%	-0.1[-0.28,0.08]
Subtotal (95% CI)	**296**	**310**		**100%**	**-0.08[-0.14,-0.02]**
Total events: 82 (NIPPV), 107 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=19.37, df=5(P=0); I^2=74.18%					
Test for overall effect: Z=2.56(P=0.01)					
2.2.2 Bilevel NIPPV					
Lista 2009	2/20	3/20		25%	-0.05[-0.25,0.15]





Analysis 2.3. Comparison 2 NIPPV vs NCPAP (by device), Outcome 3 Mortality.



Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.46, df=6(P=0.87); I²=0%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi²=0.8, df=1 (P=0.67), I²=0%					

Favours [NIPPV] 0.01 0.1 1 10 100 Favours [NCPAP]

Analysis 2.4. Comparison 2 NIPPV vs NCPAP (by device), Outcome 4 Chronic lung disease.

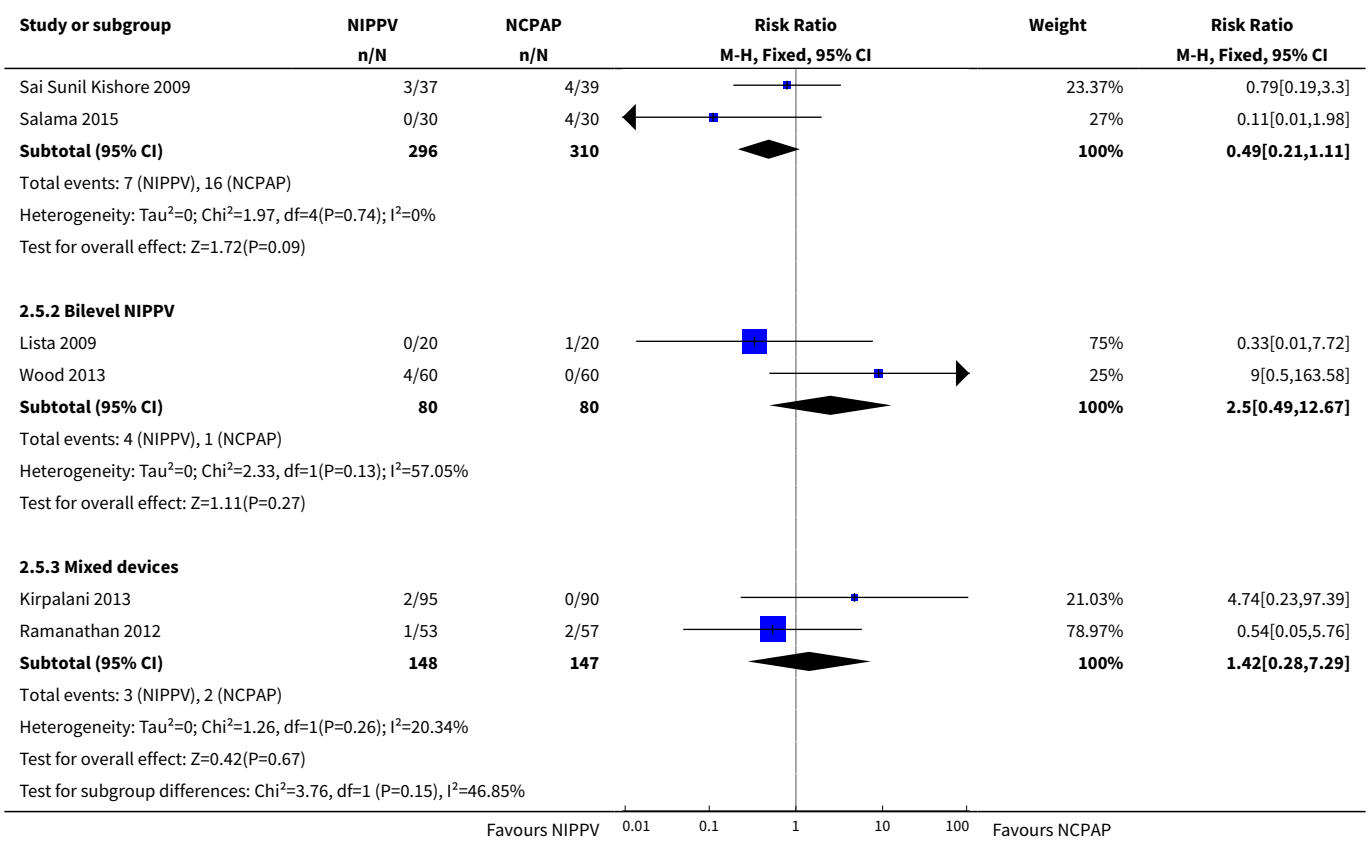
Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Ventilator-generated NIPPV					
Bisceglia 2007	2/42	4/46		10.48%	0.55[0.11,2.84]
Kugelman 2007	1/43	7/41		19.66%	0.14[0.02,1.06]
Meneses 2011	22/83	20/80		55.88%	1.06[0.63,1.79]
Sai Sunil Kishore 2009	1/32	3/30		8.5%	0.31[0.03,2.84]
Salama 2015	1/30	2/30		5.49%	0.5[0.05,5.22]
Subtotal (95% CI)	**230**	**227**		**100%**	**0.73[0.47,1.15]**
Total events: 27 (NIPPV), 36 (NCPAP)					
Heterogeneity: Tau²=0; Chi²=5.32, df=4(P=0.26); I²=24.79%					
Test for overall effect: Z=1.37(P=0.17)					
2.4.2 Bilevel NIPPV					
Lista 2009	0/20	0/20			Not estimable
Wood 2013	5/60	7/60		100%	0.71[0.24,2.13]
Subtotal (95% CI)	**80**	**80**		**100%**	**0.71[0.24,2.13]**
Total events: 5 (NIPPV), 7 (NCPAP)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.6(P=0.55)					
2.4.3 Mixed devices					
Kirpalani 2013	17/87	12/85		36.41%	1.38[0.7,2.72]
Ramanathan 2012	11/53	22/57		63.59%	0.54[0.29,1]
Subtotal (95% CI)	**140**	**142**		**100%**	**0.85[0.54,1.32]**
Total events: 28 (NIPPV), 34 (NCPAP)					
Heterogeneity: Tau²=0; Chi²=4.09, df=1(P=0.04); I²=75.57%					
Test for overall effect: Z=0.74(P=0.46)					
Test for subgroup differences: Chi²=0.23, df=1 (P=0.89), I²=0%					

Favours NIPPV 0.01 0.1 1 10 100 Favours NCPAP

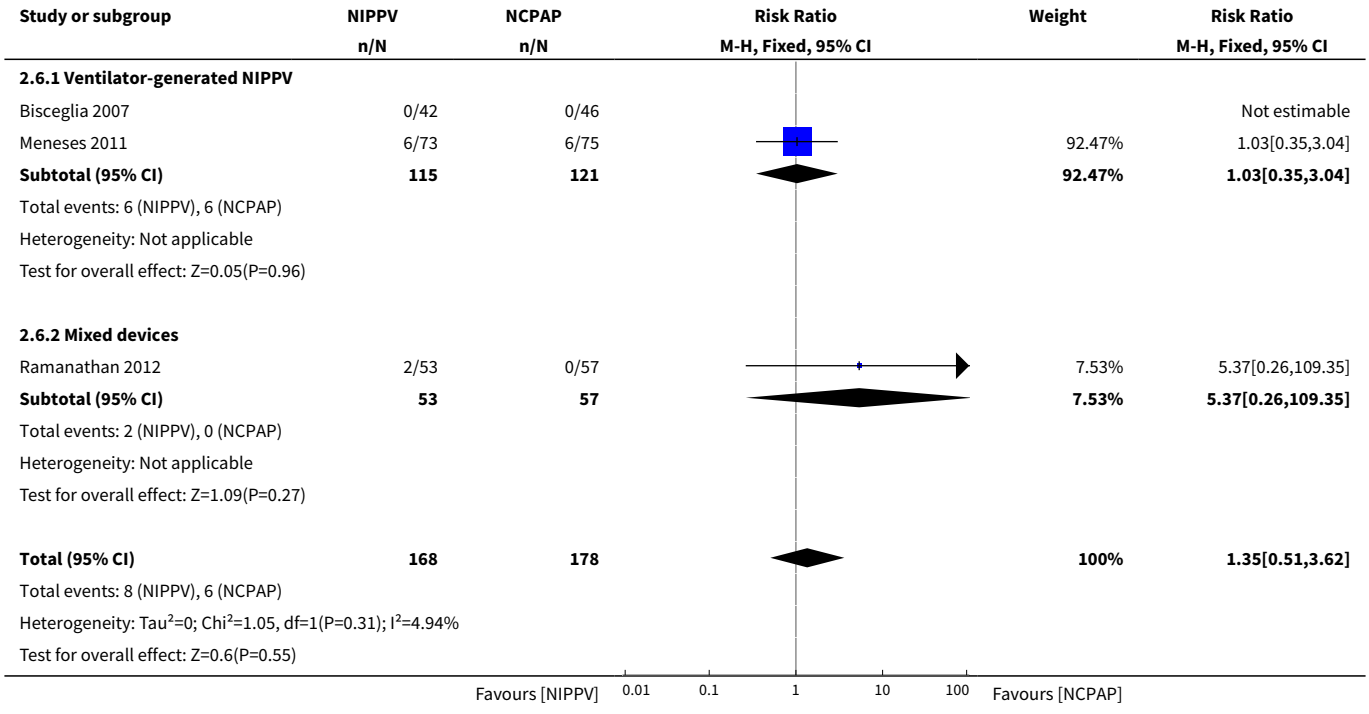
Analysis 2.5. Comparison 2 NIPPV vs NCPAP (by device), Outcome 5 Pneumothorax.

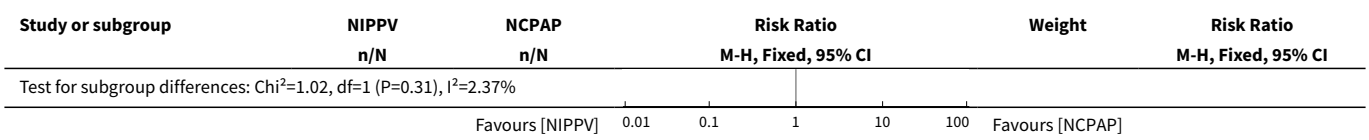
Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Ventilator-generated NIPPV					
Armanian 2014	0/44	2/54		13.5%	0.24[0.01,4.96]
Bisceglia 2007	0/42	0/46			Not estimable
Kugelman 2007	1/43	1/41		6.14%	0.95[0.06,14.75]
Meneses 2011	3/100	5/100		30%	0.6[0.15,2.44]

Favours NIPPV 0.01 0.1 1 10 100 Favours NCPAP



Analysis 2.6. Comparison 2 NIPPV vs NCPAP (by device), Outcome 6 Severe intraventricular hemorrhage (grade III/IV).



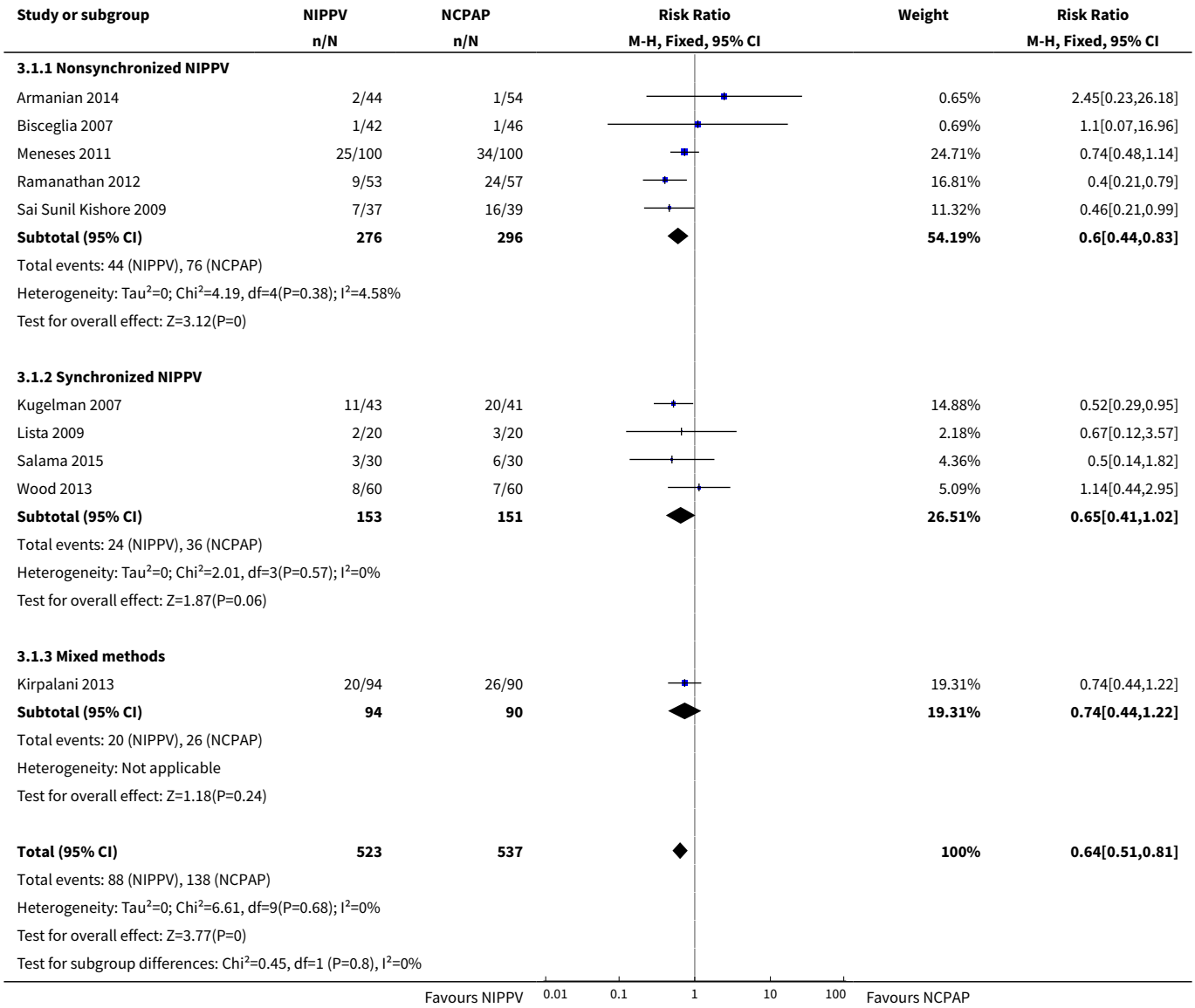


Comparison 3. NIPPV vs NCPAP (by synchronization)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory failure	10	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.51, 0.81]
1.1 Nonsynchronized NIPPV	5	572	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.44, 0.83]
1.2 Synchronized NIPPV	4	304	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.41, 1.02]
1.3 Mixed methods	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.22]
2 Need for intubation	10	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
2.1 Nonsynchronized NIPPV	5	572	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.60, 0.92]
2.2 Synchronized NIPPV	4	304	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.42, 1.06]
2.3 Mixed methods	1	184	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.44, 1.22]
3 Mortality	9	977	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.51, 1.15]
3.1 Synchronized NIPPV	3	220	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.19]
3.2 Nonsynchronized NIPPV	5	572	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.54, 1.27]
3.3 Mixed methods	1	185	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.16, 3.09]
4 Chronic lung disease	9	899	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.58, 1.06]
4.1 Nonsynchronized NIPPV	4	423	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.51, 1.08]
4.2 Synchronized NIPPV	4	304	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.18, 1.01]
4.3 Mixed methods	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.70, 2.72]
5 Pneumothorax	10	1061	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.42, 1.48]
5.1 Nonsynchronized NIPPV	5	572	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.24, 1.40]
5.2 Synchronized NIPPV	4	304	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.30, 2.43]
5.3 Mixed methods	1	185	Risk Ratio (M-H, Fixed, 95% CI)	4.74 [0.23, 97.39]

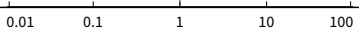
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Severe intraventricular hemorrhage (grade III/IV)	3	346	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.51, 3.62]
6.1 Synchronized NIPPV	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Nonsynchronized NIPPV	3	346	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.51, 3.62]

Analysis 3.1. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 1 Respiratory failure.



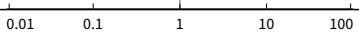
Analysis 3.2. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 2 Need for intubation.

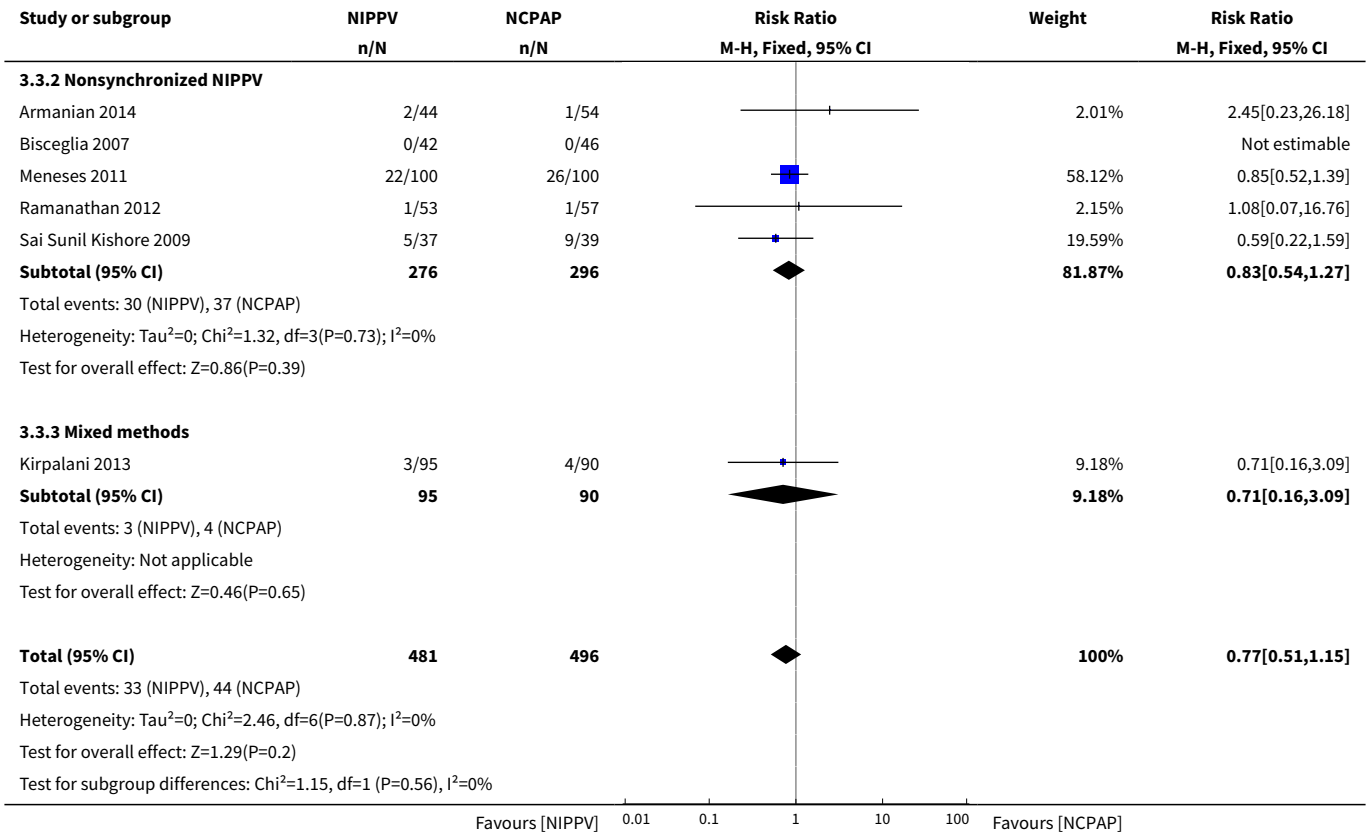
Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Nonsynchronized NIPPV					
Armanian 2014	2/44	1/54		0.54%	2.45[0.23,26.18]
Bisceglia 2007	1/42	1/46		0.57%	1.1[0.07,16.96]
Meneses 2011	58/100	64/100		38.42%	0.91[0.73,1.13]
Ramanathan 2012	9/53	24/57		13.88%	0.4[0.21,0.79]
Sai Sunil Kishore 2009	7/37	16/39		9.35%	0.46[0.21,0.99]
Subtotal (95% CI)	**276**	**296**		**62.77%**	**0.74[0.6,0.92]**
Total events: 77 (NIPPV), 106 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=8.81, df=4(P=0.07); I^2=54.57%					
Test for overall effect: Z=2.74(P=0.01)					
3.2.2 Synchronized NIPPV					
Kugelman 2007	11/43	19/41		11.68%	0.55[0.3,1.01]
Lista 2009	2/20	3/20		1.8%	0.67[0.12,3.57]
Salama 2015	3/30	6/30		3.6%	0.5[0.14,1.82]
Wood 2013	8/60	7/60		4.2%	1.14[0.44,2.95]
Subtotal (95% CI)	**153**	**151**		**21.28%**	**0.67[0.42,1.06]**
Total events: 24 (NIPPV), 35 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=1.8, df=3(P=0.61); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
3.2.3 Mixed methods					
Kirpalani 2013	20/94	26/90		15.95%	0.74[0.44,1.22]
Subtotal (95% CI)	**94**	**90**		**15.95%**	**0.74[0.44,1.22]**
Total events: 20 (NIPPV), 26 (NCPAP)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.18(P=0.24)					
Total (95% CI)	**523**	**537**		**100%**	**0.73[0.61,0.87]**
Total events: 121 (NIPPV), 167 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=11.22, df=9(P=0.26); I^2=19.79%					
Test for overall effect: Z=3.43(P=0)					
Test for subgroup differences: Chi^2=0.17, df=1 (P=0.92), I^2=0%					



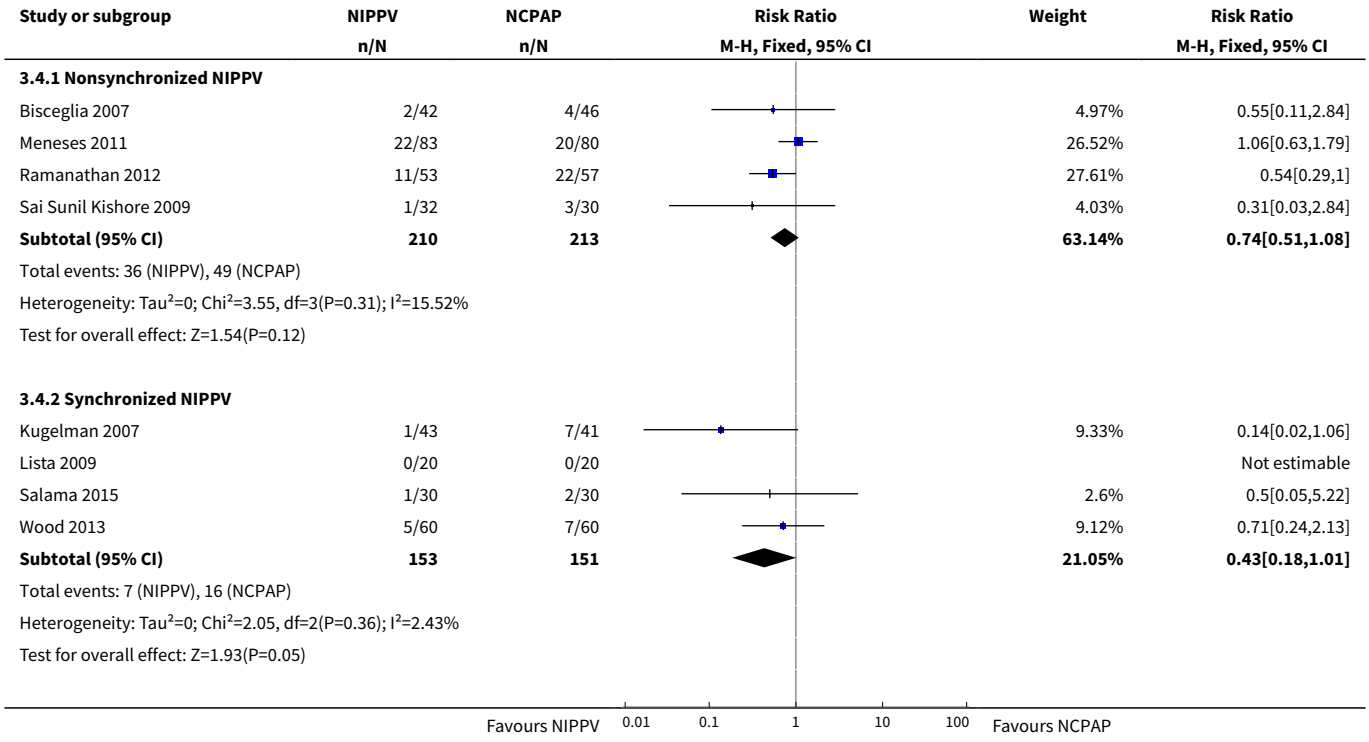
Analysis 3.3. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 3 Mortality.

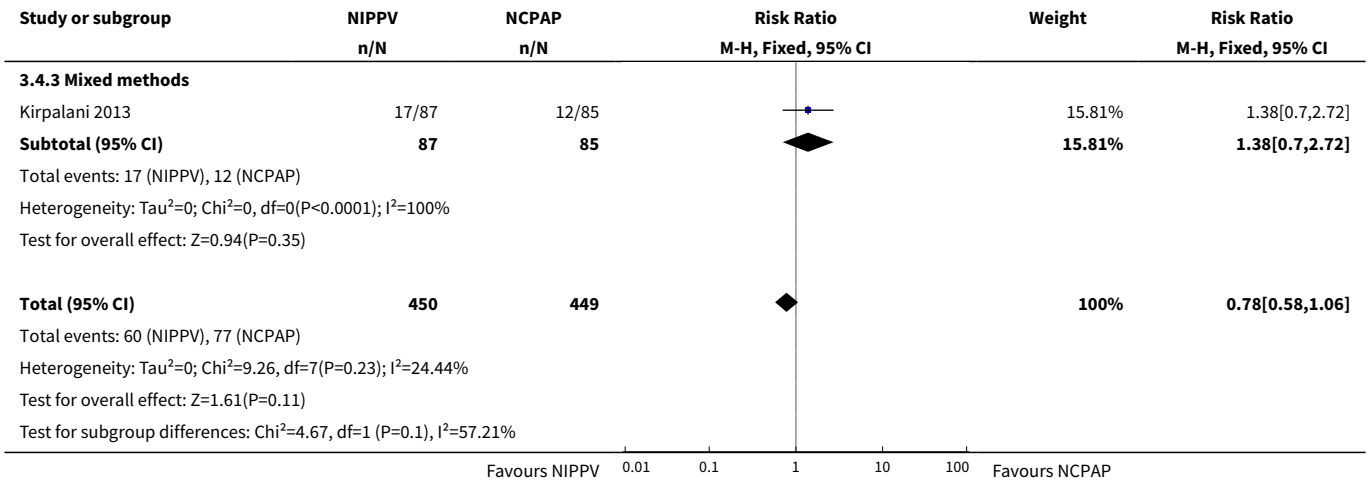
Study or subgroup	NIPPV n/N	NCPAP n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Synchronized NIPPV					
Lista 2009	0/20	0/20			Not estimable
Salama 2015	0/30	1/30		3.35%	0.33[0.01,7.87]
Wood 2013	0/60	2/60		5.59%	0.2[0.01,4.08]
Subtotal (95% CI)	**110**	**110**		**8.94%**	**0.25[0.03,2.19]**
Total events: 0 (NIPPV), 3 (NCPAP)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.82); I^2=0%					
Test for overall effect: Z=1.25(P=0.21)					



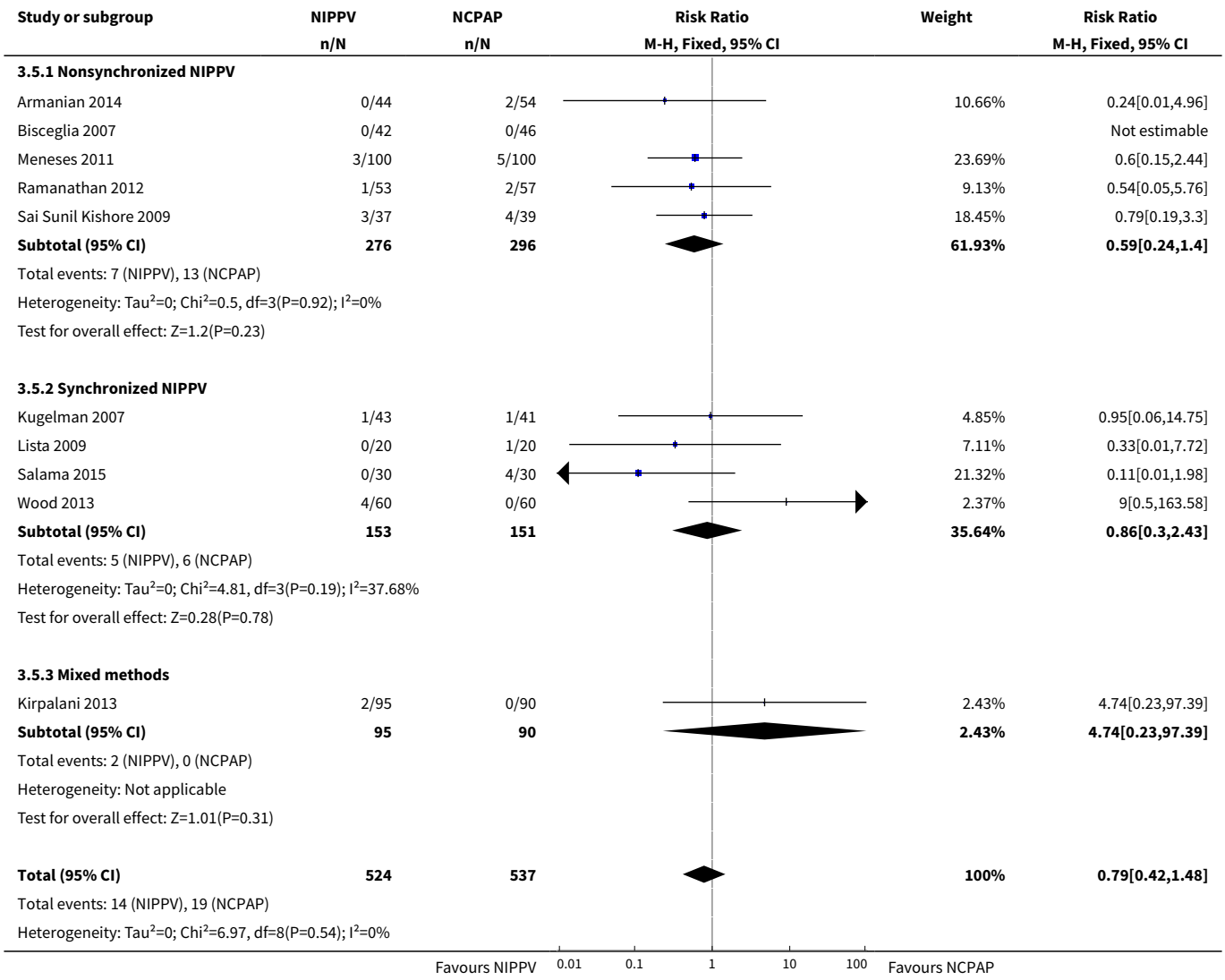


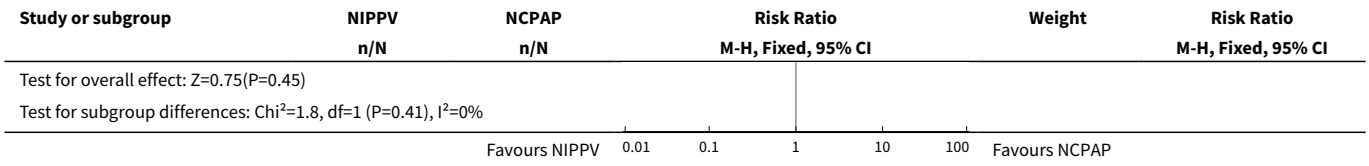
Analysis 3.4. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 4 Chronic lung disease.



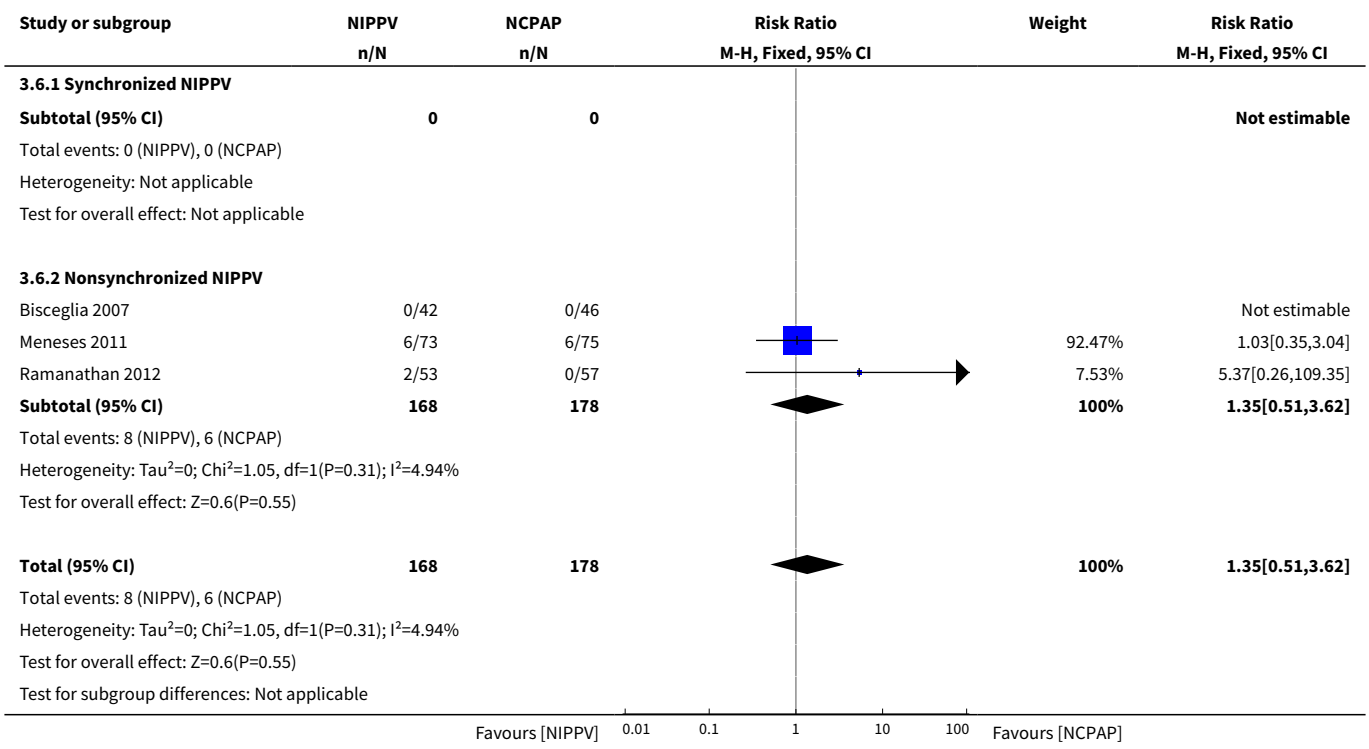


Analysis 3.5. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 5 Pneumothorax.





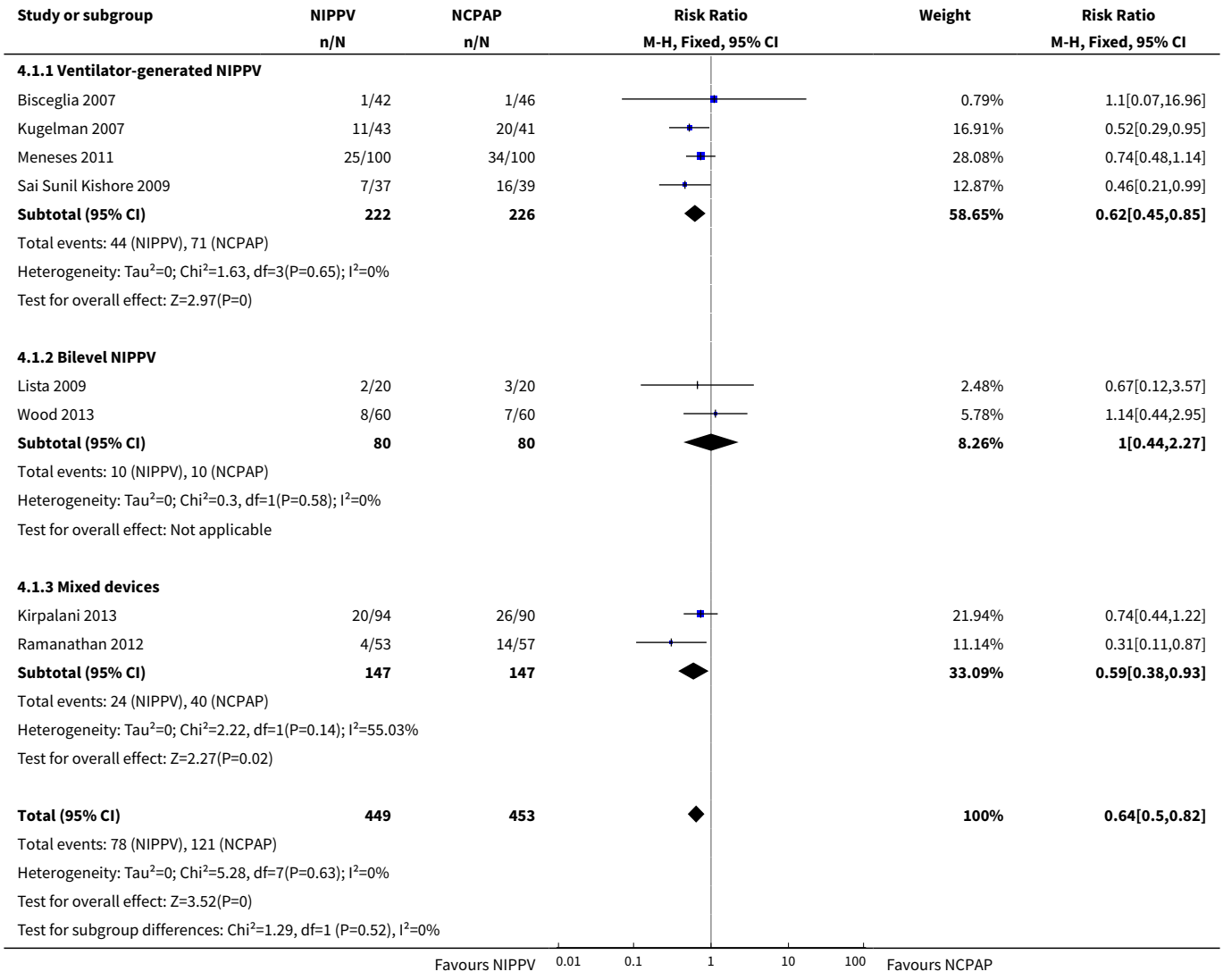
Analysis 3.6. Comparison 3 NIPPV vs NCPAP (by synchronization), Outcome 6 Severe intraventricular hemorrhage (grade III/IV).



Comparison 4. NIPPV vs NCPAP high-quality studies only (by device)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory failure (high-quality studies)	8	902	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.50, 0.82]
1.1 Ventilator-generated NIPPV	4	448	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.85]
1.2 Bilevel NIPPV	2	160	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.44, 2.27]
1.3 Mixed devices	2	294	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.38, 0.93]

Analysis 4.1. Comparison 4 NIPPV vs NCPAP high-quality studies only (by device), Outcome 1 Respiratory failure (high-quality studies).



APPENDICES

Appendix 1. Abbreviations used in this review

NIPPV: nasal intermittent positive pressure ventilation.

NCPAP: nasal continuous positive pressure ventilation.

RDS: respiratory distress syndrome.

BPD: bronchopulmonary dysplasia.

IVH: intraventricular hemorrhage.

Appendix 2. 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 randomized [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 (randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial)

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

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

Appendix 3. 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 categorized the method used to generate the allocation sequence as:
a. low risk (any truly random process, eg, random number table, computer random number generator);
b. high risk (any nonrandom process, eg, 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 categorized the method used to conceal the allocation sequence as:
a. low risk (eg, telephone or central randomization, consecutively numbered sealed opaque envelopes);
b. high risk (open random allocation, eg, unsealed or nonopaque 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 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:
a. low risk, high risk or unclear risk for participants;
b. low risk, high risk or unclear risk for personnel; or
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 randomized 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 categorized 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 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 prespecified outcomes and all expected outcomes of interest to the review have been reported);
b. high risk (when not all of the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so cannot be used; study failed 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 high risk of bias?

For each included study, we described any important concerns that we had about other possible sources of bias (eg, 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.

WHAT'S NEW

Date	Event	Description
6 February 2017	Amended	Added external source of support

CONTRIBUTIONS OF AUTHORS

ML, CB, and BL prepared the protocol for this review.

ML and CB performed a preliminary review and meta-analysis; BL updated the literature search, made independent quality assessments, and extracted data before comparing results and resolving differences for the final review.

All review authors participated in data analysis and interpretation of results of the updated review.

DECLARATIONS OF INTEREST

Review authors acknowledge no implied or actual potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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- 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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- National Institute for Health Research, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Because the technology and the terminology of these interventions have evolved in recent years, we expanded our search terms to include nasal intermittent mandatory ventilation, NIMV, nasal distending pressure, nasal positive pressure, nasal ventilation, non-invasive positive pressure ventilation, synchronized intermittent mandatory ventilation, SIMV, nasopharyngeal synchronized intermittent mandatory ventilation, bilevel CPAP, BiCPAP, BiPAP, and SiPAP. We amended the search dates to include articles written between protocol publication and the official search day for the review. Because we found the original requirement of infant enrollment in studies before the age of six hours to be too stringent, we relaxed the criteria to include studies in which nasal ventilation was described as "prophylactic" or "early."

We added methods and plans for "Summary of findings" tables and GRADE recommendations, which were not included in the original protocol.

INDEX TERMS

Medical Subject Headings (MeSH)

*Continuous Positive Airway Pressure [adverse effects]; *Intermittent Positive-Pressure Ventilation [adverse effects]; Bronchopulmonary Dysplasia [prevention & control]; Chronic Disease; Infant, Premature; Intracranial Hemorrhages; Intubation, Intratracheal [statistics & numerical data]; Oxygen Inhalation Therapy [statistics & numerical data]; Pneumothorax [epidemiology] [etiology]; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [*therapy]; Respiratory Insufficiency [*prevention & control]

MeSH check words

Humans; Infant, Newborn