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[Intervention Review]

# Continuous positive airway pressure (CPAP) for acute bronchiolitis in children

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## ABSTRACT

### Background

Acute bronchiolitis is one of the most frequent causes of emergency department visits and hospitalisation in children. There is no specific treatment for bronchiolitis except for supportive treatment, which includes ensuring adequate hydration and oxygen supplementation. Continuous positive airway pressure (CPAP) aims to widen the lungs' peripheral airways, enabling deflation of overdistended lungs in bronchiolitis. Increased airway pressure also prevents the collapse of poorly supported peripheral small airways during expiration. Observational studies report that CPAP is beneficial for children with acute bronchiolitis. This is an update of a review first published in 2015.

### Objectives

To assess the efficacy and safety of CPAP compared to no CPAP or sham CPAP in infants and children up to three years of age with acute bronchiolitis.

### Search methods

We conducted searches of CENTRAL (2017, Issue 12), which includes the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1946 to December, 2017), Embase (1974 to December 2017), CINAHL (1981 to December 2017), and LILACS (1982 to December 2017) in January 2018.

### Selection criteria

We considered randomised controlled trials (RCTs), quasi-RCTs, cross-over RCTs, and cluster-RCTs evaluating the effect of CPAP in children with acute bronchiolitis.

### Data collection and analysis

Two review authors independently assessed study eligibility, extracted data using a structured pro forma, analysed data, and performed meta-analyses.

### Main results

We included three studies with a total of 122 children (62/60 in intervention/control arms) aged up to 12 months that investigated nasal CPAP compared with supportive (or "standard") therapy. We included one new trial (72 children) that contributed data to the assessment of respiratory rate and need for mechanical ventilation for this update. The included studies were single-centre trials conducted in France, the

UK, and India. Two studies were parallel-group RCTs and one was a cross-over RCT. The evidence provided by the included studies was low quality; we assessed high risk of bias for blinding, incomplete outcome data, and selective reporting, and confidence intervals were wide.

The effect of CPAP on the need for mechanical ventilation in children with acute bronchiolitis was uncertain due to imprecision around the effect estimate (3 RCTs, 122 children; risk ratio (RR) 0.69, 95% confidence interval (CI) 0.14 to 3.36; low-quality evidence). None of the trials measured time to recovery. Limited, low-quality evidence indicated that CPAP decreased respiratory rate (2 RCTs, 91 children; mean difference (MD) -3.81, 95% CI -5.78 to -1.84). Only one trial measured change in arterial oxygen saturation, and the results were imprecise (19 children; MD -1.70%, 95% CI -3.76 to 0.36). The effect of CPAP on change in arterial partial carbon dioxide pressure ( $p\text{CO}_2$ ) was imprecise (2 RCTs, 50 children; MD -2.62 mmHg, 95% CI -5.29 to 0.05; low-quality evidence). Duration of hospital stay was similar in both CPAP and supportive care groups (2 RCTs, 50 children; MD 0.07 days, 95% CI -0.36 to 0.50; low-quality evidence). Two studies did not report about pneumothorax, but pneumothorax did not occur in one study. No studies reported occurrences of deaths. Several outcomes (change in partial oxygen pressure, hospital admission rate (from emergency department to hospital), duration of emergency department stay, and need for intensive care unit admission) were not reported in the included studies.

### Authors' conclusions

Limited, low-quality evidence suggests that breathing improved (a decreased respiratory rate) in children with bronchiolitis who received CPAP; this finding is unchanged from the 2015 review. Further evidence for this outcome was provided by the inclusion of a low-quality study for the 2018 update. Due to the limited available evidence, the effect of CPAP in children with acute bronchiolitis is uncertain for other outcomes. Larger, adequately powered trials are needed to evaluate the effect of CPAP for children with acute bronchiolitis.

## PLAIN LANGUAGE SUMMARY

### Continuous positive airway pressure (CPAP) for acute bronchiolitis in children

#### Review question

Is continuous positive airway pressure (CPAP) better or worse than supportive treatment for children with acute bronchiolitis?

#### Background

Bronchiolitis is inflammation of the small airways in the lungs, and a common cause for emergency department treatment among young children. Children usually receive supportive care that includes ensuring adequate hydration and providing supplementary oxygen as needed. Continuous positive airway pressure treatment involves providing positive air pressure by blowing air from a pump to keep airways open, and may be effective for children with bronchiolitis. This is an update of a review first published in 2015.

#### Search date

10 January 2018.

#### Study characteristics

We included three small randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method) involving a total of 122 children aged up to 12 months who were diagnosed with bronchiolitis. We included one new low-quality trial with 72 children in this update. The three studies were conducted at single centres in France, the UK, and India. All studies compared CPAP with standard therapy.

#### Study funding sources

One study was funded by a university hospital; one reported that no funding was received; and one did not mention the funding source.

#### Key results

Insufficient evidence was available to permit conclusions about the effect of CPAP on the need for mechanical ventilation in children with bronchiolitis. Limited, low-quality evidence indicated that breathing improved (respiratory rate decreased) in children who received CPAP. The length of time children spent in hospital was similar between the CPAP and the standard therapy groups. No children in the studies were reported to have died. The studies did not report on time to recovery, change in partial oxygen pressure, how often children were admitted to hospital from the emergency department, how long children were in the emergency department, and the need for intensive care admission. There were no local nasal effects, or shock as reported by one study. No children were reported to have had air in the cavity between the lungs and the chest wall, causing lung collapse (pneumothorax) as reported by one study. Two studies did not report about local nasal effects, shock, or pneumothorax. The study added for this update contributed data to the assessment of respiratory rate and need for mechanical ventilation.

#### Quality of the evidence

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We found limited, low-quality evidence related to CPAP for children with bronchiolitis. Evidence quality was reduced due to high risk of bias, losses to follow-up, selective reporting, and the wide range of values reported by the included studies.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Continuous positive airway pressure (CPAP) compared to supportive treatment for acute bronchiolitis in children

#### Continuous positive airway pressure (CPAP) compared to supportive treatment for acute bronchiolitis in children

**Patient or population:** children with acute bronchiolitis

**Settings:** inpatient

**Intervention:** CPAP

**Comparison:** supportive treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Supportive treatment	CPAP				
<b>Proportion of children requiring mechanical ventilation</b> observation Follow-up: 5 to 10 days	<b>50 per 1000</b>	<b>32 per 1000</b>	<b>RR 0.69</b> (0.14 to 3.36)	122 (3 studies)	⊕⊕⊕⊕ <b>low</b> <sup>1,2</sup>	
<b>Time to recovery</b> (hours)	<b>Study population</b>		Not estimable	0 (0 studies)	Not estimable	Data for time to recovery were not reported.
<b>Change in respiratory rate</b>	The mean change in respiratory rate in the intervention groups was <b>3.81 lower</b> (5.78 to 1.84 lower).		Mean change -3.81 (-5.78 to -1.84)	91 (2 studies)	⊕⊕⊕⊕ <b>low</b> <sup>3</sup>	

\*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **RR:** risk ratio

#### GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

<sup>1</sup>Downgraded by one level due to high risk of bias in one study, participants lost to follow-up, and selective reporting (Thia 2008).

<sup>2</sup>Wide confidence interval ([Lal 2018](#); [Thia 2008](#)).

<sup>3</sup>Downgraded by one level due to high risk of bias in two domains (blinding of participants and personnel and blinding of outcome assessment) ([Lal 2018](#)).

## BACKGROUND

### Description of the condition

Acute bronchiolitis is a frequent cause of emergency department visits and hospitalisation among infants (Hasegawa 2014; Praznik 2018; Rivera-Sepulveda 2017). Bronchiolitis, an inflammation of the small airways of the lungs, is predominantly a viral disease, usually affecting infants and children aged up to three years. The most common cause is respiratory syncytial virus (RSV) (CDC 2018). In Italy, the hospitalisation rate reported for all infants with bronchiolitis aged up to one year was 5.4% (Lanari 2015). In the USA, hospitalisation rates varied from 1.7 to 2.1 per 100 infant-seasons. 'Infant-season' is defined as the number of children multiplied by the number of seasons, for example 50 infants seen in two seasons equates to 100 infant-seasons. (Krilov 2017). Bronchiolitis occurs most frequently among non-breastfed male infants who live in crowded conditions (Meates-Dennis 2005).

Bronchiolitis typically presents with viral symptoms (sneezing, rhinorrhoea, and fever), which gradually progress to paroxysmal cough, wheezing, respiratory distress, and irritability. Chest findings are non-specific and include wheezing, with or without fine crackles. Although not required for diagnosis, chest x-ray may reveal hyperinflated lungs with patchy atelectasis. About 5% to 6% of children hospitalised with bronchiolitis respond poorly to treatment, and require intensive care management (Oakley 2017). About 75% of children admitted to intensive care units (ICU) require ventilatory support, and 18% of children requiring ventilatory support need invasive mechanical ventilation (Oakley 2017). Although uncommon, bronchiolitis may cause death; mortality rates range from 0.5% to 2% (Kabir 2003; Levy 1997). Mortality is higher in low-income countries (Scheltema 2017). Improved intensive care support has significantly reduced bronchiolitis-related mortality (Oakley 2017).

The standard management of bronchiolitis involves supportive care such as ensuring adequate fluid intake, antipyretics, and humidified oxygen supplementation if hypoxia is present (Davison 2004). Nebulised adrenaline, Hartling 2011a; Hartling 2011b, and hypertonic nebulised saline, Zhang 2017, have been found to be beneficial in acute bronchiolitis. Other therapeutic options, such as corticosteroids (Fernandes 2013), antibiotics (Farley 2014), bronchodilators (Gadomski 2014), heliox inhalation therapy (Liet 2015), chest physiotherapy (Roqué i Figuls 2016), nebulised recombinant human deoxyribonuclease (Merkus 2001; Nasr 2001), and steam inhalation (Umoren 2011), have been tried with no definitive benefit in bronchiolitis. A recent network meta-analysis of interventions for bronchiolitis found that epinephrine plus corticosteroids and epinephrine plus hypertonic saline were more effective than placebo (Guo 2018).

### Description of the intervention

Continuous positive airway pressure (CPAP) keeps airways open by administering positive pressure to the airways of spontaneously breathing patients throughout the respiratory cycle (Gupta 2016). Continuous positive airway pressure may be given to infants using nasal prongs, nasopharyngeal tube, or an infant nasal mask. Continuous positive airway pressure is administered using a commercially available circuit used in conjunction with a continuous flow source, or a ventilator. Continuous positive airway pressure devices may include provision of heated and

humidified airflow. Continuous positive airway pressure use has been associated with adverse effects, including local and systemic effects, such as nasal mucosal damage, nasal excoriation, scarring, pressure necrosis, and nasal septum distortion (Gupta 2016; Lee 2002; Robertson 1996), aspiration secondary to gastric insufflation (Kiciman 1998), pneumothorax (de Bie 2002), and decreased cardiac output due to impaired pulmonary blood flow (Lee 2002).

### How the intervention might work

The peripheral airways are most severely affected by inflammation in people with bronchiolitis. In infants with acute bronchiolitis, expiratory resistance is greater than inspiratory resistance, suggesting dynamic narrowing of the airways on expiration (Bont 2009). Acute bronchiolitis is associated with increased thoracic gas volume (air trapping) and total pulmonary resistance, with decreased dynamic compliance (Bont 2009). Infants initially compensate for the increased physiological dead space by increased respiratory rate, resulting in increased minute ventilation. Infants gradually become exhausted, and minute ventilation falls with increase in partial pressure of carbon dioxide (pCO<sub>2</sub>) and hypoxaemia. From this point, the infant may improve with oxygen supplementation, or may progress to respiratory failure.

Continuous positive airway pressure increases the functional residual capacity of lungs, which results in enlargement of the diameter of almost all airways, including the peripheral airways. The widening of the peripheral airways enables deflation of overdistended lungs in bronchiolitis. Increased airway pressure also prevents the collapse of poorly supported peripheral small airways during expiration. Continuous positive airway pressure has been used for people with bronchiolitis, and benefits have been reported in observational studies (Soong 1993). Continuous positive airway pressure may prevent the need for mechanical ventilation in infants with acute bronchiolitis.

### Why it is important to do this review

Acute bronchiolitis is a common clinical condition affecting infants and young children, yet no specific treatment is available except for supportive therapy. Continuous positive airway pressure is often used in the management of bronchiolitis on an empirical basis (i.e. based on personal experience without good evidence from the literature). We aimed to assess the role of CPAP for children with bronchiolitis.

## OBJECTIVES

To assess the efficacy and safety of CPAP compared to no CPAP or sham CPAP in infants and children up to three years of age with acute bronchiolitis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Randomised controlled trials (RCTs), quasi-RCTs, cross-over RCTs, and cluster-RCTs were eligible for inclusion.



## Types of participants

Children aged up to three years with a clinical diagnosis of acute bronchiolitis. We included all infants, regardless of respiratory syncytial virus (RSV) status.

## Types of interventions

We included CPAP treatment with any pressure level, and delivered by any type of device, by any mode (nasal prongs, face mask, etc.), and for any duration, compared to no CPAP or sham CPAP. We included studies that applied CPAP at any time after patient presentation. We excluded studies that investigated the use of high-flow nasal cannulae; this concept is addressed in another Cochrane Review (Beggs 2014). We included trials in which all children who were randomised to treatment and control arms received similar management in all other respects.

## Types of outcome measures

### Primary outcomes

1. Proportion of children requiring mechanical ventilation.
2. Time to recovery (as defined by the study).

### Secondary outcomes

1. Change in respiratory rate.
2. Change in arterial oxygen saturation.
3. Change in arterial partial pressure of carbon dioxide (pCO<sub>2</sub>) and partial pressure of oxygen (pO<sub>2</sub>).
4. Hospital admission rate (from emergency department to hospital).
5. Duration of emergency department stay.
6. Duration of hospital stay.
7. Need for intensive care unit admission.
8. Adverse events, e.g. local nasal effects, pneumothorax, and shock.
9. Mortality.

## Search methods for identification of studies

### Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2017, Issue 12), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1946 to December, 2017), Embase (1974 to December 2017), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1981 to December 2017), and LILACS (Latin American and Caribbean Health Science Information database) (1982 to December 2017) on 10 January 2018.

We used the search strategy in Appendix 1 to search CENTRAL and MEDLINE. We combined the MEDLINE search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted the search strategy to search Embase (Appendix 2), CINAHL (Appendix 3), and LILACS (Appendix 4). We did not apply any date, language, or publication restrictions.

## Searching other resources

We searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)) for completed and ongoing trials on 16 January 2018. We reviewed the reference lists of included studies to identify any additional studies. We contacted corresponding authors of included trials to ask about any additional ongoing RCTs or unpublished trials.

## Data collection and analysis

### Selection of studies

Two review authors (KRJ, JLM) independently assessed the titles and abstracts of studies obtained by the search to identify potentially relevant studies. We retrieved the full text of potentially relevant studies, and two review authors (KRJ, JLM) independently assessed these for inclusion in the review. A review author (KRJ) corresponded with study authors to clarify study eligibility where necessary. We listed excluded studies with the reasons for their exclusion. Any disagreements were resolved by discussion.

### Data extraction and management

Two review authors (KRJ, JLM) independently extracted data using a predefined data collection form in accordance with guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Data extracted included: source, eligibility, methods, participants and settings, interventions, outcomes, results, adverse effects, study funding source, and potential conflicts of interest. Any disagreements were resolved by discussion.

### Assessment of risk of bias in included studies

Two review authors (KRJ, JLM) independently assessed the risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion. We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear and provided quotes from the study report together with a justification for our judgement in the 'Risk of bias' tables. We summarised the 'Risk of bias' judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary. Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

We took risk of bias into account for studies that contributed to a given outcome when considering treatment effects.

### Assessment of bias in conducting the systematic review

We conducted the review according to a published protocol and reported deviations from it in [Differences between protocol and review](#).

### Measures of treatment effect

We entered outcome data for each study into data tables in Review Manager 5 to calculate treatment effects ([Review Manager 2014](#)). We calculated risk ratio (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes.

We undertook meta-analyses only where this was meaningful, that is where the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

### Unit of analysis issues

We planned to include RCTs, quasi-RCTs, cross-over RCTs, and cluster-RCTs. We considered data from the first study period for meta-analysis from cross-over trials. We plan that if we include cluster-RCTs in future review updates, we will conduct meta-analyses using the generic inverse-variance method in Review Manager 5 ([Review Manager 2014](#)). We plan to add standard parallel-group trials to the same generic inverse-variance meta-analysis.

### Dealing with missing data

We contacted investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study was identified as an abstract only). Where this was not possible, and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data such as standard deviations or correlation coefficients were missing and could not be obtained from the study authors, these were calculated from other available statistics, such as P values, according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Where possible, we extracted data to enable intention-to-treat analysis, which aims to include all participants randomised into a trial irrespective of what happened subsequently. We calculated and reported losses to follow-up if there was a discrepancy in the numbers randomised and the numbers analysed in each treatment group.

### Assessment of heterogeneity

We assessed clinical and methodological heterogeneity before pooling. We compared inclusion and exclusion criteria among the included studies to assess clinical heterogeneity. We assessed statistical heterogeneity by looking at forest plots, using a Chi<sup>2</sup> test and the I<sup>2</sup> statistic. Using the Chi<sup>2</sup> test, a low P value of < 0.1 (or a large Chi<sup>2</sup> test statistic relative to its degree of freedom) provided evidence of heterogeneity of intervention effects. We interpreted the value of the I<sup>2</sup> statistic as follows:

- 0% to 40%, heterogeneity might not be important;
- > 40% to 60%, moderate heterogeneity;
- > 60% to 80%, substantial heterogeneity; and

- > 80% to 100%, considerable heterogeneity.

### Assessment of reporting biases

We planned that if we were able to pool more than 10 trials, we would create and examine funnel plots to explore possible small-study and publication biases.

### Data synthesis

We carried out meta-analyses using Review Manager 5 ([Review Manager 2014](#)). We used a fixed-effect model for pooled data analysis. We used a random-effects meta-analysis if there was important (more than 40%) statistical heterogeneity among studies.

### GRADE and 'Summary of findings' table

We created a 'Summary of findings' table presenting the following outcomes: proportion of children requiring mechanical ventilation; time to recovery; and change in respiratory rate. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of the body of evidence as it relates to the studies that contributed data to the meta-analyses for the prespecified outcomes ([Atkins 2004](#)). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)), employing GRADEpro GDT software ([GRADEpro 2015](#)). We justified all decisions to downgrade the quality of evidence in footnotes, and made comments to aid the reader's understanding of the review where necessary.

### Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for the following groups.

1. CPAP with oxygen and CPAP with heliox.
2. RSV-positive and RSV-negative children.
3. Different CPAP pressure levels (< 6 cm, 6 cm to 10 cm, and > 10 cm water level (H<sub>2</sub>O)).
4. CPAP method: nasal prongs or face mask.
5. CPAP duration (< 12 hours, 12 to 24 hours, > 24 hours).
6. Trials with no CPAP and sham CPAP as comparator.
7. RCTs and cross-over RCTs.

We planned to use the Chi<sup>2</sup> test to test for subgroup interactions in Review Manager 5 ([Review Manager 2014](#)).

### Sensitivity analysis

We planned to perform sensitivity analyses to test the robustness of the results.

1. Repeating the meta-analysis after excluding studies with inadequate allocation concealment.
2. Repeating the meta-analysis after excluding studies in which the outcome evaluation was not blinded.
3. Repeating the meta-analysis imputing missing data as best-possible and worst-possible outcomes.
4. Comparing the difference in pooled analysis results by using fixed-effect and random-effects models.

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## RESULTS

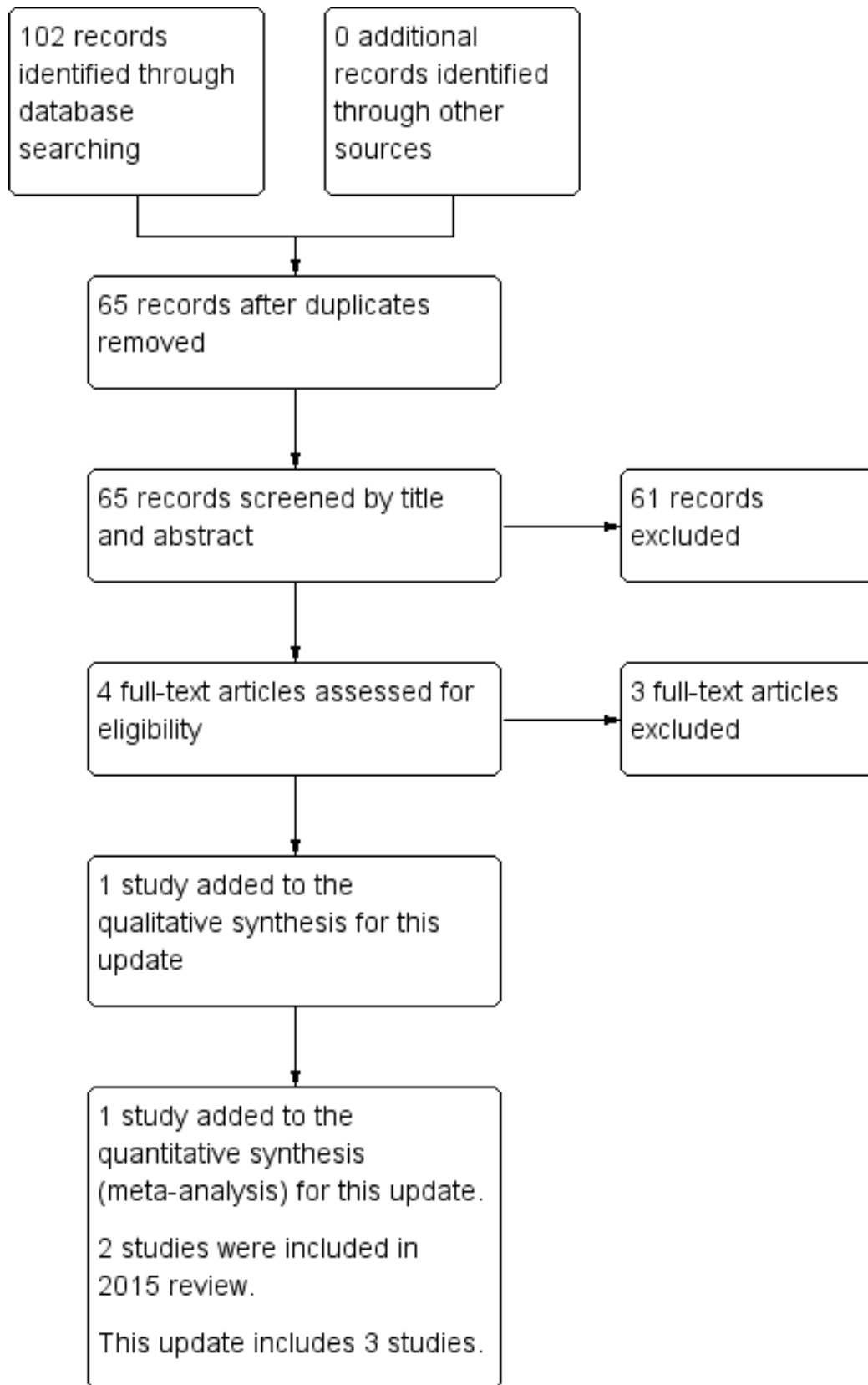
### Description of studies

We based all results on published data. We contacted study authors to request further details but received no additional information.

### Results of the search

We have presented search results for this update only. Searches in January 2018 identified 102 records ([Figure 1](#)). After removing duplicates, we screened 65 records by title and abstract. We retrieved four full-text reports for assessment, of which three studies were excluded ([Cesar 2017](#); [Chidini 2015](#); [Milési 2017](#)); see [Characteristics of excluded studies](#); [Figure 1](#). We included one new study for this update ([Lal 2018](#)).

**Figure 1. Study flow diagram for review update.**



## Included studies

We included three studies providing data from 122 children (Lal 2018; Milési 2013; Thia 2008); see [Characteristics of included studies](#)).

### Design

All included studies were single-centre trials (Lal 2018; Milési 2013; Thia 2008). Lal 2018 was described as a prospective, open-label randomised trial; Milési 2013 as a prospective, parallel-group RCT; and Thia 2008 was a randomised cross-over study.

### Sample sizes

The three included studies presented data from a total of 122 children. Sample sizes ranged from 19 children (10/9 treatment/control) in Milési 2013, to 72 children (36/36 treatment/control) in Lal 2018. We only included data from children in the first phase of the cross-over RCT (31 children; 16/15 treatment/control) by Thia 2008.

### Setting

The included studies were single-centre trials conducted in India (Lal 2018), France (Milési 2013), and the UK (Thia 2008). Two trials involved children who were inpatients (Lal 2018; Thia 2008). The study by Milési 2013 involved children being treated in a paediatric intensive care unit (PICU).

### Participants

#### Children's ages

Lal 2018 included children clinically diagnosed with bronchiolitis, but their age range was not clearly defined. Milési 2013 included infants aged up to six months, and Thia 2008 enrolled children aged up to 12 months. The mean age of children in the CPAP group was  $6.8 \pm 0.9$  weeks and  $10.92 \pm 41.33$  weeks in the trials by Milési 2013 and Thia 2008, respectively. The respective mean ages of children in the control groups were  $8.2 \pm 1.7$  weeks and  $10.5 \pm 48.93$  weeks (Milési 2013; Thia 2008).

#### Children's sex

Only Lal 2018 reported children's sex (N = 72): there were 26 boys and 10 girls in the treatment group, and 28 boys and 8 girls in the control group.

#### Respiratory syncytial virus (RSV) status

Milési 2013 included only children with RSV-positive bronchiolitis. Thia 2008 included 20 (of 31) children with RSV-positive bronchiolitis. Lal 2018 did not report RSV status.

### Study inclusion criteria

Lal 2018 included hospitalised children with a diagnosis of acute bronchiolitis. Milési 2013 included children with severe respiratory distress defined by a modified Wood's clinical asthma score (m-WCAS) > 4; no invasive or non-invasive ventilation, including nasal continuous positive airway pressure (nCPAP), before admission to PICU. Thia 2008 enrolled children with capillary pCO<sub>2</sub> measurements > 6 kPa.

None of the children in the three included trials were reported to have comorbidities.

### Study exclusion criteria

Lal 2018 excluded children in imminent need of mechanical ventilation. Milési 2013 excluded children with underlying cardiopulmonary or neuromuscular disease and who had pneumothorax on chest radiograph. Thia 2008 excluded children with congenital heart disease, neuromuscular disease, or mid-face dysmorphism that prohibited the use of nasal prongs, those who required immediate invasive ventilation, and pCO<sub>2</sub> > 12 kPa.

### Interventions

Lal 2018 used bubble CPAP delivered in the children's ward with a Gregory circuit; the pressure generated was not reported. Bubble CPAP treatment was provided for one hour once only. Children in the control arm received "standard care" in the form of adequate hydration and oxygen support through mask or hood for one hour once only. Children in the treatment group in the Milési 2013 trial received nCPAP 6 cm H<sub>2</sub>O delivered using the Infant Flow Ventilator via a mask connected to a twin injector nozzle fixed to the child using a specially designed bonnet for children for six hours. Children in the control group received a heated and humidified air/oxygen mixture delivered through a nasal cannula that allowed a maximum gas flow of 2.5 L/min. (Milési 2013). Children in the treatment group in the study by Thia 2008 received "standard treatment" (defined as minimal handling, intravenous fluids, and oxygen by nasal prongs or face mask) plus nCPAP for 12 hours followed by standard treatment alone for the next 12 hours. Children in the control group received standard treatment alone for 12 hours followed by standard treatment plus nCPAP for the next 12 hours.

### Outcomes

The primary outcome in the study by Lal 2018 was change in respiratory rate after the first hour of treatment. The secondary outcome was change in Silverman-Anderson score, and a Modified Paediatric Society of New Zealand Severity Score (MPSNZ-SS) before starting treatment and at one hour following the start of treatment (Lal 2018).

The primary outcome in Milési 2013 was clinical score for respiratory distress at baseline and at six hours after beginning treatment. Respiratory distress was evaluated with the m-WCAS. Secondary outcome measures were respiratory and cardiac rate, average blood pressure at baseline and six hours. However, the outcome measures for this study were not clearly defined in the published study report, and data were taken from information at ClinicalTrials.gov. Other secondary outcome measures were manometric: variation of oesophageal pressure at baseline and 6 hours, and gasometric: minimal fraction of inspired oxygen (FiO<sub>2</sub>) necessary to reach an oxygen saturation between 94% and 98%, transcutaneous pCO<sub>2</sub>, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) (Milési 2013).

Thia 2008 assessed change in pCO<sub>2</sub> at 12 hours of intervention as the primary outcome measure. Secondary outcomes were capillary pH, respiratory rate, pulse rate, and the need for invasive ventilatory support (Thia 2008).

### Funding sources

Lal 2018 reported that no funding was received; Milési 2013 was funded by the clinical research department of a university hospital; and Thia 2008 did not mention source of funding.

**Excluded studies**

We excluded nine studies ([Characteristics of excluded studies](#)). Three studies were not RCTs ([Balanzat 2006](#); [Javouhey 2008](#); [Smith 1993](#)); two studies investigated comparisons that were not relevant to this review ([Cesar 2017](#); [Milési 2017](#)); and four studies investigated interventions that were not relevant to this review ([Chidini 2011](#); [Chidini 2015](#); [Hough 2011](#); [Yañez 2008](#)). We excluded three studies for this update ([Cesar 2017](#); [Chidini 2015](#); [Milési 2017](#)).

**Studies awaiting classification**

We did not identify any studies awaiting classification.

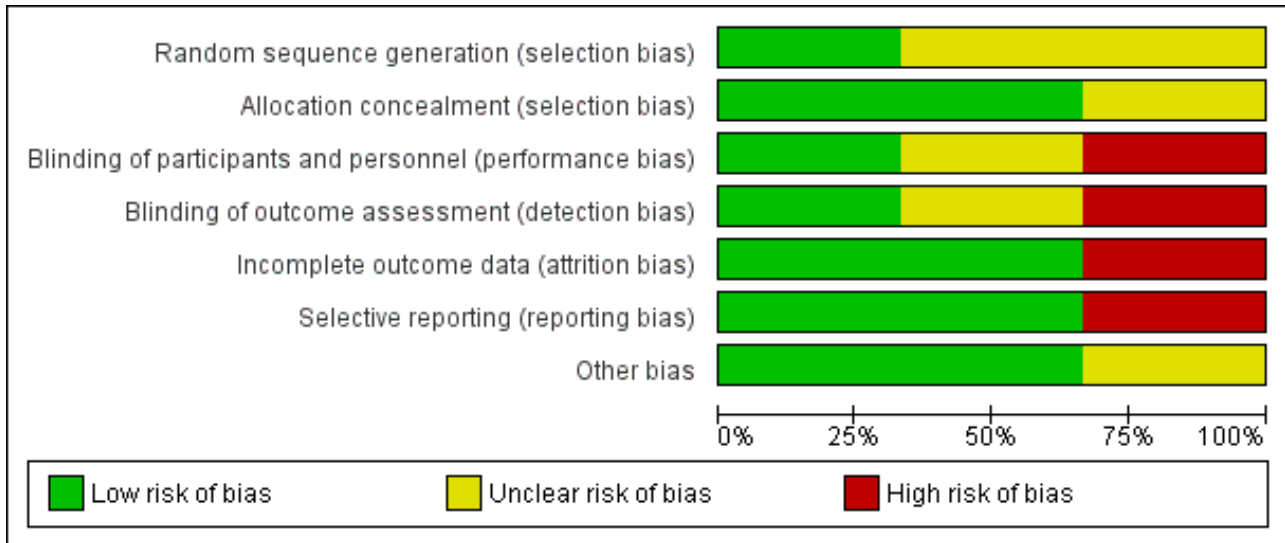
**Ongoing studies**

We did not identify any ongoing studies.

**Risk of bias in included studies**

'Risk of bias' assessments are presented in [Figure 2](#) and [Figure 3](#).

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



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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Lal 2018	+	+	-	-	+	+	+
Milési 2013	?	+	?	+	+	+	+
Thia 2008	?	?	+	?	-	-	?

**Allocation**

We assessed the method of random sequence generation as at unclear risk of bias due to inadequate reporting in two included studies (Milési 2013; Thia 2008). Lal 2018 used a computer software package for sequence generation and was assessed as at low risk of bias. We assessed allocation concealment as at low risk of bias in two studies that used sequentially numbered, opaque, and sealed envelopes (Lal 2018; Milési 2013). The method of allocation concealment was not reported for Thia 2008 and was therefore assessed as at unclear risk of bias.

**Blinding**

We assessed blinding of parents of included infants as at high risk of bias for the study by Lal 2018, which was an open-label study. Milési 2013 did not report blinding and was assessed as at unclear risk of bias. We assessed Thia 2008 as at low risk of bias for this domain.

**Incomplete outcome data**

Lal 2018 reported that four children in the treatment arm (two who required mechanical ventilation and two did not tolerate CPAP) and one child who required mechanical ventilation in the control arm did not complete the intervention; we assessed this study as at low risk of bias because data for all randomised children were included in the analysis. Milési 2013 reported no losses to follow-up and was assessed as at low risk of bias. Thia 2008 reported that two children from the control arm (one who required mechanical ventilation and another who was re-allocated to the CPAP arm) did not complete the intervention and were not included in the analysis. We assessed this study as at high risk of bias for this domain (Thia 2008).

**Selective reporting**

We assessed Lal 2018 as at low risk of bias for selective reporting, as all prespecified outcomes were reported. Milési 2013 reported all prespecified outcomes and was assessed as at low risk of bias for this domain. Thia 2008 did not report data for a secondary



outcome (capillary pH) and was assessed as at high risk of bias for this domain.

**Other potential sources of bias**

The included studies were free of other potential sources of bias.

**Effects of interventions**

See: [Summary of findings for the main comparison Continuous positive airway pressure \(CPAP\) compared to supportive treatment for acute bronchiolitis in children](#)

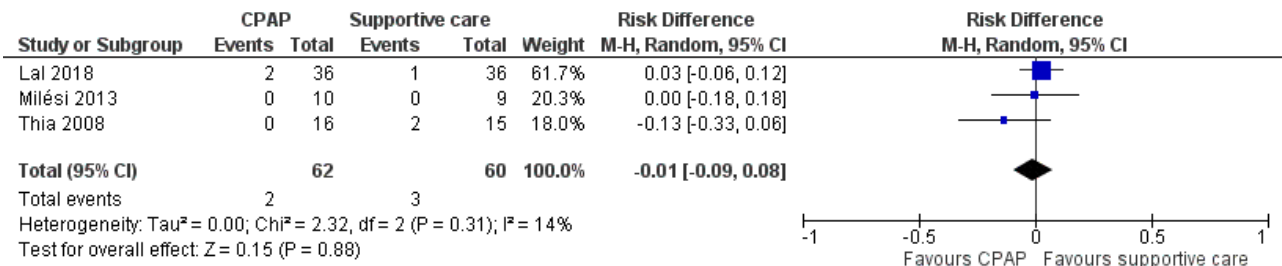
We based all results on published data. We contacted study authors to request further details but received no additional information.

**Primary outcomes**

**1. Proportion of children requiring mechanical ventilation**

In Lal 2018, two children in the CPAP group (N = 36) and one child in the control group (N = 36) required ventilation. No children in Milési 2013 required mechanical ventilation. Thia 2008 reported that two children in the control group (N = 15) and no children in the CPAP group (N = 16) required mechanical ventilation. The difference was not statistically significant (risk ratio 0.69, 95% confidence interval (CI) 0.14 to 3.36; 122 children; 3 studies; I<sup>2</sup> = 34%; Analysis 1.1; Figure 4; low-quality evidence).

**Figure 4. Forest plot of comparison: 1.1 Proportion of children requiring mechanical ventilation.**



**2. Time to recovery (as defined by the included trials)**

None of the included studies provided data regarding children's time to recovery.

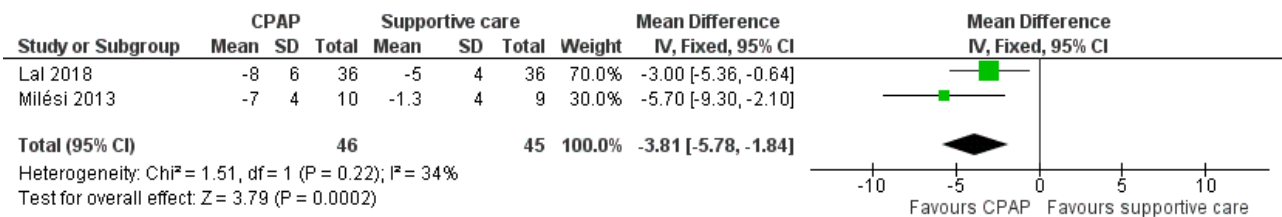
**Secondary outcomes**

**1. Change in respiratory rate**

Data for change in respiratory rate from start to end of intervention were available from two studies (Lal 2018; Milési 2013). The

respiratory rate was decreased in children in the CPAP group (mean difference (MD) -3.81, 95% CI -5.78 to -1.84; 91 children; 2 studies; I<sup>2</sup> = 34%; Analysis 2.1; Figure 5; low-quality evidence). There was no significant change in respiratory rate between groups in the study by Thia 2008. However, numerical values were not provided, and data could not be pooled for meta-analysis. Decreased respiratory rate is a beneficial effect for children with bronchiolitis.

**Figure 5. Forest plot of comparison: 2.1 Change in respiratory rate.**



**2. Change in arterial oxygen saturation**

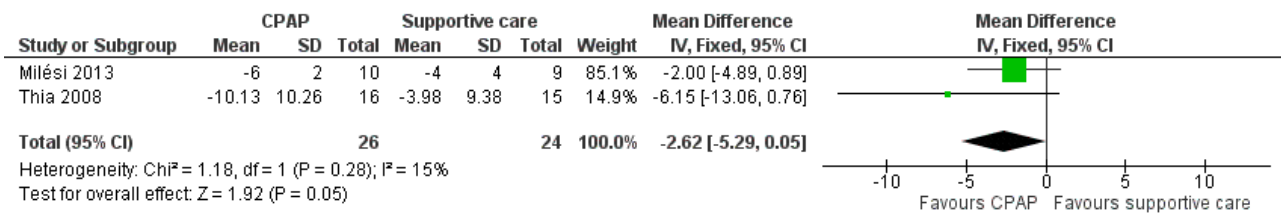
Only Milési 2013 provided data for this outcome. Change in arterial oxygen saturation did not differ between groups (MD -1.70, 95% CI -3.76 to 0.36; 19 children; I<sup>2</sup> = 0%; Analysis 2.2).

**3. Change in arterial partial pressure of carbon dioxide (pCO<sub>2</sub>) and partial pressure of oxygen (pO<sub>2</sub>)**

Two studies provided data for this outcome (Milési 2013; Thia 2008). Change in pCO<sub>2</sub> did not differ between children in the CPAP group and those in the control group (MD -2.62, 95% CI -5.29 to 0.05; 50 children; 2 studies; I<sup>2</sup> = 15%; Analysis 2.3; Figure 6).



**Figure 6. Forest plot of comparison: 2.3 Change in arterial partial pressure of carbon dioxide (mmHg).**



**4. Hospital admission rate (from emergency department to hospital)**

None of the included trials reported this outcome.

**5. Duration of emergency department stay**

None of the included trials reported this outcome.

**6. Duration of hospital stay**

Two studies reported data for this outcome (Milési 2013; Thia 2008). Duration of hospital stay was similar between intervention and control groups (MD 0.07, 95% CI -0.36 to 0.50; 50 children; 2 studies; I<sup>2</sup> = 0%; Analysis 2.4).

**7. Need for intensive care unit admission**

None of the included trials reported this outcome.

**8. Adverse events, such as local nasal effects, pneumothorax, and shock**

Two studies did not report data related to local nasal effects, pneumothorax, and shock (Milési 2013; Thia 2008). Lal 2018 reported no local nasal effects, pneumothorax, or shock in either group, although two children in the CPAP group had irritability. No other adverse events were reported.

**9. Mortality**

There were no deaths reported in the included studies.

**Subgroup and sensitivity analyses**

Subgroup and sensitivity analyses were not possible because there were too few included studies for these to be conducted.

**DISCUSSION**

**Summary of main results**

We evaluated the effects of CPAP for acute bronchiolitis in children. We included three studies that involved a total of 122 children. We found no difference in the requirement for mechanical ventilation among children treated with CPAP compared with those administered supportive care.

Limited, low-quality evidence suggests the respiratory rate among children with bronchiolitis who receive CPAP is decreased. Change in arterial partial pressure of carbon dioxide (pCO<sub>2</sub>) did not differ between children who received CPAP and those who received standard treatment. Hospital stay duration was similar between children treated with CPAP and those who received standard treatment. The included studies did not assess time to recovery, change in arterial oxygen saturation, change in partial pressure of oxygen (pO<sub>2</sub>), hospital admission rate (from emergency

department to hospital), duration of emergency department stay, or need for intensive care unit admission. Two included studies reported no events of pneumothorax or other adverse effects such as local nasal effects and shock. There were no local nasal effects, pneumothorax, and shock as reported by one study. Lal 2018 reported that two children in the CPAP group experienced irritability.

We assessed the quality of the evidence as low (Summary of findings for the main comparison).

**Overall completeness and applicability of evidence**

The three included studies were small (total of 122 children). To detect a 20% difference in the primary outcome (proportion of children requiring mechanical ventilation) with 80% power, 88 participants per group (total 176) are required. Data were not available for most of the secondary outcomes of this review. There was high risk of bias for two domains in one included trial (Thia 2008). We found some evidence to suggest that CPAP for acute bronchiolitis is beneficial in decreasing respiratory rate, but evidence was lacking for other outcomes.

**Quality of the evidence**

We found low-quality evidence for both proportion of children requiring mechanical ventilation and change in respiratory rate (Summary of findings for the main comparison). We downgraded evidence quality because of high risk of bias for incomplete outcome data (participants lost to follow-up) and selective reporting, and wide confidence intervals (Lal 2018; Thia 2008). We assessed evidence quality for change in respiratory rate as low due to high risk of bias in Lal 2018, which did not blind participants (parents of children), study personnel, or outcome assessors.

**Potential biases in the review process**

The search strategy for this review was broad and designed by the Cochrane Acute Respiratory Infections Information Specialist. It is unlikely that relevant studies were missed. Two review authors independently carried out study selection, data extraction, and analysis. There was no blinding of participants, study personnel, or outcome assessors, and this domain was assessed as at high risk of bias (see Characteristics of included studies). We assessed Milési 2013 as at unclear risk of bias for random sequence generation (method not reported) and blinding of participants and personnel (blinding not reported) (see Characteristics of included studies). We assessed Thia 2008 as at unclear risk of bias for random sequence generation (method not reported), allocation concealment (method not reported), and blinding of outcome assessment (not reported), and at high risk of bias for incomplete outcome data (two children did not complete the study and were not included in the analysis) and selective reporting (one outcome

was not reported) (see [Characteristics of included studies](#)). Data were not available for many outcomes, and we were unable to obtain additional information from trial authors. [Thia 2008](#) was a cross-over trial, and we used data from the first trial phase for meta-analysis, which may have decreased study power.

### Agreements and disagreements with other studies or reviews

[Donlan 2011](#) conducted a systematic review of CPAP use for acute bronchiolitis that included both randomised and observational studies. Only one study, [Thia 2008](#), was common to both [Donlan 2011](#) and our review. [Donlan 2011](#) reported that CPAP reduced pCO<sub>2</sub>, respiratory rate, and m-WCAS in acute bronchiolitis, but assessed the quality of the evidence as low. [Donlan 2011](#) also found no conclusive evidence that CPAP reduced need for intubation.

An excluded study, [Chidini 2011](#), compared CPAP delivered by helmet versus facial mask. [Chidini 2011](#) concluded that CPAP delivered by helmet was associated with more successful treatment outcomes, less sedation and sores, and a similar improvement in oxygenation with respect to the facial mask in cases of acute lung injury.

Another excluded study, [Yañez 2008](#), compared non-invasive ventilation using inspiratory positive airway pressure and expiratory positive airway pressure plus standard treatment (study group) to standard treatment (control group) in 50 children with acute respiratory failure. Non-invasive ventilation was associated with improvement in hypoxaemia and the signs and symptoms of acute respiratory failure with protection from endotracheal intubation ([Yañez 2008](#)).

Observational studies have suggested that CPAP is beneficial for children with acute viral bronchiolitis ([Cambonie 2008](#); [Essouri 2011](#); [Larrar 2006](#); [McNamara 1997](#); [Soong 1993](#)).

## AUTHORS' CONCLUSIONS

### Implications for practice

Several outcomes of this review were not measured in the included studies, and where data were available, findings were not sufficiently precise to enable drawing definitive conclusions for most outcomes. Limited, low-quality evidence suggests a decreased respiratory rate among children with bronchiolitis who receive continuous positive airway pressure (CPAP), but there is a lack of evidence for other outcomes.

### Implications for research

Larger, adequately powered trials are needed to evaluate the effects of CPAP in children with acute bronchiolitis. The timing and duration of CPAP application, level of CPAP, type of device for CPAP application, and both clinical (including side effects, e.g. vomiting and aspiration) and laboratory outcomes need to be evaluated in future trials.

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Soong WJ, Hwang B, Tang RB. Continuous positive airway pressure by nasal prongs in bronchiolitis. *Pediatric Pulmonology* 1993;**16**(3):163-6.

**Umoren 2011**

Umoren R, Odey F, Meremikwu MM. Steam inhalation or humidified oxygen for acute bronchiolitis in children up to three years of age. *Cochrane Database of Systematic Reviews* 2011, Issue 1. [DOI: [10.1002/14651858.CD006435.pub2](https://doi.org/10.1002/14651858.CD006435.pub2)]

**Zhang 2017**

Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database of Systematic Reviews* 2017, Issue 12. [DOI: [10.1002/14651858.CD006458.pub4](https://doi.org/10.1002/14651858.CD006458.pub4)]

**References to other published versions of this review**
**Jat 2013**

Jat KR, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database of Systematic Reviews* 2013, Issue 4. [DOI: [10.1002/14651858.CD010473](https://doi.org/10.1002/14651858.CD010473)]

**Jat 2015**

Jat KR, Mathew JL. Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database of Systematic Reviews* 2015, Issue 1. [DOI: [10.1002/14651858.CD010473.pub2](https://doi.org/10.1002/14651858.CD010473.pub2)]

**CHARACTERISTICS OF STUDIES**
**Characteristics of included studies [ordered by study ID]**
**Lal 2018**

Methods	Study design: prospective, open-label, randomised, single-centre study
	Study duration: November 2014 to March 2016



**Lal 2018** (Continued)

Participants	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Setting: inpatient, single-centre study</li> <li>• Country: India</li> <li>• Number: total 72; treatment group (36), control (36)</li> <li>• Age (mean (SD))           <ul style="list-style-type: none"> <li>* Treatment group: 4.0 (2.6) months</li> <li>* Control group: 4.7 (3.1) months</li> </ul> </li> <li>• Sex (m/f)           <ul style="list-style-type: none"> <li>* Treatment group: 26/10</li> <li>* Control group: 28/8</li> </ul> </li> <li>• Comorbidities: None</li> </ul> <p><b>Study enrolment criteria:</b> 72 children hospitalised with clinical diagnosis of acute bronchiolitis were eligible for inclusion in the study. Bronchiolitis was defined as respiratory distress (respiratory rate <math>\geq</math> 50/min) in an infant aged from 1 month to 1 year, along with wheezing on auscultation and hyperinflated lung.</p> <p><b>Exclusion criteria:</b> infants who were in imminent need of ventilator support were excluded.</p>
Interventions	<p><b>Treatment group</b></p> <ul style="list-style-type: none"> <li>• Intervention: bubble CPAP delivered in the children's ward with a Gregory circuit</li> <li>• Duration, frequency: for 1 hour, once only.</li> </ul> <p><b>Control group</b></p> <ul style="list-style-type: none"> <li>• Intervention: "standard care", which included maintenance of adequate hydration and oxygenation. Oxygen was delivered through mask or hood.</li> <li>• Duration, frequency: for 1 hour, once only.</li> </ul>
Outcomes	<p><b>Primary outcomes:</b> change in respiratory rate after the first hour of treatment</p> <p><b>Secondary outcomes:</b> change in Silverman-Anderson score, and a Modified Paediatric Society of New Zealand Severity Score (MPSNZ-SS): before starting treatment, and at 1 hour following the start of treatment</p> <p>Need for mechanical ventilation was reported.</p> <p>Time to recovery was not reported.</p>
Notes	<p>Funding source: no funding received</p> <p>Contact with study authors for additional information: yes. However, no additional information was provided.</p> <p>Other: conflict of interest stated as none</p>
<b>Risk of bias</b>	
<b>Bias</b>	<b>Authors' judgement</b> <b>Support for judgement</b>
Random sequence generation (selection bias)	Low risk                      Randomisation in blocks of 8 using computer software
Allocation concealment (selection bias)	Low risk                      Allocation done using sequentially numbered, opaque, sealed envelopes.

**Lal 2018** (Continued)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded to the intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 child in the control arm (who needed mechanical ventilation) and 4 children in the intervention arm (2 who needed mechanical ventilation and 2 who did not tolerate CPAP) did not complete the study. Intention-to-treat analysis conducted.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in study were reported.
Other bias	Low risk	Funding: declared by authors as none Competing interests: declared by authors as none

**Milési 2013**

Methods	Study design: prospective, randomised, single-centre study Duration of study: November 2006 to March 2009
Participants	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>• Setting: PICU, single-centre study</li> <li>• Country: France</li> <li>• Number: total 19; treatment group (10), control (9)</li> <li>• Age (mean (SD))           <ul style="list-style-type: none"> <li>* Treatment group: 6.8 (0.9) weeks</li> <li>* Control group: 8.2 (1.7) weeks</li> </ul> </li> <li>• Sex (m/f)           <ul style="list-style-type: none"> <li>* Treatment group: not reported</li> <li>* Control group: not reported</li> </ul> </li> <li>• Comorbidities: none</li> </ul> <p><b>Study enrolment criteria</b></p> <ul style="list-style-type: none"> <li>• RSV bronchiolitis confirmed by nasopharyngeal enzyme immuno-assay</li> <li>• Severe respiratory distress defined as m-WCAS &gt; 4</li> <li>• No invasive or non-invasive ventilation, including nCPAP, prior to PICU admission</li> <li>• No underlying cardiopulmonary or neuromuscular disease and no pneumothorax on chest radiograph</li> <li>• Authorisation signed by parents</li> </ul>
Interventions	<p><b>Active intervention:</b> nCPAP 6 cm H<sub>2</sub>O with the Infant Flow Ventilator via a mask connected to a twin injector nozzle fixed to the child by a specially designed bonnet for 6 hours</p> <p><b>Control:</b> infants in the control group continued to receive a heated and humidified air/oxygen mixture delivered through a nasal cannula, which allowed a maximum gas flow of 2.5 L/min</p>
Outcomes	<p><b>Primary outcomes:</b> clinical score for respiratory distress at baseline and at 6 hours after beginning the procedure. Respiratory distress was evaluated with m-WCAS.</p> <p><b>Secondary outcomes:</b> respiratory and cardiac rate, average blood pressure at baseline and 6 hours</p>

**Milési 2013** (Continued)

**Note:** outcome measures were not clearly defined in the published trial; these were taken from the registered trial at ClinicalTrials.gov

**Manometric:** variation of oesophageal pressure at baseline and 6 hours

**Gasometric:** minimal  $\text{FiO}_2$  necessary to reach an oxygen saturation between 94% and 98%, transcutaneous  $\text{pCO}_2$ ,  $\text{PaO}_2/\text{FiO}_2$

**Notes**

Funding source: Clinical Research Department of Montpellier University Hospital Centre.

The study was conducted at the Pediatric Intensive Care Unit, CHU Montpellier, France over 3 consecutive RSV epidemic periods, from November 2006 to March 2009.

Contact with study authors for additional information: yes. However, no additional information was provided.

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation is not clearly reported. Children "were randomly assigned" to intervention or control group.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes used.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were not aware of the allocated intervention.
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were no losses to follow-up.
Selective reporting (reporting bias)	Low risk	All defined outcomes were reported.
Other bias	Low risk	Conflicts of interest: declared by authors as none  Funding source: Clinical Research Department of Montpellier University Hospital Centre

**Thia 2008**
**Methods**

Study design: randomised cross-over, single-centre study

Duration of study: October 2002 to March 2005

**Participants**
**Inclusion criteria**

- Setting: inpatient, single-centre study
- Country: UK
- Number: total 31; treatment group (16), control (15)



**Thia 2008** (Continued)

- Age (mean (SD))
  - \* Treatment group: 10.9 (4.1) weeks
  - \* Control group: 10.5 (8.9) weeks
- Sex (m/f)
  - \* Treatment group: not reported
  - \* Control group: not reported
- Comorbidities: none

**Study enrolment criteria:** children aged up to 12 months with clinical diagnosis of bronchiolitis and capillary pCO<sub>2</sub> measurements > 6 kPa

**Exclusion criteria:** children with congenital heart disease, neuromuscular disease, and mid-face dysmorphism prohibiting the use of nasal prongs, requiring immediate invasive ventilation, and pCO<sub>2</sub> > 12 kPa were excluded

Interventions	Eligible children were randomised to receive either standard treatment plus nCPAP for 12 hours followed by standard treatment alone for the next 12 hours, or standard treatment alone for 12 hours followed by standard treatment plus nCPAP for the next 12 hours. Standard treatment was defined as minimal handling, intravenous fluids, and oxygen by nasal prongs or face mask. Nasal CPAP was applied using the Infant Flow System with pressures of 5 to 6 cm H <sub>2</sub> O.
Outcomes	<p><b>Primary outcome:</b> change in pCO<sub>2</sub> at 12 hours of intervention</p> <p><b>Secondary outcomes:</b> capillary pH, respiratory rate, pulse rate, and the need for invasive ventilatory support</p>
Notes	<p>The study was conducted over 3 winters from October 2002 to March 2005.</p> <p>Funding: not reported</p> <p>Contact with study authors for additional information: yes. However, no additional information was provided.</p>

**Risk of bias**

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	It was not possible to blind participants and personnel to the interventions due to the inherently different methods of administration. Unblinding was less likely to have introduced bias because the primary outcome was objective in nature.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	2 children (1 who required ventilation and another who shifted to CPAP) did not complete the intervention in control arm and were not included in the analysis.
Selective reporting (reporting bias)	High risk	A secondary outcome (capillary pH) mentioned in the study methods section was not reported.

**Thia 2008** (Continued)

Other bias	Unclear risk	Conflicts of interest: none
		Funding: not reported

CPAP: continuous positive airway pressure  
 FiO<sub>2</sub>: fraction of inspired oxygen  
 H<sub>2</sub>O: pressure level measures as water column  
 m-WCAS: modified Wood's clinical asthma score  
 nCPAP: nasal continuous positive airway pressure  
 PaO<sub>2</sub>/FiO<sub>2</sub>: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen  
 pCO<sub>2</sub>: arterial partial pressure of carbon dioxide  
 pH: measurement unit for acidity  
 PICU: paediatric intensive care unit  
 RSV: respiratory syncytial virus  
 SD: standard deviation

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

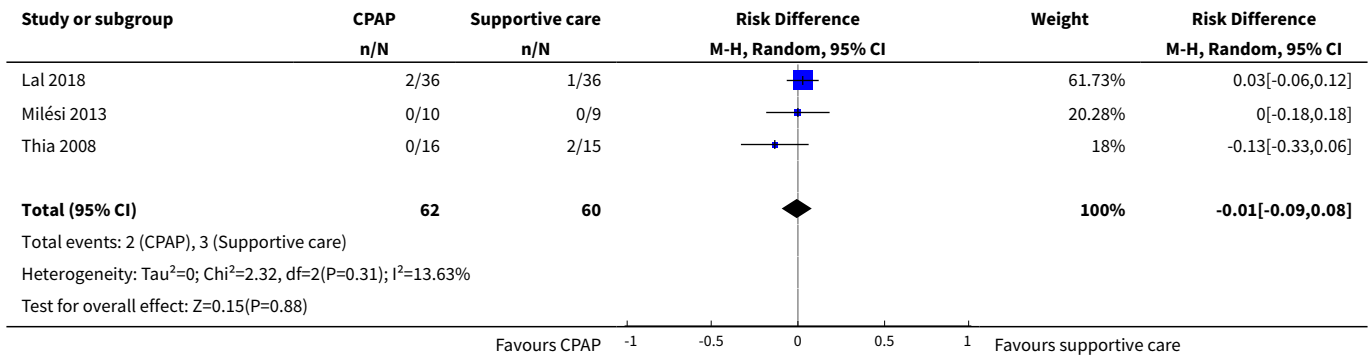
Study	Reason for exclusion
Balanzat 2006	Not RCT. Observational study
Cesar 2017	Wrong comparison. Study compared high-flow nasal canula with CPAP.
Chidini 2011	Wrong intervention. Study compared different methods of CPAP delivery rather than CPAP versus no CPAP.
Chidini 2015	Wrong intervention. Study compared different methods of CPAP delivery rather than CPAP versus no CPAP.
Hough 2011	Wrong intervention. Study compared different levels of CPAP produced by high-flow nasal prongs.
Javouhey 2008	Not RCT. Retrospective study
Milési 2017	Wrong comparison. Study compared high-flow nasal canula with CPAP.
Smith 1993	Not RCT. Study compared different levels of peak end expiratory pressure in mechanically ventilated children with bronchiolitis.
Yañez 2008	Wrong intervention. Study evaluated non-invasive ventilation rather than CPAP.

CPAP: continuous positive airway pressure  
 RCT: randomised controlled trial

**DATA AND ANALYSES**
**Comparison 1. Proportion of children requiring mechanical ventilation**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of children requiring mechanical ventilation	3	122	Risk Difference (M-H, Random, 95% CI)	-0.01 [-0.09, 0.08]

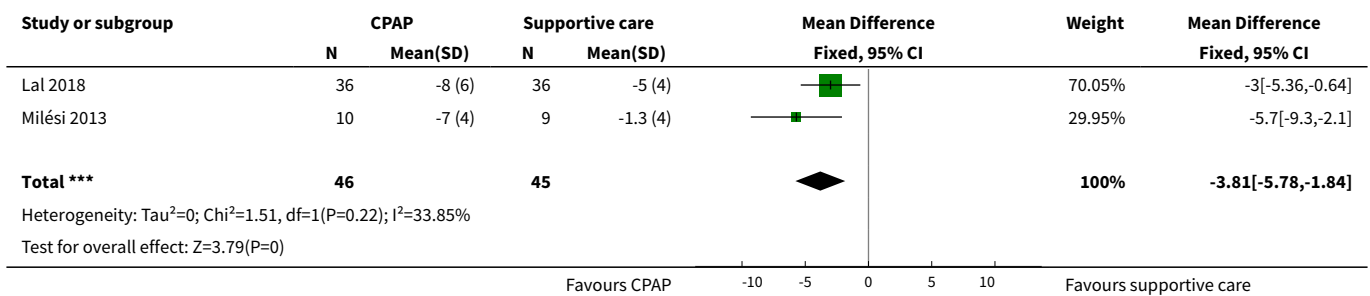
**Analysis 1.1. Comparison 1 Proportion of children requiring mechanical ventilation, Outcome 1 Proportion of children requiring mechanical ventilation.**



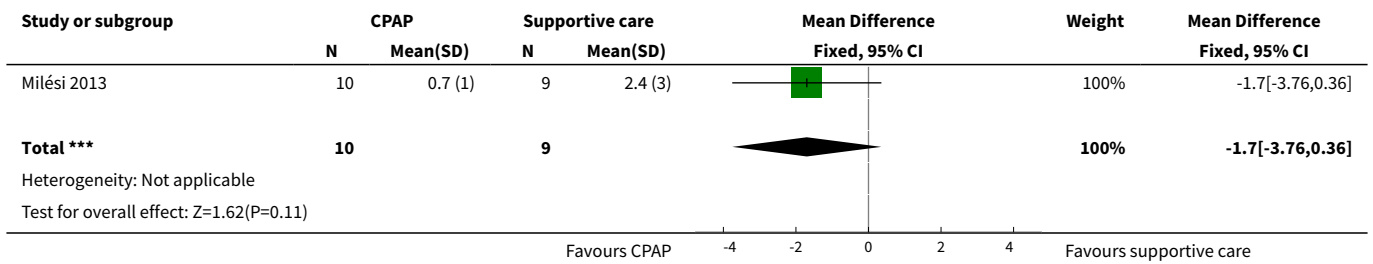
**Comparison 2. Clinical improvements**

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in respiratory rate	2	91	Mean Difference (IV, Fixed, 95% CI)	-3.81 [-5.78, -1.84]
2 Change in arterial oxygen saturation	1	19	Mean Difference (IV, Fixed, 95% CI)	-1.7 [-3.76, 0.36]
3 Change in arterial partial pressure of carbon dioxide (pCO <sub>2</sub> ) and partial pressure of oxygen (pO <sub>2</sub> )	2	50	Mean Difference (IV, Fixed, 95% CI)	-2.62 [-5.29, 0.05]
4 Duration of hospital stay (days)	2	50	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.36, 0.50]

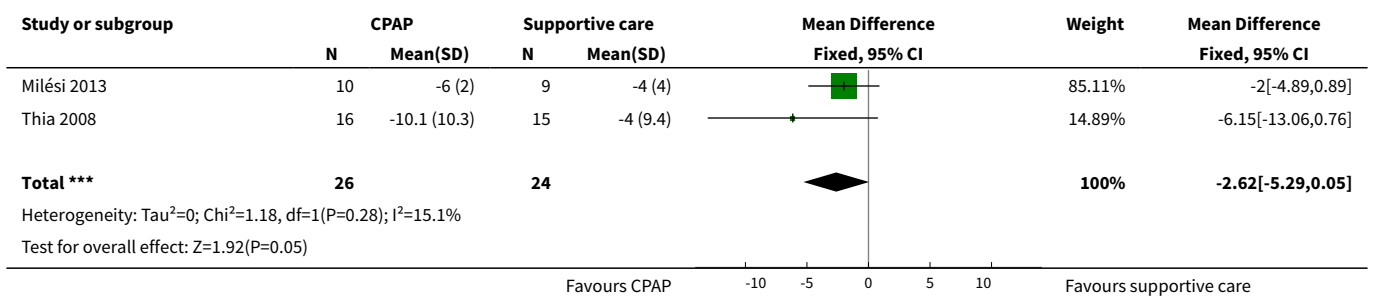
**Analysis 2.1. Comparison 2 Clinical improvements, Outcome 1 Change in respiratory rate.**



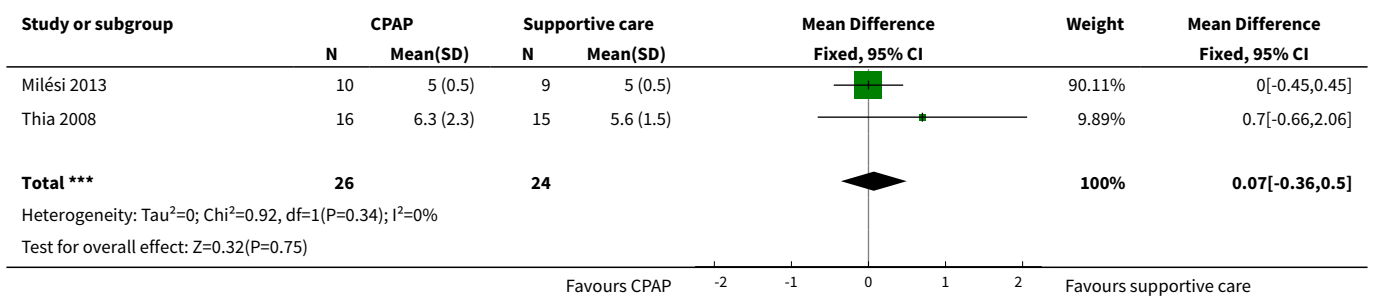
**Analysis 2.2. Comparison 2 Clinical improvements, Outcome 2 Change in arterial oxygen saturation.**



**Analysis 2.3. Comparison 2 Clinical improvements, Outcome 3 Change in arterial partial pressure of carbon dioxide (pCO<sub>2</sub>) and partial pressure of oxygen (pO<sub>2</sub>).**



**Analysis 2.4. Comparison 2 Clinical improvements, Outcome 4 Duration of hospital stay (days).**



**APPENDICES**

**Appendix 1. MEDLINE (Ovid) search strategy**

- 1 exp Bronchiolitis/
- 2 bronchiolit\*.tw.
- 3 Bronchopneumonia/
- 4 bronchopneumon\*.tw.
- 5 exp respiratory syncytial viruses/ or exp respiratory syncytial virus, human/
- 6 Respiratory Syncytial Virus Infections/
- 7 (respiratory syncytial virus\* or rsv).tw.
- 8 or/1-7
- 9 Respiratory Therapy/

10 Respiration, Artificial/  
 11 positive-pressure respiration/ or continuous positive airway pressure/  
 12 (positive pressur\* adj5 (ventilat\* or respir\* or breath\* or airway\*)),tw.  
 13 positiv\* airway\* pressur\*.tw.  
 14 continuous distend\* pressur\*.tw.  
 15 positive end expiratory pressure.tw.  
 16 (ppv or cpap or ncpap or nm-cpap or np-cpap or peep).tw.  
 17 or/9-16  
 18 8 and 17

## Appendix 2. Embase (Elsevier) search strategy

#14 \*'continuous distending pressure':ab,ti 46\*  
 #13 \*ppv\*:ab,ti OR \*cpap\*:ab,ti OR \*ncpap\*:ab,ti OR \*'nm-cpap':ab,ti OR \*'np-cpap':ab,ti 17000\*  
 #12 \*'positive airway pressure':ab,ti 6991\*  
 #11 (('positive pressure'\* OR \*'positive-pressure') NEAR/5 (\*ventilat\*\* OR \*respir\*\* OR \*breath\*\* OR \*airway\*\*)):ab,ti 5253\*  
 #10 \*'artificial ventilation'/de OR \*'positive end expiratory pressure'/de OR \*'cpap device'/de 78111\*  
 #9 \*#1\* OR \*#2\* OR \*#3\* OR \*#4\* OR \*#5\* OR \*#6\* OR \*#7\* OR \*#8\*\*28466\*  
 #8 \*rsv\*:ab,ti 7727\*  
 #7 \*'respiratory syncytial virus':ab,ti OR \*'respiratory syncytial viruses':ab,ti 8252\*  
 #6 \*'respiratory syncytial virus infection'/de 1132\*  
 #5 \*'respiratory syncytial pneumovirus'/de 10173\*  
 #4 \*'bronchopneumon\*':ab,ti 2426\*  
 #3 \*'bronchopneumonia'/de 3528\*  
 #2 \*'bronchiolit\*':ab,ti 8269\*  
 #1 \*'bronchiolitis'/exp 11323\*

## Appendix 3. CINAHL (EBSCO) search strategy

S28 S18 AND S27 15  
 S27 S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 189,818  
 S26 (MH "Quantitative Studies") 8,622  
 S25 TI placebo\* OR AB placebo\* 20,274  
 S24 TI random\* OR AB random\* 100,950  
 S23 (MH "Random Assignment") 29,181  
 S22 TI ((singl\* or doubl\* or tripl\* or trebl\*) N1 (blind\* or mask\*)) OR AB ((singl\* or doubl\* or tripl\* or trebl\*) N1 (blind\* or mask\*)) 14,743  
 S21 TI clinic\* N1 trial\* OR AB clinic\* N1 trial\* 28,628  
 S20 PT clinical trial 50,141  
 S19 (MH "Clinical Trials+") 113,828  
 S18 S9 AND S17 89  
 S17 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 14,880  
 S16 TI (ppv or cpap or ncpap or nm-cpap or np-cpap or peep) OR AB (ppv or cpap or ncpap or nm-cpap or np-cpap or peep) 1,882  
 S15 TI positive end expiratory pressur\* OR AB positive end expiratory pressur\* 627  
 S14 TI continuous distending pressure OR AB continuous distending pressure 7  
 S13 TI positive airway\* pressur\* OR AB positive airway\* pressur\* 1,306  
 S12 TI ( (positive-pressure or positive pressure) N5 (ventilat\* or respir\* or breath\* or airway\*) ) OR AB ( (positive-pressure or positive pressure) N5 (ventilat\* or respir\* or breath\* or airway\*) ) 2,199  
 S11 (MH "Positive Pressure Ventilation") OR (MH "Continuous Positive Airway Pressure") OR (MH "Positive End-Expiratory Pressure") 4,063  
 S10 (MH "Respiratory Therapy") OR (MH "Respiration, Artificial") 10,565  
 S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 1,924  
 S8 TI rsv OR AB rsv 478  
 S7 TI respiratory syncytial virus\* OR AB respiratory syncytial virus\* 693  
 S6 (MH "Respiratory Syncytial Virus Infections") 784  
 S5 (MH "Respiratory Syncytial Viruses") 283  
 S4 TI bronchopneumon\* OR AB bronchopneumon\* 43  
 S3 (MH "Bronchopneumonia") 40  
 S2 TI bronchiolit\* OR AB bronchiolit\* 748  
 S1 (MH "Bronchiolitis+") 692

## Appendix 4. LILACS (BIREME) search strategy

(mh:bronchiolitis OR bronchiolit\* OR bronquiolitis OR bronquiolite OR mh:c08.127.446.135\* OR mh:c08.381.495.146.135\* OR mh:c08.730.099.135\* OR mh:bronchopneumonia OR bronchopneumon\* OR bronconeumonia OR broncopneumonia OR mh:"Respiratory

Syncytial Viruses" OR "Virus Sincitiales Respiratorios" OR "Virus Sinciciais Respiratórios" OR "Virus Sincitial Respiratorio" OR "Virus Sincicial Respiratorio" OR "Virus Sincitiales Respiratorios" OR "Virus Sincicial Respiratório" OR mh:"Respiratory Syncytial Virus, Human" OR "Virus Sincitial Respiratorio Humano" OR "Virus Sincicial Respiratório Humano" OR mh:"Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial" OR "respiratory syncytial virus" OR "respiratory syncytial viruses" OR rsv AND (mh:"Respiratory Therapy" OR "Terapia Respiratoria" OR mh:"Respiration, Artificial" OR "Respiración Artificial" OR "Respiração Artificial" OR mh:"Positive-Pressure Respiration" OR "Respiración con Presión Positiva" OR "Respiração com Pressão Positiva" OR "Positive End-Expiratory Pressure" OR mh:"Continuous Positive Airway Pressure" OR "Presión de las Vías Aéreas Positiva Continua" OR "Pressão Positiva Contínua nas Vias Aéreas" OR "Airway Pressure Release Ventilation" OR "Ventilación Liberadora de Presión de las Vías Aéreas" OR "Pressão Positiva Contínua nas Vias Respiratórias" OR "Ventilação com Liberação de Pressão das Vias Aéreas" OR vlpva OR "Ventilação com Liberação de Pressão das Vias Respiratórias" OR "positive airway pressure" OR "continuous distending pressure" OR ppv OR cpap OR ncpap OR "nm-cpap" OR "np-cpap" OR peep OR "positive pressure ventilation" OR "positive pressure respiration" OR "positive pressure breathing") AND db:("LILACS") AND type\_of\_study:("clinical\_trials")

## WHAT'S NEW

Date	Event	Description
10 January 2018	New citation required but conclusions have not changed	The evidence for one secondary outcome (respiratory rate) was strengthened by the addition of a study with low-quality evidence. Our conclusions remain unchanged.
10 January 2018	New search has been performed	We included one new trial, (Lal 2018), and excluded three trials (Cesar 2017; Chidini 2015; Milési 2017), for this update.

## CONTRIBUTIONS OF AUTHORS

KRJ and JLM: selected studies, independently extracted data, and approved the final version of the review.

KRJ: performed analyses.

JLM: critically reviewed the analysis and provided important intellectual input for the original review and review update.

## DECLARATIONS OF INTEREST

Kana R Jat: none known

Joseph L Mathew: none known

## SOURCES OF SUPPORT

### Internal sources

- Internet and library facility from Government Medical College Hospital, Chandigarh, India.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We included both the primary outcomes and change in respiratory rate in the 'Summary of findings' table. Sufficient data were not available for the outcomes of hospital admission rate and adverse events for inclusion in the 'Summary of findings' table as specified in the protocol.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Disease; Bronchiolitis [blood] [\*therapy]; Carbon Dioxide; Continuous Positive Airway Pressure [\*methods] [statistics & numerical data]; Length of Stay; Oxygen [blood]; Partial Pressure; Randomized Controlled Trials as Topic; Respiration, Artificial [statistics & numerical data]; Respiratory Rate; Selection Bias

### MeSH check words

Humans; Infant; Infant, Newborn