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Nebulised hypertonic saline solution for acute bronchiolitis in infants (Review)

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T A B L E   O F   C O N T E N T S

[Intervention Review]

Nebulised hypertonic saline solution for acute bronchiolitis in infants

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A B S T R A C T

Background

Airway oedema (swelling) and mucus plugging are the principal pathological features in infants with acute viral bronchiolitis. Nebulised hypertonic saline solution (≥ 3%) may reduce these pathological changes and decrease airway obstruction. This is an update of a review first published in 2008, and previously updated in 2010 and 2013.

Objectives

To assess the effects of nebulised hypertonic (≥ 3%) saline solution in infants with acute bronchiolitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, Embase, CINAHL, LILACS, and Web of Science on 11 August 2017. We also searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and ClinicalTrials.gov on 8 April 2017.

Selection criteria

We included randomised controlled trials and quasi-randomised controlled trials using nebulised hypertonic saline alone or in conjunction with bronchodilators as an active intervention and nebulised 0.9% saline, or standard treatment as a comparator in children under 24 months with acute bronchiolitis. The primary outcome for inpatient trials was length of hospital stay, and the primary outcome for outpatients or emergency department trials was rate of hospitalisation.

Data collection and analysis

Two review authors independently performed study selection, data extraction, and assessment of risk of bias in included studies. We conducted random-effects model meta-analyses using Review Manager 5. We used mean difference (MD), risk ratio (RR), and their 95% confidence intervals (CI) as effect size metrics.

Main results

We identified 26 new trials in this update, of which 9 await classification due to insufficient data for eligibility assessment, and 17 trials (N = 3105) met the inclusion criteria. We included a total of 28 trials involving 4195 infants with acute bronchiolitis, of whom 2222 infants received hypertonic saline.

Hospitalised infants treated with nebulised hypertonic saline had a statistically significant shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (MD -0.41 days, 95% CI -0.75 to -0.07; P = 0.02, I² = 79%; 17 trials; 1867 infants) (GRADE quality of evidence: low). Infants who received hypertonic saline also had statistically significant lower post-inhalation clinical scores than infants who received 0.9% saline in the first three days of treatment (day 1: MD -0.77, 95% CI -1.18 to -0.36, P < 0.001; day 2: MD -1.28, 95% CI -1.91 to -0.65, P < 0.001; day 3: MD -1.43, 95% CI -1.82 to -1.04, P < 0.001) (GRADE quality of evidence: low).

Nebulised hypertonic saline reduced the risk of hospitalisation by 14% compared with nebulised 0.9% saline among infants who were outpatients and those treated in the emergency department (RR 0.86, 95% CI 0.76 to 0.98; P = 0.02, I² = 7%; 8 trials; 1723 infants) (GRADE quality of evidence: moderate).

Twenty-four trials presented safety data: 13 trials (1363 infants, 703 treated with hypertonic saline) did not report any adverse events, and 11 trials (2360 infants, 1265 treated with hypertonic saline) reported at least one adverse event, most of which were mild and resolved spontaneously.

Authors' conclusions

Nebulised hypertonic saline may modestly reduce length of stay among infants hospitalised with acute bronchiolitis and improve clinical severity score. Treatment with nebulised hypertonic saline may also reduce the risk of hospitalisation among outpatients and emergency department patients. However, we assessed the quality of the evidence as low to moderate.

PLAIN LANGUAGE SUMMARY

Is hypertonic saline solution via nebuliser effective and safe for infants with acute bronchiolitis?

Review question

Is hypertonic saline solution via nebuliser effective and safe for the treatment of infants with acute bronchiolitis, compared to normal saline solution?

Background

Acute bronchiolitis is the most common lower respiratory tract infection in children aged up to two years. Bronchiolitis occurs when small structures (bronchioles) leading to the lungs become infected, causing inflammation, swelling, and mucus production. This makes breathing difficult, especially in very young children, who develop coughs and wheezing.

Because bronchiolitis is usually caused by a virus, drug treatment is usually not effective. Hypertonic saline (sterile salt water solution) breathed in as a fine mist using a nebuliser may help relieve wheezing and breathing difficulty.

We compared nebulised hypertonic (≥ 3%) saline solution with nebulised normal (0.9%) saline for infants with acute bronchiolitis.

This is an update of a review previously published in 2008, 2010, and 2013.

Search date

11 August 2017

Study characteristics

We identified 26 new studies in this update, of which 9 await assessment and 17 trials (N = 3105) were added. We included a total of 28 trials involving 4195 infants with acute bronchiolitis.

Key results

Nebulised hypertonic saline may reduce hospital stay by 10 hours in comparison to normal saline for infants admitted with acute bronchiolitis. We found that 'clinical severity scores', which are used by doctors to assess patient health, for children treated as outpatients

or in hospital improved when administered nebulised hypertonic saline compared to normal saline. Nebulised hypertonic saline may also reduce the risk of hospitalisation by 14% among children treated as outpatients or in the emergency department. We found only minor and spontaneously resolved adverse effects from the use of nebulised hypertonic saline when given with treatment to relax airways (bronchodilators).

Reductions in hospital stay were smaller than previously thought. However, an average reduction of 10 hours in the length of hospital stay for infants is significant because bronchiolitis usually has a short duration. Nebulised hypertonic saline appears to be safe and widely available at low cost.

Quality of evidence

The quality of the evidence was low to moderate: there were inconsistencies in results among trials and risk of bias in some trials. Future large trials are therefore needed to confirm the benefits of nebulised hypertonic saline for children with bronchiolitis treated as outpatients and in hospital.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Nebulised hypertonic saline compared with nebulised 0.9% saline for acute bronchiolitis in infants

Patient or population: infants up to 24 months of age with acute bronchiolitis
Settings: outpatient, emergency department, or inpatient
Intervention: nebulised hypertonic saline ($\geq$ 3%)
Comparison: nebulised 0.9% saline or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Nebulised 0.9% saline	Nebulised hypertonic saline				
Length of hospital stay (days)	The mean length of hospital stay ranged across control groups from **1.8 to 7.4 days**.	The mean length of hospital stay in the intervention groups was on average **0.41 days shorter** (95% CI -0.75 to -0.07).	-	1867 (17 trials)	⊕⊕◯◯ **Low**[1]	The effect size of nebulised hypertonic saline shown by this updated review is only approximately one-third of that shown by the 2013 review, which included 6 inpatient trials involving 500 infants (MD -1.15 days, 95% CI -1.49 to -0.82 days). All 10 trials published in 2013 and thereafter, including 2 European multicentre studies, did not find significant effects of hypertonic saline on length of stay among inpatients with acute bronchiolitis

Clinical severity score (post-treatment) at day 1	The mean clinical severity score ranged across control groups from **3.9 to 8.8**.	The mean clinical severity score in the intervention groups was on average **0.77 lower** (95% CI -1.18 to -0.36).	-	812 (9 trials: 1 outpatient, 1 ED, 7 inpatients)	⊕⊕◯◯ **Low**[2]	The meta-analysis was based on data from only 9 trials.
Clinical severity score (post-treatment) at day 2	The mean clinical severity score ranged across control groups from **3.8 to 8.2**.	The mean clinical severity score in the intervention groups was on average **1.28 lower** (95% CI -1.91 to -0.65).	-	603 (8 trials: 1 outpatient, 1 ED, 6 inpatient)	⊕⊕◯◯ **Low**[2]	Meta-analysis was based on data from only 8 trials.
Clinical severity score (post-treatment) at day 3	The mean clinical severity score ranged across control groups from **1.9 to 7.6**.	The mean clinical severity score in the intervention groups was on average **1.43 lower** (95% CI -1.82 to -1.04).	-	499 (7 trials: 1 outpatient, 6 inpatient)	⊕⊕◯◯ **Low**[2]	Meta-analysis was based on data from only 7 trials.
Hospitalisation rate	**42 per 100**	**35 per 100**	**RR 0.86** (0.76 to 0.98)	1723 (8 trials: 1 outpatient, 7 ED)	⊕⊕⊕◯ **Moderate**[3]	
Re-admission rate	**15 per 100**	**12 per 100**	**RR 0.77** (0.48 to 1.25)	787 (6 trials: 1 inpatient, 5 ED)	⊕⊕⊕◯ **Moderate**[4]	Meta-analysis was based on data from only 6 trials
Adverse events	See comment	See comment	Not estimable	3723 (1968 received hypertonic saline) (24 trials)	Not applicable	13 trials (1363 infants, 703 treated with hypertonic saline) did not report any adverse events, and 11 trials (2360 infants, 1265 treated with hypertonic

saline) reported at least 1 adverse event; most adverse events were mild and resolved spontaneously

*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; **ED:** emergency department; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence (5 domains: limitations in design, inconsistency, indirectness, imprecision, reporting bias)
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.

The assumed risk was based on data from the included trials.
[1]We downgraded the quality of the evidence to low due to inconsistent results between studies (high heterogeneity) and risk of bias.
[2]We downgraded the quality of the evidence to low due to inconsistent results between studies (high heterogeneity) and risk of bias.
[3]We downgraded the quality of the evidence to moderate due to high clinical heterogeneity between studies.
[4]We downgraded the quality of the evidence to moderate because the meta-analysis was based on data from a small part of the included trials.

BACKGROUND

Description of the condition

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants (Klassen 1997a), and the most common causative organism is respiratory syncytial virus (RSV). Other less common pathogens include parainfluenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and *Mycoplasma pneumoniae* (García-García 2006; Henderson 1979; Jacques 2006; Rose 1987; Shay 2001). Virtually all infants are infected by RSV by the age of two years, around 40% to 50% develop involvement of the lower respiratory tract, and 1% to 2% develop severe disease leading to hospitalisation (Meissner 2003; Rakshi 1994; Shay 1999). It is estimated that globally in 2015, 1.4 million (uncertainty range (UR) 1.2 to 1.7) hospital admissions, and 27,300 (UR 20700 to 36200) in-hospital deaths were due to RSV-acute lower respiratory infection in infants younger than six months of age (Shi 2017).

The principal pathological findings in acute bronchiolitis include a peribronchial infiltrate of inflammatory cells, mucosal and submucosal oedema, necrosis and desquamation of ciliated epithelial cells, proliferation of cuboidal cells, and excess mucus secretion (Panitch 1993; Wohl 1978). The combination of airway wall swelling, sloughing of necrotic debris, increased mucus production, and impaired secretion clearance eventually leads to airway obstruction, gas trapping, atelectasis, and impaired gas exchange. The diagnosis of acute bronchiolitis is usually based on clinical grounds. Despite differences in defining bronchiolitis, it is generally accepted that acute bronchiolitis refers to the first episode of acute wheezing in children aged less than two years, starting as a viral upper respiratory infection (coryza, cough, or fever) (Panitch 1993). These criteria for diagnosis of acute bronchiolitis have also been widely used in clinical trials (Bertrand 2001; Klassen 1997b; Schuh 1992; Wainwright 2003; Zhang 2003). Direct fluorescent antibody tests, enzyme immuno-assay techniques, and cultures of the nasopharyngeal aspirate may be used to identify the causative pathogen.

Description of the intervention

The standard treatment for acute bronchiolitis remains supportive care and includes ensuring adequate oxygen exchange, fluid intake, and feeding of the infant (Panitch 2003; Wohl 2003). Convincing evidence for any other therapy is lacking. Because airway oedema and mucus plugging are the predominant pathological features in acute bronchiolitis, any therapy that can reduce these changes and improve the clearance of airway secretions may be beneficial. Epinephrine has a theoretical effect on acute bronchiolitis because it contains alpha adrenergic properties which lead to vasoconstriction and reduction of airway oedema (Wohl 1978). However, a Cochrane Review showed that nebulised epinephrine for acute bronchiolitis results in a modest short-term improvement in outpatients, but not among inpatients (Hartling 2011). Inhaled recombinant deoxyribonuclease (rhDNase), a mucolytic agent, has also been tested in hospitalised infants with acute bronchiolitis (Nasr 2001). This drug is thought to exert its major effect by enhancing airway secretion clearance. However, no significant effect was observed on clinical severity scores or length of hospital stay (Enriquez 2012). Another widely used approach is chest physiotherapy, which is thought to assist infants by enhancing the clearance of secretions and reducing ventilatory effort. However, current evidence has shown that chest physiotherapy (vibration and percussion or passive expiratory techniques) does not reduce the length of hospital stay or oxygen requirements or improve the severity of the disease respiratory parameters in hospitalised infants with acute bronchiolitis (Roqué i Figuls 2016).

Hypertonic saline has been used as a treatment for infants with acute bronchiolitis. Most randomised trials demonstrate that nebulised 3% saline may significantly reduce the length of hospital stay and improve the clinical severity score in infants with acute viral bronchiolitis (Luo 2010; Mandelberg 2003; Sarrell 2002; Tal 2006).

How the intervention might work

Hypertonic saline solution has been shown to increase mucociliary clearance in disease-free people and people with asthma, bronchiectasis, cystic fibrosis, and sinonasal diseases (Daviskas 1996; Kellett 2005; Shoseyov 1998; Wark 2009). Such benefits would also be expected in infants with acute bronchiolitis (Mandelberg 2010). The postulated mechanisms of benefit of hypertonic saline are:

- induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance (Mandelberg 2010; Robinson 1997);
- breaks the ionic bonds within the mucus gel, thereby reducing the degree of cross-linking and entanglements and lowering the viscosity and elasticity of the mucus secretion (Ziment 1978);
- stimulates cilial beat via the release of prostaglandin E2 (Assouline 1977).

Moreover, by absorbing water from the mucosa and submucosa, hypertonic saline solution can theoretically reduce oedema of the airway wall in infants with acute bronchiolitis (Mandelberg 2003; Mandelberg 2010; Sarrell 2002). Hypertonic saline inhalation can also cause sputum induction and cough, which can help to clear the sputum outside of the bronchi and thus improve airway obstruction (Mandelberg 2003).

These theoretical benefits provide the rationale for the treatment of acute bronchiolitis with nebulised hypertonic saline solution.

Why it is important to do this review

The hypothesis of this review is that nebulised hypertonic saline solution is beneficial in the management of acute bronchiolitis as assessed by clinically relevant outcomes, both in inpatients and outpatients. The establishment of a therapeutic role for hypertonic saline solution in acute bronchiolitis has relevant clinical implications. This modality may provide a cheap and effective therapy for children with acute bronchiolitis.

O B J E C T I V E S

To assess the effects of nebulised hypertonic ($\geq$ 3%) saline solution in infants with acute bronchiolitis.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials and quasi-randomised controlled trials (in which there is alternate allocation to treatment and control groups) in this review. We excluded studies including participants who had recurrent wheezing or who were intubated and ventilated, and studies that assessed pulmonary function alone.

Types of participants

Children up to 24 months of age diagnosed with acute bronchiolitis. Acute bronchiolitis was defined as the first episode of acute wheezing associated with clinical evidence of a viral infection (cough, coryza, or fever). Confirmation of viral aetiology was not necessary for study inclusion. We included studies of inpatients, emergency department patients, or outpatients.

Types of interventions

- Nebulised hypertonic saline alone versus nebulised 0.9% saline.
- Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline.
- Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline plus same bronchodilator.
- Nebulised hypertonic saline alone or plus bronchodilator versus standard treatment.

Given that we identified few studies initially in 2007, we subsequently added comparisons of nebulised hypertonic saline alone

versus nebulised 0.9% saline or no intervention (Zhang 2008). Hypertonic saline was defined as a concentration of saline greater than or equal to 3%.

Types of outcome measures

Primary outcomes

1. Length of hospital stay or time taken to be ready for discharge (inpatients).
2. Rate of hospitalisation (outpatients or emergency department patients).

Secondary outcomes

1. Clinical severity score.
2. Rate of re-admission to hospital.
3. Haemoglobin saturation (oximetry).
4. Respiratory rate.
5. Heart rate.
6. Time to resolution of symptoms or signs.
7. Duration of in-hospital oxygen supplementation.
8. Need for add-on treatment (bronchodilator, systemic corticosteroids, antibiotics, and oxygen supplementation).
9. Results of pulmonary function tests.
10. Radiological findings.
11. Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, diarrhoea, and acute urinary retention).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 4), part of the Cochrane Library (searched 11 August 2017), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE Ovid, MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily (April 2013 to 11 August 2017), Embase.com (April 2013 to 11 August 2017), CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO; May 2013 to 11 August 2017), LILACS (Latin American and Caribbean Health Science Information Database) (May 2013 to 11 August 2017), and Web of Science (May 2013 to 11 August 2017) for this update. Appendix 1 provides details of searches conducted for previous versions of this review.
We used the search strategy in Appendix 2 to search MEDLINE and CENTRAL. Because there were so few search results, we used no filter to identify randomised trials in MEDLINE. We adapted the terms to search Embase (Appendix 3), LILACS (Appendix 4), CINAHL (Appendix 5), and Web of Science (Appendix 6).

Searching other resources

We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) and US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov to identify ongoing trials on 8 April 2017. We checked reference lists of all primary studies and review articles for additional relevant trials.

Data collection and analysis

We conducted the review update according to the published protocol and reported any deviations from it in the Differences between protocol and review section.

Selection of studies

Two review authors (LZ, RAM) independently screened titles and abstracts of all studies identified as a result of the search for potential inclusion in the review. We retrieved the full-text study reports of all potentially eligible studies, and two review authors (LZ, RAM) independently screened the full-text reports to identify studies for inclusion and identify and record reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or, if required, by consulting a third review author (CW). We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in a PRISMA flow diagram (Figure 1) and Characteristics of excluded studies table. There were no language or publication restrictions.

Figure 1. Study flow diagram.
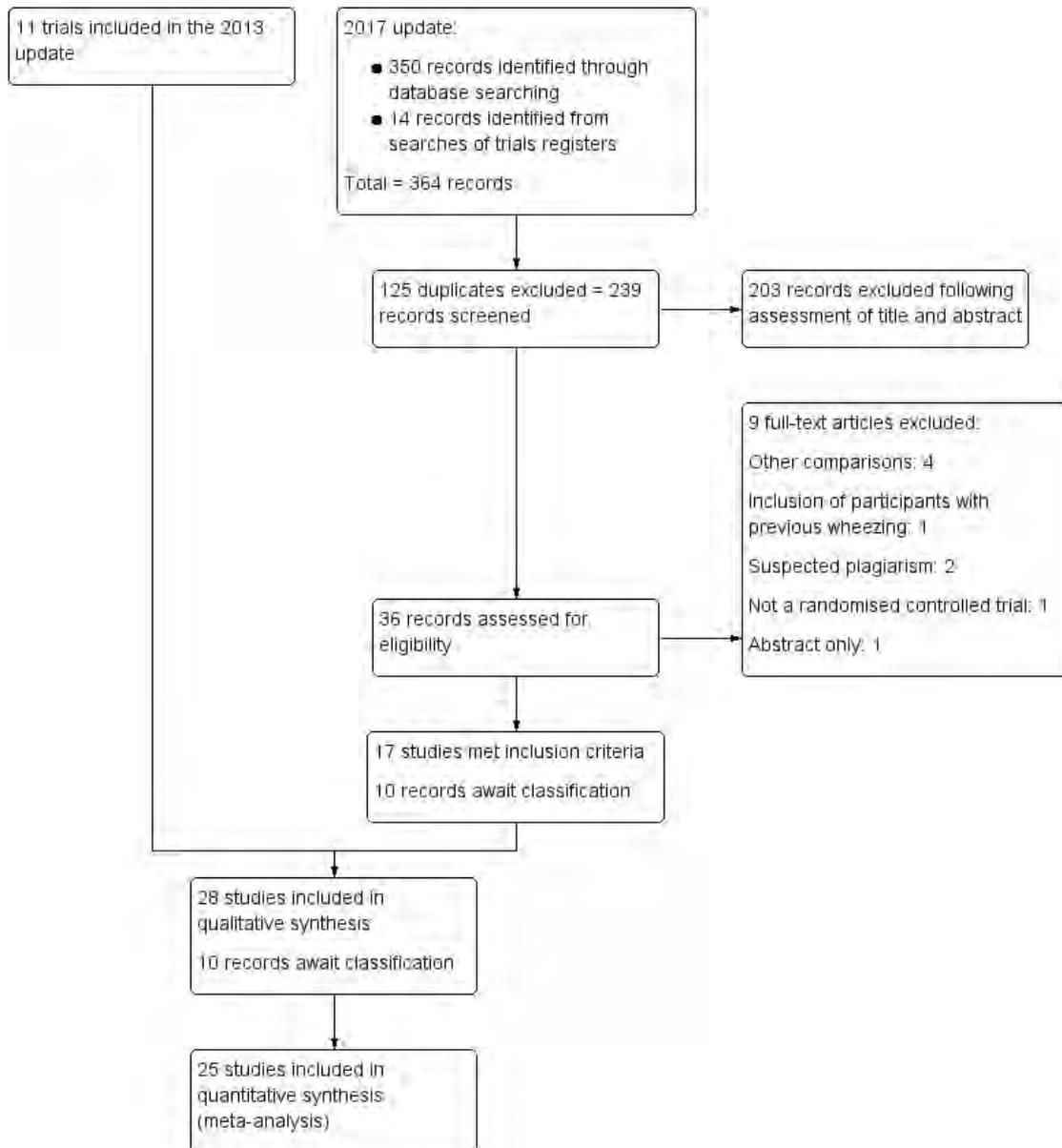
Data extraction and management

One review author (LZ) extracted study details from the included trials using a standardised data extraction form. Another review author (RAM) checked the data extraction. We resolved any disagreements by discussion. We entered the extracted the following data into Review Manager 5 (RevMan 2014).

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.

2. Participants: N, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria, and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications, and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We used Engauge digitising software to extract the first and third quartile values of length of hospital stay from a figure in Teunissen 2014. For this trial, we estimated mean and standard deviation from median and interquartile range of length of hospital stay using methods described by Wan 2014.

Assessment of risk of bias in included studies

Two review authors (LZ, RAM) independently assessed 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 or by involving a third review author (CW). 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 a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. 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, this was noted in the 'Risk of bias' table.

When considering treatment effects, we took into account the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We entered outcome data for each study into data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We used risk ratio for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes.

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

Unit of analysis issues

The participants in each intervention arm were the unit of analysis in a single parallel group design. When trials recruited multiple groups, we combined data to create hypertonic saline and normal saline groups. We used the Review Manager 5 calculator to combine groups (RevMan 2014). We combined data for the 5% and 3% saline groups into the hypertonic saline group for Al-Ansari 2010 and 7% and 3% saline groups into the hypertonic saline group for Köse 2016. We combined four groups reported by Anil 2010 (3% saline mixed with epinephrine, 3% saline mixed with salbutamol, 0.9% saline mixed with epinephrine, and 0.9% saline mixed with salbutamol) and Ipek 2011 (3% saline plus salbutamol, 3% saline alone, 0.9% saline plus salbutamol, and 0.9% saline alone) into the hypertonic and normal saline groups.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and to 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 performing sensitivity analyses.

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

We contacted the authors of seven studies for additional trial data (Köse 2016; Kuzik 2007; Luo 2010; Mandelberg 2003; Sharma 2013; Teunissen 2014; Wu 2014), of whom five responded and provided data (Köse 2016; Kuzik 2007; Luo 2010; Mandelberg 2003; Wu 2014).

Assessment of heterogeneity

We used the I² statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we reported this and explored possible causes in subgroup analysis. We used I² values of 25%, 50%, and 75% corresponding to low, moderate, and high heterogeneity, respectively (Higgins 2003).

Assessment of reporting biases

If we were able to pool more than 10 trials, we planned to create and examine a funnel plot to explore possible small-study effects and publication bias. We created the funnel plot using Stata version 11.0.

Data synthesis

We pooled data from studies we judged to be clinically homogeneous using Review Manager 5 software (RevMan 2014). If more than one study provided usable data in any single comparison, we performed meta-analysis using the random-effects model. Whenever possible, we used intention-to-treat analysis data.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: length of hospital stay; clinical severity score post-treatment at days 1, 2, and 3; rate of hospitalisation; rate of re-admission; and adverse events. We used the five factors of the GRADE approach (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence relating to the studies that contributed data to meta-analyses for outcomes (Atkins 2004). We used 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 GDT 2014). We justified all decisions to down- or upgrade the quality of studies using footnotes, and made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We performed pre-planned subgroup analysis on clinical scores according to patient status (outpatient, emergency department patient, and inpatient). For length of hospital stay, we conducted post hoc subgroup analyses according to availability of virological investigation (available versus not available), upper age limits for participants (12 months versus 18 to 24 months), hypertonic saline concentration (3% versus > 3%), administration interval (every 4 to 6 hours versus every 8 hours), co-administration with bronchodilators (β_2 agonist, epinephrine versus no), length of hospital stay in the control group (< 3 days versus ≥ 3 days), year of publication (before 2013 versus 2013 and thereafter), and risk of selection bias in the trials (low versus unclear/high). For hospitalisation rate, we conducted the same subgroup analyses, except for length of stay in the control group.

We performed post hoc random-effects meta-regression using restricted maximum likelihood (REML) estimation to investigate the potential modifiers of effects of hypertonic saline on length of hospital stay and clinical severity score. We conducted meta-regression using Stata version 11.0 (StataCorp 2009).

Sensitivity analysis

For length of hospital stay, we performed post hoc sensitivity analyses excluding open trials, trials in which mean and standard deviation were estimated from median and interquartile range, trials with withdrawal rate over 15%, and trials with very short (< two days) or very long (> six days) length of stay in the control group.

R E S U L T S

Description of studies

Results of the search

In this 2017 update, we identified 364 records from searches of databases and trials registers. After de-duplication, we assessed 239 records by title and abstract and excluded 203 that did not meet our inclusion criteria. We obtained 26 full-text reports of studies, and following assessment included 17 new trials involving 3105 participants. These were added to the 11 trials (representing 1090 participants) included in the 2013 update (Zhang 2013). Nine studies identified from searches of trials registers are awaiting classification (see Studies awaiting classification).

This update included 28 trials (4195 participants). See Characteristics of included studies.

Included studies

All 28 included studies were randomised, parallel-group, controlled trials. All but two trials were double-blinded (NCT01238848; Everard 2014). Four studies were multicentre: a hospital in the United Arab Emirates and two hospitals in Canada in Kuzik 2007; 10 centres in England and Wales in Everard 2014; two centres in the USA in Wu 2014; and 24 centres in France in Angoulvant 2017. Three trials were conducted by the same group of investigators in Israel (Mandelberg 2003; Sarrell 2002; Tal 2006), and two trials were conducted by one group of investigators in China (Luo 2010; Luo 2011). The remaining 23 studies were conducted in Argentina (NCT01238848), Canada (Grewal 2009; Kuzik 2007), China (Li 2014), France (Angoulvant 2017), India (Mahesh Kumar 2013; Pandit 2013; Sharma 2013), Italy (Miraglia

Del Giudice 2012), Nepal (Khanal 2015; Ojha 2014), the Netherlands (Teunissen 2014), Poland (Ratajczyk-Pekrul 2016), Portugal (Flores 2016), Qatar (Al-Ansari 2010), Tunisia (Tinsa 2014), Turkey (Anil 2010; Ipek 2011; Köse 2016), the UK (Everard 2014), and the USA (Florin 2014; Jacobs 2014; Wu 2014). See Figure 1.

Participants

Two trials recruited outpatient participants (N = 194) (Li 2014; Sarrell 2002); eight trials recruited emergency department participants (N = 1873) (Al-Ansari 2010; Angoulvant 2017; Anil 2010; Florin 2014; Grewal 2009; Ipek 2011; Jacobs 2014; Wu 2014); 17 trials recruited inpatients (N = 2028) (NCT01238848; Everard 2014; Flores 2016; Köse 2016; Kuzik 2007; Luo 2010; Luo 2011; Mahesh Kumar 2013; Mandelberg 2003; Miraglia Del Giudice 2012; Ojha 2014; Pandit 2013; Ratajczyk-Pekrul 2016; Sharma 2013; Tal 2006; Teunissen 2014; Tinsa 2014); and one trial recruited both outpatients and emergency department participants (N = 100) (Khanal 2015). The mean age of participants was from 2.6 to 12.5 months (range: 9 days to 24 months).

Criteria for diagnosis of viral bronchiolitis were clearly defined in all but six trials (NCT01238848; Luo 2010; Mandelberg 2003; Miraglia Del Giudice 2012; Sarrell 2002; Tal 2006).

Virological investigation was reported in 15 trials (Angoulvant 2017; Everard 2014; Flores 2016; Grewal 2009; Jacobs 2014; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Miraglia Del Giudice 2012; Ratajczyk-Pekrul 2016; Sarrell 2002; Tal 2006; Teunissen 2014; Wu 2014). The positive rate for respiratory syncytial virus (RSV) varied from 42% to 88%.

Infants who had previous wheezing episodes were excluded from all 28 trials. Infants hospitalised with severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation < 85% on room air) were excluded from all but two trials (Teunissen 2014; Wu 2014).

Interventions

The concentration of hypertonic saline was defined as 3% in all but four trials (Al-Ansari 2010; Jacobs 2014; Köse 2016; Tinsa 2014). Two concentrations were used by Al-Ansari 2010 (3% and 5%) and Köse 2016 (3% and 7%). The concentration of hypertonic saline was defined at 5% in Tinsa 2014 and 7% in Jacobs 2014. Treatment regimens of nebulised hypertonic saline (volume, interval of administration, addition of bronchodilator, and treatment duration) varied across studies, especially in emergency department-based trials (Table 1). Oxygen or compressed air-driven jet nebulisers were used for drug deliveries in all trials but Tal 2006, which used ultrasonic nebulisers.

Outcome measures

All 17 inpatient trials except Tinsa 2014 used length of hospital stay as the primary outcome measure. Length of hospital stay was defined as time from hospital admission to discharge in all but two trials (Everard 2014; Flores 2016), in which both time until fit for discharge and time until discharge were reported. We used time until fit for discharge as length of hospital stay for Everard 2014 and Flores 2016.

The same clinical severity score was used by 11 inpatient trials as a secondary outcome measure (Flores 2016; Köse 2016; Luo 2010; Luo 2011; Mahesh Kumar 2013; Mandelberg 2003; Miraglia Del Giudice 2012; Ratajczyk-Pekrul 2016; Sharma 2013; Tal 2006; Tinsa 2014). This clinical score was initially described by Wang 1992, grading respiratory rate, wheezing, retraction, and general condition on a scale from 0 to 3, with a higher score indicating increased severity. Other clinical scoring systems were used by two inpatient trials (Kuzik 2007; Ojha 2014).

For outpatient or emergency department participants, outcome measures used were rate of hospitalisation in Angoulvant 2017, Anil 2010, Florin 2014, Grewal 2009, Ipek 2011, Jacobs 2014, Sarrell 2002, and Wu 2014, and rate of re-admission (Al-Ansari 2010; Anil 2010; Florin 2014; Grewal 2009; Khanal 2015). All outpatient or emergency department trials measured clinical severity score.

Other outcome measures were haemoglobin saturation (oximetry) (Al-Ansari 2010; Anil 2010; Florin 2014; Grewal 2009; Ipek 2011; Khanal 2015; Mandelberg 2003; Pandit 2013; Tinsa 2014), heart rate (Anil 2010; Florin 2014; Ipek 2011; Khanal 2015; Mandelberg 2003; Pandit 2013; Sarrell 2002), respiratory rate (Florin 2014; Ipek 2011; Khanal 2015; Pandit 2013), time to resolution of signs and symptoms (Luo 2010; Luo 2011), and need for add-on treatment (Flores 2016; Ipek 2011; Mahesh Kumar 2013; Mandelberg 2003; Pandit 2013; Teunissen 2014; Wu 2014).

The radiological assessment score initially described by Nasr 2001 was used in two trials (Mandelberg 2003; Sarrell 2002).

Side effects associated with inhaled therapies were reported in all but four trials (Ipek 2011; Mahesh Kumar 2013; Miraglia Del Giudice 2012; Ojha 2014).

Excluded studies

We excluded nine studies in this update (Al-bahadily 2017; Bagus 2012; Bueno Campaña 2014; Flores-González 2015; Flores-González 2016; Gupta 2016; Malik 2015; Nenna 2014; Silver 2015). Reasons for exclusion were: other comparisons (Bueno Campaña 2014; Flores-González 2015; Flores-González 2016; Nenna 2014), inclusion of infants with previous history of wheezing (Silver 2015), not a randomised controlled trial (Al-bahadily 2017), and abstract only (Bagus 2012). Two trials from different groups in India presented almost identical results (Gupta 2016; Malik 2015). We contacted the editors of both journals and the corresponding authors of two papers, but neither editors nor authors provided any explanation or information. We excluded both

trials because of suspected plagiarism. These were added to studies excluded from previous versions of this review for a total of 13 excluded studies. Reasons for exclusion of the other four studies were: other comparison (Amirav 2005), abstract only (Guomo 2007), not a randomised controlled trial (Tribastone 2003), and inclusion of infants with previous history of wheezing (Kuzik 2010).

Studies awaiting classification

We identified nine records that appeared to be potentially eligible for inclusion, but published reports or unpublished data were not available (CTRI/2010/091/003065; EudraCT2009-014758-14; NCT00677729; NCT01777347; NCT01834820; NCT02029040; NCT02045238; NCT02233985; NCT02834819). We will search for published reports or seek unpublished data for assessment to include in a future update. However, if no publication has resulted from studies completed for more than five years, these records will be discarded. See Characteristics of studies awaiting classification table.

Risk of bias in included studies

Summary assessment of six key domains is described below and presented in the 'Risk of bias' tables (Characteristics of included studies) and 'Risk of bias' graph (Figure 2).

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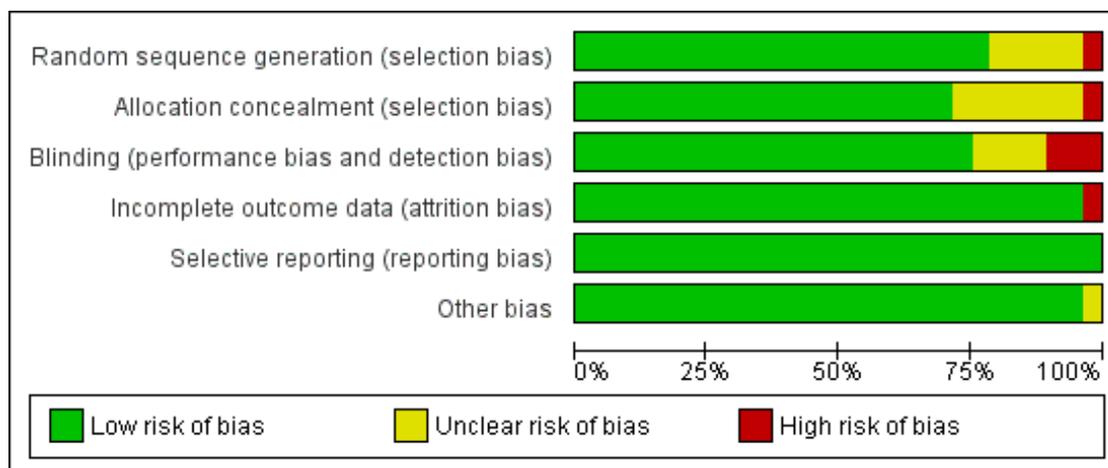
Allocation

Four trials used an online randomisation tool (Grewal 2009; Mandelberg 2003; Sarrell 2002; Tal 2006); 18 trials used a computer-based random number program (Al-Ansari 2010; Angoulvant 2017; Anil 2010; Everard 2014; Flores 2016; Florin 2014; Khanal 2015; Köse 2016; Kuzik 2007; Luo 2011; Mahesh Kumar 2013; Miraglia Del Giudice 2012; Ojha 2014; Pandit 2013; Ratajczyk-Pekrul 2016; Sharma 2013; Tinsa 2014; Wu 2014); and one trial used a random numbers table to generate the random sequence (Li 2014). Two trials used block randomisation (Jacobs 2014; Teunissen 2014), but it was unclear how blocks were chosen at random to create the allocation sequence. Ipek 2011 assigned infants to treatment groups according to the consecutive order of their admission to the emergency department. Three tri-

als did not provide information regarding random sequence generation (NCT01238848; Luo 2010; Mandelberg 2003).
Fourteen trials used sequentially numbered or coded drug containers of identical appearance for allocation concealment (Angoulvant 2017; Anil 2010; Flores 2016; Grewal 2009; Kuzik 2007; Luo 2010; Mandelberg 2003; Ojha 2014; Sarrell 2002; Sharma 2013; Tal 2006; Teunissen 2014; Tinsa 2014; Wu 2014). Six trials used sequentially numbered, sealed envelopes for allocation concealment (Al-Ansari 2010; Florin 2014; Jacobs 2014; Khanal 2015; Luo 2011; Pandit 2013). Everard 2014 used a centralised web-based randomisation system. In Miraglia Del Giudice 2012, study solutions were prepared by the local hospital pharmacy, but the method of allocation concealment was not described. Seven trials did not provide information regarding allocation concealment

(Anil 2010; NCT01238848; Ipek 2011; Köse 2016; Li 2014; Mahesh Kumar 2013; Ratajczyk-Pekrul 2016).

Blinding

In all but seven trials (NCT01238848; Everard 2014; Ipek 2011; Köse 2016; Li 2014; Mahesh Kumar 2013; Pandit 2013), infants, investigators, and care providers were blinded to group assignment. Three trials were open-label (NCT01238848; Everard 2014; Pandit 2013). Another three trials were reported as being double-blinded (Ipek 2011; Köse 2016; Mahesh Kumar 2013), but details were not provided. One trial did not provide information regarding blinding (Li 2014).

Incomplete outcome data

The number of withdrawals after randomisation was small in all but two trials; the withdrawal rate was 18% in NCT01238848 and Ojha 2014. The baseline characteristics of participants were similar between treatment groups in all 28 trials. Incomplete outcome data may thus not be a source of bias in this review. Seven trials reported using intention-to-treat analysis (Everard 2014; Florin 2014; Grewal 2009; Kuzik 2007; Mandelberg 2003; Sarrell 2002; Wu 2014).

Selective reporting

There appeared to be no evidence of selective reporting of outcomes in the included studies. All outcomes proposed in the methods or study protocols were reported in the results. The funnel plots did not suggest small-study effects and publication bias for length of hospital stay among inpatient trials (Figure 3; P = 0.29 for Egger's test).

Figure 3. Funnel plot of the weighted mean difference (WMD) of length of hospital stay (days) against its standard error. The circles represent risk estimates of each study, and the black vertical line represents the pooled effect estimate. Dashed lines represent pseudo-95% confidence limits. Egger test (P = 0.29) suggests no small-study effects.
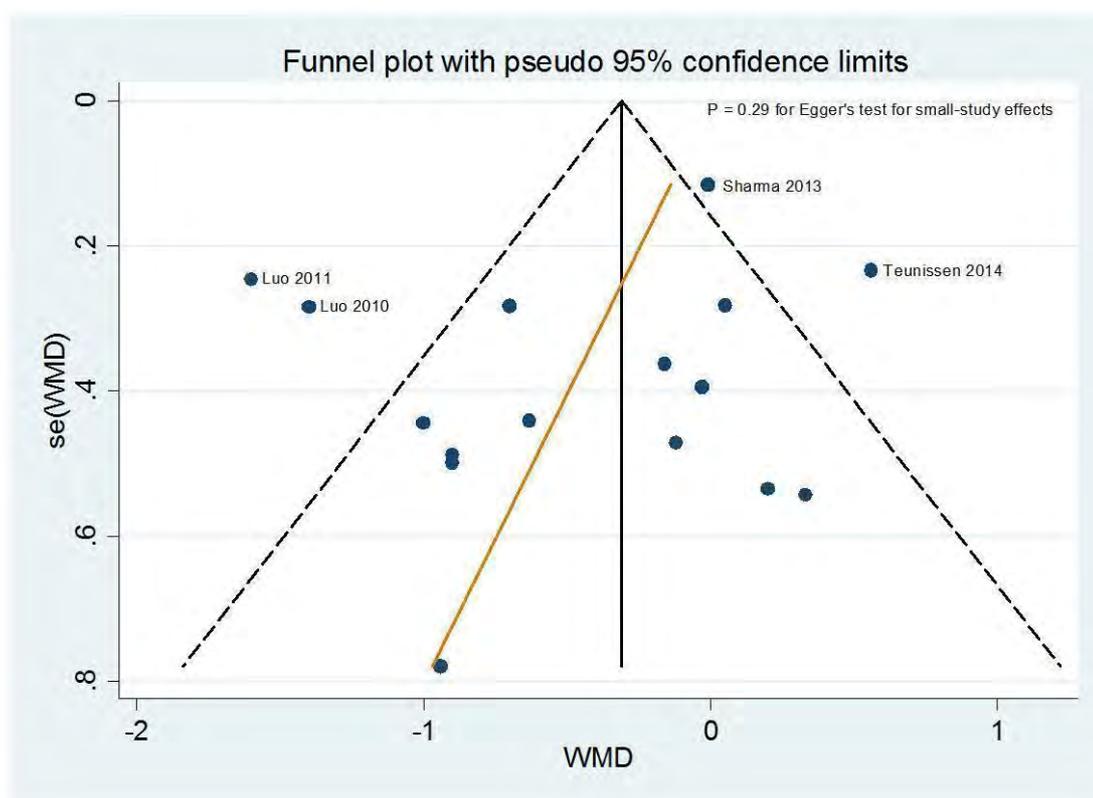
Other potential sources of bias

We observed no other potential sources of bias in the included trials.

Effects of interventions

See: **Summary of findings for the main comparison** Nebulised hypertonic saline compared with nebulised 0.9% saline for acute bronchiolitis in infants

Primary outcomes

1. Length of hospital stay or time taken to be ready for discharge (inpatients)

All but one of the 17 inpatient trials investigated length of hospital stay as the primary outcome (Tinsa 2014). Tinsa 2014 investigated clinical severity score as the primary outcome and length of stay as the secondary outcome. Two emergency department trials reported the length of stay in infants who required inpatient admission (Angoulvant 2017; Wu 2014). We did not include the data from these two trials in the meta-analysis because inpatients represent only a part of randomised participants. The pooled results of 17 trials with a total of 1867 inpatients showed that infants treated with nebulised hypertonic saline had a statistically significant shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (mean difference (MD) of -0.41 days, 95% confidence interval (CI) -0.75 to -0.07; P = 0.02; low-quality evidence; Analysis 1.1). There was significant heterogeneity in results among studies (I² = 79%).

Table 2 shows the results of seven post hoc subgroup analyses. The effect size of hypertonic saline on length of stay appeared to be greater in subgroups of trials in which virological testing was available, length of stay equal or longer than three days in the control group, use of 3% hypertonic saline, addition of epinephrine to hypertonic saline solution, and year of publication before 2013. Moderate to high levels of heterogeneity persisted in most subgroup analyses.

The meta-regression analysis did not reveal an independent effect of availability of virological testing, hypertonic saline concentration, co-administration with bronchodilators, length of hospital stay in the control group, and year of publication.

Table 3 shows the results of five post hoc sensitivity analyses. Only one sensitivity analysis excluding two trials, Luo 2010 and Luo 2011, with very long (greater than six days) and one trial, Ojha 2014, with very short (less than two days) length of hospital stay in the control group reduced the heterogeneity to a moderate level (I² from 79% to 50%), but the results were no longer statistically significant (MD of -0.22 days, 95% CI -0.48 to 0.05; P = 0.11).

2. Rate of hospitalisation (outpatients or emergency department patients)

Sarrell 2002, an outpatient trial, and seven emergency department trials, Angoulvant 2017, Anil 2010, Florin 2014, Grewal 2009, Ipek 2011, Jacobs 2014, and Wu 2014, (N = 1723) assessed the efficacy of hypertonic saline in reducing risk of hospitalisation. The pooled risk ratio (RR) was 0.86 (95% CI 0.76 to 0.98; P = 0.02; moderate-quality evidence; Analysis 1.2). There was no significant heterogeneity among studies (I² = 7%).

Table 4 shows the results of six post hoc subgroup analyses. The effect size of hypertonic saline on reduction of risk of hospitalisation appeared to be greater in the subgroups of trials in which virological testing was available and multiple doses (≥ two) of saline solutions were administered.

Secondary outcomes

1. Clinical severity scores

One outpatient trial (Sarrell 2002), one emergency department trial (Al-Ansari 2010), and seven inpatient trials, Flores 2016, Köse 2016, Luo 2010, Luo 2011, Mandelberg 2003, Miraglia Del Giudice 2012, and Tal 2006, compared post-inhalation Wang clinical severity score between infants treated with nebulised hypertonic saline and those treated with nebulised 0.9% saline on the first three days of treatment. The baseline clinical scores were comparable between groups in all nine trials.

On the first day of treatment, Sarrell 2002 (N = 65 outpatients) showed that the 3% saline group had a statistically significant lower clinical severity score compared to the 0.9% saline group (MD -1.28, 95% CI -1.92 to -0.64; P < 0.001). Seven inpatient trials (N = 576) also demonstrated significant benefits from hypertonic saline in reducing clinical severity score (pooled MD -0.82, 95% CI -1.25 to -0.38; P = 0.005; I² = 67%) (Flores 2016; Köse 2016; Luo 2010; Luo 2011; Mandelberg 2003; Miraglia Del Giudice 2012; Tal 2006). In contrast, Al-Ansari 2010 (N = 171 emergency department patients) did not show superiority of hypertonic saline over normal saline in reducing clinical score (MD -0.09, 95% CI -0.51 to 0.33; P = 0.68). The pooled results of nine trials showed a statistically significant lower clinical severity score favouring treatment with nebulised hypertonic saline over nebulised 0.9% saline on the first day of treatment (pooled MD -0.77, 95% CI -1.18 to -0.36; P < 0.001; I² = 74%; low-quality evidence; Analysis 1.3).

On the second day of treatment, Sarrell 2002 (N = 65 outpatients) showed a lower clinical severity score in the 3% saline group compared to the 0.9% saline group (MD -2.0, 95% CI -2.93 to -1.07; P < 0.001). We also observed a statistically significant difference between treatment and control groups among 467 inpatients (pooled MD -1.39, 95% CI -1.95 to -0.84; P < 0.001; I² = 76%) favouring the 3% saline group (Flores 2016; Luo 2010; Luo 2011; Mandelberg 2003; Miraglia Del Giudice 2012; Tal 2006).

Al-Ansari 2010 (N = 171 emergency department patients) did not demonstrate significant benefits of hypertonic saline in reducing clinical score (MD -0.27, 95% CI -0.63 to 0.09; P = 0.14). Meta-analysis of eight trials demonstrated superiority of nebulised 3% saline over 0.9% saline in reducing clinical severity score on the second day of treatment (pooled MD -1.28, 95% CI -1.91 to -0.65; P < 0.001; I² = 88%; low-quality evidence; Analysis 1.4). On the third day of treatment, Sarrell 2002 (N = 65 outpatients) showed a lower clinical severity score in the 3% saline group compared to the 0.9% saline group (MD -2.64, 95% CI -3.85 to -1.43; P < 0.001). Six inpatient trials (N = 434) also showed a lower clinical severity score in the 3% saline group (pooled MD -1.35, 95% CI -1.72 to -0.98; P < 0.001; I² = 57%). The pooled results from seven trials demonstrated superiority of nebulised 3% saline over 0.9% saline in reducing clinical severity score on the third day of treatment (pooled MD -1.43, 95% CI -1.82 to -1.04; P < 0.001; I² = 61%; low-quality evidence; Analysis 1.5).

We performed post hoc meta-regression analysis to explore possible causes of heterogeneity among studies regarding the effect size of hypertonic saline on clinical score during the first three days of treatment. The small number of studies enabled inclusion of only one relevant covariate in the model, which was the severity of bronchiolitis assessed by baseline clinical score in the 0.9% saline group. The meta-regression analysis yielded a regression coefficient of -0.11 (95% CI -0.35 to 0.11; P = 0.30), suggesting that disease severity did not significantly influence the effect size of hypertonic saline on clinical score.

Eight emergency department-based trials assessed short-term effects (30 minutes to 120 minutes) of up to three doses of nebulised hypertonic saline in improving clinical severity score among infants with acute bronchiolitis (Angoulvant 2017; Anil 2010; Florin 2014; Grewal 2009; Ipek 2011; Jacobs 2014; Khanal 2015; Wu 2014). Variation in scoring methods and assessment time points made conducting meta-analyses inappropriate. Only two trials showed the superiority of hypertonic saline over normal saline in improving clinical severity scores (Angoulvant 2017; Khanal 2015). Khanal 2015 found that participants who received nebulised hypertonic saline had more significant improvement in baseline clinical severity scores at the end of two hours of treatment. Angoulvant 2017 revealed that the change in Respiratory Distress Assessment Instrument (RDAI) score before and after nebulisation was greater in the hypertonic saline group than that in the normal saline group (adjusted difference -0.7, 95% CI -1.2 to -0.2; P = 0.006). Al-Ansari 2010, an emergency department trial, compared nebulised 5% and 3% hypertonic saline with nebulised 0.9% saline, given at enrolment and every four hours thereafter until child was ready for discharge. There was a small but statistically significant lower clinical score favouring treatment with nebulised 5% saline over nebulised 0.9% saline at 48 hours after randomisation (3.69 ± 1.09 versus 4.12 ± 1.11, P = 0.04) but not 24 hours after randomisation (3.75 ± 1.27 versus 3.97 ± 1.40, P = 0.38). Al-Ansari 2010 did not find a significant difference in clin-ical score at 24 hours and 48 hours after randomisation between 3% saline and 0.9% saline.

2. Rate of re-admission to hospital

Four emergency department trials, Al-Ansari 2010, Anil 2010, Grewal 2009, and Khanal 2015, and one inpatient trial, Everard 2014, included rate of re-admission after discharge as an outcome. The pooled results of these trials did not demonstrate significant benefits of nebulised hypertonic saline in reducing the risk of re-admission (pooled RR 0.77, 95% CI 0.48 to 1.25; P = 0.30; I² = 36%; moderate-quality evidence; Analysis 1.6).

3. Haemoglobin saturation (oximetry)

Eight trials reported the results of haemoglobin saturation (Anil 2010; Florin 2014; Grewal 2009; Ipek 2011; Khanal 2015; Mandelberg 2003; Pandit 2013; Tinsa 2014). Only Khanal 2015 revealed a significant difference between the hypertonic saline group and the 0.9% saline group in terms of room air saturation of oxyhaemoglobin throughout the study period, showing a significantly higher haemoglobin saturation in the hypertonic saline group than the 0.9% saline group at 60 minutes and 120 minutes after treatment.

4. Respiratory rate

Five trials reported no difference in respiratory rate between the hypertonic saline group and the 0.9% saline group (Flores 2016; Ipek 2011; Khanal 2015; Pandit 2013; Tinsa 2014).

5. Heart rate

Seven trials reported no difference in heart rate between the hypertonic saline group and the 0.9% saline group (Anil 2010; Florin 2014; Ipek 2011; Khanal 2015; Mandelberg 2003; Pandit 2013; Sarrell 2002).

6. Time to resolution of symptoms and signs

Luo 2010 and Luo 2011 reported time to resolution of wheezing, cough, and pulmonary moist crackles. The pooled results showed that infants treated with nebulised 3% saline had a shorter duration of respiratory symptoms and signs compared to those treated with nebulised 0.9% saline (pooled MD -1.19 days, 95% CI -1.54 to -0.84; P < 0.001). There was significant heterogeneity in results between studies (P < 0.001; I² = 77.0%; Analysis 1.7).

7. Duration of in-hospital oxygen supplementation

Ojha 2014 and Teunissen 2014 (both inpatient trials) reported no difference in duration of in-hospital oxygen supplementation between the hypertonic saline group and the 0.9% saline group.

8. Need for add-on treatment (bronchodilator, systemic corticosteroids, antibiotics, and oxygen supplementation)

Eight trials compared the need for add-on treatment between treatment groups (Al-Ansari 2010; Flores 2016; Kuzik 2007; Mahesh Kumar 2013; Pandit 2013; Tal 2006; Teunissen 2014; Wu 2014). None of the trials revealed a significant difference between hypertonic saline and 0.9% saline groups.

9. Results of pulmonary function tests

No included studies reported pulmonary function test results.

10. Radiological findings

In Mandelberg 2003 and Sarrell 2002 the second chest radiograph was obtained on the third day after hospital admission. The pooled results did not show a significant difference in radiological score between the hypertonic saline and 0.9% saline groups (pooled MD -0.08, 95% CI -0.90 to 0.75; P = 0.85; Analysis 1.8). There was no significant heterogeneity between studies (P = 0.95; I² = 0%).

11. Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, diarrhoea, and acute urinary retention)

Four trials did not report safety data (Ipek 2011; Mahesh Kumar 2013; Miraglia Del Giudice 2012; Ojha 2014). The remaining 24 trials involving 3723 participants reported adverse events in treatment groups. Among the 3723 participants, 1968 received nebulised hypertonic saline (3% saline: N = 1634; 5% saline: N = 165; 6% saline: N = 83; 7% saline: N = 86). Thirteen trials did not find any significant adverse events among a total of 1363 infants, of whom 703 received nebulised hypertonic saline (co-administered with bronchodilators: N = 672, 96%; hypertonic saline alone: N = 31, 4%). In the remaining 11 trials involving 2360 infants, of whom 1265 received nebulised hypertonic saline (co-administered with bronchodilators: N = 388, 31%; hypertonic saline alone: N = 877, 69%), at least one adverse event was reported. Variations in reporting and outcomes precluded the possibility of conducting meta-analysis of safety data. We narratively summarised the safety data of 11 trials (Table 5). Various adverse events were reported in both hypertonic saline and control groups; in most cases, these were mild and resolved spontaneously. Only one inpatient trial involving 142 participants who received 3% saline alone without bronchodilator reported one serious adverse event (bradycardia and desaturation), possibly related to hypertonic saline inhalation, but it resolved the following day.

DISCUSSION

Summary of main results

We included 28 trials involving 4195 infants (2222 infants received nebulised hypertonic saline) with acute viral bronchiolitis (17 inpatient trials (N = 2028); 2 outpatient trials (N = 194); 7 emergency department trials (N = 1873); 1 outpatient and emergency department trial (N = 100)) (Summary of findings for the main comparison).

Hospitalised infants treated with nebulised hypertonic saline had a statistically significant shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (MD -0.41 days, 95% CI -0.75 to -0.07; P = 0.02; 17 trials). Children who received hypertonic saline also had a statistically significant lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment (day 1: MD -0.77, 95% CI -1.18 to -0.36, P = <0.001; day 2: MD -1.28, 95% CI -1.91 to -0.65, P < 0.001; day 3: MD -1.43, 95% CI -1.82 to -1.04, P < 0.001). Nebulised hypertonic saline reduced the risk of hospitalisation by 14% compared with nebulised 0.9% saline among children treated as outpatients and in emergency departments (RR 0.86, 95% CI 0.76 to 0.98; P = 0.02; 7 trials). Among eight emergency department trials assessing short-term effects (30 minutes to 120 minutes) of up to three doses of nebulised hypertonic saline in improving clinical score, only two trials showed significant effects of the treatment. Post hoc subgroup analyses demonstrated that the effect size of nebulised hypertonic saline on length of stay among inpatients appeared to be greater in subgroups of trials in which virological testing was available, length of stay equal or longer than three days in the control group, use of 3% hypertonic saline, addition of epinephrine to hypertonic saline solution, and year of publication before 2013. However, the meta-regression analysis did not reveal independent effect of these factors on the effect size of hypertonic saline.

Among children treated as outpatients and in emergency departments, post hoc subgroup analyses revealed that the effect size of nebulised hypertonic saline on reduction of risk of hospitalisation appeared to be greater in subgroups of trials in which virological testing was available and multiple doses (≥ two) of saline solution were administered.

Twenty-four trials involving 3723 participants (of which 1968 received nebulised hypertonic saline) reported treatment safety data. Thirteen of these trials did not report any significant adverse events among a total of 1363 infants (of which 703 received nebulised hypertonic saline, mixed with bronchodilators in 96% of infants). At least one adverse event was reported in 11 trials involving 2360 infants (of which 1265 received nebulised hypertonic saline, alone in 69% of infants). In most cases, adverse events were mild and resolved spontaneously.

Overall completeness and applicability of

evidence

In this update, we found that the effect size of nebulised hypertonic saline on reducing length of stay in hospitalised infants was approximately a third of what was found in the last (2013) update of this review. Zhang 2013 included six inpatient trials involving 500 infants (MD -1.15 days, 95% CI -1.49 to -0.82 days). Moreover, all 10 trials published in 2013 and thereafter, including two European multicentre studies with relatively large sample sizes, did not find significant effects of nebulised hypertonic saline on length of stay among inpatients with bronchiolitis. We found two main differences between recently published trials and those published before 2013. Virological investigation was available in 86% of trials published before 2013, whereas such testing was available in only 30% of trials published in 2013 and thereafter. Another difference was that none of the seven older trials had a mean length of stay in the control group of less than three days, while 40% of the recently published trials had a mean length of stay in the control group of less than three days. These two factors may partially explain the inconsistency in results between older trials and trials published in 2013 and thereafter; however, the meta-regression analysis did not confirm an independent effect of these factors on the effect size of hypertonic saline.

For outpatients and emergency department patients, we found a 14% (RR 0.86, 95% CI 0.76 to 0.98) reduction in the risk of hospitalisation associated with nebulised hypertonic saline, in contrast with a 37% non-statistically significant reduction shown in the 2013 review, which included four outpatient and emergency department trials involving 380 infants (RR 0.63, 95% CI 0.37 to 1.07).

Clinical score is generally considered a relatively objective measure to assess the severity of illness. In this review, 11 trials used the clinical severity score system proposed by Wang 1992, which assesses respiratory rate, wheezing, retraction, and general condition. The benefits of nebulised hypertonic saline in improving clinical score were observed in the first three days of treatment in both outpatients and inpatients. However, most emergency department trials failed to demonstrate significant effects of hypertonic saline in improving clinical score over a short period of time (30 minutes to 120 minutes). The validity of Wang 1992 score system has not yet been assessed. Another commonly used approach for grading clinical severity was the Respiratory Distress Assessment Instrument (RDAI). However, RDAI may have poor to moderate construct validity, considerable test-retest measurement error, and does not encompass all determinants of bronchiolitis severity (Fernandes 2015).

Potential side effects, principally acute bronchospasm, remain a concern with nebulised hypertonic saline. No significant adverse events were observed in 13 trials involving 1363 infants (703 treated with nebulised hypertonic saline). Saline solutions were co-administered with bronchodilators in 96% of these infants. In contrast, there were 11 trials involving 2360 participants (1265 treated with nebulised hypertonic saline) reported at least one adverse event. The majority of patients (69%) received saline solution alone. Most adverse events were mild and resolved spontaneously. These results suggest that nebulised hypertonic saline is a safe treatment in infants with bronchiolitis, especially when administered in conjunction with a bronchodilator.

Inhalation therapy was administered via jet nebulisers in all of the included studies except for Tal 2006, which used ultrasonic nebulisers. There are some theoretical differences in the physical properties of aerosols produced by jet nebulisers and ultrasonic nebulisers, which may affect their therapeutic efficacy. On the one hand, ultrasonic nebulisers induce sputum more efficiently than jet nebulisers; on the other hand, jet nebulisers generate aerosols with smaller aerodynamic mass median diameter, which may more easily reach smaller bronchi and bronchioles. We could not provide direct evidence regarding the impact of the physical properties of aerosols generated by different types of nebulisers on the efficacy of inhaled hypertonic saline in infants with viral bronchiolitis. However, at least one trial demonstrated that both jet nebulisers and ultrasonic nebulisers are efficient methods of delivery of hypertonic saline for infants with bronchiolitis (Tal 2006).

The optimal treatment regimen for nebulised hypertonic saline in acute bronchiolitis remains unclear. Among inpatients, study solutions were given more frequently in 12 trials (every 4 to 6 hours) and less frequently in 5 trials (every 8 hours). Subgroup analysis did not reveal a significant difference in reduction of length of hospital stay between regimens. Among outpatients and emergency department patients, effect size of nebulised hypertonic saline appeared to be greater when multiple doses ($\geq$ two) of saline solutions were administered compared to a single dose.

The concentration of nebulised hypertonic saline was 3% in all but five trials (Al-Ansari 2010; Köse 2016; Li 2014; Teunissen 2014; Tinsa 2014). We did not observe the superiority of higher concentration (5%, 6%, and 7%) of hypertonic saline over 3% saline in improving clinical outcomes. On the contrary, subgroup analysis showed a larger effect of 3% saline on reducing length of hospital stay among inpatients compared to hypertonic saline with higher concentration.

We included trials conducted in high- and low-income countries and in different settings (inpatient, outpatient, and emergency department). The evidence derived from this review thus may have wide applicability. However, as all but two included trials only recruited infants with mild to moderate bronchiolitis (Teunissen 2014; Wu 2014), care should be taken when extrapolating the findings of this review to infants with more severe bronchiolitis, such as those requiring mechanical ventilation, intensive care, or with oxygen saturation readings below 85% on room air. The underlying airway pathological changes may differ between severe and mild to moderate bronchiolitis, so different responses to treatments with hypertonic saline may be expected in children with more severe illness. Further trials are needed to assess the potential effects of nebulised hypertonic saline in infants hospitalised with severe acute bronchiolitis.

Despite our findings that the effects of nebulised hypertonic saline on reduction in length of hospital stay are smaller than were previously estimated, a reduction of 10 hours in length of hospital stay in infants with bronchiolitis may still be considered clinically relevant given the relatively short disease course, high prevalence, and huge burden of illness on healthcare systems around the world. Moreover, nebulised hypertonic saline may have benefits on other outcomes such as rate of hospitalisation and clinical severity score in infants with acute bronchiolitis, providing a good safety profile and low cost.

Quality of the evidence

We had no serious concerns on three domains of the GRADE approach (indirectness, imprecision, and publication bias). We downgraded the quality of the evidence to low for length of hospital stay due to high levels of statistical heterogeneity and potential risk of selection bias in one-third of the included trials. High heterogeneity could be expected given variations among trials in definitions of acute bronchiolitis, disease severity, standard care, intervention regimen, criteria for discharge, and risk of potential bias. We conducted several subgroup analyses to investigate the potential sources of heterogeneity, but moderate to high levels of heterogeneity persisted in most subgroup analyses.

We downgraded the quality of the evidence to low for clinical severity score due to high heterogeneity and risk of bias, as mentioned above.

In spite of the fact that there was no statistically significant heterogeneity, we downgraded the quality of evidence to moderate for rate of hospitalisation due to substantial clinical heterogeneity between studies.

Potential biases in the review process

We searched for both published and unpublished trials to identify all relevant studies. We obtained additional trial data from five principal investigators. All included inpatient trials contributed data for meta-analysis of length of hospital stay. However, the results of meta-analyses of some secondary outcomes, such as clinical severity score and rate of re-admission, may be biased because only some included trials contributed data for analysis. The number of trials and participants in outpatient and emergency department settings was limited: Wu 2014 and Angoulvant 2017 contributed 73% of weight to the overall summary estimate of effects of hypertonic saline on reduction of risk of hospitalisation. All studies except for Everard 2014 used 0.9% saline as the comparison. The use of normal saline enables the trial to be double-blind, however normal saline is not technically a placebo, as high-volume normal saline inhalation could potentially have physiological effects by improving airway mucociliary clearance, which may have beneficial effects on acute bronchiolitis (Wohl 2003). Use of normal saline as the control may tend to minimise the effect size of hypertonic saline.

Agreements and disagreements with other studies or reviews

Four published systematic reviews addressed efficacy and safety of nebulised hypertonic saline in children with acute bronchiolitis (Badgett 2015; Chen 2014; Maguire 2015; Zhang 2015). We comparatively summarised the main findings of these four reviews in Table 6.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence suggests that nebulised hypertonic saline may modestly reduce the length of hospital stay among infants hospitalised with acute viral bronchiolitis and improve clinical severity scores. Nebulised hypertonic saline may also reduce the risk of hospitalisation among outpatients and emergency department patients. Treatment with nebulised hypertonic saline has a good safety profile. However, the quality of evidence in this review was insufficient to support routine use of nebulised hypertonic saline in infants with acute bronchiolitis.

Implications for research

Further multicentre randomised trials are required to evaluate the efficacy and safety of nebulised hypertonic saline in infants with acute bronchiolitis, in inpatient, outpatient, and emergency department settings. There are some common challenges for all clinical trials in infants with acute bronchiolitis. The currently used definition of 'bronchiolitis' may include a heterogeneous group of patients with different underlying aetiologies and pathologies. The development of valid diagnostic criteria for acute bronchiolitis in infants is urgently needed. There is a lack of robust and well-accepted efficacy outcome measures. Length of hospital stay and rate of hospitalisation are the most clinically important endpoints, but they are usually more susceptible to bias. Well-defined valid admission and discharge criteria should thus be used. Further trials should have sufficient statistical power to detect modest but clinically relevant effects of the intervention. The optimal treatment regimen of nebulised hypertonic saline for infants with acute bronchiolitis remains to be determined. The mechanism of action of nebulised hypertonic saline in infants with viral bronchiolitis also needs to be addressed in future studies.

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Zhang 2016

Zhang L, Mendoza-Sassi RA, Klassen TP, Wainwright C. Nebulized hypertonic saline for acute bronchiolitis: a systematic review [erratum]. *Pediatrics* 2016;**137**(4): e20160017. [DOI: 10.1542/peds.2016-0017

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Al-Ansari 2010

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: paediatric emergency facility in Qatar Assessed for eligibility: 187 Randomised: 115 hypertonic saline group (5% saline: 57; 3% saline: 58); 56 normal saline group Completed: 115 hypertonic saline group; 56 normal saline group Gender (male): 59.1% Age (mean ± SD): 3.8 ± 2.8 months in 3% saline group; 4.0 ± 2.5 months in 5% saline group; 3.3 ± 2.4 months in normal saline group Inclusion criteria: infants aged ≤ 18 months, with a prodromal history of viral upper respiratory tract infection, followed by wheezing or crackles, or both on auscultation and Wang clinical severity score ≥ 4 Exclusion criteria: born at ≤ 34 weeks' gestation, previous history of wheezing, steroid use within 48 h of presentation, obtundation and progressive respiratory failure requiring ICU admission, history of apnoea within 24 hours before presentation, SaO_2 ≤ 85% on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease, or immunodeficiency
Interventions	Intervention groups: Group 1: nebulised 5% hypertonic saline (5 mL) plus 1.5 mL of epinephrine Group 2: nebulised 3% hypertonic saline (5 mL) plus 1.5 mL of epinephrine Control group: nebulised 0.9% normal saline (5 mL) plus 1.5 mL of epinephrine Treatment was given every 4 hours, until the patient was ready for discharge. Nebulised medications were delivered through a tight-fitting face mask by pressurised oxygen with the flow meter set at 10 L/min
Outcomes	• Wang clinical severity score • Oxygen saturation • Length of stay • Need for ICU admission • Rate of re-admission • Adverse events
Notes	Virological identification not available

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation program
Allocation concealment (selection bias)	Low risk	Sequentially numbered and sealed envelopes

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 (9.3%) withdrawals after randomisation; baseline characteristics between treatment groups were balanced
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Angoulvant 2017

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: 24 paediatric emergency departments in France Assessed for eligibility: 2445 Randomised: 387 hypertonic saline group; 390 normal saline group Completed: 385 hypertonic saline group; 387 normal saline group Gender (male): 60.2% Age: median (interquartile range): 3 (2 to 5) months in hypertonic saline group; 3 (2 to 5) months in normal saline group Inclusion criteria: infants aged 6 weeks to 12 months with first episode of moderate to severe bronchiolitis defined as viral upper respiratory tract infection plus wheezing or crackles, or both on chest auscultation with respiratory distress Exclusion criteria: premature birth (birth before 37 weeks of gestation), immunologic, cardiac or chronic pulmonary disease, bone malformation of the chest, previous use of nebulised hypertonic saline, inability to communicate with the family (a language barrier or lack of telephone for contact), need of admission to a paediatric ICU
Interventions	Intervention groups: nebulised 3% hypertonic saline (4 mL) Control groups: nebulised 0.9% normal saline (4 mL) Study medication was given at 0 and 30 min using a jet nebuliser through a firmly applied face mask with an oxygen flow rate of 6 L/min
Outcomes	- Hospital admission up to 24 hours after enrolment - Admission within 28 days - Changes in RDAI score - Duration of symptoms - Length of hospital stay for hospitalised infants - Adverse events
Notes	RSV positive: 84.5% in hypertonic saline group; 88.2% in control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random allocation sequence using a 1:1 ratio and permutation blocks with a block size of 4, stratified according to centre
Allocation concealment (selection bias)	Low risk	The investigational pharmacy prepared the study drugs in sequentially numbered and visually identical packets. Randomisation codes were kept secure until data entry was complete
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Hospitalisation data were not available for 5 infants (2 in hypertonic saline group and 3 in normal saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Anil 2010

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: emergency department of a teaching hospital in Turkey Assessed for eligibility: 190 Randomised: 75 hypertonic saline group; 111 normal saline group Completed: 75 hypertonic saline group; 111 normal saline group Gender (male): 64.5% Age (mean ± SD): 9.5 ± 5.3 months (range 1.5 to 24 months) Inclusion criteria: infants with diagnosis of bronchiolitis requiring a history of upper respiratory infection and the presence of bilateral wheezing or crackles, or both on chest auscultation, plus clinical severity score between 1 and 9 Exclusion criteria: prematurity, any underlying disease (e.g. cystic fibrosis, bronchopulmonary dysplasia, and cardiac or renal disease), prior history of wheezing, atopic dermatitis, allergic rhinitis or asthma, SaO_2 < 85% on room air, clinical severity score > 9, obtunded consciousness, progressive respiratory failure requiring mechanical ventilation, previous treatment with bronchodilators, and any steroid therapy within 2 weeks
Interventions	Intervention groups: Group 1: nebulised 3% hypertonic saline (4 mL) plus 1.5 mg epinephrine Group 2: nebulised 3% hypertonic saline (4 mL) plus 2.5 mg salbutamol Control groups:

Anil 2010 (*Continued*)

	Group 3: nebulised 0.9% normal saline (4 mL) plus 1.5 mg epinephrine Group 4: nebulised 0.9% normal saline (4 mL) plus 2.5 mg salbutamol Group 5: nebulised 0.9% normal saline (4 mL) alone The study drug was administered at 0 and 30 min by Medic-Aid Sidestream nebuliser (Medic-Aid Ltd., West Sussex, UK) using a face mask with continuous flow of 100% oxygen at 6 L/min
Outcomes	• Wang clinical severity score • Oxygen saturation • Heart rate • Rate of hospitalisation • Rate of re-admission • Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation program
Allocation concealment (selection bias)	Unclear risk	Study medications were identical in appearance and odour, but no other details were provided regarding allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Everard 2014

Methods	Design: multicentre, parallel-group, open, randomised controlled trial
Participants	Setting: assessment units and paediatric wards of 10 participating centres in England and Wales Assessed for eligibility: 772 Randomised: 158 hypertonic saline group (3% saline); 159 standard care group Completed: 141 hypertonic saline group; 149 standard care group Gender (male): 54.5%

	Age (mean ± SD): 3.3 ± 2.6 months in hypertonic saline group; 3.4 ± 2.8 months in standard care group Inclusion criteria: infants < 12 months with diagnosis of bronchiolitis defined as an apparent viral respiratory tract infection associated with airways obstruction manifest by hyperinflation, tachypnoea and subcostal recession with widespread crepitations on auscultation, needing supplementary oxygen for SaO_2 of < 92% in air Exclusion criteria: history of wheezy bronchitis or asthma, gastro-oesophageal reflux, previous lower respiratory tract infections, risk factors for severe disease, carers lacking fluent English in the absence of translator service, and requiring admission to high dependency or intensive care units at presentation
Interventions	Intervention group: 4 mL 3% saline + standard care Control group: standard care Hypertonic saline given every 6 h, administered via PARI Sprint nebuliser with appropriate face mask, until primary outcome achieved
Outcomes	• Time to fit for discharge (75% of usual intake and SaO$_2$ ≥ 92% for 6 h at room air) • Actual time to discharge • Re-admission within 28 days from randomisation • Health care usage • Duration of respiratory symptoms postdischarge • Infant Toddler Quality of Life • Adverse events
Notes	RSV positive: 58.5% in hypertonic saline group; 64.4% in control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation in blocks of size two, four, and six, stratified by hospital
Allocation concealment (selection bias)	Low risk	Centralised web-based randomisation system
Blinding (performance bias and detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Low risk	27 (8.5%) withdrawals after randomisation (17 hypertonic saline group, 10 control group); baseline characteristics between treatment groups were balanced
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.

Other bias	Low risk	No other bias found.

Flores 2016

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: paediatric ward of a general urban hospital in Portugal Assessed for eligibility: not stated Randomised: 38 hypertonic saline group (3% saline); 40 normal saline group Completed: 33 hypertonic saline group; 35 normal saline group Gender (male): 52.9% Age (mean ± SD): 3.3 ± 2.4 months hypertonic saline group; 3.8 ± 2.5 months normal saline group Inclusion criteria: infants aged < 12 months with acute bronchiolitis, defined as an apparent viral respiratory tract infection manifest by nasal discharge and wheezy cough, with presence of fine inspiratory crackles and/or high-pitched expiratory wheeze, even apnoea Exclusion criteria: previous episodes of wheezing, personal history of prematurity (gestational age < 34 weeks), physician diagnosis of eczema, food allergy, or chronic (cardiac, respiratory, immunological, neurological, or metabolic) disease and high severity criteria (coma, respiratory rate > 80 breaths/minute, SaO_2 < 88% on room air or need for assisted ventilation)
Interventions	Intervention group: nebulised 3% hypertonic saline (3 mL) plus 0.25 mL (1.25 mg) salbutamol Control group: nebulised 0.9% normal saline (3 mL) plus 0.25 mL (1.25 mg) salbutamol Treatment was given every 6 h until discharge. All inhaled therapies were delivered through a tight-fitting face mask from an oxygen-driven nebuliser (Cirrus 2 Nebuliser, Wokingham, Berkshire, UK), connected to a source of pressurised oxygen from the wall, set to a flow rate of 6 L/min
Outcomes	• Length of hospital stay (fit to discharge and actual discharge) • Wang severity score • Need for supplemental oxygen and tube feeding and their duration • Need for other treatments (further doses of salbutamol, nebulised epinephrine, systemic corticosteroids, antibiotics, or diuretics) • Adverse events
Notes	RSV positive: 87.9% in hypertonic saline group; 82.9% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation

Allocation concealment (selection bias)	Low risk	Both solutions were similar in appearance and smell, were stored in identical syringes, and were labelled only by a code number. Randomisation list was concealed by the pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 (12.8%) withdrawals after randomisation (5 hypertonic saline group, 5 control group); baseline characteristics between treatment groups were balanced
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Florin 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: urban paediatric emergency department in USA Assessed for eligibility: 2256 Randomised: 31 hypertonic saline group (3% saline); 31 normal saline group Completed: 31 hypertonic saline group; 31 normal saline group Gender (male): 45.2% Age (mean ± SD): 7.2 ± 5.1 months in hypertonic saline group; 6.1 ± 3.6 months in normal saline group Inclusion criteria: children aged 2 months up to 24 months presenting to the emergency department with acute bronchiolitis, defined as a first episode of wheezing associated with signs and symptoms of respiratory distress and upper respiratory infection, with RDAI score of 4 to 15 (moderate to severe) Exclusion criteria: infants with a history of wheezing or asthma, bronchodilator therapy prior to the current illness, chronic lung or heart disease, critical illness, inability to receive nebulised medications, and infants with non-English-speaking guardians
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) Control group: nebulised 0.9% normal saline (4 mL) Treatment delivered using a jet nebuliser with an oxygen flow rate of 8 L/min. Study medication was given within 90 minutes after albuterol administration
Outcomes	• Respiratory assessment change score (RACS) • Heart rate • Respiratory rate • Oxygen saturation • Rate of hospitalisation

	• Physician clinical impression (i.e. overall rating of clinical severity, categorised as mild, moderate, or severe) • Parental perception of improvement in breathing and feeding (i.e. improved, worse, or unchanged) • Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random permuted block randomisation
Allocation concealment (selection bias)	Low risk	The investigational pharmacy prepared the study medications, which were stored in sequentially numbered envelopes with blinded syringes labelled only with the study number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Grewal 2009

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: emergency department of a children's hospital in Canada Assessed for eligibility: not stated Randomised: 24 hypertonic saline group; 24 normal saline group Completed: 23 hypertonic saline group; 23 normal saline group Gender (male): 60.9% Age (mean ± SD): 5.6 ± 4.0 months in hypertonic saline group; 4.4 ± 3.4 months in normal saline group Inclusion criteria: infants aged 6 weeks to 12 months presenting with a first episode of wheezing and clinical symptoms of a viral respiratory infection, plus an initial SaO_2 of 85% or more but 96% or less, and RDAI score $\geq$ 4 Exclusion criteria: pre-existing cardiac or pulmonary disease, previous diagnosis of asthma by a physician, any previous use of bronchodilators (except for treatment of the current

	illness), severe disease requiring resuscitation room care, inability to take medication using a nebuliser, inability to obtain informed consent secondary to a language barrier, or no phone access for follow-up
Interventions	Intervention group: nebulised 3% hypertonic saline (2.5 mL) plus 0.5 mL 2.25% racaemic epinephrine Control group: nebulised 0.9% normal saline (2.5 mL) plus 0.5 mL 2.25% racaemic epinephrine Both groups received inhalation solutions at 0 minutes. Each treatment was given by nebuliser with continuous flow of oxygen at 6 L/min. 2 doses of the study drug were available for each infant such that, if the physician felt that a second dose of racaemic epinephrine was needed during the 120-minute study period, the infant received the same drug combination again
Outcomes	• Respiratory assessment change score • Oxygen saturation • Rate of hospitalisation • Rate of re-admission • Adverse events
Notes	RSV positive: 82.6% in hypertonic saline group; 81.8% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Website randomisation scheme
Allocation concealment (selection bias)	Low risk	The solutions prepared by the hospital pharmacy were similar in appearance and smell, stored in identical syringes, labelled only by a code number, and placed in the research cupboard within the emergency department
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (4.1%) withdrawals (1 hypertonic saline group; 1 normal saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Ipek 2011

Methods	Design: quasi-randomised, double-blind, parallel-group, controlled trial
Participants	Setting: paediatric emergency department of a training and research hospital in Turkey Eligible: not stated Randomised: 60 hypertonic saline group; 60 normal saline group Completed: 60 hypertonic saline group; 60 normal saline group Gender (male): 59.2% Age (mean ± SD): 7.9 ± 3.9 months Inclusion criteria: age < 2 years, a history of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation, and a clinical severity score of 4 to 8 on admission Exclusion criteria: infants with clinical severity score < 4 or > 8, SaO_2 < 85% on room air, chronic cardiac illness, premature birth, birth weight < 2500 g, history of recurrent wheezing episodes, proven immune deficiency, severe neurological disease, age < 1 month or > 2 years, consolidation or atelectasis on a chest roentgenogram
Interventions	Intervention groups: Group 1: nebulised 3% hypertonic saline (4 mL) plus salbutamol 0.15 mg/kg Group 2: nebulised 3% hypertonic saline (4 mL) alone Control groups: Group 1: nebulised 0.9% hypertonic saline (4 mL) plus salbutamol 0.15 mg/kg Group 2: nebulised 0.9% hypertonic saline (4 mL) alone The treatment was given every 20 min until 3 doses had been administered (0, 20, and 40 min). All inhaled therapies were delivered via a compressor nebuliser through a face mask with continued flow of oxygen at 4 to 5 L/min (Mini Compressor Nebulizer, CN-02WD, Ace-Tec Co., Ltd., Guangdong, China)
Outcomes	- Wang clinical severity score - Oxygen saturation - Respiratory rate - Heart rate - Corticosteroid need - Rate of hospitalisation - Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Infants were assigned to 1 of 4 groups according to the consecutive order of their admission to the short-stay unit
Allocation concealment (selection bias)	High risk	As stated above

Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was stated to be double-blind, but no details were provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Jacobs 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: emergency department of an urban tertiary care centre in the USA Assessed for eligibility: 128 Randomised: 52 hypertonic saline group; 49 normal saline group Completed: 52 hypertonic saline group; 49 normal saline group Gender (male): 63.3% Age (mean ± SD): 6.0 ± 3.9 months in hypertonic saline group; 5.6 ± 3.3 months in normal saline group Inclusion criteria: infants aged 6 weeks to 18 months presenting to the emergency department with acute bronchiolitis, defined as viral respiratory illness and first episode of wheeze, and a modified Wang clinical severity score of ≥ 4 Exclusion criteria: previous history of wheezing, any use of bronchodilators within 2 hours of presentation, gestational age ≤ 34 weeks, history of congenital heart disease or chronic pulmonary or chronic renal disease, $SaO_2 \leq 85\%$ at the time of recruitment, severe disease requiring ICU admission, or inability to obtain informed consent
Interventions	Intervention group: nebulised 7% hypertonic saline (3 mL) plus 2.25% racaemic epinephrine (0.5 mL) Control group: nebulised 0.9% hypertonic saline (3 mL) plus 2.25% racemic epinephrine (0.5 mL) The medication was given via a nebuliser driven by oxygen flow at 6 L/min after initial screening and assessment. If admitted, the infant continued to receive the same designated medication every 6 h until discharge or 24 h after admission
Outcomes	• Modified Wang clinical severity score • Rate of hospitalisation • Discharge rate at 23 h (observation status) • Length of hospital stay • Adverse events
Notes	RSV positive: 68% in hypertonic saline group; 50% in control group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation in blocks of 10, but it is unclear how to choose blocks at random to create the allocation sequence
Allocation concealment (selection bias)	Low risk	Sequentially numbered, concealed envelopes containing either 7% or 0.9% saline solution
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Khanal 2015

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: emergency and outpatient departments of a children's hospital in Nepal Assessed for eligibility: 146 Randomised: 50 hypertonic saline group (3% saline); 50 normal saline group Completed: 49 hypertonic saline group; 50 normal saline group Gender (male): 48% Age (mean ± SD): 9.8 ± 5.0 months in hypertonic saline group; 9.5 ± 4.2 months in normal saline group Inclusion criteria: infants aged 6 weeks to 2 years with acute bronchiolitis defined as the first episode of acute wheezing, starting as a viral upper respiratory infection (coryza, cough or fever), with Wang clinical severity score between 1 and 9 Exclusion criteria: any underlying disease (e.g. cystic fibrosis, bronchopulmonary dysplasia, and cardiac or renal disease), prior history of wheezing, diagnosed case of asthma, SaO₂ < 85% on room air, clinical severity score > 9, progressive respiratory distress requiring mechanical ventilation, previous treatment with bronchodilators within last 4 h, and any steroid therapy within 48 h
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) plus L-epinephrine (1.5 mg) Control group: nebulised 0.9% normal saline (4 mL) plus L-epinephrine (1.5 mg) The study drug was administered at 0 and 30 min by a jet nebuliser using a face mask
Outcomes	• Wang clinical severity score • Oxygen saturation • Respiratory rate

Khanal 2015 *(Continued)*

- Heart rate
- Discharge readiness at the end of 2 h of observation
- Re-admission rate within 24 h following discharge
- Socioeconomic burden of illness
- Adverse events

Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation (in blocks of 10)
Allocation concealment (selection bias)	Low risk	Study solutions were labelled with the codes and wrapped in an envelope bearing the respective codes. Study solutions were identical in appearance and odour
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (1%) withdrawal after randomisation in hypertonic saline group
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Kuzik 2007

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient wards of 3 regional tertiary care hospitals, 1 in United Arab Emirates and 2 in Canada Eligible: not stated Randomised: 47 hypertonic saline group; 49 normal saline group Completed: 45 hypertonic saline group; 46 normal saline group Gender (male): 59.4% Age (mean ± SD): 4.7 ± 4.2 months (range 10 days to 18 months) Inclusion criteria: infants with diagnosis of moderately severe bronchiolitis requiring a history of a preceding viral upper respiratory infection, the presence of wheezing or crackles on chest auscultation, plus either an SaO_2 < 94% in room air or RDAI score ≥ 4 Exclusion criteria: previous episode of wheezing, chronic cardiopulmonary disease or immunodeficiency, critical illness at presentation requiring admission to intensive care,

	the use of nebulised hypertonic saline within the previous 12 h, or premature birth (gestational age ≤ 34 weeks)
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) Control group: nebulised 0.9% normal saline (4 mL) The treatment was given every 2 h for 3 doses, followed by every 4 h for 5 doses, followed by every 6 h until discharge. All inhaled therapies were delivered to a settled infant from a standard oxygen-driven hospital nebuliser through a tight-fitting face mask or head box, whichever the infant tolerated better
Outcomes	• Length of hospital stay • Treatments received during the study • Adverse events
Notes	RSV positive: 62% in hypertonic saline group; 75% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation program
Allocation concealment (selection bias)	Low risk	Study solutions were prepared by a research pharmacist and were identical in appearance and odour. The identity of the study solutions was blinded to all participants, care providers, and investigators
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 (5.2%) withdrawals after randomisation (2 hypertonic saline group; 3 normal saline group); intention-to-treat analysis used
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Köse 2016

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient wards of a children's hospital in Turkey Assessed for eligibility: not stated Randomised: 35 (3% saline group); 34 (7% saline group); 35 (normal saline group)

	Completed: 35 (3% saline group); 32 (7% saline group); 35 (normal saline group) Gender (male): 40.3% Age: median (min-max): 7.6 (2 to 23) months in 3% saline group; 7.7 (1 to 24) months in 7% saline group; 7.6 (1 to 18) months in 0.9% saline group Inclusion criteria: infants aged 1 to 24 months with clinical diagnosis of bronchiolitis, defined as the first wheezing episode followed by a viral upper respiratory infection, with crackles on auscultation, and Wang clinical severity score $\geq$ 4 Exclusion criteria: infants with clinical severity score < 4, SaO_2 < 80% in room air, chronic cardiopulmonary or neurological disease, premature birth, birth weight < 2500 g, history of recurrent wheezing episodes, proven immune deficiency, age < 1 month or > 2 years, proven or suspected acute bacterial infection, previous treatment with bronchodilators or corticosteroids, the presence of symptoms > 7 days, consolidation or atelectasis on a chest roentgenogram
Interventions	Intervention groups: Nebulised 3% hypertonic saline (2.5 mL) plus salbutamol (0.15 mg/kg) Nebulised 7% hypertonic saline (2.5 mL) plus salbutamol (0.15 mg/kg) Control group: nebulised 0.9% normal saline (2.5 mL) plus salbutamol (0.15 mg/kg) 2 doses were given at 30-minute interval, followed by every 6 h until discharge
Outcomes	• Length of hospital stay • Wang severity score • Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated stratified randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was stated to be double-blind, but no details were provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (1.9%) withdrawals after randomisation in 7% saline group
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Li 2014

Methods	Design: randomised, parallel-group, controlled trial
Participants	Setting: outpatient department of a children's hospital in China Assessed for eligibility: not stated Randomised: 85 hypertonic saline groups (5% saline: 41; 3% saline: 44); 44 normal saline group Completed: 82 hypertonic saline groups (5% saline: 40; 3% saline: 42); 42 normal saline group Gender (male): 73.3% Age: median (quartiles): 6.7 (3.1) months in 3% saline group; 6.7 (3.6) months in 5% saline group; 7.6 (3.9) months in 0.9% saline group Inclusion criteria: infants aged 2 months to 18 months with clinical diagnosis of acute bronchiolitis and Wang clinical severity score ≥ 4 Exclusion criteria: severe bronchiolitis (respiratory rate > 80 breaths per minute, SaO$_2$ < 85% on room air or need for mechanical ventilation), immunological deficiency diseases, cardiac diseases, neurological or metabolic diseases, chronic respiratory diseases, prematurity, and previous history of wheezing
Interventions	Intervention groups: Nebulised 3% hypertonic saline (3 mL) Nebulised 5% hypertonic saline (3 mL) Control group: nebulised 0.9% normal saline (3 mL) The study drug was administered by a jet nebuliser, twice daily for 3 days
Outcomes	• Wang clinical severity score • Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generated using a random number table.
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 (3.8%) withdrawals after randomisation (1 5% saline group, 2 3% saline group, 2 normal saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Luo 2010

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient wards of a teaching hospital for children in China Eligible: not stated Randomised: 50 hypertonic saline group; 43 normal saline group Completed: 50 hypertonic saline group; 43 normal saline group Gender (male): 60.2% Age (mean ± SD): 6.0 ± 4.3 months in hypertonic saline group; 5.6 ± 4.5 months in normal saline group Inclusion criteria: infants with a diagnosis of mild to moderately severe bronchiolitis Exclusion criteria: age > 24 months, previous episode of wheezing, chronic cardiac and pulmonary disease, immunodeficiency, accompanying respiratory failure, requiring mechanical ventilation, inhaling the nebulised 3% hypertonic saline solution and salbutamol 12 h before treatment, and premature infants born at less than 34 weeks gestation
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) plus 2.5 mg salbutamol Control group: nebulised 0.9% normal saline (4 mL) plus 2.5 mg salbutamol Infants in each group received 3 treatments every day, delivered at intervals of 8 h until discharge using air-compressed nebulisers
Outcomes	• Length of hospital stay • Duration of symptoms and signs • Wang clinical severity score • Adverse events
Notes	RSV positive: 70% in hypertonic saline group; 69.7% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details were reported.
Allocation concealment (selection bias)	Low risk	No detectable difference in colour, smell, or other physical properties between the therapeutic packages containing 0.9% saline solution or 3% saline solution. The codes of the therapeutic packages were not available to the investigators, nurses, or parents
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.

Other bias	Low risk	No other bias found.

Luo 2011

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a teaching hospital for children in China Assessed for eligibility: not stated Randomised: 64 hypertonic saline group; 62 normal saline group Completed: 57 hypertonic saline group; 55 normal saline group Gender (male): 56.3% Age (mean ± SD): 5.9 ± 4.1 months in hypertonic saline group; 5.8 ± 4.3 months in normal saline group Inclusion criteria: infants aged < 24 months with a first episode of wheezing, hospitalised for treatment of moderate to severe bronchiolitis Exclusion criteria: age > 24 months, previous episode of wheezing, chronic cardiac and pulmonary disease, immunodeficiency, accompanying respiratory failure, requiring mechanical ventilation, inhaling the nebulised 3% hypertonic saline solution 12 h before treatment, and prematurity with birth at < 34 weeks of gestation
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) Control group: nebulised 0.9% normal saline (4 mL) The treatment was given every 2 h for 3 doses, followed by every 4 h for 5 doses, followed by every 6 h until discharge. All inhaled treatments were delivered to infants from standard air-compressed nebulisers (PARI Corporation, Stanford, Germany)
Outcomes	• Length of hospital stay • Duration of symptoms and signs • Wang clinical severity score • Adverse events
Notes	RSV positive: 73.7% in hypertonic saline group; 72.7% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation program
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed, opaque envelopes
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

Incomplete outcome data (attrition bias) All outcomes	Low risk	14 (11.1%) withdrawals (7 infants from each group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Mahesh Kumar 2013

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a teaching hospital in India Assessed for eligibility: 78 Randomised: 20 hypertonic saline group; 20 normal saline group Completed: 20 hypertonic saline group; 20 normal saline group Gender (male): 62.5% Age (mean ± SD): 5.9 ± 3.8 months Inclusion criteria: children aged < 2 years, hospitalised with acute bronchiolitis defined as the first episode of lower respiratory tract infection with wheeze and having a moderate respiratory distress with clinical severity score between 4 and 8 Exclusion criteria: children with pre-existing cardiac disease, previous wheezing episodes, severe disease (clinical severity score > 8) requiring mechanical ventilation (SaO_2 < 85% on room air, cyanosis, obtunded consciousness, and/or progressive respiratory failure)
Interventions	Intervention group: nebulised 3% hypertonic saline (3 mL) plus salbutamol (0.15 mg/kg) Control group: nebulised 0.9% normal saline (3 mL) plus salbutamol (0.15 mg/kg) The medication was given via a nebuliser driven by oxygen flow at 5 to 6 L/min, every 6 h until ready for discharge
Outcomes	• Length of hospital stay • Wang clinical severity score • Number of add-on nebulisation
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial was stated as double-blind, but no details were provided

Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Mandelberg 2003

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: paediatric inpatient ward, Edith Wolfson Medical Center, Israel Eligible: not stated Randomised: 27 (3% saline group); 26 (0.9% saline group) Completed: 27 hypertonic saline group; 25 normal saline group Gender (male): 57.7% Age (mean ± SD): 2.9 ± 2.1 months (range 0.5 to 12 months) Inclusion criteria: infants with clinical presentation of viral bronchiolitis with temperature > 38 ºC that led to hospitalisation Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, SaO_2 < 85% in room air, changes in consciousness and/or progressive respiratory failure requiring mechanical ventilation
Interventions	Intervention group: nebulised 3% saline solution (4 mL) plus 1.5 mg epinephrine Control group: nebulised 0.9% saline solution (4 mL) plus 1.5 mg epinephrine The treatment was given 3 times/day at intervals of 8 h, until the infant was ready for discharge. All inhaled treatments were delivered using a nebuliser (Aeromist Nebulizer Set 61400; B&F Medical by Allied; Toledo, OH) connected to a source of pressurised oxygen at a flow rate of 5 L/min
Outcomes	- Length of hospital stay - Wang clinical severity score - Oxygen saturation - Pulse rate - Radiograph assessment score - Number of add-on treatments - Adverse events
Notes	RSV positive: 85% in hypertonic saline group; 88% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details provided.

Mandelberg 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Study solutions were similar in colour, smell, and other physical properties. The code of the therapeutic package (hypertonic saline versus normal saline solution) was deposited with the statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (1.8%) withdrawal after randomisation
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Miraglia Del Giudice 2012

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: division of paediatrics of a general hospital in Italy Assessed for eligibility: 136 Randomised: 53 hypertonic saline group; 56 normal saline group Completed: 52 hypertonic saline group; 54 normal saline group Gender (male): 65.1% Age (mean ± SD): 4.8 ± 2.3 months in hypertonic saline group; 4.2 ± 1.6 months in normal saline group Inclusion criteria: children aged under 2 years with a diagnosis of bronchiolitis, defined as the first episode of wheezing and clinical symptoms of a viral respiratory infection and SaO_2 < 94% in room air and significant respiratory distress Exclusion criteria: pre-existing cardiac or pulmonary diseases, premature birth < 36 weeks of gestational age, previous diagnosis of asthma, initial SaO_2 ≤ 85% or respiratory distress severe enough to require resuscitation
Interventions	Intervention group: nebulised 3.0% hypertonic saline (the volume not reported) plus 1. 5 mg epinephrine Control group: nebulised 0.9% normal saline (the volume not reported) plus 1.5 mg epinephrine Study solutions were given at intervals of 6 h until discharge. Each treatment was delivered by a nebuliser with continuous flow of oxygen at 6 L/min through a tight-fitting face mask
Outcomes	• Length of hospital stay • Wang clinical severity score
Notes	RSV positive: 80.7% in hypertonic saline group; 83.3% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based randomisation program
Allocation concealment (selection bias)	Unclear risk	Study solutions were prepared by the local hospital pharmacy, but the method of allocation concealment was not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 withdrawals (1 hypertonic saline group; 2 normal saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

NCT01238848

Methods	Design: randomised, open-label, parallel-group, controlled trial
Participants	Setting: inpatient ward of a children's hospital, Buenos Aires, Argentina Assessed for eligibility: not stated Randomised: 50 hypertonic saline group; 50 normal saline group Completed: 37 hypertonic saline group; 45 normal saline group Gender (male): 50.0% Age (mean ± SD): 4.5 ± 3.8 months Inclusion criteria: infants aged 1 to 24 months, hospitalised for first episode of bronchiolitis, with severity score ≥ 5 and oxygen saturation ≥ 97% Exclusion criteria: chronic respiratory or cardiovascular disease, respiratory failure
Interventions	Intervention group: nebulised 3.0% normal saline (3 mL) plus albuterol (0.25 mg/kg/day) Control group: nebulised 0.9% normal saline (3 mL) plus albuterol (0.25 mg/kg/day) Study solutions were given 4 times a day for 5 days.
Outcomes	• Length of hospital stay • Length of oxygen use • Clinical severity score • Adverse events
Notes	Virological identification not available

(*Continued*)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial was stated as randomised, but no details were provided
Allocation concealment (selection bias)	Unclear risk	No details provided
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	High risk	18 (18%) withdrawals (13 hypertonic saline group, 5 normal saline group); unbalanced attrition between treatment groups
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported
Other bias	Low risk	No other bias found

Ojha 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a teaching hospital in Nepal Assessed for eligibility: 104 Randomised: 36 hypertonic saline group; 36 normal saline group Completed: 28 hypertonic saline group; 31 normal saline group Gender (male): 74% Age (mean ± SD): 8.5 ± 5.0 months Inclusion criteria: children aged over 6 weeks up to 24 months, hospitalised with acute bronchiolitis, defined as the first episode of wheezing associated with tachypnoea, increased respiratory effort, and an upper respiratory tract infection Exclusion criteria: previous episode of wheezing, chronic cardiac and pulmonary disease, immunodeficiency, accompanying respiratory failure, requiring mechanical ventilation, inhaling the nebulised 3% hypertonic saline solution and salbutamol 12 h before treatment, premature infants born at less than 34 weeks gestation, SaO_2 < 85% on room air
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) Control group: nebulised 0.9% normal saline (4 mL) The treatment was given every 8 h until discharge.
Outcomes	• Length of hospital stay • Clinical severity score • Duration of oxygen supplementation

Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	The random numbers were kept in a sealed envelope. The solutions looked similar in appearance and smell and were kept in 2 identical containers, labelled only by a code number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	13 (18%) withdrawals after randomisation (8 hypertonic saline group; 5 normal saline group); baseline characteristics between treatment groups were balanced
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Pandit 2013

Methods	Design: randomised, non-blind, parallel-group, controlled trial
Participants	Setting: paediatric department of a government multi-speciality hospital in India Assessed for eligibility: not stated Randomised: 51 hypertonic saline group; 49 normal saline group Completed: 51 hypertonic saline group; 49 normal saline group Gender (male): not reported Age: mean age: not reported Inclusion criteria: infants aged 2 months to 12 months, admitted with clinical diagnosis of acute bronchiolitis, defined as the first attack of wheezing after a short history of cough with or without fever of less than 7 days duration Exclusion criteria: recurrent episodes of wheezing, 1 or more episodes of respiratory distress in past, family history of asthma, atopy, congenital heart disease, history of prematurity or mechanical ventilation in newborn period, very sick patients with shock, seizures, heart rate > 180/min, respiratory rate > 100/min and adjudged to be in incipient respiratory failure, severe malnutrition, consolidation lung on chest X-ray

Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) plus 1:1000 adrenaline (1 mL) Control group: nebulised 0.9% normal saline (4 mL) plus 1:1000 adrenaline (1 mL) The medication was given 3 times with an interval of 1 hour, via a nebuliser driven by oxygen flow at 6 to 8 L/min
Outcomes	- Length of hospital stay - RDAI - Oxygen saturation - Respiratory rate - Heart rate - Number of add-on treatments - Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Group allocation was concealed in an opaque envelope.
Blinding (performance bias and detection bias) All outcomes	High risk	Non-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Ratajczyk-Pekrul 2016

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a general hospital in Poland Assessed for eligibility: 80 Randomised: 41 hypertonic saline group; 37 normal saline group Completed: 41 hypertonic saline group; 36 normal saline group Gender (male): 58.9% Age (mean): 5.34 months in hypertonic saline group; 4.43 months in normal saline group

	Inclusion criteria: children aged 0 to 18 months, hospitalised with acute bronchiolitis, defined as prolonged expiration, wheezes, and crepitations, with a history of a preceding viral upper respiratory infection, and with SaO_2 $\leq$ 95% or Wang score $\geq$ 5 Exclusion criteria: preterm babies < 34 weeks, chronic cardiac or respiratory disease, immunological deficiencies, 2 or more episodes of bronchial obstruction, treatment with systemic glucocorticosteroids, received a hypertonic saline nebulisation in 24 hours prior to admission, or with SaO_2 < 85%
Interventions	Intervention group: nebulised 3% hypertonic saline (3 mL) plus salbutamol (0.15 mg/kg, max 1.5 mg) Control group: nebulised 0.9% normal saline (3 mL) plus salbutamol (0.15 mg/kg, max 1.5 mg) The medication was given 6 times daily until discharge, via a nebuliser driven by oxygen flow at 6 to 8 L/min
Outcomes	• Length of hospital stay • Improvement in clinical severity score at 24, 48, and 72 h after hospital admission • Adverse events
Notes	RSV positive: 51% in hypertonic saline group; 56% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	No details provided.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 (5.1%) withdrawals (2 infants from each group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Unclear risk	No other bias found.

Sarrell 2002

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: Paediatrics and Adolescent Ambulatory Community Clinic of General Health Services of Petach-Tikva, Israel Eligible: not stated

Sarrell 2002 *(Continued)*

	Randomised: 70 Completed: 33 (3% saline group); 32 (0.9% saline group) Gender (male): 59% Age (mean ± SD): 12.5 ± 6.0 months (range 3 to 24 months) Inclusion criteria: infants with clinical presentation of mild to moderate viral bronchiolitis Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age ≥ 24 months, SaO_2 < 96% on room air, and need for hospitalisation
Interventions	Intervention group: nebulised 3% saline solution (2 mL) plus 5 mg (0.5 mL) terbutaline Control group: nebulised 0.9% saline solution (2 mL) plus 5 mg (0.5 mL) terbutaline The treatment was given 3 times/day at intervals of 8 h for 5 days
Outcomes	• Wang clinical severity score • Hospitalisation rate • Radiograph assessment score • Pulse rate • Adverse events
Notes	RSV positive: 82% in hypertonic saline group; 78% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4, using an on-line randomiser
Allocation concealment (selection bias)	Low risk	Study solutions were similar in colour, smell, and other physical properties. The code of the therapeutic package (hypertonic saline versus normal saline solution) was deposited with the statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 (7.1%) withdrawals after randomisation
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Sharma 2013

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a tertiary care teaching hospital in India Assessed for eligibility: 277 Randomised: 125 hypertonic saline group; 125 normal saline group Completed: 125 hypertonic saline group; 123 normal saline group Gender (male): 76.2% Age (mean ± SD): 8.5 ± 5.0 months Inclusion criteria: infants aged 1 to 24 months, hospitalised with moderate (clinical severity score 3 to 6) acute bronchiolitis, defined by the first episode of wheezing along with prodrome of upper respiratory tract infection Exclusion criteria: children with obtunded consciousness, cardiac disease, chronic respiratory disease, previous wheezing episode, progressive respiratory distress requiring respiratory support other than supplemental oxygen, use of nebulised hypertonic saline within the previous 12 h
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) plus salbutamol (2.5 mg) Control group: nebulised 0.9% normal saline (4 mL) plus salbutamol (2.5 mg) The medication was given via a jet nebuliser with tight-fitting face mask, driven by oxygen flow at 7 L/min, every 4 h until the infant was ready for discharge
Outcomes	• Length of hospital stay • Wang clinical severity score • Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Study solutions were similar in colour, smell, and other physical properties. The code of the therapeutic package (hypertonic saline versus normal saline solution) was deposited with the statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 (0.8%) withdrawals after randomisation in normal saline group
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.

Other bias	Low risk	No other bias found.

Tal 2006

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: paediatric inpatient ward, Wolfson Medical Center, Israel Eligible: not stated Randomised: 22 hypertonic saline group; 22 normal saline group Completed: 21 hypertonic saline group; 20 normal saline group Gender (male): 56.1% Age (mean ± SD): 2.6 ± 1.0 months (range 1 to 5 months) Inclusion criteria: infants with clinical presentation of viral bronchiolitis that led to hospitalisation Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, SaO_2 < 85% on room air, obtunded consciousness and/or progressive respiratory failure requiring mechanical ventilation
Interventions	Intervention group: nebulised 3% saline solution (4 mL) plus 1.5 mg epinephrine Control group: nebulised 0.9% saline solution (4 mL) plus 1.5 mg epinephrine The treatment was given 3 times/day at intervals of 8 h, until the infant was ready for discharge. All inhaled treatments were delivered using an ultrasonic nebuliser (Omron UI, OMRON Matsusaka Co. Ltd, Japan)
Outcomes	• Length of hospital stay • Wang clinical severity score • Adverse events
Notes	RSV positive: 86% in hypertonic saline group; 75% in normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4, using an online randomiser
Allocation concealment (selection bias)	Low risk	Study solutions were similar in colour, smell, and other physical properties. The code of the therapeutic package (hypertonic saline versus normal saline solution) was deposited with the statistician
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

Incomplete outcome data (attrition bias) All outcomes	Low risk	3 (6.8%) withdrawals after randomisation (1 hypertonic saline group; 2 normal saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Teunissen 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient wards of 11 general hospitals and 1 tertiary medical centre in the Netherlands Assessed for eligibility: not stated Randomised: 97 (3% saline group); 102 (6% saline group); 93 (normal saline group) Completed: 84 (3% saline group); 83 (6% saline group); 80 (normal saline group) Gender (male): 57.1% Age: median 3.4 months (range 10 days to 23 months) Inclusion criteria: children aged birth to 24 months, hospitalised with mild to severe (Wang clinical severity score $\geq$ 3) viral bronchiolitis, defined as symptoms of an upper respiratory tract infection with wheezing, tachypnoea, and dyspnoea Exclusion criteria: Wang clinical severity score improved at least 2 points after inhalation of 2.5 mg salbutamol, haemodynamically important congenital heart disease, chronic pre-existent lung disease, T-cell immunodeficiency, treatment with corticosteroids, and previous wheezing, (food) allergy, or eczema
Interventions	Intervention groups: Nebulised 3% hypertonic saline (4 mL) plus salbutamol (2.5 mg) Nebulised 6% hypertonic saline (4 mL) plus salbutamol (2.5 mg) Control group: nebulised 0.9% normal saline (4 mL) plus salbutamol (2.5 mg) The solutions were given via a HOT Top Plus Nebuliser (Intersurgical, Uden, Netherlands) with a tight-fitting face mask, driven by oxygen flow at 6 to 8 L/min, every 8 h until discharge
Outcomes	• Length of hospital stay • Transfer to a paediatric intensive care unit because of respiratory insufficiency • Need and duration of supplemental oxygen or tube feeding • Adverse events
Notes	RSV positive: 83.7% in 3% saline group; 91.4% in 6% saline group; 88.6% in control group

Risk of bias

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Block randomisation (in blocks of 6), but it is unclear how to choose blocks at random to create the allocation sequence
Allocation concealment (selection bias)	Low risk	Study solutions were identical in vial packaging, colour, smell, and other physical characteristics. The trial codes were kept by the pharmacist
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	43 (14.7%) withdrawals after randomisation (13 (3% saline group), 18 (6% saline group), 12 (normal saline group)); baseline characteristics between treatment groups were balanced
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Tinsa 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: inpatient ward of a children's hospital in Tunisia
Assessed for eligibility: not stated
Randomised: 32 (5% saline group); 37 (5% saline + epinephrine group); 28 (normal saline group)
Completed: 31 (5% saline group); 37 (5% saline + epinephrine group); 26 (normal saline group)
Gender (male): 61.7%
Age (mean ± SD): 3.7 ± 2.8 months in 5% saline group; 3.2 ± 2.5 months in 5% saline + epinephrine group; 3.0 ± 2.4 months in normal saline group
Inclusion criteria: children aged 1 to 12 months, hospitalised with moderate (Wang clinical severity score of 3) bronchiolitis, defined as an acute infection of the lower respiratory tract, preceded by or accompanied by fever or rhinitis, or both, and characterised by expiratory wheezing and increased respiratory effort
Exclusion criteria: prematurity (gestational age at birth < 34 weeks), underlying chronic cardiac or pulmonary disease (e.g. bronchopulmonary dysplasia, cystic fibrosis), recurrent wheezing, severe respiratory distress (apnoeas, heart rate > 200 beats per minute, respiratory rate > 80 breaths/minute, profound lethargy, duration of illness exceeding 15 days)

Interventions	Intervention groups: Nebulised 5% hypertonic saline (4 mL) Nebulised 5% hypertonic saline (2 mL) plus standard epinephrine (2 mL) Control group: nebulised 0.9% normal saline (4 mL) The solutions were given via a jet nebuliser with a tight-fitting face mask, driven by oxygen flow at 6 to 7 L/min, every 4 h until discharge
Outcomes	- Wang clinical severity score - Length of hospital stay - Oxygen saturation - Rerpiratory rate - Adverse events
Notes	Virological identification not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Study solutions were similar in appearance and smell and were stored in identical syringes, labelled only by a code number
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 (3.1%) withdrawals after randomisation (2 normal saline group, 1 hypertonic saline group)
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

Wu 2014

Methods	Design: randomised, double-blind, parallel-group, controlled trial
Participants	Setting: emergency departments of 2 urban freestanding tertiary children's hospitals in USA Assessed for eligibility: 1254 Randomised: 211 hypertonic saline group; 197 normal saline group Completed: 211 hypertonic saline group; 197 normal saline group Gender (male): 56.8%

	Age (mean ± SD): 6.5 ± 5.1 months in hypertonic saline group; 6.4 ± 5.3 months in normal saline group Inclusion criteria: children younger than 24 months with a primary diagnosis of viral bronchiolitis during bronchiolitis season Exclusion criteria: children with a prior illness with wheezing or bronchodilator use, premature (gestational age < 34 weeks), cyanotic congenital heart disease, chronic lung disease, or tracheostomy
Interventions	Intervention group: nebulised 3% hypertonic saline (4 mL) Control group: nebulised 0.9% normal saline (4 mL) The solutions were given via a small-volume wall nebuliser at study entry. Emergency department physicians could order 2 additional treatments every 20 minutes to a maximum of 3 inhaled doses. Admitted infants continued receiving study medication, every 8 h until discharge
Outcomes	- Admission rate - Length of hospital stay - RDAI - Supplemental treatment use - Adverse events
Notes	RSV positive: 65.6% hypertonic saline group; 59.2% normal saline group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Saline solutions were prepared by the investigational pharmacy and stored in sequentially numbered identical vials
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals reported at emergency department setting.
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Low risk	No other bias found.

ICU: intensive care unit
RDAI: Respiratory Distress Assessment Instrument
RSV: respiratory syncytial virus

SaO₂ : oxygen saturation
SD: standard deviation

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

Study	Reason for exclusion
Al-bahadily 2017	Not an RCT. The authors classified the study design as "prospective case second multicenter study" in the Abstract and "Prospective comparison study" in the Methods. We contacted the first author for more details about study design, but did not receive a reply
Amirav 2005	Study of drug delivery (hood versus face mask)
Bagus 2012	Abstract available only
Bueno Campaña 2014	Other comparison (hypertonic saline versus high flow therapy)
Flores-González 2015	Other comparison (epinephrine versus placebo)
Flores-González 2016	Other comparison (epinephrine versus placebo)
Guomo 2007	Abstract available only
Gupta 2016	Suspected plagiarism. This trial presented results identical to those of the Malik 2015 trial. We contacted the first authors of both trials and the editors of the journals in which the trials were published, but neither authors nor editors provided clarification
Kuzik 2010	Inclusion of infants with previous history of wheezing
Malik 2015	Suspected plagiarism. This trial presented results identical to those of the Gupta 2016 trial. We contacted the first authors of both trials and the editors of the journals in which the trials were published, but neither authors nor editors provided clarification
Nenna 2014	Other comparison (hypertonic saline + 0.1% hyaluronic acid versus 0.9% saline)
Silver 2015	Inclusion of infants with previous history of wheezing
Tribastone 2003	Not an RCT (summary of Sarrell 2002)

RCT: randomised controlled trial

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

CTRI/2010/091/003065

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Consecutive patients with moderate to severe bronchiolitis, aged 2 months to 2 years, of either sex, admitted to the hospital during the study period
Interventions	Nebulised hypertonic saline versus nebulised normal saline
Outcomes	Primary outcome: Length of hospital stay (the time between study entry and the time at which the infant reached protocol-defined discharge criteria as measured by study physician) Secondary outcomes: Change in clinical severity scores Change in oxygen saturation (pulse oximetry)
Notes	Starting date: July 2009 Completion of data collection: February 2013 Last updated: 3 April 2017 Contact information: Lopamudra Mishra, 27A South Sinthee Road Kolkata 700050 Kolkata, West Bengal, India; email: lopamudra83.cmc@gmail.com

EudraCT2009-014758-14

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Infants under the age of 12 months with a clinical diagnosis of bronchiolitis
Interventions	Nebulised 3% hypertonic saline plus salbutamol
Outcomes	Primary outcomes: Duration of hospital stay Secondary outcomes: Duration of supplemental oxygen requirement
Notes	Starting date: May 2010 Last updated: 19 March 2012

NCT00677729

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Infants aged up to 24 months, presenting to ED or outpatient department with moderately severe viral bronchiolitis defined as history of viral upper respiratory tract infection within previous 7 days, presence of wheezing or crackles, or both on chest auscultation, and RDAI score > 4 (of 17) or transcutaneous oxygen saturation < 94% in room air

Interventions	Nebulised 3% hypertonic saline (4 mL) plus 1.0 mg salbutamol versus nebulised 0.9% normal saline (4 mL) plus 1.0 mg salbutamol Study solutions were given every 20 minutes for a total of 3 doses
Outcomes	Primary outcome: rate of admission to hospital 1 hour after treatment end Secondary outcomes: change in the RDAI score between study entry and post-treatment
Notes	Starting date: June 2008 Completion of data collection: April 2009 Last updated: November 2015 Contact information: Brian Kuzik, MD, The Royal Victoria Hospital of Barrie, Ontario, Canada L4M 6M2

NCT01777347

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Children aged 6 weeks to 12 months with first moderate-to-severe episode of acute viral bronchiolitis (history of viral upper respiratory tract infection plus wheezing or crackles, or both on chest auscultation with respiratory distress), admitted in ED
Interventions	Nebulised 3% hypertonic saline (4 mL) versus nebulised 0.9% normal saline (4 mL) 2 doses of study solutions were given every 20 minutes.
Outcomes	Primary outcomes: Admission rate at 24 hours Secondary outcomes: Change in RDAI score at 2 hours Number of participants with adverse events at 2 hours Length of hospitalisation for hospitalised infant Health care utilisation within 1 month after discharge
Notes	Starting date: October 2012 Completion of data collection: April 2014 Last updated: 25 July 2014 Contact information: Vincent Gajdos, MD, PhD, Assistance Publique Hôpitaux de Paris - Paris Sud Medical School

NCT01834820

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Children under 2 years of age diagnosed with mild to moderate bronchiolitis, presenting to outpatient Department of Hospital General Naval de Alta Especialidad, Mexico
Interventions	Intervention 1: epinephrine and dexamethasone 1 dose of nebulised dexamethasone (4 mg) was given, followed by 2 doses of nebulised 1:1000 epinephrine (3 mL) at an interval of 20 minutes on the first day. Nebulised dexamethasone (4 mg) was given every 24 hours for 3 days Intervention 2: 3% hypertonic saline

	3 doses of nebulised 3% saline (4 mL) were given every 20 minutes on the first day of treatment, followed by nebulised 3% saline (4 mL) every 24 hours for 3 days Active comparator: 0.9% normal saline 3 doses of nebulised 0.9% normal saline (4 mL) were given at an interval of 20 minutes on the first day of treatment, followed by nebulised 0.9% normal saline (4 mL) every 24 hours for 3 days
Outcomes	Primary outcome: Rate of hospital admissions until 7 days after treatment Secondary outcomes: Number of participants with adverse events in each arm of treatment Change from baseline CBSS after 3 treatments in the first day Change from baseline heart rate after 3 treatments in the first day Change from baseline oxygen saturation after 3 treatments in the first day
Notes	Starting date: January 2013 Completion of data collection: June 2015 Last updated: 4 July 2015 Contact information: José Luis Rodríguez Cuevas, Hospital General Naval de Alta Especialidad, México, Distrito Federal, Distrito Federal, Mexico 04480

NCT02029040

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Children aged 2 to 12 months, presenting to ED with a diagnosis of bronchiolitis (RDAI score = 6) defined as the first episode of wheezing or crackles, or both in a child younger than 12 months who has physical findings of a viral respiratory infection and there is no other explanation for the wheezing and/or crackles
Interventions	Nebulised 3% hypertonic saline (3 mL) versus nebulised 0.9% normal saline (3 mL) A single dose of study solution was given.
Outcomes	Primary outcomes: Respiratory assessment change score (RACS) at 15 minutes and 1 hour Secondary outcomes: Rate of hospitalisations at 24 hours Return to ED within 7 days following discharge
Notes	Starting date: December 2013 Completion of data collection: December 2014 Last updated: 3 May 2016 Contact information: Mohamed Badawy, MD, University of Texas Southwestern Medical Center

NCT02045238

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Children aged up to 12 months with clinical diagnosis of bronchiolitis (viral respiratory disease and first episode of wheezing) and with moderate respiratory distress, defined as having at least 2 of the following criteria: SaO_2 < 93%, respiratory rate > 60, and/or RDAI score > 4
Interventions	Nebulised 3% hypertonic saline (5 mL) versus nebulised 0.9% normal saline (5 mL) Study solutions were initially given every 2 hours, then every 4 hours if the following criteria were met: SaO_2 > 94%, respiratory rate < 60, and RDAI score < 4
Outcomes	Primary outcomes: Rate of admission at 24 hours Time to ready for discharge at 24 hours (room air oxygen saturation > 94%, respiratory rate < 60, and RDAI score < 4 over a 4-hour period) Secondary outcomes: Actual time to discharge at 24 hours Rate of re-admission within 5 days after discharge Incidence of adverse effects during 24-hour treatment period
Notes	Starting date: July 2013 Completion of data collection: December 2014 Last updated: 5 January 2015 Contact information: Mateus D Leme, MD, Sao Paulo University, Brazil

NCT02233985

Methods	Randomised, double-blind, parallel-group, controlled trial
Participants	Children aged 2 to 24 months attending the paediatric emergency service with moderate to severe bronchiolitis, defined as first episode of wheezing associated with respiratory distress and a history of upper respiratory tract infection
Interventions	Nebulised 3% hypertonic saline (4 mL) plus salbutamol (100 mcg/kg) versus nebulised 0.9% normal saline (4 mL) plus salbutamol (100 mcg/kg) 3 doses of study solutions were initially given at an interval of 20 minutes, then every 4 hours during the entire hospital stay
Outcomes	Primary outcomes: Respiratory distress score (at baseline, 30 minutes after the end of the first 3 continuous nebulisation sessions, at 4 hours, 8 hours, and every 24 hours during the entire hospital stay) Length of hospital stay (hours) Secondary outcomes: Hospital re-admission within 30 days after discharge Frequency of complications within 30 days after discharge
Notes	Starting date: August 2013 Completion of data collection: April 2015 Last updated: 25 January 2017 Contact information: Gloria P Sosa-Bustamante, MD, Unidad Medica de Alta Especialidad Bajio 48. Hospital de

Gineco - Pediatria, Instituto Mexicano del Seguro Social, Mexico

NCT02834819

Methods	Randomised, single-blind (investigator), parallel-group, controlled trial
Participants	Children aged 3 to 18 months, presenting to Children's Hospital Colorado Emergency Department with diagnosis of bronchiolitis and persistent hypoxia following initial supportive care
Interventions	Nebulised 3% hypertonic saline (4 mL) plus standard care versus standard care alone A single dose of study solution was given.
Outcomes	Primary outcomes: Hospitalisation rate at any point during enrolment visit or up to 7 days after enrolment visit Need for supplemental oxygen at time of hospital discharge for up to 7 days Persistent hypoxia at baseline and 90 minutes postintervention Secondary outcomes: Adverse outcomes during enrolment visit or within 7 days following enrolment visit Hospital admission within 7 days following discharge from enrolment visit Postintervention clinical severity score during enrolment visit - 90 minutes after randomisation Pre-intervention clinical severity score during enrolment visit following randomisation Unscheduled return ED visits 7 days post-enrolment visit
Notes	Starting date: September 2013 Completion of data collection: September 2015 Last updated: 14 July 2016 Contact information: Cortney Braund, MD, University of Colorado, Denver

CBSS: Clinical Bronchiolitis Severity Score
ED: emergency department
RDAI: Respiratory Distress Assessment Instrument

SaO₂ : oxygen saturation

D A T A   A N D   A N A L Y S E S

Comparison 1.   Hypertonic saline versus normal saline (0.9%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of hospital stay (days)	17	1867	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.75, -0.07]
2 Rate of hospitalisation	8	1723	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.76, 0.98]
3 Clinical severity score (post-treatment) at day 1	9	812	Mean Difference (IV, Random, 95% CI)	-0.77 [-1.18, -0.36]
3.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.92, -0.64]
3.2 Emergency department patients	1	171	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.51, 0.33]
3.3 Inpatients	7	576	Mean Difference (IV, Random, 95% CI)	-0.82 [-1.25, -0.38]
4 Clinical severity score (post-treatment) at day 2	8	703	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.91, -0.65]
4.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	0.00 [-2.93, -1.07]
4.2 Emergency department patients	1	171	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.63, 0.09]
4.3 Inpatients	6	467	Mean Difference (IV, Random, 95% CI)	-1.39 [-1.95, -0.84]
5 Clinical severity score (post-treatment) at day 3	7	499	Mean Difference (IV, Random, 95% CI)	-1.43 [-1.82, -1.04]
5.1 Outpatients	1	65	Mean Difference (IV, Random, 95% CI)	-2.64 [-3.85, -1.43]
5.2 Inpatients	6	434	Mean Difference (IV, Random, 95% CI)	-1.35 [-1.72, -0.98]
6 Rate of re-admission	6	787	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.48, 1.25]
7 Time for resolution of symptoms/signs	2	615	Mean Difference (IV, Random, 95% CI)	-1.19 [-1.54, -0.84]
7.1 Wheezing	2	205	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.43, -0.89]
7.2 Cough	2	205	Mean Difference (IV, Random, 95% CI)	-1.01 [-1.35, -0.66]
7.3 Pulmonary moist crackles	2	205	Mean Difference (IV, Random, 95% CI)	-1.30 [-2.28, -0.32]
8 Radiological assessment score	2	117	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.90, 0.75]

Analysis 1.1. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 1 Length of hospital stay (days).

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 1 Length of hospital stay (days)

Study or subgroup	Hypertonic saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Mandelberg 2003	27	3 (1.2)	25	4 (1.9)		5.4 %	-1.00 [-1.87, -0.13]
Tal 2006	21	2.6 (1.4)	20	3.5 (1.7)		5.1 %	-0.90 [-1.86, 0.06]
Kuzik 2007	45	2.6 (1.9)	46	3.5 (2.9)		4.9 %	-0.90 [-1.91, 0.11]
Luo 2010	50	6 (1.2)	43	7.4 (1.5)		6.9 %	-1.40 [-1.96, -0.84]
Luo 2011	57	4.8 (1.2)	55	6.4 (1.4)		7.2 %	-1.60 [-2.08, -1.12]
NCT01238848	37	5.8 (2.7)	45	5.47 (2.1)		4.6 %	0.33 [-0.73, 1.39]
Miraglia Del Giudice 2012	52	4.9 (1.3)	54	5.6 (1.6)		6.9 %	-0.70 [-1.25, -0.15]
Mahesh Kumar 2013	20	2.25 (0.89)	20	2.88 (1.76)		5.5 %	-0.63 [-1.49, 0.23]
Pandit 2013	51	3.92 (1.72)	49	4.08 (1.9)		6.2 %	-0.16 [-0.87, 0.55]
Sharma 2013	125	2.65 (0.89)	123	2.66 (0.93)		8.1 %	-0.01 [-0.24, 0.22]
Teunissen 2014	167	3.03 (1.95)	80	2.47 (1.6)		7.3 %	0.56 [0.10, 1.02]
Everard 2014	142	3.76 (3.05)	149	3.7 (2.82)		6.3 %	0.06 [-0.62, 0.74]
Tinsa 2014	31	3.6 (1.7)	26	4.5 (3.8)		3.0 %	-0.90 [-2.48, 0.68]
Ojha 2014	28	1.87 (0.96)	31	1.82 (1.18)		6.9 %	0.05 [-0.50, 0.60]
Flores 2016	33	4.9 (2.4)	35	4.7 (2.3)		4.4 %	0.20 [-0.92, 1.32]
Köse 2016	67	3.08 (2.11)	35	3.2 (2.35)		5.2 %	-0.12 [-1.05, 0.81]
Ratajczyk-Pekrul 2016	41	3.06 (1.61)	37	3.11 (1.63)		6.1 %	-0.05 [-0.77, 0.67]
Total (95% CI)	**994**		**873**			**100.0 %**	**-0.41 [-0.75, -0.07]**

Heterogeneity: Tau² = 0.36; Chi² = 76.46, df = 16 (P<0.00001); I² =79%

Test for overall effect: Z = 2.36 (P = 0.018)

Test for subgroup differences: Not applicable

-4   -2   0   2   4

Favours hypertonic saline   Favours 0.9% saline

Analysis 1.2. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 2 Rate of hospitalisation.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 2 Rate of hospitalisation

Study or subgroup	Hypertonic saline	0.9% saline	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
	n/N	n/N			
Sarrell 2002	2/33	3/32		0.6 %	0.65 [0.12, 3.62]
Grewal 2009	8/23	13/23		3.6 %	0.62 [0.32, 1.20]
Anil 2010	1/75	1/74		0.2 %	0.99 [0.06, 15.48]
Ipek 2011	5/60	8/60		1.5 %	0.63 [0.22, 1.80]
Florin 2014	22/31	20/31		12.6 %	1.10 [0.78, 1.55]
Jacobs 2014	22/52	24/49		8.5 %	0.86 [0.56, 1.32]
Wu 2014	61/211	84/197		20.0 %	0.68 [0.52, 0.89]
Angoulvant 2017	185/385	202/387		53.0 %	0.92 [0.80, 1.06]
Total (95% CI)	**870**	**853**		**100.0 %**	**0.86 [0.76, 0.98]**

Total events: 306 (Hypertonic saline), 355 (0.9% saline)

Heterogeneity: Tau^2 = 0.00; Chi^2 = 7.53, df = 7 (P = 0.38); I^2 =7%

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable

0.01 0.1 1 10 100

Favours hypertonic saline   Favours 0.9% saline

Analysis 1.3.   Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 3 Clinical severity score (post-treatment) at day 1.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 3 Clinical severity score (post-treatment) at day 1

Study or subgroup	Hypertonic saline		0.9% saline		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
1 Outpatients							
Sarrell 2002	33	4.36 (1.05)	32	5.64 (1.54)		11.1 %	-1.28 [-1.92, -0.64]
Subtotal (95% CI)	**33**		**32**			**11.1 %**	**-1.28 [-1.92, -0.64]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.90 (P = 0.000095)							
2 Emergency department patients							
Al-Ansari 2010	115	3.88 (1.13)	56	3.97 (1.4)		13.2 %	-0.09 [-0.51, 0.33]
Subtotal (95% CI)	**115**		**56**			**13.2 %**	**-0.09 [-0.51, 0.33]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.42 (P = 0.68)							
3 Inpatients							
Mandelberg 2003	27	7.7 (1.54)	25	7.81 (1.49)		9.5 %	-0.11 [-0.93, 0.71]
Tal 2006	21	6.25 (1.1)	20	7 (1)		11.1 %	-0.75 [-1.39, -0.11]
Luo 2010	50	3.4 (1.2)	43	4.9 (1.7)		11.5 %	-1.50 [-2.11, -0.89]
Luo 2011	57	5.7 (1.5)	55	7.3 (1.7)		11.6 %	-1.60 [-2.19, -1.01]
Miraglia Del Giudice 2012	52	8 (1.3)	54	8.8 (1.6)		12.0 %	-0.80 [-1.35, -0.25]
Köse 2016	69	4.4 (1.2)	35	4.6 (1.7)		11.3 %	-0.20 [-0.83, 0.43]
Flores 2016	33	5.8 (2.1)	35	6.3 (1.7)		8.7 %	-0.50 [-1.41, 0.41]
Subtotal (95% CI)	**309**		**267**			**75.7 %**	**-0.82 [-1.25, -0.38]**
Heterogeneity: Tau² = 0.23; Chi² = 18.36, df = 6 (P = 0.01); I² =67%							
Test for overall effect: Z = 3.64 (P = 0.00027)							
Total (95% CI)	**457**		**355**			**100.0 %**	**-0.77 [-1.18, -0.36]**
Heterogeneity: Tau² = 0.29; Chi² = 31.30, df = 8 (P = 0.00012); I² =74%							
Test for overall effect: Z = 3.67 (P = 0.00024)							
Test for subgroup differences: Chi² = 10.86, df = 2 (P = 0.00), I² =82%							

-10   -5   0   5   10

Favours hypertonic saline   Favours 0.9% saline

Analysis 1.4.   Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 4 Clinical severity score (post-treatment) at day 2.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 4 Clinical severity score (post-treatment) at day 2

Study or subgroup	Hypertonic saline		0.9% saline		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
1 Outpatients							
Sarrell 2002	33	2.77 (1.4)	32	4.77 (2.31)		11.2 %	-2.00 [-2.93, -1.07]
Subtotal (95% CI)	**33**		**32**			**11.2 %**	**-2.00 [-2.93, -1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.21 (P = 0.000026)							
2 Emergency department patients							
Al-Ansari 2010	115	3.85 (1.16)	56	4.12 (1.11)		14.2 %	-0.27 [-0.63, 0.09]
Subtotal (95% CI)	**115**		**56**			**14.2 %**	**-0.27 [-0.63, 0.09]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.47 (P = 0.14)							
3 Inpatients							
Mandelberg 2003	24	6.41 (1.4)	25	6.92 (1.62)		11.7 %	-0.51 [-1.36, 0.34]
Tal 2006	20	5.35 (1.3)	20	6.45 (1)		12.5 %	-1.10 [-1.82, -0.38]
Luo 2010	50	2.2 (1.1)	43	3.8 (1.5)		13.4 %	-1.60 [-2.14, -1.06]
Luo 2011	57	3.5 (1.1)	55	5.9 (1.5)		13.7 %	-2.40 [-2.89, -1.91]
Miraglia Del Giudice 2012	52	6.8 (1.4)	54	8.2 (1.7)		13.2 %	-1.40 [-1.99, -0.81]
Flores 2016	33	5.9 (2.3)	34	6.8 (2.4)		10.1 %	-0.90 [-2.03, 0.23]
Subtotal (95% CI)	**236**		**231**			**74.6 %**	**-1.39 [-1.95, -0.84]**
Heterogeneity: Tau^2 = 0.35; Chi^2 = 20.43, df = 5 (P = 0.001); I^2 =76%							
Test for overall effect: Z = 4.92 (P < 0.00001)							
Total (95% CI)	**384**		**319**			**100.0 %**	**-1.28 [-1.91, -0.65]**
Heterogeneity: Tau^2 = 0.69; Chi^2 = 57.02, df = 7 (P<0.00001); I^2 =88%							
Test for overall effect: Z = 3.99 (P = 0.000065)							
Test for subgroup differences: Chi^2 = 18.88, df = 2 (P = 0.00), I^2 =89%							

```
          -10    -5     0     5    10
      Favours hypertonic saline   Favours 0.9% saline
```

Analysis 1.5. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 5 Clinical severity score (post-treatment) at day 3.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 5 Clinical severity score (post-treatment) at day 3

Study or subgroup	Hypertonic saline		0.9% saline		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Outpatients							
Sarrell 2002	33	1.77 (2.4)	32	4.41 (2.57)		7.7 %	-2.64 [-3.85, -1.43]
Subtotal (95% CI)	**33**		**32**			**7.7 %**	**-2.64 [-3.85, -1.43]**
Heterogeneity: not applicable							
Test for overall effect: Z = 4.28 (P = 0.000019)							
2 Inpatients							
Mandelberg 2003	21	5.81 (1.68)	23	6.08 (2.03)		8.8 %	-0.27 [-1.37, 0.83]
Tal 2006	13	4.7 (1.5)	14	5.72 (1)		10.5 %	-1.02 [-1.99, -0.05]
Luo 2010	45	1.5 (0.5)	40	2.9 (0.7)		26.1 %	-1.40 [-1.66, -1.14]
Luo 2011	57	2.4 (0.9)	55	4.1 (1.1)		23.3 %	-1.70 [-2.07, -1.33]
Miraglia Del Giudice 2012	52	5.8 (1.4)	54	7.6 (1.6)		18.1 %	-1.80 [-2.37, -1.23]
Flores 2016	29	5.5 (3.2)	31	5.6 (2.7)		5.5 %	-0.10 [-1.60, 1.40]
Subtotal (95% CI)	**217**		**217**			**92.3 %**	**-1.35 [-1.72, -0.98]**
Heterogeneity: Tau^2 = 0.10; Chi^2 = 11.60, df = 5 (P = 0.04); I^2 =57%							
Test for overall effect: Z = 7.13 (P < 0.00001)							
Total (95% CI)	**250**		**249**			**100.0 %**	**-1.43 [-1.82, -1.04]**
Heterogeneity: Tau^2 = 0.13; Chi^2 = 15.20, df = 6 (P = 0.02); I^2 =61%							
Test for overall effect: Z = 7.17 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 3.99, df = 1 (P = 0.05), I^2 =75%							

-10   -5   0   5   10
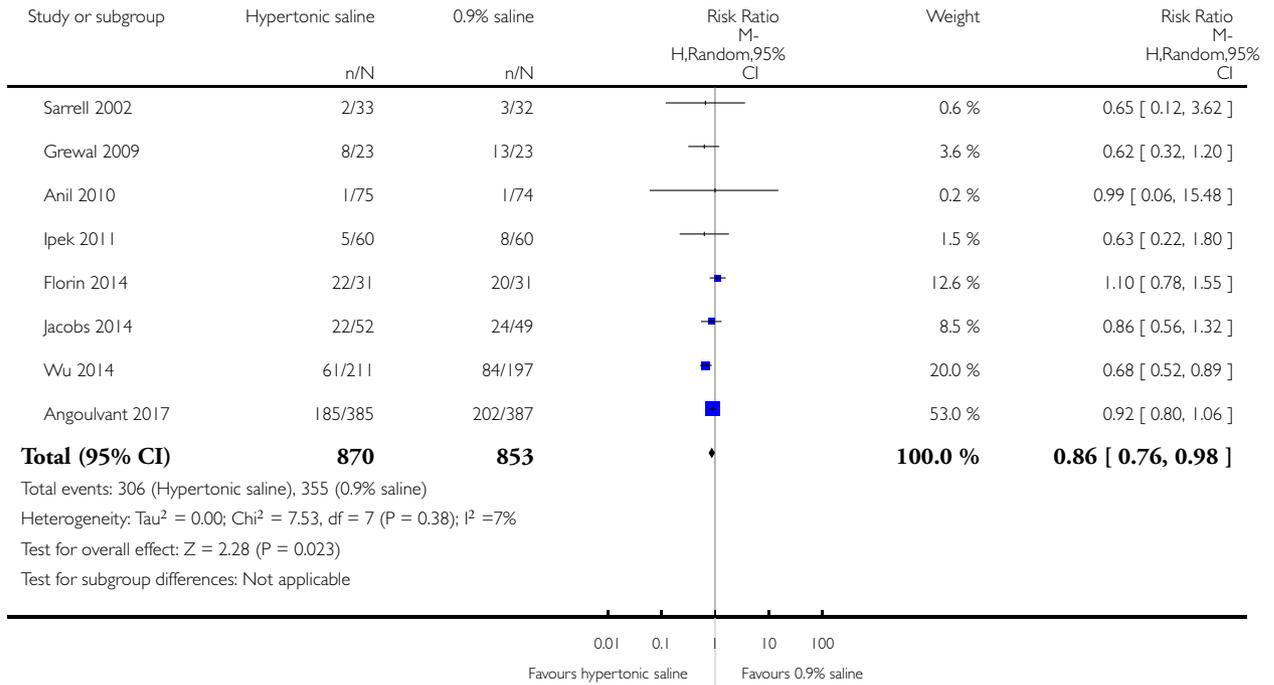
Favours hypertonic saline   Favours 0.9% saline

Analysis 1.6. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 6 Rate of re-admission.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 6 Rate of re-admission

Study or subgroup	Hypertonic saline n/N	0.9% saline n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Al-Ansari 2010	18/115	7/56		20.2 %	1.25 [0.56, 2.82]
Anil 2010	11/75	11/74		21.4 %	0.99 [0.46, 2.13]
Everard 2014	4/128	7/140		11.9 %	0.63 [0.19, 2.09]
Florin 2014	4/26	1/27		4.6 %	4.15 [0.50, 34.75]
Grewal 2009	8/23	13/23		24.9 %	0.62 [0.32, 1.20]
Khanal 2015	5/50	15/50		17.0 %	0.33 [0.13, 0.85]
Total (95% CI)	**417**	**370**		**100.0 %**	**0.77 [0.48, 1.25]**

Total events: 50 (Hypertonic saline), 54 (0.9% saline)

Heterogeneity: Tau^2 = 0.13; Chi^2 = 7.85, df = 5 (P = 0.16); I^2 =36%

Test for overall effect: Z = 1.04 (P = 0.30)

Test for subgroup differences: Not applicable

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          0.01    0.1     1     10    100
       Favours hypertonic saline   Favours 0.9% saline
```

Analysis 1.7. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 7 Time for resolution of symptoms/signs.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)
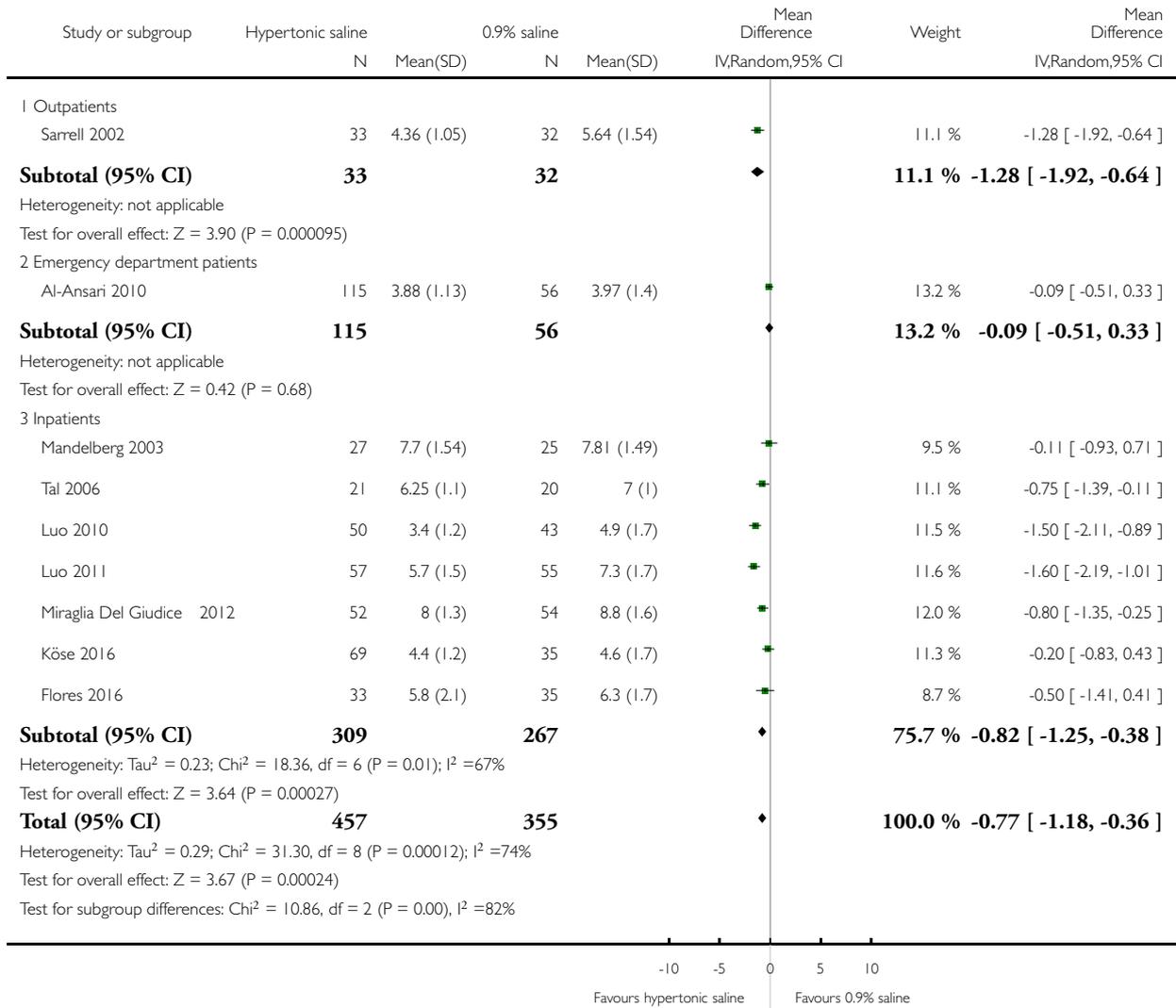
Outcome: 7 Time for resolution of symptoms/signs

Study or subgroup	Hypertonic saline		0.9% saline		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 Wheezing							
Luo 2010	50	2.7 (0.9)	43	3.8 (1.1)		18.1 %	-1.10 [-1.51, -0.69]
Luo 2011	57	3.6 (0.9)	55	4.8 (1)		19.4 %	-1.20 [-1.55, -0.85]
Subtotal (95% CI)	**107**		**98**			**37.4 %**	**-1.16 [-1.43, -0.89]**
Heterogeneity: Tau² = 0.0; Chi² = 0.13, df = 1 (P = 0.72); I² =0.0%							
Test for overall effect: Z = 8.46 (P < 0.00001)							
2 Cough							
Luo 2010	50	5.3 (0.8)	43	6.3 (0.9)		19.4 %	-1.00 [-1.35, -0.65]
Luo 2011	57	4.3 (7)	55	5.5 (0.9)		3.2 %	-1.20 [-3.03, 0.63]
Subtotal (95% CI)	**107**		**98**			**22.6 %**	**-1.01 [-1.35, -0.66]**
Heterogeneity: Tau² = 0.0; Chi² = 0.04, df = 1 (P = 0.83); I² =0.0%							
Test for overall effect: Z = 5.76 (P < 0.00001)							
3 Pulmonary moist crackles							
Luo 2010	50	5.4 (0.8)	43	6.2 (0.9)		19.4 %	-0.80 [-1.15, -0.45]
Luo 2011	57	4.4 (0.9)	55	6.2 (0.7)		20.5 %	-1.80 [-2.10, -1.50]
Subtotal (95% CI)	**107**		**98**			**40.0 %**	**-1.30 [-2.28, -0.32]**
Heterogeneity: Tau² = 0.47; Chi² = 18.26, df = 1 (P = 0.00002); I² =95%							
Test for overall effect: Z = 2.61 (P = 0.0091)							
Total (95% CI)	**321**		**294**			**100.0 %**	**-1.19 [-1.54, -0.84]**
Heterogeneity: Tau² = 0.13; Chi² = 21.98, df = 5 (P = 0.00053); I² =77%							
Test for overall effect: Z = 6.65 (P < 0.00001)							
Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² =0.0%							

```
                    -4   -2    0    2    4
          Favours hypertonic saline    Favours 0.9% saline
```
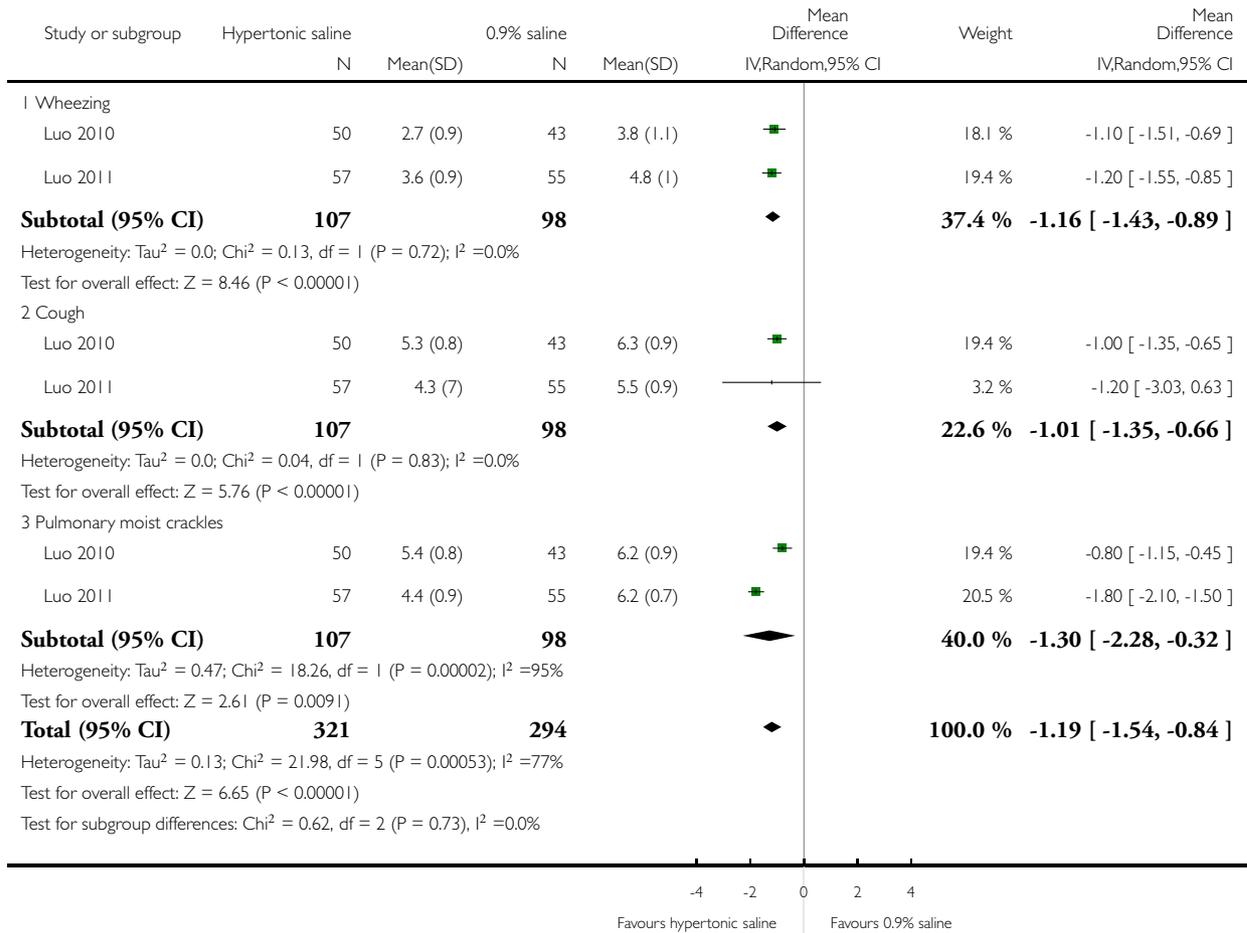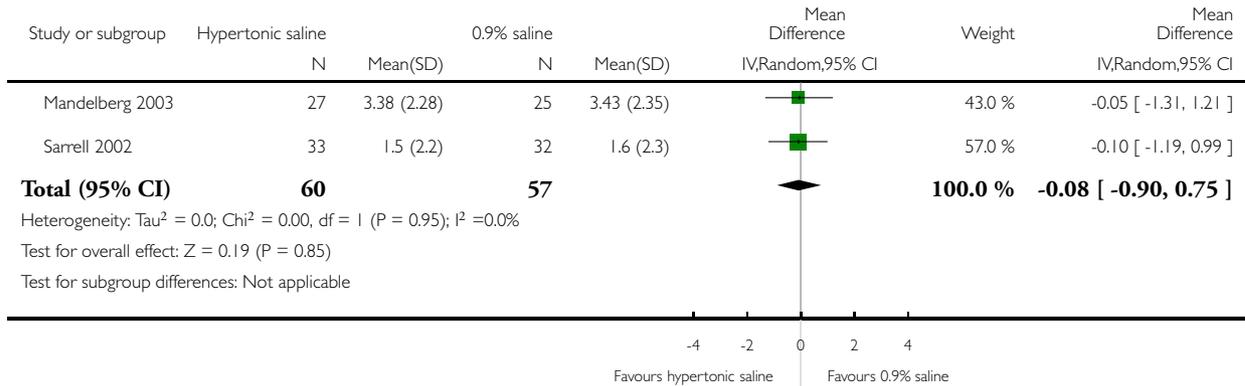
Analysis 1.8.   Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 8 Radiological assessment score.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 Hypertonic saline versus normal saline (0.9%)

Outcome: 8 Radiological assessment score

Study or subgroup	Hypertonic saline		0.9% saline		Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
	N	Mean(SD)	N	Mean(SD)			
Mandelberg 2003	27	3.38 (2.28)	25	3.43 (2.35)		43.0 %	-0.05 [-1.31, 1.21]
Sarrell 2002	33	1.5 (2.2)	32	1.6 (2.3)		57.0 %	-0.10 [-1.19, 0.99]
Total (95% CI)	**60**		**57**			**100.0 %**	**-0.08 [-0.90, 0.75]**

Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.00, df = 1 (P = 0.95); I^2 =0.0%

Test for overall effect: Z = 0.19 (P = 0.85)

Test for subgroup differences: Not applicable

```
        -4    -2    0     2     4
  Favours hypertonic saline   Favours 0.9% saline
```

ADDITIONAL TABLES

Table 1.   Treatment regimens of nebulised hypertonic saline

Study ID	Saline concentration	Saline volume	Bronchodilator administered	Administration interval	Treatment duration
Outpatient trials					
Li 2014	3%, 5%	3 mL	None	Twice daily	3 days
Sarrell 2002	3%	2 mL	Terbutaline 5 mg	Every 8 hours	5 days
Emergency department trials					
Al-Ansari 2010	3%, 5%	5 mL	Epinephrine 1.5 mL	Every 4 hours	Until discharge
Anil 2010	3%	4 mL	Epinephrine 1.5 mL or salbutamol 2.5 mg	Every 30 minutes	Until 2 doses had been administered
Florin 2014	3%	4 mL	None	Within 90 minutes after albuterol administration	Single dose

Table 1. Treatment regimens of nebulised hypertonic saline *(Continued)*

Grewal 2009	3%	2.5 mL	2.25% racemic epinephrine 0.5 mL	If needed, the second dose was given during the 120-minute study period	Up to 2 doses
Ipek 2011	3%	4 mL	Salbutamol 0.15 mg/kg	Every 20 minutes	Until 3 doses had been administered
Jacobs 2014	7%	3 mL	Racemic epinephrine 0.5 mL	Study solution was given after initial screening and assessment	Single dose (if the infant was admitted, the same solution was given every 6 h until discharge or 24 h after the admission)
Khanal 2015	3%	4 mL	Epinephrine 1.5 mg	Study solution was given at 0 and 30 minutes.	Until 2 doses had been administered
Wu 2014	3%	4 mL	None	Emergency department physicians could order 2 additional doses every 20 minutes	Up to 3 doses
Angoulvant 2017	3%	4 mL	None	Study solution was given at 0 and 30 minutes.	Until 2 doses had been administered
Inpatient trials					
NCT01238848	3%	3 mL	Albuterol 0.25 mg/kg/day	4 times a day	5 days
Everard 2014	3%	4 mL	None	Every 6 hours	Until fit for discharge
Flores 2016	3%	3 mL	Salbutamol 0.25 mL (1.25 mg)	Every 6 hours	Until discharge
Mahesh Kumar 2013	3%	3 mL	Salbutamol 0.15 mg/kg	Every 6 hours	Until ready for discharge
Miraglia Del Giudice 2012	3%	? mL	Epinephrine 1.5 mg	Every 6 hours	Until discharge
Köse 2016	3%, 7%	2.5 mL	Salbutamol 0.15 mg/kg	2 doses were given at 30-minute interval, followed by every 6	Until discharge

Table 1. Treatment regimens of nebulised hypertonic saline *(Continued)*

				hours	
Kuzik 2007	3%	4 mL	Albuterol was added in 37% of the treatments, and racemic epinephrine was added in 23% of the treatments by attending physicians	Every 2 hours for 3 doses, followed by every 4 hours for 5 doses, and then every 6 hours	Until discharge
Luo 2010	3%	4 mL	Salbutamol 2.5 mg	Every 8 hours	Until discharge
Luo 2011	3%	4 mL	None	Every 2 hours for 3 doses, followed by every 4 hours for 5 doses, and then every 6 hours	Until discharge
Mandelberg 2003	3%	4 mL	Epinephrine 1.5 mg	Every 8 hours	Until discharge
Sharma 2013	3%	4 mL	Salbutamol 2.5 mg	Every 4 hours	Until ready for discharge
Pandit 2013	3%	4 mL	Epinephrine 1.0 mL	3 doses were given at 1-hour intervals, followed by every 6 hours	Until discharge
Ojha 2014	3%	4 mL	None	Every 8 hours	Until discharge
Ratajczyk-Pekrul 2016	3%	3 mL	Salbutamol 0.15 mg/ kg	Every 4 hours	Until discharge
Tal 2006	3%	4 mL	Epinephrine 1.5 mg	Every 8 hours	Until discharge
Teunissen 2014	3%, 6%	4 mL	Salbutamol 2.5 mg	Every 8 hours	Until discharge
Tinsa 2014	5%	4 mL	Epinephrine 2 mL	Every 4 hours	Until discharge

Table 2. Subgroup analyses on length of hospital stay among inpatients

Subgroups	Length of hospital stay (days)				
	Trial (n)	Participants (N)	Effect size (MD, 95% CI)	P values	Heterogeneity (I²)
Virological investigation					

Available	10	1179	-0.58 (-1.12 to -0.04)	0.03	84%
Not available	7	688		0.60	0%
			-0.05 (-0.24 to 0.13)		
Upper age limits for infants					
12 months	6	609	-0.37 (-0.79 to 0.04)	0.08	23%
18 to 24 months	11	1258	-0.41 (-0.86 to 0.03)	0.07	86%
Hypertonic saline solution plus bronchodilator					
β_2 agonist	9	1049	-0.22 (-0.67 to 0.22)	0.32	81%
Epinephrine	5	356	-0.65 (-1.01 to -0.30)	P < 0.001	0%
No	3	462		0.39	79%
			-0.51 (-1.67 to 0.65)		
Administration interval*					
A	12	1375	-0.38 (-0.77 to 0.002)	0.05	75%
B	5	492		0.22	88%
			-0.51 (-1.35 to 0.32)		
Hypertonic saline concentration					
3%	14	1461	-0.49 (-0.86 to -0.13)	0.01	52%
> 3%	3	406		0.79	79%
			0.09 (-0.65 to 0.85)		
Length of stay in the control group					
< 3 days	4	594	0.07 (-0.29 to 0.44)	0.69	59%
≥ 3 days	13	1273	-0.59 (-0.97 to -0.20)	0.003	68%
Risk of selection bias					
Low	11	1366	-0.37 (-0.81 to 0.06)	0.09	82%
Unclear/high	6	501	-0.51 (-1.02 to 0.004)	0.05	64%
Year of publication					
Before 2013	7	577	-0.98 (-1.41 to -0.55)	P < 0.001	59%
2013 and thereafter	10	1290		0.75	3%
			0.02 (-0.15 to 0.20)		

Abbreviations: CI: confidence interval; MD: mean difference

*A: every 4 to 6 hours; B: every 8 hours

Table 3. Sensitivity analyses: length of hospital stay among inpatients

Length of hospital stay			
Effect size (RR, 95% CI)	**Heterogeneity (I²)**	**Trials excluded from analysis**	**Reasons for exclusion**
-0.51 (-0.91 to -0.11)	82%	NCT01238848; Everard 2014; Pandit 2013	Open trials
-0.49 (-0.83 to -0.15)	75%	Teunissen 2014	Mean and standard deviation were estimated from median and interquartile range
-0.49 (-0.87 to -0.11)	80%	NCT01238848; Ojha 2014	Withdrawal rate > 15% or data obtained from a part of study sample
-0.45 (-0.78 to -0.12)	80%	Everard 2014	Did not use 0.9% saline as the control
-0.22 (-0.48 to 0.05)	50%	Luo 2010; Luo 2011; Ojha 2014	Very short (< 2 days) or very long (> 6 days) length of stay in the control group

Abbreviations: CI: confidence interval; RR: risk ratio

Table 4. Subgroup analyses: hospitalisation rate among outpatients and emergency department patients

Subgroups	Hospitalisation rate (%)				
	Trial (n)	**Participants (N)**	**Effect size (RR, 95% CI)**	**P values**	**Heterogeneity (I²)**
Virological investigation					
Available	5	1392	0.81 (0.69 to 0.96)	0.01	21%
Not available	3	331	1.04 (0.75 to 1·44)	0.81	0%
Upper age limits for infants					
12 months	2	818	0.86 (0.64 to 1.15)	0.31	26%
18 to 24 months	6	905	0.82 (0.66 to 1.01)	0.06	9%
Hypertonic saline solution plus bronchodilator*					
β_2 agonist	3	257	0.65 (0.28 to 1.55)	0.34	0%
Epinephrine	3	224	0.78 (0.54 to 1.12)	0.18	0%
No	3	1242	0.87 (0.68 to 1.11)	0.27	65%
Administration interval**					

| A | 3 | 209 | 0.91 (0.67 to 1.23) | 0.54 | 24% |
| B | 5 | 1514 | 0.83 (0.70 to 0.98) | 0.02 | 11% |

Hypertonic saline concentration					
3%	7	1622	0.85 (0.71 to 1.00)	0.05	20%
> 3%	1	101	0.86 (0.56 to 1.32)	0.50	-

Risk of selection bias					
Low	6	1454	0.85 (0.72 to 1.00)	0.06	29%
Unclear/high	2	269	0.66 (0.24 to 1.78)	0.42	0%

Year of publication					
Before 2013	4	380	0.63 (0.37 to 1.06)	0.08	0%
2013 and thereafter	4	1343	0.87 (0.72 to 1.05)	0.15	48%

Abbreviations: CI: confidence interval; RR: risk ratio

*Anil 2010 used two intervention groups: hypertonic saline plus salbutamol and hypertonic saline plus epinephrine.

**Regimen A: single dose; regimen B: multiple doses (≥ 2).

Table 5. Narrative summary: adverse events of treatment reported in 11 trials

Trials	Comparisions	Narrative summary
Everard 2014	3% saline (N = 142) versus standard care (N = 143)	6 AEs were possibly related to saline treatment, including 1 SAE, bradycardia and desaturation, which resolved the following day. The remaining 5 non-SAEs were: bradycardia (self correcting), desaturation, coughing fit, and increased respiratory rate (all of which were resolved within 1 day); and a chest infection, which resolved after 6 days
Flores 2016	3% saline + salbutamol (N = 33) versus 0.9% saline + salbutamol (N = 35)	Exacerbation of coughing and excessive rhinorrhoea were more common in the 3% saline group (45.5% and 57.6%) than in the 0.9% saline group (20% and 31.4%). There was no significant difference in bronchial constriction and agitation between the 2 groups. Apnoea, cyanosis, saturation dips, tachycardia, and vomiting were not observed
Grewal 2009	3% saline + epinephrine (N = 23) versus 0.9% saline + epinephrine (N = 23)	Adverse events were noted in 4 infants (vomiting 3; diarrhoea 1) in the hypertonic saline group. No additional bronchodilators were given to any enrolled infant during the study period

Table 5. Narrative summary: adverse events of treatment reported in 11 trials *(Continued)*

Köse 2016	3% saline + salbutamol (N = 35), 7% saline + salbutamol (N = 32) versus 0.9% saline + salbutamol (N = 35)	No AEs were reported in the 3% and 0.9% saline groups. In the 7% saline group, bronchospasm was observed in 2 infants, and exacerbation of coughing was observed in another 2 infants. Both bronchospasm and cough was observed during nebulisation in 1 infant
Kuzik 2007	3% saline (N = 47) versus 0.9% saline (N = 49)	No infants were withdrawn by the medical staff due to AEs, although 5 infants were withdrawn at parents' request due to perceived AEs, only 2 of which were from the hypertonic saline group (1 presented with vigorous crying and another with agitation)
Li 2014	5% saline (N = 40), 3% saline (N = 42) versus 0.9% saline (N = 42)	No AEs were observed in the 3% and 0.9% saline groups. 4 infants from the 5% saline group presented with paroxysmal cough during saline inhalation
Luo 2011	3% saline (N = 57) versus 0.9% saline (N = 55)	No infants were withdrawn by the medical staff due to AEs. Coughing and wheezing did not worsen during saline inhalation. Although 5 infants had hoarse voices, only 2 of these were from the hypertonic saline group, and the symptom disappeared after 3 to 4 days
Pandit 2013	3% saline + epinephrine (N = 51) versus 0.9% saline + epinephrine (N = 49)	No AEs were observed in the 3% saline group. In the 0.9% saline group, 3 infants had vomiting, and 1 infant had diarrhoea
Teunissen 2014	3%, 6% saline + salbutamol (N = 167) versus 0.9% saline + salbutamol (N = 80)	A substantial number of AEs (cough, bronchospasm, agitation, desaturation, etc.) were noted in all treatment groups. Except for cough, which occurred more significantly in the hypertonic saline groups (P = 0.03), no differences were found between groups. Withdrawals due to AEs did not differ between groups (4.3%, 6.1%, and 7.9% in the 3%, 6%, and 0.9% saline groups, respectively; P = 0.59)
Wu 2014	3% saline (N = 211) versus 0.9% saline (N = 197)	3 infants in the normal saline group and 4 infants in the hypertonic saline group withdrew owing to parent request. Of these parent requests, 1 in the normal saline group and 2 in the hypertonic saline group were attributed to worsening cough. For these 3 infants, pre-treatment and post-treatment vital signs and Respiratory Distress Assessment Instrument score were the same or improved, and no intervention or additional treatment was necessary
Angoulvant 2017	3% saline (N = 385) versus 0.9% saline (N = 387)	No SAEs were reported. Mild AEs occurred 57 times among 50 infants: in 35 of 392 infants (8.9%) in the HS group versus 15 of 384 infants (3.9%) in the NS

Table 5. Narrative summary: adverse events of treatment reported in 11 trials *(Continued)*

			group (risk difference 5.0%, 95% confidence interval 1. 6% to 8.4%; P = 0.005). Worsening of cough without respiratory distress was the most frequent AE, occurring in 26 infants (6.6%) in the HS group and 3 infants (0.8%) in the NS group. Bronchospasm occurred in 3 infants (0.8%) in the NS group

Abbreviations:
AE: adverse event
HS: hypertonic saline
NS: normal saline
SAE: serious adverse event

Table 6. Comparative summary: main findings of 4 systematic reviews addressing efficacy and safety of nebulised hypertonic saline for infants with acute bronchiolitis

Review	Trials included (n)	Participants (N)	Hospital length-of-stay reduction (MD, 95% CI)	Clinical score reduction (MD, 95% CI)	Hospitalisation rate reduction (RR, 95% CI)	Re-admission rate reduction (RR, 95% CI)	Other findings
Chen 2014	11	1070 (infants with previous wheeze excluded)	-0.96 (-1.38 to -0.54) (6 trials)	Day 1: -0.77 (-1.30 to -0.24) Day 2: -0.85 (-1.30 to -0.39) Day 3: -1.14 (-1.69 to -0.58) (6 trials)	0.59 (0.37 to 0.93) (5 trials)	1.08 (0.68 to 1.73) (3 trials)	None
Badgett 2015	19	2441	-0.42 (-0.72 to -0.11) (19 trials)	-	-	-	-
Maguire 2015	15	1922	-0.36 (-0.50 to -0.22) (15 trials)	-1.36 (-1.52 to -1.20) (5 trials)	-	-	-
Zhang 2015	24	3209 (infants with previous wheeze excluded)	-0.51 (-0.91 to -0.11) (14 trials)*	Day 1: -0.99 (-1.48 to -0.50) Day 2: -1.45 (-2.06 to -0.85) Day 3: -1.44 (-1.78 to -1.11) (5 trials)	0.80 (0.67 to 0.96) (7 trials)	Re-admission to hospital 1.45 (0.67 to 3.14) (4 trials) Re-admission to	No significant difference between the hypertonic saline group and the control group in terms of oxygen satura-

Table 6. Comparative summary: main findings of 4 systematic reviews addressing efficacy and safety of nebulised hypertonic saline for infants with acute bronchiolitis *(Continued)*

						emergency department 0.78 (0.46 to 1.32) (5 trials)	tion, duration of oxygen supplementation, respiratory rate, heart rate, radiograph scores, and parental perception of improvement

Abbreviations: CI: confidence interval; MD: mean difference; RR: risk ratio

*Zhang 2015 included one unpublished inpatient trial (NCT01488448) that included infants with previous wheeze. In the erratum (Zhang 2016), removal of this trial from the meta-analysis changed the results of hypertonic saline on length of hospital stay from MD -0.45 days (95% CI -0.82 to -0.08) to MD -0.51 days (95% CI -0.91 to -0.11).

APPENDICES

Appendix 1. Previous search

For the 2013 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 4, part of *The Cochrane Library*, www.thecochranelibrary.com (accessed 8 May 2013), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE (May 2010 to April week 4, 2013), EMBASE (June 2010 to April 2013) and LILACS (June 2010 to May 2013). We broadened our search to include two further databases and searched CINAHL (1981 to May 2013) and Web of Science (1955 to May 2013). We used the search strategy detailed in Appendix 2 to search MEDLINE and CENTRAL. As there were so few search results we used no filter to identify randomised trials in MEDLINE. We adapted the search terms to search EMBASE (Appendix 3), LILACS (Appendix 4), CINAHL (Appendix 5) and Web of Science (Appendix 6).

For the 2010 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2010, Issue 2), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, OLDMEDLINE (1951 to 1965), MEDLINE (1966 to May Week 4, 2010), EMBASE (1974 to June 2010) and LILACS (1985 to June 2010).

For the original search we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 4), which contains the Cochrane Acute Respiratory Infections Group Specialised Register, OLDMEDLINE (1951 to 1965), MEDLINE (1966 to November 2007), EMBASE (1974 to November 2007) and LILACS (November 2007).

For the original search and the 2010 update the following search terms were combined with the highly sensitive search strategy as recommended by The Cochrane Collaboration (Dickersin 1994) to search MEDLINE. These terms were adapted to search CENTRAL, EMBASE and LILACS as required.

MEDLINE (OVID)

1 exp Bronchiolitis/
2 bronchiolit$.mp.
3 exp Respiratory Syncytial Viruses/
4 exp Respiratory Syncytial Virus Infections/
5 (respiratory syncytial vir$ or RSV).mp.
6 exp Parainfluenza Virus 1, Human/

7 exp Parainfluenza Virus 2, Human/
8 exp Parainfluenza Virus 3, Human/
9 exp Respirovirus Infections/
10 exp Adenoviridae Infections/
11 exp Influenza, Human/
12 (parainfluenza or adenovirus$ or influenza).mp.
13 or/1-12
14 exp Saline Solution, Hypertonic/
15 hypertonic saline.mp.
16 exp Sodium Chloride/
17 saline.mp.
18 or/14-17
19 exp "Nebulizers and Vaporizers"/
20 (nebulis$ or nebuliz$).mp.
21 exp Administration, Inhalation/
22 inhal$.mp.
23 exp Aerosols/
24 aerosol$.mp.
25 or/19-24
26 13 and 18 and 25
27 from 26 keep 1-79

There were no language or publication restrictions.

Appendix 2. MEDLINE (Ovid) search strategy

1 exp Bronchiolitis/
2 (bronchiolit* or wheez*).tw.
3 respiratory syncytial viruses/ or respiratory syncytial virus, human/
4 Respiratory Syncytial Virus Infections/
5 (respiratory syncytial virus* or rsv).tw.
6 parainfluenza virus 1, human/ or parainfluenza virus 3, human/
7 Parainfluenza Virus 2, Human/
8 Respirovirus Infections/
9 Adenovirus Infections, Human/
10 Rhinovirus/
11 Influenza, Human/
12 exp influenzavirus a/ or exp influenzavirus b/
13 (parainfluenza* or respirovirus* or adenovirus* or rhinovirus* or influenza*).tw.
14 or/1-13
15 Saline Solution, Hypertonic/
16 (hypertonic adj3 (saline or solution*)).tw.
17 Sodium Chloride/
18 (sodium chloride or saline).tw.
19 or/15-18
20 exp "Nebulizers and Vaporizers"/
21 (nebuli* or vapor* or vapour* or atomi*).tw.
22 Administration, Inhalation/
23 inhal*.tw.
24 Aerosols/
25 aerosol*.tw.
26 or/20-25

27 14 and 19 and 26

Appendix 3. Embase.com search strategy

24. #12 AND #16 AND #23
23. #17 OR #18 OR #19 OR #20 OR #21 OR #22
22. aerosol*:ab,ti
21. 'aerosol'/de
20. inhal*:ab,ti
19. 'inhalational drug administration'/de
18. nebuli*:ab,ti OR vapour*:ab,ti OR vapour*:ab,ti OR atomi*:ab,ti
17. 'nebulizer'/exp
16. #13 OR #14 OR #15
15. 'sodium chloride':ab,ti OR saline:ab,ti
14. (hypertonic NEAR/3 (saline OR solution*)):ab,ti
13. 'hypertonic solution'/de OR 'sodium chloride'/de
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
11. parainfluenza*:ab,ti OR respirovirus*:ab,ti OR adenovirus*:ab,ti OR rhinovirus*:ab,ti OR influenza*:ab,ti
10. 'influenza virus'/de OR 'influenza virus a'/exp OR 'influenza virus b'/de OR 'influenza'/exp
9. 'rhinovirus infection'/de
8. 'human adenovirus infection'/de
7. 'respirovirus infection'/de
6. 'parainfluenza virus 1'/de OR 'parainfluenza virus 2'/de OR 'parainfluenza virus 3'/de
5. 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti
4. 'respiratory syncytial virus infection'/de
3. 'respiratory syncytial pneumovirus'/de
2. bronchiolit*:ab,ti
1. 'bronchiolitis'/exp

Appendix 4. LILACS search strategy

> Search > (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 wheez$ OR MH:"Respiratory Syncytial Viruses" OR "Virus Sinciatiales Respiratorios" OR "Vírus Sinciciais Respiratórios" OR "Respiratory Syncytial Virus, Human" OR "Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial" OR rsv "respiratory syncytial virus" OR "respiratory syncytial virus infection" OR "respiratory syncytial virus infections") AND (MH:"Saline Solution, Hypertonic" OR "Solución Salina Hipertónica" OR "Solução Salina Hipertônica" OR "Hypertonic Saline Solution" OR "Solución Hipertónica de Cloruro de Sodio" OR "Solução Salina Hipertônica" OR "Solução Hipertônica de Cloreto de Sódio" OR MH:"Sodium Chloride" OR "sodium chloride" OR "Cloruro de Sodio" OR "Cloreto de Sódio" OR salin$) AND (MH:"Nebulizers and Vaporizers" OR MH: E07.605$ OR atomi$ OR inhal$ OR vapor$ OR vapour$ OR nebuli$ OR Inala$ OR MH:Aerosols OR aerosol$ OR Aerossóis OR MH:"Administration, Inhalation" OR "Administración por Inhalación" OR "Administração por Inalação")

Appendix 5. CINAHL (EBSCO) search strategy

S22 S10 and S15 and S21
S21 S16 or S17 or S18 or S19 or S20
S20 TI (inhal* or aerosol*) OR AB (inhal* or aerosol*)
S19 (MH "Aerosols")
S18 (MH "Administration, Inhalation")
S17 TI (nebuli* or vapor* or vapour* or atomi*) OR AB (nebuli* or vapor* or vapour* or atomi*)
S16 (MH "Nebulizers and Vaporizers")
S15 S11 or S12 or S13 or S14
S14 TI (sodium chloride or saline) OR AB (sodium chloride or saline)
S13 (MH "Sodium Chloride")
S12 TI (hypertonic N3 (salin* or solut*)) OR AB (hypertonic N3 (salin* or solut*))
S11 (MH "Saline Solution, Hypertonic")
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
S9 TI (influenza* or flu) OR AB (influenza* or flu)
S8 (MH "Influenzavirus A+") OR (MH "Influenzavirus B+")
S7 (MH "Influenza") OR (MH "Influenza, Human") OR (MH "Influenza A H5N1") OR (MH "Influenza, Pandemic (H1N1) 2009") OR (MH "Influenza, Seasonal")
S6 TI (parainfluenza* or respirovirus* or adenovirus* or rhinovirus*) OR AB (parainfluenza* or respirovirus* or adenovirus* or rhinovirus*)
S5 TI (respiratory syncytial virus* or rsv) OR AB (respiratory syncytial virus* or rsv)
S4 (MH "Respiratory Syncytial Virus Infections")
S3 (MH "Respiratory Syncytial Viruses")
S2 TI (bronchiolit* or wheez*) OR AB (bronchiolit* or wheez*)
S1 (MH "Bronchiolitis+")

Appendix 6. Web of Science (Thomson Reuters) search strategy

# 3	93	#2 AND #1 *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 2	1,322,438	Topic=(random* or placebo* or ((single or double) NEAR/1 blind*) or allocat* or (clinical NEAR/1 trial*)) OR Title=(trial) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*
# 1	173	Topic=(bronchiolit* or wheez* or "respiratory syncytial virus" or "respiratory syncytial viruses" or rsv or parainfluenza* or "respirovirus infection" or "respirovirus infections" or rhinovirus* or adenovirus* or influenza*) AND Topic=((hypertonic NEAR/3 (salin* or solut*)) or "sodium chloride" or saline) AND Topic=(nebuli* or vapor* or vapour* or atomi* or inhal* or aerosol*) *Databases=SCI-EXPANDED, CPCI-S Timespan=All Years* *Lemmatization=On*

WHAT'S NEW

Last assessed as up-to-date: 11 August 2017.

Date	Event	Description
11 August 2017	New search has been performed	We conducted updated searching and new analyses. We created and examined a funnel plot to explore possible small-study effects and publication bias. We revised the review text. We included 17 new trials in this updated review (Angoulvant 2017; NCT01238848; Everard 2014; Flores 2016; Florin 2014; Jacobs 2014; Khanal 2015; Köse 2016; Li 2014; Mahesh Kumar 2013; Ojha 2014; Pandit 2013; Ratajczyk-Pekrul 2016; Sharma 2013; Teunissen 2014; Tinsa 2014; Wu 2014). We excluded nine new trials (Al-bahadily 2017; Bagus 2012; Bueno Campaña 2014; Flores-González 2015; Flores-González 2016; Gupta 2016; Malik 2015; Nenna 2014; Silver 2015). Nine studies await classification (CTRI/2010/091/003065; EudraCT2009-014758-14; NCT00677729; NCT01777347; NCT01834820; NCT02029040; NCT02045238; NCT02233985; NCT02834819). We conducted additional post hoc subgroup, sensitivity, and meta-regression analyses
11 August 2017	New citation required and conclusions have changed	Nebulised hypertonic saline may modestly reduce the length of hospital stay among infants hospitalised with acute bronchiolitis and improve clinical severity score. Nebulised hypertonic saline may also reduce the risk of hospitalisation among outpatients and emergency department patients

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2008

Date	Event	Description
8 May 2013	New search has been performed	Searches conducted. We included four new trials and performed new analyses (Al-Ansari 2010; Miraglia Del Giudice 2012; Ipek 2011; Luo 2011). Our conclusions remain unchanged.
7 June 2010	New search has been performed	Searches conducted. We included three new trials and conducted new analyses (Anil 2010; Grewal 2009; Luo 2010). The conclusions remain unchanged.

10 May 2010	New search has been performed	Searches conducted. We included three new trials and performed new analyses (Anil 2010; Grewal 2009; Luo 2010). Our conclusions remain unchanged.
13 May 2009	Amended	No changes; republished to fix technical problem.
18 February 2008	Amended	Converted to new review format.
13 November 2007	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Linjie Zhang conceived the idea and wrote the draft protocol, primary review, and review updates.

Linjie Zhang and Raúl A Mendoza-Sassi were responsible for study selection, quality assessment, data collection, and data analysis.

Raúl A Mendoza-Sassi, Claire Wainwright, and Terry P Klassen provided input in the writing of the protocol and primary and updated reviews.

All authors approved the final version of this review update.

DECLARATIONS OF INTEREST

Linjie Zhang: None known.

Raúl A Mendoza-Sassi: None known.

Claire Wainwright: received travel grants from the North American Cystic Fibrosis Foundation and the European Cystic Fibrosis Society, travel and accommodation expenses from Novartis Pharmaceuticals and Vertex Pharmaceuticals, and travel and accommodation expenses from the University of Miami; has served as a consultant for/an advisory board member for Vertex Pharmaceuticals; has previously and is currently receiving grants or grants pending from the National Health and Medical Research Council (Australia), and has previously and currently is receiving funds from Vertex Pharmaceuticals for site costs associated with clinical trial participation and has previously received funds from Ablynx, and Novo Nordisk Phamaceuticals for site participation in clinical trials; and her institution has previously received payment for her providing lectures from Novartis Pharmaceuticals and Vertex Pharmaceuticals. None of the declared benefits were received in relation to this review or review topic or scope.

Terry P Klassen: None known.

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External sources

- National Council for Scientific and Technological Development (CNPq), Brazil.
Fellowship of research productivity (PQ)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the very limited number of studies that were identified initially (Zhang 2011), we added the comparison of nebulised hypertonic saline alone versus nebulised 0.9% saline since the first version of the review. We also clarified the population according to age and changed the title to specify infants. We performed post hoc subgroup analyses, post hoc meta-regression, and post hoc sensitivity analyses in the updated review. We also created and examined a funnel plot to explore possible small-study effects and publication bias. Cochrane Review methods have evolved over time, and these have been applied.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Airway Obstruction; Bronchiolitis, Viral [*therapy]; Bronchodilator Agents [administration & dosage]; Length of Stay; Nebulizers and Vaporizers; Patient Readmission [statistics & numerical data]; Randomized Controlled Trials as Topic; Saline Solution, Hypertonic [*administration & dosage]; Severity of Illness Index

MeSH check words

Humans; Infant