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# Nebulised hypertonic saline solution for acute bronchiolitis in infants



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

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[Intervention Review]

# Nebulised hypertonic saline solution for acute bronchiolitis in infants

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## ABSTRACT

### Background

Airway oedema and mucus plugging are the predominant pathological features in infants with acute viral bronchiolitis. Nebulised hypertonic saline solution may reduce these pathological changes and decrease airway obstruction.

### Objectives

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

### Search methods

We searched CENTRAL 2013, Issue 4, OLDMEDLINE (1951 to 1965), MEDLINE (1966 to April week 4, 2013), EMBASE (1974 to May 2013), LILACS (1985 to May 2013) and Web of Science (1955 to May 2013).

### Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs using nebulised hypertonic saline alone or in conjunction with bronchodilators as an active intervention and nebulised 0.9% saline as a comparator in infants up to 24 months of age with acute bronchiolitis.

### Data collection and analysis

Two review authors independently performed study selection, data extraction and assessment of risk of bias in included studies. We conducted meta-analyses using the Cochrane statistical package RevMan 5.2. We used the random-effects model for meta-analyses. We used mean difference (MD) and risk ratio (RR) as effect size metrics.

### Main results

We included 11 trials involving 1090 infants with mild to moderate acute viral bronchiolitis (500 inpatients, five trials; 65 outpatients, one trial; and 525 emergency department patients, four trials). All but one of the included trials were of high quality with a low risk of bias. A total of 560 patients received hypertonic saline (3% saline n = 503; 5% saline n = 57). Patients treated with nebulised 3% saline had a significantly shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline (MD -1.15 days, 95% confidence interval (CI) -1.49 to -0.82, P < 0.00001). The hypertonic saline group also had a significantly lower post-inhalation clinical score than the 0.9% saline group in the first three days of treatment (day 1: MD -0.88, 95% CI -1.36 to -0.39, P = 0.0004; day

2: MD -1.32, 95% CI -2.00 to -0.64, P = 0.001; day 3: MD -1.51, 95% CI -1.88 to -1.14, P < 0.00001). The effects of improving clinical score were observed in both outpatients and inpatients. Four emergency department-based trials did not show any significant short-term effects (30 to 120 minutes) of up to three doses of nebulised 3% saline in improving clinical score and oxygen saturation. No significant adverse events related to hypertonic saline inhalation were reported.

**Authors' conclusions**

Current evidence suggests nebulised 3% saline may significantly reduce the length of hospital stay among infants hospitalised with non-severe acute viral bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations.

## PLAIN LANGUAGE SUMMARY

**Hypertonic saline solution administered via nebuliser for acute bronchiolitis in infants**

Acute viral bronchiolitis is the most common lower respiratory tract infection in infants up to two years old. Currently there is no effective treatment so standard treatment remains supportive care. Airway oedema (abnormal accumulation of fluid) and mucus plugging can cause wheezing and difficulty breathing in these patients. Nebulised hypertonic saline may be a beneficial treatment to manage acute bronchiolitis because it can improve airway hygiene. This review was conducted to assess the effects of hypertonic (≥ 3%) saline solution administered via a nebuliser in infants with acute bronchiolitis, compared with nebulised normal (0.9%) saline. The establishment of a therapeutic role for hypertonic saline solution may provide a cheap and effective therapy for these patients.

We included 11 randomised trials involving 1090 infants with mild to moderate bronchiolitis. All but one of the 11 trials are considered as high-quality studies with low risk of error (i.e. bias) in their conclusions. Meta-analysis suggests that nebulised hypertonic saline could lead to a reduction of 1.2 days in the mean length of hospital stay among infants hospitalised for non-severe acute bronchiolitis and improve the clinical severity score in both outpatient and inpatient populations. No significant short-term effects (at 30 to 120 minutes) of one to three doses of nebulised hypertonic saline were observed among emergency department patients. However, more trials are needed to address this question. There were no significant adverse effects noted with the use of nebulised hypertonic saline when administered along with bronchodilators.

Given the clinically relevant benefit and good safety profile, nebulised hypertonic saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis.

## 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 (≥ 3%)**
**Comparison: nebulised 0.9% saline**

| 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 **3.5 to 7.4 days** | The mean length of hospital stay in the intervention groups was on average **1.15 days shorter** (95% CI -1.49 to -0.82) | | 500 (6 inpatient trials) | ⊕⊕⊕⊕ **high** | |
| **Clinical severity score (post-treatment) at day 1** The clinical score of Wang 1992 in which each of 4 symptoms and signs (respiratory rate, wheezing, retraction and general condition) was graded on a scale of 0 to 3, with increased severity receiving a higher score | The mean clinical severity score ranged across control groups from **3.97 to 8.8** | The mean clinical severity score in the intervention groups was on average **0.88 lower** (95% CI -1.36 to -0.39) | | 640 (7 trials: 1 outpatient, 1 emergency department, 5 inpatients) | ⊕⊕⊕⊕ **high** | Given the small number of participants, the small number of inhalations (up to three doses) and short monitoring time (up to 120 minutes post-inhalation), further large RCTs with multiple doses of hypertonic saline over a longer period of time are still needed for evaluating the effect of nebulised hypertonic saline in improving clinical score among |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | infants with acute bronchiolitis seen in emergency departments |
| **Clinical severity score (post-treatment) at day 2**<br>The clinical score of Wang 1992 as described above | 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 **1.32 lower** (95% CI -2.00 to -0.64) | | 636 (7 trials: 1 outpatient, 1 emergency department, 5 inpatients) | ⊕⊕⊕⊕ **high** | The same comments as described above |
| **Clinical severity score (post-treatment) at day 3**<br>The clinical score of Wang 1992 as described above | The mean clinical severity score ranged across control groups from **2.9 to 7.6** | The mean clinical severity score in the intervention groups was on average **1.51 lower** (95% CI -1.88 to -1.14) | | 439 (6 trials: 1 outpatient, 5 inpatients) | ⊕⊕⊕⊕ **high** | The same comments as described above |
| **Rate of hospitalisation**<br>Duration of follow-up: 5 days for outpatient trial; up to 120 minutes for emergency department trial | **25 per 189** | **16 per 191** | **RR 0.63** (0.37 to 1.07) | 380 (4 trials: 1 outpatient, 3 emergency department trials) | ⊕⊕⊕◯ **moderate** | Low statistical power due to small sample sizes may have contributed to the negative result. Further large RCTs are required to evaluate the efficacy of nebulised hypertonic saline in preventing hospitalisation among infants with acute viral bronchiolitis seen in outpatient settings or emergency departments |
| **Rate of readmission**<br>Duration of follow-up: up to 1 week after discharge. | **22 per 153** | **32 per 213** | **RR 1.05** (0.62 to 1.76) | 366 (3 emergency department trials) | ⊕⊕⊕◯ **moderate** | Further large RCTs are required to evaluate the efficacy of nebulised hypertonic saline in reducing the rate of readmission |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | | among infants with acute viral bronchiolitis seen in inpatient settings, outpatient settings or emergency departments |
| **Adverse events** | See comment | See comment | Not estimable | 1090 (560 received hypertonic saline) (11 trials) | ⊕⊕⊕⊕ **high** | No significant adverse events related to hypertonic saline inhalation were observed in any of the 11 trials. No patients were withdrawn from the trial by the medical staff because of adverse events or clinical deterioration |

*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; **RCT:** randomised controlled trial; **RR:** risk ratio.

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

# BACKGROUND

## Description of the condition

Acute bronchiolitis is the most frequent lower respiratory tract infection in infants (Klassen 1997a). Most cases are viral in origin, with the leading cause being the respiratory syncytial virus (RSV). Other less common pathogens include parainfluenza viruses, adenovirus, influenza A and B, rhinovirus, human metapneumovirus and *Mycoplasma pneumoniae* (*M. pneumoniae*) (Garcia-Garcia 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). Over the last few decades, an increasing trend in the rate of hospitalisation of children with bronchiolitis has been observed in the USA and Canada (Langley 2003; Njoo 2001; Shay 1999).

In acute bronchiolitis, the principal pathological findings 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 the definition of bronchiolitis differing from country to country, it is generally accepted that acute bronchiolitis refers to the first episode of acute wheezing in children less than two years of age, 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 immunoassay 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). There is a lack of convincing evidence for any other therapy. As airway oedema and mucus plugging are the predominant pathological features in acute bronchiolitis, any therapeutic modality which can reduce these pathological 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 recent 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 on the 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, the current evidence concludes that chest physiotherapy (vibration and percussion or passive expiratory techniques) does not reduce the length of hospital stay, oxygen requirements or improve the severity of the disease, respiratory parameters in hospitalised infants with acute bronchiolitis (Roqué i Figuls 2012).

Hypertonic saline has been recently introduced 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 normal individuals and in patients 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 are as follows: 1) hypertonic saline induces an osmotic flow of water into the mucus layer, rehydrating the airway surface liquid and improving mucus clearance (Mandelberg 2010; Robinson 1997); 2) hypertonic saline 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); 3) hypertonic saline 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). The above mentioned 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.

# OBJECTIVES

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

# METHODS

## Criteria for considering studies for this review

### Types of studies

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

### Types of participants

Infants up to 24 months of age with the diagnosis of 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

1. Nebulised hypertonic saline alone versus nebulised 0.9% saline
2. Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline
3. Nebulised hypertonic saline plus bronchodilator versus nebulised 0.9% saline plus same bronchodilator
4. Nebulised hypertonic saline alone or plus bronchodilator versus no intervention

Given the very limited number of studies that were identified initially, we added the comparison of nebulised hypertonic saline alone versus nebulised 0.9% saline. 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 scores
2. Rate of readmission to hospital
3. Haemoglobin saturation (oximetry)
4. Respiratory rate
5. Heart rate
6. Time for the resolution of symptoms/signs
7. Duration of in-hospital oxygen supplementation
8. Results of pulmonary function tests
9. Radiological findings
10. Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, diarrhea and acute urinary retention)

## Search methods for identification of studies

### Electronic searches

For this 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). See Appendix 1 for details of the previous search.

We used the following search strategy 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 2), LILACS (Appendix 3), CINAHL (Appendix 4) and Web of Science (Appendix 5).

#### MEDLINE (OVID)

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

There were no language or publication restrictions.

## Data collection and analysis

### Selection of studies

Two review authors (LZ, RAM) independently assessed the titles and abstracts of all studies identified by the searches. We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to make a clear decision for their inclusion. We excluded articles that did not meet the inclusion criteria. We noted the reasons for their exclusion (see Characteristics of excluded studies table). We resolved any disagreements between the two review authors about study inclusion by discussion.

### Data extraction and management

One review author (LZ) extracted study details from the included trials using a standardised data extraction form. These were checked by another review author (RAM). We resolved any disagreements by discussion. We entered the extracted data into RevMan 2012. We extracted the following data.

1. Study characteristics: publication status, year, country of study and setting.
2. Methods: method of allocation, blinding of participants and assessment of outcome, exclusion of participants after randomisation, proportion of follow-up losses and intention-to-treat analysis.
3. Participants: sample size, age, sex, and inclusion and exclusion criteria.
4. Intervention: concentration of saline, volume of saline, interval of administration, treatment duration and co-interventions.
5. Control: nebulised 0.9% saline or nil.
6. Outcomes: primary and secondary outcomes as described previously. For continuous outcomes, we extracted sample size, mean and standard deviation for each group. For dichotomous outcomes, we extracted sample size and number of events for each group.

When the trial recruited multiple groups, we combined them into the hypertonic saline group and the normal saline group. In the trial of Al-Ansari 2010, we combined 5% saline group and 3% saline group into the hypertonic saline group. In the trial of Anil 2010, we combined four groups (3% saline mixed with epinephrine, 3% saline mixed with salbutamol, 0.9% saline mixed with epinephrine and 0.9% saline mixed with salbutamol) into the hypertonic saline group and the normal saline group. In the trial of Ipek 2011, we combined four groups (3% saline plus salbutamol, 3% saline alone, 0.9% saline plus salbutamol and 0.9% saline alone) into the hypertonic saline group and the normal saline group.

### Assessment of risk of bias in included studies

Two review authors (LZ, RAM) independently assessed the potential risk of bias in included studies according to The Cochrane Collaboration's 'Risk of bias' tool (Higgins 2011). Assessment results are summarised in the 'Risk of bias' tables.

### Measures of treatment effect

We synthesised dichotomous data using risk ratios (RR) and 95% confidence intervals (CI) as the effect measures. We used the mean difference (MD) and 95% CI as the metrics of effect size for continuous outcomes.

### Dealing with missing data

We contacted three principal investigators (Kuzik 2007; Luo 2010; Mandelberg 2003) for additional data on clinical score and methodological aspects. All three trial authors responded and provided the requested data.

### Assessment of heterogeneity

We assessed heterogeneity in results between studies using the Cochrane Q test ($P < 0.1$ considered significant) and the $I^2$ statistic. The $I^2$ statistic ranges from 0% to 100% and measures the degree of inconsistency across studies, with values of 25%, 50% and 75% corresponding to low, moderate and high heterogeneity, respectively (Higgins 2003).

### Assessment of reporting biases

Reporting biases, especially publication bias, may be expected to occur in the majority of systematic reviews. Unfortunately there is no reliable method to detect publication bias. To minimise the potential reporting biases, we used no language restrictions for the literature searches. We contacted experts and searched the currently available trial registration databases for additional published or unpublished trials.

### Data synthesis

We performed the meta-analyses using the Cochrane statistical package RevMan 5.2 (RevMan 2012). We used the random-effects model for meta-analyses. We conducted random effects meta-regression using Stata version 11.0 (Stata-Corp, College Station, TX, USA). Whenever possible, we used intention-to-treat (ITT) analysis data.

### Subgroup analysis and investigation of heterogeneity

We performed pre-planned subgroup analysis according to patient status (outpatient, emergency department patient and inpatient). The severity of disease and treatment regime (concentration of saline, volume, interval of inhalation, drug delivery and duration of treatment) may also contribute to heterogeneity in effect sizes across studies. We conducted post hoc random-effects meta-regression using Restricted Maximum Likelihood Estimation (REML) to explore these possible causes of heterogeneity between studies.

# RESULTS

## Description of studies

### Results of the search

The initial search of electronic databases in 2007 retrieved a total of 261 citations (Zhang 2008). After reviewing the titles and abstracts, we identified seven papers as being potentially relevant, which we reviewed in full text. Four trials met all the criteria for study selection and were included in the initial review.

The update search in 2010 (Zhang 2011) retrieved 39 citations and three additional trials were identified and included in the updated review.

This 2013 updated search retrieved 158 citations from the electronic databases. From them we identified four new trials. Therefore, a total of 11 trials were included in this updated review. See the Characteristics of included studies table.

### Included studies

All 11 studies were randomised, double-blind, parallel-group, controlled trials. One study was a multi-centre trial involving one hospital in the United Arab Emirates and two hospitals in Canada (Kuzik 2007). 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 five studies were conducted in Turkey (Anil 2010; Ipek 2011), Canada (Grewal 2009), Qatar (Al-Ansari 2010) and Italy (Giudice 2012).

#### Participants

One trial recruited outpatient participants (Sarrell 2002), four trials recruited emergency department participants (Al-Ansari 2010; Anil 2010; Grewal 2009; Ipek 2011) and six trials recruited inpatients (Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006). The mean age of participants varied from 2.6 to 12.5 months (range: 9 days to 24 months). The criteria for diagnosis of viral bronchiolitis were clearly defined by seven trials (Al-Ansari 2010; Anil 2010; Giudice 2012; Grewal 2009; Ipek 2011; Kuzik 2007; Luo 2011). Virological investigation was available in all trials except two (Anil 2010; Ipek 2011) and the positive rate for respiratory syncytial virus (RSV) varied from 42% to 88%. Patients with a previous wheezing episode were excluded in all 11 trials. Patients hospitalised with severe bronchiolitis (requiring mechanical ventilation or intensive care, or oxygen saturation < 85% on room air) were also excluded in all inpatient trials.

#### Interventions

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

#### Outcome measures

All six inpatient trials (Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) used length of hospital stay as the primary outcome measure. The same clinical severity score was used by five trials (Giudice 2012; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) as the secondary outcome measure. This clinical score was initially described by Wang (Wang 1992), grading respiratory rate, wheezing, retraction and general condition from 0 to 3, with increased severity receiving a higher score. For outpatients or emergency department participants (Al-Ansari 2010; Anil 2010; Grewal 2009; Ipek 2011; Sarrell 2002), rate of

hospitalisation, rate of readmission and/or clinical severity score were used as the outcome measures.

Other outcome measures used in the trials were haemoglobin saturation (oximetry) (Al-Ansari 2010; Anil 2010; Grewal 2009; Ipek 2011; Mandelberg 2003), pulse rate (Anil 2010; Ipek 2011; Mandelberg 2003; Sarrell 2002), respiratory rate (Ipek 2011) and time for the resolution of symptoms/signs (Luo 2010; Luo 2011). The radiological assessment score initially described by Nasr 2001 was used by two trials (Mandelberg 2003; Sarrell 2002).

Side effects associated with inhaled therapies were reported in all 10 trials.

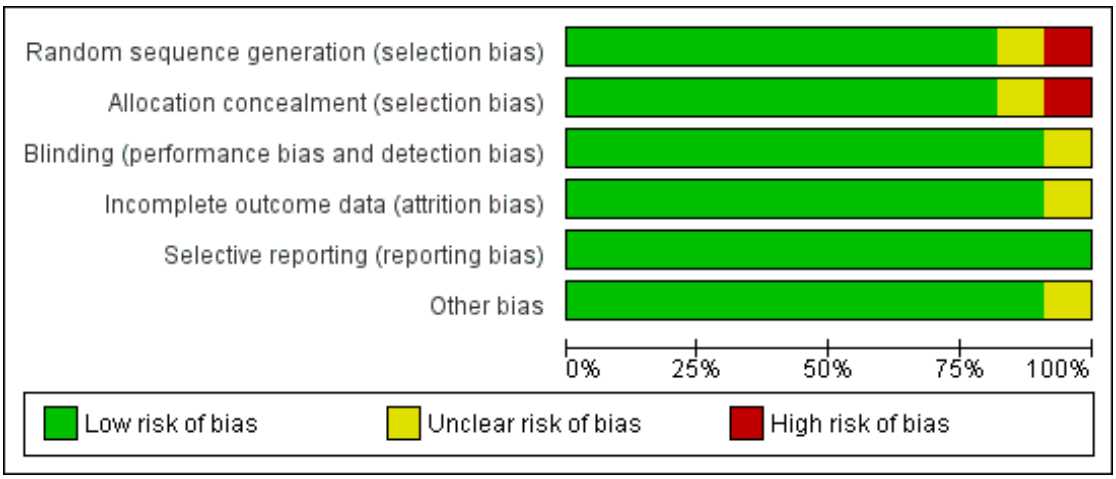
### Excluded studies

We excluded four studies from the review. The reasons for exclusion are summarised in the Characteristics of excluded studies table.

## Risk of bias in included studies

All but one (Ipek 2011) of the 11 included trials were of high methodological quality with low risk of bias. Summary assessment of six key domains is described below and presented in Figure 1.

**Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**




### Allocation

Four trials (Grewal 2009; Mandelberg 2003; Tal 2006; Sarrell 2002) used an online randomiser and six (Al-Ansari 2010; Anil 2010; Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011) used a computer-based random number program to generate the random sequence. All but four trials (Al-Ansari 2010; Giudice 2012; Ipek 2011; Luo 2011) used sequentially numbered drug containers of identical appearance for allocation concealment. Two trials (Al-Ansari 2010; Luo 2011) used sequentially numbered, opaque, sealed envelopes for allocation concealment. In the trial of Giudice 2012, study solutions were prepared by the local hospital pharmacy, but the method of allocation concealment was not described. The trial of Ipek 2011 assigned patients to treatment groups according to the consecutive order of their admission to the emergency department.

### Blinding

In all but one (Ipek 2011) of the 11 included trials, participants, care providers and investigators were blinded to group assignment. The trial of Ipek 2011 was stated to be double-blinded, but no details were provided.

### Incomplete outcome data

The number of participants with missing data was small in all 11 trials. Thus, incomplete outcome data may not be a source of bias in this review. Intention-to-treat (ITT) analysis was used by three trials (Grewal 2009; Kuzik 2007; Sarrell 2002).

### Selective reporting

There was no evidence of selective reporting of outcomes in the included studies.

### Other potential sources of bias

No other potential sources of bias were observed in the included trials.

## Effects of interventions

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

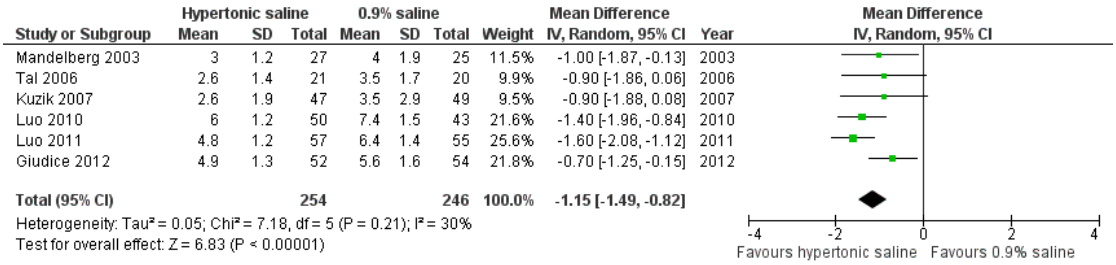
Eleven RCTs involving 1090 infants with mild to moderate acute viral bronchiolitis (500 inpatients, 65 outpatients and 525 emergency department patients) compared nebulised hypertonic saline to nebulised 0.9% saline.

### Primary outcome

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

All six inpatient trials (Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) demonstrated a benefit of nebulised 3% saline in reducing the duration of hospitalisation. The pooled results show that infants treated with nebulised 3% saline had a statistically significant shorter mean length of hospital stay compared to those treated with nebulised 0.9% saline, with a pooled mean difference (MD) of -1.15 days (95% confidence interval (CI) -1.49 to -0.82, P < 0.00001) (Analysis 1.1) (Figure 2). This represents a 22.7% reduction from the mean length of hospital stay in the 0.9% saline group. There was no significant heterogeneity in results between studies (P = 0.21; $I^2$ statistic = 30%).

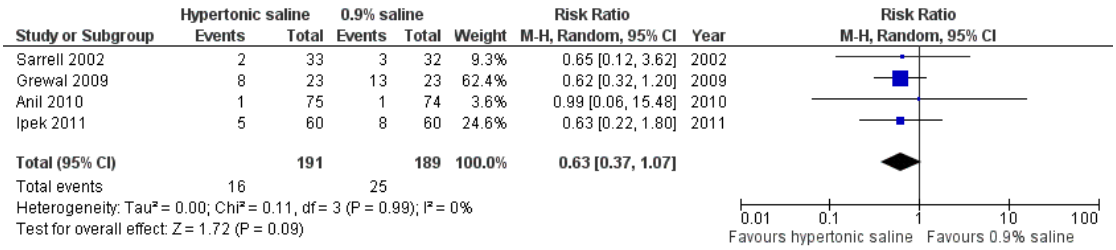
**Figure 2. Hypertonic saline versus 0.9% saline: length of hospital stay (days)**




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

One outpatient trial (Sarrell 2002) and three emergency department trials (Anil 2010; Grewal 2009; Ipek 2011) with a combined total of 380 participants assessed the efficacy of nebulised 3% saline in reducing the risk of hospitalisation. There was no significant reduction in rate of hospitalisation. The pooled risk ratio (RR) was 0.63 (95% CI 0.37 to 1.07, P = 0.09) (Analysis 1.2) (Figure 3). There was no significant heterogeneity between studies (P = 0.99; $I^2$ statistic = 0%).

**Figure 3. Hypertonic saline versus 0.9% saline: rate of hospitalisation.**



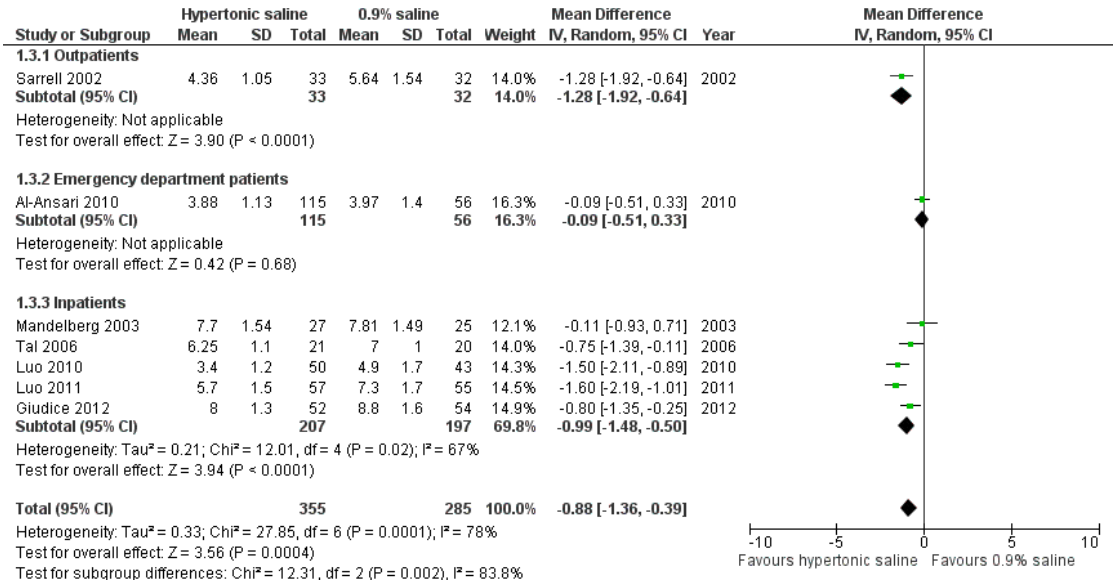

## Secondary outcomes

### 1. Clinical severity scores

One outpatient (Sarrell 2002), one emergency (Al-Ansari 2010) and five inpatient trials (Giudice 2012; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) used the Wang 1992 clinical severity score as an outcome. All seven trials compared the post-inhalation clinical scores 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 the two groups in all seven trials.

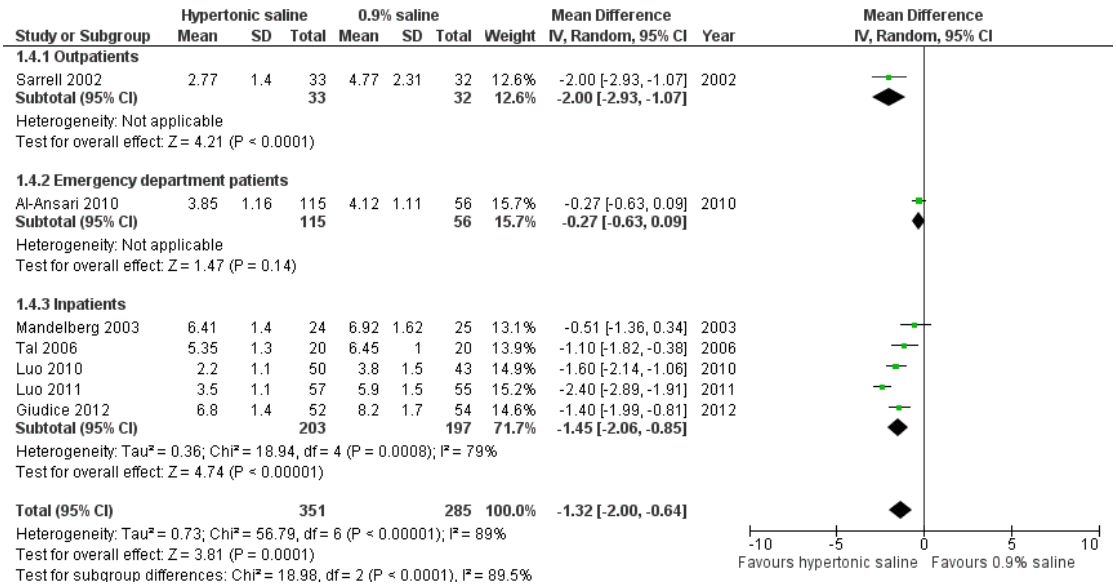
On the first day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed that the 3% saline group had a statistically significant lower post-inhalation clinical score compared to the 0.9% saline group, with a MD of -1.28 (95% CI -1.92 to -0.64, P < 0.0001) (Analysis 1.3.1). Five inpatient trials (Giudice 2012; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) with a total of 404 patients also demonstrated significant benefits of hypertonic saline in reducing clinical score (pooled MD -0.99, 95% CI -1.48 to -0.50, P < 0.00001) (Analysis 1.3.3), in spite of significant heterogeneity between studies (P = 0.02; $I^2$ statistic = 67%). In contrast, one emergency department trial (Al-Ansari 2010) with 171 patients did not show the 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 from all seven trials showed a significantly lower post-inhalation clinical score favouring treatment with nebulised hypertonic saline over nebulised 0.9% saline on the first day of treatment, with a pooled MD of -0.88 (95% CI -1.36 to -0.39, P = 0.0004) (Analysis 1.3) (Figure 4). This difference represents a 13.6% reduction from the mean clinical score in the 0.9% saline group on the first day of treatment. There was significant heterogeneity in results between studies (P = 0.0001; $I^2$ statistic = 78%).

**Figure 4. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 1**



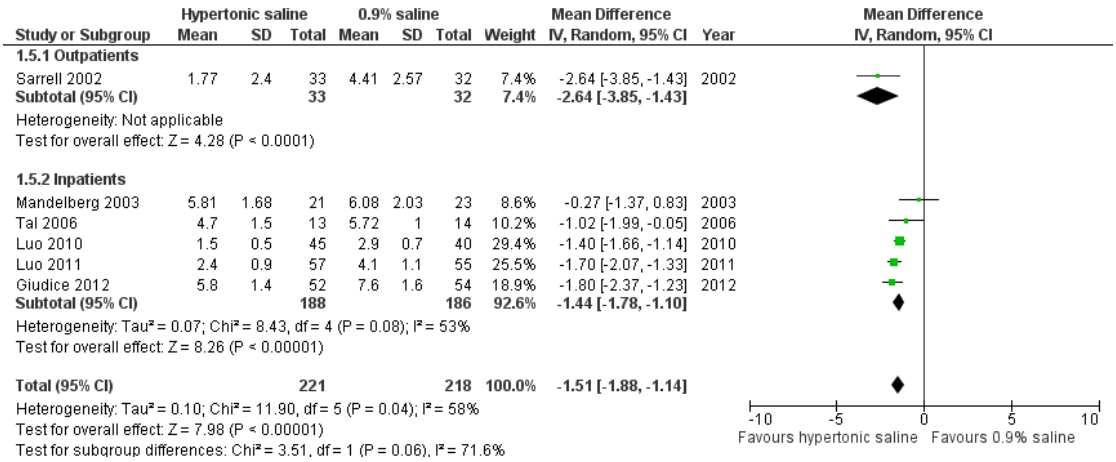
On the second day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed a lower post-inhalation clinical score in the 3% saline group compared to the 0.9% saline group, with a MD of -2.0 (95% CI -2.93 to -1.07, P < 0.0001) (Analysis 1.4.1). A significant difference between the treatment and control groups was also observed among 400 inpatients (Giudice 2012; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006), with a pooled MD of -1.45 favouring 3% saline group (95% CI -2.06 to -0.85, P < 0.00001) (Analysis 1.4.3). There was significant heterogeneity between inpatient trials (P = 0.0008; $I^2$ statistic = 79%). One emergency department trial (n = 171) (Al-Ansari 2010) failed to show significant benefits of hypertonic saline in reducing clinical score (MD -0.27, 95% CI -0.63 to 0.09, P = 0.14) (Analysis 1.4.2). The meta-analysis of seven trials demonstrated the superiority of nebulised 3% saline over 0.9% saline in reducing the post-inhalation clinical score on the second day of treatment, with a pooled MD of -1.32 (95% CI -2.00 to -0.64, P < 0.0001) (Analysis 1.4) (Figure 5). This difference represents a 23.0% reduction from the mean clinical score in the 0.9% saline group for the second day of treatment. Significant heterogeneity was found between studies (P < 0.00001; $I^2$ statistic = 89%).

**Figure 5. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 2**



On the third day of treatment, one outpatient trial (n = 65) (Sarrell 2002) showed a lower post-inhalation clinical score in the 3% saline group compared to the 0.9% saline group, with a MD of -2.64 (95% CI -3.85 to -1.43, P < 0.0001) (Analysis 1.5.1). The five inpatient trials (n = 374) (Giudice 2012; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) also showed a lower post-inhalation clinical score in the 3% saline group (pooled MD -1.44, 95% CI -1.78 to -1.10, P < 0.00001) (Analysis 1.5.2). Moderate heterogeneity was observed between inpatient trials (P = 0.08; $I^2$ statistic = 53%). The pooled results from these five trials demonstrated the superiority of nebulised 3% saline over 0.9% saline in reducing the post-inhalation clinical score on the third day of treatment (pooled MD -1.51, 95% CI -1.88 to -1.14, P < 0.00001) (Analysis 1.5) (Figure 6). This difference represents a 29.4% reduction from the mean clinical score in the 0.9% saline group. There was significant heterogeneity between studies (P = 0.04; $I^2$ statistic = 58%).

**Figure 6. Hypertonic saline versus 0.9% saline: clinical severity score (post-treatment) at day 3.**




To explore the possible causes of heterogeneity across studies regarding the effect size of hypertonic saline on clinical score during the first three days of treatment, we performed post hoc meta-regression in which the effect estimate (mean difference of clinical score) is predicated by one or more explanatory variables (potential effect modifiers or covariates). The small number of studies allowed us to include only one relevant covariate in the model which was the severity of bronchiolitis assessed by clinical score in the 0.9% saline group. The meta-regression yielded a regression coefficient of 0.05 (95% CI -0.15 to 0.25, P = 0.59), suggesting that the severity of disease did not significantly influence the effect size of hypertonic saline.

Three emergency department-based trials (Anil 2010; Grewal 2009; Ipek 2011) assessed short-term effects (30 to 120 minutes) of up to three doses of nebulised 3% saline in improving clinical score among infants with acute bronchiolitis. No significant benefits were observed. There were also no significant effects on oxygen saturation. Another emergency department trial (Al-Ansari 2010) showed 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). This trial did not find a significant difference in clinical score at 24 hours and 48 hours after randomisation between 3% saline and 0.9% saline.

**2. Rate of readmission to hospital**

Three emergency department trials with a total of 366 participants (Al-Ansari 2010; Anil 2010; Grewal 2009) used rate of readmission as an outcome. The pooled results of these trials did not demonstrate significant benefits of nebulised hypertonic saline in reducing the risk of readmission (pooled RR 1.05, 95% CI 0.62 to 1.76, P = 0.87) (Analysis 1.6). There was no significant heterogeneity between studies (P = 0.81; $I^2$ statistic = 0%).

#### 3. Haemoglobin saturation (oximetry)

Five trials (Al-Ansari 2010; Anil 2010; Grewal 2009; Ipek 2011; Mandelberg 2003) did not find 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.

#### 4. Respiratory rate

One trial (Ipek 2011) reported no difference in respiratory rate between the hypertonic saline group and the 0.9% saline group.

#### 5. Heart rate

Four trials (Anil 2010; Ipek 2011; Mandelberg 2003; Sarrell 2002) reported no difference in pulse rate between the hypertonic saline group and the 0.9% saline group.

#### 6. Time for the resolution of symptoms/signs

Two trials (Luo 2010; Luo 2011) reported the time for the resolution of wheezing, cough and pulmonary moist crackles. The pooled results of two trials show that infants treated with nebulised 3% saline had a shorter duration of respiratory symptoms and sign compared to those treated with nebulised 0.9% saline, with a pooled MD of -1.19 days (95% CI -1.54 to -0.84, P < 0.00001). There was significant heterogeneity in results between studies (P = 0.0005; $I^2$ statistic = 77.0%) (Analysis 1.7).

#### 7. Duration of in-hospital oxygen supplementation

Not reported on.

#### 8. Results of pulmonary function tests

Not reported on.

#### 9. Radiological findings

In two trials (Mandelberg 2003; Sarrell 2002), the second chest radiograph was obtained on the third days after hospital admission. The pooled results of two trials did not show significant difference in radiological score between the hypertonic saline group and the 0.9% saline group (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; $I^2$ statistic = 0%).

#### 10. Adverse events (tachycardia, hypertension, pallor, tremor, nausea, vomiting, diarrhea and acute urinary retention)

No significant adverse events related to hypertonic saline inhalation were observed in 11 trials. No patients were withdrawn from the trial by the medical staff because of adverse events or clinical deterioration. In the trial of Grewal 2009, three participants presented with vomiting and one presented with diarrhea during the study period. All four participants were enrolled in the 3% saline group, but these symptoms might not be directly related to nebulised hypertonic saline.

## DISCUSSION

### Summary of main results

In this review, we defined the length of hospital stay as the primary outcome to measure the efficacy of nebulised hypertonic saline among inpatients with viral bronchiolitis. Despite differences in inhalation mixture and delivery intervals across the studies, the effect sizes of the treatment with 3% saline inhalation reported by six independent studies (Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) were similar. That is, there was approximately a one-day reduction in the duration of hospitalisation. The pooled results from these five trials demonstrate that nebulised 3% saline could produce a reduction of 1.15 days in the mean length of hospital stay. This represents a 22.7% reduction from the mean length of hospitalisation in the normal saline group. Given the high prevalence of viral bronchiolitis in infants and the tremendous burden of this illness related to hospitalisation, this reduction may be considered clinically relevant and may potentially have a positive economic impact for both the health system and the individual families.

The benefit of nebulised hypertonic saline in reducing the rate of hospitalisation was assessed by four trials, one in outpatients (Sarrell 2002) and three in emergency departments (Anil 2010; Grewal 2009; Ipek 2011). The pooled results of these four trials showed a 37% reduction in the risk of hospitalisation among participants treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation. However, this reduction was not statistically significant. Low statistical power due to small sample sizes may have contributed to this negative result. Further large RCTs are required to evaluate the efficacy of nebulised hypertonic saline in preventing hospitalisation among infants with acute viral bronchiolitis seen at outpatient setting or emergency department. The effects of hypertonic saline in reducing the rate of readmission were assessed by three emergency department trials (Al-Ansari

2010; Anil 2010; Grewal 2009). The pooled results of three trials did not demonstrate significant benefits of nebulised hypertonic saline in reducing the risk of readmission. Caution should be taken when interpreting the results of these three emergency department-based trials, given the small number of participants, the small number of inhalations (up to three doses) and short monitoring time (up to 120 minutes post-inhalation). Further large RCTs with multiple doses of hypertonic saline over a longer period of time are still needed.

Clinical score is generally considered a relatively objective measure to assess the severity of illness. There are two clinical severity scoring systems more commonly used by randomised trials involving infants with viral bronchiolitis. One is a Respiratory Distress Assessment Instrument (RDAI) which assesses chest retractions and auscultatory findings, and provides a score ranging from 0 to 17, with a higher score indicating more severe respiratory distress (Lowell 1987). The other scoring system, initially described by Wang, assesses respiratory rate, wheezing, retraction and general condition, providing a score ranging from 0 to 12, with increased severity receiving a higher score (Wang 1992). In this review, seven trials utilised the clinical severity score system proposed by Wang 1992. The pooled results from these seven trials (one outpatient, one emergency department and five inpatient) demonstrate a statistically significant lower mean post-inhalation score among infants treated with 3% saline inhalation compared to those treated with 0.9% saline inhalation in the first three days of treatment. The magnitude of reduction in the severity score produced by 3% saline inhalation may be considered clinically relevant because it represents a reduction of up to 29% from the mean clinical score in the 0.9% saline group. The benefits of nebulised hypertonic saline in improving clinical score are observed in both outpatients and inpatients, but not in emergency department patients over a short period of time (30 to 120 minutes). There is significant heterogeneity across studies regarding effect size of hypertonic saline on clinical score, especially between inpatient trials. We used post hoc meta-regression to explore the possible causes of heterogeneity, however, the small number of studies allowed us to include only the severity of bronchiolitis in the model and no significant association was found between the severity of disease and the effect size of hypertonic saline. Despite the substantial heterogeneity, the size of effect but not the direction of effect varies across studies, indicating that nebulised hypertonic saline is beneficial to different degrees in improving clinical score among infants with bronchiolitis. The potential effect modifiers have not been identified by this review, but they may include patient characteristics and treatment regimens.

The potential side effects, principally acute bronchospasm, remain a concern with nebulised hypertonic saline. This review included 560 infants receiving hypertonic saline (3% saline: n = 503; 5% saline: n = 57) in repeated doses and no significant adverse events were reported. In nine trials (Al-Ansari 2010; Anil 2010; Giudice 2012; Grewal 2009; Ipek 2011; Luo 2010; Mandelberg 2003; Sarrell 2002), the participants received hypertonic saline inhalation in conjunction with bronchodilators. In one trial (Kuzik 2007), the study protocol defined the use of nebulised 3% saline alone, but bronchodilators were added into the study solution in 60% of the treatments by attending physicians. Only 57 patients in the trial of Luo 2011 and 30 patients in the trial of Ipek 2011 used 3% saline alone. Therefore, this review could not provide convincing evidence regarding the safety of nebulised hypertonic saline alone in infants with viral bronchiolitis. Given the possibility of acute bronchospasm induced by hypertonic saline in asthmatics and the difficulty in distinguishing between asthma and viral bronchiolitis in infants, it would seem reasonable to administer hypertonic saline in conjunction with bronchodilators to avoid any possible broncho-constrictive effect. The safety of nebulised hypertonic saline, even in higher concentration (5% to 7%), has recently been reported in patients with cystic fibrosis (Wark 2009) and the authors attributed the good safety profile of the therapy to the co-administration of hypertonic saline with bronchodilators. In the trial of Al-Ansari 2010, no significant adverse events were observed among 57 patients receiving nebulised 5% saline mixed with 1.5 ml of epinephrine.

The inhalation therapy was administrated via jet nebulisers in all but one trial (Tal 2006), in which ultrasonic nebulisers were used. Theoretically, there are some differences in the physical properties of aerosols produced by jet nebulisers and ultrasonic nebulisers, which may affect their therapeutical efficacies. 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. This review 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 (Tal 2006) demonstrated that both jet nebulisers and ultrasonic nebulisers are an efficient method of delivery of hypertonic saline in these patients. Further studies are required to compare the efficacy of nebulised hypertonic saline delivered by different nebulisers in infants with viral bronchiolitis.

The optimal treatment regime of nebulised hypertonic saline in acute bronchiolitis remains unclear. One outpatient (Sarrell 2002) and six inpatient trials (Giudice 2012; Kuzik 2007; Luo 2010; Luo 2011; Mandelberg 2003; Tal 2006) used multiple daily doses during several days. All seven trials demonstrated significant effects of hypertonic saline in reducing length of hospital stay, improving clinical severity score or both. The most commonly used delivery regime was three times daily at intervals of eight hours (Luo 2010; Mandelberg 2003; Sarrell 2002; Tal 2006), and more frequent deliveries may not yield an additional benefit (Giudice 2012; Kuzik 2007). In contrast, three emergency department-based trials (Anil 2010; Grewal 2009; Ipek 2011) used small numbers of inhalations during a short period (up to three inhalations within 120 min-

utes) and all trials failed to show significant effects of hypertonic saline in improving clinical score/oxygen saturation or in reducing the risk of hospitalisation/readmission. These results may suggest that nebulised hypertonic saline is effective for acute bronchiolitis only when the treatment is given at multiple daily doses during a reasonable period of time.

The concentration of nebulised hypertonic saline was 3% in all but one trial (Al-Ansari 2010). In this emergency department trial, two concentrations of hypertonic saline (3% and 5%) were used. No superiority of 5% saline over 3% saline was observed in improving clinical score at 24 hours and 48 hours after randomisation. However, further studies are still needed to establish the optimal concentration and treatment regime of nebulised hypertonic saline in infants with viral bronchiolitis.

### Overall completeness and applicability of evidence

This review included trials conducted in both high-income and low-income countries and in different settings (inpatient, outpatient and emergency department). Thus evidence derived from this review may have a wide applicability. However, all 11 trials included in this review recruited only infants with mild to moderate bronchiolitis, so caution should be taken when extrapolating the findings of this review to patients with more severe bronchiolitis, such as those requiring mechanical ventilation, intensive care or having an oxygen saturation reading 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 more severe cases. Further trials are needed to assess the potential effects of nebulised hypertonic saline in infants hospitalised with severe acute bronchiolitis.

### Quality of the evidence

All but one of the 11 included trials are of high methodological quality with low risk of bias. However, some methodological considerations should be mentioned. Firstly, eight trials (Al-Ansari 2010; Anil 2010; Giudice 2012; Ipek 2011; Luo 2010; Luo 2011 Mandelberg 2003; Tal 2006) did not use an intention-to-treat analysis. This analysis strategy aims to maintain the unbiased group comparison afforded by randomisation and to deal with the problem of non-compliance and protocol deviation. As the number of participants withdrawn after randomisation was small in all these trials, the lack of application of an intention-to-treat principle was unlikely to cause significant bias. Secondly, the sample size of this review was relatively small and the statistical power of the study might be not sufficient for some outcome measures, such as rate of hospitalisation and rate of readmission among outpatients or emergency department patients. The small number of studies included in the review also precludes an analytic approach to heterogeneity across studies, however, this is a substantial heterogeneity only for clinical score but not other outcomes.

### Potential biases in the review process

The strength of this review is that all but one of the included trials have high quality and low risk of bias. The main concern regarding potential biases of this review is publication bias. We did not use funnel plots or other analytic approaches to deal with the potential publication bias, given the lack of reliable methods and relatively small number of included studies.

### Agreements and disagreements with other studies or reviews

To the best of our knowledge, there is no other systematic review or traditional narrative review which assesses the efficacy and safety of nebulised hypertonic saline in infants with acute bronchiolitis. We also failed to find observational studies that address this question. This precludes a comparison of findings between this review and other studies.

## AUTHORS' CONCLUSIONS

### Implications for practice

Nebulised 3% saline produces a 1.2 day reduction in the mean length of hospital stay, compared to nebulised normal saline, among infants hospitalised with non-severe acute bronchiolitis. This therapy also significantly reduces clinical severity score among outpatients and inpatients with mild to moderate bronchiolitis. Given the clinically relevant benefit and good safety profile, nebulised 3% saline used in conjunction with bronchodilators should be considered an effective and safe treatment for infants with mild to moderate acute viral bronchiolitis.

### Implications for research

Further large randomised controlled trials, preferably multi-centred, are still required to evaluate the effectiveness of nebulised hypertonic saline in infants with acute viral bronchiolitis, principally in infants who attend the emergency department and infants hospitalised with severe acute bronchiolitis. The optimal delivery intervals, duration of treatment and concentration of saline, and the most effective delivery devices remain to be determined. The mechanism of action of nebulised hypertonic saline in patients with viral bronchiolitis also needs to be addressed in future studies.

## ACKNOWLEDGEMENTS

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* *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<br>Eligible: 87<br>Randomised: 115 HS group (5% saline: 57; 3% saline: 58); 56 NS group<br>Completed: 115 HS group; 56 NS group<br>Gender (male): 41.5%<br>Age: median age 3.1 months, range 9 days to 14.7 months<br>Inclusion criteria: Infants aged ≤ 18 months, with a prodromal history of viral upper respiratory tract infection, followed by wheezing and/or crackles on auscultation and a Wang bronchiolitis severity score of ≥ 4<br>Exclusion criteria: born at ≤ 34 weeks' gestation, previous history of wheezing, steroid use within 48 hours of presentation, obtundation and progressive respiratory failure requiring intensive care unit (ICU) admission, history of apnoea within 24 hours before presentation, oxygen saturation ≤ 85% on room air at the time of recruitment, history of a diagnosis of chronic lung disease, congenital heart disease or immunodeficiency |
| Interventions | Test groups:<br>Group 1: nebulised 5% hypertonic saline (5 ml) plus 1.5 ml of epinephrine<br>Group 2: nebulised 3% hypertonic saline (5 ml) plus 1.5 ml of epinephrine<br>Control groups: nebulised 0.9% normal saline (5 ml) plus 1.5 ml of epinephrine<br>The 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 | Clinical severity score<br>Oxygen saturation<br>Length of stay<br>Need for ICU admission<br>Rate of readmission<br>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 |

**Al-Ansari 2010** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised patients completed the trial |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Anil 2010**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: emergency department of a teaching hospital in Turkey<br>Eligible: 190<br>Randomised: 75 HS group; 111 NS group<br>Completed: 75 HS group;111 NS group<br>Gender (male): 64.5%<br>Age: mean age 9.5 months, range 1.5 to 24 months<br>Inclusion criteria: infants with diagnosis of bronchiolitis, which required a history of upper respiratory infection and the presence of bilateral wheezing and/or crackles on chest auscultation, plus clinical severity score between 1 and 9<br>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, oxygen saturation ($SaO_2$) < 85% on room air, CS score > 9, obtunded consciousness, progressive respiratory failure requiring mechanical ventilation, previous treatment with bronchodilators, and any steroid therapy within 2 weeks |
| Interventions | Test groups:<br>Group 1: nebulised 3% hypertonic saline (4 ml) plus 1.5 mg of epinephrine<br>Group 2: nebulised 3% hypertonic saline (4 ml) plus 2.5 mg of salbutamol<br>Control groups:<br>Group 3: nebulised 0.9% normal saline (4 ml) plus 1.5 mg of epinephrine<br>Group 4: nebulised 0.9% normal saline (4 ml) plus 2.5 mg of salbutamol<br>Group 5: nebulised 0.9% normal saline (4 ml) alone<br>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 | Clinical severity score<br>Oxygen saturation<br>Heart rate<br>Rate of hospitalisation<br>Rate of readmission<br>Adverse events |

**Anil 2010** (*Continued*)

| | | |
|---|---|---|
| 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 drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 4 withdrawals (2 protocol deviation, 2 parents refused to participate in the study) |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Giudice 2012**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: Division of Pediatrics, Saint Mary Hospital in Pozzuoli, Naples, Italy<br>Eligible: 109<br>Randomised: 53 HS group; 56 NS group<br>Completed: 752 HS group; 54 NS group<br>Gender (male): 65.1%<br>Age: mean (SD): 4.8 (2.3) months HS group; 4.2 (1.6) months NS group<br>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 oxygen saturation < 94% in room air and significant respiratory distress<br>Exclusion criteria: pre-existing cardiac or pulmonary diseases, premature birth < 36 weeks of gestational age, previous diagnosis of asthma, initial oxygen saturation ≤ 85% or respiratory distress severe enough to require resuscitation |
| Interventions | Test group: nebulised 3.0% normal saline (? ml) plus 1.5 mg of epinephrine<br>Control group: nebulised 0.9% normal saline (? ml) plus 1.5 mg of epinephrine<br>Study solutions were given at intervals of 6 hours 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<br>Clinical score |

**Giudice 2012** (*Continued*)

| | |
|---|---|
| Notes | - |

***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)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 3 withdrawals due to parent refusal to participate in study (1 HS group; 2 NS group) |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Grewal 2009**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: emergency department of a children's hospital in Canada<br>Eligible: 48<br>Randomised: 24 HS group; 24 NS group<br>Completed: 23 HS group; 23 NS group<br>Gender (male): 60.9%<br>Age: mean age 5 months, range 6 weeks to 12 months<br>Inclusion criteria: infants presenting with a first episode of wheezing and clinical symptoms of a viral respiratory infection, plus an initial oxygen saturation of 85% or more but 96% or less, and Respiratory Distress Assessment Instrument (RDAI) score >= 4<br>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 | Test group: nebulised 3% hypertonic saline (2.5 ml) plus 0.5 ml of 2.25% racaemic epinephrine<br>Control group: nebulised 0.9% normal saline (2.5 ml) plus 0.5 ml of 2.25% racaemic epinephrine<br>Both groups received inhalation solutions at 0 minutes. Each treatment was given by |

**Grewal 2009** (*Continued*)

| | |
|---|---|
| | nebuliser with continuous flow of oxygen at 6 L/min. Two doses of the study drug were available for each patient such that, if the physician felt that a second dose of racaemic epinephrine was needed during the 120-minute study period, the patient received the same drug combination again |
| Outcomes | Clinical severity score<br>Oxygen saturation<br>Rate of hospitalisation<br>Rate of readmission<br>Adverse events |
| Notes | RSV positive: 82.6% in HS group; 81.8% in NS 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 | Sequentially numbered drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 1 withdrawal due to age > 12 months (HS) , 1 inadvertently discharged prior to completion of study period (NS)<br>Intention-to-treat analysis used |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Ipek 2011**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: Paediatric Emergency Department of a training and research hospital in Turkey<br>Eligible: not stated<br>Randomised: 60 HS group; 60 NS group<br>Completed: 60 HS group; 60 NS group<br>Gender (male): 59.2%<br>Age: mean age 7.96 ± 3.91 months<br>Inclusion criteria: age < 2 years, a history of preceding viral upper respiratory infection followed by wheezing and crackles on auscultation, and a Clinical Bronchiolitis Severity |

| | |
|---|---|
| | Score (CBSS) of 4 to 8 on admission<br>Exclusion criteria: infants with CBSS < 4 or > 8, oxygen saturation < 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 | Test groups:<br>Group 1: nebulised 3% hypertonic saline (4 ml) plus salbutamol 0.15 mg/kg<br>Group 2: nebulised 3% hypertonic saline (4 ml) alone<br>Control groups:<br>Group 1: nebulised 0.9% hypertonic saline (4 ml) plus salbutamol 0.15 mg/kg<br>Group 2: nebulised 0.9% hypertonic saline (4 ml) alone<br>The treatment was given every 20 min until 3 doses had been administered (0, 20 and 40th min). All inhaled therapies were delivered via a compressor nebuliser through a facemask with continued flow of oxygen at 4e5 L/min (Minicompressor nebuliser, CN-02WD, Ace-Tec Co., Ltd., Guangdong, China) |
| Outcomes | Changes in clinical score after the treatment<br>Oxygen saturation<br>Respiratory rate<br>Heart beat rate<br>Corticosteroid need<br>Rate of hospitalisation<br>Adverse events |
| Notes | Virological identification not available |

***Risk of bias***

| **Bias** | **Authors' judgement** | **Support for judgement** |
|---|---|---|
| Random sequence generation (selection bias) | High risk | Patients 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)<br>All outcomes | Unclear risk | The trial was stated to be double-blind, but no details were provided |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | All randomised patients completed the trial |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Unclear risk | - |

**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<br>Eligible: not stated<br>Randomised: 47 HS group; 49 NS group<br>Completed: 45 HS group; 46 NS group<br>Gender (male): 59%<br>Age: mean age 4.7 months, range 10 days to 18 months<br>Inclusion criteria: infants with diagnosis of moderately severe bronchiolitis, which required a history of a preceding viral upper respiratory infection, the presence of wheezing or crackles on chest auscultation, plus either an oxygen saturation of < 94% in room air or RDAI score of >= 4<br>Exclusion criteria: previous episode of wheezing, chronic cardiopulmonary disease or immunodeficiency, critical illness at presentation requiring admission to intensive care, the use of nebulised HS within the previous 12 hours, or premature birth (gestational age <= 34 weeks) |
| Interventions | Test group: nebulised 3% hypertonic saline (4 ml)<br>Control group: nebulised 0.9% normal saline (4 ml)<br>The treatment was given every 2 hours for 3 doses, followed by every 4 hours for 5 doses, followed by every 6 hours 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 was better tolerated by the infant |
| Outcomes | Length of hospital stay<br>Treatments received during the study<br>Adverse events |
| Notes | RSV positive: 62% in HS group; 75% in NS 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 drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 2 patients from HS group and 3 from NS group were withdrawn at parental request because of perceived adverse effects of therapy |

**Kuzik 2007** (*Continued*)

| | | |
|---|---|---|
| | | Intention-to-treat analysis used |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Luo 2010**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: inpatient wards of a teaching hospital for children in China<br>Eligible: not stated<br>Randomised: 50 HS group; 43 NS group<br>Completed: 50 HS group; 43 NS group<br>Gender (male): 60.2%<br>Age: mean age 5.8 months, range 1 to 16.5 months<br>Inclusion criteria: infants with a diagnosis of mild to moderately severe bronchiolitis<br>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 | Test group: nebulised 3% hypertonic saline (4 ml) plus 2.5 mg of salbutamol<br>Control group: nebulised 0.9% normal saline (4 ml) plus 2.5 mg of salbutamol<br>Patients 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<br>Duration of symptoms and signs<br>Clinical score<br>Adverse events |
| Notes | RSV positive: 70% in HS group; 69.7% in NS 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 | Sequentially numbered drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |

**Luo 2010** (*Continued*)

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All randomised patients completed the trial |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Luo 2011**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: inpatient wards of a teaching hospital for children in China<br>Eligible: 135<br>Randomised: 64 HS group; 62 NS group<br>Completed: 57 HS group; 55 NS group<br>Gender (male): 56.3%<br>Age: mean age: 5.9 ± 4.1 months in HS group; 5.8 ± 4.3 months in NS group<br>Inclusion criteria: infants aged < 24 months with a first episode of wheezing, hospitalised for treatment of moderate to severe bronchiolitis<br>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% HS solution 12 h before treatment, and prematurity, with birth at < 34 weeks of gestation |
| Interventions | Test group: nebulised 3% hypertonic saline (4 ml)<br>Control group: nebulised 0.9% normal saline (4 ml)<br>The treatment was given every 2 hours for 3 doses, followed by every 4 hours for 5 doses, followed by every 6 hours until discharge. All inhaled treatments were delivered to infants from standard air-compressed nebulisers (PARI Corporation, Starnford, Germany) |
| Outcomes | Length of hospital stay<br>Duration of symptoms and signs<br>Clinical score<br>Adverse events |
| Notes | RSV positive: 73.7% in HS group; 72.7% in NS 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 |

**Luo 2011** (*Continued*)

| | | |
|---|---|---|
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | - |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Mandelberg 2003**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: inpatient ward, the Edith Wolfson Medical Center, Israel<br>Eligible: 61<br>Randomised: 31 (0.9% saline group); 30 (3% saline group)<br>Completed: 25 HS group; 27 NS group<br>Gender (male): 57.7%<br>Age: mean age 2.9 months, range 0.5 to 12 months<br>Inclusion criteria: infants with clinical presentation of viral bronchiolitis with temperatures > 38 ºC that lead to hospitalisation<br>Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, oxygen saturation < 85% in room air, changes in consciousness and/or progressive respiratory failure requiring mechanical ventilation |
| Interventions | Test group: nebulised 3% saline solution (4 ml) plus 1.5 mg epinephrine<br>Control group: nebulised 0.9% saline solution (4 ml) plus 1.5 mg epinephrine<br>The treatment was given 3 times/day at intervals of 8 hours, until the patient was ready for discharge. All inhaled treatments were delivered using a nebuliser (Aeromist Nebuliser 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<br>Change in clinical severity score<br>Others: pulse rate, saturation on room air, radiograph assessment score, number of add-on treatments, adverse events |
| Notes | RSV positive: 85% in HS group; 88% in NS 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 |

**Mandelberg 2003** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Sequentially numbered drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 14 patients were withdrawn from the trial (7 patients in each group discharged within 12 h after enrolment) |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Sarrell 2002**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial |
| Participants | Setting: The Paediatrics and Adolescent Ambulatory Community Clinic of General Health Services of Petach-Tikva, Israel<br>Eligible: not stated<br>Randomised: 70<br>Completed: 32 (0.9% saline group); 33 (3% saline group)<br>Gender (male): 59%<br>Age: mean age 12.5 months, range 3 to 24 months<br>Inclusion criteria: infants with clinical presentation of mild-to-moderate viral bronchiolitis<br>Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age >= 24 months, oxygen saturation < 96% on room air, and need for hospitalisation |
| Interventions | Test group: nebulised 3% saline solution (2 ml) plus 5 mg (0.5 ml) terbutaline<br>Control group: nebulised 0.9% saline solution (2 ml) plus 5 mg (0.5 ml) terbutaline<br>The treatment was given 3 times/day at intervals of 8 hours for 5 days |
| Outcomes | Change in clinical severity score<br>Hospitalisation rate<br>Others: radiograph assessment score, pulse rate, adverse events |
| Notes | RSV positive: 82% in HS group; 78% in NS 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 |

**Sarrell 2002** (*Continued*)

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Low risk | Sequentially numbered drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | 5 patients were withdrawn, but the reasons were not stated<br>Intention-to-treat analysis used |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

**Tal 2006**

| | |
|---|---|
| Methods | Design: randomised, double-blind, parallel-group, controlled trial<br>Randomisation: randomisation in blocks of 4, using an online randomiser<br>Blinding: double-blind<br>Withdrawals/drop-outs: 2 patients from the 0.9% saline group were withdrawn, 1 because of clinical deterioration and another because of parental refusal. 1 patient from the 3% saline group was withdrawn because of protocol violation |
| Participants | Setting: inpatient ward, the Wolfson Medical Center, Israel<br>Eligible: unclear<br>Randomised: 22 (0.9% saline group); 22 (3% saline group)<br>Completed: 20 (0.9% saline group); 21 (3% saline group)<br>Gender (male): 56.1%<br>Age: mean age 2.6 months, range 1 to 5 months<br>Inclusion criteria: infants with clinical presentation of viral bronchiolitis that led to hospitalisation<br>Exclusion criteria: cardiac disease, chronic respiratory disease, previous wheezing episode, age > 12 months, oxygen saturation < 85% on room air, obtunded consciousness and/or progressive respiratory failure requiring mechanical ventilation |
| Interventions | Test group: nebulised 3% saline solution (4 ml) plus 1.5 mg epinephrine<br>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 hours, until the patient 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<br>Change in clinical severity score |
| Notes | RSV positive: 86% in HS group; 75% in NS group |

***Risk of bias***

**Tal 2006** (*Continued*)

| 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 | Sequentially numbered drug containers of identical appearance |
| Blinding (performance bias and detection bias)<br>All outcomes | Low risk | Double-blind |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 2 patients from the 0.9% saline group were withdrawn, 1 because of clinical deterioration and another because of parental refusal. 1 patient from the 3% saline group was withdrawn because of protocol violation |
| Selective reporting (reporting bias) | Low risk | - |
| Other bias | Low risk | - |

CS = clinical severity
h = hours
HS = hypertonic saline
ICU = intensive care unit
NS = normal saline
RDAI = Respiratory Distress Assessment Instrument
RSV = respiratory syncytial virus
$SaO_2$ = oxygen saturation

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

| Study | Reason for exclusion |
|---|---|
| Amirav 2005 | Study of drug delivery (hood versus face-mask) |
| Guomo 2007 | Abstract only |
| Kuzik 2010 | Inclusion of patients with previous history of wheezing |
| Tribastone 2003 | Summary of Sarrell 2002 |

## DATA AND ANALYSES

### 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) | 6 | 500 | Mean Difference (IV, Random, 95% CI) | -1.15 [-1.49, -0.82] |
| 2 Rate of hospitalisation | 4 | 380 | Risk Ratio (M-H, Random, 95% CI) | 0.63 [0.37, 1.07] |
| 3 Clinical severity score (post-treatment) at day 1 | 7 | 640 | Mean Difference (IV, Random, 95% CI) | -0.88 [-1.36, -0.39] |
| 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 | 5 | 404 | Mean Difference (IV, Random, 95% CI) | -0.99 [-1.48, -0.50] |
| 4 Clinical severity score (post-treatment) at day 2 | 7 | 636 | Mean Difference (IV, Random, 95% CI) | -1.32 [-2.00, -0.64] |
| 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 | 5 | 400 | Mean Difference (IV, Random, 95% CI) | -1.45 [-2.06, -0.85] |
| 5 Clinical severity score (post-treatment) at day 3 | 6 | 439 | Mean Difference (IV, Random, 95% CI) | -1.51 [-1.88, -1.14] |
| 5.1 Outpatients | 1 | 65 | Mean Difference (IV, Random, 95% CI) | -2.64 [-3.85, -1.43] |
| 5.2 Inpatients | 5 | 374 | Mean Difference (IV, Random, 95% CI) | -1.44 [-1.78, -1.10] |
| 6 Rate of readmission | 3 | 366 | Risk Ratio (M-H, Random, 95% CI) | 1.05 [0.62, 1.76] |
| 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) | | 11.5 % | -1.00 [ -1.87, -0.13 ] |
| Tal 2006 | 21 | 2.6 (1.4) | 20 | 3.5 (1.7) | | 9.9 % | -0.90 [ -1.86, 0.06 ] |
| Kuzik 2007 | 47 | 2.6 (1.9) | 49 | 3.5 (2.9) | | 9.5 % | -0.90 [ -1.88, 0.08 ] |
| Luo 2010 | 50 | 6 (1.2) | 43 | 7.4 (1.5) | | 21.6 % | -1.40 [ -1.96, -0.84 ] |
| Luo 2011 | 57 | 4.8 (1.2) | 55 | 6.4 (1.4) | | 25.6 % | -1.60 [ -2.08, -1.12 ] |
| Giudice 2012 | 52 | 4.9 (1.3) | 54 | 5.6 (1.6) | | 21.8 % | -0.70 [ -1.25, -0.15 ] |
| **Total (95% CI)** | **254** | | **246** | | | **100.0 %** | **-1.15 [ -1.49, -0.82 ]** |

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 7.18$, df = 5 (P = 0.21); $I^2 = 30\%$

Test for overall effect: Z = 6.83 (P < 0.00001)

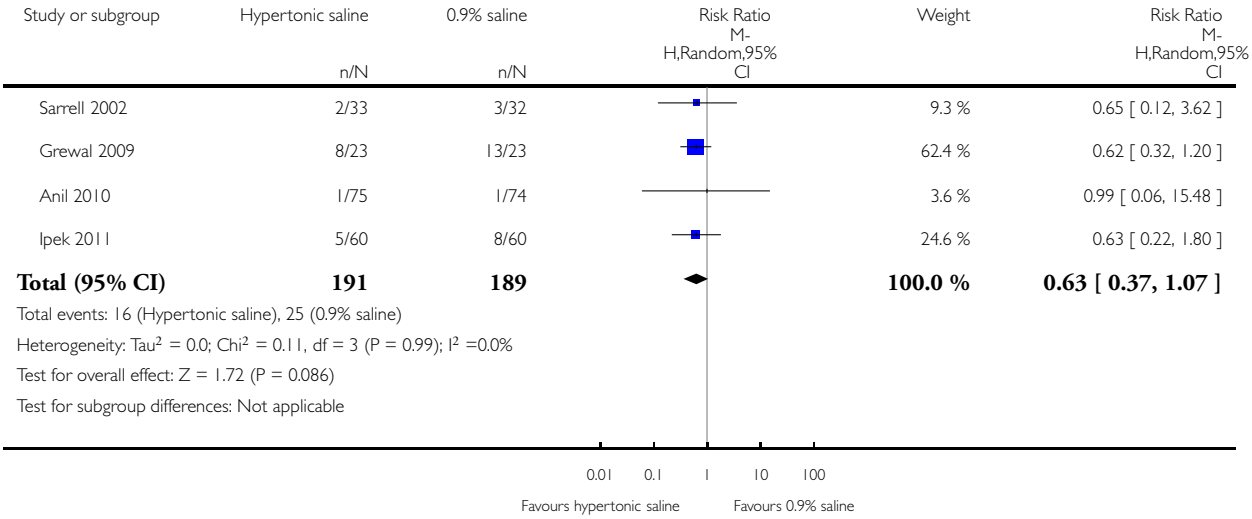
Test for subgroup differences: Not applicable

## 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



## 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 N | Mean(SD) | 0.9% saline N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Outpatients | | | | | | | |
| Sarrell 2002 | 33 | 4.36 (1.05) | 32 | 5.64 (1.54) | | 14.0 % | -1.28 [ -1.92, -0.64 ] |
| **Subtotal (95% CI)** | **33** | | **32** | | | **14.0 %** | **-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) | | 16.3 % | -0.09 [ -0.51, 0.33 ] |
| **Subtotal (95% CI)** | **115** | | **56** | | | **16.3 %** | **-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) | | 12.1 % | -0.11 [ -0.93, 0.71 ] |
| Tal 2006 | 21 | 6.25 (1.1) | 20 | 7 (1) | | 14.0 % | -0.75 [ -1.39, -0.11 ] |
| Luo 2010 | 50 | 3.4 (1.2) | 43 | 4.9 (1.7) | | 14.3 % | -1.50 [ -2.11, -0.89 ] |
| Luo 2011 | 57 | 5.7 (1.5) | 55 | 7.3 (1.7) | | 14.5 % | -1.60 [ -2.19, -1.01 ] |
| Giudice 2012 | 52 | 8 (1.3) | 54 | 8.8 (1.6) | | 14.9 % | -0.80 [ -1.35, -0.25 ] |
| **Subtotal (95% CI)** | **207** | | **197** | | | **69.8 %** | **-0.99 [ -1.48, -0.50 ]** |
| Heterogeneity: $Tau^2$ = 0.21; $Chi^2$ = 12.01, df = 4 (P = 0.02); $I^2$ =67% | | | | | | | |
| Test for overall effect: Z = 3.94 (P = 0.000081) | | | | | | | |
| **Total (95% CI)** | **355** | | **285** | | | **100.0 %** | **-0.88 [ -1.36, -0.39 ]** |
| Heterogeneity: $Tau^2$ = 0.33; $Chi^2$ = 27.85, df = 6 (P = 0.00010); $I^2$ =78% | | | | | | | |
| Test for overall effect: Z = 3.56 (P = 0.00038) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 12.31, df = 2 (P = 0.00), $I^2$ =84% | | | | | | | |

### 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 N | Mean(SD) | 0.9% saline N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Outpatients | | | | | | | |
| Sarrell 2002 | 33 | 2.77 (1.4) | 32 | 4.77 (2.31) | | 12.6 % | -2.00 [ -2.93, -1.07 ] |
| **Subtotal (95% CI)** | **33** | | **32** | | | **12.6 %** | **-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) | | 15.7 % | -0.27 [ -0.63, 0.09 ] |
| **Subtotal (95% CI)** | **115** | | **56** | | | **15.7 %** | **-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) | | 13.1 % | -0.51 [ -1.36, 0.34 ] |
| Tal 2006 | 20 | 5.35 (1.3) | 20 | 6.45 (1) | | 13.9 % | -1.10 [ -1.82, -0.38 ] |
| Luo 2010 | 50 | 2.2 (1.1) | 43 | 3.8 (1.5) | | 14.9 % | -1.60 [ -2.14, -1.06 ] |
| Luo 2011 | 57 | 3.5 (1.1) | 55 | 5.9 (1.5) | | 15.2 % | -2.40 [ -2.89, -1.91 ] |
| Giudice 2012 | 52 | 6.8 (1.4) | 54 | 8.2 (1.7) | | 14.6 % | -1.40 [ -1.99, -0.81 ] |
| **Subtotal (95% CI)** | **203** | | **197** | | | **71.7 %** | **-1.45 [ -2.06, -0.85 ]** |
| Heterogeneity: $Tau^2$ = 0.36; $Chi^2$ = 18.94, df = 4 (P = 0.00081); $I^2$ =79% | | | | | | | |
| Test for overall effect: Z = 4.74 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **351** | | **285** | | | **100.0 %** | **-1.32 [ -2.00, -0.64 ]** |
| Heterogeneity: $Tau^2$ = 0.73; $Chi^2$ = 56.79, df = 6 (P<0.00001); $I^2$ =89% | | | | | | | |
| Test for overall effect: Z = 3.81 (P = 0.00014) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 18.98, df = 2 (P = 0.00), $I^2$ =89% | | | | | | | |

## 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 N | Mean(SD) | 0.9% saline N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference IV,Random,95% CI |
|---|---|---|---|---|---|---|---|
| 1 Outpatients | | | | | | | |
| Sarrell 2002 | 33 | 1.77 (2.4) | 32 | 4.41 (2.57) | | 7.4 % | -2.64 [ -3.85, -1.43 ] |
| **Subtotal (95% CI)** | **33** | | **32** | | | **7.4 %** | **-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) | | 8.6 % | -0.27 [ -1.37, 0.83 ] |
| Tal 2006 | 13 | 4.7 (1.5) | 14 | 5.72 (1) | | 10.2 % | -1.02 [ -1.99, -0.05 ] |
| Luo 2010 | 45 | 1.5 (0.5) | 40 | 2.9 (0.7) | | 29.4 % | -1.40 [ -1.66, -1.14 ] |
| Luo 2011 | 57 | 2.4 (0.9) | 55 | 4.1 (1.1) | | 25.5 % | -1.70 [ -2.07, -1.33 ] |
| Giudice 2012 | 52 | 5.8 (1.4) | 54 | 7.6 (1.6) | | 18.9 % | -1.80 [ -2.37, -1.23 ] |
| **Subtotal (95% CI)** | **188** | | **186** | | | **92.6 %** | **-1.44 [ -1.78, -1.10 ]** |
| Heterogeneity: $Tau^2$ = 0.07; $Chi^2$ = 8.43, df = 4 (P = 0.08); $I^2$ =53% | | | | | | | |
| Test for overall effect: Z = 8.26 (P < 0.00001) | | | | | | | |
| **Total (95% CI)** | **221** | | **218** | | | **100.0 %** | **-1.51 [ -1.88, -1.14 ]** |
| Heterogeneity: $Tau^2$ = 0.10; $Chi^2$ = 11.90, df = 5 (P = 0.04); $I^2$ =58% | | | | | | | |
| Test for overall effect: Z = 7.98 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2$ = 3.51, df = 1 (P = 0.06), $I^2$ =72% | | | | | | | |

## Analysis 1.6. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 6 Rate of readmission.

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

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

Outcome: 6 Rate of readmission

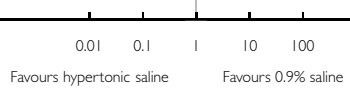
| Study or subgroup | Hypertonic saline n/N | 0.9% saline n/N | Risk Ratio M-H,Random,95% CI | Weight | Risk Ratio M-H,Random,95% CI |
|---|---|---|---|---|---|
| Al-Ansari 2010 | 18/115 | 7/56 | | 40.7 % | 1.25 [ 0.56, 2.82 ] |
| Anil 2010 | 11/75 | 11/74 | | 45.2 % | 0.99 [ 0.46, 2.13 ] |
| Grewal 2009 | 3/23 | 4/23 | | 14.1 % | 0.75 [ 0.19, 2.98 ] |
| **Total (95% CI)** | **213** | **153** | | **100.0 %** | **1.05 [ 0.62, 1.76 ]** |

Total events: 32 (Hypertonic saline), 22 (0.9% saline)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.43$, df = 2 (P = 0.81); $I^2 = 0.0\%$

Test for overall effect: Z = 0.17 (P = 0.87)

Test for subgroup differences: Not applicable



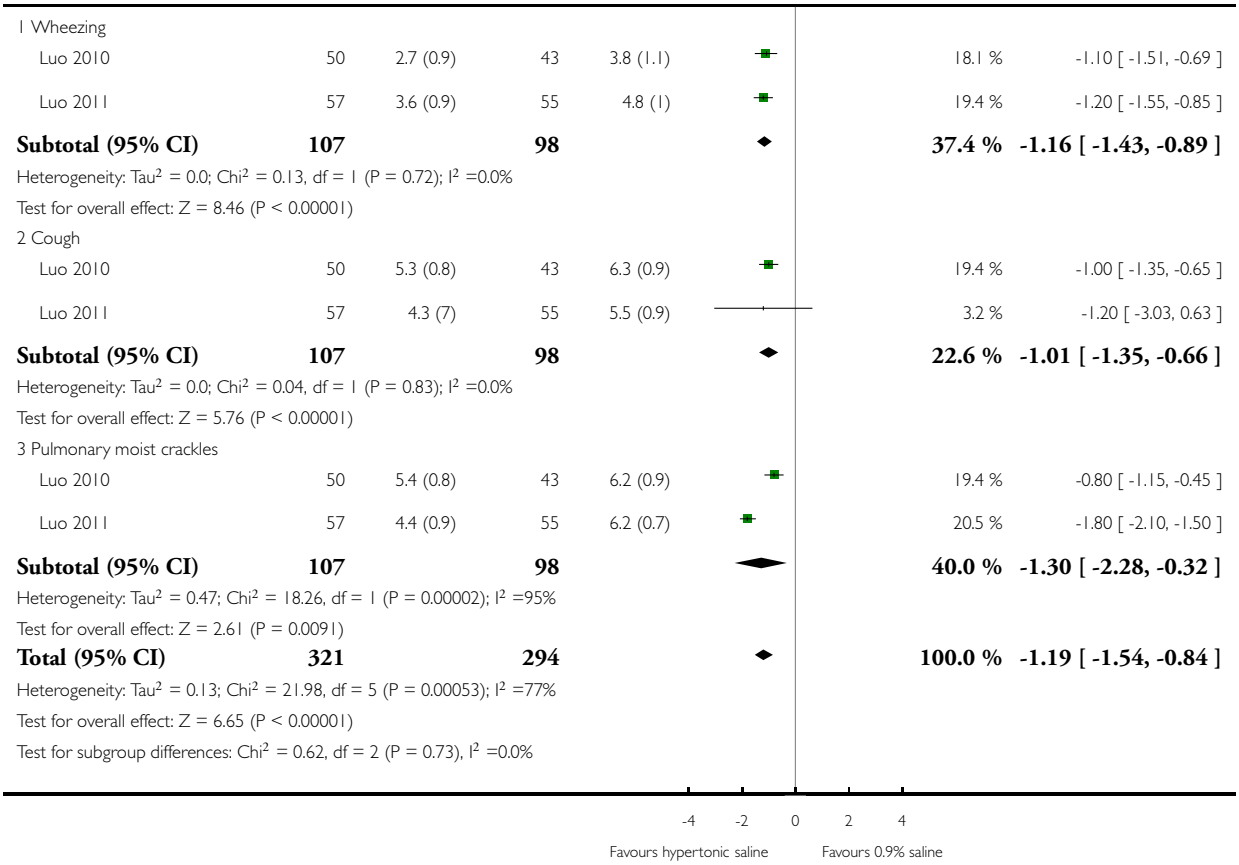
## Analysis 1.7. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 7 Time for resolution of symptoms/signs.

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 N | Mean(SD) | 0.9% saline N | Mean(SD) | Mean Difference IV,Random,95% CI | Weight | Mean Difference 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: $Tau^2 = 0.0$; $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$ | | | | | | | |
| 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: $Tau^2 = 0.0$; $Chi^2 = 0.04$, df = 1 (P = 0.83); $I^2 = 0.0\%$ | | | | | | | |
| 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: $Tau^2 = 0.47$; $Chi^2 = 18.26$, df = 1 (P = 0.00002); $I^2 = 95\%$ | | | | | | | |
| Test for overall effect: Z = 2.61 (P = 0.0091) | | | | | | | |
| **Total (95% CI)** | **321** | | **294** | | | **100.0 %** | **-1.19 [ -1.54, -0.84 ]** |
| Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 21.98$, df = 5 (P = 0.00053); $I^2 = 77\%$ | | | | | | | |
| Test for overall effect: Z = 6.65 (P < 0.00001) | | | | | | | |
| Test for subgroup differences: $Chi^2 = 0.62$, df = 2 (P = 0.73), $I^2 = 0.0\%$ | | | | | | | |

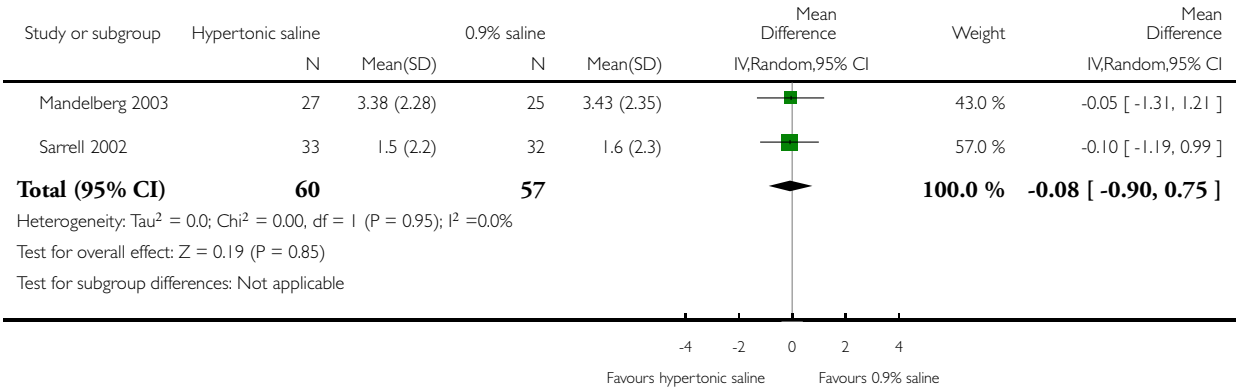


**Analysis 1.8. Comparison 1 Hypertonic saline versus normal saline (0.9%), Outcome 8 Radiological assessment score.**

Review: Nebulised hypertonic saline solution for acute bronchiolitis in infants

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

Outcome: 8 Radiological assessment score




## ADDITIONAL TABLES

**Table 1. Treatment regimens of nebulised hypertonic saline**

| Study ID | Concentration of saline | Volume of saline | Addition of bronchodilator | Interval of administration | Treatment duration |
|---|---|---|---|---|---|
| **Outpatient trial** | | | | | |
| Sarrell 2002 | 3% | 2 ml | Terbutaline 5 mg | Every 8 hours | 5 days |
| **Emergency -based trial** | | | | | |
| 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 administrated |
| Grewal 2009 | 3% | 2.5 ml | 2.25% racaemic epinephrine 0.5 ml | If needed, the second dose was given during the 120-minute study period | Up to 2 doses |

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

| | | | | | |
|---|---|---|---|---|---|
| Ipek 2011 | 3% | 4 ml | Salbutamol 0.15 mg/kg | Every 20 minutes | Until 3 doses had been administrated |
| **Inpatient trial** | | | | | |
| Giudice 2012 | 3% | ? ml | Epinephrine 1.5 mg | Every 6 hours | Until discharge |
| Kuzik 2007 | 3% | 4 ml | Albuterol was added in 37% of the treatments and racaemic 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 | | 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 |
| Tal 2006 | 3% | 4 ml | Epinephrine 1.5 mg | Every 8 hours | Until discharge |

# APPENDICES

## Appendix 1. Previous search

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).

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. 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 3. 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 Sincitiales 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 4. 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 5. Web of Science (Thomson Reuters) search strategy

| | | |
|---|---|---|
| # 3 | **93** | #2 AND #1<br>*Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*<br>*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)<br>*Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*<br>*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*)<br>*Databases=SCI-EXPANDED, CPCI-S Timespan=All Years*<br>*Lemmatization=On* |

## WHAT'S NEW

Last assessed as up-to-date: 8 May 2013.

| Date | Event | Description |
|---|---|---|
| 8 May 2013 | New search has been performed | Searches conducted. We included four new trials (Al-Ansari 2010; Giudice 2012; Ipek 2011; Luo 2011) and performed new analyses. Our conclusions remain unchanged |
| 8 May 2013 | New citation required but conclusions have not changed | Our conclusions remain unchanged. |

## HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 4, 2008

| Date | Event | Description |
|---|---|---|
| 7 June 2010 | New search has been performed | Searches conducted. We included three new trials (Anil 2010; Grewal 2009; Luo 2010) and conducted new analyses. The 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 (LZ) conceived the idea and wrote the draft protocol, the primary review and updated the review.

LZ and Raúl A Mendoza-Sassi (RAM) were responsible for study selection, quality assessment, data collection and data analysis.

RAM, Claire Wainwright (CW) and Terry P Klassen (TPK) provided input for writing the protocol and review.

The final version of the updated review was approved by all authors.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT


### Internal sources

- Faculty of Medicine, Universidade Federal do Rio Grande, Brazil.

### External sources

- No sources of support supplied


## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the very limited number of studies that were identified initially, we added the comparison of nebulised hypertonic saline alone versus nebulised 0.9% saline. We also clarified the population according to the age and changed the title to specify infants.

## NOTES

We performed post hoc meta-regression in the updated review.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Acute Disease; Bronchiolitis, Viral [*therapy]; Bronchodilator Agents [administration & dosage]; Nebulizers and Vaporizers; Randomized Controlled Trials as Topic; Saline Solution, Hypertonic [*administration & dosage]

### MeSH check words

Humans; Infant