Epinephrine for bronchiolitis (Review)

Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, Klassen TP, Patel H, Fernandes RM

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2011, Issue 6

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[Intervention Review]

Epinephrine for bronchiolitis

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Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 6, 2011.
Review content assessed as up-to-date: 26 September 2010.

Citation: Hartling L, Bialy LM, Vandermeer B, Tjosvold L, Johnson DW, Plint AC, Klassen TP, Patel H, Fernandes RM. Epinephrine for bronchiolitis. *Cochrane Database of Systematic Reviews* 2011, Issue 6. Art. No.: CD003123. DOI: 10.1002/14651858.CD003123.pub3.

ABSTRACT

Background

Bronchodilators are commonly used for acute bronchiolitis, despite uncertain effectiveness.

Objectives

To examine the efficacy and safety of epinephrine in children less than two with acute viral bronchiolitis.

Search methods

We searched CENTRAL (2010, Issue 3) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE (1950 to September Week 2, 2010), EMBASE (1980 to September 2010), Scopus (1823 to September 2010), PubMed (March 2010), LILACS (1985 to September 2010) and Iran MedEx (1998 to September 2010).

Selection criteria

We included randomized controlled trials comparing epinephrine to placebo or another intervention involving children less than two years with acute viral bronchiolitis. Studies were included if the trials presented data for at least one quantitative outcome of interest.

We selected primary outcomes a priori, based on clinical relevance: rate of admission by days one and seven of presentation for outpatients, and length of stay (LOS) for inpatients. Secondary outcomes included clinical severity scores, pulmonary function, symptoms, quality of life and adverse events.

Data collection and analysis

Two review authors independently screened the searches, applied inclusion criteria, assessed risk of bias and graded the evidence. We conducted separate analyses for different comparison groups (placebo, non-epinephrine bronchodilators, glucocorticoids) and for clinical setting (inpatient, outpatient).

Main results

We included 19 studies (2256 participants). Epinephrine versus placebo among outpatients showed a significant reduction in admissions at Day 1 (risk ratio (RR) 0.67; 95% confidence interval (CI) 0.50 to 0.89) but not at Day 7 post-emergency department visit. There was no difference in LOS for inpatients. Epinephrine versus salbutamol showed no differences among outpatients for admissions at Day 1 or 7. Inpatients receiving epinephrine had a significantly shorter LOS compared to salbutamol (mean difference -0.28; 95% CI -0.46 to -0.09). One large RCT showed a significantly shorter admission rate at Day 7 for epinephrine and steroid combined versus placebo (RR 0.65; 95% CI 0.44 to 0.95). There were no important differences in adverse events.

Authors' conclusions

This review demonstrates the superiority of epinephrine compared to placebo for short-term outcomes for outpatients, particularly in the first 24 hours of care. Exploratory evidence from a single study suggests benefits of epinephrine and steroid combined for later time points. More research is required to confirm the benefits of combined epinephrine and steroids among outpatients. There is no evidence of effectiveness for repeated dose or prolonged use of epinephrine or epinephrine and dexamethasone combined among inpatients.

PLAIN LANGUAGE SUMMARY

Epinephrine for acute viral bronchiolitis in children less than two years of age

Bronchiolitis is the most common acute infection of the airways and lungs during the first years of life. It is caused by viruses, the most common being respiratory syncytial virus. The illness starts similarly to a cold, with symptoms such as a runny nose, mild fever and cough. It later leads to fast, troubled and often noisy breathing (for example, wheezing). While the disease is often mild for most healthy babies and young children, it is a major cause of clinical illness and financial health burden worldwide. Hospitalizations have risen in high-income countries, there is substantial healthcare use, and bronchiolitis may be linked with preschool wheezing disorders and the child later developing asthma.

There is variation in how physicians manage bronchiolitis, reflecting the absence of clear scientific evidence for any treatment approach. Bronchodilators are drugs that are often used for asthma attacks to relax the muscles in the airways so that breathing is easier. Epinephrine is one type of bronchodilator. With several new trials having been published since the 2004 publication of this Cochrane Review it is important to incorporate the most recent evidence.

Our systematic review found 19 studies involving 2256 children that use epinephrine for the treatment of bronchiolitis in acute care settings. When comparing epinephrine with placebo, no differences were found for length of hospital stay but there is some indication that epinephrine is effective for reducing hospital admissions. Exploratory results from one large, high-quality trial suggest that combined treatment with systemic glucocorticoids (dexamethasone) and epinephrine may significantly reduce admissions. There is insufficient evidence to support the use of epinephrine for the treatment of bronchiolitis among children admitted to the hospital.

The evidence shows no important differences in adverse effects with epinephrine over the short-term with long-term safety not being assessed. Some limitations of this review include the quality of the included studies and inconsistent timing of measurement across studies which limited the number of children included in some meta-analyses. Further research is needed to confirm the efficacy, applicability and long-term safety of epinephrine as a treatment for bronchiolitis.

In summary, our systematic review provides evidence that epinephrine is more effective than placebo for bronchiolitis in outpatients. Recent research suggests combined epinephrine and steroids may be effective for outpatients. There is no evidence to support the use of epinephrine for inpatients.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Epinephrine versus placebo for acute viral bronchiolitis

Patient or population: patients with acute viral bronchiolitis
Settings: outpatients and inpatients
Intervention: epinephrine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Epinephrine versus placebo				
Admissions at enrollment or <24 hours (outpatients only)	Study population		RR 0.67 (0.5 to 0.89)	995 (5 studies)	⊕⊕⊕◯ moderate	
	185 per 1000	124 per 1000 (92 to 165)				
	Medium-risk population					
	190 per 1000	127 per 1000 (95 to 169)				
Admissions overall up to 7 days (outpatients only)	Study population		RR 0.81 (0.63 to 1.03)	875 (3 studies)	⊕⊕◯◯ low	
	251 per 1000	203 per 1000 (158 to 259)				
	Medium-risk population					
	255 per 1000	207 per 1000 (161 to 263)				

Length of stay (inpatients only)		The mean length of stay (inpatients only) in the intervention groups was **0.35 lower** (0.87 lower to 0.17 higher)	292 (2 studies)	⊕⊕⊕○ **moderate**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

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

BACKGROUND

Description of the condition

Bronchiolitis is an acute lower respiratory tract infection (LRTI) that affects children less than two years of age (Klassen 1997). It is characterized by fever, coryza, cough, expiratory wheezing, apnea in the very young, and respiratory distress (i.e. increased respiratory rate, chest wall indrawing, thoracic-abdominal asynchrony) (Klassen 1997). Bronchiolitis is most commonly associated with respiratory syncytial virus (RSV) (Kini 2001; Shay 2001; Smyth 2006).

Bronchiolitis is the most frequent acute LRTI in infants and is one of the main reasons that children younger than one year require hospitalization (Everard 1995; Klassen 1997; Wright 1989). It is estimated that 11% to 12% of infants are afflicted (Flores 1997). Approximately 3% of infants are hospitalized with bronchiolitis and rates of hospitalization have been increasing over time (Langley 2003; Shay 1999; Van Woensel 2002). The prevalence and morbidity associated with bronchiolitis mean that the economic burden placed on health services is substantial (Hall 1999; Paramore 2004; Pelletier 2006). According to a recent review the global incidence of RSV-associated bronchiolitis is a major cause of hospital admissions and mortality (Nair 2010).

Description of the intervention

Despite the frequency of the condition, there remains considerable controversy regarding its management (Mallory 2003; Panitch 2003). This has resulted in substantial practice variation both within centres and across geographic regions, reflecting the absence of clear evidence for any single treatment approach. In part, this controversy stems from the fact that superficially, infants with acute viral bronchiolitis resemble older children with asthma. For example, both groups commonly present with the symptoms of a recent viral illness, respiratory distress and wheezing. Systematic reviews have assessed the use of bronchodilators, β_2 agonists, epinephrine, glucocorticoids, hypertonic saline, antibiotics, surfactant, ribavirin and chest physiotherapy (Bialy 2006). All of these reviews, with the exception of treatment with nebulized hypertonic saline, have failed to show consistent and relevant effects (Zhang 2008). Nebulized hypertonic saline may significantly improve some outcomes, but replication of this effect in large randomized controlled trials (RCTs) is needed (Zhang 2008). While bronchodilators have proven to be of substantive benefit in children with asthma, their effects on infants with bronchiolitis have been less dramatic. Pathophysiologically, we know that bronchiolitis and asthma are, in fact, distinct conditions. There has also been a lack of consistency in determining relevant outcomes to evaluate the effectiveness of interventions and the outcomes used may not be clinically meaningful. For example, a 2% to 3% difference in hemoglobin oxygen saturation has been used as a primary outcome measure; though the relevance of this outcome is questionable.

How the intervention might work

Historically, children were offered good supportive care including fluids and oxygen (Panitch 2003). Clinical trials have provided conflicting evidence regarding the benefit of pharmacological interventions. Much of the debate involves the role of bronchodilators (Everard 1995; Mallory 2003). The use of bronchodilators, though costly and widespread, is not without harm, therefore effectiveness requires rigorous review (Kini 2001). A systematic review by Kellner and colleagues examined the effectiveness of bronchodilators and showed modest short-term improvement in patients with mild to moderate bronchiolitis (Kellner 1996). The review grouped all bronchodilators and compared these to placebo; they did not examine the relative efficacy of different bronchodilators. In a 2010 Cochrane systematic review, Gadomski et al examined the effectiveness of all bronchodilators (other than epinephrine) and found that they did not improve oxygen saturation, reduce hospital admission after outpatient treatment, shorten the duration of hospitalization or reduce the time to resolution of illness at home (Gadomski 2010). Although there were small improvements in clinical scores for outpatients, the authors cautioned that this must be weighed against the costs and adverse effects of bronchodilators (Gadomski 2010).

Epinephrine has a theoretical benefit because it contains alpha adrenergic properties in addition to the beta adrenergic effect. Wohl and Chernick suggested that bronchiolitis may benefit from the vasoconstricting effects and reduction of edema offered by the alpha adrenergic effect (Wohl 1978). The mechanisms of different bronchodilators vary, therefore we chose to specifically investigate the efficacy of epinephrine in the treatment of bronchiolitis.

Why it is important to do this review

There continues to be substantial variation in the management of bronchiolitis worldwide (Babl 2008; Barben 2008; Christakis 2005; Plint 2004), likely stemming from lack of evidence for any single approach. Several new trials have been published since the 2004 publication of this Cochrane Review (Hartling 2004). Of particular interest is a multi-centre trial involving 800 children in Canada, examining epinephrine and dexamethasone, alone or combined utilizing a factorial design (Plint 2009). This pivotal trial adds substantially to the evidence and provides a strong signal for an update of the earlier review (Shojania 2007). This trial also raises new questions about the benefit of combining epinephrine and steroids, therefore it is critical to incorporate these results along with other recently published trials to determine whether this new evidence can inform practice.

OBJECTIVES

The objective of this review was to compare the effects of epinephrine (any route of administration) versus placebo or other active interventions (i.e. other bronchodilators, glucocorticoids) in infants less than two years of age with acute viral bronchiolitis. For outpatients the effects of epinephrine was measured based on the rate of admission on Day 1 and 7 and for inpatients by length of stay.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) evaluating the efficacy of epinephrine versus placebo or another active intervention in the treatment of bronchiolitis were considered for inclusion. We considered all studies regardless of language or publication status.

Types of participants

All studies of infants and young children up to 24 months of age were considered for inclusion. We defined bronchiolitis as a first episode of wheezing, respiratory distress and clinical evidence of respiratory infection (for example, cough, coryza or fever). We included studies of inpatients or outpatients (ambulatory care or emergency department, or both). We excluded studies in the intensive care setting or with intubated or ventilated participants (or both). Patients admitted to the intensive care unit with bronchiolitis were not included as they are a distinct subset of patients which require specific focus in terms of disease description, interventions and outcomes.

Types of interventions

We considered studies for inclusion if participants were randomized between receiving epinephrine or receiving placebo or another active intervention. We made no restrictions for dose, duration or routes of administration. Epinephrine could be administered alone or combined with co-interventions (for example, glucocorticoids), with or without a fixed study protocol.

Types of outcome measures

We selected primary outcomes a priori based on clinical relevance and patient importance; secondary outcomes assessed other relevant health domains (clinical severity, pulmonary function, healthcare use, patient/parent-reported symptoms and status, and harms). We included studies if they reported numeric data on at least one primary or secondary outcome assessed within the first month after acute bronchiolitis. We considered different timings of outcome assessment, based on a priori relevance and available data.

Primary outcomes

1. Rate of admission by Day 1 and Day 7 for outpatients.
2. Length of stay for inpatients.

Secondary outcomes

1. Change in clinical score, oxygen saturation (oximetry), respiratory rate and heart rate.
2. Hospital re-admissions for inpatients.
3. Return healthcare visits.
4. Length of stay for outpatients.
5. Pulmonary function tests.
6. Duration of symptoms and quality of life.
7. Short and long-term adverse events.

We selected the following time points and intervals for secondary outcomes: clinical scores, oxygen saturation, respiratory and heart rate, 60 and 120 minutes, 3 to 6, 6 to 12, 12 to 24, 24 to 72 hours, and 3 to 10 days; re-admissions and return visits, Days 1 to 10 and Days 11 to 30. When available we used these time points for both inpatient and outpatient outcomes. However, the majority of outpatient data are reported for the earlier time points. We also considered data on all other outcomes when reported.

Search methods for identification of studies

We designed an inclusive search strategy as part of a comprehensive systematic review evaluating the effect of three types of interventions in bronchiolitis (steroids, epinephrine and other bronchodilators).

Electronic searches

We searched CENTRAL (2010, Issue 3) which contains the Acute Respiratory Infections Group's Specialized Register, MEDLINE Ovid Version (1950 to September Week 2, 2010), EMBASE Ovid Version (1980 to September 2010), Scopus® (1823 to September 2010), PubMed (March 2010), LILACS (1985 to September 2010) and IRAN MedEx (1998 to September 2010). We examined the reference lists of all selected articles for relevant studies. We developed the searches by scanning search strategies of relevant systematic reviews and examining index terms of potentially relevant studies. We applied a validated RCT filter and modified this for each database (Glanville 2006). We applied no year or language restrictions. Full search strategies can be found in Appendix 1 to Appendix 7.

To identify unpublished studies and those in progress we searched the following clinical trials registers on 3 March and 26 November 2009:

1. ClinicalTrials.gov; Current Controlled Trials;
2. ClinicalStudyResults.org;
3. Australian New Zealand Clinical Trials Registry;
4. IFPMA Clinical Trials Portal;
5. UMIN Clinical Trials Registry;
6. rct zoeken (http://www.trialregister.nl/trialreg/index.asp) - Netherlands Trial Register - Dutch Cochrane Centre; and
7. ICTRP Search Portal - World Health Organization.

Searching other resources

We searched the following conference proceedings: Canadian Pediatric Society, Pediatric Academic Societies and Society for Academic Emergency Medicine (2004 to 2009); European Respiratory Society (2003 to 2009); American Thoracic Society and European Society for Pediatric Research (2006 to 2009).

We identified additional published, unpublished and ongoing studies by handsearching reference lists of relevant reviews and included or excluded studies, as well as contacting topic specialists.

Data collection and analysis

Selection of studies

Four review authors (LB, LH, NH, RF) screened the titles, keywords and abstracts (when available) to determine if an article met the inclusion criteria. Two review authors independently screened each article and rated articles as 'include', 'exclude' or 'unclear'. One or more of the review authors retrieved the full text of all articles classified as 'include' or 'unclear' for detailed review. Two review authors (LB, LH, NH or RF) independently assessed each study using a standard inclusion/exclusion form. Disagreements were resolved by consensus or third-party adjudication.

Data extraction and management

One review author (LB, LH, HM, AM or RF) extracted data from English trials and a second review author (LB, LH, AM or RF) independently verified the data. One review author (OT) extracted data from Turkish (OT) and one review author (MK) extracted data from Farsi reports. We used a standard form that described the following: characteristics of the study (design, method of randomization, withdrawals/dropouts); participants (age, gender); intervention (type, dose, route of administration, timing and duration of therapy, co-interventions); control (agent and dose); outcomes (types of outcome measures, timing of outcomes, adverse effects); whether or not the study used an intention-to-treat protocol; funding source; and results.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' tool (Higgins 2011) to assess for potential for bias in the included studies. We pilot tested the 'Risk of bias' tool on a sample of five studies. We used results from this pilot to adapt decision rules based on the *Cochrane Handbook for Systematic Reviews of Interventions* guidance regarding application of the tool (rules available from review authors). Two review authors (LH, LB or RF) independently evaluated the risk of bias of included trials. Differences were resolved by consensus reached after discussion. Only one review author assessed studies published in Turkish (OT) and Farsi (MK).

As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), we grouped outcomes into classes with similar risks of bias for the assessment of blinding and incomplete outcome data. The classes and associated outcomes included: 1) administrative - rate of admission, length of hospitalization, hospital re-admission, return to any healthcare facility; 2) clinical scores/parameters - change in clinical scores, oxygen saturation, respiratory rate, heart rate; 3) patient-reported quality of life measures, assessment of well-being; 4) pulmonary function - forced expiratory volume, other pulmonary function tests; and 5) other - adequate fluid intake, duration of oxygen therapy, adverse events, etc.

For the selective outcome reporting domain, we used the search strategies described to identify trial protocols or trial registers. When these were available, we compared the stated pre-specified outcomes with the paper reported outcomes. If not available, we compared outcomes reported in the methods and results sections of the reports.

The overall (study level) assessment of risk of bias for each study was based on recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If one or more domains were assessed as having a high risk of bias, we rated the overall score as high. Only if all domains were rated as having a low risk of bias was the overall score considered low. We rated all other studies as unclear for overall risk of bias.

We chose a priori to explore the impact of summarized risk of bias at a study level by performing sensitivity analyses of the primary outcomes restricted to studies with a low overall risk of bias, whenever feasible.

Grading the body of evidence

We used the Evidence-Based Practice Centers GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach, based on the standard GRADE system, to assess the domain-specific and overall strength of evidence (Guyatt 2008; Owens 2009). We evaluated the outcomes which were judged to be most relevant: length of hospital stay (LOS) or admission rate; clinical severity scores; and adverse events. We examined the following four domains: risk of bias, consistency, directness and precision.

We graded the overall strength of evidence as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research may change our confidence in the estimate of effect and may change the estimate), low (further research is likely to change the confidence in the estimate of effect and is likely to change the estimate), or insufficient (evidence either is unavailable or does not permit estimation of an effect).
Two review authors (LH, RF) independently graded the body of evidence using GRADE guidance and decision rules adapted to the clinical and research context. For the risk of bias domain, we considered all evidence as high or medium, as we only included RCTs. For the precision domain, there is limited evidence of the minimal clinically important difference for all outcomes studied. We considered a priori the following clinical thresholds of significance, based on expert opinion: a relative reduction of 20% or more for dichotomous outcomes, and a reduction in LOS of 0.5 days or more. We used GRADE guidelines for the remaining domains (GRADEpro 2009). All decisions were made explicitly and we calculated inter-rater agreement (available from authors). Two review authors (LH, RF) resolved discrepancies through consensus.

Measures of treatment effect

We pooled dichotomous variables using risk ratios (RR). We analyzed measurement scale outcomes as continuous variables. For continuous variables measured on the same scale (for example, respiratory rate), we calculated mean differences for individual studies and calculated mean differences (MD) for the pooled estimates. For continuous variables measured on different scales (for example, different clinical scores) we calculated mean differences for separate studies and calculated standardized mean differences (SMD) for the pooled estimates. We used changes from baseline for all continuous variables when available, otherwise we used unadjusted final scores. We conducted separate analyses for the different types of control groups (i.e. placebo, non-epinephrine bronchodilators, glucocorticoids) and clinical setting (i.e. inpatient or outpatient).

Unit of analysis issues

Some studies with more than two intervention groups were eligible to contribute with several comparisons between arms to a single pair-wise meta-analysis. We included data from these arms with no transformation when the comparisons were independent, i.e. with no intervention group in common (for example, a trial with four independent arms (1) 'epinephrine + placebo', (2) 'epinephrine + dexamethasone', (3) 'placebo + dexamethasone' and (4) 'placebo + placebo' contributed both comparisons 1 versus 4 and 2 versus 3 to the overall epinephrine versus placebo comparison). These arms are shown separately in each forest plot, with the same study identification. If needed and feasible, we pooled the active groups to avoid double-counting of the comparator group when there was more than one active group (for example, when there were two steroid groups versus placebo). No treatment groups were included twice in the same meta-analysis.
We extracted and included both 'at the margins' and 'inside the table' data for factorial trials whenever reported. These are shown separately in each forest plot with the same study identification (see Data and analyses). There were no further unit of analysis issues.

Dealing with missing data

We extracted information on incomplete outcome data and we identified trials that performed adequate intention-to-treat analysis. We only included data for participants whose results were reported; we did not impute missing data for drop-outs (available case analysis). We addressed the potential impact of the missing data in the assessment of risk of bias (incomplete outcome data domain).
When means were not given they were estimated from graphs or imputed from medians if possible. Otherwise, the study would be excluded from the meta-analysis. Standard deviations, when not given, were computed from available data (i.e. standard errors, confidence intervals or P values). Failing this we estimated them from ranges and inter-quartile ranges, or imputed them from a similar study. To estimate standard deviations of change from baseline values, we estimated correlation at 0.5 when it was not available.
When data were unavailable for one of the predefined timings of outcome measurement, we used the time point closest to the planned timing, or any time point in the range. If there was more than one time point, we chose the one with the largest magnitude of change. We did not contact authors of the individual trials to obtain additional data.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic. A value greater than 50% was considered to be substantial heterogeneity (Higgins 2002; Higgins 2003).

Assessment of reporting biases

We did not assess publication bias due to the small number of trials in each outcome, comparison and clinical setting group included in the review.

Data synthesis

We meta-analyzed quantitative results within the different comparisons when studies were consistent on clinical grounds and had available outcome data. There were no restrictions based on risk of bias. We performed meta-analyses separately for studies involving inpatients and outpatients.

We combined results using random-effects models regardless of heterogeneity, due to expected differences in interventions, outcomes and measurement instruments (for example, clinical scores measuring different clinical features or weighting these differently). We also calculated fixed-effects in a sensitivity analysis. We carried out meta-analyses of dichotomous outcomes using Mantel-Haenszel methods (Borenstein 2009). We used inverse variance methods for continuous outcomes and measurement scales. All results are reported with 95% CI and we used Review Manager (RevMan 2011).

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting subgroup analyses based on the protocolized use of steroids (use of steroids was part of, and defined by, the study protocol versus steroid given at the discretion of the attending physician). This subgroup was decided upon based on a recent trial suggesting a possible positive interaction ('synergism') between steroids and epinephrine. Our aim was to subgroup trials in which steroid use was fixed by protocol in all participants (epinephrine + fixed steroid versus placebo + fixed steroid), from those in which steroid use was at the discretion of the physician or not allowed ('pure' epinephrine versus placebo). Differences between these subgroups could be attributed to positive or negative (i.e. 'synergistic' or 'antagonistic') interactions between treatments when combined. We planned to perform subgroup analyses only on the review's primary outcomes.

Sensitivity analysis

We decided a priori to perform sensitivity analyses on primary outcome results of trials with overall low risk of bias. We also checked for differences in the direction and magnitude of primary outcome results when using fixed-effect models, as well as using pooled data from all factorial trial arms ('at the margins data').

RESULTS

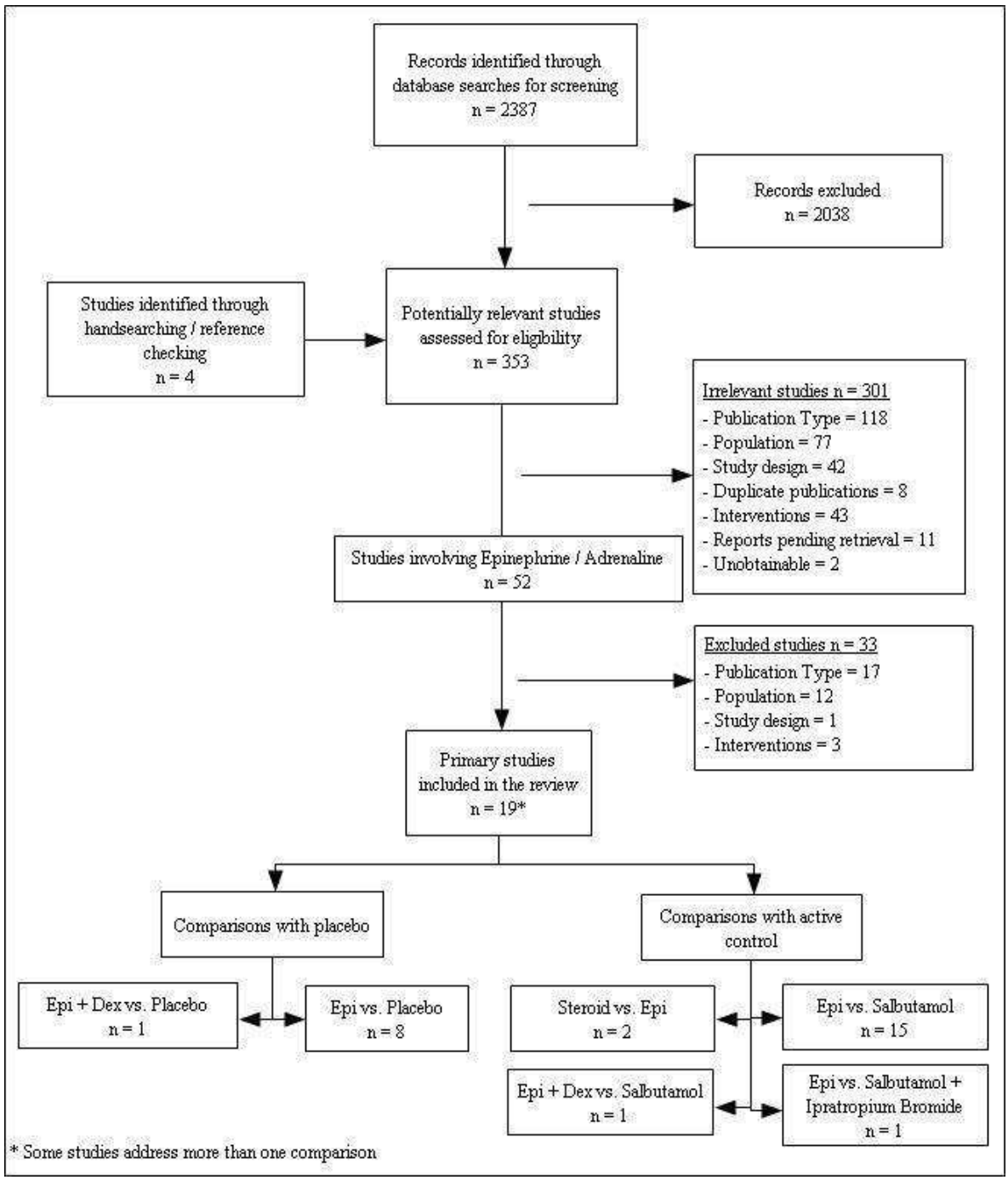
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The search strategy identified 2387 citations from electronic databases (Figure 1). After screening titles and abstracts, 349 studies were assessed to be potentially relevant. Four additional studies were identified for further examination by contact with experts or handsearching the reference lists from previous systematic reviews.

Figure 1. Flow of citations through the search and screening procedures, studies included in the review, and comparisons addressed



Included studies

We reviewed the full text of 353 reports using the pre-defined inclusion criteria resulting in 301 irrelevant studies and 33 excluded studies in this review. A total of 19 reports of RCTs are included in this review (Figure 1).

The 19 included studies ranged in sample size from 27 to 800 and included a total of 2256 participants. For detailed information on each study refer to the Characteristics of included studies tables. Nine studies involved 773 inpatients (Abu-Shukair 2001; Abul-Ainine 2002; Bertrand 2001; Bilan 2007; John 2006; Kadir 2009; Patel 2002a; Sanchez 1993; Wainwright 2003) and 10 involved 1483 outpatients (Anil 2010a; Barlas 1998a; Beck 2007; Khashabi 2005a; Kuyucu 2004a; Menon 1995; Mull 2004; Okutan 1998a; Plint 2009a; Ralston 2005a). Ten studies only included children at one year of age or younger and three studies described atopic status of participants (Anil 2010a; Beck 2007; Plint 2009a). In all 19 studies epinephrine was administered via nebulization. Five studies used racemic epinephrine (Barlas 1998a; Mull 2004; Patel 2002a; Ralston 2005a; Sanchez 1993), 12 used L-epinephrine (Abul-Ainine 2002; Anil 2010a; Beck 2007; Bertrand 2001; John 2006; Kadir 2009; Khashabi 2005a; Kuyucu 2004a; Menon 1995; Okutan 1998a; Plint 2009a; Wainwright 2003), and for two studies information on the type of epinephrine was not available (Abu-Shukair 2001; Bilan 2007). Most trials reported administering epinephrine in multiple doses (n = 12) with all others being delivered as a single dose (n = seven). Placebo was compared to an active treatment in nine studies with eight studies reporting the use of saline (Abul-Ainine 2002; Anil 2010a; Khashabi 2005a; Okutan 1998a; Patel 2002a; Plint 2009a; Ralston 2005a; Wainwright 2003) and one study did not indicate the type of placebo used (Barlas 1998a).

A wide range of outcomes was reported. The primary outcomes varied across studies: clinical score (Anil 2010a; Barlas 1998a; Beck 2007; Bertrand 2001; Kadir 2009; Khashabi 2005a; Okutan 1998a; Sanchez 1993); length of stay (Bilan 2007; Patel 2002a; Wainwright 2003); oxygen saturation (Menon 1995); admission rates (Plint 2009a); admission rates for those on home oxygen therapy (Ralston 2005a); heart rate and/or respiratory rate (Abu-Shukair 2001; Abul-Ainine 2002; John 2006); clinical score and respiratory rate (Mull 2004); and clinical score, respiratory rate and heart rate (Kuyucu 2004a). Secondary outcomes included: clinical score; oxygen saturation; respiratory rate; heart rate; blood pressure; activity status; time in oxygen; need for supplemental oxygen; adequate fluid intake; duration of hospitalization; rate of hospitalization; temperature; pulmonary functions; duration of symptoms; return to healthcare facility; and 'improvement' as defined by the individual trials. Most of the outcomes reported were short-term (i.e. within minutes or hours of treatment) with few studies evaluating longer-term outcomes (for example, participants' progression over several days). Due to inconsistency or lack of reporting, the following pre-defined outcomes were not meta-analyzed: quality of life (none reported), pulmonary functions (Sanchez 1993) and participant/provider report of symptoms (Barlas 1998a; Bilan 2007; Khashabi 2005a; Plint 2009a).

The majority of studies assessing clinical score used the Respiratory Distress Assessment Instrument (RDAI) (Abu-Shukair 2001; Abul-Ainine 2002; Khashabi 2005a; Kuyucu 2004a; Menon 1995; Mull 2004; Plint 2009a) with other assessments done through the modification of existing clinical scores (Barlas 1998a; Beck 2007; Bertrand 2001; Okutan 1998a; Sanchez 1993) and respiratory effort score (Wainwright 2003).

The majority (n = 16) of studies were published in English, with two of the studies published in Turkish (Barlas 1998a; Okutan 1998a) and one in Farsi (Bilan 2007). Most studies were conducted in high-income countries: Australia (Wainwright 2003); Canada (Menon 1995; Patel 2002a; Plint 2009a; Sanchez 1993); Chile (Bertrand 2001); England (Abul-Ainine 2002); Israel (Beck 2007); Turkey (Anil 2010a; Barlas 1998a; Kuyucu 2004a; Okutan 1998a) and the United States (Mull 2004; Ralston 2005a). Five of the studies were conducted in low-income countries, including Jordan (Abu-Shukair 2001); Iran (Bilan 2007; Khashabi 2005a); India (John 2006); and Bangladesh (Kadir 2009).

Excluded studies

For this update we revised the inclusion criteria to include only studies that defined bronchiolitis as the first episode of wheezing. As a result of this new criterion five studies included in the original review have been excluded from this update (Hariprakash 2003; Kristjansson 1993; Lowell 1987; Ray 2002; Reijonen 1995). For detailed information on reasons for exclusion refer to the Characteristics of excluded studies table.

Risk of bias in included studies

Domain-specific and overall risk of bias assessments are detailed in the Characteristics of included studies table and summarized by outcome and study in Figure 2 and Figure 3, respectively. Of the 19 included studies 42% (n = eight) had an overall risk of bias rating of 'Unclear' (Abu-Shukair 2001; Abul-Ainine 2002; Anil 2010a; Barlas 1998a; Bilan 2007; John 2006; Khashabi 2005a; Okutan 1998a), 32% (n = six) a rating of 'Low' (Beck 2007; Menon 1995; Mull 2004; Patel 2002a; Plint 2009a; Ralston 2005a) and 26% (n = five) a rating of 'High' (Bertrand 2001; Kadir 2009; Kuyucu 2004a; Sanchez 1993; Wainwright 2003).

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

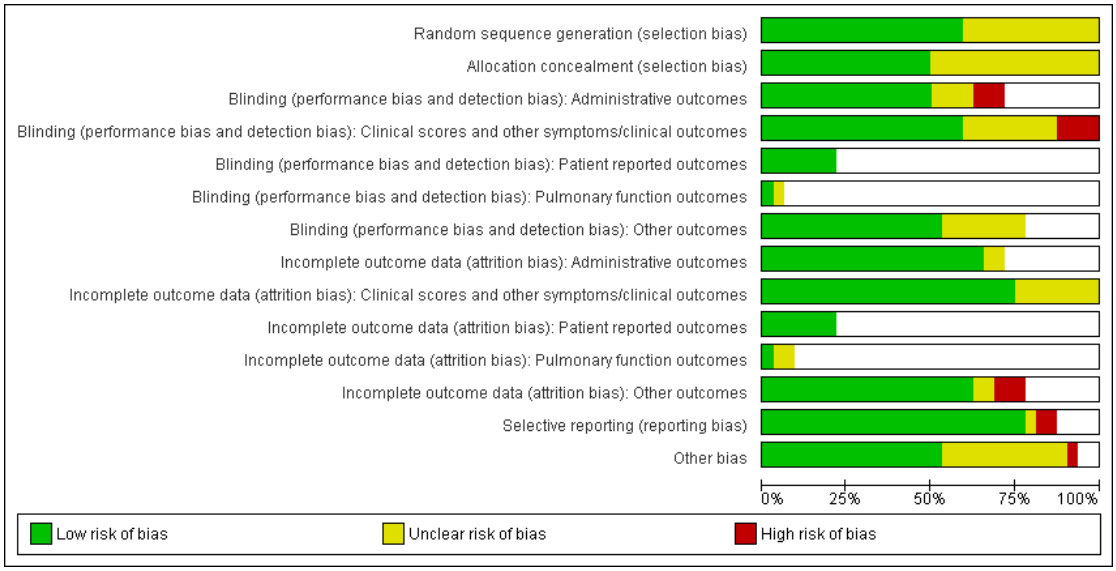
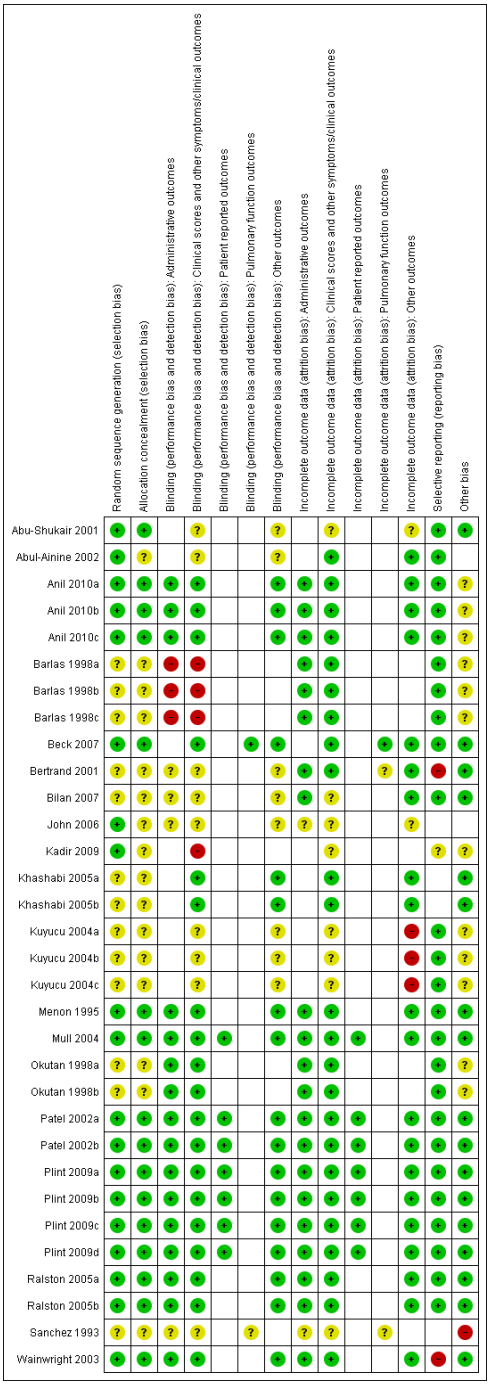


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Randomization sequence

Twelve studies reported an adequate method of generating the randomization sequence (Abu-Shukair 2001; Abul-Ainine 2002; Anil 2010a; Beck 2007; John 2006; Kadir 2009; Menon 1995; Mull 2004; Patel 2002a; Plint 2009a; Ralston 2005a; Wainwright 2003).

Allocation

Nine studies adequately concealed the randomization sequence from the investigators (Abu-Shukair 2001; Anil 2010a; Beck 2007; Menon 1995; Mull 2004; Patel 2002a; Plint 2009a; Ralston 2005a; Wainwright 2003).

Blinding

All 19 of the trials assessed either an administrative outcome or clinical severity parameter; 12 of these trials adequately blinded participants and investigators.

Incomplete outcome data

Incomplete outcome reporting was adequately addressed in 11 of 13 for the review primary outcomes; 13 of 18 for clinical severity score.

Selective reporting

Thirteen studies adequately reported outcomes in methods/protocol and results (Abu-Shukair 2001; Abul-Ainine 2002; Anil 2010a; Barlas 1998a; Beck 2007; Bilan 2007; Kuyucu 2004a; Menon 1995; Mull 2004; Okutan 1998a; Patel 2002a; Plint 2009a; Ralston 2005a), four studies had unclear reporting (John 2006; Kadir 2009; Khashabi 2005a; Sanchez 1993), and two studies did not adequately report all outcomes in the methods/protocol and results (Bertrand 2001; Wainwright 2003). We identified three studies with protocols (Beck 2007; Plint 2009a; Wainwright 2003) that were used to assist in the assessment of selective outcome reporting.

Other potential sources of bias

The studies were assessed for bias with respect to potential for inappropriate influence of funder, important imbalances in baseline characteristics, and use of a cross-over design. Twelve studies were at low risk of bias for other sources of bias (Abu-Shukair 2001; Abul-Ainine 2002; Beck 2007; Bertrand 2001; Bilan 2007; Khashabi 2005a; Menon 1995; Mull 2004; Patel 2002a; Plint 2009a; Ralston 2005a; Wainwright 2003), six studies were unclear (Anil 2010a; Barlas 1998a; John 2006; Kadir 2009; Kuyucu 2004a; Okutan 1998a), and one study was inadequate due to the utilization of a cross-over study design (Sanchez 1993).

Effects of interventions

See: **Summary of findings for the main comparison** Epinephrine versus placebo for acute viral bronchiolitis; **Summary of findings 2** Epinephrine versus salbutamol/albuterol for acute viral bronchiolitis; **Summary of findings 3** Epinephrine and steroid versus placebo for acute viral bronchiolitis; **Summary of findings 4** Epinephrine versus steroid for acute viral bronchiolitis

We stratified results by comparison (i.e. epinephrine versus placebo, epinephrine versus salbutamol, epinephrine versus steroid, epinephrine and steroid versus placebo, epinephrine and steroid versus salbutamol, epinephrine versus salbutamol and ipratropium bromide) and by setting (i.e. inpatient versus outpatient). Supplementary data tables are available for strength of evidence (Table 1) and adverse events (Table 2). Summary of findings are provided for the following comparisons: epinephrine versus placebo (Summary of findings for the main comparison), epinephrine versus salbutamol (Summary of findings 2), epinephrine and steroid versus placebo (Summary of findings 3) and epinephrine versus steroid (Summary of findings 4).

Epinephrine versus placebo

Nine studies compared epinephrine and placebo; these comparisons involved a total of 1354 patients (677 epinephrine; 677 placebo). The studies were published between 1995 and 2010 and were conducted in Canada (n = two), the US (n = one), Australia (n = one), Turkey (n = three), England (n = one) and Iran (n = one). Three studies involved inpatients (n = 333) and six studies involved outpatients (n = 1021). Three studies used racemic epinephrine while six studies used L-epinephrine. Epinephrine was administered by nebulizer in all studies.

The overall risk of bias was low for three studies, unclear for five studies and high for one study. The latter study was assessed as high risk overall due to potential selective outcome reporting: a number of outcomes were reported in the results but not mentioned in the methods section of the report. Studies were rated unclear overall primarily due to unclear reporting with respect to sequence generation and allocation concealment.

Inpatients (three studies)

Our primary outcome (length of stay: LOS) was reported and declared as the primary outcome in two studies. The primary outcomes for the third study were respiratory rate and heart rate. There was no statistically significant difference in LOS (mean dif-

ference (MD) -0.35; 95% confidence interval (CI) -0.87 to 0.17; two studies, 292 participants) (Analysis 1.3).

There were also no differences in clinical score, oxygen saturation, respiratory rate at any of the time points measured. The only significant difference in terms of physiological measures was for heart rate at 60 minutes post-treatment, which favored placebo (MD 13.06; 95% CI 1.19 to 24.92; two studies, 225 participants) (Analysis 1.11).

There were no significant differences in other administrative outcomes, including hospital readmission after discharge and return visits to the emergency department (ED) or any healthcare provider.

One study reported on adverse events and found no occurrences of vomiting, pallor, tremor or arrhythmias.

There was no change in the results for LOS and clinical scores when only low risk of bias studies were included.

The strength of evidence was moderate for inpatient studies, i.e. there was moderate evidence suggesting no difference in length of stay or clinical score at 60 minutes.

Outpatients (six studies)

Our primary outcome for outpatients (admission rate) was assessed in five studies and was declared as the primary outcome in two studies. The timing of assessment differed: Ralston 2005a measured admission within 24 hours of study enrolment; Plint 2009a reported admission rates up to seven days and by Day 22 after enrolment; timing was not specified by Barlas et al. The primary outcome was clinical score in two studies and not specified in two studies. Physiological measures were commonly assessed; the timing of assessments as well as other outcomes assessed in each study are detailed in the Characteristics of included studies table.

The primary outcome of admission rate at Day 1 was significant in favor of epinephrine (RR 0.67; 95% CI 0.50 to 0.89; five studies; n = 995) (Analysis 1.1). However, admission rate by Day 7 was not significantly different between groups. Differences in results for admission at Day 1 were seen for subgroups that used steroids (RR 0.74; 95% CI 0.45 to 1.23; one study, 400 participants) (Analysis 1.15) versus those that did not (RR 0.62; 95% CI 0.40 to 0.94; five studies, 595 participants) (Analysis 1.15). However, the CIs overlapped. When analyses for admission at Day 1 were restricted to trials with low risk of bias, results were no longer statistically significant (RR 0.77; 95% CI 0.56 to 1.07; three studies, 842 participants) (Analysis 1.16). For admission up to Day 7, results were significant when steroids were used (RR 0.67; 95% CI 0.45 to 0.98; one study; 400 participants) versus no steroid use (RR 0.90; 95% CI 0.64 to 1.26; one study; 400 participants) (Analysis 1.17). While the point estimates differed substantially between these subgroups, the Cls overlapped.

Results favored epinephrine in terms of change in clinical score at 60 and 120 minutes (standardized mean difference (SMD) -0.40; 95% CI -0.58 to -0.23; five studies, n = 975; and SMD -0.73; 95% CI -1.13 to -0.33; two studies, n = 105, respectively) (Analysis 1.4). There was no significant difference between groups in oxygen saturation at 60 and 120 minutes or respiratory rate at 60 minutes. Results favored placebo in terms of change in heart rate at 60 minutes, although there was no difference between groups at 120 minutes post-treatment. There was no difference in return visits (RR 0.98; 95% CI 0.81 to 1.19; two studies, n = 800) (Analysis 1.13).

Three studies reported on adverse events (n = 944). One study observed pallor (11% epinephrine, 8% placebo), vomiting (2% epinephrine, 1.5% placebo), tremors (2% epinephrine, 1% placebo) and hypertension (0.5% epinephrine, 0% placebo). However, the occurrence was not significantly different between groups. The other study found no occurrences of tachycardia, withdrawal due to worsening clinical status, or discontinuation of study medications due to adverse events.

The strength of evidence favoring epinephrine was rated as moderate for admissions Day 1 and low for admissions Day 7. In terms of clinical score, the strength of evidence favoring epinephrine was considered high at 60 minutes and low at 120 minutes. Details for each strength of evidence domain are detailed in Table 1.

Epinephrine versus salbutamol

Fifteen studies compared epinephrine versus salbutamol/albuterol; these comparisons involved 957 randomized participants (480 epinephrine; 477 salbutamol). The studies were published between 1993 and 2010 and were conducted in Canada (n = three), Turkey (n = four), the USA (n = two), Iran (n = two), Jordan (n = one), India (n = one), Israel (n = one) and Chile (n = two). Six studies involved inpatients (n = 430) and nine studies involved outpatients (n = 527). Four studies used racemic epinephrine while eight studies used L-epinephrine and in two studies the type of epinephrine was unknown. Epinephrine was administered by nebulizer in all studies.

'Risk of bias' was low in four studies, unclear in seven studies and high in four studies. Studies were assessed at high risk of bias due to selective outcome reporting, incomplete outcome reporting, cross-over study design and limited baseline characteristics. Many studies were unclear in their reporting of sequence generation (n = seven), allocation concealment (n = eight), and blinding (n = six).

Inpatients (six studies)

Our primary outcome for inpatients (length of stay) was reported in four studies and declared as the primary outcome in one study. The primary outcomes for one study were respiratory rate, heart rate and clinical score. The remaining studies (n = four) did not specify a primary outcome. The other outcomes assessed are detailed the Characteristics of included studies table.

There was a statistically significant difference in the primary outcome of length of stay favoring epinephrine (MD -0.28; 95% CI -

0.46 to -0.09; four studies, 261 participants) (Analysis 2.3). However, the implications of this result need to be interpreted in light of the above findings showing no difference for epinephrine versus placebo. The result was not significant when restricted to one trial at low risk of bias.

There were significant differences favoring epinephrine for change in clinical score at both 60 minutes and 120 minutes post-treatment (SMD -0.79; 95% CI -1.45 to -0.13; four studies, 248 participants; and SMD -0.52; 95% CI -0.86 to -0.18; one study, 140 participants, respectively) (Analysis 2.6). Change in oxygen saturation was significant and favored epinephrine at 60 minutes. However, there was no difference between groups at 120 minutes based on data from one study. There was a significant difference favoring epinephrine in change in respiratory rate at 60 minutes but not 120 minutes. There were no significant differences in heart rate at 60 minutes or 120 minutes. Further, there were no significant differences in hospital readmissions after discharge.

Two studies reported on adverse events. One study found no cases of pallor, vomiting or tremors (n = 46). The second study (n = 30) reported no cases of tremor, increased blood pressure after nebulization or tachycardia among the epinephrine group; the authors did not report on adverse events for the salbutamol group.

The strength of evidence for inpatients was moderate for length of stay and low for clinical score, however the findings varied by outcome. There were no differences for overall length of stay, while results favored epinephrine in terms of clinical score at 60 and 120 minutes. Details for each strength of evidence domain are detailed in Table 1.

Outpatients (nine studies)

Our primary outcome for outpatients (admission rate) was assessed in seven studies, and was declared as the primary outcome in one study. The primary outcome for the remaining studies was clinical score (n = three), oxygen saturation (n = one), respiratory rate (n = one) or not specified (n = three). The other outcomes assessed in each study are detailed in the Characteristics of included studies table.

The primary outcomes of admission rate at Day 1 and Day 7 were not significantly different between treatment groups (RR 0.67; 95% CI 0.41 to 1.09; seven studies, n = 444 and RR 1.05; 95% CI 0.71 to 1.54, two studies; n = 212, respectively) (Analysis 2.1; Analysis 2.2).

Clinical score and heart rate were compared at 60 and 120 minutes, 12 to 24 hours, and 3 to 10 days post-treatment. Respiratory rate was assessed at 60 and 120 minutes, 12 to 24 hours, and > 24 hours. Significant differences were found favoring epinephrine for clinical score at 3 to 10 days and respiratory rate at 60 minutes and > 24 hours. Oxygen saturation was assessed at 60 and 120 minutes but no differences were found. Return visits to any healthcare facility was not significantly different between groups overall or for the two time points measured (i.e. 2 to 10 days, 10 to 30 days).

Three studies reported on adverse events. One study (n = 66) reported on pallor (one epinephrine, zero albuterol), vomiting (one epinephrine, five albuterol), and tremors (zero epinephrine, zero albuterol). The second study (n = 40) reported cases of tachycardia (zero epinephrine, two albuterol) but reported no cases of withdrawal due to worsening clinical status or discontinuation of study medications due to adverse events. The third study (n = 186) reported no cases of tremor or increased heart rate in the epinephrine or albuterol groups.

Epinephrine versus steroid

Two studies compared steroids and epinephrine; these comparisons involved a total of 444 patients (230 steroid; 214 epinephrine). One study examined prednisolone (n = 15) and budesonide (n = 15), and one study examined dexamethasone (n = 200). The studies were published in 1995 and 2009 and were conducted in Turkey and Canada. Both studies involved outpatients. There were no studies that compared steroids and epinephrine among inpatients.

'Risk of bias' was unclear in one study and low in the other study. The study that was rated unclear did not describe methods for sequence generation, allocation concealment and blinding, and did not report any funding source.

Our primary outcome for outpatients (admission rate) was assessed in both studies, and was declared as the primary outcome in one study. The primary outcome in the other study was clinical score. A variety of other outcomes were assessed and are detailed in the Characteristics of included studies table.

The primary outcomes of admission rate at Day 1 and Day 7 were not significantly different between groups.

Results favored epinephrine over steroids in terms of change in clinical score at 60 minutes (SMD 0.31; 95% CI 0.12 to 0.50; two studies, 442 participants) (Analysis 3.3). There was no significant difference for change in clinical score at 120 minutes or three to six hours, possibly due to the small numbers of participants for these comparisons. There was a significant difference in oxygen saturation at 60 minutes favoring epinephrine, but no significant difference at 120 minutes or three to six hours, again possibly due to the small numbers of participants available for comparison at these latter time points. There was no significant difference in respiratory rate at 60 minutes post-treatment. Results favored steroids in terms of change in heart rate at 60 minutes, although there was no difference between groups at 120 minutes and three to six hours post-treatment. Based on one study, there was no significant difference between groups in return visits to any healthcare facility.

One study reported on adverse events and noted the following reactions which did not differ substantially between groups: pallor (11% epinephrine, 7.5% dexamethasone), vomiting (2% epinephrine, 2.5% dexamethasone), tremors (2% epinephrine, 2.5% dexamethasone), and hypertension (0.5% epinephrine,

0.5% dexamethasone).
The strength of evidence was rated moderate among outpatient studies in terms of admissions (no difference between groups) and high for clinical score 60 minutes post-treatment (favoring epinephrine over steroids). The strength of evidence was low for clinical score at other time points due to the small number of patients and only a single study for these comparisons. Details for each strength of evidence domain are detailed in Table 1.

Epinephrine and steroid versus placebo

One study compared epinephrine and dexamethasone versus placebo among 399 outpatients. The study was conducted in Canada and was rated as low risk of bias. For our primary outcomes, no significant difference was observed at Day 1. However, a significant difference favoring epinephrine and dexamethasone was observed for Day 7 (RR 0.65; 95% CI 0.44 to 0.95) (Analysis 4.2). The number needed to treat for this comparison is 11 (95% CI 7 to 76).
A significant difference favoring epinephrine and dexamethasone was also observed for clinical score at 60 minutes. No differences were observed for respiratory rate or oxygen saturation at 60 minutes. A significant difference favoring placebo was found for heart rate at 60 minutes. The study observed the following adverse events: pallor (11.5% epi + dex; 8% placebo); vomiting (1% epi + dex; 1.5% placebo); tremor (2% epi + dex; 1% placebo); and hypertension (0% in both groups).
The strength of evidence for admissions at Day 1 and Day 7 was rated as low due to unknown consistency and imprecision resulting from the small number of events. The strength of evidence for clinical score at 60 minutes was considered moderate demonstrating superiority of epinephrine and dexamethasone combined. Details for each strength of evidence domain are detailed in Table 1.

Epinephrine and steroid versus salbutamol

One small study (n = 35) compared epinephrine and dexamethasone versus salbutamol among outpatients. The study did not evaluate our primary outcome of length of stay. The study measured clinical score at 120 minutes, 24 to 48 hours, and 3 to 10 days. The only significant difference in clinical score was at 3 to 10 days. Respiratory rate was assessed at 120 minutes, 12 to 24 hours, and > 24 hours; a significant difference was observed at > 24 hours. Heart rate was assessed at 120 minutes, 24 to 72 hours, and 3 to 10 days; there were no significant differences at any time point assessed. The study did not report any adverse effects.
The strength of evidence for admissions at Day 1 and Day 7 was insufficient. The strength of evidence for clinical score was considered low and only favored epinephrine and dexamethasone at the longest of the three time points assessed (i.e. 3 to 10 days). Details for each strength of evidence domain are detailed in Table 1.

Epinephrine versus salbutamol and ipratropium bromide

One study compared epinephrine versus salbutamol and ipratropium bromide among 60 inpatients. This study did not evaluate our primary outcome of length of stay. The study measured clinical score and oxygen saturation at six to 12 hours. The only significant difference was in the clinical score which favored epinephrine. The study was at high risk of bias due to lack of blinding. The strength of evidence for this finding is considered low.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Epinephrine versus salbutamol/albuterol for acute viral bronchiolitis

Patient or population: patients with acute viral bronchiolitis
Settings: outpatients and inpatients
Intervention: epinephrine versus salbutamol/albuterol

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Epinephrine versus salbutamol/albuterol				
Admissions at enrollment or <24 hours (outpatients only)	Study population		RR 0.67 (0.41 to 1.09)	444 (7 studies)	⊕⊕⊕◯ moderate	
	225 per 1000	151 per 1000 (92 to 245)				
	Medium-risk population					
	133 per 1000	89 per 1000 (55 to 145)				
Admissions overall up to 7 days (outpatients only)	Study population		RR 1.05 (0.71 to 1.54)	212 (2 studies)	⊕⊕⊕◯ moderate	
	262 per 1000	275 per 1000 (186 to 403)				
	Medium-risk population					
	167 per 1000	175 per 1000 (119 to 257)				

Length of stay (inpatients only)		The mean length of stay (inpatients only) in the intervention groups was **0.28 lower** (0.46 to 0.09 lower)	261 (4 studies)	⊕⊕⊕○ **moderate**

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

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

Epinephrine and steroid versus placebo for acute viral bronchiolitis

Patient or population: patients with acute viral bronchiolitis
Settings: outpatients
Intervention: epinephrine and steroid versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Epinephrine and steroid versus placebo				
Admissions at enrollment or <24 hours (outpatients only)	Study population		RR 0.64 (0.4 to 1.04)	401 (1 study)	⊕⊕◯◯ low	
	179 per 1000	115 per 1000 (72 to 186)				
	Medium-risk population					
	179 per 1000	115 per 1000 (72 to 186)				
Admissions overall up to 7 days (outpatients only)	Study population		RR 0.64 (0.44 to 0.95)	400 (1 study)	⊕⊕◯◯ low	
	264 per 1000	169 per 1000 (116 to 251)				
	Medium-risk population					
	264 per 1000	169 per 1000 (116 to 251)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

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

Epinephrine versus steroid for acute viral bronchiolitis

Patient or population: patients with acute viral bronchiolitis
Settings: outpatients
Intervention: epinephrine versus steroid

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Epinephrine versus steroid				
Admissions (outpatients only)	Study population		RR 1.12 (0.66 to 1.88)	444 (2 studies)	⊕⊕⊕◯ **moderate**	
	136 per 1000	152 per 1000 (90 to 256)				
	Medium-risk population					
	73 per 1000	82 per 1000 (48 to 137)				
Admissions overall up to 7 days (outpatients only)	Study population		RR 1.08 (0.77 to 1.52)	399 (1 study)	⊕⊕⊕◯ **moderate**	
	236 per 1000	255 per 1000 (182 to 359)				
	Medium-risk population					
	236 per 1000	255 per 1000 (182 to 359)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

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

DISCUSSION

Summary of main results

This review provides evidence of the effectiveness of epinephrine in outpatients for outcomes of most clinical relevance, specifically admission rates during the first 24 hours. This is supported by positive results for secondary outcomes, in particular short-term changes in clinical scores.

This review provides preliminary evidence for the effectiveness of epinephrine and dexamethasone combined for outcomes of most clinical relevance among outpatients. This is based on a single large trial with low risk of bias which demonstrated a relative risk reduction of 35%. Based on the study's baseline risk, 11 children with bronchiolitis would need to be treated to reduce one admission. These were unadjusted results from a factorial randomized controlled trial (RCT) which should be interpreted cautiously since significant findings may arise from multiple comparisons.

There is no evidence of effectiveness for repeated dose or prolonged use of epinephrine or epinephrine and dexamethasone combined among inpatients. While epinephrine compared to salbutamol showed a significant difference for length of stay, the finding is tempered by the fact that there were no differences in length of stay for epinephrine versus placebo.

The evidence shows no important differences in adverse effects with epinephrine over the short-term.

Although severity of illness was reported overall in many of the studies, due to variability of scales used it is difficult to assess which populations are most sensitive to these treatments. For outpatient results comparing epinephrine to placebo most of the population ranges from mild to moderate severity with some possibly severe; and for epinephrine compared to steroid the population ranges from moderate to severe.

Overall completeness and applicability of evidence

The findings from this review add substantially to the current evidence base regarding the use of epinephrine in acute viral bronchiolitis. For this update we used revised methodology at all stages of the review, including more precise inclusion criteria and predefined clinically relevant primary outcomes. We also devised a new approach to analysis in order to accommodate for the use of epinephrine alone or in combination with steroids, and the presence of different comparisons. A substantial amount of new data was added, including up to 800 participants from the largest RCT performed to date in bronchiolitis. We used a comprehensive search strategy to capture all potentially relevant trials. We were unable to test for publication bias due to the small number of studies within each category of comparison, outcome and clinical setting.

This review included only first-time wheezers so results could be directly pertinent to infants with 'typical' viral bronchiolitis, as opposed to children with acute recurrent wheezing (i.e. episodic/viral or multiple-trigger wheeze) or a formal diagnosis of asthma. We acknowledge that there is no standard definition of bronchiolitis (DiTraglia 2004; Weinberger 2003; Weinberger 2007), in part due to regional variation in semantics between North America and UK, which is likely to exist throughout the world. Differences in definitions are based on factors like age of the child, number of previous wheezing episodes, and acute clinical findings. For example, in the UK, 'crackles' are often key to a diagnosis of bronchiolitis, while older children with wheeze may be considered a distinct subgroup (Everard 2009). A first episode of wheezing may be a first manifestation of wheezing phenotypes with heterogeneous pathological, genetic, viral or environmental determinants and distinct prognosis (Brand 2008; Martinez 2005; Sly 2008). However, research is still ongoing to identify simple, valid and universal discriminative and/or prognostic tools to distinguish prospectively between them (Brand 2008; Sly 2008). Our choice of bronchiolitis definition was meant to allow a pragmatic interpretation of results by clinicians in different settings, and findings are likely to be applicable to children with different bronchiolitis definitions.

The applicability of the findings from this review is driven by the individual trial characteristics. There was variation between the trials in delivery of interventions including the type of epinephrine, number of administrations and dosage. We were unable to assess the impact of these variations due to the small number of studies in each comparison.

The effectiveness of interventions may also vary according to a number of patient factors such as age, severity or stage of illness, co-morbidities, viral etiology, and atopic status of the patient, family or both. There were insufficient data presented at the trial level to allow for comparisons within these important subgroups. Ten studies included only children less than one year of age. Seven of these studies involved inpatients, therefore there were insufficient numbers of studies within the comparative groups to examine differences with respect to younger (<= 12 months) versus older (up to two years) children. The trials most often involved children without co-morbidities. Individual trials varied in terms of the disease severity of their sample ranging from mild to severe disease, although data were rarely available for these subgroups within trials. Inpatient versus outpatient status may be a proxy for severity or response to treatment which may explain the differences in effect, particularly lack of clear effect among inpatients. Further, we excluded studies in the intensive care unit (ICU) setting or involving children requiring intubation or mechanical ventilation which likely represent children with more severe disease or complicating co-morbidities. Data were not available to examine effects due to different viral etiology. In the seven studies that described the viral etiology of their participants, the majority (> 50%) were positive for respiratory syncytial virus. Two studies described the atopic status of participants and found it present in approximately 10%

and 13.3%; subgroup analyses at the trial level showed no important differences in effect for the trial with 10% atopy in participants.

Results from one trial show that a combination of epinephrine with systemic dexamethasone may have a significant and clinically relevant effect in reducing admissions of outpatients by Day 7, when compared to placebo. Caution may be advised when interpreting whether these findings are true and generalizable. Recent empirical evidence suggests that reliance on evidence from a single precise well-conducted trial is reasonable (Glasziou 2010).This was a factorial trial with methodological caveats, and interpretation of results is problematic since interaction between treatments was not anticipated. It is not clear how to handle possible additive/synergistic or subtractive/antagonistic effects at a systematic review level. These results should be considered exploratory; replication of these findings is needed to improve our confidence in the direction, precision and magnitude of the effect estimate. Further, additional research is required to assess the applicability of combination therapy to other populations, specifically inpatients, and to examine differences within the combination schemes, such as doses of steroids.

Results suggesting a benefit from epinephrine and dexamethasone should be balanced against incomplete data on harms. Safety concerns are expected regarding the widespread use of epinephrine and steroids in young children with viral wheezing, particularly with repeated high steroid doses (Bush 2009; Frey 2009). Our results do not suggest any serious or frequent short-term expected or unexpected harms from epinephrine or steroids in infants with bronchiolitis in the absence of co-morbidities. However, the power to detect important differences was limited due to the infrequent occurrence of events. Adverse event detection at the trial level was also heterogeneous. Current data from RCTs and observational studies in croup suggest a favorable short-term safety profile from both dexamethasone and epinephrine (Bjornson 2008; Zhang 2005b). Corticosteroids also raise long-term safety issues. Their use in prematurity for neonatal respiratory distress has been associated with effects on adrenal function, cardiovascular responses, somatic and lung growth, and neurodevelopment (Doyle 2010; Karemaker 2008b; Karemaker 2008a; Onland 2008; Wilson-Costello 2009). Evidence is scarce, however, regarding effects of short-term use in otherwise healthy term infants. Further pharmacoepidemiologic data are needed to permit adequate short and long-term risk-benefit assessments.

Quality of the evidence

Our risk of bias and strength of evidence assessments provide clarity around the limitations of this body of evidence. Two key factors affected the strength of evidence: potential risk of bias in the included studies and sparsity of data for many of the outcomes and comparisons, which resulted in imprecise estimates and unknown consistency of estimates across studies. The trials varied in their risk of bias with six at low risk, five high and eight unclear. The domains that resulted in high overall risk of bias were selective outcome reporting in two trials, missing outcome data in one trial, and use of cross-over design in one trial which we deemed to be inappropriate for this condition. The domains that consistently contributed to unclear overall ratings were sequence generation, allocation concealment and blinding. This information provides clear direction for enhanced reporting of future trials.

Sparsity of data was a result of a large number of comparisons as well as variability in the choice of outcomes and timing of outcome assessments. Within trials, this also led to frequent uncertainties regarding selective outcome reporting. The message around consistency and relevance of outcomes is not new to this field. The absence of standardized, validated and patient-important outcome measures and instruments in this area has been a challenge for evidence synthesis and poses a threat to the validity of trial results. Our primary outcomes were based on the increased use of hospital services, and its clear implications for patients and families. However, there is no evidence or guidance supporting the choice of outcomes that are methodologically sound and patient-important. The diversity of primary outcomes chosen by different included trials reflects this, and caused heterogeneous sample size calculations. Timings of assessment are also important and were not standardized. Additionally, validity of admissions and length of stay is limited by inadequate reporting of hospitalization and discharge criteria, given the wide variation in bronchiolitis management. Many factors besides disease severity and treatment response may contribute to these outcomes (for example, social, family, health service related factors), and this may ultimately impact treatment effects. While most trials assessed clinical scores, the choice of instruments was inconsistent. Their compositions often encompass different disease domains, and scale structures differed, which limits comparability between results. While the Respiratory Distress Assessment Instrument (RDAI) was used in a considerable number of trials, its clinimetric properties are not well known. Importantly, responsiveness and clinically important differences have not been defined, thus limiting the clinical interpretation of findings. The heterogeneity in post-acute symptom assessment instruments, as well as the absence of any quality of life measures highlights under representation of patient-important domains. Further work is needed to define a core set of clinically important efficacy and safety outcome measures and timing of assessments, for trials and systematic reviews in this field.

Potential biases in the review process

Strengths of this updated review rest primarily on a revision of methods used and investigation of new hypotheses stemming from recent evidence. Some limitations have been described previously; others should also be highlighted. We did not obtain data from authors of included studies, which might have clarified risk of bias assessments and further added to reported trial characteristics and

secondary outcome results. Our approach to the investigation of synergism/antagonism was exploratory, since there is scarce guidance on how to handle this issue at a systematic review level. The same holds for the use of factorial trial results in systematic reviews when interaction is observed. Limitations of subgroup analyses are well known and have been addressed. Grading of evidence was limited by the lack of evidence regarding clinically relevant differences in studied outcomes. Finally, we were unable to assess for publication bias due to the small number of studies within each outcome, comparison and patient subgroup.

Agreements and disagreements with other studies or reviews

The earlier version of this review published in 2004 (Hartling 2004) showed "some evidence to support the use of epinephrine among outpatients." This was based on findings for clinical parameters from a small number of studies of varying internal validity. Overall the review found that the findings lacked consistency. One of the largest sources of inconsistency in the earlier review arose from the six different scoring systems used across the component studies. This resulted in statistically significant heterogeneity between studies. The present review adds substantially more data to the comparisons of interest. Further, the focus on different outcomes of clinical and patient importance (i.e. admission rates for outpatients and length of stay for inpatients) avoids overreliance on the clinical scores and the challenges they present for interpretation. The findings from the present review increase our confidence in the effectiveness of epinephrine among outpatients. However, the lack of evidence for epinephrine among inpatients remains.

AUTHORS' CONCLUSIONS

Implications for practice

1. There is evidence that epinephrine is effective for outpatients in terms of outcomes of clinical importance, including admissions within 24 hours and short-term changes in clinical scores and other clinical parameters. There were no important differences reported in adverse effects.

2. Combined epinephrine and high-dose systemic dexamethasone may be effective in reducing outpatient admissions in moderately severe bronchiolitis, with few short-term adverse effects. Efficacy, harms and applicability of this promising finding need to be clarified further.

3. There is insufficient evidence to support the use of epinephrine, with or without steroids, for the treatment of bronchiolitis among inpatients.

Implications for research

1. A large RCT is needed to replicate and complement findings from combination therapy with epinephrine and steroids for outpatients. An additional aim could include assessing the minimum efficacious steroid dose.

2. The strategy of combined epinephrine and steroids could be evaluated in inpatient settings.

3. Data are needed to assess the long-term safety of combination treatment with epinephrine and steroids.

4. Future trials should use standardized sets of outcome measures in this field.

ACKNOWLEDGEMENTS

We thank Marlene Dorgan and Ellen Crumley for their assistance with searching for the initial review. We thank Dr. Metin Gulmezoglum for his assistance with translation and data extraction of the Turkish studies for the initial review. We would like to acknowledge the previous review authors Kelly Russell and Natasha Wiebe for their work on the original document.

The authors gratefully acknowledge the following individuals for their contributions to the most recent update: Ms. Annabritt Chisholm (article retrieval), Ms. Heather McPhee (study inclusion, quality assessment and data extraction), Ms. Nicola Hooton (study selection), Ms. Andrea Milne (screening, study inclusion, quality assessment and data extraction), Dr. Özge Tunçalp (Turkish translation), Joy Lee (Korean translation), João Franco (Spanish translation), Mohammad Karkhaneh (Farsi translation) and Paolo Valerio (Dutch translation). Finally we thank the following people for commenting on this updated review: Thiagarajan Jaiganesh, Vishal Jatana, Sara Ahronheim, Robert Ware and Inge Axelsson.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Abu-Shukair 2001

Methods	Randomized, controlled trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in Jordan, inpatients 140 inpatients < 18 months with acute bronchiolitis *Group 1* Sample size: 68 Age, mean: 7.4 months Males, N (%): 46 (68) *Group 2* Sample size: 72 Age, mean: 7.1 months Males, N (%): 50 (70)
Interventions	*Group 1*: salbutamol (0.03 ml/kg of 5 mg/ml solution diluted with 0.9% saline to total 3 ml) *Group 2*: 3 ml of 1:1000 epinephrine. Administered at 0 and 30 min via nebulizer with continuous flow of oxygen at 6 L/min
Outcomes	*Primary outcome* Not specified *Secondary outcome** SaO_2, respiratory rate, heart rate, adverse events, clinical score (RDAI) *Outcomes measured at baseline, 30, 60, 120 minutes
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RDAI; oxygen saturation; respiratory rate; heart rate

Abu-Shukair 2001 (*Continued*)

Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Adverse events
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RDAI; oxygen saturation; respiratory rate; heart rate
Incomplete outcome data (attrition bias) Other outcomes	Unclear risk	Adverse events
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Abul-Ainine 2002

Methods	Randomized, double-blind, placebo-controlled trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in England, inpatients 38 children (between 30 days to 1 year) admitted with clinical diagnosis of moderately severe acute bronchiolitis (within the first 4 days of illness); first-time wheezers only *Group 1* Sample size: 19 Age: < 6 months, N (%): 14 (73.7), > 6 months, N (%): 5 (26.3) Males, N (%): 10 (42.6) *Group 2* Sample size: 19 Age: < 6 months, N (%): 13 (68.4), > 6 months, N (%): 6 (31.6) Males, N (%): 8 (42.1)
Interventions	*Group 1*: single dose (3 ml) of levo-adrenaline (3 mg) *Group 2*: 0.9% saline placebo Treatments nebulized in 100% oxygen at 6 L/min
Outcomes	*Primary outcome* Respiratory rate, heart rate *Secondary outcome* SaO_2, clinical score (RDAI), activity status Outcomes measured at 20 minutes pre-treatment, baseline, and 20, 40, 60 minutes post-treatment
Notes	Funding: PARI Medical Ltd provided nebulizer Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo
Risk of bias	

Abul-Ainine 2002 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RDAI; oxygen saturation; respiratory rate; heart rate
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Adverse events; activity status
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RDAI; oxygen saturation; respiratory rate; heart rate
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Adverse events; activity status
Selective reporting (reporting bias)	Low risk	

Anil 2010a

Methods	Randomized, double-blind, placebo-controlled trial. No withdrawals reported Parallel design, single-centre, 5 arms
Participants	Conducted in Turkey, outpatients 186 children (between 6 weeks to 24 months) admitted with first episode of acute bronchiolitis and a clinical severity score between 1 and 9 (mild to moderate) *Group 1* Sample size: 38 Age, mean ± SD: 10.4 ± 5.7 months Males, N (%): 26 (68.4) *Group 2* Sample size: 39 Age, mean ± SD: 9.4 ± 5.0 months Males, N (%): 29 (74.3) *Group 3* Sample size: 36 Age, mean ± SD: 9.0 ± 6.2 months Males, N (%): 20 (55.5) *Group 4* Sample size: 36 Age, mean ± SD: 9.7 ± 6.2 months

Anil 2010a (*Continued*)

	Males, N (%): 23 (63.8) *Group 5* Sample size: 37 Age, mean ± SD: 9.1 ± 4.4 Males, N (%): 22 (59.4)
Interventions	*Group 1*: inhalation of epinephrine, 1.5 mg, diluted to 4 ml with 0.9% saline *Group 2*: inhalation of epinephrine, 1.5 mg, diluted to 4 ml with 3% saline *Group 3*: inhalation of salbutamol, 2.5 mg, diluted to 4 ml with 0.9% saline *Group 4*: inhalation of salbutamol, 2.5 mg, diluted to 4 ml with 3% saline *Group 5*: inhalation of 4 ml 0.9% saline Treatments nebulized in 100% oxygen at 6 L/min, 2 doses administered at 0 and 30 minutes
Outcomes	*Primary outcome* Not specified *Secondary outcome* Clinical severity score, SaO_2, HR, admissions from ED, number of readmissions of those discharged from ED, tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects Outcomes measured prior to each drug administration (0 and 30 minutes), 60 and 120 minutes post-treatment
Notes	Funding: not specified Language of publication: English This study contributed to the following comparisons: epinephrine (Group 1) versus salbutamol (Group 3)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR
Blinding (performance bias and detection bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects

Anil 2010a (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Anil 2010b

Methods	See Anil 2010a
Participants	See Anil 2010a
Interventions	See Anil 2010a
Outcomes	See Anil 2010a
Notes	This study contributed to the following comparisons: epinephrine (Group 2) versus salbutamol (Group 4)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR

Anil 2010b (*Continued*)

Blinding (performance bias and detection bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Anil 2010c

Methods	See Anil 2010a
Participants	See Anil 2010a
Interventions	See Anil 2010a
Outcomes	See Anil 2010a
Notes	This study contributed to the following comparisons: epinephrine (Group 1) versus placebo (Group 5)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR

Anil 2010c (*Continued*)

Blinding (performance bias and detection bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Admissions from ED, number of readmissions of those discharged from ED
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	Clinical severity score, SaO_2, HR
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Tremor, study withdrawal due to worsening symptoms, discontinuation of any study drug due to side effects
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Barlas 1998a

Methods	Randomized trial. No withdrawals reported Parallel design, single-centre, multi-arm (6)
Participants	Conducted in Turkey, outpatients 90 children (less than 24 months of age) presenting to emergency outpatient clinic with first episode of wheezing and clinical score between 4 and 10 (mild to moderate) *Group 1 to 6 (all participants)* Sample size: 15 (total 90) Age, mean ± SD: 8.52 ± 0.59 months Males, N (%): 50 (56)
Interventions	*Group 1*: placebo - mist tent (nebulized) *Group 2*: albuterol (nebulized); 0.15 mg/kg; every hour during the first 4 h *Group 3*: prednisolone (IV); 2 mg/kg; single dose *Group 4*: albuterol + prednisolone (nebulized + I); 0.15 mg/kg (alb) + 2 mg/kg (pre); single dose for both interventions *Group 5*: racemic adrenaline (epinephrine) (nebulized); 0.1 ml/kg; every 2 h during the first 4 h *Group 6*: budesonide (nebulized); 0.5 mg; single dose
Outcomes	*Primary outcome* Not specified *Secondary outcome* Hospital admission, SaO_2*, heart rate*, observation period, number improved with initial tx, and additional tx *Outcomes measured at baseline, 60, 120 minutes and 4 hours

Barlas 1998a (*Continued*)

Notes	Funding: not mentioned Language of publication: Turkish This study contributed to the following comparison: epinephrine versus placebo (Barlas 1998a); epinephrine versus salbutamol (Barlas 1998b); and epinephrine versus steroid (prednisolone + budesonide) (Barlas 1998c)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	High risk	Hospital admission, observation period
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	High risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, observation period
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Barlas 1998b

Methods	See Barlas 1998a
Participants	See Barlas 1998a
Interventions	See Barlas 1998a
Outcomes	See Barlas 1998a
Notes	This study contributed to the following comparison: epinephrine versus placebo (Barlas 1998a); epinephrine versus salbutamol (Barlas 1998b); and epinephrine versus steroid (prednisolone + budesonide) (Barlas 1998c)

Barlas 1998b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	High risk	Hospital admission, observation period
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	High risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, observation period
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Barlas 1998c

Methods	See Barlas 1998a
Participants	See Barlas 1998a
Interventions	See Barlas 1998a
Outcomes	See Barlas 1998a
Notes	This study contributed to the following comparison: epinephrine versus placebo (Barlas 1998a); epinephrine versus salbutamol (Barlas 1998b); and epinephrine versus steroid (prednisolone + budesonide) (Barlas 1998c)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Barlas 1998c (*Continued*)

Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	High risk	Hospital admission, observation period
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	High risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, observation period
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, HR, clinical score, no. improved with initial tx, additional tx
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Beck 2007

Methods	Randomized, double-blind, controlled trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in Israel, outpatients (emergency department) 27 children (2 to 12 months of age) presenting to emergency department with first episode of respiratory distress and RSV-positive *Group 1* Sample size: 12 Age, mean ± SD: 4.9 ± 0.8 months Males, N (%): 8 (66.7) *Group 2* Sample size: 15 Age, mean ± SD: 4 ± 1.35 months Males, N (%): 11 (77.3)
Interventions	*Group 1*: epinephrine (1 mg diluted in 2 ml 0.9% saline) *Group 2*: albuterol (2.5 mg diluted in 2.5 ml 0.9% saline) Via nebulizer at 0.4 ml/min in 5L/min O_2 flow. Single treatment of interventions
Outcomes	*Primary outcome* Not specified

Beck 2007 (*Continued*)

	Secondary outcome Clinical score*, respiratory rate*, heart rate*, acoustic breath sounds, computerized wheeze rate, computerized crackle count *Outcomes measured at baseline, 10, 30 minutes
Notes	Funding: government Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, HR, clinical score
Blinding (performance bias and detection bias) Pulmonary function outcomes	Low risk	Acoustic breath sounds
Blinding (performance bias and detection bias) Other outcomes	Low risk	Computerized wheeze rate, computerized crackle count
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, HR, clinical score
Incomplete outcome data (attrition bias) Pulmonary function outcomes	Low risk	Acoustic breath sounds
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Computerized wheeze rate, computerized crackle count
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Bertrand 2001

Methods	Randomized, double-blind, controlled trial Two participants (one per group) had worsening of clinical condition and were transferred to PICU; these participants were excluded from analysis
Participants	Conducted in Chile, inpatients 30 children (less than 1 year of age) admitted with acute bronchiolitis (first episode of wheezing) *Group 1* Sample size: 14 Age, mean ± SD: 3.7 ± 0.6 months Males, N (%): 7 (50) *Group 2* Sample size: 16 Age, mean ± SD: 3.9 ± 0.4 months Males, N (%): 9 (56)
Interventions	*Group 1*: salbutamol (0.5 ml (2.5 mg) + 3.5 ml 0.9% saline) *Group 2*: epinephrine (0.5 ml (0.5 mg) + 3.5 ml saline) Via nebulizer. Interventions administered every 2 to 4 h during hospitalization; measurements done at baseline, 24 and 36 hours
Outcomes	*Primary outcome* Not specified *Secondary outcome* Clinical score (60 min, 24 and 36 hours), SaO_2, respiratory rate*, heart rate*, duration of oxygen therapy, length of hospital stay, hospital re-admission (2 weeks after discharge) , adverse events, blood pressure *Outcomes measured at baseline, 24 and 36 hours
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Unclear risk	LOS, hospital re-admission
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, BP, clinical score

Bertrand 2001 (*Continued*)

Blinding (performance bias and detection bias) Other outcomes	Unclear risk	AE, duration O_2 therapy
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	LOS, hospital re-admission
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, BP, clinical score
Incomplete outcome data (attrition bias) Pulmonary function outcomes	Unclear risk	AE, duration O_2 therapy
Incomplete outcome data (attrition bias) Other outcomes	Low risk	
Selective reporting (reporting bias)	High risk	
Other bias	Low risk	

Bilan 2007

Methods	Randomized trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in Iran, inpatients 100 children (2 to 12 months of age) admitted to hospital with bronchiolitis with lower respiratory tract infection, fever, rhinitis, tachypnea, wheezing and dyspnea *Group 1* Sample size: 50 Age, mean ± SD: 6 ± 4 months Males, N (%): 30 (60) *Group 2* Sample size: 50 Age, mean ± SD: 5 ± 3.6 months Males, N (%): 28 (56)
Interventions	*Group 1*: salbutamol (2 puffs via spacer every 4 hours) *Group 2*: epinephrine (1/1000 0.2 mg/kg with 3.5 cc saline via spray) Interventions administered every 4 hours
Outcomes	*Primary outcome* Not specified *Secondary outcome* Length of stay and return to normal feeding

Bilan 2007 (*Continued*)

Notes	Funding: not mentioned Language of publication: Farsi This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Unclear risk	LOS, hospital re-admission (2 weeks after d/c)
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, BP, clinical score
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	AE, duration O_2 therapy
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	LOS, hospital re-admission (2 weeks after d/c)
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, BP, clinical score
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE, duration O_2 therapy
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

John 2006

Methods	Randomized trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in India, inpatients 30 children (2 to 12 months of age) diagnosed with bronchiolitis based on history of coryza and/or fever followed by respiratory distress; moderately severe to severe bron-

John 2006 (*Continued*)

	chiolitis with respiratory distress with difficulty in feeding, nasal flare, chest retractions, and hypoxia requiring supplemental oxygen *Group 1* Sample size: 15 Age, mean ± SD: 6.67 ± 3.01 months Males, N (%): 10 (66.7) *Group 2* Sample size: 15 Age, mean ± SD: 6.73 ± 2.95 months Males, N (%): 9 (60)
Interventions	*Group 1*: epinephrine (0.5 ml/kg; maximum of 2.5 ml with 3 ml saline via nebulizer) *Group 2*: salbutamol (0.15 mg/kg with 3 ml saline via nebulizer) Interventions administered at 0, 30, 60 minutes and then 4-hourly until child was stable
Outcomes	*Primary outcome* Not specified *Secondary outcome* Length of stay, clinical score (RDAI)*, SaO_2*, respiratory rate*, heart rate* *Outcomes measured at baseline, 10, 40 and 70 minutes
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Lottery method
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Unclear risk	LOS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Adverse events
Incomplete outcome data (attrition bias) Administrative outcomes	Unclear risk	LOS

John 2006 (*Continued*)

Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	Unclear risk	Adverse events

Kadir 2009

Methods	Randomized trial. No withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in Bangladesh, inpatients 60 children (less than 2 years of age) with acute bronchiolitis presenting with respiratory distress and wheeze following an attack of coryza with evidence of hyperinflation on chest x-ray, hypoxemia and clinical score > 4 *Group 1* Sample size: 30 Age: 28 (93%) in first year, 2 (7%) in second year Males, N (%): 21 (70) *Group 2* Sample size: 30 Age: 24 (80%) in first year, 6 (20%) in second year Males, N (%): 21 (70)
Interventions	*Group 1*: combined salbutamol (0.15 mg/kg) and ipratropium bromide (250 μg in 1 ml) *Group 2*: L-adrenaline (0.01 ml/kg of 1:1000 dilutions) Interventions nebulized and administered at 0 and 6 hours
Outcomes	*Primary outcome* Not specified *Secondary outcome* MRDAI (Modified Respiratory Distress Assessment Instrument), SaO_2, respiratory rate, coryza, respiratory distress, cyanosis, ronchi, crepitation, evidence of hyperinflation on chest x-ray, white blood cell counts Outcomes measured at baseline and 30 min after each tx
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol + ipratropium bromide

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Kadir 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	High risk	MRDAI, SaO_2, respiratory rate
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	MRDAI, SaO_2, respiratory rate
Selective reporting (reporting bias)	Unclear risk	NS
Other bias	Unclear risk	NS

Khashabi 2005a

Methods	Randomized, double-blind trial. No withdrawals reported Parallel design, single-centre, multi-arm (3)
Participants	Conducted in Iran, outpatients (emergency department) 72 children (2 to 24 months of age) presenting to emergency department with a diagnosis of viral bronchiolitis, including: acute viral lower respiratory tract infection; fever; rhinitis; tachypnea; expiratory wheezing; increased respiratory effort; and mild to moderate severity bronchiolitis *Group 1* Sample size: 24 Age, mean: 8.9 months Males, N (%): 5 (20.8) *Group 2* Sample size: 24 Age, mean: 10.5 months Males, N (%): 6 (25) *Group 3* Sample size: 24 Age, mean: 7.9 months Males, N (%): 9 (37.5)
Interventions	*Group 1*: epinephrine (0.1 ml/kg of 1:10000 solution + saline to 5 ml) *Group 2*: salbutamol (0.15 mg/kg + saline to 5 ml) *Group 3*: placebo (5 ml saline) Administered via nebulizer in 8 L/min O_2 flow, 3 doses at 20-minute intervals
Outcomes	*Primary outcome* Not specified

Khashabi 2005a (*Continued*)

	Secondary outcome Clinical score (RDAI)*, SaO_2*, respiratory rate*, number ready to go home at end of treatment *Outcomes measured at baseline, 10, 20, 30 and 40 minutes
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo (Khashabi 2005a) and epinephrine versus salbutamol (Khashabi 2005b)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Low risk	Number ready to go home at end of tx
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Number ready to go home at end of tx
Other bias	Low risk	

Khashabi 2005b

Methods	See Khashabi 2005a
Participants	See Khashabi 2005a
Interventions	See Khashabi 2005a
Outcomes	See Khashabi 2005a
Notes	This study contributed to the following comparisons: epinephrine versus placebo (Khashabi 2005a) and epinephrine versus salbutamol (Khashabi 2005b)

Khashabi 2005b (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Low risk	Number ready to go home at end of tx
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Number ready to go home at end of tx
Other bias	Low risk	

Kuyucu 2004a

Methods	Randomized, double-blind controlled study; not ITT for follow-up outcomes (21 patients did not attend follow-up visits at 24 hours or Day 5 and were not included in analysis) Parallel design, single-centre, multi-arm (4)
Participants	Conducted in Turkey, outpatients 69 children (2 to 21 months) attending pediatric outpatient clinic or ED with first episode of wheezing *Group 1* Sample size: 26 Age, mean ± SD: 7.2 ± 0.8 months *Group 2* Sample size: 24 Age, mean ± SD: 7.9 ± 1.0 months *Group 3* Sample size: 19 Age, mean ± SD: 9.6 ± 1.3 months *Group 4* Sample size: 21

Kuyucu 2004a (*Continued*)

	Age, mean ± SD: 9.9 ± 1.7 months
Interventions	*Group 1*: epinephrine + dexamethasone (3 ml (3 mg) of 1:1000 L-epinephrine + 0.6 mg/kg of dexamethasone) *Group 2*: salbutamol + dexamethasone (0.15 mg/kg of 1 mg/ml solution of salbutamol added to 0.9% saline to total 3 ml + 0.6 mg/kg of dexamethasone) *Group 3*: epinephrine + placebo (3 ml (3 mg) of 1:1000 L-epinephrine) *Group 4*: salbutamol + placebo (0.15 mg/kg of 1 mg/ml solution of salbutamol added to 0.9% saline solution to make a total of 3 ml) 3 doses administered to each participant
Outcomes	*Primary outcome* Respiratory rate*, heart rate*, clinical score* (RDAI) *Secondary outcome* Additional medication, follow-up rate, adverse events *Outcomes measured at baseline, 120 minutes, 24 hours, 5 days
Notes	Funding: not mentioned Language of publication: English This study contributed to the following comparisons:epinephrine versus salbutamol (Kuyucu 2004a and Kuyucu 2004b); epinephrine + steroid versus salbutamol (Kuyucu 2004c)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Additional medication, follow-up rate, AE
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	High risk	Additional medication, follow-up rate, AE
Selective reporting (reporting bias)	Low risk	

Kuyucu 2004a (*Continued*)

Other bias	Unclear risk	NS

Kuyucu 2004b

Methods	See Kuyucu 2004a	
Participants	See Kuyucu 2004a	
Interventions	This study contributed to the following comparisons: epinephrine versus salbutamol (Kuyucu 2004a and Kuyucu 2004b); epinephrine + steroid versus salbutamol (Kuyucu 2004c)	
Outcomes	See Kuyucu 2004a	
Notes	See Kuyucu 2004a	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Additional medication, follow-up rate, AE
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	High risk	Additional medication, follow-up rate, AE
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Kuyucu 2004c

Methods	See Kuyucu 2004a
Participants	See Kuyucu 2004a
Interventions	This study contributed to the following comparisons: epinephrine versus salbutamol (Kuyucu 2004a and Kuyucu 2004b); epinephrine + steroid versus salbutamol (Kuyucu 2004c)
Outcomes	See Kuyucu 2004a
Notes	See Kuyucu 2004a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Unclear risk	Additional medication, follow-up rate, AE
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	RR, HR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	High risk	Additional medication, follow-up rate, AE
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Menon 1995

Methods	Randomized centrally by pharmacy using table of random numbers; controlled trial; double-blind. One participant excluded after randomization (did not meet inclusion criteria); no withdrawals reported Parallel design, single-centre, 2 arms
Participants	Conducted in Canada, outpatients 42 children (between 6 weeks and 1 year) presenting to emergency department with first episode of wheezing *Group 1* Sample size: 21 *Group 2* Sample size: 21
Interventions	*Group 1*: salbutamol (0.3 ml of 5 mg/ml solution + 2.7 ml of 0.9% saline) *Group 2*: L-epinephrine (3 ml of 1:1000) Via nebulizer. One inhalation
Outcomes	*Primary outcome* SaO_2* *Secondary outcome* Clinical score (RDAI)*, heart rate*, respiratory rate*, length of stay in ED or hospital, admission to hospital *Outcomes measured at baseline, 30, 60, 90 minutes
Notes	Funding: other Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to health-care facility (24 h after d/c)
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, RDAI
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE

Menon 1995 (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to health-care facility (24 h after d/c)
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, RDAI
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Mull 2004

Methods	Randomized, double-blind, controlled trial. Seven participants excluded after enrolment; no withdrawals or losses to follow up Parallel design, single-centre, 2 arms
Participants	Conducted in USA, outpatients 66 moderately ill children (between 0 to 12 months) presenting to emergency department of a tertiary care centre with first-time episode of acute wheezing *Group 1* Sample size: 34 Age, mean ± SD: 4.7 ± 2.6 months Males, N (%): 19 (55.9) *Group 2* Sample size: 32 Age, mean ± SD: 4.1 ± 2.0 months Males, N (%): 17 (53.1)
Interventions	*Group 1*: nebulized 2.25% racemic epinephrine (0.9 mg/kg) *Group 2*: nebulized 0.5% albuterol (0.15 mg/kg) (n = 32) with 2 ml of 0.9% isotonic sodium chloride solution Delivered via face mask with continuous flow of 100% oxygen at 6 L/min in 3 doses at 0, 30 and 60 minutes
Outcomes	*Primary outcome* Clinical score (RDAI)*, respiratory rate* *Secondary outcome* SaO_2*, hospitalization rate, adverse events, hospital re-admission, return to physician, 72-hour relapse rate, time well enough to go home *Outcomes measured at baseline, 30, 60, 90, 120, 150 minutes
Notes	Funded in part by Nephron Pharmaceuticals Company Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Mull 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, time to d/c, re-admission to hospital, relapse rate
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, SaO_2, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Return to physician
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, time to d/c, re-admission to hospital, relapse rate
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, SaO_2, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Return to physician
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Okutan 1998a

Methods	Randomized trial. Participants were sedated with oral chloral hydrate (80 mg/kg) and kept in supine position. After 1 hour (or after the child was asleep) pulse oximeter was fitted and clinical scoring made. Extent of follow up or whether ITT analysis done unknown Parallel design, single-centre, multi-arms (3)
Participants	Conducted in Turkey, outpatients 45 children (ages 3 to 18 months) *Group 1* Sample size: 16 Age, mean ± SD: 7.8 ± 4.1 months *Group 2* Sample size: 19 Age, mean ± SD: 7.7 ± 3.8 months *Group 3* Sample size: 10 Age, mean ± SD: 9 ± 5.8 months Males, % (total): 28
Interventions	*Group 1*: epinephrine (0.2 mg/kg; 1 mg/ml; 3 ml) *Group 2*: salbutamol (0.15 mg/kg; 2.5 mg/2.5 ml; 3 ml) *Group 3*: placebo (0.9% NaCl; 3 ml) Number and timing of doses unclear
Outcomes	*Primary outcome* Not specified *Secondary outcome* Respiratory rate, pulse rate, clinical score (RDAI), SaO_2, arterial BP Outcomes measured at 15, 30, 45, 60 and 120 minutes
Notes	Funding: not mentioned Language of publication: Turkish This study contributed to the following comparisons: epinephrine versus placebo (Okutan 1998a); epinephrine versus salbutamol (Okutan 1998b)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	

Okutan 1998a (*Continued*)

Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, BP, RDAI
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, BP, RDAI
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Okutan 1998b

Methods	See Okutan 1998a
Participants	See Okutan 1998a
Interventions	This study contributed to the following comparisons: epinephrine versus placebo (Okutan 1998a); epinephrine versus salbutamol (Okutan 1998b)
Outcomes	See Okutan 1998a
Notes	See Okutan 1998a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, BP, RDAI

Okutan 1998b (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, BP, RDAI
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	NS

Patel 2002a

Methods	Randomized, double-blind study. Intention-to-treat analysis performed; 10 participants withdrew (epi = 1, sal = 4, pla = 5) Parallel design, single-centre, multi-arm (3)
Participants	Conducted in Canada, inpatients 149 hospitalized infants with moderate-severe bronchiolitis (ages 0 to 12 months), who were previously well, were randomized into 3 treatment groups *Group 1* Sample size: 50 Age, mean ± SD: 4.2 ± 3.1 months Males, N (%): 28 (56) *Group 2* Sample size: 51 Age, mean ± SD: 3.9 ± 2.9 months Males, N (%): 35 (69) *Group 3* Sample size: 48 Age, mean ± SD: 4.7 ± 2.9 months Males, N (%): 25 (52)
Interventions	*Group 1*: racemic epinephrine (0.03 ml/kg/dose of a 2.25% solution) *Group 2*: saline placebo (0.03 ml/kg/dose of 0.9% sodium chloride) *Group 3*: salbutamol (0.03 ml/kg/dose of a 5 mg/ml solution) Treatment administered every 1 to 6 h for 10 to 15 min via nebulizer with continuous flow 100% oxygen at 6 to 7 L/min, frequency changes at the discretion of medical team
Outcomes	*Primary outcome* Length of stay *Secondary outcome* SaO_2,* clinical score (RDAI), hospital or ICU readmission**, return to healthcare facility**, adequate fluid intake*, medication requirements* * Outcomes measured 2 times per day **Outcomes measured 7 days after discharge

Patel 2002a (*Continued*)

Notes	Funding: other Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo (Patel 2002a); epinephrine versus salbutamol (Patel 2002b)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital or ICU readmission, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Medication requirements
Blinding (performance bias and detection bias) Other outcomes	Low risk	Adequate fluid intake
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital or ICU readmission, return to healthcare facility
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Medication requirements
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Adequate fluid intake
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Patel 2002b

Methods	See Patel 2002a
Participants	
Interventions	50 infants received epinephrine (0.03 ml/kg/dose of a 2.25% solution) and 51 were given salbutamol (0.03 ml/kg/dose of a 5 mg/ml solution)
Outcomes	
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital or ICU readmission, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Medication requirements
Blinding (performance bias and detection bias) Other outcomes	Low risk	Adequate fluid intake
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital or ICU readmission, return to healthcare facility
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Medication requirements
Incomplete outcome data (attrition bias) Other outcomes	Low risk	Adequate fluid intake

Patel 2002b (*Continued*)

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Plint 2009a

Methods	Randomized, double-blind, controlled trial Data were not available on the primary outcome for 3 participants (one each of epinephrine-dexamethasone, epinephrine and dexamethasone groups); these participants were not included in the intention-to-treat analysis. Because of a pharmacy error, a total of 23 participants in the epinephrine-dexamethasone group and 23 participants in the placebo-dexamethasone group received dexamethasone at 80% of the planned dose; these participants were included in the analysis Factorial design, multi-centre (8), multi-arm (4)
Participants	Conducted in Canada, outpatients (emergency department) 797 children (6 to 24 months) presenting to the emergency department with bronchiolitis and a RDAI score between 4 and 15 (mild to severe), and first episode wheezing associated with upper respiratory tract infection *Group 1* Sample size: 200 Age, median: 5 months Males, N (%): 124 (62) *Group 2* Sample size: 199 Age, median: 5 months Males, N (%): 122 (61.3) *Group 3* Sample size: 200 Age, median: 5 months Males, N (%): 127 (63.5) *Group 4* Sample size: 201 Age, median: 5 months Males, N (%): 120 (59.7)
Interventions	*Group 1*: epinephrine + dexamethasone *Group 2*: epinephrine + placebo *Group 3*: dexamethasone + placebo *Group 4*: placebo + placebo Dosages as follows: epi: 3 ml in 1:1000 saline; dex: 1.0 mg/kg weight (max 10 mg) then 0.6 mg/kg (max 10 mg) after ED. Mode of administration for epinephrine was nebulized in O_2 flow 8 L/min, and dexamethasone was oral. Two doses of treatment administered at 30 minutes apart; oral dexamethasone after first nebulization of epinephrine in ED, followed by 5 once daily doses of oral dexamethasone after leaving ED

Plint 2009a (*Continued*)

Outcomes	*Primary outcome* Hospital admission at Day 7 and 22 *Secondary outcome* Length of stay for those admitted, SaO_2, respiratory rate, heart rate, return to healthcare facility (within 22 days), duration of symptoms (22 days), temperature, adverse events * Outcomes measured at baseline, 30 and 60 minutes
Notes	Funding: government Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo (Plint 2009a and Plint 2009b); epinephrine versus dexamethasone (Plint 2009c); epinephrine + dexamethasone versus placebo (Plint 2009d)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Duration of symptoms
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Duration of symptoms

Plint 2009a (*Continued*)

Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Plint 2009b

Methods	See Plint 2009a
Participants	See Plint 2009a
Interventions	This study contributed to the following comparisons: epinephrine versus placebo (Plint 2009a and Plint 2009b); epinephrine versus dexamethasone (Plint 2009c); epinephrine + dexamethasone versus placebo (Plint 2009d)
Outcomes	See Plint 2009a
Notes	See Plint 2009a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Duration of symptoms
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE

Plint 2009b (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Duration of symptoms
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Plint 2009c

Methods	See Plint 2009a
Participants	See Plint 2009a
Interventions	This study contributed to the following comparisons: epinephrine versus placebo (Plint 2009a and Plint 2009b); epinephrine versus dexamethasone (Plint 2009c); epinephrine + dexamethasone versus placebo (Plint 2009d)
Outcomes	See Plint 2009a
Notes	See Plint 2009a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI

Plint 2009c (*Continued*)

Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Duration of symptoms
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	Duration of symptoms
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Plint 2009d

Methods	See Plint 2009a
Participants	See Plint 2009a
Interventions	This study contributed to the following comparisons: epinephrine versus placebo (Plint 2009a and Plint 2009b); epinephrine versus dexamethasone (Plint 2009c); epinephrine + dexamethasone versus placebo (Plint 2009d)
Outcomes	See Plint 2009a
Notes	See Plint 2009a

Risk of bias

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

Plint 2009d (*Continued*)

Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission, LOS, return to healthcare facility
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	SaO_2, RR, HR, temperature, RDAI
Blinding (performance bias and detection bias) Patient reported outcomes	Low risk	Duration of symptoms
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	
Incomplete outcome data (attrition bias) Patient reported outcomes	Low risk	
Incomplete outcome data (attrition bias) Other outcomes	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ralston 2005a

Methods	Randomized, double-blind, controlled trial. No withdrawals reported Parallel design, single-centre, multi-arm (3)
Participants	Conducted in USA, outpatients (emergency department) 65 children (6 weeks to 24 months) with mild to moderate bronchiolitis (first episode of wheezing) presenting to urgent care clinic *Group 1* Sample size: 25 Age, mean ± SD: 7.3 ± 5.1 months Males, N (%): 15 (60) *Group 2* Sample size: 23

Ralston 2005a (*Continued*)

	Age, mean ± SD: 7.7 ± 6.0 months Males, N (%): 15 (65) *Group 3* Sample size: 17 Age, mean ± SD: 7.9 ± 5.2 months Males, N (%): 6 (35)
Interventions	*Group 1*: 0.9% saline placebo *Group 2*: racemic albuterol (salbutamol) sulfate (5 mg) *Group 3*: racemic epinephrine (5 mg) All drugs given in 3 ml nebulized doses via mask with continuous flow of oxygen at 6 L/min. Study drug given at 0 and 30 min. Third dose given at 60 min if RDAI score > 8 or room air oxygen saturation < 90%
Outcomes	*Primary outcome* Hospital admission or received home oxygen *Secondary outcome* Clinical score (RDAI) (measured at 60 minutes if 2 doses, 90 minutes if 3 doses), adverse events (heart rate > 200, withdrawal from study due to deteriorating status, discontinuation due to side effects)
Notes	Funding: Dept HHS/NIH/NCRR/GCRC (USA); American Academy of Pediatrics Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo (Ralston 2005a); epinephrine versus salbutamol (Ralston 2005b)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RDAI
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE; home oxygen management

Ralston 2005a (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RDAI
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE; home oxygen management
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Ralston 2005b

Methods	See Ralston 2005a
Participants	See Ralston 2005a
Interventions	This study contributed to the following comparisons: epinephrine versus placebo (Ralston 2005a); epinephrine versus salbutamol (Ralston 2005b)
Outcomes	See Ralston 2005a
Notes	See Ralston 2005a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	Hospital admission
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RDAI
Blinding (performance bias and detection bias) Other outcomes	Low risk	AE; home oxygen management

Ralston 2005b (*Continued*)

Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	Hospital admission
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RDAI
Incomplete outcome data (attrition bias) Other outcomes	Low risk	AE; home oxygen management
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Sanchez 1993

Methods	Randomized, controlled trial, double-blind, cross-over study. Results from cross-over arms not differentiated in the analysis. 8 participants did not complete study because of inadequate sedation or technical problems; they were excluded from the analysis Cross-over design, single-centre, 2 arms
Participants	Conducted in Canada, inpatients 32 inpatients (less than 1 year of age) with diagnosis of acute bronchiolitis. All patients being treated with inhaled salbutamol. Mild to moderate cases *Group 1 and 2* Sample size: 32 Age, mean ± SEM (range): 4.6 ± 0.5 (1 to 10) months
Interventions	*Group 1*: albuterol (0.03 ml/kg of 5 mg/ml solution diluted to total of 2 ml in 0.9% NaCl) *Group 2*: racemic epinephrine (0.1 ml/kg of 2.25% solution diluted to total 2 ml in 0.9% NaCl) Via nebulizer. One inhalation
Outcomes	*Primary outcome* Not specified *Secondary outcome* Length of stay, clinical score (12-point scale)*, SaO_2*, respiratory rate*; heart rate*. Pulmonary mechanics measured under sedation: tidal volume; minute ventilation; inspiratory, expiratory and total pulmonary resistance; duration of inspiration as fraction of total breath duration; dynamic compliance *Outcomes measured at baseline and 20 to 30 minutes post-treatment
Notes	Funding: pharmaceutical and other Language of publication: English This study contributed to the following comparisons: epinephrine versus salbutamol

Risk of bias

Sanchez 1993 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	NS
Allocation concealment (selection bias)	Unclear risk	NS
Blinding (performance bias and detection bias) Administrative outcomes	Unclear risk	LOS, hospital re-admission
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, clinical score
Blinding (performance bias and detection bias) Pulmonary function outcomes	Unclear risk	Pulmonary tests
Incomplete outcome data (attrition bias) Administrative outcomes	Unclear risk	LOS, hospital re-admission
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Unclear risk	SaO_2, RR, HR, clinical score
Incomplete outcome data (attrition bias) Pulmonary function outcomes	Unclear risk	Pulmonary tests
Other bias	High risk	

Wainwright 2003

Methods	Randomized, placebo-controlled, double-blind study. No withdrawals reported. Data analyzed on an intention-to-treat basis Parallel design, multi-centre (4), 2 arms
Participants	Conducted in Australia, inpatients 194 inpatients (less than 1 year of age) with clinical diagnosis of bronchiolitis; first-time wheezing only; mild, moderate and severe cases included *Group 1* Sample size: 99 Age, mean ± SD: 4.52 ± 3.01 months Males, N (%): 70 (70.7) *Group 2* Sample size: 95 Age, mean ± SD: 4.35 ± 2.95 months

Wainwright 2003 (*Continued*)

	Males, N (%): 61 (64.2)
Interventions	*Group 1*: adrenaline (isomer epinephrine) (4 ml 1%) *Group 2*: placebo (4 ml normal saline) Three doses administered at 4-hour intervals within 24 hours after admission to hospital. Treatment nebulized with oxygen flow at 6 L/min
Outcomes	*Primary outcome* Length of stay and time to be ready for discharge *Secondary outcome* Respiratory rate*, heart rate*, hospital readmission at 1 month, chest recession, time in oxygen, highest oxygen flow rates, need for supplemental parenteral fluids, blood pressure *Outcomes measured at 30 and 60 minutes after each dose
Notes	Funding: none Language of publication: English This study contributed to the following comparisons: epinephrine versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Administrative outcomes	Low risk	LOS, time ready for discharge, hospital readmission
Blinding (performance bias and detection bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, HR, BP, respiratory effort score
Blinding (performance bias and detection bias) Other outcomes	Low risk	Supplemental O_2
Incomplete outcome data (attrition bias) Administrative outcomes	Low risk	LOS, time ready for discharge, hospital readmission
Incomplete outcome data (attrition bias) Clinical scores and other symptoms/clinical outcomes	Low risk	RR, HR, BP, respiratory effort score

Wainwright 2003 (*Continued*)

Incomplete outcome data (attrition bias) Other outcomes	Low risk	Supplemental O_2
Selective reporting (reporting bias)	High risk	
Other bias	Low risk	

AE: adverse events
BP: blood pressure
d/c: discharge
ED: emergency department
epi: epinephrine
h: hour
HR: heart rate
ICU: Intensive Care Unit
ITT: intention-to-treat
IV: intravenous
LOS: length of stay
min: minute
NaCl: sodium chloride
O_2: oxygen
PICU: Pediatric Intensive Care Unit
pla: placebo
RDAI: Respiratory Distress Assessment Index
RR: respiratory rate
RSV: respiratory syncytial virus
NS: not specified
sal: salbutamol
SaO_2: oxygen saturation
SD: standard deviation
SEM: standard error of the mean
tx: treatment

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

Study	Reason for exclusion
Altamirano 2002	Unclear if first episode of wheezing
Altinel 2003	Unclear if first episode of wheezing
Carter 1993	Letter
Carvajal 2001	Study is not randomized

(*Continued*)

Frohna 2009	Commentary
Grewal 2009	Used saline as intervention not epinephrine
Guill 2003	Letter
Gurkan 2004	Unclear if first episode of wheezing
Hariprakash 2003	Recurrent wheezing
King 2003	Comment
Klassen 2003	Commentary
Kristjansson 1993	Not first episode of wheezing
Langley 2005	Unclear if first episode of wheezing
Lopez Andreu 2002	Letter
Lowell 1987	Not first episode of wheezing
Martinon-Torres 2002	Review
Meates 2002	Review
Mesquita 2009	Protocolized use of epinephrine
Misra 2003	Review
Okutan 2002	Letter
Patel 2001	Unclear if first episode of wheezing
Ray 2002	First or second episode of wheezing
Reijonen 1995	Not first episode of wheezing
Rusconi 1996	Letter
Saseen 2004	Review
Schumacher 2010	Commentary
Simsek 2005	Unclear if first episode of wheezing
Tal 2006	Used saline as intervention not epinephrine

(*Continued*)

Valverde 2005	Letter
Van Aerde 2003	Commentary
Walsh 2008	Unclear if first episode of wheezing
Waseem 2006	Editorial
Zhang 2005	Review

DATA AND ANALYSES

Comparison 1. Epinephrine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions at enrollment or < 24 hours (outpatients only)	6	995	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.89]
2 Admissions overall up to 7 days (outpatients only)	3	875	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.63, 1.03]
3 Length of stay (inpatients only)	2	292	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.87, 0.17]
4 Clinical score - all (outpatients)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 minutes	6	975	Std. Mean Difference (IV, Random, 95% CI)	-0.40 [-0.58, -0.23]
4.2 120 minutes	2	105	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-1.13, -0.33]
5 Clinical score - all (inpatients)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 minutes	2	232	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.49, 0.40]
6 Oxygen saturation - all (outpatients)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 60 minutes	5	949	Mean Difference (IV, Random, 95% CI)	0.61 [-0.14, 1.36]
6.2 120 minutes	2	105	Mean Difference (IV, Random, 95% CI)	-0.05 [-1.22, 1.13]
7 Oxygen saturation - all (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 60 minutes	1	38	Mean Difference (IV, Random, 95% CI)	-0.4 [-1.56, 0.76]
8 Respiratory rate - all (outpatients)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 60 minutes	3	844	Mean Difference (IV, Random, 95% CI)	-3.22 [-7.10, 0.65]
9 Respiratory rate - all (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 60 minutes	1	38	Mean Difference (IV, Random, 95% CI)	2.80 [-2.97, 8.57]
10 Heart rate - all (outpatients)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 60 minutes	4	901	Mean Difference (IV, Random, 95% CI)	7.85 [5.63, 10.06]
10.2 120 minutes	2	105	Mean Difference (IV, Random, 95% CI)	1.76 [-5.96, 9.47]
11 Heart rate - all (inpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 60 minutes	2	225	Mean Difference (IV, Random, 95% CI)	13.06 [1.19, 24.92]
12 Hospital readmissions (inpatients)	2	292	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.05, 1.86]
12.1 2 to 10 days	1	98	Risk Ratio (M-H, Random, 95% CI)	0.14 [0.01, 2.59]
12.2 10 to 30 days	1	194	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.04, 5.20]
13 Return visits (ED or any healthcare provider) - (outpatients)	2	800	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.19]
13.1 10 to 30 days	2	800	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.81, 1.19]
14 Return visits (ED or any healthcare provider) - (inpatients)	1	98	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.39]
14.1 2 to 10 days	1	98	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.76, 1.39]
15 Admissions at enrollment or < 24 hours (outpatients only) - subgroup analysis 'synergism'	6	995	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.50, 0.89]

15.1 Protocolized use of steroid	1	400	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.45, 1.23]
15.2 No protocolized use of steroid	5	595	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.40, 0.94]
16 Admissions at enrollment or < 24 hours (outpatients only) only low overall RoB	3	842	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.56, 1.07]
17 Admissions overall up to 7 days (outpatients only) - subgroup analysis 'synergism'	2	800	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.59, 1.05]
17.1 Protocolized use of steroid	1	400	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.45, 0.98]
17.2 No protocolized use of steroid	1	400	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.64, 1.26]
18 Length of stay (inpatients only) only low overall RoB	1	98	Mean Difference (IV, Random, 95% CI)	-0.15 [-1.05, 0.76]
19 Clinical score - all (outpatients) only low RoB	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
19.1 60 minutes	2	796	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.46, -0.18]

Comparison 2. Epinephrine versus salbutamol/albuterol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions at enrollment or < 24 hours (outpatients only)	9	444	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.41, 1.09]
2 Admissions overall up to 7 days (outpatients only)	3	212	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.71, 1.54]
3 Length of stay (inpatients only)	4	261	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.46, -0.09]
4 Length of stay (outpatients only)	1	42	Mean Difference (IV, Random, 95% CI)	0.46 [-0.27, 1.20]
5 Clinical score - all (outpatients)	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 minutes	8	397	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.32, 0.08]
5.2 120 minutes	7	356	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.31, 0.11]
5.3 12 to 24 hours	2	69	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.86, 0.44]
5.4 3 to 10 days	2	69	Std. Mean Difference (IV, Random, 95% CI)	-0.50 [-0.98, -0.02]
6 Clinical score - all (inpatients)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 60 minutes	4	248	Std. Mean Difference (IV, Random, 95% CI)	-0.79 [-1.45, -0.13]
6.2 120 minutes	1	140	Std. Mean Difference (IV, Random, 95% CI)	-0.52 [-0.86, -0.18]
7 Oxygen saturation - all (outpatients)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 60 minutes	6	335	Mean Difference (IV, Random, 95% CI)	-0.37 [-1.18, 0.43]
7.2 120 minutes	5	287	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.63, 0.34]
8 Oxygen saturation - all (inpatients)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 60 minutes	3	218	Mean Difference (IV, Random, 95% CI)	1.32 [0.51, 2.12]
8.2 120 minutes	1	140	Mean Difference (IV, Random, 95% CI)	1.5 [-0.22, 3.22]
9 Respiratory rate - all (outpatients)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only

9.1 60 minutes	4	183	Mean Difference (IV, Random, 95% CI)	-3.75 [-7.43, -0.08]
9.2 120 minutes	4	177	Mean Difference (IV, Random, 95% CI)	-2.59 [-6.08, 0.89]
9.3 12 to 24 hours	2	69	Mean Difference (IV, Random, 95% CI)	-3.44 [-10.64, 3.76]
9.4 > 24 hours	2	69	Mean Difference (IV, Random, 95% CI)	-6.88 [-11.05, -2.71]
10 Respiratory rate - all (inpatients)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 60 minutes	3	218	Mean Difference (IV, Random, 95% CI)	-5.20 [-8.33, -2.07]
10.2 120 minutes	1	140	Mean Difference (IV, Random, 95% CI)	1.0 [-4.30, 6.30]
11 Heart rate - all (outpatients)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 60 minutes	5	248	Mean Difference (IV, Random, 95% CI)	0.30 [-3.67, 4.27]
11.2 120 minutes	6	290	Mean Difference (IV, Random, 95% CI)	1.35 [-4.76, 7.45]
11.3 12 to 24 hours	2	69	Mean Difference (IV, Random, 95% CI)	-3.56 [-16.58, 9.47]
11.4 3 to 10 days	2	69	Mean Difference (IV, Random, 95% CI)	-3.97 [-13.85, 5.91]
12 Heart rate - all (inpatients)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
12.1 60 minutes	3	218	Mean Difference (IV, Random, 95% CI)	0.89 [-0.97, 2.76]
12.2 120 minutes	1	140	Mean Difference (IV, Random, 95% CI)	-5.0 [-10.30, 0.30]
13 Hospital readmissions (inpatients)	2	131	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.1 2 to 10 days	1	101	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 10 to 30 days	1	30	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Return visits (ED or any healthcare provider) - (outpatients)	2	76	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.28, 2.42]
14.1 2 to 10 days	1	41	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.30, 3.64]
14.2 10 to 30 days	1	35	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.05, 3.44]
15 Return visits (ED or any healthcare provider) - (inpatients)	1	101	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.84, 1.61]
15.1 10 to 30 days	1	101	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.84, 1.61]
16 Length of stay (inpatients only) only low RoB overall	1	101	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.01, 0.88]
17 Admissions at enrollment or < 24 hours (outpatients only) only low RoB overall	3	148	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.28, 1.56]
18 Clinical score - all (outpatients) only low RoB	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
18.1 60 minutes	3	135	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.57, 0.11]
18.2 120 minutes	2	108	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.64, 0.42]

Comparison 3. Epinephrine versus steroid

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (outpatients only)	2	444	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.66, 1.88]
2 Admissions overall up to 7 days (outpatients only)	1	399	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.77, 1.52]
3 Clinical score - all (outpatients)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 minutes	2	442	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.12, 0.50]

3.2 120 minutes	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.27, 0.98]
3.3 3 to 6 hours	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.42 [-0.20, 1.05]
4 Oxygen saturation - all (outpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 minutes	2	442	Mean Difference (IV, Random, 95% CI)	-0.99 [-1.46, -0.52]
4.2 120 minutes	1	45	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.07, 0.94]
4.3 3 to 6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.74, 0.57]
5 Respiratory rate - all (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 minutes	1	397	Mean Difference (IV, Random, 95% CI)	0.38 [-1.44, 2.20]
6 Heart rate - all (outpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 60 minutes	2	442	Mean Difference (IV, Random, 95% CI)	-7.56 [-11.34, -3.79]
6.2 120 minutes	1	45	Mean Difference (IV, Random, 95% CI)	0.44 [-7.59, 8.47]
6.3 3 to 6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-0.20 [-8.09, 7.69]
7 Return visits (ED or any healthcare provider) (outpatients)	1	399	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]
7.1 10 to 30 days	1	399	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.93, 1.38]

Comparison 4. Epinephrine and steroid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions at enrollment or < 24 hours (outpatients only)	1	401	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.40, 1.04]
2 Admissions overall up to 7 days (outpatients only)	1	400	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.95]
3 Clinical score (outpatients only)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 minutes	1	399	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.54, -0.14]
4 Oxygen saturation (outpatients only)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 minutes	1	399	Mean Difference (IV, Random, 95% CI)	0.04 [-0.53, 0.61]
5 Respiratory rate (outpatients only)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 minutes	1	399	Mean Difference (IV, Random, 95% CI)	-1.16 [-3.06, 0.74]
6 Heart rate (outpatients only)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 60 minutes	1	399	Mean Difference (IV, Random, 95% CI)	8.44 [4.85, 12.03]
7 Return visits (outpatients only)	1	400	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.90, 1.38]
7.1 10 to 30 days	1	400	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.90, 1.38]

Comparison 5. Epinephrine and steroid versus salbutamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical score - all scores (inpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 120 minutes	1	35	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.87, 0.52]
1.2 12 to 24 hours	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-0.70, 0.70]
1.3 3 to 10 days	1	35	Std. Mean Difference (IV, Random, 95% CI)	-1.22 [-1.98, -0.46]
2 Respiratory rate - all (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 120 minutes	1	35	Mean Difference (IV, Random, 95% CI)	-3.10 [-9.51, 3.31]
2.2 12 to 24 hours	1	35	Mean Difference (IV, Random, 95% CI)	-2.80 [-9.96, 4.36]
2.3 > 24 hours	1	35	Mean Difference (IV, Random, 95% CI)	-13.70 [-20.56, -6.84]
3 Heart rate - all (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 120 minutes	1	35	Mean Difference (IV, Random, 95% CI)	-3.20 [-12.20, 5.80]
3.2 24 to 72 hours	1	35	Mean Difference (IV, Random, 95% CI)	-1.40 [-9.36, 6.56]
3.3 3 to 10 days	1	35	Mean Difference (IV, Random, 95% CI)	-6.30 [-14.21, 1.61]

Comparison 6. Epinephrine versus salbutamol and ipratropium bromide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical score (inpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 6 to 12 hours	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.60 [-1.12, -0.09]
2 Oxygen saturation (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 6 to 12 hours	1	60	Mean Difference (IV, Random, 95% CI)	0.37 [-0.82, 1.56]

Analysis 1.1. Comparison 1 Epinephrine versus placebo, Outcome 1 Admissions at enrollment or < 24 hours (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 1 Admissions at enrollment or < 24 hours (outpatients only)

Study or subgroup	Epinephrine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Anil 2010c	0/38	0/37		0.0 [0.0, 0.0]
Barlas 1998a	0/15	3/15		0.14 [0.01, 2.55]
Khashabi 2005a	8/24	18/24		0.44 [0.24, 0.82]
Plint 2009a	23/200	31/200		0.74 [0.45, 1.23]
Plint 2009b	29/199	36/201		0.81 [0.52, 1.27]
Ralston 2005a	2/17	5/25		0.59 [0.13, 2.69]
Total (95% CI)	**493**	**502**		**0.67 [0.50, 0.89]**

Total events: 62 (Epinephrine), 93 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.76$, df = 4 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 2.72 (P = 0.0065)

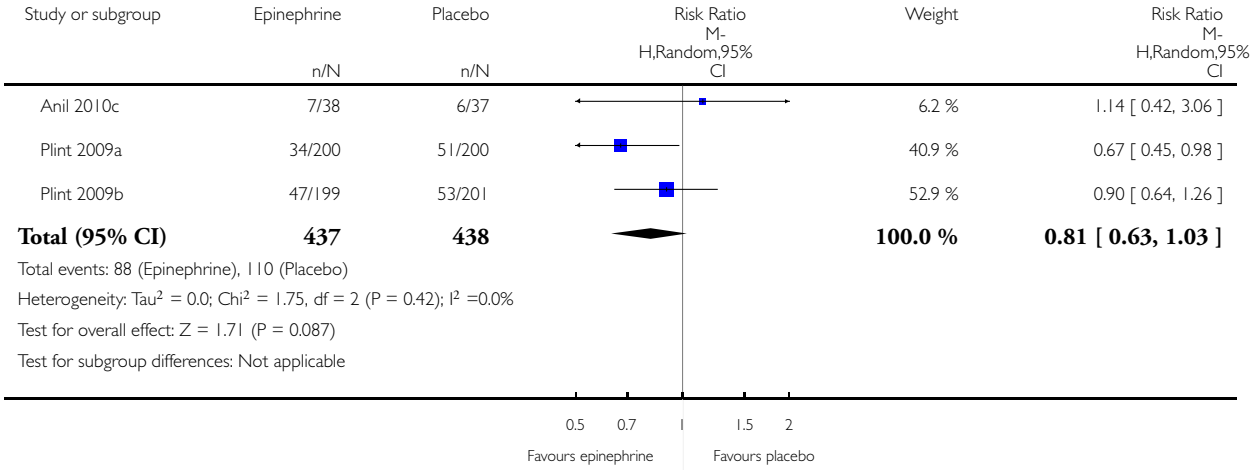
Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Epinephrine versus placebo, Outcome 2 Admissions overall up to 7 days (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 2 Admissions overall up to 7 days (outpatients only)

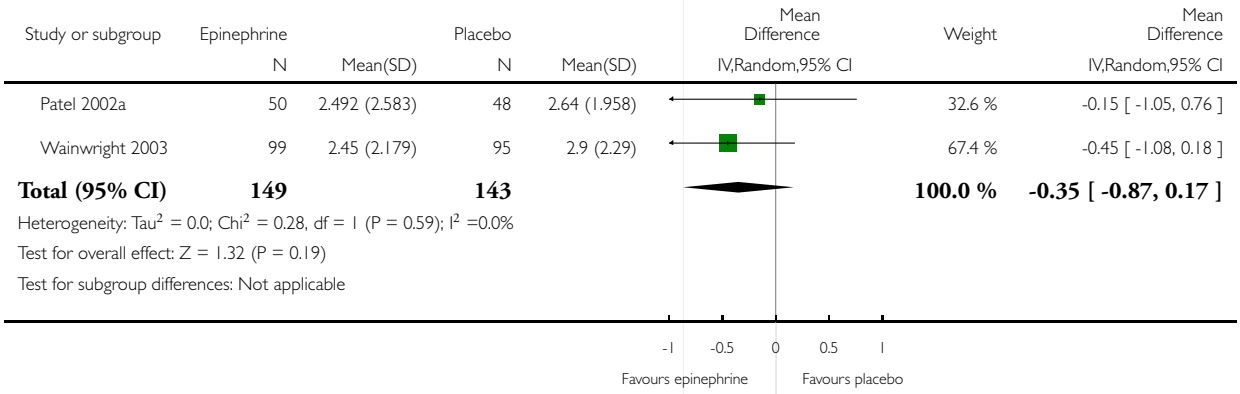


Analysis 1.3. Comparison 1 Epinephrine versus placebo, Outcome 3 Length of stay (inpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 3 Length of stay (inpatients only)



Analysis 1.4. Comparison 1 Epinephrine versus placebo, Outcome 4 Clinical score - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 4 Clinical score - all (outpatients)

Study or subgroup	Epinephrine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 60 minutes							
Anil 2010c	38	-1.8 (1.153)	37	-1.5 (1.114)		12.1 %	-0.26 [-0.72, 0.19]
Barlas 1998a	15	-1.93 (1.589)	15	-0.54 (1.96)		5.1 %	-0.76 [-1.50, -0.01]
Khashabi 2005a	24	-7.5 (4)	24	-2.7 (5.2)		7.5 %	-1.02 [-1.62, -0.41]
Okutan 1998a	16	-1.09 (1.26)	10	-0.1 (1.47)		4.3 %	-0.71 [-1.53, 0.10]
Plint 2009a	199	-2.5 (2.58)	199	-1.75 (2.4)		35.5 %	-0.30 [-0.50, -0.10]
Plint 2009b	198	-2.45 (2.32)	200	-1.65 (2.42)		35.5 %	-0.34 [-0.53, -0.14]
Subtotal (95% CI)	**490**		**485**			**100.0 %**	**-0.40 [-0.58, -0.23]**
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 6.94$, df = 5 (P = 0.23); $I^2 = 28\%$							
Test for overall effect: Z = 4.50 (P < 0.00001)							
2 120 minutes							
Anil 2010c	38	-2.5 (1.2)	37	-1.8 (0.748)		72.1 %	-0.69 [-1.16, -0.22]
Barlas 1998a	15	-3.53 (2.74)	15	-1.27 (2.54)		27.9 %	-0.83 [-1.58, -0.08]
Subtotal (95% CI)	**53**		**52**			**100.0 %**	**-0.73 [-1.13, -0.33]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.61 (P = 0.00030)							

Analysis 1.5. Comparison 1 Epinephrine versus placebo, Outcome 5 Clinical score - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 5 Clinical score - all (inpatients)

Study or subgroup	Epinephrine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 60 minutes							
Abul-Ainine 2002	19	-1.6 (8.282)	19	-3.9 (7.41)		31.7 %	0.29 [-0.35, 0.93]
Wainwright 2003	99	-0.483 (1.538)	95	-0.2 (1.293)		68.3 %	-0.20 [-0.48, 0.08]
Subtotal (95% CI)	**118**		**114**			**100.0 %**	**-0.04 [-0.49, 0.40]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 1.85$, df = 1 (P = 0.17); $I^2 = 46\%$

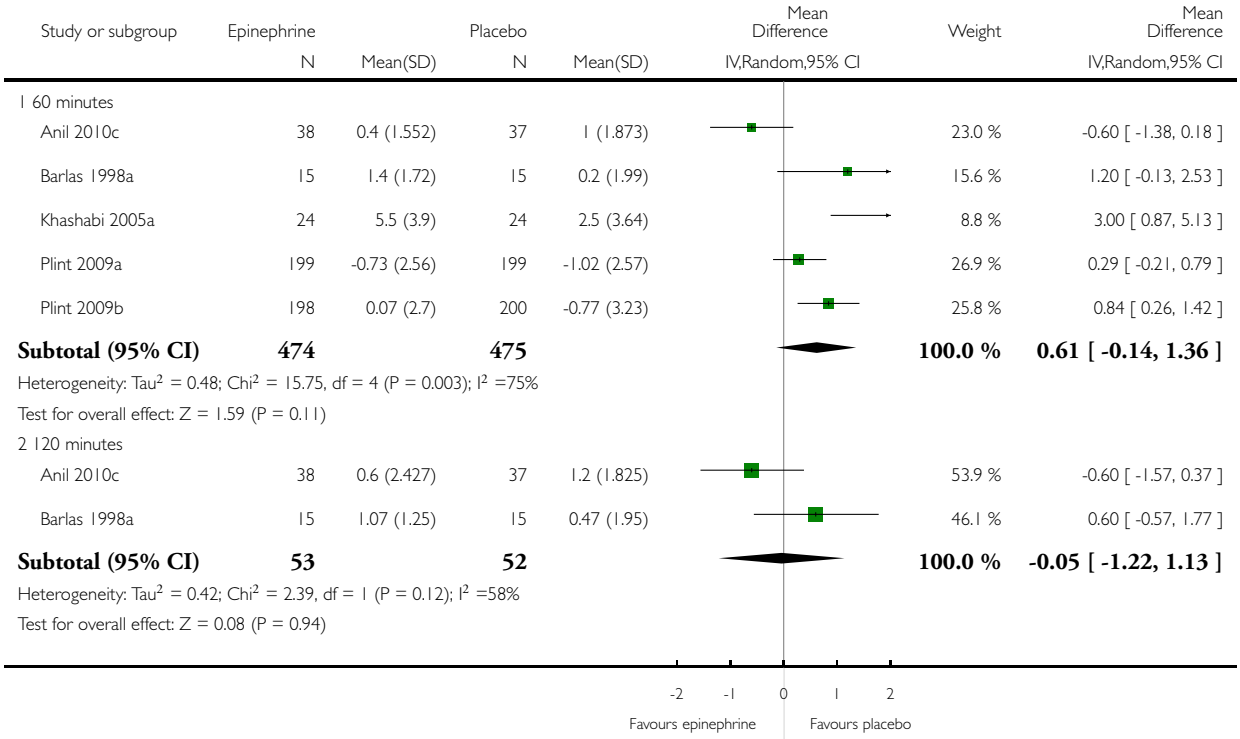
Test for overall effect: Z = 0.20 (P = 0.84)

Analysis 1.6. Comparison 1 Epinephrine versus placebo, Outcome 6 Oxygen saturation - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 6 Oxygen saturation - all (outpatients)

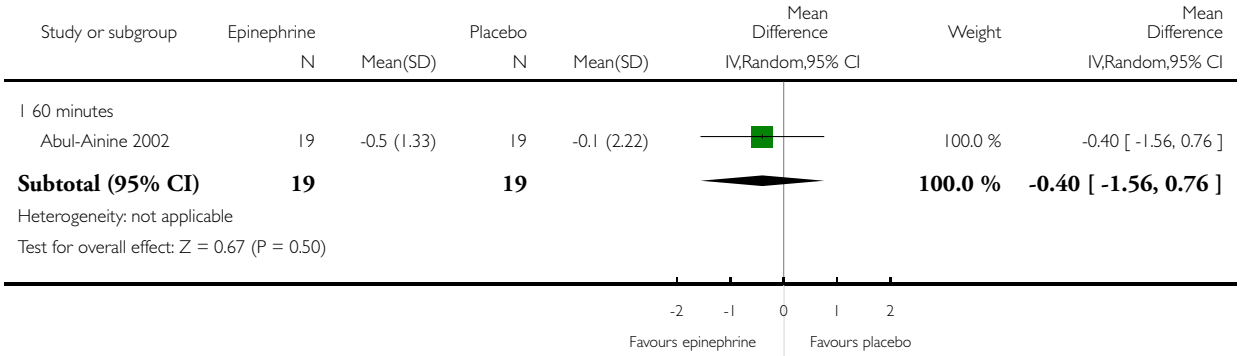


Analysis 1.7. Comparison 1 Epinephrine versus placebo, Outcome 7 Oxygen saturation - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 7 Oxygen saturation - all (inpatients)

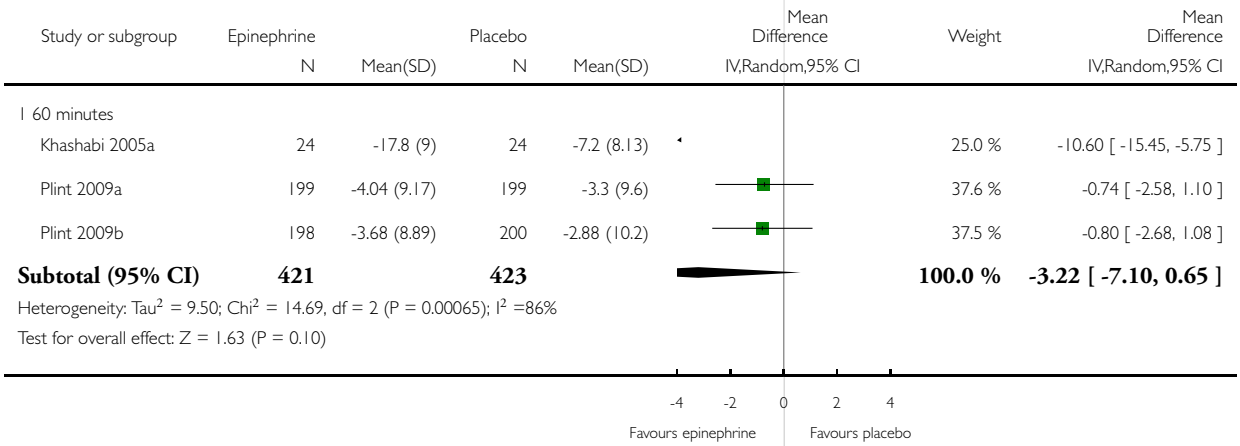


Analysis 1.8. Comparison 1 Epinephrine versus placebo, Outcome 8 Respiratory rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 8 Respiratory rate - all (outpatients)

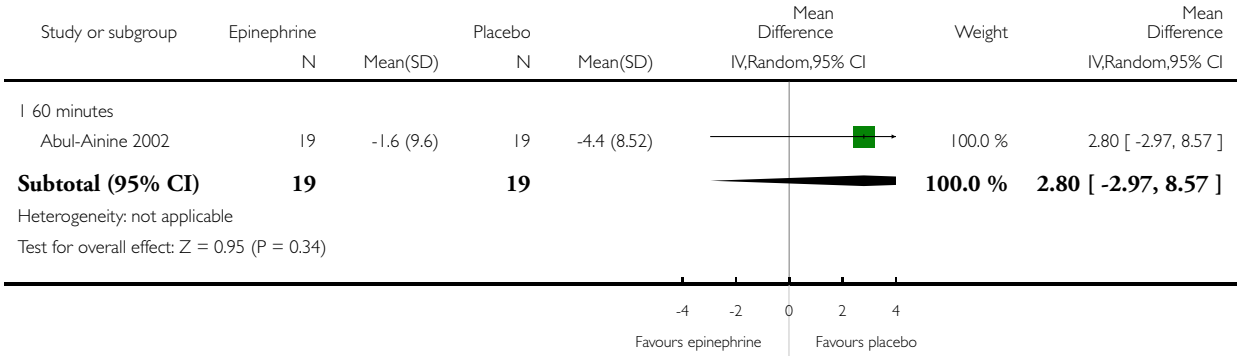


Analysis 1.9. Comparison 1 Epinephrine versus placebo, Outcome 9 Respiratory rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 9 Respiratory rate - all (inpatients)

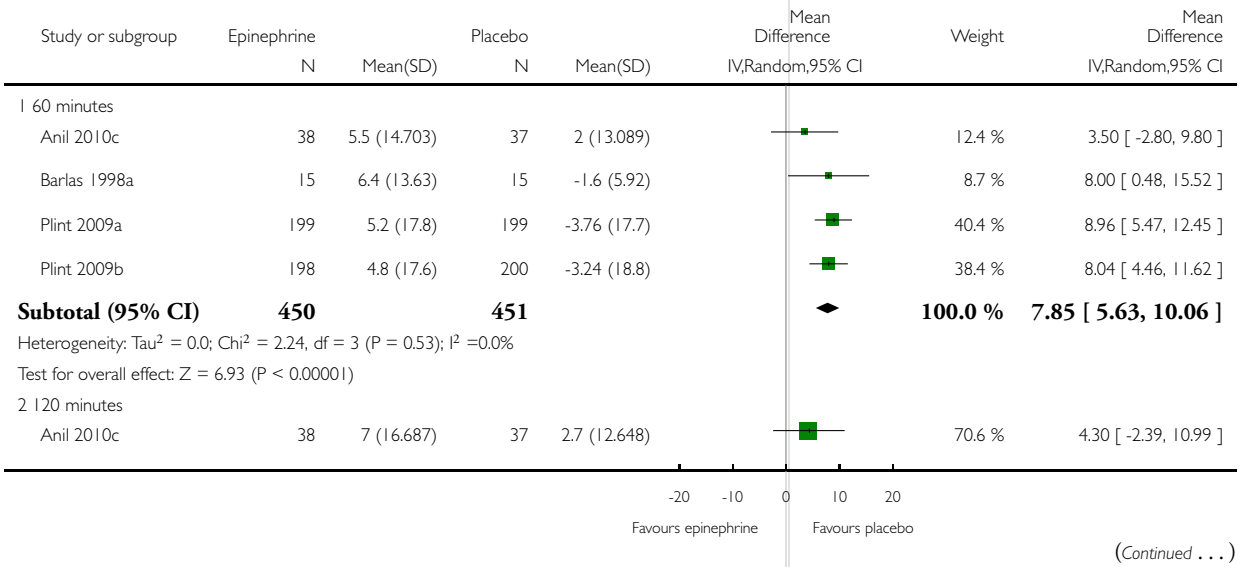


Analysis 1.10. Comparison 1 Epinephrine versus placebo, Outcome 10 Heart rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 10 Heart rate - all (outpatients)



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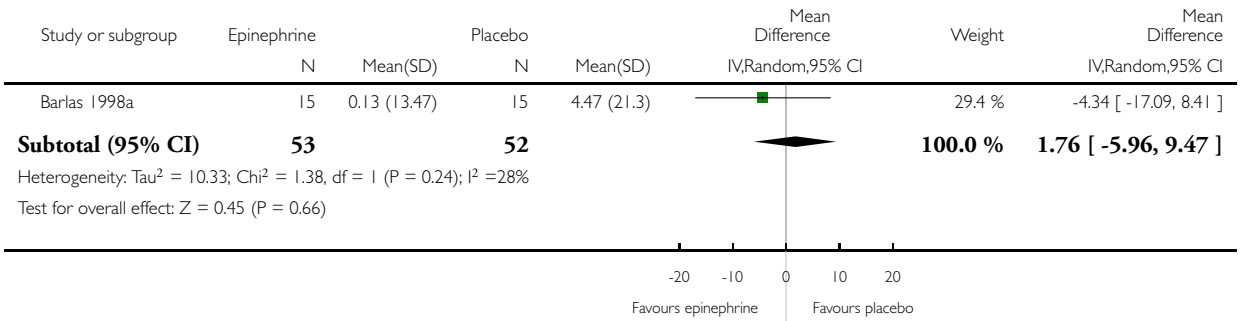
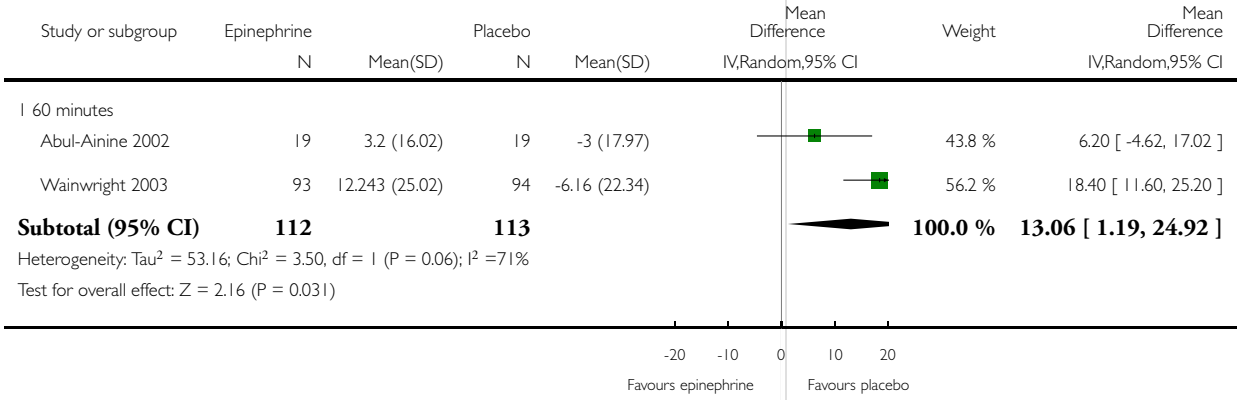


Analysis 1.11. Comparison 1 Epinephrine versus placebo, Outcome 11 Heart rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 11 Heart rate - all (inpatients)

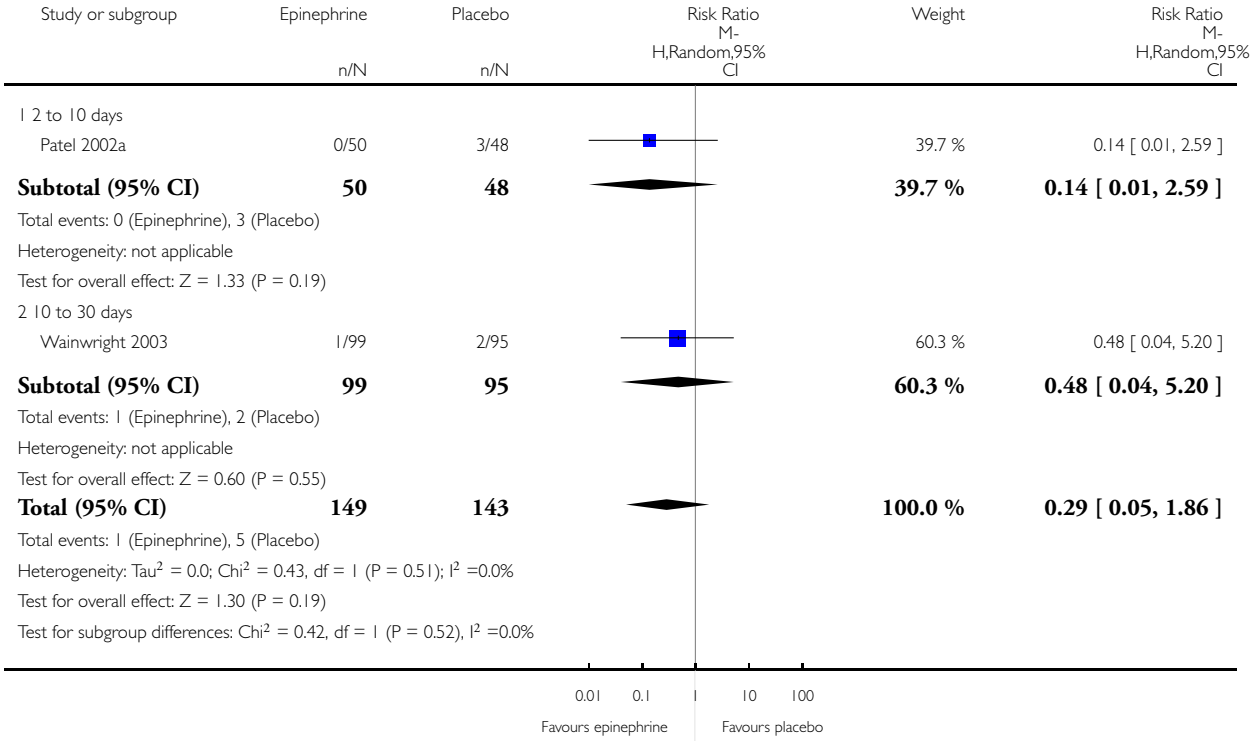


Analysis 1.12. Comparison 1 Epinephrine versus placebo, Outcome 12 Hospital readmissions (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 12 Hospital readmissions (inpatients)

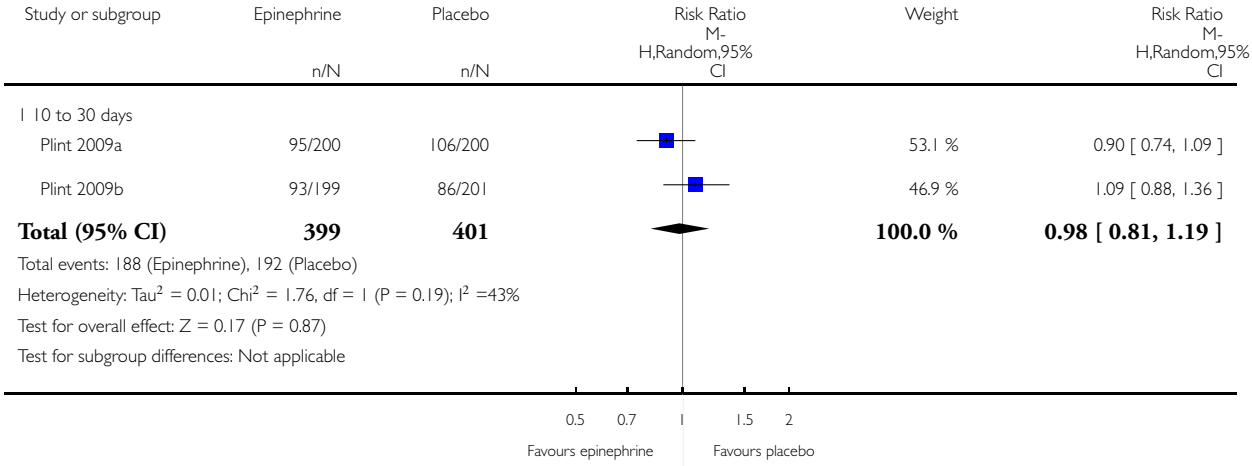


Analysis 1.13. Comparison 1 Epinephrine versus placebo, Outcome 13 Return visits (ED or any healthcare provider) - (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 13 Return visits (ED or any healthcare provider) - (outpatients)

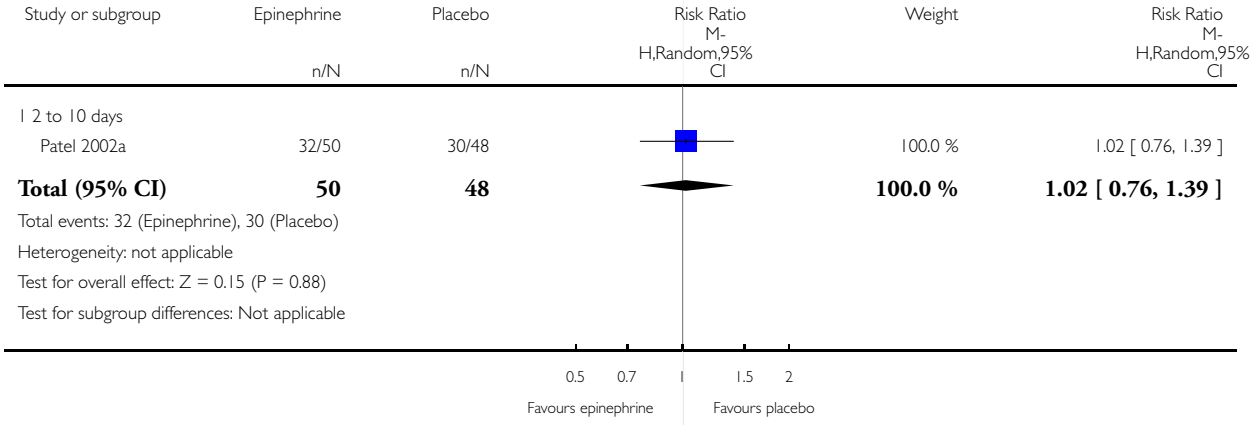


Analysis 1.14. Comparison 1 Epinephrine versus placebo, Outcome 14 Return visits (ED or any healthcare provider) - (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 14 Return visits (ED or any healthcare provider) - (inpatients)



Analysis 1.15. Comparison 1 Epinephrine versus placebo, Outcome 15 Admissions at enrollment or < 24 hours (outpatients only) - subgroup analysis 'synergism'.

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 15 Admissions at enrollment or < 24 hours (outpatients only) - subgroup analysis 'synergism'

Study or subgroup	Epinephrine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Protocolized use of steroid				
Plint 2009a	23/200	31/200		0.74 [0.45, 1.23]
Subtotal (95% CI)	**200**	**200**		**0.74 [0.45, 1.23]**
Total events: 23 (Epinephrine), 31 (Placebo)				
Heterogeneity: not applicable				
Test for overall effect: Z = 1.16 (P = 0.24)				
2 No protocolized use of steroid				
Anil 2010c	0/38	0/37		0.0 [0.0, 0.0]
Barlas 1998a	0/15	3/15		0.14 [0.01, 2.55]
Khashabi 2005a	8/24	18/24		0.44 [0.24, 0.82]
Plint 2009b	29/199	36/201		0.81 [0.52, 1.27]
Ralston 2005a	2/17	5/25		0.59 [0.13, 2.69]
Subtotal (95% CI)	**293**	**302**		**0.62 [0.40, 0.94]**
Total events: 39 (Epinephrine), 62 (Placebo)				
Heterogeneity: Tau^2 = 0.03; Chi^2 = 3.53, df = 3 (P = 0.32); I^2 =15%				
Test for overall effect: Z = 2.24 (P = 0.025)				
Total (95% CI)	**493**	**502**		**0.67 [0.50, 0.89]**
Total events: 62 (Epinephrine), 93 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.76, df = 4 (P = 0.44); I^2 =0.0%				
Test for overall effect: Z = 2.72 (P = 0.0065)				
Test for subgroup differences: Chi^2 = 0.30, df = 1 (P = 0.58), I^2 =0.0%				

Analysis 1.16. Comparison 1 Epinephrine versus placebo, Outcome 16 Admissions at enrollment or < 24 hours (outpatients only) only low overall RoB.

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 16 Admissions at enrollment or < 24 hours (outpatients only) only low overall RoB

Study or subgroup	Epinephrine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Plint 2009a	23/200	31/200		42.2 %	0.74 [0.45, 1.23]
Plint 2009b	29/199	36/201		53.1 %	0.81 [0.52, 1.27]
Ralston 2005a	2/17	5/25		4.6 %	0.59 [0.13, 2.69]
Total (95% CI)	**416**	**426**		**100.0 %**	**0.77 [0.56, 1.07]**

Total events: 54 (Epinephrine), 72 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.20$, df = 2 (P = 0.90); $I^2 = 0.0\%$

Test for overall effect: Z = 1.56 (P = 0.12)

Test for subgroup differences: Not applicable

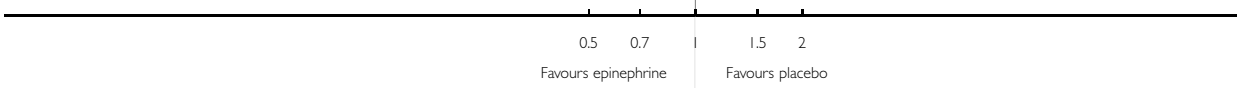
Analysis 1.17. Comparison 1 Epinephrine versus placebo, Outcome 17 Admissions overall up to 7 days (outpatients only) - subgroup analysis 'synergism'.

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 17 Admissions overall up to 7 days (outpatients only) - subgroup analysis 'synergism'

Study or subgroup	Epinephrine n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Protocolized use of steroid					
Plint 2009a	34/200	51/200		44.9 %	0.67 [0.45, 0.98]
Subtotal (95% CI)	**200**	**200**		**44.9 %**	**0.67 [0.45, 0.98]**
Total events: 34 (Epinephrine), 51 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.05 (P = 0.040)					
2 No protocolized use of steroid					
Plint 2009b	47/199	53/201		55.1 %	0.90 [0.64, 1.26]
Subtotal (95% CI)	**199**	**201**		**55.1 %**	**0.90 [0.64, 1.26]**
Total events: 47 (Epinephrine), 53 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.63 (P = 0.53)					
Total (95% CI)	**399**	**401**		**100.0 %**	**0.78 [0.59, 1.05]**
Total events: 81 (Epinephrine), 104 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 1.26, df = 1 (P = 0.26); I^2 =21%					
Test for overall effect: Z = 1.65 (P = 0.099)					
Test for subgroup differences: Chi^2 = 1.26, df = 1 (P = 0.26), I^2 =21%					

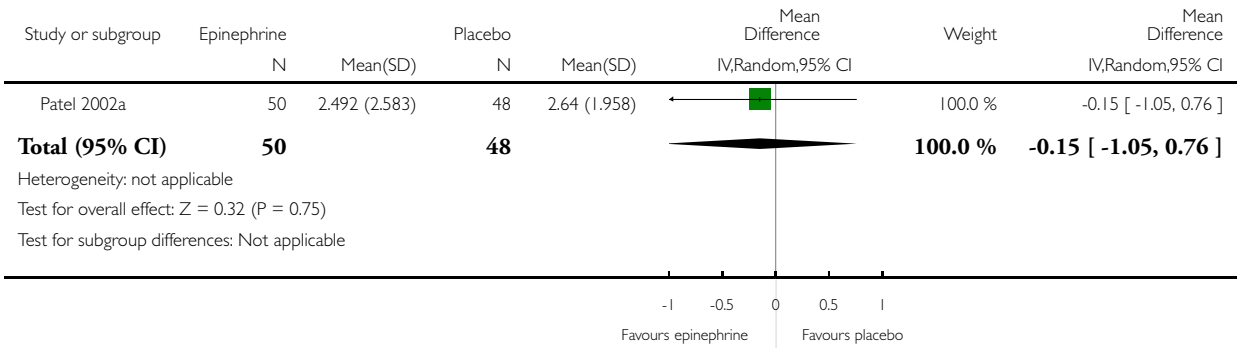


Analysis 1.18. Comparison 1 Epinephrine versus placebo, Outcome 18 Length of stay (inpatients only) only low overall RoB.

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 18 Length of stay (inpatients only) only low overall RoB

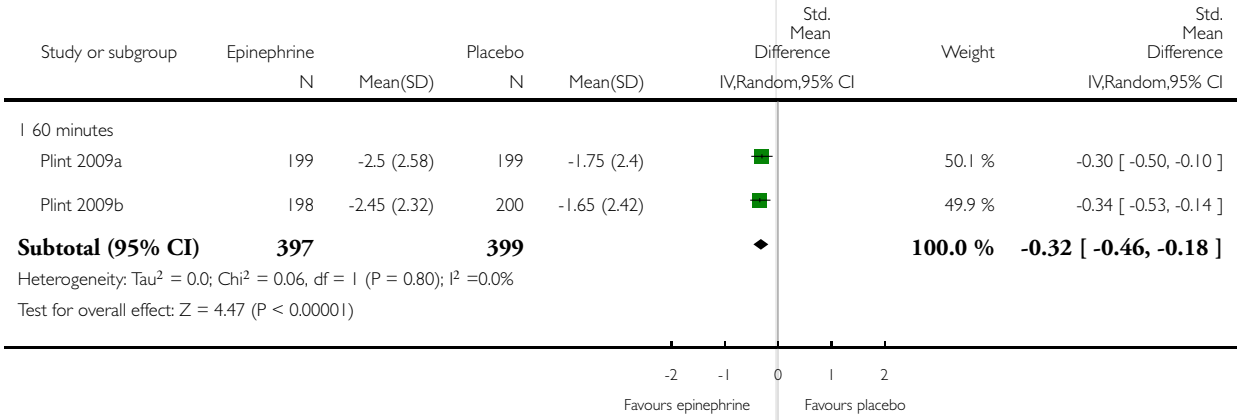


Analysis 1.19. Comparison 1 Epinephrine versus placebo, Outcome 19 Clinical score - all (outpatients) only low RoB.

Review: Epinephrine for bronchiolitis

Comparison: 1 Epinephrine versus placebo

Outcome: 19 Clinical score - all (outpatients) only low RoB



Analysis 2.1. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 1 Admissions at enrollment or < 24 hours (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 1 Admissions at enrollment or < 24 hours (outpatients only)

Study or subgroup	Epinephrine n/N	Salbutamol/Albuterol n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Anil 2010a	0/38	1/36		0.32 [0.01, 7.52]
Anil 2010b	1/39	0/36		2.78 [0.12, 66.02]
Barlas 1998b	0/15	2/15		0.20 [0.01, 3.85]
Khashabi 2005b	8/24	12/24		0.67 [0.33, 1.33]
Kuyucu 2004a	0/11	0/12		0.0 [0.0, 0.0]
Kuyucu 2004b	0/23	0/23		0.0 [0.0, 0.0]
Menon 1995	7/21	17/21		0.41 [0.22, 0.78]
Mull 2004	16/34	12/32		1.25 [0.71, 2.22]
Ralston 2005b	2/17	6/23		0.45 [0.10, 1.97]
Total (95% CI)	**222**	**222**		**0.67 [0.41, 1.09]**

Total events: 34 (Epinephrine), 50 (Salbutamol/Albuterol)

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.68$, df = 6 (P = 0.19); $I^2 = 31\%$

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 2.2. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 2 Admissions overall up to 7 days (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 2 Admissions overall up to 7 days (outpatients only)

Study or subgroup	Epinephrine n/N	Salbutamol/Albuterol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Anil 2010a	7/38	4/36		11.4 %	1.66 [0.53, 5.19]
Anil 2010b	5/39	6/36		12.4 %	0.77 [0.26, 2.30]
Mull 2004	18/32	17/31		76.2 %	1.03 [0.66, 1.60]
Total (95% CI)	**109**	**103**		**100.0 %**	**1.05 [0.71, 1.54]**

Total events: 30 (Epinephrine), 27 (Salbutamol/Albuterol)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.94$, df = 2 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.23 (P = 0.82)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 3 Length of stay (inpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

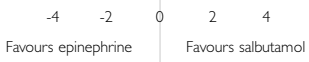
Outcome: 3 Length of stay (inpatients only)

Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol/Albuterol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bertrand 2001	16	4.1 (4.4)	14	5.2 (3.742)		0.4 %	-1.10 [-4.01, 1.81]
Bilan 2007	50	3.47 (1.31)	50	3.91 (1.31)		12.9 %	-0.44 [-0.95, 0.07]
John 2006	15	4.203 (0.281)	15	4.46 (0.284)		82.9 %	-0.26 [-0.46, -0.06]
Patel 2002b	50	2.492 (2.583)	51	2.56 (2.25)		3.8 %	-0.07 [-1.01, 0.88]
Total (95% CI)	**131**		**130**			**100.0 %**	**-0.28 [-0.46, -0.09]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.92$, df = 3 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 2.95 (P = 0.0031)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 4 Length of stay (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 4 Length of stay (outpatients only)

Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol/Albuterol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Menon 1995	21	1.729 (1.267)	21	1.27 (1.158)		100.0 %	0.46 [-0.27, 1.20]
Total (95% CI)	**21**		**21**			**100.0 %**	**0.46 [-0.27, 1.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.23 (P = 0.22)

Test for subgroup differences: Not applicable

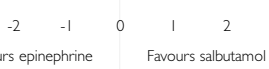
Analysis 2.5. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 5 Clinical score - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 5 Clinical score - all (outpatients)

Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol/Albuterol N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 60 minutes							
Anil 2010a	38	-1.8 (1.153)	36	-1.3 (1.015)		18.3 %	-0.45 [-0.92, 0.01]
Anil 2010b	39	-1.5 (1.277)	36	-1.7 (0.917)		19.0 %	0.18 [-0.28, 0.63]
Barlas 1998b	15	-1.93 (1.589)	15	-2.27 (1.73)		7.6 %	0.20 [-0.52, 0.92]
Beck 2007	12	0.08 (0.77)	15	0.2 (0.68)		6.8 %	-0.16 [-0.92, 0.60]
Khashabi 2005b	24	-7.5 (4)	24	-7 (4.2)		12.2 %	-0.12 [-0.69, 0.45]
Menon 1995	21	6.4 (2.6)	21	6.7 (2.1)		10.7 %	-0.12 [-0.73, 0.48]
Mull 2004	34	-4.02 (1.4)	32	-3.44 (2)		16.6 %	-0.33 [-0.82, 0.15]
Okutan 1998b	16	-1.09 (1.26)	19	-1.23 (1.85)		8.8 %	0.09 [-0.58, 0.75]
Subtotal (95% CI)	**199**		**198**			**100.0 %**	**-0.12 [-0.32, 0.08]**
Heterogeneity: Tau² = 0.0; Chi² = 5.54, df = 7 (P = 0.59); I² =0.0%							
Test for overall effect: Z = 1.20 (P = 0.23)							
2 120 minutes							
Anil 2010a	38	-2.5 (1.2)	36	-2 (1.229)		20.5 %	-0.41 [-0.87, 0.05]
Anil 2010b	39	-1.6 (1.277)	36	-1.8 (0.8544)		21.2 %	0.18 [-0.27, 0.63]
Barlas 1998b	15	-3.53 (2.74)	15	-3.42 (1.77)		8.5 %	-0.05 [-0.76, 0.67]
Kuyucu 2004a	23	-3.5 (0.959)	23	-3.2 (1.439)		13.0 %	-0.24 [-0.82, 0.34]
Kuyucu 2004b	11	-3.2 (0.995)	12	-3.3 (1.386)		6.5 %	0.08 [-0.74, 0.90]
Menon 1995	21	6.6 (2.5)	21	7.5 (1.7)		11.6 %	-0.41 [-1.02, 0.20]
Mull 2004	34	-4.76 (1.4)	32	-4.99 (2)		18.7 %	0.13 [-0.35, 0.62]
Subtotal (95% CI)	**181**		**175**			**100.0 %**	**-0.10 [-0.31, 0.11]**
Heterogeneity: Tau² = 0.0; Chi² = 5.51, df = 6 (P = 0.48); I² =0.0%							
Test for overall effect: Z = 0.93 (P = 0.35)							
3 12 to 24 hours							
Kuyucu 2004a	23	-3.9 (0.959)	23	-3.3 (1.439)		59.5 %	-0.48 [-1.07, 0.10]
Kuyucu 2004b	11	-3.7 (0.995)	12	-3.9 (1.039)		40.5 %	0.19 [-0.63, 1.01]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-0.21 [-0.86, 0.44]**



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Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol/Albuterol N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
Heterogeneity: Tau² = 0.09; Chi² = 1.70, df = 1 (P = 0.19); I² =41%							
Test for overall effect: Z = 0.64 (P = 0.52)							
4 3 to 10 days							
Kuyucu 2004a	23	-5 (0.48)	23	-4.7 (0.48)		65.9 %	-0.61 [-1.21, -0.02]
Kuyucu 2004b	11	-4.5 (0.663)	12	-4.3 (0.693)		34.1 %	-0.28 [-1.11, 0.54]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-0.50 [-0.98, -0.02]**
Heterogeneity: Tau² = 0.0; Chi² = 0.41, df = 1 (P = 0.52); I² =0.0%							
Test for overall effect: Z = 2.04 (P = 0.041)							

Analysis 2.6. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 6 Clinical score - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 6 Clinical score - all (inpatients)

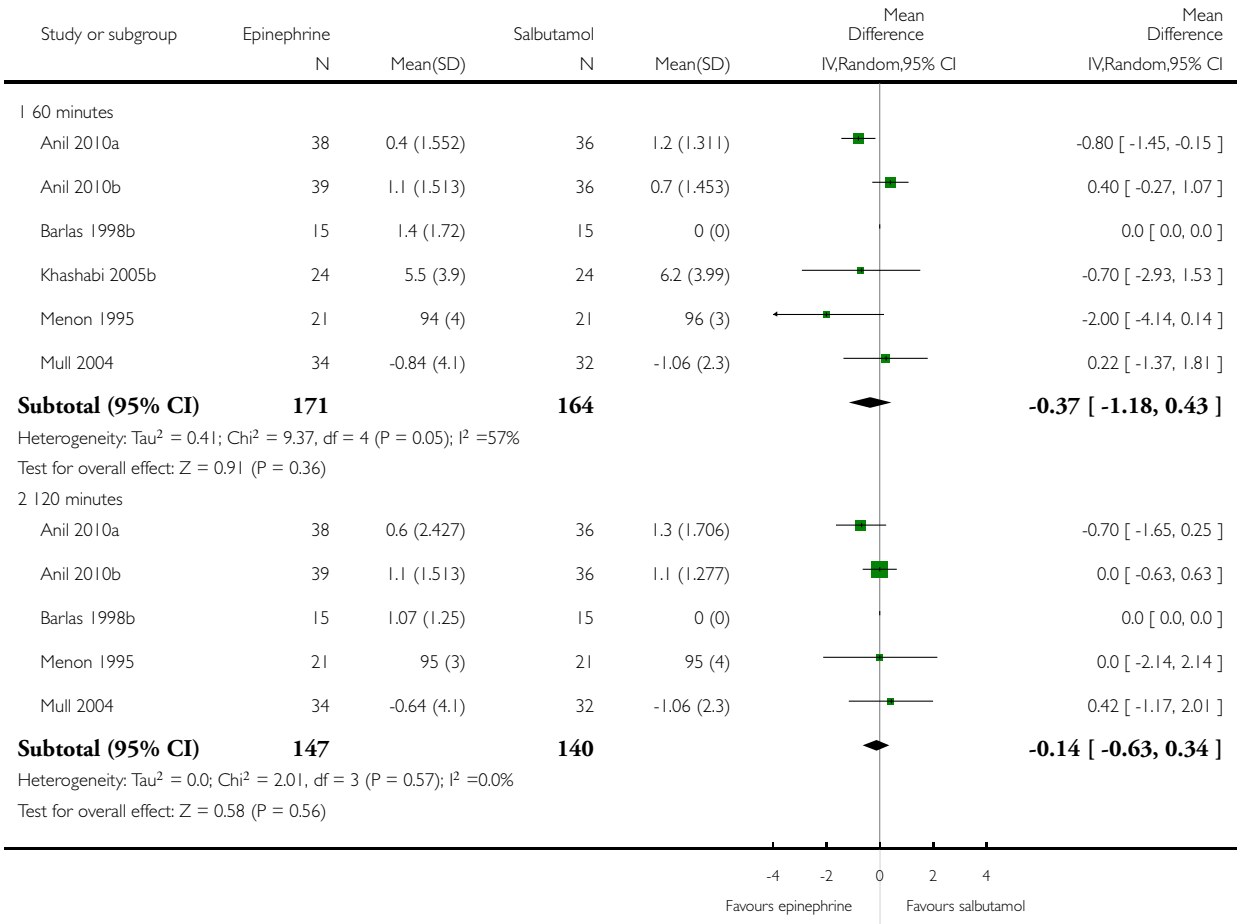
Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol/Albuterol N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 60 minutes							
Abu-Shukair 2001	72	-1.4 (1.141)	68	-1.1 (1.141)		30.3 %	-0.26 [-0.59, 0.07]
Bertrand 2001	16	-0.9 (1.6)	14	-0.3 (1.497)		23.5 %	-0.38 [-1.10, 0.35]
John 2006	15	-5.33 (0.72)	15	-3.93 (0.59)		20.2 %	-2.07 [-2.98, -1.16]
Sanchez 1993	24	-1.8 (1.47)	24	-0.4 (1.96)		26.0 %	-0.79 [-1.38, -0.21]
Subtotal (95% CI)	**127**		**121**			**100.0 %**	**-0.79 [-1.45, -0.13]**
Heterogeneity: Tau² = 0.34; Chi² = 14.44, df = 3 (P = 0.002); I² =79%							
Test for overall effect: Z = 2.36 (P = 0.018)							
2 120 minutes							
Abu-Shukair 2001	72	-2 (1.914)	68	-1 (1.914)		100.0 %	-0.52 [-0.86, -0.18]
Subtotal (95% CI)	**72**		**68**			**100.0 %**	**-0.52 [-0.86, -0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.02 (P = 0.0025)							

Analysis 2.7. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 7 Oxygen saturation - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 7 Oxygen saturation - all (outpatients)



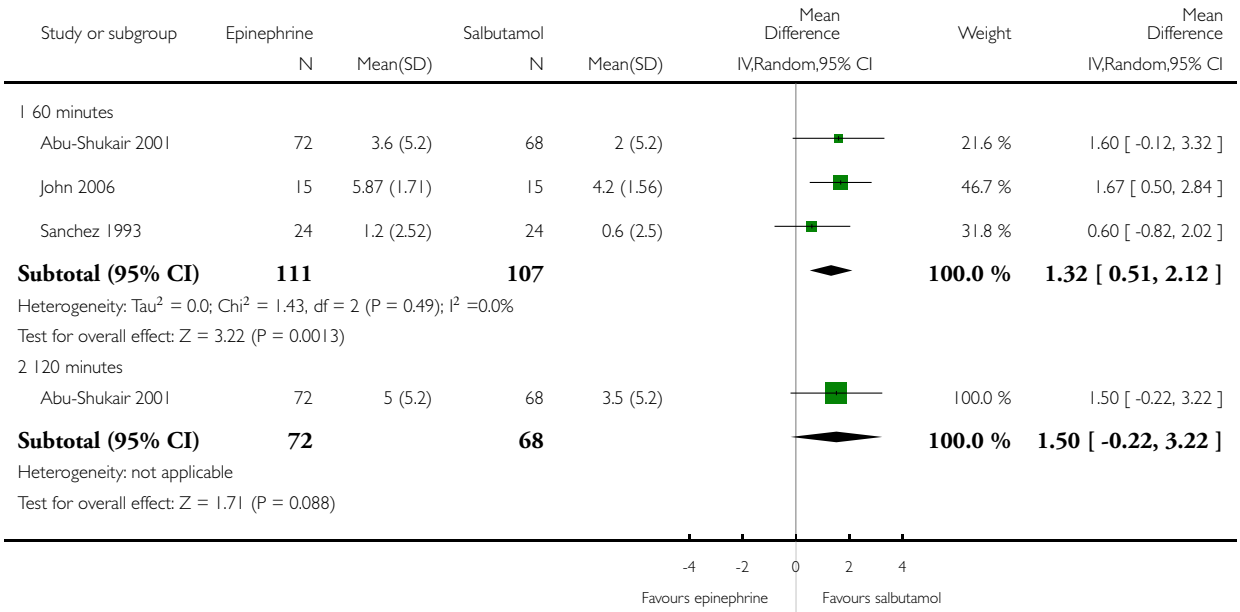
Analysis 2.8. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 8 Oxygen saturation - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 8 Oxygen saturation - all (inpatients)

Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 minutes							
Abu-Shukair 2001	72	3.6 (5.2)	68	2 (5.2)		21.6 %	1.60 [-0.12, 3.32]
John 2006	15	5.87 (1.71)	15	4.2 (1.56)		46.7 %	1.67 [0.50, 2.84]
Sanchez 1993	24	1.2 (2.52)	24	0.6 (2.5)		31.8 %	0.60 [-0.82, 2.02]
Subtotal (95% CI)	**111**		**107**			**100.0 %**	**1.32 [0.51, 2.12]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.43$, df = 2 (P = 0.49); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.22 (P = 0.0013)							
2 120 minutes							
Abu-Shukair 2001	72	5 (5.2)	68	3.5 (5.2)		100.0 %	1.50 [-0.22, 3.22]
Subtotal (95% CI)	**72**		**68**			**100.0 %**	**1.50 [-0.22, 3.22]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.71 (P = 0.088)							



Analysis 2.9. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 9 Respiratory rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 9 Respiratory rate - all (outpatients)

Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 minutes							
Beck 2007	12	0 (16)	15	0.7 (16)		9.2 %	-0.70 [-12.85, 11.45]
Khashabi 2005b	24	-17.8 (9)	24	-11.8 (9.71)		48.1 %	-6.00 [-11.30, -0.70]
Menon 1995	21	50 (13)	21	55 (16)		17.4 %	-5.00 [-13.82, 3.82]
Mull 2004	34	-5.77 (13.5)	32	-6.03 (16.5)		25.3 %	0.26 [-7.04, 7.56]
Subtotal (95% CI)	**91**		**92**			**100.0 %**	**-3.75 [-7.43, -0.08]**
Heterogeneity: Tau² = 0.0; Chi² = 2.17, df = 3 (P = 0.54); I² =0.0%							
Test for overall effect: Z = 2.00 (P = 0.045)							
2 120 minutes							
Kuyucu 2004a	23	-24 (8.2)	23	-19 (10.02)		37.2 %	-5.00 [-10.29, 0.29]
Kuyucu 2004b	11	-18.4 (9.16)	12	-20.9 (9.66)		19.0 %	2.50 [-5.19, 10.19]
Menon 1995	21	49 (11)	21	54 (12)		22.8 %	-5.00 [-11.96, 1.96]
Mull 2004	34	-6.76 (13.5)	32	-6.44 (16.5)		21.0 %	-0.32 [-7.62, 6.98]
Subtotal (95% CI)	**89**		**88**			**100.0 %**	**-2.59 [-6.08, 0.89]**
Heterogeneity: Tau² = 1.21; Chi² = 3.31, df = 3 (P = 0.35); I² =9%							
Test for overall effect: Z = 1.46 (P = 0.14)							
3 12 to 24 hours							
Kuyucu 2004a	23	-27.3 (10.58)	23	-20.6 (11.58)		55.9 %	-6.70 [-13.11, -0.29]
Kuyucu 2004b	11	-23.8 (9.77)	12	-24.5 (10.09)		44.1 %	0.70 [-7.42, 8.82]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-3.44 [-10.64, 3.76]**
Heterogeneity: Tau² = 13.45; Chi² = 1.97, df = 1 (P = 0.16); I² =49%							
Test for overall effect: Z = 0.94 (P = 0.35)							
4 > 24 hours							
Kuyucu 2004a	23	-39.1 (8.13)	23	-31.9 (9.01)		70.7 %	-7.20 [-12.16, -2.24]
Kuyucu 2004b	11	-31.5 (8.17)	12	-25.4 (10.6)		29.3 %	-6.10 [-13.80, 1.60]
Subtotal (95% CI)	**34**		**35**			**100.0 %**	**-6.88 [-11.05, -2.71]**
Heterogeneity: Tau² = 0.0; Chi² = 0.06, df = 1 (P = 0.81); I² =0.0%							
Test for overall effect: Z = 3.23 (P = 0.0012)							

Analysis 2.10. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 10 Respiratory rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 10 Respiratory rate - all (inpatients)

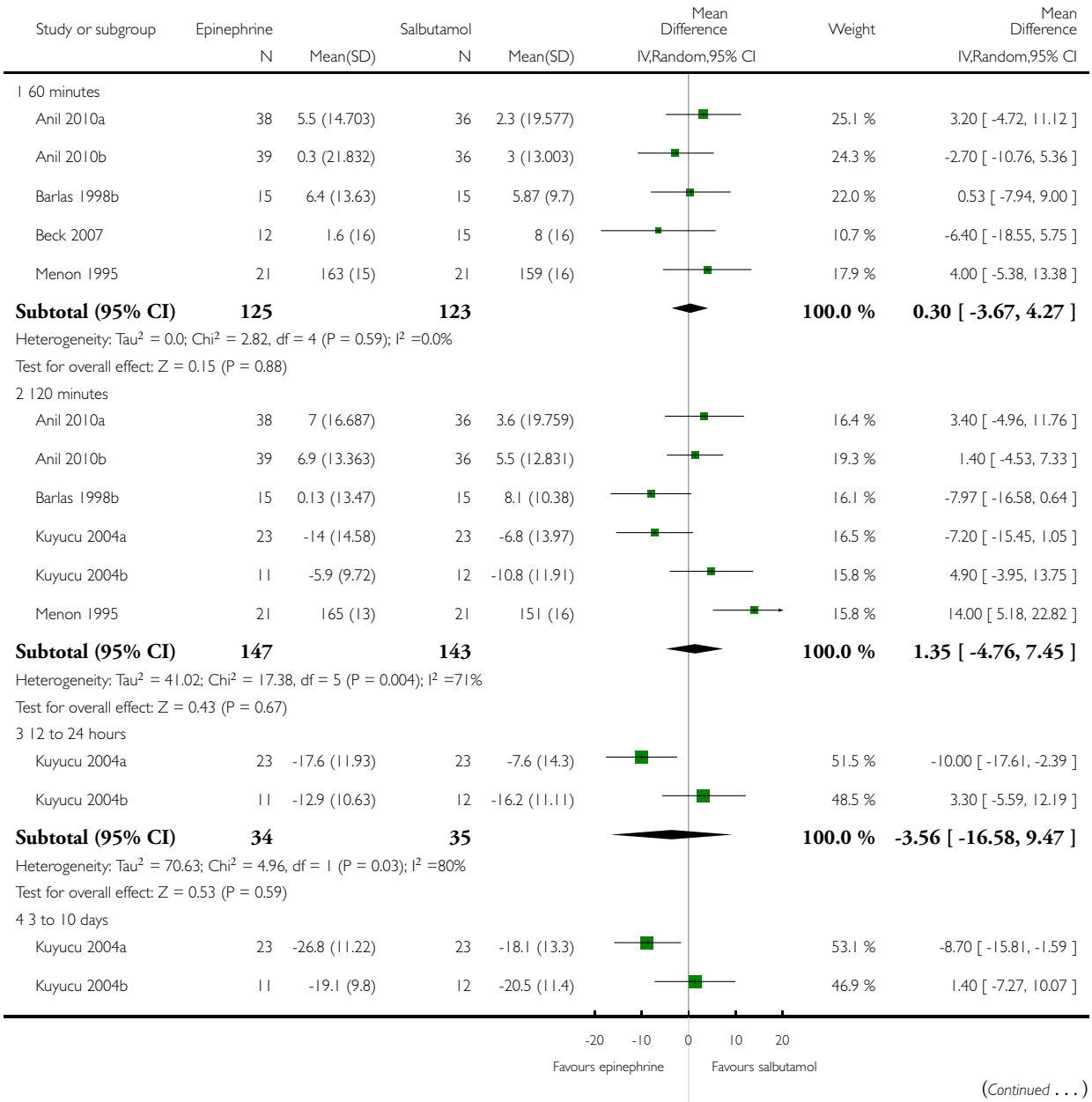
Study or subgroup	Epinephrine N	Mean(SD)	Salbutamol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 minutes							
Abu-Shukair 2001	72	-6 (16)	68	-5 (16)		20.4 %	-1.00 [-6.30, 4.30]
John 2006	15	-16.67 (3.17)	15	-9.07 (1.91)		42.0 %	-7.60 [-9.47, -5.73]
Sanchez 1993	24	-11 (4.4)	24	-6.2 (4.45)		37.6 %	-4.80 [-7.30, -2.30]
Subtotal (95% CI)	**111**		**107**			**100.0 %**	**-5.20 [-8.33, -2.07]**
Heterogeneity: $Tau^2 = 5.14$; $Chi^2 = 7.04$, df = 2 (P = 0.03); $I^2 = 72\%$							
Test for overall effect: Z = 3.26 (P = 0.0011)							
2 120 minutes							
Abu-Shukair 2001	72	-8 (16)	68	-9 (16)		100.0 %	1.00 [-4.30, 6.30]
Subtotal (95% CI)	**72**		**68**			**100.0 %**	**1.00 [-4.30, 6.30]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.37 (P = 0.71)							

Analysis 2.11. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 11 Heart rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 11 Heart rate - all (outpatients)



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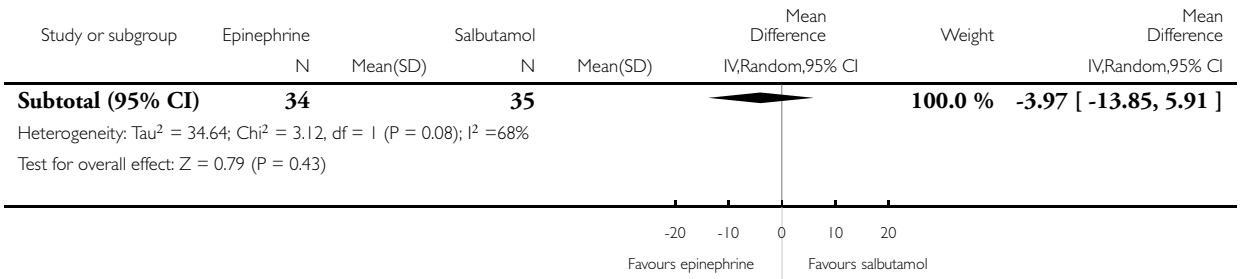
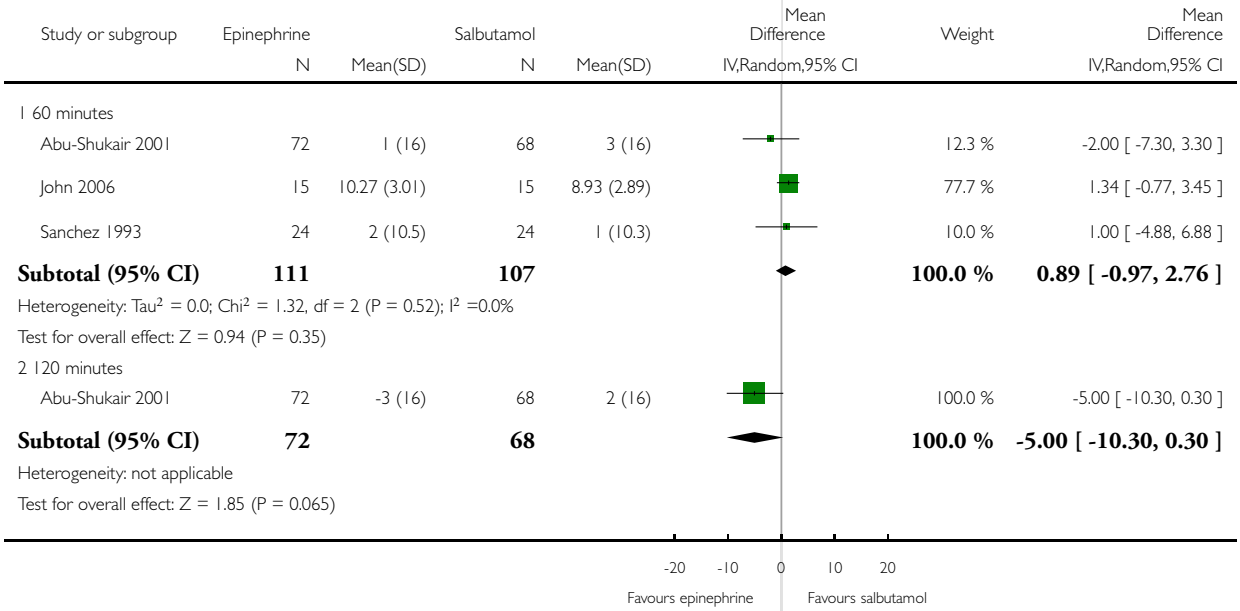


Analysis 2.12. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 12 Heart rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 12 Heart rate - all (inpatients)



Analysis 2.13. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 13 Hospital readmissions (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 13 Hospital readmissions (inpatients)

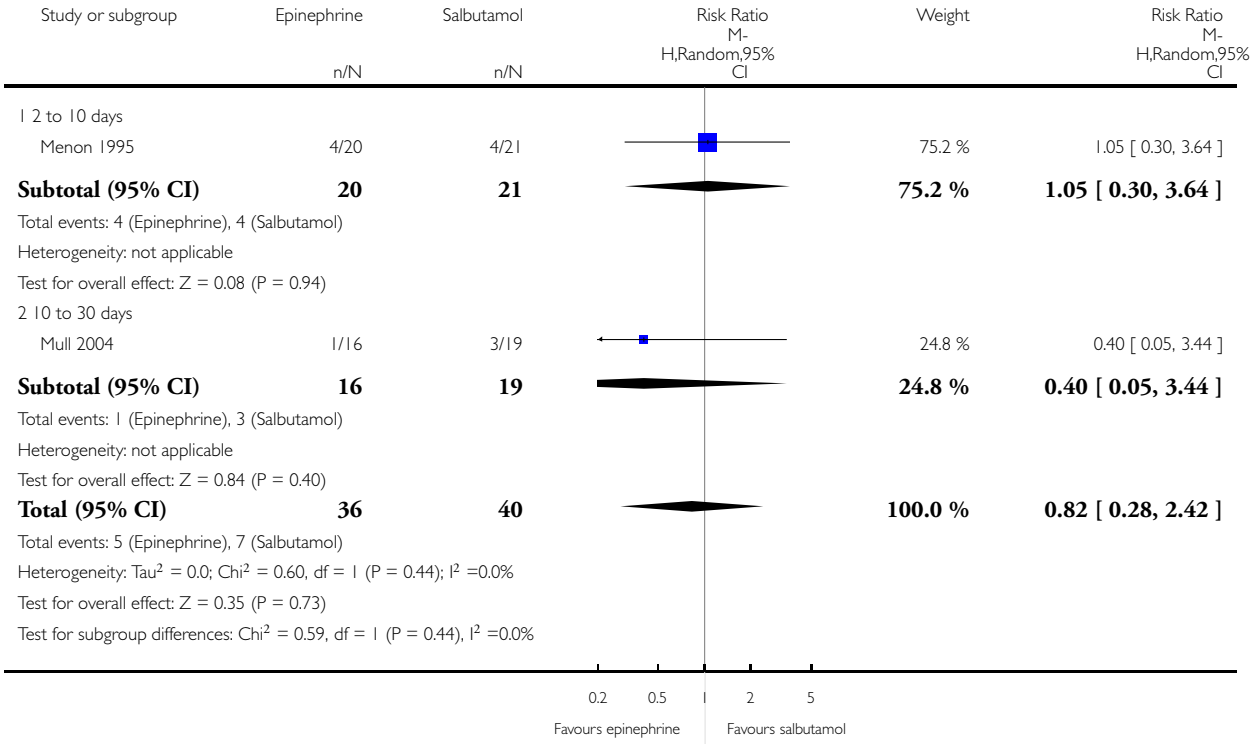
Study or subgroup	Epinephrine n/N	Salbutamol n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 2 to 10 days				
Patel 2002b	0/50	0/51		0.0 [0.0, 0.0]
Subtotal (95% CI)	**50**	**51**		**0.0 [0.0, 0.0]**
Total events: 0 (Epinephrine), 0 (Salbutamol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 10 to 30 days				
Bertrand 2001	0/16	0/14		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**14**		**0.0 [0.0, 0.0]**
Total events: 0 (Epinephrine), 0 (Salbutamol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**66**	**65**		**0.0 [0.0, 0.0]**
Total events: 0 (Epinephrine), 0 (Salbutamol)				
Heterogeneity: Tau² = ï½; Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi² = 0.0, df = -1 (P = 0.0), I² =0.0%				

Analysis 2.14. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 14 Return visits (ED or any healthcare provider) - (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 14 Return visits (ED or any healthcare provider) - (outpatients)

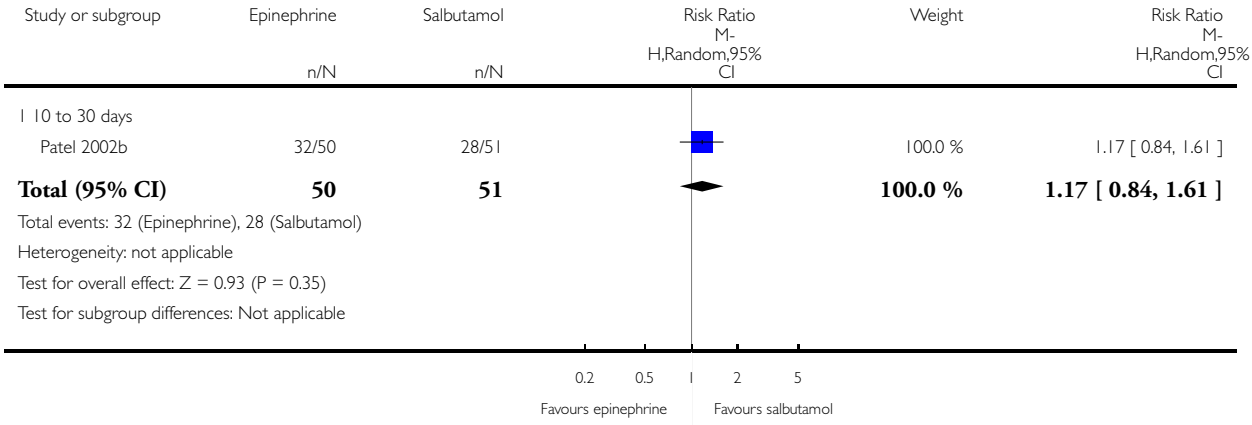


Analysis 2.15. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 15 Return visits (ED or any healthcare provider) - (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 15 Return visits (ED or any healthcare provider) - (inpatients)

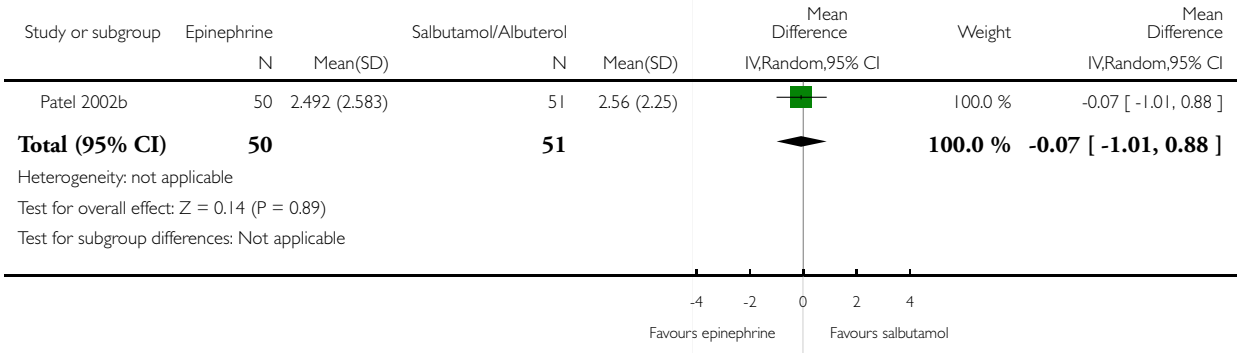


Analysis 2.16. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 16 Length of stay (inpatients only) only low RoB overall.

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 16 Length of stay (inpatients only) only low RoB overall

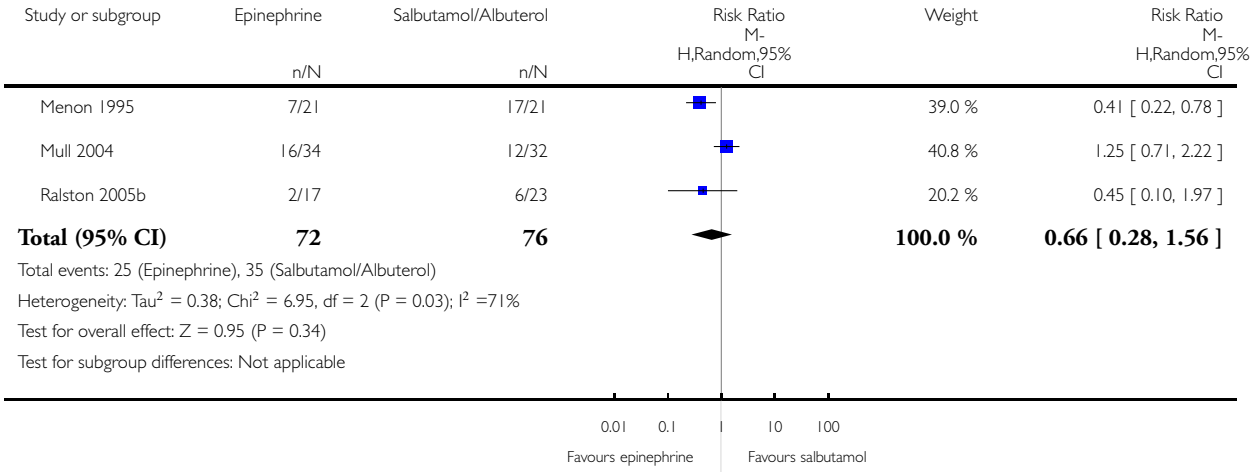


Analysis 2.17. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 17 Admissions at enrollment or < 24 hours (outpatients only) only low RoB overall.

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 17 Admissions at enrollment or < 24 hours (outpatients only) only low RoB overall

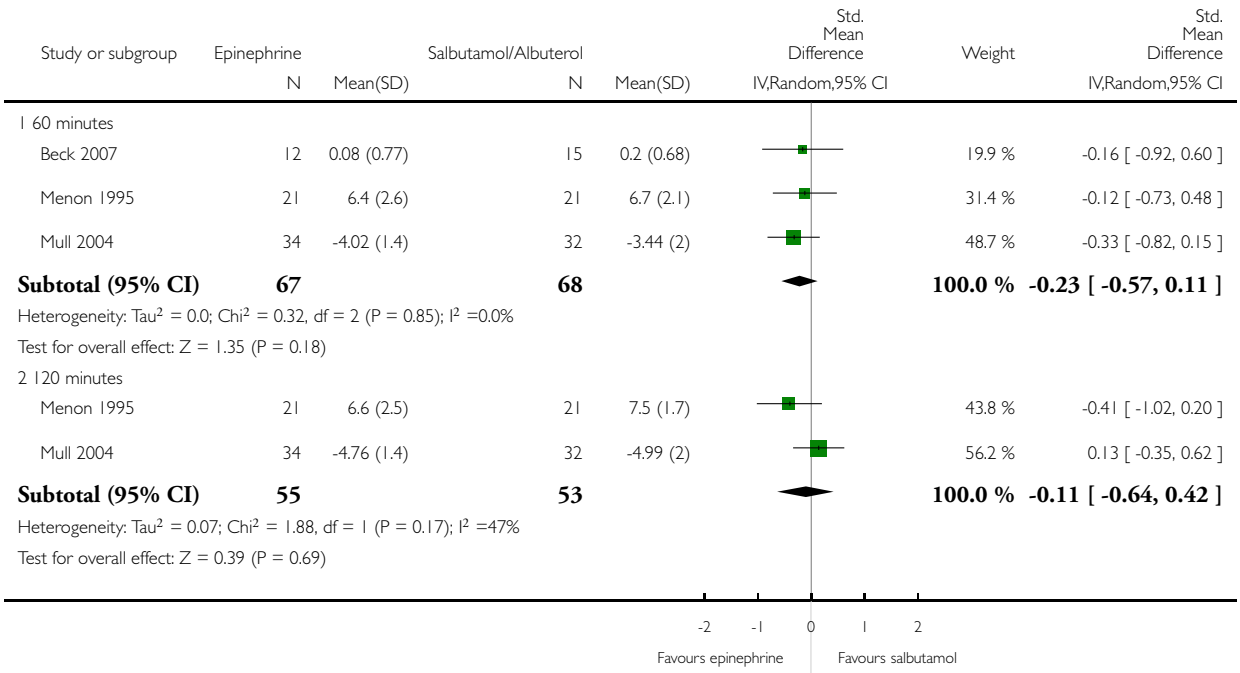


Analysis 2.18. Comparison 2 Epinephrine versus salbutamol/albuterol, Outcome 18 Clinical score - all (outpatients) only low RoB.

Review: Epinephrine for bronchiolitis

Comparison: 2 Epinephrine versus salbutamol/albuterol

Outcome: 18 Clinical score - all (outpatients) only low RoB



Analysis 3.1. Comparison 3 Epinephrine versus steroid, Outcome 1 Admissions (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 1 Admissions (outpatients only)

Study or subgroup	Steroid n/N	Epinephrine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Barlas 1998c	4/30	0/15		3.3 %	4.65 [0.27, 81.01]
Plint 2009c	31/200	29/199		96.7 %	1.06 [0.67, 1.70]
Total (95% CI)	**230**	**214**		**100.0 %**	**1.12 [0.66, 1.88]**

Total events: 35 (Steroid), 29 (Epinephrine)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 1.02$, df = 1 (P = 0.31); $I^2 = 2\%$

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Epinephrine versus steroid, Outcome 2 Admissions overall up to 7 days (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 2 Admissions overall up to 7 days (outpatients only)

Study or subgroup	Steroid n/N	Epinephrine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Plint 2009c	51/200	47/199		100.0 %	1.08 [0.77, 1.52]
Total (95% CI)	**200**	**199**		**100.0 %**	**1.08 [0.77, 1.52]**

Total events: 51 (Steroid), 47 (Epinephrine)

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Epinephrine versus steroid, Outcome 3 Clinical score - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 3 Clinical score - all (outpatients)

Study or subgroup	Steroid N	Mean(SD)	Epinephrine N	Mean(SD)	Std. Mean Difference IV,Random,95% CI	Weight	Std. Mean Difference IV,Random,95% CI
1 60 minutes							
Barlas 1998c	30	-1.135 (1.72)	15	-1.93 (1.589)		9.0 %	0.47 [-0.16, 1.09]
Plint 2009c	199	-1.75 (2.4)	198	-2.45 (2.32)		91.0 %	0.30 [0.10, 0.49]
Subtotal (95% CI)	**229**		**213**			**100.0 %**	**0.31 [0.12, 0.50]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.25$, df = 1 (P = 0.61); $I^2 = 0.0\%$							
Test for overall effect: Z = 3.23 (P = 0.0012)							
2 120 minutes							
Barlas 1998c	30	-2.65 (2.28)	15	-3.53 (2.74)		100.0 %	0.35 [-0.27, 0.98]
Subtotal (95% CI)	**30**		**15**			**100.0 %**	**0.35 [-0.27, 0.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
3 3 to 6 hours							
Barlas 1998c	30	-2.915 (2.67)	15	-3.95 (1.75)		100.0 %	0.42 [-0.20, 1.05]
Subtotal (95% CI)	**30**		**15**			**100.0 %**	**0.42 [-0.20, 1.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.32 (P = 0.19)							

Analysis 3.4. Comparison 3 Epinephrine versus steroid, Outcome 4 Oxygen saturation - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 4 Oxygen saturation - all (outpatients)

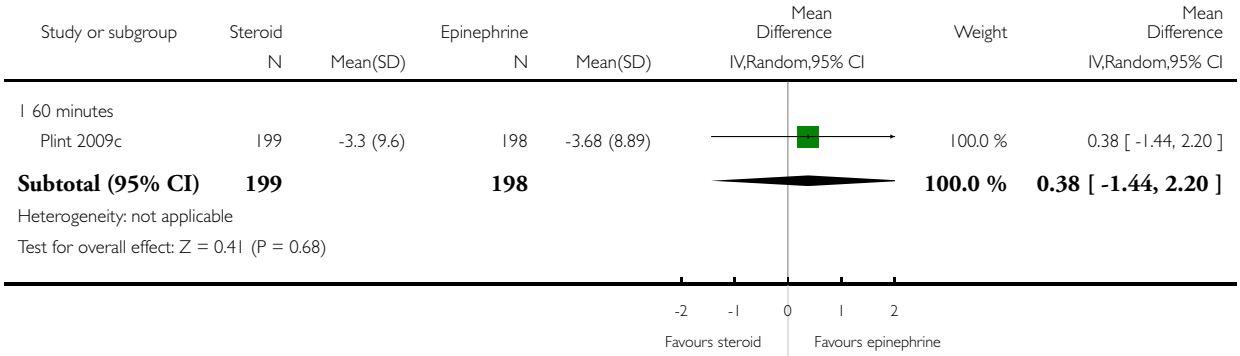
Study or subgroup	Steroid N	Mean(SD)	Epinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 minutes							
Barlas 1998c	30	0.87 (2.018)	15	1.4 (1.72)		17.4 %	-0.53 [-1.66, 0.60]
Plint 2009c	199	-1.02 (2.57)	198	0.07 (2.7)		82.6 %	-1.09 [-1.61, -0.57]
Subtotal (95% CI)	**229**		**213**			**100.0 %**	**-0.99 [-1.46, -0.52]**
Heterogeneity: Tau² = 0.0; Chi² = 0.78, df = 1 (P = 0.38); I² =0.0%							
Test for overall effect: Z = 4.13 (P = 0.000037)							
2 120 minutes							
Barlas 1998c	30	1.005 (2.172)	15	1.07 (1.25)		100.0 %	-0.07 [-1.07, 0.94]
Subtotal (95% CI)	**30**		**15**			**100.0 %**	**-0.07 [-1.07, 0.94]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.13 (P = 0.90)							
3 3 to 6 hours							
Barlas 1998c	30	0.795 (1.804)	15	1.38 (1.89)		100.0 %	-0.58 [-1.74, 0.57]
Subtotal (95% CI)	**30**		**15**			**100.0 %**	**-0.58 [-1.74, 0.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.99 (P = 0.32)							

Analysis 3.5. Comparison 3 Epinephrine versus steroid, Outcome 5 Respiratory rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 5 Respiratory rate - all (outpatients)

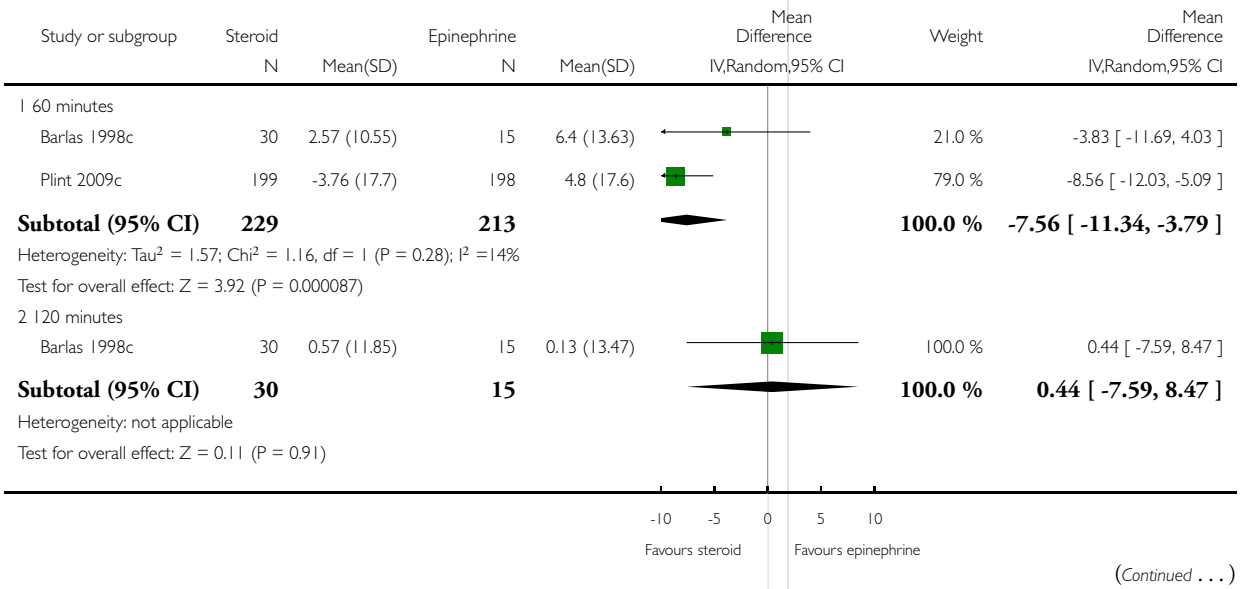


Analysis 3.6. Comparison 3 Epinephrine versus steroid, Outcome 6 Heart rate - all (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

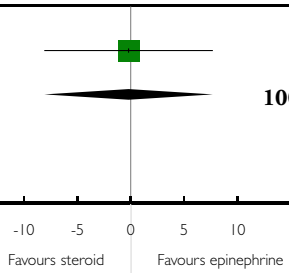
Outcome: 6 Heart rate - all (outpatients)



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Steroid N	Mean(SD)	Epinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
3 3 to 6 hours							
Barlas 1998c	30	1.2 (12.17)	15	1.4 (12.99)		100.0 %	-0.20 [-8.09, 7.69]
Subtotal (95% CI)	**30**		**15**			**100.0 %**	**-0.20 [-8.09, 7.69]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.05 (P = 0.96)							



Analysis 3.7. Comparison 3 Epinephrine versus steroid, Outcome 7 Return visits (ED or any healthcare provider) (outpatients).

Review: Epinephrine for bronchiolitis

Comparison: 3 Epinephrine versus steroid

Outcome: 7 Return visits (ED or any healthcare provider) (outpatients)

Study or subgroup	Steroid n/N	Epinephrine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 10 to 30 days					
Plint 2009c	106/200	93/199		100.0 %	1.13 [0.93, 1.38]
Total (95% CI)	**200**	**199**		**100.0 %**	**1.13 [0.93, 1.38]**
Total events: 106 (Steroid), 93 (Epinephrine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.25 (P = 0.21)					
Test for subgroup differences: Not applicable					

Analysis 4.1. Comparison 4 Epinephrine and steroid versus placebo, Outcome 1 Admissions at enrollment or < 24 hours (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 1 Admissions at enrollment or < 24 hours (outpatients only)

Study or subgroup	Epi+Steroid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Plint 2009d	23/200	36/201		100.0 %	0.64 [0.40, 1.04]
Total (95% CI)	**200**	**201**		**100.0 %**	**0.64 [0.40, 1.04]**
Total events: 23 (Epi+Steroid), 36 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.79 (P = 0.074)					
Test for subgroup differences: Not applicable					

Analysis 4.2. Comparison 4 Epinephrine and steroid versus placebo, Outcome 2 Admissions overall up to 7 days (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 2 Admissions overall up to 7 days (outpatients only)

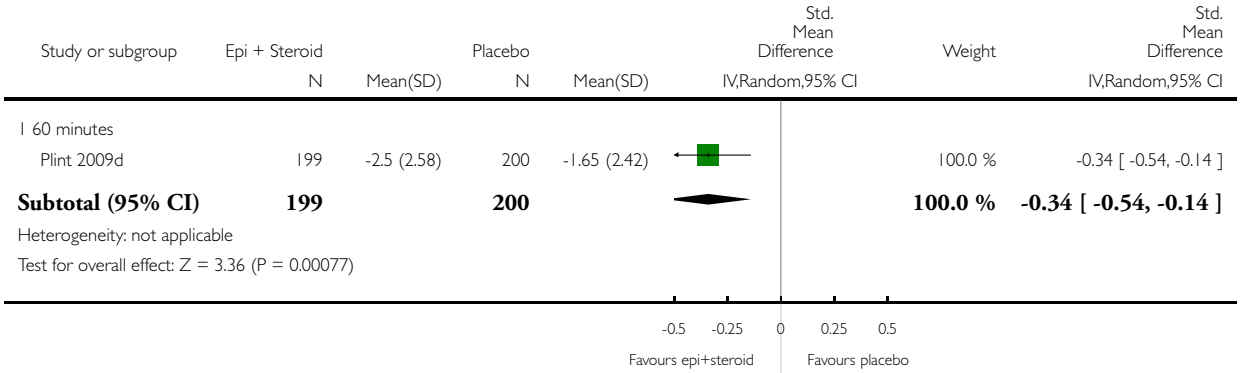
Study or subgroup	Epi+Steroid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Plint 2009d	34/199	53/201		100.0 %	0.65 [0.44, 0.95]
Total (95% CI)	**199**	**201**		**100.0 %**	**0.65 [0.44, 0.95]**
Total events: 34 (Epi+Steroid), 53 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.22 (P = 0.027)					
Test for subgroup differences: Not applicable					

Analysis 4.3. Comparison 4 Epinephrine and steroid versus placebo, Outcome 3 Clinical score (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 3 Clinical score (outpatients only)

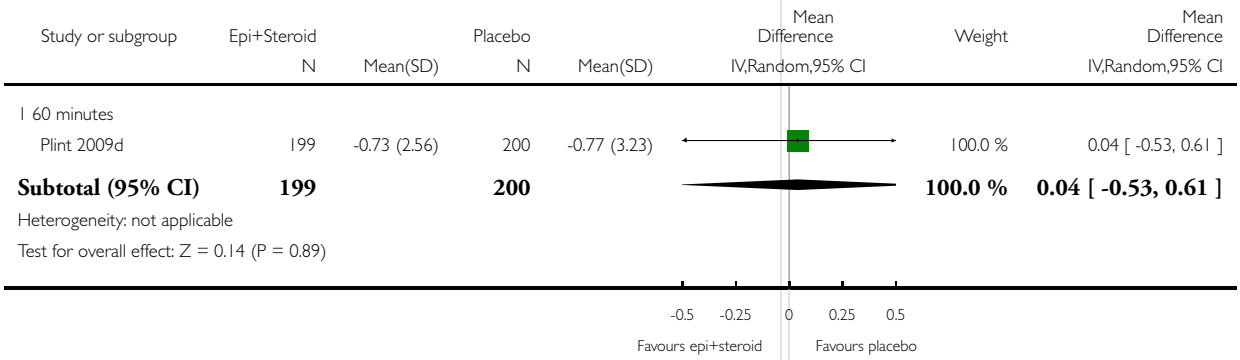


Analysis 4.4. Comparison 4 Epinephrine and steroid versus placebo, Outcome 4 Oxygen saturation (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 4 Oxygen saturation (outpatients only)

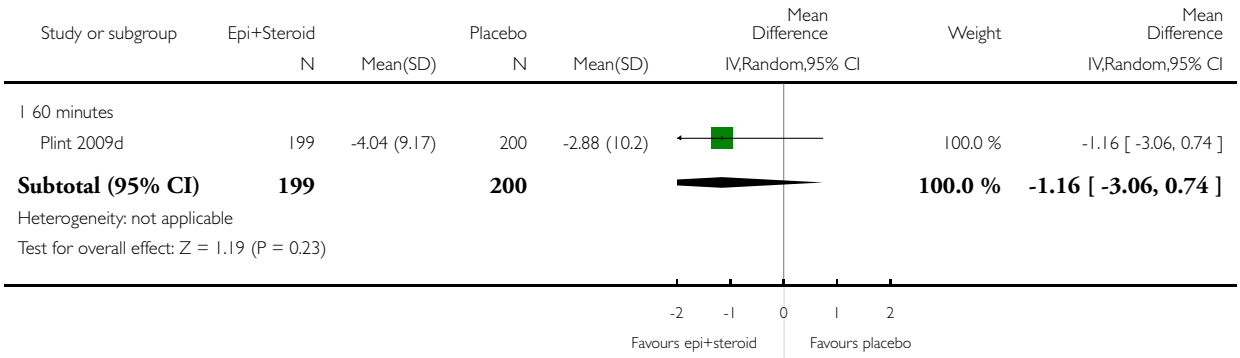


Analysis 4.5. Comparison 4 Epinephrine and steroid versus placebo, Outcome 5 Respiratory rate (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 5 Respiratory rate (outpatients only)

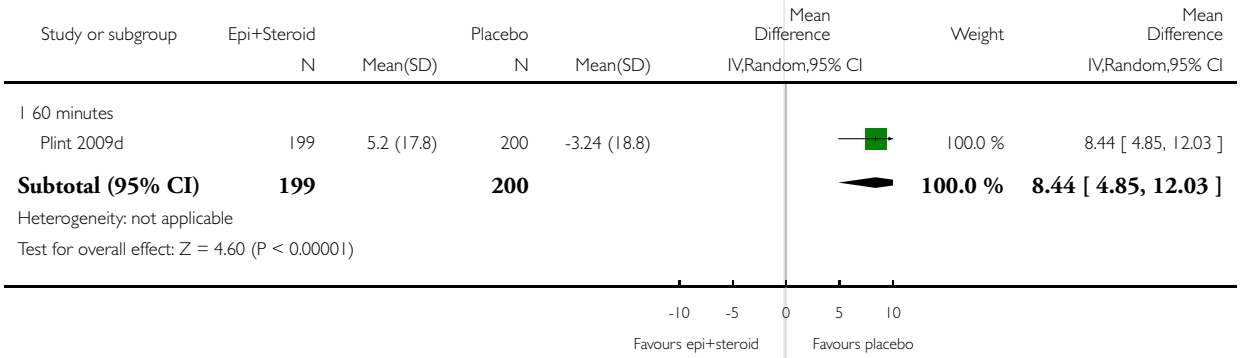


Analysis 4.6. Comparison 4 Epinephrine and steroid versus placebo, Outcome 6 Heart rate (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 6 Heart rate (outpatients only)

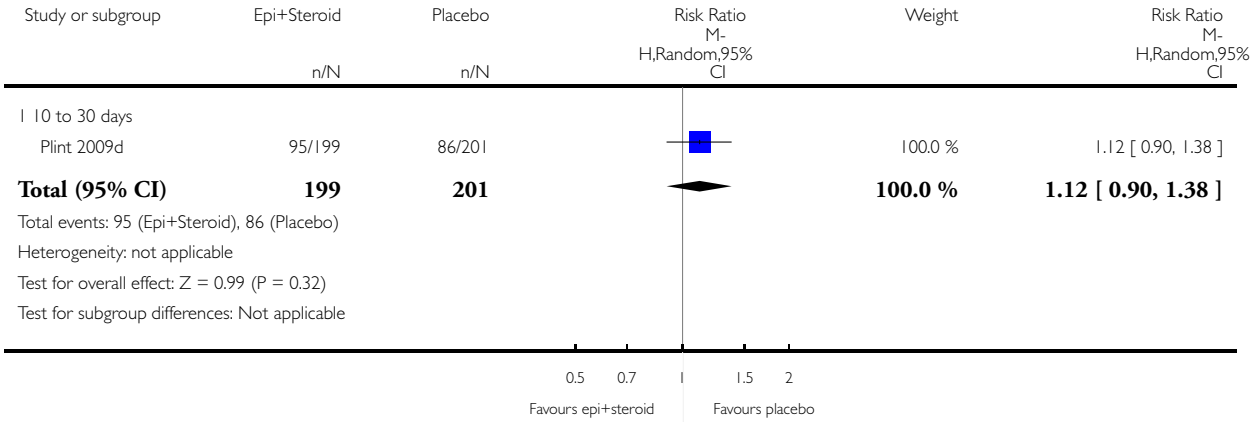


Analysis 4.7. Comparison 4 Epinephrine and steroid versus placebo, Outcome 7 Return visits (outpatients only).

Review: Epinephrine for bronchiolitis

Comparison: 4 Epinephrine and steroid versus placebo

Outcome: 7 Return visits (outpatients only)

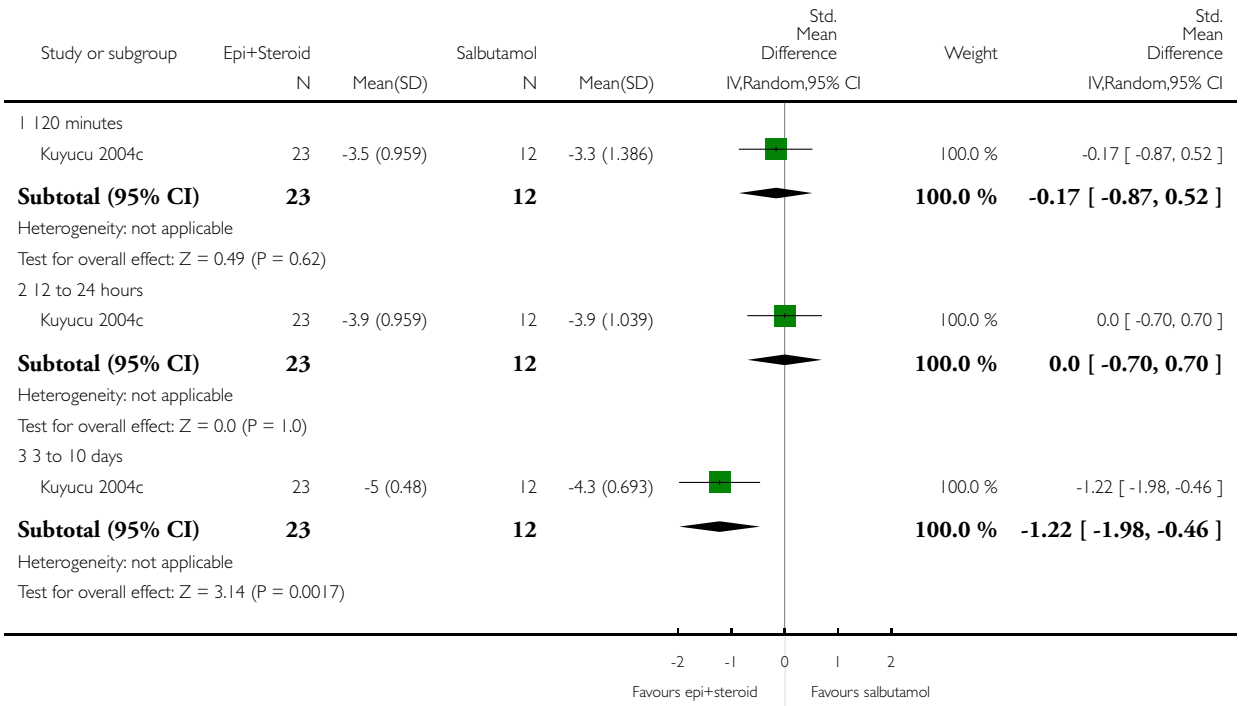


Analysis 5.1. Comparison 5 Epinephrine and steroid versus salbutamol, Outcome 1 Clinical score - all scores (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 5 Epinephrine and steroid versus salbutamol

Outcome: 1 Clinical score - all scores (inpatients)

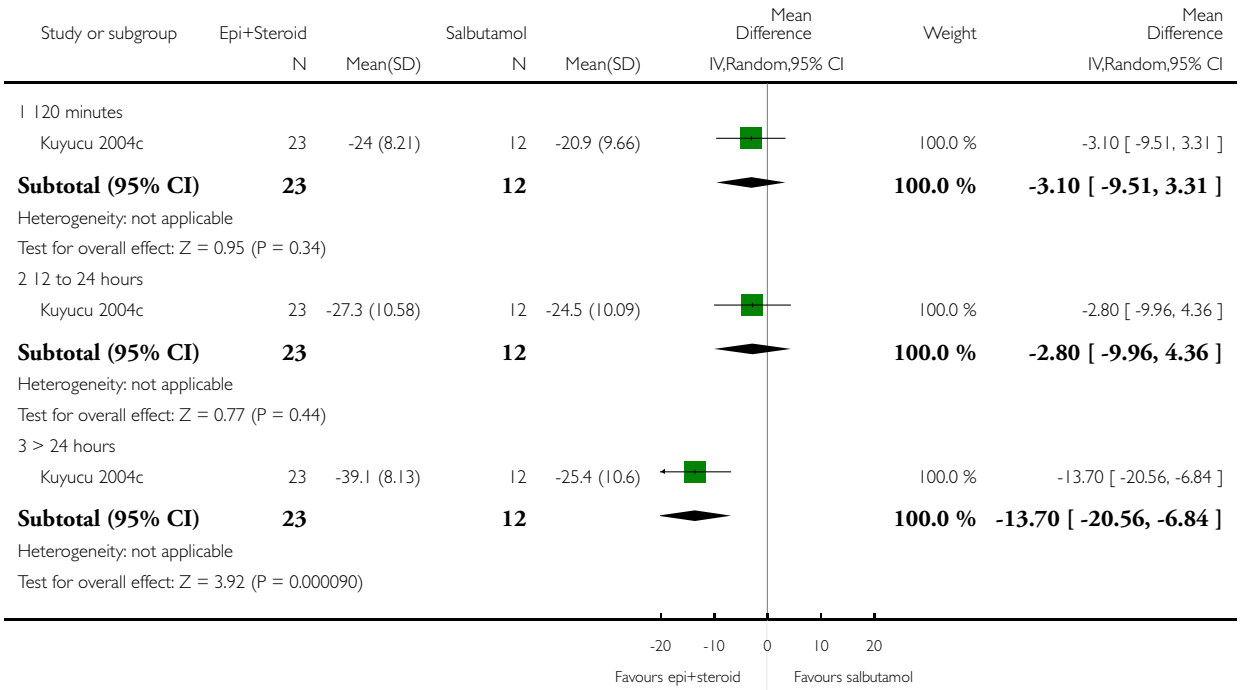


Analysis 5.2. Comparison 5 Epinephrine and steroid versus salbutamol, Outcome 2 Respiratory rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 5 Epinephrine and steroid versus salbutamol

Outcome: 2 Respiratory rate - all (inpatients)



Analysis 5.3. Comparison 5 Epinephrine and steroid versus salbutamol, Outcome 3 Heart rate - all (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 5 Epinephrine and steroid versus salbutamol

Outcome: 3 Heart rate - all (inpatients)

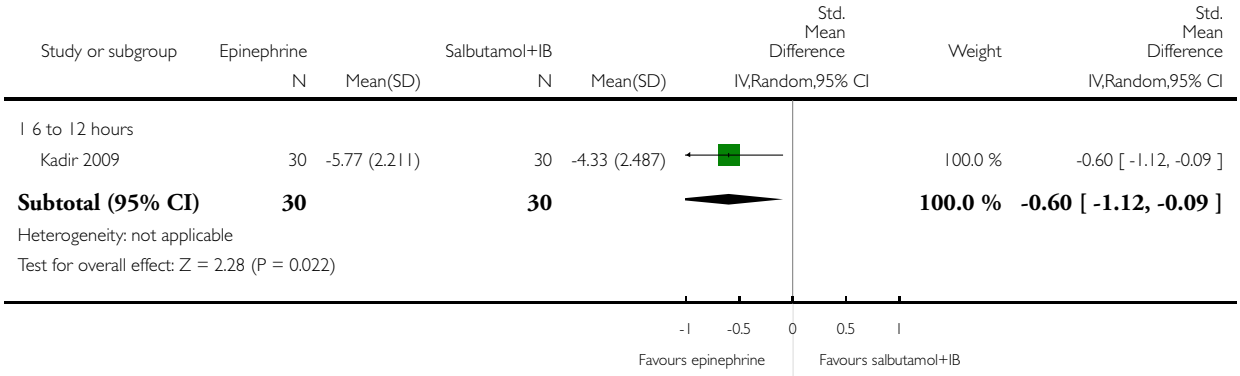
Study or subgroup	Epi+Steroid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 120 minutes							
Kuyucu 2004c	23	-14 (14.6)	12	-10.8 (11.91)		100.0 %	-3.20 [-12.20, 5.80]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-3.20 [-12.20, 5.80]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.70 (P = 0.49)							
2 24 to 72 hours							
Kuyucu 2004c	23	-17.6 (11.93)	12	-16.2 (11.11)		100.0 %	-1.40 [-9.36, 6.56]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-1.40 [-9.36, 6.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.34 (P = 0.73)							
3 3 to 10 days							
Kuyucu 2004c	23	-26.8 (11.22)	12	-20.5 (11.4)		100.0 %	-6.30 [-14.21, 1.61]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-6.30 [-14.21, 1.61]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.56 (P = 0.12)							

Analysis 6.1. Comparison 6 Epinephrine versus salbutamol and ipratropium bromide, Outcome 1 Clinical score (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 6 Epinephrine versus salbutamol and ipratropium bromide

Outcome: 1 Clinical score (inpatients)

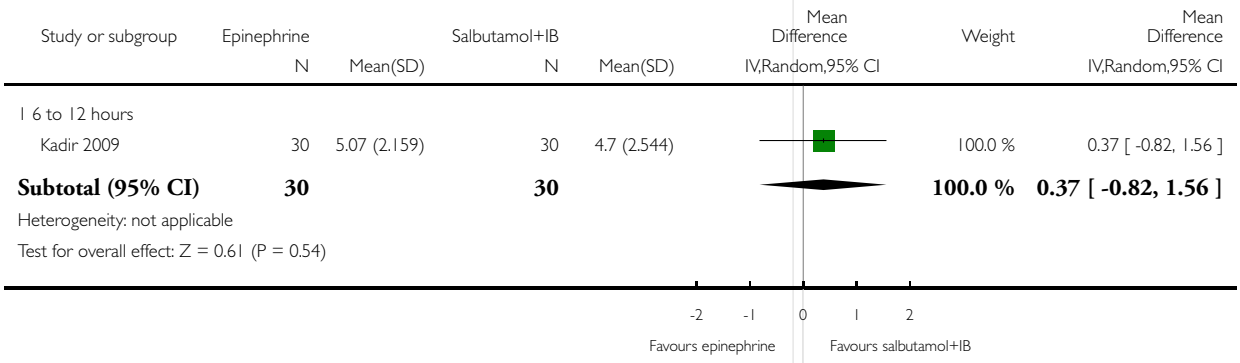


Analysis 6.2. Comparison 6 Epinephrine versus salbutamol and ipratropium bromide, Outcome 2 Oxygen saturation (inpatients).

Review: Epinephrine for bronchiolitis

Comparison: 6 Epinephrine versus salbutamol and ipratropium bromide

Outcome: 2 Oxygen saturation (inpatients)



ADDITIONAL TABLES

Table 1. GRADE strength of evidence

Population	Outcome	Number of studies	Number of participants	GRADE domains				Strength of evidence	Intervention favored
				Risk of bias	Consistency	Directness	Precision		
Epinephrine versus placebo									
Inpatient	Length of stay	2	292	medium	consistent	direct	imprecise	moderate	no difference
	Clinical score (60 minutes)	2	232	medium	consistent	direct	imprecise	moderate	no difference
Outpatient	Admissions (Day 1)	4	920	low	consistent	direct	imprecise	moderate	epinephrine
	Admissions (up to Day 7)	1	800	low	unknown	direct	imprecise	low	no difference
	Clinical score (60 minutes)	4	900	low	consistent	direct	precise	high	epinephrine
	Clinical score (120 minutes)	1	30	medium	unknown	direct	imprecise	low	epinephrine
Epinephrine versus salbutamol									
Inpatient	Length of stay	4	261	medium	consistent	direct	precise	moderate	epinephrine
	Clinical score (60 minutes)	4	148	medium	inconsistent	direct	precise	low	epinephrine
	Clinical score (120 minutes)	1	140	medium	unknown	direct	imprecise	low	epinephrine
Outpatient	Admissions (Day 1)	7	444	low	consistent	direct	imprecise	moderate	no difference

Table 1. GRADE strength of evidence (*Continued*)

	Admissions (up to Day 7)	2	212	low	consistent	direct	imprecise	moderate	no difference
	Clinical score (60 minutes)	7	397	low	consistent	direct	precise	moderate	no difference
	Clinical score (120 minutes)	5	356	low	consistent	direct	precise	moderate	no difference
	Clinical score (12 to 24 hours)	1	69	medium	unknown	direct	imprecise	low	no difference
	Clinical score (3 to 10 days)	1	69	medium	unknown	direct	imprecise	low	epinephrine
Epinephrine + dexamethasone versus placebo									
Outpatient	Admissions (Day 1)	1	401	low	unknown	direct	imprecise	low	no difference
	Admissions (up to Day 7)	1	401	low	unknown	direct	imprecise	low	epinephrine + dexamethasone
	Clinical score (60 minutes)	1	399	low	unknown	direct	precise	moderate	epinephrine + dexamethasone
Epinephrine + dexamethasone versus salbutamol									
Outpatient	Clinical score (120 minutes)	1	35	medium	unknown	direct	imprecise	low	no difference
	Clinical score (12 to 24 hours)	1	35	medium	unknown	direct	imprecise	low	no difference

Table 1. GRADE strength of evidence (*Continued*)

	Clinical score (3 to 10 days)	1	35	medium	unknown	direct	imprecise	low	epinephrine + dexamethasone

Table 2. Adverse events

Comparison	Adverse event		Total (N)	Study	Results	Number of events/total (%)	Notes
Epi versus placebo Epi versus salbutamol	Cardiovascular	Arrhythmias	111	Ralston 2005	1) saline placebo 2) racemic albuterol sulfate 3) racemic epi	0/25 (0) 2/23 (9) 0/17 (0)	tachycardia
				Bertrand 2001	1) salbutamol 2) epi	NR 0/16 (0)	tachycardia
				John 2006	1) epi 2) salbutamol	0/15 (0) 0/15 (0)	tachyarrhythmia
		Hypertension / others	54	Bertrand 2001	1) salbutamol 2) epi	NR 0/16 (0)	hypertension
				Abul-Ainine 2002	1) levo-adrenaline 2) saline placebo	0/19 (0) 0/19 (0)	vomiting, pallor, tremor, arrhythmia
	General	Tremor	981	Anil 2010	1) epi + 0.9% saline 2) epi + 3% saline 3) salbutamol + 0.9% saline 4) salbutamol + 3% saline	0/38 (0) 0/39 (0) 0/36 (0) 0/36 (0)	
				Kuyucu 2004	1) epi + dex 2) salbutamol + dex 3) epi + placebo 4) salbutamol + placebo	0/23 (0) 0/23 (0) 0/11 (0) 0/12 (0)	

Table 2. Adverse events (*Continued*)

				Plint 2009	1) epi + dex 2) epi + placebo 3) placebo + dex 4) placebo + placebo	4/200 (2) 4/199 (2) 5/200 (2.5) 2/201 (1)	
				Mull 2004	1) racemic epi 2) albuterol sulfate	0/34 (0) 0/32 (0)	
				Bertrand 2001	1) salbutamol 2) epi	NR 0/16 (0)	
				John 2006	1) epi 2) salbutamol	0/15 (0) 0/15 (0)	
		Pallor / flushing	965	Kuyucu 2004	1) epi + dex 2) salbutamol + dex 3) epi + placebo 4) salbutamol + placebo	0/23 (0) 0/23 (0) 0/11 (0) 0/12 (0)	
				Plint 2009	1) epi + dex 2) epi + placebo 3) placebo + dex 4) placebo + placebo	23/200 (11.5) 22/199 (11.1) 15/200 (7.5) 16/201 (8)	
				John 2006	1) epi 2) salbutamol	0/15 (0) 0/15 (0)	
				Mull 2004	1) racemic epi 2) albuterol sulfate	1/34 (3) 0/32 (0)	
		Vomiting	935	Mull 2004	1) racemic epi 2) albuterol sulfate	1/34 (3) 5/32 (15.6)	
				Kuyucu 2004	1) epi + dex 2) salbutamol + dex 3) epi + placebo 4) salbutamol + placebo	0/23 (0) 0/23 (0) 0/11 (0) 0/12 (0)	

Table 2. Adverse events (*Continued*)

				Plint 2009	1) epi + dex 2) epi + placebo 3) placebo + dex 4) placebo + placebo	2/200 (1) 4/199 (2) 5/200 (2.5) 3/201 (1.5)	
		Agitation / others	30	John 2006	1) epi 2) salbutamol	0/15 (0) 0/15 (0)	irritability

Dex: dexamethasone
Epi: epinephrine
NR: not reported

APPENDICES

Appendix 1. Search strategy: Cochrane Central Register of Controlled Trials - Ovid version

1. exp BRONCHIOLITIS/
2. (bronchiolitis or wheez*).mp. [mp=title, original title, abstract, mesh headings, heading words, keyword]
3. exp Respiratory Syncytial Viruses/ or exp exp Respiratory Syncytial Virus Infections/
4. Respiratory Syncytial Virus$.mp.
5. or/1-4
6. exp Bronchodilator Agents/
7. exp Adrenergic Agents/
8. exp Glucocorticoids/ or exp Adrenal Cortex Hormones/
9. (Glucocorticoid* or Corticosteroid*).mp.
10. exp Anti-Inflammatory Agents/
11. exp Drug Therapy, combination/
12. exp Epinephrine/
13. adrenal cortex hormone*.ti,ab.
14. (epinephrine or adrenalin*).mp.
15. albuterol.mp.
16. beclomet?asone.mp.
17. betamet?asone.mp.
18. budesonide.mp.
19. dexamet?asone.mp.
20. salbutamol.mp.
21. ipratropium.mp.
22. prednisolone.mp.
23. prednisone.mp.
24. methylprednisone.mp.
25. terbutaline.mp.
26. fluticasone.mp.

27. exp Orciprenaline/ or (orciprenaline or fenoterol).mp.
28. aminophylline.mp.
29. androstadienes.mp.
30. hydrocortisone.mp.
31. or/6-30
32. 5 and 31
33. exp Infant/
34. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp.
35. or/33-34
36. 32 and 35

Appendix 2. Search strategy: EMBASE - Ovid version

1. exp BRONCHIOLITIS/
2. (bronchiolitis or wheez*).mp.
3. exp Respiratory Syncytial Pneumovirus/
4. Respiratory Syncytial Virus$.mp.
5. or/1-4
6. exp Bronchodilating Agents/
7. exp Adrenergic Receptor Stimulating Agents/
8. exp Glucocorticoid/ or exp corticosteroid/
9. (glucocorticoid* or corticosteroid*).mp.
10. exp Anti-Inflammatory Agent/
11. exp Drug combination/
12. exp Adrenalin/
13. adrenal cortex hormone*.ti,ab.
14. (epinephrine or adrenalin*).mp.
15. albuterol.mp.
16. betamet?asone.mp.
17. beclomet?asone.mp.
18. budesonide.mp.
19. exp Dexamethasone/ or dexametha?one.mp.
20. salbutamol.mp.
21. ipratropium.mp.
22. exp Prednisolone/ or prednisolone.mp.
23. exp Prednisone/ or prednisone.mp.
24. methylprednisone.mp.
25. terbutaline.mp.
26. fluticasone.mp.
27. Orciprenaline/ or Fenoterol/ or (orciprenaline or fenoterol).mp.
28. aminophylline.mp.
29. androstadienes.mp.
30. exp hydrocortisone/
31. hydrocortisone.mp.
32. or/6-31
33. 5 and 32
34. exp clinical trial/
35. randomi?ed.ti,ab.
36. placebo.ti,ab.
37. dt.fs.
38. randomly.ti,ab.
39. trial.ti,ab.

40. groups.ti,ab.
41. or/34-40
42. animal/
43. human/
44. 42 not (42 and 43)
45. 41 not 44
46. 33 and 45
47. limit 46 to (child or preschool child <1 to 6 years>)
48. exp Infant/
49. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp.
50. 48 or 49
51. 46 and 50
52. 47 or 51

Appendix 3. Search strategy: IRAN MedEx

(Bronchiolitis or bronquiolitis or broncho-alveolites virales or bronchiolite*)

Appendix 4. Search strategy: LILACS BIREME/OPAS/OMS - Latin American and Caribbean Center on Health Sciences Information

wheeze OR Sibilancias OR bronquiolitis OR bronchiolitis OR bronquiolite [Words] and infant OR pediatric OR newborn OR nacidos OR Lactentes OR lactantes OR pediátrica [Words]

Appendix 5. Search strategy: MEDLINE - Ovid version

1. exp BRONCHIOLITIS/
2. (bronchiolitis or wheez*).mp.
3. exp Respiratory Syncytial Viruses/ or exp Respiratory Syncytial Virus Infections/
4. Respiratory Syncytial Virus$.mp.
5. or/1-4
6. exp Bronchodilator Agents/
7. exp Adrenergic Agents/
8. exp Glucocorticoids/ or exp Adrenal Cortex Hormones/
9. (Glucocorticoid* or Corticosteroid*).mp.
10. exp Anti-Inflammatory Agents/
11. exp Drug Therapy, combination/
12. exp Epinephrine/
13. (epinephrine or adrenalin*).mp.
14. albuterol.mp.
15. betamet?asone.mp.
16. beclomet?asone.mp.
17. budesonide.mp.
18. dexamet?asone.mp.
19. salbutamol.mp.
20. ipratropium.mp.
21. prednisolone.mp.
22. prednisone.mp.
23. methylprednisone.mp.
24. terbutaline.mp.
25. fluticasone.mp.

26. exp Orciprenaline/ or (orciprenaline or fenoterol).mp.
27. aminophylline.mp.
28. androstadienes.mp.
29. hydrocortisone.mp.
30. or/6-29
31. 5 and 30
32. randomized controlled trial.pt.
33. clinical trial.pt.
34. randomi?ed.ti,ab.
35. placebo.ti,ab.
36. dt.fs.
37. randomly.ti,ab.
38. trial.ti,ab.
39. groups.ti,ab.
40. or/32-39
41. animals/
42. humans/
43. 41 not (41 and 42)
44. 40 not 43
45. 44 and 31
46. exp Infant/
47. (Infant* or infancy or Newborn* or Baby* or Babies or Neonat* or Preterm* or Prematur* or Postmatur*).mp.
48. or/46-47
49. 45 and 48

Appendix 6. Search strategy: PubMed - U.S. National Library of Medicine

Searched for a few of pre 1965 older articles identified through reference lists

Appendix 7. Scopus - Elsevier B.V.

(((TITLE(bronchiolitis OR wheez*) AND TITLE-ABS-KEY(steroid* OR glucocorticoid* OR corticosteroid*))) AND KEY("epinephrine" OR "adrenaline" OR "albuterol" OR "corticosteroids" OR "hydrocortisone" OR "steroids" OR ("inhaled steroids") OR "salbutamol" OR "betamethasone" OR "beclomethasone" OR "dexamethasone" OR "steroid" OR ("inhaled budesonide") OR "glucocorticoids" OR "bronchodilator" OR ("steroid use") OR "prednisolone" OR "methylprednisone" OR ("oral prednisolone") OR "prednisone" OR "ipratropium" OR "terbutaline" OR "orciprenaline" OR "fenoterol" OR "aminophylline" OR "androstadienes" OR "hydrocortisone")) AND (TITLE-ABS-KEY("Clinical Trial" OR "Clinical Trials" OR "Randomized Controlled Trial*" OR "Random Allocation" OR "double-blind method" OR "single-blind method" OR placebos OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective)) AND (infan* OR newborn* OR neonat* OR baby OR babies)
(((TITLE(bronchiolitis) AND TITLE-ABS-KEY(steroid* OR glucocorticoid*OR corticosteroid*))) AND KEY("epinephrine" OR "albuterol" OR "corticosteroids" OR "hydrocortisone" OR "steroids" OR ("inhaled steroids") OR "salbutamol" OR "dexamethasone" OR "steroid" OR ("inhaled budesonide") OR "glucocorticoids"OR "bronchodilator"OR ("steroid use") OR "prednisolone" OR ("oral prednisolone") OR "prednisone")) AND (TITLE-ABS-KEY("Clinical Trial" OR "Clinical Trials" OR "Randomized Controlled Trial*" OR "Random Allocation" OR "double-blind method" OR "single-blind method" OR placebosOR research design OR comparativestudy OR evaluationstudies OR follow-up studies OR prospective))

FEEDBACK

Epinephrine for bronchiolitis, 2 January 2007

Summary

You used change from baseline in clinical score. In your Fig. 2, you have shown SDs for changes for the trial by Abul-Ainine 2001, but we could not find any SDs for change in clinical score in this article. We believe your result is wrong as you found epinephrine to be better than the control, but the trial authors' fig. 1 shows that the opposite is true. We estimated SDs from the trial report's fig. 1 after 60 min. and got SDs of 3.99 and 3.86, which are similar to your reported SDs for changes of 4.12 and 4.04. We calculated SMD based on values after treatment and got 0.32, in contrast to your finding of -0.44 (which seems to be wrong as it should have a positive sign according to fig. 1).

We have the same problem with the second trial, the one by Kristjansson 1993, where we could not find any SDs for change in clinical score in the article. We estimated SDs from the trial report's fig. 1 after 60 min. and got SDs of 0.76 and 1.38, whereas you got SDs of 0.77 and 1.15 for changes. We calculated SMD based on values after treatment and got -0.62 (-1.38 to 0.15), or nearly identical results to yours, -0.62 (-1.37 to 0.13). Does this mean that you did not use changes from baseline, which your review states, but values after treatment?

Reply

We are in the process of updating this review and will take into consideration your comments in our update.

We have confirmed that our original calculation for the SMD in the Abul-Ainine trial was incorrect - it should be in the other direction. I believe that your other concerns stem from the difficulty in extracting from graphs and methods of SD imputation. The concerns for the second trial appear trivial as the estimates are almost identical.

The updated review will incorporate these observations. However, I don't think that these discrepancies would have changed our overall conclusions.

Lisa Hartling

Contributors

Gøtzsche PC, Hróbjartsson A, Maric K, Tendal B

Feedback added 4 January 2007

WHAT'S NEW

Last assessed as up-to-date: 26 September 2010.

Date	Event	Description
27 September 2010	New citation required and conclusions have changed	Searches were conducted in September 2010 (March 2010 for PubMed). Seven new studies were added to this update. For this update we revised the inclusion criteria to only include studies that defined bronchiolitis as the first episode of wheezing. As a result of this new criterion five studies included in the original review have been excluded from this update (Hariprakash 2003; Kristjansson 1993; Lowell 1987;

(*Continued*)

		Ray 2002; Reijonen 1995). The conclusions have changed to recommend the superiority of epinephrine compared to placebo for short-term outcomes for outpatients, particularly in the first 24 hours of care. Six new authors have participated in this update: Liza Bialy, Ben Vandermeer, Lisa Tjosvold, David W Johnson, Amy C Plint and Ricardo M Fernandes
27 September 2010	New search has been performed	Searches conducted.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 1, 2004

Date	Event	Description
18 July 2008	Amended	Converted to new review format.
3 January 2007	Feedback has been incorporated	Feedback and reply added.
26 November 2003	New search has been performed	Searches conducted. Review first published Issue 1, 2004

CONTRIBUTIONS OF AUTHORS

LH contributed to protocol development, searching, relevance and inclusion screening, quality assessment, data extraction, analysis and writing the review.

LB contributed to relevance and inclusion screening, quality assessment, data extraction, analysis and writing the review.

BV contributed to protocol development, analysis and editing the review.

LT contributed to the development and execution of the search strategy and editing the review.

DWJ contributed to relevance and inclusion screening, analysis and editing the review.

ACP contributed to relevance and inclusion screening, analysis and editing the review.

TPK contributed to protocol development, relevance and inclusion screening, analysis and editing the review.

HP contributed to review of protocol, interpretation of results and editing the review.

RMF contributed to protocol development, searching, relevance and inclusion screening, quality assessment, data extraction, analysis and writing the review.

DECLARATIONS OF INTEREST

ACP, HP, DWJ and TPK are authors and/or co-authors on trials included in this review. No other declarations of interest are noted.

SOURCES OF SUPPORT

Internal sources

- Alberta Research Centre for Health Evidence (ARCHE), Canada.

External sources

- Canadian Institutes of Health Research, Canada.
- Programme for Advanced Medical Education (Fundação Calouste Gulbenkian, Fundação Champalimaud, Ministério da Saúde and Fundação para a Ciência e Tecnologia), Portugal.

Ricardo M Fernandes (Fellowship)

NOTES

We made the following changes to this 2010 update based on consultations with clinicians and authors.

1. We modified the inclusion criteria to include definitions of bronchiolitis that specified first episode of wheezing.

2. The outcome 'improvement' has been excluded.

3. Analyses of return visits, hospital re-admissions, risk of bias and synergies of drug combinations have been added.

4. Comparisons of epinephrine plus dexamethasone versus placebo, epinephrine plus dexamethasone versus salbutamol, epinephrine versus salbutamol plus ipratropium bromide have been added.

5. The search strategy for this review along with *Glucocorticoids for acute viral bronchiolitis in infants and young children* (Fernandes 2010) were part of a comprehensive synthesis project evaluating the effect of various interventions in bronchiolitis, i.e. bronchodilators, epinephrine and steroids.

6. Based on the data available in the included studies the time points from the previous review (change from baseline at 30, 60 and 90 minutes) have been modified to include the following: change from baseline at 60 minutes, 120 minutes, three to six hours, 6 to 12 hours, 12 to 24 hours, 24 to 72 hours and 3 to 10 days.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Albuterol [therapeutic use]; Bronchiolitis [*drug therapy]; Bronchodilator Agents [adverse effects; *therapeutic use]; Epinephrine [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans; Infant