Glucocorticoids for acute viral bronchiolitis in infants and young children (Review)

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

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TABLE OF CONTENTS

[Intervention Review]

Glucocorticoids for acute viral bronchiolitis in infants and young children

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ABSTRACT

Background

Previous systematic reviews have not shown clear benefit of glucocorticoids for acute viral bronchiolitis, but their use remains considerable. Recent large trials add substantially to current evidence and suggest novel glucocorticoid-including treatment approaches.

Objectives

To review the efficacy and safety of systemic and inhaled glucocorticoids in children with acute viral bronchiolitis.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2009, issue 4); MEDLINE (1950 to November 2009); EMBASE (1980 to Week 47 2009); LILACS (1982 to November 2009); Scopus® (1823 to November 2009); and IRAN MedEx (1998 to November 2009).

Selection criteria

Randomised controlled trials (RCTs) comparing short-term systemic or inhaled glucocorticoids versus placebo or another intervention in children < 24 months with acute bronchiolitis (first episode with wheezing). Our primary outcomes were: admissions by days 1 and 7 for outpatient studies; and length of stay (LOS) for inpatient studies. Secondary outcomes included clinical severity parameters, healthcare use, pulmonary function, symptoms, quality of life and harms.

Data collection and analysis

Two authors independently extracted data on study and participant characteristics, interventions and outcomes. We assessed risk of bias and graded strength of evidence. Inpatient and outpatient results were meta-analysed separately using random-effects models. We pre-specified subgroup analyses, including the combined use of protocolised bronchodilators.

Main results

We included 17 trials (2596 participants); only two had low overall risk of bias. Baseline severity, glucocorticoid schemes, comparators and outcomes were heterogeneous. Glucocorticoids did not significantly reduce outpatient admissions by days 1 and 7 when compared to placebo (pooled risk ratios (RRs) 0.92; 95% CI 0.78 to 1.08; and 0.86; 95% CI 0.7 to 1.06, respectively). There was no benefit in LOS for inpatients (mean difference -0.18 days; 95% CI -0.39 to 0.04). Unadjusted results from a large factorial low risk of bias RCT found combined high-dose systemic dexamethasone and inhaled epinephrine reduced admissions by day 7 (baseline risk of admission 26%; RR 0.65, 95% CI 0.44 to 0.95; number needed to treat 11, 95% CI 7 to 76), with no differences in short-term adverse effects. No other comparisons showed relevant differences in primary outcomes.

Authors' conclusions

Current evidence does not support a clinically relevant effect of systemic or inhaled glucocorticoids on admissions or length of hospitalization. Combined dexamethasone and epinephrine may reduce outpatient admissions, but results are exploratory and safety data limited. Future research should further assess the efficacy, harms and applicability of combined therapy.

PLAIN LANGUAGE SUMMARY

Glucocorticoids for acute viral bronchiolitis in infants and young children under 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 similar 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. Hospitalisations 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. Anti-inflammatory drugs like glucocorticoids (for example, prednisolone or dexamethasone) have been used based on apparent similarities between bronchiolitis and asthma. However, no clear benefit of their use has been shown.

Our systematic review found 17 controlled studies involving 2596 affected children that used these drugs acutely and assessed short-term outcomes. When comparing glucocorticoids to placebo, no differences were found for either hospital admissions or length of hospital stay. There was no substantial benefit in other health outcomes. These findings are consistent and likely to be applicable in diverse settings.

Exploratory results from one large high-quality trial suggest that combined treatment of systemic glucocorticoids (dexamethasone) and bronchodilators (epinephrine) may significantly reduce hospital admissions. There were no relevant short-term adverse effects that were any different from those seen with an inactive placebo, while long-term safety was not assessed. Further research is needed to confirm the efficacy, safety and applicability of this promising approach.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Glucocorticoid versus placebo for acute viral bronchiolitis in infants and young children

Patient or population: patients with acute viral bronchiolitis in infants and young children
Settings: outpatients and inpatients
Intervention: glucocorticoid versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Steroid versus Placebo	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk[1]	Corresponding risk			
	Placebo	Steroid			
Admissions (outpatients) Follow-up: day 1	**Medium risk population**		**RR 0.92** (0.78 to 1.08)	1762 (8)	high
	162 per 1000	**149 per 1000** (126 to 175)			
Admissions (outpatients) Follow-up: day 7	**Medium risk population**		**RR 0.86** (0.7 to 1.06)	1530 (5)	moderate
	250 per 1000	**215 per 1000** (175 to 265)			
Length of stay (inpatients) days.	The mean length of stay ranged across control groups from 0.8 to 6.6 days	The mean length of stay in the intervention groups was **0.18 lower** (0.39 lower to 0.04 higher)		633 (8)	high

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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; LoS: length of stay

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.

[1] Assumed risk for admissions was based on the median control group risks across the studies included in the meta-analysis (medium risk)

BACKGROUND

Description of the condition

Acute viral bronchiolitis is the most common acute infection of the lower respiratory tract during the first year of life (Wright 1989). It is diagnosed clinically in infants and young children, based on a history of rhinorrhea and low-grade fever that progress to cough and respiratory distress, with findings of tachypnea, chest retractions, and wheeze, crackles, or both, on examination (Bush 2007; Chernick 2006; Smyth 2006; Taussig 2008). Respiratory syncytial virus (RSV) is responsible for the majority of cases, usually in seasonal epidemics (Smyth 2006; Welliver 2009; Yusuf 2007). Other viral agents, particularly rhinovirus, human metapneumovirus, bocavirus, and adenovirus, may also be involved as single or dual infections (Calvo 2010; Kusel 2006; Mansbach 2008a; Smyth 2006). Although bronchiolitis is usually a straightforward diagnosis, some variability in its definition exists. This may be due to poor agreement on the identification of early childhood wheezing phenotypes, and worldwide differences in disease semantics (Brand 2008; Everard 2009; Mansbach 2008).

Bronchiolitis is a major cause of clinical morbidity, and its financial health burden is substantial. Population-based studies in developed countries suggest an incidence ratio of approximately 10% within the first year of life, with hospital admissions up to 3% (Koehoorn 2008; Mansbach 2005; Shay 1999; Wright 1989). While mortality is rare, hospitalizations have increased steadily in North America and Europe over the past 10 to 20 years (Langley 2003; Shay 1999; van Woensel 2002), with rising inpatient health care costs (Langley 1997; Paramore 2004; Pelletier 2006). Additionally, a majority of cases with mild illness cared for in the community are responsible for a considerable number of outpatient visits, loss of parental work time and decreased quality of life (Carroll 2008; Mansbach 2007; Robbins 2006).The disease burden attributable to RSV infection in developing countries is being increasingly studied (Nokes 2008). A recent review highlighted the impact of RSV disease, including bronchiolitis, as a major cause of childhood morbidity and mortality at a global level (Nair 2010).

Bronchiolitis involves acute inflammation of the bronchiolar airways initiated by viral infection, regardless of the causative agent. Airway oedema, necrosis and mucous plugging are the hallmark pathological features, and air flow obstruction ensues (Chernick 2006; Taussig 2008). Factors underlying the severity of bronchiolitis are only partially understood, but clinical determinants include lower age, prematurity, chronic lung, heart or neurological disease, immunodeficiency, and ethnicity (Damore 2008; Figueras-Aloy 2008; Meissner 2003; Opavsky 1995; Simoes 2003; Simoes 2007; Simoes 2008). Identifying genetic risk markers for severe bronchiolitis is complex (Amanatidou 2009; Miyairi 2008), and evidence is disputed regarding the influence of pre- and post-natal factors such as environmental exposures and types of viral agent(s) (Simoes 2007; Sly 2010). Basic, translational and clinical research studies are elucidating the association between bronchiolitis, preschool wheezing disorders and later asthma (Martinez 2005; Perez-Yarza 2007; Singh 2007; Sly 2010).

Description of the intervention

The current treatment of bronchiolitis is controversial. There is substantial variation in its management throughout the world, reflecting the absence of clear evidence for any single treatment approach (Babl 2008; Barben 2003; Brand 2000; Gonzalez 2010; Mallory 2003; Mansbach 2005; Plint 2004). Systematic reviews have assessed the use of bronchodilators, heliox, epinephrine, glucocorticoids, hypertonic saline, antibiotics, surfactant, ribavirin, and chest physiotherapy (Blom 2007; Fuller 2006; Gadomski 2006; Hartling 2004; Liet 2010; Liza 2006; Patel 2004; Patel 2008; Perrotta 2007; Spurling 2007; Ventre 2010; Ventre 2010a; Zhang 2008). Nebulised hypertonic saline may significantly improve some outcomes, but replication of this effect in large RCTs is needed (Zhang 2008). All other synthesis reviews failed to show consistent and relevant effects, and no routine treatment is recommended by most evidence-based clinical practice guidelines worldwide (AAP 2006; Baumer 2007; Turner 2008).

The case of glucocorticoids highlights the uncertainties of research in this field. Trials assessing their use date back to the 1960s, with different potencies (for example, prednisolone, dexamethasone), modes of administration (for example, systemic, inhaled), dosages and regimens of these drugs having been recommended (Connolly 1969; Leer 1969). However, results from randomized clinical trials (RCTs) have been heterogeneous, leading to ongoing controversy regarding their use. In 2000, a systematic review with meta-analysis showed a small but statistically significant reduction in length of stay (LOS) and clinical scores for inpatients treated with systemic glucocorticoids compared to placebo (Garrison 2000). A later Cochrane review failed to confirm these findings for inpatients, and found no difference in outpatient studies (Patel 2004). Differences in participants, care settings and outcomes may account for these conflicting results, and have led to distinct interpretations (Everard 2009; Hall 2007; Weinberger 2003; Weinberger 2007). While guideline implementation has changed prescription patterns, glucocorticoids are still widely used (Barben 2000; Barben 2008; David 2010).

How the intervention might work

Glucocorticoid use in bronchiolitis was originally thought to have equivalent benefits to those with acute asthma. Similarities between clinical findings were expected to express equivalent biological and physiological mechanisms (Leer 1969). It is recognised that inflammation plays a significant role in the pathogenesis of bronchiolitis (Halfhide 2008). However, evidence suggests there is heterogeneity in inflammatory pathways and mediators activated

in different wheezing phenotypes which may underlie bronchiolitis (for example, neutrophil- versus eosinophil-mediated inflammation) (Halfhide 2008). This was thought to be associated with factors such as age or atopy (Weinberger 2007). The interplay between the cytotoxic effects of direct viral infection and the host immune response is also unclear (Collins 2008; Halfhide 2008) which might explain findings suggesting a limited biological effect of anti-inflammatory interventions in bronchiolitis (Buckingham 2002; Somers 2009). Recent evidence has also fostered debate regarding the risks and benefits of glucocorticoids in acute virus-induced asthma and wheezing in preschool children (Bush 2009; Ducharme 2009; Panickar 2009). Potential benefits need to be considered in light of possible short- and long-term adverse effects.

Why it is important to do this review

The latest Cochrane review was withdrawn in 2008 for being out of date (Patel 2008). Various RCTs were published since, including the two largest multi-centre studies in this area which include 1400 participants overall (Corneli 2007; Plint 2009). These two pivotal trials add substantially to the evidence, and provide a strong signal for an update of relevant systematic reviews (Shojania 2007).
These recent trials also raise new questions and potentially novel approaches that warrant closer investigation. Specifically, one trial showed a relevant clinical benefit when combining glucocorticoids and epinephrine, with a defined protocol for epinephrine use (Plint 2009). While the interactive effect of glucocorticoids and bronchodilators has emerged as a potential treatment option, it has not been examined at the systematic review level. It is critical to incorporate these results into the current body of evidence, and to decide whether this new evidence can affect practice.

OBJECTIVES

To systematically review the evidence on the efficacy and safety of systemic and inhaled glucocorticoids for the treatment of infants and young children with acute viral bronchiolitis.

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs irrespective of risk of bias, sample size, publication status, or language of publication.

Types of participants

Studies should include infants and young children ≤ 24 months of age with acute viral bronchiolitis. Bronchiolitis was defined clinically as a first episode of acute wheezing, respiratory distress and clinical evidence of a viral infection (cough, coryza, fever). Many bronchiolitis trial reports do not specify clinical findings required for participant inclusion (King 2004); we included all studies if other diagnoses (for example, pneumonia) could be excluded. We did not restrict inclusion based on specific findings on examination (for example, crackles) or viral aetiology.
We excluded studies which included any participant with a history of wheezing or respiratory distress (one or more previous episodes), a formal diagnosis of asthma, or if reporting of these items was unclear. We focused on first time wheezing so results could be directly pertinent to infants with "typical" viral bronchiolitis, as opposed to children with acute recurrent wheezing. We did not exclude trials based on other reported participant characteristics, including gestational age and co-morbidities.
We included studies of both inpatients and outpatients (ambulatory care and/or emergency department), and excluded trials in the intensive care setting or with intubated and/or ventilated participants.

Types of interventions

The interventions of interest were short-term systemic or inhaled glucocorticoids administered for the acute care of bronchiolitis. We considered all types of glucocorticoids, dosages, durations and routes of administration. Glucocorticoids could be administered alone or combined with co-interventions (for example, bronchodilators), used with or without a fixed protocol. We excluded trials assessing the use of longer courses of glucocorticoids started during the acute phase for the prevention of post-bronchiolitic wheezing.
Comparators included either placebo or another intervention (for example, bronchodilators, other glucocorticoid). Inhaled isotonic saline is frequently used as a placebo control for inhaled drugs. We excluded studies comparing different doses or regimens of the same glucocorticoid.

Types of outcome measures

We selected primary outcomes based a priori 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 outcomes 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 days one and seven for outpatient studies.
2. Length of stay (LOS) for inpatient studies.

Secondary outcomes

1. Clinical severity scores.
2. O_2 saturation, respiratory rate, and heart rate.
3. Hospital re-admissions (for inpatient studies), and return healthcare visits (for all studies); LOS (for outpatient studies).
4. Pulmonary function tests.
5. Symptoms and quality of life.
6. Short- and long-term adverse events.

We selected the following time points and intervals for clinical scores, O_2 saturation, respiratory and heart rate: 60 and 120 minutes, three to six hours, six to 12 hours, 12 to 24 hours, 24 to 72 hours, and three to 10 days. The time points selected for re-admissions and return visits were days 1 to 10, and 11 to 30. We also considered data on all other reported outcomes.

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 (glucocorticoids, epinephrine, and other bronchodilators) (Hartling 2010).

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1950 to November Week 2, 2009), EMBASE (1980 to Week 47, 2009), LILACS (Latin American and Caribbean Center on Health Sciences Information) (1982 to November 25, 2009), Scopus® (1823 to November 25, 2009) and IRAN MedEx (1998 to November 26, 2009).

We developed search strings by scanning search strategies of relevant systematic reviews and examining index terms of potentially relevant studies. We applied and modified a validated RCT filter according to each database (Glanville 2006). We applied no publication or language restrictions. The search strings for each database can be found in Appendix 1 to Appendix 6.

Searching other resources

To identify unpublished studies and studies in progress we searched the following clinical trials registers on 3 March, 2009 and again 26 November, 2009: ClinicalTrials.gov; Current Controlled Trials; ClinicalStudyResults.org; Australian New Zealand Clinical Trials Registry; IFPMA Clinical Trials Portal; UMIN Clinical Trials Registry; rct zoeken - Nederlands Trialregister - Dutch Cochrane Centre; and ICTRP Search Portal - World Health Organisation.

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

We identified additional published, unpublished or ongoing studies by handsearching reference lists and included or excluded studies of relevant reviews. In addition, we contacted topic specialists.

Data collection and analysis

Selection of studies

Four review authors (LB, LH, NH or RF) independently screened the titles, keywords and abstracts (when available) to determine if an article met the inclusion criteria. The full text of all articles classified as "include" or "unclear" were independently assessed for inclusion by these authors using a standardized form. Three review authors (TK, AP or DJ) resolved disagreements by consensus or an arbitrator.

Data extraction and management

We extracted data using a standardized form in paper or electronic format and then entered it into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA) (form available from authors). Seven review authors extracted data (LB, LH, AM, HM, RF, OT or JF) and three review authors (LB, AM or RF) independently checked for accuracy and completeness. We resolved discrepancies by consensus or in consultation with a third review author (TK, AP or DJ). All quantitative data were checked by the statistician (BV) during analysis.

Extracted data included study characteristics, funding, inclusion/exclusion criteria, participant characteristics, interventions, outcomes and results. When needed, we extracted trial results from figures.

Assessment of risk of bias in included studies

We used the Cochrane 'Risk of bias' assessment tool, which includes six domains: sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias (Higgins 2009). We assessed blinding and incomplete outcome data separately for the following groups of outcomes: healthcare use (rate of admission, LOS, hospital re-admissions, and return healthcare visits); clinical parameters (clinical severity scores, O_2 saturation, respiratory rate, and heart rate); pulmonary function; patient/parent-reported outcomes (symptoms, and quality of life measures) and other outcomes such as adverse events.

Three review authors (LB, LH or RF) independently assessed the risk of bias of the included studies. One reviewer (OT) assessed study reports written in Turkish. We pilot tested the risk of bias tool on a sample of five studies, and used the results to adapt decision rules (available from authors). Where trial protocols or trial registers were unavailable, we assessed selective outcome reporting by comparing outcomes reported in the methods and results sections. The overall (study level) risk of bias was based on individual domain assessments ("high" if one or more domains were high; "low" if all domains were low; "unclear" for all other studies). We resolved discrepancies by consensus among three review authors (LB, LH and RF).

Whenever feasible, we performed sensitivity analyses of the primary outcomes restricted to studies with low overall risk of bias.

Grading the body of evidence

We used the Evidence-Based Practice Centers Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, based on the standard GRADE system (GRADE 2009; Owens 2010), to assess domain-specific and overall strength of evidence on relevant outcomes (length of stay or admission rate; clinical severity scores; and adverse events). Two review authors (LH, RF) independently graded the body of evidence using adapted decision rules.

We examined the following domains: risk of bias, consistency, directness, and precision. Risk of bias was considered as low or medium, as we only included RCTs. There is limited evidence regarding clinically significant and patient-important changes in this field, therefore we defined a priori thresholds of clinical relevance based on expert opinion and GRADE guidance (risk ratio reduction > 20% for admissions, reduction in LOS > 0.5 days; clinical scale effect sizes based on GRADE guidance) (GRADE 2009). Overall strength of evidence was graded "high", "moderate" or "low" based on the likelihood of further research changing our confidence in the estimate of effect (when evidence was unavailable or did not permit estimation of an effect, it was considered insufficient).

All decisions were made explicitly and inter-rater agreement was calculated (data available from authors). We resolved discrepancies by consensus among two review authors (LH, RF).

Measures of treatment effect

Dichotomous variables were pooled using risk ratios (RRs). The number needed to treat to benefit (NNTB) was derived for significant results from primary outcomes. Since the only comparison with significant differences was based on a single trial, the NNTB is shown for that trial's baseline risk.

We analysed measurement scale outcomes as continuous variables. For continuous variables measured on the same scale (for example, respiratory rate), we calculated mean differences (MD) for individual studies, and mean differences (MD) for the pooled estimates. For those measured on different scales (for example, clinical scores), we calculated mean differences for separate studies and standardized mean differences (SMD) for the pooled estimates. We used changes from baseline for all continuous variables.

Unit of analysis issues

Some multi-arm or factorial studies with more than two intervention groups were eligible to contribute several comparisons to a single meta-analysis (for example, a trial might compare glucocorticoid versus placebo in two arms, and glucocorticoid + bronchodilator versus placebo + bronchodilator in another two arms, with both contributing to the overall glucocorticoid versus placebo comparison). When the comparisons were independent, i.e. with no intervention group in common, we included data from these arms with no transformation (shown separately in each forest plot). 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, two glucocorticoid groups versus placebo). We did not include any treatment groups twice in the same meta-analysis.

Guidance regarding the analysis of factorial trials mandates caution when results suggest positive interaction/additive effects ("synergism") between study treatments (McAlister 2003; Montgomery 2003). This was the case for a large trial included in this review. We therefore chose to include comparisons separately in meta-analysis ("within the table analysis"; for example, for the glucocorticoid versus placebo comparison, we included glucocorticoid + bronchodilator versus placebo + bronchodilator and glucocorticoid + placebo versus double placebo). We also performed sensitivity analysis pooling all arms ("at the margins data").

Dealing with missing data

We extracted information on incomplete outcome data and we classified trials that performed intention-to-treat (ITT) analysis according to the *Cochrane Handbook of Systematic Reviews of Interventions* guidance (either ITT with all data, ITT with imputation of missing data, ITT with available case analysis, per-protocol analysis, and treatment-received analysis) (Higgins 2009).

We did not impute missing data for drop-outs (available case analysis). Unreported means were estimated from figures or imputed from medians if possible. Standard deviations (SDs) were computed from available data (i.e. standard errors, confidence intervals [CI] or P values) when missing. Failing this, we estimated them from ranges and inter-quartile ranges, or imputed them from a similar study. When standard deviations of change from baseline values were unavailable, we estimated correlation at 0.5 (Follmann 1992; Wiebe 2006). We occasionally encountered clinical score results presented as dichotomous data, for example, using a cut-off score or time-to-event analysis. When methods were feasible and assumptions judged reasonable, we used existing approaches to re-express odds ratios as standardized mean differences, thus

allowing dichotomous and continuous data to be pooled together (Higgins 2009). When data were unavailable for one of the predefined timings of outcome measurement, we used the time point closest 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 trial authors of the individual studies to obtain additional data.

Assessment of heterogeneity

We quantified statistical heterogeneity using the I^2 statistic. We used the following intervals for interpreting I^2 statistic values: 0% to 30% low heterogeneity; 30% to 50% moderate heterogeneity; 50% to 75% substantial heterogeneity; and 75% to 100% considerable heterogeneity (Higgins 2009). We investigated heterogeneity as described in the Subgroup analysis and investigation of heterogeneity section.

Assessment of reporting biases

We assessed reporting biases for the main comparisons and primary outcomes by visual interpretation of funnel plots and testing for funnel plot asymmetry (Egger test) (Higgins 2009).

Data synthesis

We meta-analysed quantitative results within the different comparisons when studies were consistent on clinical grounds and had available outcome data; we imposed no restrictions based on risk of bias. We performed separate meta-analyses 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. We calculated fixed-effect models in a sensitivity analysis. We conducted meta-analyses of dichotomous outcomes using Mantel-Haenszel methods. We used inverse variance methods for continuous outcomes and measurement scales, and combined dichotomous and continuous data into a standardized mean difference whenever needed (Higgins 2009). All results are reported with 95% CI. We used Review Manager software for data management and analysis (RevMan 2008).

Subgroup analysis and investigation of heterogeneity

We planned to investigate heterogeneity by conducting subgroup analyses based on pre-specified study- and participant-level characteristics. The following subgroups were considered:

1. Protocolised use of bronchodilators (studies with protocolised use versus no/unclear protocolised use).
2. RSV status (studies with all participants exclusively RSV positive versus some RSV negative or unspecified RSV status).
3. Age of participants (studies with all participants exclusively less than 12 months of age versus some participants older than 12 months or unspecified age).
4. Atopy (studies with all participants exclusively atopic versus some participants not atopic or unspecified atopic status).
5. Glucocorticoid: type of glucocorticoids; and daily and overall dose (high versus low).

We explored potential positive or negative (i.e. "synergistic" or "antagonistic") interactions between glucocorticoids and bronchodilators by distinguishing trials where bronchodilator use was protocolised (i.e. comparing glucocorticoids + bronchodilator vs placebo + bronchodilator), from studies where use was either at the discretion of the physician or not allowed (Gurusamy 2009). The choice of other subgroups was based on clinical or biologic evidence suggesting possible effect modification of glucocorticoid effects by these characteristics. We chose a priori to use both drug type and dose as parameters to explore distinct glucocorticoid pharmacokinetic and pharmacodynamic properties; dosing was based on prednisolone equivalents.

We planned to perform subgroup analyses only on the review's primary outcomes. Data was also collected from studies that analysed these subgroups at a study-level. We assessed subgroup differences comparing changes in effect estimate and CI overlap; statistical tests or meta-regression techniques were not used.

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

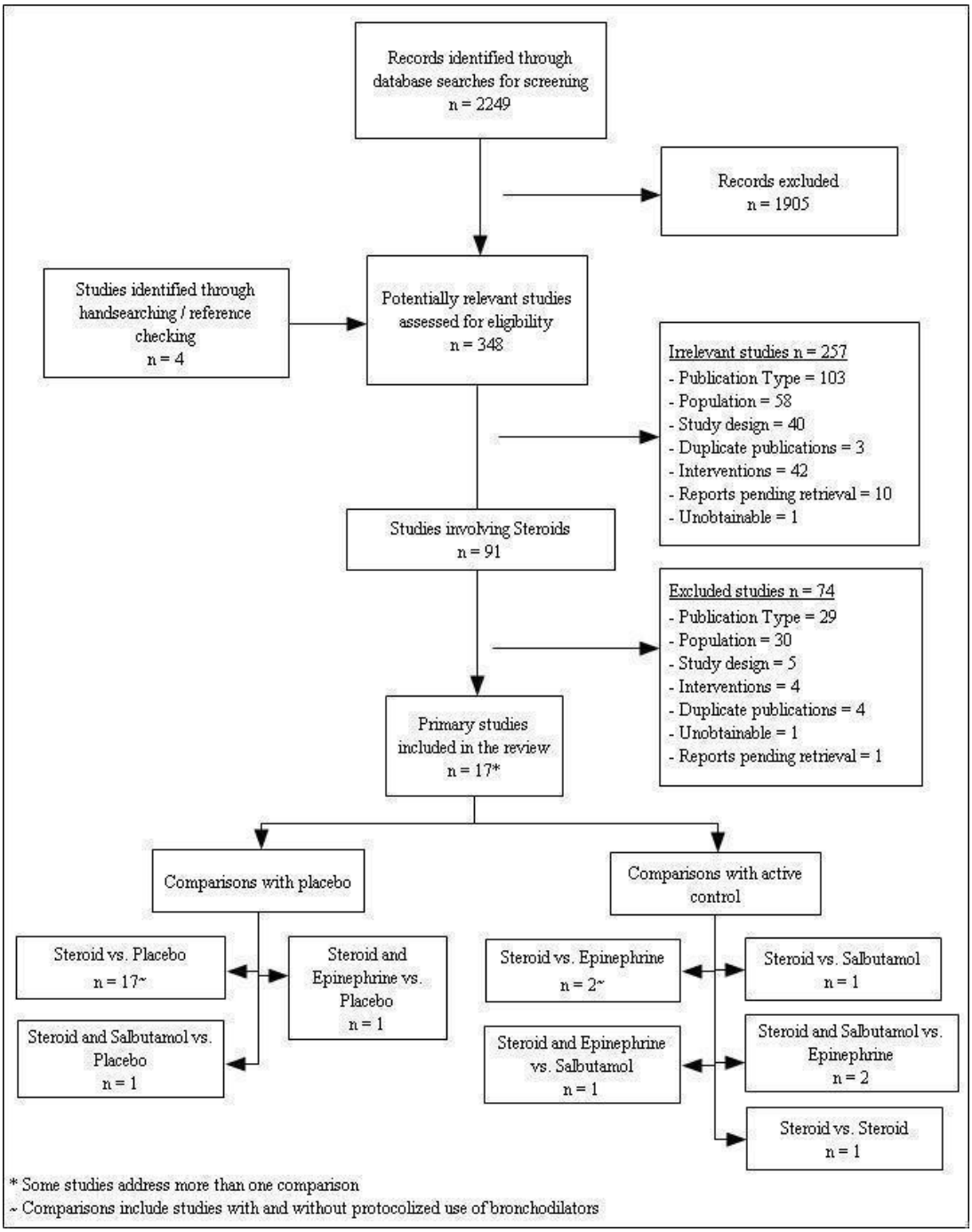
See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

The comprehensive search of all electronic databases identified 2249 records, of which 344 were potentially relevant. Through handsearching we identified four more studies, and overall 348 full-text articles were assessed for eligibility. Of these, 91 studies used glucocorticoids, 74 of which were excluded, including seven from the previous review version. One ongoing trial identified through register searches was subsequently found to have been terminated. Six trials included in the previous review version were also included in this update, and 11 new trials were added.

Figure 1 shows the flow of citations during the search, screening and eligibility stages, as well as all motives for exclusion.

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



Included studies

We included 17 trials with 2596 randomized participants. Details on the methods, participants, interventions and outcomes of each included trial are shown in Characteristics of included studies table.

We considered different comparisons separately between glucocorticoids, alone or with fixed co-interventions, and either placebo or active controls. Included trials contributed to one or more comparisons, depending on trial arms (Figure 1). There were three comparisons with placebo: glucocorticoid versus placebo (all 17 included trials, 2596 randomized participants); glucocorticoid and salbutamol versus placebo (one trial, 30 participants) (Barlas 1998); and glucocorticoid and epinephrine versus placebo (one trial, 401 participants) (Plint 2009). Five comparisons with active control were considered: glucocorticoid versus epinephrine (two trials, 444 participants) (Barlas 1998; Plint 2009); glucocorticoid versus salbutamol (one trial, 45 participants) (Barlas 1998); glucocorticoid versus glucocorticoid (one trial, 30 participants) (Barlas 1998); glucocorticoid and epinephrine versus salbutamol (one trial, 35 participants) (Kuyucu 2004); and glucocorticoid and salbutamol versus epinephrine (two trials, 64 participants) (Barlas 1998; Kuyucu 2004).

Design, centres and sample sizes

Fifteen trials were parallel-designed, 14 of which were double-armed (Bentur 2005; Berger 1998; Cade 2000; Corneli 2007; De Boeck 1997; Goebel 2000; Gomez 2007; Klassen 1997; Mesquita 2009; Richter 1998; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007; Zhang 2003) and one was six-armed (Barlas 1998). Barlas 1998 included three glucocorticoid arms, one placebo and two active comparators. Two trials were factorial two-by-two: Kuyucu 2004 randomized glucocorticoid/placebo and salbutamol/epinephrine, while Plint 2009 randomized glucocorticoid/placebo and epinephrine/placebo.

Eleven trials were single-centred and five included multiple centres (range: 2 to 20) (Cade 2000; Corneli 2007; Goebel 2000; Plint 2009; Teeratakulpisarn 2007); one trial did not clearly report this item (Bentur 2005). All trials were conducted in a single country, either in North America (six in the United States and Canada) (Corneli 2007; Goebel 2000; Klassen 1997; Plint 2009; Roosevelt 1996; Schuh 2002); Central and South America (three in Mexico, Brazil and Paraguay) (Gomez 2007; Mesquita 2009; Zhang 2003); Europe and the Middle East (seven in Turkey, United Kingdom [UK], Israel and Belgium) (Barlas 1998; Bentur 2005; Berger 1998; Cade 2000; De Boeck 1997; Kuyucu 2004; Richter 1998); or Asia (one in Thailand) (Teeratakulpisarn 2007).

Sample size calculations were reported in 12 trials (Bentur 2005; Berger 1998; Cade 2000; Corneli 2007; Klassen 1997; Mesquita 2009; Plint 2009; Richter 1998; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007; Zhang 2003); the outcome used for sample size calculation was the reported primary outcome in all except one trial (Richter 1998). The overall median number of participants per trial was 72 (range 32 to 800), with two large trials counting 600 and 800 (Corneli 2007; Plint 2009, respectively), and all others less than 200.

Funding was reported in nine studies, three of which had pharmaceutical industry support (Cade 2000; Richter 1998; Schuh 2002).

Setting and participants

Outpatients were included in eight trials, with 1824 randomized participants and a median of 85 participants per trial (range: 42 to 800) (Barlas 1998; Berger 1998; Corneli 2007; Goebel 2000; Kuyucu 2004; Mesquita 2009; Plint 2009; Schuh 2002). Outpatient settings mostly included pediatric emergency departments. Nine trials included inpatients only, with 772 participants and a median of 61 participants per trial (range: 32 to 179) (Bentur 2005; Cade 2000; De Boeck 1997; Gomez 2007; Klassen 1997; Richter 1998; Roosevelt 1996; Teeratakulpisarn 2007; Zhang 2003). Few details were reported regarding criteria for hospitalization and the type of admission unit in which patients received care, except for one inpatient trial report (Teeratakulpisarn 2007).

In most trials bronchiolitis was defined by clinical findings; wheezing was always required. Three trials restricted inclusion to bronchodilator responders (Goebel 2000 - outpatients; Teeratakulpisarn 2007 and Zhang 2003 - inpatients). Seven trials only included participants under the age of 12 months, all of which had a mean or median participant age below six months (Bentur 2005; Cade 2000; Corneli 2007; Plint 2009; Richter 1998; Roosevelt 1996; Zhang 2003).

Bronchiolitis severity thresholds were used for inclusion in eight outpatient (Barlas 1998; Berger 1998; Corneli 2007; Goebel 2000; Kuyucu 2004; Mesquita 2009; Plint 2009; Schuh 2002) and two inpatient trials (Gomez 2007; Klassen 1997). Severity was based on clinical scales or respiratory parameters, and thresholds varied. The Respiratory Distress Assessment Instrument (RDAI) baseline score thresholds were more than two (Gomez 2007); four (Kuyucu 2004; Plint 2009) and six (Corneli 2007; Klassen 1997; Schuh 2002) (less than four usually considered mild bronchiolitis).

Thirteen trials reported testing for RSV at least in a portion of participants, and three trials only included RSV-positive patients (Bentur 2005; Cade 2000; De Boeck 1997). Prevalence of RSV in the remaining 10 trials varied from 33% to 89% (Barlas 1998; Berger 1998; Corneli 2007; Goebel 2000; Klassen 1997; Mesquita 2009; Plint 2009; Richter 1998; Roosevelt 1996; Schuh 2002).

Atopic status was reported in nine trials (Barlas 1998; Berger 1998; Cade 2000; Plint 2009; Richter 1998; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007; Zhang 2003), while one trial reported a family history of wheezing (Corneli 2007). Definitions for atopy and methods of assessment were rarely provided, and when reported were heterogeneous. No trials excluded participants with a history of atopy.

Children with the following medical conditions were frequently excluded: cardiac or pulmonary disease (all trials except Teeratakulpisarn 2007), immunodeficiency (Bentur 2005; Cade 2000; Corneli 2007; De Boeck 1997; Goebel 2000; Plint 2009; Richter 1998; Schuh 2002), or neurological disease (Bentur 2005; Goebel 2000; Mesquita 2009; Schuh 2002). All or some premature infants were explicitly excluded in seven trials (Cade 2000; Corneli 2007; De Boeck 1997; Goebel 2000; Plint 2009; Schuh 2002; Teeratakulpisarn 2007). Other criteria for exclusion were length of illness and glucocorticoid-related parameters (previous use, history of adverse events, specific contraindications).

Subgroup analyses within studies were reported in five trials (Bentur 2005; Cade 2000; Corneli 2007; Plint 2009; Teeratakulpisarn 2007), two of which being pre-specified (Corneli 2007; Plint 2009). Subgroups were based on age, RSV status, family or personal history of atopy and eczema, duration and severity of illness, and exposure to smoke and/or dampness.

Interventions

There was heterogeneity regarding the choice of glucocorticoid, its dosage, route of administration and duration of treatment. Dexamethasone was the most frequently tested drug (11 trials). Nine trials used systemic dexamethasone, either oral (Corneli 2007; Klassen 1997; Mesquita 2009; Plint 2009; Schuh 2002), intramuscular (Kuyucu 2004; Roosevelt 1996; Teeratakulpisarn 2007), or intravenous (De Boeck 1997). Single-day doses were administered during one to five days. Initial dosing was higher (0.5 to 1 mg/kg), with later doses from 0.15 to 0.6 mg/kg. The highest overall dose was seen in Plint 2009 and Schuh 2002 (1 mg/kg followed by 0.6 mg/kg for five days), and the lowest in Mesquita 2009 (single-dose 0.5 mg/kg). Two trials used inhaled dexamethasone (0.2 mg to 0.25 mg every four or six hours), at least for one day, or until discharge for inpatients (Bentur 2005; Gomez 2007). Systemic prednisone or prednisolone were tested in four trials, three oral (Berger 1998; Goebel 2000; Zhang 2003) and one intravenous (Barlas 1998). Duration varied between one and five days (1 to 2 mg/kg/day, once or twice daily). Three trials used inhaled budesonide (0.5 mg to 1 mg, once or twice daily) for one to six weeks (Barlas 1998; Cade 2000; Richter 1998).

Details on placebos were reported in nine trials. Inhaled placebos included mist (Barlas 1998) and 0.9% saline (Bentur 2005; Richter 1998). Oral placebo solutions were described in four trials (Goebel 2000; Klassen 1997; Plint 2009; Schuh 2002), while Roosevelt 1996 and Teeratakulpisarn 2007 used intramuscular saline. Protocolised standard of care was used as a control arm in Zhang 2003.

Active control arms included epinephrine, salbutamol, and glucocorticoids. Eleven trials used protocolised bronchodilators in both glucocorticoid and placebo arms. The choice of bronchodilator, its dose and frequency varied substantially. Seven trials used salbutamol (Barlas 1998; Berger 1998; Goebel 2000; Gomez 2007; Klassen 1997; Kuyucu 2004; Schuh 2002), four used epinephrine (Bentur 2005; Kuyucu 2004; Mesquita 2009; Plint 2009) and one used salbutamol and ipratropium bromide (De Boeck 1997). Nebulised salbutamol was administered during emergency department stay (first two to four hours), or each four to six hours at home or during hospitalization (1.5 to 2.5 mg, or 0.15 mg/kg). Oral administration was also allowed in Goebel 2000. Nebulised epinephrine was administered every six hours to inpatients, or once or twice in the emergency department for outpatients (1 mg to 3 mg). All other trials used bronchodilators at the discretion of the attending physician, often with guidance on the choice of drug and dosage. Additional use of glucocorticoids was often restricted. Supportive measures, i.e. oxygen and intravenous or nasogastric fluids, were usually reported. Data on the use of bronchodilator co-interventions were often reported as an outcome.

Outcomes

Pre-defined primary outcomes were specified in twelve trials (Cade 2000; Corneli 2007; Goebel 2000; Klassen 1997; Kuyucu 2004; Mesquita 2009; Plint 2009; Richter 1998; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007; Zhang 2003), three of which reported more than one primary outcome (Kuyucu 2004; Richter 1998; Teeratakulpisarn 2007). Only the two largest trials used admission as a primary outcome (Corneli 2007; Plint 2009). Other primary outcomes included clinical scales (Goebel 2000; Klassen 1997; Kuyucu 2004; Mesquita 2009; Richter 1998; Schuh 2002), clinical severity parameters or duration of disease (Kuyucu 2004; Roosevelt 1996; Teeratakulpisarn 2007), and symptoms (Cade 2000; Zhang 2003). Timings of primary outcome assessment were reported in 11 trials, six of which used multiple time points. Sample size calculations were either not reported or based on secondary outcomes in Goebel 2000, Kuyucu 2004, and Richter 1998.

Reported outcomes included healthcare use domains and clinical severity parameters (all trials), pulmonary function (De Boeck 1997), patient/parent-reported symptoms and status (seven trials: Berger 1998; Cade 2000; Plint 2009; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007; Zhang 2003), and other outcomes, including adverse events (10 trials: Bentur 2005; Cade 2000; Corneli 2007; Klassen 1997; Kuyucu 2004; Plint 2009; Richter 1998; Roosevelt 1996; Teeratakulpisarn 2007; Zhang 2003). Not all outcome and time point results were reported (see selective outcome reporting in Risk of bias in included studies).

Admission rates were assessed in all eight outpatient trials, both by day 1 (all trials) and day 7 (three trials; Corneli 2007; Plint 2009; Schuh 2002). Kuyucu 2004 and Goebel 2000 reported admissions by days 5 and 6, respectively, and were pooled with day 7 results. LOS was reported in eight of nine inpatient trials (except Roosevelt 1996) and three outpatient trials (Berger 1998; Corneli 2007; Goebel 2000). Criteria for admission or discharge were rarely reported. Considerable variability was found in control group admission event rates (from 0% to 44% by day 1, and

0% to 49% by day 7) and mean LOS (0.8 to 6.6 days) (Table 1). Hospital re-admissions for inpatients and return healthcare visits up to one month were mentioned in six trials, with variable assessment methods (Berger 1998; Klassen 1997; Plint 2009; Roosevelt 1996; Schuh 2002; Teeratakulpisarn 2007).

Clinical severity scales were assessed in all except one trial (Zhang 2003), often using more than one scale (Corneli 2007; Plint 2009; Richter 1998; Schuh 2002). Measurement instruments were developed specifically for nine trials (Barlas 1998; Bentur 2005; Berger 1998; Cade 2000; De Boeck 1997; Goebel 2000; Richter 1998; Roosevelt 1996; Teeratakulpisarn 2007), mostly based on previous scales by Schuh 1990, Tal 1983, and Westley 1978. The RDAI was used in eight trials (Corneli 2007; Gomez 2007; Klassen 1997; Kuyucu 2004; Mesquita 2009; Plint 2009; Richter 1998; Schuh 2002). Corneli 2007 and Plint 2009 also used the Respiratory Assessment Change Score (RACS), based on RDAI and respiratory rate (both originally reported by Lowell 1987). All scales included items on wheezing and accessory muscle use; other respiratory items (for example, timing or location of wheezing) or disease domains (for example, general status, nutrition) were less frequently used. Internal scale structure and item weighting varied considerably. Conditions of assessment (for example, child status, fever, blinding) and raters were rarely reported. Oxygen saturation and respiratory rates were reportedly measured in all trials, and heart rate in all trials except Goebel 2000, Richter 1998, Teeratakulpisarn 2007, and Zhang 2003. Heterogeneity in timings of repeated measurements was found; the two most frequently time points assessed were 60 minutes and 3 to 6 hours.

Measurement of patient/parent-reported symptoms was inconsistent. Five trials reported symptoms data (Cade 2000; Plint 2009; Richter 1998; Roosevelt 1996; Teeratakulpisarn 2007). There were differences in the specific symptoms addressed (for example, respiratory, feeding), the measurement instrument used (i.e. questionnaires, diaries), and the time points of assessment. No trial reported the use of generic or disease-specific quality of life instruments.

Other reported outcomes included temperature measurements (Corneli 2007; Plint 2009; Roosevelt 1996), time to resolution or length of illness (Roosevelt 1996; Zhang 2003), and duration of oxygen therapy or fluids (Bentur 2005; Richter 1998; Roosevelt 1996; Teeratakulpisarn 2007; Zhang 2003).

Adverse events were mentioned in six trials (Corneli 2007; Goebel 2000; Klassen 1997; Kuyucu 2004; Plint 2009; Teeratakulpisarn 2007). Five of these studies assessed specific gastrointestinal, endocrine or infectious complications (Table 2). There was heterogeneity and incomplete reporting regarding which adverse events were pre-specified, their definitions and measurement methods. All adverse effects were short-term and no study assessed long-term harms.

Excluded studies

We excluded 74 papers after the initial screening procedure (Figure 1 and Characteristics of excluded studies table). The most frequent motives for exclusion included inappropriate population (for example, trials including participants with a history of previous wheezing, or > 24 months old), type of publication and non-RCT study design.

Risk of bias in included studies

Domain-specific and overall risk of bias assessments are detailed in Characteristics of included studies table and summarised by outcome and study in Figure 2 and Figure 3, respectively.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.*#*Overall risk of bias assessments are exclusive#For multi-arm studies (Barlas 1998, Kuyucu 2004 and Plint 2009), we included one overall assessment for all trial comparisons, and two assessments for each separate comparison of glucocorticoids versus placebo (with or without protocolized bronchodilator, or with epinephrine or salbutamol)

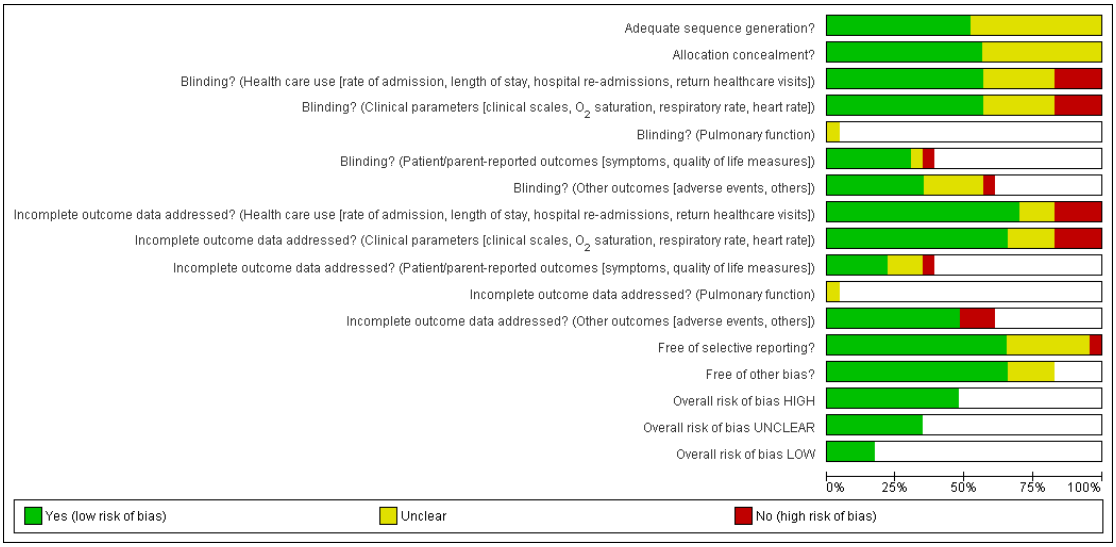


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.#For multi-arm studies (Barlas 1998, Kuyucu 2004 and Plint 2009), we included one overall assessment for all trial comparisons, and two assessments for each separate comparison of glucocorticoids versus placebo (with or without protocolized bronchodilator, or with epinephrine or salbutamol)**

Overall risk of bias was assessed as "low" in two trials, as "high" in seven and "unclear" in eight. The glucocorticoid and epinephrine versus placebo comparison included one low risk of bias trial. All other comparisons included mostly high risk of bias trials.

Adequate sequence generation and allocation concealment was found in 10 and 11 trials, respectively. Blinding was considered adequate in 11 out of 17 trials for the review primary outcomes and clinical severity parameters. Incomplete reporting explained most "unclear" assessments. Incomplete outcome data was adequately addressed in 12 out of 17 studies for the review primary outcomes, and 11 out of 17 for clinical severity outcomes; it was unclear or inadequate when there was imbalanced attrition between groups, mostly in longer follow-up assessments.

Nine out of 17 studies were considered free from risk of selective outcome reporting. Assessment of this item was challenging given the large number of outcomes reported, the diversity of measurement time points, and the fact that trial protocols were not available. Using trial registry searches, we identified three trial registers and used that data to complete assessments (Corneli 2007; Plint 2009; Teeratakulpisarn 2007).

Regarding publication bias and small study effects, there was no asymmetry in funnel plots for the primary outcomes in the glucocorticoids versus placebo comparison by visual inspection or statistical testing (Egger test for admissions and length of stay, P = 0.98 and P = 0.77, respectively) (Figure 4; Figure 5).

Figure 4. Funnel plot of comparison: 1 Steroid versus placebo, outcome: 1.1 Admissions (days 1 and 7) (outpatients) - review primary outcome.

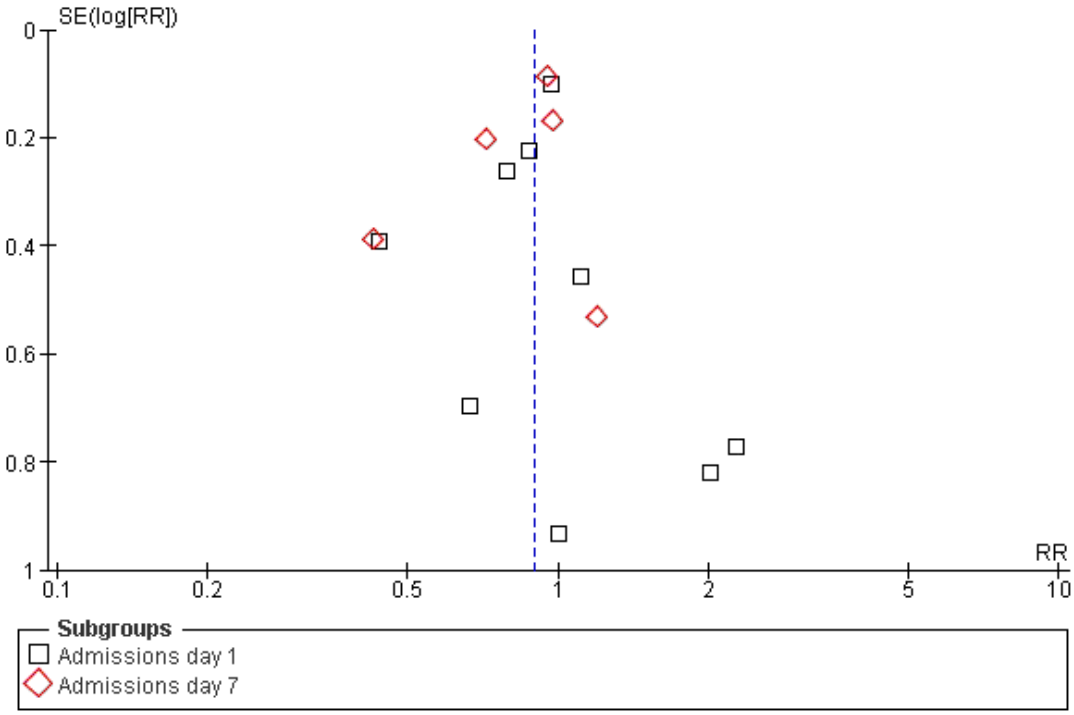
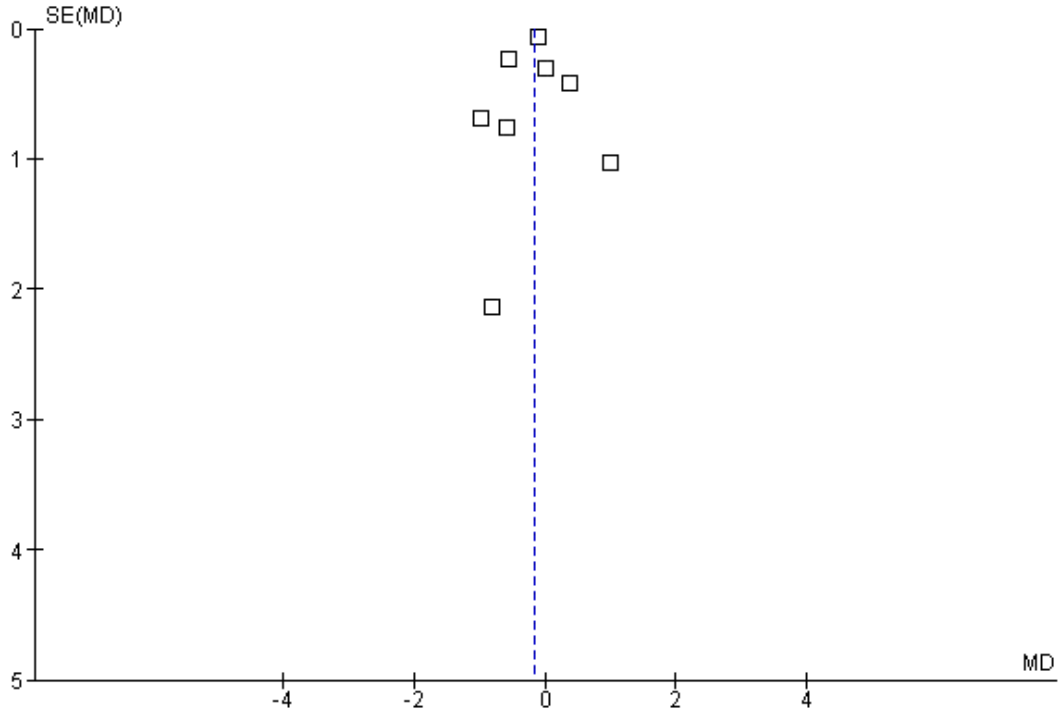


Figure 5. Funnel plot of comparison: 1 Steroid versus placebo, outcome: 1.2 Length of stay (inpatients) - review primary outcome.



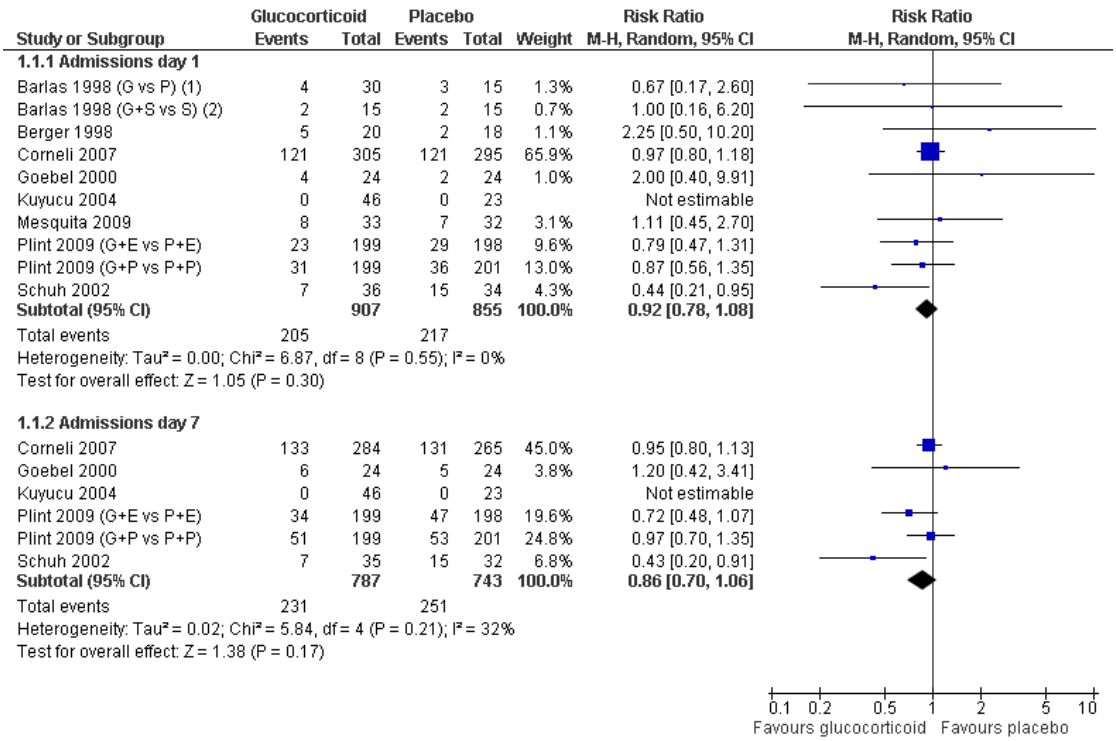
Other types of bias assessed as "unclear" included baseline imbalances, or active arm contamination with other related co-interventions (Kuyucu 2004 and Schuh 2002, respectively).

Effects of interventions

See: **Summary of findings for the main comparison** Glucocorticoid versus placebo: summary of findings; **Summary of findings 2** Glucocorticoid and epinephrine versus placebo: summary of findings

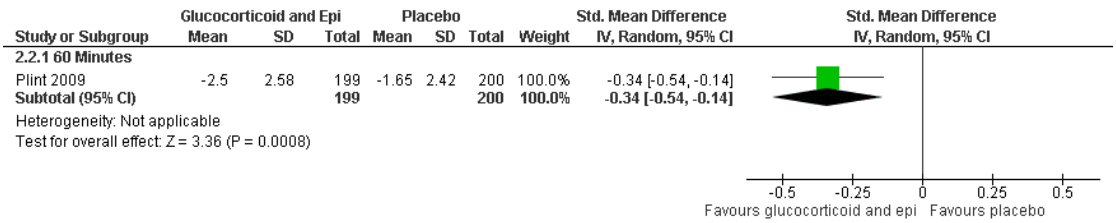
Results are summarised by comparison, setting and outcome. All results from meta-analyses are shown in summary Data and analyses table, and supplementary data can be found in Additional tables. For the two main comparisons - glucocorticoid versus placebo and glucocorticoid and bronchodilator versus placebo - we report forest plots of results from primary outcomes and clinical scores (Figure 6 to Figure 7). We also performed GRADE assessments for these comparisons (Table 3; Table 4), and summary findings are shown in Summary of findings for the main comparison and Summary of findings 2, with different baseline assumed risks. All meta-analyses used random-effects models; fixed-effect models did not modify the direction and magnitude of results unless mentioned.

Figure 6. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.1 Admissions (days 1 and 7) (outpatients) - review primary outcome.



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately;
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Figure 7. Forest plot of comparison: 5 Steroid and epinephrine versus placebo, outcome: 5.2 Clinical scale scores (outpatients) (change from baseline data).



Glucocorticoid versus placebo

Outpatients

Primary outcomes

All eight outpatient studies reported admissions by day 1, and five also reported admissions by day 7. Incomplete outcome data due to losses of follow-up limited analysis to 1762 participants by day

1 (out of 1824 randomized), and 1530 participants by day 7 (out of 1612 randomized).

The pooled RRs for admissions by days 1 and 7 were 0.92 (95% CI 0.78 to 1.08) and 0.86 (95% CI 0.7 to 1.06), respectively, with no significant differences between groups (Analysis 1.1; Figure 6). Heterogeneity was low for day 1 results and moderate for day 7 (I^2 statistic = 0% and 31%, respectively). There was no relevant change in the magnitude or direction of results when using pooled data from both Plint 2009 arms. Sensitivity analyses of trials with low overall risk of bias only included Plint 2009; RRs for admissions by days 1 and 7 were 0.83 (95% CI 0.6 to 1.16) and 0.85 (95% CI 0.64 to 1.14), respectively (Analysis 1.22). Overall strength of evidence for these findings was high for day 1 results and moderate for day 7, the latter due to some imprecision in the effect estimate (Table 3; Summary of findings for the main comparison).

Subgroup analyses of studies using protocolised bronchodilator are shown in Analysis 1.15 and Analysis 1.16 (Figure 8; Figure 9). For admissions by day 7, the estimate for RR was 0.68 (95% CI 0.44 to 1.05) for protocolised bronchodilator trials (four trials, 581 participants), and 0.95 (95% CI 0.82 to 1.11) for other trials (two trials, 949 participants). While RRs for both days 1 and 7 were lower in protocolised bronchodilator trials, the CIs between subgroups overlapped. Heterogeneity was low in both subgroups.

Figure 8. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.15 Admissions at day 1 (outpatients) - subgroup analysis protocolized use of bronchodilator.

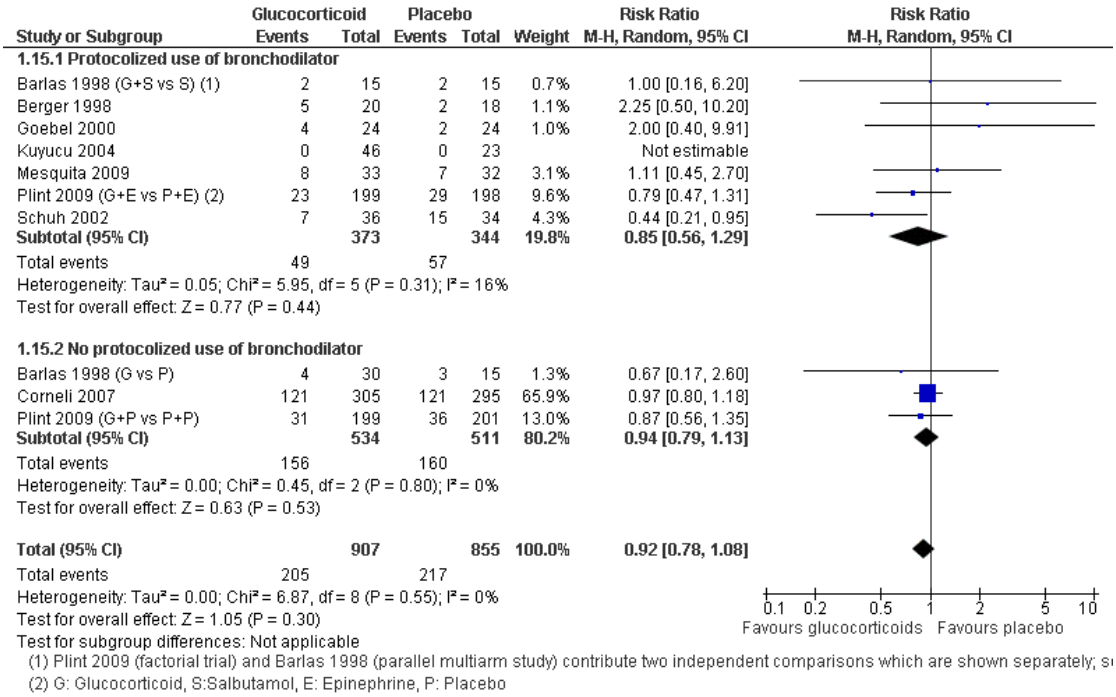
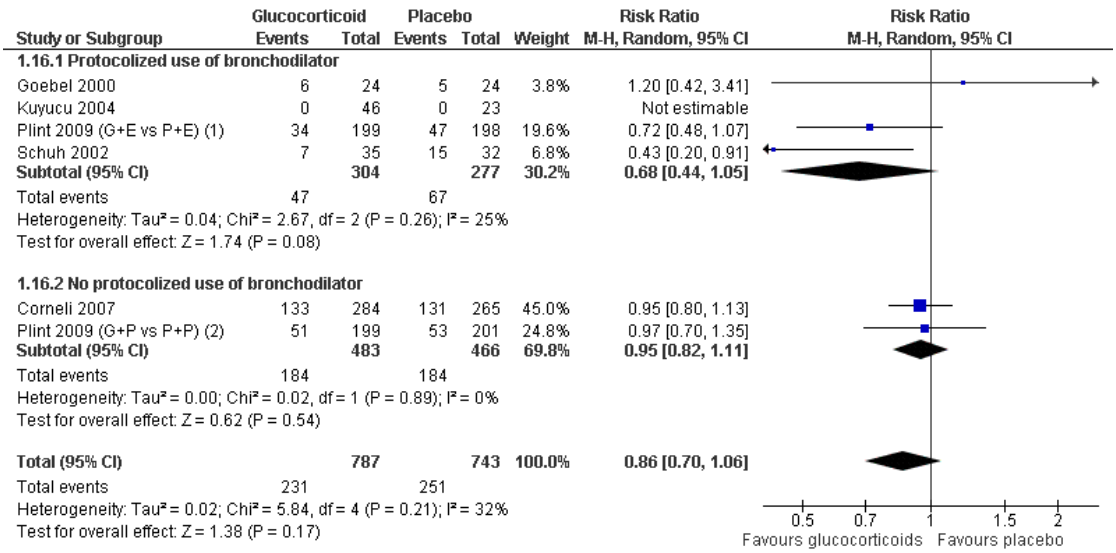


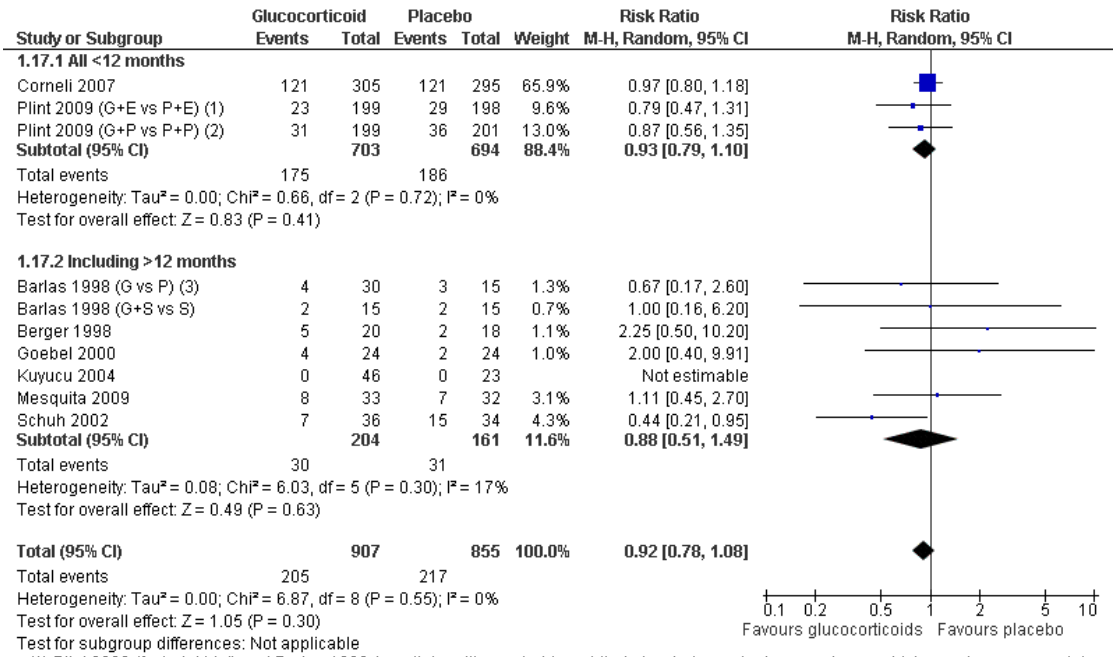
Figure 9. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.16 Admissions within 7 days (outpatients) - subgroup analysis protocolized use of bronchodilator.



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; s
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

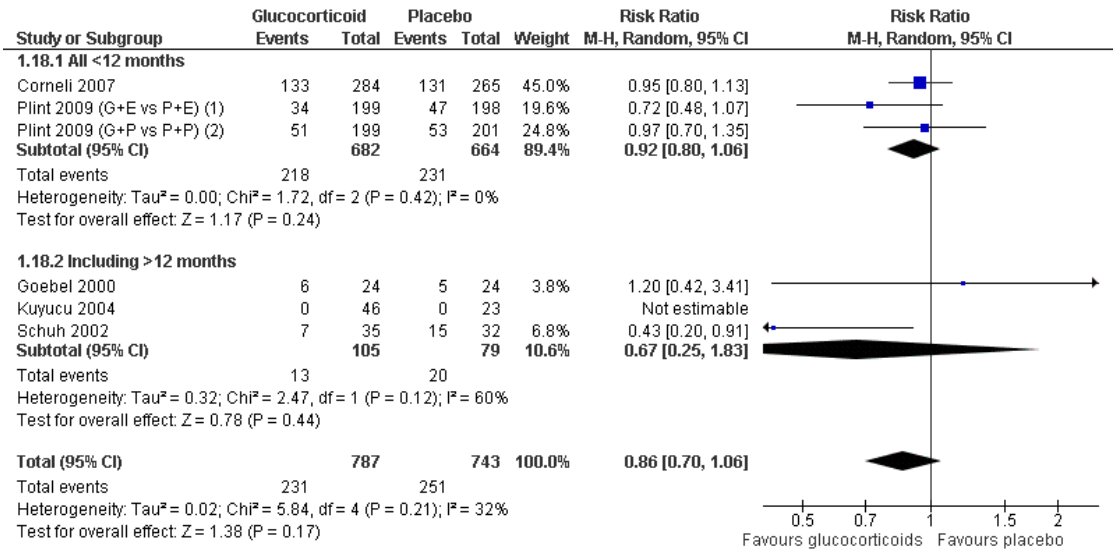
The two largest outpatient studies only included participants under 12 months of age, while six smaller studies also included older patients (Analysis 1.17; Analysis 1.18; and Figure 10; Figure 11). For admissions by day 7, estimates were 0.92 (95% CI 0.80 to 1.06) and 0.67 (95% CI 0.25 to 1.83), for < 12 months (two trials, 1346 participants) and trials including older participants (three trials, 184 participants), respectively. Trials including older participants had a lower effect estimate, but a large CI overlapped with the other subgroup and there was substantial heterogeneity (I^2 statistic = 60%).

Figure 10. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.17 Admissions at day 1 (outpatients) - subgroup analysis age.



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; s
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo
(3) Multi-arm study; contributes two comparisons to this analysis (G: Glucocorticoid, S:Salbutamol, P: Placebo)

Figure 11. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.18 Admissions within 7 days (outpatients) - subgroup analysis age.



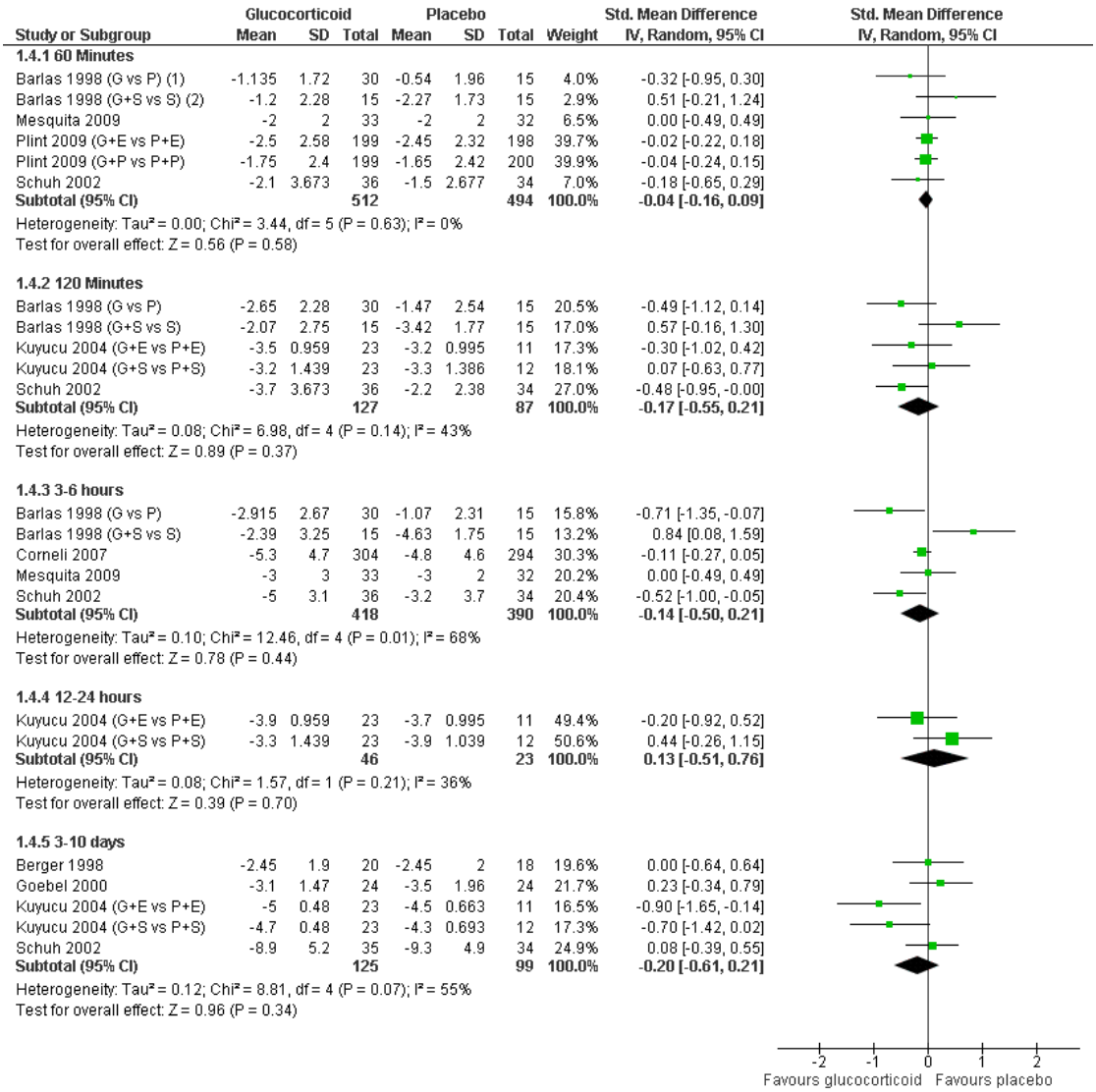
(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; s
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

No subgroup analysis according to RSV or atopic status was performed, since no outpatient trial restricted inclusion based on these parameters. We chose not to perform analyses based on glucocorticoid type or dose due to heterogeneity in glucocorticoid schemes. Corneli 2007 and Plint 2009 reported pre-specified subgroup analyses based on atopic status, with no statistically significant differences. Plint 2009 also reported no differences according to RSV status, duration of illness and severity.

Secondary outcomes

Clinical score data were available for time points/intervals between 60 minutes and 3 to 10 days (Analysis 1.4; Figure 12). Different sets of studies with different scales contributed to each time point, with most data at 60 minutes (four trials, 1006 participants) and 3 to 6 hours (four trials, 808 participants); no trial assessed the period between 24 to 72 hours. There were no significant differences between groups at any time point. Strength of evidence for these findings was high at 60 minutes, with precise and consistent results (SMD -0.04; 95% CI -0.16 to 0.09; I^2 statistic = 0%). Results at 120 minutes and 3 to 6 hours showed some heterogeneity (I^2 statistic = 43% and 68%, respectively), with overall moderate strength of evidence. Evidence was weaker for later results at 12 to 24 hours and between 3 to 10 days, with imprecision and substantial heterogeneity (I^2 statistic = 55%).

Figure 12. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.4 Clinical scale scores (outpatients) (change from baseline data).



(1) Kuyucu 2004 and Plint 2009 (factorial trials) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown se
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Six trials reported outcome data on oxygen saturation between 60 minutes and 24 to 72 hours (Analysis 1.6). Data were most frequently reported at 60 minutes (three trials, 936 participants) and 3 to 6 hours (four trials, 808 participants). At 3 to 6 hours, results favoured placebo (MD -0.43; 95% CI -0.84 to -0.02; units: %), while for all other time points there were no significant differences between groups.

Respiratory and heart rate data were both reported in six outpatient trials, between 60 minutes and 3 to 10 days (Analysis 1.8; Analysis 1.10). The most frequently assessed time points for both outcomes were 60 minutes and 3 to 6 hours; no trial assessed the period 24 to 72 hours. There were no significant differences between groups for any of these outcomes, at any of the earlier or later time points.

Regarding other health services outcomes, pooled data from three trials (255 participants) reporting LOS of admitted patients did not show significant differences between groups (Analysis 1.3). Return to healthcare visits for bronchiolitis symptoms were only assessed in two trials (863 participants), both showing considerable event rate for a three to four week follow-up period (26% to 53% in all groups; Table 5). Pooled results did not show significant differences between groups (RR 1.04; 95% CI 0.80 to 1.35) (Analysis 1.14).

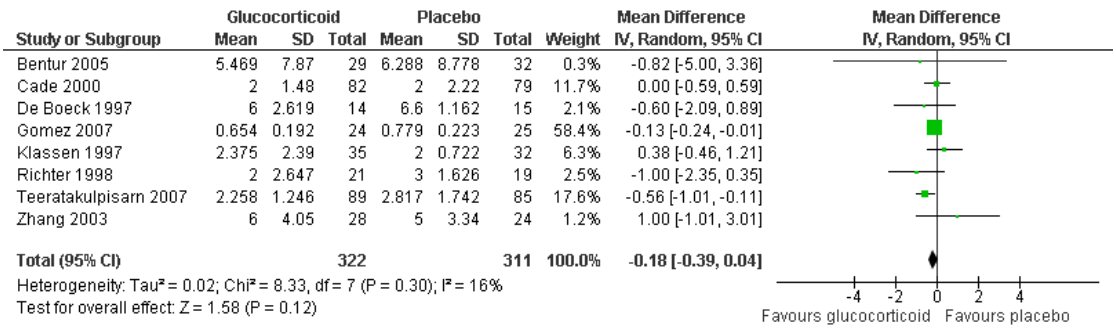
Plint 2009 reported data on parent-reported symptoms regarding time to return to normal feeding, sleeping, breathing and no coughing (Table 6). There were no statistically significant differences between glucocorticoid and placebo groups. No outpatient trials assessed or reported pulmonary function or quality of life outcomes.

Inpatients

Primary outcomes

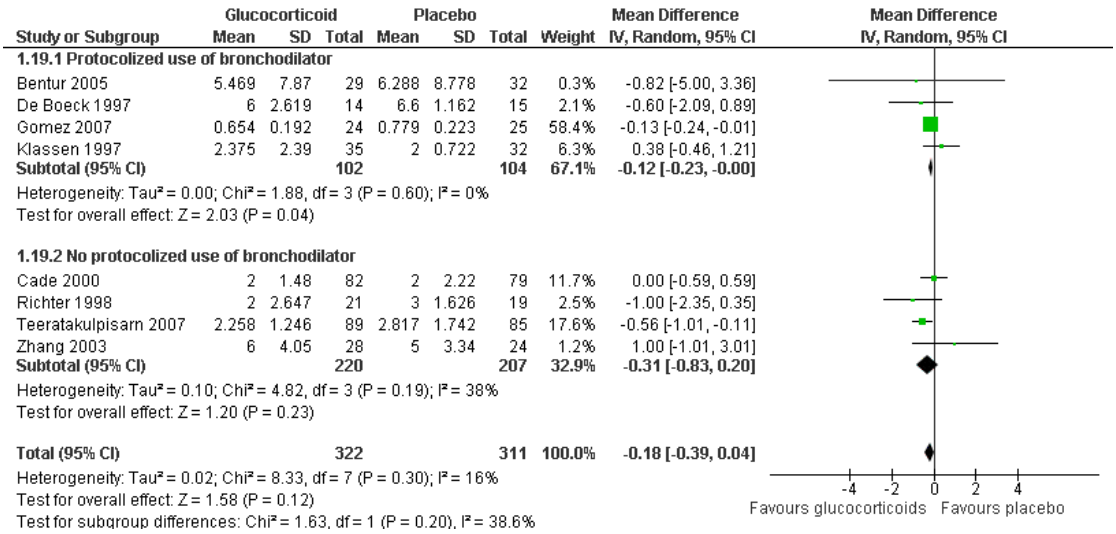
Eight inpatient trials reported data on LOS (633 participants), with no significant mean difference between glucocorticoid and placebo groups (MD -0.18 days, 95% CI -0.39 to 0.04; I^2 statistic = 16%) (Analysis 1.2; Figure 13). On a sensitivity analysis using fixed-effect models and including all studies, the mean difference reached statistical significance favoring glucocorticoids, with a similar magnitude (MD -0.14 days, 95% CI -0.25 to -0.03). Only one trial had low risk of bias (Klassen 1997). Strength of evidence was graded high given its precision, consistency, and risk of bias assessments for all included trials (Table 3; Summary of findings for the main comparison).

Figure 13. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.2 Length of stay (inpatients) - review primary outcome.



Subgroup analyses of studies with or without protocolised bronchodilators showed mean LOS differences of -0.12 days (95% CI -0.23 to -0.00; four trials, 206 participants) and -0.31 days (95% CI -0.83 to 0.20; four trials, 427 participants), respectively (Analysis 1.19; Figure 14). The subgroup with protocolised bronchodilator showed a statistically significant reduction in LOS, but CIs overlapped between subgroups. Heterogeneity was low in the protocolised group results (I^2 statistic = 0%), and moderate in the other subgroup (I^2 statistic = 38%).

Figure 14. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.19 Length of stay (inpatients) - subgroup analysis protocolized use of bronchodilator.



Subgroup analyses according to age and RSV status are shown in Analysis 1.20 and Analysis 1.21 (Figure 15; Figure 16). CIs overlapped between subgroups in both parameters. Heterogeneity was low in both < 12 months and RSV-only trial results, and moderate in the other subgroups.

Figure 15. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.20 Length of stay (inpatients) - subgroup analysis age.

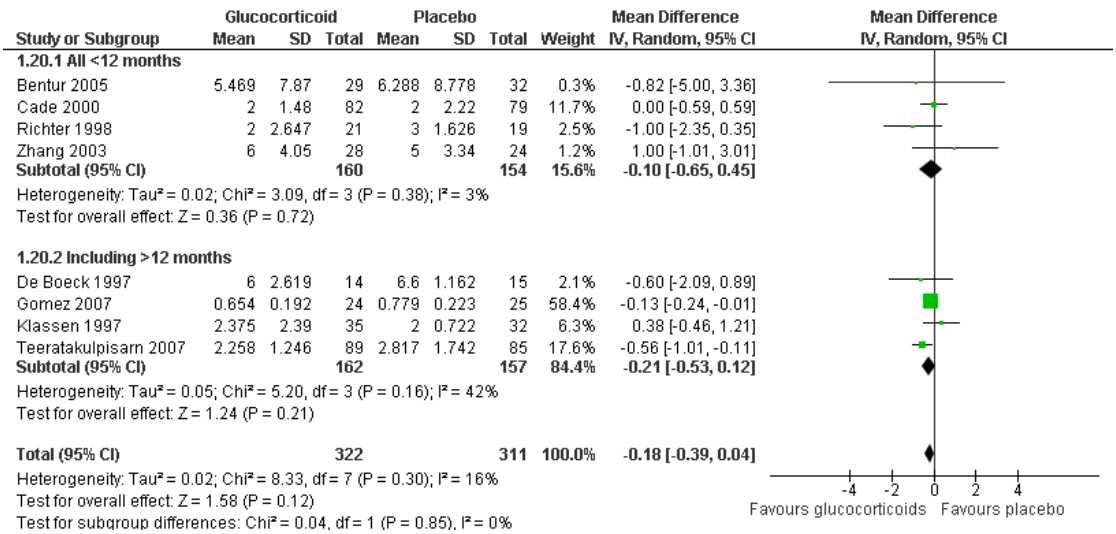
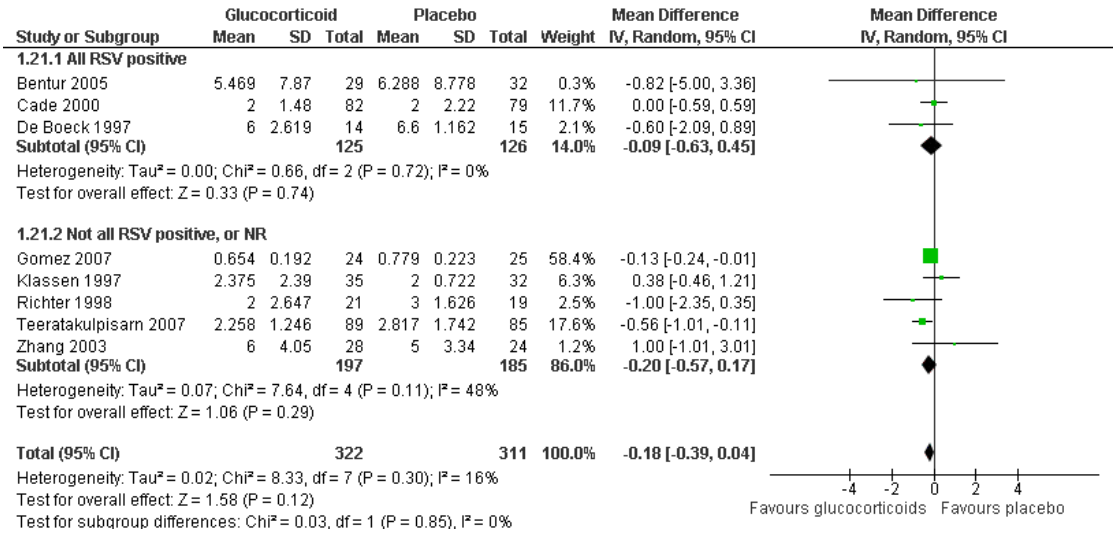


Figure 16. Forest plot of comparison: 1 Steroid versus placebo, outcome: 1.21 Length of stay (inpatients) - subgroup analysis RSV status.

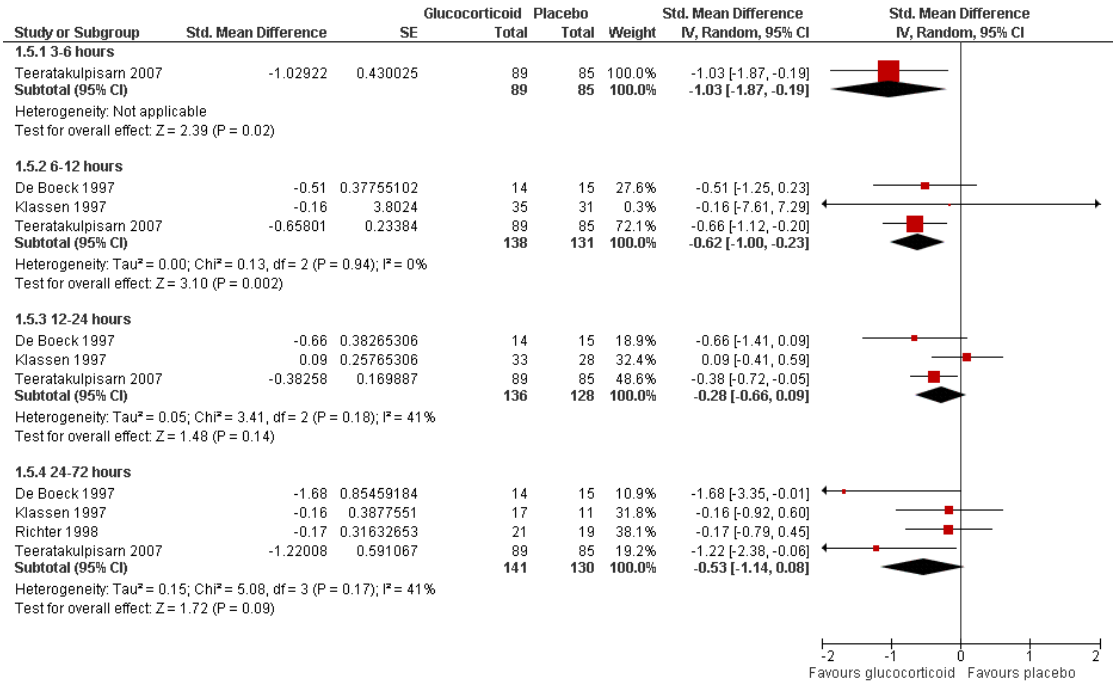


We did not perform subgroup analyses based on atopic status and glucocorticoid type and dose for the reasons mentioned previously.

Secondary outcomes

Clinical score data were only available for intervals between 3 to 6 hours and 24 to 72 hours (Analysis 1.5; Figure 17). Glucocorticoids were favoured at earlier time points (3 to 6 hours, one trial, 174 participants: SMD -1.03; 95% CI -1.87 to -0.19; and 6 to 12 hours, three trials, 269 participants: SMD -0.62; 95% CI -1.00 to -0.23). There were no statistically significant differences at later time points. Overall strength of evidence for these findings was assessed as low or moderate, due to imprecision and low or unknown consistency, often with considerable heterogeneity.

Figure 17. Forest plot of comparison: 1 Glucocorticoid versus placebo, outcome: 1.6 Clinical scores (inpatients) (change from baseline data).



Only two trials reported outcomes of oxygen saturation and respiratory rate at time points between 6 to 12 hours and 24 to 72 hours, one of which also reported heart rate at 12 to 24 hours (Analysis 1.7; Analysis 1.9; Analysis 1.11). There were no significant differences between groups for any outcome or time point.

Both hospital re-admissions and return healthcare visits were reported by three inpatient studies, with distinct durations of follow-up; no significant differences were found between groups (Table 5; Analysis 1.12; Analysis 1.13).

Three inpatient trials reported data on parent-reported symptoms (Table 6). Different sets of symptoms were measured at distinct time points, and methods of measurement and analysis varied. In Teeratakulpisarn 2007 time to being symptom free was significantly shorter in the glucocorticoid group, while Cade 2000 used a different analysis and did not shown any statistically significant differences. There were no differences regarding respiratory symptoms and feeding in both Cade 2000 and Roosevelt 1996. No inpatient trials assessed or reported quality of life outcomes.

De Boeck 1997 reported results from pulmonary function tests on day three. No differences were found in minute ventilation, dynamic lung compliance, and inspiratory and expiratory pulmonary resistance, both before and after nebulized bronchodilator.

All patients

Adverse events

Six trials reported adverse events. Five assessed specific glucocorticoid-related harms including the two largest studies (Table 2). We considered all harms data together regardless of patient setting in order to adequately assess the safety profile of glucocorticoids. Data were available from 600 to 1579 participants for each safety outcome. We did not pool results given the heterogeneity in definitions, methods and timings of assessment. Individual trial analysis did not show significant differences between glucocorticoids and placebo regarding the occurrence of vomiting, gastrointestinal bleeding, hypertension, pneumonia or varicella.

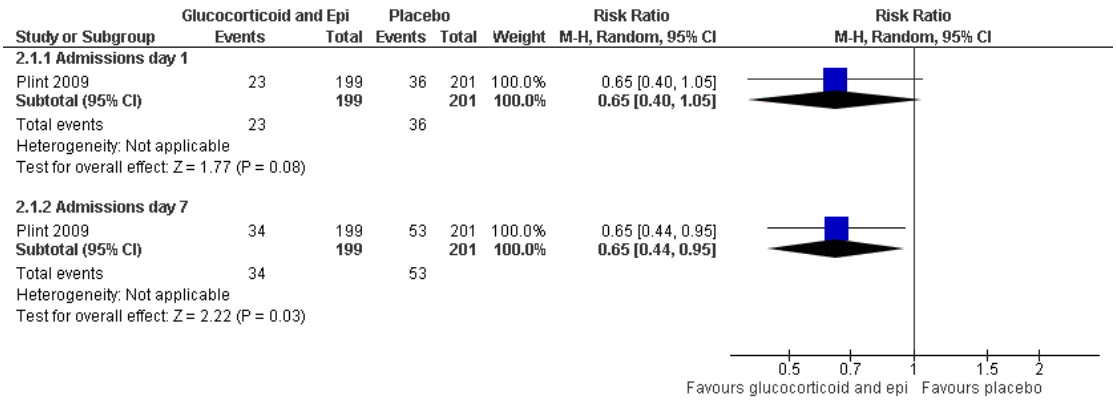
Glucocorticoid and bronchodilator (epinephrine or salbutamol) versus placebo

Both outpatient trials assessing either of these comparisons used different severity thresholds for patient inclusion: RDAI score above four in Plint 2009 (moderate disease), and scores between 4-10 using a trial-specific clinical scale in Barlas 1998 (mild to moderate disease).

Primary outcomes

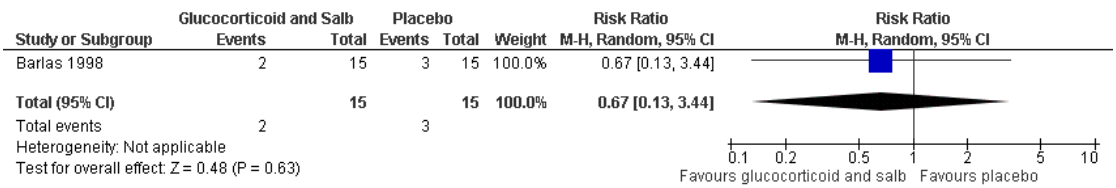
The factorial trial Plint 2009 included a comparison of oral dexamethasone and nebulized epinephrine against double placebo (399 analysed participants). This was the largest trial included in the review, with low overall risk of bias. The RRs for admissions by days 1 and 7 were 0.65 (95% CI 0.40 to 1.05) and 0.65 (95% CI 0.44 to 0.95), respectively (Analysis 2.1; Figure 18). There was a statistically significant reduction in admissions by day 7, with a relative risk reduction estimate of 35%. Absolute risk reduction was 9% (95% CI 1 to 17), and the NNTB to reduce one admission by day 7 was 11 (95% CI 7 to 76); these results were obtained through unadjusted analysis. However, the factorial trial design requires special methodological considerations, since this was not the study's main comparison, and there was an unanticipated additive/synergistic effect between epinephrine and dexamethasone. The authors therefore also reported analyses adjusted for multiple comparisons. Risk ratio for admissions by day 7 was 0.65 (95% CI 0.41 to 1.03), above the threshold for statistical significance. Overall strength of evidence was graded as low for these results given their imprecision and the fact that they were obtained from a single trial (Table 4; Summary of findings 2).

Figure 18. Forest plot of comparison: 5 Steroid and epinephrine versus placebo, outcome: 5.1 Admissions (days 1 and 7) (outpatients) - review primary outcome.



Barlas 1998, a small high risk of bias trial, compared systemic glucocorticoids (intravenous prednisolone) and nebulized salbutamol versus placebo. Admissions by day 1 (30 participants) showed no statistically significant differences between groups (RR 0.67; 95% CI 0.13 to 3.44) (Analysis 3.1; Figure 19).

Figure 19. Forest plot of comparison: 6 Steroid and salbutamol versus placebo, outcome: 6.1 Admissions (day 1) (outpatients) - review primary outcome.



Secondary outcomes

For the glucocorticoid and epinephrine versus placebo comparison, data on clinical scores, oxygen saturation, respiratory and heart rate were only available at 60 minutes. Clinical score results favoured glucocorticoid and epinephrine (SMD -0.34; 95% CI -0.54 to -0.14) (Analysis 2.2; Figure 7), while having a higher heart rate (MD 8.44; 95% CI 4.85 to 12.03) (Analysis 2.5). No differences were found between groups regarding oxygen saturation and respiratory rate (Analysis 2.3; Analysis 2.4). There were also no differences regarding return healthcare visits for bronchiolitis symptoms (RR 1.11; 95% CI 0.89 to 1.38) (Table 5; Analysis 2.6). Symptom results showed reduced time to normal feeding and quiet breathing in the glucocorticoid and epinephrine group (mean symptom duration ratios: 0.63, 95% CI 0.5 to 0.8 and 0.83, 95% CI 0.69 to 1.00) (Table 6). No differences were found in time to normal breathing and time to no coughing.

Results for clinical scores, oxygen saturation, and heart rate at 60 minutes, 120 minutes and 3 to 6 hours did show any differences between groups in the single trial comparing glucocorticoid and salbutamol versus placebo (Analysis 3.2; Analysis 3.3; Analysis 3.4). No further secondary outcomes were assessed in this comparison.

Other comparisons

These included glucocorticoid versus bronchodilator (epinephrine or salbutamol), glucocorticoid and bronchodilator (epinephrine or salbutamol) versus bronchodilator (epinephrine or salbutamol), and direct comparisons between different types of glucocorticoid (prednisolone versus budesonide). All trials were performed in the outpatient setting, and all except one were small-sized and had a high risk of bias.

Primary outcomes

The glucocorticoid versus epinephrine comparison included data from two trials (444 participants) for admissions by day 1, and one trial by day 7 (399 participants). Risk of bias was low for one trial, and high for the other. The pooled RRs for admissions were 1.12 (95% CI 0.66 to 1.88) (day 1) and 1.08 (95% CI 0.77 to 1.52) (day 7), with no significant differences between groups (Analysis 4.1). Only one small high risk of bias trial assessed day 1 admissions for both glucocorticoid versus salbutamol (45 participants) and glucocorticoid and salbutamol versus epinephrine comparisons (30 participants), with no differences between arms (Analysis 5.1; Analysis 7.1). There were no events in the trial comparing glucocorticoid and salbutamol versus epinephrine, and glucocorticoid and epinephrine versus salbutamol (Analysis 6.1; Analysis 7.1).

Barlas 1998 multi-arm trial also performed an unblinded comparison between systemic prednisolone and inhaled budesonide, with no statistically significant differences in admissions by day 1 (Analysis 8.1).

Secondary outcomes

When compared to glucocorticoid at 60 minutes, epinephrine use was associated with lower clinical scores (SMD 0.31; 95% CI 0.12 to 0.50) and higher oxygen saturation (MD -0.99; 95% CI -1.46 to -0.52; units: %) (two trials, 442 participants), while heart rate was lower with glucocorticoids (MD -7.56 bpm; 95% CI -11.34 to -3.79), and there were no differences in respiratory rate (Analysis 4.2; Analysis 4.3; Analysis 4.4; Analysis 4.5). There were no differences in the single trial assessing clinical scores and heart rate at later time points.

Salbutamol was also favoured when compared to glucocorticoids, in clinical scores at 60 minutes and 3 to 6 hours (SMD 0.65, 95% CI 0.01 to 1.28; and SMD 0.70, 95% CI 0.06 to 1.34, respectively), with no differences at 120 minutes (Analysis 5.2). Oxygen saturation at 60 minutes, 120 minutes and 3 to 6 hours were similar, and heart rate at 120 minutes was lower in glucocorticoid group (MD -7.53 bpm; 95% CI -14.28 to -0.78), with no differences at 60 minutes (Analysis 5.3; Analysis 5.4).

At 3 to 10 days, clinical scores and respiratory rate results favoured glucocorticoids and epinephrine as compared to salbutamol (SMD -1.22; 95% CI -1.98 to -0.46, and MD -13.70; 95% CI -20.56 to -6.84, respectively) (Analysis 6.2; Analysis 6.3; Analysis 6.4). There were no other differences at earlier time points and regarding heart rate.

Oxygen saturation at 60 and 120 minutes was higher in the epinephrine group when compared to glucocorticoid and salbutamol (MD -1.54; 95% CI -2.85 to -0.23, and MD -1.27; 95% CI -2.41 to -0.13, respectively) (Analysis 7.2; Analysis 7.3; Analysis 7.4; Analysis 7.5). No other statistically significant differences were found in clinical scores, oxygen saturation or respiratory or heart rate at other time points.

When comparing systemic prednisolone and inhaled budesonide, oxygen saturation results favoured budesonide at 60 minutes and 120 minutes (MD -1.46; 95% CI -2.74 to -0.18, and MD -1.73; 95% CI -3.06 to -0.40, respectively), and heart rate was lower with prednisolone at 3 to 6 hours (Analysis 8.3; Analysis 8.4). No differences were found in all other outcomes and time points (Analysis 8.2).

Plint 2009 reported safety assessments comparing glucocorticoid and epinephrine (Table 2). Pallor was observed in 7.5% of participants in the glucocorticoid group, compared to 11.1% in the epinephrine group. There were no significant differences in vomiting, bleeding, hypertension, varicella and tremor between glucocorticoids and epinephrine. No other trial from any of the other comparisons reported adverse events data.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Glucocorticoid and epinephrine versus placebo for acute viral bronchiolitis in infants and young children

Patient or population: patients with acute viral bronchiolitis in infants and young children
Settings: outpatients
Intervention: glucocorticoid and epinephrine versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Steroid versus Placebo	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Placebo	Steroid				
Admissions (outpatients) Follow-up: day 1	**179 per 1000**	**115 per 1000** (72 to 186)	**RR 0.65** (0.4 to 1.05)	400 (1)	Low	NNT: not calculated for non-significant findings
Admissions (outpatients) Follow-up: day 7	**264 per 1000**	**169 per 1000** (116 to 251)	**RR 0.65** (0.44 to 0.95)	400 (1)	Low	NNT: 11 [95% CI 7-76] (based on unadjusted analysis results)

*The basis for the **assumed risk** (for example, the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) 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.

[1] Assumed risk for admissions was based on the control group risk in the single study included (Plint 2009).

DISCUSSION

Summary of main results

Findings from this updated review add substantially to the current evidence base on use of glucocorticoids in acute viral bronchiolitis. Methods were revised since the last Cochrane citation (Patel 2004), and substantial new data were added from recent large studies. We included 17 trials (2596 participants) comparing glucocorticoids (alone or combined) versus placebo or active control. Only two studies had low overall risk of bias. Variability was found in control group admission rates and LOS, and baseline severity varied. Types of glucocorticoid schemes, active comparators and reported outcome definitions, instruments and timings of assessment were also heterogeneous.

Results do not suggest a clinically relevant stand-alone effect of systemic or inhaled glucocorticoids in either outpatient and inpatient settings (Summary of findings for the main comparison). Strength of evidence was moderate to high, indicating our confidence in effect estimates. There were no significant differences in outpatient admissions by days 1 and 7, and pooled RR estimates favoring glucocorticoids were below commonly used thresholds for clinical relevance. There were also no differences in any secondary outcomes, particularly clinical scores, oxygen saturation and respiratory symptoms. For inpatient trials, precise and consistent results did not show differences in LOS. The lower boundary of the pooled estimate CI was about nine hours, likely excluding a large clinically relevant benefit from glucocorticoids. While clinical score results were superior during the first day of treatment, no consistent differences were found at later time points or in any other secondary outcomes. Subgroup analyses according to age and RSV status did not suggest effect modification by these factors; heterogeneity did not allow adequate analysis of atopy and glucocorticoid type or dose.

Exploratory evidence suggests that combined glucocorticoids and bronchodilators may have clinically relevant benefits. A large factorial trial with low risk of bias found that high-dose systemic glucocorticoids (dexamethasone) with epinephrine reduced admissions by day 7 when compared to placebo, in outpatients with moderately severe bronchiolitis (Summary of findings 2). The unadjusted RR reduction estimate was 36%, and 11 children with bronchiolitis had to be treated to reduce one admission given the study's baseline risk. Clinical scores and symptoms results supported this benefit. However, these are the findings of a single study, and should be interpreted cautiously. There were methodological issues with trial design, and results may have arisen by chance. Further evidence regarding combined therapy is scarce and imprecise. Exploratory subgroup analyses was not conclusive as to an additive/synergistic effect of glucocorticoids combined with bronchodilators.

No relevant differences were reported in short-term general and intervention-specific adverse effects for these comparisons. However, balancing harms and benefits of glucocorticoids alone or combined was hampered by the lack of long-term safety data.

Overall completeness and applicability of evidence

These results rule out a significant stand alone benefit from glucocorticoids for the acute care of bronchiolitis. Previous trials and systematic reviews have used heterogeneous bronchiolitis definitions (DiTraglia 2004; Weinberger 2003; Weinberger 2007). There is no international standard definition, due to variation in semantics and clinical findings (for example, in the UK, 'crackles' are often key to diagnosis, as opposed to 'wheeze' in North America) (Everard 2009). We focused on first time wheezing in younger children so results could be directly pertinent to infants with "typical" viral bronchiolitis, as opposed to those with acute recurrent wheezing or asthma. 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 prospectively distinguish between them (Brand 2008; Sly 2008). While some parameters linked with different bronchiolitis classifications may help identify children at risk of later wheezing and asthma (for example, age, previous wheezing episodes) (Castro-Rodriguez 2000; Elphick 2007), scarce evidence supports the validity of these classifications (Elphick 2004; Everard 2009; Schultz 2010; Smyth 2006). We used a pragmatic definition for bronchiolitis, and our results are likely applicable to young children with first episodes of viral infection including wheezing.

Our findings of heterogeneity in bronchiolitis severity and glucocorticoids schemes did not affect the consistency of results. Baseline disease in outpatients was often moderate, but the use of different clinical criteria and scales limited the comparison between trials, particularly in inpatients. The wide range of control group admission rates and lengths of stay can be partially explained by differing disease severity, but it also reflects variation in bronchiolitis management, for example, different admission/ discharge criteria and standards of care (Babl 2008; Barben 2003; Brand 2000; Christakis 2005; Gonzalez 2010; Mallory 2003; Mansbach 2005). Variability in drug use patterns is also known to exist, and likely explains the large number of therapeutic approaches tested in included studies. Our findings were consistent in trials performed worldwide, and results likely apply to settings with different resources and management strategies.

Most studies were restricted to healthy infants, often excluding children with chronic conditions and prematurity. Lack of evidence for this subset of patients is problematic, since many are particularly at risk of adverse outcomes (Damore 2008; Figueras-Aloy 2008; Meissner 2003; Opavsky 1995). Epidemiological studies have highlighted the short- and long-term impact of RSV disease in prematurity (Figueras-Aloy 2008; Simoes 2008), and underlying changes in respiratory pathophysiology may limit external validity of our results in these populations.

Results from subgroup analyses did not identify any subset of par-

ticipants with a different response to glucocorticoids. Older aged and atopic children are at higher risk of recurrent wheezing and asthma (Castro-Rodriguez 2000), and both factors have been traditionally proposed as markers of underlying glucocorticoid-responsive wheezing phenotypes (Weinberger 2007). We found no conclusive evidence of such effect with age. We were unable to study atopy, but subgroup analyses from a few studies did not identify any significant differences. It has also been suggested that the response to glucocorticoids is different according to the causative virus (Korppi 2007; Lehtinen 2007). RSV and rhinovirus infection are associated with recurrent wheezing, the latter being a stronger predictor and possibly more responsive to glucocorticoids (Jackson 2008; Korppi 2007; Lehtinen 2007; Stein 1999). We found no differences according to RSV status, while other viral aetiologies were not reported. There are, however, potential methodological reasons for our negative results. Definition, ascertainment and reporting of subgroups were heterogeneous, and the use of aggregated data reduced power to investigate these hypotheses. While access to individual patient data might overcome some of these limitations (Higgins 2009), it is plausible that there may not be a glucocorticoid-responsive phenotype in "typical" viral bronchiolitis. It is known that each of these factors per se has limited prognostic accuracy in defining wheezing phenotypes, reflecting their heterogeneity (Brand 2008; Simpson 2010; Sly 2008). Accumulating evidence also shows that glucocorticoids have reduced effectiveness in later acute recurrent wheezing (Bush 2009; Panickar 2009). Using current definitions, our results suggest that none of these factors modify the effect of glucocorticoids in bronchiolitis.

We found promising exploratory results from one large trial using combined dexamethasone with epinephrine for moderately severe outpatients. Although reliance on findings from single precise well-conducted trials is often reasonable (Glasziou 2010), in this factorial trial the additive interaction between treatments was unanticipated, and this limits the interpretation of its results (McAlister 2003; Montgomery 2003). Our observational and exploratory subgroup analyses of protocolised bronchodilators may indirectly support an additive effect, but findings were not conclusive for both outpatients and inpatients. The latter often have factors that distinguish them from outpatients, for example, severity, duration of symptoms or non-response to initial bronchodilators, and these may affect response to therapy. Replication is therefore needed to improve our confidence in the direction, precision and magnitude of the effect estimates for outpatients, and its applicability for inpatients.

Whether results from combination therapy can be generalisable to different glucocorticoid or bronchodilator schemes is not known. Our positive results were shown with systemic dexamethasone, which is favoured in another common viral respiratory disorder, croup (Bjornson 2008). Its pharmacokinetic properties (i.e. long half-life) may account for this, but underlying pathological changes are distinct between conditions. Plint 2009 used multiple high-doses of dexamethasone. A previous dose-finding trial suggested similar results with a single high-dose, although there was no placebo comparator (Schuh 2008); the lowest efficacious dose remains unknown. The choice of bronchodilator is also undecided. Recent findings from an updated systematic Review on epinephrine in bronchiolitis show a reduction in first day outpatient admissions, as well as other short-term severity outcomes (Hartling 2010, updating results from Hartling 2004). This might explain part of the early benefit of combined therapy seen in Plint 2009. However, evidence is insufficient to assess whether combined epinephrine is superior to combined salbutamol. The wide variation in bronchiolitis drug management warrants further research to assess the adequate choice of glucocorticoid and bronchodilator.

Evidence from basic and translational research may support a synergistic effect of combined therapy, but it is not clear how this reconciles with lack of effect of glucocorticoids alone. Inflammation pathways and mediators involved in bronchiolitis seem to be distinct from those in glucocorticoid-sensitive asthma. Research has recently focused on the role of innate immunity and specific cytokine dysregulation patterns, and some early wheezing phenotypes have been shown to have prominent neutrophilic inflammation (Bont 2009; Halfhide 2008). This might explain the limited biological action of glucocorticoids alone, and phenotype specificities could determine differential drug effectiveness in children with apparently similar clinical findings (Buckingham 2002; Lehtinen 2007; Somers 2009). Paradoxically, clinical and biological synergism between glucocorticoids and bronchodilators has been a major topic in asthma treatment (Giembycz 2008). Two-way molecular interactions exist, including beta$_2$-agonist-stimulated glucocorticoid-mediated gene transcription (Kaur 2008), and glucocorticoid-induced increase in the transcription of the ß$_2$-receptor gene (Black 2009). Epinephrine's α-adrenergic vasoconstricting and edema-reducing activity may also confer an additional short-term benefit. Whether these mechanisms are involved in acute bronchiolitis therapy, and the role of specific types and doses of bronchodilators and glucocorticoids is unknown.

These positive results should be balanced against incomplete data on harms. Safety concerns are expected regarding the widespread use of epinephrine and glucocorticoids in young children with viral wheezing, particularly with repeated high glucocorticoid doses (Bush 2009; Frey 2009). Current data from RCTs and observational studies in croup suggest a favorable short-term safety profile from both dexamethasone and epinephrine (Bjornson 2008; Zhang 2005). Considering all trials, our results do not suggest any serious or frequent short-term expected or unexpected harms from glucocorticoids in the absence of co-morbidities. However, the power to detect important differences was limited due to the infrequent occurrence of events, and adverse event detection was heterogeneous. Glucocorticoids 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 2008; Karemaker 2008a; Onland 2008; Wilson-Costello 2009). Evidence is scarce, however, regarding effects of short-term use in otherwise healthy term infants, and none of these were studied in included trials. Further pharmacoepidemiologic data is needed to permit adequate short and long-term risk-benefit assessments.

Quality of the 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, with imprecise estimates and unknown consistency across studies.

A majority of trials had unclear risk of bias, usually due to incomplete or inadequate reporting, and many comparisons only included small trials at high risk of bias. Inadequate allocation concealment and blinding were likely to be relevant given the nature of interventions (for example, inhaled versus systemic administration) and outcome assessments (for example, physician-based admissions or discharge decisions). Incomplete outcome data was often found, with losses of follow-up in outpatient trials. However, for the main glucocorticoid versus placebo comparison, sensitivity analyses restricted to low risk of bias trials did not change the direction or magnitude of results for primary outcomes, highlighting their consistency.

Sparsity of data was a result of a large number of comparisons as well as variability in the choice of outcomes and timing of 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 (Flores 1997; King 2004; Klassen 1996). The absence of standardized, validated and patient-important outcome measures has been a serious threat to bronchiolitis trial validity. Our primary outcomes focused on hospital use, which has clear implications for patients, families and health services. However, there is no guidance supporting the choice of methodologically sound and patient-important outcomes. Lack of reporting of admission and discharge criteria is also problematic given the wide variation in bronchiolitis management. Additionnaly, the choice of clinical scales was inconsistent. The RDAI was used in a considerable number of trials, but its clinimetric properties - for example, responsiveness and clinically important difference - are not well known, which limits the interpretation of findings. This was compounded by the absence of quality of life measures. 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 all methods used, in order to explore new hypotheses stemming from recent evidence while addressing issues from previous studies.

Some limitations have been described in the discussion; others should also be highlighted. We did not obtain further 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. There is scarce guidance on how to investigate synergism/antagonism at a systematic review level, therefore our approach should be considered exploratory, including our use of factorial trial results. However, we performed sensitivity analyses of different analysis methods and these did not show a change in the direction of results. Our choice of outcome time intervals may have been source of heterogeneity, although it was limited by the variability of reported data. Limitations of subgroup analyses are well known and have been addressed. Grading of evidence was limited by the lack of guidance regarding clinically relevant differences in studied outcomes.

Agreements and disagreements with other studies or reviews

Three previous systematic reviews assessed the use of glucocorticoids in acute bronchiolitis, two of which also performed meta-analysis (Garrison 2000; King 2004; Patel 2004). None of the reviews included data from the two recent large glucocorticoid outpatient trials. There was some discordance in inclusion criteria regarding population and interventions: Garrison 2000 only included inpatient trials, Garrison 2000 and Patel 2004 were restricted to systemic glucocorticoidsm, and no review excluded previous wheezing. Choice of primary outcomes and their definitions, timings and analysis also differed. While Garrison 2000 highlighted a statistically significant reduction in LOS for inpatients, this analysis used a modified outcome definition. When comparing similar analyses for this outcome, quantitative results were comparable between all reviews, including ours, and suggest no relevant benefit from glucocorticoids in inpatients. Outpatient descriptive and quantitative results from Patel 2004 and King 2004 also found no difference in admissions. No previous review assessed the hypothesis of synergism between glucocorticoids and bronchodilators at an analysis level, while subgroup analyses assessing possible dose-response and effect modifiers like age and RSV status showed similar negative results.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence does not support a clinically relevant effect of systemic or inhaled glucocorticoids on admissions or LOS, when used alone in infants with bronchiolitis defined as a first episode of wheezing. Clinical score results suggest some short-term benefit of glucocorticoids for inpatients, but no differences were found

in other secondary outcomes. Absence of treatment effects was consistent throughout studies despite substantial heterogeneity regarding included populations, interventions, and outcomes, and this finding is likely to be applicable in diverse settings.

Exploratory results from a single large trial suggest combined high-dose systemic dexamethasone and epinephrine may reduce outpatient admissions in moderately severe bronchiolitis. These findings should be interpreted cautiously and may have arisen by chance. While no relevant differences were reported in short-term adverse events, long-term safety data were missing. Efficacy, harms and applicability of combined therapy needs to be clarified further.

Implications for research

A large RCT is needed to replicate and complement findings from combination therapy with glucocorticoid and bronchodilator for outpatients. Additional aims could include assessing the minimum efficacious glucocorticoid dose and the most adequate co-intervention. This strategy could also be tested in inpatient settings. Choice of comparators should take into account the wide variability in bronchodilator use, so that valid results may be more easily implemented. Further investigation of parent-reported outcomes is needed, as well as data to assess the long-term safety of this association. Future trials should use standardized sets of outcome measures in this field.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Barlas 1998

Methods	Parallel design, multi-arm (6) Single-centre, conducted in Turkey
Participants	Outpatients (emergency department/outpatient clinic) *Inclusion/exclusion criteria* Inclusion criteria: age < 24 months; 1st episode of wheezing; clinical score between 4-10 (mild-moderate) Exclusion criteria: patients with history of premature heart disease, chronic heart and lung problems, prior diagnosis of bronchial asthma, used bronchodilators and anti-inflammatory medications *Participant characteristics (all groups)* Sample size: randomized (N): 90, analysed - all outcomes (N): 90 (unclear what type of analysis was performed regarding ITT and missing data) Age, mean±SD: 8.52±0.59 Males, N (%): 50 (56) RSV status: 19/57 positive Atopic status: 4/86 (family)
Interventions	*GROUP 1* Drug name: placebo - mist tent Dose: NR Mode of administration: nebulized Timing/duration: NR *GROUP 2* Drug name: albuterol Dose: 0.15 mg/kg Mode of administration: nebulized Timing/duration: every hour during the first 4h *GROUP 3 (with glucocorticoid)* Drug name: prednisolone Dose: 2 mg/kg Mode of administration: IV Timing/duration: single dose *GROUP 4 (with glucocorticoid)* Drug name: albuterol + prednisolone Dose: 0.15 mg/kg (alb) + 2 mg/kg (pre) Mode of administration: nebulized + IV Timing/duration: single dose for both interventions *GROUP 5* Drug name: racaemic adrenaline (epinephrine) Dose: 0.1 mL/kg Mode of administration: nebulized Timing/duration: every 2h during the first 4h *GROUP 6 (with glucocorticoid)*

Barlas 1998 (*Continued*)

	Drug name: budesonide Dose: 0.5 mg Mode of administration: nebulized Timing/duration: single dose Additional co interventions for all groups: NR Protocolised use of bronchodilators with glucocorticoids: yes (Group 4 - salbutamol)
Outcomes	Primary outcome/outcome *used to calculate sample size* NR Secondary outcome*s* Hospital admission by day 1; SaO2*; heart rate*; clinical scale*: developed for this trial - 15 point score, based on respiratory rate, wheezing, retractions, nostril movement, and general patient condition; length of observation period; improvement with initial therapy; additional therapy *time points: baseline, 60, 120 minutes, 4 hours
Funding	NR
Notes	Language of publication: Turkish Study did not report any study-level subgroup analyses Results from groups 3 and 6 were combined for some analyses This study contributed to the following comparisons in this review: steroid versus placebo (with two comparisons: steroid versus placebo - "Barlas 1998 (G versus P)"; and steroid+salbutamol versus salbutamol - "Barlas 1998 (G+S versus S)"); steroid versus epinephrine; steroid versus salbutamol; prednisolone versus budesonide; steroid+salbutamol versus. Placebo; steroid+salbutamol versus epinephrine

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	

Barlas 1998 (*Continued*)

Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Free of selective reporting?	Low risk	
Overall risk of bias HIGH	Low risk	

Barlas 1998 (G vs P)

Methods	(see Barlas 1998)
Participants	(see Barlas 1998)
Interventions	(see Barlas 1998) This glucocorticoid versus placebo comparison includes pooled data from Groups 3 and 6 (prednisolone and budesonide) versus Group 1 (placebo)
Outcomes	(see Barlas 1998)
Funding	(see Barlas 1998)
Notes	(see Barlas 1998)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	High risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	

Barlas 1998 (G vs P) (*Continued*)

Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Free of selective reporting?	Low risk	
Overall risk of bias HIGH	Low risk	

Barlas 1998 (G+S vs S)

Methods	(see Barlas 1998)
Participants	(see Barlas 1998)
Interventions	(see Barlas 1998) This glucocorticoid+salbutamol versus salbutamol comparison includes data from Group 4 (prednisolone and albuterol) versus Group 2 (albuterol)
Outcomes	(see Barlas 1998)
Funding	(see Barlas 1998)
Notes	(see Barlas 1998)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	High risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	

Barlas 1998 (G+S vs S) (*Continued*)

Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Free of selective reporting?	Low risk	
Overall risk of bias HIGH	Low risk	

Bentur 2005

Methods	Parallel design, two-arm Centres: NR, conducted in Israel
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion criteria: age 3-12 months; 1st episode wheezing/dyspnoea; RSV present; parental consent Exclusion criteria: previous therapy with systemic glucocorticoids; inhaled β_2-agonists prior to admission; other chronic diseases *Participant characteristics* *All groups* Sample size: randomized (N): NR, analysed - trial / review primary outcomes (N): 61 (unclear what type of analysis was performed regarding ITT and missing data) *GROUP 1* Sample size: randomized (N): NR, analysed - trial / review primary outcomes (N): 29 Age, mean±SD: 3.3±2.5 Males, N (%): 14 (48.3) RSV status: All positive *GROUP 2* Sample size: randomized (N): NR, analysed - trial / review primary outcomes (N): 32 Age, mean±SD: 3.8±2.0 Males, N (%): 14 (43.8) RSV status: all positive Atopic status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone + epinephrine Dose: 0.25 mg (dex) + 1 ml (epi) Mode of administration: nebulized in 5 L/minutepre-specif100% O_2 Timimg/duration: every 6h until discharge *GROUP 2* Drug name: placebo - 0.9% saline + epinephrine Dose: 0.5 mL (0.9% sal) + 1 ml (epi) Mode of administration: nebulized in 5 L/minute pre-specif 100% O_2 Timimg/duration: every 6h until discharge Additional co interventions for all groups: O_2 therapy if SaO_2 < 92%; IV fluids if respiratory rate > 60 bpm Protocolised use of bronchodilators with glucocorticoids: yes (epinephrine)

Outcomes	Primary outcome NR / *Outcome used to calculate sample size* Clinical scale developed for this trial - 10 points score, based on respiratory rate, wheezing, retraction, general condition, oxygen saturation Secondary outcome*s* Length of stay (and time-to-discharge analysis); SaO_2*; respiratory rate*; heart rate*; duration of O_2 and IV fluids; clinical status#; hospital re-admissions#; wheezing exacerbations# *time points: baseline, every 8 hours #time points: 1 week, 1 mo., 3 mo. post discharge
Funding	NR
Notes	Study reported stratified results for premature and term infants; no specific interaction term This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	

Bentur 2005 (*Continued*)

Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias HIGH	Low risk	

Berger 1998

Methods	Parallel design, two-arm Single-centre, conducted in Israel (affiliations: Shaare Zedek Medical Center, Jerusalem)
Participants	Outpatients (emergency department) Inclusion/exclusion *criteria* Inclusion criteria: age ≤18 months; 1st episode of wheezing associated with low-grade fever, rhinitis, tachypnea and increased respiratory effort; otherwise healthy infant Exclusion criteria: chronic cardiopulmonary disease; asthma; proven or suspected acute bacterial infection; previous therapy with glucocorticoids; symptoms > 7d; fever > 38.5°C; severe bronchiolitis (clinical score > 7) *Participant characteristics* *All groups* Sample size: randomized (N): 42, analysed - trial / review primary outcomes (N): 38 (per-protocol analysis was used) *GROUP 1* Sample size: randomized (N): NR, analysed - trial / review primary outcomes (N): 20 Age, mean±SD: 5.2±0.7 Males, N (%): NR RSV status: 50% positive Atopic status: 1/20 (infant), 3/20 (family) *GROUP 2* Sample size: randomized (N): NR, analysed - trial / review primary outcomes (N): 18 Age, mean±SD: 4.8±0.9 Males, N (%): NR RSV status: 50% positive Atopic status: 0 (infant), 4/20 (family)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: prednisone Dose: 1 mg/kg Mode of administration: oral Timimg/duration: twice daily, 3 days *GROUP 2* Drug name: placebo (NR) Dose: 1 mg/kg Mode of administration: Oral Timimg/duration: twice daily, 3 days Additional co interventions for all groups: inhaled albuterol solution 0.03 mL/kg/dose (0.15 mg/kg/dose) every 4-6 hours; O_2 and hydration as needed Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol)

Berger 1998 (*Continued*)

Outcomes	Primary outcome NR / *Outcome used to calculate sample size* Clinical scale developed for this trial - 9 points score, based on respiratory rate, wheezing, accessory muscle use Secondary outcomes Initial hospital admission (usually within 4 h); SaO_2*; respiratory rate*; well-being#; return healthcare visits#; medications#; recurrent symptoms (by 2 years) *time points: baseline, 3 days #time points: 7 days
Funding	NR
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Unclear risk	Unclear
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Unclear risk	Unclear

Berger 1998 (*Continued*)

Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

Cade 2000

Methods	Parallel design, two-arm Multi-centre (5), conducted in the UK (West Yorkshire hospitals)
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion criteria: age < 12 mo.; confirmed RSV; informed consent; randomized within 12 hours admission Exclusion criteria: hx hospitalization with respiratory tract illness; chronic respiratory illness; congenital heart disease; prematurity; pre-existing immunodeficiencies; recent exposure to varicella or tuberculosis; prolonged exposure to systemic glucocorticoids *Participant characteristics* *All groups* Sample size: randomized (N): 165, analysed - trial primary outcome (N): 155 (ITT with available case analysis was used), analysed - review primary outcome (N): 161 (ITT with available case analysis was used) *GROUP 1* Sample size: randomized (N): 83, analysed - trial primary outcome (N): 79, analysed - review primary outcome (N): 82 Age, mean±SD: 4.3±2.8 Males, N (%): 45 (54.9) RSV status: all positive Atopic status: 43/82 present (infant) *GROUP 2* Sample size: randomized (N): 82, analysed - trial primary outcome (N): 76, analysed - review primary outcome (N): 79 Age, mean±SD: 4.0±2.8 Males, N (%): 47 (59.5) RSV status: All positive Atopic status: 38/79 present (infant)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: budesonide Dose: 1 mg Mode of administration: nebulized 10 minutes Timimg/duration: twice daily, 14-21 days *GROUP 2* Drug name: placebo (NR) Dose: NR Mode of administration: nebulized 10 minutes Timimg/duration: twice daily, 14-21 days

Cade 2000 (*Continued*)

	Additional co interventions for all groups: 6.5 L/minute O_2 therapy; reported use of ipratropium bromide, B_2 agonists, oral/IV glucocorticoids, antibiotics Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome/outcome *used to calculate sample size* Coughing or wheezing episodes (within 12 mo.; proportion with at least one episode) Secondary outcome*s* LOS; clinical scale developed for this trial - 11 points score, based on heart rate, respiratory rate, supplemental oxygen requirements, and the presence or absence of chest wall retractions*; additional medication use*#; hospital readmission#; return health-care visits#; respiratory symptoms# *time points: during hospitalization #time points: first 28 days, by 12 months (personal diaries, nurse visits, medical records)
Funding	Astra Foundation - full financial support grant
Notes	Study reported analyses of some outcomes by initial severity score, duration of symptoms at presentation, atopic history, and exposure to cigarette smoke or damp in the household; no specific interaction term This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Unclear risk	Unclear
Blinding? Other outcomes [adverse events, others]	Unclear risk	Unclear
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	

Cade 2000 (*Continued*)

Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Unclear risk	Unclear
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	High risk	
Free of other bias?	Low risk	
Overall risk of bias HIGH	Low risk	

Corneli 2007

Methods	Parallel design, two-arm Multi-centre (20), conducted in the US (centres from the Pediatric Emergency Care Applied Research Network - PECARN)
Participants	Outpatients (emergency department) Inclusion/exclusion *criteria* Inclusion criteria: age 2-12 mo.; 1st episode of bronchiolitis (no wheezing, asthma, no previous use of bronchodilators); within 7 days onset; moderate to severe (RDAI $\geq$ 6) Exclusion criteria: prior adverse event to dexamethasone; heart or lung disease; premature birth (< 36 weeks); immunosuppression or immunodeficiency; therapy with glucocorticoids in previous 14 d; active or recent exposure to varicella; critically ill; parent inability to speak English/Spanish *Participant characteristics* *All groups* Sample size: randomized (N): 600, analysed - review / trial primary outcome (N): 600 (ITT with all data was used; also performed per-protocol analysis) *GROUP 1* Sample size: randomized (N): 305, analysed - review / trial primary outcome (N): 305 Age, mean±SD: 5.1±2.6 months Males, N (%): 190 (62.5) RSV status: 85/127 positive *GROUP 2* Sample size: randomized (N): 295, analysed - review / trial primary outcome (N): 295 Age, mean±SD: 5.1±2.8 months Males, N (%): 178 (60.5) RSV status: 81/142 positive Atopic status: NR (reported family history of wheezing)

Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone Dose: 1 mL/kg (max 12 mg); oral solution = 1 mg/mL of liquid from generic dexamethasone phosphate injection solution Mode of administration: oral Timimg/duration: 1 dose *GROUP 2* Drug name: placebo (NR) Dose: 1 mL/kg (max 12 mg) Mode of administration: oral Timimg/duration: 1 dose Additional co-interventions for all groups: reported use of albuterol, epinephrine Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome/outcome *used to calculate sample size* Hospital admission (at 4 hours) Secondary outcome*s* Length of stay for admitted patients; SaO_2*; respiratory rate *; heart rate *; temperature*; clinical scale: Respiratory Assessment Change Score, a change score based on RDAI and respiratory rate change from baseline*; hospital re-admission#; return health care visits# ; adverse events# *time points: 4 hours #time points: within 7-10 days
Funding	Grant from the Maternal and Child Health Research program and cooperative agreements with the Emergency Medical Services for Children program of the Maternal and Child Health Bureau, Health Resources and Services Administration
Notes	Study reported subgroup analyses of patients with eczema or a family history of asthma (pre-specified), RSV positive, and aged <6 months; adjusted analysis plan with interaction terms This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 sat-	Low risk	

Corneli 2007 (*Continued*)

uration, respiratory rate, heart rate]		
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Unclear risk	Unclear
Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

De Boeck 1997

Methods	Parallel design, two-arm Single-centre, conducted in Belgium (affiliation: University Hospital Leuven)
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion criteria: age < 24 months; detection of RSV; 1st episode of wheezing or shortness of breath; onset of illness within the previous 5 days; informed consent Exclusion criteria: Heart, lung or immune disorder; premature infants born before 34 weeks *Participant characteristics* *All groups* Sample size: randomized (N): 32, analysed - all trial outcomes (N): 29 (per protocol analysis was used) *GROUP 1* Sample size: randomized (N): NR, analysed - all trial outcomes (N): 14 Age: 6.2 (median), 3.7-7.5 (IQR) months RSV status: all positive *GROUP 2* Sample size: randomized (N): NR, analysed - all trial outcomes (N): 15 Age: 7.1 (median), 4.4-8.9 (IQR) RSV status: all positive Males, N (%): NR

De Boeck 1997 (*Continued*)

	Atopic status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone Dose: 0.6 mg/kg Mode of administration: IV Timimg/duration: day 1, 2 doses of 0.6 mg/kg; days 2 and 3, 0.15 mg/kg *GROUP 2* Drug name: placebo (NR) Dose: NR Mode of administration: IV Timimg/duration: day 1, 2 doses of 0.6 mg/kg; days 2 and 3, 0.15 mg/kg Additional co-interventions for all groups: salbutamol (0.5%); 0.25 mL, ipratropium bromide (0.025%), 0.5 mL; both aerosolised every 6 h; also reported use of antibiotics Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol+ipratropium)
Outcomes	Primary outcome/outcome *used to calculate sample size* NR Secondary outcome*s* LOS; SaO_2*; respiratory rate*; clinical scale modified from Tal et al - 12 points score; pulmonary function tests (minute ventilation, dynamic lung compliance, and airway resistance - PEDS, MAS, Inc., Hatfield, Pa.) (before/after aerosol and day 3) *time points: every 12hours until day 3
Funding	NR
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Pulmonary function	Unclear risk	Unclear

De Boeck 1997 (*Continued*)

Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Incomplete outcome data addressed? Pulmonary function	Unclear risk	Unclear
Free of selective reporting?	Unclear risk	Unclear
Overall risk of bias UNCLEAR	Low risk	

Goebel 2000

Methods	Parallel design, two-arm Multi-centre (2), conducted in the US (University of South Alabama)
Participants	Outpatients (pediatric emergency department / children's clinic) Inclusion/exclusion *criteria* Inclusion Criteria: age 23 months of age or younger; viral respiratory tract infection; 1st time wheeze that did not clear completely after 1 dose of nebulized albuterol Exclusion criteria: history of immune defect; neurological disease with possible aspiration; gastroesophageal reflux; congenital or acquired chronic heart or lung disease; mechanical ventilation; birth < 36 weeks; temp > 38.5°C (rectal); antibiotic therapy < 1 week or antipyretic therapy < 8 hours before enrolment; concomitant bacterial infection; emesis precluding oral medications; initial bronchiolitis score < 2 or > 9 *Participant characteristics* *All groups* Sample size: randomized (N): 51, analysed - primary trial outcome (N): 32 (per protocol analysis was used), analysed - review primary outcome (N): 48 (per protocol analysis was used) *GROUP 1* Sample size: randomized (N): NR, analysed - primary trial outcome (N): 17, analysed - review primary outcome (N): 24 Age: 4.0 (median); 0-13 (range) months Males, N (%): 6 (25) RSV status: 11 positive *GROUP 2* Sample size: randomized (N): NR, analysed - primary trial outcome (N): 15, analysed - review primary outcome (N): 24 Age: 4.5 (median); 0-16 (range) Males, N (%): 8 (33.3) RSV status: 15 positive Atopic status: NR

Goebel 2000 (*Continued*)

Interventions	*GROUP 1 (with glucocorticoid)* Drug name: prednisolone Dose: 2 mg/kg/day Mode of administration: oral Timimg/duration: twice per day for 5 days *GROUP 2* Drug name: placebo - similar in appearance and taste, 100 mL each of water and glycerin with 5 mL of cherry-flavoured Kool-Aid and 100 mg of quinine Dose: equal volume per body weight Mode of administration: oral Timimg/duration: twice per day for 5 days Additional co interventions for all groups: albuterol initially 1 dose (0.15 mg/kg), continued at 0.3 mg/kg/d three times a day by mouth or 0.15 mg/kg/dose q.i.d. by nebulizer Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol)
Outcomes	Primary outcome Clinical scale modified from Tal et al: 12 point score, based on respiratory rate, flaring or retractions, oxygen saturation on room air, and wheezing* *Outcome used to calculate sample size* NR Secondary outcome*s* Hospital admission - initial and later; adverse events *time points: days 2, 3, 6, full convalescence
Funding	NR
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	

Goebel 2000 (*Continued*)

Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias HIGH	Low risk	

Gomez 2007

Methods	Parallel design, two-arm Single-centre, conducted in Mexico (Hospital General de Zona 1, San Luis Potosi)
Participants	Inpatients (emergency department and infant pediatric department) Inclusion/exclusion *criteria* Inclusion Criteria: age 1-18 mo.; observed in the ED of the centre; clinical and radiological diagnosis of bronchiolitis; < 72 hours of evolution of symptoms; RDAI score > 2, Silvermann-Andersen score > 0; informed consent Exclusion criteria: previous bronchospasm/bronchiolitis; congenital heart disease; chronic lung disease; possible bronchopneumonia; children treated with salbutamol/dexamethasone in the previous 48 hours *Participant characteristics* *All groups* Sample size: randomized (N): NR , Analysed - trial primary outcomes (N): 49 (unclear what type of analysis was performed regarding ITT and missing data) *GROUP 1* Sample size: randomized (N): NR, Analysed - all trial outcomes (N): 24 Age, mean±SD: 5.7±1.3 months Males, N (%): 12 (50) *GROUP 2* Sample size: randomized (N): NR, Analysed - primary trial outcome (N): 25 Age, mean±SD: 5.22±1.6 months Males, N (%): 13 (52) RSV status: NR Atopic status: NR
Interventions	*GROUP 1* Drug name: salbutamol Dose: 0.3 mL/1.5mg Mode of administration: nebulized in 5 L/minute of O2 Timimg/duration: every 4 hours for 24 hours (total 6 doses)

	GROUP 2 (with glucocorticoid) Drug name: salbutamol + dexamethasone Dose: 0.3 mL/1.5mg (salb) + dexamethasone: 0.5 mL/2mg Mode of administration: nebulized Timimg/duration: every 4 hours for 24 hours (total 6 doses) Additional co interventions for all groups: NR Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol)
Outcomes	*Primary outcome /outcome used to calculate sample size* NR *Secondary outcomes* LOS; SaO_2*; respiratory rate*; heart rate*; clinical scale: RDAI, 17 points score based on wheezing and retractions* *time points: every 4 hours until 24 hours
Funding	NR
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Free of selective reporting?	Unclear risk	Unclear

Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

Klassen 1997

Methods	Parallel design, two-arm Single-centre, conducted in Canada (Children's Hospital of Eastern Ontario)
Participants	Inpatients (inpatient wards, pediatric tertiary hospital) Inclusion/exclusion criteria Inclusion Criteria: age > 6 weeks < 15 mo.; 1st time wheeze; evidence of viral infection (rhinorrhea/ temp > 37.5°C); admitted to inpatient ward; SaO_2 < 95%; RDAI score > 6 Exclusion criteria: underlying disease that might affect cardiopulmonary status; asthma; wheezing/cough previously treated with bronchodilators; therapy with glucocorticoids within the past 2 week; history of adverse events to glucocorticoids *Participant characteristics* *All groups* Sample size: randomized (N): 72 (5 ineligible), analysed - trial / review primary outcome (N): 67 (ITT with available case analysis was used) *GROUP 1* Sample size: randomized (N): 35, analysed - trial / review primary outcomes (N): 35 Age, mean: 4.68; 3.6-5.76 (95% CI) Males, N (%): 22 (63) RSV status: 30 (86%) positive *GROUP 2* Sample size: randomized (N): 37, analysed - trial / review primary trial outcome (N): 32 Age, mean: 4.68; 3.6-5.64 (95% CI) Males, N (%): 15 (47) RSV status: 28 (88%) positive Atopic status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone (clear 70% sucrose solution + dex sodium phosphate) Dose: 1st: 0.5 mg/kg; 2nd and others: 0.3 mg/kg Mode of administration: oral Timimg/duration: 3 doses max: at admission, once each of the following mornings or until discharge (if before) *GROUP 2* Drug name: placebo (70% sucrose solution) Dose: NR Mode of administration: oral Timimg/duration: 3 doses max: at admission, once each of the following mornings or until discharge (if before) Additional co interventions for all groups: salbutamol by nebulisation, 0.15 mg/kg every 4 hours for first 24 hours, O_2 concentration of 35% in a plastic tent; reported use of additional bronchodilators and antibiotics

	Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol)
Outcomes	*Primary outcome /outcome used to calculate sample size* Clinical scale: RDAI, 17 points score based on wheezing and retractions (at 24 h; other time points*) *Secondary outcomes* LOS; SaO_2*; respiratory rate*; heart rate*; hospital readmission (1 week); return health-care visits; adverse events, number of nebulisation; additional medications * time points: 12, 24, 36, 48, 60 hours
Funding	Grant from Physicians Services Inc, Toronto, Ontario, Canada
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	

Free of other bias?	Low risk	
Overall risk of bias LOW	Low risk	

Kuyucu 2004

Methods	Double-randomisation / factorial design, four arms Single-centre, conducted in Turkey (Faculty of Medicine, Mersin University)
Participants	Outpatients (pediatric outpatient clinics and emergency department) Inclusion/exclusion *criteria* Inclusion Criteria: age 2-21 mo.; admitted with 1st episode of wheezing; clinical findings compatible with acute bronchiolitis; RDAI $\geq$ 4 Exclusion criteria: history of wheezing; previous therapy with bronchodilators; previous diagnosis of asthma or allergic bronchitis; personal history of atopic dermatitis or allergic rhinitis; chronic cardiac or pulmonary disease; any glucocorticoid therapy in the previous 2 week; signs of severe respiratory disease; bacterial infection; parental history of asthma or atopic disease *Participant characteristics* *All groups* Sample size: randomized (N): 90, analysed - trial / review primary outcome (N): 69 (ITT with available case analysis was used) *GROUP 1* Sample size: randomized (N): 26, analysed - trial / review primary outcomes (N): 23 Age, mean±SD: 7.2±0.8 months *GROUP 2* Sample size: randomized (N): 24, analysed - trial / review primary trial outcome (N): 23 Age, mean±SD: 7.9±1.0 months *GROUP 3* Sample size: randomized (N): 19, analysed - trial / review primary trial outcome (N): 11 Age, mean±SD: 9.6±1.3 months GROUP 4 Sample size: randomized (N): 21, analysed - trial / review primary trial outcome (N): 12 Age, mean±SD: 9.9±1.7 months Males, N (%): NR RSV status NR Atopic status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: epinephrine + dexamethasone Dose: 3 mL (3 mg) of 1:1000 L-epinephrine + 0.6 mg/kg (dex) Mode of administration: nebulized with O_2, flow 5-6 L/minute for 10 minutes (epi) + IM (dex) Timimg/duration: epinephrine - initial dose, if no improvement at 120 minutes, then 2nd dose given; dexamethasone single dose *GROUP 2 (with glucocorticoid)* Drug name: salbutamol + dexamethasone

	Dose: 0.15 mg/kg of 1 mg/mL solution of salbutamol added to 0.9% saline to total 3 mL+ 0.6 mg/kg (dex) Mode of administration: nebulized with O_2, flow 5-6 L/minute for 10 minutes (epi) + IM (dex) Timimg/duration: salbutamol - initial dose, if no improvement at 120 minutes, then 2nd dose given; dexamethasone single dose *GROUP 3* Drug name: epinephrine + placebo (NR) Dose: 3 mL (3 mg) of 1:1000 L-epinephrine Mode of administration: nebulized with O_2, flow 5-6 L/minute for 10 minutes (epi) + IM (pla) Timimg/duration: epinephrine - initial dose, if no improvement at 120 minutes, then 2nd dose given; placebo single dose *GROUP 4* Drug name: salbutamol + placebo (NR) Dose: 0.15 mg/kg of 1 mg/mL solution of salbutamol added to 0.9% saline solution to make a total of 3 mL Mode of administration: nebulized with O2, flow 5-6 L/minute for 10 minutes (epi) + IM (pla) Timimg/duration: salbutamol - initial dose, if no improvement at 120 minutes, then 2nd dose given; placebo single dose Additional co-interventions for all groups: NR Protocolised use of bronchodilators with glucocorticoids: yes (epinephrine Group 1, salbutamol Group 2)
Outcomes	Primary outcome Respiratory rate*; heart rate*; clinical scale*: RDAI, 17 points score based on wheezing and retractions *Outcome used to calculate sample size* NR Secondary outcome*s* Admissions; additional medication; adverse events; respiratory complaints (2 months) *time points: 30, 60, 90, 120 minutes, 24 hours, 5days
Funding	NR
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus. Placebo, steroids + epinephrine versus salbutamol, steroids + salbutamol versus epinephrine Factorial design not reported explicitly; analysis was "inside the table", and did not aggregate group results

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear

Kuyucu 2004 (*Continued*)

Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Other outcomes [adverse events, others]	Unclear risk	Unclear
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	High risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Unclear
Overall risk of bias HIGH	Low risk	

Kuyucu 2004 (G+E vs P+E)

Methods	(see Kuyucu 2004)
Participants	(see Kuyucu 2004)
Interventions	(see Kuyucu 2004) This glucocorticoid versus placebo comparison includes data from Group 1 (epinephrine + dexamethasone) versus Group 3 (epinephrine + placebo)
Outcomes	(see Kuyucu 2004)
Funding	(see Kuyucu 2004)
Notes	(see Kuyucu 2004)

Kuyucu 2004 (G+E vs P+E) (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Other outcomes [adverse events, others]	Unclear risk	Unclear
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	High risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Unclear
Overall risk of bias HIGH	Low risk	

Kuyucu 2004 (G+S vs P+S)

Methods	(see Kuyucu 2004)
Participants	(see Kuyucu 2004)
Interventions	(see Kuyucu 2004) This glucocorticoid versus placebo comparison includes data from Group 1 (salbutamol + dexamethasone) versus Group 3 (salbutamol + placebo)

Kuyucu 2004 (G+S vs P+S) (*Continued*)

Outcomes	(see Kuyucu 2004)	
Funding	(see Kuyucu 2004)	
Notes	(see Kuyucu 2004)	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Other outcomes [adverse events, others]	Unclear risk	Unclear
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	High risk	
Free of selective reporting?	Low risk	
Free of other bias?	Unclear risk	Unclear
Overall risk of bias HIGH	Low risk	

Mesquita 2009

Methods	Parallel design, two arms. Single-centre, conducted in Paraguay (Hospital General Pediátrico "Niños de Acosta Ñu", Asunción)
Participants	Outpatients (pediatric emergency department) Inclusion/exclusion *criteria* Inclusion Criteria: age 2-24 mo.; 1st episode of bronchiolitis defined as respiratory distress, respiratory rate 40-80 bpm, wheezing; < 7 d after onset of cold Exclusion criteria: clinical or radiological pneumonia; cardiopulmonary congenital malformations; bronchopulmonary dysplasia; cystic fibrosis; foreign body aspirations; neurological alteration; previous wheezing or asthma episode; inhaled or systemic glucocorticoid < 15 d; β_2-agonists < 4 hours; history of atopy in the child (dermatitis or allergic rhinitis) or parental asthma; severe wheezing attack (respiratory rate $\geq$ 100/minute and/or heart rate $\geq$ 200/minute and/or shock or lethargy) *Participant characteristics* *All groups* Sample size: randomized (N): 80 , analysed - trial/review primary outcomes (N): 65 (per-protocol analysis was used) *GROUP 1* Sample size: randomized (N): NR, analysed - trial/review primary outcomes (N): 33 Age, mean±SD: 7.3 ± 4 months Males, N (%): 19 (58) RSV status: 17/29 positive *GROUP 2* Sample size: randomized (N): NR, analysed - trial / review primary trial outcome (N): 32 (available case analysis was used) Age, mean±SD: 5.9 ± 3 months Males, N (%): 15 (47) RSV status: 19/23 positive Atopic status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone Dose: 0.5 mg/kg (1 mL/kg) Mode of administration: oral Timimg/duration: 1 dose *GROUP 2* Drug name: placebo (NR) Dose: 1 mL/kg Mode of administration: oral Timimg/duration: 1 dose Cointerventions: Additional co interventions for all groups: all patients received 4 mL physiological solution during a 6-minute. nebulisation with 0_2 flow of 6 L/minute; after 30 minutes, a dose of 1 mL L-adrenaline solution (1:1000, 1 mL = 1 mg) was received by nebulisation Protocolised use of bronchodilators with glucocorticoids: yes (epinephrine)

Outcomes	Primary outcome/outcome *used to calculate sample size* Clinical scale*: RDAI, 17 points score based on wheezing and retractions (at 4 h; other time points*) Secondary outcome*s* Hospital admission (at 4 hours); SaO_2*; respiratory rate*; heart rate* *time points: 60 minutes, 4 hours
Funding	NR (Lab. Formula Magistral, Asunción, Paraguay provided drugs)
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Free of selective reporting?	Unclear risk	Unclear
Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

Plint 2009

Methods	Factorial design, four arms Multi-centre (8), conducted in Canada (hospitals are members of the research group Pediatric Emergency Research Canada)
Participants	Outpatients (pediatric emergency department) Inclusion/exclusion *criteria* Inclusion Criteria: age 6-12 mo.; RDAI: 4-15; 1st episode wheezing associated with upper respiratory tract infection; presenting bronchiolitis Exclusion criteria: prior bronchodilator treatment in the emergency department; oral or inhaled glucocorticoid during previous 2 week; previous episode of wheezing or history of asthma; previous bronchodilator use; chronic cardiopulmonary disease; immunodeficiency; serious distress (defined as a pulse rate >200 beats per minute, a respiratory rate > 80 breaths per minute, or an RDAI score >15); lethargy; exposed to varicella < 3 week; < 37 week gestation who had a corrected age of less than 6 weeks at presentation; communication barriers with family *Participant characteristics* *All groups* Sample size: randomized (N): 800, analysed - trial / review primary outcome (N): 797 (ITT with available case analysis was performed) *GROUP 1* Sample size: randomized (N): 200, analysed - trial / review primary outcomes (N): 199 Age: 5 (median) 3-7 (interquartile range) months Males, N (%): 124 (62) RSV status: 128 (64) positive Atopic status: 28 (14) present (infant) *GROUP 2* Sample size: randomized (N): 199, analysed - trial / review primary trial outcome (N): 198 Age: 5 (median) 3-7 (interquartile range) months Males, N (%): 122 (61) RSV status: 129 (65) positive Atopic status: 20 (10) present (infant) *GROUP 3* Sample size: randomized (N): 200, analysed - trial / review primary trial outcome (N): 199 Age: 5 (median) 3-7 (interquartile range) months Males, N (%): 127 (64) RSV status: 127 (64) positive Atopic status: 19 (9.5) present (infant) GROUP 4 Sample size: randomized (N): 201, analysed - trial / review primary trial outcome (N): 201 Age: 5 (median) 3-7 (interquartile range) months Males, N (%): 120 (60) RSV status: 136 (68) positive Atopic status: 22 (10.9) present (infant)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: epinephrine + dexamethasone (generic dexamethasone phosphate injection solution mixed with Ora-Plus and Ora-Sweet - Paddock Laboratories)

	Dose: 3mL 1:1000 solution (epi)+ 1.0 mg/kg weight (max 10 mg) then 0.6 mg/kg (max 10 mg) after ED (dex) Mode of administration: nebulized in O_2 flow 8L/minute (epi) + oral (dex) Timimg/duration: nebulise 2 doses 30 minutes apart (epi); oral after 1st nebulisation in ED, followed by 5, 1x daily doses after leaving ED (dex) *GROUP 2* Drug name: epinephrine + placebo (Ora-Plus and Ora-Sweet) Dose: 3mL 1:1000 solution (epi) + placebo Mode of administration: nebulized in O_2 flow 8L/minute (epi) + oral (pla) Timimg/duration: nebulise 2 doses 30 minutes apart (epi); oral after 1st nebulisation in ED, followed by 5, 1x daily doses after leaving ED (pla) *GROUP 3 (with glucocorticoid)* Drug name: dexamethasone + placebo (saline) Dose: 1.0 mg/kg weight (max 10 mg) then 0.6 mg/kg (max 10 mg) after ED (dex) + 3 ml (pla) Mode of administration: oral (dex) + nebulized in O_2 flow 8L/minute (pla) Timimg/duration: nebulise 2 doses 30 minutes apart (pla); oral after 1st nebulisation in ED, followed by 5, 1x daily doses after leaving ED (dex) *GROUP 4* Drug name: placebo (saline) + placebo (Ora-Plus and Ora-Sweet) Dose: 3 ml + oral Mode of administration: nebulized in O_2 flow 8L/minute + oral Timimg/duration: nebulise 2 doses 30 minutes apart; oral after 1st nebulisation in ED, followed by 5, 1x daily doses after leaving ED Additional co-interventions for all groups: O_2 if SaO_2 < 92%; acetaminophen (15mg/kg) if fever; additional interventions allowed after 90' - reported use of other bronchodilators and antibiotics Protocolised use of bronchodilators with glucocorticoids: yes (epinephrine Group 1)
Outcomes	Primary outcome/outcome *used to calculate sample size* Hospital admission by day 7 Secondary outcome*s* Hospital admission by day 1 and day 22; SaO_2*; respiratory rate*; heart rate*, temperature*; RDAI: 17 points score based on wheezing and retractions*; time to discharge (time between the triage time at the enrolment and the time of discharge from the last emergency department visit or from the last hospitalization for each patient within the next 7 days); return healthcare visits#; symptoms (length / severity)#; adverse events *time points: 30, 60, 120, 240 minutes. #time points: within 22d
Funding	Grants from the Canadian Institutes of Health Research and Alberta Children's Hospital Foundation
Notes	Study reported a priori subgroup analyses of presence or absence of atopy, RSV status, and duration of illness at presentation; adjusted analysis plan with interaction terms This study contributed to the following comparisons in this review: steroid versus placebo, steroids + epinephrine versus placebo Analysis of factorial design was "inside the table", due to results suggesting unanticipated synergism between epinephrine and dexamethasone

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias LOW	Low risk	

Plint 2009 (G+E vs P+E)

Methods	See Plint 2009
Participants	See Plint 2009
Interventions	See Plint 2009 This glucocorticoid and epinephrine versus placebo and epinephrine comparison includes data from Group 1 (glucocorticoid and epinephrine) versus Group 2 (placebo and epinephrine)
Outcomes	See Plint 2009
Funding	See Plint 2009
Notes	See Plint 2009

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	

Plint 2009 (G+E vs P+E) (*Continued*)

Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias LOW	Low risk	

Plint 2009 (G+P vs P+P)

Methods	See Plint 2009
Participants	See Plint 2009
Interventions	See Plint 2009 This glucocorticoid versus placebo comparison includes data from Group 3 (dexamethasone + placebo) versus Group 4 (placebo and placebo)
Outcomes	See Plint 2009
Funding	See Plint 2009
Notes	See Plint 2009

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	

Plint 2009 (G+P vs P+P) (*Continued*)

Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias LOW	Low risk	

Richter 1998

Methods	Parallel design, two arms Single-centre, conducted in the UK (affiliation: Royal Alexandra Children's Hospital Brighton)
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion Criteria: age < 12 mo.; no history of wheezing; hospitalized with clinical features of bronchiolitis (tachypnea, recession, wheezing, crepitations) Exclusion criteria: congenital abnormality; pre-existing pulmonary disease; immune deficiency; need for assisted ventilation *Participant characteristics* *All groups* Sample size: randomized (N): 40 , analysed - trial primary outcomes (N): 39 (ITT with available case analysis was performed), analysed - review primary outcomes (N): 40 (ITT with all data was performed) *GROUP 1* Sample size: randomized (N): 21, analysed - trial primary outcomes (N): 20, analysed -

	review primary outcomes (N): 21 Age: 4.08 (median); 1.1-10.15 (range) months Males, N (%): 12 (57) RSV status: 16 (76) positive Atopic status: 18 (86) present (family) *GROUP 2* Sample size: randomized (N): 19, analysed - trial primary outcomes (N): 19, analysed - review primary outcomes (N): 19 Age: 2.7 (median); 0.9-7.82 (range) months Males, N (%): 10 (52.6) RSV status: 17 (89) positive Atopic status: 12 (63) present (family)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: budesonide Dose: 1 mg in 2 mL then 0.5 mg in 2 mL Mode of administration: nebulized with O2, flow 6 L/minute Timimg/duration: 1 mg/2mL - twice daily for 5 d; 0.5 mg/2 mL - 2 x daily for 6 weeks *GROUP 2* Drug name: placebo Dose: 2 mL 0.9% saline Mode of administration: nebulized with O_2, flow 6 L/minute Timimg/duration: twice daily for 6 weeks Additional co interventions for all groups: no restrictions on use of other drug treatments Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome Clinical scale adapted from Wesley et al, based on respiratory rate, 0_2 concentration required to keep O_2 > 92%, wheeze, degree of recession, and need for IV fluids or nasogastric tube feeding (at 48 hours; other time points*) Clinical scale*: RDAI, 17 points score based on wheezing and retractions (at 4 hours; other time points*) *Outcome used to calculate sample size* Wheezing episodes in the early months after bronchiolitis (no specific time point or definition) Secondary outcomes Duration and maximum requirements of O_2 therapy; LOS; hospital re-admission (6 mo.); symptoms (diary; based on Noble et al, daytime and nighttime cough and wheeze) #¶; inhaled bronchodilators#¶; length and growth rate# *time points: twice daily until discharge, 48 hours #time points: daily until 6 weeks ¶time points: until 6 months, when symptomatic, and by 6-week periods
Funding	Astra Clinical Research Unit, and Rockinghorse Appeal
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo
Risk of bias	

Richter 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Unclear risk	Unclear
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Unclear risk	Unclear
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Unclear risk	Unclear
Blinding? Other outcomes [adverse events, others]	Unclear risk	Unclear
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Unclear risk	Unclear
Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

Roosevelt 1996

Methods	Parallel design, two arms. Single-centre, conducted in the US (The Children's Memorial Hospital, Chicago)
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion Criteria: age < 12 months; bronchiolitis (lower respiratory tract infection characterized by wheezing); 1st episode of wheezing; requiring inpatient management; examined in ED Exclusion criteria: age: < 4 week old; needing admission to ICU; history of congenital heart disease; history of intubation, ventilation, or O_2 therapy

	Participant characteristics *All groups* Sample size: randomized (N): 122 , analysed - trial primary outcomes (N): 118 (per-protocol analysis was performed) *GROUP 1* Sample size: randomized (N): NR, analysed - trial primary outcomes (N): 65 Age, mean±SD: 5.3 ± 3.7 months Males, N (%): 41 (63) RSV status: 39 (60) positive Atopic status: 26 (40) present (family) *GROUP 2* Sample size: randomized (N): NR, analysed - trial primary outcomes (N): 53 Age, mean±SD: 5.0 ± 2.5 months Males, N (%): 33 (62) RSV status: 40 (76) positive Atopic status: 23 (43) present (family)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone Dose: 1 mg/kg Mode of administration: IM Timimg/duration: every 24 hours for max 3 doses *GROUP 2* Drug name: placebo (saline) Dose: equivalent volume Mode of administration: IM Timimg/duration: every 24 hours for max 3 doses Additional co interventions for all groups: left at the discretion of physician Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome Time to resolution (number of 12-hour periods needed for the following criteria to be met: SaO_2 > 95% while receiving no supplemental oxygen, accessory muscle score of 0, a wheeze of 0 or 1, and resumption of normal feeding) *Outcomes used to calculate sample size* Time to resolution; duration of O_2 therapy Secondary outcomes use of co-interventions; clinical scale adapted from Schuh et al: 6 points score based on accessory muscle use and wheeze*; SaO_2*; respiratory rate*; heart rate*; blood pressure*; temperature*; occult blood in the stool; return healthcare visits#; hospital re-admissions#; symptoms# *time points: every 12 hours until resolution #time points: 10-14 d
Funding	Green Bay Foundation-James P Gorter Family Fund
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Roosevelt 1996 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	Unclear
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	High risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias HIGH	Low risk	

Schuh 2002

Methods	Parallel design, two arms Single-centre, conducted in Canada (Hospital for Sick Children, University of Toronto)
Participants	Outpatients (pediatric emergency department) Inclusion/exclusion *criteria* Inclusion Criteria: age 8 week-23 months, 1st wheezing episode associated with respiratory distress and URTI; RDAI $\geq$ 6 at baseline Exclusion criteria: history of wheezing or bronchodilator therapy; prematurity; neonatal ventilation; chronic lung/cardiac disease; aspiration, neurologic/neuromuscular problems; immunodeficiency; critically ill infants requiring immediate airway stabilization; previous oral or inhaled glucocorticoids; exposed to varicella < 21 days of arrival *Participant characteristics* *All groups* Sample size: randomized (N): 71, analysed - trial primary outcomes (N): 70 (ITT with available case analysis was performed), analysed - review primary outcomes (N): 67 (ITT with available case analysis was performed) *GROUP 1* Sample size: randomized (N): NR, analysed - trial primary outcomes (N): 36, analysed - review primary outcomes (N): 35 Age, mean±SD: 6.1 ± 3.5 months Males, N (%): 20 (56) RSV status: 15/28 positive Atopic status: 30 (83) present (infant) *GROUP 2* Sample size: randomized (N): NR, analysed - trial primary outcomes (N): 35, analysed - review primary outcomes (N): 32 Age, mean±SD: 6.9 ± 3.9 months Males, N (%): 23 (68) RSV status: 15/30 positive Atopic status: 18 (53) present (infant)
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone (prepared from the intravenous dexamethasone solution flavoured with wild cherry syrup) Dose: 1 mg/kg (first dose) and then 0.6 mg/kg/day (if discharged) Mode of administration: oral Timimg/duration: single dose if admitted, five days if discharged *GROUP 2* Drug name: placebo Dose: Identical colour, texture, taste, and smell Mode of administration: oral Timimg/duration: single dose if admitted, five days if discharged Additional co interventions for all groups: nebulized albuterol 2.5 mg/dose in 3 ml normal saline with oxygen flow of 6-7 l/minute at 0, 30, 60 and 120 minutes during the observation period; albuterol (1.5 mg - 0.3 mL) 4 times daily with the same nebulizer if discharged home. All decisions regarding the need for further treatment and hospitalization were made by the attending physicians not involved in the study; they were requested not to administer additional therapy (other than acetaminophen for fever) un-

Schuh 2002 (*Continued*)

	less the patient's condition deteriorated significantly; use of bronchodilators is reported. Hospitalised patients were given nebulized albuterol only and supportive treatment as indicated Protocolised use of bronchodilators with glucocorticoids: yes (salbutamol)
Outcomes	Primary outcome/outcome *used to calculate sample size* Clinical scale: Respiratory Assessment Change Score, a change score based on RDAI and respiratory rate change from baseline (at 240'; other time points*) Secondary outcome*s* Hospital admission (at 4 hours., 7daysand 28 d); RDAI: 17 points score based on wheezing and retractions*; respiratory rate*; SaO_2 (4 hours), heart rate (4 hours); additional treatments#; return healthcare visits# *time points: 60', 120', 180', 240', 7 days #time points: 7 days, 28 days
Funding	Grants from the Medical Research Council of Canada and Merck Frosst, Canada
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	

Schuh 2002 (*Continued*)

Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Unclear risk	Unclear
Free of selective reporting?	Unclear risk	Unclear
Free of other bias?	Unclear risk	Unclear
Overall risk of bias UNCLEAR	Low risk	

Teeratakulpisarn 2007

Methods	Parallel design, two arms Multi-centre (2), conducted in Thailand (two tertiary hospitals in the northeast)
Participants	Inpatients Inclusion/exclusion *criteria* Inclusion Criteria: age 4 week-24 months; 1st episode wheezing with tachypnea; increased respiratory effort; URTI; criteria for hospitalization: < 3 months, respiratory rate > 60 bpm (<12 months) or > 50 bpm (≥ 12 months), SaO_2 < 95%, apathy/refusal to eat Exclusion criteria: symptoms > 7 d; admission to ICU with intubation; history of: intubation, asthma, atopy with good response to 1st dose β_2-agonist; therapy with glucocorticoid < 2 week; contraindication to glucocorticoid therapy; premature birth *Participant characteristics* *All groups* Sample size: randomized (N): 179, analysed - trial / review primary outcomes (N): 174 (per-protocol analysis was performed) *GROUP 1* Sample size: randomized (N): 90, analysed - trial /review primary outcomes (N): 89 Age, mean±SD: 10.2 ± 5.5 months Males, N (%): 55 (62) Atopic status: 26 (29) present (family) *GROUP 2* Sample size: randomized (N): 89, analysed - trial /review primary outcomes (N): 85 Age, mean±SD: 11.2 ± 5.9 months Males, N (%): 55 (65) Atopic status: 24 (28) present (family) RSV status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: dexamethasone Dose: 0.6 mg/kg Mode of administration: intramuscular injection Timimg/duration: 1 dose *GROUP 2*

	Drug name: placebo Dose: equivalent volume of saline Mode of administration: intramuscular injection Timimg/duration: 1 dose Additional co interventions for all groups: use of epinephrine, β_2-agonist nebulisation, O_2 permitted and reported (both study groups were similarly treated following the National Treatment Guidelines for Acute Respiratory Infection in Children, Thailand); also reported use of antibiotics. The investigators monitored the treatment regimens in order to avoid any additional form of glucocorticoid being added to either group until the study endpoint was reached Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome/outcome *used to calculate sample size* time from the study entry to resolution of respiratory distress, recognized by a total clinical score of 3 and an oxygen saturation 95% at room air together with a respiratory rate score of 0 or 1, a wheezing score of 0 or 1, and a retraction muscle score of 0 or 1. Clinical scale developed for this trial, modified from De Boeck et al. and Tal et al. - 12 points score based on respiratory rate, wheezing, accessory respiratory muscle retraction, and oxygen saturation* Secondary outcome*s* duration of O_2 therapy; LOS; hospital re-admission#, return health-care visits#; duration of symptoms#; adverse events; additional medications *time points: every 6 hours until the study endpoint was reached #time points: 2-week intervals, until 1 month
Funding	Grant sponsor: The National Research Council of Thailand
Notes	Study reported subgroup analysis in children under 12 months; no specific interaction term This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	
Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	

Teeratakulpisarn 2007 (*Continued*)

Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Blinding? Other outcomes [adverse events, others]	Low risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return healthcare visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Unclear risk	Unclear
Free of other bias?	Low risk	
Overall risk of bias UNCLEAR	Low risk	

Zhang 2003

Methods	Parallel design, two arms Single-centre, conducted in Brazil (teaching hospital of the Federal University of Rio Grande, Rio Grande)
Participants	Inpatients (30-bed pediatric inpatient ward) Inclusion/exclusion criteria Inclusion Criteria: age < 12 months, diagnosis of bronchiolitis, 1st episode of wheezing with respiratory distress, history of upper respiratory tract infection Exclusion criteria: age < 4 weeks; any chronic cardiac or pulmonary disease; congenital abnormality; immediate favorable response to administration of single dose nebulized fenoterol; received glucocorticoids < 4 weeks; severe initial disease requiring intensive care *Participant characteristics* *All groups* Sample size: randomized (N): 52, analysed - trial primary outcomes (N): 50 (ITT with available case analysis was performed), analysed - review primary outcomes (N): 52 (ITT with all data was performed)

Zhang 2003 (*Continued*)

	GROUP 1 Sample size: randomized (N): 28, analysed - trial primary outcomes (N): 26 , analysed - review primary outcomes (N): 28 Age, mean±SD: 4.0 ± 2.5 months Males, N (%): 21 (75) Atopic status: 23 (82.1) present (family) *GROUP 2* Sample size: randomized (N): 24, analysed - trial / review primary outcomes (N): 24 Age, mean±SD: 3.4 ± 1.8 months Males, N (%): 20 (83.3) Atopic status: 21 (87.5) present (family) RSV status: NR
Interventions	*GROUP 1 (with glucocorticoid)* Drug name: prednisolone + standard care (see below) Dose: 1 mg/kg Mode of administration: oral Timimg/duration: 1st at enrolment; once daily at 8:00 am for 4 days (total 5 days of treatment); if hospital stay <5 d, remaining doses given at home *GROUP 2* Drug name: standard care Dose: judged by attending physician based on standard protocol: O_2 therapy, fluid replacement, nebulized fenoterol Mode of administration: NR Timimg/duration: NR Additional co interventions for all groups: standard care as stated above; attending paediatricians were advised against prescribing any glucocorticoid for recruited patients (use of IV hydrocortisone was reported) Protocolised use of bronchodilators with glucocorticoids: no
Outcomes	Primary outcome/outcome *used to calculate sample size* prevalence of post bronchiolitic wheeze (at 1, 3, 6, 12 mo) Secondary outcome*s* LOS; duration of O_2 therapy; time to clinical resolution - defined as the days needed for the following criteria to be met: pulse blood oxygen saturation above 95% without supplemental oxygen, absence of chest retractions and respiratory rate less than upper limits for age (< 2 months 60 b.p.m.; 2-12 months 50 b.p.m.)
Funding	Research Support Foundation of Rio Grande do Sul
Notes	Study did not report any study-level subgroup analyses This study contributed to the following comparisons in this review: steroid versus placebo

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	

Zhang 2003 (*Continued*)

Allocation concealment?	Low risk	
Blinding? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	High risk	
Blinding? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	High risk	
Blinding? Patient/parent-reported outcomes [symptoms, quality of life measures]	High risk	
Blinding? Other outcomes [adverse events, others]	High risk	
Incomplete outcome data addressed? Health care use [rate of admission, length of stay, hospital re-admissions, return health-care visits]	Low risk	
Incomplete outcome data addressed? Clinical parameters [clinical scales, O2 saturation, respiratory rate, heart rate]	Low risk	
Incomplete outcome data addressed? Patient/parent-reported outcomes [symptoms, quality of life measures]	Low risk	
Incomplete outcome data addressed? Other outcomes [adverse events, others]	Low risk	
Free of selective reporting?	Low risk	
Free of other bias?	Low risk	
Overall risk of bias HIGH	Low risk	

ITT = intention-to-treat
IV = intravenous
h = hour
NR = not reported
bpm = beats per minute
mo = month
ED = emergency department
RDAI = Respiratory Distress Assessment Instrument

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

Study	Reason for exclusion
Anonymous 1989	Publication type: commentary
Bacharier 2008	Population: children aged 12 to 59 months with moderate-to-severe recurrent intermittent wheezing
Berger 1996	Publication type and duplicate: abstract of later published trial
Bibi 2004	Population: clinical definition of bronchiolitis uncertain
Blom 2007	Publication type: Cochrane systematic review
Bont 2006	Publication type: letter to editor
Buckingham 2002	Population: intensive care unit patients who were intubated and mechanically ventilated
Bülow 1999	Population: clinical definition of bronchiolitis uncertain
Callen Blecua 2000	Intervention:inhaled glucocorticoid therapy given for 3 months after mild bronchiolitis
Chao 2003	Population: clinical definition of bronchiolitis uncertain
Chipps 2008	Publication type: letter to editor
Connolly 1969	Population: clinical definition of bronchiolitis uncertain
Cornell 2007	Publication type: review
Csonka 2003	Population: children aged 6 to 35 months, clinical definition of bronchiolitis uncertain, and recurrent wheezing
da Silva 2007	Article pending retrieval
Dabbous 1966	Population: clinical definition of bronchiolitis uncertain
Daugbjerg 1993	Population: history of recurrent wheezing
Dennis 1963	Study design: not randomized
Doornebal 2009	Study design: not randomized
Ermers 2008	Population: clinical definition of bronchiolitis uncertain and some participants required mechanical ventilation
Filippskii 1983	Population: children aged 0 months to 3 years
Fox 1999	Population: clinical definition of bronchiolitis uncertain and history of recurrent wheezing

(*Continued*)

Garrison 2000	Publication type: meta-analysis
Hall 2008	Publication type: commentary
Hoekstra 2004	Publication type: letter to editor
Jartti 2002	Publication type: review
Jartti 2006	Population: first or second episode of wheezing
Jartti 2007	Population: children aged 3 months to 16 years, clinical definition of bronchiolitis uncertain, and recurrent wheezing
Kajosaari 2000	Population: clinical definition of bronchiolitis uncertain
Kelm-Kahl 2008	Publication type: review
Kitowicz 2007	Publication type: review
Koumbourlis 2009	Publication type: letter to editor
Leer 1969a	Population: children aged 0 to 30 months, clinical definition of bronchiolitis uncertain, and recurrent wheezing
Leer 1969b	Publication type: letter to editor
Lin 1991	Population: ages below 36 months
Mallol 1987	Population: clinical definition of bronchiolitis uncertain
Merkus 2005	Publication type: letter to editor
Milner 1997	Publication type: letter to editor
O'Callaghan 1989	Publication type: letter to editor
Oommen 2003	Publication type: children aged 1-5 years with recurrent episodic viral wheeze
Oski 1961	Study design: not randomized
Panickar 2009	Population: children between the ages of 10 months and 60 months, possibly with recurrent wheezing
Park 1997	Population: history of recurrent wheezing
Patel 2004	Publication type: Cochrane systematic review
Patel 2008	Duplicate: abstract of RCT by Plint et al (included)

(*Continued*)

Plint 2008	Duplicate: abstract of RCT by Plint et al (included)
Poets 2005	Publication type: review
Rajeshwari 2006	Publication type: commentary
Ranganathan 2003	Publication type: review
Renzi 2003	Unobtainable (abstract from conference proceedings)
Sammartino 1995	Publication type: letter to editor
Sano 2000	Population: history of recurrent wheeze
Schuh 2004	Publication type: commentary
Schuh 2008	Intervention: single versus multiple doses of the same glucocorticoid (dexamethasone)
Smith 2008	Publication type: review
Spencer 1989	Publication type: letter to editor
Springer 1990	Study design: not randomized
Sussman 1964	Study design: not randomized
Tal 1982	Population: history of recurrent wheezing
Tofts 2009	Publication type: letter to editor
Uhereczky 2001	Population: children aged 3 to 36 months, history of recurrent wheezing
Van Bever 1996	Publication type: letter to editor
van Woensel 1997	Publication type: letter to editor
van Woensel 2000	Population and intervention: Not a study of acute effects of glucocorticoids; this study measured the follow-up incidence of recurrent wheezing in treated infants
van Woensel 2003a	Population: involved intensive care unit patients who were intubated and mechanically ventilated
van Woensel 2003b	Population: involved intensive care unit patients who were intubated and mechanically ventilated
Wardrope 2000	Duplicate: RCT by Cade et al (included)
Webb 1986	Publication type: history of recurrent wheezing

(*Continued*)

Weinberger 2004	Publication type: letter to editor
Weinberger 2007	Publication type: letter to editor
Wong 2000	Intervention: 3 months inhaled glucocorticoids
Yaffe 1970	Publication type: commentary
Zuerlein 1990	Population: children aged 5 to 27 months, clinical definition of bronchiolitis uncertain

DATA AND ANALYSES

Comparison 1. Glucocorticoid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (days 1 and 7) (outpatients) - review primary outcome	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Admissions day 1	10	1762	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
1.2 Admissions day 7	6	1530	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.06]
2 Length of stay (inpatients) - review primary outcome	8	633	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
3 Length of stay (outpatients)	3	255	Mean Difference (IV, Random, 95% CI)	0.10 [-0.81, 1.01]
4 Clinical scores (outpatients)	11		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 Minutes	6	1006	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.16, 0.09]
4.2 120 Minutes	5	214	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.55, 0.21]
4.3 3-6 hours	5	808	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.50, 0.21]
4.4 12-24 hours	2	69	Std. Mean Difference (IV, Random, 95% CI)	0.13 [-0.51, 0.76]
4.5 3-10 days	5	224	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.61, 0.21]
5 Clinical scores (inpatients)	4		Std. Mean Difference (Random, 95% CI)	Subtotals only
5.1 3-6 hours	1	174	Std. Mean Difference (Random, 95% CI)	-1.03 [-1.87, -0.19]
5.2 6-12 hours	3	269	Std. Mean Difference (Random, 95% CI)	-0.62 [-1.00, -0.23]
5.3 12-24 hours	3	264	Std. Mean Difference (Random, 95% CI)	-0.28 [-0.66, 0.09]
5.4 24-72 hours	4	271	Std. Mean Difference (Random, 95% CI)	-0.53 [-1.14, 0.08]
6 O_2 saturation (outpatients)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 60 Minutes	5	936	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.73, 0.19]
6.2 120 Minutes	2	75	Mean Difference (IV, Random, 95% CI)	-0.10 [-1.56, 1.37]
6.3 3-6 hours	5	808	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.84, -0.02]
6.4 24-72 hours	1	38	Mean Difference (IV, Random, 95% CI)	0.20 [-1.01, 1.41]
7 O_2 saturation (inpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 6-12 hours	1	67	Mean Difference (IV, Random, 95% CI)	-0.7 [-1.98, 0.58]
7.2 12-24 hours	2	116	Mean Difference (IV, Random, 95% CI)	-0.44 [-2.04, 1.16]
7.3 24-72 hours	1	67	Mean Difference (IV, Random, 95% CI)	1.10 [-0.77, 2.97]
8 Respiratory rate (outpatients)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 60 Minutes	3	861	Mean Difference (IV, Random, 95% CI)	-0.24 [-1.51, 1.03]
8.2 120 Minutes	2	69	Mean Difference (IV, Random, 95% CI)	-1.95 [-9.30, 5.39]
8.3 3-6 hours	3	733	Mean Difference (IV, Random, 95% CI)	-1.12 [-3.07, 0.82]
8.4 12-24 hours	2	69	Mean Difference (IV, Random, 95% CI)	0.15 [-7.10, 7.40]
8.5 3-10 days	4	174	Mean Difference (IV, Random, 95% CI)	-1.64 [-7.89, 4.61]
9 Respiratory rate (inpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 6-12 hours	1	66	Mean Difference (IV, Random, 95% CI)	-4.0 [-11.45, 3.45]
9.2 12-24 hours	2	110	Mean Difference (IV, Random, 95% CI)	-1.22 [-5.08, 2.64]
9.3 24-72 hours	1	28	Mean Difference (IV, Random, 95% CI)	-1.90 [-15.37, 11.57]
10 Heart rate (outpatients)	9		Mean Difference (IV, Random, 95% CI)	Subtotals only
10.1 60 Minutes	5	936	Mean Difference (IV, Random, 95% CI)	0.46 [-1.62, 2.55]
10.2 120 Minutes	4	144	Mean Difference (IV, Random, 95% CI)	-3.54 [-8.83, 1.75]
10.3 3-6 hours	5	808	Mean Difference (IV, Random, 95% CI)	-0.65 [-7.01, 5.71]

10.4 12-24 hours	2	69	Mean Difference (IV, Random, 95% CI)	1.85 [-11.18, 14.88]
10.5 3-10 days	3	136	Mean Difference (IV, Random, 95% CI)	0.43 [-8.32, 9.18]
11 Heart rate (inpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 12-24 hours	1	49	Mean Difference (IV, Random, 95% CI)	-9.0 [-18.99, 0.99]
12 Hospital readmissions (inpatients)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12.1 2-10 days	1	67	Risk Ratio (M-H, Random, 95% CI)	3.66 [0.43, 31.03]
12.2 10-30 days	2	292	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.11, 1.53]
13 Return healthcare visits (inpatients)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
13.1 2-10 days	1	67	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.86, 1.42]
13.2 10-30 days	2	292	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.30, 4.96]
14 Return healthcare visits (outpatients)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 10-30 days	3	863	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.35]
15 Admissions at day 1 (outpatients) - subgroup analysis protocolized use of bronchodilator	10	1762	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
15.1 Protocolized use of bronchodilator	7	717	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.29]
15.2 No protocolized use of bronchodilator	3	1045	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.79, 1.13]
16 Admissions within 7 days (outpatients) - subgroup analysis protocolized use of bronchodilator	6	1530	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.06]
16.1 Protocolized use of bronchodilator	4	581	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.44, 1.05]
16.2 No protocolized use of bronchodilator	2	949	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.11]
17 Admissions at day 1 (outpatients) - subgroup analysis age	10	1762	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.78, 1.08]
17.1 All <12 months	3	1397	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.79, 1.10]
17.2 Including >12 months	7	365	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.51, 1.49]
18 Admissions within 7 days (outpatients) - subgroup analysis age	6	1530	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.70, 1.06]
18.1 All <12 months	3	1346	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
18.2 Including >12 months	3	184	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.25, 1.83]
19 Length of stay (inpatients) - subgroup analysis protocolized use of bronchodilator	8	633	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
19.1 Protocolized use of bronchodilator	4	206	Mean Difference (IV, Random, 95% CI)	-0.12 [-0.23, -0.00]
19.2 No protocolized use of bronchodilator	4	427	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.83, 0.20]
20 Length of stay (inpatients) - subgroup analysis age	8	633	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
20.1 All <12 months	4	314	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.65, 0.45]

20.2 Including >12 months	4	319	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.53, 0.12]
21 Length of stay (inpatients) - subgroup analysis RSV status	8	633	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.39, 0.04]
21.1 All RSV positive	3	251	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.63, 0.45]
21.2 Not all RSV positive, or NR	5	382	Mean Difference (IV, Random, 95% CI)	-0.20 [-0.57, 0.17]
22 Admissions (days 1 and 7) (outpatients) - sensitivity analysis with only low overall RoB	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Admissions day 1	2	797	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.60, 1.16]
22.2 Admissions day 7	2	797	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.64, 1.14]
23 Length of stay (inpatients) - sensitivity analysis with only low overall RoB	1	67	Mean Difference (IV, Random, 95% CI)	0.38 [-0.46, 1.21]

Comparison 2. Glucocorticoid and epinephrine versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (days 1 and 7) (outpatients) - review primary outcome	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Admissions day 1	1	400	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.40, 1.05]
1.2 Admissions day 7	1	400	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.44, 0.95]
2 Clinical scores (outpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 Minutes	1	399	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.54, -0.14]
3 O_2 saturation (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 Minutes	1	399	Mean Difference (IV, Random, 95% CI)	0.04 [-0.53, 0.61]
4 Respiratory rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 Minutes	1	399	Mean Difference (IV, Random, 95% CI)	-1.16 [-3.06, 0.74]
5 Heart rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 Minutes	1	399	Mean Difference (IV, Random, 95% CI)	8.44 [4.85, 12.03]
6 Return healthcare visits (outpatients)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 10-30 days	1	399	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.89, 1.38]

Comparison 3. Glucocorticoid and salbutamol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (day 1) (outpatients) - review primary outcome	1	30	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.13, 3.44]
2 Clinical scores (outpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 Minutes	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.30 [-1.02, 0.42]
2.2 120 Minutes	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.94, 0.50]
2.3 3-6 hours	1	30	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-1.18, 0.27]
3 O_2 saturation (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.75, 1.07]
3.2 120 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-0.67 [-2.04, 0.70]
3.3 3-6 hours	1	30	Mean Difference (IV, Random, 95% CI)	-1.08 [-2.43, 0.27]
4 Heart rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	4.67 [-1.89, 11.23]
4.2 120 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-1.87 [-14.10, 10. 36]
4.3 3-6 hours	1	30	Mean Difference (IV, Random, 95% CI)	4.3 [-2.38, 10.98]

Comparison 4. Glucocorticoid versus epinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (days 1 and 7) (outpatients) - review primary outcome	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Admissions day 1	2	444	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.66, 1.88]
1.2 Admissions day 7	1	399	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.77, 1.52]
2 Clinical scores (outpatients)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 Minutes	2	442	Std. Mean Difference (IV, Random, 95% CI)	0.31 [0.12, 0.50]
2.2 120 Minutes	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.35 [-0.27, 0.98]
2.3 3-6 hours	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.42 [-0.20, 1.05]
3 O_2 saturation (outpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 Minutes	2	442	Mean Difference (IV, Random, 95% CI)	-0.99 [-1.46, -0.52]
3.2 120 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	-0.07 [-1.07, 0.94]
3.3 3-6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.74, 0.57]
4 Respiratory rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 Minutes	1	397	Mean Difference (IV, Random, 95% CI)	0.38 [-1.44, 2.20]
5 Heart rate (outpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 Minutes	2	442	Mean Difference (IV, Random, 95% CI)	-7.56 [-11.34, -3.79]
5.2 120 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	0.44 [-7.59, 8.47]
5.3 3-6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-0.20 [-8.09, 7.69]

Comparison 5. Glucocorticoid versus salbutamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (day 1) (outpatients) - review primary outcome	1	45	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.21, 4.86]
2 Clinical scores (outpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 Minutes	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.65 [0.01, 1.28]
2.2 120 Minutes	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-0.27, 0.98]
2.3 3-6 hours	1	45	Std. Mean Difference (IV, Random, 95% CI)	0.70 [0.06, 1.34]
3 O_2 saturation (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	0.93 [-0.71, 2.57]
3.2 120 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	0.22 [-0.88, 1.33]
3.3 3-6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-0.03 [-0.95, 0.88]
4 Heart rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	-3.30 [-9.49, 2.89]
4.2 120 Minutes	1	45	Mean Difference (IV, Random, 95% CI)	-7.53 [-14.28, -0.78]
4.3 3-6 hours	1	45	Mean Difference (IV, Random, 95% CI)	-5.12 [-12.39, 2.15]

Comparison 6. Glucocorticoid and epinephrine versus salbutamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (day 1) (outpatients) - review primary outcome	1	35	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Clinical scores (outpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 120 Minutes	1	35	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.87, 0.52]
2.2 12-24 hours	1	35	Std. Mean Difference (IV, Random, 95% CI)	0.0 [-0.70, 0.70]
2.3 3-10 days	1	35	Std. Mean Difference (IV, Random, 95% CI)	-1.22 [-1.98, -0.46]
3 Respiratory rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 120 Minutes	1	35	Mean Difference (IV, Random, 95% CI)	-3.10 [-9.51, 3.31]
3.2 12-24 hours	1	35	Mean Difference (IV, Random, 95% CI)	-2.80 [-9.96, 4.36]
3.3 3-10 days	1	35	Mean Difference (IV, Random, 95% CI)	-13.70 [-20.56, -6.84]
4 Heart rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 120 Minutes	1	35	Mean Difference (IV, Random, 95% CI)	-3.20 [-12.20, 5.80]
4.2 12-24 hours	1	35	Mean Difference (IV, Random, 95% CI)	-1.40 [-9.36, 6.56]
4.3 3-10 days	1	35	Mean Difference (IV, Random, 95% CI)	-6.30 [-14.21, 1.61]

Comparison 7. Glucocorticoid and salbutamol versus epinephrine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (day 1) (outpatients) - review primary outcome	2	64	Risk Ratio (M-H, Random, 95% CI)	5.00 [0.26, 96.13]
2 Clinical scores (outpatients)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 Minutes	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-0.36, 1.08]
2.2 120 Minutes	2	64	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.26, 0.77]
2.3 12-24 hrs	1	34	Std. Mean Difference (IV, Random, 95% CI)	0.30 [-0.43, 1.02]
2.4 3-10 days	1	34	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.88, 0.56]
3 O_2 saturation (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-1.54 [-2.85, -0.23]
3.2 120 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-1.27 [-2.41, -0.13]
4 Respiratory rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 120 Minutes	1	34	Mean Difference (IV, Random, 95% CI)	-0.60 [-7.39, 6.19]
4.2 12-24 hours	1	34	Mean Difference (IV, Random, 95% CI)	3.20 [-4.27, 10.67]
4.3 3-10 days	1	34	Mean Difference (IV, Random, 95% CI)	-0.40 [-6.47, 5.67]
5 Heart rate (outpatients)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 60 Minutes	1	30	Mean Difference (IV, Random, 95% CI)	-3.33 [-12.37, 5.71]
5.2 120 Minutes	2	64	Mean Difference (IV, Random, 95% CI)	0.62 [-5.38, 6.62]
5.3 12-24 hrs	1	34	Mean Difference (IV, Random, 95% CI)	5.30 [-3.28, 13.88]
5.4 3-10 days	1	34	Mean Difference (IV, Random, 95% CI)	1.0 [-6.94, 8.94]

Comparison 8. Glucocorticoid versus glucocorticoid (prednisolone versus budesonide)

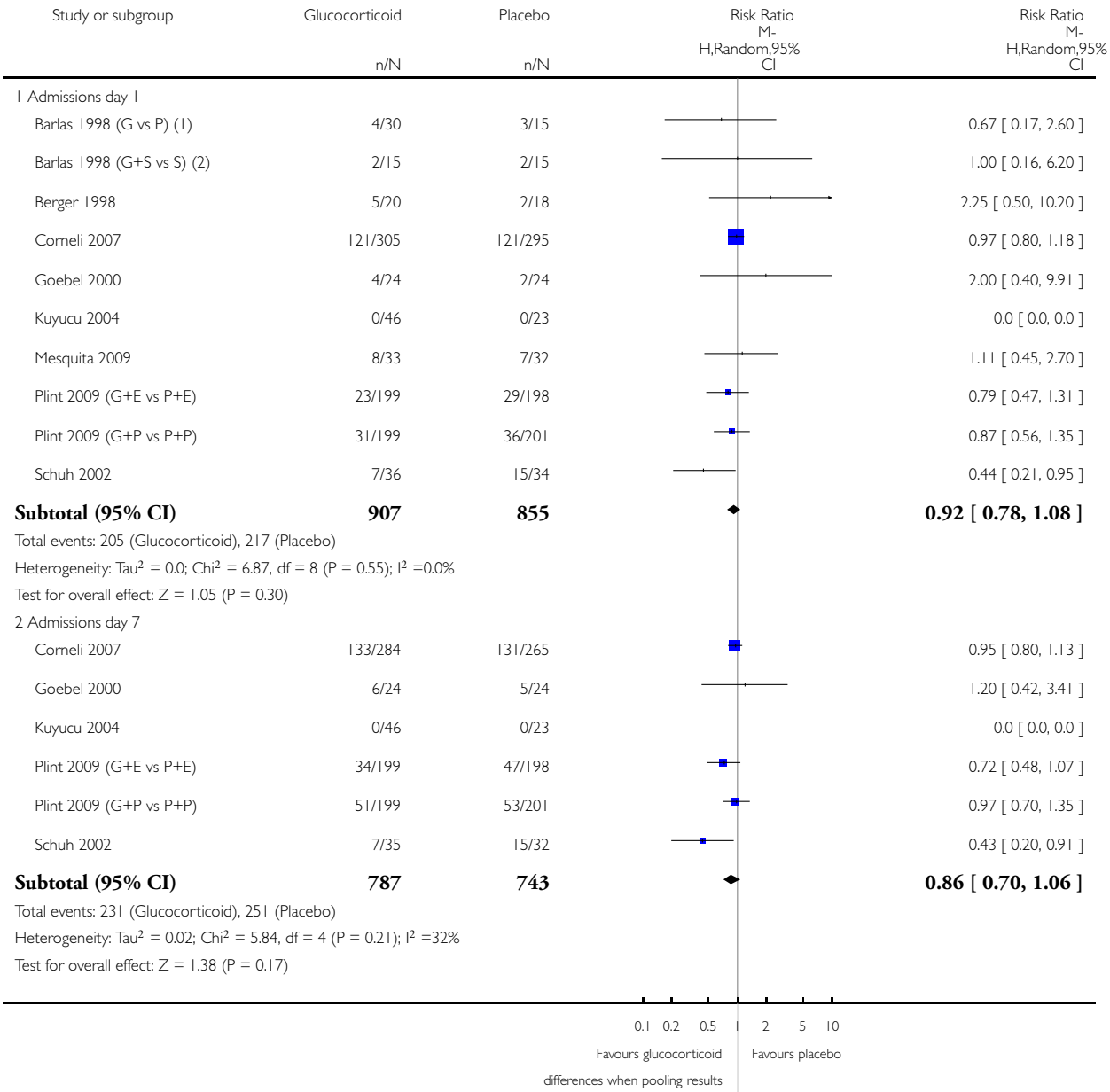
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Admissions (day 1) (outpatients) - review primary outcome	1	30	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.35, 25.68]
2 Clinical scores (outpatients)	1		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 60 minutes	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.40 [-0.33, 1.12]
2.2 120 minutes	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.66 [-0.08, 1.40]
2.3 3-6 hours	1	30	Std. Mean Difference (IV, Random, 95% CI)	0.23 [-0.49, 0.95]
3 O_2 saturation (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 60 minutes	1	30	Mean Difference (IV, Random, 95% CI)	-1.46 [-2.74, -0.18]
3.2 120 minutes	1	30	Mean Difference (IV, Random, 95% CI)	-1.73 [-3.06, -0.40]
3.3 3-6 hours	1	30	Mean Difference (IV, Random, 95% CI)	-1.17 [-2.37, 0.03]
4 Heart rate (outpatients)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 60 minutes	1	30	Mean Difference (IV, Random, 95% CI)	-5.93 [-13.29, 1.43]
4.2 120 minutes	1	30	Mean Difference (IV, Random, 95% CI)	-7.39 [-15.57, 0.79]
4.3 3-6 hours	1	30	Mean Difference (IV, Random, 95% CI)	-10.8 [-18.71, -2.89]

Analysis 1.1. Comparison 1 Glucocorticoid versus placebo, Outcome 1 Admissions (days 1 and 7) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 1 Admissions (days 1 and 7) (outpatients) - review primary outcome



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.2. Comparison 1 Glucocorticoid versus placebo, Outcome 2 Length of stay (inpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

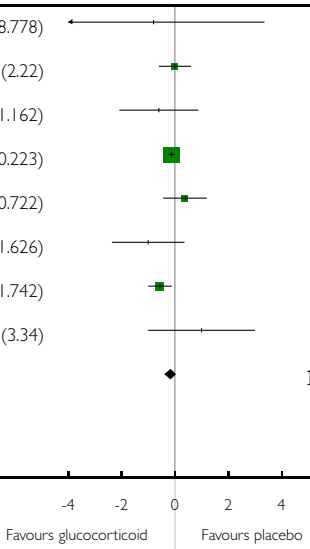
Comparison: 1 Glucocorticoid versus placebo

Outcome: 2 Length of stay (inpatients) - review primary outcome

Study or subgroup	Glucocorticoid		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Bentur 2005	29	5.469 (7.87)	32	6.29 (8.778)		0.3 %	-0.82 [-5.00, 3.36]
Cade 2000	82	2 (1.48)	79	2 (2.22)		11.7 %	0.0 [-0.59, 0.59]
De Boeck 1997	14	6 (2.619)	15	6.6 (1.162)		2.1 %	-0.60 [-2.09, 0.89]
Gomez 2007	24	0.654 (0.192)	25	0.78 (0.223)		58.4 %	-0.13 [-0.24, -0.01]
Klassen 1997	35	2.375 (2.39)	32	2 (0.722)		6.3 %	0.38 [-0.46, 1.21]
Richter 1998	21	2 (2.647)	19	3 (1.626)		2.5 %	-1.00 [-2.35, 0.35]
Teeratakulpisarn 2007	89	2.258 (1.246)	85	2.82 (1.742)		17.6 %	-0.56 [-1.01, -0.11]
Zhang 2003	28	6 (4.05)	24	5 (3.34)		1.2 %	1.00 [-1.01, 3.01]
Total (95% CI)	**322**		**311**			**100.0 %**	**-0.18 [-0.39, 0.04]**

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.33$, df = 7 (P = 0.30); $I^2 = 16\%$

Test for overall effect: Z = 1.58 (P = 0.12)



Analysis 1.3. Comparison 1 Glucocorticoid versus placebo, Outcome 3 Length of stay (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

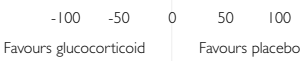
Outcome: 3 Length of stay (outpatients)

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Berger 1998	5	5 (2.105)	2	8 (2.828)		4.2 %	-3.00 [-7.33, 1.33]
Corneli 2007	121	2.55 (1.32)	121	2.27 (1.32)		86.8 %	0.28 [-0.05, 0.61]
Goebel 2000	4	2.3 (1.7)	2	2.5 (1.7)		9.0 %	-0.20 [-3.09, 2.69]
Total (95% CI)	**130**		**125**			**100.0 %**	**0.10 [-0.81, 1.01]**

Heterogeneity: $Tau^2 = 0.22$; $Chi^2 = 2.29$, df = 2 (P = 0.32); $I^2 = 13\%$

Test for overall effect: Z = 0.21 (P = 0.83)

Test for subgroup differences: Not applicable



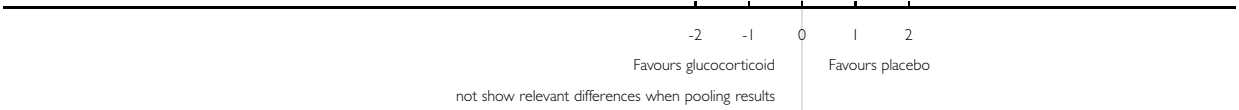
Analysis 1.4. Comparison 1 Glucocorticoid versus placebo, Outcome 4 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 4 Clinical scores (outpatients)

Study or subgroup	Glucocorticoid 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							
Barlas 1998 (G vs P) (1)	30	-1.135 (1.72)	15	-0.54 (1.96)		4.0 %	-0.32 [-0.95, 0.30]
Barlas 1998 (G+S vs S) (2)	15	-1.2 (2.28)	15	-2.27 (1.73)		2.9 %	0.51 [-0.21, 1.24]
Mesquita 2009	33	-2 (2)	32	-2 (2)		6.5 %	0.0 [-0.49, 0.49]
Plint 2009 (G+E vs P+E)	199	-2.5 (2.58)	198	-2.45 (2.32)		39.7 %	-0.02 [-0.22, 0.18]
Plint 2009 (G+P vs P+P)	199	-1.75 (2.4)	200	-1.65 (2.42)		39.9 %	-0.04 [-0.24, 0.15]
Schuh 2002	36	-2.1 (3.673)	34	-1.5 (2.677)		7.0 %	-0.18 [-0.65, 0.29]
Subtotal (95% CI)	**512**		**494**			**100.0 %**	**-0.04 [-0.16, 0.09]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.44$, df = 5 (P = 0.63); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.56 (P = 0.58)							
2 120 Minutes							
Barlas 1998 (G vs P)	30	-2.65 (2.28)	15	-1.47 (2.54)		20.5 %	-0.49 [-1.12, 0.14]
Barlas 1998 (G+S vs S)	15	-2.07 (2.75)	15	-3.42 (1.77)		17.0 %	0.57 [-0.16, 1.30]
Kuyucu 2004 (G+E vs P+E)	23	-3.5 (0.959)	11	-3.2 (0.995)		17.3 %	-0.30 [-1.02, 0.42]
Kuyucu 2004 (G+S vs P+S)	23	-3.2 (1.439)	12	-3.3 (1.386)		18.1 %	0.07 [-0.63, 0.77]
Schuh 2002	36	-3.7 (3.673)	34	-2.2 (2.38)		27.0 %	-0.48 [-0.95, 0.00]
Subtotal (95% CI)	**127**		**87**			**100.0 %**	**-0.17 [-0.55, 0.21]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.98$, df = 4 (P = 0.14); $I^2 = 43\%$							
Test for overall effect: Z = 0.89 (P = 0.37)							
3 3-6 hours							
Barlas 1998 (G vs P)	30	-2.915 (2.67)	15	-1.07 (2.31)		15.8 %	-0.71 [-1.35, -0.07]
Barlas 1998 (G+S vs S)	15	-2.39 (3.25)	15	-4.63 (1.75)		13.2 %	0.84 [0.08, 1.59]
Corneli 2007	304	-5.3 (4.7)	294	-4.8 (4.6)		30.3 %	-0.11 [-0.27, 0.05]
Mesquita 2009	33	-3 (3)	32	-3 (2)		20.2 %	0.0 [-0.49, 0.49]
Schuh 2002	36	-5 (3.1)	34	-3.2 (3.7)		20.4 %	-0.52 [-1.00, -0.05]
Subtotal (95% CI)	**418**		**390**			**100.0 %**	**-0.14 [-0.50, 0.21]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 12.46$, df = 4 (P = 0.01); $I^2 = 68\%$							



not show relevant differences when pooling results

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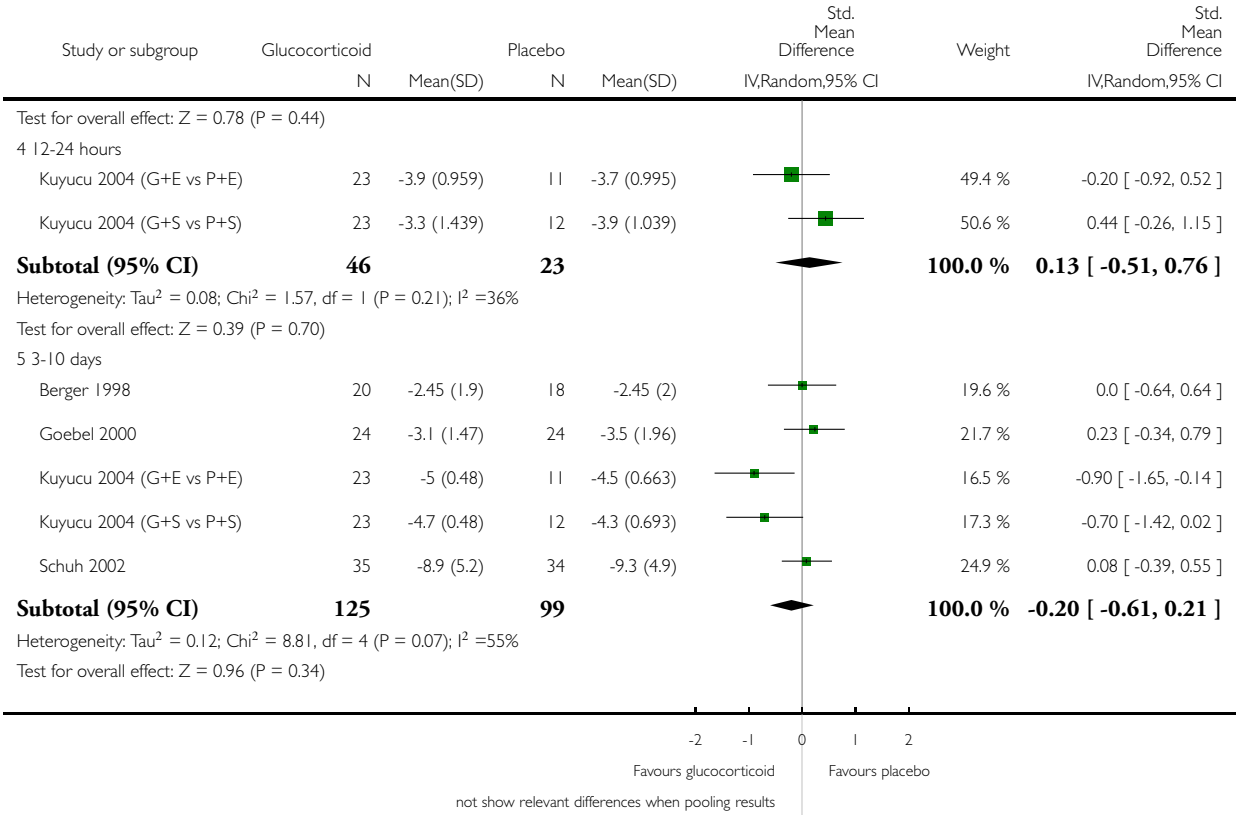


(1) Kuyucu 2004 and Plint 2009 (factorial trials) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did

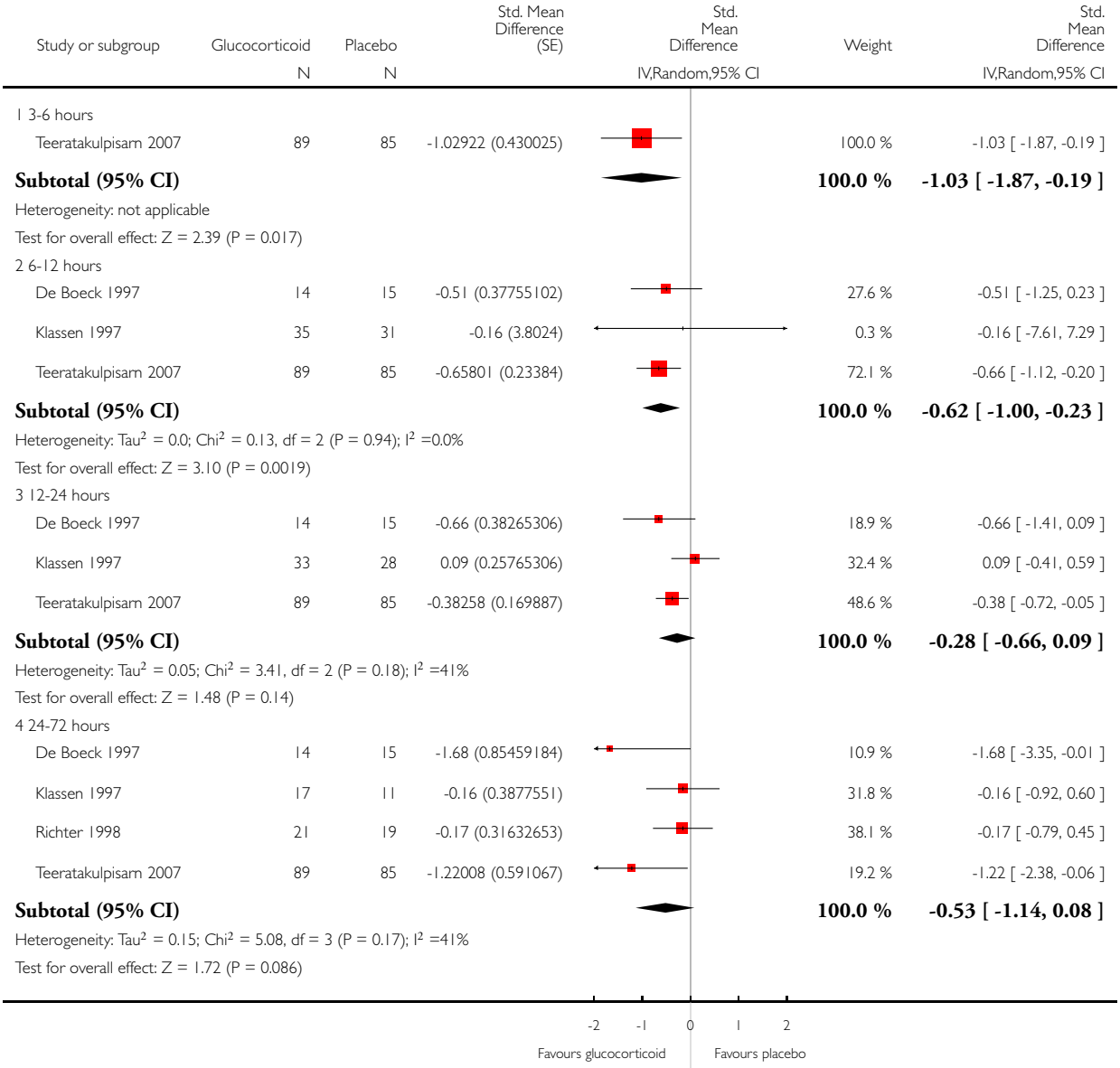
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.5. Comparison 1 Glucocorticoid versus placebo, Outcome 5 Clinical scores (inpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 5 Clinical scores (inpatients)

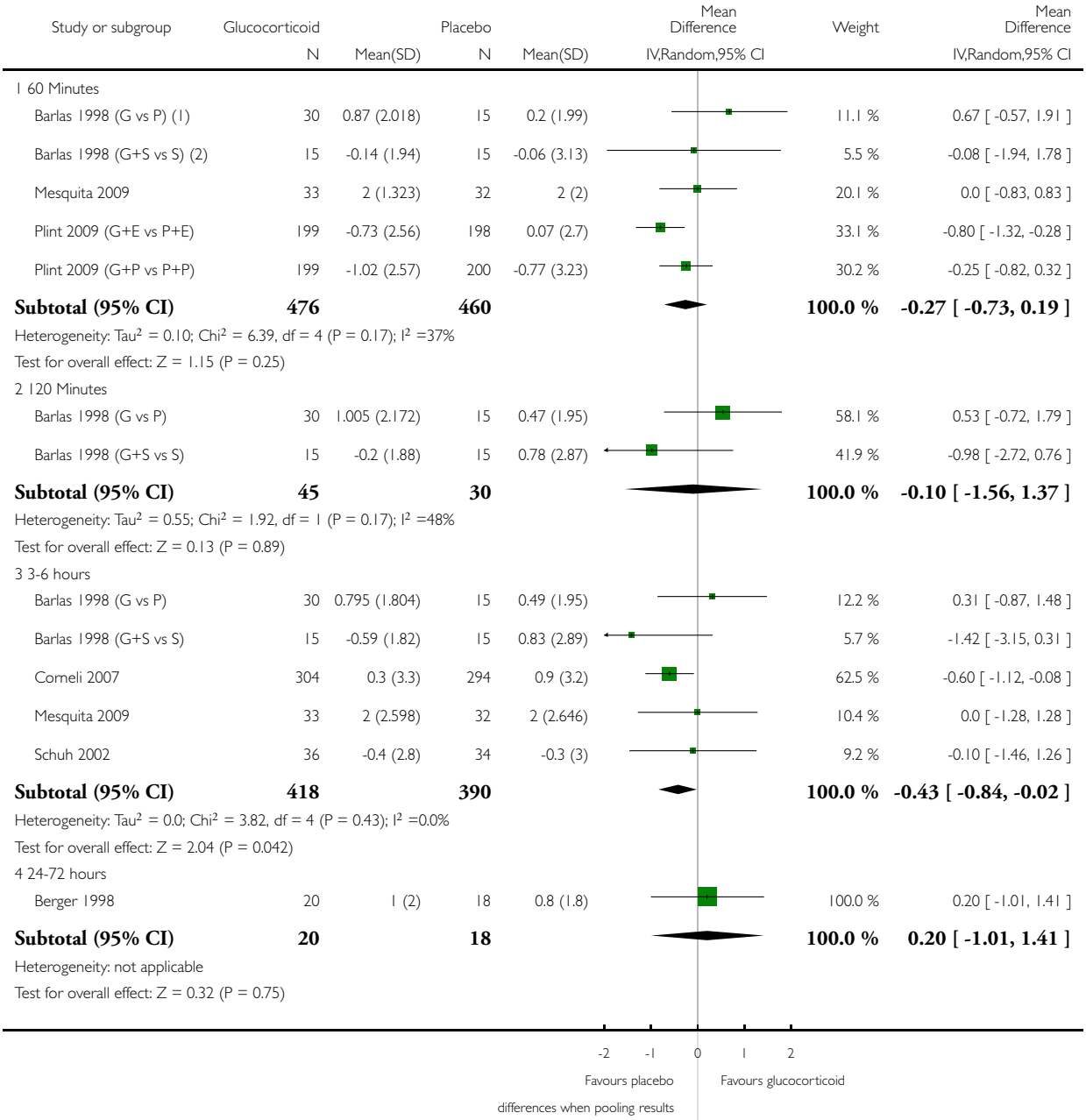


Analysis 1.6. Comparison 1 Glucocorticoid versus placebo, Outcome 6 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 6 O_2 saturation (outpatients)



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.7. Comparison 1 Glucocorticoid versus placebo, Outcome 7 O_2 saturation (inpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 7 O_2 saturation (inpatients)

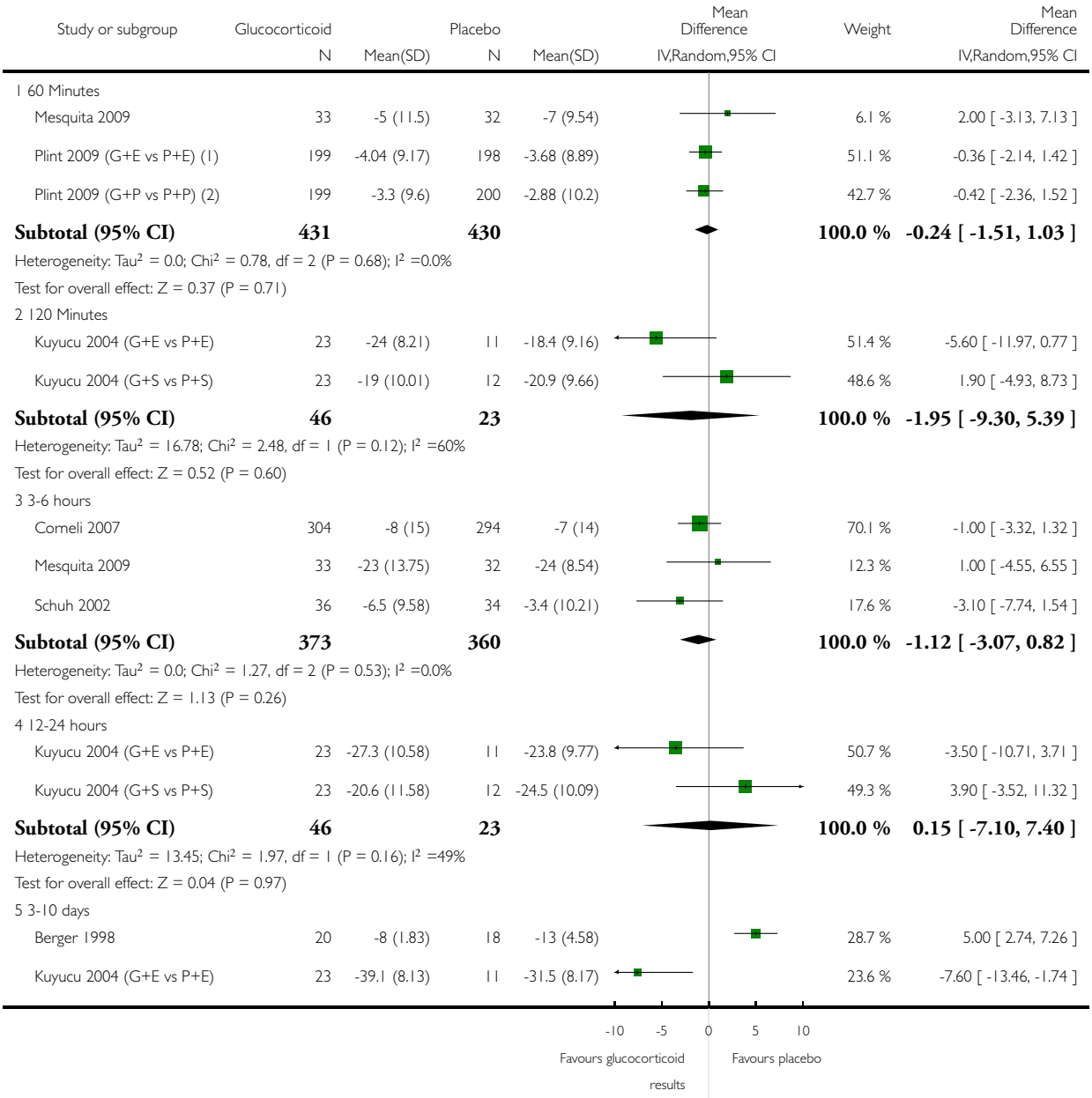
Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 6-12 hours							
Klassen 1997	35	0.7 (2.5)	32	1.4 (2.8)		100.0 %	-0.70 [-1.98, 0.58]
Subtotal (95% CI)	**35**		**32**			**100.0 %**	**-0.70 [-1.98, 0.58]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.08 (P = 0.28)							
2 12-24 hours							
Gomez 2007	24	87 (5.3)	25	86 (5.8)		24.4 %	1.00 [-2.11, 4.11]
Klassen 1997	35	1 (3.6)	32	1.9 (3.1)		75.6 %	-0.90 [-2.51, 0.71]
Subtotal (95% CI)	**59**		**57**			**100.0 %**	**-0.44 [-2.04, 1.16]**
Heterogeneity: Tau^2 = 0.21; Chi^2 = 1.13, df = 1 (P = 0.29); I^2 =12%							
Test for overall effect: Z = 0.53 (P = 0.59)							
3 24-72 hours							
Klassen 1997	35	2.3 (3.8)	32	1.2 (4)		100.0 %	1.10 [-0.77, 2.97]
Subtotal (95% CI)	**35**		**32**			**100.0 %**	**1.10 [-0.77, 2.97]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.15 (P = 0.25)							

Analysis 1.8. Comparison 1 Glucocorticoid versus placebo, Outcome 8 Respiratory rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 8 Respiratory rate (outpatients)



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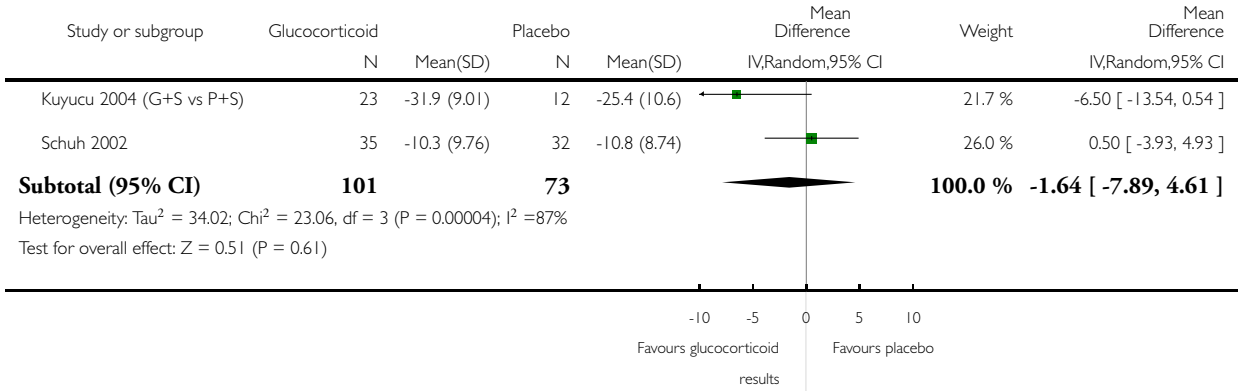


(1) Kuyucu 2004 and Plint 2009 (factorial trials) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant differences when pooling

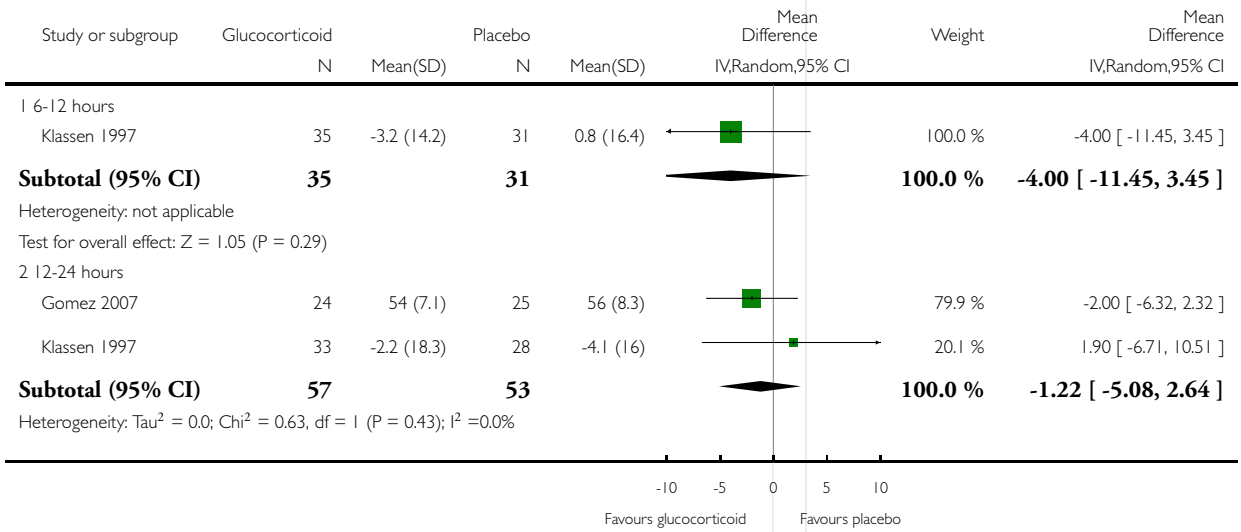
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.9. Comparison 1 Glucocorticoid versus placebo, Outcome 9 Respiratory rate (inpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 9 Respiratory rate (inpatients)



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Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Test for overall effect: Z = 0.62 (P = 0.54)							
3 24-72 hours							
Klassen 1997	17	-5.6 (16.9)	11	-3.7 (18.3)		100.0 %	-1.90 [-15.37, 11.57]
Subtotal (95% CI)	**17**		**11**			**100.0 %**	**-1.90 [-15.37, 11.57]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.28 (P = 0.78)							

Analysis 1.10. Comparison 1 Glucocorticoid versus placebo, Outcome 10 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 10 Heart rate (outpatients)

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 Minutes							
Barlas 1998 (G vs P) (1)	30	2.57 (10.55)	15	-1.6 (5.92)		18.8 %	4.17 [-0.65, 8.99]
Barlas 1998 (G+S vs S) (2)	15	3.07 (11.54)	15	5.87 (9.7)		7.5 %	-2.80 [-10.43, 4.83]
Mesquita 2009	33	-6 (21.52)	32	-4 (22.52)		3.8 %	-2.00 [-12.71, 8.71]
Plint 2009 (G+E vs P+E)	199	5.2 (17.8)	198	4.8 (17.6)		36.0 %	0.40 [-3.08, 3.88]
Plint 2009 (G+P vs P+P)	199	-3.76 (17.7)	200	-3.24 (18.8)		34.0 %	-0.52 [-4.10, 3.06]
Subtotal (95% CI)	**476**		**460**			**100.0 %**	**0.46 [-1.62, 2.55]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.47, df = 4 (P = 0.48); I^2 =0.0%							
Test for overall effect: Z = 0.44 (P = 0.66)							
2 120 Minutes							
Barlas 1998 (G vs P)	30	0.57 (11.85)	15	4.47 (21.3)		16.8 %	-3.90 [-15.48, 7.68]

not show relevant differences when pooling results

(*Continued* . . .)

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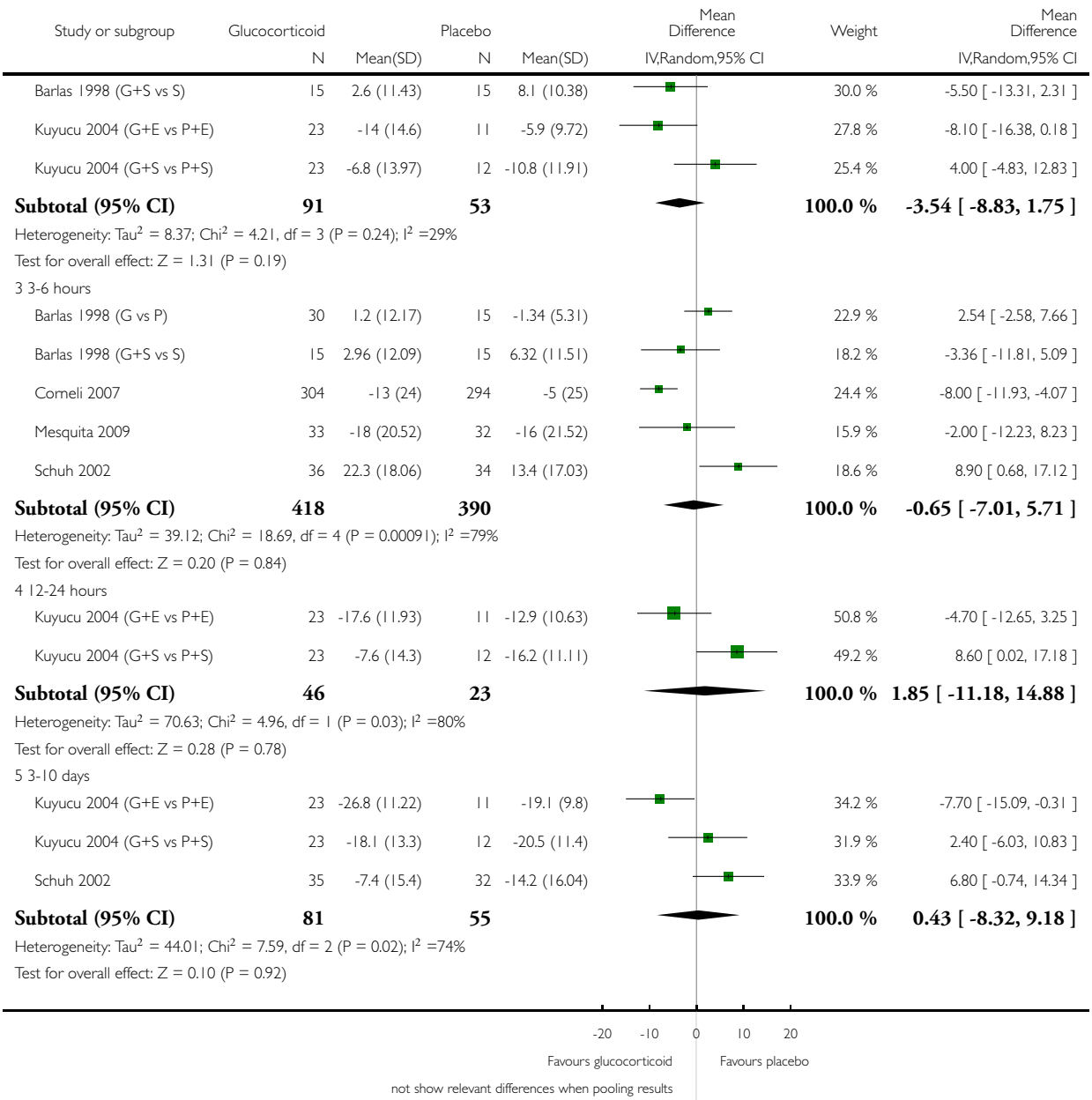


(1) Kuyucu 2004 and Plint 2009 (factorial trials) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.11. Comparison 1 Glucocorticoid versus placebo, Outcome 11 Heart rate (inpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 11 Heart rate (inpatients)

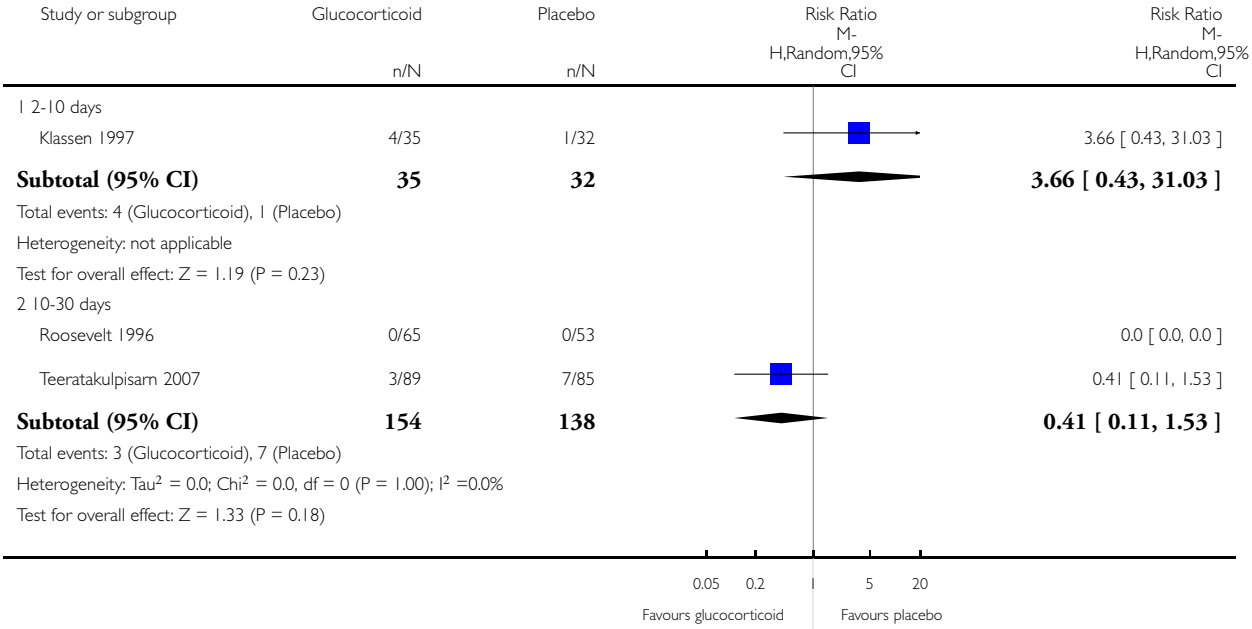
Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 12-24 hours							
Gomez 2007	24	2 (22.87)	25	11 (10.25)		100.0 %	-9.00 [-18.99, 0.99]
Subtotal (95% CI)	**24**		**25**			**100.0 %**	**-9.00 [-18.99, 0.99]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.77 (P = 0.078)							

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

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 12 Hospital readmissions (inpatients)



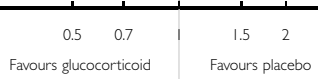
Analysis 1.13. Comparison 1 Glucocorticoid versus placebo, Outcome 13 Return healthcare visits (inpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 13 Return healthcare visits (inpatients)

Study or subgroup	Glucocorticoid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 2-10 days					
Klassen 1997	29/35	24/32		100.0 %	1.10 [0.86, 1.42]
Subtotal (95% CI)	**35**	**32**		**100.0 %**	**1.10 [0.86, 1.42]**
Total events: 29 (Glucocorticoid), 24 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.78 (P = 0.44)					
2 10-30 days					
Roosevelt 1996	16/65	5/53		46.3 %	2.61 [1.02, 6.66]
Teeratakulpisarn 2007	17/89	26/85		53.7 %	0.62 [0.37, 1.07]
Subtotal (95% CI)	**154**	**138**		**100.0 %**	**1.21 [0.30, 4.96]**
Total events: 33 (Glucocorticoid), 31 (Placebo)					
Heterogeneity: Tau^2 = 0.89; Chi^2 = 6.88, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 0.27 (P = 0.79)					



Analysis 1.14. Comparison 1 Glucocorticoid versus placebo, Outcome 14 Return healthcare visits (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 14 Return healthcare visits (outpatients)

Study or subgroup	Glucocorticoid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 10-30 days					
Plint 2009 (G+E vs P+E) (1)	95/199	93/198		44.0 %	1.02 [0.83, 1.25]
Plint 2009 (G+P vs P+P)	106/199	86/200		44.2 %	1.24 [1.01, 1.52]
Schuh 2002	9/35	14/32		11.9 %	0.59 [0.30, 1.17]
Subtotal (95% CI)	**433**	**430**		**100.0 %**	**1.04 [0.80, 1.35]**
Total events: 210 (Glucocorticoid), 193 (Placebo)					
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.04$, df = 2 (P = 0.08); $I^2 = 60\%$					
Test for overall effect: Z = 0.29 (P = 0.77)					

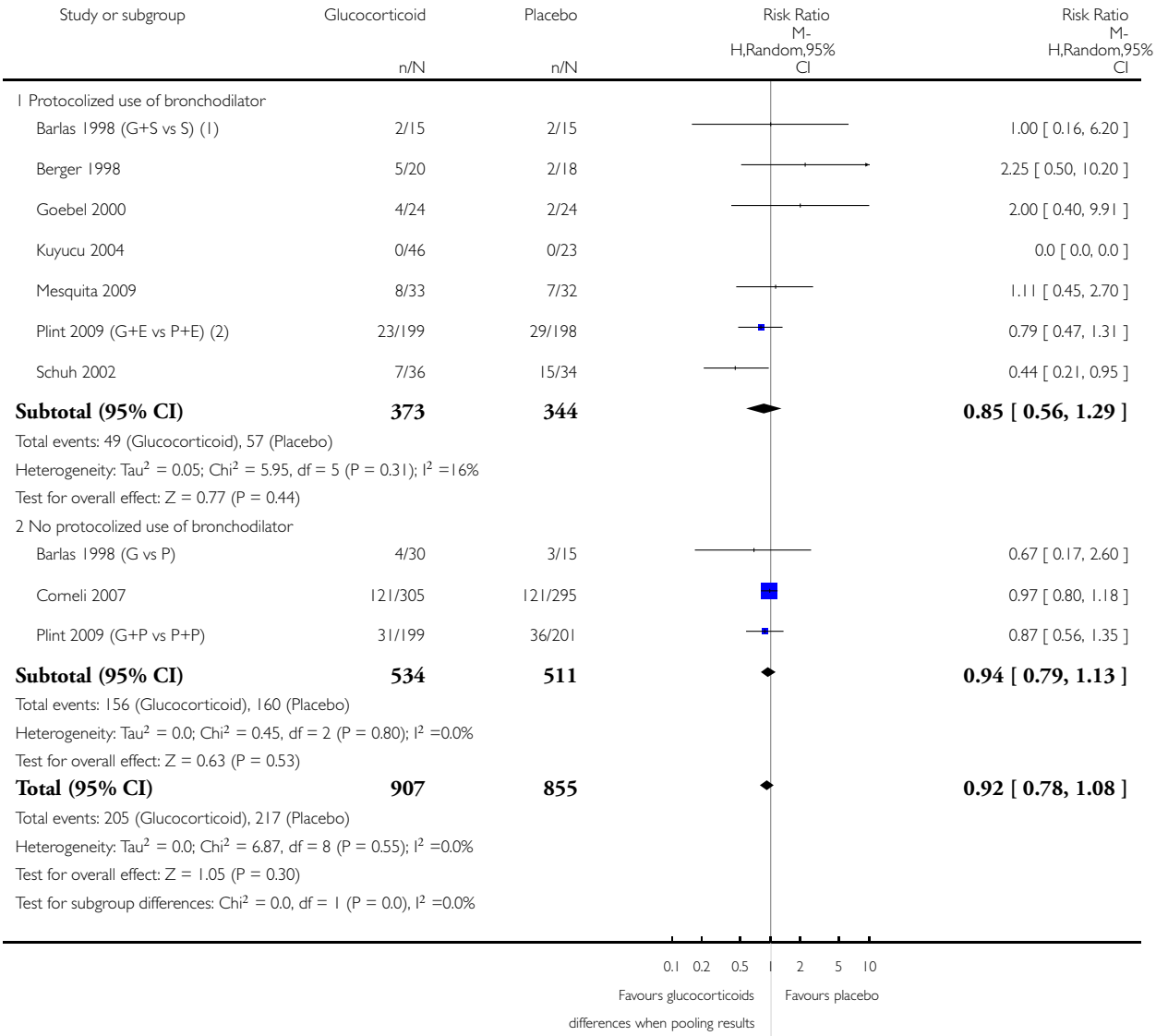
(1) Plint 2009 (factorial trial) contributes two independent comparisons which are shown separately; sensitivity analysis did not show relevant differences when pooling results

Analysis 1.15. Comparison 1 Glucocorticoid versus placebo, Outcome 15 Admissions at day 1 (outpatients) - subgroup analysis protocolized use of bronchodilator.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 15 Admissions at day 1 (outpatients) - subgroup analysis protocolized use of bronchodilator



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

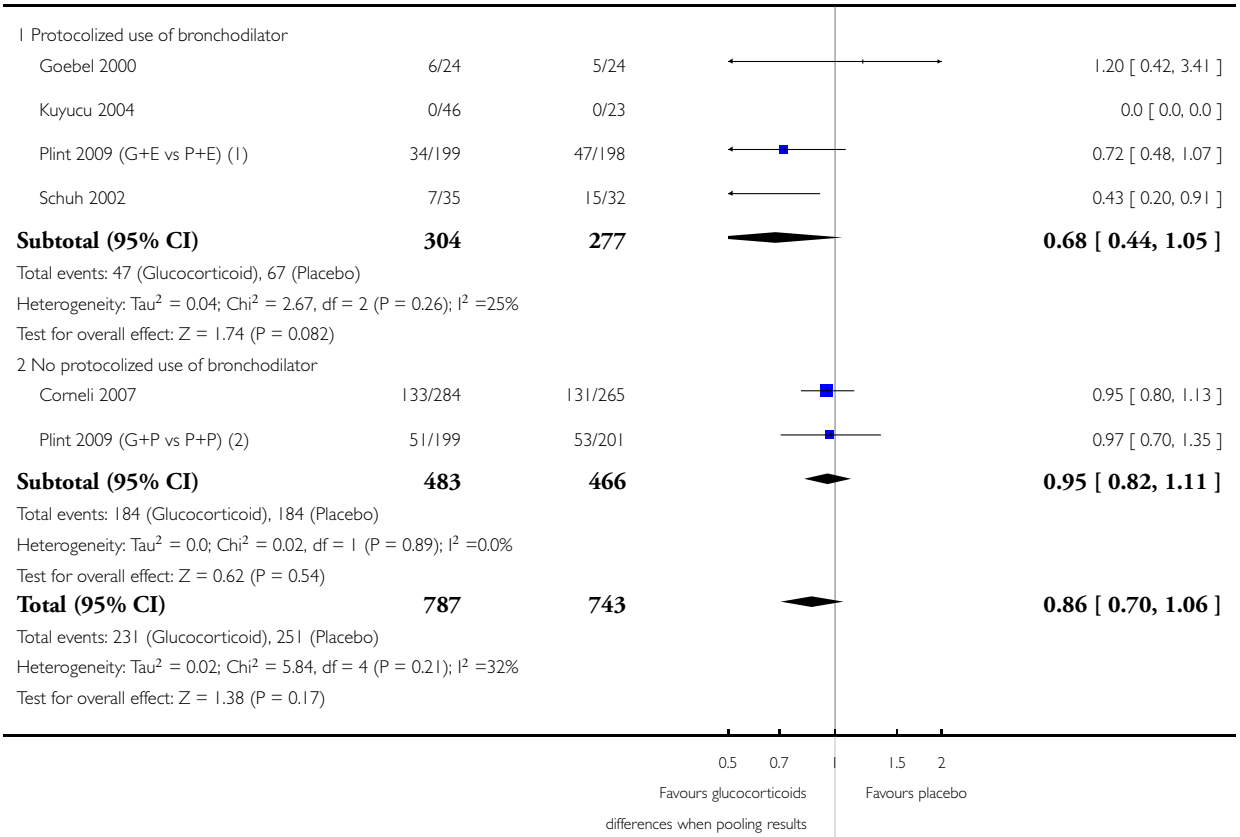
Analysis 1.16. Comparison 1 Glucocorticoid versus placebo, Outcome 16 Admissions within 7 days (outpatients) - subgroup analysis protocolized use of bronchodilator.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 16 Admissions within 7 days (outpatients) - subgroup analysis protocolized use of bronchodilator

Study or subgroup	Glucocorticoid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Protocolized use of bronchodilator				
Goebel 2000	6/24	5/24		1.20 [0.42, 3.41]
Kuyucu 2004	0/46	0/23		0.0 [0.0, 0.0]
Plint 2009 (G+E vs P+E) (1)	34/199	47/198		0.72 [0.48, 1.07]
Schuh 2002	7/35	15/32		0.43 [0.20, 0.91]
Subtotal (95% CI)	**304**	**277**		**0.68 [0.44, 1.05]**
Total events: 47 (Glucocorticoid), 67 (Placebo)				
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 2.67$, df = 2 (P = 0.26); $I^2 = 25\%$				
Test for overall effect: Z = 1.74 (P = 0.082)				
2 No protocolized use of bronchodilator				
Corneli 2007	133/284	131/265		0.95 [0.80, 1.13]
Plint 2009 (G+P vs P+P) (2)	51/199	53/201		0.97 [0.70, 1.35]
Subtotal (95% CI)	**483**	**466**		**0.95 [0.82, 1.11]**
Total events: 184 (Glucocorticoid), 184 (Placebo)				
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0.0\%$				
Test for overall effect: Z = 0.62 (P = 0.54)				
Total (95% CI)	**787**	**743**		**0.86 [0.70, 1.06]**
Total events: 231 (Glucocorticoid), 251 (Placebo)				
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 5.84$, df = 4 (P = 0.21); $I^2 = 32\%$				
Test for overall effect: Z = 1.38 (P = 0.17)				



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

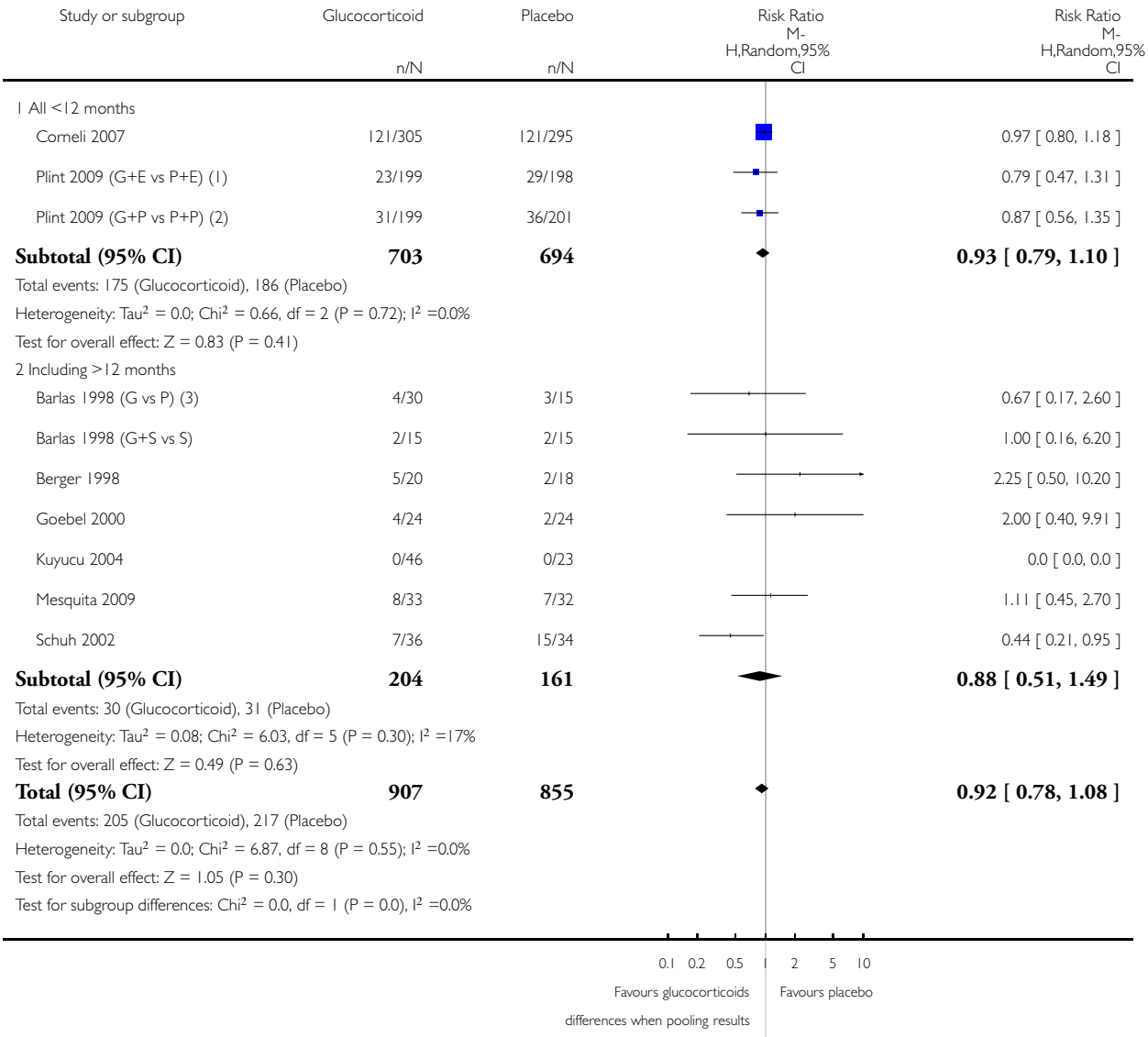
(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.17. Comparison 1 Glucocorticoid versus placebo, Outcome 17 Admissions at day 1 (outpatients) - subgroup analysis age.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 17 Admissions at day 1 (outpatients) - subgroup analysis age



(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

(3) Multi-arm study; contributes two comparisons to this analysis (G: Glucocorticoid, S:Salbutamol, P: Placebo)

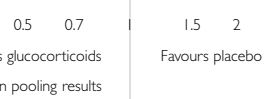
Analysis 1.18. Comparison 1 Glucocorticoid versus placebo, Outcome 18 Admissions within 7 days (outpatients) - subgroup analysis age.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 18 Admissions within 7 days (outpatients) - subgroup analysis age

Study or subgroup	Glucocorticoid n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 All <12 months				
Corneli 2007	133/284	131/265		0.95 [0.80, 1.13]
Plint 2009 (G+E vs P+E) (1)	34/199	47/198		0.72 [0.48, 1.07]
Plint 2009 (G+P vs P+P) (2)	51/199	53/201		0.97 [0.70, 1.35]
Subtotal (95% CI)	**682**	**664**		**0.92 [0.80, 1.06]**
Total events: 218 (Glucocorticoid), 231 (Placebo)				
Heterogeneity: Tau^2 = 0.0; Chi^2 = 1.72, df = 2 (P = 0.42); I^2 =0.0%				
Test for overall effect: Z = 1.17 (P = 0.24)				
2 Including >12 months				
Goebel 2000	6/24	5/24		1.20 [0.42, 3.41]
Kuyucu 2004	0/46	0/23		0.0 [0.0, 0.0]
Schuh 2002	7/35	15/32		0.43 [0.20, 0.91]
Subtotal (95% CI)	**105**	**79**		**0.67 [0.25, 1.83]**
Total events: 13 (Glucocorticoid), 20 (Placebo)				
Heterogeneity: Tau^2 = 0.32; Chi^2 = 2.47, df = 1 (P = 0.12); I^2 =60%				
Test for overall effect: Z = 0.78 (P = 0.44)				
Total (95% CI)	**787**	**743**		**0.86 [0.70, 1.06]**
Total events: 231 (Glucocorticoid), 251 (Placebo)				
Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.84, df = 4 (P = 0.21); I^2 =32%				
Test for overall effect: Z = 1.38 (P = 0.17)				



differences when pooling results

(1) Plint 2009 (factorial trial) and Barlas 1998 (parallel multiarm study) contribute two independent comparisons which are shown separately; sensitivity analysis did not show relevant

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

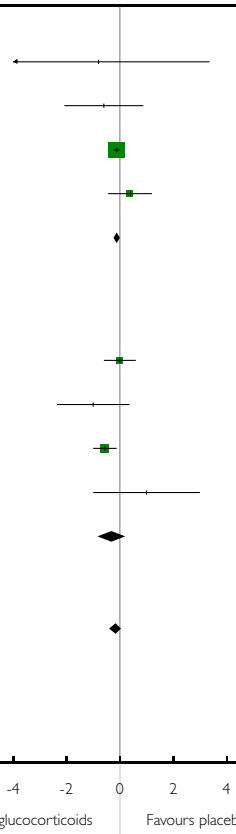
Analysis 1.19. Comparison 1 Glucocorticoid versus placebo, Outcome 19 Length of stay (inpatients) - subgroup analysis protocolized use of bronchodilator.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 19 Length of stay (inpatients) - subgroup analysis protocolized use of bronchodilator

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Protocolized use of bronchodilator							
Bentur 2005	29	5.469 (7.87)	32	6.29 (8.778)		0.3 %	-0.82 [-5.00, 3.36]
De Boeck 1997	14	6 (2.619)	15	6.6 (1.162)		2.1 %	-0.60 [-2.09, 0.89]
Gomez 2007	24	0.654 (0.192)	25	0.78 (0.223)		58.4 %	-0.13 [-0.24, -0.01]
Klassen 1997	35	2.375 (2.39)	32	2 (0.722)		6.3 %	0.38 [-0.46, 1.21]
Subtotal (95% CI)	**102**		**104**			**67.1 %**	**-0.12 [-0.23, 0.00]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.88$, df = 3 (P = 0.60); $I^2 = 0.0\%$							
Test for overall effect: Z = 2.03 (P = 0.043)							
2 No protocolized use of bronchodilator							
Cade 2000	82	2 (1.48)	79	2 (2.22)		11.7 %	0.0 [-0.59, 0.59]
Richter 1998	21	2 (2.647)	19	3 (1.626)		2.5 %	-1.00 [-2.35, 0.35]
Teeratakulpisarn 2007	89	2.258 (1.246)	85	2.82 (1.742)		17.6 %	-0.56 [-1.01, -0.11]
Zhang 2003	28	6 (4.05)	24	5 (3.34)		1.2 %	1.00 [-1.01, 3.01]
Subtotal (95% CI)	**220**		**207**			**32.9 %**	**-0.31 [-0.83, 0.20]**
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 4.82$, df = 3 (P = 0.19); $I^2 = 38\%$							
Test for overall effect: Z = 1.20 (P = 0.23)							
Total (95% CI)	**322**		**311**			**100.0 %**	**-0.18 [-0.39, 0.04]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.33$, df = 7 (P = 0.30); $I^2 = 16\%$							
Test for overall effect: Z = 1.58 (P = 0.12)							
Test for subgroup differences: $Chi^2 = 1.63$, df = 1 (P = 0.20), $I^2 = 39\%$							



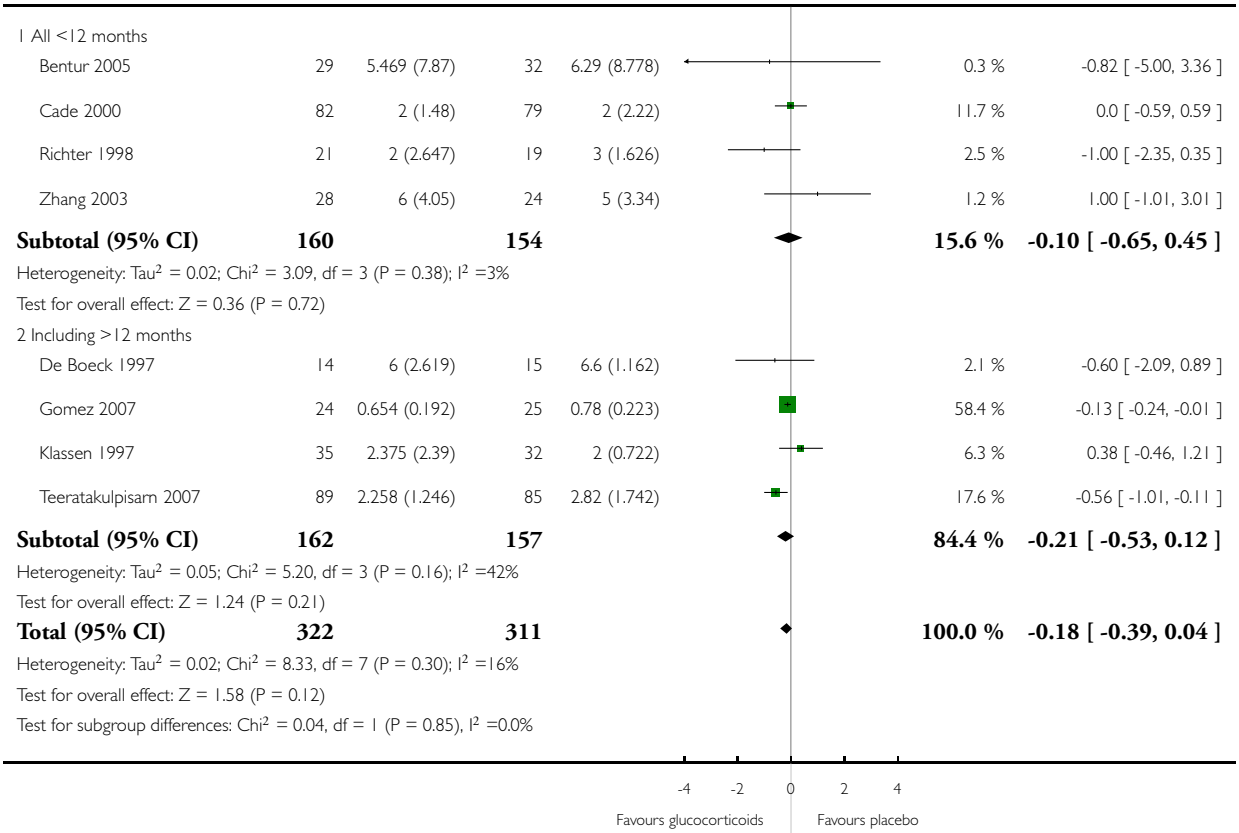
Analysis 1.20. Comparison 1 Glucocorticoid versus placebo, Outcome 20 Length of stay (inpatients) - subgroup analysis age.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 20 Length of stay (inpatients) - subgroup analysis age

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 All <12 months							
Bentur 2005	29	5.469 (7.87)	32	6.29 (8.778)		0.3 %	-0.82 [-5.00, 3.36]
Cade 2000	82	2 (1.48)	79	2 (2.22)		11.7 %	0.0 [-0.59, 0.59]
Richter 1998	21	2 (2.647)	19	3 (1.626)		2.5 %	-1.00 [-2.35, 0.35]
Zhang 2003	28	6 (4.05)	24	5 (3.34)		1.2 %	1.00 [-1.01, 3.01]
Subtotal (95% CI)	**160**		**154**			**15.6 %**	**-0.10 [-0.65, 0.45]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.09$, df = 3 (P = 0.38); $I^2 = 3\%$							
Test for overall effect: Z = 0.36 (P = 0.72)							
2 Including >12 months							
De Boeck 1997	14	6 (2.619)	15	6.6 (1.162)		2.1 %	-0.60 [-2.09, 0.89]
Gomez 2007	24	0.654 (0.192)	25	0.78 (0.223)		58.4 %	-0.13 [-0.24, -0.01]
Klassen 1997	35	2.375 (2.39)	32	2 (0.722)		6.3 %	0.38 [-0.46, 1.21]
Teeratakulpisarn 2007	89	2.258 (1.246)	85	2.82 (1.742)		17.6 %	-0.56 [-1.01, -0.11]
Subtotal (95% CI)	**162**		**157**			**84.4 %**	**-0.21 [-0.53, 0.12]**
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 5.20$, df = 3 (P = 0.16); $I^2 = 42\%$							
Test for overall effect: Z = 1.24 (P = 0.21)							
Total (95% CI)	**322**		**311**			**100.0 %**	**-0.18 [-0.39, 0.04]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.33$, df = 7 (P = 0.30); $I^2 = 16\%$							
Test for overall effect: Z = 1.58 (P = 0.12)							
Test for subgroup differences: $Chi^2 = 0.04$, df = 1 (P = 0.85), $I^2 = 0.0\%$							



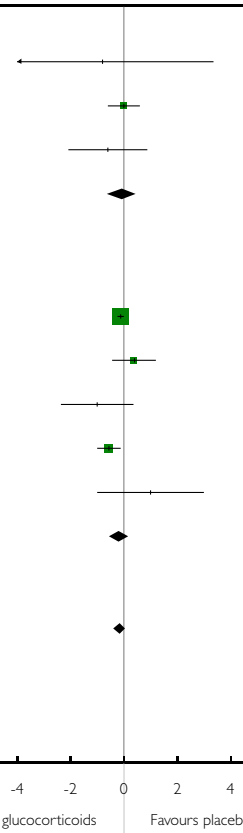
Analysis 1.21. Comparison 1 Glucocorticoid versus placebo, Outcome 21 Length of stay (inpatients) - subgroup analysis RSV status.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 21 Length of stay (inpatients) - subgroup analysis RSV status

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 All RSV positive							
Bentur 2005	29	5.469 (7.87)	32	6.29 (8.778)		0.3 %	-0.82 [-5.00, 3.36]
Cade 2000	82	2 (1.48)	79	2 (2.22)		11.7 %	0.0 [-0.59, 0.59]
De Boeck 1997	14	6 (2.619)	15	6.6 (1.162)		2.1 %	-0.60 [-2.09, 0.89]
Subtotal (95% CI)	**125**		**126**			**14.0 %**	**-0.09 [-0.63, 0.45]**
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.66$, df = 2 (P = 0.72); $I^2 = 0.0\%$							
Test for overall effect: Z = 0.33 (P = 0.74)							
2 Not all RSV positive, or NR							
Gomez 2007	24	0.654 (0.192)	25	0.78 (0.223)		58.4 %	-0.13 [-0.24, -0.01]
Klassen 1997	35	2.375 (2.39)	32	2 (0.722)		6.3 %	0.38 [-0.46, 1.21]
Richter 1998	21	2 (2.647)	19	3 (1.626)		2.5 %	-1.00 [-2.35, 0.35]
Teeratakulpisarn 2007	89	2.258 (1.246)	85	2.82 (1.742)		17.6 %	-0.56 [-1.01, -0.11]
Zhang 2003	28	6 (4.05)	24	5 (3.34)		1.2 %	1.00 [-1.01, 3.01]
Subtotal (95% CI)	**197**		**185**			**86.0 %**	**-0.20 [-0.57, 0.17]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 7.64$, df = 4 (P = 0.11); $I^2 = 48\%$							
Test for overall effect: Z = 1.06 (P = 0.29)							
Total (95% CI)	**322**		**311**			**100.0 %**	**-0.18 [-0.39, 0.04]**
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 8.33$, df = 7 (P = 0.30); $I^2 = 16\%$							
Test for overall effect: Z = 1.58 (P = 0.12)							
Test for subgroup differences: $Chi^2 = 0.03$, df = 1 (P = 0.85), $I^2 = 0.0\%$							

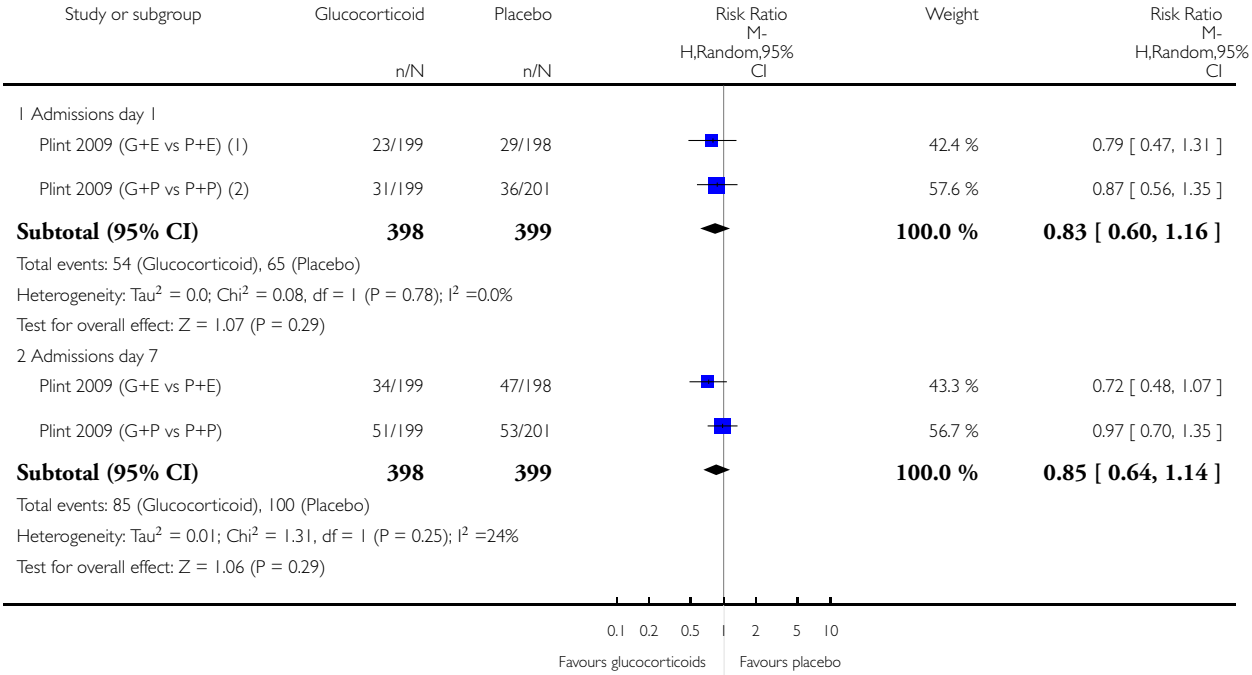


Analysis 1.22. Comparison 1 Glucocorticoid versus placebo, Outcome 22 Admissions (days 1 and 7) (outpatients) - sensitivity analysis with only low overall RoB.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 22 Admissions (days 1 and 7) (outpatients) - sensitivity analysis with only low overall RoB



(1) Plint 2009 (factorial trial) contributes two independent comparisons which are shown separately; sensitivity analysis did not show relevant differences when pooling results

(2) G: Glucocorticoid, S:Salbutamol, E: Epinephrine, P: Placebo

Analysis 1.23. Comparison 1 Glucocorticoid versus placebo, Outcome 23 Length of stay (inpatients) - sensitivity analysis with only low overall RoB.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 1 Glucocorticoid versus placebo

Outcome: 23 Length of stay (inpatients) - sensitivity analysis with only low overall RoB

Study or subgroup	Glucocorticoid N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Klassen 1997	35	2.375 (2.39)	32	2 (0.722)		100.0 %	0.38 [-0.46, 1.21]
Total (95% CI)	**35**		**32**			**100.0 %**	**0.38 [-0.46, 1.21]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.89 (P = 0.38)

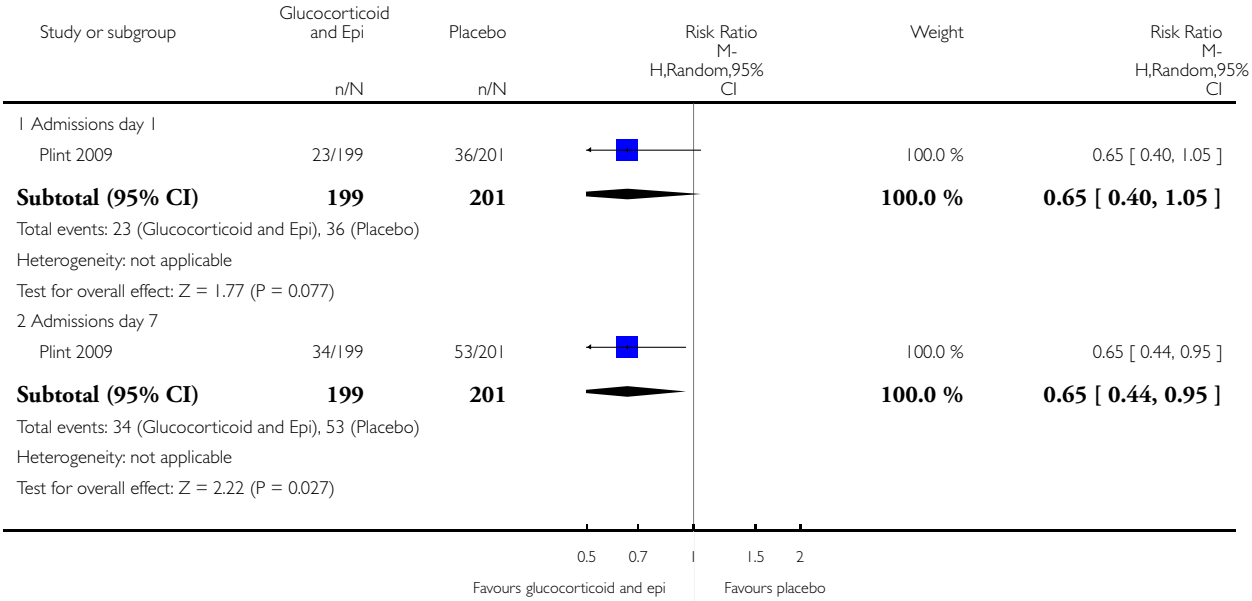
Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 1 Admissions (days 1 and 7) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 1 Admissions (days 1 and 7) (outpatients) - review primary outcome

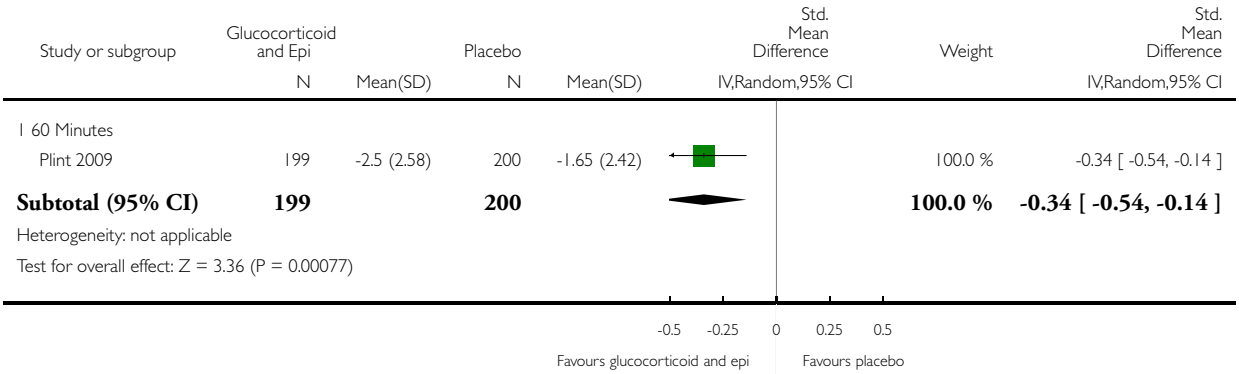


Analysis 2.2. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 2 Clinical scores (outpatients)

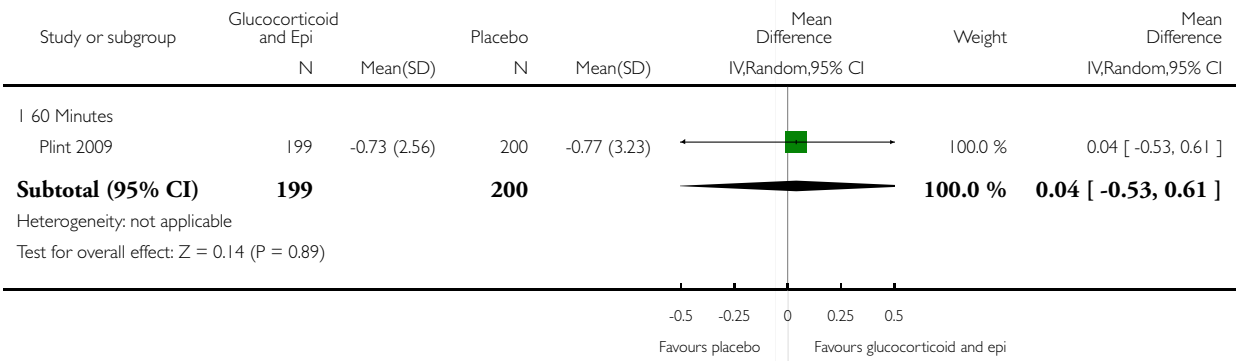


Analysis 2.3. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 3 O_2 saturation (outpatients)

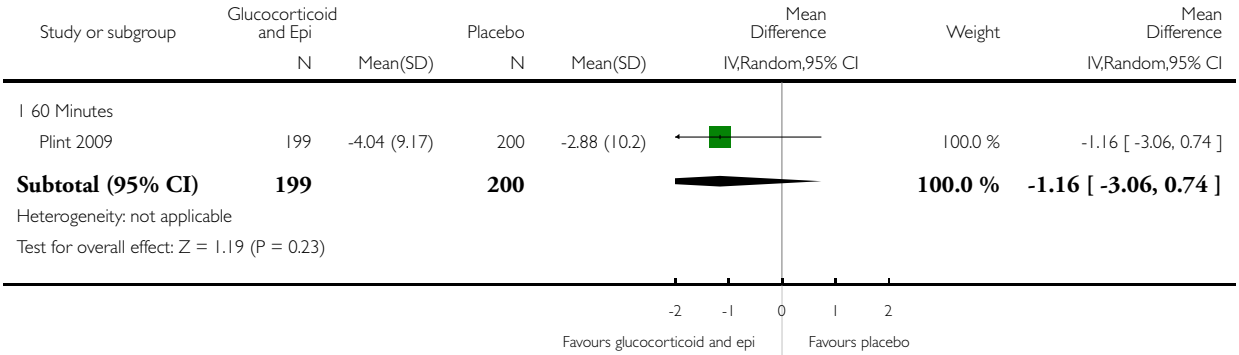


Analysis 2.4. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 4 Respiratory rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 4 Respiratory rate (outpatients)

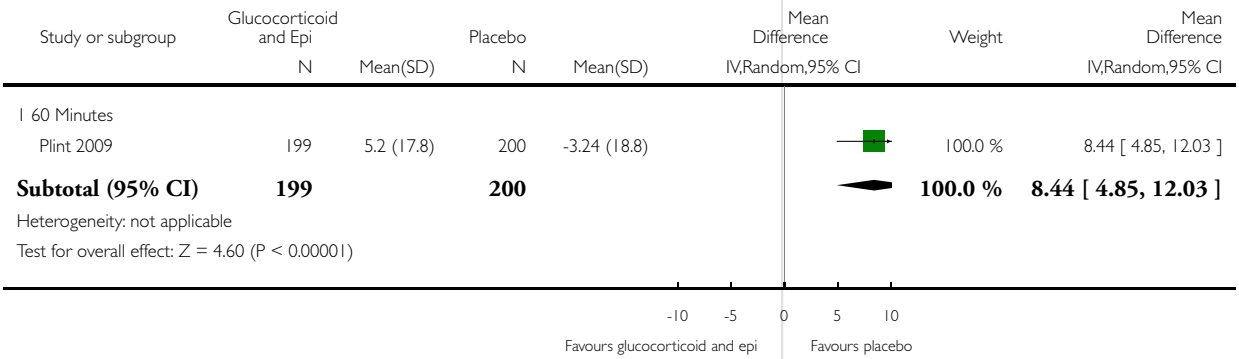


Analysis 2.5. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 5 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 5 Heart rate (outpatients)

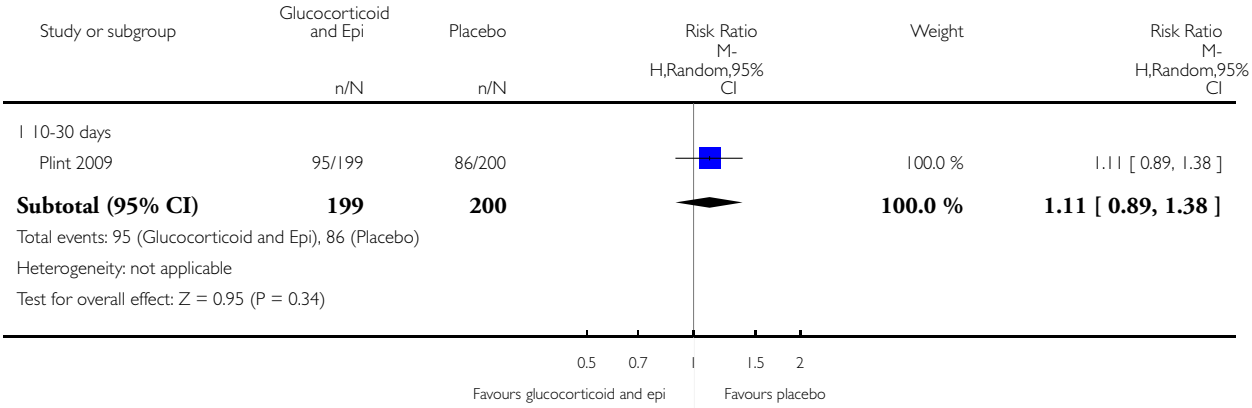


Analysis 2.6. Comparison 2 Glucocorticoid and epinephrine versus placebo, Outcome 6 Return healthcare visits (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 2 Glucocorticoid and epinephrine versus placebo

Outcome: 6 Return healthcare visits (outpatients)

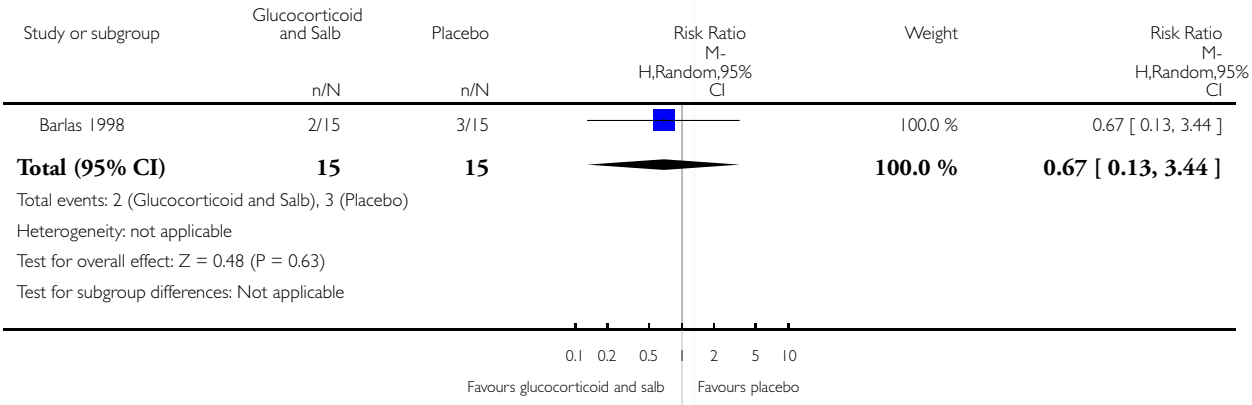


Analysis 3.1. Comparison 3 Glucocorticoid and salbutamol versus placebo, Outcome 1 Admissions (day 1) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 3 Glucocorticoid and salbutamol versus placebo

Outcome: 1 Admissions (day 1) (outpatients) - review primary outcome



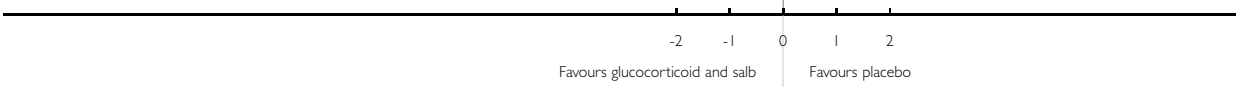
Analysis 3.2. Comparison 3 Glucocorticoid and salbutamol versus placebo, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 3 Glucocorticoid and salbutamol versus placebo

Outcome: 2 Clinical scores (outpatients)

Study or subgroup	Glucocorticoid and Salb 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							
Barlas 1998	15	-1.2 (2.28)	15	-0.54 (1.96)		100.0 %	-0.30 [-1.02, 0.42]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.30 [-1.02, 0.42]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.82 (P = 0.41)							
2 120 Minutes							
Barlas 1998	15	-2.07 (2.75)	15	-1.47 (2.54)		100.0 %	-0.22 [-0.94, 0.50]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.22 [-0.94, 0.50]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.60 (P = 0.55)							
3 3-6 hours							
Barlas 1998	15	-2.39 (3.25)	15	-1.07 (2.31)		100.0 %	-0.46 [-1.18, 0.27]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.46 [-1.18, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.23 (P = 0.22)							



Analysis 3.3. Comparison 3 Glucocorticoid and salbutamol versus placebo, Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 3 Glucocorticoid and salbutamol versus placebo

Outcome: 3 O_2 saturation (outpatients)

Study or subgroup	Glucocorticoid and Salb		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 60 Minutes							
Barlas 1998	15	-0.14 (1.94)	15	0.2 (1.99)		100.0 %	-0.34 [-1.75, 1.07]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.34 [-1.75, 1.07]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.47 (P = 0.64)							
2 120 Minutes							
Barlas 1998	15	-0.2 (1.88)	15	0.47 (1.95)		100.0 %	-0.67 [-2.04, 0.70]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-0.67 [-2.04, 0.70]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.96 (P = 0.34)							
3 3-6 hours							
Barlas 1998	15	-0.59 (1.82)	15	0.49 (1.95)		100.0 %	-1.08 [-2.43, 0.27]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.08 [-2.43, 0.27]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.57 (P = 0.12)							

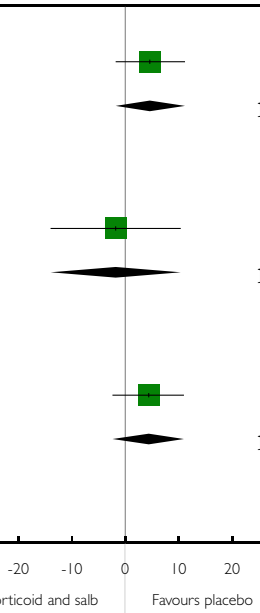
Analysis 3.4. Comparison 3 Glucocorticoid and salbutamol versus placebo, Outcome 4 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 3 Glucocorticoid and salbutamol versus placebo

Outcome: 4 Heart rate (outpatients)

Study or subgroup	Glucocorticoid and Salb N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 Minutes							
Barlas 1998	15	3.07 (11.54)	15	-1.6 (5.92)		100.0 %	4.67 [-1.89, 11.23]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**4.67 [-1.89, 11.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.39 (P = 0.16)							
2 120 Minutes							
Barlas 1998	15	2.6 (11.43)	15	4.47 (21.3)		100.0 %	-1.87 [-14.10, 10.36]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.87 [-14.10, 10.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.30 (P = 0.76)							
3 3-6 hours							
Barlas 1998	15	2.96 (12.09)	15	-1.34 (5.31)		100.0 %	4.30 [-2.38, 10.98]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**4.30 [-2.38, 10.98]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.26 (P = 0.21)							

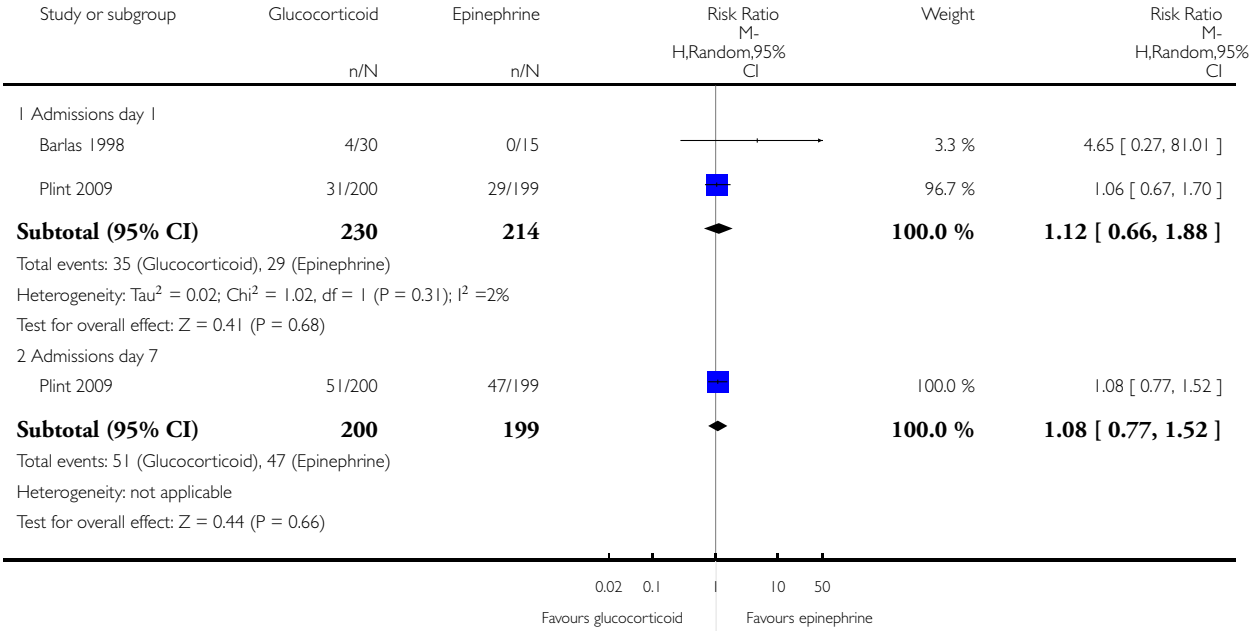


Analysis 4.1. Comparison 4 Glucocorticoid versus epinephrine, Outcome 1 Admissions (days 1 and 7) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 4 Glucocorticoid versus epinephrine

Outcome: 1 Admissions (days 1 and 7) (outpatients) - review primary outcome



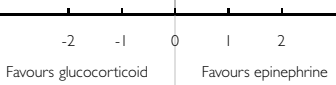
Analysis 4.2. Comparison 4 Glucocorticoid versus epinephrine, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 4 Glucocorticoid versus epinephrine

Outcome: 2 Clinical scores (outpatients)

Study or subgroup	Glucocorticoid 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 1998	30	-1.135 (1.72)	15	-1.93 (1.589)		9.0 %	0.47 [-0.16, 1.09]
Plint 2009	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 1998	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 3-6 hours							
Barlas 1998	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 4.3. Comparison 4 Glucocorticoid versus epinephrine, Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 4 Glucocorticoid versus epinephrine

Outcome: 3 O_2 saturation (outpatients)

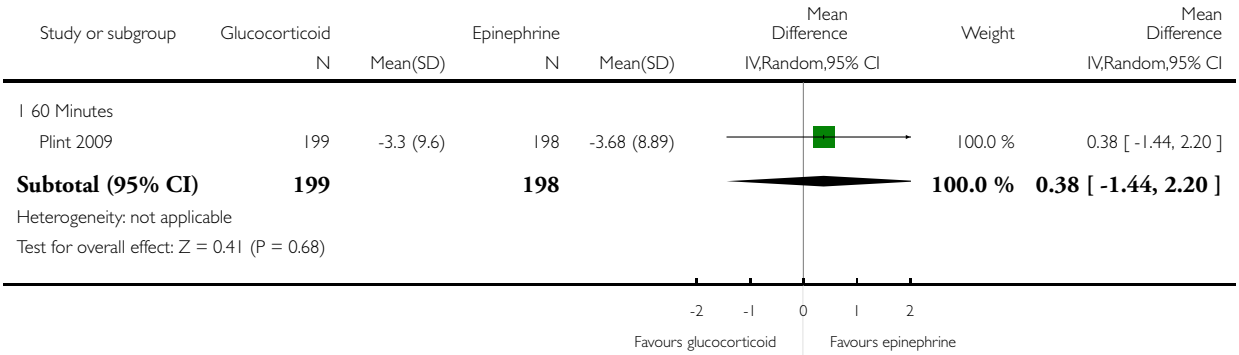
Study or subgroup	Glucocorticoid N	Mean(SD)	Epinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 Minutes							
Barlas 1998	30	0.87 (2.018)	15	1.4 (1.72)		17.4 %	-0.53 [-1.66, 0.60]
Plint 2009	199	-1.02 (2.57)	198	0.07 (2.7)		82.6 %	-1.09 [-1.61, -0.57]
Subtotal (95% CI)	**229**		**213**			**100.0 %**	**-0.99 [-1.46, -0.52]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.78, df = 1 (P = 0.38); I^2 =0.0%							
Test for overall effect: Z = 4.13 (P = 0.000037)							
2 120 Minutes							
Barlas 1998	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 3-6 hours							
Barlas 1998	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 4.4. Comparison 4 Glucocorticoid versus epinephrine, Outcome 4 Respiratory rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 4 Glucocorticoid versus epinephrine

Outcome: 4 Respiratory rate (outpatients)

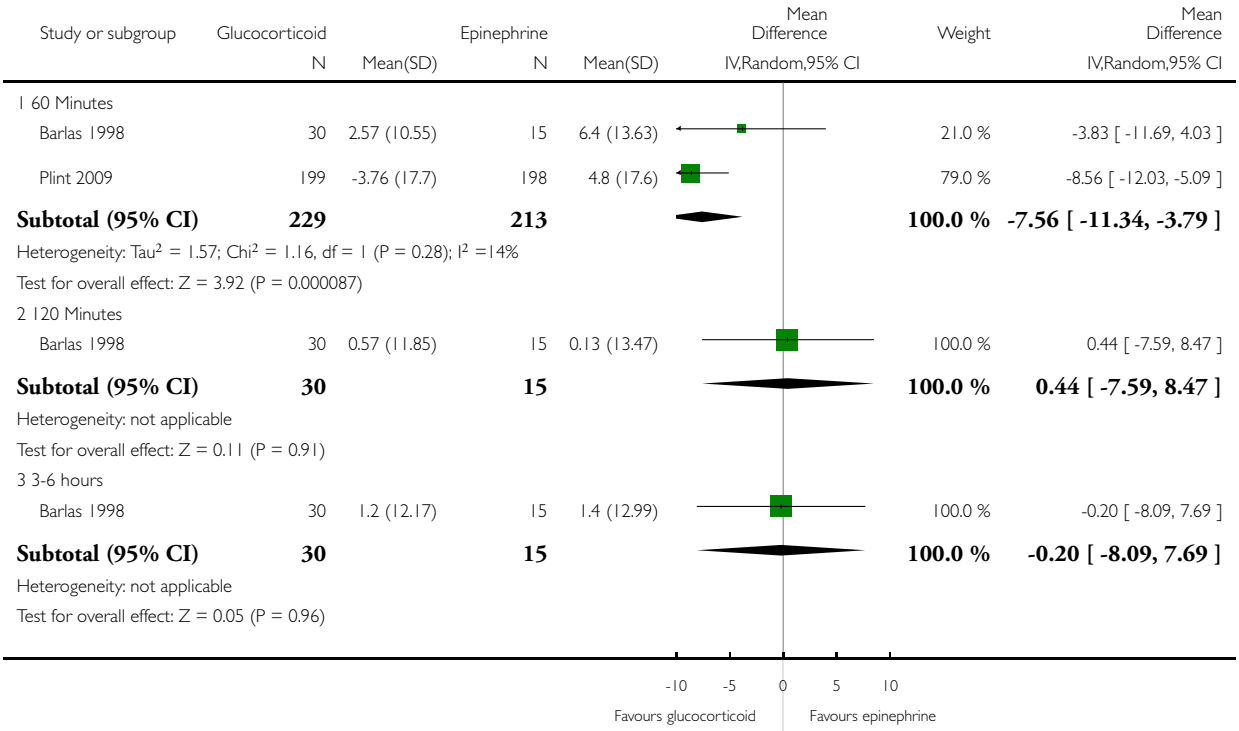


Analysis 4.5. Comparison 4 Glucocorticoid versus epinephrine, Outcome 5 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 4 Glucocorticoid versus epinephrine

Outcome: 5 Heart rate (outpatients)



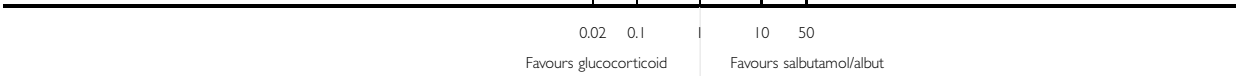
Analysis 5.1. Comparison 5 Glucocorticoid versus salbutamol, Outcome 1 Admissions (day 1) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 5 Glucocorticoid versus salbutamol

Outcome: 1 Admissions (day 1) (outpatients) - review primary outcome

Study or subgroup	Glucocorticoid n/N	Salbutamol n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Barlas 1998	4/30	2/15		100.0 %	1.00 [0.21, 4.86]
Total (95% CI)	**30**	**15**		**100.0 %**	**1.00 [0.21, 4.86]**
Total events: 4 (Glucocorticoid), 2 (Salbutamol)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Not applicable					

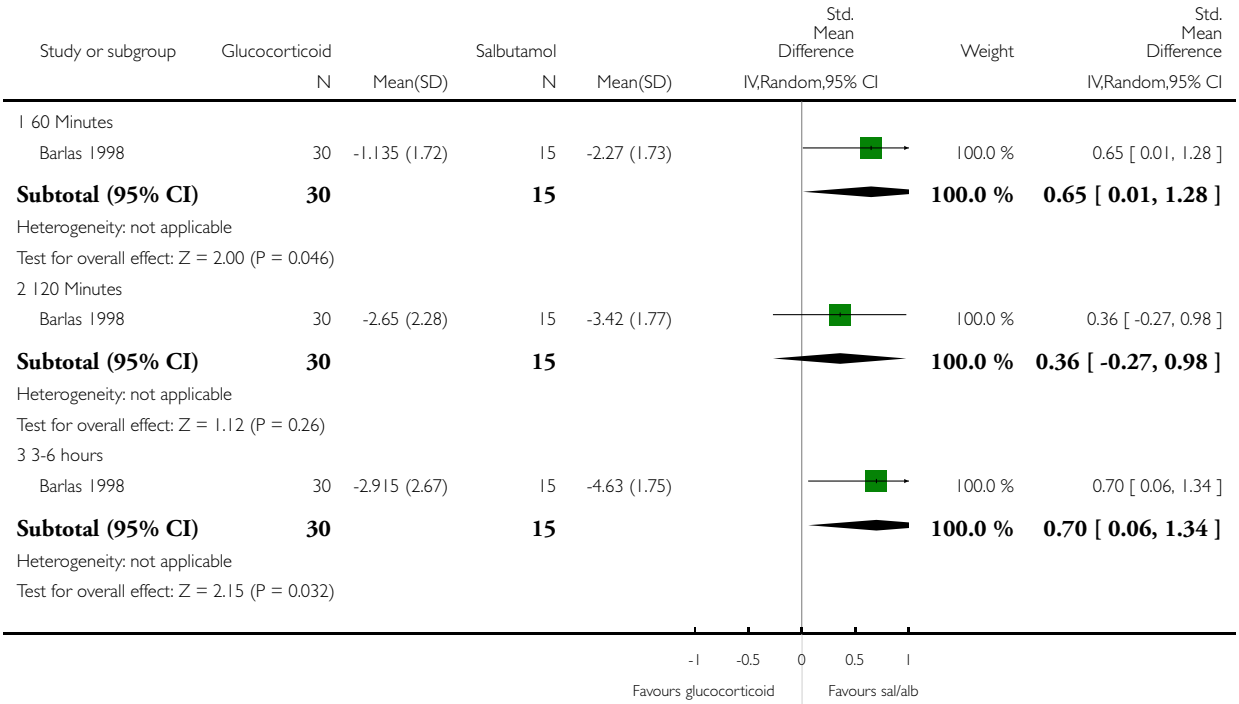


Analysis 5.2. Comparison 5 Glucocorticoid versus salbutamol, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 5 Glucocorticoid versus salbutamol

Outcome: 2 Clinical scores (outpatients)

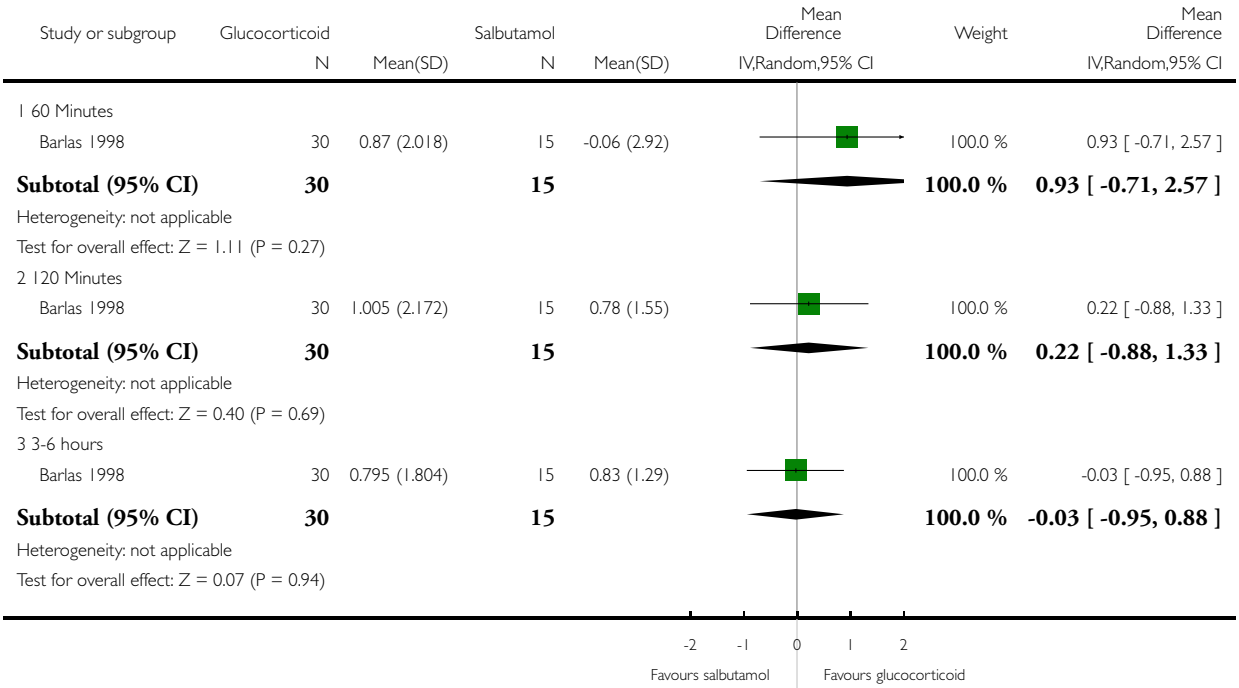


Analysis 5.3. Comparison 5 Glucocorticoid versus salbutamol, Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 5 Glucocorticoid versus salbutamol

Outcome: 3 O_2 saturation (outpatients)

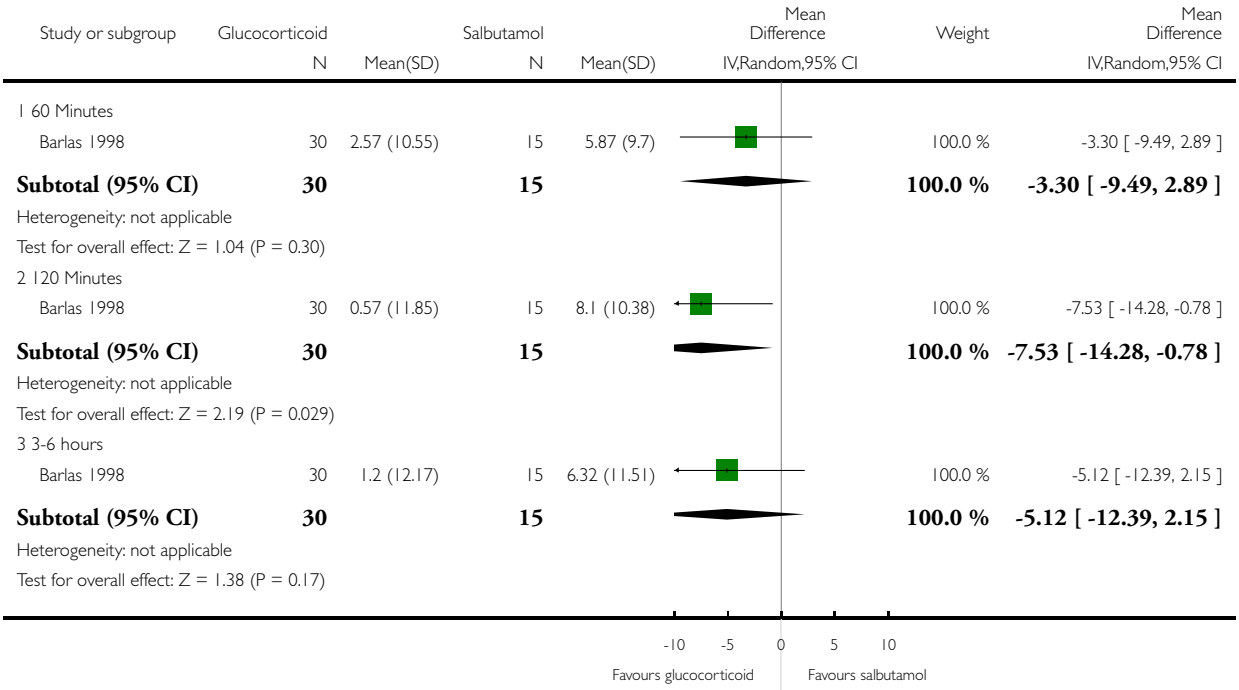


Analysis 5.4. Comparison 5 Glucocorticoid versus salbutamol, Outcome 4 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 5 Glucocorticoid versus salbutamol

Outcome: 4 Heart rate (outpatients)



Analysis 6.1. Comparison 6 Glucocorticoid and epinephrine versus salbutamol, Outcome 1 Admissions (day 1) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 6 Glucocorticoid and epinephrine versus salbutamol

Outcome: 1 Admissions (day 1) (outpatients) - review primary outcome

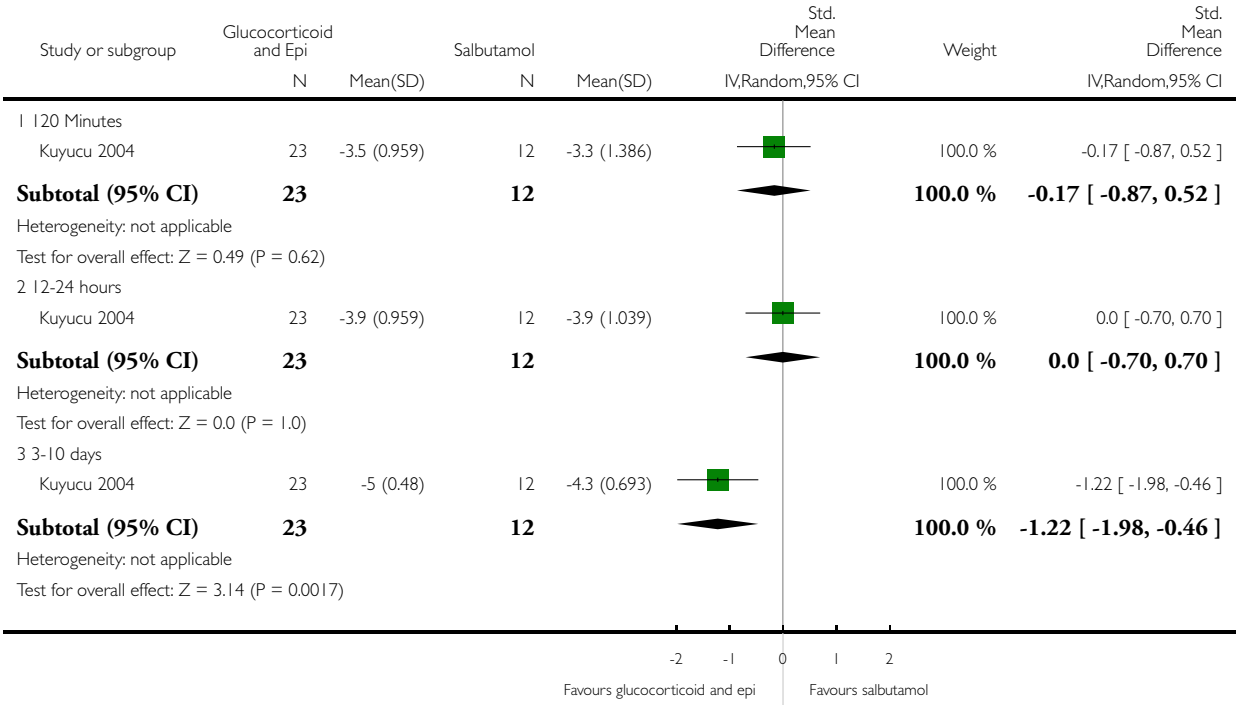
Study or subgroup	Glucocorticoid and Epi n/N	Salbutamol n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Kuyucu 2004	0/23	0/12		0.0 [0.0, 0.0]
Total (95% CI)	**23**	**12**		**0.0 [0.0, 0.0]**
Total events: 0 (Glucocorticoid and Epi), 0 (Salbutamol)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				

Analysis 6.2. Comparison 6 Glucocorticoid and epinephrine versus salbutamol, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 6 Glucocorticoid and epinephrine versus salbutamol

Outcome: 2 Clinical scores (outpatients)



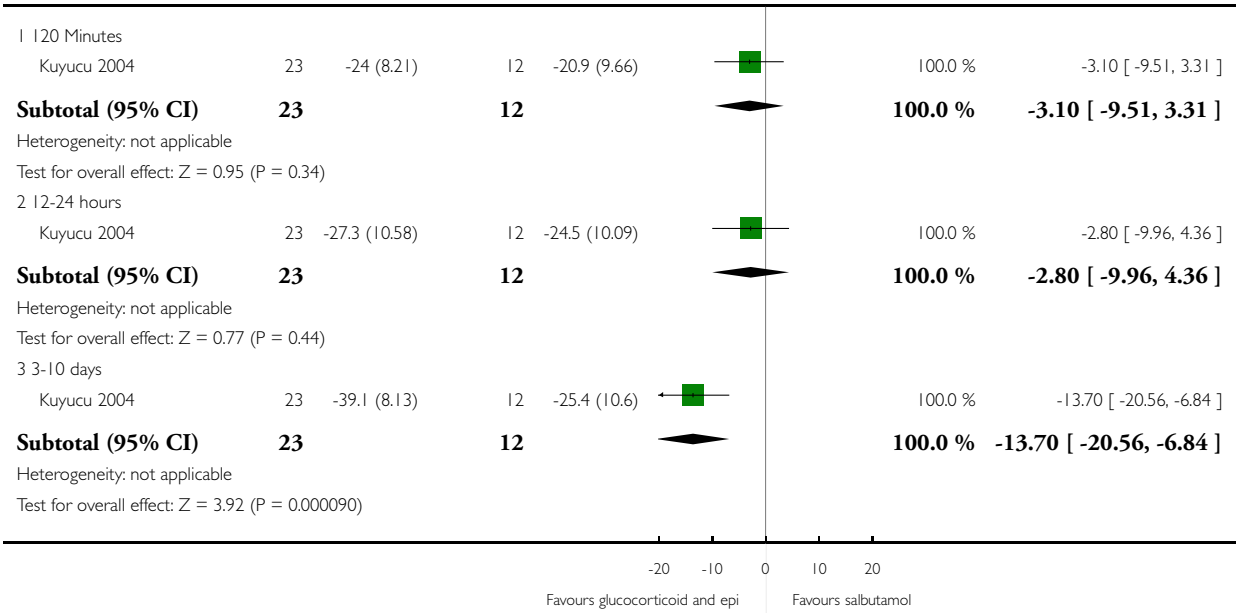
Analysis 6.3. Comparison 6 Glucocorticoid and epinephrine versus salbutamol, Outcome 3 Respiratory rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 6 Glucocorticoid and epinephrine versus salbutamol

Outcome: 3 Respiratory rate (outpatients)

Study or subgroup	Glucocorticoid and Epi N	Mean(SD)	Salbutamol N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 120 Minutes							
Kuyucu 2004	23	-24 (8.21)	12	-20.9 (9.66)		100.0 %	-3.10 [-9.51, 3.31]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-3.10 [-9.51, 3.31]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.95 (P = 0.34)							
2 12-24 hours							
Kuyucu 2004	23	-27.3 (10.58)	12	-24.5 (10.09)		100.0 %	-2.80 [-9.96, 4.36]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-2.80 [-9.96, 4.36]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.77 (P = 0.44)							
3 3-10 days							
Kuyucu 2004	23	-39.1 (8.13)	12	-25.4 (10.6)		100.0 %	-13.70 [-20.56, -6.84]
Subtotal (95% CI)	**23**		**12**			**100.0 %**	**-13.70 [-20.56, -6.84]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.92 (P = 0.000090)							



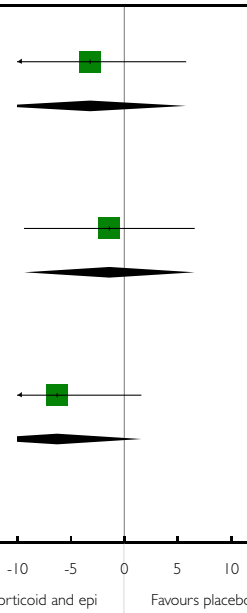
Analysis 6.4. Comparison 6 Glucocorticoid and epinephrine versus salbutamol, Outcome 4 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 6 Glucocorticoid and epinephrine versus salbutamol

Outcome: 4 Heart rate (outpatients)

Study or subgroup	Glucocorticoid and Epi		Salbutamol		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
1 120 Minutes							
Kuyucu 2004	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 12-24 hours							
Kuyucu 2004	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 3-10 days							
Kuyucu 2004	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)							

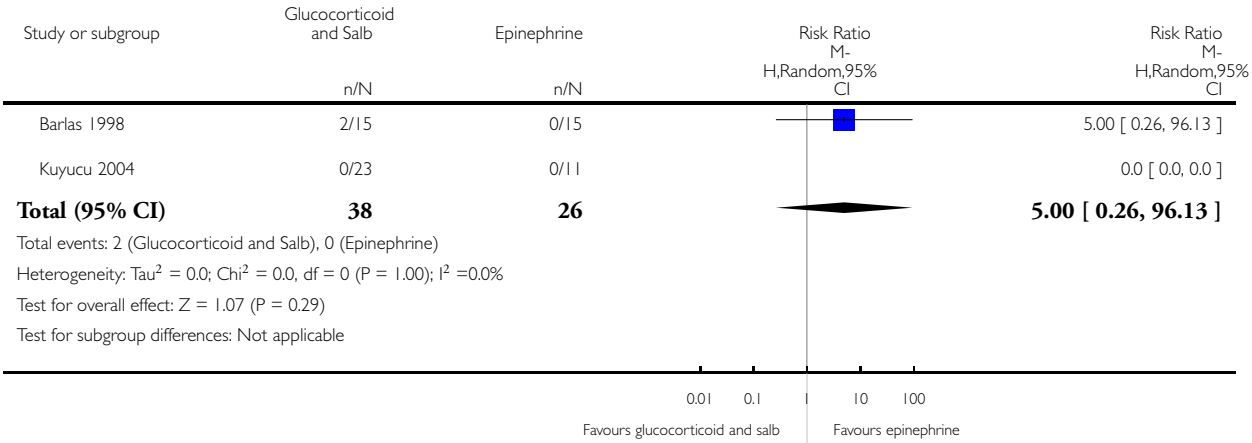


Analysis 7.1. Comparison 7 Glucocorticoid and salbutamol versus epinephrine, Outcome 1 Admissions (day 1) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 7 Glucocorticoid and salbutamol versus epinephrine

Outcome: 1 Admissions (day 1) (outpatients) - review primary outcome



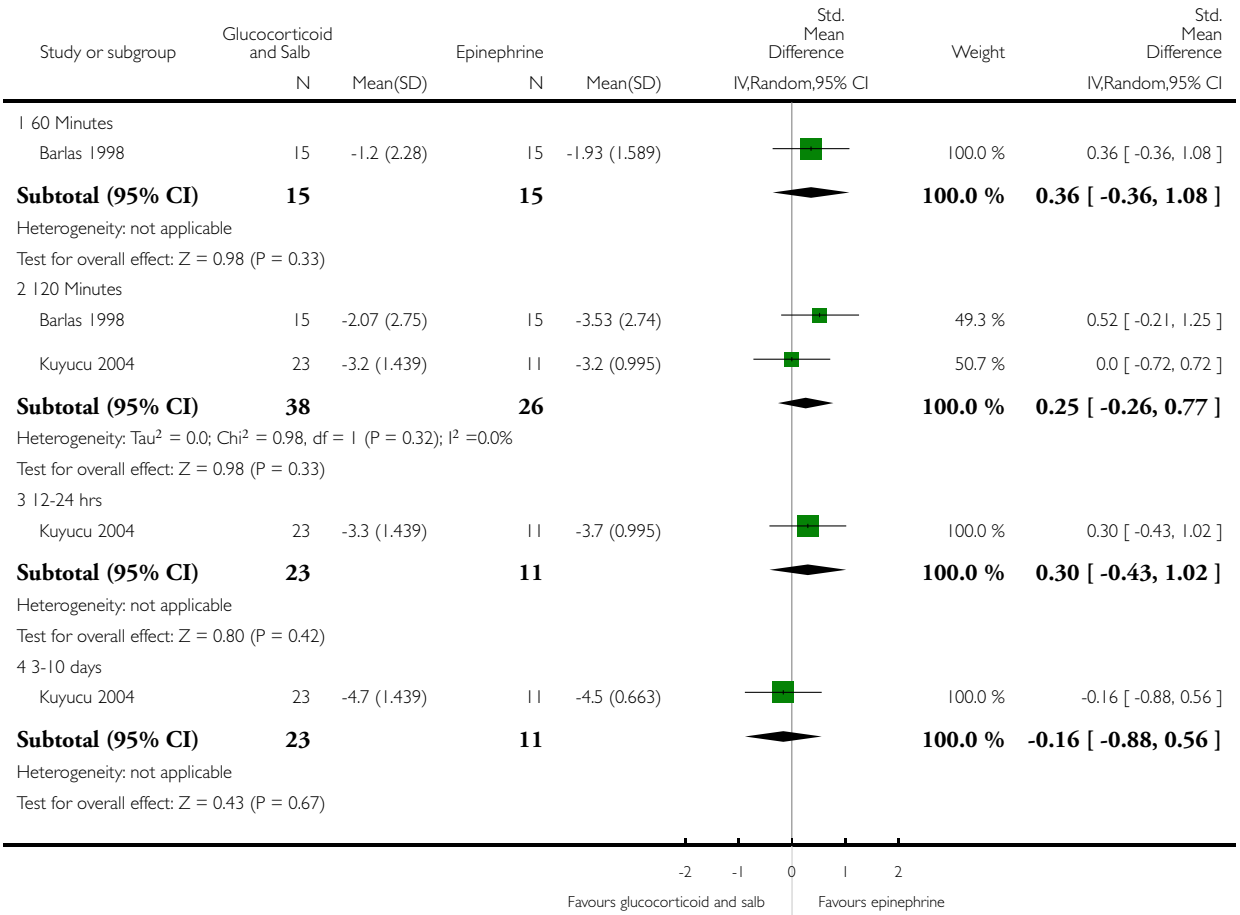
Analysis 7.2. Comparison 7 Glucocorticoid and salbutamol versus epinephrine, Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 7 Glucocorticoid and salbutamol versus epinephrine

Outcome: 2 Clinical scores (outpatients)

Study or subgroup	Glucocorticoid and Salb 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 1998	15	-1.2 (2.28)	15	-1.93 (1.589)		100.0 %	0.36 [-0.36, 1.08]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**0.36 [-0.36, 1.08]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.98 (P = 0.33)							
2 120 Minutes							
Barlas 1998	15	-2.07 (2.75)	15	-3.53 (2.74)		49.3 %	0.52 [-0.21, 1.25]
Kuyucu 2004	23	-3.2 (1.439)	11	-3.2 (0.995)		50.7 %	0.0 [-0.72, 0.72]
Subtotal (95% CI)	**38**		**26**			**100.0 %**	**0.25 [-0.26, 0.77]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.98, df = 1 (P = 0.32); I^2 =0.0%							
Test for overall effect: Z = 0.98 (P = 0.33)							
3 12-24 hrs							
Kuyucu 2004	23	-3.3 (1.439)	11	-3.7 (0.995)		100.0 %	0.30 [-0.43, 1.02]
Subtotal (95% CI)	**23**		**11**			**100.0 %**	**0.30 [-0.43, 1.02]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.80 (P = 0.42)							
4 3-10 days							
Kuyucu 2004	23	-4.7 (1.439)	11	-4.5 (0.663)		100.0 %	-0.16 [-0.88, 0.56]
Subtotal (95% CI)	**23**		**11**			**100.0 %**	**-0.16 [-0.88, 0.56]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.43 (P = 0.67)							



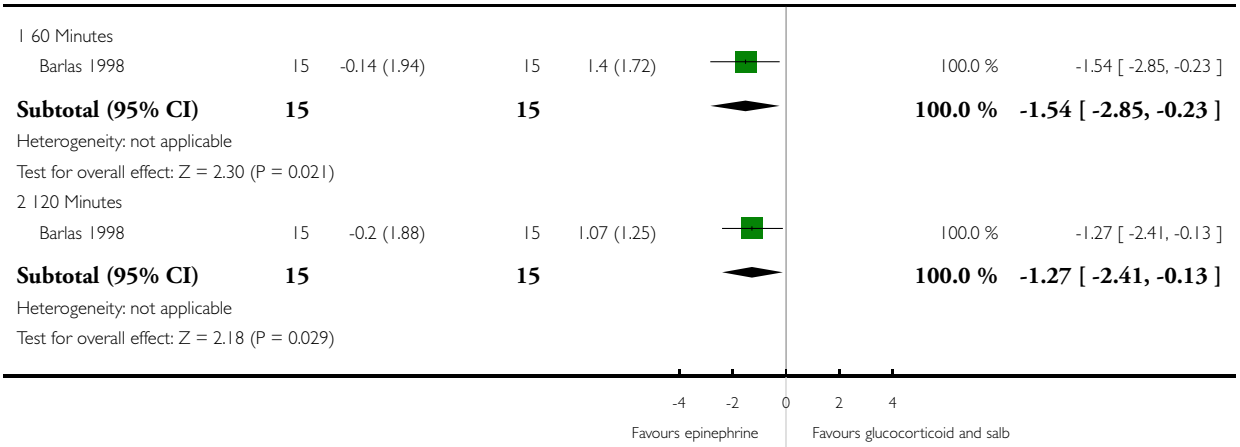
Analysis 7.3. Comparison 7 Glucocorticoid and salbutamol versus epinephrine, Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 7 Glucocorticoid and salbutamol versus epinephrine

Outcome: 3 O_2 saturation (outpatients)

Study or subgroup	Glucocorticoid and Salb N	Mean(SD)	Epinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 Minutes							
Barlas 1998	15	-0.14 (1.94)	15	1.4 (1.72)		100.0 %	-1.54 [-2.85, -0.23]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.54 [-2.85, -0.23]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.30 (P = 0.021)							
2 120 Minutes							
Barlas 1998	15	-0.2 (1.88)	15	1.07 (1.25)		100.0 %	-1.27 [-2.41, -0.13]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.27 [-2.41, -0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.18 (P = 0.029)							

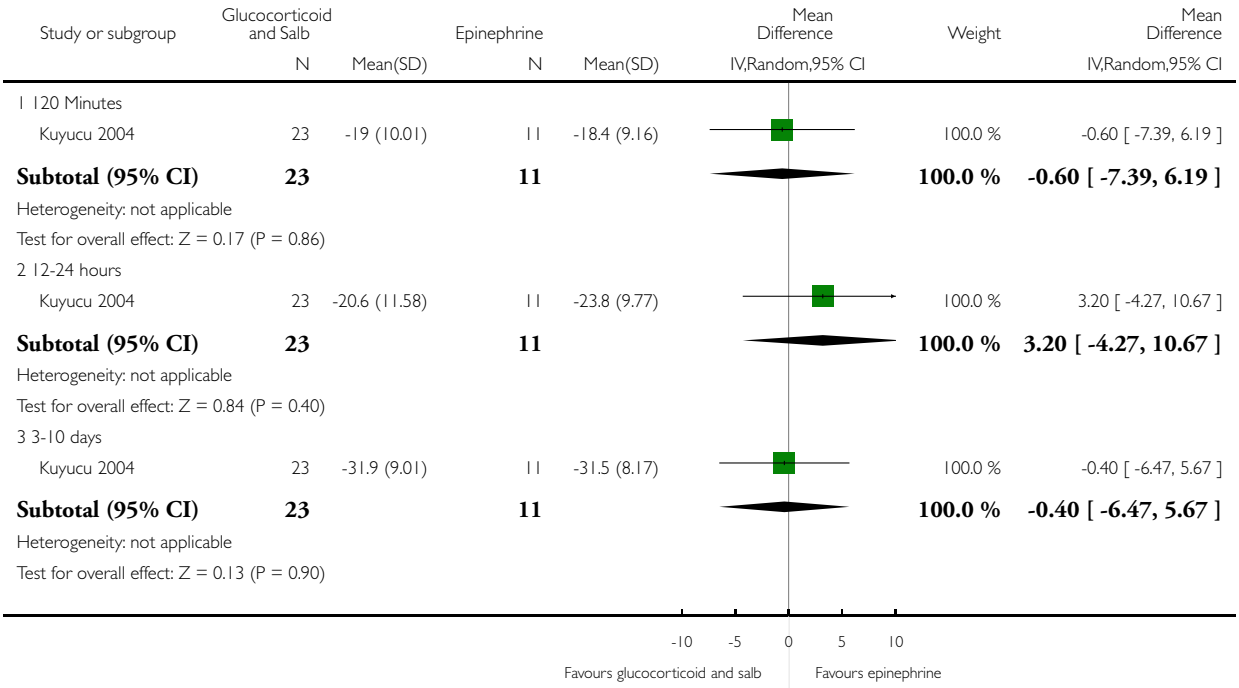


Analysis 7.4. Comparison 7 Glucocorticoid and salbutamol versus epinephrine, Outcome 4 Respiratory rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 7 Glucocorticoid and salbutamol versus epinephrine

Outcome: 4 Respiratory rate (outpatients)



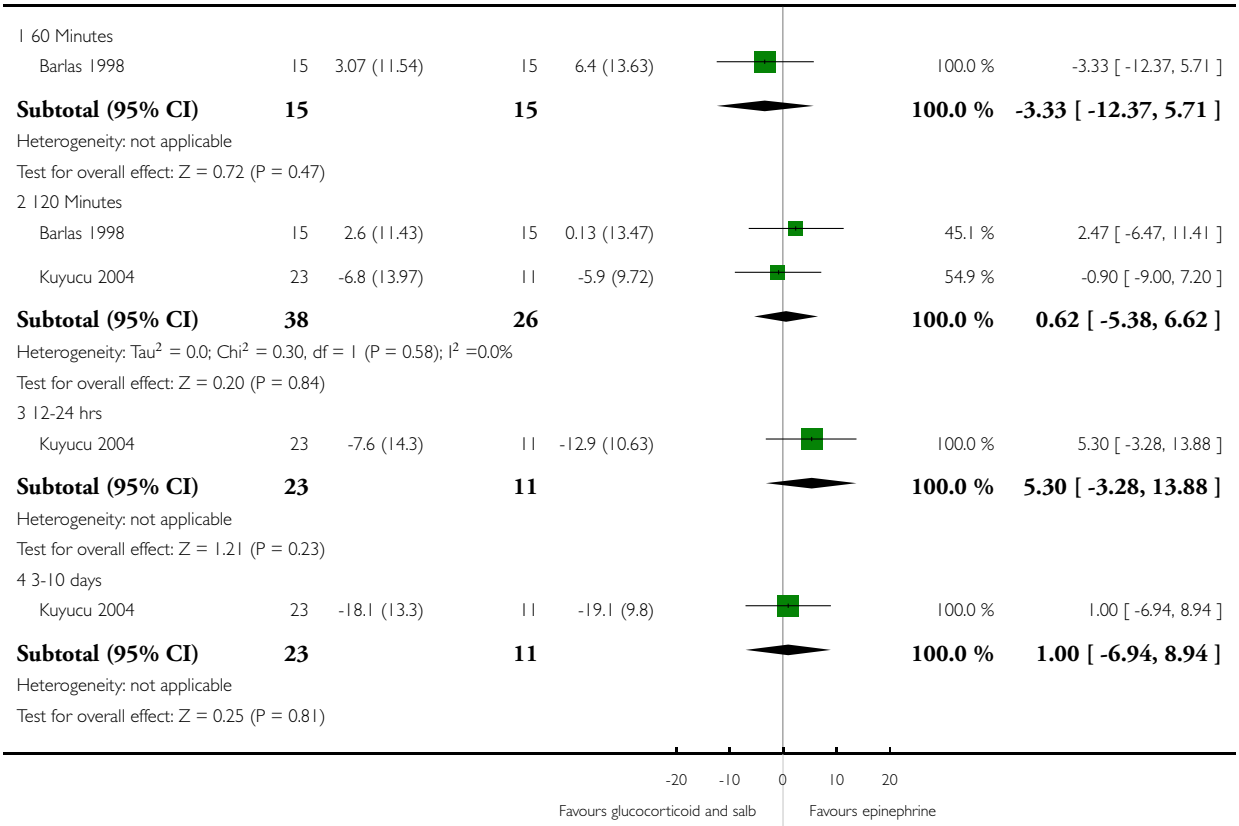
Analysis 7.5. Comparison 7 Glucocorticoid and salbutamol versus epinephrine, Outcome 5 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 7 Glucocorticoid and salbutamol versus epinephrine

Outcome: 5 Heart rate (outpatients)

Study or subgroup	Glucocorticoid and Salb N	Mean(SD)	Epinephrine N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 Minutes							
Barlas 1998	15	3.07 (11.54)	15	6.4 (13.63)		100.0 %	-3.33 [-12.37, 5.71]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-3.33 [-12.37, 5.71]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.72 (P = 0.47)							
2 120 Minutes							
Barlas 1998	15	2.6 (11.43)	15	0.13 (13.47)		45.1 %	2.47 [-6.47, 11.41]
Kuyucu 2004	23	-6.8 (13.97)	11	-5.9 (9.72)		54.9 %	-0.90 [-9.00, 7.20]
Subtotal (95% CI)	**38**		**26**			**100.0 %**	**0.62 [-5.38, 6.62]**
Heterogeneity: Tau^2 = 0.0; Chi^2 = 0.30, df = 1 (P = 0.58); I^2 =0.0%							
Test for overall effect: Z = 0.20 (P = 0.84)							
3 12-24 hrs							
Kuyucu 2004	23	-7.6 (14.3)	11	-12.9 (10.63)		100.0 %	5.30 [-3.28, 13.88]
Subtotal (95% CI)	**23**		**11**			**100.0 %**	**5.30 [-3.28, 13.88]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.21 (P = 0.23)							
4 3-10 days							
Kuyucu 2004	23	-18.1 (13.3)	11	-19.1 (9.8)		100.0 %	1.00 [-6.94, 8.94]
Subtotal (95% CI)	**23**		**11**			**100.0 %**	**1.00 [-6.94, 8.94]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.25 (P = 0.81)							

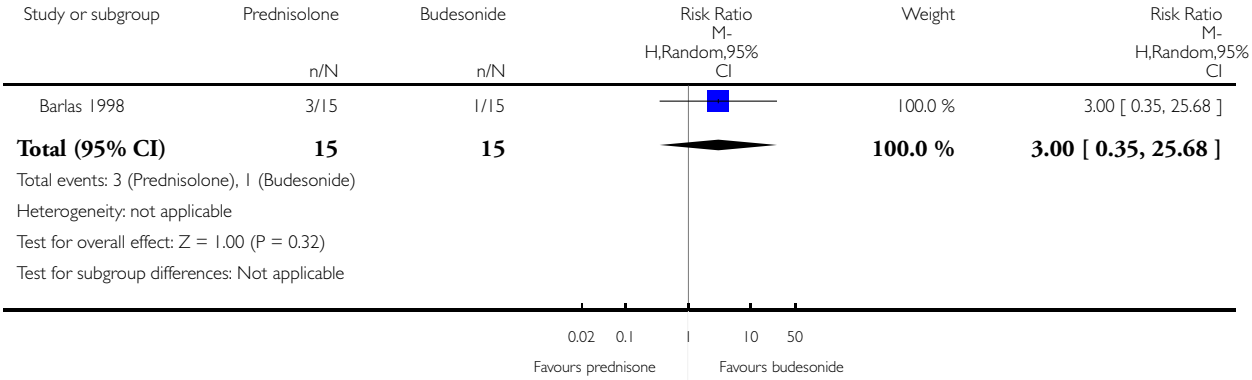


Analysis 8.1. Comparison 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide), Outcome 1 Admissions (day 1) (outpatients) - review primary outcome.

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide)

Outcome: 1 Admissions (day 1) (outpatients) - review primary outcome

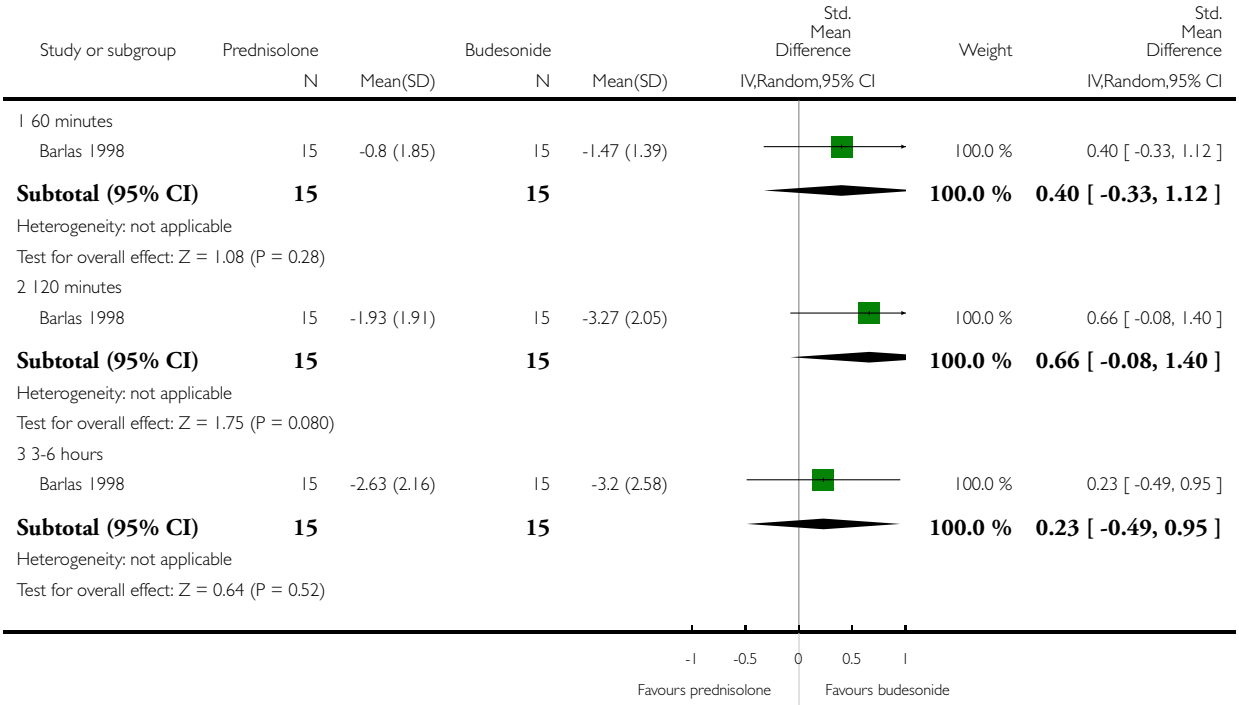


Analysis 8.2. Comparison 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide), Outcome 2 Clinical scores (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide)

Outcome: 2 Clinical scores (outpatients)



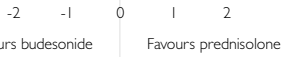
Analysis 8.3. Comparison 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide), Outcome 3 O_2 saturation (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide)

Outcome: 3 O_2 saturation (outpatients)

Study or subgroup	Prednisolone N	Mean(SD)	Budesonide N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 60 minutes							
Barlas 1998	15	0.14 (1.62)	15	1.6 (1.93)		100.0 %	-1.46 [-2.74, -0.18]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.46 [-2.74, -0.18]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.24 (P = 0.025)							
2 120 minutes							
Barlas 1998	15	0.14 (1.65)	15	1.87 (2.05)		100.0 %	-1.73 [-3.06, -0.40]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.73 [-3.06, -0.40]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.55 (P = 0.011)							
3 3-6 hours							
Barlas 1998	15	0.21 (1.59)	15	1.38 (1.75)		100.0 %	-1.17 [-2.37, 0.03]
Subtotal (95% CI)	**15**		**15**			**100.0 %**	**-1.17 [-2.37, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.92 (P = 0.055)							

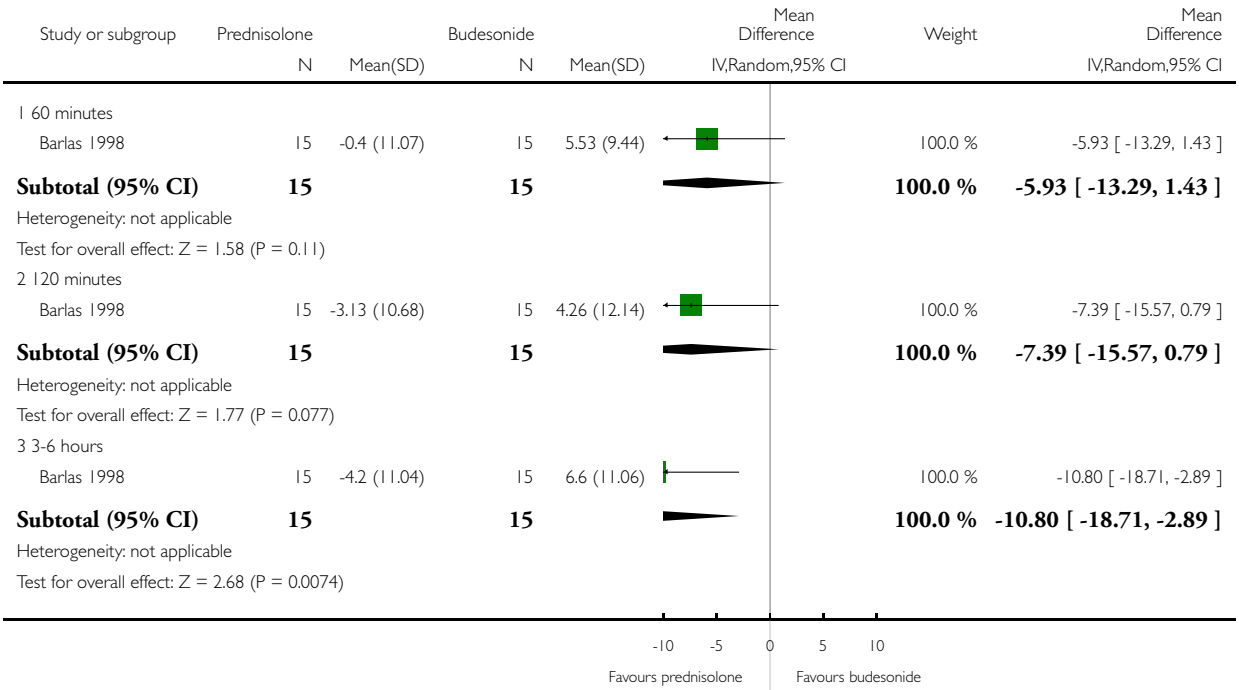


Analysis 8.4. Comparison 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide), Outcome 4 Heart rate (outpatients).

Review: Glucocorticoids for acute viral bronchiolitis in infants and young children

Comparison: 8 Glucocorticoid versus glucocorticoid (prednisolone versus budesonide)

Outcome: 4 Heart rate (outpatients)



ADDITIONAL TABLES

Table 1. Placebo group risk of admission/length of stay

Study	Number of Participants (placebo group)	Placebo group		
		Risk of admission day 1 (%)	Risk of admission day 7 (%)	Length of stay (mean ± SD days)
OUTPATIENT STUDIES (RISK OF ADMISSION)				
Barlas 1998	30	17%	NR	NA
Berger 1998	18	11%	NR	NA

Table 1. Placebo group risk of admission/length of stay (*Continued*)

Corneli 2007	295	41%	49%	NA
Goebel 2000	24	8%	21%	NA
Kuyucu 2004	11	0%	0%	NA
Mesquita 2009	32	22%	NR	NA
Plint 2009	201	18%	26%	NA
Schuh 2002	34	44%	47%	NA
INPATIENT STUDIES (LENGTH OF STAY)				
Bentur 2005	32	NA	NA	6.3 ± 8.8
Cade 2000	79	NA	NA	2 ± 2.2
De Boeck 1997	15	NA	NA	6.6 ± 1.2
Gomez 2007	25	NA	NA	0.8 ± 0.2
Klassen 1997	32	NA	NA	2 ± 0.7
Richter 1998	19	NA	NA	3 ± 1.6
Teeratakulpisarn 2007	85	NA	NA	2.8 ± 1.7
Zhang 2003	24	NA	NA	5 ± 3.3

Table 2. Harms - adverse events

Adverse Event		Number of Participants	Study	Glucocorticoid-including Group	Placebo or Comparator Group	Notes
GLUCOCORTICOID versus PLACEBO, GLUCOCORTICOID versus EPINEPHRINE, GLUCOCORTICOID AND EPINEPHRINE versus PLACEBO						
Gastrointestinal	Vomiting	1466	Plint 2009*	D+E: 2/199 (1) D+P: 5/199 (2.5) P+E: 4/198 (2) P+P: 3/201 (1.5)		Observed in the emergency department by research nurse
			Kuyucu 2004*	No events in either group (D+E, D+S, P+E, P+S)		Methods/ timings NR

Table 2. Harms - adverse events (*Continued*)

			Corneli 2007	16/305 (5.2)	14/295 (4.7)	Within 20 minutes after administration of the study medication
	Bleeding	1576	Corneli 2007	No events in either group		#
			Teeratakulpisarn 2007	2/90 (2)	1/89 (1)	Occult blood; also assessed diarrhea separately. Methods/timings NR
			Plint 2009	D+E: 17/199 (8.5) D+P: 12/199 (6) P+E: 14/198 (7) P+P: 16/201 (8)		Dark stools; reported by families during the 22 day telephone follow-up. No patient had more than one episode
Endocrine	Hypertension	1397	Plint 2009	D+E: 0/199 (0) D+P: 1/199 (0.5) P+E: 1/198 (0.5) P+P: 0/201 (0)		Observed in infants admitted to hospital.
			Corneli, 2007	No events in either group		#
Infectious	Pneumonia	851	Corneli, 2007	1/305 (3.3)	2/295 (7)	Also assessed empyema separately.
			Teeratakulpisarn, 2007	0/90 (0)	3/89 (3.4)	Methods/timings NR
			Klassen, 1997	1/35 (3)	1/37 (3)	Methods/timings NR
	Varicella	1397	Corneli, 2007	No events in either group		#
			Plint 2009	No events in either group (D+E, D+P, P+E, P+P)		Observed in infants admitted to hospital.
General	Tremor	866	Kuyucu, 2004	No events in either group (D+E, D+S, P+E, P+S)		Methods/timings NR

Table 2. Harms - adverse events (*Continued*)

			Plint 2009	D+E: 4/199 (2) D+P: 5/199 (2.5) P+E: 4/198 (2) P+P: 2/201 (1)	Observed in the emergency department by research nurse
	Pallor/flushing	866	Kuyucu 2004	No events in either group (D+E, D+S, P+E, P+S)	Methods/ timings NR
			Plint 2009	D+E: 23/199 (11.5) D+P: 15/199 (7.5) P+E: 22/198 (11.1) P+P: 16/201 (8)	Observed in the emergency department by research nurse

Additional reported adverse events: Goebel 2000 reported toxicity data: one patient was "jittery"; no evidence of further treatment complications. Plint 2009 also reported hyperkalaemia observed in infants admitted to hospital (only one case was noted in the dexamethasone group).

*epinephrine - E; dexamethasone - D; salbutamol - S; placebo - P

#Corneli 2007: Study clinicians and research assistants monitored the infants for adverse events during observation in the emergency department. Subsequent adverse events were determined at follow-up. A patient safety committee, made up of people not involved with patient enrolment, tracked all adverse events.

Table 3. GRADE assessments: glucocorticoid versus placebo

Population	Outcome	Number of studies	Number of Participants	GRADE domains				Strength of evidence	Intervention favoured
				Risk of bias	Consistency	Directness	Precision		
GLUCOCORTICOID versus PLACEBO									
Inpatients	Length of stay	8	633	medium	consistent	direct	Precise	high	no difference
	Clinical score : 3-6 hours	1	26	medium	unknown	direct	Imprecise	low	glucocorticoid
	Clinical score : 6-12 hours	3	175	medium	consistent	direct	Imprecise	moderate	glucocorticoid
	Clinical score : 12-24 hours	3	230	medium	consistent	direct	Imprecise	moderate	no difference (glucocorticoid favoured)

Table 3. GRADE assessments: glucocorticoid versus placebo (*Continued*)

	Clinical score : 24-72 hours	4	113	medium	inconsistent	direct	Imprecise	low	no difference (glucocorticoid favoured; very close to significant)
Outpatients	Admissions day 1	8	1762	medium	consistent	direct	Precise	high	no difference
	Admissions up to day 7	5	1530	low	consistent	direct	Imprecise	moderate	no difference
	Clinical score: 60 minutes	4	1006	low	consistent	direct	Precise	high	no difference
	Clinical score: 120 minutes	3	214	medium	consistent	direct	Imprecise	moderate	no difference
	Clinical score: 3-6 hours	2	808	medium	inconsistent	direct	Precise	moderate	no difference
	Clinical score: 12-24 hours	1	69	medium	unknown	direct	Imprecise	low	no difference
	Clinical score: 3-10 days	4	224	medium	inconsistent	direct	Imprecise	low	no difference
Inpatients/ Outpatients	Adverse events	5	1123	low	consistent	direct	Precise	moderate	no difference

Table 4. GRADE assessments: glucocorticoid and epinephrine versus placebo

Population	Outcome	Number of studies	Number of Participants	GRADE domains				Strength of evidence	Intervention favoured
				Risk of bias	Consistency	Directness	Precision		

Table 4. GRADE assessments: glucocorticoid and epinephrine versus placebo (*Continued*)

GLUCOCORTICOID AND EPINEPHRINE versus PLACEBO									
Outpatients	Admissions day 1	1	400	low	unknown	direct	imprecise	low	favours epi+dex but NS
	Admissions day 7	1	400	low	unknown	direct	imprecise	low	epi+dex
	Clinical score: 60 minutes	1	400	low	unknown	direct	precise	moderate	epi+dex
	Adverse events	1	400	low	unknown	direct	imprecise	low	no difference

Table 5. Hospital re-admissions and return healthcare visits (in- and outpatients)

Study	Population	Duration of follow-up	Glucocorticoid-including Group	Placebo or Comparator Group	Notes
GLUCOCORTICOID AND EPINEPHRINE versus PLACEBO: HOSPITAL RE-ADMISSIONS					
Roosevelt 1996	Inpatients	Days 1-14	0	0	(no events in either group)
Klassen 1997	Inpatients	Days 1-7	4/35 (11%)	1/32 (3%)	P = 0.36
Teeratakulpisarn 2007	Inpatients	Days 1-30	3/89 (3%)	7/85 (8%)	
GLUCOCORTICOID versus PLACEBO: RETURN HEALTHCARE VISITS*					
Plint 2009 (epinephrine - E; dexamethasone - D; placebo - P)	Outpatients	Days 1-22	D+E 95/199(48%)	P+E 93/198 (47%)	Return to the health care provider for bronchiolitis symptoms Difference between dexamethasone+placebo versus placebo+placebo, was significant in the unadjusted analysis (P = 0.04)
			D+P 106/199 (53%)	P+P 86/201 (43%)	
Schuh 2002	Outpatients	Days 7-28	9/35 (26%)	14/32 (44%)	Medical visits for continuing symptoms; P = 0.069

Table 5. Hospital re-admissions and return healthcare visits (in- and outpatients) (*Continued*)

Klassen 1997	Inpatients	Days 1-7	29/35 (83%)	24/32 (75%)	P = 0.77
Roosevelt 1996	Inpatients	Days 1-14	16/65 (25%)	5/53 (9%)	P = 0.01; reported on visits made by the physician; 69% were for non-respiratory difficulties
Teeratakulpisarn 2007	Inpatients	Days 1-30	17/89 (19%)	26/85 (31%)	Visit to emergency room or a private clinic because of respiratory symptoms
GLUCOCORTICOID versus EPINEPHRINE: RETURN HEALTHCARE VISITS					
Plint 2009 (dexamethasone+placebo versus epinephrine+placebo)	Outpatients	Days 1-22	106/199 (53%)	93/198 (47%)	
GLUCOCORTICOID AND EPINEPHRINE versus PLACEBO: RETURN HEALTHCARE VISITS					
Plint 2009 (dexamethasone+epinephrine versus placebo+placebo)	Outpatients	Days 1-22	95/198 (48%)	86/201 (43%)	

*Berger 1998: no difference between groups, but did not report quantitative data.
Data presented as n/N (%)

Table 6. Symptoms and quality of life (in- and outpatients)*

Study	Population	Duration of follow-up	Parameter	Glucocorticoid-including Group	Placebo or Comparator Group	Notes
GLUCOCORTICOID versus PLACEBO						
Teeratakulpisarn 2007	Inpatients	Days 1-30	Time from treatment to being symptom free - mean±SD	7.0±5.9	9.0±6.4	P = 0.035
Cade 2000	Inpatients	Days 1-28	Time taken for half of infants to become asymptomatic for	10 (10-13)	12 (10-16)	HR 1.41 (95% CI 0.98 to 2.04), P = 0.07

Table 6. Symptoms and quality of life (in- and outpatients)* (*Continued*)

			48 hours (95% CI) - time to event analysis			
			Days with coughing or wheezing episodes - mean±SD	17.0±7.6 days	17.1±8.5	Mean difference: 0.91 days (95% CI -2.72 to 2.41) , P = 0.91
Roosevelt 1996#	Inpatients	Day 10-14	No current difficulty breathing - n/N (%)	45/45 (100)	37/42 (88)	P = 0.07
			Feeding and drinking well - n/N (%)	45/45 (100)	40/42 (95)	P = 0.57
GLUCOCORTICOID versus PLACEBO, GLUCOCORTICOID versus EPINEPHRINE, GLUCOCORTICOID AND EPINEPHRINE versus PLACEBO						
Plint 2009 (epinephrine - E; dexamethasone - D; placebo - P)	Outpatients	Days 1-22	Time to return to normal feeding - median (IQR)	D+E: 0.6 (0.2 - 1.3) D+P: 0.8 (0.3 - 1.9) P+E: 0.5 (0.2 - 1.2) P+P: 0.9 (0.3 - 2.1)		Time to return to normal feeding - mean symptom duration ratio D+ E versus P+P: 0.63 (unadjusted 95% CI 0. 5-0.8).¶ Time to return to quiet breathing - mean symptom duration ratio D+ E versus P+P: 0.83 (unadjusted 95% CI 0. 69-1.00) No other reported comparison was statistically significant in adjusted analysis
			Time to return to normal sleeping - median (IQR)	D+E: 0.7 (0.2 - 1.7) D+P: 0.8 (0.3 - 1.9) P+E: 0.8 (0.3 - 1.9) P+P: 0.8 (0.3 - 1.8)		
			Time to no coughing - median (IQR)	D+E: 12.6 (7.8 - 18.5) D+P: 13.8 (8.5 - 20.2) P+E: 13.2 (8.1 - 19.3) P+P: 13.3 (8.2 - 19.5)		
			Time to quiet breathing - median (IQR)	D+E: 3.1 (1.4 - 6.1) D+P: 3.7 (1.6 - 7.1) P+E: 3.6 (1.5 - 6.9) P+P: 3.7 (1.6 - 7.2)		

*Units in days unless otherwise stated; no study assessed or reported data from generic or disease-specific quality of life instruments; Richter 1998 also reported number of symptom-free days for a 6 week follow-up period

#Roosevelt 1996 primary outcome was time to resolution (defined as number of 12h periods needed to achieve: O_2 saturation > 95% at room air, accessory muscle score = 0, wheeze = 0 or 1, and normal feeding); only association measures were reported: HR 1.3 (95% CI 0.9 to 1.3), P = 0.22

¶time to symptom relief was analysed by means of parametric survival models with Weibull distributions assumed; 95% CI adjusted for multiple analysis in a factorial trial

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 Corticoglucocorticoid*).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 corticoglucocorticoid/
9. (glucocorticoid* or corticoglucocorticoid*).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 Corticoglucocorticoid*).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. randomised 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. Scopus - Elsevier B.V.

(((TITLE(bronchiolitis OR wheez*) AND TITLE-ABS-KEY(glucocorticoid* OR glucocorticoid* OR corticoglucocorticoid*))) AND KEY("epinephrine" OR "adrenaline" OR "albuterol" OR "corticoglucocorticoids" OR "hydrocortisone" OR "glucocorticoids" OR ("inhaled glucocorticoids") OR "salbutamol" OR "betamethasone" OR "beclomethasone" OR "dexamethasone" OR "glucocorticoid" OR ("inhaled budesonide") OR "glucocorticoids" OR "bronchodilator" OR ("glucocorticoid 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 "Randomised 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(glucocorticoid* OR glucocorticoid*OR corticoglucocorticoid*))) AND KEY("epinephrine" OR "albuterol" OR "corticoglucocorticoids" OR "hydrocortisone" OR "glucocorticoids" OR ("inhaled glucocorticoids") OR "salbutamol" OR "dexamethasone" OR "glucocorticoid" OR ("inhaled budesonide") OR "glucocorticoids"OR "bronchodilator"OR ("glucocorticoid use") OR "prednisolone" OR ("oral prednisolone") OR "prednisone")) AND (TITLE-ABS-KEY("Clinical Trial" OR "Clinical Trials" OR "Randomised 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))

WHAT'S NEW

Last assessed as up-to-date: 24 November 2009.

Date	Event	Description
16 September 2010	Amended	Corrected references and text in Results - Effects of interventions - Glucocorticoid and bronchodilator (epinephrine or salbutamol) versus placebo

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2004

Date	Event	Description
1 May 2010	New citation required and conclusions have changed	A new team of authors have updated this previously withdrawn review. Current evidence suggests combined glucocorticoids and epinephrine may be effective in reducing outpatient admissions in this patient group
25 November 2009	New search has been performed	Searches conducted. Eleven new trials (Barlas 1998; Bentur 2005; Cade 2000; Corneli 2007; Gomez 2007; Kuyucu 2004; Mesquita 2009; Plint 2009; Richter 1998; Teeratakulpisarn 2007; Zhang 2003) have been included and 61 new trials have been excluded in this update
9 January 2008	Amended	Converted to new review format.
4 January 2007	Feedback has been incorporated	Feedback added.
26 May 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Ricardo M Fernandes (RF): guarantor of the review, involved at all phases. Contribution: review update design and implementation, search strategy, screening of search results, data extraction and entry, risk of bias and GRADE assessments, data analysis, interpretation of results, manuscript writing and revision.

Liza M Bialy (LB): screening results, data extraction and entry, risk of bias assessments, manuscript writing and revision.

Ben Vandermeer (BV): review update design, data entry and analysis, manuscript revision.

Lisa Tjosvold (LT): search strategy and implementation, article retrieval, manuscript revision.

Amy C Plint (AC): review update, screening of search results, interpretation of results, manuscript revision.

Hema Patel (HP): protocol design, screening of search results, interpretation of results, manuscript revision. Responsible for the previous Cochrane review (2004).

David W Johnson (DJ): review update, screening of search results, interpretation of results, manuscript revision.

Terry P Klassen (TK): review update, interpretation of results, manuscript revision.

Lisa Hartling (LH): review update and implementation, screening of search results, risk of bias and GRADE assessments, interpretation of results, manuscript writing and revision.

DECLARATIONS OF INTEREST

AC, HP, DJ and TK are authors of one or more RCTs included in this review. Assessment of eligibility, risk of bias and strength of evidence of these trials were performed by other review authors. The review authors declare no other real or perceived conflicts of interest.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The Protocol limited the selection to studies testing systemic glucocorticoids only; we later decided to also include studies with inhaled glucocorticoids. Not all planned subgroup analyses were performed due to the reduced number of trials and data heterogeneity. There were no other differences between the withdrawn review and this update.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Ambulatory Care; Bronchiolitis, Viral [*drug therapy]; Glucocorticoids [*therapeutic use]; Hospitalization; Infant, Newborn; Randomized Controlled Trials as Topic; Respiratory Sounds [etiology]

MeSH check words

Humans; Infant