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Safety of Corticosteroids in Young Children with Acute Respiratory Conditions: A Systematic Review and Meta-Analysis

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ABSTRACT (300 words)

Objective: To systematically review adverse events (AEs) with short-term corticosteroid use for respiratory conditions in young children.

Design: Systematic review of primary studies. Literature searches were conducted in Medline, Cochrane CENTRAL, Embase, and regulatory agencies. Study selection and methodological quality (McHarm scale) involved duplicate independent reviews. One reviewer extracted with another reviewer verifying data. Meta-analyses used Peto odds ratios (pOR) and Mantel-Haenszel risk differences (random effects model), with 95% confidence intervals (CI). Subgroup analyses were conducted for respiratory condition and dose.

Eligibility criteria and outcome measure(s): Children <6 years with an acute respiratory condition, given inhaled (high-dose) or systemic corticosteroids up to 14 days, were eligible. We extracted AEs as reported by study authors and used a categorization model by organ systems.

Results: Eighty-five studies (11,505 children) were included; most were randomized trials (n=68). Methodological quality was poor overall due to lack of assessment and inadequate reporting of AEs. Meta-analysis of six studies (1,373 children) found fewer cases of vomiting comparing oral dexamethasone with prednisone (pOR 0.29, 95% CI 0.17 to 0.48; I²=0%). The mean difference in change-from-baseline height after one year between inhaled corticosteroid and placebo was 0.10 cm (two studies, n=268; 95% CI -0.47, 0.67). Results from five studies with heterogeneous interventions, comparators, and measurements, were not pooled; one study found a smaller mean change in height *z*-score with recurrent high-dose inhaled fluticasone over one year. No statistically significant differences were found comparing systemic or inhaled corticosteroid with placebo, or between corticosteroids, for other AEs; CIs around estimates were often wide, due to small samples and few events.

Conclusions: Evidence suggests that short-term high-dose inhaled or systemic corticosteroids use is not associated with an increase in AEs across organ systems. Uncertainties remain, particularly for recurrent use and growth outcomes, due to low study quality, poor reporting and imprecision.

Strengths and limitations of this study:

- Examined safety outcomes associated with short-term corticosteroid use across multiple common acute respiratory conditions in young children
- Broad range of adverse events captured across organ systems
- Inconsistent definitions, assessments and reporting of adverse events
- Extensive variation in corticosteroid formulations and dosages within and between studies
- Did not examine long-term corticosteroid use (more than 14 days)

INTRODUCTION

Corticosteroids are the cornerstone of treatment for many common pediatric respiratory conditions including croup and asthma.¹⁻³ These conditions often result in presentation to urgent and emergency care settings, in otherwise healthy children. Previous studies examining corticosteroid use in chronic asthma have demonstrated the potential for short- and long-term adverse events, particularly growth inhibition, bone disease, and adrenal suppression.⁴⁻⁶ While corticosteroids have demonstrated effectiveness for the acute treatment of many respiratory indications, clinicians are faced with considerable uncertainty regarding short-term safety, particularly among the youngest children.¹

Previous systematic reviews have examined corticosteroids in preschool or school-aged asthma or wheezing;^{4, 7, 8} however, most focused on efficacy and were restricted to randomized controlled trials (RCTs). These reviews also focused on a specific underlying condition, disease severity, or particular corticosteroid, and mostly for longer-term administration (e.g., for recurrent, persistent or chronic asthma). Current guidance on systematic assessment of harms highlights the need to include data from observational studies when considering safety outcomes.⁹ As well, it has been suggested that it may be useful to have a wider view of the evidence across a number of similar indications.¹⁰ Recent knowledge synthesis approaches have studied specific safety outcomes across conditions to increase power, with the assumption that some safety outcomes are not confounded by condition.¹⁰ Such a comprehensive approach to knowledge synthesis in this area is critical to inform treatment decisions, reduce practice variation, and optimize management of young children who seek care due to acute respiratory illness.

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The goal of this study was to synthesize evidence regarding the safety of short course corticosteroid use in young children (less than six years) with acute respiratory conditions.

METHODS

This review followed internationally recommended methods and standards for systematic reviews.¹¹⁻¹³ An *a priori* protocol was developed (available from authors).

Literature search

Original database searches were conducted September 2014 in Ovid Medline, the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library, and Ovid Embase. Additional sources included regulatory agency databases: Drugs@FDA, Health Canada's Drug Products Database, and the European Medicines Agency's European Public Assessment Reports. Search strategies combined index terms and keywords for respiratory illnesses, children and drug classes identified in the Global Initiative for Asthma (GINA)¹⁴ guidelines. Study design filters were applied to limit results to RCTs and observational studies. Update searches were executed in Medline and CENTRAL in February 2016, and then again in July 2017. Detailed search strategies are in Supplement 1.

Eligibility criteria

We included primary studies involving children up to six years old treated with single or recurrent systemic (any dose) or high-dose inhaled (as defined by the GINA guidelines¹⁴) corticosteroids for up to 14 days for an acute respiratory condition in an inpatient or outpatient setting. See Supplement 2 for detailed eligibility criteria.

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Given the lack of standardized terminology for safety, we gathered information on all potentially drug-related harm outcomes¹⁵ from studies including, but not limited to: adverse drug reactions, adverse drug events, medication errors, side effects and potential adverse drug events. For consistency these outcomes are referred to in the manuscript as adverse events (AEs). Studies that did not report or mention AEs were excluded. Due to resource constraints and mean age of the studies, no attempt was made to contact study authors if no harms were reported in the text, or when there was potentially missing data; such efforts are unlikely to yield additional data.

Study selection

Two reviewers independently screened the titles and abstracts of all records using *a priori* selection criteria. Full texts of potentially eligible studies were reviewed by two reviewers independently using a standard form. Disagreements were resolved through consensus or consultation with a third reviewer.

Data extraction

One reviewer extracted data using a structured form, with verification by a second reviewer. Data were extracted on study characteristics (design features), patient characteristics (age, sex, baseline characteristics), respiratory conditions, interventions (type, dose, duration, route of administration, timing, co-interventions, rescue medications), outcomes (types and timing), care setting, funding sources, and results.

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AEs were extracted as reported by study authors and categorized using a published model based on organ systems (see Results).¹⁶ A panel of clinicians with specialties in pediatrics, emergency medicine, respiratory medicine and clinical pharmacology rated each AE in order of clinical severity independent of knowledge of the study results.

Assessment of methodological quality

Two reviewers independently assessed the methodological quality of studies using the McMaster Quality Assessment Scale for Harms (McHarm)¹⁷; disagreements were resolved through discussion.

Data synthesis

A comparative summary of AEs for studies with more than one treatment arm was presented to provide an overall picture of which interventions had a high risk of specific AEs. Data for AEs were pooled using a Peto odds ratio (pOR) and a risk difference (RD) using a Mantel-Haenszel random effects model, with 95% confidence intervals (CI). Studies that reported at least one event in at least one treatment arm were included in the analysis of pORs and all comparative studies were used for analysis of RD. One AE (growth) was reported as a continuous outcome and data were pooled using a mean difference (MD; in cm). The I² statistic was presented to quantify the magnitude of statistical heterogeneity between studies.¹⁸ Subgroup analyses from study-level data were conducted for respiratory condition and dose (single versus multi-dose) using Cochran's Q (α =0.05) to detect statistical heterogeneity. Studies contributing no numerical data for analysis (e.g., single arm studies, studies that reported no AEs overall) are summarized in Supplement 3. Assessment of small-study bias (for meta-analyses with at least eight studies)

was planned using the funnel plot and Egger's test;¹⁹ however, this was not conducted due to inadequate number of studies for each outcome. Analyses were conducted using Review Manager Version 5.3 (Cochrane Collaboration).²⁰ Graphs were constructed using TIBCO Spotfire S+ Workbench, Version 3.4.²¹

RESULTS

Database and grey literature searches yielded 9,134 records. Eighty-six papers (85 studies)²²⁻¹⁰⁷ involving 11,505 participants were included (Figure 1). Characteristics of the included studies are in Supplement 3. There was large variation in corticosteroid type, dose, duration and route of administration, both for systemic and inhaled corticosteroids. Methodological quality of studies was poor overall due to inadequate reporting of how AEs were defined and collected ere. (Supplement 4).

Adverse events

Results below are presented according to the categories in Table 1. Figures 2, 3 and 4 display forest plots of AEs comparing systemic corticosteroid to placebo, inhaled corticosteroid to placebo, and systemic dexamethasone to another systemic corticosteroid, respectively. Results of meta-analyses and subgroup analyses are in Supplement 5, with effect estimates and 95% CIs. There was large variation in the number of studies and number of patients with available data for meta-analysis across comparisons and outcomes. Further, for four safety outcomes there were no events in both study arms (double-zero) across studies. In most cases the subgroup analyses by dose and condition did not differ substantially from the overall results. Studies reporting no AEs overall are summarized in Supplement 6.

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Infections & Respiratory System

The number of studies contributing to each meta-analysis ranged from one to seven (range 58 to 2,178 children). There were no statistically significant differences between: a) *systemic corticosteroid compared to placebo* for severe infections,^{29, 73, 95, 98} systemic infections,^{29, 39, 42, 82} infections of the lung/trachea,^{29, 39, 53, 73, 95, 97, 104} and the upper respiratory tract,^{29, 42, 53, 64, 66, 73} and voice complaints⁴² (estimated pORs between 0.15 and 1.26) and b) *inhaled corticosteroid compared to placebo* for severe infections,⁴⁴ systemic infections,^{42, 44} lung/trachea,⁴⁴ infections of the upper respiratory tract ^{36, 42, 44, 64-66} or voice complaints^{36, 42, 99, 100} (estimated pORs between 0.54 and 1.51). No study comparing *dexamethasone with another corticosteroid* reported infections or respiratory AEs.

Gastro-Intestinal Tract (GI)

The number of studies contributing to each meta-analysis ranged from one to seven (range 97 to 3,176 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for GI bleeding,^{29, 31, 39, 64, 82, 86, 104} vomiting,^{29, 37, 39, 41, 69, 80, 82} abdominal pain,²⁹ or diarrhea;^{41, 76, 104} and b) *inhaled corticosteroid and placebo* for GI bleeding,⁶⁴ vomiting,^{36, 44, 68, 84, 100} or diarrhea.^{36, 44} Estimated pORs for both comparisons ranged from 0.89 to 1.10.

Meta-analysis of six studies $(1,373 \text{ children})^{24, 26, 40, 48, 51, 79}$ found fewer cases of vomiting in patients who received *dexamethasone compared with another corticosteroid*, although the number of events was small (12/663 versus 51/710 cases; pOR 0.29, 95% CI 0.17, 0.48; I²=0%). These studies focused on asthma (n=3),^{26, 40, 79} croup (n=2),^{48, 51} or both (n=1);²⁴ all compared

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oral dexamethasone with oral prednisone. No statistically significant difference was found for abdominal pain between *dexamethasone and another corticosteroid*.^{24, 26, 51}

CNS & Behaviour Effects

The number of studies for each meta-analysis ranged from one to five (range 70 to 1,159 children). The estimated pORs for the *systemic corticosteroid and placebo* were 1.44 for tremor/jitteriness,^{37, 54, 69, 76, 82} 1.95 for behaviour change,^{29, 41, 66, 76} and 0.11 for headache,³⁷ with no statistically significant differences. There were also no differences between *inhaled corticosteroid and placebo* for behaviour change;^{66, 84, 100} and *dexamethasone and another corticosteroid* for behaviour change,^{51, 56} headache,^{26, 51} or tremor/jitteriness,⁵¹ the latter with an estimated pOR of 6.63 from a small study (n=87) with only one reported event.

Dermatologic Conditions

The number of studies per meta-analysis ranged from one to four (range 32 to 1,079 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for rash and hives,^{29, 41, 66} albeit with an estimated pOR of 7.59 (4/536 versus 0/543; 95% CI 1.07, 54.01); and b) *inhaled corticosteroid and placebo* for rash,^{36, 44, 84} hives⁶⁶ and burning sensation⁶⁷ (estimated pORs 0.88 and 0.14, respectively). No events of phlebitis were reported comparing *dexamethasone to another corticosteroid*.⁵⁶

Endocrine/metabolic & Musculoskeletal Systems

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There were no statistically significant differences for electrolyte abnormalities between *systemic corticosteroid and placebo* (estimated pOR 3.08)^{29, 46, 82, 101} and *dexamethasone to another corticosteroid* (estimated pOR 0.18).¹⁰¹

Pooled data for linear growth between inhaled corticosteroid and placebo included two studies (n=263) using recurrent doses for acute wheeze with follow-up at one year.^{27,44} The estimated change-from-baseline height was small (MD 0.10 cm; 95% CI -0.47 to 0.67; I²=9%). Five studies reported measurements of growth (height and weight) ranging from one to three years of follow-up, which could not be pooled due to heterogeneous interventions, comparators, or outcome measurements.^{28, 30, 44, 57, 70} Three studies included data on inhaled corticosteroid versus placebo. One RCT on asthma⁵⁷ (n=20) comparing budesonide and placebo found no signs of growth retardation by height measurements at 12 months or after up to six treatments. An RCT of episodic wheeze²⁸ (n=294) found height at three years of age was unaffected in children receiving budesonide or placebo. One RCT of inhaled fluticasone propionate at very high doses (1500 mcg daily during upper respiratory infections) versus placebo in recurrent wheeze⁴⁴ reported additional outcome data on height that was not pooled in the meta-analysis mentioned above. There was a smaller mean change in height z score in the corticosteroid group over one year (MD -0.24; 95% CI -0.40 to -0.08; adjusted results).⁴⁴ Furthermore, mean weight was significantly lower at one-year follow-up in the fluticasone group (n=62) versus placebo (n=67); two children given fluticasone and one given placebo met criteria for 'failure to thrive'.⁴⁴ Finally, two small trials did not report group differences for other comparisons: total and mean height growth (at eight to 19 months) for intravenous (IV) dexamethasone versus inhaled budesonide in asthma (n=18);⁷⁰ weight and height gains at two years for theophylline and metaproterenol with

or without systemic prednisone on prevention of wheeze during upper respiratory infections in asthma (n=32).³⁰

Five studies reported on adrenal function/suppression, with few children contributing data for this outcome.^{44, 56, 57, 70, 88} The RCT of high-dose inhaled fluticasone propionate versus placebo (99 children with data)⁴⁴ found no significant differences between groups in basal cortisol (baseline and 12 months). Another RCT in asthma reported no differences in serum cortisol and urinary cortisol/creatinine after 10 days of inhaled budesonide or placebo (16 children with data). A subgroup who received oral betamethasone (n=9) showed significant changes from baseline after three days, but no differences at 12 to 14 days.⁵⁷ Two studies included comparisons between different corticosteroids. One RCT⁸⁸ in acute asthma compared IV prednisolone (n=20) with nebulized budesonide (n=30) and found significant levels of suppressed serum cortisol in the prednisolone group, albeit not considered pathologic by the study authors. Although another RCT^{56} comparing intramuscular (IM) dexamethasone with oral prednisone for asthma (n=32) found lower median urinary cortisol/creatinine in the former group at day 14, there was no statistically significant difference. An RCT⁷⁰ comparing IV dexamethasone (n=9) with inhaled budesonide (n=9) found no significant differences between groups from baseline for blood pressure and blood glucose measurements.

Five studies reported on bone health biomarkers, three of which compared inhaled corticosteroids and placebo; no pooled analyses were performed.^{28, 44, 57, 60, 91} One RCT²⁸ compared inhaled budesonide (n=294) with placebo in episodic wheeze and found no effect on bone mineral density over three years. The RCT comparing high-dose inhaled fluticasone

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propionate with placebo (n=59 children with data) in viral wheeze⁴⁴ reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT⁵⁷ comparing inhaled budesonide with placebo (n=20) in asthma found transient decreased levels of bone and collagen markers post-treatment and in a subset of children who received oral betamethasone, with no difference between groups. A study of patients with acute respiratory illness⁹¹ compared hydrocortisone (n=28), methylprednisone (n=21) and controls (n=51) and found decreased levels of osteocalcin and alkaline phosphatase in younger children two days post-treatment; these effects were reversed 12 days after treatment. A non-randomized controlled trial (nRCT) of 36 asthma patients⁶⁰ compared IV methylprednisolone of three different durations and found that all had decreasing levels of serum osteocalcin that correlated with increasing duration of treatment.

Cardiovascular System

No significant differences were found between *systemic corticosteroid and placebo* in three bronchiolitis studies reporting hypertension (estimated pOR 1).^{31, 39, 82} Single studies with up to 110 children did not report events for arrhythmia⁴² and congestive heart failure⁴⁶ (*systemic or inhaled corticosteroid versus placebo*); and arrhythmia²⁶ or hypertension⁵⁶ (*dexamethasone with another corticosteroid*).

General AEs/ Other Symptoms

Meta-analyses included a total of two studies (range 197 to 869 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for pallor;^{69,}

⁸² and b) *dexamethasone with another corticosteroid* for dizziness⁵¹ or excessive urination.²⁶ No study comparing *inhaled corticosteroid with placebo* reported general AEs.

Immune System & Oncology

One study (95 participants)³⁸ compared *systemic corticosteroid and placebo* and found no occurrences of immunosuppression. No other study reported immune system-related AEs.

DISCUSSION

This systematic review of studies in which short-course corticosteroids were administered to children under six years of age for acute respiratory conditions, included 85 studies involving more than 11,000 patients. These studies used a variety of delivery routes, doses, formulations and duration of corticosteroids. Overall, the evidence suggests that short-term corticosteroid use is not associated with a significant increase in AEs across organ systems. However, given the low quality of included studies, the heterogeneous and poor reporting of AEs, and the lack of precision of results, considerable uncertainties remain regarding the safety of high-dose inhaled or systemic corticosteroids for these indications in this age range. Importantly, these results can help guide future research in the collection and reporting of AEs, particularly concerning measures of growth and behavioral outcomes; this in turn is needed to help inform shared decision-making between clinicians and parents/caregivers of young children.

A common concern when using corticosteroids in young children is effect on growth. Results from a single, small trial (n=129) of recurrent high-dose inhaled fluticasone propionate in wheezing preschoolers were heterogeneous across outcome measures, but suggested a small

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significant risk of growth suppression.⁴⁴ Observational data have also suggested that multiple corticosteroid bursts can increase the risk of growth suppression, fractures, bone mineral accretion and osteopenia in children with underlying respiratory disease.^{5, 6, 108} Conversely, a pooled analysis using change-from-baseline linear growth did not find significant differences, albeit the other included study used a substantially lower equivalent dose of inhaled corticosteroid.¹⁰⁹ Further, results from individual studies reporting transient differences in bone and adrenal biomarkers are of unclear clinical relevance, particularly for previously healthy children and single use. This calls for caution and monitoring of linear growth, particularly when use of high-dose inhaled or systemic corticosteroid is recurrent.

We found no other statistically significant differences between systemic or inhaled corticosteroid and placebo, or between dexamethasone and other systemic corticosteroid, including subgroup analyses by respiratory condition or dose, for AEs across organ systems. Due to small sample sizes and low number of events, these results should be interpreted with caution. While we found increased pORs when comparing systemic corticosteroids for behavioural outcomes such as tremor/jitteriness and behaviour change, there were wide confidence intervals around estimates. No study examined neurodevelopmental outcomes after corticosteroid administration; ideally, studies should assess children for potentially related long-term AEs using validated instruments in this domain. Results from case series and case reports added anecdotal evidence of rare cases of hypersensitivity, infection or behavioral AEs, which have been described.^{110, 111} While the estimated increased pOR for rash and hives was close to statistical significance, no other differences were found in systemic or severe infections as well as immunosuppression.

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This review did not ascertain a clear safety advantage between systemic or inhaled corticosteroids compared with placebo. When comparing between different systemic corticosteroids, evidence favored oral dexamethasone over oral prednisone for vomiting (pOR 0.029; 95% CI 0.17 to 0.48; I²=0%). Differences in palatability and tolerability between corticosteroids are well known to parents, healthcare providers and researchers, and can influence adherence to medication in children.¹¹² Further, different specific formulations of corticosteroid (e.g., prednisolone tablets versus prednisolone syrup) have been shown to influence taste and vomiting.²⁴ However, cost and access to better tolerated formulations may be problematic. Subgroup analyses also found no significant differences between groups by respiratory condition or dose (single versus multiple) for these outcomes. Due to extensive variation in dosing within and across studies, we were unable to analyze data or draw further conclusions with respect to dosage or differences between specific molecules. It should be noted that among the eight RCTs^{34, 42, 45, 50, 64, 66, 70, 88} directly comparing systemic and inhaled routes of corticosteroid administration, none contributed meaningful data for meta-analysis. The decision to initiate corticosteroid and the selection of drug, dose and mode of administration must consider these uncertainties on harms, as well as existing evidence on comparative potency and clinical effectiveness. The risk-benefit rationale is less established for repeated acute use in younger children, such as in recurrent wheezing.¹¹³

Strengths and limitations

We conducted a comprehensive systematic review of the literature following rigorous methods, including grey literature, to minimize potential for publication and selection bias. We examined safety outcomes across multiple acute respiratory conditions using 'baskets' of outcomes in each

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organ system to increase our ability to detect rare events and the precision of our estimates.¹⁶ This approach is reflective of clinical practice where corticosteroids are used across many respiratory diseases, even if the evidence base is not entirely robust for children. A recent systematic review also assessed the toxicity of short-course oral corticosteroids in children across clinical conditions.¹¹⁴ However, there was scarce overlap in respiratory conditions across included studies, and authors mostly provided estimates of the incidence of AEs within treatment groups rather than comparative treatment effects. Studies in adults have also adopted similar approaches to estimate incidence rates of AEs. For example, findings from a recent retrospective cohort in adults showed a significant increase in rates of sepsis, venous thromboembolism and fracture.¹¹⁵

This review was limited by the quality of the primary literature, particularly regarding the definition, assessment and reporting of AEs. This underscores the challenges researchers encounter when attempting to synthesize safety data due to sparse and poor reporting,¹¹⁶ and highlights the urgent need to enhance detection and reporting of AEs. Common nomenclature (e.g., www.meddra.org) and standardized approaches to collection of AE data should be implemented to help draw comparisons across studies. Further, safety reporting was not a primary focus of the studies, AEs were rarely defined a priori, and methods for ascertaining AEs were usually absent. While the McHarm scale is recommended to be used in conjunction with other quality assessment tools to evaluate the broader elements of study quality, we used it exclusively to assess methodological quality since the primary focus of this review was on AEs. The AEs reported typically reflect what is detected by a healthcare provider; it is difficult to discern what is reported by patients as well as what patients consider important. The duration of

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surveillance of most studies was insufficient to detect many of the long-term AEs potentially associated with corticosteroid use. Although the present study suggests that single doses of systemic or inhaled corticosteroids may result in few AEs, recurrent courses may lead to long-term risks, as cumulative dosing has been shown to be a determinant of safety.¹⁰⁸ Finally, there was variation within and across studies with respect to maintenance corticosteroids, and concomitant and rescue medications. Due to the variation in corticosteroids and extensive range of AEs reported (including when a single study contributes to an outcome or in cases of zero events, where meta-analysis was not feasible or meaningful) amongst varied study designs of overall poor quality, we did not attempt to rate the quality of the body of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

CONCLUSION

This is the most comprehensive systematic review to date examining the safety of corticosteroids for managing acute respiratory conditions among young children, an age group of great clinical concern. While the existing evidence suggests that short-term high-dose inhaled or systemic corticosteroids is not associated with a significant increase in AEs across organ systems, uncertainties remain due to low quality of studies, poor reporting and lack of precision of results.

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Organ system	AE - category	AE – specific	No. of studies	No. of participants
Infection & Respiratory	Severe infections		5	1235
	1)	Sepsis	1	32
	2)	Superinfection	2	354
	3)	UTI	1	720
	4)	Streptococcal infection	1	129
	Systemic infections		5	1635
	1)	Fever	3	963
	2)	Common	2	792
		viral/bacterial/fungal		
		infection		
	3)	Varicella	3	1449
	Lung/trachea		10	2053
	1)	Empyema	1	600
	2)	Pneumonia	8	2051
	3)	Respiratory distress	2	2
	Upper respiratory tract		14	2457
	1)	Bacterial tracheitis	5	1023
	2)	Sinusitis	2	849
	3)	Croup	2	131
	4)	Viral parotitis	1	27
	5)	Pharyngitis	1	129
	6)	Persistent cough	1	27
	7)	Oral thrush	3	837
	8)	Otitis media	4	1173
	9)	Ear, nose, throat infection	3	862
	10)	Nasal discharge	1	720
	11)	Eye discharge	1	720
	Voice complaints		5	794
GI	GI bleeding		8	2669
	1)	Bleeding	5	1577
	2)	Gross hematochezia	1	118
	3)	Occult blood in stools	2	292
	4)	Dark stools	1	800
	Vomiting		27	6067
	1)	Vomiting	24	5983
	2)	Nausea	6	586
	3)	Palatability	3	170
	Abdominal pain		5	1332
	Diarrhea		8	1346
	1)	Diarrhea	7	1217
	2)	Gastroenteritis	1	129
CNS & Behaviour	Tremor/jitteriness		8	1274
	1)	Tremor	7	1226
	2)	Jittery	1	48
	Behaviour change		14	2078
	1)	Violent behaviour	1	198
	2)	Mood change	7	1430
	3)	Hyperactivity	2	268

Table 5. Number of studies and participants reporting adverse events*

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38 39 40	
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52 53	
55 54 55	
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60	

	4)	Restlessness	3	297
	5)	New sleep problems	3	408
	6)	Emotional distress due to	1	82
		nebulizer mask		
	7)	Psychosis	1	1
	Headache		3	291
Dermatological	Burn		1	198
	Integument		10	1954
	1)	Hives	2	199
	2)	Rash	8	1954
	3)	Eczema	1	129
	4)	Eye irritation	2	211
	5)	Tongue irritation	1	82
	6)	Positive wheal	1	1
	7)	Bleeding from ear	1	720
	Phlebitis		1	32
Endocrine/Metabolic	Fluid and electrolyte		7	1849
& Musculoskeletal	abnormalities			
	1)	Hyperkalemia	1	800
	2)	Hyperglycemia	3	154
	3)	Glycosuria	1	125
	4)	Sodium retention	1	50
	5)	Dehydration	1	720
	Growth		6	731
	Adrenal suppression		5	249
	Bone health		5	579
Cardiovascular	Arrhythmia		3	312
	1)	Tachycardia	2	178
	2)	Palpitations	1	134
	Hypertension		5	1491
	Congestive heart failure		1	50
General	General complaints		5	1146
	1)	Dizziness	1	87
	2)	Pallor	2	869
	3)	Excessive urination	1	134
	4)	Normal tooth eruption	1	56
	Hematology, gum bleeding		1	1
Immune System & Oncology	Immunosuppression		4	147
	1)	Immunosuppression	3	146
	2)	Tumor cell proliferation	1	1

AE: adverse event; CNS: central nervous system; GI: gastro-intestinal; no.: number; URT: upper respiratory tract * Each adverse event was clustered into its related organ system; a panel of clinicians ranked each AE category and its corresponding adverse events in order of clinical significance/severity. The organ systems are presented in order of frequency of reporting, beginning with the most frequently reported (i.e., Infection & respiratory).

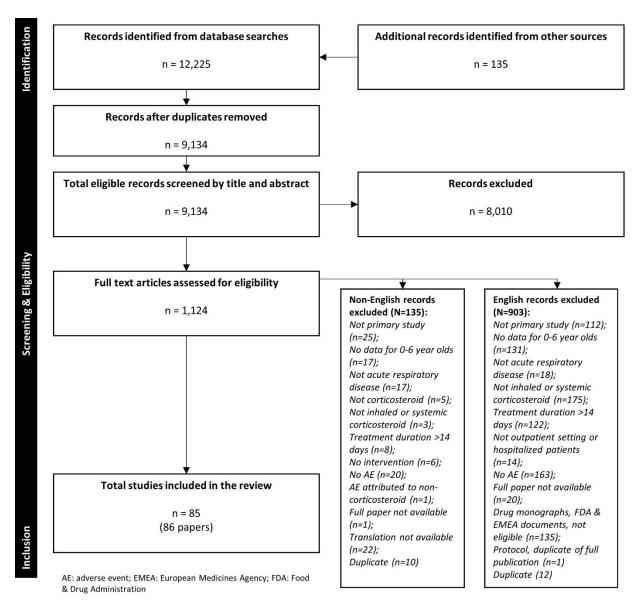


Figure 1. PRISMA study flow selection



BMJ Open

<figure><figure></figure></figure>					
<figure><figure></figure></figure>		No. of	No./Total	Odds ratio	Odds ratio
Seven infections 4 0552 2554 Systems infections 4 0552 2554 Systems infections 4 0505 40083 Lagytytecha 7 1855 26293 Voice complaints 1 001 007 G G blooking 7 31/1287 31/1260 Voice complaints 1 0559 1561 Selenbe Tremorfilterines 5 22559 14058 G blooking 4 7758 3571 Behaviour change 4 77588 3571 Behaviour change 4 7758 3572 Behaviour change 4 7758 3572	Outcome				
Systemic inflations 4 50295 40083 Lungbraches 7 108955 28928 Voise compliants 1 001 027 G theeding 7 201/1287 31/1262 Voise compliants 1 1029 17661 Diarbas 3 10254 92230 CHS & Behaviour change 4 7588 3571 Behaviour change 5 22559 14508 Cardio Cardio Cardio But none Skin Dum none Skin Dum none Skin Dum home Lungmostynession 1 047 048 Skin Stare	Inf & Resp			1	
Langhrachen7189552892800URT6967176560Visice compliants10/010/27G010/28731/126210/00(0.60,167)Visiting738/160334/157310/00(0.60,176)Abdominal pain11/2591/26110/00(0.60,176)Diarbas310/2549/23010/00(0.60,176)Use diabase10/371/3310/00(0.60,176)Construct change40/371/33Hestache10/310/27Hypertension31/7271/714Congestive haart fulaws10/250/25CardioNa100(0.60,1599)NAManal appression30/250/25Paid & electrolyte abnormalities 45/8321/818Gorothnonee10/00(0.61,199)Integrament34/536Na100(0.62,160)10/00(0.62,160)Hentology, gan bakelingnoneeIntegrament34/536Ontone System10/07Immunonspression10/47Out010/07Manal appression10/47Out010/00 (0.62,160)Hentology, gan bakelingnoneIntegrament34/536Out010/00 (0.62,160)Hentology, gan bakelingnoneIntegrament10/47Out01Int	Severe infections	4	0/552 2/554		0.15 (0.01, 2.45)
URT696717656121 (0.44, 3.33)Voice complaints10.010.027100 (0.60, 1.67)Globeding731/128731/1282100 (0.60, 1.67)Nomining738/160334/1573101 (0.06, 51.11)Disches3102549/230109 (0.43, 2.73)URT dio71.5251.4508109 (0.43, 2.73)Disches52.255514/50814/00 (0.65, 652)Balaviour change47/5883/571Headelle10.0371/33Congetive heart failure10.025Na100 (0.65, 159)NaCongetive heart failure10.025None10.025Balaviour change45/832Phild & electrolyte absormalities 45/832Na100 (0.65, 159)Na100 (0.65, 159)RoothnoneAdvental appressionnoneAdvental appressionnoneBalaviour change4Out0.25OutnoneAdvental appressionnoneAdvental complaints2Balavis3Out0.02Balavis1Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21Out0.21 <t< td=""><td>Systemic infections</td><td>4 5</td><td>5/1095 4/1083</td><td></td><td>1.26 (0.34, 4.68)</td></t<>	Systemic infections	4 5	5/1095 4/1083		1.26 (0.34, 4.68)
Voice complaints 1 031 027 G G G Heading 7 31/1227 31/1227 Voming 7 38/1603 34/1373 Abdominal pain 1 1/359 1/361 Diarbas 3 10/254 9/259 Headicele 1 0/37 1/33 CHS & Behav Tremorfitterines 5 22/559 14/508 Behaviour change 4 7/588 3/571 Headicele 1 0/37 1/23 Cardio Arrythmia 1 0/31 0/27 Hypertension 3 1/227 1/714 G Headicele 5 852 1/818 Headicele 3 10/25 0/25 FridoMetabMuse Phild & electoryle abnormalities 4 5/832 1/818 Stein Diarbase Stein General General General General General General General General Headicogy, gam bleding none Theomore System Themacoppearies none Stein General General General Headicogy, gam bleding none Theomore System Theomore Systemic Frigure 2. Forest plot of adverse events – systemic versus placebo	Lung/trachea	7 1	18/955 28/928		0.61 (0.34, 1.12)
G Gildesting 7 31/287 31/287 34/373 Addominal pain 1 1039 1/361 Diarbas 3 10254 9/230 Gildesting 4 7/588 34/573 Belaviour charge 4 7/588 34/571 Belaviour charge 4 7/588 34/571 Belaviour charge 4 7/588 34/571 Belaviour charge 4 7/588 34/571 Belaviour charge 4 7/588 34/571 Cardio Arrythmia 1 0/01 0/27 Arrythmia 1 0/01 0/27 Gardio Arrythmia 1 0/01 0/27 Boars 1 0/25 0/25 Fordoffetabline Barn none Advand repression none Advand repression none Barn none Advand repression none Barn none Barn none Barn none Mathini 2 3 38/46 38/423 General General General General General Innume System Innume System Innume System Innume System Struct 2. Forest plot of adverse events – systemic versus placebo	URT	6	9/671 7/656	en	1.21 (0.44, 3.33)
Gi biesding 7 31/267 31/262 Vomiting 7 38/1003 34/1573 Jun 10254 9230 CIS & Behav Twenorifiterines 3 10/254 9230 CIS & Behav Twenorifiterines 5 22/559 14/508 Jun 00/06, 161) Jun 00, 06, 159) NA Stan General General General General General General General General General General General General General General General General General General General Jun 00, 052, 160) Jun 00, 062, 160) Heating Jun 00, 062, 160) Heating Jun 00, 062, 160) Heating Jun 00, 06, 1594) General General Jun 00, 06, 1594) General Jun 00, 06, 1594) General General Jun 00, 06, 1594) Jun 00, 06, 1594) Jun 00, 06, 1594) Jun 00, 06, 1594) Jun 00, 062, 160) Jun 00, 062, 160) Jun 00, 052, 160) Heating Jun 00, 06, 1594) Jun 00, 062, 160) Jun 00, 052, 160, 160, 160, 160, 160, 160, 160, 160		1	0/31 0/27		NA
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Abdominal pain 1 1/359 1/361 Diarbea 3 10254 9/230 CNS & Behav Twenor/jitterines 5 2/2/559 1/4/508 Behaviour change 4 7/588 3/571 Headache 1 0/37 1/3 Carolo Arrythmia 1 0/31 0/27 Hypertension 3 1/727 1/7/4 Hypertension 3 1/727 1/7/4 Hypertension 3 1/727 1/7/4 Crowth none Headawal suppression none Skin Durn none Skin General General General Immunosupression 1 0/47 0/48 Ma Heatology, gun bleeding none Hammony pression 1 0/47 0/48 Ma String Heatology, gun bleeding none Humuno System This 2, 58/46 38/423 Hematology, gun bleeding none Humuno System This 2, Forest plot of adverse events – systemic versus placebo					
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Tremotifiteriness 5 22559 14/508 14/508 14/508 14/508 14/508 12/571 14/50(75,5,6,52) 15(5,5,52) 15(3 1	10/254 9/230		1.09 (0.43, 2.73)
Behaviour change 4 7/58 3/571 195 0.55, 6.92) Headache 1 0/37 1/33 0.11 (0.00, 5.68) Cardio Arythmia 1 0/31 0.27 NA Hypertension 3 1/727 1/714 100 (0.06, 15.99) Congestive heart failure 1 0/25 0/25 NA EndoMetabMusc Fhaid & electrolyte abnormalities 4 5/832 1/618 30.8 (0.60, 15.94) Growth none Adrenal suppression none Skin Burn none Heagment 3 4/536 0/543 7.59 (1.07, 54.01) Phabitis none General General General General Ma Ma 1.00 (0.62, 1.60) Hematology, gun bleeding none Immuno System Immuno System Thomas System 1 0/47 0/48 NA Figure 2. Forest plot of adverse events – systemic versus placebo					1.44.49.61.0.00
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Cardio Arythmia 1 0/31 0/27 Hypertension 3 1/727 1/714 Hypertension 3 1/727 1/714 Congestive least falue 1 0/25 0/25 Foundetabluss Growth none Adrenal suppression none Skin Dun none Integument 3 4/536 0/543 Plubitis none Ceneral Ceneral Ceneral Ceneral Ceneral Ceneral Ceneral Complaints 2 38/446 38/423 Humanoappession 1 0/47 0/48 MA System Integument 1 0/47 0/48 Figure 2. Forest plot of adverse events – systemic versus placebo					
Arythmia 1 0/31 0/27 Hypertension 3 1/727 1/714 Congestive heart failure 1 0/25 0/25 EndoMetabMuse Phuid & electrolyte abnormalities 4 5/832 1/818 Growth none Adrenal appression none Skin Durn none Skin Durn none General General complaints 2 38/446 38/423 Hematology, gun bleeding none Immune System Immune System Immune System Immune System Immune System I Immune System I Imm		1	0/57 1/33	at the second	0.11 (0.00, 5.68)
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Congestive heart failure 1 0/25 0/25 EndoMetabMusc Paid & electrolyte abnormalities 4 5/832 1/818 Growth none Adrenal suppression none Skin Dum none Integument 3 4/536 0/543 Philebitis none General General General General Immune System Immune System Immune System Immune System Immune System Immune System Immune System Immune System Immune System I 0/47 0/48 MA MA MA MA MA MA MA MA MA MA					
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Fhid & electrolyte abnormalities 4 5832 1/818 308 (0.60, 15.94) Growth nome 4dremal suppression nome Adremal suppression nome 9 Skin 1 0.543 7.59 (1.07, 54.01) Phild its nome 9 7.59 (1.07, 54.01) Phild its nome 9 1.00 (0.62, 1.60) General of General of General of Nome 1.00 (0.62, 1.60) 1.00 (0.62, 1.60) Hematology, gun bleeding nome 1.00 (0.62, 1.60) Immune System 1.00 (0.62, 1.60) NA Immune System 1.00 (0.62, 1.60) NA Favours systemic Favours placebo NA			د2/0 دم		API
Growth none Advenal suppression none Skin Burn none Integument 3 4/536 0/543 Phibbitis none General General complaints 2 38/446 38/423 Hematology, gun bleeding none Immune System Immune System Immune System Immune System 1 0/47 0/48 MA Figure 2. Forest plot of adverse events – systemic versus placebo		nalities 4	5/832 1/818		3.08 (0.60.15.94)
Adrenal suppression none Skin Durn none Integument 3 4/536 0/543 Pilabitis none General General General General complaints 2 38/446 38/423 Hematology, gun bleeding none Immune System Inumnosysession 1 0/47 0/48 MA Second 1 1 0/47 0/48 MA Favours systemic Favours placebo					2.00 (0.00, 12.94)
Skin Durn none Integument 3 4/536 0/543 Pilabitis none General General General complaints 2 38/446 38/423 Hematology, gun bleeding none Immune System Inumanosupression 1 0/47 0/48 MA Figure 2. Forest plot of adverse events – systemic versus placebo					
Burn nome Integument 3 4/536 0/543 Phlabitis nome 7.59 (1.07, 54.01) General					
Integunent 3 4/536 0/543 Phlebitis none General General General complaints 2 38/446 38/423 Hematology, gun bleeding none Immune System Immune System Immune System Immune System Favours systemic Favours placebo Figure 2. Forest plot of adverse events – systemic versus placebo		none			
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General General General complaints 2 38/46 38/423 Hematology, gun bleeding none Immune System Inumuno supression 1 0/47 0/48 0.01 0.1 1 10 100 Favours systemic Favours placebo Figure 2. Forest plot of adverse events – systemic versus placebo					
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6.01 0.1 1 10 100 Favours systemic Favours placebo Figure 2. Forest plot of adverse events – systemic versus placebo	Immune System				
Favours systemic Favours placebo Figure 2. Forest plot of adverse events – systemic versus placebo	Imminosupression	1	0/47 0/48		NA
Favours systemic Favours placebo Figure 2. Forest plot of adverse events – systemic versus placebo					
Figure 2. Forest plot of adverse events – systemic versus placebo					0
				Favours systemic Favours placebo	
	Figure ? Forest	t plat of	advance ever	ta sustamia varsus placaba	
	rigure 2. rores	r h10r 01	auverse evel	is – systemic versus placebo	

Figure 2. Forest plot of adverse events – systemic versus placebo

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	No. of	No./	Total	Odds ra	atio	Odds ratio	
Outcome	Studies	Inhaled	Placebo	95% C	CL	95% CI	
Inf & Resp				E			
Severe infections	1	2/62	4/67	<u>. 8</u>		0.54 (0.11, 2.77)	
Systemic infections	2	18/91	20/94			0.96 (0.45, 2.05)	
Lung/trachea	1	13/62	10/67			1.51 (0.61, 3.70)	
URT	6	24/495	24/499		2027	1.03 (0.57, 1.85)	
Voice complaints	4	38/343	43/337			0.85 (0.53, 1.36)	
GI							
GI Bleeding	1	0/48	0/49			NA	
Voniting	s	28/421	28/420		<u>-</u>	1.00 (0.58, 1.72)	
Abdominal pain	none						
Diarrhea	2	41/326	46/328			0.89 (0.57, 1.40)	
Skin							
Burn	1	0/27	1/27		10	0.14 (0.00, 6.82)	
Integument	4	24/432	27/436		-1	0.88 (0.50, 1.56)	
Abdominal pain	none						
EndoMetabMusc							
Fluid & electrolyte abnorm	ıs none						
Adrenal suppression	1	5/6	4/10		20 22	5.21 (0.72, 37.57)	
CNS & Behav							
Tremor/jitteriness	none						
Behaviour change	3	6/134	7/135		it)	0.81 (0.26, 2.54)	
Headache	none						
Cardio							
Anythmia	1	0/29	0/27			NA	
Hypertension	none						
Congestive heart failure	none						
General							
General complaints	none						
Hematology, gum bleeding	none						
Immune System							
Imminosupression	none						

Figure 3. Forest plot of adverse events – inhaled versus placebo

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3								
4		No. of	No./Tota		Odds ra		Odds ratio	1 ²
5	Outcome Gl	studies	Dexamethasone	Other	95% C	.1	95% CI	
6	GI bleeding	none						
	Vomiting	6	12/663	51/710			0.29 (0.17, 0.48)	0
7	Abdominal pain	3	29/188	48/264	_	_0	0.96 (0.57, 1.61)	0
8	Diarrhea	none						
9	CNS & Behav							
10	Tremor/jitteriness	1	1/46	0/41		÷	6.63 (0.13, 336.21)	NA
11	Behaviour change	2	35/60	38/57	6	-	0.73 (0.34, 1.56)	0
12	Headache General	2	7/102	4/95			1.63 (0.46, 5.74)	NA
	General complaints	2	3/102	3/95			0.90 (0.18, 4.61)	11
13	Hematology, gum bleeding	none	5/102	2022			0.30 (0.10, 4.01)	÷.
14	Cardio							
15	Anythmia	1	0/56	0/54			NA	NA
16	Hypertension	1	0/15	0/17			NA	NA
17	Congestive heart failure	none						
18	EndoMetabMusc							
	Fluid & electrolyte abnorms	1	1/33	2/15			0.18 (0.01, 2.17)	NA
19	Growth	none						
20	Adrenal suppresion Skin	none						
21	Burn	none						
22	Integument	none						
23	Phlebitis	1	0/15	0/17			NA	NA
	Inf & Resp							
24	Severe infections	none						
25	Systemic infections	none						
26	Lung/trachea	none						
27	URT	none						
28	Voice complaints Immune System	none						
29	Immuno suppression	none						
	mananosappression	10010						
30					0.01 0.1 1	10 100		
31					Favours dexamethasone	Favours other		
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33 r	igure 4. Fores	st pio	t of adver	se even	ts – dexamethason	ie versus otne	r	
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3	Supplement 1. Search strategy
4 5	
6	Database for original search: Ovid Medline(R) 1946 to September Week 1 2014
7	Databases for update searches: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed
8	Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
9	Date original search conducted: 14 September 2014
10	Date first update search conducted: 24 February 2016
11 12	Date second update search conducted: 31 July 2017
12	Strategy:
14	
15	1. Adrenal Cortex Hormones/
16	2. Anti-Inflammatory Agents/
17	3. Beclomethasone/
18 19	4. Budesonide/
20	
21	5. exp Glucocorticoids/
22	6. exp Hydroxycorticosteroids/
23	7. Pregnenediones/
24	8. Triamcinolone Acetonide/
25 26	9. adrenal cortex hormone*.tw,nm.
20	10. advair*.tw,nm.
28	11. alvesco*.tw,nm.
29	12. azmacort*.tw,nm.
30	13. becl?met*.tw,nm.
31	14. beclazone*.tw,nm.
32 33	15. beclo?ort*.tw,nm.
33 34	16. beclovent*.tw,nm.
35	17. beconase*.tw,nm.
36	18. becotide*.tw,nm.
37	19. betamet?asone*.tw,nm.
38	20. betnesol*.tw,nm.
39 40	21. budesonide*.tw,nm.
41	22. ciclesonide*.tw,nm.
42	23. clobetasol*.tw,nm.
43	24. cortiso*.tw,nm.
44	25. cortodoxone*.tw,nm.
45	26. corticosteroid*.tw,nm.
46 47	27. decadron*.tw,nm.
48	28. depo medrone*.tw,nm.
49	29. desoximet?asone*.tw,nm.
50	30. dexamethasone*.tw,nm.
51	31. deflazacort*.tw,nm.
52 53	32. diflucortolone*.tw,nm.
54	33. flixotide*.tw,nm.
55	34. flumethasone*.tw,nm.
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58 50	Supplement 1 - Page 1 of 13
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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3	35. flunisolide*.tw,nm.
4 r	36. fluocino*.tw,nm.
5 6	37. fluocortolone*.tw,nm.
7	38. fluorometholone*.tw,nm.
8	39. flurandrenolone*.tw,nm.
9	40. fluticasone*.tw,nm.
10	41. glucocortico*.tw,nm.
11	
12	42. hydrocortisone*.tw,nm.
13	43. hydroxycorticostero*.tw,nm.
14 15	44. hydrocortone*.tw,nm.
16	45. hydroxypregnenolone*.tw,nm.
10	46. kenacort*.tw,nm.
18	47. kenalog*.tw,nm.
19	48. medrone*.tw,nm.
20	49. methylprednisolone*.tw,nm.
21	50. mometasone furoate*.tw,nm.
22	51. nasonex*.tw,nm.
23	52. paramethasone*.tw,nm.
24 25	53. predniso*.tw,nm.
25	
27	54. pregnenolone*.tw,nm.
28	55. pulmicort*.tw,nm.
29	56. qvar*.tw,nm.
30	57. rhinocort*.tw,nm.
31	58. seretide*.tw,nm.
32	59. solu cortef*.tw,nm.
33 34	60. symbicort*.tw,nm.
35	61. tetrahydrocortisol*.tw,nm.
36	62. triamcinolone*.tw,nm.
37	63. tricort*.tw,nm.
38	64. vanceril*.tw,nm.
39	65. or/1-64
40	66. Acute Disease/ and (asthma* or pneumonia* or wheez*).mp.
41 42	67. exp Asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
42	68. Bronchial Hyperreactivity/
44	69. Bronchial Spasm/
45	
46	70. exp Bronchiolitis/
47	71. Croup/
48	72. exp Dyspnea/
49 50	73. Emergencies/ and (asthma* or pneumonia* or wheez*).mp.
50 51	74. Emergency Medical Services/ and (asthma* or pneumonia* or wheez*).mp.
52	75. Emergency Services, Hospital/ and (asthma* or pneumonia* or wheez*).mp.
53	76. exp Pharyngitis/
54	77. exp Pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
55	78. exp Respiratory Syncytial Viruses/
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58 50	Supplement 1 - Page 2 of 13
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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80. Rhinitis/

81. exp Sinusitis/

- 82. Status Asthmaticus/
- 83. Respiratory Sounds/ and (acute* or emergenc* or exacerbation* or severe*).mp.
- 84. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw.
- 85. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw.
- 86. (bronch* adj3 (constrict* or spas*)).tw.
- 87. bronchiolitis*.tw.
- 88. bronchoconstrict*.tw.
- 89. bronchospasm*.tw.
- 90. croup*.tw.
- 91. dyspne*.tw.
- 92. (lung* adj2 (disease* or infect*)).tw.
- 93. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
- 94. (nasosinusit* or rhinosinusit*).tw.
- 95. pharyngitis*.tw.
- 96. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
- 97. rhinit*.tw.
- 98. sinusit*.tw.
- 99. tonsillitis*.tw.
- 100. or/66-99
- 101. exp child/
- 102. exp infant/
- 103. exp Pediatrics/
- 104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).mp.
- 105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).mp.
 - 106. or/101-105
- 107. and/65,100,106 [steroids/respiratory illness/children]
- 108. randomized controlled trial.pt.
- 109. controlled clinical trial.pt.
- 110. randomi?ed.ab.
- 111. placebo.ab.
- 112. drug therapy.fs.
- 113. randomly.ab.
 - 114. trial.ab.
 - 115. groups.ab.
 - 116. or/108-115
 - 117. exp Case control studies/
 - 118. case reports.pt.
 - 119. Cross-sectional studies/
- 120. exp Cohort Studies/
- 121. Epidemiologic studies/
- 5 122. case control.tw.

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2 3	
4	123. (case adj (report* or study or studies or series)).tw.
5	124. cohort analy*.tw.
6	125. (cohort adj (study or studies)).tw.
7	126. cross sectional.tw.
8	127. (follow up adj (study or studies)).tw.
9 10	128. longitudinal.tw.
11	129. (observational adj (study or studies)).tw.
12	130. retrospective.tw.
13	131. or/117-130
14	132. 116 or 131
15	133. exp animals/ not humans.sh.
16 17	134. 132 not 133
18	135. 107 and 134
19	136. (comment or editorial or letter or meta analysis or review).pt.
20	137. 135 not 136
21	138. remove duplicates from 137
22 23	
23 24	Database for original search: Ovid Medline(R) In-Process & Other Non-Indexed Citations, September 12,
25	2014
26	Date original search conducted: 14 September 2014
27	Strategy:
28 29	
29 30	1. adrenal cortex hormone*.tw,nm.
31	2. advair*.tw,nm.
32	3. alvesco*.tw,nm.
33	4. azmacort*.tw,nm.
34	5. becl?met*.tw,nm.
35 36	6. beclazone*.tw,nm.
37	7. beclo?ort*.tw,nm.
38	8. beclovent*.tw,nm.
39	
40	9. beconase*.tw,nm. 10. becotide*.tw,nm. 11. betamet?asona*.tw.nm
41 42	11. betamet?asone*.tw,nm.
43	12. betnesol*.tw,nm.
44	13. budesonide*.tw,nm.
45	14. ciclesonide*.tw,nm.
46	15. clobetasol*.tw,nm.
47 48	16. cortiso*.tw,nm.
40 49	17. cortodoxone*.tw,nm.
50	
51	18. corticosteroid*.tw,nm.
52	19. decadron*.tw,nm.
53	20. depo medrone*.tw,nm.
54 55	21. desoximet?asone*.tw,nm.
55 56	22. dexamethasone*.tw,nm.
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58	Supplement 1 - Page 4 of 13
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60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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23. deflazacort*.tw.nm. 24. diflucortolone*.tw,nm. 25. flixotide*.tw,nm. 26. flumethasone*.tw,nm. 27. flunisolide*.tw,nm. 28. fluocino*.tw,nm. 29. fluocortolone*.tw,nm. 30. fluorometholone*.tw,nm. 31. flurandrenolone*.tw,nm. 32. fluticasone*.tw,nm. 33. glucocortico*.tw,nm. 34. hydrocortisone*.tw,nm. n. ۲ (asthma* or allow* or 35. hydroxycorticostero*.tw,nm. 36. hydrocortone*.tw,nm. 37. hydroxypregnenolone*.tw,nm. 38. kenacort*.tw,nm. 39. kenalog*.tw,nm. 40. medrone*.tw,nm. 41. methylprednisolone*.tw,nm. 42. mometasone furoate*.tw,nm. 43. nasonex*.tw,nm. 44. paramethasone*.tw,nm. 45. predniso*.tw,nm. 46. pregnenolone*.tw,nm. 47. pulmicort*.tw,nm. 48. qvar*.tw,nm. 49. rhinocort*.tw,nm. 50. seretide*.tw,nm. 51. solu cortef*.tw,nm. 52. symbicort*.tw,nm. 53. tetrahydrocortisol*.tw,nm. 54. triamcinolone*.tw,nm. 55. tricort*.tw,nm. 56. vanceril*.tw,nm. 57. or/1-56 58. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw. 59. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw. 60. (bronch* adj3 (constrict* or spas*)).tw. 61. bronchiolitis*.tw. 62. bronchoconstrict*.tw. 63. bronchospasm*.tw. 64. croup*.tw. 65. dyspne*.tw. 66. (lung* adj2 (disease* or infect*)).tw.

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3	67. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
4	68. (nasosinusit* or rhinosinusit*).tw.
5	69. pharyngitis*.tw.
6	70. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
7	
8 9	71. rhinit*.tw.
9 10	72. sinusit*.tw.
11	73. tonsillitis*.tw.
12	74. or/58-73
13	75. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).tw.
14	76. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).tw.
15	77. or/75,76
16	78. and/57,74,77
17	
18	79. randomi?ed.tw.
19	80. placebo.tw.
20	81. randomly.tw.
21 22	82. trial.tw.
22	83. groups.tw.
23	84. or/79-83
25	85. case control.tw.
26	86. (case adj (report* or study or studies or series)).tw.
27	87. cohort analy*.tw.
28	
29	88. (cohort adj (study or studies)).tw.
30	89. cross sectional.tw.
31	90. (follow up adj (study or studies)).tw.
32	91. longitudinal.tw.
33	92. (observational adj (study or studies)).tw.
34 35	93. retrospective.tw.
36	94. or/85-93
37	95. 84 or 94
38	96. 78 and 95
39	
40	97. (comment* or editorial* or letter*).mp.
41	98. 96 not 97
42	99. remove duplicates from 98
43	
44	Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library
45	Date original search conducted: 14 September 2014
46 47	Date first update search conducted: 24 February 2016
47 48	Date second update search conducted: 31 July 2017
49	
50	Strategy:
51	· · · · · · · · · · · · · · · · · · ·
52	1. [mh ^ "Adrenal Cortex Hormones"]
53	2. [mh ^ "Anti-Inflammatory Agents"]
54	3. [mh ^ Beclomethasone]
55	4. [mh ^ Budesonide]
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58 50	Supplement 1 - Page 6 of 13
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
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2 3	
4	5. [mh Glucocorticoids]
5	6. [mh Hydroxycorticosteroids]
6	7. [mh ^ Pregnenediones]
7	8. [mh ^ "Triamcinolone Acetonide"]
8 9	9. "adrenal cortex" next hormone*:ti,ab,kw
9 10	10. advair*:ti,ab,kw
10	11. alvesco*:ti,ab,kw
12	12. azmacort*:ti,ab,kw
13	13. becl?met*:ti,ab,kw
14	14. beclazone*:ti,ab,kw
15	15. beclo?ort*:ti,ab,kw 🔨
16	16. beclovent*:ti,ab,kw
17 18	17. beconase*:ti,ab,kw
19	18. becotide*:ti,ab,kw
20	19. betamet?asone*:ti,ab,kw
21	20. betnesol*:ti,ab,kw
22	21. budesonide*:ti,ab,kw
23	22. ciclesonide*:ti,ab,kw
24 25	23. clobetasol*:ti,ab,kw
25	
27	24. cortiso*:ti,ab,kw
28	25. cortodoxone*:ti,ab,kw
29	26. corticosteroid*:ti,ab,kw
30	27. decadron*:ti,ab,kw
31 22	28. depo next medrone*:ti,ab,kw
32 33	29. desoximet?asone*:ti,ab,kw
34	30. dexamethasone*:ti,ab,kw
35	31. deflazacort*:ti,ab,kw
36	32. diflucortolone*:ti,ab,kw
37	33. flixotide*:ti,ab,kw
38	34. flumethasone*:ti,ab,kw
39 40	35. flunisolide*:ti,ab,kw
40	36. fluocino*:ti,ab,kw
42	37. fluocortolone*:ti,ab,kw
43	38. fluorometholone*:ti,ab,kw
44	39. flurandrenolone*:ti,ab,kw
45	40. fluticasone*:ti,ab,kw
46 47	41. glucocortico*:ti,ab,kw
47 48	42. hydrocortisone*:ti,ab,kw
49	43. hydroxycorticostero*:ti,ab,kw
50	44. hydrocortone*:ti,ab,kw
51	45. hydroxypregnenolone*:ti,ab,kw
52	46. kenacort*:ti,ab,kw
53 54	
54 55	47. kenalog*:ti,ab,kw
55	48. medrone*:ti,ab,kw
57	
58	Supplei
59	For peer review only - http://bmiopen.hmi.com/site/about/guidelines.xk
60	FOLDEELIEVIEW OUV - UTD://DUIJODED.DUITCOU/SITE/ADOUT/OUDOEUNES XI

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1 2	
3	49. methylprednisolone*:ti,ab,kw
4	50. mometasone next furoate*:ti,ab,kw
5	51. nasonex*:ti,ab,kw
6 7	52. paramethasone*:ti,ab,kw
8	53. predniso*:ti,ab,kw
9	54. pregnenolone*:ti,ab,kw
10	55. pulmicort*:ti,ab,kw
11	56. qvar*:ti,ab,kw
12	• • • •
13 14	57. rhinocort*:ti,ab,kw
14	58. seretide*:ti,ab,kw
16	59. solu next cortef*:ti,ab,kw
17	60. symbicort*:ti,ab,kw
18	61. tetrahydrocortisol*:ti,ab,kw
19	62. triamcinolone*:ti,ab,kw
20	63. tricort*:ti,ab,kw
21 22	64. vanceril*:ti,ab,kw
23	65. {OR #1-#64}
24	66. [mh ^ "Acute Disease"] and (asthma* or pneumonia* or wheez*)
25	67. [mh Asthma] and (acute* or emergenc* or exacerbation* or severe*)
26	68. [mh "Bronchial Hyperreactivity"]
27	69. [mh "Bronchial Spasm"]
28 29	70. [mh Bronchiolitis]
29 30	71. [mh ^ Croup]
31	72. [mh Dyspnea]
32	73. [mh ^ Emergencies] and (asthma* or pneumonia* or wheez*)
33	74. [mh ^ "Emergency Medical Services"] and (asthma* or pneumonia* or wheez*)
34	75. [mh ^ "Emergency Services, Hospital"] and (asthma* or pneumonia* or wheez*)
35	76. [mh Pharyngitis]
36 37	77. [mh Pneumonia] and (acute* or emergenc* or exacerbation* or severe*)
38	· · · · · ·
39	78. [mh "Respiratory Syncytial Viruses"]
40	79. [mh "Respiratory Syncytial Virus Infections"]
41	80. [mh Rhinitis]
42	81. [mh Sinusitis]
43 44	82. [mh ^ "Status Asthmaticus"]
45	83. [mh ^ "Respiratory Sounds"] and (acute* or emergenc* or exacerbation* or severe*)
46	84. ((acute* or emergenc* or exacerbation* or severe*) near/5 (asthma* or pneumonia* or
47	wheez*)):ti,ab,kw
48	85. (breath* near/2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)):ti,ab,kw
49	86. (bronch* near/3 (constrict* or spas*)):ti,ab,kw
50 51	87. bronchiolitis*:ti,ab,kw
52	88. bronchoconstrict*:ti,ab,kw
53	89. bronchospasm*:ti,ab,kw
54	90. croup*:ti,ab,kw
55	91. dyspne*:ti,ab,kw
56	
57 59	Constant of A. Dere
58 59	Supplement 1 - Page

- 92. (lung* near/2 (disease* or infect*)):ti,ab,kw
- 93. (("naso pharynx" or nasopharynx* or "para nasal" or paranasal* or sinus*) near/3 (infect* or inflam*)):ti,ab,kw
- 94. (nasosinusit* or rhinosinusit*):ti,ab,kw
- 95. pharyngitis*:ti,ab,kw
- 96. (respiratory* near/2 (attack* or infect* or inflam* or virus*)):ti,ab,kw
- 97. rhinit*:ti,ab,kw
- 98. sinusit*:ti,ab,kw
- 99. tonsillitis*:ti,ab,kw
- 100. {or #66-#99}

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- 101. [mh child]
- 102. [mh infant]
- 103. [mh Pediatrics]
- 104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*):ti,ab,kw
- 105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*):ti,ab,kw
 - 106. {or #101-#105}
 - 107. #65 and #100 and #106
 - 108. #65 and #100 and #106 in Trials
 - Database: Ovid Embase 1974 to 2014 September 12 Date original search conducted: 14 September 2014 Strategy:
 - 1. antiinflammatory agent/
 - 2. beclometasone/
 - 3. budesonide/
 - 4. corticosteroid/
 - 5. exp glucocorticoid/
 - 6. hydroxycorticosteroid/
 - 7. pregnane derivitative/
 - 8. triamcinolone acetonide/
 - 9. adrenal cortex hormone*.tw,tn.
 - 10. advair*.tw,tn.
 - 11. alvesco*.tw,tn.
- 12. azmacort*.tw,tn.
- 13. becl?met*.tw,tn.
 - 14. beclazone*.tw,tn.
 - 15. beclo?ort*.tw,tn.
 - 16. beclovent*.tw,tn.
 - 17. beconase*.tw,tn.
- 18. becotide*.tw,tn.
 - 19. betamet?asone*.tw,tn.
 - 20. betnesol*.tw,tn.
- 21. budesonide*.tw,tn.

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1 2 3 22. ciclesonide*.tw.tn. 4 23. clobetasol*.tw,tn. 5 24. cortiso*.tw,tn. 6 25. cortodoxone*.tw,tn. 7 8 26. corticosteroid*.tw,tn. 9 27. decadron*.tw,tn. 10 28. depo medrone*.tw,tn. 11 29. desoximet?asone*.tw,tn. 12 30. dexamethasone*.tw,tn. 13 14 31. deflazacort*.tw,tn. 15 32. diflucortolone*.tw,tn. 16 33. flixotide*.tw,tn. 17 ,tn. *w,tn. 34. flumethasone*.tw,tn. 18 35. flunisolide*.tw,tn. 19 20 36. fluocino*.tw,tn. 21 37. fluocortolone*.tw,tn. 22 38. fluorometholone*.tw,tn. 23 39. flurandrenolone*.tw,tn. 24 25 40. fluticasone*.tw,tn. 26 41. glucocortico*.tw,tn. 27 42. hydrocortisone*.tw,tn. 28 43. hydroxycorticostero*.tw,tn. 29 44. hydrocortone*.tw,tn. 30 31 45. hydroxypregnenolone*.tw,tn. 32 46. kenacort*.tw,tn. 33 47. kenalog*.tw,tn. 34 48. medrone*.tw,tn. 35 49. methylprednisolone*.tw,tn. 36 37 50. mometasone furoate*.tw,tn. 38 51. nasonex*.tw,tn. 39 52. paramethasone*.tw,tn. 40 53. predniso*.tw,tn. 41 42 54. pregnenolone*.tw,tn. 43 55. pulmicort*.tw,tn. 44 56. qvar*.tw,tn. 45 57. rhinocort*.tw,tn. 46 58. seretide*.tw,tn. 47 59. solu cortef*.tw,tn. 48 49 60. symbicort*.tw,tn. 50 61. tetrahydrocortisol*.tw,tn. 51 62. triamcinolone*.tw,tn. 52 63. tricort*.tw.tn. 53 54 64. vanceril*.tw,tn. 55 65. or/1-64 56 57 58

1 2	
2 3	66. acute disease/ and (asthma* or pneumonia* or wheez*).mp.
4	67. exp asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
5	68. exp breathing disorder/ and (acute* or emergenc* or exacerbation* or severe*).mp.
6	
7	69. bronchospasm/
8 9	70. bronchus hyperreactivity/
10	71. exp bronchiolitis/
11	72. croup/
12	73. exp dyspnea/
13	74. emergency/ and (asthma* or pneumonia* or wheez*).mp.
14	75. emergency health service/ and (asthma* or pneumonia* or wheez*).mp.
15	76. exp emergency treatment/ and (asthma* or pneumonia* or wheez*).mp.
16 17	77. emergency ward/ and (asthma* or pneumonia* or wheez*).mp.
18	78. exp pharyngitis/
19	79. exp pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
20	80. Respiratory syncytial pneumovirus/
21	81. respiratory syncytial virus infection/
22	82. exp rhinitis/
23	83. exp sinusitis/
24 25	84. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw.
26	85. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw.
27	
28	86. (bronch* adj3 (constrict* or spas*)).tw.
29	87. bronchiolitis*.tw.
30	88. bronchoconstrict*.tw.
31 22	89. bronchospasm*.tw.
32 33	90. croup*.tw.
34	91. dyspne*.tw.
35	92. (lung* adj2 (disease* or infect*)).tw.
36	93. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
37	94. (nasosinusit* or rhinosinusit*).tw.
38	95. pharyngitis*.tw.
39 40	96. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
40 41	97. rhinit*.tw.
42	98. sinusit*.tw.
43	99. tonsillitis*.tw.
44	100. or/66-99
45	101. exp child/
46	102. exp infant/
47 48	103. exp Pediatrics/
40 49	•
50	104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).mp.
51	105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).mp.
52	106. or/101-105
53	107. and/65,100,106
54	108. crossover procedure/
55 56	109. double blind procedure/
56 57	
58	Supplement 1 - Page 11 of 1
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4	110. randomized controlled trial/
5	110. single blind procedure/
6	111. allocat*.tw.
7	112. assign*.tw.
8	113. cross over*.tw.
9 10	114. crossover*.tw.
10	115. doubl* adj blind*.tw.
12	116. factorial*.tw.
13	117. placebo*.tw.
14	118. random*.tw.
15	119. singl* adj blind*.tw.
16 17	120. volunteer*.tw.
17	121. or/108-120
19	122. exp case control study/
20	123. case report/
21	124. case study/
22	125. cross-sectional study/
23	126. cohort analysis/
24 25	127. case control.tw.
25	
27	128. (case adj (report* or study or studies or series)).tw.
28	129. cohort analy*.tw.
29	130. (cohort adj (study or studies)).tw.
30	131. cross sectional.tw.
31	132. (follow up adj (study or studies)).tw.
32 33	133. longitudinal.tw.
34	134. (observational adj (study or studies)).tw.
35	135. retrospective.tw.
36	136. or/122-135
37	137. 121 or 136
38	138. animals/ not (animals/ and humans/)
39 40	139. 137 not 138
40	140. 107 and 139
42	141. (editorial or journal editorial or journal letter or journal note or letter or review).pt.
43	142. 140 not 141
44	143. limit 142 to embase
45	
46 47	Database: Drugs@FDA
48	URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
49	Date original search conducted: 5 September 2014
50	Strategy:
51	Strategy.
52	Searched Drugs@FDA for drug name keywords:
53 54	
54 55	1. beclametasone dipropionate
56	2. budesonide
57	
58	Supplement 1
59	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
60	To peer review only - http://binjopen.binj.com/site/about/guideimes.xhtml

ement 1 - Page **12** of **13**

- 3. ciclesonide
- 4. fluticasone propionate
- 5. mometasone furoate
- 6. triamcinolone acetonide

Retrieved all available medical and statistical reviews for drugs in these classes with systemic routes of administration

Database: Health Canada Drug Products Database URL: <u>http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php</u>

Date original search conducted: 8 September 2014 Strategy:

Searched Health Canada Drug Products Database for drug name keywords:

- 1. beclomethasone
- 2. budesonide
- 3. ciclesonide
- 4. fluticasone propionate
- 5. mometasone furoate
- 6. triamcinolone acetonide

Retrieved all available monographs for drugs in these classes with systemic routes of administration

Database: European Medicines Agency's European Public Assessment Reports **URL**:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b 01ac058001d124

Date original search conducted: 9, 10 September 2014 **Strategy**:

Searched EMA reports for drug name keywords:

- 1. beclomethasone
- 2. beclometasone
- 3. beclamethasone
- 4. beclometasone
- 5. budesonide
- 6. ciclesonide
- 7. fluticasone
- 8. mometasone
- 9. triamcinolone acetonide
- 10. Also searched for "corticosteroids" as a pharmaco therapeutic group

Retrieved all available reports for drugs in these classes with systemic routes of administration

Review	ver ID:	Date:	/	/2015	Record ID:		
Criteria	3					Yes	
1. PUB	LICATION TYPE						
a. P	rimary research (RCTs, o	cohort studi	es, cas	e control studi	es, case reports, and case		
series)							
Exclud	2:						
•	Systematic reviews, le	tters to edite	or, con	nmentaries			
2. Pop	ulation						
a.	Children ≤6 years of ag	ge, where ag	e subg	roups data is a	vailable:		
Jnclea							
•	If aggregate/subgroup	data include	e but a	re not limited	to age ≤6 years		
Exclud	2:						
•	e: If data is reported in a	ggregate wit	h olde:	r ages			
	e: If data is reported in a DITION Children with acute re			2.	wing):		_
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis			2.	owing):		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup	spiratory dis		2.	owing):		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p	spiratory dis	ease (a	any of the follo	2		
• 8. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial w Respiratory distress du	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
8. CON a. • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs	any of the follo scess, effusion, her viruses	2		
8. CON a. • • • • • • • • • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs irus/ot bodie	any of the follo scess, effusion, her viruses s	2		
a. • • • • • • • • • • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome e: patients in NICU, PICU	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs irus/ot bodie	any of the follo scess, effusion, her viruses s	2		

	* and systemic (IV, IM, oral) corticosteroids used for ≤14 days per			
course, inc	luding (but not limited to):			
 Beclometh 				
 Budesonid 				
Ciclesonide				
 Dexametha 	asone			
Fluticasone	e propionate			
 Mometaso 	ne furoate			
 Prednisolo 	ne			
Prednisone				
 Triamcinol 	one acetonide			
 combination 	on therapies (e.g. ICS + short-acting beta-agonists)			
Exclude				
 topical (no 	n-systemic) corticosteroid therapy			
* inhaled (moderation	te- to high-dose) corticosteroids, following GINA guidelines for low			
doses for children	5 years and younger (see Box 6-6 below).			
5. Comparator gro	up (where relevant)			
a. Any comparis	on, including non-pharmacologic interventions which may act similarly			
to a				
placebo				
6. OUTCOME				
Adverse drug react	ion, side effect, adverse effects/events, adverse reactions	\Box	\Box	
U				
7. Setting				
Focus is on outpati	ent settings (e.g. ambulatory, ED), and hospitalised patients			
		_	_	
Exclude				
• patients in	NICU, PICU			
Comments:				

GINA Global Strategy for Asthma Management and Prevention: http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Jun11.pdf

Box 6-6. Low daily doses of inhaled corticosteroids for children 5 years and younger

Drug	Low daily dose (mcg)		
Beclometasone dipropionate (HFA)	100		
Budesonide pMDI + spacer	200		

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Budenoside nebulized	500
Fluticasone proprionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studied below age 4 years
Triamcinolone acetonide	Not studied in this age group

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Supplement 3	Characteristics of included studies
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a.	Summary characteristics of included studies	p. 1-2
b.	Summary characteristics of included studies - comparisons	р. З
c.	Characteristics of included studies	р. 4-76

Supplement 3a. Summary characteristics of included studies

Study characteristic	N (% ¹)
Country	
Canada	15 (18)
US	15 (18)
Australia	7 (8)
UK	5 (6)
Denmark	4 (5)
Finland	4 (5)
Italy, Netherlands, Taiwan, Thailand	3, each (14)
China, Greece, Ireland, Israel, Japan, Saudi Arabia (SA), Spain, Sweden,	2, each (21)
Turkey	
Brazil, Germany, Mexico, Qatar	1, each (5)
SA & UK	1 (1)
Study designs	
RCT (all)	68 (80)
2-arm	52 (61)
3-arm	7 (8)
4-arm non-factorial	1 (1)
factorial 4 x4	4 (5)
crossover	2 (2)
trial registry	1 (1)
conference abstract	1 (1)
Non-RCT	5 (6)
Cohort	4 (5)
Case control	1 (1)
Case series	4 (5)
Case report	3 (4)
Number of centres	
Single centre	56 (66)
Multi-centre	24 (28)
Unclear/NR	5 (6)
Setting	
Inpatient	41 (48)
Outpatient	22 (26)
Inpatient & outpatient	21 (25)
NR	1 (1)

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Funding	
Not reported	35 (41)
Non-industry	25 (29)
Industry	9 (11)
Industry & non-industry	15 (18)
No direct funding	1 (1)
Year of publication, median (range)	2002 (1964-201
Respiratory condition	
Asthma	27 (32)
Croup	22 (26)
Bronchiolitis	15 (18)
Wheeze	14 (16)
Asthma/croup, palatability & tolerability of CS	2 (2)
Pharyngitis	1 (1)
Shortness of breath	1 (1)
Refractory pneumonia	1 (1)
Bronchiolitis & laryngitis	1 (1)
Bronchiolitis, viral wheeze & croup	1 (1)

CS: corticosteroid; N: number of studies; NR: not reported; RCT: randomized controlled trial; SA: Saudi Arabia; UK: United Kingdom; US: United States

¹ sum of percentages may not total 100 due to rounding

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Number of treatment groups	Comparison	No. of studies	No. of studies	
		(no. of patients)	contributing	
			data	
			(no. of patients)	
2-arms	Systemic CS vs. placebo/no intervention/standard care	26 (4166)	15 (1425)	
	Systemic CS vs. systemic CS	12 (1683)	5 (1051)	
	Systemic CS vs. non-CS	2 (180)	0	
	Systemic CS vs. inhaled CS	3 (124)	1 (18)	
	Systemic CS vs. systemic CS + placebo	1 (125)	0	
	Inhaled CS vs. placebo/no intervention	14 (2367)	8 (1234)	
	Inhaled CS vs. non-CS	1 (66)	0	
3-arms	Systemic CS vs. systemic CS vs. no intervention	2 (180)	1 (80)	
	Systemic CS vs. systemic CS vs. systemic CS	5 (624)	2 (99)	
	Systemic CS vs. inhaled CS vs. non-CS/placebo	2 (208)	2 (183)	
	Systemic CS vs. inhaled CS vs. combined (systemic + inhaled)	1 (198)	1 (197)	
	Systemic CS + non-CS vs. inhaled CS + sal + non-CS vs. inhaled CS + sal	1 (238)	0	
	Inhaled CS vs. inhaled CS vs. no CS	1 (80)	1 (80)	
4-arms	Systemic CS vs. inhaled CS vs. non-CS vs. placebo	1 (114)	1 (114)	
	Systemic CS + sal dose1 vs. systemic CS + sal dose2 vs. sal dose1 +	1 (70)	1 (70)	
	placebo vs. sal dose2 + placebo			
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal +	1 (69)	1 (69)	
	placebo	Þ		
	Systemic CS + non-CS vs. systemic CS + placebo vs. non-CS + placebo vs.	1 (800)	1 (800)	
	placebo + placebo			
	Systemic CS + sal vs. systemic CS + placebo vs. sal + placebo vs. placebo	1 (32)	0	
Non-comparative (case	Systemic CS	5 (5)	0	
reports/series)	Mode of administration NR	2 (3)	0	

CS: corticosteroid; no.: number; NR: not reported; sal: salbutamol; vs.: versus

Author,	Study	Respirato	Comparators,	Co-	Time points	Outcome
year	design	ry	no. of	interventions;	for	related t
Country	Setting	condition	participants	Maintenance	assessment	adverse
Funding	No. of	Age		CS	s;	events
source	centres	(range)			FU	
Alangari	RCT	Asthma	1) Budesonide	Salbutamol,	Baseline, at	The most
2014	ED	2-12y	500mcg/dose, 3	ipratropium &	1h, 2h, 3h	frequentl
Saudi	1		doses 20min	prednisolone	and 4h	reported
Arabia			apart (neb),		from the	adverse
Non-			n=458	No CS in	start of	effects w
industry			2) Placebo	preceding 7d	medication	fine trem
funded			saline, 3 doses		s;	(17 cases)
			20min apart		FU 72h	palpitatio
			(neb), n=448		post-	(11 cases)
					discharge	None of t
						reported
						adverse
						effects wa
						serious, a
						none was
						significan
			L			different
						between
						two grou
Alansari	RCT	Bronchiol	1)	Epinephrine,	At study	Daily
2013	Pediatri	itis	Dexamethasone	oxygen &	entry, then	telephone
Qatar	С	<=18mo	1.0mg first day,	hydration	assessed if	surveillan
Non-	emerge		then 0.6mg for		ready for	days)
industry	ncy unit		4d (oral) + sal,	No CS in	discharge	revealed
funded	1		5d total (neb),	preceding 48h	at 12h, 18h,	particular
			n=102		24h, 36h &	effect
			2) Placebo (oral)		48h;	concerns
			+ sal, 5d total		FU by	either
			(neb), n=98		telephone	treatmen
					1wk post-	group.
					discharge	
Aljebab	Cohort,	Asthma/c	SA	NR	After each	In SA and
2017	3-arm	roup,	1)		dose	UK,
Saudi	Pediatri	palatabili	Dexamethasone	Most patients	(within	dexameth
Arabia &	c ED of	ty &	0.5mg/5mL	in	10min) &	ne had th
UK	hospital	tolerabilit	elixir (oral),	prednisolone	daily on D1-	highest
Unfunded		у	n=33	groups had	D5	palatabili

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2					
3	(SA &	2-10y	2) Prednisolone	received oral	scores and
4 5	UK)	(SA);	base 5.0mg	steroids	prednisolone
6	2	2-16y	tablets (oral),	previously;	base tablets
7		(UK)	n=52	however,	had the
8			3) Prednisolone	most patients	lowest.
9			sodium	and none had	Palatability
10			phosphate	received oral	scores
11 12			15.0mg/mL	steroids	improved for
12			syrup (oral),	previously in	all
14			n=37	the SA & UK	formulations
15			11-57	dexamethaso	of
16			UK	ne groups,	prednisolone
17			1)	respectively	with each
18 19			Dexamethasone	respectively	
20					subsequent
20			2.0mg/5mL		daily dose.
22			elixir (oral),		In SA,
23			n=53		prednisolone
24			2) Prednisolone		base tablets
25			base 5.0mg		were
26 27			tablet (oral),		associated
27			n=38		with more
29			3) Prednisolone		nausea (24 vs.
30			sodium		7 patients)
31			phosphate 🦊		and vomiting
32			5.0mg soluble		(5 vs. 0
33			tablets (oral),	ez	patients) than
34 35			n=42	4	sodium
36					phosphate
37					syrup.
38					In the UK,
39					vomiting
40					occurred
41 42					more
42					
44					frequently
45					with
46					prednisolone
47					base (8
48					patients) than
49 50					sodium
51					phosphate
52					soluble
53					tablets (2
54					patients)
55					(p=0.041).
56	ı	L			

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						In both centres, dexamethaso ne was associated with less side effects. Vomiting (1 vs. 0 patients), nausea (7 vs.
			Per C			3 patients), and abdominal pain (10 vs. 8 patients) occurred more with dexamethaso ne sodium phosphate solution than dexamethaso
Alshehr 2005 Saudi Arabia Funding NR	RCT Emerge ncy rooms & outpati ent clinics 3	Croup 3mo-9y	1) Dexamethasone 0.6mg/kg, single dose (oral), n=36 2) Dexamethasone 0.15mg/kg, single dose (oral), n=36	Mist therapy, racemic epinephrine, oxygen & antibiotics No CS in preceding 4wk	12h & 24h after treatment & change in total croup scores per 12h intervals within & between study groups	ne elixir. Two patients developed bronchopneu monia on second day of admission as confirmed by chest x-ray and one patient had bacterial tracheitis. All these three patients were in group A (0.6 mg/kg dexamethaso ne). No adverse events were

				2	dex vs. 1 pred); Headache (0 dex vs. 0 pred); Palpitation (r dex vs. 0 pred); Excessive urination (0
Bacharier RCT, 3- 2008 arm	At least 2 wheeze	1) Montelukast 4.0mg once	Albuterol, prednisolone	Clinic visits 4wk after	dex vs. 1 pred) The 3 groups did not diffe

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Non-	Clinical	in last	placebo ICS	asthma	on, then	several othe
industry &	center	year	twice daily for	medications	every 8wk;	outcomes
industry	5	12-59mo	7d (neb), n=95		FU by	assessed ove
funded			2) Budesonide	No more than	phone 2wk	the 1-year
			1.0mg twice	6 courses of	after	trial, includir
			daily (neb) +	CS in past year	randomizati	oral
			placebo LTRA		on,	corticostero
			once daily (neb),		followed by	use, health
			n=96		calls 4wk	care use,
					after each	-
			3) conventional			linear growt
		\sim	therapy +		scheduled	quality of lif
			placebo		clinic visit	and
			(systemic +			frequencies
			inhaled), n=47		Linear	adverse
					growth in	events.
			Multiple		height or	
			courses over 1yr		length	
					(assessmen	
					t method	
					NR) from	
					baseline to	
					study end	
					(12mo)	
Bisgaard	RCT	Wheeze	1) Budesonide	NR	Height &	Safety, as
2006	Clinical	1mo	400mcg/day for		bone	evaluated by
Denmark	researc	Into	2wk (MDI),	NR	mineral	height and
Non-	h unit		n=149	NIX		bone miner
					density	
industry &	1		2) Placebo once		measured	density, we
industry			daily for 2wk		using	not affected
funded			(MDI), n=145		Harpenden	by treatmer
					stadiometry	the height a
			Multiple		at 3yrs of	three years
			courses over		age	age measur
			3yrs			by
						stadiometry
						and bone
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						ultrasonogr
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						unaffected b
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						treatment
						group.
Bjornson	RCT	Croup	1)	Mist,	D1, D2, D3,	Among th
2004	Pediatri	mean	Dexamethasone	antibiotics &	D7 & D21	720 patier
Canada	c ED	35+/-23	0.6mg, max.	nebulized	after day of	there wer
Non-	4	mo	20.0mg, single	epinephrine	treatment;	cases of
industry &			dose (oral),	or beta-	FU	gastrointe
industry			n=359	agonists	interview	al bleedin
funded			2) Placebo		with parent	complicat
			solution, single	No CS in	on D7 and	varicella,
		$\mathbf{\wedge}$	dose (oral),	preceding 2wk	chart and	bacterial
			n=361		administrati	tracheitis.
					ve database	There we
					review	cases of
						pneumon
						in the
						dexameth
						ne group)
						these case
						were
						managed
			\sim			an outpat
						basis, with
						significant sequelae.
				\mathbf{O}		Repeated
						short cour
						of oral
						corticoste
						s are not
						associated
				•		with long-
						term nega
						effects on
						bone
						metabolis
						bone den
						or adrena
						function.
						There we
						no serious
						adverse
						events
						attributab

0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 8 9 0 0 1 2 3 4 5 5 6 7 8 8 9 0 1 1 2 3 4 5 5 6 7 8 8 1 7 8 8 1 7 8 8 1 7 8 8 1 7 8 1 8 1 8 1 1 1 1 1 1 1 1 1 1 1 1 1					to therapy in any children in our study. However, the study was not sufficiently powered to exclude the possibility of rare adverse events. Supplementar y Table 1 list of adverse events, n (dex vs. placebo): Abnormal bowel movements (6 vs. 5); Fever (5 vs. 4); Pneumonia (3 vs. 4); Vomiting or gastroenteriti s (3 vs. 4); Otitis media (1 vs. 5); Bronchitis (3 vs. 1); Sore throat (1 vs. 2); Streptococcal throat infection (1 vs. 1); Abdominal pain (1 vs. 1); Rash (2 vs. 0); Dehydration (1 vs. 0); Febrile seizure (1 vs. 0);
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						RSV infectio
						(1 vs. 0);
						Uncomplica ⁻
						d varicella ((
						vs. 1);
						Urinary trac
						infection (0
						vs. 1);
						Irritability (1
						vs. 1);
						Eye dischar
						(1 vs. 0);
						Sinusitis (0
						1);
						Bleeding fro
						ear (0 vs. 1)
			6			Nasal
						discharge (1
						vs. 0)
Brunette	NRCT	Asthma	1) Theophylline	None	Monthly or	No side effe
1988	Hospita	<6y	8.0mg/kg every		every	was observe
Canada	I		6-8h (oral) +	NR	second	in a particul
Funding NR	1		metaproterenol		month,	case which
			0.3-0.7 mg/kg 🥢		depending	received
			every 6-8h 🔹 🔹		on severity	longer
			(oral)+		of disease;	duration of
			prednisone	4		corticostero
			1.0mg/kg/day		Growth	(high
			for 7-14d (oral),		(mean	cumulative
			n=16		height gain	corticosterc
			2) Theophylline		in cm/yr	dose).
			8.0mg/kg every		and height	Growth and
			6-8h (oral) +		as	weight gain
			metaproterenol		percentile	for all child
			0.3-0.7mg/kg		of normal	were within
			every 6-8h for		distribution	the normal
			7-14d (oral),) assessed	range durin
			n=16		(assessmen	the two
					t method	periods.
			Multiple		NR) at the	
			courses over 1yr		end of each	
					of two 1-yr	
			1	1	periods	

Buckingha	RCT	RSV	1)	Other	Enrolment	Serious
m 2002	Pediatri	(bronchio	Dexamethasone	treatment	& daily until	adverse
USA	С	litis)	0.5mg/kg/dose	(not specified)	discharge;	events
Non-	hospital	<24mo	every 12h for 4d		FU 30d	occurre
industry	2		(IV), n=22	No CS in	after	patient
funded			2) Placebo	preceding 3wk	enrolment	dexam
			saline every 12h			ne gro
			for 4d (IV), n=19			infant
						develo
						progre
						respira
						failure
						did no
						improv
						high-
						freque
						oscilla
						ventila
						extrac
						Imem
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Bulow 1999 Denmark Non- industry funded	RCT Pediatri c hospital 3	RSV (bronchio litis) 0-2y	1) Prednisolone 5.0mg/ml at dose of 2mg/kg/day, first dose at enrolment and for 4d (oral), or methylprednisol one for patients with IV line (40.0mg/ml at dose of 1.5mg/kg/day) for 5d (IV), n=73 2) quinine hydrochloride (or saline for patients with IV line) for 5d (IV), n=74	Beta-2- agonist, antibiotics, oxygen & hydration No CS in preceding month	Enrolment & 5d; FU 1mo & at 1y	drug. No patients in either group had microscopic or gross gastrointestin al bleeding, and no patients required antihypertens ve therapy during the study. A total of 11 patients (7 in the prednisolone group and 4 i the placebo group) did no complete the treatment because of side effects, primarily vomiting (8 patients), which were mild in all cases.
Chang 2008 Australia Non- industry & industry funded	RCT Pediatri c & general ED 3	Asthma 2-15y	1) Prednisolone 1.0mg/kg (max. 50.0mg/day) for 3d + placebo solution for 2d (oral), n=101 2) Prednisolone 1.0mg/kg (max.	NR No maintenance CS or CS preceding presentation	24h, 48h, D5, D7, D10, D14 & D28	There were five recorded adverse events, with no significant difference between groups. In the 3-day group,

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			50.0mg/day) for			two parents
			5d (oral), n=100			reported that
						their child ha
						behavioural
						disturbance
						(cranky and
						irritable) and
						one had a
						rash, while
						two children
						in the 5-day
						group had
						behavioural
						disturbance
						(angry and
						aggressive).
Chen 2008	RCT, 3-	Asthma	1) Budesonide	NR	0.5h before	All three
China	arm	1-14y	0.5mg (neb) +		& post-	groups of
Funding NR	Pediatri		sal +	No CS within	treatment	children
	с		ipratropium; 1-	48h	& 5d post-	showed no
	outpati		6yo (n=32); 6-		treatment	adverse
	ent,		14yo (n=21)			effects.
	hospital		2) Budesonide			
	ward,		0.2-0.4mg (neb)			
	or ED		+ sal +			
	1		ipratropium; 1-			
			6yo (n=25); 6-	4		
			14yo (n=16)			
			3)			
			Dexamethasone		5	
			2.0mg (<2yo),			
			4.0mg (2-6yo)			
			(IV); 1-6yo			
			(n=15); 6-14yo			
			(n=14)			
Chub-	RCT	Croup	1)	Epinephrine,	0, 1h, 2h,	There was no
Appakarn	Pediatri	6mo-5y	Dexamethasone	mist,	3h, 4h, 6h,	significant
2007	С		0.5ml/kg of 0.15	antibiotics &	8h, 10h &	adverse
Thailand	hospital		mg/kg, single	oxygen	12h post-	reaction fron
Funding NR	ward		dose (IV), n=20		treatment	dexamethaso
	1		2)	No CS in		ne treatment
			Dexamethasone	preceding 2wk		in either
			0.5 ml/kg of	1		group.

			0.6mg/kg, single			
	-		dose (IV), n=21			
Clavenna	RCT	Wheeze	1)	Paracetamol,	Entry visit,	No
2014	Family	1-5y	Beclomethason	nasal saline	D11 (or	differences
Italy	pediatri		e 400mcg (1ml)	irrigation &	prior if	were found
Non-	c health		twice daily for	antibiotics	requested	the incident
industry &	units		10d (neb),		by parents)	of adverse
industry	9		n=264	No CS in	& daily	events
funded			2) Placebo twice	preceding	diary	reported by
			daily for 10d	month	symptom	parents at t
			(neb), n=261		recording	end of the
					during 10d	therapy.
					treatment	Table 4 AEs
						reported by
						parents, n
						(beclo vs.
						placebo):
						Any AEs (97
						vs. 98)
						Hoarseness
						(34 vs. 34);
						Diarrhea (27
						vs. 35);
			L			Skin rash (19
						vs. 22);
						Vomiting (19
				4		vs. 20);
						Candidiasis
						(12 vs. 15);
					4	Others (25 v
						26)
						Two serious
						adverse
						events were
						reported by
						pediatrician
						1 hospital
						admission fo
						urinary tract
						infection in
						the
						beclometha
						ne group an
						1

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Connett 1994 UK Non- industry funded	RCT, factoria l Hospita l 1	Asthma >18mo	1) Prednisolone 2.0mg/kg single dose (oral) + sal 0.15mg/kg every 30min for 3h (max. 5.0mg) (neb), n=18 2) Prednisolone 2.0mg/kg single dose (oral) + sal 5.0mg every 1- 4h as needed (neb), n=19 3) Placebo single dose (oral) + sal 0.15mg/kg every 30min for 3h (neb), n=15 4) Placebo single dose (oral) plus sal 5.0mg every 1- 4h as needed (neb), n=18	NR No CS in preceding 2wk	On arrival, after nebulizatio n & at treatment completion	hospitalization n for adenoidectory y and tonsillectomy in the placebor group. Neither adverse event was drug related. Tremor and hyperactivity were more commonly reported in those children receiving the more intensive nebuliser regimen but symptoms were mild and self-limiting in most instances. Vomiting was more a feature of disease severity than any particular treatment group. There was no significant change in heart and respiratory rates
						change in heart and

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						though there was a trend towards decreasing tachypnoea i all four groups.
Connolly 1969 Ireland Funding NR	RCT Hospita I 1	RSV Bronchiol itis 0-2y	1) Prednisolone D1=15.0mg; D2-3=10.0mg; D4-5=5.0mg; D6-7=2.5mg (NR, likely IV), n=47 2) Placebo (NR, likely IV), n=48	Ampicillin, oxygen NR	FU 1mo & 1y	There was no evidence in this trial that prednisolone treatment of the patients affected the antibody response. In the dosage used in this trial, prednisolone had no beneficial or harmful effects on th course of the disease in severely ill children. There were no deaths.
Corneli 2007 USA Non- industry & industry funded	RCT ED 20	Bronchiol itis 2-12mo	1) Dexamethasone 1.0mg/kg (max. 12mg), single dose (oral), n=305 2) Placebo solution 1.0ml/kg (max. 12ml), NR (oral), n=295	Not specified No CS in preceding 14d	Baseline, 1h & 4 h; FU at 7-10d by telephone	There were few adverse events. No infant had gastrointesti al bleeding, hypertension or complicated varicella. Vomiting within 20 mi after administratio

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						n of study
						medication
						(5.5% in dex;
						4.7% in
						placebo).
						Pneumonia
						was
						diagnosed in
						three infants
						two were in
						the placebo
						group, and a
						empyema
						developed in
						one of these
						two infants.
Cronin	RCT	Asthma	1)	Regular	Baseline &	Seven
2016	Tertiary	2-16y	Dexamethasone	inhaled	D4 for	patients in th
Ireland	hospital	,	0.3mg/kg (max.	bronchodilato	primary	PRED group
Non-	ED		12.0mg) single	rs prior to	outcome;	(5.7%)
industry	1		dose, n=123	enrolment in	14d period	vomited
funded	1		2) Prednisolone	trial	for adverse	within 30
Tunaca			1.0mg/kg per	that	events	minutes of
			day, once daily	No IV or oral	events	the dose of
			(max. 40.0mg)	CS in previous		steroid on da
			for 3d, n=122	4wk		1 in the ED
			101 50, 11–122	400 K		
						compared with none in
						the DEX grou (absolute
					5	
						difference -
						5.7%; 95%Cl
						9.9% to -
						1.54%). Seve
						patients
						vomited afte
						the
						prednisolone
						dose on day
						and 6 vomite
						after the dos
						on day 3. A
						total of 14
						patients

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						vomited after at least 1 dose of prednisolone. No other adverse events attributable to the study medications were noted.
Csonka 2003 Finland Non- industry funded	RCT Pediatri c ED 1	Viral respirator y infection- induced lower airway disease 6-35mo	1) Prednisolone 2.0mg/kg in ED followed by 2.0mg/kg/day for 3d (oral), n=113 2) Placebo 10.0mL fructose in water (in ED) followed by subsequent doses for 3d, n=117	NR	Diary recordings twice daily for 14d; examinatio n by physician 14d-21d post-ED visit	Fifteen children (4 in the placebo group and 11 in the prednisolone group) discontinued the study medication because of perceived side effects. The reported reactions were mild and resolved without
					2	special interventions. These included vomiting (4 vs 9), diarrhea (6 vs 6), rash (0 vs 2), and restlessness (2 vs 3) in the placebo and prednisolone groups, respectively.

Daugbjerg	RCT, 4-	First or	1) Prednisolone	NR	Daily for 5d	No side
1993	arm	recurrent	4.0-6.0mg/kg on		or until	effects were
Denmark	Pediatri	wheeze	admission; D2-	No CS	discharge	observed,
Non-	с	0-18mo	3=1.6-2.6mg/kg	preceding		specifically r
industry &	depart		(oral) +	study		hoarseness,
industry	ment		terbutaline			oral
funded	5		0.12-0.2mg/kg			candidiasis o
			(4ml) every 4h			continued
			until discharge			fever, in any
			or for 5d (neb),			of the group
			n=31			No significar
			2) Placebo			tachycardia
			solution (oral) +			was found in
			budesonide			the treatme
			0.5mg every 4h			groups
			until discharge			compared
			or for 5d (neb) +			with placebo
			terbutaline			
			0.12-0.2mg/kg			
			(4ml) every 4h			
			until discharge			
			or for 5d, n=29			
			3) Placebo			
			solution (oral) +			
			placebo (neb) + <			
			terbutaline			
			0.12-0.2mg/kg			
			every 4h until			
			discharge or for		•	
			5d (neb), n=27		5	
			4) Placebo			
			solution (oral) + placebo (neb) +			
			placebo (neb) +			
			(neb), n=27			
Dawson	RCT	Asthma	1) Prednisolone	None	D1 to D5	Twenty-one
1993	Hospita	<6.5y	1.0mg/kg			of the
Australia			tablets, every	NR		children
Industry	1		24h for 5d			taking the
funded			(oral), n=25			solution too
			2) Prednisolone			it easily on
			1.0mg/kg			day 3,
			solution, every			compared to
						two in the

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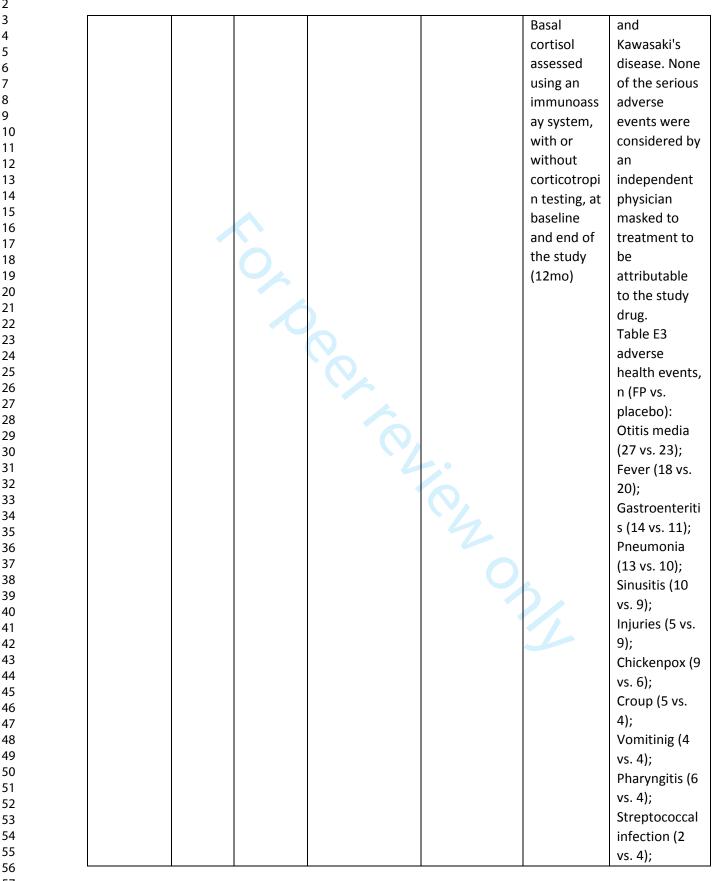
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· · · · · ·	I			
		24h for 5d		tablet group
		(oral), n=26		on the same
				day. A
				difference
				was noted on
				day 1 with
				regard to
				mood change
				but there was
				no significant
				difference at
				any stage
				between the
				groups in
				terms of
				excitability.
				The only
				, children who
				appeared to
				be nauseated
				on day 1 were
				, eight children
				receiving the
				tablet
				treatment.
			\sim	Thereafter,
			· La	only one child
				in the tablet
				group
				experienced
				severe nausea
				although the
				incidence of
				mild nausea
				was evenly
				distributed.
				We could not
				demonstrate
				any statistical
				difference
				between the
				two
				treatments in
				terms of their

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						propensity cause vomiting (d all five day abdominal pain frequency (days 2-5), nausea (da 2-5) or mo change (da 2-5). As a result of persistent vomiting, t parents of two childro
			10×			receiving tablets stopped treatment premature
Ducharme	RCT	>=3	1)Fluticasone	Albuterol,	Monthly	Thirteen
2009	Hospita	wheeze	propionate	nasal saline	telephone	serious
Canada		episodes	250mcg (3	irrigation	contacts	adverse
Non-	5	in	doses twice		and a	events (4 i
industry &		lifetime,	daily at start of	No more than	medical	fluticason
industry		onset of	URTI) until 48h	1 dose of CS in	visit every	group and
funded		URTI	elapsed without	preceding	4mo;	placebo)
		1-6y	symptoms, for	6mo or 2	5	occurred i
			max. 10d (MDI),	doses in	Growth	children
			n=62	preceding	assessed	during the
			2) Placebo (3	12mo	using an	study peri
			doses twice		upright	namely,
			daily at start of		stadiomete	pneumoni
			URTI until 48h		r at	seizure,
			elapsed without		baseline,	admission
			symptoms		every	an intensi
			(MDI), n=67		month, and	care unit,
					at the end	burn,
			Multiple		of follow-	respirator
			courses over 6-		up (6-	syncytial v
			12mo		12mo);	infection,
1	1	1	1		1	atelectasis

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3					Conjunctivitis (2 vs. 3); Eczema (6 vs. 1); Rash (5 vs. 2); Serous otitis media (4 vs. 2) Author reports harms separately from adverse health events: harm defined as failure to thrive, defined by a weight below the 3rd percentile at the end of the study period or a decrease in weight by at least 2 major percentile lines on the Centers for Diseases Control and Prevention growth charts. The gain in height and weight was significantly lower in children treated with fluticasone than in children given
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						placebo, with a difference between the groups of 5 percentage points. Two children in the fluticasone group and 1 in the placebo group met the definition of failure to thrive; the number needed to harm was not significant. There were no significant group differences in the change in lumbar bone mineral density, bone mineral content, or bone age; low values for these and cortisol were normal when repeated or when corticotropin testing was
Eboriadou	RCT 3-	Croup	1) L-eninenhrine	Οχνσερ	Before	performed.
Eboriadou 2010	RCT, 3- arm	Croup 6mo-5v	1) L-epinephrine 5.0ml (1 of	Oxygen	Before treatment	performed. The L-
2010	arm	Croup 6mo-5y	5.0ml (1 of		treatment	performed. The L- epinephrine
2010 Greece	arm Pediatri	-	5.0ml (1 of 1:1000mg/ml),	No CS in	treatment & at 15min,	performed. The L- epinephrine group was the
2010	arm	-	5.0ml (1 of 1:1000mg/ml), 5-10min (neb),		treatment & at 15min, 20min,	performed. The L- epinephrine group was the only group
2010 Greece	arm Pediatri	-	5.0ml (1 of 1:1000mg/ml),	No CS in	treatment & at 15min,	performed. The L- epinephrine group was the

			2)		120min	treatment
			Dexamethasone		post-	Tremor an
			0.6mg/kg (max.		treatment;	tachycard
			8mg), single		patients	were
			dose (IM), n=19		asked to	observed
			3)		return if	children f
			Beclomethason		relapse in	Group A,
			e dipropionate		next 24h	had receiv
			200mcg (MDI),			LE and we
			n=20			resolved a
						2 hours, w
						the action
						LE wear of
Eden 1967	RCT	Croup	1)	Oxygen,	Every 6h for	No untow
USA	Hospita	8mo-5y	Dexamethasone	humidity &	total 48h	effects we
Industry	1		0.10mg/kg at	tetracycline		noted. The
funded	1		0.1cc/kg/dose			were no
			every 6h for	NR		episodes o
			48h, total daily			congestive
			0.40mg (IM),			heart failu
			n=25			or sodium
			2) Control			retention.
			preparation			
			0.1cc/kg/dose 🥢			
			every 6h for 48h <			
			(IM), n=25			
Escobedo	RCT	Asthma	1)	Saline,	Baseline &	We detec
Chavez	Hospita	1mo-14y	Methylprednisol	salbutamol &	discharge	no side
1992	l ed		one 3.0mg/kg,	oxygen		effects wi
Mexico	1		single dose (IM)		5	the use of
Industry			+ placebo 4.5ml	No CS in		methylpre
funded			+ sal 0.5ml	preceding 15d		olone in a
			every 4h (neb),			single dos
			n=25			any treatr
			2)			failures th
			Aminophylline			merited th
			5.0mg/kg every			use of
			6h (IV) + sal 70			methylxar
			mcg/kg every 8h			es or
			+ oxygen (neb),			additional
			n=25			steroid do
Fifoot 2007	RCT, 3-	Croup	1) Prednisolone	Antipyretics or	Baseline &	No patien
Australia	arm	6mo-6y	0.2ml/kg of	nebulized	hourly up	suffered a
	1	1	1.0mg/kg, single	adrenaline	1	adverse

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Non-	Pediatri		dose (oral),		to 4h post-	outcomes
industry	c ED		n=34	No CS in	treatment;	from receivin
funded	1		2)	preceding wk	FU 1wk by	study steroid
			Dexamethasone		telephone	either at
			0.2ml/kg of		following	index
			0.15mg/kg,		index visit	presentation
			single dose			or during the
			(oral), n=34			follow-up
			3)			period. One
			Dexamethasone			patient from
			0.2ml/kg of			each group
		$\langle \cdot \rangle$	0.6mg/kg, single			vomited their
			dose (oral),			first dose of
		$\mathbf{O}_{\mathbf{A}}$	n=31			medication,
			11-21			-
						all except one
						(dex
			\mathbf{O}			0.6mg/kg)
						tolerated
F '1	D.CT			A .1.1111		second dose.
Fitzgerald	RCT	Croup	1) Budesonide	Additional	Baseline,	Six patients in
1996	Pediatri	6mo-6y	2.0mg (4ml) for	medications	30min,	each
Canada	c ED		5min (neb),	permitted 2h	60min,	treatment
Industry	3		n=35	after study	90min,	group
funded			2) Adrenaline 🦊		120min,	reported
			4.0mg (4ml) for <	No CS in	12h & 24h	adverse
			5min (neb),	preceding 4wk	post-	events. These
			n=31	4	treatment	included
						vomiting, an
						erythematou
					5	rash,
						diarrhea,
						wakefulness,
						excessively
						active
						behavior,
						wheezing, an
						a nosebleed.
						These were
						minor and die
						not result in
						withdrawal
						from the
						study or
						require
						1.544.00

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			specific treatment.
Francis 1997 (trial Australia registry Funding NR data) Acute care setting 4	<pre>≤48mo propionate y 1.0mg twice daily (neb) + placebo tablets once daily (oral)</pre>	NR D1 to D7	Most frequent adverse events – on- therapy, n (FP vs. pred): Nausea & vomiting (7 vs. 1); Diarrhoea (3 vs. 0); Normal tooth eruption (2 vs 1); Ear, nose and throat infections (2 vs. 0); Psychomotor disorders (2 vs. 0); Temperature regulation disturbances (2 vs. 0); Temperature regulation disturbances (2 vs. 0); Asthma (1 vs. 2); Hoarseness/d ysphonia (0 vs. 2); Serious adverse events - on- therapy: Subjects with non-fatal SAEs (2 vs. 0): Ketonuria, glycosuria and hyperglycaem ia (1 vs. 0);

GarbuttRCTCroup1)AcetaminopheFUNo s2013Primary1-8yDexamethasonen & ibuprofeninterviewsadveUSAcare0.6mg/kg (max.at D1 to D4everNon-office18mg), singleNo CS& D11;occuindustry10dose, followedprecedingFU chartStudfundeduby placebo forcurrent croupreviewdid r
by pacebolicity in content croup in review dubits in re 2d, 2 doses total (oral), n=46 2) Prednisolone 2.0mg/kg/d (max. 60mg/d) for 3d (oral), n=41 P = 1 4). T com effect iden with quess visit P = 1 4). T com effect iden with quess stor (13% Tabli advest stor P = 1 4). T com effect iden visit

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		0				New sleep problems (18 vs. 13); Stomach pain (9 vs. 7); Headache (7 vs. 4); Vomiting (3 vs. 7); Nausea (3 vs. 4); Dizziness (3 vs. 2); Tremor (1 vs. 0)
Ghirga	NRCT	Wheeze -	1)	NR	Twice daily	At this
2002 Italy	NR, "ambul	early URTI	Beclomethason e 400mcg 3	NR		writing, four years after
Funding NR	atory	before	doses daily for			the study was
	infants"	signs of	5d (neb), n=12			completed, n
	1	wheeze	2) Control (no			apparent
		7-12mo	intervention),			adverse
			n=13			effects were
			L			reported.
			Multiple	6		Plasma
			courses - 4			cortisol
			treatment	4		measured in
			periods of 5d			four patients
			(12 infants			receiving at
			completed 48		5	least 2
			treatment			treatment
			periods in group			periods of 5
			1)			days a month
C:11 2017	Calcart	Creation	1)	ND	A. A. A F	was normal.
Gill 2017 Canada	Cohort Pediatri	Croup	1) Dexamethasone	NR	AM of admission	Single-dose oral
Funding NR	C	>2y (mean	0.6mg/kg (max	No chronic	& D1, D3 &	dexamethas
	c hospital	4.7y vs.	12mg), single	glucocorticoid	D7	ne 0.6mg/kg
	ED	4.8y)	dose, n=22	therapy or any	07	for croup is
	1	,	2) Controls	glucocorticoid		not associate
	-		diagnosed with	s within 10d		with
			viral URTI (no	of ED visit		decreased
			dexamethasone			endogenous
			1	1		5

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		or antibiotics),			levels in
		n=5			children.
					A 3-year-old
					previously
					healthy boy
					returned to
					the ED within
					24 hours and
					was given a
					diagnosis of
					pneumonia.
					He was
					discharged
					home from
					the ED with
					oral
					antibiotics,
					and his
		et te			symptoms
					resolved by 7
					days. The
					other, also a
					3-year-old
					boy, returned
					to the ED 4
					days after
			CZ		dexamethaso
					ne administratio
					n for
				5.	
					unilateral
					facial
					swelling.
					Serologic
					testing for
					paramyxoviru
					s (mumps)
					was negative,
					and he was
					given a
					diagnosis of
					viral parotitis.
					His symptoms
					resolved by 7

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2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43							days. Four participants visited their primary care physician within 7 days of dexamethaso ne administratio n. One patient was healthy, another was given a diagnosis of otitis media and treated with oral antibiotics, and two patients who had persistent coughs were prescribed salbutamol. None of the participants were admitted to hospital, and there were no serious adverse events or
41 42						4	
46	Goebel	RCT	Bronchiol	1) Prednisone	NR	Clinical	One patient in
47	2000	Pediatri	itis	2.0mg/kg/day		scores on	the
48 49	USA	c ED or	≤23mo	for 5d (oral) +	NR	D0, D2, D3	prednisolone
49 50	Funding NR	childre		albuterol		& D6;	group was
50 51		n's		0.3mg/kg/day		FU when	observed by
52		clinic		(or		convalesce	his caretakers
53		2		0.15mg/kg/dose		nce	to be "jittery"
54				(neb)) for 5d		completed	at times after
55				(oral), n=24			enrollment.
56				(01ai), 11-24			enioninent.
57							

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			2) Placebo solution (oral) + albuterol 0.3mg/kg/day (or 0.15mg/kg/dose (neb)) for 5d			This resolved after a decrease in the albutero dose. No evidence of treatment
		^	(oral), n=24			complication was observe in any of the other patients.
Grant 1996 USA	Cohort Primary	Asthma 2-14y	1) Prednisone 2.0mg/kg (max.	Bronchodilato rs as needed	NR	Ninety-four episodes of acute
Non- industry funded	care clinic & teachin g		60mg/day), single dose intermittent for 6mo (oral),	NR		infection occurred in subjects and
	hospital ED		n=86 2) Placebo (NR),			222 episode of symptom
	1		n=86			of infection occurred in
			Multiple courses over 1yr			subjects (table 1
			•	C4		episodes of infection, number of
				0		doses, and association between
					1	doses and frequency o infection). N
						difference was observe
						in the mear number of
						doses of
						prednisone received by
						those with t infection
						compared with those

BMJ Open

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						without the infection. No correlation was observed between the
D 1 2 3 4 5 5 7						number of doses of prednisone received and the number of episodes of each infection. This
3 9 0 1 2 3 4 5 5			ee.			included all episodes of otitis media, streptococcal pharyngitis, pneumonia, and urinary
7 3 9 0 1 2 3 4 5			í C			tract infection; eight (73%) episodes of chickenpox; eight (57%) episodes of
5 7 3 9 0 1	DCT	Asthma	1)	Albutaral		skin infections; and 14 (88%) episodes of ringworm.
2 Gries 2000 3 USA 4 Funding NR 5 7 8 9 0 1 2	RCT Tertiary care center 1	Asthma 6mo-7y	 Dexamethasone Tmg/kg/dose single dose, (IV), n=15 Prednisolone 2mg/kg/dose, twice daily for d (oral), n=17 	Albuterol No CS in preceding 2wk	D3, D5, D7, D14 & D28; Urinary cortisol/cre atinine assessed by radioimmu noassay (standard	Ten of the 17 children who received PO Pred took the prednisone without much difficulty. However, 3 children missed more

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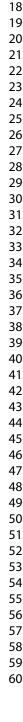
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60

						PO Prec
						group,
						this dif
						was no
						statisti
						signific
Hedlin	RCT	Asthma –	1) Budesonide	Beta-agonists	D10 & D13;	There
1999 ¹	Pediatri	first sign	400mcg, 4 times	and/or		no sigr
Sweden	с	of URTI	daily for 3d then	theophylline	Routine	differe
Funding NR	hospital	1-3y	twice daily for		height	betwe
	1		7d (MDI), n=9	NR	measureme	pretre
			2) Placebo, 4		nts	and po
			times daily for 3		(assessmen	treatm
			days then twice		t method	serum
			daily for 7d		NR) were	cortise
			(MDI), n=11		taken	osteod
					(timing of	ICTP a
			Multiple		assessment	cortise
						nine ra
			courses over		s NR);	
			1yr, or max. 6			the gr
			treatments		Serum	(the
					cortisol (on	compa
			*subgroup of		D8-10 of	was m
			children from 🦊		second	the ch
			Svedmyr 1999		course of	who h
			with		study	assess
			therapeutic	4	medication,	before
			failure from		morning of	after
			budesonide		day after	budes
			given 3d course		third dose,	lacebo
			(6.0mg, 4.0mg,		and at 12-	weret
			and 2.0mg on		14d after	any sig
			respective days)		therapy)	differe
			of oral		and urinary	betwe
			betamethasone		cortisol/cre	active
					atinine (in	placek
					the night	treate
					after third	group
					dose of	was, h
					betamethas	notew
					one and at	that th
					12-14d	cortiso
					after	nine ra
					therapy)	decre

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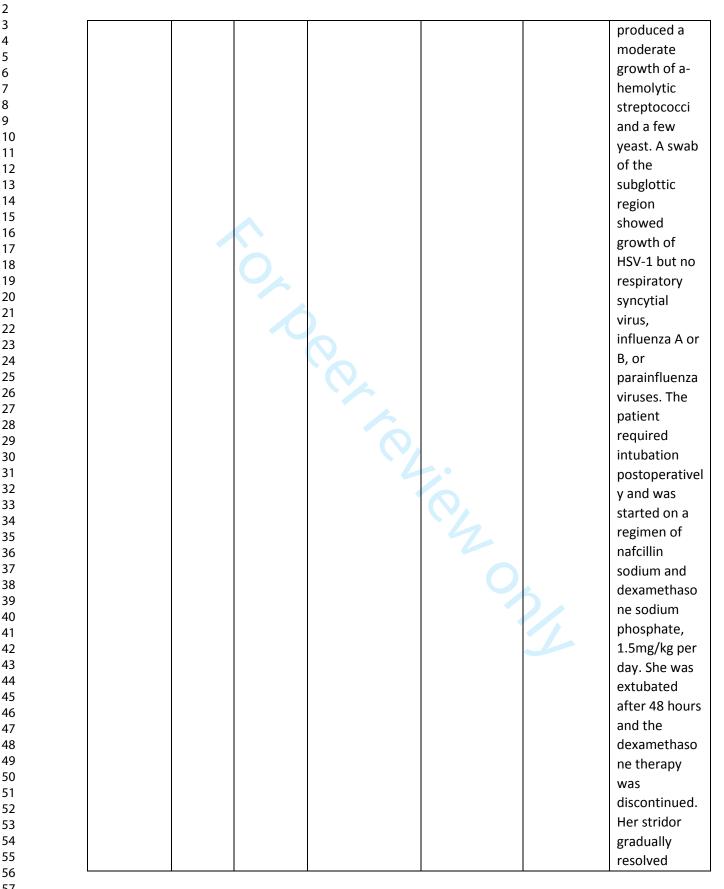
		ſ	I		1	1
					assessed by	5/6 children
					radioimmu	studied in the
					noassay	active group
						and in 4/10 ir
						the placebo
						group.
						Neither this
						change nor
						the differenc
						was
						statistically
						, significant.
						PIIINP
						decreased
						after both
						budesonide
						and placebo
			\sim			treatment
			$\mathbf{\hat{\mathbf{A}}}$			periods (p<
						0.05). Short
						courses of
						oral
						betamethaso
						ne have
						pronounced
						systemic
						effects,
						whereas 10c
						of high doses of budesonic
					5	
						do not
						produce
						significant
						systemic
						effects.
Husby	RCT	Croup	1) Budesonide	Antibiotics	Baseline &	No side
1993	Pediatri	3mo-4.9y	1000mcg (2ml		2h post-	effects were
Denmark	С		500mcg/ml),	No CS	treatment	reported.
Funding NR	hospital		two doses	preceding		
	1		30min apart	study		
			(neb), n=20			
			2) Placebo			
			saline 0.9%			



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			doses 30min apart (neb),			
Inglis 1993	Case	Croup	n=16 Case 1)	Case 1:	NR	Case 1:
USA	report,	18mo;	Prednisolone	racemic		Twenty day
Funding NR	2	18110, 14mo	1.0mg/kg, twice	epinephrine,		into illness
		14110	daily for 4d (NR)			
	Hospita			acyclovir sodium		airway
	1		Case 2)			endoscopy
			Dexamethasone	Case 2:		revealed
			0.3mg/kg, 3	amoxicillin/cla		shallow
		\frown	doses in 24h	vulanate		mucosal
			(NR)	potassium,		ulcerations
				cefuroxime		patient's
				sodium		glottis and
						subglottis,
						a normal
			\mathbf{O}			appearing
						tracheobro
						hial tree.
						Cultures w
						positive fo
						HSV-1,
						Staphyloco
						s aureus ai
			•			a-hemolyt
						streptococ
				4		;
						Case 2: On
						day 11 of
					5	illness, airv
						endoscopy
						revealed
						severe
						subglottic
						edema and
						ulceration,
						purulent
						tracheal
						secretions,
						but norma
						tracheal
						mucosa. A
						tracheal
					1	aspirate

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						spontaneou
						y over the
						next 7 days
						without
						further
						interventio
Jan 2000	Non-	Asthma	1) Group A:	NR	D1 to D3	An acute
Taiwan	RCT	NR	Methylprednisol			effect of
Funding NR	Pediatri		one	NR		glucocortic
0	с		1.0mg/kg/6h			therapy on
	hospital		(IV) for 1d,			the
	clinic		n=NR			suppressio
	1		2) Group B:			of osteobla
	1	$\mathbf{O}_{\mathbf{A}}$				
			Methylprednisol			was
			one			biochemic
			1.0mg/kg/6h			revealed b
			(IV) for 2d,			the finding
			n=NR			reduced
			3) Group C:			serum
			Methylprednisol			osteocalci
			one			levels; this
			1.0mg/kg/6h			suggests th
			(IV) for 3d,			early chan
			n=NR			in serum
			•			osteocalcir
				CZ		may be a
				4		useful
						indicator f
						patients at
						high risk o
						bone loss.
				•		Levels of
						serum
						osteocalci
						progressiv
						declined w
						increasing
						duration o
						GC therapy
						with tende
						toward a
						decrease c
						serum
						phosphate

		0				However, serum calcium levels remained unchanged before and after therapy. Osteocalcin levels (µg/L): Group A - 2.7 +/- 3.; Group B - 2.2 +/- 1.9; Group C - 1.8
Jartti 2006 Finland Non- industry and industry funded	RCT Pediatri C hospital 1	First or second wheeze episode 3mo- 35mo	1) Prednisolone 5.0mg tablets, first dose 2.0mg/kg then 2.0mg/kg/day in 3 divided doses for 3d (oral), n=46 2) Placebo tablets, in 3 divided doses for 3d, n=32	Albuterol, beta-2- agonists, antibiotics, & racemic epinephrine No CS in preceding 4 weeks	Study entry & twice daily during hospitalizati on, daily diary notes for 2wk post- discharge; FU visit & phone call 2wk post- discharge	+/- 1.5 The prednisolone treatment was well tolerated. No clinically significant adverse effects occurred.
Jartti 2007 Finland Non- industry and industry funded	RCT Pediatri c hospital 1	At least third wheeze 3mo-7y	1) Prednisolone 5.0mg tablets, first dose 2.0mg/kg then 2.0mg/kg/day in 3 divided doses for 3d (oral), n=23 2) Placebo for 3d, n=35	Salbutamol & antibiotics No CS in preceding 4wk	discharge Study entry & twice daily during hospitalizati on, daily diary notes for 2wk post- discharge; FU visit & phone call 2wk post- discharge	The prednisolone treatment was well tolerated. No clinically significant adverse effects occurred.
Jartti 2015 Finland	RCT	Wheeze – first acute	1) Prednisolone first dose 2.0mg/kg, then	NR	2wk daily diary; FU at 2wk, 2mo &	There were no difference in the

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Non-	Univers	rhinoviru	2mg/kg/d in 2	No previous	12mo post-	incidence
industry	ity	s-induced	divided doses	systemic or	discharge	adverse
and	hospital	3-23mo	for 3d (max.	inhaled CS	_	events
industry	1	(mean	60.0mg/day),	treatment		between t
funded		13.2mo	n=34			prednisolo
		vs.	2) Placebo, n=40			and place
		12.2mo)				groups
			Multiple			(results no
			courses over 1yr			shown). N
						clinically
						significant
						adverse
						events we
						reported.
Johnson	RCT	Croup	1)	Humidified	Baseline, 2h	Two patie
1996	Pediatri	mean	Dexamethasone	oxygen	& 4h post-	with
Canada	c ED	15mo vs.	10.0mg (4ml) -		treatment	neutroper
Non-	1	17mo	10.0mg (<8kg),	No CS in		treated w
industry			15.0mg (8-12kg)	preceding 2wk		dexameth
funded			or 20.0mg			ne had a
			(>12kg), 10min			clinical co
			(neb), n=28			consisten
			2) Control,			with bacte
			saline (4ml), 🧹			tracheitis.
			10min (neb), 🔹			
			n=27			
Johnson	RCT	Croup	1) Budesonide	Racemic	Study entry	No child h
1998	Pediatri	3mo-9y	4.0mg for 20min	epinephrine &	& hourly	gastrointe
Canada	c ED		(neb), n=48	mist therapy	for 5h post-	al bleedin
Industry	2		2)		treatment	bacterial
funded			Dexamethasone	No CS in	until	tracheitis.
			0.6mg/kg, single	preceding 4wk	discharge;	
			dose (IM), n=47		FU 72h	
			3)Placebo		post-	
			suspension,		discharge	
			single dose for			
			20min (neb),			
			n=49			
Klassen	RCT	Croup	1) Budesonide	Racemic	Baseline &	No advers
1994	Pediatri	3mo-5y	2.0mg (4ml),	epinephrine	hourly for	events we
Canada	c ED		single dose	or	4h;	noted in t
Non-	1		(neb), n=27	dexamethaso	FU at 1wk	budesonic
industry			2) Placebo	ne, or oxygen		group. No
funded			saline 0.9%	tent		patient in

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			(4ml), single			group had
			dose (neb),	No CS in		clinical
			n=27	preceding 2wk		deterioratior
						either in the
						emergency
						department
						or after
						discharge.
						One patient i
						the placebo
						group had a
						burning
						sensation on
						the face.
Klassen	RCT	Croup	1)	Racemic	Baseline &	Two patients
1996	Pediatri	3m-5y	Dexamethasone	epinephrine &	hourly for	in the
Canada	c ED		0.6mg/kg (oral)	croup tent	4h;	budesonide
Non-	1		+ budesonide		, FU 1wk	group and 1
industry			2.0mg (4ml)	No CS in		patient in the
funded			(neb), n=25	preceding 2		placebo grou
lanaca			2)	weeks		vomited thei
			Dexamethasone	Weeks		initial doses of
			0.6mg/kg (oral)			dexamethaso
			+ placebo saline			ne within
			0.9% (4ml)			30min and
			(neb), n=25	\sim		required
			(1105), 11-25			readministra
						on of
						dexamethaso
						ne, which wa
						subsequently
						tolerated in
						all 3 patients
Klassen	RCT	Croup	1) Budesonide	Epinephrine,	Baseline &	All parents
1998	Pediatri	3mo-5y	2.0mg (4ml)	supplemental	hourly for	were asked
Canada	c ED	эшо-эү	••••	glucocorticoid	4h;	about the
Non-			(neb) + placebo	s & mist	4n; FU 1wk	
	2		syrup (oral),			presence of
industry funded			n=65	therapy	post-	oral thrush
funded			2)		enrolment	and only 1
			Dexamethasone	No CS in		parent whose
			0.6mg/kg (oral)	preceding 2wk		child was in
			+ placebo saline			the
			4ml (neb), n=69			budesonide
						group

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2							
3				3) Budesonide			reported this
4				2.0mg (4ml)			condition at
5 6				(neb) +			the 1-week
7				dexamethasone			follow-up.
8				0.6mg/kg (oral),			Parents of 1
9				n=64			patient
10				11-04			treated with
11							
12							dexamethaso
13							ne reported
14 15							hives, and
16							parents of 1
17							patient
18							treated with
19							dexamethaso
20							ne reported
21							violent
22 23							behavior.
25 24							Parents of 1
25							patient who
26				e (e			had received
27							budesonide
28							and
29							dexamethaso
30 31							
32							ne reported
33							their child to
34							be more
35							hyperactive
36							than usual.
37	Киуиси	RCT	Bronchiol	1) Epinephrine	NR	Baseline,	No side-
38 39	2004	Pediatri	itis	3ml of 1:1000		30min,	effects such
40	Turkey	с	2-21mo	solution for	No CS in	60min,	as pallor,
41	Funding NR	outpati		10min (neb) +	preceding 2wk	90min &	vomiting or
42		ent		dexamethasone		120min,	tremor were
43		clinic		0.6mg/kg, single		then 24h,	encountered
44		and ED		dose (IM), n=23		5d;	in the
45		1		2) Sal		FU by	patients.
46 47		-		0.15mg/kg of		regular	
47 48				1mg/ml solution		hospital	
49				added to 0.9%		visits in	
50							
51				saline for 10min		subsequent	
52				(neb) +		2mo	
53				dexamethasone			
54				0.6mg/kg, single			
55 56				dose (IM), n=23			
50							

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			2) Epipophrina			
			3) Epinephrine 3ml of 1:1000			
			solution for			
			10min (neb) +			
			placebo saline,			
			single dose (IM),			
			n=11			
			4) Sal			
			0.15mg/kg			
			(1mg/ml			
		\land	solution added			
			to 0.9% saline)			
		$\mathbf{O}_{\mathbf{A}}$	for 10min (neb)			
			+ placebo saline, single			
			dose (IM), n=12			
Lai 2005	RCT	Asthma	1) Budesonide	Terbutaline	On	The mea
China	Hospita	1-5y	0.05mg/kg	(as needed)	admission,	of blood
Funding NR		,	every 12h (neb),	0.25mg/kg	at	pressure
-	pediatri		n=9	every 6h to a	discharge &	(systolic
	С		2)	max. of 5.0mg	at follow-	diastolic
	inpatie		Dexamethasone		up;	blood gl
	nt ward		0.1mg/kg every	NR		and seru
	1		8h (neb), n=9 🦢		Growth	potassiu
			N Audition In		(mean	revealed
			Multiple courses over 8-		height) assessed	significa
			19mo		(assessed	changes betweer
			19110		t method	admissic
					NR) at	discharg
					baseline	either gr
					and	of patier
					approximat	(Table 3)
					ely 8-19mo	Thus, the
					after	were no
					randomizati	adverse
					on;	effects ir these
					Adrenal	patients
					suppression	Table 4 a
					assessed	shows th
					from blood	there we
					pressure	significar
					(systolic	differenc

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					and diastolic) and blood glucose at baseline and approximat ely 8-19mo after randomizati on	total height growth, mear rate of height increase, systolic or diastolic blood pressure, or blood glucose between the treatment groups.
Langton Hewer 1998 UK Funding NR	RCT Hospita I 1	Asthma 1-15y	1) Prednisolone 0.5mg/kg/day until discharge (max. 60.0mg/day) (oral), n=35 2) Prednisolone 1.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=33 3) Prednisolone 2.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=30	Bronchodilato rs (nebulized) No CS in preceding 14d	Baseline, Oh, 12h, 24h, 36h, 48h, 60h & 72h; FU 2wks post- enrollment	No serious short-term side-effects were noted but hyperactivity related to nebulized B2 agonist therapy was seen. No side effect possibl attributable to prednisolone therapy was noted in any of the three treatment groups. Three childre in prednisolone 2.0mg group were withdrawn because of vomiting, a diagnosis of pneumonia o the parents

						withdrew
						consent.
Lee 2001 Taiwan Funding NR	Case report Pediatri c clinic of hospital 1	Asthma 5y	1) Terbutaline solution (loading dose: 5.0mg/kg/dose, maintaining dose: 0.6mg/kg/h); Methylprednisol one (BW 21kg, 2.0mg/kg/dose, 40.0mg every 6h) (IV), and; Procaterol 12.5mcg twice daily (oral)	NR	D1 to D3	Consent. On day 3 of admission the patient was found to have major behaviour changes and hyperventilat on. She started screaming unreasonably gazing forward and sometimes upward and became panic She had visua hallucinations
Leer 1969 USA Industry funded	RCT Hospita I 5	Bronchiol itis <30mo	1) Betamethasone, 1.0mg/5lb first dose and 0.5mg/5lb every 12h (total 3.5mg/5lb (6 doses) for 72h) (IM/IV), n=148 2) Aqueous vehicle, 5cc every 12h for 72h for total 6 doses (IM/IV), n=149	Mist, oxygen, parenteral fluids & antibiotics NR	Clinical signs every 6h	and delusion. There were no detrimental corticosteroid effects in any of the patients. The corticosteroid neither increased the incidence of staphylococca l or other bacterial pneumonias nor masked superinfection
Lehmann 2008 Germany	Case report Pediatri	Asthma 2y	1) Prednisolone- 21-hydrogen	None 3wk washout	Post skin prick test	s. Patient had been on well- tolerated
Germany	reulati		21-invulugell			lucialeu

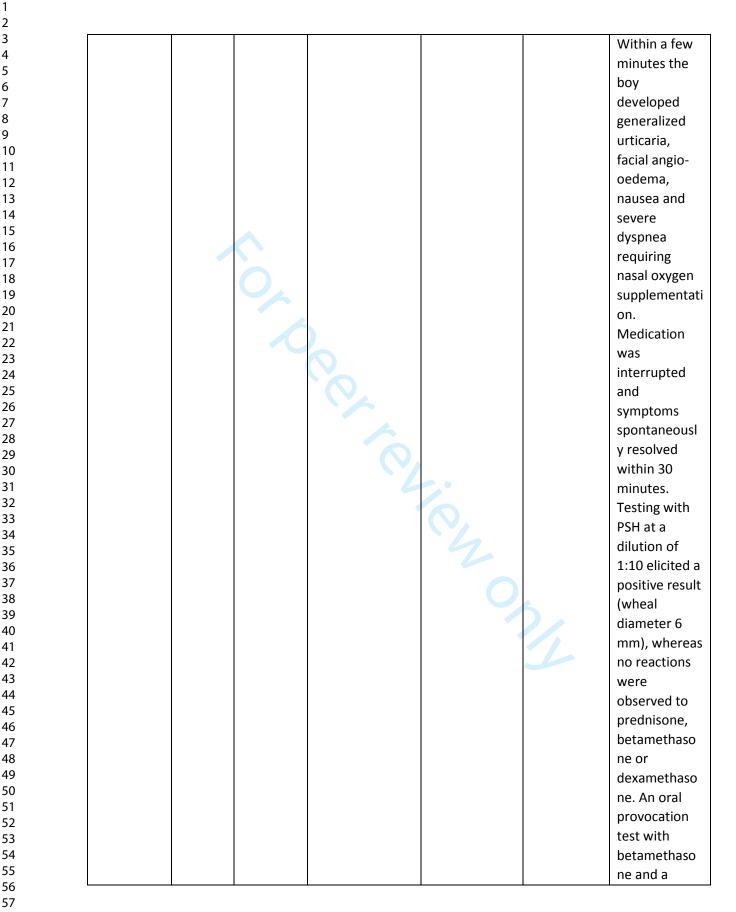
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Allergol	succinate (PSH)	under long-	therapy o
ogy	50.0mg (IV)	term	100mcg
Clinic	2) Prednisone	maintenance	inhaled
1	(100.0mg,	therapy of	fluticasor
-	suppository)	daily 100mcg	dipropion
	3)	fluticasone	daily for
	Betamethasone		
		propionate	frequent
	(dose NR, oral)	(inhaled) and	recurring
	4)	intermittent	episodes
	Dexamethasone	prednisone	asthmatio
	(dose NR, IV)	suppositories	exacerba
			, with
			intermitte
	6		prednisor
			supposito
			for acute
			bronchop
			onary
			obstructio
			with no
	0		occurren
			adverse
			events ar
			other
			glucocort
			preparati
			Patient w
			admitted
			departme
			due to se
			bronchos
			m (neithe
			bronchoc
			rs nor rec
			administe
			prednisor
			provided
			symptom
			relief) and
			given 50r
			prednisol
			21-hydro
			succinate
			intravenc

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						titrated intravenous dexamethaso ne challenge test were tolerated without any complications.
Leipzig 1979 USA Funding NR	RCT Hospita I 2	Croup 8mo-5y	1) Dexamethasone 0.3mg/kg (4mg/ml) 2 doses 2h apart (IM), n=16 2) Placebo saline, two doses 2h apart (IM), n=14	Vaponephrine , mist tent therapy & racemic epinephrine NR	Baseline, 12h & 24h NR	We observed no adverse effects or late relapses.
Lin 1991 Taiwan Funding NR	NRCT Hospita I 1	Acute wheeze <36mo	1) Group A: <12mo old (n=29): hydrocortisone 5.0mg/kg loading dose (IV) plus 2.5mg/kg/dose every 6h for 3d + meptin liquid (procaterol hydrochloride) 1.25mcg/kg/dos e on admission, then twice daily (oral) 2) Group B: >12mo old (n=23): hydrocortisone 5.0mg/kg loading dose (IV) plus 2.5mg/kg/dose every 6h for 3d + meptin liquid	IV fluid, oxygen & antibiotics NR	Daily for 5d	Regarding side effects, two patients in Group B and one patient each in Groups A and C had tremor. One patient in Group A had irritability, and another had diarrhea.

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			(procaterol			
			hydrochloride)			
			1.25mcg/kg/dos			
			e on admission,			
			then twice daily			
			(oral)			
			3) Group C: No			
			hydrocortisone			
			or procaterol (n=28)			
Lucas-	RCT	Asthma	1) Prednisolone	Bronchodilato	6d to 8d	Vomiting wa
Bouwman	Hospita	3mo-8y	1.0mg/kg	rs (inhaled)	after index	observed in
2001	1	(mean	tablets, twice		visit	23% of
Netherland	1	2y)	daily for 5d	NR		patients usi
s Funding NR			(oral), n=NR 2) Prednisolone			crushed tablets, and
i unung ivit			1.0mg/kg			none of the
			solution, twice			patients on
			daily for 5d			oral solution
			(oral), n=NR			
Nahum	Case	Asthma -	1)	NR	D1 & D2;	He presente
2009	series	5у	Methylprednisol		FU 3mo	with
Israel Funding NR	(n=3, 1 case		one 2.0mg/kg for 2d (IV)		post- discharge	wheezing, received an
i unung ini	relevan				uischarge	intravenous
	t)					bolus of
	Pediatri			4		methylpred
	c ED					olone sodiu
	1					succinate
					5	(2mg/kg), a immediatel
						developed
						restlessness
						and facial ra
						which
						resolved
						spontaneou
						y. On the
						following da he received
						again the
						same
						medication
						and

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				1			I
							immediately
							developed
							respiratory
							distress and
							cyanosis with
							oxygen
							desaturation
							of 89%. He
							recovered
							with oxygen
							supplementat
							on and was
		•					treated
			U,				afterward
							with oral
							betamethaso
							ne sodium
				\sim			phosphate
							without
							adverse
							events.
Dr	aniagua	RCT	Asthma	1)	NR	NR;	No
	016	(confer	>12mo	Dexamethasone		FU at 7d &	differences
	pain	ence	>12110	, NR, 2 doses	NR	15d post-	were found
-	unding NR	abstrac		(oral), n=287		ED visit	regarding
		t)		2)	\sim		vomits (2.1%
		e, Pediatri		Prednisone/pre			vs 4.1%).
		c ED		dnisolone, NR,			V3 4.170J.
		1		5d (NR), n=290			
D:	anickar	RCT	Wheeze	1) Prednisolone	Albuterol,	4h, 12h &	No clinically
	009	Pediatri	10-60mo	10.0mg/day	oxygen &	24h after	significant
		c ED	10 00110	(10ml) once	antibiotics	albuterol &	adverse
	lon-	3		daily for 10-	antibiotics	daily post-	events were
	ndustry	5		24mo old (oral);	NR	discharge;	reported to
	unded			20.0mg/day		FU by	the patient
1u	unacu			(10ml) once		phone 1mo	safety
				daily for >24mo		post-	committee. In
				old (oral), for		discharge	one child in
				5d, n=343		uischarge	the
				<u> </u>			the
							prodpicalana
				2) Placebo			prednisolone
				2) Placebo solution (10ml)			group,
				2) Placebo solution (10ml) once daily for			group, parents
				2) Placebo solution (10ml)			group,

						vomiting to the study drug and discontinued the medication after discharge from hospital.
Panigada 2014 Italy Funding NR	Case report Pediatri c Pulmon ary and Allergy Unit 1	Progressi ve shortness of breath, subseque nt diagnosis of inflamma tory myofibro blastic tumor cell proliferat ion 5y	Albuterol (inhaled) + prednisone 1.0mg/kg (28.70kg) (oral), n=1	NR	NR	The child was sent home on inhaled albuterol and prednisone to be tapered and discontinued after 7-10 days. Fifteen days after first presentation, 1 day after the discontinuation n of prednisone, the boy was readmitted because of progressive shortness of breath. He had moderate-to- severe dyspnoea, inspiratory, and expiratory wheezes: SaO2 was 97% in room air, RR 39 breaths/min.

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3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 30 31 32 33 34 35 36 37 38 9 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 57 58				er re			Spirometry demonstrated to significant changes in FVC (1.43L), a decrease in FEV1 (1.29L) and a "box- shaped" flow/volume loop, consistent with fixed large airway obstruction. A computed tomography (CT) scan showed an endoluminal mass in the superior portion of the trachea, 15mm from glottis, nearly completely occluding the lumen. Tracheostomy was performed, followed by bronchoscopy . Histological examination of the biopsies showed spindle cells surrounded by collagenous stroma,
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						displaying
						strong
						positivity for
						vimentin,
						focal positivity
						for a-smooth
						muscle actin,
						and weak
						positivity for
						clusterin. No
						desmin, ALK,
						S100, CD21,
						and CD 23
						expression
						was detected
						A diagnosis of
						IMT of the
						trachea was
						performed
						and a
						complete
						surgical
						resection of
			L			the neoplasm
						was carried
						out.
Plint 2009	RCT	Bronchiol	1) Epinephrine	Bronchodilato	Baseline to	Adverse
Canada	Pediatri	itis	3ml 1:1000, 2	rs (albuterol,	30min,	events were
Non-	c ED	6wk-	doses 30min	epinephrine)	60min,	uncommon
industry	8	12mo	apart (neb) +	& antibiotics	120min &	(see
and			dexamethasone		240min;	Supplementa
industry			1.0mg/kg (max	No CS in	FU daily	y Appendix).
funded			10mg) in ED	preceding 2wk	until D7,	Pallor was
			plus 5 once-		then every	reported in 7
			daily		2d until	infants (9.5%)
			0.6mg/kg/dose,		D14 &	tremor in 15
			total 6d (oral),		every 3d	(1.9%), and
			n=200		until D22	vomiting in 14
			2) Epinephrine			(1.8%), with
			3ml 1:1000, 2			no significant
			doses 30min			differences
			apart (neb) +			among the
			placebo, total			groups. One
			6d (oral), n=199			hospitalized

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			3) Placebo 2			infant in
			doses 30min			group 2 and
			apart (neb) +			one in group 3
			dexamethasone			had mild,
			1.0mg/kg (max			transient
			10mg), total 6d			hypertension,
			(oral), n=200			which
			4) Placebo 2			resolved
			doses 30min			rapidly.
			apart (neb) +			Supplementar
			Placebo solution			y table: side
			(max 12ml),			effects and
		$\mathbf{O}_{\mathbf{A}}$	total 6d (oral),			adverse
			n=201			events, n (Epi
						+ Dex vs. Epi
						vs. Dex vs.
						Placebo):
						Tremor (4 vs.
						4 vs. 5 vs. 2);
						Pallor (23 vs.
						22 vs. 15 vs.
						16);
						Vomiting (2
			L	•		vs. 4 vs. 5 vs.
						3);
						Varicella (0 in
				4		all groups);
						Dark stools
						(17 vs. 14 vs.
						12 vs. 16);
						Hypertension
				•		(0 vs. 1 vs. 1
						vs. 0);
						Hyperkalemia
						(0 vs. 0 vs. 1
						(0 vs. 0 vs. 1 vs. 0)
Razi 2015	RCT	Asthma	1) Budesonide	Standard care:	Every 4h	No drug-
					until	related
Turkey	Hospita	7-72mo	1.0mg/2ml, 2	methylprednis		
Funding NR			doses for up to	olone	discharge	adverse
	1		5d, n=50	1.0mg/kg/day,		effects were
			2) Sterile saline	for up to 5d		identified
			2ml, 2 doses for	(IV) + sal		during
			up to 5d, n=50	0.15mg/kg		hospitalizatio
				every 4h +		

Roberts 1999	RCT Women	Croup 6mo-8y	1) Budesonide 2.0mg (4ml) for	ipratropium bromide 250mcg every 6h NR NR	Baseline, 2h, 6h &	The adverse effects in b
Australia Industry funded	's and Childre n's Hospita I 1		10min each dose, every 12h (max. 4 doses) (neb), n=42 2) Placebo for 10min each dose, every 12h (max. 4 doses) (neb), n=40	No CS in preceding 4wk	12h after first dose, then 12- hourly up to 48h if in hospital; FU by telephone 1d & 3d post- discharge	groups wer attributable to either manifestati s of the disease stat or the mod of drug administrat n (Table 3). Four patien (3 placebo, budesonide experienced an exacerbatic in symptom to the point causing intervention
				0	2	treatment mode outsi of the protocol nebulised adrenaline) These exacerbatic occurred shortly after beginning nebulisatio and were apparently induced du to distress

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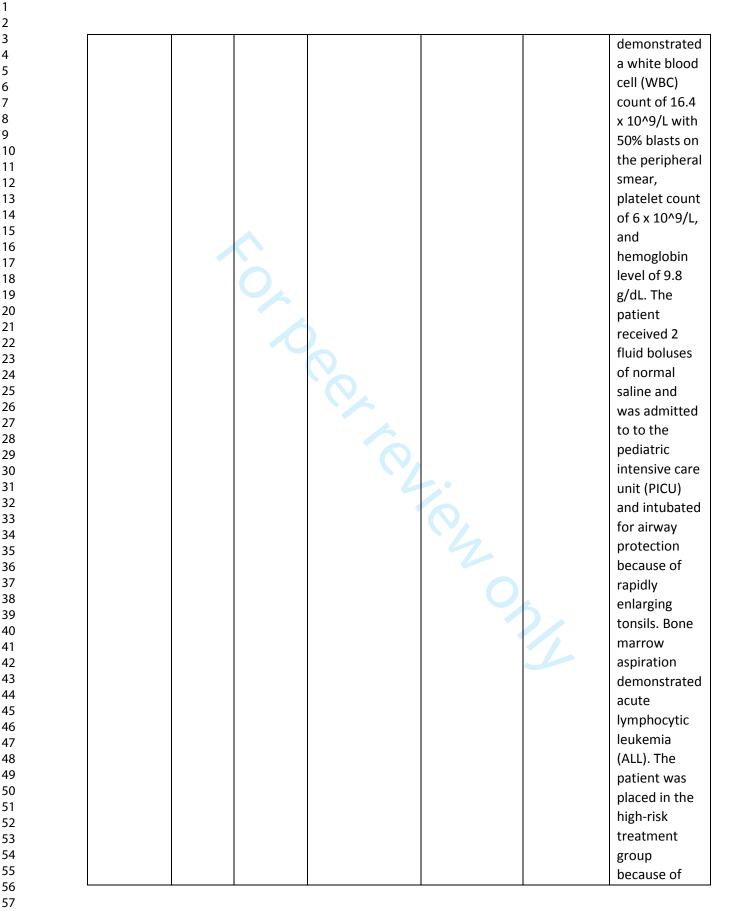
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54					caused by using the nebuliser mask. All four of these patients had severe croup symptoms (croup score >=8) at the time of nebulisation. The nebuliser mask was poorly accepted in up to 18% of patients in this study if the four exacerbations were considered to be mediated by nebuliser- induced emotional distress. Table 3 adverse effect profile, n (Bud vs. placebo): Emotional distress (5 vs. 6); Vomiting (2 vs. 3); Rash (0 vs. 2); Eye irritation (1 vs. 1); Irritated tongue (0 vs.
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Roorda	RCT	Croup	1) Fluticasone	NR	Admission,	No side
1998	Hospita	4-52mo	propionate		30min, 2h,	effects of the
Netherland	1		1000mcg, 2	No CS in	6h, 12h &	treatment
S	NR		divided doses	preceding 48h	24h	regimens
Funding NR			30min apart			were reporte
-			(MDI), n=9			during the
			2) Placebo (NR),			study.
			n=8			,
Roosevelt	RCT	Bronchiol	1)	Antibiotics,	Admission	Three
1996	ED	itis	, Dexamethasone	bronchodilato	& every	patients had
USA	1	<12mo	1.0mg/kg every	rs & tribavirin	12h;	occult blood
Non-	-		24h for max. 3		FU 1wk	in their stool
industry			doses (IM),	NR	post-	two were in
funded		U,	n=65		discharge	the
Tunueu			2) Placebo		uischarge	dexamethasc
			-			
			saline, every 24h for max. 3			ne group. No
						episodes of
			doses (IM),			gross
			n=53			haematochez
						a were
						observed.
Sadowitz	Case	Pharyngit	Dexamethasone	NR	NR	The patient
2012	series	is	10.0mg single			was given a
USA	(n=4, 1	Зу	dose (oral?) + 🦢	NR		10-mg dose o
Funding NR	case		acetaminophen <			dexamethaso
	relevan		+ amoxicillin,			ne in additio
	t)		n=1	4		to
	ED					acetaminoph
	1					n and
					4	amoxicillin;
						she was able
						to tolerate
						liquids and
						was
						discharged.
						The patient
						returned to
						the ED 2 days
						later with
						persistent
						-
						complaints of
						fever and sor
						throat, now
	1	1	1	1	1	with an

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	dexamethase ne administration n before the diagnosis of ALL and in the absence of a pretreatmen CBC count following the guidelines for high-risk leukemia established b the Children' Oncology Group. Induction therapy include IV daunorubicing decadron, asparaginase and vincristine.

						chemotherap y at this time.
Saito 2017	RCT	Asthma	1) Budesonide	At admission,	Daily;	Serum cortiso
Japan	Pediatri	<3y	1.0mg/dose,	received	,,	levels in the
Funding NR	С	- /	twice daily	hydrocortison	Serum	BIS and PSL
	depart		(neb), n=30	e (IV) & one	cortisol	groups at the
	ment of		2) Prednisolone	inhalation of	assessed	time of
	hospital		0.5mg/kg, 3	procaterol;	(assessmen	admission
	1		times daily (IV),	LTRA for	t method	were
			n=20	wheezing	NR) on	15.0mcg/dL
				episodes	admission	and
					and D4 of	17.2mcg/dL
				NR	hospitalizati	(p>0.05),
					on	respectively.
						However,
						serum levels
			0			on the fourth
						day of
						hospitalizatio
						n were
						17.0mcg/dL
						and
						10.9mcg/dL,
						with
						significant
						suppression i
						the PSL group
						Adverse
					•	events did no
					5	occur in eithe
Schuh 2008	RCT	Bronchiol	1)	Albuterol	Baseline,	group. The mean
Canada	Pediatri	itis	Dexamethasone		D4 & D6	blood
Non-	c ED	8wk-	1.0mg/kg in ED	Baseline	(home	pressure
industry	1	23mo	+ 4 doses	reports 3	visits);	increased
funded	-	251110	0.15mg/kg	patients with	FU by	from 96.1+/-
			starting 24h	prior inhaled	telephone	8.8 mmHg to
			later, total 5d	ICS	on D28	99.5+/-14.8
			(oral), n=61		-	mmHg in the
			2)			single-dose
			 Dexamethasone			group and
			1.0mg in ED + 4			from 96.4+/-
			doses placebo			7.9 mmHg to
			syrup starting			103+/-

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			24h later, total			16.8mmHg i
			5d (oral), n=64			the multiple
						dose group.
						Bag urine w
						obtained on
						day 6 visit ir
						47 study
						infants and
						tested
						positive for
						glucose in 1
						child
						belonging to
						the multiple
						dose group.
Schuh 2009	RCT	Asthma	1) Montelukast	Albuterol &	48h & D8	In the
Canada	Pediatri	>=2y	1.0mg/kg:	fluticasone		montelukas
Industry	c ED	-,	2-5y=4.0mg;			group,
funded	1		6-14y=5.0mg;	>1 single dose		adverse
landed	-		and,	or oral		effects
			15-17y=10.0mg	prednisolone		developed i
			at 24h, 48h,	or >250mcg		3 patients.
			72h, 96h & 120h	per day of		One patient
			(oral), n=67	inhaled		experienced
			2)	fluticasone		facial swelli
			Prednisone/pre	within 72h		of unknown
			dnisolone	Within 7211		etiology at 9
			1.0mg/kg: 2-			hours,
			5y=4.0mg;			another
			6-14y=5.0mg;			patient had
			and 15-			vomiting an
			17y=10.0mg at			diarrhea at
			24h, 48h, 72h,			hours, and
			96h & 120h			the third
			(oral), n=63			patient
						complained
						abdominal
						and leg pair
						on day 4.
						None of the
						patients
						-
						required treatment f
			1			these event

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for 3 days (NR), n=21 3) Control, 3d, n=51

						the maximu renal phosphate reabsorptio decrease in the maximu renal
						phosphate reabsorptio were
		\sim				significant b
<u></u>	DOT			A . I I'	E	transient.
Sparrow	RCT De dia tri	Croup	1)	Adrenaline	Enrolment,	No adverse
2006 Australia	Pediatri c ED	mean 37mo	Dexamethasone	No CS	30min post- treatment,	events were noted in
Funding NR	1	(28.8) vs.	0.2ml/kg of 0.15 mg/kg, single	preceding	hourly for	either group
	T	(20.0) vs. 45mo	dose (oral),	study	next 4h &	
		(31.6)	n=68	study	every 4h	
		(51.0)	2) Prednisolone		until	
			0.2ml/kg of		discharge;	
			1.0mg/kg, single		FU 7d-10d	
			dose (oral),		post-	
			n=65		discharge	
Stafford	NRCT	Asthma/c	1) Prednisolone	NR	Daily	No significa
1998	Pediatri	roup	5.0mg/ml	6		differences
Australia	С	1-12y	solution (oral),	NR		were found
Industry	hospital		n=8	4		regarding th
and non-	or ED		2) PredMix			incidence o
industry	1		5.0mg/ml			nausea,
funded			solution (oral),		5	vomiting an
			n=46			abdominal
			3)			pain, or any
			Dexamethasone			the objectiv
			5.0mg/ml (oral),			parameters
CL	DOT	A	n=80			tested.
Storr 1987	RCT Dediatri	Asthma	1) Prednisolone	Salbutamol	Admission,	Prednisolon
UK	Pediatri	NR (mean	30.0mg (<5yo),	5.0mg in 2ml	4h, 12h,	has a bitter
Non-	C bosnital	5y)	otherwise	saline (neb), on admission	24h & 36h	aftertaste.
industry &	hospital 1		60.0mg, max.	& 3 times or		Most childre disliked the
industry funded	T		dose 3.0mg/kg (range 1.0-	more daily		drink. 2
TUTUEU			(range 1.0- 3.0mg/kg) single	when		children in
			dose (oral),	indicated		each group
				Indicated		each group

			2) Placebo solution identical to treatment, single dose (oral), n=73	No CS in preceding 48h		almost immediately and were consequently excluded. There were no observed side-effects related to the single prednisolone dose.
Sumboonn anonda 1997 Thailand Funding NR	RCT Pediatri c hospital 1	Croup <5y	1) Dexamethasone 0.5mg/kg/d, 3d (IM/IV), n=14 2) Control, n=18	Aerosolized adrenaline, antibiotics, IV fluid & cool mist NR	Admission, 24h & 48h; FU 3wks post- discharge	Complications included pneumonia in 4 controls, Acinetobacter sepsis in 1 control and bacterial tracheitis in 1 cases.
Sung 1998 Canada Non- industry funded	RCT Tertiary pediatri c hospital 1	Asthma >6mo or <18y	1) Budesonide 4000mcg (4ml), single dose (neb), n=24 2) Placebo, single dose (neb), n=20	Salbutamol 0.15mg/kg every 30min for 3 doses, then hourly for 4 doses	Baseline, discharge & 7d to 10d post- treatment	No adverse effects were noted in either group.
Super 1989 USA Funding NR	RCT General hospital or childre n's hospital 2	Croup NR (mean 16mo)	1) Dexamethasone 0.6mg/kg, single dose (IM), n=16 2) Placebo saline, single dose (IM), n=13	Mist, racemic epinephrine, oxygen & antibiotics	Baseline, 30min, and every 12h until discharge	In two dexamethaso ne-treated patients in the main study, including one with a culture- positive influenza A viral infection, laryngotrachei tis progressed to pneumonia.

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2 3							The other
4							patient was
5							the one who
6 7							received a
8							second
9							
10							injection of
11							dexamethaso
12							ne. At the
13							time of his
14							second
15 16							injection, he
17							had
18							roentgenogra
19							phic evidence
20							of
21							pneumonia.
22			1				We did not
23 24							encounter any
24 25				C. C			side effects
<u>2</u> 6							
27							directly
28							attributable
29							to
30							dexamethaso
31 32				L			ne.
32 33	Sussman	RCT	Bronchiol	1)	Oxygen,	Daily	Adverse
34	1964	Hospita	itis	Dexamethasone	penicillin &		reactions to
35	USA	1	1-25mo;	0.1mg in divided	streptomycin		steroid
86	Non-	NR	Laryngitis	daily dose every			therapy were
37	industry		15mo-	6h:	NR		not noted on
88	funded		10y	D1-		4	clinical
39				9=0.2ml/lb/day;			examination
10 1				D10-	•		and
12				11=0.1ml/lb/da			superinfection
3				y;			s, bacterial or
14				y, D12-			viral
45							
46				13=0.05ml/lb/d			dissemination
47				ay;			, were not
48				D14=0.02ml/lb/			encountered.
49 50				day (IM), n=31			
51				2) Sodium			
52				chloride			
				0.15mEq/ml for			
52 53 54 55				14d (IM), n=26			

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Svedmyr	RCT,	Asthma	1) Budesonide	Maintenance	NR	Ten adverse
1995	crossov	3-10y	0.2mg 4 times	bronchodilato		events were
Sweden	er		daily for first 3d,	rs permitted		reported in
Funding NR	NR		0.2mg 3 times			the
			daily for next 3d	No CS in		budesonide
			and 0.2mg twice	preceding		group and
			daily for last 3d	month		nine in the
			(neb), n=NR (all			placebo
			groups=26)			group. There
			2) Placebo (NR),			were two
			n=NR (all			cases of
			groups=26)			dysphonia in
						the
			Multiple			budesonide
			courses;			group. The
			17 children			other events
			completed one			were
			paired (Grp			correlated
			1&2) treatment;			more to the
			15 children			children's
			completed 4			URTI such as
			paired			headache,
			treatments			diarrhoea,
			L			epistaxis or
			•			sore throat.
						There were
				4		no significant
						differences
						between the
					5	two groups.
Svedmyr	RCT	Asthma –	1) Budesonide	Beta-agonists	Daily for	In the
1999 ¹	Pediatri	first sign	400mcg, 4 times	and/or	10d	budesonide
Sweden	с	of URTI	daily for 3d then	theophylline		group a 24-
Funding NR	hospital	1-3y	twice daily for			month-old gir
	4		7d (MDI), n=28	No CS in		discontinued
			2) Placebo, 4	preceding		treatment
			times daily for	2mo		during the
			3d then twice			first
			daily for 7d			treatment
			(MDI), n=27			period
						because of a
			Multiple			suspected
			courses over			side effect.
						The child

 1	1		
	1yr, or max. 6		became
	treatments		emotionally
			unstable and
			vomited after
			inhaling the
			study drug.
			Almost 1 y
			later, she
			used
			budesonide
			for 10 d with
			no side
			effects at all.
			The symptom
			of hoarseness
			a well-known
			side effect
			with ICS, is of
			special
			interest. Nine
			children
			reported 18
			episodes of
			hoarseness in
			the placebo
			group,
			compared
			with 2
			children
		6	reporting 4
			episodes in
			the
			budesonide
			group. This
			difference
			was
			statistically
			significant (p
			= 0.024).
			Figure 4 – bar
			chart of
			adverse
			events
			(counts, only

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		< 01 K				otitis, hoarseness, sore throat, conjunctiviti croup, stomach ach diarrhea, agitation, sleep disturbances and aggressivene s.
Tagarro 2014 Spain Non- industry funded	Cohort Univers ity hospital 1	Bronchiol itis 0-6mo	 Dexamethasone Dexamethasone Omg single dose, or for 6d, or 1.0mg on first day plus O.6mg for 5d, 6d total (likely oral), n=33 Prednisone 1.0-2.0mg for 5d (likely oral), n=15 No steroids, dose/duration NR, n=32 	Adrenaline & salbutamol NR	NR	No significar adverse effects attributable to steroids o bronchodilat rs were foun in the clinica records, apa from hyperglycem a. Hyperglycem a was found in 4 out of 2: patients tested (17%) Two of them had received PRD, one of them DXM and one no
Tal 1983 Israel	RCT Hospita	Acute wheeze 1-12mo	1) Dexamethasone 0.3mg/kg	Oral/IV fluid & humidified oxygen	Admission, 3h after first IM	steroids. One infant developed a remarkable

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Non-		1		(4mg/ml) on		dose &	tremor as a
indus	stry			admission + 0.1	NR	each	side effect o
funde				mg/kg every 8h		morning	salbutamol.
				(IM), n=8		(8am) until	No other sid
				2) a) Sal solution		discharge	effects or
				2.5mg (0.5ml),		uischarge	complicatio
				on admission &			of the
				every 6h (neb);			treatment
				b) Sal syrup,			were
				0.15mg/kg,			documente
			\wedge	every 8h (oral);			
				and,			
				c) Placebo saline			
				(IM), n=8			
				3)			
				Dexamethasone			
				0.3mg/kg			
				(4mg/ml) on			
				admission +			
				0.1mg/kg every			
				8h (IM);			
				a) Sal solution			
				2.5mg (0.5ml),			
				on admission &			
				every 6h (neb); <			
				and,			
				b) Sal syrup,			
				0.15mg/kg,			
				every 8h (oral),			
				n=8		5	
				4) Placebo			
				saline			
				0.075ml/kg on			
				admission, then			
				0.025ml/kg			
				every 8h during			
				next 3d (IM),			
				n=8			
Tamu	ura	Case	Refractor	Methylprednisol	NR	NR	All cases:
2008		series	y	one 30.0mg/kg			There were
Japar		Medical	, mycoplas	once daily for	NR		no adverse
-	ing NR	center,	ma	3d (IV), n=1			events in a
		inpatie	pneumon				patients
		nt	-				during ster
1		110	ia		1	1	I uuillig stere

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Teeratakul RCT Bronchiol 1) Epinephrine, Baseline &				daily for 3 days. Six hours after the initiation of steroid therapy, she became afebrile. On the next day, dyspnea was resolved. Chest radiograph on that day showed dramatic improvement. Five days after the initiation of steroid therapy, laboratory findings were normalized. She was discharged on the 17th day of admission without sequelae.
	aratakul PCT Pronchiol 1)	Eninonhrino	Pacolino 9	sequelae. Soon after
pisarn 2007 Pediatri itis Dexamethasone salbutamol, IV every 6h	,			study
			•	
Thailandc4wk-0.6mg/kg, singlefluids,until study				endpoint, but
		antimicrobial	endpoint	before being
outpati 24mo dose (IM), n=89 antimicrobial endpoint	outpati 24mo dose (IM), n=89	antimicrobial	endpoint	before being
outpati 24mo dose (IM), n=89 antimicrobial endpoint (resolution	outpati 24mo dose (IIVI), n=89	antimicrobial	-	discharged,

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Г	Non-	ent or		2) Saline	drugs &	of	systemic CS
				solution	-		
	industry	ED			oxygen	respiratory	was
	funded	2		0.6mg/kg, single		distress);	prescribed to
				dose (IM), n=85	No CS in	FU at 2wk	seven children
					preceding 2wk	intervals for	(four in the
						at least	dexamethaso
						1mo	ne group)
							because of re-
							wheezing.
							None of the
			\sim				children
							received
							theophylline
							or ribavirin.
							Three childre
							(two in the
			K				dexamethaso
				\mathbf{N}			ne group)
				eet tev			developed
							occult blood
							in stools. Six
							children
							(three in the
					•		dexamethaso
							ne group) had
							subsequent
							diarrhea.
							Three childre
							(all in the
						•	-
						5	placebo
							group) had
							subsequent
							pneumonia
							with
							suspicious
							bacterial
							causes and
							required
							additional
							antibiotics.
							Table 5 -
							probable
							adverse
							outcomes of

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						treatment up to 1 month post- treatment, n (Dex vs. Placebo): Occult blood in stools (2 vs. 1); Pneumonia (0 vs. 0); Diarrhea (3 vs. 3)
van	RCT	Bronchiol	1) Prednisolone	Oxygen,	Baseline &	In the present
Woensel	Hospita	itis	powder	bronchodilato	daily for 7d	study no
1997	1	<2y	1.0mg/kg/day in	rs, or		clinically
Netherland	1		2 divided doses	antibiotics		significant
S			for 7d (oral),			side effects of
Non-			n=27	No CS in		prednisolone
industry			2) Placebo in 2	preceding		were found.
funded			divided doses	2mo		
			for 7d (oral), n=27			
Webb 1986	RCT,	Persisten	1) Prednisolone	Bronchodilato	Daily for 5d	There were
UK	crossov	t wheeze	1.0mg/kg, twice <	r & antibiotics	& clinical	no side
Non-	er	<18mo	daily for 5d		exam 3d	effects
industry	"unit",		(oral), n=NR	NR	after	reported by
funded	outpati		(total patients in		treatment	the parents
	ent		study = 38)		course (D8)	and none was
	1		2) Placebo,		5	detected on
			twice daily for			clinical
			5d (oral), n=18			examination
			crossed over			at the time of review three
			Multiple			days after
			courses;			completing
			38 children			the five day
			completed a			course of
			total of 56			treatment.
			treatment			
			courses			
Zhang 2003	RCT	Bronchiol	1) Prednisolone	IV	Enrolment,	The potential
Brazil	Pediatri	itis	1.0mg (oral) +	hydrocortison	1mo, 3mo,	side-effects o
	с	<12mo	standard care	e in first 24h	6mo &	prednisolone

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Non-	hospital	for 5d (NR),	after	12mo after	were not
industry	ward	n=28	hospitalization	discharge	included as
funded	1	2) Standard care			outcome
		(oxygen, fluid	No CS in		measures in
		replacement,	preceding 4wk		this study as
		nebulised			the safety of
		fenoterol) for			short-term
		5d (NR), n=24			steroid
					therapy has
					been well
					confirmed.
					the time of
					analysis of t
					data, all 52
					patients'
					hospital
		0			records wer
					reviewed an
					no adverse
					event was
					noted in the
					patients who
					received
					prednisolon

¹Hedlin 1999 and Svedmyr 1999 are associated publications; Svedmyr 1999 reports on an RCT comparing budesonide with placebo, and Hedlin 1999 reports systemic effects on a subgroup of these children with moderate to severe asthma exacerbations who required additional treatment (with oral betamethasone) and/or hospitalization;

admin: administration; BW: birthweight; cc: cubic centrimetre(s); CCT: controlled clinical trial; cm: centimeter(s); CS: corticosteroid; d/D: day(s); ED: emergency department; FP: fluticasone propionate; FU: follow-up; g: gram(s); h: hour(s); IM: intramuscular; IV: intravenous; kg: kilogram(s); L: litre(s); max.: maximum; mcg: microgram(s); MDI: metered-dose inhaler; mg: milligram(s); mL: milliliter(s); mo: month(s); neb: nebulized; NR: not reported; NRCT: non-randomized clinical trial; RCT: randomized clinical trial; RSV: respiratory syncytial virus; SA: Saudi Arabia; sal: salbutamol; UK: United Kingdom; URTI: upper respiratory tract infection; vs: versus; wk: week(s); y: year(s); yo: year old

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Supplement 4	Methodological quality of included studies
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a.	Summary of methodological quality assessments	р. 1-2
b.	Methodological quality assessments of included studies	р. 3-6

Supplement 4a. Summary of methodological quality assessments

Mc	Harm* criteria	Rating	No. of studies (% ²)		
1)	Were the harms PRE-DEFINED using standardized or precise definitions?	Yes	6 (7)		
		No	79 (93)		
		Unsure	0		
2)	Were SERIOUS events precisely defined?	Yes	2 (2)		
		No	83 (98)		
		Unsure	0		
3)	Were SEVERE events precisely defined?	Yes	0		
		No	85 (100)		
		Unsure	0		
4)	Were the number of DEATHS in each study group specified OR were the	Yes	10 (12)		
	reason(s) for not specifying them given?	No	75 (88)		
		Unsure	0		
5)	Was the mode of harms collection specified as ACTIVE?	Yes	46 (54)		
		No	37 (44)		
		Unsure	2 (2)		
6)	Was the mode of harms collection specified as PASSIVE?	Yes	11 (13)		
		No	73 (86)		
		Unsure	1 (1)		
7)	Did the study specify WHO collected the harms?	Yes	22 (26)		
		No	63 (74)		
		Unsure	0		
8)	Did the study specify the TRAINING or BACKGROUND of who ascertained	Yes	20 (24)		
	the harms?	No	65 (76)		
		Unsure	0		
9)	Did the study specify the TIMING and FREQUENCY of collection of the	Yes	39 (46)		
	harms?	No	45 (53)		
		Unsure	1 (1)		
10)	Did the author(s) use STANDARD scale(s) or checklist(s) for harms	Yes	6 (7)		
	collection?	No	76 (89)		
		Unsure	3 (4)		
11)	Did the authors specify if the harms reported encompass ALL the events	Yes	80 (94)		
	collected or a selected SAMPLE?	No	2 (2)		
		Unsure	3 (4)		
12)	Was the NUMBER of participants that withdrew or were lost to follow-up	Yes	24 (28)		
·	specified for each study group?	No	61 (72)		

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	Unsure	0
13) Was the TOTAL NUMBER of participants affected by harms specified for	Yes	16 (19)
each study arm?	No	69 (81)
	Unsure	0
14) Did the author(s) specify the NUMBER for each TYPE of harmful event for	Yes	43 (51)
each study group?	No	39 (46)
	Unsure	3 (4)
15) Did the author(s) specify the type of analyses undertaken for harms data?	Yes	10 (12)
	No	75 (88)
	Unsure	0

JIS/SLLL LIDO due to *methodological quality of publications/studies as assessed by the McHarm scale¹

² sum of percentages may not total 100 due to rounding

Supplement 4b. Methodological quality assessments of included studies

	efined		fined		Mode of co	ollection		ckground	uency of	d for AE	II AE	and ow-up	arm	f AE	/sis
Study (year)	Harms pre-defined	Serious AE defined	Severe AE defined	Deaths specified	ACTIVE	PASSIVE	Who collected AE	Training/ background of assessors	Timing/ frequency of AE collection	Checklist used for AE	Encompass all AE	Withdrawal and losses to follow-up	AE in each ar specified	# and type of specified	Type of analysis
Alangari (2014)	Ν	Ν	N	N	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
Alansari (2013)	Ν	Ν	Ν	Ν	Y	Ν	Y	Y	Y	Ν	Υ	Y	Ν	Ν	Ν
Aljebab (2017)	Υ	Ν	Ν	N	Υ	Υ	Υ	Y	Y	U	Υ	Y	Ν	Y	Y
Alshehr (2005)	Ν	Ν	Ν	N	N	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Y	Ν
Altamimi (2006)	Ν	Ν	Ν	Ν	Y	Ν	Y	Y	Y	Ν	Y	Y	Ν	Y	Ν
Bacharier (2008)	Ν	Ν	Ν	Ν	N	Ν	Ν	Ν	Ν	Ν	Υ	Y	Ν	Ν	Ν
Bisgaard (2006)	Υ	N	N	Ν	Y	Ν	N	N	Y	Ν	Ν	Y	Y	U	Y
Bjornson (2004)	Ν	Ν	N	Ν	Y	N	Υ	Y	Y	Ν	Y	N	Ν	Y	Ν
Brunette (1988)	Υ	Ν	N	Ν	Y	Ν	N	Ν	Y	Y	Y	N	Ν	Y	Y
Buckingham															
(2002)	Ν	Ν	Ν	Y	Y	Ν	Y	Υ	Y	Ν	Y	Ν	Ν	Y	Ν
Bulow (1999)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	Ν	Ν	Y	Ν	Y	Ν	Ν
Chang (2008)	Ν	Ν	N	Ν	Y	Ν	N	N	Y	N	Y	Y	Y	Y	Ν
Chen (2008)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	Ν	Y	Ν	Ν	Ν	Ν
Chub-Appakarn															
(2007)	N	N	N	N	Ν	Ν	N	N	N	Ν	Y	N	N	N	Ν
Clavenna (2014)	Ν	Ν	N	N	Y	Y	Y	Y	Y	Ν	Y	Y	N	N	Ν
Connett (1994)	N	Ν	Ν	Ν	Ν	Ν	N	N	Ν	Ν	Y	N	Ν	Y	Ν
Connolly (1969)	Ν	Ν	Ν	Y	Y	Ν	N	Ν	Y	Ν	Y	Ν	Ν	Y	Ν
Corneli (2007)	Ν	N	N	N	Y	Ν	Y	Y	Y	Ν	Y	Y	N	N	Ν
Cronin (2016)	Ν	N	N	N	Y	Y	Y	Y	Y	Ν	Y	Y	N	Y	Ν
Csonka (2003)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Υ	Y	Y	Y	Ν

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Daughiarg (1002)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
Daugbjerg (1993)						Y	Y	Y			Y Y				
Dawson (1993)	N	N	N	N	Y				Y	U		N	N	N	N
Ducharme (2009)	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Eboriadou (2010)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	U	N
Eden (1967)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	U	N
Escobedo Chavez (1992)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Fifoot (2007)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N
Fitzgerald (1996)	N	N	N	N	U	U	N	N	Y	N	Y	Y	N	N	Y
Francis (1997)	N	Y	N	N	N	N	N	N	N	N	U	Y	Y	N	N
Garbutt (2013)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N.	N	N	N
Ghirga (2002)	N	N	N	N	N	N	N	N	N	N	Ŷ	N	N	N	N
Gill (2017)	N	N	N	Y	Y	N	N	N	Y	N	Y	N	N	Y	Y
Goebel (2000)	N	N	N	N	Y	N	Y	Y	Y	N	N	N	N	Y	N
Grant (1996)	N	N	N	N	Y	Υ	N	N	Y	N	Y	N	N	N	Y
Gries (2000)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	Y
Hedlin (1999) ¹	Ν	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Husby (1993)	Ν	N	N	N	U	N	Y	N	Y	N	Y	N	N	N	N
Inglis (1993)	Ν	Ν	N	Y	Y	Y	N	Ν	Y	N	Y	Y	Y	Y	N
Jan (2000)	Ν	Ν	N	Ν	Y	N	N	N	Y	Y	Y	N	N	N	N
Jartti (2006)	N	N	N	Ν	N	Ν	N	Ν	Ν	N	Y	N	Ν	N	N
Jartti (2007)	Ν	Ν	N	Ν	N	Ν	N	N	N	N	Y	Ν	N	Ν	N
Jartti (2015)	Ν	Ν	N	Ν	N	Ν	N	N	Ν	N	U	Y	N	Ν	N
Johnson (1996)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Johnson (1998)	Ν	N	N	N	N	N	N	N	N	N	U	N	N	Y	N
Klassen (1994)	Ν	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Klassen (1996)	Ν	Ν	Ν	Ν	N	Ν	N	Ν	Ν	N	Y	Ν	Ν	Y	Ν
Klassen (1998)	Ν	Ν	Ν	Ν	Y	Υ	Y	Y	U	N	Y	Y	Ν	Y	Ν
Kuyucu (2004)	Ν	Ν	Ν	Ν	N	Ν	N	Ν	Ν	N	Y	Ν	Ν	Ν	Ν
Lai (2005)	N	N	N	N	Y	N	Ν	Ν	Y	Y	Y	N	Ν	N	Y

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2																
3	Langton-Hewer															
4 5	(1998)	N	Ν	N	N	Ν	Ν	Ν	N	N	N	Y	N	N	Y	N
6	Lee (2001)	N	N	N	Y	Y	Ν	N	N	Y	N	Y	Y	Y	Y	N
7	Leer (1969)	Ν	Ν	N	N	Ν	N	N	N	N	N	Y	N	Y	Y	Ν
8 9	Lehmann (2008)	Ν	Ν	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
9 10	Leipzig (1979)	N	N	N	N	N	Ν	N	N	N	N	Y	N	N	N	N
11	Lin (1991)	N	N	N	N	N	Ν	N	N	N	N	Y	N	N	Y	N
12	Lucas-Bouwman															
13 14	(2001)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	Y	Y	N	Y	N
15	Nahum (2009)	Ν	Ν	Ν	Y	Y	Ν	Ν	Ν	Y	N	Y	Y	Y	Y	Ν
16	Paniagua (2017)	Ν	Ν	Ν	N	Y	Ν	Ν	Ν	Ν	N	Y	Ν	N	Y	Ν
17 18	Panickar (2009)	Ν	Ν	Ν	N	Y	Y	Y	Y	Y	Ν	Y	Ν	Ν	Y	Ν
19	Panigada (2014)	Ν	Ν	Ν	Ν	Y	N	Ν	Ν	Y	Ν	Y	Y	Y	Y	Ν
20	Plint (2009)	Ν	Ν	Ν	N	Y	N	Y	Y	Y	N	Y	N	N	Y	Ν
21	Razi (2015)	Ν	Ν	Ν	N	Ν	Ν	Ν	Ν	Ν	N	Y	Ν	N	Ν	Ν
22 23	Roberts (1999)	Ν	Ν	Ν	Ν	Ν	N	Ν	N	Ν	Ν	Y	Ν	Ν	Y	Ν
24	Roorda (1998)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
25	Roosevelt (1996)	Ν	Ν	Ν	Ν	Y	Ν	Y	Y	Y	Ν	Y	Ν	Ν	Y	Ν
26 27	Sadowitz (2012)	Ν	Ν	Ν	Ν	Y	Y	Ν	Ν	Y	Ν	Y	Y	Y	Y	Ν
28	Saito (2017)	Ν	Ν	Ν	Ν	Y	Ν	Ν	N	Ν	Ν	Y	Ν	Ν	Ν	Ν
29	Schuh (2008)	Ν	Ν	Ν	Ν	Y	Ν	Y	Y	Υ	Υ	Y	Ν	Ν	Ν	Ν
30	Schuh (2009)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	Ν	Y	Y	Ν	Y	Ν
31 32	Siomou (2003)	Y	Ν	Ν	Ν	Y	Ν	Ν	Ν	Y	U	Y	Ν	Ν	Ν	Ν
33	Sparrow (2006)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
34	Stafford (1998)	Y	Ν	Ν	Ν	Y	Ν	Ν	Ν	Y	Y	Y	Ν	Ν	Y	Ν
35 36	Storr (1987)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
37	Sumboonnanonda															
38	(1997)	Ν	Ν	Ν	N	Y	Ν	N	N	Y	N	Y	Ν	N	Y	Ν
39 40	Sung (1998)	Ν	Ν	Ν	N	Y	Y	Y	Y	Ν	N	Υ	Ν	N	Ν	Ν
40 41	Super (1989)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Υ	Ν	Ν	Ν	Ν

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1															
² ³ Sussman (1964)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
4 5 Svedmyr (1995)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
6 Svedmyr (1999) ¹	N	N	Ν	N	Y	N	Y	Ν	Y	Y	Y	Ν	Y	Y	Y
7 Tagarro (2014)	N	N	Ν	N	N	N	N	Ν	N	Ν	Y	Ν	Ν	Y	N
8 9 Tal (1983)	N	N	Ν	Y	N	N	Ν	Ν	N	Ν	Y	Ν	Ν	N	Ν
10 Tamura (2008)	N	N	N	N	Y	N	Ν	Ν	N	Ν	Y	Ν	Ν	N	N
11 Teeratakulpisarn															
¹² (2007)	Ν	Ν	Ν	N	Y	Ν	Y	Y	Υ	Ν	Y	Ν	Ν	Y	Ν
13 van Woensel															
15 (1997)	N	Ν	Ν	Y	N	N	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
16 Webb (1986)	N	N	N	N	Y	Y	Ν	Ν	Y	Ν	Y	Ν	Ν	N	N
17 18 Zhang (2003)	N	Ν	N	N	Y	Ν	N	Ν	N	Ν	Y	Ν	Ν	N	N

¹ Hedlin 1999 and Svedmyr 1999 are associated publications; the two papers are assessed as one study

N: no; U: unsure; Y: yes

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1. Chou R, Aronson N, Atkins DL, et al. Accessing harms when comparing medication interventions. In: Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD; 2008. - M

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Supplement 5 Effect estimates for all adverse events with subgroups

a. Infection & respiratory system	р. 2-4
b. Gastro-intestinal tract	p. 5-7
c. CNS & behaviour effects	р. 8-9
d. Dermatologic conditions	p. 10
e. Endocrine/ metabolic & musculoskeletal systems	p. 11
f. Cardiovascular system	p. 12
g. General adverse events/ other symptoms	p. 13
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The tables below report results of meta-analyses for adverse events, organized by organ systems.

Effect estimates were calculated for studies with more than one treatment arm, using risk difference (RD) for all comparative studies and, using Peto odds ratio (pOR) for studies that reported at least one event in at least one treatment arm. Shaded rows indicate all studies contributing to an outcome, for the specified comparison, without subgroup analysis. When data was available, subgroup analyses (non-shaded rows) using study-level data were conducted for dose (single versus multi-dose) and for respiratory condition (e.g., bronchiolitis).

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Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients with events/total no. of patients	Comparison 2 – no. of patients with events/total no. of patients	RD (95% CI)	l ² (%)	Peto OR (95% CI)	
Severe infections, overall	Systemic vs. placebo		4	0/552	2/554	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	
Severe infections, by dose	Systemic vs. placebo	Single dose	1	0/359	1/361	0.00 (-0.01, 0.00)	NA	0.14 (0.00, 6.86)	
	Systemic vs. placebo	Multi-dose	3	0/193	1/193	0.00 (-0.01, 0.01)	0	0.17 (0.00, 8.79)	
Severe infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/179	0/175	0.00 (-0.01, 0.01)	0	NA	
	Systemic vs. placebo	Croup	2	0/373	2/379	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	
Severe infections, overall	Inhaled vs. placebo		1	2/62	4/67	-0.03 (-0.10, 0.04)	NA	0.54 (0.11, 2.77)	
Systemic infections, overall	Systemic vs. placebo		4	5/1095	4/1083	0.00 (0.00, 0.00)	0	1.26 (0.34, 4.68)	
Systemic infections, by dose	Systemic vs. placebo	Single dose	2	5/664	4/656	0.00 (-0.01, 0.01)	0	1.26 (0.34, 4.68)	
	Systemic vs. placebo	Multi-dose	2	0/431	0/427	0.00 (-0.01, 0.01)	0	NA	
Systemic infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/705	0/695	0.00 (0.00, 0.00)	0	NA	
	Systemic vs. placebo	Croup	1	5/359	4/361	0.00 (-0.01, 0.02)	NA	1.26 (0.34, 4.68)	
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	

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Systemic infections, overall	Inhaled vs. placebo	Multi-dose, wheeze	2	18/91	20/94	0.00 (-0.06, 0.06)	0	0.96 (0.45, 2.05)	NA
Lung/trachea, overall	Systemic vs. placebo		7	18/955	28/928	-0.01 (-0.02, 0.01)	37	0.61 (0.34, 1.12)	0
Lung/trachea, by dose	Systemic vs. placebo	Single dose	5	6/793	9/761	0.00 (-0.01, 0.00)	0	0.57 (0.20, 1.62)	0
	Systemic vs. placebo	Multi-dose	2	12/162	19/167	-0.09 (-0.29, 0.10)	69	0.63 (0.30, 1.33)	57
Lung/trachea, by condition	Systemic vs. placebo	Bronchiolitis	3	12/542	19/529	-0.02 (-0.05, 0.02)	61	0.61 (0.29, 1.28)	30
	Systemic vs. placebo	Croup	4	6/413	9/399	-0.02 (-0.12, 0.07)	40	0.61 (0.21, 1.76)	6
Lung/trachea, overall	Inhaled vs. placebo	Multi-dose, wheeze	1	13/62	10/67	0.06 (-0.07, 0.19)	NA	1.51 (0.61, 3.70)	NA
URT, overall	Systemic vs. placebo		6	9/671	7/656	0.00 (-0.01, 0.01)	0	1.21 (0.44, 3.33)	0
URT, by dose	Systemic vs. placebo	Single dose	4	1/492	1/480	0.00 (-0.01, 0.01)	0	0.46 (0.02, 10.18)	0
	Systemic vs. placebo	Multi-dose	2	8/179	6/176	0.01 (-0.03, 0.05)	0	1.36 (0.47, 3.96)	NA
URT, by condition	Systemic vs. placebo	Bronchiolitis	1	8/148	6/149	0.01 (-0.03, 0.06)	NA	1.36 (0.47, 3.96)	NA
URT, by condition	Systemic vs. placebo	Croup	4	1/492	1/480	0.00 (-0.01, 0.01)	0	0.46 (0.02, 10.18)	0
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
URT, overall	Inhaled vs. placebo		6	24/495	24/499	0.00 (-0.02, 0.02)	0	1.03 (0.57, 1.85)	21
URT, by dose	Inhaled vs. placebo	Single dose	3	2/140	0/144	0.00 (-0.02, 0.03)	14	7.40 (0.45 <i>,</i> 121.47)	NA
	Inhaled vs. placebo	Multi-dose	3	22/355	24/355	-0.01 (-0.04, 0.03)	0	0.93 (0.51, 1.71)	0

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URT, by condition	Inhaled vs. placebo	Croup	3	2/140	0/144	0.00 (-0.02, 0.03)	14	7.40 (0.45 <i>,</i> 121.47)	NA
	Inhaled vs. placebo	Wheeze	3	22/355	24/355	-0.01 (-0.04, 0.03)	0	0.93 (0.51, 1.71)	0
Voice complaints, overall	Systemic vs. placebo		1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
Voice complaints, overall	Inhaled vs. placebo	All multi- dose	4	38/343	43/337	-0.01 (-0.10, 0.07)	64	0.85 (0.53, 1.36)	73
Voice complaints, by condition	Inhaled vs. placebo	Asthma	2	4/50	9/49	-0.08 (-0.046, 0.31)	90	0.39 (0.12, 1.26)	81
	Inhaled vs. placebo	Wheeze	2	34/293	34/288	0.00 (-0.04, 0.04)	0	0.99 (0.59, 1.64)	NA

al; NA not application, con RD: risk difference; CI: confidence interval; NA not applicable/estimable; no.: number; Peto OR: Peto odds ratio; URI=upper respiratory tract;

vs.: versus

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Supplement 6b. Gastro-intestinal tract

Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD	l ²	Peto OR	²
	vs.		of	1 –	2 –	(95% CI)	(%)	(95% CI)	(%)
	Comparison 2		studies	no. of	no. of				
				patients	patients				
				with	with				
	$\mathbf{\wedge}$			events/total	events/total				
				no. of	no. of				
				patients	patients				
Bleeding, overall	Systemic vs. placebo		7	31/1287	31/1262	0.00 (0.00, 0.00)	0	1.00 (0.60, 1.67)	0
Bleeding, by dose	Systemic vs. placebo	Single dose	4	2/800	1/790	0.00 (0.00, 0.00)	0	1.87 (0.19, 18.27)	NA
	Systemic vs. placebo	Multi-dose	3	29/487	30/472	0.00 (-0.02,	0	0.96 (0.57, 1.64)	0
		6				0.02)			
Bleeding, by condition	Systemic vs. placebo	Bronchiolitis	5	31/881	31/852	0.00 (-0.01,	0	1.00 (0.60, 1.67)	0
						0.01)			
	Systemic vs. placebo	Croup	2	0/406	0/410	0.00 (-0.01,	0	NA	NA
						0.01)			
Bleeding, overall	Inhaled vs. placebo	Single dose,	1	0/48	0/49	0.00 (-0.04,	NA	NA	NA
		croup				0.04)			
Vomiting, overall	Systemic vs. placebo		7	38/1603	34/1573	0.00 (0.00, 0.01)	0	1.10 (0.69, 1.76)	17
Vomiting, by dose	Systemic vs. placebo	Single dose	4	21/747	23/712	0.00 (-0.02,	0	0.87 (0.47, 1.59)	24
						0.01)			
	Systemic vs. placebo	Multi-dose	3	17/856	11/861	0.00 (-0.01,	37	1.58 (0.75, 3.36)	0
						0.02)			
Vomiting, by condition	Systemic vs. placebo	Asthma	1	1/37	5/33	-0.11 (-0.27,	33	0.19 (0.03, 1.02)	0
						0.06)			
	Systemic vs. placebo	Bronchiolitis	3	24/751	21/718	0.00 (-0.02,	0	1.12 (0.62, 2.04)	0
						0.02)			
	Systemic vs. placebo	Croup	1	3/359	4/361	0.00 (-0.02,	NA	0.75 (0.17, 3.34)	NA
						0.01)			

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	Systemic vs. placebo	Wheeze	2	10/456	4/461	0.02 (-0.06, 0.11)	87	2.55 (0.87, 7.46)	0
Vomiting, overall	Inhaled vs. placebo		5	28/421	28/420	0.00 (-0.03, 0.04)	0	1.00 (0.58, 1.72)	0
Vomiting, by dose	Inhaled vs. placebo	Single dose	1	2/25	1/25	0.04 (-0.09 <i>,</i> 0.17)	NA	2.00 (0.20, 20.20)	NA
	Inhaled vs. placebo	Multi-dose	4	26/396	27/395	0.00 (-0.03 <i>,</i> 0.03)	0	0.96 (0.55, 1.67)	0
Vomiting, by condition	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06, 0.13)	NA	7.13 (0.14, 359.55)	NA
	Inhaled vs. placebo	Croup	2	4/67	4/65	0.00 (-0.08, 0.08)	0	0.97 (0.23, 4.00)	0
	Inhaled vs. placebo	Wheeze	2	23/326	24/328	0.00 (-0.04, 0.04)	0	0.96 (0.53, 1.74)	0
Vomiting, overall	Dexamethasone vs. other steroid		6	12/663	51/710	-0.06 (-0.09, - 0.02)	58	0.29 (0.17, 0.48)	0
Vomiting, by dose	Dexamethasone vs. other steroid	Single dose	5	6/376	39/420	-0.08 (-0.11, - 0.05)	47	0.23 (0.12, 0.42)	0
	Dexamethasone vs. other steroid	Multi-dose	1	6/287	12/290	-0.02 (-0.05, - 0.01)	NA	0.51 (0.20, 1.30)	NA
Vomiting, by condition	Dexamethasone vs. other steroid	Asthma	3	6/466	28/466	-0.05 (-0.11, 0.00)	77	0.26 (0.13, 0.52)	52
	Dexamethasone vs. other steroid	Croup	2	5/111	8/75	-0.04 (-0.16, 0.08)	64	0.46 (0.14, 1.45)	0
	Dexamethasone vs. other steroid	Other conditions	1	1/86	15/169	-0.08 (-0.13, - 0.02)	3	0.25 (0.09, 0.72)	0
Abdominal pain, overall	Systemic vs. placebo	Single dose, croup	1	1/359	1/361	0.00 (-0.01, 0.01)	NA	1.01 (0.06, 16.11)	NA
Abdominal pain, overall	Dexamethasone vs. other steroid		3	29/188	48/264	-0.01 (-0.07, 0.05)	0	0.96 (0.57, 1.61)	0

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1									
Abdominal pain, by condition	Dexamethasone vs. other steroid	Asthma	1	2/56	3/54	-0.02 (-0.10, 0.06)	NA	0.64 (0.11, 3.79)	NA
		Croup	1	9/46	7/41	0.02 (-0.14, 0.19)	NA	1.18 (0.40, 3.47)	NA
		Other conditions	1	18/86	38/169	-0.01 (-0.12, 0.10)	0	0.94 (0.50, 1.77)	0
0 1 Diarrhea, overall 2	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03, 0.04)	0	1.09 (0.43, 2.73)	0
3 Diarrhea, by dose 4	Systemic vs. placebo	Single dose	1	3/89	3/85	0.00 (-0.06, 0.05)	NA	0.95 (0.19, 4.84)	NA
5 6 7	Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
8 Diarrhea, by condition 9	Systemic vs. placebo	Bronchiolitis	1	3/89	3/85	0.00 (-0.06, 0.05)	NA	0.95 (0.19, 4.84)	NA
0 11 2	Systemic vs. placebo	Wheeze	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
 Diarrhea, overall Diarrhea, overall PD: rick difference 	Inhaled vs. placebo	Multi-dose, wheeze	2	41/326	46/328	-0.01 (-0.09, 0.08)	37	0.89 (0.57, 1.40)	44
6 KD. Tisk differe 7 18 9 0 1 2 3 4	ence; CI: confidence interval; NA:	пот аррпсарте е	stillable,	no number,			us		
5 6 7 8 9 0 1 2 3						Supj	olement	5 - Page 7 of 14	
4 5 6 7	For peer re	view only - http://	/bmjopen.k	omj.com/site/a	bout/guidelines.	xhtml			

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Supplement 6c.	CNS &	behavior	effects
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Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients with events/total no. of	Comparison 2 – no. of patients with events/total no. of	RD (95% CI)	l ² (%)	Peto OR (95% Cl)	l ² (%)
2 3 Tremor/jitteriness, overall 4	Systemic vs. placebo		5	patients 22/559	patients 14/508	0.01 (-0.01, 0.03)	0	1.44 (0.71, 2.92)	0
5 6 7	Systemic vs. placebo	Single dose	2	9/83	7/56	0.00 (-0.08, 0.08)	0	1.15 (0.36, 3.66)	0
8 9	Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
⁰ Tremor/jitteriness, by 1 2 condition	Systemic vs. placebo	Asthma	1	9/37	7/33	0.01 (-0.16, 0.18)	0	1.15 (0.36, 3.66)	0
3		Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
4		Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
5 6 7	Dexamethasone vs. other steroid	Single dose, croup	1	1/46	0/41	0.02 (-0.04, 0.08)	NA	6.63 (0.13, 336.21)	NA
 Behaviour change, overall 9 	Systemic vs. placebo		4	7/588	3/571	0.00 (-0.01, 0.02)	19	1.95 (0.55, 6.92)	0
 ⁰ Behaviour change, by dose 2 	Systemic vs. placebo	Single dose	2	1/423	1/426	0.00 (-0.01, 0.01)	0	1.01 (0.06, 16.11)	NA
3	Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
5 Behaviour change, by	Systemic vs. placebo	Croup	2	1/423	1/426	0.00 (-0.01, 0.01)	0	1.01 (0.06, 16.11)	NA
7 8 9	Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
⁰ Behaviour change, overall	Inhaled vs. placebo		3	6/134	7/135	-0.01 (-0.04, 0.03)	0	0.81 (0.26, 2.54)	0

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Inhaled vs. placebo Multi-dose 2 6/70 6/67 0.02 (-0.06, 0.10) 0 0.95 (0.28, 3.15) 11 Behaviour change, by condition Inhaled vs. placebo Asthma 1 1/28 0/27 0.04 (-0.06, 0.13) NA 7.13 (0.14, 359.55) NA condition Inhaled vs. placebo Croup 2 5/106 7/108 -0.02 (-0.05, 0.02) 0 0.66 (0.20, 2.18) 0 Behaviour change, overall Dexamethasone vs. other steroid All single dose 2 35/60 38/57 -0.08 (-0.25, 0.09) 0 0.73 (0.34, 1.56) 0 Behaviour change, by condition Dexamethasone vs. other steroid Asthma 1 10/14 14/16 -0.16 (-0.45, 0.13) NA 0.38 (0.06, 2.21) NA Condition vs. other steroid Croup 1 25/46 24/41 -0.04 (-0.25, 0.17) NA 0.85 (0.36, 1.97) NA Headache, overall Dexamethasone vs. other steroid Single dose, asthma 1 0/37 1/33 -0.02 (-0.10, 0.07) 0 0.11 (0.00, 5.68)	Inhaled vs. placebo Multi-dose 2 6/70 6/67 0.02 (-0.06, 0.10) 0 0.95 (0.00) Behaviour change, by condition Inhaled vs. placebo Asthma 1 1/28 0/27 0.04 (-0.06, 0.13) NA 7.13 (0.00) Behaviour change, by condition Inhaled vs. placebo Croup 2 5/106 7/108 -0.02 (-0.05, 0.02) 0 0.66 (0.00) Behaviour change, overall Dexamethasone vs. other steroid All single dose 2 35/60 38/57 -0.08 (-0.25, 0.09) 0 0.73 (0.00) Behaviour change, by Dexamethasone vs. other steroid Asthma 1 10/14 14/16 -0.16 (-0.45, 0.13) NA 0.38 (0.00)	.28, 3.15) 11 .14, 359.55) NA .20, 2.18) 0 .34, 1.56) 0
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vs. other steroid vs. Single dose, asthma 1 0/37 1/33 -0.02 (-0.10, 0.07) 0 0.11 (0.00, 5.68) Nu Headache, overall Dexamethasone All single 2 7/102 4/95 0.02 (-0.08, 0.11) 51 1.63 (0.46, 5.74) Nu Headache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA NA Nu Headache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA NA Nu Headache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA NA NA Meadache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA 1.63 (0.46, 5.74) N. RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto Ods ratio; vs.: versus V V V V V V V V V V V V V V V V V V V		.06, 2.21) NA
placebo asthma n n n n n n n Headache, overall Dexamethasone All single 2 7/102 4/95 0.02 (-0.08, 0.11) 51 1.63 (0.46, 5.74) N. Headache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA NA NA Meadache, by condition Dexamethasone Asthma 1 0/56 0/54 0.00 (-0.03, 0.03) NA NA NA Meadache, by condition Dexamethasone Asthma 1 7/46 4/41 0.05 (-0.08, 0.19) NA 1.63 (0.46, 5.74) N. RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus Supplement 5 - Page 9 of 14		.36, 1.97) NA
vs. other steroid dose loc loc <thloc< th=""> loc loc<td></td><td>.00, 5.68) NA</td></thloc<>		.00, 5.68) NA
vs. other steroid Croup 1 7/46 4/41 0.05 (-0.08, 0.19) NA 1.63 (0.46, 5.74) NA RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus V		.46, 5.74) NA
RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus		NA
Supplement 5 - Page 9 of 14	Croup 1 7/46 4/41 0.05 (-0.08, 0.19) NA 1.63 (0	.46, 5.74) NA
		ge 9 of 14

Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD	²	Peto OR	²
	VS.		of	1 – no. of	2 – no. of	(95% CI)	(%)	(95% CI)	(%)
	Comparison 2		studies	patients	patients				
				with	with				
				events/total	events/total				
				no. of	no. of				
				patients	patients				
Burn, overall	Inhaled vs. placebo	Single dose,	1	0/27	1/27	-0.04 (-0.13, 0.06)	NA	0.14 (0.00, 6.82)	NA
		croup							
Integument, overall	Systemic vs.		3	4/536	0/543	0.01 (0.00, 0.01)	0	7.59 (1.07, 54.01)	0
	placebo								
Integument, by dose	Systemic vs.	Single dose	2	2/423	0/426	0.01 (0.00, 0.01)	0	7.45 (0.47, 119.36)	NA
	placebo								
	Systemic vs.	Multi-dose	1	2/133	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
	placebo			\mathbf{O}					
Integument, by condition	Systemic vs.	Croup	2	2/423	0/426	0.01 (0.00, 0.01)	0	7.45 (0.47, 119.36)	NA
	placebo	-							
	Systemic vs.	Wheeze	1	2/113	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
	placebo								
Integument, overall	Inhaled vs. placebo		4	24/432	27/436	-0.01 (-0.04, 0.02)	11	0.88 (0.50, 1.56)	37
Integument, by dose	Inhaled vs. placebo	Single dose	1	0/64	1/68	-0.01 (-0.06, 0.03)	NA	0.14 (0.00, 7.25)	NA
	Inhaled vs. placebo	Multi-dose	3	24/368	26/368	-0.01 (-0.05, 0.04)	38	0.92 (0.52, 1.63)	49
Integument, by condition	Inhaled vs. placebo	Croup	2	0/106	3/108	-0.02 (-0.06, 0.01)	0	0.13 (0.01, 1.27)	0
0	Inhaled vs. placebo	Wheeze	2	24/326	24/328	0.01 (-0.05, 0.07)	46	1.00 (0.56, 1.80)	47
Phlebitis, overall	Dexamethasone vs.	Single dose,	1	0/15	0/17	0.00 (-0.11, 0.11)	NA	NA	NA
	other steroid	asthma	-	0,10	0/1/	0.00 (0.11, 0.11)			

RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus

Adverse event	Comparison 1 vs. Comparison 2	Subgrou	p No. of studies	Comparison 1 – no. of patients with events/tota no. of patients	2 – no. of patients with	RD (95% CI)	l ² (%)		eto OR 5% CI)	² (%)
Fluid & electrolyte abnormalities, overall	Systemic vs. placebo		4	5/832	1/818	0.00 (0.00, 0.01) 0	3.08 (0.	60, 15.94)	0
Fluid & electrolyte abnormalities, by dose	Systemic vs. placebo	Single dose	e 1	1/359	0/361	0.00 (0.00, 0.01) NA	7.43 (0.	15, 374.47)	NA
3	Systemic vs. placebo	Multi-dose	e 3	4/473	1/457	0.00 (-0.01, 0.01	L) 0	2.56 (0.	42, 15.61)	0
Fluid & electrolyte abnormalities, by condition	Systemic vs. placebo	Bronchioli	tis 2	4/448	1/432	0.00 (-0.01, 0.01	L) O	2.56 (0.	42, 15.61)	0
)	Systemic vs. placebo	Croup	2	1/384	0/386	0.00 (0.00, 0.01) 0	7.43 (0.	15, 374,47)	NA
Fluid & electrolyte abnormalities, overall	Dexamethasone vs. other steroid	Multi-dose bronchiolit		1/33	2/15	-0.10 (-0.28, 0.0	8) NA	0.18 (0.	01, 2.17)	NA
Adrenal suppression, overall	Inhaled vs. placebo	Multi-dose asthma	e, 1	5/6	4/10	0.43 (0.01, 0.86) NA	5.21 (0.	72, 37.57)	NA
Adverse e		nparison 1 vs. nparison 2	Subgrou		o. Compariso f 1 – total	2/	ersus Me Differ (95%	ence	l ² (%)	
Linear growth CI: confidence inter	val; no.: number; vs.:	•	Multi-dose, w	heeze 2	154	109	0.10 (-0.4	17, 0.67)	9	

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Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients	Comparison 2 – no. of patients	RD (95% CI)	l² (%)	Peto OR (95% Cl)	l² (%)
	~			with events/total no. of patients	with events/total no. of patients				
Arrhythmia, overall	Systemic vs. placebo	Multi-dose, wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
Arrhythmia, overall	Inhaled vs. placebo	Multi-dose, wheeze	1	0/29	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
Arrhythmia, overall	Dexamethasone vs. other steroid	Multi-dose, asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	NA	NA	NA
Hypertension, overall	Systemic vs. placebo	All bronchiolitis	3	1/727	1/714	0.00 (-0.01, 0.01)	0	1.00 (0.06, 15.99)	50
Hypertension, by dose	Systemic vs. placebo	Single dose	1	0/305	0/295	0.00 (-0.01, 0.01)	NA	NA	NA
	Systemic vs. placebo	Multi-dose	2	1/422	1/419	0.00 (-0.01, 0.01)	0	1.00 (0.06, 15.99)	50
Hypertension, overall	Dexamethasone vs. other steroid	Single dose, asthma	1	0/15	0/17	0.00 (-0.11, 0.11)	NA	NA	NA
Congestive heart failure, overall	Systemic vs. placebo	Multi-dose, croup	1	0/25	0/25	0.00 (-0.07, 0.07)	NA	NA	NA
RD: risk differend	ce; Cl: confidence interval;	NA: not applical	ole/estimat	ble; no.: numbe	r; Peto OR: Peto	o odds ratio; vs.: vers	us		

Supplement 6g. General adverse events/ other symptoms

4 _[eral adverse events/ oth		Na	Comparison	Comparison	RD	²	Peto OR	²
5	Adverse event	Comparison 1	Subgroup	No.	Comparison	-				
6		VS.		of	1 – no. of	2 – no. of	(95% CI)	(%)	(95% CI)	(%)
7 8		Comparison 2		studies	patients	patients				
9					with	with				
10					events/total	events/total				
11					no. of	no. of				
12					patients	patients		-		-
13	General complaints ¹ , overall	Systemic vs. placebo	All	2	38/446	38/423	0.00 (-0.04, 0.04)	0	1.00 (0.62, 1.60)	0
14			bronchiolitis							
16	General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, 0.09)	0	NA	NA
17		Systemic vs. placebo	Multi-dose	1	38/400	38/400	0.00 (-0.04, 0.04)	0	1.00 (0.62, 1.60)	0
	General complaints ² , overall	Dexamethasone vs.		2	3/102	3/95	-0.01 (-0.06, 0.03)	0	0.90 (0.18, 4.61)	11
19		other steroid								
20 21	General complaints, by	Dexamethasone vs.	Asthma	1	0/56	1/54	-0.02 (-0.07, 0.03)	NA	0.13 (0.00, 6.58)	NA
22	condition	other steroid),					
23		Dexamethasone vs.	Croup	1	3/46	2/41	0.01 (-0.08, 0.11)	NA	1.29 (0.21, 7.81)	NA
24		other steroid								
25	¹ Two studies reporte	ed pallor				1				
26 27	² One study reported	excessive urination; one	study reported	dizziness						
28	RD: risk difference; C	I: confidence interval; N	A: not applicable,	/estimable	; no.: number; F	Peto OR: Peto o	dds ratio; vs.: versus			
29										
30										
31										
32 33										
34										
35										
36										
37										
38										

Supplement 6h. Immune system & oncology

Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD	²	Peto OR	²
	VS.		of	1 –no.# of	2 – no. of	(95% CI)	(%)	(95% CI)	(%)
	Comparison 2		studies	patients	patients				
				with	with				
				events/total	events/total				
				no. of	no. of				
				patients	patients				
nmunosuppression, overall	Systemic vs. placebo		1	0/47	0/48	0.00 (-0.04, 0.04)	NA	NA	NA
	confidence interval; NA:								

Supplement 6. Studies reporting no adverse events

Study	Condition	Comparisons - main	Study design	Study sample	AE reporting
Alansari 2013	bronchiolitis	systemic vs. placebo	RCT	200	No AE overall; 7 days follow-up revealed no side effect concerns in treatment groups.
Brunette 1988	asthma, before signs of wheeze	systemic vs. systemic	nRCT	32	No AE overall; Growth and weight gains for all children were within normal range.
Chen 2008	asthma	systemic vs. inhaled vs. inhaled	RCT, 3-arm	123	No AE overall; All 3 groups reported no adverse effects.
Chub-Uppakarn 2007	croup	systemic vs. systemic	RCT	41	No AE overall; No significant adverse reaction from dexamethasone treatment in either group.
Escobedo Chavez 1992	asthma	systemic vs. non- corticosteroid	RCT	50	No AE overall; We detected no side effects from the use of methylprednisolone in a single dose.
Fifoot 2007	croup	systemic vs. systemic vs. systemic	RCT, 3-arm	99	No AE overall; One patient in each group vomited their first dose of medication; all except one (dexamethasone 0.6mg/kg) tolerated their repeat dose; no patient suffered any adverse outcomes from receiving study steroid, either at index presentation or during the follow-up period.

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Ghirga 2002	wheeze - recurrent,	inhaled vs. no	RCT	26	No AE overall;
	early in URTI	intervention			No apparent adverse effects reported 4 year
					post-study.
Husby 1993	croup	inhaled vs. placebo	RCT	36	No AE overall;
					No side effects were reported.
Jartti 2006	wheeze - acute	systemic vs. placebo	RCT	78	No AE overall;
					Prednisolone treatment well tolerated; no
		6			clinically significant adverse effects occurred
Jartti 2007	wheeze - recurrent	systemic vs. placebo	RCT	58	No AE overall;
					Prednisolone treatment well tolerated; no
		Co.			clinically significant adverse effects occurred
Klassen 1994	croup	inhaled vs. placebo	RCT	54	One patient in placebo group had a burning
					sensation on the face. No adverse events
			C/		noted in budesonide group.
Langton Hewer 1998	asthma	systemic vs. systemic	RCT, 3-arm	98	No AE overall;
		vs. systemic			No side effect possibly attributable to
					prednisolone therapy was noted in any of th
				O	three treatment groups.
Leipzig 1979	croup	systemic vs. placebo	RCT	30	No AE overall;
					Observed no adverse effects or late relapses
Razi 2015	asthma	inhaled vs. placebo	RCT	100	No AE overall;
					No drug-related adverse effects were
					identified during hospitalization.
Roorda 1998	croup	inhaled vs. placebo	RCT	17	No AE overall;
					No side effects of treatment regimens were
					reported.

Saito 2017	asthma	systemic vs. inhaled	RCT	50	No AE overall;
					Adverse events did not occur in either group
					Serum cortisol levels on the 4th day of
					hospitalization were 17.0mcg/dL and
					10.9mcg/dL with significant suppression in
					the prednisolone group.
Schuh 2009	asthma	systemic vs. non-	RCT	130	No AE overall;
		corticosteroid			No adverse effects developed in children
		4			given prednisolone after discharge.
Sparrow 2006	croup	systemic vs. systemic	RCT	133	No AE overall;
					No adverse events in either group.
Storr 1987	asthma	systemic vs. placebo	RCT	140	No AE overall;
			4		There were no observed side effects related
			$\mathbf{Q}_{\mathbf{r}}$		to the single prednisolone dose.
Sung 1998	asthma	inhaled vs. placebo	RCT	44	No AE overall;
					No adverse effects in either group.
Super 1989	croup	systemic vs. placebo	RCT	33	No AE overall;
					Did not encounter any side effects directly
					attributable to dexamethasone.
Tal 1983	wheeze - acute	systemic + sal;	RCT, 2x2	32	No AE overall;
		systemic + placebo;			No other side effects or complications were
		sal + placebo;			documented, aside from tremor (1 infant) as
		placebo			side effect of salbutamol.
Tamura 2008	refractory	systemic	CS (#1)	1	No AE overall;
	pneumonia (5 year				No adverse events in any patients during
	old)				steroid treatment.

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van Woensel 1997	bronchiolitis	systemic vs. placebo	RCT	54	No AE overall; No clinically significant side effects of prednisolone were found.
Webb 1986	wheeze	systemic vs. placebo	RCT	38	No AE overall; No side effects reported by parents and none detected on clinical exam 3 days after completing 5-day treatment course.
Zhang 2003	bronchiolitis	systemic vs. standard care	RCT	52	No AE overall; Potential side-effects of prednisolone not included as outcome measures in this study as short-term steroid therapy has been well confirmed. At time of analysis, no adverse events were noted in patients who received prednisolone.
AE: adverse events; respiratory tract inf		on-randomised controlle	d trial; RCT: rai	ndomised cont	trolled trial; sal: salbutamol; URTI: upper

Section/ topic (page no)	Item	PRISMA checklist item	PRISMA harms (minimum)	Recommendations for reporting harms in systematic reviews (desirable)	Check if done
Title Title (3)	1	Identify the report as a systematic review, meta-analysis, or both.	Specifically mention "harms" or other related terms, or the harm of interest in the review.		Title page, p. 1-2
Abstract Structured summary (4)	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	_	Abstracts should report any analysis of harms undertaken in the review, if harms are a primary or secondary outcome.	p. 3
Introduction Rationale (5)	3	Describe the rationale for the review in the context of what is already known.		It should clearly describe in introduction or in methods section which events are considered harms and provide a clear rationale for the specific harm(s), condition(s), and patient group(s) included in the review.	p. 4
Objectives (5)	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	0	PICOS format should be specified, although in systematic reviews of harms the selection criteria for P, C, and O may be very broad (same intervention may have been used for heterogeneous indications in a diverse range of patients)	p. 5
Methods Protocol and registration (6)	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	_	No specific additional information is required for systematic reviews of harms.	 p. 5; protocol reference # reported in funding source (p. 20)
Eligibility criteria (6)	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication		Report how handled relevant studies (based on population and intervention) when the	20) p. 5-6;

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2 3 4 5 6			status) used as criteria for eligibility, giving rationale.		outcomes of interest were not reported. Report choices for specific study designs	Supplement 2 - Eligibility criteria for study inclusion
7 8	Information (7)	7	Describe all information sources (eg,	—	and length of follow-up. Report if only searched	p. 5;
9 10 11 12 13 14	sources (7)		databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.		for published data, or also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished	Supplement 1- Search strategy
15 16 17					data, provide the source and the process of obtaining it.	
18 19 20 21 22 23 24	Search (7)	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.		If additional searches were used specifically to identify adverse events, authors should present the full search process so it can be replicated.	Supplement 1 - Search strategy
25 26 27	Study selection (8)	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable,	—	If only included studies reporting on adverse events of interest,	p. 6; Supplement 2 -
28 29 30 31 32 33 34 35 36			included in the meta-analysis).		defined if screening was based on adverse event reporting in title/abstract or full text. If no harms reported in the text, report if any attempt was made to retrieve relevant data from authors.	Eligibility criteria for study inclusion
38 39 40	Data collection process (9)	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	- 0	No specific additional information is required for systematic reviews of harms.	р. 6-7
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59	Data items (9)	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.		Report the definition of the harm and seriousness used by each included study (if applicable). Report if multiple events occurred in the same individuals, if this information is available. Consider if the harm may be related to factors associated with participants (eg, age, sex, use of medications) or provider (eg, years of practice, level of	p. 6-7

1 2 3 4 5 6 7 8					training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details	
9 10 11 12					regarding the specific methods used to capture harms (active/passive and timing of adverse event).	
15 ⁱ 16 ^s 17 18	Risk of bias in individual studies (10)	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	_	The risk of bias assessment should be considered separately for outcomes of benefit and harms.	p. 7
	Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	_	No specific additional information is required for systematic reviews of harms.	p. 7-8
24	Synthesis of results (11)	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I ²) for each meta- analysis.	Specify how zero events were handled, if relevant.	or numity.	p. 7-8
29 a	Risk of bias across studies (11)	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	el.ez	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	p. 7
37 /	Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	- 0	Sensitivity analyses may be affected by different definitions, grading, and attribution of adverse events, as adverse events are typically infrequent or reported using heterogeneous classifications. Report the number of participants and studies included in each subgroup.	p. 7
51 §	Results Study selection (13)	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	_	If a review addresses both efficacy and harms, display a flow diagram specific for each (efficacy and harm).	p. 8; Figure 1 - PRISMA study flow selection
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1 2						
3 4 5 6 7 8 9 10 11 12 13 14 15 16 17	Study characteristics (14)	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period.	Add additional characteristics to: "P" (population) patient risk factors that were considered as possibly affecting the risk of the harm outcome. "I" (intervention) professional expertise/skills if relevant (for example if the intervention is a procedure). "T" (time) timing of all harms assessments and the length of follow-up.	p. 8; Supplement 3 - Characteristics of included studies
18 19 20 21 22 23 24 25 26 27 28 29 30	Risk of bias within studies (15)	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-	Consider the possible sources of biases that could affect the specific harm under consideration within the review. Sample selection, dropouts and measurement of adverse events should be evaluated separately from the outcomes of benefit as described in item 12, above.	p. 8; Supplement 4 - Methodological quality of included studies
31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 90 51 52 54 55 56 57 58	Results of individual studies (16) Synthesis of results (17)	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Describe any assessment of possible causality.	Report the actual numbers of adverse events in each study, separately for each intervention. If included data from unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	 p. 8; Supplement 3 - Characteristics of included studies p. 8-14; Table 1 - Number of studies and participants reporting adverse events; Figures 2-4 - Forest plots of adverse events; Supplement 5 - Effect estimates for all adverse events with subgroups; Supplement 6 - Studies reporting no adverse events
59 60			For peer review only - http://bmjoj	pen.bmj.com/site/about/	guidelines.xhtml	

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1 2						
3 4 5 6 7 8	Risk of bias across studies (18)	22	Present results of any assessment of risk of bias across studies (see item 15).	_	No specific additional information is required for systematic reviews of harms. See item 15 above.	p. 8; Supplement 4 - Methodological quality of included studies
9 10 11		23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression (see item		No specific additional information is required for systematic reviews	p. 8; Supplement 5 -
12 13 14 15	D		16)).		of harms.	Effect estimates for all adverse events with subgroups
16	Discussion	24	Communication and findings including		No monifie additional	- 14.16
17 18 19 20	Summary of evidence (18)	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	_	No specific additional information is required for systematic reviews of harms.	p. 14-16
21 22	Limitations	25	Discuss limitations at study and outcome		Recognise possible	p. 16-18
22	(18)		level (eg, risk of bias), and at review level		limitations of meta-	
25 24			(eg, incomplete retrieval of identified		analysis for rare adverse	
24 25			research, reporting bias).		events (ie, quality and	
26					quantity of data), issues	
27					noted previously related to collection and	
28					reporting.	
29	Conclusions	26	Provide a general interpretation of the		State conclusions in	p. 18
30	(19)	20	results in the context of other evidence,		coherence with the	p. 10
31	(1))		and implications for future research.		review findings. When	
32			and implications for fature research.		adverse events were not	
33					identified we caution	
34					against the conclusion	
35					that the intervention is	
36					"safe," when, in reality,	
37					its safety remains	
38					unknown.	
39	Funding					
40	Funding (19)	27	Describe sources of funding for the	_	No specific additional	p. 20
41			systematic review and other support (eg,		information is required	
42			supply of data); role of funders for the		for systematic reviews	
43			systematic review.		of harms.	
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Safety of Corticosteroids in Young Children with Acute Respiratory Conditions: A Systematic Review and Meta-Analysis

Medicina Molecular, University of Lisbon Wingert, Aireen; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence Vandermeer, Ben; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Featherstone, Robin; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Ali, Samina; University of Alberta, Pediatrics; Women & Children's Health Research Institute, Pediatrics, University of Alberta Plint, AMy; University of Calgary, Pediatrics, Emergency Medicine, Community Health Sciences Rowe, Brian; University of Alberta, Emergency Medicine; University of Alberta, School of Public Health Johnson, David; University of Alberta, Pediatrics, Faculty of Medicine, Pediatrics, Emergency Medicine, and Physiology and Pharmacology Allain, Dominic; University of Alberta, Pediatrics; Faculty of Medicine & Dentistry Klassen, Terry; Manitoba Institute of Child Health & Associate Dean of Academic, Faculty of Medicine, University of Maintoba Hartling, Lisa; University of Alberta, Pediatrics; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence Primary Subject Heading Paediatrics Secondary Subject Heading: Respiratory medicine	Journal:	BMJ Open
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ABSTRACT (300 words)

Objective Adverse events (AEs) associated with short-term corticosteroid use for respiratory conditions in young children.

Design Systematic review of primary studies.

Data sources Medline, Cochrane CENTRAL, Embase, and regulatory agencies were searched September 2014; search was updated in 2017.

Eligibility criteria Children <6 years with acute respiratory condition, given inhaled (high-dose) or systemic corticosteroids up to 14 days.

Data extraction and synthesis One reviewer extracted with another reviewer verifying data. Study selection and methodological quality (McHarm scale) involved duplicate independent reviews. We extracted AEs reported by study authors and used a categorization model by organ systems. Meta-analyses used Peto odds ratios (pOR) and DerSimonian Laird inverse variance method utilizing Mantel-Haenszel Q statistic, with 95% confidence intervals (CI). Subgroup analyses were conducted for respiratory condition and dose.

Results Eighty-five studies (11,505 children) were included; 68 were randomized trials. Methodological quality was poor overall due to lack of assessment and inadequate reporting of AEs. Meta-analysis (six studies; n=1,373) found fewer cases of vomiting comparing oral dexamethasone with prednisone (pOR 0.29, 95% CI 0.17 to 0.48; I²=0%). The mean difference in change-from-baseline height after one year between inhaled corticosteroid and placebo was 0.10 cm (two studies, n=268; 95% CI -0.47, 0.67). Results from five studies with heterogeneous interventions, comparators, and measurements, were not pooled; one study found a smaller mean change in height *z*-score with recurrent high-dose inhaled fluticasone over one year. No significant differences were found comparing systemic or inhaled corticosteroid with placebo, or between corticosteroids, for other AEs; CIs around estimates were often wide, due to small samples and few events.

Conclusions Evidence suggests that short-term high-dose inhaled or systemic corticosteroids use is not associated with an increase in AEs across organ systems. Uncertainties remain, particularly for recurrent use and growth outcomes, due to low study quality, poor reporting and imprecision.

Strengths and limitations of this study:

- Examined safety outcomes associated with short-term corticosteroid use across multiple common acute respiratory conditions in young children
- Broad range of adverse events captured across organ systems
- Inconsistent definitions, assessments and reporting of adverse events
- Extensive variation in corticosteroid formulations and dosages within and between studies
- Did not examine long-term corticosteroid use (more than 14 days)

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INTRODUCTION

Corticosteroids are the cornerstone of treatment for many common pediatric respiratory conditions including croup and asthma.¹⁻³ These conditions often result in presentation to urgent and emergency care settings, in otherwise healthy children. Previous studies examining corticosteroid use in chronic asthma have demonstrated the potential for short- and long-term adverse events, particularly growth inhibition, bone disease, and adrenal suppression.⁴⁻⁶ While corticosteroids have demonstrated effectiveness for the acute treatment of many respiratory indications, clinicians are faced with considerable uncertainty regarding short-term safety, particularly among the youngest children.¹

Previous systematic reviews have examined corticosteroids in preschool or school-aged asthma or wheezing;^{4, 7, 8} however, most focused on efficacy and were restricted to randomized controlled trials (RCTs). These reviews also focused on a specific underlying condition, disease severity, or particular corticosteroid, and mostly for longer-term administration (e.g., for recurrent, persistent or chronic asthma). Current guidance on systematic assessment of harms highlights the need to include data from observational studies when considering safety outcomes.⁹ As well, it has been suggested that it may be useful to have a wider view of the evidence across a number of similar indications.¹⁰ Recent knowledge synthesis approaches have studied specific safety outcomes across conditions to increase power, with the assumption that some safety outcomes are not confounded by condition.¹⁰ Such a comprehensive approach to knowledge synthesis in this area is critical to inform treatment decisions, reduce practice variation, and optimize management of young children who seek care due to acute respiratory illness.

The goal of this study was to synthesize evidence regarding the safety of short course corticosteroid use in young children (less than six years) with acute respiratory conditions.

METHODS

This review followed internationally recommended methods and standards for systematic reviews.¹¹⁻¹³ An *a priori* protocol was developed (available from authors).

Patient and Public Involvement

Patients and/or the public were not involved in the design or conduct of this systematic review.

Literature search

Original database searches were conducted September 2014 in Ovid Medline, the Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library, and Ovid Embase. Additional sources included regulatory agency databases: Drugs@FDA, Health Canada's Drug Products Database, and the European Medicines Agency's European Public Assessment Reports. Search strategies combined index terms and keywords for respiratory illnesses, children and drug classes identified in the Global Initiative for Asthma (GINA)¹⁴ guidelines. Study design filters were applied to limit results to RCTs and observational studies. Update searches were executed in Medline and CENTRAL in February 2016, and then again in July 2017. Detailed search strategies are in Supplement 1.

Eligibility criteria

We included primary studies involving population (P): children up to six years old; intervention (I): treated with single or recurrent systemic (any dose) or high-dose inhaled (as defined by the GINA guidelines¹⁴) corticosteroids for up to 14 days; comparator (C): any comparator; outcome (O): any adverse event; timing (T): any timing; and, setting (S): any inpatient or outpatient setting providing care to children with an acute respiratory condition. See Supplement 2 for detailed eligibility criteria.

Given the lack of standardized terminology for safety, we gathered information on all potentially drug-related harm outcomes¹⁵ from studies including, but not limited to: adverse drug reactions, adverse drug events, medication errors, side effects and potential adverse drug events. For consistency these outcomes are referred to in the manuscript as adverse events (AEs). Studies that did not report or mention AEs were excluded. Due to resource constraints and mean age of the studies, no attempt was made to contact study authors if no harms were reported in the text, or when there was potentially missing data; such efforts are unlikely to yield additional data.

Study selection

Two reviewers independently screened the titles and abstracts of all records using *a priori* selection criteria. Full texts of potentially eligible studies were reviewed by two reviewers independently using a standard form. Disagreements were resolved through consensus or consultation with a third reviewer.

Data extraction

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One reviewer extracted data using a structured form, with verification by a second reviewer. Data were extracted on study characteristics (design features), patient characteristics (age, sex, baseline characteristics), respiratory conditions, interventions (type, dose, duration, route of administration, timing, co-interventions, rescue medications), outcomes (types and timing), care setting, funding sources, and results.

AEs were extracted as reported by study authors and categorized using a published model based on organ systems (see Results).¹⁶ A panel of clinicians with specialties in pediatrics, emergency medicine, respiratory medicine and clinical pharmacology rated each AE in order of clinical severity independent of knowledge of the study results.

Assessment of methodological quality

Two reviewers independently assessed the methodological quality of studies using the McMaster Quality Assessment Scale for Harms (McHarm)¹⁷; disagreements were resolved through discussion.

Data synthesis

A comparative summary of AEs for studies with more than one treatment arm was presented to provide an overall picture of which interventions had a high risk of specific AEs. Risk differences were pooled using the DerSimonian Laird inverse variance random effects method utilizing the Mantel-Haenszel Q statistic. Binary data were also pooled using the Peto odds ratios (pORs) fixed effects method.¹⁸ Studies that reported at least one event in at least one treatment arm were included in the analysis of pORs and all comparative studies were used for analysis of

RD. One AE (growth) was reported as a continuous outcome and data were pooled using a DerSimonian Laird inverse variance random effects method as a mean difference (MD; in cm). The I² statistic was presented to quantify the magnitude of statistical heterogeneity between studies; while the I² has the potential to be misinterpreted, it is the standard in the field and we chose to present the statistic for informational purposes.¹⁹ Subgroup analyses from study-level data were conducted for respiratory condition and dose (single versus multi-dose) using Cochran's Q (α =0.05) to detect statistical heterogeneity. Studies contributing no numerical data for analysis (e.g., single arm studies, studies that reported no AEs overall) are summarized in Supplement 3. Assessment of small-study bias (for meta-analyses with at least eight studies) was planned using the funnel plot and Egger's test;²⁰ however, this was not conducted due to inadequate number of studies for each outcome. Analyses were conducted using Review Manager Version 5.3 (Cochrane Collaboration).²¹ Graphs were constructed using TIBCO ich Spotfire S+ Workbench, Version 3.4.²²

RESULTS

Database and grey literature searches yielded 9,134 records. Eighty-six papers (85 studies)²³⁻¹⁰⁸ involving 11,505 participants were included (Figure 1). Characteristics of the included studies are in Supplement 3. There was large variation in corticosteroid type, dose, duration and route of administration, both for systemic and inhaled corticosteroids. Methodological quality of studies was poor overall due to inadequate reporting of how AEs were defined and collected (Table 1; Supplement 4).

Adverse events

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Results below are presented according to the categories in Table 2. Figures 2, 3 and 4 display forest plots of AEs comparing systemic corticosteroid to placebo, inhaled corticosteroid to placebo, and systemic dexamethasone to another systemic corticosteroid, respectively. Results of meta-analyses and subgroup analyses are in Supplement 5, with effect estimates and 95% CIs. Forest plots from meta-analyses are in Supplement 6. There was large variation in the number of studies and number of patients with available data for meta-analysis across comparisons and outcomes. Further, for four safety outcomes there were no events in both study arms (double-zero) across studies. In most cases the subgroup analyses by dose and condition did not differ substantially from the overall results. Studies reporting no AEs overall are summarized in Supplement 7.

Infections & Respiratory System

The number of studies contributing to each meta-analysis ranged from one to seven (range 58 to 2,178 children). There were no statistically significant differences between: a) *systemic corticosteroid compared to placebo* for severe infections,^{30,74,96,99} systemic infections,^{30,40,43,83} infections of the lung/trachea,^{30,40,54,74,96,98,105} and the upper respiratory tract,^{30,43,54,65,67,74} and voice complaints⁴³ (estimated pORs between 0.15 and 1.26) and b) *inhaled corticosteroid compared to placebo* for severe infections,⁴⁵ systemic infections,^{43,45} lung/trachea,⁴⁵ infections of the upper respiratory tract ^{37,44,45,65-67} or voice complaints^{37,43,100,101} (estimated pORs between 0.54 and 1.51). No study comparing *dexamethasone with another corticosteroid* reported infections or respiratory AEs.

Gastro-Intestinal Tract (GI)

The number of studies contributing to each meta-analysis ranged from one to seven (range 97 to 3,176 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for GI bleeding,^{30, 32, 40, 65, 83, 87, 105} vomiting,^{30, 38, 40, 42, 70, 81, 83} abdominal pain,³⁰ or diarrhea;^{42, 77, 105} and b) *inhaled corticosteroid and placebo* for GI bleeding,⁶⁵ vomiting,^{37, 45, 69, 85, 101} or diarrhea.^{37, 45} Estimated pORs for both comparisons ranged from 0.89 to 1.10.

Meta-analysis of six studies (1,373 children)^{25, 27, 41, 49, 52, 80} found fewer cases of vomiting in patients who received *dexamethasone compared with another corticosteroid*, although the number of events was small (12/663 versus 51/710 cases; pOR 0.29, 95% CI 0.17, 0.48; I²=0%). These studies focused on asthma (n=3),^{27, 41, 80} croup (n=2),^{49, 52} or both (n=1);²⁵ all compared oral dexamethasone with oral prednisone. No statistically significant difference was found for abdominal pain between *dexamethasone and another corticosteroid*.^{25, 27, 52}

4.

CNS & Behaviour Effects

The number of studies for each meta-analysis ranged from one to five (range 70 to 1,159 children). The estimated pORs for the *systemic corticosteroid and placebo* were 1.44 for tremor/jitteriness,^{38, 55, 70, 77, 83} 1.95 for behaviour change,^{30, 42, 67, 77} and 0.11 for headache,³⁸ with no statistically significant differences. There were also no differences between *inhaled corticosteroid and placebo* for behaviour change;^{67, 85, 101} and *dexamethasone and another corticosteroid* for behaviour change,^{52, 57} headache,^{27, 52} or tremor/jitteriness,⁵² the latter with an estimated pOR of 6.63 from a small study (n=87) with only one reported event.

Dermatologic Conditions

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The number of studies per meta-analysis ranged from one to four (range 32 to 1,079 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for rash and hives,^{30, 42, 67} albeit with an estimated pOR of 7.59 (4/536 versus 0/543; 95% CI 1.07, 54.01); and b) *inhaled corticosteroid and placebo* for rash,^{37, 45, 85} hives⁶⁷ and burning sensation⁶⁸ (estimated pORs 0.88 and 0.14, respectively). No events of phlebitis were reported comparing *dexamethasone to another corticosteroid*.⁵⁷

Endocrine/metabolic & Musculoskeletal Systems

There were no statistically significant differences for electrolyte abnormalities between *systemic corticosteroid and placebo* (estimated pOR 3.08)^{30, 47, 83, 102} and *dexamethasone to another corticosteroid* (estimated pOR 0.18).¹⁰²

Pooled data for linear growth between *inhaled corticosteroid and placebo* included two studies (n=263) using recurrent doses for acute wheeze with follow-up at one year.^{28, 45} The estimated change-from-baseline height was small (MD 0.10 cm; 95% CI -0.47 to 0.67; I²=9%). Five studies reported measurements of growth (height and weight) ranging from one to three years of follow-up, which could not be pooled due to heterogeneous interventions, comparators, or outcome measurements.^{29, 31, 45, 58, 71} Three studies included data on inhaled corticosteroid versus placebo. One RCT on asthma⁵⁸ (n=20) comparing budesonide and placebo found no signs of growth retardation by height measurements at 12 months or after up to six treatments. An RCT of episodic wheeze²⁹ (n=294) found height at three years of age was unaffected in children receiving budesonide or placebo. One RCT of inhaled fluticasone propionate at very high doses (1500 mcg daily during upper respiratory infections) versus placebo in recurrent wheeze⁴⁵

reported additional outcome data on height that was not pooled in the meta-analysis mentioned above. There was a smaller mean change in height *z* score in the corticosteroid group over one year (MD -0.24; 95% CI -0.40 to -0.08; adjusted results).⁴⁵ Furthermore, mean weight was significantly lower at one-year follow-up in the fluticasone group (n=62) versus placebo (n=67); two children given fluticasone and one given placebo met criteria for 'failure to thrive'.⁴⁵ Finally, two small trials did not report group differences for other comparisons: total and mean height growth (at eight to 19 months) for intravenous (IV) dexamethasone versus inhaled budesonide in asthma (n=18);⁷¹ weight and height gains at two years for theophylline and metaproterenol with or without systemic prednisone on prevention of wheeze during upper respiratory infections in asthma (n=32).³¹

Five studies reported on adrenal function/suppression, with few children contributing data for this outcome.^{45, 57, 58, 71, 89} The RCT of high-dose inhaled fluticasone propionate versus placebo (99 children with data)⁴⁵ found no significant differences between groups in basal cortisol (baseline and 12 months). Another RCT in asthma reported no differences in serum cortisol and urinary cortisol/creatinine after 10 days of inhaled budesonide or placebo (16 children with data). A subgroup who received oral betamethasone (n=9) showed significant changes from baseline after three days, but no differences at 12 to 14 days.⁵⁸ Two studies included comparisons between different corticosteroids. One RCT⁸⁹ in acute asthma compared IV prednisolone (n=20) with nebulized budesonide (n=30) and found significant levels of suppressed serum cortisol in the prednisolone group, albeit not considered pathologic by the study authors. Although another RCT⁵⁷ comparing intramuscular (IM) dexamethasone with oral prednisone for asthma (n=32) found lower median urinary cortisol/creatinine in the former group at day 14, there was no

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statistically significant difference. An RCT⁷¹ comparing IV dexamethasone (n=9) with inhaled budesonide (n=9) found no significant differences between groups from baseline for blood pressure and blood glucose measurements.

Five studies reported on bone health biomarkers, three of which compared inhaled corticosteroids and placebo: no pooled analyses were performed.^{29, 45, 58, 61, 92} One RCT²⁹ compared inhaled budesonide (n=294) with placebo in episodic wheeze and found no effect on bone mineral density over three years. The RCT comparing high-dose inhaled fluticasone propionate with placebo (n=59 children with data) in viral wheeze⁴⁵ reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT⁵⁸ comparing inhaled budesonide with placebo (n=20) in asthma found transient decreased levels of bone and collagen markers post-treatment and in a subset of children who received oral betamethasone, with no difference between groups. A study of patients with acute respiratory illness⁹² compared hydrocortisone (n=28), methylprednisone (n=21) and controls (n=51) and found decreased levels of osteocalcin and alkaline phosphatase in younger children two days post-treatment; these effects were reversed 12 days after treatment. A non-randomized controlled trial (nRCT) of 36 asthma patients⁶¹ compared IV methylprednisolone of three different durations and found that all had decreasing levels of serum osteocalcin that correlated with increasing duration of treatment.

Cardiovascular System

No significant differences were found between *systemic corticosteroid and placebo* in three bronchiolitis studies reporting hypertension (estimated pOR 1).^{32, 40, 83} Single studies with up to

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110 children did not report events for arrhythmia⁴³ and congestive heart failure⁴⁷ (*systemic or inhaled corticosteroid versus placebo*); and arrhythmia²⁷ or hypertension⁵⁷ (*dexamethasone with another corticosteroid*).

General AEs/ Other Symptoms

Meta-analyses included a total of two studies (range 197 to 869 children). There were no statistically significant differences between: a) *systemic corticosteroid and placebo* for pallor;^{70, 83} and b) *dexamethasone with another corticosteroid* for dizziness⁵² or excessive urination.²⁷ No study comparing *inhaled corticosteroid with placebo* reported general AEs.

Immune System & Oncology

One study (95 participants)³⁹ compared *systemic corticosteroid and placebo* and found no occurrences of immunosuppression. No other study reported immune system-related AEs.

DISCUSSION

This systematic review of studies in which short-course corticosteroids were administered to children under six years of age for acute respiratory conditions, included 85 studies involving more than 11,000 patients. These studies used a variety of delivery routes, doses, formulations and duration of corticosteroids. Overall, the evidence suggests that short-term corticosteroid use is not associated with a significant increase in AEs across organ systems. However, given the low quality of included studies, the heterogeneous and poor reporting of AEs, and the lack of precision of results, considerable uncertainties remain regarding the safety of high-dose inhaled or systemic corticosteroids for these indications in this age range.

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A common concern when using corticosteroids in young children is effect on growth. Results from a single, small trial (n=129) of recurrent high-dose inhaled fluticasone propionate in wheezing preschoolers were heterogeneous across outcome measures, but suggested a small significant risk of growth suppression.⁴⁵ Observational data have also suggested that multiple corticosteroid bursts can increase the risk of growth suppression, fractures, bone mineral accretion and osteopenia in children with underlying respiratory disease.^{5, 6, 109} Conversely, a pooled analysis using change-from-baseline linear growth did not find significant differences, albeit the other included study used a substantially lower equivalent dose of inhaled corticosteroid.¹¹⁰ Further, results from individual studies reporting transient differences in bone and adrenal biomarkers are of unclear clinical relevance, particularly for previously healthy children and single use. This calls for caution and monitoring of linear growth, particularly when use of high-dose inhaled or systemic corticosteroid is recurrent.

We found no other statistically significant differences between systemic or inhaled corticosteroid and placebo, or between dexamethasone and other systemic corticosteroid, including subgroup analyses by respiratory condition or dose, for AEs across organ systems. Due to small sample sizes and low number of events, these results should be interpreted with caution. While we found increased pORs when comparing systemic corticosteroids for behavioural outcomes such as tremor/jitteriness and behaviour change, there were wide confidence intervals around estimates. No study examined neurodevelopmental outcomes after corticosteroid administration; ideally, studies should assess children for potentially related long-term AEs using validated instruments in this domain. Results from case series and case reports added anecdotal evidence of rare cases

of hypersensitivity, infection or behavioral AEs, which have been described.^{111, 112} While the estimated increased pOR for rash and hives was close to statistical significance, no other differences were found in systemic or severe infections as well as immunosuppression.

This review did not ascertain a clear safety advantage between systemic or inhaled corticosteroids compared with placebo. When comparing between different systemic corticosteroids, evidence favored oral dexamethasone over oral prednisone for vomiting (pOR 0.029; 95% CI 0.17 to 0.48; I²=0%). Differences in palatability and tolerability between corticosteroids are well known to parents, healthcare providers and researchers, and can influence adherence to medication in children.¹¹³ Further, different specific formulations of corticosteroid (e.g., prednisolone tablets versus prednisolone syrup) have been shown to influence taste and vomiting.²⁵ However, cost and access to better tolerated formulations may be problematic. Subgroup analyses also found no significant differences between groups by respiratory condition or dose (single versus multiple) for these outcomes. Due to extensive variation in dosing within and across studies, we were unable to analyze data or draw further conclusions with respect to dosage or differences between specific molecules. It should be noted that among the eight RCTs^{35, 43, 46, 51, 65, 67, 71, 89} directly comparing systemic and inhaled routes of corticosteroid administration, none contributed meaningful data for meta-analysis. The decision to initiate corticosteroid and the selection of drug, dose and mode of administration must consider these uncertainties on harms, as well as existing evidence on comparative potency and clinical effectiveness. The risk-benefit rationale is less established for repeated acute use in younger children, such as in recurrent wheezing.¹¹⁴

Strengths and limitations

We conducted a comprehensive systematic review of the literature following rigorous methods, including grey literature, to minimize potential for publication and selection bias. We examined safety outcomes across multiple acute respiratory conditions using 'baskets' of outcomes in each organ system to increase our ability to detect rare events and the precision of our estimates.¹⁶ This approach is reflective of clinical practice where corticosteroids are used across many respiratory diseases, even if the evidence base is not entirely robust for children. A recent systematic review also assessed the toxicity of short-course oral corticosteroids in children across clinical conditions.¹¹⁵ However, there was scarce overlap in respiratory conditions across included studies, and authors mostly provided estimates of the incidence of AEs within treatment groups rather than comparative treatment effects. Studies in adults have also adopted similar approaches to estimate incidence rates of AEs. For example, findings from a recent retrospective cohort in adults showed a significant increase in rates of sepsis, venous thromboembolism and fracture.¹¹⁶

This review was limited by the quality of the primary literature, particularly regarding the definition, assessment and reporting of AEs. This underscores the challenges researchers encounter when attempting to synthesize safety data due to sparse and poor reporting,¹¹⁷ and highlights the urgent need to enhance detection and reporting of AEs. For example, it is worthwhile noting that 26 studies reported 'no AEs' or 'no significant AE' which could not be included in pooled estimates; this may be a reflection of these studies being under-powered to detect statistically significant findings (especially for rare AEs) and/or AEs that may or may not be considered of special interest and/or clinically important. Such blanket statements are

problematic for interpretation, highlighting the need for study authors to clearly report AEs of interest pre- and post-study conduct. Common nomenclature (e.g., www.meddra.org) and standardized approaches to collection of AE data should be implemented to help draw comparisons across studies. Further, safety reporting was not a primary focus of the studies, AEs were rarely defined a priori, and methods for ascertaining AEs were usually absent. While the McHarm scale is recommended to be used in conjunction with other quality assessment tools to evaluate the broader elements of study quality, we used it exclusively to assess methodological quality since the primary focus of this review was on AEs. The AEs reported typically reflect what is detected by a healthcare provider; it is difficult to discern what is reported by patients as well as what patients consider important. The duration of surveillance of most studies was insufficient to detect many of the long-term AEs potentially associated with corticosteroid use. Although the present study suggests that single doses of systemic or inhaled corticosteroids may result in few AEs, recurrent courses may lead to long-term risks, as cumulative dosing has been shown to be a determinant of safety.¹⁰⁹ Finally, there was variation within and across studies with respect to maintenance corticosteroids, and concomitant and rescue medications. Due to the variation in corticosteroids and extensive range of AEs reported (including when a single study contributes to an outcome or in cases of zero events, where meta-analysis was not feasible or meaningful) amongst varied study designs of overall poor quality, we did not attempt to rate the quality of the body of the evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE¹¹⁸) approach.

CONCLUSION

This is the most comprehensive systematic review to date examining the safety of corticosteroids for managing acute respiratory conditions among young children, an age group of great clinical concern. While the existing evidence suggests that short-term high-dose inhaled or systemic corticosteroids is not associated with an increase in AEs across organ systems, uncertainties remain due to low quality of studies, poor reporting and lack of precision of results. Importantly, these results can help guide future research in the collection and reporting of AEs, particularly concerning measures of growth and behavioral outcomes; this in turn is needed to help inform shared decision-making between clinicians and parents/caregivers of young children.

- Table 1. Summary of methodological quality assessments
- Table 2. Number of studies and participants reporting adverse events

Figures

- Figure 1. PRISMA study flow selection
- Figure 2. Forest plot of adverse events systemic versus placebo
- Figure 3. Forest plot of adverse events inhaled versus placebo
- Figure 4. Forest plot of adverse events dexamethasone versus other

Supplementary data

Supplement 1	- Search strategy
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- Supplement 2 Eligibility criteria for study inclusion
- Supplement 3 Characteristics of included studies
 - a. Summary characteristics of included studies
 - b. Summary characteristics of included studies comparisons
 - c. Characteristics of included studies
- Supplement 4 Methodological quality assessments of included studies
- Supplement 5 Effect estimates for all adverse events with subgroups
 - a. Infection & respiratory system
 - b. Gastro-intestinal tract
 - c. CNS & behaviour effects
 - d. Dermatologic conditions
 - e. Endocrine/ metabolic & musculoskeletal system
 - f. Cardiovascular system
 - g. General adverse events/ other symptoms
 - h. Immune system & oncology
 - Supplement 6 Forest plots of adverse events
 - Systemic vs. placebo
 - a. Infection & respiratory system
 - b. Gastro-intestinal tract
 - c. CNS & behaviour effects
 - d. Dermatologic conditions
 - e. Endocrine/ metabolic & musculoskeletal system
 - f. Cardiovascular system
 - g. General adverse events/ other symptoms
 - h. Immune system & oncology

Inhaled vs. placebo

- a. Infection & respiratory system
- b. Gastro-intestinal tract

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3	c. CNS & behaviour effects
4	d. Dermatologic conditions
5	-
6 7	e. Endocrine/ metabolic & musculoskeletal system
8	f. Cardiovascular system
9	Dexamethasone vs. Other steroid
10	a. Gastro-intestinal tract
11	b. CNS & behaviour effects
12	c. Dermatologic conditions
13	d. Endocrine/ metabolic & musculoskeletal system
14 15	-
16	e. Cardiovascular system
17	f. General adverse events/ other symptoms
18	Supplement 7 - Studies reporting no adverse events
19	
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Table 1. Summary of methodological quality assessments

Mc	Harm* criteria	Rating	No. of studies (% ²)
1)	Were the harms PRE-DEFINED using standardized or precise definitions?	Yes	6 (7)
		No	79 (93)
		Unsure	0
2) Were SEI	Were SERIOUS events precisely defined?	Yes	2 (2)
		No	83 (98)
		Unsure	0
3)	Were SEVERE events precisely defined?	Yes	0
		No	85 (100)
		Unsure	0
4)	Were the number of DEATHS in each study group specified OR were the	Yes	10 (12)
	reason(s) for not specifying them given?	No	75 (88)
		Unsure	0
5)	Was the mode of harms collection specified as ACTIVE?	Yes	46 (54)
		No	37 (44)
		Unsure	2 (2)
6)	Was the mode of harms collection specified as PASSIVE?	Yes	11 (13)
		No	73 (86)
		Unsure	1(1)
7)	7) Did the study specify WHO collected the harms?	Yes	22 (26)
		No	63 (74)
		Unsure	0
8)	Did the study specify the TRAINING or BACKGROUND of who ascertained the	Yes	20 (24)
	harms?	No	65 (76)
		Unsure	0
9)	Did the study specify the TIMING and FREQUENCY of collection of the harms?	Yes	39 (46)
		No	45 (53)
		Unsure	1(1)
10)	Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	Yes	6 (7)
) Did the author(s) use STANDARD scale(s) or checklist(s) for harms collection?	No	76 (89)
		Unsure	3 (4)
11)	Did the authors specify if the harms reported encompass ALL the events collected	Yes	80 (94)
	or a selected SAMPLE?	No	2 (2)
		Unsure	3 (4)
12)	Was the NUMBER of participants that withdrew or were lost to follow-up	Yes	24 (28)
	specified for each study group?	No	61 (72)
		Unsure	0
13)	Was the TOTAL NUMBER of participants affected by harms specified for each	Yes	16 (19)
	study arm?	No	69 (81)
		Unsure	0
14)	Did the author(s) specify the NUMBER for each TYPE of harmful event for each	Yes	43 (51)
	study group?	No	39 (46)
		Unsure	3 (4)
15)	Did the author(s) specify the type of analyses undertaken for harms data?	Yes	10 (12)
		No	75 (88)
		Unsure	0

*methodological quality of publications/studies as assessed by the McHarm scale¹

² sum of percentages may not total 100 due to rounding

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Organ system	AE - category	AE – specific	No. of studies	No. of participants
Infection & Respiratory	Severe infections		5	1235
	1)	Sepsis	1	32
	2)	Superinfection	2	354
	3)	UTI	1	720
	4)	Streptococcal infection	1	129
	Systemic infections	•	5	1635
	1)	Fever	3	963
	2)	Common viral/bacterial/fungal	2	792
	2)	infection Variable	2	1440
	3)	Varicella	3	1449
	Lung/trachea		10	2053
	1)	Empyema Drawwania	1	600
	2)	Pneumonia Despiratore distance	8	2051
		Respiratory distress	2	2
	Upper respiratory tract		14	2457
	1)	Bacterial tracheitis	5	1023
	2)	Sinusitis	2	849
	3)	Croup	2	131
	4)	Viral parotitis	1	27
	5)	Pharyngitis	1	129
	6)	Persistent cough	1	27
	7)	Oral thrush	3	837
	8)	Otitis media	4	1173
	9)	Ear, nose, throat infection	3	862
	10)	Nasal discharge	1	720
	11)	Eye discharge	1	720
~-	Voice complaints		5	794
GI	GI bleeding		8	2669
	1)	Bleeding	5	1577
	2)	Gross hematochezia	1	118
	3)	Occult blood in stools	2	292
	4)	Dark stools	1	800
	Vomiting		27	6067
	1)	Vomiting	24	5983
	2)	Nausea	6	586
	3)	Palatability	3	170
	Abdominal pain		5	1332
	Diarrhea	D' 1	8	1346
	1)	Diarrhea	7	1217
	2)	Gastroenteritis	1	129
CNS & Behaviour	Tremor/jitteriness	Tromor	8	1274
	1)	Tremor	7	1226
	2)	Jittery	1	48
	Behaviour change	Violant babania	14	2078
	1)	Violent behaviour	1	198
	2)	Mood change	7	1430
	3)	Hyperactivity	2	268

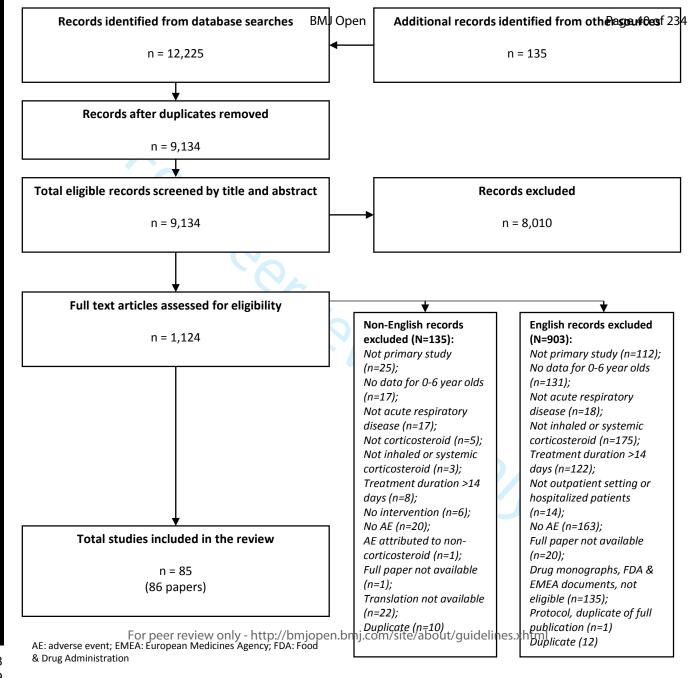
Table 2. Number of studies and participants reporting adverse events*

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	4)	Restlessness	3	297
	5)	New sleep problems	3	408
	6)	Emotional distress due to	1	82
		nebulizer mask		
	7)	Psychosis	1	1
	Headache		3	291
Dermatological	Burn		1	198
	Integument		10	1954
	1)	Hives	2	199
	2)	Rash	8	1954
	3)	Eczema	1	129
	4)	Eye irritation	2	211
	5)	Tongue irritation	1	82
	6)	Positive wheal	1	1
	7)	Bleeding from ear	1	720
	Phlebitis	0	1	32
Endocrine/Metabolic	Fluid and electrolyte		7	1849
& Musculoskeletal	abnormalities			
	1)	Hyperkalemia	1	800
	2)	Hyperglycemia	3	154
	3)	Glycosuria	1	125
	4)	Sodium retention	1	50
	5)	Dehydration	1	720
	Growth		6	731
	Adrenal suppression		5	249
	Bone health		5	579
Cardiovascular	Arrhythmia		3	312
	1)	Tachycardia	2	178
	2)	Palpitations	1	134
	Hypertension		5	1491
	Congestive heart failure		1	50
General	General complaints		5	1146
	1)	Dizziness	1	87
	2)	Pallor	2	869
	3)	Excessive urination	1	134
	4)	Normal tooth eruption	1	56
	Hematology, gum bleeding		1	1
Immune System &	Immunosuppression		4	147
Oncology	1)	Immunosuppression	3	146
	2)	Tumor cell proliferation	1	1

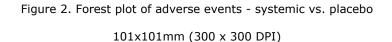
AE: adverse event; CNS: central nervous system; GI: gastro-intestinal; no.: number; URT: upper respiratory tract * Each adverse event was clustered into its related organ system; a panel of clinicians ranked each AE category and its corresponding adverse events in order of clinical significance/severity. The organ systems are presented in order of frequency of reporting, beginning with the most frequently reported (i.e., Infection & respiratory).

Screening & Eligibility



lnclusion

	No. of	No./	Fotal	Peto	Odds ratio		Peto Odds ratio	
Outcome	Studies	Systemic	Placebo		95% CI		95% CI	12
Inf & Resp					1			
Severe infections	4	0/552	2/554		+-		0.15 (0.01, 2.45)	0
Systemic infections	4	5/1095	4/1083	_			1.26 (0.34, 4.68)	NA
Lung/trachea	7	18/955	28/928	-	- +		0.61 (0.34, 1.12)	0
URT	6	9/671	7/656	-			1.21 (0.44, 3.33)	0
Voice complaints	1	0/31	0/27				NA	NA
GI								
GI bleeding	7	31/1287	31/1262		-#-		1.00 (0.60, 1.67)	0
Vomiting	7	38/1603	34/1573		-		1.10 (0.69, 1.76)	17
Abdominal pain	1	1/359	1/361				1.01 (0.06, 16.11)	NA
Diarrhea	3	10/254	9/230	-	-		1.09 (0.43, 2.73)	0
CNS & Behav								
Tremon/jitteriness	5	22/559	14/508		-+ B		1.44 (0.71, 2.92)	0
Behaviour change	4	7/588	3/571				1.95 (0.55, 6.92)	0
Headache	1	0/37	1/33		<u> </u>		0.11 (0.00, 5.68)	NA
Cardio								
Anythmia	1	0/31	0/27				NA	NA
Hypertension	3	1/727	1/714		-		1.00 (0.06, 15.99)	50
Congestive heart failure	1	0/25	0/25				NA	NA
EndoMetabMusc								
Fluid & electrolyte abnorn	ualitie#	5/832	1/818		—		3.08 (0.60, 15.94)	0
Growth	none							
Adrenal suppression	none							
Skin								
Bum	none							
Integament	3	4/536	0/543			_	7.59 (1.07, 54.01)	0
Phlebitis	none							
General								
General complaints	2	38/446	38/423		_ + _		1.00 (0.62, 1.60)	0
Hematology, gun bleeding	none							
Immune System								
Immunosupression	1	0/47	0/48				NA	NA
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				Favours systemic	Favours placebo			



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14	Outcome	No. of Studies	No./	Total Placebo	Peto Odds ratio 95% Cl	Peto Odds ratio 95% Cl	1 ²
15	Inf & Resp Severe infections	1				0.54 (0.11, 2.77)	NA
16	Systemic infections	2	2/62 18/91	4/67 20/94	_	0.96 (0.45, 2.05)	NA
17	Lung/trachea URT	1 6	13/62 24/495	10/67 24/499		1.51 (0.61, 3.70) 1.03 (0.57, 1.85)	NA 21
	Voice complaints Gl	4	38/343	43/337	-=-	0.85 (0.53, 1.36)	73
18	GI Bleeding Vomiting	1 5	0/48 28/421	0/49 28/420	-+-	NA 1.00 (0.58, 1.72)	NA 0
19	Abdominal pain Diamhea	none 2	41/326	46/328		0.89 (0.57, 1.40)	44
20	Skin Burn	1	0/27	1/27		0.14 (0.00, 6.82)	NA
21	Integument Abdominal pain	4 none	24/432	27/436		0.88 (0.50, 1.56)	37
22	EndoMetabMusc Fluid & electrolyte abnorm	ns none					
23	Adrenal suppression CNS & Behav	1	5/6	4/10		5.21 (0.72, 37.57)	NA
24	Tremor/jitteriness Behaviour change	none 3	6/134	7/135		0.81 (0.26, 2.54)	0
25	Headache Cardio	none	0154		_	0.01 (0.20, 2.24)	0
26	Anythmia	1	0/29	0/27		NA	NA
27	Hypertension Congestive heart failure	none					
28	General General complaints	none					
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			No. of No./Total Peto Odds ratio Peto Odds ratio Outcome Studies Dezamethasone Other 95% CI 95% CI	Outcom Status Description 95% Cl 95% Cl 95% Cl Gd	virtuance Butter 95% CI 95% CI 95% CI 95% CI I None 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.29 (0.17, 0.49) 0.50 (0.13, 3.120) 0.50 (0.12, 1.70) 0.50 (0.12, 1.70) 0.50 (0.12, 1.70) 0.50 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70) 0.51 (0.12, 1.70)	states setue beeder setue setue setue setue setue blacking muting 6 12663 51/10 $$ 0.29 (0.17, 0.49) 0.29 (0.05, 0.57, 1.81) setue 3 2018 48.624 $$ 0.29 (0.07, 0.41, 1.65) setue 3 1.46 0.40 $$ 0.50 (0.07, 0.41, 1.65) setue 2 3.070 3.05 $$ 0.50 (0.07, 0.41, 1.65) setue 3 7.022 4.05 $$ 0.50 (0.37, 0.41, 1.65) setue 3 7.02 4.05 $$ 0.50 (0.57, 0.41, 1.65) setue 3 7.02 3.05 $$ 0.50 (0.41, 4.61) setue 3 0.15 0.56 0.54 NA setue 3 0.55 0.54 NA setue 3 0.55 0.54 NA setue 3 0.05 0.54 NA setue 3 0.05 0.07 N				2	Jopen		
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Figure 4. Forest plot of adverse events - dexamethasone vs. other

101x101mm (300 x 300 DPI)

2	
3	Supplement 1. Search strategy
4 5	
6	Database for original search: Ovid Medline(R) 1946 to September Week 1 2014
7	Databases for update searches: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed
8	Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
9	Date original search conducted: 14 September 2014
10	Date first update search conducted: 24 February 2016
11 12	Date second update search conducted: 31 July 2017
13	Strategy:
14	
15	1. Adrenal Cortex Hormones/
16	2. Anti-Inflammatory Agents/
17	3. Beclomethasone/
18 19	4. Budesonide/
20	5. exp Glucocorticoids/
21	6. exp Hydroxycorticosteroids/
22	
23	7. Pregnenediones/
24	8. Triamcinolone Acetonide/
25 26	9. adrenal cortex hormone*.tw,nm.
20	10. advair*.tw,nm.
28	11. alvesco*.tw,nm.
29	12. azmacort*.tw,nm.
30	13. becl?met*.tw,nm.
31 32	14. beclazone*.tw,nm.
33	15. beclo?ort*.tw,nm.
34	16. beclovent*.tw,nm.
35	17. beconase*.tw,nm.
36	18. becotide*.tw,nm.
37	19. betamet?asone*.tw,nm.
38 39	20. betnesol*.tw,nm.
40	21. budesonide*.tw,nm.
41	22. ciclesonide*.tw,nm.
42	23. clobetasol*.tw,nm.
43	24. cortiso*.tw,nm.
44 45	25. cortodoxone*.tw,nm.
45 46	26. corticosteroid*.tw,nm.
47	27. decadron*.tw,nm.
48	28. depo medrone*.tw,nm.
49	29. desoximet?asone*.tw,nm.
50	30. dexamethasone*.tw,nm.
51 52	31. deflazacort*.tw,nm.
52 53	32. diflucortolone*.tw,nm.
54	33. flixotide*.tw,nm.
55	34. flumethasone*.tw,nm.
56	
57 59	
58 59	Supplement 1 - Page 1 of 13
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

1 2

2	
3	35. flunisolide*.tw,nm.
4	36. fluocino*.tw,nm.
5 6	37. fluocortolone*.tw,nm.
7	38. fluorometholone*.tw,nm.
8	39. flurandrenolone*.tw,nm.
9	40. fluticasone*.tw,nm.
10	41. glucocortico*.tw,nm.
11	42. hydrocortisone*.tw,nm.
12 13	43. hydroxycorticostero*.tw,nm.
13	44. hydrocortone*.tw,nm.
15	•
16	45. hydroxypregnenolone*.tw,nm.
17	46. kenacort*.tw,nm.
18	47. kenalog*.tw,nm.
19 20	48. medrone*.tw,nm.
20 21	49. methylprednisolone*.tw,nm.
22	50. mometasone furoate*.tw,nm.
23	51. nasonex*.tw,nm.
24	52. paramethasone*.tw,nm.
25	53. predniso*.tw,nm.
26 27	54. pregnenolone*.tw,nm.
27 28	55. pulmicort*.tw,nm.
29	56. qvar*.tw,nm.
30	57. rhinocort*.tw,nm.
31	58. seretide*.tw,nm.
32	59. solu cortef*.tw,nm.
33 34	60. symbicort*.tw,nm.
34 35	61. tetrahydrocortisol*.tw,nm.
36	62. triamcinolone*.tw,nm.
37	63. tricort*.tw,nm.
38	64. vanceril*.tw,nm.
39	65. or/1-64
40 41	66. Acute Disease/ and (asthma* or pneumonia* or wheez*).mp.
42	67. exp Asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
43	68. Bronchial Hyperreactivity/
44	69. Bronchial Spasm/
45	70. exp Bronchiolitis/
46 47	71. Croup/
47 48	72. exp Dyspnea/
49	73. Emergencies/ and (asthma* or pneumonia* or wheez*).mp.
50	74. Emergency Medical Services/ and (asthma* or pneumonia* or wheez*).mp.
51	75. Emergency Services, Hospital/ and (asthma* or pneumonia* or wheez*).mp.
52	76. exp Pharyngitis/
53 54	77. exp Pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
55	78. exp Respiratory Syncytial Viruses/
56	70. CAP ACSPITATORY Syncytian viruses/
57	
58	Supplement 1 - Page 2 of 13
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml
00	

84. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw.

93. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.

83. Respiratory Sounds/ and (acute* or emergenc* or exacerbation* or severe*).mp.

85. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw.

104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).mp. 105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).mp.

79. exp Respiratory Syncytial Virus Infections/

86. (bronch* adj3 (constrict* or spas*)).tw.

92. (lung* adj2 (disease* or infect*)).tw.

94. (nasosinusit* or rhinosinusit*).tw.

108. randomized controlled trial.pt.109. controlled clinical trial.pt.

117. exp Case control studies/

119. Cross-sectional studies/120. exp Cohort Studies/121. Epidemiologic studies/

96. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.

107. and/65,100,106 [steroids/respiratory illness/children]

80. Rhinitis/ 81. exp Sinusitis/

82. Status Asthmaticus/

87. bronchiolitis*.tw.88. bronchoconstrict*.tw.89. bronchospasm*.tw.

95. pharyngitis*.tw.

97. rhinit*.tw.
98. sinusit*.tw.
99. tonsillitis*.tw.
100. or/66-99
101. exp child/
102. exp infant/
103. exp Pediatrics/

106. or/101-105

110. randomi?ed.ab.
 111. placebo.ab.
 112. drug therapy.fs.
 113. randomly.ab.
 114. trial.ab.
 115. groups.ab.
 116. or/108-115

118. case reports.pt.

122. case control.tw.

90. croup*.tw.
 91. dyspne*.tw.

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3 4	123. (case adj (report* or study or studies or series)).tw.
5	124. cohort analy*.tw.
6	125. (cohort adj (study or studies)).tw.
7	126. cross sectional.tw.
8	127. (follow up adj (study or studies)).tw.
9	128. longitudinal.tw.
10 11	129. (observational adj (study or studies)).tw.
12	130. retrospective.tw.
13	131. or/117-130
14	132. 116 or 131
15	133. exp animals/ not humans.sh.
16 17	134. 132 not 133
17	135. 107 and 134
19	136. (comment or editorial or letter or meta analysis or review).pt.
20	137. 135 not 136
21	138. remove duplicates from 137
22	
23 24	Database for original search: Ovid Medline(R) In-Process & Other Non-Indexed Citations, September 12,
24 25	2014
26	Date original search conducted: 14 September 2014
27	Strategy:
28	Stategy.
29	1. adrenal cortex hormone*.tw,nm.
30 31	 adrenal cortex hormone*.tw,nm. advair*.tw,nm. alvesco*.tw,nm. azmacort*.tw,nm. becl?met*.tw,nm. beclazone*.tw,nm.
32	3. alvesco*.tw,nm.
33	4. azmacort*.tw,nm.
34	4. dzindcort*.tw.nm.
35	5. becl?met*.tw,nm.
36 37	6. beclazone*.tw,nm.
38	7. beclo?ort*.tw,nm.
39	8. beclovent*.tw,nm.
40	9. beconase*.tw,nm. 10. becotide*.tw,nm.
41	10. becotide*.tw,nm.
42	
43 44	12. betnesol*.tw,nm.
44 45	13. budesonide*.tw,nm.
46	14. ciclesonide*.tw,nm.
47	15. clobetasol*.tw,nm.
48	16. cortiso*.tw,nm.
49	17. cortodoxone*.tw,nm.
50 51	18. corticosteroid*.tw,nm.
52	19. decadron*.tw,nm.
53	20. depo medrone*.tw,nm.
54	21. desoximet?asone*.tw,nm.
55	22. dexamethasone*.tw,nm.
56	
57 58	Supplement 1 - Page 4 of 13
58 59	Supplement 1 - Page 4 01 13
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

23. deflazacort*.tw.nm. 24. diflucortolone*.tw,nm. 25. flixotide*.tw,nm. 26. flumethasone*.tw,nm. 27. flunisolide*.tw,nm. 28. fluocino*.tw,nm. 29. fluocortolone*.tw,nm. 30. fluorometholone*.tw,nm. 31. flurandrenolone*.tw,nm. 32. fluticasone*.tw,nm. 33. glucocortico*.tw,nm. 34. hydrocortisone*.tw,nm. n. ۲ (asthma* or allow* or 35. hydroxycorticostero*.tw,nm. 36. hydrocortone*.tw,nm. 37. hydroxypregnenolone*.tw,nm. 38. kenacort*.tw,nm. 39. kenalog*.tw,nm. 40. medrone*.tw,nm. 41. methylprednisolone*.tw,nm. 42. mometasone furoate*.tw,nm. 43. nasonex*.tw,nm. 44. paramethasone*.tw,nm. 45. predniso*.tw,nm. 46. pregnenolone*.tw,nm. 47. pulmicort*.tw,nm. 48. qvar*.tw,nm. 49. rhinocort*.tw,nm. 50. seretide*.tw,nm. 51. solu cortef*.tw,nm. 52. symbicort*.tw,nm. 53. tetrahydrocortisol*.tw,nm. 54. triamcinolone*.tw,nm. 55. tricort*.tw,nm. 56. vanceril*.tw,nm. 57. or/1-56 58. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw. 59. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw. 60. (bronch* adj3 (constrict* or spas*)).tw. 61. bronchiolitis*.tw. 62. bronchoconstrict*.tw. 63. bronchospasm*.tw. 64. croup*.tw. 65. dyspne*.tw. 66. (lung* adj2 (disease* or infect*)).tw.

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3 4	67. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
5	68. (nasosinusit* or rhinosinusit*).tw.
6	69. pharyngitis*.tw.
7	70. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
8	71. rhinit*.tw.
9	72. sinusit*.tw.
10 11	73. tonsillitis*.tw.
11	74. or/58-73
13	75. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).tw.
14	76. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).tw.
15	77. or/75,76
16	78. and/57,74,77
17	79. randomi?ed.tw.
18 19	80. placebo.tw.
20	81. randomly.tw.
21	
22	82. trial.tw.
23	83. groups.tw.
24	84. or/79-83
25 26	85. case control.tw.
26 27	86. (case adj (report* or study or studies or series)).tw.
28	87. cohort analy*.tw.
29	88. (cohort adj (study or studies)).tw.
30	89. cross sectional.tw.
31	90. (follow up adj (study or studies)).tw.
32	91. longitudinal.tw.
33 34	92. (observational adj (study or studies)).tw.
35	93. retrospective.tw.
36	94. or/85-93
37	95. 84 or 94
38	96. 78 and 95
39	97. (comment* or editorial* or letter*).mp.
40 41	98. 96 not 97
41	99. remove duplicates from 98
43	
44	Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library
45	Date original search conducted: 14 September 2014
46	Date first update search conducted: 24 February 2016
47	
48 49	Date second update search conducted: 31 July 2017
50	Strategy:
51	
52	1. [mh ^ "Adrenal Cortex Hormones"]
53	2. [mh ^ "Anti-Inflammatory Agents"]
54	3. [mh ^ Beclomethasone]
55 56	4. [mh ^ Budesonide]
56 57	
58	Supplement 1 - Page 6 or
59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

of **13**

2 3 5. [mh Glucocorticoids] 4 6. [mh Hydroxycorticosteroids] 5 7. [mh ^ Pregnenediones] 6 8. [mh ^ "Triamcinolone Acetonide"] 7 8 9. "adrenal cortex" next hormone*:ti,ab,kw 9 10. advair*:ti,ab,kw 10 11. alvesco*:ti,ab,kw 11 12. azmacort*:ti,ab,kw 12 13. becl?met*:ti,ab,kw 13 14 14. beclazone*:ti,ab,kw 15 15. beclo?ort*:ti,ab,kw 16 16. beclovent*:ti,ab,kw 17 17. beconase*:ti,ab,kw 18 19 18. becotide*:ti,ab,kw 20 19. betamet?asone*:ti,ab,kw 21 20. betnesol*:ti,ab,kw 22 21. budesonide*:ti,ab,kw 23 22. ciclesonide*:ti,ab,kw 24 25 23. clobetasol*:ti,ab,kw 26 24. cortiso*:ti,ab,kw 27 25. cortodoxone*:ti,ab,kw 28 26. corticosteroid*:ti,ab,kw 29 27. decadron*:ti,ab,kw 30 31 28. depo next medrone*:ti,ab,kw 32 29. desoximet?asone*:ti,ab,kw 33 30. dexamethasone*:ti,ab,kw 34 31. deflazacort*:ti,ab,kw 35 32. diflucortolone*:ti,ab,kw 36 37 33. flixotide*:ti,ab,kw 38 34. flumethasone*:ti,ab,kw 39 35. flunisolide*:ti,ab,kw 40 36. fluocino*:ti,ab,kw 41 42 37. fluocortolone*:ti,ab,kw 43 38. fluorometholone*:ti,ab,kw 44 39. flurandrenolone*:ti,ab,kw 45 40. fluticasone*:ti,ab,kw 46 41. glucocortico*:ti,ab,kw 47 42. hydrocortisone*:ti,ab,kw 48 49 43. hydroxycorticostero*:ti,ab,kw 50 44. hydrocortone*:ti,ab,kw 51 45. hydroxypregnenolone*:ti,ab,kw 52 46. kenacort*:ti,ab,kw 53 47. kenalog*:ti,ab,kw 54 55 48. medrone*:ti,ab,kw 56 57 58 59 60

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ab,kw v

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2 3	49. methylprednisolone*:ti,ab,kw
4	50. mometasone next furoate*:ti,ab,kw
5	51. nasonex*:ti,ab,kw
6	
7 8	52. paramethasone*:ti,ab,kw
9	53. predniso*:ti,ab,kw
10	54. pregnenolone*:ti,ab,kw
11	55. pulmicort*:ti,ab,kw
12	56. qvar*:ti,ab,kw
13 14	57. rhinocort*:ti,ab,kw
14 15	58. seretide*:ti,ab,kw
16	59. solu next cortef*:ti,ab,kw
17	60. symbicort*:ti,ab,kw
18	61. tetrahydrocortisol*:ti,ab,kw
19 20	62. triamcinolone*:ti,ab,kw
20 21	63. tricort*:ti,ab,kw
22	64. vanceril*:ti,ab,kw
23	65. {OR #1-#64}
24	66. [mh ^ "Acute Disease"] and (asthma* or pneumonia* or wheez*)
25	67. [mh Asthma] and (acute* or emergenc* or exacerbation* or severe*)
26 27	68. [mh "Bronchial Hyperreactivity"]
27	69. [mh "Bronchial Spasm"]
29	70. [mh Bronchiolitis]
30	71. [mh ^ Croup]
31	72. [mh Dyspnea]
32	73. [mh ^ Emergencies] and (asthma* or pneumonia* or wheez*)
33 34	74. [mh ^ "Emergency Medical Services"] and (asthma* or pneumonia* or wheez*)
35	75. [mh ^ "Emergency Services, Hospital"] and (asthma* or pneumonia* or wheez*)
36	76. [mh Pharyngitis]
37	77. [mh Pneumonia] and (acute* or emergenc* or exacerbation* or severe*)
38	78. [mh "Respiratory Syncytial Viruses"]
39 40	79. [mh "Respiratory Syncytial Virus Infections"]
40	80. [mh Rhinitis]
42	81. [mh Sinusitis]
43	82. [mh ^ "Status Asthmaticus"]
44	83. [mh ^ "Respiratory Sounds"] and (acute* or emergenc* or exacerbation* or severe*)
45 46	84. ((acute* or emergenc* or exacerbation* or severe*) near/5 (asthma* or pneumonia* or
46 47	wheez*)):ti,ab,kw
48	85. (breath* near/2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)):ti,ab,kw
49	86. (bronch* near/3 (constrict* or spas*)):ti,ab,kw
50	87. bronchiolitis*:ti,ab,kw
51 52	88. bronchoconstrict*:ti,ab,kw
52 53	89. bronchospasm*:ti,ab,kw
54	90. croup*:ti,ab,kw
55	91. dyspne*:ti,ab,kw
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58 59	Supplement 1 - Pag
59 60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

- 92. (lung* near/2 (disease* or infect*)):ti,ab,kw
- 93. (("naso pharynx" or nasopharynx* or "para nasal" or paranasal* or sinus*) near/3 (infect* or inflam*)):ti,ab,kw
- 94. (nasosinusit* or rhinosinusit*):ti,ab,kw
- 95. pharyngitis*:ti,ab,kw
- 96. (respiratory* near/2 (attack* or infect* or inflam* or virus*)):ti,ab,kw
- 97. rhinit*:ti,ab,kw
- 98. sinusit*:ti,ab,kw
- 99. tonsillitis*:ti,ab,kw
- 100. {or #66-#99}

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- 101. [mh child]
- 102. [mh infant]
- 103. [mh Pediatrics]
- 104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*):ti,ab,kw
- 105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*):ti,ab,kw
 - 106. {or #101-#105}
 - 107. #65 and #100 and #106
 - 108. #65 and #100 and #106 in Trials
 - Database: Ovid Embase 1974 to 2014 September 12 Date original search conducted: 14 September 2014 Strategy:
 - 1. antiinflammatory agent/
 - 2. beclometasone/
 - 3. budesonide/
 - 4. corticosteroid/
 - 5. exp glucocorticoid/
 - 6. hydroxycorticosteroid/
 - 7. pregnane derivitative/
 - 8. triamcinolone acetonide/
 - 9. adrenal cortex hormone*.tw,tn.
 - 10. advair*.tw,tn.
 - 11. alvesco*.tw,tn.
- 12. azmacort*.tw,tn.
- 13. becl?met*.tw,tn.
- 14. beclazone*.tw,tn.
- 15. beclo?ort*.tw,tn.
- 16. beclovent*.tw,tn.
- 17. beconase*.tw,tn.
- 18. becotide*.tw,tn.
 - 19. betamet?asone*.tw,tn.
 - 20. betnesol*.tw,tn.
- 21. budesonide*.tw,tn.

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1 2 3 22. ciclesonide*.tw.tn. 4 23. clobetasol*.tw,tn. 5 24. cortiso*.tw,tn. 6 25. cortodoxone*.tw,tn. 7 8 26. corticosteroid*.tw,tn. 9 27. decadron*.tw,tn. 10 28. depo medrone*.tw,tn. 11 29. desoximet?asone*.tw,tn. 12 30. dexamethasone*.tw,tn. 13 14 31. deflazacort*.tw,tn. 15 32. diflucortolone*.tw,tn. 16 33. flixotide*.tw,tn. 17 ,tn. *w,tn. 34. flumethasone*.tw,tn. 18 35. flunisolide*.tw,tn. 19 20 36. fluocino*.tw,tn. 21 37. fluocortolone*.tw,tn. 22 38. fluorometholone*.tw,tn. 23 39. flurandrenolone*.tw,tn. 24 25 40. fluticasone*.tw,tn. 26 41. glucocortico*.tw,tn. 27 42. hydrocortisone*.tw,tn. 28 43. hydroxycorticostero*.tw,tn. 29 44. hydrocortone*.tw,tn. 30 31 45. hydroxypregnenolone*.tw,tn. 32 46. kenacort*.tw,tn. 33 47. kenalog*.tw,tn. 34 48. medrone*.tw,tn. 35 49. methylprednisolone*.tw,tn. 36 37 50. mometasone furoate*.tw,tn. 38 51. nasonex*.tw,tn. 39 52. paramethasone*.tw,tn. 40 53. predniso*.tw,tn. 41 42 54. pregnenolone*.tw,tn. 43 55. pulmicort*.tw,tn. 44 56. qvar*.tw,tn. 45 57. rhinocort*.tw,tn. 46 58. seretide*.tw,tn. 47 59. solu cortef*.tw,tn. 48 49 60. symbicort*.tw,tn. 50 61. tetrahydrocortisol*.tw,tn. 51 62. triamcinolone*.tw,tn. 52 63. tricort*.tw.tn. 53 54 64. vanceril*.tw,tn. 55 65. or/1-64 56 57 58

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2 3 66. acute disease/ and (asthma* or pneumonia* or wheez*).mp. 4 67. exp asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp. 5 68. exp breathing disorder/ and (acute* or emergenc* or exacerbation* or severe*).mp. 6 69. bronchospasm/ 7 8 70. bronchus hyperreactivity/ 9 71. exp bronchiolitis/ 10 72. croup/ 11 73. exp dyspnea/ 12 74. emergency/ and (asthma* or pneumonia* or wheez*).mp. 13 14 75. emergency health service/ and (asthma* or pneumonia* or wheez*).mp. 15 76. exp emergency treatment/ and (asthma* or pneumonia* or wheez*).mp. 16 77. emergency ward/ and (asthma* or pneumonia* or wheez*).mp. 17 78. exp pharyngitis/ 18 79. exp pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp. 19 20 80. Respiratory syncytial pneumovirus/ 21 81. respiratory syncytial virus infection/ 22 82. exp rhinitis/ 23 83. exp sinusitis/ 24 25 84. ((acute* or emergenc* or exacerbation* or severe*) adj5 (asthma* or pneumonia* or wheez*)).tw. 26 85. (breath* adj2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)).tw. 27 86. (bronch* adj3 (constrict* or spas*)).tw. 28 87. bronchiolitis*.tw. 29 88. bronchoconstrict*.tw. 30 31 89. bronchospasm*.tw. 32 90. croup*.tw. 33 91. dyspne*.tw. 34 92. (lung* adj2 (disease* or infect*)).tw. 35 93. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw. 36 37 94. (nasosinusit* or rhinosinusit*).tw. 38 95. pharyngitis*.tw. 39 96. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw. 40 97. rhinit*.tw. 41 98. sinusit*.tw. 42 43 99. tonsillitis*.tw. 44 100. or/66-99 45 101. exp child/ 46 102. exp infant/ 47 103. exp Pediatrics/ 48 49 104. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).mp. 50 105. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).mp. 51 106. or/101-105 52 107. and/65,100,106 53 108. crossover procedure/ 54 55 109. double blind procedure/ 56 57 58 59

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4	110. randomized controlled trial/
5	110. single blind procedure/
6	111. allocat*.tw.
7	112. assign*.tw.
8	113. cross over*.tw.
9 10	114. crossover*.tw.
10	115. doubl* adj blind*.tw.
12	116. factorial*.tw.
13	117. placebo*.tw.
14	118. random*.tw.
15	119. singl* adj blind*.tw.
16 17	120. volunteer*.tw.
17 18	121. or/108-120
19	122. exp case control study/
20	123. case report/
21	124. case study/
22	125. cross-sectional study/
23	126. cohort analysis/
24 25	120. control.tw.
25	
27	128. (case adj (report* or study or studies or series)).tw.
28	129. cohort analy*.tw.
29	130. (cohort adj (study or studies)).tw.
30	131. cross sectional.tw.
31	132. (follow up adj (study or studies)).tw.
32 33	133. longitudinal.tw.
34	134. (observational adj (study or studies)).tw.
35	135. retrospective.tw.
36	136. or/122-135
37	137. 121 or 136
38	138. animals/ not (animals/ and humans/)
39	139. 137 not 138
40 41	140. 107 and 139
41	141. (editorial or journal editorial or journal letter or journal note or letter or review).pt.
43	142. 140 not 141
44	143. limit 142 to embase
45	
46	Database: Drugs@FDA
47	URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
48 49	
50	Date original search conducted: 5 September 2014
51	Strategy:
52	
53	Searched Drugs@FDA for drug name keywords:
54	1. beclametasone dipropionate
55 56	2. budesonide
56 57	
58	Supplement 1
59	
60	For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

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- 3. ciclesonide
- 4. fluticasone propionate
- 5. mometasone furoate
- 6. triamcinolone acetonide

Retrieved all available medical and statistical reviews for drugs in these classes with systemic routes of administration

Database: Health Canada Drug Products Database URL: <u>http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php</u>

Date original search conducted: 8 September 2014 Strategy:

Searched Health Canada Drug Products Database for drug name keywords:

- 1. beclomethasone
- 2. budesonide
- 3. ciclesonide
- 4. fluticasone propionate
- 5. mometasone furoate
- 6. triamcinolone acetonide

Retrieved all available monographs for drugs in these classes with systemic routes of administration

Database: European Medicines Agency's European Public Assessment Reports **URL**:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b 01ac058001d124

Date original search conducted: 9, 10 September 2014 **Strategy**:

Searched EMA reports for drug name keywords:

- 1. beclomethasone
- 2. beclometasone
- 3. beclamethasone
- 4. beclometasone
- 5. budesonide
- 6. ciclesonide
- 7. fluticasone
- 8. mometasone
- 9. triamcinolone acetonide
- 10. Also searched for "corticosteroids" as a pharmaco therapeutic group

Retrieved all available reports for drugs in these classes with systemic routes of administration

Review	ver ID:	Date:	/	/2015	Record ID:		
Criteria	1					Yes	
1. PUB	LICATION TYPE						
a. P	rimary research (RCTs, o	cohort studi	es, cas	e control studi	es, case reports, and case		
series)							
Exclud	2:						
•	Systematic reviews, le	tters to edite	or, con	nmentaries			
2. Pop	ulation						
a.	Children ≤6 years of ag	ge, where ag	e subg	roups data is a	vailable:		
Jnclea							
•	If aggregate/subgroup	data include	e but a	re not limited	to age ≤6 years		
Exclud	2:						
•	e: If data is reported in a	ggregate wit	h olde:	r ages			
	e: If data is reported in a DITION Children with acute re			2.	wing):		_
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis			2.	owing):		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup	spiratory dis		2.	owing):		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p	spiratory dis	ease (a	any of the follo	2		
• 8. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute re Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis	spiratory dis	ease (a	any of the follo	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial w Respiratory distress du	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
• 3. CON	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi	ease (a no abs	any of the follo scess, effusion, her viruses	2		
8. CON a. • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs	any of the follo scess, effusion, her viruses	2		
8. CON a. • • • • • • • • • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs irus/ot bodie	any of the follo scess, effusion, her viruses s	2		
a. • • • • • • • • • • • • • • • • • • •	e: If data is reported in a DITION Children with acute rea Bronchiolitis Croup Acute wheeze/asthma Acute uncomplicated p Pharyngitis/tonsillitis Peritonsillar abcess Acute sinusitis Respiratory syncytial v Respiratory distress du PFAPA syndrome e: patients in NICU, PICU	spiratory dis oneumonia (irus/ rhinovi ue to foreign	ease (a no abs irus/ot bodie	any of the follo scess, effusion, her viruses s	2		

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	All inhaled [*] and systemic (IV, IM, oral) corticosteroids used for ≤14 days per		
	course, including (but not limited to):		
•	Beclomethasone		
•	Budesonide		
•	Ciclesonide		
•	Dexamethasone		
•	Fluticasone propionate		
٠	Mometasone furoate		
•	Prednisolone		
•	Prednisone		
•	Triamcinolone acetonide		
•	combination therapies (e.g. ICS + short-acting beta-agonists)		
Exclude			
٠	topical (non-systemic) corticosteroid therapy		
* inhale	ed (moderate- to high-dose) corticosteroids, following GINA guidelines for low		
doses fo	or children 5 years and younger (see Box 6-6 below).		
5. Com	parator group (where relevant)	 	
a. Ar	parator group (where relevant) ny comparison, including non-pharmacologic interventions which may act similarly		
a. Ar to a	y comparison, including non-pharmacologic interventions which may act similarly		
a. Ar to a			
a. Ar to a pla	acebo		
a. Ar to a pla 6. OUT(acebo		
a. Ar to a pla 6. OUT(Adverse	acebo COME e drug reaction, side effect, adverse effects/events, adverse reactions		
a. Ar to a pla 6. OUT(Adverse 7. Setti	acebo COME e drug reaction, side effect, adverse effects/events, adverse reactions		
a. Ar to a pla 6. OUT(Adverse 7. Setti	acebo COME e drug reaction, side effect, adverse effects/events, adverse reactions		
a. Ar to a pla 6. OUT(Adverse 7. Setti Focus is	acebo COME e drug reaction, side effect, adverse effects/events, adverse reactions ng s on outpatient settings (e.g. ambulatory, ED), and hospitalised patients		
a. Ar to a pla 6. OUT(Adverse 7. Setti	acebo COME e drug reaction, side effect, adverse effects/events, adverse reactions ng s on outpatient settings (e.g. ambulatory, ED), and hospitalised patients		

GINA Global Strategy for Asthma Management and Prevention: http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Jun11.pdf

Box 6-6. Low daily doses of inhaled corticosteroids for children 5 years and younger

Drug	Low daily dose (mcg)		
Beclometasone dipropionate (HFA)	100		
Budesonide pMDI + spacer	200		

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Budenoside nebulized	500
Fluticasone proprionate (HFA)	100
Ciclesonide	160
Mometasone furoate	Not studied below age 4 years
Triamcinolone acetonide	Not studied in this age group

Supplement 3 Characteristics of included studies

a. Summary characteristics of included studies	p. 1-2
b. Summary characteristics of included studies - comparisons	р. 3-4
c. Characteristics of included studies	p. 5-77

Supplement 3a. Summary characteristics of included studies

Study characteristic	N (% ¹)
Country	
Canada	15 (18)
US	15 (18)
Australia	7 (8)
UK	5 (6)
Denmark	4 (5)
Finland	4 (5)
Italy, Netherlands, Taiwan, Thailand	3, each (14)
China, Greece, Ireland, Israel, Japan, Saudi Arabia (SA), Spain, Sweden, Turkey	2, each (21)
Brazil, Germany, Mexico, Qatar	1, each (5)
SA & UK	1 (1)
Study designs	
RCT (all)	68 (80)
2-arm	52 (61)
3-arm	7 (8)
4-arm non-factorial	1 (1)
factorial 4 x4	4 (5)
crossover	2 (2)
trial registry	1 (1)
conference abstract	1 (1)
Non-RCT	5 (6)
Cohort	4 (5)
Case control	1 (1)
Case series	4 (5)
Case report	3 (4)
Number of centres	
Single centre	56 (66)
Multi-centre	24 (28)
Unclear/NR	5 (6)
Setting	
Inpatient	41 (48)
Outpatient	22 (26)
Inpatient & outpatient	21 (25)
NR	1 (1)
Funding	

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Not reported	35 (41)
Non-industry	25 (29)
Industry	9 (11)
Industry & non-industry	15 (18)
No direct funding	1 (1)
Year of publication, median (range)	2002 (1964-201
Respiratory condition	
Asthma	27 (32)
Croup	22 (26)
Bronchiolitis	15 (18)
Wheeze	14 (16)
Asthma/croup, palatability & tolerability of CS	2 (2)
Pharyngitis	1 (1)
Shortness of breath	1 (1)
Refractory pneumonia	1 (1)
Bronchiolitis & laryngitis	1 (1)
Bronchiolitis, viral wheeze & croup	1 (1)

CS: corticosteroid; N: number of studies; NR: not reported; RCT: randomized controlled trial; SA: Saudi Arabia; UK: United Kingdom; US: United States

¹ sum of percentages may not total 100 due to rounding

Number of treatment groups	Comparison	No. of studies	No. of studies
		(no. of patients)	contributing
			data
			(no. of patients)
2-arms	Systemic CS vs. placebo/no intervention/standard care	26 (4166)	15 (3035)
	Systemic CS vs. systemic CS	12 (1683)	5 (1051)
	Systemic CS vs. non-CS	2 (180)	0
	Systemic CS vs. inhaled CS	3 (124)	1 (18)
	Systemic CS vs. systemic CS + placebo	1 (125)	0
	Systemic CS + inhaled CS vs. systemic CS + placebo	1 (50)	1 (50)
	Inhaled CS vs. placebo/no intervention	14 (2367)	8 (1234)
	Inhaled CS vs. non-CS	1 (66)	0
3-arms	Systemic CS vs. systemic CS vs. no intervention	2 (180)	1 (80)
	Systemic CS vs. systemic CS vs. systemic CS	5 (624)	2 (354)
	Systemic CS vs. inhaled CS vs. non-CS/placebo	1 (144)	1 (144)
	Systemic CS vs. inhaled CS vs. no CS	1 (64)	1 (39)
	Systemic CS vs. inhaled CS vs. inhaled CS	1 (123)	0
	Systemic CS vs. inhaled CS vs. combined (systemic + inhaled)	1 (198)	1 (197)
	Systemic CS + non-CS vs. inhaled CS + sal + non-CS vs. inhaled CS + sal	1 (238)	0
	Inhaled CS vs. inhaled CS vs. no CS	1 (80)	1 (80)
4-arms	Systemic CS + terb vs. inhaled CS + terb + placebo vs. non-CS + terb +	1 (114)	1 (114)
	placebo vs. placebo		
	Systemic CS + sal dose1 vs. systemic CS + sal dose2 vs. sal dose1 +	1 (70)	1 (70)
	placebo vs. sal dose2 + placebo		
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal +	1 (69)	1 (69)
	placebo		
	Systemic CS + non-CS vs. systemic CS + placebo vs. non-CS + placebo vs.	1 (800)	1 (800)
	placebo + placebo		
	Systemic CS + sal vs. systemic CS + placebo vs. sal + placebo vs. placebo	1 (32)	0
	Systemic CS	5 (5)	0

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Non-comparative (case reports/series)	Mode of administration NR	2 (3)	0
CS: corticosteroid; no.: num	ber; NR: not reported; sal: salbutamol; terb: terbutaline; vs.: v	ersus	
		Supple	ement 3 - Page 4 of 7 7
	For peer review only - http://bmjopen.bmj.com/site/abo		-

Supplem	ent 3c. Cha	racteristics of i	ncluded studies			
Author, year Country Funding	Study design Setting No. of	Respiratory condition Age (range)	Comparators, no. of participants	Co-interventions; Maintenance CS	Time points for assessment s;	Outcomes related to adverse events
source	centres				FU	
Alangari 2014 Saudi Arabia Non- industry funded	RCT ED 1	Asthma 2-12y	1) Budesonide 500mcg/dose, 3 doses 20min apart (neb), n=458 2) Placebo saline, 3 doses 20min apart (neb), n=448	Salbutamol, ipratropium & prednisolone No CS in preceding 7d	Baseline, at 1h, 2h, 3h and 4h from the start of medication s; FU 72h post- discharge	The most frequently reported adverse effects were fine tremors (17 cases) an palpitations (11 cases). None of the reported adverse effects was serious, and none was significantly different between the
Alansari 2013 Qatar Non- industry funded	RCT Pediatri c emerge ncy unit 1	Bronchiolitis <=18mo	 Dexamethasone Deginst day, then 0.6mg for 4d (oral) + sal, 5d total (neb), n=102 Placebo (oral) + sal, 5d total (neb), n=98 	Epinephrine, oxygen & hydration No CS in preceding 48h	At study entry, then assessed if ready for discharge at 12h, 18h, 24h, 36h & 48h; FU by telephone 1wk post- discharge	two groups. Daily telephone surveillance days) revealed no particular sid effect concerns in either treatment group.
Aljebab 2017 Saudi Arabia & UK Unfunded	Cohort, 3-arm Pediatri c ED of hospital (SA & UK)	Asthma/cro up, palatability & tolerability 2-10y (SA); 2-16y (UK)	SA 1) Dexamethasone 0.5mg/5mL elixir (oral), n=33	NR Most patients in prednisolone groups had received oral steroids previously;	After each dose (within 10min) & daily on D1- D5	In SA and the UK, dexamethas ne had the highest palatability scores and

2	2) Prednisolone	however, most	predni
	base 5.0mg	patients and none	base ta
	tablets (oral),	had received oral	had th
	n=52	steroids previously	lowest
	3) Prednisolone	in the SA & UK	Palata
	sodium	dexamethasone	scores
	phosphate	groups,	improv
	15.0mg/mL	respectively	all
	syrup (oral),		formu
	n=37		of
			predni
	UK		with e
	1)		subsec
	Dexamethasone		daily d
	2.0mg/5mL		In SA,
	elixir (oral),		predni
	n=53		base ta
	2) Prednisolone		were
	base 5.0mg		associa
	tablet (oral),		with m
	n=38		nausea
	3) Prednisolone		7 patie
	sodium		
			and vo
	phosphate		(5 vs. (
	5.0mg soluble		patien
	tablets (oral),		sodiun
	n=42		phosp
			syrup.
			In the
			vomiti
			occurr
			more
		_	freque
			with
			predni
			base (8
			patien
			sodiun
			phosp
			soluble
			tablets
			patien
			(p=0.0

						In both centres, dexametha ne was associated with less si effects. Vomiting (1 vs. 0 patients), nausea (7 v 3 patients) and abdominal pain (10 vs patients) occurred more with dexametha ne sodium phosphate solution th dexametha ne elixir.
Alshehr 2005 Saudi Arabia	RCT Emerge ncy rooms	Croup 3mo-9y	1) Dexamethasone 0.6mg/kg, single dose (oral),	Mist therapy, racemic epinephrine, oxygen &	12h & 24h after treatment & change in	dexametha ne elixir. Two patien developed bronchopn monia on
Funding NR	& outpati ent clinics 3		n=36 2) Dexamethasone 0.15mg/kg, single dose (oral), n=36	antibiotics No CS in preceding 4wk	total croup scores per 12h intervals within & between study groups	second day admission a confirmed chest x-ray and one patient hac bacterial tracheitis.
						these three patients we in group A (0.6 mg/kg dexametha ne). No adverse events wer

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						noted in
						group B
						patients
						patient l
						clinical
						deterior
						either in
						emerger
						room or
						discharg
						no child
						gastroin
						al bleed
						bacteria
						infectior
Altamimi	RCT	Asthma	1)	Salbutamol	2d & 5d	Two sub
2006	Pediatri	2-16y	Dexamethasone		post-	in the
Canada	С	,	0.6mg/kg (max	No CS in preceding	discharge &	predniso
Non-	hospital		18mg), single	2wk	every week	group
industry &	1		dose (oral),		to a	dropped
, industry			n=67		maximum	because
, funded			2) Prednisolone		of 3wk	repeate
			1.0mg/kg (max			vomiting
			30mg) twice			effects (
			daily (oral),			5) <i>,</i> n:
			n=67			Abdomi
			_	CZ O		pain (2 d
						3 pred);
						Vomitin
						dex vs. 1
						pred);
						Headach
						dex vs. 0
						pred);
						Palpitati
						dex vs. (
						pred);
						Excessiv
						urinatio
						dex vs. 1
						pred)
Bacharier	RCT, 3-	At least 2	1) Montelukast	Albuterol,	Clinic visits	The 3 gr
2008	arm	wheeze	4.0mg once	prednisolone &	4wk after	did not o
			daily (oral) +	μ		significa

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Non-	Clinical	episodes in	placebo ICS	other non-asthma	on, then	several oth
industry &	center	last year	twice daily for	medications	every 8wk;	outcomes
industry	5	12-59mo	7d (neb), n=95		FU by	assessed ov
funded			2) Budesonide	No more than 6	phone 2wk	the 1-year
			1.0mg twice	courses of CS in	after	trial, includi
			daily (neb) +	past year	randomizati	oral
			placebo LTRA		on,	corticostero
			once daily (neb),		followed by	use, health
			n=96		calls 4wk	care use,
			3) conventional		after each	linear growt
			therapy +		scheduled	quality of lif
			placebo		clinic visit	and
			(systemic +			frequencies
			inhaled), n=47		Linear	adverse
					growth in	events.
			Multiple		height or	
			courses over 1yr		length	
					(assessmen	
					t method	
					NR) from	
					baseline to	
					study end	
					(12mo)	
Bisgaard	RCT	Wheeze	1) Budesonide 🧹	NR	Height &	Safety, as
2006	Clinical	1mo	400mcg/day for	5	bone	evaluated b
Denmark	researc		2wk (MDI),	NR	mineral	height and
Non-	h unit		n=149	4	density	bone miner
industry &	1		2) Placebo once		measured	density, we
industry			daily for 2wk		using	not affected
funded			(MDI), n=145		Harpenden	by treatmer
					stadiometry	the height a
			Multiple		at 3yrs of	three years
			courses over		age	age measur
			3yrs			by
						stadiometry
						and bone
						mineral
						density
						measured b
						ultrasonogr
						hy at the
						phalanx we
			1	1	I	unaffected

						treatment
Diaracan	RCT	Croup	1)	Mist, antibiotics &	D1, D2, D3,	group.
Bjornson	Pediatri	Croup	Dexamethasone		D1, D2, D3, D7 & D21	Among the
2004		mean 35+/-		nebulized		720 patien
Canada	c ED	23 mo	0.6mg, max.	epinephrine or	after day of	there were
Non-	4		20.0mg, single	beta-agonists	treatment;	cases of
industry &			dose (oral),		FU	gastrointe
industry			n=359	No CS in preceding	interview	al bleedin
funded			2) Placebo	2wk	with parent	complicat
			solution, single		on D7 and	varicella, o
			dose (oral),		chart and	bacterial
			n=361		administrati	tracheitis.
					ve database	There we
					review	cases of
						pneumon
			6			in the
						dexameth
						ne group)
						these case
						were
						managed
						an outpat
						-
						basis, with
						significant
						sequelae.
						Repeated
						short cou
						of oral
						corticoste
						s are not
						associated
						with long-
				-		term nega
						effects on
						bone
						metabolis
						bone dens
						or adrena
						function.
						There we
						no serious
						adverse
						events
						attributab
			1			

59 60

	to theraj any child in our st Howeve study wa sufficien powered exclude possibili rare adv events. Supplem y Table 1 of adver events, r vs. place Abnorm bowel moveme vs. 5); Fever (5 4); Pneumo vs. 4); Vomiting gastroer s (3 vs. 4) Otitis me (1 vs. 5); Bronchit vs. 1); Sore thra vs. 2); Streptoc throat infection vs. 1); Sore thra vs. 2); Streptoc throat infection vs. 1); Abdomin pain (1 v Rash (2 v Dehydra (1 vs. 0); Febrile s (1 vs. 0);
--	--

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						RSV infect (1 vs. 0); Uncomplic d varicella vs. 1); Urinary tra infection (vs. 1); Irritability
		<0<<				vs. 1); Eye discha (1 vs. 0); Sinusitis (C 1); Bleeding fi ear (0 vs. 1 Nasal
						discharge (vs. 0)
Brunette	NRCT	Asthma	1) Theophylline	None	Monthly or	No side eff
1988	Hospita	<6y	8.0mg/kg every		every	was observ
Canada	I		6-8h (oral) +	NR	second	in a partic
Funding NR	1		metaproterenol		month,	case which
			0.3-0.7 mg/kg 🧹	•	depending	received
			every 6-8h		on severity	longer
			(oral)+		of disease;	duration o
			prednisone	4		corticoste
			1.0mg/kg/day		Growth	(high
			for 7-14d (oral),		(mean	cumulative
			n=16		height gain	corticoster
			2) Theophylline		in cm/yr	dose).
			8.0mg/kg every		and height	Growth an
			6-8h (oral) +		as	weight gai
			metaproterenol		percentile	for all child
			0.3-0.7mg/kg		of normal	were with
			every 6-8h for		distribution	the norma
			7-14d (oral),) assessed	range duri
			n=16		(assessmen	the two
					t method	periods.
			Multiple		NR) at the	
			courses over 1yr		end of each	
					of two 1-yr	
					periods	

Buckingha	RCT	RSV	1)	Other treatment	Enrolment	Serious
m 2002	Pediatri	(bronchioliti	Dexamethasone	(not specified)	& daily until	adverse
USA	с	s)	0.5mg/kg/dose		discharge;	events
Non-	hospital	<24mo	every 12h for 4d	No CS in preceding	FU 30d	occurred in
industry	2		(IV), n=22	3wk	after	patients in
funded			2) Placebo		enrolment	dexametha
			saline every 12h			ne group. (
			for 4d (IV), n=19			infant
						developed
						progressiv
						respiratory
						failure that
						did not
						improve w
						high-
			5			frequency
						oscillatory
			\mathbf{N}			ventilation
			, C			extracorpo
						Imembrar
						oxygenatio
						support w
			\sim			withdrawr
						and this in
						died on st
						day 38. Another
						subject
						developed
						pneumoth
						x, which
						resolved
						following
						placement
						a pigtail
						thoracoto
						catheter, o
						study day
						Neither
						adverse ev
						was judgeo
						be related
						administra
			1			n of the stu

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						drug. No patients in either gro had microscop or gross gastrointe al bleedin and no patients required antihyper ve therap
						during the
Dulau	DCT		1) Due du la class	Data 2 and sist	Faugles st	study.
Bulow 1999 Denmark	RCT Pediatri c	RSV (bronchioliti s)	1) Prednisolone 5.0mg/ml at dose of	Beta-2-agonist, antibiotics, oxygen & hydration	Enrolment & 5d; FU 1mo &	A total of patients (the
Non- industry	hospital 3	0-2y	2mg/kg/day, first dose at	No CS in preceding	at 1y	prednisol group and
funded			enrolment and for 4d (oral), or methylprednisol one for patients	month		the placel group) did complete treatmen
			with IV line (40.0mg/ml at dose of	e4		because of side effect primarily
			 1.5mg/kg/day) for 5d (IV), n=73 2) quinine hydrochloride 	05		vomiting patients), which we mild in al
			(or saline for patients with IV line) for 5d (IV), n=74		2	cases.
Chang	RCT	Asthma	1) Prednisolone	NR	24h, 48h,	There we
2008	Pediatri	2-15y	1.0mg/kg (max.		D5, D7,	five recor
Australia	с&		50.0mg/day) for	No maintenance CS	D10, D14 &	adverse
Non- industry &	general ED		3d + placebo solution for 2d	or CS preceding presentation	D28	events, w no signifi
industry &	3		(oral), n=101	presentation		difference
funded			2) Prednisolone			between
-			1.0mg/kg (max.			groups. Ir
						3-day gro

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			50.0mg/day) for			two parents
			5d (oral), n=100			reported tha
						their child ha
						behavioural
						disturbance
						(cranky and
						irritable) and
						one had a
						rash, while
						two children
						in the 5-day
						group had
						behavioural
						disturbance
			•			(angry and
						aggressive).
Chen 2008	RCT, 3-	Asthma	1) Budesonide	NR	0.5h before	All three
China	arm	1-14y	0.5mg (neb) +		& post-	groups of
Funding NR	Pediatri		sal +	No CS within 48h	treatment	children
	с		ipratropium; 1-		& 5d post-	showed no
	outpati		6yo (n=32); 6-		treatment	adverse
	ent,		14yo (n=21)			effects.
	hospital		2) Budesonide			
	ward,		0.2-0.4mg (neb)			
	or ED		+ sal +	5		
	1		ipratropium; 1-			
			6yo (n=25); 6-	4		
			14yo (n=16)			
			3)			
			Dexamethasone			
			2.0mg (<2yo),			
			4.0mg (2-6yo)			
			(IV); 1-6yo			
			(n=15); 6-14yo			
			(n=14)			
Chub-	RCT	Croup	1)	Epinephrine, mist,	0, 1h, 2h,	There was no
Appakarn	Pediatri	6mo-5y	Dexamethasone	antibiotics &	3h, 4h, 6h,	significant
2007 The sile and	C		0.5ml/kg of 0.15	oxygen	8h, 10h &	adverse
Thailand	hospital		mg/kg, single		12h post-	reaction from
Funding NR	ward		dose (IV), n=20	No CS in preceding	treatment	dexamethas
	1		2)	2wk		ne treatmen
			Dexamethasone			in either
			0.5 ml/kg of			group.

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			0.6mg/kg, single dose (IV), n=21			
Clavenna 2014 Italy Non- industry & industry funded	RCT Family pediatri c health units 9	Wheeze 1-5y	1) Beclomethason e 400mcg (1ml) twice daily for 10d (neb), n=264 2) Placebo twice	Paracetamol, nasal saline irrigation & antibiotics No CS in preceding month	Entry visit, D11 (or prior if requested by parents) & daily diary	No differences were found the incider of adverse events reported b
		10	daily for 10d (neb), n=261		symptom recording during 10d treatment	parents at end of the therapy. Table 4 AE reported b parents, n
			66			(beclo vs. placebo): Any AEs (9 vs. 98)
			C, C			Hoarsenes (34 vs. 34); Diarrhea (2 vs. 35); Skin rash (2
				CZ		vs. 22); Vomiting (vs. 20); Candidiasi
				0)		(12 vs. 15) Others (25 26) Two seriou
						adverse events wer reported b pediatricia
						1 hospital admission urinary tra infection ii
						the beclometh ne group a 1

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5.0mg every 1- 4h as needed (neb), n=19 3) Placebo single dose (oral) + sal 0.15mg/kg every 30min for 3h (neb), n=15 4) Placebo single dose (oral) plus sal 5.0mg every 1- 4h as needed (oral) plus sal 5.0mg every 1- 4h as needed (neb), n=18regimen but symptoms were mild a self-limiting most instances. Vomiting wa more a feature of disease severity that any particula treatment group. There was no	Connett 1994 UK Non- industry funded	RCT, factoria l Hospita l 1	Asthma >18mo	1) Prednisolone 2.0mg/kg single dose (oral) + sal 0.15mg/kg every 30min for 3h (max. 5.0mg) (neb), n=18 2) Prednisolone 2.0mg/kg single	NR No CS in preceding 2wk	On arrival, after nebulizatio n & at treatment completion	hospitalizati n for adenoidecto y and tonsillectom in the placel group. Neither adverse eve was drug related. Tremor and hyperactivit were more commonly reported in those childro receiving the more intensive
3h (neb), n=15feature of disease4) Placebosingle dosesingle doseseverity that any particula(oral) plus salany particula treatment5.0mg every 1-treatment group. There was no				2) Prednisolone 2.0mg/kg single dose (oral) + sal 5.0mg every 1- 4h as needed (neb), n=19 3) Placebo single dose (oral) + sal 0.15mg/kg	icz		more intensive nebuliser regimen but symptoms were mild an self-limiting most
				3h (neb), n=15 4) Placebo single dose (oral) plus sal 5.0mg every 1- 4h as needed			feature of disease severity than any particula treatment group. There

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						though th
						was a tre
						towards
						decreasi
						tachypno
						all four
						groups.
Connolly	RCT	RSV	1) Prednisolone	Ampicillin, oxygen	FU 1mo &	There wa
1969	Hospita	Bronchiolitis	D1=15.0mg;		1y	evidence
Ireland	I	0-2y	D2-3=10.0mg;	NR		this trial
Funding NR	1		D4-5=5.0mg;			predniso
			D6-7=2.5mg			treatmen
			(NR, likely IV),			the patie
			n=47			affected
			2) Placebo (NR,			antibody
			likely IV), n=48			response
						the dosag
						used in th
						trial,
						prednisol
						had no
						beneficia
						harmful
						effects or
						course of
						disease ir
				· La		severely
						children.
						There we
						no death
Corneli	RCT	Bronchiolitis	1)	Not specified	Baseline, 1h	There we
2007	ED	2-12mo	Dexamethasone		& 4 h;	few adve
USA	20		1.0mg/kg (max.	No CS in preceding	FU at 7-10d	events. N
Non-	20		12mg), single	14d	by	infant ha
industry &			dose (oral),	110	telephone	gastroint
industry			n=305		telephone	al bleedir
funded			2) Placebo			hyperten
landed			solution			or
			1.0ml/kg (max.			complica
			12ml), NR (oral),			varicella.
			n=295			Varicella. Vomiting
			11-293			-
						within 20
						after
		1	1	1		administr

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						n of study medication (5.5% in dex 4.7% in placebo). Pneumonia was diagnosed in three infants two were in the placebo group, and a empyema developed in one of these two infants.
Cronin 2016 Ireland Non- industry funded	RCT Tertiary hospital ED 1	Asthma 2-16y	1) Dexamethasone 0.3mg/kg (max. 12.0mg) single dose, n=123 2) Prednisolone 1.0mg/kg per day, once daily (max. 40.0mg) for 3d, n=122	Regular inhaled bronchodilators prior to enrolment in trial No IV or oral CS in previous 4wk	Baseline & D4 for primary outcome; 14d period for adverse events	Seven patients in t PRED group (5.7%) vomited within 30 minutes of the dose of steroid on d 1 in the ED compared with none in the DEX grou (absolute difference - 5.7%; 95%CI
						9.9% to - 1.54%). Seve patients vomited after the prednisolon dose on day and 6 vomit after the do on day 3. A total of 14 patients

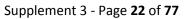
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						vomited aft
						at least 1 do
						of
						prednisolor
						No other
						adverse
						events
						attributable
						to the study
						medication
						were noted
Csonka	RCT	Viral	1) Prednisolone	NR	Diary	Fifteen
2003	Pediatri	respiratory	2.0mg/kg in ED		recordings	children (4
Finland	c ED	infection-		NR	-	
			followed by	NR	twice daily	the placebo
Non-	1	induced	2.0mg/kg/day		for 14d;	group and 2
industry		lower	for 3d (oral),		examinatio	in the
funded		airway	n=113		n by	prednisolo
		disease	2) Placebo		physician	group)
		6-35mo	10.0mL fructose		14d-21d	discontinue
			in water (in ED)		post-ED	the study
			followed by 🦰		visit	medication
			subsequent			because of
			doses for 3d,			perceived s
			n=117			effects. The
						reported
						reactions
				4		were mild a
						resolved
				CZ O		without
				U,		special
						interventio
						These
						included
						vomiting (4
						9), diarrhea
						vs 6), rash
						vs 2), and
						restlessnes
						(2 vs 3) in t
						placebo an
						prednisolo
						groups,
						respectively

1993 Denmark Non- industry & industry	arm Pediatri	recurrent				
Non- industry &	Pediatri		4.0-6.0mg/kg on		or until	effects we
industry &		wheeze	admission; D2-	No CS preceding	discharge	observed
-	С	0-18mo	3=1.6-2.6mg/kg	study		specifical
inductry	depart		(oral) +			hoarsene
muustiy	ment		terbutaline			oral
funded	5		0.12-0.2mg/kg			candidias
			(4ml) every 4h			continue
			until discharge			fever, in a
			or for 5d (neb),			of the gro
			n=31			No signifi
			2) Placebo			tachycard
			solution (oral) +			was found
			budesonide			the treat
			0.5mg every 4h			groups
			until discharge			compare
			or for 5d (neb) +			with plac
			terbutaline			
			0.12-0.2mg/kg			
			(4ml) every 4h			
			until discharge			
			or for 5d, n=29			
			3) Placebo			
			solution (oral) +			
			placebo (neb) +			
			terbutaline			
			0.12-0.2mg/kg	2		
			every 4h until			
			discharge or for			
			5d (neb), n=27			
			4) Placebo			
			solution (oral) +			
			placebo (neb) +			
			placebo saline			
			(neb), n=27			
Dawson	RCT	Asthma	1) Prednisolone	None	D1 to D5	Twenty-o
1993	Hospita	<6.5y	1.0mg/kg			of the
Australia		,	tablets, every	NR		children
Industry	1		24h for 5d	-		taking the
funded	-		(oral), n=25			solution t
			2) Prednisolone			it easily o
			1.0mg/kg			day 3,
			solution, every			compare
						two in the

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	(oral), n=26		on the same day. A difference
			-
			difference
			was noted on
			day 1 with
			regard to
			mood change
			but there was
			no significant
			difference at
			any stage
			between the
			groups in
			terms of
	5		excitability.
			The only
			children who
			appeared to
			be nauseated
			on day 1 were
			eight children
			receiving the
			tablet
			treatment.
			Thereafter,
			only one child
			in the tablet
			group
			experienced
			severe nausea
			although the
			incidence of
			mild nausea
			was evenly
			distributed.
			We could not
			demonstrate
			any statistical
			difference
			between the
			two
			treatments in
			terms of their



						propensity cause
						vomiting (
						all five day
						abdomina
						pain for a second
						frequency
						(days 2-5)
						nausea (da
						2-5) or mo
						change (d
						2-5). As a
						result of
						persistent
						vomiting,
						parents of
						two childr
						receiving
						tablets
						stopped
						treatment
						premature
Ducharme	RCT	>=3 wheeze	1)Fluticasone	Albuterol, nasal	Monthly	Thirteen
2009	Hospita	episodes in	propionate 🧹	saline irrigation	telephone	serious
Canada	1	lifetime,	250mcg (3		contacts	adverse
Non-	5	onset of	doses twice	No more than 1	and a	events (4
industry &		URTI	daily at start of	dose of CS in	medical	fluticason
industry		1-6y	URTI) until 48h	preceding 6mo or 2	visit every	group and
funded			elapsed without	doses in preceding	4mo;	placebo)
			symptoms, for	12mo		occurred
			max. 10d (MDI),		Growth	children
			n=62		assessed	during the
			2) Placebo (3		using an	study peri
			doses twice		upright	namely,
			daily at start of		stadiomete	pneumon
			URTI until 48h		r at	seizure,
			elapsed without		baseline,	admission
			symptoms		every	an intensi
			(MDI), n=67		month, and	care unit,
					at the end	burn,
			Multiple		of follow-	respirator
			courses over 6-		up (6-	syncytial v
			12mo		12mo);	infection,
	1	I	1			atelectasis

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				Basal cortisol assessed using an immunoass ay system, with or without corticotropi n testing, at baseline and end of the study (12mo)	and Kawasaki's disease. None of the serious adverse events were considered by an independent physician masked to treatment to be attributable to the study drug. Table E3 adverse health events, n (FP vs. placebo): Otitis media (27 vs. 23); Fever (18 vs. 20); Gastroenteriti s (14 vs. 11); Pneumonia (13 vs. 10); Sinusitis (10 vs. 9); Injuries (5 vs. 9); Chickenpox (9 vs. 6); Croup (5 vs. 4); Vomitinig (4 vs. 4); Pharyngitis (6 vs. 4); Streptococcal infection (2 vs. 4);
--	--	--	--	--	---

(2 vs. Eczer 1); Rash Serou medi 2) Autho repor separ from healt harm as fai thrive defin weigh the 3 perce the e study or a c in we at lea majo perce lines Cente Disea Contr										Rash (5 vs. 2) Serous otitis media (4 vs. 2) Author reports harm separately from adverse health events harm defined as failure to thrive, defined by a weight below the 3rd percentile at the end of th study period or a decrease in weight by at least 2 major percentile lines on the Centers for Diseases Control and Prevention growth
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			2)		120min	treatment.
			Dexamethasone		post-	Tremor and
			0.6mg/kg (max.		treatment;	tachycardia
			8mg), single		patients	were
			dose (IM), n=19		asked to	observed ir
			3)		return if	children fro
			Beclomethason		relapse in	Group A, w
			e dipropionate		next 24h	had receive
			200mcg (MDI),			LE and were
			n=20			resolved af
						2 hours, wh
						the action o
						LE wear off
Eden 1967	RCT	Croup	1)	Oxygen, humidity &	Every 6h for	No untowa
USA	Hospita	8mo-5y	Dexamethasone	tetracycline	total 48h	effects were
Industry	1		0.10mg/kg at			noted. Ther
funded	1		0.1cc/kg/dose	NR		were no
			every 6h for			episodes of
			48h, total daily			congestive
			0.40mg (IM),			heart failur
			n=25			or sodium
			2) Control			retention.
			preparation			
			0.1cc/kg/dose 🧹	•		
			every 6h for 48h			
			(IM), n=25			
Escobedo	RCT	Asthma	1)	Saline, salbutamol	Baseline &	We detecte
Chavez	Hospita	1mo-14y	Methylprednisol	& oxygen	discharge	no side
1992	l ed		one 3.0mg/kg,			effects with
Mexico	1		single dose (IM)	No CS in preceding		the use of
Industry			+ placebo 4.5ml	15d		methylpred
funded			+ sal 0.5ml			olone in a
			every 4h (neb),			single dose
			n=25			any treatme
			2)			failures that
			Aminophylline			merited the
			5.0mg/kg every			use of
			6h (IV) + sal 70			methylxant
			mcg/kg every 8h			es or
			+ oxygen (neb),			additional
			n=25			steroid dos
Fifoot 2007	RCT, 3-	Croup	1) Prednisolone	Antipyretics or	Baseline &	No patient
Australia	arm	6mo-6y	0.2ml/kg of	nebulized	hourly up	suffered an
			1.0mg/kg, single	adrenaline		adverse

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Non-	Pediatri		dose (oral),		to 4h post-	outcomes
industry funded	c ED 1	< 0, <	n=34 2) Dexamethasone 0.2ml/kg of 0.15mg/kg, single dose (oral), n=34 3) Dexamethasone 0.2ml/kg of 0.6mg/kg, single dose (oral), n=31	No CS in preceding wk	treatment; FU 1wk by telephone following index visit	from receiving study steroid, either at index presentation or during the follow-up period. One patient from each group vomited their first dose of medication, all except one (dex 0.6mg/kg)
Fitzgerald 1996 Canada Industry funded	RCT Pediatri c ED 3	Croup 6mo-6y	1) Budesonide 2.0mg (4ml) for 5min (neb), n=35 2) Adrenaline 4.0mg (4ml) for 5min (neb), n=31	Additional medications permitted 2h after study No CS in preceding 4wk	Baseline, 30min, 60min, 90min, 120min, 12h & 24h post- treatment	tolerated second dose. Six patients ir each treatment group reported adverse events. These included vomiting, an erythematous rash, diarrhea,
						wakefulness, excessively active behavior, wheezing, an a nosebleed. These were minor and die not result in withdrawal from the study or require

						specific
						treatment
Francis	RCT	Asthma	1) Fluticasone	NR	D1 to D7	Most freq
1997	(trial	≤48mo	propionate			adverse
Australia	registry		1.0mg twice	No CS treatment		events – o
Funding NR	data)		daily (neb) +	for >7d in		therapy, n
	Acute		placebo tablets	preceding 4wk		vs. pred):
	care		once daily (oral)			Nausea &
	setting		for 7d, n=37			vomiting (
	4		2) Prednisolone			vs. 1);
			(dose NR) daily			Diarrhoea
			for 7d (oral),			vs. 0);
			n=19			Normal to
			_			eruption (
						1);
			5			Ear, nose a
						throat
						infections
						vs. 0);
						Psychomo
						disorders
						vs. 0);
						Temperatu
						regulation
						disturband
						(2 vs. 0);
						Asthma (1
						2);
						Hoarsenes
				U,		ysphonia (
						vs. 2);
						Serious
						adverse
						events - or
						therapy:
						Subjects w
						non-fatal S
						(2 vs. 0): Kotopuria
						Ketonuria,
						glycosuria
						hyperglyca
						ia (1 vs. 0)

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FU interviews at D1 to D4 & D11; FU chart review within 28d of index visit	Acetaminophen & ibuprofen No CS preceding current croup episode	1) Dexamethasone 0.6mg/kg (max. 18mg), single dose, followed by placebo for 2d, 2 doses total (oral), n=46 2) Prednisolone 2.0mg/kg/d (max. 60mg/d) for 3d (oral), n=41	Croup 1-8y	RCT Primary care office 10	Garbutt 2013 USA Non- industry funded

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		~O_				New sleep problems (1 vs. 13); Stomach pa (9 vs. 7); Headache (7 vs. 4); Vomiting (3 vs. 7); Nausea (3 v 4); Dizziness (3 vs. 2); Tremor (1 v 0)
Ghirga 2002 Italy Funding NR	NRCT NR, "ambul atory infants" 1	Wheeze - early URTI before signs of wheeze 7-12mo	1) Beclomethason e 400mcg 3 doses daily for 5d (neb), n=12 2) Control (no intervention), n=13 Multiple courses - 4 treatment periods of 5d (12 infants completed 48 treatment periods in group 1)	NR	Twice daily	At this writing, four years after the study w completed, apparent adverse effects were reported. Plasma cortisol measured in four patient receiving at least 2 treatment periods of 5 days a mont was normal
Gill 2017 Canada Funding NR	Cohort Pediatri c hospital ED 1	Croup >2y (mean 4.7y vs. 4.8y)	 Dexamethasone 0.6mg/kg (max 12mg), single dose, n=22 2) Controls diagnosed with viral URTI (no dexamethasone 	NR No chronic glucocorticoid therapy or any glucocorticoids within 10d of ED visit	AM of admission & D1, D3 & D7	Single-dose oral dexamethas ne 0.6mg/kg for croup is not associat with decreased endogenous glucocortico

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3			or antibiotics)		levels in
4			or antibiotics),		
5			n=5		children.
6					A 3-year-old
7					previously
8					healthy boy
9 10					returned to
11					the ED within
12					24 hours and
13					was given a
4					diagnosis of
5					pneumonia.
16					He was
7 8					discharged
19					home from
20					the ED with
21		0,	5		oral
22					antibiotics,
23 24			\mathbf{N}		and his
24 25			C. X.		symptoms
<u>2</u> 6					
<u>2</u> 7					resolved by 7
28					days. The
29					other, also a
30					3-year-old
31 32			-		boy, returned
33					to the ED 4
34					days after
35					dexamethaso
86					ne
87 88					administratio
89					n for
10					unilateral
41					facial
12					swelling.
13					Serologic
14 15					testing for
15 16					paramyxoviru
10 17					s (mumps)
18					was negative,
19					and he was
50					given a
51					diagnosis of
52 53					viral parotitis.
55 54					His symptoms
55					resolved by 7
56					i conveu by /

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						days. Four participants visited their primary care physician within 7 day of dexamethas ne administratio n. One patie was healthy, another was given a diagnosis of otitis media and treated with oral antibiotics,
				iezo		and two patients who had persister coughs were prescribed salbutamol. None of the participants were admitted to
					2	hospital, and there were n serious adverse events or
Goebel	RCT	Bronchiolitis	1) Prednisone	NR	Clinical	deaths. One patient

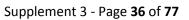
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			2) Placebo			This reso
			solution (oral) +			after a
			albuterol			decrease
			0.3mg/kg/day			the albut
						dose. No
			(or			
			0.15mg/kg/dose			evidence
			(neb)) for 5d			treatme
			(oral), n=24			complica
						was obse
						in any of
						other
						patients
Grant 1996	Cohort	Asthma	1) Prednisone	Bronchodilators as	NR	Ninety-f
USA	Primary	2-14y	2.0mg/kg (max.	needed		episodes
Non-	care		60mg/day),			acute
industry	clinic &		single dose	NR		infectior
, funded	teachin		intermittent for			occurred
	g		6mo (oral),			subjects
	hospital		n=86			222 epis
	ED		2) Placebo (NR),			of sympt
	1		n=86			of infect
	-					occurred
			Multiple			subjects
			courses over 1yr			(table 1
			courses over typ			episodes
				ez		infectior
						number
						doses, a
						associati
						betweer
						doses an
						frequent
						infection
						differend
						was obse
						in the m
						number
						doses of
						predniso
						received
						those wi
						infectior
						compare
						with tho

		< 0, , ,				without the infection. No correlation was observed between the number of doses of prednisone received and the number of episodes of each infection. This included all episodes of otitis media, streptococcal
			C.C.	iez os		pharyngitis, pneumonia, and urinary tract infection; eight (73%) episodes of chickenpox; eight (57%) episodes of skin infections; and 14 (88%) episodes of
Gries 2000 USA Funding NR	RCT Tertiary care center 1	Asthma 6mo-7y	1) Dexamethasone 1.7mg/kg/dose single dose, (IV), n=15 2) Prednisolone 2.2mg/kg/dose, twice daily for 5d (oral), n=17	Albuterol No CS in preceding 2wk	D3, D5, D7, D14 & D28; Urinary cortisol/cre atinine assessed by radioimmu noassay (standard methods) on D14	ringworm. Ten of the 17 children who received PO Pred took the prednisone without much difficulty. However, 3 children missed more than 75% of their doses

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			because of refusal to take their medicine, and another 4 missed approximately one third of the doses despite force and coaxing by their parents. There were no complications from the IM injections including no cases of persistent swelling, bruising, soreness, or atrophy at the injection site. Patients with any personality changes within the first 5 days (%): IM dex - 10/14 (71); oral pred - 14/16 (87). The median urinary cortisol/creati nine value for the IM Dex group was lower than that for the
--	--	--	--



						PO Pred
						group, bu
						this differ
						was not
						statistical
						significant
Hedlin	RCT	Asthma –	1) Budesonide	Beta-agonists	D10 & D13;	There we
1999 ¹	Pediatri	first sign of	400mcg, 4 times	and/or theophylline		no signific
Sweden	С	URTI	daily for 3d then		Routine	difference
Funding NR	hospital	1-3y	twice daily for	NR	height	between
-	1		7d (MDI), n=9		measureme	pretreatm
			2) Placebo, 4		nts	and post-
			times daily for 3		(assessmen	treatmen
			days then twice		t method	serum
			daily for 7d		NR) were	cortisol,
			(MDI), n=11		taken	osteocalc
					(timing of	ICTP and
			Multiple		assessment	cortisol/c
			courses over		s NR);	nine ratio
			1yr, or max. 6		5 NN),	the group
			treatments		Serum	(the
			treatments			-
			****		cortisol (on	compariso
			*subgroup of		D8-10 of	was made
			children from		second	the childr
			Svedmyr 1999		course of	who had
			with		study	assessme
			therapeutic		medication,	before an
			failure from		morning of	after
			budesonide		day after	budesoni
			given 3d course		third dose,	lacebo) no
			(6.0mg, 4.0mg,		and at 12-	were ther
			and 2.0mg on		14d after	any signif
			respective days)		therapy)	difference
			of oral		and urinary	between
			betamethasone		cortisol/cre	active and
					atinine (in	placebo
					the night	treated
					after third	groups. It
					dose of	was, how
					betamethas	notewort
					one and at	that the u
					12-14d	cortisol/c
					after	nine ratio
					therapy)	decreased

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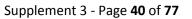
					assessed by radioimmu noassay	5/6 children studied in the active group and in 4/10 in the placebo group. Neither this change nor the difference was statistically significant. PIIINP decreased after both budesonide and placebo treatment periods (p< 0.05). Short courses of oral betamethaso ne have pronounced systemic effects, whereas 10d of high doses of budesonid do not produce significant systemic effects.
Husby 1993 Denmark Funding NR	RCT Pediatri c hospital 1	Croup 3mo-4.9y	1) Budesonide 1000mcg (2ml 500mcg/ml), two doses 30min apart (neb), n=20 2) Placebo saline 0.9% (2ml), two	Antibiotics No CS preceding study	Baseline & 2h post- treatment	No side effects were reported.

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			doses 30min apart (neb),			
			n=16			
Inglis 1993	Case	Croup	Case 1)	Case 1: racemic	NR	Case 1:
USA	report,	18mo;	Prednisolone	epinephrine,		Twenty o
Funding NR	2	14mo	1.0mg/kg, twice	acyclovir sodium		into illne
0	Hospita		daily for 4d (NR)	Case 2:		airway
	1		Case 2)	amoxicillin/clavulan		endosco
			Dexamethasone	ate potassium,		revealed
			0.3mg/kg, 3	cefuroxime sodium		shallow
			doses in 24h			mucosal
			(NR)			ulceratio
			(111)			patient's
						glottis ar
						subglotti
			5			a norma
						appearin
			\mathbf{N}			tracheok
						hial tree
						Cultures
						positive
						HSV-1,
			\sim			
						Staphylo
						s aureus
						a-hemol
						streptoc
						;
						Case 2: C
						day 11 o
						illness, a
						endosco
						revealed
						severe
						subglotti
						edema a
						ulceratio
						purulent
						tracheal
						secretion
						but norn
						tracheal
						mucosa.
						tracheal
						aspirate

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				produced a moderate growth of a- hemolytic streptococci and a few yeast. A swab of the subglottic region showed growth of HSV-1 but no respiratory syncytial virus, influenza A or B, or parainfluenza viruses. The patient required intubation postoperativel y and was started on a regimen of nafcillin sodium and dexamethaso ne sodium phosphate, 1.5mg/kg per day. She was extubated after 48 hours and the dexamethaso ne therapy was discontinued. Her stridor
--	--	--	--	---



						spontane
						y over th
						next 7 da
						without
						further
						intervent
Jan 2000	Non-	Asthma	1) Group A:	NR	D1 to D3	An acute
Taiwan	RCT	NR	Methylprednisol			effect of
Funding NR	Pediatri		one	NR		glucocor
	с		1.0mg/kg/6h			therapy
	hospital		(IV) for 1d,			the
	clinic		n=NR			suppress
	1		2) Group B:			of osteol
			Methylprednisol			was
			one			biochem
			1.0mg/kg/6h			revealed
			(IV) for 2d,			the findi
			n=NR			reduced
			3) Group C:			serum
			Methylprednisol			osteocal
			one			levels; th
			1.0mg/kg/6h			suggests
			(IV) for 3d,			early cha
			n=NR			in serum
			n=NR			osteocal
				C2		may be a useful
						indicator
						patients
						high risk
						bone los
						Levels of
						serum
						osteocal
						progress
						declined
						increasir
						duration
						GC thera
						with ten
						toward a
						decrease
						serum
						phospha

						However, serum calciu levels remained unchanged before and after therapy Osteocalcin levels (μg/L) Group A - 2.7 +/- 3.; Group B - 2.7 +/- 1.9;
			þ			Group C - 1.8 +/- 1.5
Jartti 2006 Finland Non- industry and industry funded	RCT Pediatri c hospital 1	First or second wheeze episode 3mo-35mo	1) Prednisolone 5.0mg tablets, first dose 2.0mg/kg then 2.0mg/kg/day in 3 divided doses for 3d (oral), n=46 2) Placebo tablets, in 3 divided doses for 3d, n=32	Albuterol, beta-2- agonists, antibiotics, & racemic epinephrine No CS in preceding 4 weeks	Study entry & twice daily during hospitalizati on, daily diary notes for 2wk post- discharge; FU visit & phone call 2wk post- discharge	The prednisolone treatment was well tolerated. No clinically significant adverse effects occurred.
Jartti 2007 Finland Non- industry and industry funded	RCT Pediatri c hospital 1	At least third wheeze 3mo-7y	1) Prednisolone 5.0mg tablets, first dose 2.0mg/kg then 2.0mg/kg/day in 3 divided doses for 3d (oral), n=23 2) Placebo for 3d, n=35	Salbutamol & antibiotics No CS in preceding 4wk	Study entry & twice daily during hospitalizati on, daily diary notes for 2wk post- discharge; FU visit & phone call 2wk post- discharge	The prednisolone treatment was well tolerated. No clinically significant adverse effects occurred.
Jartti 2015 Finland	RCT	Wheeze – first acute	1) Prednisolone first dose 2.0mg/kg, then	NR	2wk daily diary; FU at 2wk, 2mo &	There were no differenc in the

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Non-	Univers	rhinovirus-	2mg/kg/d in 2	No previous	12mo post-	incidence o
industry	ity	induced	divided doses	systemic or inhaled	discharge	adverse
and	hospital	3-23mo	for 3d (max.	CS treatment		events
industry	1	(mean	60.0mg/day),			between t
funded		13.2mo vs.	n=34			prednisolo
		12.2mo)	2) Placebo, n=40			and placeb
						groups
			Multiple			(results no
			courses over 1yr			shown). No
						clinically
						significant
						adverse
						events wer
						reported.
Johnson	RCT	Croup	1)	Humidified oxygen	Baseline, 2h	Two patier
1996	Pediatri	mean 15mo	Dexamethasone		& 4h post-	with
Canada	c ED	vs. 17mo	10.0mg (4ml) -	No CS in preceding	treatment	neutropen
Non-	1		10.0mg (<8kg),	2wk		treated wit
industry			15.0mg (8-12kg)			dexametha
funded			or 20.0mg			ne had a
			(>12kg), 10min			clinical cou
			(neb), n=28			consistent
			2) Control,			with bacte
			saline (4ml),			tracheitis.
			10min (neb),			
			n=27			
Johnson	RCT	Croup	1) Budesonide	Racemic	Study entry	No child ha
1998	Pediatri	3mo-9y	4.0mg for 20min	epinephrine & mist	& hourly	gastrointes
Canada	c ED		(neb), n=48	therapy	for 5h post-	al bleeding
Industry	2		2)		treatment	bacterial
funded			Dexamethasone	No CS in preceding	until	tracheitis.
			0.6mg/kg, single	4wk	discharge;	
			dose (IM), n=47		FU 72h	
			3)Placebo		post-	
			suspension, single dose for		discharge	
			20min (neb),			
			n=49			
Klassen	RCT	Croup	1) Budesonide	Racemic	Baseline &	No adverse
1994	Pediatri	3mo-5y	2.0mg (4ml),	epinephrine or	hourly for	events wer
Canada	c ED	5110-59	single dose	dexamethasone, or	4h;	noted in th
Non-	1		(neb), n=27	oxygen tent	FU at 1wk	budesonid
industry			2) Placebo		. O GU IWK	group. No
funded			saline 0.9%			patient in t
lanaca			Sume 0.570			patientint

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			(4ml), single	No CS in preceding		group had
			dose (neb),	2wk		clinical
			n=27			deteriora
						either in
						emergen
						departm
						or after
						discharge
						One pati
						the place
						group ha
						burning
						sensatio
						the face.
Klassen	RCT	Croup	1)	Racemic	Baseline &	Two pati
1996	Pediatri	3m-5y	Dexamethasone	epinephrine &	hourly for	in the
Canada	c ED		0.6mg/kg (oral)	croup tent	4h;	budeson
Non-	1		+ budesonide		FU 1wk	group an
industry			2.0mg (4ml)	No CS in preceding		patient i
funded			(neb), n=25	2 weeks		placebo
			2)			vomited
			Dexamethasone			initial do
			0.6mg/kg (oral)			dexamet
			+ placebo saline			ne withir
			0.9% (4ml)			30min ar
			(neb), n=25			required
				4		readmini
						on of
						dexamet
						ne, whicl
						subseque
						tolerated
						all 3 patie
Klassen	RCT	Croup	1) Budesonide	Epinephrine,	Baseline &	All paren
1998	Pediatri	3mo-5y	2.0mg (4ml)	supplemental	hourly for	were ask
Canada	c ED		(neb) + placebo	glucocorticoids &	, 4h;	about th
Non-	2		syrup (oral),	mist therapy	FU 1wk	presence
industry			n=65		post-	oral thru
funded			2)	No CS in preceding	enrolment	and only
			Dexamethasone	2wk		parent w
			0.6mg/kg (oral)			child was
			+ placebo saline			the
			4ml (neb), n=69			budeson
						group

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			3) Budesonide			reported th
			2.0mg (4ml)			condition a
			(neb) +			the 1-week
			dexamethasone			follow-up.
			0.6mg/kg (oral),			Parents of 2
			n=64			patient
						treated wit
						dexametha
						ne reported
						, hives, and
						parents of
						patient
						treated wit
						dexametha
						ne reported
			6			violent
						behavior.
			\mathbf{O}			Parents of 2
			\mathbf{O}^{\prime}			patient who
						had receive
						budesonide
						and
						dexametha
						ne reported
						their child t
						be more
				4		hyperactive
						than usual.
Киуиси	RCT	Bronchiolitis	1) Epinephrine	NR	Baseline,	No side-
2004	Pediatri	2-21mo	3ml of 1:1000		30min,	effects such
Turkey	с		solution for	No CS in preceding	60min,	as pallor,
Funding NR	outpati		10min (neb) +	2wk	90min &	vomiting or
	ent		dexamethasone		120min,	tremor wer
	clinic		0.6mg/kg, single		then 24h,	encountere
	and ED		dose (IM), n=23		5d;	in the
	1		2) Sal		FU by	patients.
			0.15mg/kg of		regular	
			1mg/ml solution		hospital	
			added to 0.9%		visits in	
			saline for 10min		subsequent	
			(neb) +		2mo	
			dexamethasone			
			0.6mg/kg, single			
	1	1	dose (IM), n=23			

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59

			3) Epinephrine			
			3ml of 1:1000			
			solution for			
			10min (neb) +			
			placebo saline,			
			single dose (IM),			
			n=11			
			4) Sal			
			0.15mg/kg			
			(1mg/ml			
			solution added			
			to 0.9% saline)			
			for 10min (neb)			
			+ placebo			
			saline, single			
			dose (IM), n=12			
Lai 2005	RCT	Asthma	1) Budesonide	Terbutaline (as	On	The meas
China	Hospita	1-5y	0.05mg/kg	needed) 0.25mg/kg	admission,	of blood
Funding NR	I		every 12h (neb),	every 6h to a max.	at	pressure
	pediatri		n=9	of 5.0mg	discharge &	(systolic a
	С		2)		at follow-	diastolic),
	inpatie		Dexamethasone	NR	up;	blood glu
	nt ward		0.1mg/kg every			and serur
	1		8h (neb), n=9 🛛 <		Growth	potassiun
				0	(mean	revealed
			Multiple		height)	significan
			courses over 8-	4	assessed	changes
			19mo		(assessmen	between
					t method	admissior
					NR) at	discharge
					baseline	either gro
					and	of patient
					approximat	(Table 3).
					ely 8-19mo	Thus, the
					after	were no
					randomizati	adverse
					on;	effects in
					Adversel	these
					Adrenal	patients.
					suppression	Table 4 al
					assessed from blood	shows that
					from blood	there we
					pressure	significan difference
		1	1	1	(systolic	atterenc

Funding NR60.0mg/day) (oral), n=35 2) Prednisolone 1.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=33 3) Prednisolone 2.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=33 a) Prednisolone 2.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=3014d72h; FU 2wks post- enrollmentbut hyperactiv post- enrollmentV1.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=3014dFU 2wks post- enrollmenthyperactiv nebulized to agonist therapy way seen. No si effect poss attributable to prednisolo therapy way noted in an of the three treatment groups. Three child in prednisolo	Langton Hewer 1998	RCT Hospita I	Asthma 1-15y	1) Prednisolone 0.5mg/kg/day until discharge	Bronchodilators (nebulized)	and diastolic) and blood glucose at baseline and approximat ely 8-19mo after randomizati on Baseline, Oh, 12h, 24h, 36h,	total height growth, mea rate of heigh increase, systolic or diastolic blood pressure, or blood glucos between the treatment groups. No serious short-term side-effects
	UK Funding NR	1		(oral), n=35 2) Prednisolone 1.0mg/kg/day until discharge (max. 60.0mg/day) (oral), n=33 3) Prednisolone 2.0mg/kg/day until discharge (max. 60.0mg/day)		FU 2wks post-	hyperactivit related to nebulized Bi agonist therapy was seen. No sid effect possil attributable to prednisolon therapy was noted in any of the three treatment groups. Three childr in prednisolon 2.0mg group

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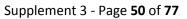
						withdrew
						consent.
Lee 2001	Case	Asthma	1) Terbutaline	NR	D1 to D3	On day 3
Taiwan	report	5y	solution			admissio
Funding NR	Pediatri		(loading dose:			patient w
	c clinic		5.0mg/kg/dose,			found to
	of		maintaining			major
	hospital		dose:			behaviou
	1		0.6mg/kg/h);			changes a
			Methylprednisol			hyperven
			one (BW 21kg,			on. She
			2.0mg/kg/dose,			started
			40.0mg every			screamin
			6h) (IV), and;			unreason
			Procaterol			gazing
			12.5mcg twice			forward a
			daily (oral)			sometim
						upward a
						became p
						She had v
						hallucina
						and delus
Leer 1969	RCT	Bronchiolitis	1)	Mist, oxygen,	Clinical	There we
USA	Hospita	<30mo	Betamethasone,	parenteral fluids &	signs every	no
Industry	1		1.0mg/5lb first	antibiotics	6h	detrimen
funded	5		dose and			corticost
			0.5mg/5lb every	NR		effects in
			12h (total			of the
			3.5mg/5lb (6			patients.
			doses) for 72h)			corticost
			(IM/IV), n=148			neither
			2) Aqueous			increased
			vehicle, 5cc			incidence
			every 12h for			staphylo
			72h for total 6			l or other
			doses (IM/IV),			bacterial
			n=149			pneumor
						nor mask
						superinfe
						s.
Lehmann	Case	Asthma	1)	None	Post skin	Patient h
2008	report	2у	Prednisolone-		prick test	been on
Germany	Pediatri		21-hydrogen	3wk washout		tolerated
Funding NR				period (but under		long-tern

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Allergol	succinate (PSH)	long-term	therapy of
ogy	50.0mg (IV)	maintenance	100mcg
Clinic	2) Prednisone	therapy of daily	inhaled
1	, (100.0mg,	100mcg fluticasone	fluticasone
	suppository)	propionate	dipropionate
	3)	(inhaled) and	daily for
	Betamethasone	intermittent	frequently
	(dose NR, oral)	prednisone	recurring
	4)	suppositories	episodes of
	⁴) Dexamethasone	suppositories	asthmatic
			exacerbation
	(dose NR, IV)		
			, with
			intermittent
			prednisone
			suppositories
			for acute
			bronchopulm
	Peer re		onary
			obstruction
			with no
			occurrence o
			adverse
			events and n
			other
			glucocorticoi
			preparations
		CZ2	Patient was
			admitted to
			department
			due to severe
			bronchospas
			m (neither
			bronchodilat
			rs nor rectall
			administered
			prednisone
			provided
			symptom
			relief) and
			given 50mg o
			prednisolone
			21-hydrogen
			succinate
			intravenously

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0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 6 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 6 7 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 7 8 9 0 0 1 2 3 4 5 5 6 7 7 8 9 0 0 1 2 3 4 5 5 6 7 8 9 0 0 1 2 3 4 5 5 6 7 7 8 9 0 0 1 2 3 1 1 2 3 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 1 2 3 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 1 2 3 1 1 1 2 3 1 1 1 2 3 1 1 1 1 1 1 1 1 1 1 1 1 1		Within a few minutes the boy developed generalized urticaria, facial angio- oedema, nausea and severe dyspnea requiring nasal oxygen supplementati on. Medication was interrupted and symptoms spontaneousl y resolved within 30 minutes. Testing with PSH at a dilution of 1:10 elicited a positive result (wheal diameter 6 mm), whereas no reactions were observed to prednisone, betamethaso ne or dexamethaso ne. An oral provocation test with
1 2		provocation



Leipzig 1979 USA Funding NR	RCT Hospita I 2	Croup 8mo-5y	1) Dexamethasone 0.3mg/kg (4mg/ml) 2 doses 2h apart (IM), n=16 2) Placebo saline, two	Vaponephrine, mist tent therapy & racemic epinephrine NR	Baseline, 12h & 24h NR	titrated intravenous dexametha ne challeng test were tolerated without any complication We observe no adverse effects or la relapses.
Lin 1991 Taiwan Funding NR	NRCT Hospita I 1	Acute wheeze <36mo	doses 2h apart (IM), n=14 1) Group A: <12mo old (n=29): hydrocortisone 5.0mg/kg loading dose (IV) plus 2.5mg/kg/dose every 6h for 3d + meptin liquid (procaterol hydrochloride) 1.25mcg/kg/dos e on admission, then twice daily (oral) 2) Group B: >12mo old (n=23): hydrocortisone 5.0mg/kg loading dose (IV) plus 2.5mg/kg/dose every 6h for 3d + meptin liquid	IV fluid, oxygen & antibiotics NR	Daily for 5d	Regarding side effects two patien in Group B and one patient eac in Groups A and C had tremor. On patient in Group A ha irritability, and anothe had diarrhe

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Lucas- Bouwman 2001 Netherland s Funding NR	RCT Hospita I 1	Asthma 3mo-8y (mean 2y)	(procaterol hydrochloride) 1.25mcg/kg/dos e on admission, then twice daily (oral) 3) Group C: No hydrocortisone or procaterol (n=28) 1) Prednisolone 1.0mg/kg tablets, twice daily for 5d (oral), n=NR 2) Prednisolone 1.0mg/kg	Bronchodilators (inhaled) NR	6d to 8d after index visit	Vomiting observed 23% of patients u crushed tablets, ar none of th
Nahum 2009	Case series	Asthma 5y	solution, twice daily for 5d (oral), n=NR 1) Methylprednisol	NR	D1 & D2; FU 3mo	patients o oral soluti He preser with
Israel Funding NR	(n=3, 1 case relevan t) Pediatri c ED 1		one 2.0mg/kg for 2d (IV)	HEN ON	post- discharge	wheezing, received a intravenou bolus of methylpre olone sodi succinate (2mg/kg), immediate developed restlessne and facial which resolved spontaned y. On the following he receive again the same medicatio and

						immediately developed respiratory distress and cyanosis wit oxygen desaturatio of 89%. He recovered with oxyger supplement on and was treated afterward with oral betamethas
Paniagua	RCT	Asthma		NR	NR;	ne sodium phosphate without adverse events. No
2016 Spain Funding NR	(confer ence abstrac t) Pediatri c ED 1	>12mo	Dexamethasone , NR, 2 doses (oral), n=287 2) Prednisone/pre dnisolone, NR, 5d (NR), n=290	NR	FU at 7d & 15d post- ED visit	differences were found regarding vomits (2.19 vs 4.1%).
Panickar 2009 UK Non- industry funded	RCT Pediatri c ED 3	Wheeze 10-60mo	1) Prednisolone 10.0mg/day (10ml) once daily for 10- 24mo old (oral); 20.0mg/day (10ml) once daily for >24mo old (oral), for 5d, n=343 2) Placebo solution (10ml) once daily for 5d (oral), n=344	Albuterol, oxygen & antibiotics NR	4h, 12h & 24h after albuterol & daily post- discharge; FU by phone 1mo post- discharge	No clinically significant adverse events were reported to the patient safety committee. one child in the prednisolor group, parents attributed excess

						vomitin
						the stu
						drug ar
						discont
						the
						medica
						after
						dischar
						from h
Panigada	Case	Progressive	Albuterol	NR	NR	The chi
2014	report	shortness of	(inhaled) +			sent ho
Italy	Pediatri	breath,	prednisone	NR		inhaled
Funding NR	С	subsequent	1.0mg/kg			albuter
	Pulmon	diagnosis of	(28.70kg) (oral),			predni
	ary and	inflammator	n=1			be tape
	Allergy	y	5			and
	Unit	, myofibrobla				discont
	1	stic tumor				after 7
		cell				days. F
		proliferation				days at
		5y				presen
		<i></i>				1 day a
						the
						discon
						n of
						predni:
						the bo
				ilen o		readm
						becaus
						progre
						shortn
						breath
				4		had
						moder
						severe
						dyspno
						inspira
						and
						expirat
						wheez
						SaO2 v
						in roor
						RR 39
						breath

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surrounded by collagenous

1

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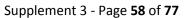
2 3					1		
, 1							displaying
5							strong
5							positivity for
7							vimentin,
3							focal positivity
9							for a-smooth
10 11							muscle actin,
12							and weak
13							positivity for
14							clusterin. No
5							desmin, ALK,
6 7							S100, CD21,
8							and CD 23
19							expression
20							was detected.
21				5			A diagnosis of
22 23							IMT of the
23 24							trachea was
25							performed
26							and a
27							complete
28 29							surgical
30							resection of
31							the neoplasm
32							was carried
33 34							out.
35	Plint 2009	RCT	Bronchiolitis	1) Epinephrine	Bronchodilators	Baseline to	Adverse
6	Canada	Pediatri	6wk-12mo	3ml 1:1000, 2	(albuterol,	30min,	events were
7	Non-	c ED		doses 30min	epinephrine) &	60min,	uncommon
8 9	industry	8		apart (neb) +	antibiotics	120min &	(see
0	and			dexamethasone		240min;	Supplementar
1	industry			1.0mg/kg (max	No CS in preceding	FU daily	y Appendix).
2	funded			10mg) in ED	2wk 🧹	until D7,	Pallor was
3 4				plus 5 once-		then every	reported in 76
14 15				daily		2d until	infants (9.5%),
16				0.6mg/kg/dose,		D14 &	tremor in 15
47				total 6d (oral),		every 3d	(1.9%), and
48				n=200		until D22	vomiting in 14
49 50				2) Epinephrine			(1.8%), with
51				3ml 1:1000, 2			no significant
52				doses 30min			differences
53				apart (neb) +			among the
54 55				placebo, total			groups. One
JJ	1	1	1	6d (oral), n=199		1	hospitalized

				up to 5d, n=50	bromide 250mcg every 6h		hospitalizatio n.
				2ml, 2 doses for	+ ipratropium		during
				2) Sterile saline	0.15mg/kg every 4h		identified
		1		5d, n=50	up to 5d (IV) + sal		effects were
	Funding NR	I		doses for up to	e 1.0mg/kg/day, for	discharge	adverse
	Turkey	Hospita	7-72mo	1.0mg/2ml, 2	methylprednisolon	until	related
ĺ	Razi 2015	RCT	Asthma	1) Budesonide	Standard care:	Every 4h	No drug-
							vs. 0)
							(0 vs. 0 vs. 1
							Hyperkalemia
							vs. 0);
							(0 vs. 1 vs. 1
							Hypertension
							12 vs. 16);
							(17 vs. 14 vs.
							Dark stools
					4		all groups);
							Varicella (0 in
							3);
							vs. 4 vs. 5 vs.
							Vomiting (2
							16);
				ie, c			22 vs. 15 vs.
							Pallor (23 vs.
							4 vs. 5 vs. 2);
							Tremor (4 vs.
							Placebo):
				6			vs. Dex vs.
							+ Dex vs. Epi
				n=201			events, n (Epi
				total 6d (oral),			adverse
				(max 12ml),			effects and
				Placebo solution			y table: side
				apart (neb) +			Supplementar
				doses 30min			rapidly.
				(oral), n=200 4) Placebo 2			resolved
							hypertension, which
				1.0mg/kg (max 10mg), total 6d			
				1.0mg/kg (max			had mild, transient
				apart (neb) + dexamethasone			one in group 3
				doses 30min			group 2 and

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59

				NR		
Roberts	RCT	Croup	1) Budesonide	NR	Baseline,	The adverse
1999	Women	6mo-8y	2.0mg (4ml) for		2h, 6h &	effects in bo
Australia	's and		10min each	No CS in preceding	12h after	groups were
Industry	Childre		dose, every 12h	4wk	first dose,	attributable
, funded	n's		(max. 4 doses)		then 12-	to either
	Hospita		(neb), n=42		hourly up	manifestatio
			2) Placebo for		to 48h if in	s of the
	1		10min each		hospital;	disease stat
	1		dose, every 12h		FU by	or the mode
			-		-	
			(max. 4 doses)		telephone	of drug
			(neb), n=40		1d & 3d	administrat
					post-	n (Table 3).
					discharge	Four patien
						(3 placebo,
						budesonide
						experience
						an
						exacerbatic
						in symptom
						to the point
						causing
						interventio
						treatment
						mode outsi
						of the
						protocol
						nebulised
						adrenaline)
						These
						exacerbatic
						occurred
						shortly afte
						beginning
						nebulisatio
						and were
						apparently
						induced due
						to distress
						caused by
						using the
						nebuliser
						mask. All fo



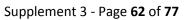
						of these patients had severe croup symptoms (croup score >=8) at the time of nebulisation. The nebulise mask was poorly accepted in up to 18% of patients in this study if the four exacerbation were considered to be mediated by nebuliser- induced emotional distress. Table 3 adverse effec profile, n (Bu vs. placebo): Emotional distress (5 vs 6); Vomiting (2 vs. 3); Rash (0 vs. 2) Eye irritation (1 vs. 1); Irritated tongue (0 vs. 1)
Roorda 1998	RCT Hospita	Croup 4-52mo	1) Fluticasone propionate 1000mcg, 2	NR No CS in preceding	Admission, 30min, 2h,	1) No side effects of the

			30min apart (MDI), n=9 2) Placebo (NR), n=8			during th study.
Roosevelt 1996 USA Non- industry funded	RCT ED 1	Bronchiolitis <12mo	1) Dexamethasone 1.0mg/kg every 24h for max. 3 doses (IM), n=65 2) Placebo saline, every 24h for max. 3 doses (IM), n=53	Antibiotics, bronchodilators & tribavirin NR	Admission & every 12h; FU 1wk post- discharge	Three patients l occult blo in their si two were the dexamet ne group episodes gross haemato a were
Sadowitz 2012 USA Funding NR	Case series (n=4, 1 case relevan t) ED 1	Pharyngitis 3y	Dexamethasone 10.0mg single dose (oral?) + acetaminophen + amoxicillin, n=1	NR	NR	observed The patie was given 10-mg do dexamet ne in add to acetamin n and amoxicill she was a to tolerar liquids ar was discharge The patie returned the ED 2 later with persister complain fever and throat, n with an inability tolerate of fluids. Pertinen

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					physical examination findings included pulse rate of 166 beats per minutes; oral temperature of 40.3 degrees C; dry, erythematous membranes with blood clots; and sores over the tonsils and posterior oropharynx. The tonsils had markedly enlarged from the previous visit. Multiple petechiae were present on the soft palate, with blood noted to be oozing from gums after throat exam. No palpable lymph nodes were found. A completed blood cell (CBC) count demonstrated a white blood cell (WBC) count of 16.4
--	--	--	--	--	---

2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34 45 46 47 48 49 50 51 52 53 54 55 56					x 10^9/L with 50% blasts on the peripheral smear, platelet count of 6 x 10^9/L, and hemoglobin level of 9.8 g/dL. The patient received 2 fluid boluses of normal saline and was admitted to to the pediatric intensive care unit (PICU) and intubated for airway protection because of rapidly enlarging tonsils. Bone marrow aspiration demonstrated acute lymphocytic leukemia (ALL). The patient was placed in the high-risk treatment group because of dexamethaso ne administratio
--	--	--	--	--	---



Japan Funding NR	Pediatri	<3y	1.0mg/dose,	received hydrocortisone (IV)		levels in the BIS and PSL
Saito 2017	RCT	Asthma	1) Budesonide	At admission,	Daily;	Serum cortis
						y at this time
						chemotherap
						maintenance
						continues or
						remission an
						and achieved
						complication
						survived the
						The patient
						and osteonecros
						peritonitis
						ulcer with
						duodenal
				1		by a rupture
						complicated
						was
						of treatmen
						initial course
						The patient's
						vincristine.
						and
						asparaginas
						decadron,
						daunorubici
			5			include IV
						therapy
						Induction
						Group.
						Oncology
						the Children
						established
						high-risk leukemia
						guidelines fo
						following the
						CBC count
						pretreatmer
						absence of a
						ALL and in th

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	depart		twice daily	& one inhalation of	Serum	groups
	ment of		(neb) <i>,</i> n=30	procaterol; LTRA	cortisol	time of
	hospital		2) Prednisolone	for wheezing	assessed	admiss
	1		0.5mg/kg, 3	episodes	(assessmen	were
			times daily (IV),		t method	15.0mc
			n=20	NR	NR) on	and
					admission	17.2m
					and D4 of	(p>0.0
					hospitalizati	respec
					on	Howev
						serum
						on the
						day of
						hospita
						n were
			5			17.0m
						and
						10.9m
						with
						signific
						suppre
						the PS
						Advers
			6	•		events
				0		occur i
						group.
Schuh 2008	RCT	Bronchiolitis	1)	Albuterol	Baseline,	The m
Canada	Pediatri	8wk-23mo	Dexamethasone		D4 & D6	blood
Non-	c ED		1.0mg/kg in ED	Baseline reports 3	(home	pressu
industry	1		+ 4 doses	patients with prior	visits);	increa
funded			0.15mg/kg	inhaled ICS	FU by	from 9
			starting 24h		telephone	8.8 mr
			later, total 5d	-	on D28	99.5+/
			(oral), n=61			mmHg
			2)			single-
			Dexamethasone			group
			1.0mg in ED + 4			from 9
			doses placebo			7.9 mr
			syrup starting			103+/-
			24h later, total			16.8m
			5d (oral), n=64			the mu
						dose g
						Bag ur
			1	1		obtain

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	Schuh 2009 Canada Industry funded	RCT Pediatri c ED 1	Asthma >=2y	1) Montelukast 1.0mg/kg: 2-5y=4.0mg; 6-14y=5.0mg; and, 15-17y=10.0mg at 24h, 48h, 72h, 96h & 120h (oral), n=67 2) Prednisone/pre dnisolone 1.0mg/kg: 2- 5y=4.0mg; 6-14y=5.0mg; and 15- 17y=10.0mg at 24h, 48h, 72h, 96h & 120h (oral), n=63	Albuterol & fluticasone >1 single dose or oral prednisolone or >250mcg per day of inhaled fluticasone within 72h	48h & D8	day 6 visit in 47 study infants and tested positive for glucose in 1 child belonging to the multiple dose group. In the montelukast group, adverse effects developed in 3 patients. One patient experienced facial swellin of unknown etiology at 9 hours, another patient had vomiting and diarrhea at 7 hours, and the third patient complained abdominal and leg pain
required				96h & 120h	0		the third patient complained abdominal and leg pain on day 4. None of the patients

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						"event
						questi
						No adv
						effects
						develo
						the ch
						given
						predn
						after
						discha
Siomou	Case	Bronchiolitis	1)	NR	Baseline, 2	In sum
2003	control,	, viral	Hydrocortisone		days after	short-
Greece	3-arm	wheezing,	10.0mg/kg/day	Never/no CS in last	cs	cortic
Industry	Pediatri	or croup	for 3d (NR),	2mo	administrati	admir
funded	с	2mo-10y	n=28		on & 12d	n to cl
	hospital	,	2)		after end of	sufferi
	1		Methylprednisol		therapy	acute
			one 2.0mg/kg			respira
			for 3 days (NR),			diseas
			n=21			to par
			3) Control, 3d,			revers
			n=51			inhibit
						bone
				iez		forma
						marke
						espec
						detec
						the >1
						old ch
				U,		witho
						affect
						bone
						resorp
						marke
						fall in
						serum
						phosp
						levels
						decrea
						the ma
						renal
						phosp
						reabso
						decrea

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Sparrow	RCT	Croup	1)	Adrenaline	Enrolment,	the maximum renal phosphate reabsorption were significant but transient. No adverse
2006 Australia Funding NR	Pediatri c ED 1	mean 37mo (28.8) vs. 45mo (31.6)	Dexamethasone 0.2ml/kg of 0.15 mg/kg, single dose (oral), n=68 2) Prednisolone 0.2ml/kg of 1.0mg/kg, single dose (oral), n=65	No CS preceding study	30min post- treatment, hourly for next 4h & every 4h until discharge; FU 7d-10d post- discharge	events were noted in either group.
Stafford 1998 Australia Industry and non- industry funded	NRCT Pediatri c hospital or ED 1	Asthma/cro up 1-12y	 Prednisolone 5.0mg/ml solution (oral), n=8 PredMix 5.0mg/ml solution (oral), n=46 3) Dexamethasone 5.0mg/ml (oral), n=80 	NR	Daily	No significant differences were found regarding the incidence of nausea, vomiting and abdominal pain, or any o the objective parameters tested.
Storr 1987 UK Non- industry & industry funded	RCT Pediatri c hospital 1	Asthma NR (mean 5y)	1) Prednisolone 30.0mg (<5yo), otherwise 60.0mg, max. dose 3.0mg/kg (range 1.0- 3.0mg/kg) single dose (oral), n=67 2) Placebo solution identical to treatment,	Salbutamol 5.0mg in 2ml saline (neb), on admission & 3 times or more daily when indicated No CS in preceding 48h	Admission, 4h, 12h, 24h & 36h	Prednisolone has a bitter aftertaste. Most children disliked the drink. 2 children in each group vomited almost immediately and were consequently excluded.

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			single dose			There w
			(oral), n=73			no obse
						side-eff
						related
						single
						prednise
						dose.
Sumboonn	RCT	Croup	1)	Aerosolized	Admission,	Complic
anonda	Pediatri	-	Dexamethasone		24h & 48h;	included
		<5y		adrenaline,	-	
1997	C ·····		0.5mg/kg/d, 3d	antibiotics, IV fluid	FU 3wks	pneumo
Thailand	hospital		(IM/IV), n=14	& cool mist	post-	4 contro
Funding NR	1		2) Control, n=18		discharge	Acineto
				NR		sepsis ir
						control
						bacteria
						tracheit
						cases.
Sung 1998	RCT	Asthma	1) Budesonide	Salbutamol	Baseline,	No adve
Canada	Tertiary	>6mo or	4000mcg (4ml),	0.15mg/kg every	discharge &	effects
Non-	, pediatri	<18y	single dose	30min for 3 doses,	7d to 10d	noted ir
industry	C	/	(neb), n=24	then hourly for 4	post-	either g
funded	- hospital		2) Placebo,	doses	treatment	
Turfucu	1		single dose		treatment	
	Ŧ		(neb), n=20			
Super 1989	RCT	Croup	1)	Mist, racemic	Baseline,	In two
USA	General	NR (mean	Dexamethasone	epinephrine,	30min, and	dexame
Funding NR		16mo)	0.6mg/kg, single		every 12h	ne-treat
Fulluling INK	hospital	10110)		oxygen &	-	
	or		dose (IM), n=16	antibiotics	until	patients
	childre		2) Placebo		discharge	main st
	n's		saline, single			includin
	hospital		dose (IM), n=13			with a
	2					culture-
						positive
						influenz
						viral info
						laryngo
						tis prog
						to
						pneumo
						The oth
						patient
						the one
						received
						second

						injection of dexametha ne. At the time of his second injection, h had roentgenog phic evider of pneumonia We did not encounter side effects directly attributabl to dexametha
Sussman	RCT	Bronchiolitis	1)	Oxygen, penicillin &	Daily	ne. Adverse
1964	Hospita	1-25mo;	Dexamethasone	streptomycin		reactions t
USA	1	Laryngitis	0.1mg in divided			steroid
Non-	NR	15mo-10y	daily dose every	NR		therapy w
industry		-	6h:			not noted
funded			D1-	6		clinical
			9=0.2ml/lb/day;			examinatio
			D10-	4		and
			11=0.1ml/lb/da			superinfec
			у;			s, bacteria
			D12-			viral
			13=0.05ml/lb/d			disseminat
			ay;			, were not
			D14=0.02ml/lb/			encounter
			day (IM), n=31 2) Sodium			
			chloride			
			0.15mEq/ml for			
			14d (IM), n=26			
Svedmyr	RCT,	Asthma	1) Budesonide	Maintenance	NR	Ten adver
1995	crossov	3-10y	0.2mg 4 times	bronchodilators		events we
Sweden	er		daily for first 3d,	permitted		reported i
Funding NR	NR		0.2mg 3 times			the
			daily for next 3d	No CS in preceding		budesonid
			and 0.2mg twice	month		group and

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			daily for last 3d			nine in the
			(neb), n=NR (all			placebo
			groups=26)			group. There
			2) Placebo (NR),			were two
			n=NR (all			cases of
			groups=26)			dysphonia in
			groups-20)			the
			Multiple			budesonide
			Multiple			
			courses;			group. The
			17 children			other events
			completed one			were
			paired (Grp			correlated
			1&2) treatment;			more to the
			15 children			children's
			completed 4			URTI such as
			paired			headache,
			treatments			diarrhoea,
						epistaxis or
						sore throat.
						There were
						no significant
						differences
						between the
						two groups.
Svedmyr	RCT	Asthma –	1) Budesonide	Beta-agonists	Daily for	In the
1999 ¹	Pediatri	first sign of	400mcg, 4 times	and/or theophylline	10d	budesonide
Sweden	с	URTI	daily for 3d then	4		group a 24-
Funding NR	hospital	1-3y	twice daily for	No CS in preceding		month-old gir
	4		7d (MDI), n=28	2mo		discontinued
			2) Placebo, 4			treatment
			times daily for			during the
			3d then twice			first
			daily for 7d			treatment
			, (MDI), n=27			period
			(<i>m</i>			because of a
			Multiple			suspected
			courses over			side effect.
			1yr, or max. 6			The child
			treatments			became
			treatments			emotionally
						unstable and
						vomited after
						inhaling the
	1	1	1	1	1	study drug.

			Almost 1 y
			later, she
			used
			budesonid
			for 10 d w
			no side
			effects at a
			The sympt
			of hoarsen
			a well-kno
			side effect
			with ICS, is
			special
			interest. N
			children
	5		reported 1
			episodes o
			hoarsenes
			the placeb
	6		group,
			compared
			with 2
			children
			reporting
			episodes in
			the
		4	budesonid
			group. This
			difference
			was
			statistically
			significant
			= 0.024).
			Figure 4 –
			chart of
			adverse
			events
			(counts, or
			once per
			treatment
			period),
			including
			vomiting, otitis,
			ouus,

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						hoarse sore th
						conjur
						croup,
						stoma
						diarrh
						agitati
						sleep
						distur
						and
						aggres
						s.
Tagarro	Cohort	Bronchiolitis	1)	Adrenaline &	NR	No sigi
2014	Univers	0-6mo	Dexamethasone	salbutamol		advers
Spain	ity		1.0mg single			effects
Non-	, hospital		dose, or for 6d,	NR		attribu
industry	1		or 1.0mg on			to ster
, funded			first day plus			bronch
			0.6mg for 5d, 6d			rs wer
			total (likely			in the
			oral), n=33			record
			2) Prednisone			from
			1.0-2.0mg for			hyperg
			5d (likely oral),			a.
			n=15			Hyper
			3) No steroids,			a was
			dose/duration	· La		in 4 ou
			NR, n=32	ez		patien
			NN, 11-32			tested
						Two of
						had re
						PRD, o
						them [
						and or
						steroid
Tal 1983	RCT	Acute	1)	Oral/IV fluid &	Admission,	One in
Israel	Hospita	wheeze	Dexamethasone	humidified oxygen	3h after	develo
Non-		1-12mo	0.3mg/kg		first IM	remar
industry	1		(4mg/ml) on	NR	dose &	tremo
funded	-		admission + 0.1		each	side ef
.unucu			mg/kg every 8h		morning	salbuta
			(IM), n=8		(8am) until	No oth
			2) a) Sal solution		discharge	effects
			2.5mg (0.5ml),		alsenange	compli
	1	1	2.5116 (0.5111),			Compl

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			on admission &			of the
			every 6h (neb);			treatment
			b) Sal syrup,			were
			0.15mg/kg,			documented.
			every 8h (oral);			
			and,			
			c) Placebo saline			
			, (IM), n=8			
			3)			
			Dexamethasone			
			0.3mg/kg			
			(4mg/ml) on			
			admission +			
			0.1mg/kg every			
			8h (IM);			
			a) Sal solution			
			2.5mg (0.5ml),			
			on admission &			
			every 6h (neb);			
			and,			
			b) Sal syrup, 📥			
			0.15mg/kg,			
			every 8h (oral),			
			n=8			
			4) Placebo	6		
			saline			
			0.075ml/kg on	4		
			admission, then			
			0.025ml/kg			
			every 8h during			
			next 3d (IM),			
			n=8			
Tamura	Case	Refractory	Methylprednisol	NR 🧹	NR	All cases:
2008	series	mycoplasma	one 30.0mg/kg			There were
Japan	Medical	pneumonia	once daily for	NR		no adverse
Funding NR	center,	5y (n=6 <i>,</i>	3d (IV), n=1			events in any
	inpatie	range 3y-9y)				patients
	nt					during steroid
	1					treatment;
						Case patient
						1: On the 10t
						clinical day,
						we initiated
			1		1	methylpredni

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						olone pulse therapy once daily for 3 days. Six hours after the initiation of steroid
		< 0, <	0			therapy, she became afebrile. On the next day dyspnea was resolved. Chest radiograph o that day showed dramatic
				ien		improvemen Five days after the initiation of steroid therapy, laboratory findings were normalized.
Teeratakul	RCT	Bronchiolitis	1)	Epinephrine,	Baseline &	She was discharged o the 17th day of admission without sequelae. Soon after
pisarn 2007 Thailand Non- industry funded	Pediatri c outpati ent or ED 2	4wk-24mo	Dexamethasone 0.6mg/kg, single dose (IM), n=89 2) Saline solution 0.6mg/kg, single dose (IM), n=85	salbutamol, IV fluids, antimicrobial drugs & oxygen No CS in preceding 2wk	every 6h until study endpoint (resolution of respiratory distress); FU at 2wk	study endpoint, bu before being discharged, systemic CS was prescribed to seven childro

		at least	ne group)
		1mo	because of re
		Into	wheezing.
			None of the
			children
			received
			theophylline
			or ribavirin.
			Three childre
			(two in the
			dexamethaso
			ne group)
			developed
			occult blood
			in stools. Six
	5		children
			(three in the
	2010		dexamethaso
			ne group) had
			subsequent
			diarrhea.
			Three childre
			(all in the
			placebo
			group) had
			subsequent
			pneumonia
			with
			suspicious
			bacterial
			causes and
			required
			additional
			antibiotics.
			Table 5 -
			probable
			adverse
			outcomes of
			treatment up
			to 1 month
			post-
			treatment, n
			(Dex vs.
			Placebo):
I			1 1000000

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						Occult I in stool 1); Pneumo vs. 0);
						Diarrhe
	RCT	Bronchiolitis	1) Due duis a la vie	0	Baseline &	3)
van Woensel 1997 Netherland s	Hospita I 1	<2y	 Prednisolone powder 1.0mg/kg/day in 2 divided doses for 7d (oral), 	Oxygen, bronchodilators, or antibiotics No CS in preceding	daily for 7d	In the p study n clinicall significa side eff
Non- industry funded		0	n=27 2) Placebo in 2 divided doses for 7d (oral), n=27	2mo		prednis were fo
Webb 1986	RCT,	Persistent	1) Prednisolone	Bronchodilator &	Daily for 5d	There w
UK	crossov	wheeze	1.0mg/kg, twice	antibiotics	& clinical	no side
Non-	er	<18mo	daily for 5d		exam 3d	effects
industry	"unit",		(oral), n=NR	NR	after	reporte
funded	outpati		(total patients in		treatment	the par
	ent		study = 38)		course (D8)	and nor
	1		2) Placebo,			detecte
			twice daily for			clinical
			5d (oral), n=18			examin
			crossed over			at the t
			Multiple			review
			Multiple courses;	O,		days aft comple
			38 children	0		the five
			completed a			course
			total of 56			treatme
			treatment			
			courses			
Zhang 2003	RCT	Bronchiolitis	1) Prednisolone	IV hydrocortisone	Enrolment,	The pot
Brazil	Pediatri	<12mo	1.0mg (oral) +	in first 24h after	1mo, 3mo,	side-eff
Non-	С		standard care	hospitalization	6mo &	prednis
industry	hospital		for 5d (NR),		12mo after	were no
funded	ward		n=28	No CS in preceding	discharge	include
	1		2) Standard care	4wk		outcom
			(oxygen, fluid			measur
			replacement, nebulised			this stu the safe

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		fenoterol) for		short-term
		5d (NR), n=24		steroid
				therapy has
				been well
				confirmed. At
				the time of
				analysis of the
				data, all 52
				patients'
				hospital
				records were
				reviewed and
				no adverse
				event was
		•		noted in the
				patients who
		5		received
				prednisolone.
11	1 1000		 	T

¹Hedlin 1999 and Svedmyr 1999 are associated publications; Svedmyr 1999 reports on an RCT comparing budesonide with placebo, and Hedlin 1999 reports systemic effects on a subgroup of these children with moderate to severe asthma exacerbations who required additional treatment (with oral betamethasone) and/or hospitalization;

admin: administration; BW: birthweight; cc: cubic centrimetre(s); CCT: controlled clinical trial; cm: centimeter(s); CS: corticosteroid; d/D: day(s); ED: emergency department; FP: fluticasone propionate; FU: follow-up; g: gram(s); h: hour(s); IM: intramuscular; IV: intravenous; kg: kilogram(s); L: litre(s); max.: maximum; mcg: microgram(s); MDI: metered-dose inhaler; mg: milligram(s); mL: milliliter(s); mo: month(s); neb: nebulized; NR: not reported; NRCT: non-randomized clinical trial; RCT: randomized clinical trial; RSV: respiratory syncytial virus; SA: Saudi Arabia; sal: salbutamol; UK: United Kingdom; URTI: upper respiratory tract infection; vs: versus; wk: week(s); y: year(s); yo: year old

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Supplement 4. Methodological quality assessments of included studies								

4 5 6 7						Mode of co	ollection		d of	of AE			pecified	fied	pecified	
8 9 10 11 12 13 14 15	Study (year)	Harms pre-defined	Serious AE defined	Severe AE defined	Deaths specified	ACTIVE	PASSIVE	Who collected AE	Training/ background of assessors	Timing/ frequency o collection	Checklist used for AE	Encompass all AE	Withdrawal and losses to follow-up specified	AE in each arm specified	No. and type of AE specified	Type of analysis
16	Alangari (2014)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	N	Y	Ν	Ν	Ν	Ν
17 18	Alansari (2013)	Ν	Ν	Ν	N	Y	Ν	Y	Y	Y	Ν	Y	Y	Ν	Ν	Ν
19	Aljebab (2017)	Y	Ν	Ν	Ν	Y	Υ	Y	Y	Y	U	Y	Y	Ν	Y	Y
20	Alshehr (2005)	Ν	Ν	Ν	Ν	Ν	N	Ν	Ν	Ν	Ν	Y	Ν	Ν	Y	Ν
21	Altamimi (2006)	Ν	Ν	Ν	Ν	Y	Ν	Y	Y	Y	Ν	Y	Y	Ν	Y	Ν
22 23	Bacharier (2008)	Ν	Ν	Ν	Ν	Ν	N	N	N	Ν	Ν	Y	Y	Ν	Ν	Ν
24	Bisgaard (2006)	Y	N	N	N	Y	Ν	Ν	N	Y	Ν	Ν	Y	Y	U	Υ
25	Bjornson (2004)	N	N	N	N	Y	Ν	Y	Y	Y	Ν	Y	N	N	Y	Ν
26 27	Brunette (1988)	Y	N	N	N	Y	Ν	N	Ν	Y	Y	Y	N	N	Y	Y
27	Buckingham															
29	(2002)	Ν	Ν	Ν	Y	Y	Ν	Y	Y	Y	Ν	Y	Ν	Ν	Y	Ν
30	Bulow (1999)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	N	N	Y	Ν	Υ	Ν	Ν
31 32	Chang (2008)	Ν	Ν	Ν	Ν	Υ	Ν	Ν	Ν	Y	Ν	Y	Y	Υ	Y	Ν
33	Chen (2008)	N	N	N	N	Ν	Ν	N	Ν	Ν	N	Y	N	N	N	Ν
34	Chub-Appakarn															
35	(2007)	N	N	N	N	Ν	Ν	N	Ν	Ν	Ν	Y	N	N	N	Ν
36 37	Clavenna (2014)	Ν	Ν	Ν	Ν	Y	Y	Y	Y	Y	Ν	Y	Y	Ν	Ν	Ν
38	Connett (1994)	Ν	N	N	N	Ν	Ν	Ν	Ν	Ν	Ν	Y	N	N	Y	Ν
39	Connolly (1969)	Ν	N	N	Y	Y	Ν	Ν	Ν	Y	Ν	Y	N	N	Y	Ν
40 41	Corneli (2007)	Ν	Ν	Ν	Ν	Y	Ν	Υ	Υ	Υ	Ν	Y	Y	Ν	Ν	Ν

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1																
2 3	Cronin (2016)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N
4 5	Csonka (2003)	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N
6	Daugbjerg (1993)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
7	Dawson (1993)	N	N	N	N	Y	Y	Y	Y	Y	U	Y	N	N	N	N
8 9	Ducharme (2009)	Y	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
9 10	Eboriadou (2010)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	U	Ν
11	Eden (1967)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	U	Ν
12	Escobedo Chavez															
13 14	(1992)	N	Ν	Ν	N	N	Ν	N	N	N	Ν	Y	Ν	N	N	Ν
15	Fifoot (2007)	Ν	Ν	Ν	N	N	Ν	Ν	Ν	Ν	N	Y	Y	Ν	Ν	Ν
16	Fitzgerald (1996)	Ν	Ν	Ν	Ν	U	U	Ν	Ν	Y	Ν	Y	Υ	Ν	Ν	Υ
17 18	Francis (1997)	Ν	Y	Ν	N	N	Ν	Ν	Ν	Ν	Ν	U	Y	Y	Ν	Ν
19	Garbutt (2013)	Ν	Ν	Ν	Ν	Y	N	Y	Y	Y	Ν	Y	Ν	Ν	Ν	Ν
20	Ghirga (2002)	Ν	Ν	Ν	Ν	Ν	N	Ν	Ν	Ν	Ν	Y	Ν	N	Ν	Ν
21 22	Gill (2017)	Ν	Ν	Ν	Y	Y	Ν	Ν	Ν	Y	Ν	Y	Ν	N	Y	Y
22	Goebel (2000)	Ν	Ν	Ν	Ν	Y	N	Y	Y	Y	Ν	Ν	Ν	N	Y	Ν
24	Grant (1996)	Ν	Ν	Ν	Ν	Y	Y	Ν	Ν	Y	Ν	Y	Ν	N	Ν	Y
25	Gries (2000)	Ν	Ν	Ν	N	Y	Ν	Y	Y	Y	Ν	Y	Ν	N	Y	Y
26 27	Hedlin (1999) ¹	N	Ν	Ν	N	Y	Ν	Y	Ν	Y	Y	Y	Ν	Y	Y	Y
28	Husby (1993)	N	Ν	Ν	N	U	Ν	Y	N	Y	N	Y	Ν	N	Ν	Ν
29	Inglis (1993)	N	Ν	Ν	Y	Y	Y	N	N	Υ	N	Y	Y	Y	Y	Ν
30 31	Jan (2000)	N	Ν	N	N	Y	Ν	N	N	Y	Y	Y	Ν	Ν	N	Ν
32	Jartti (2006)	N	Ν	Ν	N	Ν	Ν	N	N	N	N	Y	Ν	Ν	N	Ν
33	Jartti (2007)	N	Ν	Ν	N	Ν	Ν	N	N	Ν	Ν	Y	Ν	N	Ν	Ν
34 35	Jartti (2015)	Ν	Ν	Ν	N	Ν	Ν	N	N	N	N	U	Y	Ν	N	Ν
35 36	Johnson (1996)	N	Ν	Ν	N	Ν	Ν	N	N	Ν	Ν	Y	Ν	N	Y	Ν
37	Johnson (1998)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	U	Ν	N	Y	Ν
38	Klassen (1994)	Ν	Ν	Ν	N	N	N	N	N	Ν	Ν	Y	Ν	N	Y	Ν
39 40	Klassen (1996)	N	Ν	Ν	N	Ν	N	N	N	Ν	Ν	Y	Ν	N	Y	Ν
41	Klassen (1998)	Ν	Ν	Ν	Ν	Y	Y	Y	Y	U	Ν	Y	Y	Ν	Y	Ν

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1 2																
3	Киуиси (2004)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
4 5	Lai (2005)	N	N	N	N	Y	Ν	Ν	Ν	Y	Y	Y	N	N	N	Y
6	Langton-Hewer															
7	(1998)	N	Ν	N	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	N	Y	Ν
8 9	Lee (2001)	N	N	N	Y	Y	N	Ν	Ν	Y	Ν	Y	Y	Y	Y	N
10	Leer (1969)	N	N	N	Ν	Ν	N	N	Ν	N	Ν	Y	N	Y	Y	Ν
11	Lehmann (2008)	N	N	N	Y	Y	N	N	Ν	Y	Ν	Y	Y	Y	Y	N
12	Leipzig (1979)	N	N	N	N	Ν	Ν	Ν	Ν	Ν	Ν	Y	N	N	N	N
13 14	Lin (1991)	N	N	N	N	Ν	Ν	Ν	Ν	Ν	Ν	Y	N	N	Y	N
15	Lucas-Bouwman															
16	(2001)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Y	N	Y	Ν
17 18	Nahum (2009)	N	Ν	Ν	Y	Y	Ν	Ν	Ν	Υ	Ν	Y	Y	Y	Υ	Ν
10	Paniagua (2017)	N	Ν	Ν	Ν	Y	N	N	Ν	N	Ν	Y	N	N	Y	Ν
20	Panickar (2009)	N	Ν	Ν	Ν	Y	Y	Υ	Y	Υ	Ν	Y	N	N	Y	Ν
21	Panigada (2014)	N	N	N	Ν	Y	N	Ν	Ν	Y	Ν	Y	Y	Y	Y	Ν
22 23	Plint (2009)	N	Ν	Ν	Ν	Y	N	Υ	Y	Υ	Ν	Y	Ν	N	Υ	Ν
24	Razi (2015)	N	N	N	Ν	Ν	Ν	Ν	N	N	Ν	Y	N	N	Ν	Ν
25	Roberts (1999)	N	N	N	N	Ν	N	N	Ν	N	Ν	Y	N	N	Y	N
26	Roorda (1998)	N	N	N	Ν	Ν	Ν	Ν	Ν	N	Ν	Y	N	N	N	N
27 28	Roosevelt (1996)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	Ν
29	Sadowitz (2012)	N	N	N	N	Y	Y	Ν	Ν	γ	N	Y	Y	Y	Y	N
30	Saito (2017)	N	N	N	N	Y	N	Ν	Ν	N	N	Y	N	N	N	N
31 32	Schuh (2008)	N	N	N	Ν	Y	Ν	Y	Y	Y	Y	Y	N	N	N	N
33	Schuh (2009)	N	N	N	N	Ν	Ν	Ν	Ν	Ν	Ν	Y	Y	N	Y	N
34	Siomou (2003)	Y	N	Ν	N	Y	Ν	Ν	Ν	Y	U	Y	N	N	N	Ν
35 36	Sparrow (2006)	N	Ν	N	Ν	Ν	N	Ν	Ν	N	Ν	Y	Ν	N	Ν	Ν
30 37	Stafford (1998)	Y	N	N	N	Y	Ν	Ν	Ν	Y	Y	Y	N	N	Y	Ν
38	Storr (1987)	N	N	N	N	Ν	Ν	Ν	Ν	N	Ν	Y	N	N	N	Ν
39	Sumboonnanonda		1													
40 41	(1997)	Ν	Ν	N	Ν	Y	Ν	Ν	Ν	Y	Ν	Y	Ν	Ν	Y	Ν

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2																
3	Sung (1998)	N	N	Ν	N	Y	Y	Y	Y	N	N	Y	N	Ν	Ν	Ν
4 5	Super (1989)	N	N	N	N	N	N	Ν	Ν	N	N	Y	N	N	Ν	Ν
6	Sussman (1964)	N	N	N	Ν	Y	N	Ν	Ν	N	N	Y	N	N	Y	Ν
7	Svedmyr (1995)	N	N	Ν	N	N	N	Ν	N	N	N	Y	Ν	Y	N	N
8 9	Svedmyr (1999) ¹	Ν	Ν	Ν	Ν	Υ	Ν	Y	Ν	Y	Y	Y	Ν	Y	Y	Y
10	Tagarro (2014)	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Υ	Ν
11	Tal (1983)	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
12 13	Tamura (2008)	Ν	Ν	N	N	Y	Ν	Ν	Ν	Ν	Ν	Y	Ν	N	Ν	Ν
14 15	Teeratakulpisarn (2007)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
16	van Woensel															
17 18	(1997)	Ν	Ν	Ν	Y	N	Ν	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
19	Webb (1986)	Ν	Ν	Ν	Ν	Y	Y	Ν	Ν	Y	Ν	Y	Ν	Ν	Ν	Ν
20	Zhang (2003)	Ν	Ν	Ν	Ν	Y	N	Ν	Ν	Ν	Ν	Y	Ν	Ν	Ν	Ν
21 22					associated	l publication	s; the two pa	apers are	assessed	as one st	udy					
23 24 25 26	N: no; No REFEREN(, o. unsu	iic, ii yes												
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41	 1. Chou R, Aronson N, Atkins DL, et al. Accessing harms when comparing medication interventions. In: Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD; 2008. 2. Additional and the second seco															
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Supplement 5	Effect estimates for all adverse events with subgroups	
	a. Infection & respiratory system	р. 2-4
	b. Gastro-intestinal tract	p. 5-7
	c. CNS & behaviour effects	p. 8-9
	d. Dermatologic conditions	p. 10
	e. Endocrine/ metabolic & musculoskeletal systems	p. 11
	f. Cardiovascular system	p. 12
	g. General adverse events/ other symptoms	p. 13

h. Immune system & oncology

The tables below report results of meta-analyses for adverse events, organized by organ systems.

Effect estimates were calculated for studies with more than one treatment arm, using risk difference (RD) for all comparative studies and, using Peto odds ratio (pOR) for studies that reported at least one event in at least one treatment arm. Shaded rows indicate all studies contributing to an outcome, for the specified comparison, without subgroup analysis. When data was available, subgroup analyses (non-shaded rows) using study-level data were conducted for dose (single versus multi-dose) and for respiratory condition (e.g., bronchiolitis).

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Supplement 5a. Infection & respiratory system

Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD	l ²	Peto OR	l ²
	vs.		of	1 – no. of	2 – no. of	(95% CI)	(%)	(95% CI)	(%)
	Comparison 2		studies	patients with	patients with				
				events/total	events/total				
				no. of	no. of				
				patients	patients				
Severe infections, overall	Systemic vs.		4	0/552	2/554	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
	placebo								
Severe infections, by dose	Systemic vs.	Single dose	1	0/359	1/361	0.00 (-0.01, 0.00)	NA	0.14 (0.00, 6.86)	NA
	placebo								
	Systemic vs.	Multi-dose	3	0/193	1/193	0.00 (-0.01, 0.01)	0	0.17 (0.00, 8.79)	NA
	placebo		0						
Severe infections, by	Systemic vs.	Bronchiolitis	2	0/179	0/175	0.00 (-0.01, 0.01)	0	NA	NA
condition	placebo								
	Systemic vs.	Croup	2	0/373	2/379	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
	placebo								
Severe infections, overall	Inhaled vs. placebo		1	2/62	4/67	-0.03 (-0.10,	NA	0.54 (0.11, 2.77)	NA
						0.04)			
Systemic infections, overall	Systemic vs.		4	5/1095	4/1083	0.00 (0.00, 0.00)	0	1.26 (0.34, 4.68)	NA
	placebo								
Systemic infections, by	Systemic vs.	Single dose	2	5/664	4/656	0.00 (-0.01, 0.01)	0	1.26 (0.34, 4.68)	NA
dose	placebo								
	Systemic vs.	Multi-dose	2	0/431	0/427	0.00 (-0.01, 0.01)	0	NA	NA
	placebo								
Systemic infections, by	Systemic vs.	Bronchiolitis	2	0/705	0/695	0.00 (0.00, 0.00)	0	NA	NA
condition	placebo								
	Systemic vs.	Croup	1	5/359	4/361	0.00 (-0.01, 0.02)	NA	1.26 (0.34, 4.68)	NA
	placebo								
	Systemic vs.	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
	placebo								

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Systemic infections, overall	Inhaled vs. placebo	Multi-dose, wheeze	2	18/91	20/94	0.00 (-0.06, 0.06)	0	0.96 (0.45, 2.05)	NA
Lung/trachea, overall	Systemic vs. placebo		7	18/955	28/928	-0.01 (-0.02, 0.01)	37	0.61 (0.34, 1.12)	0
Lung/trachea, by dose	Systemic vs. placebo	Single dose	5	6/793	9/761	0.00 (-0.01, 0.00)	0	0.57 (0.20, 1.62)	0
	Systemic vs. placebo	Multi-dose	2	12/162	19/167	-0.09 (-0.29, 0.10)	69	0.63 (0.30, 1.33)	57
Lung/trachea, by condition	Systemic vs. placebo	Bronchiolitis	3	12/542	19/529	-0.02 (-0.05, 0.02)	61	0.61 (0.29, 1.28)	30
	Systemic vs. placebo	Croup	4	6/413	9/399	-0.02 (-0.12, 0.07)	40	0.61 (0.21, 1.76)	6
Lung/trachea, overall	Inhaled vs. placebo	Multi-dose, wheeze	1	13/62	10/67	0.06 (-0.07, 0.19)	NA	1.51 (0.61, 3.70)	NA
URT, overall	Systemic vs. placebo		6	9/671	7/656	0.00 (-0.01, 0.01)	0	1.21 (0.44, 3.33)	0
URT, by dose	Systemic vs. placebo	Single dose	4	1/492	1/480	0.00 (-0.01, 0.01)	0	0.46 (0.02, 10.18)	0
	Systemic vs. placebo	Multi-dose	2	8/179	6/176	0.01 (-0.03, 0.05)	0	1.36 (0.47, 3.96)	NA
URT, by condition	Systemic vs. placebo	Bronchiolitis	1	8/148	6/149	0.01 (-0.03, 0.06)	NA	1.36 (0.47, 3.96)	NA
URT, by condition	Systemic vs. placebo	Croup	4	1/492	1/480	0.00 (-0.01, 0.01)	0	0.46 (0.02, 10.18)	0
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
URT, overall	Inhaled vs. placebo		6	24/495	24/499	0.00 (-0.02, 0.02)	0	1.03 (0.57, 1.85)	21
URT, by dose	Inhaled vs. placebo	Single dose	3	2/140	0/144	0.00 (-0.02, 0.03)	14	7.40 (0.45 <i>,</i> 121.47)	NA
	Inhaled vs. placebo	Multi-dose	3	22/355	24/355	-0.01 (-0.04, 0.03)	0	0.93 (0.51, 1.71)	0

URT, by condition	Inhaled vs. placebo	Croup	3	2/140	0/144	0.00 (-0.02, 0.03)	14	7.40 (0.45,	NA
								121.47)	
	Inhaled vs. placebo	Wheeze	3	22/355	24/355	-0.01 (-0.04, 0.03)	0	0.93 (0.51, 1.71)	0
Voice complaints, overall	Systemic vs. placebo		1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
Voice complaints, overall	Inhaled vs. placebo	All multi- dose	4	38/343	43/337	-0.01 (-0.10, 0.07)	64	0.85 (0.53, 1.36)	73
Voice complaints, by condition	Inhaled vs. placebo	Asthma	2	4/50	9/49	-0.08 (-0.46, 0.31)	90	0.39 (0.12, 1.26)	81
	Inhaled vs. placebo	Wheeze	2	34/293	34/288	0.00 (-0.04, 0.04)	0	0.99 (0.59, 1.64)	NA

al; NA not applicable, com RD: risk difference; CI: confidence interval; NA not applicable/estimable; no.: number; Peto OR: Peto odds ratio; URT=upper respiratory tract;

vs.: versus

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Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients with events/total no. of patients	Comparison 2 – no. of patients with events/total no. of patients	RD (95% CI)	l ² (%)	Peto OR (95% CI)	² (%
Bleeding, overall	Systemic vs. placebo		7	31/1287	31/1262	0.00 (0.00, 0.00)	0	1.00 (0.60, 1.67)	0
Bleeding, by dose	Systemic vs. placebo	Single dose	4	2/800	1/790	0.00 (0.00, 0.00)	0	1.87 (0.19, 18.27)	NA
	Systemic vs. placebo	Multi-dose	3	29/487	30/472	0.00 (-0.02, 0.02)	0	0.96 (0.57, 1.64)	0
Bleeding, by condition	Systemic vs. placebo	Bronchiolitis	5	31/881	31/852	0.00 (-0.01, 0.01)	0	1.00 (0.60, 1.67)	0
	Systemic vs. placebo	Croup	2	0/406	0/410	0.00 (-0.01, 0.01)	0	NA	NA
Bleeding, overall	Inhaled vs. placebo	Single dose, croup	1	0/48	0/49	0.00 (-0.04 <i>,</i> 0.04)	NA	NA	NA
Vomiting, overall	Systemic vs. placebo		7	38/1603	34/1573	0.00 (0.00, 0.01)	0	1.10 (0.69, 1.76)	17
Vomiting, by dose	Systemic vs. placebo	Single dose	4	21/747	23/712	0.00 (-0.02, 0.01)	0	0.87 (0.47, 1.59)	24
	Systemic vs. placebo	Multi-dose	3	17/856	11/861	0.00 (-0.01, 0.02)	37	1.58 (0.75, 3.36)	0
Vomiting, by condition	Systemic vs. placebo	Asthma	1	1/37	5/33	-0.11 (-0.27, 0.06)	33	0.19 (0.03, 1.02)	0
	Systemic vs. placebo	Bronchiolitis	3	24/751	21/718	0.00 (-0.02, 0.02)	0	1.12 (0.62, 2.04)	0
	Systemic vs. placebo	Croup	1	3/359	4/361	0.00 (-0.02, 0.01)	NA	0.75 (0.17, 3.34)	N/

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	Systemic vs. placebo	Wheeze	2	10/456	4/461	0.02 (-0.06, 0.11)	87	2.55 (0.87, 7.46)	0
Vomiting, overall	Inhaled vs. placebo		5	28/421	28/420	0.00 (-0.03, 0.04)	0	1.00 (0.58, 1.72)	0
Vomiting, by dose	Inhaled vs. placebo	Single dose	1	2/25	1/25	0.04 (-0.09, 0.17)	NA	2.00 (0.20, 20.20)	N
	Inhaled vs. placebo	Multi-dose	4	26/396	27/395	0.00 (-0.03, 0.03)	0	0.96 (0.55, 1.67)	0
Vomiting, by condition	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06, 0.13)	NA	7.13 (0.14, 359.55)	N
	Inhaled vs. placebo	Croup	2	4/67	4/65	0.00 (-0.08, 0.08)	0	0.97 (0.23, 4.00)	0
	Inhaled vs. placebo	Wheeze	2	23/326	24/328	0.00 (-0.04, 0.04)	0	0.96 (0.53, 1.74)	0
Vomiting, overall	Dexamethasone vs. other steroid		6	12/663	51/710	-0.06 (-0.09 <i>,</i> - 0.02)	58	0.29 (0.17, 0.48)	0
Vomiting, by dose	Dexamethasone vs. other steroid	Single dose	5	6/376	39/420	-0.07 (-0.11, - 0.02)	47	0.23 (0.12, 0.42)	0
	Dexamethasone vs. other steroid	Multi-dose	1	6/287	12/290	-0.02 (-0.05, - 0.01)	NA	0.51 (0.20, 1.30)	N
Vomiting, by condition	Dexamethasone vs. other steroid	Asthma	3	6/466	28/466	-0.05 (-0.11, 0.00)	77	0.26 (0.13, 0.52)	52
	Dexamethasone vs. other steroid	Croup	2	5/111	8/75	-0.04 (-0.16, 0.08)	64	0.46 (0.14, 1.45)	0
	Dexamethasone vs. other steroid	Other conditions	1	1/86	15/169	-0.08 (-0.13, - 0.02)	3	0.25 (0.09, 0.72)	0
Abdominal pain, overall	Systemic vs. placebo	Single dose, croup	1	1/359	1/361	0.00 (-0.01, 0.01)	NA	1.01 (0.06, 16.11)	N
Abdominal pain, overall	Dexamethasone vs. other steroid		3	29/188	48/264	-0.01 (-0.07, 0.05)	0	0.96 (0.57, 1.61)	0

1 2										
3 4 5	Abdominal pain, by condition	Dexamethasone vs. other steroid	Asthma	1	2/56	3/54	-0.02 (-0.10, 0.06)	NA	0.64 (0.11, 3.79)	NA
5 6 7			Croup	1	9/46	7/41	0.02 (-0.14, 0.19)	NA	1.18 (0.40, 3.47)	NA
8 9 10			Other conditions	1	18/86	38/169	-0.01 (-0.12, 0.10)	0	0.94 (0.50, 1.77)	0
10 11 12	Diarrhea, overall	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03, 0.04)	0	1.09 (0.43, 2.73)	0
13 14 15	Diarrhea, by dose	Systemic vs. placebo	Single dose	1	3/89	3/85	0.00 (-0.06, 0.05)	NA	0.95 (0.19, 4.84)	NA
16 17		Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
18 19 20	Diarrhea, by condition	Systemic vs. placebo	Bronchiolitis	1	3/89	3/85	0.00 (-0.06, 0.05)	NA	0.95 (0.19, 4.84)	NA
20 21 22		Systemic vs. placebo	Wheeze	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
23 24	Diarrhea, overall	Inhaled vs. placebo	Multi-dose, wheeze	2	41/326	46/328	-0.01 (-0.09, 0.08)	37	0.89 (0.57, 1.40)	44
25 26 27	RD: risk differe	nce; CI: confidence interval; NA: i	not applicable/e	stimable;	no.: number;			us		
28 29										
30 31										
32 33 34										
35 36										
37 38 39										
39 40 41										
42 43							Supp	olement	5 - Page 7 of 14	
44 45		For peer rev	view only - http://	′bmjopen.k	omj.com/site/a	bout/guidelines.x	html			

Supplement 5c. CNS & behavior effects

4 5 6	Adverse event	Comparison 1 vs.	Subgroup	No. of	Comparison 1 – no. of	Comparison 2 – no. of	RD (95% CI)	l ² (%)	Peto OR (95% CI)	l ² (%)
7 8 9 10 11 12		Comparison 2	•	studies	patients with events/total no. of patients	patients with events/total no. of patients				
13 14	Tremor/jitteriness, overall	Systemic vs. placebo		5	22/559	14/508	0.01 (-0.01, 0.03)	0	1.44 (0.71, 2.92)	0
15 16 17	Tremor/jitteriness, by dose	Systemic vs. placebo	Single dose	2	9/83	7/56	0.00 (-0.08, 0.08)	0	1.15 (0.36, 3.66)	0
18 19		Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
20 21 22	Tremor/jitteriness, by condition	Systemic vs. placebo	Asthma	1	9/37	7/33	0.01 (-0.16, 0.18)	0	1.15 (0.36, 3.66)	0
23			Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
24			Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
25 26 27	Tremor/jitteriness, overall	Dexamethasone vs. other steroid	Single dose, croup	1	1/46	0/41	0.02 (-0.04, 0.08)	NA	6.63 (0.13, 336.21)	NA
28 29	Behaviour change, overall	Systemic vs. placebo		4	7/588	3/571	0.00 (-0.01, 0.02)	19	1.95 (0.55, 6.92)	0
30 31 32	Behaviour change, by dose	Systemic vs. placebo	Single dose	2	1/423	1/426	0.00 (-0.01, 0.01)	0	1.01 (0.06, 16.11)	NA
33 34		Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
35 36 37	Behaviour change, by condition	Systemic vs. placebo	Croup	2	1/423	1/426	0.00 (-0.01, 0.01)	0	1.01 (0.06, 16.11)	NA
37 38 39		Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
40	Behaviour change, overall	Inhaled vs. placebo		3	6/134	7/135	-0.01 (-0.04, 0.03)	0	0.81 (0.26, 2.54)	0

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Behaviour change, by dose	Inhaled vs. placebo	Single dose	1	0/64	1/68	-0.01 (-0.06, 0.03)	NA	0.14 (0.00, 7.25)	NA
	Inhaled vs. placebo	Multi-dose	2	6/70	6/67	0.02 (-0.06, 0.10)	0	0.95 (0.28, 3.15)	11
Behaviour change, by condition	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06, 0.13)	NA	7.13 (0.14, 359.55)	NA
	Inhaled vs. placebo	Croup	2	5/106	7/108	-0.02 (-0.05, 0.02)	0	0.66 (0.20, 2.18)	0
Behaviour change, overall	Dexamethasone vs. other steroid	All single dose	2	35/60	38/57	-0.08 (-0.25, 0.09)	0	0.73 (0.34, 1.56)	0
2 Behaviour change, by 3 condition	Dexamethasone vs. other steroid	Asthma	1	10/14	14/16	-0.16 (-0.45, 0.13)	NA	0.38 (0.06, 2.21)	NA
5	Dexamethasone vs. other steroid	Croup	1	25/46	24/41	-0.04 (-0.25, 0.17)	NA	0.85 (0.36, 1.97)	NA
7 Headache, overall 3	Systemic vs. placebo	Single dose, asthma	1	0/37	1/33	-0.02 (-0.10, 0.07)	0	0.11 (0.00, 5.68)	NA
Headache, overall	Dexamethasone vs. other steroid	All single dose	2	7/102	4/95	0.02 (-0.08, 0.11)	51	1.63 (0.46, 5.74)	NA
2 Headache, by condition	Dexamethasone vs. other steroid	Asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	NA	NA	NA
		Croup	1	7/46	4/41	0.05 (-0.08, 0.19)	NA	1.63 (0.46, 5.74)	NA
6 RD: risk difference 7 8	; CI: confidence interva	al; NA: not appl	icable/es	timable; no.: nui	nber; Peto O	R: Peto odds ratio; vs.: v	ersus		

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Supplement 5d. Dermatologic conditions

	Adverse event	Comparison 1 vs.	Subgroup	No. of	Comparison 1 – no. of	Comparison 2 – no. of	RD (95% CI)	²	Peto OR (95% CI)	l ² (%)
) 1 2		vs. Comparison 2		studies	patients with events/total no. of patients	patients with events/total no. of patients	(93% CI)	(%)	(95% CI)	(70)
3 4	Burn, overall	Inhaled vs. placebo	Single dose, croup	1	0/27	1/27	-0.04 (-0.13, 0.06)	NA	0.14 (0.00, 6.82)	NA
5 7	Integument, overall	Systemic vs. placebo		3	4/536	0/543	0.01 (0.00, 0.01)	0	7.59 (1.07, 54.01)	0
3	Integument, by dose	Systemic vs. placebo	Single dose	2	2/423	0/426	0.01 (0.00, 0.01)	0	7.45 (0.47, 119.36)	NA
) 1 2		Systemic vs. placebo	Multi-dose	1	2/133	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
3	Integument, by condition	Systemic vs. placebo	Croup	2	2/423	0/426	0.01 (0.00, 0.01)	0	7.45 (0.47, 119.36)	NA
5		Systemic vs. placebo	Wheeze	1	2/113	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
3	Integument, overall	Inhaled vs. placebo		4	24/432	27/436	-0.01 (-0.04, 0.02)	11	0.88 (0.50, 1.56)	37
)	Integument, by dose	Inhaled vs. placebo	Single dose	1	0/64	1/68	-0.01 (-0.06, 0.03)	NA	0.14 (0.00, 7.25)	NA
)		Inhaled vs. placebo	Multi-dose	3	24/368	26/368	-0.01 (-0.05, 0.04)	38	0.92 (0.52, 1.63)	49
1 7	Integument, by condition	Inhaled vs. placebo	Croup	2	0/106	3/108	-0.02 (-0.06, 0.01)	0	0.13 (0.01, 1.27)	0
3		Inhaled vs. placebo	Wheeze	2	24/326	24/328	0.01 (-0.05, 0.07)	46	1.00 (0.56, 1.80)	47
1	Phlebitis, overall	Dexamethasone vs. other steroid	Single dose, asthma	1	0/15	0/17	0.00 (-0.11, 0.11)	NA	NA	NA

RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus

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Advo	Com		son 1 son 2	usculoskelet Subgrou		Compar 1 – no patier with events/ no. c patier	. of nts n total e	Comparison 2 – no. of patients with events/total no. of patients	RD (95% CI)	l ² (%)		eto OR 95% CI)	² (%)
Fluid & elec		Systemic vs.	placebo		4	5/832	1	l/818	0.00 (0.00, 0.01)	0	3.08 (0.	60, 15.94)	0
abnormaliti Fluid & elec abnormaliti	rolyte	Systemic vs.	placebo	Single dos	e 1	1/359	C	0/361	0.00 (0.00, 0.01)) NA	7.43 (0.	15, 374.47)	NA
3	· ,	Systemic vs.	placebo	Multi-dose	2 3	4/473	1	L/457	0.00 (-0.01, 0.01	.) 0	2.56 (0.	42, 15.61)	0
Fluid & elec	rolyte es, by condition	Systemic vs.	placebo	Bronchioli	tis 2	4/448	1	1/432	0.00 (-0.01, 0.01	.) 0	2.56 (0.	42, 15.61)	0
)		Systemic vs. placebo		Croup	2	1/384	C	0/386	0.00 (0.00, 0.01)	0	7.43 (0.	15, 374.47)	NA
Fluid & elec		Dexamethas other steroid		Multi-dose bronchioli	· · · · · · · · · · · · · · · · · · ·	1/33	2	2/15	-0.10 (-0.28, 0.0	8) NA	0.18 (0.	01, 2.17)	NA
Adrenal sup	pression, overall	Inhaled vs. p	lacebo	Multi-dose asthma	e, 1	5/6	4	4/10	0.43 (0.01, 0.86)	NA	5.21 (0.	72, 37.57)	NA
3 9 0 1 <u>2</u> 3 4 5	RD: risk difference;		Compa	NA: not appl arison 1 /s. arison 2	icable/estimab	p	umber; F No. of studies	Compariso 1 – total	7	ersus Me Differ (95%	ence	l ² (%)	
б	Linear growth		Inhaled v	s. placebo	Multi-dose, w	heeze	2	154	109	0.10 (-0.4	17, 0.67)	9	
7 8 9 0 1 2 3	Cl: confidence inter	rval; no.: numt	ber; vs.: ve	rsus						pplement	- Dama	11 - 6 1 4	

Supplement 5f. Cardiovascular system

4	Supplement Si. Ca	irdiovascular system	1	- T	1	1				
4 5	Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD	l ²	Peto OR	l ²
6		vs.		of	1 – no. of	2 – no. of	(95% CI)	(%)	(95% CI)	(%)
7 8		Comparison 2		studies	patients with	patients with				
9					events/total	events/total				
10 11					no. of	no. of				
12					patients	patients				
13 14	Arrhythmia, overall	Systemic vs. placebo	Multi-dose, wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
15 16 17	Arrhythmia, overall	Inhaled vs. placebo	Multi-dose, wheeze	1	0/29	0/27	0.00 (-0.07, 0.07)	NA	NA	NA
18 19	Arrhythmia, overall	Dexamethasone vs. other steroid	Multi-dose, asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	NA	NA	NA
20 21 22	Hypertension, overall	Systemic vs. placebo	All bronchiolitis	3	1/727	1/714	0.00 (-0.01, 0.01)	0	1.00 (0.06, 15.99)	50
23	Hypertension, by dose	Systemic vs. placebo	Single dose	1	0/305	0/295	0.00 (-0.01, 0.01)	NA	NA	NA
24		Systemic vs. placebo	Multi-dose	2	1/422	1/419	0.00 (-0.01, 0.01)	0	1.00 (0.06, 15.99)	50
25 26 27	Hypertension, overall	Dexamethasone vs. other steroid	Single dose, asthma	1	0/15	0/17	0.00 (-0.11, 0.11)	NA	NA	NA
28	Congestive heart failure,	Systemic vs. placebo	Multi-dose,	1	0/25	0/25	0.00 (-0.07, 0.07)	NA	NA	NA
29	overall		croup							
30 31 32 33 34 35 36		; CI: confidence interval;	NA: not applicat	ole/estimat	ole; no.: numbe	r; Peto OR: Peto	o odds ratio; vs.: vers	us		
37 38 39										
40										
41 42										
43							Suppl	ement !	5 - Page 12 of 14	
44 45		For pe	er review only - h	ttp://bmjop	en.bmj.com/site	/about/guidelin	es.xhtml			

4 5 6 7 8 9 10	Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients with events/total no. of	Comparison 2 – no. of patients with events/total no. of	RD (95% CI)	² (%)	Peto OR (95% CI)	² (%)
11 12					patients	patients				
13 14	General complaints ¹ , overall	Systemic vs. placebo	All bronchiolitis	2	38/446	38/423	0.00 (-0.04, 0.04)	0	1.00 (0.62, 1.60)	0
15	General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, 0.09)	0	NA	NA
10		Systemic vs. placebo	Multi-dose	1	38/400	38/400	0.00 (-0.04, 0.04)	0	1.00 (0.62, 1.60)	0
18 19	General complaints ² , overall	Dexamethasone vs. other steroid		2	3/102	3/95	-0.01 (-0.06, 0.03)	0	0.90 (0.18, 4.61)	11
20 21 22	General complaints, by condition	Dexamethasone vs. other steroid	Asthma	1	0/56	1/54	-0.02 (-0.07, 0.03)	NA	0.13 (0.00, 6.58)	NA
23 24		Dexamethasone vs. other steroid	Croup	1	3/46	2/41	0.01 (-0.08, 0.11)	NA	1.29 (0.21, 7.81)	NA
26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41		d excessive urination; one Cl: confidence interval; NA	• •		no.: number; F	Peto OR: Peto o	dds ratio; vs.: versus			
42 43 44 45 46		For peer	review only - http	://bmjopen	bmj.com/site/ak	oout/guidelines.		nent 5	- Page 13 of 14	

Supplement 5h. Immune system & oncology

Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 –no.# of patients with events/total	Comparison 2 – no. of patients with events/total	RD (95% CI)	l ² (%)	Peto OR (95% CI)	l ² (%)
				no. of	no. of	0.00/0.04.0.04			
mmunosuppression, overall RD: risk difference; Cl:	Systemic vs. placebo	not applicable/	1 estimable;	0/47 no.: number; P	0/48 reto OR: Peto o	0.00 (-0.04, 0.04) dds ratio; vs.: versus	NA	NA	NA
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3	Supplement 6	Forest plots of adverse events	
4	••	Systemic vs. Placebo	
5		a. Infection & respiratory system	p. 2-12
6 7		b. Gastro-intestinal tract	p. 13-22
8		c. CNS & behaviour effects	p. 23-29
9		d. Dermatologic conditions	p. 30-32
10		e. Endocrine/ metabolic & musculoskeletal systems	p. 33-35
11		f. Cardiovascular system	p. 35-35 p. 36-38
12		g. General adverse events/ other symptoms	p. 30-38 p. 39-40
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14		h. Immune system & oncology Inhaled vs. Placebo	p. 41
15			· 42.47
16		a. Infection & respiratory system	p. 42-47
17		b. Gastro-intestinal tract	p. 48-51
18 19		c. CNS & behaviour effects	p. 52-54
20		d. Dermatologic conditions	p. 55-57
20		 e. Endocrine/ metabolic & musculoskeletal systems 	p. 58
22		f. Cardiovascular system	p. 59
23		Dexamethasone vs. Other steroid	
24		a. Gastro-intestinal tract	р. 60-63
25		b. CNS & behaviour effects	р. 64-66
26		c. Dermatologic conditions	p. 67
27		d. Endocrine/ metabolic & musculoskeletal systems	p. 68
28		e. Cardiovascular system	р. 69
29		f. General adverse events/ other symptoms	р. 70-71
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SYSTEMIC vs. PLACEBO – Infection & Respiratory

Severe infections

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	0	359	1	361	73.6%	-0.00 [-0.01, 0.00]	
Leer 1969	0	148	0	149	25.2%	0.00 [-0.01, 0.01]	+
Sumboonnanonda 1997	0	14	1	18	0.2%	-0.06 [-0.21, 0.10]	
Sussman 1964	0	31	0	26	1.0%	0.00 [-0.07, 0.07]	
Total (95% CI)		552		554	100.0%	-0.00 [-0.01, 0.00]	4
Total events	0		2				
Heterogeneity: Tau ² = 0.00); Chi ² = 0.	75, df=	= 3 (P = 0	.86); I ^z :	= 0%		
Test for overall effect: Z = (`				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3jornson 2004	0	359	1	361	50.4%	0.14 [0.00, 6.86]	
_eer 1969	0	148	0	149		Not estimable	
Sumboonnanonda 1997	0	14	1	18	49.6%	0.17 [0.00, 8.79]	
Bussman 1964	0	31	0	26		Not estimable	
iotal (95% Cl)		552		554	100.0%	0.15 [0.01, 2.45]	
Fotal events	0		2				
Heterogeneity: Chi ² = 0.01,	, df = 1 (P	= 0.94)	; l² = 0%				0.001 0.1 1 10
est for overall effect: Z = 1	.33 (P = 0	.18)					Favours systemic Favours placebo

Severe infections (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.23.1 Single-dose						· · ·	
Bjornson 2004	0	359	1	361	73.6%	-0.00 [-0.01, 0.00]	
Subtotal (95% CI)		359		361	73.6%	-0.00 [-0.01, 0.00]	•
Total events	0		1				
Heterogeneity: Not applica	ible						
Test for overall effect: Z = 0).71 (P = 0	1.48)					
1.23.2 Multi-dose							
Leer 1969	0	148	0	149	25.2%	0.00 [-0.01, 0.01]	+
Sumboonnanonda 1997	0	14	1	18	0.2%	-0.06 [-0.21, 0.10]	
Sussman 1964	0	31	0	26	1.0%	0.00 [-0.07, 0.07]	
Subtotal (95% CI)		193		193	26.4%	-0.00 [-0.01, 0.01]	•
Total events	0		1				
Heterogeneity: Tau ² = 0.00	l; Chi ^z = 0.	92, df=	= 2 (P = 0	.63); I²:	= 0%		
Test for overall effect: Z = 0	0.06 (P = 0	1.95)					
Total (95% CI)		552		554	100.0 %	-0.00 [-0.01, 0.00]	•
Total events	0		2				
Heterogeneity: Tau ² = 0.00	l; Chi² = 0.	75, df=	= 3 (P = 0	.86); l²:	= 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z = 0).64 (P = 0	1.52)					Favours systemic Favours placebo
Test for subgroup differen	ces: Chi ^z a	= 0.10,	df = 1 (P :	= 0.76)	, I² = 0%		

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Severe infections (by dose) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.24.1 Single-dose							
Bjornson 2004	0	359	1	361	50.4%	0.14 [0.00, 6.86]	
Subtotal (95% CI)		359		361	50.4%	0.14 [0.00, 6.86]	
Total events	0		1				
Heterogeneity: Not applical	ble						
Test for overall effect: Z = 1	.00 (P = 0	.32)					
1.24.2 Multi-dose							
Leer 1969	0	148	0	149		Not estimable	
Sumboonnanonda 1997	0	14	1	18	49.6%	0.17 [0.00, 8.79]	
Sussman 1964	0	31	0	26		Not estimable	
Subtotal (95% Cl)		193		193	49.6%	0.17 [0.00, 8.79]	
Total events	0		1				
Heterogeneity: Not applical	ble						
Test for overall effect: Z = 0	.88 (P = 0	.38)					
Total (95% CI)		552		554	100.0%	0.15 [0.01, 2.45]	
Total events	0		2				
Heterogeneity: Chi ² = 0.01,	df = 1 (P	= 0.94)	; I² = 0%				0.002 0.1 1 10
Test for overall effect: Z = 1	.33 (P = 0	.18)					Favours systemic Favours placebo
Test for subgroup difference	es: Chi ² =	= 0.01,	df = 1 (P :	= 0.94)	, I² = 0%		

Severe infections (by condition)

Chuch and Cale and an	Syster		Place		Wainha	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.25.1 Bronchiolitis							
Leer 1969	0	148	0	149	25.2%	0.00 [-0.01, 0.01]	+
Sussman 1964	0	31	0	26	1.0%	0.00 [-0.07, 0.07]	
Subtotal (95% Cl)		179		175	26.2%	0.00 [-0.01, 0.01]	♦
Total events	0		0				
Heterogeneity: Tau ² = 0.00): Chi ² = 0.	.00. df=	= 1 (P = 1	.00); i ž :	= 0%		
Test for overall effect: Z = 0	•	•					
restion overall effect. Z = c	5.00 (i – i	.00)					
1.25.2 Croup							
Bjornson 2004	0	359	1	361	73.6%	-0.00 [-0.01, 0.00]	
Sumboonnanonda 1997	0	14	1	18	0.2%	-0.06 [-0.21, 0.10]	
Subtotal (95% Cl)		373		379	73.8%	-0.00 [-0.01, 0.00]	•
Total events	0		2				
Heterogeneity: Tau ² = 0.00): Chi ² = 0.	.75. df=	= 1 (P = 0	.39); P :	= 0%		
Test for overall effect: Z = 0				// ·			
		,					
Total (95% CI)		552		554	100.0%	-0.00 [-0.01, 0.00]	•
Total events	0		2				
Heterogeneity: Tau ² = 0.00); Chi ² = 0.	75, df=	= 3 (P = 0,	.86); l² :	= 0%	-	
			•				-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z = 0	J.64 (P = U	1.521					Favours systemic Favours placebo

Severe infections (by condition) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.26.1 Bronchiolitis							
Leer 1969	0	148	0	149		Not estimable	
Sussman 1964	0	31	0	26		Not estimable	
Subtotal (95% Cl)		179		175		Not estimable	
Total events	0		0				
Heterogeneity: Not applica	ble						
Test for overall effect: Not :		1					
1.26.2 Croup							
Bjornson 2004	0	359	1	361	50.4%	0.14 [0.00, 6.86]	_
Sumboonnanonda 1997	0	14	1	18	49.6%	0.17 [0.00, 8.79]	
Subtotal (95% Cl)		373		379	100.0%	0.15 [0.01, 2.45]	
Total events	0		2				
Heterogeneity: Chi ² = 0.01	, df = 1 (P	= 0.94)	; l² = 0%				
Test for overall effect: Z = 1	.33 (P = 0	.18)					
Total (95% CI)		552		554	100.0%	0.15 [0.01, 2.45]	
Total events	0		2				
Heterogeneity: Chi ² = 0.01	, df = 1 (P	= 0.94)	; l² = 0%				0.005 0.1 1 10 200
Test for overall effect: Z = 1	.33 (P = 0	.18)					Favours systemic Favours placebo
Test for subgroup differen	ces: Not a	pplicat	ole				r avours systemic in ravours platebo

Systemic infections

	Syster	mic	Place	Placebo		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Bjornson 2004	5	359	4	361	7.8%	0.00 [-0.01, 0.02]	- - -	
Corneli 2007	0	305	0	295	48.4%	0.00 [-0.01, 0.01]		
Daugbjerg 1993	0	31	0	27	0.5%	0.00 [-0.07, 0.07]		
Plint 2009	0	200	0	199	21.5%	0.00 [-0.01, 0.01]	+	
Plint 2009	0	200	0	201	21.7%	0.00 [-0.01, 0.01]	+	
Total (95% CI)		1095		1083	100.0%	0.00 [-0.00, 0.00]	4	
Total events	5		4					
Heterogeneity: Tau ² =	= 0.00; Ch	i² = 0.2	1, df = 4 ((P = 1.0	0); I² = 09	6 –		
Test for overall effect	Z = 0.10	(P = 0.9	92)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo	

Systemic infections - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	5	359	4	361	100.0%	1.26 [0.34, 4.68]	
Corneli 2007	0	305	0	295		Not estimable	
Daugbjerg 1993	0	31	0	27		Not estimable	
Plint 2009	0	200	0	199		Not estimable	
Plint 2009	0	200	0	201		Not estimable	
Total (95% CI)		1095		1083	100.0%	1.26 [0.34, 4.68]	
Total events	5		4				
Heterogeneity: Not ap	plicable						0.05 0.2 1 5 20
Test for overall effect:	Z=0.34	(P = 0.7	73)				0.05 0.2 1 5 20 Favours systemic Favours placebo

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Systemic infections (by dose)

	Systen	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.29.1 Single-dose							
Bjornson 2004	5	359	4	361	7.8%	0.00 [-0.01, 0.02]	_ +
Corneli 2007	0	305	0	295	48.4%	0.00 [-0.01, 0.01]	+
Subtotal (95% Cl)		664		656	56.2%	0.00 [-0.01, 0.01]	•
Total events	5		4				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 0.2	4, df = 1 (P = 0.6	2); I² = 0 9	, 0	
Test for overall effect	: Z = 0.13 (P = 0.9	90)				
1.29.2 Multi-dose							
Daugbjerg 1993	0	31	0	27	0.5%	0.00 [-0.07, 0.07]	
Plint 2009	0	200	0	199	21.5%	0.00 [-0.01, 0.01]	+
Plint 2009	0	200	0	201	21.7%	0.00 [-0.01, 0.01]	+
Subtotal (95% Cl)		431		427	43.8%	0.00 [-0.01, 0.01]	♦
Total events	0		0				
Heterogeneity: Tau ² =	= 0.00; Chi	z = 0.0	0, df = 2 (P = 1.0	0); I ^z = 09	6	
Test for overall effect	: Z = 0.00 (P = 1.0)0)				
Total (95% CI)		1095		1083	100.0%	0.00 [-0.00, 0.00]	•
Total events	5		4				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 0.2	1, df = 4 (P = 1.0	0); I^z = 0 9	6 .	
Test for overall effect					-0.1 -0.05 0 0.05 0.1		
Test for subaroup dif				1 (P =	0.93), I ^z =	0%	Favours systemic Favours placebo
stemic infectio	ns (by d	lose)	– Peto				
,	- () -						

Systemic infections (by dose) – Peto

Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
5	359	4	361	100.0%	1.26 [0.34, 4.68]	
0	305	0	295		Not estimable	
	664		656	100.0 %	1.26 [0.34, 4.68]	
5		4				
oplicable						
Z=0.34 ((P = 0.7)	73)				
0	31	0	27		Not estimable	
0	200	Ō	199		Not estimable	
0	200	0	201		Not estimable	
	431		427		Not estimable	
0		0				
oplicable						
Not appli	cable					
	1095		1083	100.0%	1.26 [0.34, 4.68]	
5		4				
oplicable						0.1 0.2 0.5 1 2 5 10
Z=0.34 ((P = 0.7)	73)				Favours systemic Favours placebo
foroncoc:	Noton	nlionhlo				r avours systemic in avours placebo
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Systemic infections (by condition)

	Syster		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.31.1 Bronchiolitis							
Corneli 2007	0	305	0	295	48.4%	0.00 [-0.01, 0.01]	•
Plint 2009	0	200	0	199	21.5%	0.00 [-0.01, 0.01]	+
Plint 2009	0	200	0	201	21.7%	0.00 [-0.01, 0.01]	<u>+</u>
Subtotal (95% CI)		705		695	91.7%	0.00 [-0.00, 0.00]	•
Total events	0		0				
Heterogeneity: Tau ² =	•		•	P = 1.0	0); I² = 09	6	
Test for overall effect: .	Z = 0.00	(P = 1.0	10)				
1.31.2 Croup							
Bjornson 2004	5	359	4	361	7.8%	0.00 [-0.01, 0.02]	+
Subtotal (95% CI)		359		361	7.8%	0.00 [-0.01, 0.02]	•
Total events	5		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=0.34 ((P = 0.7	3)				
1.31.3 Wheeze							
Daugbjerg 1993	0	31	0	27	0.5%	0.00 [-0.07, 0.07]	
Subtotal (95% CI)		31		27	0.5%	0.00 [-0.07, 0.07]	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.00	(P = 1.0	10)				
Total (95% CI)		1095		1083	100.0%	0.00 [-0.00, 0.00]	•
Total events	5		4				
Heterogeneity: Tau ² =	0.00; Ch	i ^z = 0.2 ⁴	1, df = 4 (P = 1.0	0); I ^z = 09	6 —	-0.1 -0.05 0 0.05 0.1
Test for overall effect: .	Z = 0.10 ((P = 0.9	12)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo
Test for subgroup diffe	erences:	Chi ^z = I	D.11, df=	2 (P =	0.95), I ^z =	0%	avours systemic i avours pracebo
ystemic infectior	ns (by d	condit	tion) –	Peto			
•							

Systemic infections (by condition) – Peto

	Systen	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
1.32.1 Bronchiolitis							
Corneli 2007	0	305	0	295		Not estimable	
Plint 2009	0	200	0	199		Not estimable	
Plint 2009	0	200	0	201		Not estimable	
Subtotal (95% CI)		705		695		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
1.32.2 Croup							
Bjornson 2004	5	359	4	361	100.0%	1.26 [0.34, 4.68]	
Subtotal (95% CI)		359		361	100.0%	1.26 [0.34, 4.68]	
Total events	5		4				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.34 (P = 0.7	3)				
1.32.3 Wheeze							
Daugbjerg 1993	0	31	0	27		Not estimable	
Subtotal (95% CI)		31		27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
Total (95% CI)		1095		1083	100.0%	1.26 [0.34, 4.68]	
Total events	5		4				
Heterogeneity: Not ap	plicable						0.1 0.2 0.5 1 2 5 10
Test for overall effect:	7 = 0 34 (P = 0.7	3)				
			97				Favours systemic Favours placebo

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Lung/trachea

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	3	359	4	361	37.4%	-0.00 [-0.02, 0.01]	•
Corneli 2007	0	305	1	295	46.0%	-0.00 [-0.01, 0.01]	•
Gill 2017	1	22	0	5	0.4%	0.05 [-0.20, 0.29]	
Leer 1969	12	148	15	149	5.1%	-0.02 [-0.08, 0.05]	
Sumboonnanonda 1997	0	14	4	18	0.5%	-0.22 [-0.43, -0.01]	
Super 1989	2	18	1	15	0.6%	0.04 [-0.15, 0.24]	
Teeratakulpisarn 2007	0	89	3	85	9.9%	-0.04 [-0.08, 0.01]	
Total (95% CI)		955		928	100.0%	-0.01 [-0.02, 0.01]	•
Total events	18		28				
Heterogeneity: Tau ² = 0.00	; Chi ² = 9.	51, df=	6 (P = 0.	.15); I²÷	= 37%		-0.5 -0.25 0 0.25
Test for overall effect: Z = 0	.99 (P = 0	.32)					-0.5 -0.25 0 0.25 Favours systemic Favours placebo

Lung/trachea – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bjornson 2004	3	359	4	361	16.3%	0.75 [0.17, 3.34]	
Corneli 2007	0	305	1	295	2.4%	0.13 [0.00, 6.60]	·
Gill 2017	1	22	0	5	1.4%	3.41 [0.02, 530.01]	
Leer 1969	12	148	15	149	58.0%	0.79 [0.36, 1.74]	— — —
Sumboonnanonda 1997	0	14	4	18	8.4%	0.14 [0.02, 1.12]	
Super 1989	2	18	1	15	6.6%	1.68 [0.16, 17.61]	
Teeratakulpisarn 2007	0	89	3	85	7.0%	0.13 [0.01, 1.23]	
Total (95% CI)		955		928	100.0%	0.61 [0.34, 1.12]	•
Total events	18		28				
Heterogeneity: Chi ² = 6.02	, df = 6 (P	= 0.42)	; I² = 0%				
Test for overall effect: Z = 1	.59 (P = 0	.11)					0.01 0.1 1 10 10 Favours systemic Favours placebo

Lung/trachea (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.35.1 Single dose							
Bjornson 2004	3	359	4	361	37.4%	-0.00 [-0.02, 0.01]	•
Corneli 2007	0	305	1	295	46.0%	-0.00 [-0.01, 0.01]	•
Gill 2017	1	22	0	5	0.4%	0.05 [-0.20, 0.29]	
Super 1989	2	18	1	15	0.6%	0.04 [-0.15, 0.24]	
Teeratakulpisarn 2007	0	89	3	85	9.9%	-0.04 [-0.08, 0.01]	
Subtotal (95% CI)		793		761	94.4%	-0.00 [-0.01, 0.00]	
Total events	6		9				
Heterogeneity: Tau ² = 0.00	; Chi ² = 2.	43, df=	• 4 (P = 0.	.66); l² :	= 0%		
Test for overall effect: Z = 1	.03 (P = 0	.30)					
1.35.2 Multi-dose							
Leer 1969	12	148	15	149	5.1%	-0.02 [-0.08, 0.05]	
Sumboonnanonda 1997	0	14	4	18	0.5%	-0.22 [-0.43, -0.01]	
eanipeennanonaa reer	0	14	-			-0.22 [-0.40, -0.01]	
Subtotal (95% CI)	0	162	-	167	5.6%	-0.09 [-0.29, 0.10]	
	12		19	167	5.6%		
Subtotal (95% CI)	12	162	19				
Subtotal (95% CI) Total events	12 ; Chi ² = 3.	162 22, df=	19				
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01	12 ; Chi ² = 3.	162 22, df=	19				
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01	12 ; Chi ² = 3.	162 22, df=	19	.07); I² :			
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = 0	12 ; Chi ² = 3.	162 22, df = .33)	19	.07); I² :	= 69%	-0.09 [-0.29, 0.10]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = 0 Total (95% CI)	12 ; Chi² = 3.).97 (P = 0 18	162 22, df = .33) 955	19 = 1 (P = 0. 28	.07); I ^z : <mark>928</mark>	= 69% 100.0%	-0.09 [-0.29, 0.10]	
Subtotal (95% CI) Total events Heterogeneity: Tau ² = 0.01 Test for overall effect: Z = 0 Total (95% CI) Total events	12 ; Chi ² = 3. 0.97 (P = 0 18 ; Chi ² = 9.	162 22, df = .33) 955 51, df =	19 = 1 (P = 0. 28	.07); I ^z : <mark>928</mark>	= 69% 100.0%	-0.09 [-0.29, 0.10]	-0.5 -0.25 0 0.25 Favours systemic Favours placebo

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Lung/trachea (by dose) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
1.36.1 Single dose							
Bjornson 2004	3	359	4	361	16.3%	0.75 [0.17, 3.34]	
Corneli 2007	0	305	1	295	2.4%	0.13 [0.00, 6.60]	
Gill 2017	1	22	0	5	1.4%	3.41 [0.02, 530.01]	· · · · ·
Super 1989	2	18	1	15	6.6%	1.68 [0.16, 17.61]	
Teeratakulpisarn 2007	0	89	3	85	7.0%	0.13 [0.01, 1.23]	
Subtotal (95% CI)		793		761	33.7%	0.57 [0.20, 1.62]	
Total events	6		9				
Heterogeneity: Chi ² = 3.67,	df = 4 (P :	= 0.45)	; I ² = 0%				
Test for overall effect: Z = 1.							
1.36.2 Multi-dose							
Leer 1969	12	148	15	149	58.0%	0.79 [0.36, 1.74]	
Sumboonnanonda 1997	0	14	4	18	8.4%	0.14 [0.02, 1.12]	
Subtotal (95% CI)		162		167	66.3%	0.63 [0.30, 1.33]	◆
Total events	12		19				
Heterogeneity: Chi ² = 2.33,	df = 1 (P :	= 0.13)	; I ² = 57%	,			
Test for overall effect: Z = 1.	21 (P = 0	.23)					
Total (95% CI)		955		928	100.0%	0.61 [0.34, 1.12]	
Total events	18	000	28	520	100.070	0.01 [0.04, 1.12]	•
Heterogeneity: Chi ² = 6.02,		- 0.425					
Test for overall effect: Z = 1.			,1 - 0 %				0.002 0.1 i 10 50
		r .	46 - 4 (D -		17 - 0.07		Favours systemic Favours placebo
Test for subgroup differenc	es. chi==	= 0.0Z,	ui = 1 (P :	= 0.88)	. 1- = 0%		
ung/trachaa (by can	dition						
ung/trachea (by con	ultion						
	Sustan		Diacab	_		Diele Difference	Disk Difference

Study or Subgroup	events	TUID	Events	rotdl	weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
1.37.1 Bronchiolitis							
Corneli 2007	0	305	1	295	46.0%	-0.00 [-0.01, 0.01]	•
Leer 1969	12	148	15	149	5.1%	-0.02 [-0.08, 0.05]	
Teeratakulpisarn 2007	0	89	3	85	9.9%	-0.04 [-0.08, 0.01]	
Subtotal (95% CI)		542		529	61.0%	-0.02 [-0.05, 0.02]	•
Total events	12		19				
Heterogeneity: Tau ² = 0.00	l; Chi ² = 5.:	18, df=	2 (P = 0	.07); l²:	= 61%		
Test for overall effect: Z = 0).88 (P = 0	.38)					
1.37.2 Croup							
Bjornson 2004	3	359	4	361	37.4%	-0.00 [-0.02, 0.01]	•
Gill 2017	1	22	0	5	0.4%	0.05 [-0.20, 0.29]	
Sumboonnanonda 1997	0	14	4	18	0.5%	-0.22 [-0.43, -0.01]	
Super 1989	2	18	1	15	0.6%	0.04 [-0.15, 0.24]	
Subtotal (95% CI)		413		399	39.0%	-0.02 [-0.12, 0.07]	-
Total events	6		9				
Heterogeneity: Tau ² = 0.00	l; Chi² = 5.I	01, df=	3 (P = 0,	.17); I²÷	= 40%		
Test for overall effect: Z = 0	.44 (P = 0	.66)					
Total (95% CI)		955		928	100.0%	-0.01 [-0.02, 0.01]	•
Total events	18		28				
Heterogeneity: Tau ² = 0.00	⊡ ⊂hi≅ – Q i	51 df=	6 (P = 0)	15): IF:	= 37%		-0.5 -0.25 0 0.25

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	Syster		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.38.1 Bronchiolitis	_						
Corneli 2007	0	305	1	295	2.4%	0.13 [0.00, 6.60]	
Leer 1969 Teoretekulaisean 2007	12 0	148 89	15	149 85	58.0% 7.0%	0.79 [0.36, 1.74]	
Teeratakulpisarn 2007 Subtotal (95% CI)	U	542	3	529	67.3%	0.13 [0.01, 1.23] 0.61 [0.29, 1.28]	
Total events	12	012	19	020	011070	0101 [0120, 1120]	•
Heterogeneity: Chi ² = 2.84	. –	= 0.24);		6			
Test for overall effect: Z = 1							
1.38.2 Croup							
Bjornson 2004	3	359	4	361	16.3%	0.75 [0.17, 3.34]	
Gill 2017	1	22	0	5	1.4%	3.41 [0.02, 530.01]	
Sumboonnanonda 1997 Super 1989	0	14 18	4	18 15	8.4% 6.6%	0.14 [0.02, 1.12] 1.68 [0.16, 17.61]	
Subtotal (95% CI)	2	413	1	399	32.7%	0.61 [0.21, 1.76]	
Total events	6		9				
Heterogeneity: Chi ² = 3.18	.df=3(P:	= 0.37);	; ² = 6%				
Test for overall effect: Z = 0).91 (P = 0	.36)					
Total (95% CI)		955		928	100.0%	0.61 [0.34, 1.12]	-
Total events	18		28				
Heterogeneity: Chi ² = 6.02			; l² = 0%				0.002 0.1 1 10 50
Test for overall effect: Z = 1 Test for subgroup differen		· ·	df = 1 /D	- 1.00\	12 - 0%		Favours systemic Favours placebo
restion subgroup differen	ues. Unifie	- 0.00, 1	ui — I (F	- 1.00)	1 - 070		
URT							
0							
_	vstemic		lacebo			isk Difference	Risk Difference

	Syster	nic	Placel	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	0	359	0	361	94.7%	0.00 [-0.01, 0.01]	
Daugbjerg 1993	0	31	0	27	0.7%	0.00 [-0.07, 0.07]	
Gill 2017	1	22	0	5	0.0%	0.05 [-0.20, 0.29]	
Johnson 1998	0	47	0	49	1.8%	0.00 [-0.04, 0.04]	
Klassen 1998	0	64	1	65	1.6%	-0.02 [-0.06, 0.03]	
Leer 1969	8	148	6	149	1.2%	0.01 [-0.03, 0.06]	_
Total (95% Cl)		671		656	100.0%	-0.00 [-0.01, 0.01]	4
Total events	9		7				
Heterogeneity: Tau ² =	= 0.00; Ch	² = 1.6	5, df = 5 (l	P = 0.8	9); i² = 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect	: Z = 0.02 (P = 0.9	18)				Favours systemic Favours placebo
							Tavouis systemic Tavouis placebo
IRT – Peto							
	Syste	mic	Place	ebo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	0	359	0	361		Not estimable	
Bjornson 2004 Daugbjerg 1993	0 0	359 31	0 0			Not estimable Not estimable	
,	0 0 1			27		Not estimable	

URT – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	0	359	0	361		Not estimable	
Daugbjerg 1993	0	31	0	27		Not estimable	
Gill 2017	1	22	0	5	4.0%	3.41 [0.02, 530.01]	
Johnson 1998	0	47	0	49		Not estimable	
Klassen 1998	0	64	1	65	6.7%	0.14 [0.00, 6.93]	
Leer 1969	8	148	6	149	89.3%	1.36 [0.47, 3.96]	
Total (95% CI)		671		656	100.0%	1.21 [0.44, 3.33]	-
Total events	9		7				
Heterogeneity: Chi ² =	1.39, df=	2 (P =	0.50); l² :	= 0%			0.001 0.1 1 10 1000
Test for overall effect	Z = 0.37 ((P = 0.7	71)				Favours systemic Favours placebo

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URT (by dose)

	Syster		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.41.1 Single Dose							\perp
Bjornson 2004	0	359	0	361	94.7%	0.00 [-0.01, 0.01]	
Gill 2017	1	22	0	5	0.0%	0.05 [-0.20, 0.29]	
Johnson 1998	0	47	0	49	1.8%	0.00 [-0.04, 0.04]	
Klassen 1998	0	64	1	65	1.6%	-0.02 [-0.06, 0.03]	
Subtotal (95% Cl)		492		480	98.1%	-0.00 [-0.01, 0.01]	•
Total events	1		1				
Heterogeneity: Tau ²	= 0.00; Ch	i ² = 0.8	0, df = 3 ((P = 0.8)	(5); I² = 0 9	6	
Test for overall effec	t: Z = 0.08	(P = 0.9)	33)				
1.41.2 Multi-Dose							
Daugbjerg 1993	0	31	0	27	0.7%	0.00 [-0.07, 0.07]	
Leer 1969	8	148	6		1.2%	0.01 [-0.03, 0.06]	
Subtotal (95% Cl)		179		176	1.9%	0.01 [-0.03, 0.05]	•
Total events	8		6				
Heterogeneity: Tau²	= 0.00; Ch	i² = 0.1	3, df = 1 ((P = 0.7	2); I² = 09	6	
Test for overall effec	t: Z = 0.45	(P = 0.6	65)				
Fotal (95% CI)		671		656	100.0%	-0.00 [-0.01, 0.01]	•
Total events	9		7				
Heterogeneity: Tau ²	= 0.00; Ch	i ^z = 1.6	5. df = 5 ((P = 0.8	9); I² = 0 9	6	
Test for overall effec				•			-0.2 -0.1 Ó 0.1 0.2
Test for subaroup di				1 (P =	0.65), I ² =	: 0%	Favours systemic Favours placebo
RT (by dose) –	Peto						
						<u> </u>	

URT (by dose) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.42.1 Single Dose							
Bjornson 2004	0	359	0	361		Not estimable	
Gill 2017	1	22	0	5	4.0%	3.41 [0.02, 530.01]	
Johnson 1998	0	47	0	49		Not estimable	
Klassen 1998	0	64	1	65	6.7%	0.14 [0.00, 6.93]	
Subtotal (95% Cl) 👘		492		480	10.7%	0.46 [0.02, 10.18]	
Total events	1		1				
Heterogeneity: Chi² =	•			= 0%			
Heterogeneity: Chi² =	•			= 0%			
Heterogeneity: Chi² = Test for overall effect	•			= 0%			
Heterogeneity: Chi ² = Test for overall effect 1.42.2 Multi-Dose	•			= 0% 27		Not estimable	
Heterogeneity: Chi ² : Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993	t: Z = 0.49 ((P = 0.6	62)		89.3%	Not estimable 1.36 (0.47, 3.96)	
Heterogeneity: Chi [≇] Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993 Leer 1969	t: Z = 0.49 (0	(P = 0.6 31	52) ⁽⁷⁾ 0	27	89.3% 89.3 %		-
Heterogeneity: Chi [≆] Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993 Leer 1969 Subtotal (95% CI)	t: Z = 0.49 (0	(P = 0.6 31 148	52) ⁽⁷⁾ 0	27 149		1.36 [0.47, 3.96]	-
Heterogeneity: Chi [≇] Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993 Leer 1969 Subtotal (95% CI) Total events	t: Z = 0.49 (0 8 8	(P = 0.6 31 148	62) 0 6	27 149		1.36 [0.47, 3.96]	*
Total events Heterogeneity: Chi ² - Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993 Leer 1969 Subtotal (95% CI) Total events Heterogeneity: Not a Test for overall effect	t: Z = 0.49 (0 8 pplicable	(P = 0.8 31 148 179	52) ⁽¹⁾ 0 6 6	27 149		1.36 [0.47, 3.96]	*
Heterogeneity: Chi [≢] Test for overall effect 1.42.2 Multi-Dose Daugbjerg 1993 Leer 1969 Subtotal (95% CI) Total events Heterogeneity: Not a	t: Z = 0.49 (0 8 pplicable	(P = 0.8 31 148 179	52) ⁽¹⁾ 0 6 6	27 149 176		1.36 [0.47, 3.96]	

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1						
2						
3 4	URT (by condition	ו)				
5	Study or Subgroup	Systemic Events Total	Placebo Events Total	Moight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
6 7	1.43.1 Bronchiolitis					
8	Leer 1969 Subtotal (95% CI)	8 148 148	6 149 149		0.01 [-0.03, 0.06] 0.01 [-0.03, 0.06]	-
9 10	Total events Heterogeneity: Not ap	8 nlicable	6			
11	Test for overall effect:		8)			
12	1.43.2 Croup					<u> </u>
13 14	Bjornson 2004 Gill 2017	0 359 1 22	0 361 0 5		0.00 [-0.01, 0.01] 0.05 [-0.20, 0.29]	_
15	Johnson 1998 Klassen 1998	0 47 0 64	0 49 1 65	1.8%	0.00 [-0.04, 0.04] -0.02 [-0.06, 0.03]	
16 17	Subtotal (95% CI)	492	480		-0.02 [-0.00, 0.03] -0.00 [-0.01, 0.01]	•
17	Total events Heterogeneity: Tau² =	1 0.00; Chi² = 0.8(1), df = 3 (P = 0.8	35); I² = 0%	6	
19	Test for overall effect:					
20 21	1.43.3 Wheeze					
22	Daugbjerg 1993 Subtotal (95% CI)	0 31 31	0 27 27		0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07]	-
23	Total events Heterogeneity: Not ap	0 nlicable	0			
24 25	Test for overall effect:		0)			
26	Total (95% CI)	671		100.0%	-0.00 [-0.01, 0.01]	•
27 28	Total events Heterogeneity: Tau² =	9 0.00; Chi² = 1.6	7 5. df = 5 (P = 0.8	39); I² = 0%	6 –	
29	Test for overall effect: Test for subgroup diff	Z = 0.02 (P = 0.9	8)			-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo
30	restion subgroup uni	erences. Chi – i	5.52, ui – 2 (r –	0.05),1 -	0.0	
31 32						
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58 59						Supplement 6 - Page 11 of 71
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URT (by condition) - Peto

	Syster		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.44.1 Bronchiolitis							
Leer 1969	8	148	6	149	89.3%	1.36 [0.47, 3.96]	
Subtotal (95% CI)	, v	148		149	89.3%	1.36 [0.47, 3.96]	
Total events	8	110	6	140	001010	100 [0111, 0100]	
			0				
Heterogeneity: Not ap	•						
Test for overall effect:	Z=0.56 ((P = 0.5	58)				
1.44.2 Croup							
Bjornson 2004	0	359	0	361		Not estimable	
Gill 2017	1	22	0	5	4.0%	3.41 [0.02, 530.01]	
Johnson 1998	0	47	0	49		Not estimable	
Klassen 1998	0	64	1	65	6.7%	0.14 [0.00, 6.93]	•
Subtotal (95% CI)		492		480	10.7%	0.46 [0.02, 10.18]	
	4	102		100	10.1 /4	0.40 [0.02, 10.10]	
Total events	1		1	~~			
Heterogeneity: Chi ² =	•	•		= 0%			
Test for overall effect:	Z=0.49 ((P = 0.6	52)				
1.44.3 Wheeze							
Daugbjerg 1993	0	31	0	27		Not estimable	
Subtotal (95% CI)	-	31	-	27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	-		0				
	•	aabla					
Test for overall effect:	могарри	capie					
Total (95% CI)		671		656	100.0%	1.21 [0.44, 3.33]	-
i u sui ju u iu uij							
Total events Heterogeneity: Chi² = Test for overall effect:	Z= 0.37 ((P = 0.7	'1)		0.52). ぼ=		0.002 0.1 1 10 Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff	1.39, df = Z = 0.37 ((P = 0.7	0.50); l ² = '1)		0.52), l² =		0.002 0.1 1 10 Favours systemic Favours placebo
Total events Heterogeneity: Chi² = Test for overall effect:	1.39, df = Z = 0.37 ((P = 0.7	0.50); l ² = '1)		0.52), l² =		0.002 0.1 1 10 Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff	1.39, df = Z = 0.37 ((P = 0.7 Chi² = I	0.50); l ² = '1)	1 (P =	0.52), l² =		0.002 0.1 1 10 Favours systemic Favours placebo Risk Difference
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff	1.39, df = Z = 0.37 (erences: System	(P = 0.7 Chi ² = 1 hic	0.50); I ² = '1) 0.42, df = Placeb	1 (P = 0		:0%	Favours systemic Favours placebo Risk Difference
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup dif /oice complaints	1.39, df = Z = 0.37 (erences: System	(P = 0.7 Chi ² = 1 hic	0.50); I ² = '1) 0.42, df = Placeb	1 (P = o Total		0% Risk Difference	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993	1.39, df = Z = 0.37 (erences: System Events	(P = 0.7 Chi ² = 1 nic Total	0.50); I ² = '1) 0.42, df = Placeb <u>Events</u>	1 (P = o Total	Weight	Risk Difference M-H, Random, 95% CI	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup dif /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI)	1.39, df = Z = 0.37 (erences: System <u>Events</u> 0	(P = 0.7 Chi ² = 1 hic Total 31	0.50); I ² = '1) 0.42, df = Placeb <u>Events</u> 0	1 (P = o <u>Total</u> 27	<u>Weight</u> 100.0%	0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07]	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events	1.39, df = Z = 0.37 (erences: System Events 0 0	(P = 0.7 Chi ² = 1 hic Total 31	0.50); I ² = '1) 0.42, df = Placeb <u>Events</u>	1 (P = o <u>Total</u> 27	<u>Weight</u> 100.0%	0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07]	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup dif /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI)	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 plicable	(P = 0.7 Chi² = 1 nic <u>Total</u> 31 31	0.50); * = '1) 0.42, df = Placeb <u>Events</u> 0	1 (P = o <u>Total</u> 27	<u>Weight</u> 100.0%	0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07]	Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events Heterogeneity: Not ap	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 plicable	(P = 0.7 Chi² = 1 nic <u>Total</u> 31 31	0.50); * = '1) 0.42, df = Placeb <u>Events</u> 0	1 (P = o <u>Total</u> 27	<u>Weight</u> 100.0%	0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07]	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events Heterogeneity: Not ap	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 plicable Z = 0.00 (f	(P = 0.7 Chi² = 1 nic <u>Total</u> 31 31	0.50); * = '1) 0.42, df = Placeb <u>Events</u> 0	1 (P = o <u>Total</u> 27	<u>Weight</u> 100.0%	0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07]	Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 plicable Z = 0.00 (f – Peto	(P = 0.7 Chi ^z = 1 nic <u>Total</u> 31 31 P = 1.0	0.50); ² = 1) 0.42, df = Placeb <u>Events</u> 0 0 0	1 (P = 0 <u>Total</u> 27 27	<u>Weight</u> 100.0%	: 0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07]	Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 0 plicable Z = 0.00 (f – Peto System	(P = 0.7 Chi ² = 1 nic <u>Total</u> 31 31 P = 1.01 nic	0.50); ² = 1) 0.42, df = Placeb Events 0 0 0 0 Placel	1 (P = 0 <u>Total</u> 27 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07]	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	1.39, df = Z = 0.37 (erences: <u>System</u> <u>Events</u> 0 plicable Z = 0.00 (f – Peto	(P = 0.7 Chi ² = 1 nic <u>Total</u> 31 31 P = 1.01 nic	0.50); ² = 1) 0.42, df = Placeb Events 0 0 0 0 Placel	1 (P = 0 <u>Total</u> 27 27	<u>Weight</u> 100.0% 100.0 %	: 0% Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07]	Favours systemic Favours placebo
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993	1.39, df = Z = 0.37 (erences: Events 0 0 plicable Z = 0.00 (f – Peto System Events	(P = 0.7 Chi ² = 1 iic 31 31 P = 1.01 nic <u>Total</u> 31	0.50); ² = 1) 0.42, df = Placeb Events 0 0 0 0 0 Placel Events	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl)	1.39, df = Z = 0.37 (erences: Events 0 0 plicable Z = 0.00 (f - Peto System Events 0	(P = 0.7 Chi ² = 1 nic <u>Total</u> 31 31 P = 1.0 nic <u>Total</u>	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 27 bo	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints /oice complaints Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0	(P = 0.7 Chi ² = 1 iic 31 31 P = 1.01 nic <u>Total</u> 31	0.50); ² = 1) 0.42, df = Placeb Events 0 0 0 0 0 Placel Events	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl)	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0	(P = 0.7 Chi ² = 1 iic 31 31 P = 1.01 nic <u>Total</u> 31	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio Peto, Fixed, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints /oice complaints Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0 0 0 0 0 0 0 0 0 0 0 0	(P = 0.7 Chi ² = 1 iic <u>Total</u> 31 31 P = 1.0 nic <u>Total</u> 31 31	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio Peto, Fixed, 95% Cl 0.1 0.2 0.5 1 2 5 10
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints /oice complaints Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0 0 0 0 0 0 0 0 0 0 0 0	(P = 0.7 Chi ² = 1 iic <u>Total</u> 31 31 P = 1.0 nic <u>Total</u> 31 31	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio Peto, Fixed, 95% Cl
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints /oice complaints Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0 0 0 0 0 0 0 0 0 0 0 0	(P = 0.7 Chi ² = 1 iic <u>Total</u> 31 31 P = 1.0 nic <u>Total</u> 31 31	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio Peto, Fixed, 95% Cl 0.1 0.2 0.5 1 2 5 10
Total events Heterogeneity: Chi ² = Test for overall effect: Test for subgroup diff /oice complaints /oice complaints Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: /oice complaints Study or Subgroup Daugbjerg 1993 Total (95% Cl) Total events Heterogeneity: Not ap	1.39, df = Z = 0.37 (erences: System Events 0 0 plicable Z = 0.00 (f - Peto System Events 0 0 0 0 0 0 0 0 0 0 0 0 0	(P = 0.7 Chi ² = 1 iic <u>Total</u> 31 31 P = 1.0 nic <u>Total</u> 31 31	0.50); * = 1) 0.42, df = Placeb Events 0 0 0 0 0 0 0 0 0 0 0 0 0	1 (P = 0 <u>Total</u> 27 27 bo <u>Total</u> 27	<u>Weight</u> 100.0% 100.0 %	Risk Difference <u>M-H, Random, 95% CI</u> 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] 0.00 [-0.07, 0.07] Peto Odds Ratio Peto, Fixed, 95% CI Not estimable	Favours systemic Favours placebo Risk Difference M-H, Random, 95% Cl -0.2 -0.1 0 0.1 0 Favours systemic Favours placebo Peto Odds Ratio Peto, Fixed, 95% Cl 0.1 0.2 0.5 1 2 5 10

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SYSTEMIC vs. PLACEBO - GI

GI bleeding

	Syster		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	0	359	0	361	56.0%	0.00 [-0.01, 0.01]	#
Buckingham 2002	0	22	0	19	0.2%	0.00 [-0.09, 0.09]	
Corneli 2007	0	305	0	295	38.9%	0.00 [-0.01, 0.01]	•
Johnson 1998	0	47	0	49	1.0%	0.00 [-0.04, 0.04]	+
Plint 2009	17	200	14	199	0.6%	0.01 [-0.04, 0.07]	
Plint 2009	12	200	16	201	0.7%	-0.02 [-0.07, 0.03]	-+
Roosevelt 1996	0	65	0	53	1.5%	0.00 [-0.03, 0.03]	+
Teeratakulpisarn 2007	2	89	1	85	1.1%	0.01 [-0.03, 0.05]	+-
Total (95% CI)		1287		1262	100.0%	0.00 [-0.00, 0.00]	
Total events	31		31				
Heterogeneity: Tau ² = 0.1	00; Chi ^z =	1.20, d	f=7(P=	0.99);1	²=0%	+	0.5 -0.25 0 0.25 0.5
Test for overall effect: Z =	= 0.04 (P =	0.97)				-L	0.5 -0.25 Ó 0.25 0.5 Favours systemic Favours placebo

GI bleeding – Peto

	Systen	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	0	359	0	361		Not estimable	
Buckingham 2002	0	22	0	19		Not estimable	
Corneli 2007	0	305	0	295		Not estimable	
Johnson 1998	0	47	0	49		Not estimable	
Plint 2009	17	200	14	199	49.6%	1.23 [0.59, 2.55]	
Plint 2009	12	200	16	201	45.2%	0.74 [0.34, 1.59]	
Roosevelt 1996	0	65	0	53		Not estimable	
Teeratakulpisarn 2007	2	89	1	85	5.1%	1.87 [0.19, 18.27]	
Fotal (95% CI)		1287		1262	100.0%	1.00 [0.60, 1.67]	+
Total events	31		31				
Test for overall effect: Z =	= 0.01 (P =	0.99)					Favours systemic Favours placebo
Test for overall effect: Z =	= 0.01 (P =	0.99)					Favours systemic Favours placebo
Test for overall effect: Z =	= 0.01 (P =	0.99)					Favours systemic Favours placebo
Test for overall effect: Z =	= 0.01 (P =	0.99)					Favours systemic Favours placebo
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					
Fest for overall effect: Z =	= 0.01 (P =	0.99)					
Test for overall effect: Z =	= 0.01 (P =	0.99)					

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GI bleeding (by dose)

Study or Subgroup 1.3.1 Single Dose Bjornson 2004 Corneli 2007	0		Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	-						
-,	-						
Corneli 2007		359	0	361	56.0%	0.00 [-0.01, 0.01]	
	0	305	0	295	38.9%	0.00 [-0.01, 0.01]	+
Johnson 1998	0	47	0	49	1.0%	0.00 [-0.04, 0.04]	
Teeratakulpisarn 2007	2	89	1	85	1.1%	0.01 [-0.03, 0.05]	_
Subtotal (95% CI)		800		790	97.0%	0.00 [-0.00, 0.00]	+
Total events	2		1				
Heterogeneity: Tau ² = 0.00	l; Chi² =	0.54, d	f=3(P=	0.91); I	P≃=0%		
Test for overall effect: Z = 0).06 (P =	0.95)					
1.3.2 Multi-Dose							
Buckingham 2002	0	22	0	19	0.2%	0.00 [-0.09, 0.09]	
Plint 2009	17	200	14	199	0.6%	0.01 [-0.04, 0.07]	
Plint 2009	12	200	16	201	0.7%	-0.02 [-0.07, 0.03]	
Roosevelt 1996	0	65	0	53	1.5%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		487		472	3.0%	-0.00 [-0.02, 0.02]	•
Total events	29		30				
Heterogeneity: Tau² = 0.00	l; Chi z =	0.88, d	f=3(P=	0.83); I	l²=0%		
Test for overall effect: Z = 0).12 (P =	0.91)					
Fotal (95% CI)		1287		1262	100.0%	0.00 [-0.00, 0.00]	4
Total events	31		31				
Heterogeneity: Tau ² = 0.00	; Chi ^z =	1.20, d	f = 7 (P =	0.99); (l²=0%	_	
Test for overall effect: Z = 0	•						-0.1 -0.05 0 0.05 0.1
Test for subaroup differend			2. df = 1 (F	^o = 0.91	0), I ² = 0%	5	Favours systemic Favours placebo

GI bleeding (by dose) – Peto

	Syster	nic	Place	hn		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup					Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.4.1 Single Dose							
Bjornson 2004	0	359	0	361		Not estimable	
Corneli 2007	0	305	0	295		Not estimable	
Johnson 1998	0	47	0	49		Not estimable	
Teeratakulpisarn 2007 - Subtotal (95% Cl)	2	89 800	1	85 790	5.1% 5.1 %	1.87 [0.19, 18.27] 1.87 [0.19, 18.27]	
Total events	2	000	1	790	J. 170	1.07 [0.19, 10.27]	
Heterogeneity: Not appli	_		1				
Test for overall effect: Z =		0.60\					
	0.04 () =	0.00)					
1.4.2 Multi-Dose							
Buckingham 2002	0	22	0	19		Not estimable	
Plint 2009	17	200	14	199	49.6%	1.23 [0.59, 2.55]	- -
Plint 2009	12	200	16	201	45.2%	0.74 [0.34, 1.59]	
Roosevelt 1996	0	65	0	53		Not estimable	
Subtotal (95% CI)		487		472	94.9%	0.96 [0.57, 1.64]	•
Total events	29		30				
Heterogeneity: Chi ² = 0.8			5); I² = 09	6			
Test for overall effect: Z =	: 0.14 (P =	0.89)					
T-4-1 (05%) ON		1287		1262	100.0%	1.00 [0.60, 1.67]	•
Total (95% CI)		1201		1202	100.070		

22	
56	

GI bleeding (by condition)

Events		Funnta	Total	Mainht	Risk Difference	
	Total	Events	Total	vveight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
_		_				
0	22	0	19	0.2%	0.00 [-0.09, 0.09]	
0	305	0	295	38.9%	0.00 [-0.01, 0.01]	
-	65	0	53	1.5%	0.00 [-0.03, 0.03]	
2	89	1	85		0.01 [-0.03, 0.05]	4
	881		852	43.0%	0.00 [-0.01, 0.01]	•
•		31 f = 5 (P =	0.95); I	²=0%		
0	359	0	361	56.0%	0.00 (-0.01, 0.01)	•
-		-				
Ŭ		Ŭ				
Ο		Ο			1	Ĭ
0; Chi ² = 0		-	1.00); I	²= 0%		
	1287		1262	100.0%	0.00 [-0.00, 0.00]	•
31		31				
	1.20, dt		0.99); I	²=0%		-0.2 -0.1 0 0.1 0
), df = 1 (F	P = 0.93	7), j² = 0%)	Favours systemic Favours placebo
dition)	- Pet	0				
Syster	nic	Place			Peto Odds Ratio	Peto Odds Ratio
Syster	nic	Place		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
Syster	nic	Place		Weight		
Syster	nic	Place Events	Total			
Syster Events	nic Total	Place Events	Total		Peto, Fixed, 95% Cl	
Syster Events 0	nic <u>Total</u> 22 305	Place Events 0 0	Total 19 295		Peto, Fixed, 95% Cl Not estimable Not estimable	
Syster Events 0 0 17	mic Total 22 305 200	Place Events 0 0 14	Total 19 295 199	49.6%	Peto, Fixed, 95% Cl Not estimable Not estimable 1.23 [0.59, 2.55]	
Syster Events 0 0 17 12	nic Total 22 305 200 200	Place Events 0 0 14 16	Total 19 295 199 201	49.6% 45.2%	Peto, Fixed, 95% Cl Not estimable Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59]	
Syster Events 0 0 17 12 0	nic Total 22 305 200 200 65	Place Events 0 0 14 16 0	Total 19 295 199 201 53	49.6% 45.2%	Peto, Fixed, 95% Cl Not estimable Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable	
Syster Events 0 0 17 12	nic Total 22 305 200 200 65 89	Place Events 0 0 14 16	Total 19 295 199 201 53 85	49.6% 45.2% 5.1%	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27]	
Syster Events 0 0 17 12 0 2	nic Total 22 305 200 200 65	Place Events 0 0 14 16 0 1	Total 19 295 199 201 53 85	49.6% 45.2%	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27]	
Syster Events 0 0 17 12 0	mic Total 22 305 200 200 65 89 881 P = 0.5	Place <u>Events</u> 0 0 14 16 0 1 31	Total 19 295 199 201 53 85 852	49.6% 45.2% 5.1%	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27]	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1	mic Total 22 305 200 200 65 89 881 P = 0.5	Place <u>Events</u> 0 0 14 16 0 1 31	Total 19 295 199 201 53 85 852	49.6% 45.2% 5.1%	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27]	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1	mic Total 22 305 200 200 65 89 881 P = 0.5	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I [≈] = 0	Total 19 295 199 201 53 85 852 %	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27]	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (l 0.01 (P =	mic Total 203 200 200 65 89 881 P = 0.5 0.99)	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I [≈] = 0	Total 19 295 199 201 53 85 852 %	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67]	
Syster <u>Events</u> 0 0 17 12 0 2 31 8, df = 2 (I 0.01 (P =	mic <u>Total</u> 22 305 200 200 65 89 881 P = 0.5 0.99) 359	Place <u>Events</u> 0 0 14 16 0 1 31 31 ;5); ² = 0 ⁻ 0	Total 19 295 199 201 53 85 852 %	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable	
Syster <u>Events</u> 0 0 17 12 0 2 31 8, df = 2 (I 0.01 (P =	mic <u>Total</u> 22 305 200 200 65 89 881 P = 0.5 0.99) 359 47	Place <u>Events</u> 0 0 14 16 0 1 31 31 ;5); ² = 0 ⁻ 0	Total 19 295 199 201 53 85 852 % 361 49	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable	
Syster <u>Events</u> 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0 0	mic <u>Total</u> 22 305 200 200 65 89 881 P = 0.5 0.99) 359 47	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ² = 0 0 0 0	Total 19 295 199 201 53 85 852 % 361 49	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable	
Syster <u>Events</u> 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0	mic Total 200 200 65 89 881 P = 0.5 0.99) 359 47 406	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ² = 0 0 0 0	Total 19 295 199 201 53 85 852 % 361 49	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0 0 0 0 0 0 0 0 0 0 0	mic Total 22 305 200 65 89 881 P = 0.5 0.99) 359 47 406	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ² = 0 0 0 0	Total 19 295 199 201 53 852 852 % 361 49 410	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable Not estimable	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (I 0.01 (P = 0 0 0 0 cable tapplicab	mic Total 200 200 65 89 881 P = 0.5 0.99) 359 47 406	Place Events 0 14 16 0 1 31 (5); I ² = 0 0 0 0 0	Total 19 295 199 201 53 852 852 % 361 49 410	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable Not estimable	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	mic Total 22 305 200 65 89 881 P = 0.5 0.99) 359 47 406 le 1287	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ^a = 0 0 0 0 0 31 31 31 31 31 31 31 31 31 31	Total 19 295 199 201 53 852 852 % 361 49 410 1262	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable Not estimable	
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	mic Total 22 305 200 65 89 881 P = 0.6 0.99) 359 47 406 lle 1287 P = 0.5	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ^a = 0 0 0 0 0 31 31 31 31 31 31 31 31 31 31	Total 19 295 199 201 53 852 852 % 361 49 410 1262	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable Not estimable	Peto, Fixed, 95% Cl
Syster Events 0 0 17 12 0 2 31 8, df = 2 (1 0.01 (P = 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	mic Total 22 305 200 65 89 881 P = 0.6 0.99) 359 47 406 lle 1287 P = 0.5	Place <u>Events</u> 0 0 14 16 0 1 31 (5); I ^a = 0 0 0 0 0 31 31 31 31 31 31 31 31 31 31	Total 19 295 199 201 53 852 852 % 361 49 410 1262	49.6% 45.2% 5.1% 100.0 %	Peto, Fixed, 95% Cl Not estimable 1.23 [0.59, 2.55] 0.74 [0.34, 1.59] Not estimable 1.87 [0.19, 18.27] 1.00 [0.60, 1.67] Not estimable Not estimable Not estimable	
	0; Chi ² = - 0.06 (P = 0 0 0; Chi ² = (0.00 (P = 31 0; Chi ² = - 0.04 (P =	$\begin{array}{cccc} 12 & 200 \\ 0 & 65 \\ 2 & 89 \\ 881 \\ 31 \\ 0; Chi^2 = 1.20, dt \\ 0.06 (P = 0.95) \\ 0 & 359 \\ 0 & 47 \\ 406 \\ 0 \\ 0; Chi^2 = 0.00, dt \\ 0.00 (P = 1.00) \\ 1287 \\ 31 \\ 0; Chi^2 = 1.20, dt \\ 0.04 (P = 0.97) \\ \end{array}$	$\begin{array}{ccccc} 12 & 200 & 16 \\ 0 & 65 & 0 \\ 2 & 89 & 1 \\ & & & & \\ & & & & \\ 31 & & & & \\ 31 & & & & \\ 31 & & & & \\ 31 & & & & \\ 31 & & & & \\ 31 & & & & \\ 0 & & & & & \\ 0 & & & & & \\ 0 & & & &$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{cccccccccccccccccccccccccccccccccccc$	12 200 16 201 0.7% $-0.02[-0.07, 0.03]$ 0 65 0 53 1.5% $0.00[-0.03, 0.03]$ 2 89 1 85 1.1% $0.00[-0.03, 0.03]$ 31 31 31 $0.00[-0.01, 0.01]$ 31 31 $0.00[-0.01, 0.01]$ 0 359 0 361 56.0% $0.00[-0.01, 0.01]$ 0 459 0 $0.00[-0.04, 0.04]$ $0.00[-0.04, 0.04]$ 0 406 410 57.0% $0.00[-0.01, 0.01]$ 0 0 0 $0.00[-0.04, 0.04]$ 0 0 0 $0.00[-0.00, 0.00]$ 0 0 0 $0.00[-0.00, 0.00]$ 0 0 $0.00[-0.00, 0.00]$ $0.00[-0.00, 0.00]$ 0 0 $0.00[-0.00, 0.00]$ $0.00[-0.00, 0.00]$ 0 1 31 31 0 0 $0.00[-0.00, 0.00]$ $0.00[-0.00, 0.00]$ 31 31 31 $0.00[-0.00, 0.00]$ 31 31 $0.00[-0.00, 0.00]$ </td

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.6.1 Bronchiolitis							
Buckingham 2002	0	22	0	19		Not estimable	
Corneli 2007	0	305	0	295		Not estimable	
Plint 2009	17	200	14	199	49.6%	1.23 [0.59, 2.55]	
Plint 2009	12	200	16	201	45.2%	0.74 [0.34, 1.59]	
Roosevelt 1996	0	65	0	53		Not estimable	
Teeratakulpisarn 2007	2	89	1	85	5.1%	1.87 [0.19, 18.27]	
Subtotal (95% CI)		881		852	100.0%	1.00 [0.60, 1.67]	-
Total events	31		31				
Heterogeneity: Chi ² = 1.1	18, df = 2 (I	P = 0.5	5); I² = 09	6			
Test for overall effect: Z =	= 0.01 (P =	0.99)					
1.6.2 Croup							
Bjornson 2004	0	359	0	361		Not estimable	
Johnson 1998	0	47	0	49		Not estimable	
Subtotal (95% CI)		406		410		Not estimable	
Total events	0		0				
Heterogeneity: Not appli	cable						
Test for overall effect: No)t applicab	le					
T-4-1 (0/0% CI)		4207		4000	400.0%	4 00 10 00 4 071	
Total (95% CI)	~ .	1287	~ .	1202	100.0%	1.00 [0.60, 1.67]	
Total events	31		31	,			
Heterogeneity: Chi ² = 1.1			5); I* = 09	6			0.05 0.2 1 5 20
Test for overall effect: Z =		,	- 1- 1 -				Favours systemic Favours placebo
Test for subgroup differe	inces: Not	applic	able				

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Vomiting

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	3	359	4	361	19.7%	-0.00 [-0.02, 0.01]	+
Connett 1994	1	18	4	15	0.1%	-0.21 [-0.46, 0.04]	
Connett 1994	0	19	1	18	0.2%	-0.06 [-0.19, 0.08]	
Corneli 2007	17	305	14	295	3.2%	0.01 [-0.03, 0.04]	+-
Csonka 2003	9	113	4	117	1.1%	0.05 [-0.01, 0.11]	<u> </u>
Kuyucu 2004	0	23	0	11	0.3%	0.00 [-0.13, 0.13]	
Kuyucu 2004	0	23	0	12	0.3%	0.00 [-0.12, 0.12]	
Panickar 2009	1	343	0	344	62.6%	0.00 [-0.01, 0.01]	•
Plint 2009	2	200	4	199	7.1%	-0.01 [-0.03, 0.01]	
Plint 2009	5	200	3	201	5.4%	0.01 [-0.02, 0.04]	
Total (95% CI)		1603		1573	100.0%	0.00 [-0.00, 0.01]	
Total events	38		34				
Heterogeneity: Tau ² =	: 0.00; Ch	i ² = 7.4:	5. df = 9 ((P = 0.5	9); I² = 09	6 -	
Test for overall effect:	•				-71.		-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Vomiting – Peto

Connett 1994	1	18	4	15	0.1%	-0.21 [-0.46, 0.04]	· · · · · · · · · · · · · · · · · · ·
Connett 1994	0	19	1	18	0.2%	-0.06 [-0.19, 0.08]	
Corneli 2007	17	305	14	295	3.2%	0.01 [-0.03, 0.04]	
Csonka 2003	9	113	4	117	1.1%	0.05 [-0.01, 0.11]	
Kuyucu 2004	Ō	23	Ó	11	0.3%	0.00 [-0.13, 0.13]	
Kuyucu 2004	Õ	23	Õ	12	0.3%	0.00 [-0.12, 0.12]	
Panickar 2009	1	343	0	344	62.6%	0.00 [-0.01, 0.01]	
Plint 2009	2	200	4	199	7.1%	-0.01 [-0.03, 0.01]	
Plint 2009	2 5	200	4	201	5.4%	0.01 [-0.02, 0.04]	
						0.00 [-0.00, 0.01]	
Total (95% CI) Total events	38	1603	34	1973	100.0%	0.00 [-0.00, 0.01]	
Heterogeneity: Tau ² =		-745) – N E(a) · I≊ – ∩∞.		
Test for overall effect:				- 0.08			-0.2 -0.1 0 0.1 0.2
restior overall ellect.	Z = 0.01 (i	0.0	0				Favours systemic Favours placebo
′omiting – Peto							
	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	-				Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	3	359	4	361	10.1%	0.75 [0.17, 3.34]	
Connett 1994	1	18	4	15	6.3%	0.20 [0.03, 1.34]	
Connett 1994	0	18		15		• • •	
			1		1.5%	0.13 [0.00, 6.46]	-
Corneli 2007	17	305	14	295	42.8%	1.18 [0.57, 2.44]	
Csonka 2003	9	113	4	117	17.9%	2.34 [0.76, 7.14]	T -
Kuyucu 2004	0	23	0	11		Not estimable	
Kuyucu 2004	0	23	0	12		Not estimable	
Panickar 2009	1	343	0	344	1.5%	7.41 [0.15, 373.47]	
Plint 2009	2	200	4	199	8.6%	0.51 [0.10, 2.54]	
Plint 2009	5	200	3	201	11.4%	1.67 [0.41, 6.77]	
Total (95% Cl)		1603		1573	100.0%	1.10 [0.69, 1.76]	•
Total events	38		34				ſ
Heterogeneity: Chi ² =		7 (P =		= 17%			· · · · · · · · · · · · · · · · · · ·
Test for overall effect							0.002 0.1 1 10 50 Favours systemic Favours placebo

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Vomiting (by dose)

	Systen		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.9.1 Single Dose							
Bjornson 2004	3	359	4	361	19.7%	-0.00 [-0.02, 0.01]	+
Connett 1994	1	18	4	15	0.1%	-0.21 [-0.46, 0.04]	
Connett 1994	0	19	1	18	0.2%	-0.06 [-0.19, 0.08]	
Corneli 2007	17	305	14	295	3.2%	0.01 [-0.03, 0.04]	+
Kuyudu 2004	0	23	0	11	0.3%	0.00 [-0.13, 0.13]	
Kuyudu 2004	0	23	0	12	0.3%	0.00 [-0.12, 0.12]	
Subtotal (95% CI)		747		712	23.8%	-0.00 [-0.02, 0.01]	•
Total events	21		23				
Heterogeneity: Tau ² =	= 0.00; Chi	²= 3.7	3, df = 5 (P = 0.5	9); I ^z = 09	6	
Test for overall effect:	Z=0.33 (P = 0.7	74)				
1.9.2 Multi-Dose							
Csonka 2003	9	113	4	117	1.1%	0.05 [-0.01, 0.11]	
Panickar 2009	1	343	0	344	62.6%	0.00 [-0.01, 0.01]	•
Plint 2009	2	200	4	199	7.1%	-0.01 [-0.03, 0.01]	-
Plint 2009	5	200	3	201	5.4%	0.01 [-0.02, 0.04]	- -
Subtotal (95% CI)		856		861	76.2%	0.00 [-0.01, 0.02]	•
Total events	17		11				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 4.7	6, df = 3 (P = 0.1	9); I^z = 37	%	
Test for overall effect:	Z=0.49 (P = 0.6	63)				
Total (95% CI)		1603		1573	100.0%	0.00 [-0.00, 0.01]	•
Total events	38		34				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 7.4	5, df = 9 (P = 0.5	9); I² = 09	6	-0.5 -0.25 0 0.25
Test for overall effect:	Z= 0.51 (P = 0.6	51)				-0.5 -0.25 Ó 0.25 Favours systemic Favours placebo
Test for subgroup diff	ferences:	Chi ⁼=	0.34. df=	1 (P =	0.56), l ² =	0%	Favours systemic Favours placepo
omiting (by dos	e) – Pet	0					
0 ()	-,						

Vomiting (by dose) – Peto

omiting (by dos	e) – Peto	C					
	Systen	nic	Place	hn		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	-				Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.10.1 Single Dose							
Bjornson 2004	3	359	4	361	10.1%	0.75 [0.17, 3.34]	
Connett 1994	1	18	4	15	6.3%	0.20 [0.03, 1.34]	
Connett 1994	0	19	1	18	1.5%	0.13 [0.00, 6.46]	
Corneli 2007	17	305	14	295	42.8%	1.18 [0.57, 2.44]	
Kuyudu 2004	0	23	0	11		Not estimable	
Kuyucu 2004 Subtotal (95% CI)	0	23 747	0	12 712	60.6%	Not estimable 0.87 [0.47, 1.59]	•
Total events	21		23				
Heterogeneity: Chi ² =	- 2 D A df -	3 (P -	0.07\-12-	- D 4 07			
Test for overall effect	•			= 24%			
- ,	•			= 24%			
Test for overall effect	•			- 24%	17.9%	2.34 [0.76, 7.14]	
Test for overall effect 1.10.2 Multi-Dose	:Z=0.46(P = 0.6	4)		17.9% 1.5%	2.34 [0.76, 7.14] 7.41 [0.15, 373.47]	
Test for overall effect 1.10.2 Multi-Dose Csonka 2003	: Z = 0.46 (9	P = 0.6 113	4) 4	117			
Test for overall effect 1.10.2 Multi-Dose Csonka 2003 Panickar 2009	: Z = 0.46 (9 1	P = 0.6 113 343	4) 4 4 0	117 344	1.5%	7.41 [0.15, 373.47]	
Test for overall effect 1.10.2 Multi-Dose Csonka 2003 Panickar 2009 Plint 2009 Plint 2009	: Z = 0.46 (9 1 2	P = 0.6 113 343 200 200	4) 4 0 4	117 344 199 201	1.5% 8.6% 11.4%	7.41 [0.15, 373.47] 0.51 [0.10, 2.54] 1.67 [0.41, 6.77]	
Test for overall effect 1.10.2 Multi-Dose Csonka 2003 Panickar 2009 Plint 2009 Plint 2009 Subtotal (95% CI)	Z = 0.46 (9 1 2 5 17 : 2.99, df =	P = 0.6 113 343 200 200 856 3 (P =	4) 4 0 4 3 11 0.39); I ² =	117 344 199 201 861	1.5% 8.6% 11.4%	7.41 [0.15, 373.47] 0.51 [0.10, 2.54] 1.67 [0.41, 6.77]	
Test for overall effect 1.10.2 Multi-Dose Csonka 2003 Panickar 2009 Plint 2009 Plint 2009 Subtotal (95% Cl) Total events Heterogeneity: Chi ² =	Z = 0.46 (9 1 2 5 17 : 2.99, df =	P = 0.6 113 343 200 200 856 3 (P =	4) 4 0 4 3 11 0.39); I ² =	117 344 199 201 861 = 0%	1.5% 8.6% 11.4%	7.41 [0.15, 373.47] 0.51 [0.10, 2.54] 1.67 [0.41, 6.77]	

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Vomiting (by condition)

Study or Subgroup	Systen Events		Placet Events		Weight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
1.11.1 Asthma	LYGING	Total	Eventa	rotar	ricigitt	men, rondom, 55/8 Cr	men, realidoni, 55 /a Gi
	4	40		45	0.400	0.04 1.0 46 0.041	
Connett 1994	1	18	4	15	0.1%	-0.21 [-0.46, 0.04]	
Connett 1994	0	19	1	18	0.2%	-0.06 [-0.19, 0.08]	
Subtotal (95% CI)		37		33	0.3%	-0.11 [-0.27, 0.06]	
Total events	1		5				
Heterogeneity: Tau ² : Test for overall effect	•			P = 0.2	2); I^z = 33'	%	
1.11.2 Bronchiolitis							
Corneli 2007	17	305	14	295	3.2%	0.01 [-0.03, 0.04]	+
Kuyudu 2004	0	23	0	11	0.3%	0.00 [-0.13, 0.13]	
Kuyudu 2004	0	23	0	12	0.3%	0.00 [-0.12, 0.12]	
Plint 2009	2	200	4	199	7.1%	-0.01 [-0.03, 0.01]	-
Plint 2009	5	200	3	201	5.4%	0.01 [-0.02, 0.04]	+
Subtotal (95% CI)		751		718	16.3%	0.00 [-0.02, 0.02]	♦
Total events	24		21				
Heterogeneity: Tau ² : Test for overall effect	= 0.00; Chi		, df = 4 (F	° = 0.8	2); I² = 0%		
1.11.3 Croup							
Bjornson 2004 Subtotal (95% Cl)	3	359 359	4	361 361	19.7% 19.7 %	-0.00 [-0.02, 0.01] - 0.00 [-0.02, 0.01]	t
Total events	3		4				1
Heterogeneity: Not a							
Test for overall effect		P = 0.7	1)				
1.11.4 Wheeze							
Csonka 2003	9	113	4	117	1.1%	0.05 [-0.01, 0.11]	+
Panickar 2009	1	343	0	344	62.6%	0.00 [-0.01, 0.01]	
Subtotal (95% CI)		456		461	63.8%	0.02 [-0.06, 0.11]	
Total events	10		4				
Heterogeneity: Tau ² : Test for overall effect	•			° = 0.0	05); I² = 8	7%	
Total (95% CI)		1603		1573	100.0%	0.00 [-0.00, 0.01]	
Total events	38		34				
		2 2 4 5	df = 0.70	^o = 0.5	9); I² = 0%		
Heterogeneity: Tau ² : Test for overall effect	= 0.00; Chi				.,,)	-0.5 -0.25 0 0.25 Eavours systemic Favours placebo
Heterogeneity: Tau ² :	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				-0.5 -0.25 0 0.25 Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				-0.5 -0.25 0 0.25 Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				-0.5 -0.25 0 0.25 Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				-0.5 -0.25 0 0.25 Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				-0.5 -0.25 0 0.25 Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo
Heterogeneity: Tau²: Test for overall effect	= 0.00; Chi :: Z = 0.51 (P = 0.6	1)				Favours systemic Favours placebo

	System	nic	Place	ho		Peto Odds Ratio	D.	to Odds Ratio	
Study or Subgroup	-				Weight	Peto, Fixed, 95% Cl		o, Fixed, 95% Cl	
1.12.1 Asthma									
Connett 1994	1	18	4	15	6.3%	0.20 [0.03, 1.34]	• •		
Connett 1994 Subtotel (05% CD	0	19 37	1	18 33	1.5% 7.8 %	0.13 (0.00, 6.46) 0.19 (0.03, 1.02)	•		
Subtotal (95% Cl) Total events	1	37	5	77	7.070	0.19[0.03, 1.02]			
Heterogeneity: Chi ² =		1 (P =		= 0%					
Test for overall effect	•	•							
1.12.2 Bronchiolitis									
Corneli 2007 Kuyucu 2004	17 0	305 23	14 0	295 11	42.8%	1.18 [0.57, 2.44]			
καγάζα 2004 Κάγαςα 2004	0	23	0	12		Not estimable Not estimable			
Plint 2009	2	200	4	199	8.6%	0.51 [0.10, 2.54]		•	
Plint 2009	5	200	3	201	11.4%	1.67 [0.41, 6.77]	-		
Subtotal (95% CI)		751		718	62.8%	1.12 [0.62, 2.04]		-	
Total events	24		21						
Heterogeneity: Chi ² =	•			= 0%					
Test for overall effect	. Z = 0.38 (P = 0.7	1)						
1.12.3 Croup									
Bjornson 2004	3	359	4	361	10.1%	0.75 [0.17, 3.34]			
Subtotal (95% CI)		359		361	10.1%	0.75 [0.17, 3.34]			
Total events	3		4						
Heterogeneity: Not ap		D - 0 -	43						
Test for overall effect	: Z = 0.37 (P = 0.7	1)						
1.12.4 Wheeze									
Csonka 2003	9	113	4	117	17.9%	2.34 [0.76, 7.14]			
Panickar 2009	1	343	0	344	1.5%	7.41 [0.15, 373.47]			
Subtotal (95% CI)		456		461	19.3%	2.55 [0.87, 7.46]			
Total events	10		4	0.07					
Heterogeneity: Chi² = Test for overall effect	•	•		= 0%					
restion overall effect	. 2 - 1.7 ((r – 0.U	(3)						
Total (95% CI)		1603		1573	100.0%	1.10 [0.69, 1.76]		+	
Total events	38		34			· · ·			
Heterogeneity: Chi² =				= 17%			0.05 0.2		
Test for overall effect			•	a	o oo:	66 OW		temic Favours placebo	4
Test for subgroup dif	rerences: I	Uni*=1	0.80, df=	3 (P =	0.08), I* =	- 55.9%			
Abdominal pain									
Study or Subgroup	System Events	Total	Placeb Events	Total	-	Risk Difference M-H, Random, 95% Cl		iisk Difference , Random, 95% Cl	
Bjornson 2004	1	359	1	361	100.0%	0.00 [-0.01, 0.01]			
Total (95% CI)		359		361	100.0%	0.00 [-0.01, 0.01]			
Total events	1		1						
Heterogeneity: Not ap	•						-1 -0.5	0 0.5	
Test for overall effect:	Z = 0.00 (F	^o = 1.0	D)					temic Favours placebo	

Abdominal pain - Peto

	Syster	nic	Place	bo		Peto Odds Ratio		Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl		Peto, Fixe	ed, 95% Cl	
Bjornson 2004	1	359	1	361	100.0%	1.01 [0.06, 16.11]				
Total (95% CI)		359		361	100.0%	1.01 [0.06, 16.11]				
Total events	1		1							
Heterogeneity: Not ap Test for overall effect:	•	(P = 1.0	10)				L 0.01	0.1 Favours systemic	1 10 Favours placebo	100

Diarrhea

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Csonka 2003	6	113	6	117	34.4%	0.00 [-0.06, 0.06]	+
Lin 1991	1	52	0	28	26.9%	0.02 [-0.05, 0.08]	
Teeratakulpisarn 2007	3	89	3	85	38.7%	-0.00 [-0.06, 0.05]	-+-
Total (95% CI)		254		230	100.0%	0.01 [-0.03, 0.04]	•
Total events	10		9				
Heterogeneity: Tau ² = 0.0	00; Chi ^z =	0.26, d	f= 2 (P =	0.88);	I²=0%		
Test for overall effect: Z =	= 0.30 (P =	0.76)					-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Diarrhea – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Csonka 2003	6	113	6	117	62.9%	1.04 [0.33, 3.31]	— —
Lin 1991	1	52	0	28	5.0%	4.66 [0.08, 283.63]	
Teeratakulpisarn 2007	3	89	3	85	32.1%	0.95 [0.19, 4.84]	
Total (95% CI)		254		230	100.0%	1.09 [0.43, 2.73]	+
Total events	10		9				
Heterogeneity: Chi ² = 0.5	51, df = 2 (P = 0.7	7); l² = 09	6			
Test for overall effect: Z =	= 0.18 (P =	0.86)					0.005 0.1 1 10 200 Favours systemic Favours placebo

Diarrhea (by dose)

	Syster	nic	Place	00		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.17.1 Single Dose							
Teeratakulpisarn 2007 Subtotal (95% Cl)	3	89 89	3	85 85	38.7% 38.7 %	-0.00 [-0.06, 0.05] - 0.00 [-0.06, 0.05]	
Total events	3		3				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	0.06 (P =	0.95)					
1.17.2 Multi-Dose							
Csonka 2003	6	113	6	117	34.4%	0.00 [-0.06, 0.06]	
Lin 1991	1	52	0	28	26.9%	0.02 [-0.05, 0.08]	_
Subtotal (95% Cl)		165		145	61.3%	0.01 [-0.03, 0.05]	-
Total events	7		6				
Heterogeneity: Tau ² = 0.0	00; Chi ² = 1	0.18, d	f=1 (P=	0.67);1	²=0%		
Test for overall effect: Z =	0.43 (P =	0.67)					
Total (95% CI)		254		230	100.0%	0.01 [-0.03, 0.04]	-
Total events	10		9				

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Diarrhea (by dose) - Peto

	Systen	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.18.1 Single Dose							
Teeratakulpisarn 2007	3	89	3	85	32.1%	0.95 [0.19, 4.84]	_
Subtotal (95% CI)		89		85	32.1%	0.95 [0.19, 4.84]	
Total events	3		3				
Heterogeneity: Not applic:	able						
Test for overall effect: Z = I	0.06 (P =	0.95)					
1.18.2 Multi-Dose							
Csonka 2003	6	113	6	117	62.9%	1.04 [0.33, 3.31]	
Lin 1991	1	52	0	28	5.0%	4.66 [0.08, 283.63]	
Subtotal (95% CI)		165		145	67.9%	1.16 [0.38, 3.54]	-
Total events	7		6				
Heterogeneity: Chi ² = 0.48	3, df = 1 (F	P = 0.4	9); I ^z = 09	6			
Test for overall effect: Z = I	0.26 (P =	0.80)					
Total (95% Cl)		254		230	100.0%	1.09 [0.43, 2.73]	+
Total events	10		9				
Heterogeneity: Chi ² = 0.51	, df = 2 (F	P = 0.7	7); I² = 09	6			
Test for overall effect: Z =	0.18 (P =	0.86)					0.002 0.1 1 10 Favours systemic Favours placebo
Test for subgroup differen	ices: Chi ^z	= 0.04	4, df = 1 (l	P = 0.8	5), I ^z = 0%		Favouis systemit Favouis platebo

Diarrhea (by condition)

						D: 1 D:07	B : 1 B:27
Church and Carls and an	Syster		Placel			Risk Difference	Risk Difference
Study or Subgroup 1.19.1 Bronchiolitis	Events	Total	Events	Total	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Teeratakulpisarn 2007	3	89	3	85	38.7%	-0.00 [-0.06, 0.05]	
Subtotal (95% CI)	Ŭ	89	Ŭ	85	38.7%	-0.00 [-0.06, 0.05]	
Total events	3		3				
Heterogeneity: Not appli	cable						
Test for overall effect: Z =	= 0.06 (P =	0.95)					
1.19.2 Wheeze							
Csonka 2003	6	113	6	117	34.4%	0.00 [-0.06, 0.06]	+
Lin 1991	1	52	0	28	26.9%	0.02 [-0.05, 0.08]	
Subtotal (95% CI)		165		145	61.3%	0.01 [-0.03, 0.05]	-
	7		6				
Total events	0.0.01.2	018 d	f=1 (P=	0.67);1	l²=0%		
	uu; Chif=	0.10,0					
Heterogeneity: Tau ² = 0.							
Total events Heterogeneity: Tau² = 0. Test for overall effect: Z = Total (95% CI)				230	100.0%	0.01 [-0.03, 0.04]	•

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Diarrhea (by condition) – Peto

Study or Subgroup	Systemic Events Total	Placebo Events Total	Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.20.1 Bronchiolitis Teeratakulpisarn 2007	3 89	3 85	32.1%	0.95 [0.19, 4.84]	
Subtotal (95% CI)	89	85	32.1%	0.95 [0.19, 4.84]	
Total events Heterogeneity: Not applic	3 able	3			
Test for overall effect: Z =					
1.20.2 Wheeze	6 440	C 447	62.00	4 04 10 00 0 041	
Csonka 2003 Lin 1991	6 113 1 52	6 117 0 28	62.9% 5.0%	1.04 [0.33, 3.31] 4.66 [0.08, 283.63]	T
Subtotal (95% CI)	165	145	67.9%	1.16 [0.38, 3.54]	•
Total events	7 0 46 - 470 - 0 44	6 20. 17 - 001			
Heterogeneity: Chi ² = 0.4 Test for overall effect: Z =		a); I= U%			
Total (95% Cl)	254		100.0%	1.09 [0.43, 2.73]	•
Total events	10 1 df= 270 = 0.7	9 2): 1 2 - 00/			
Heterogeneity: Chi ² = 0.5 Test for overall effect: Z =		/); F= 0%			0.002 0.1 1 10 500
Test for subgroup differe		, df = 1 (P = 0.8	5), I² = 09	6	Favours systemic Favours placebo
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					Supplement 6 - Page 22 of 71
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SYSTEMIC vs. PLACEBO – CNS & Behaviour

Tremor/jitteriness

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Connett 1994	7	18	5	15	0.3%	0.06 [-0.27, 0.38]	
Connett 1994	2	19	2	18	0.8%	-0.01 [-0.21, 0.19]	
Goebel 2000	1	24	0	24	2.7%	0.04 [-0.07, 0.15]	_
Kuyudu 2004	0	23	0	11	1.9%	0.00 [-0.13, 0.13]	
Kuyucu 2004	0	23	0	12	2.2%	0.00 [-0.12, 0.12]	
Lin 1991	3	52	1	28	3.6%	0.02 [-0.07, 0.12]	-
Plint 2009	4	200	4	199	41.1%	-0.00 [-0.03, 0.03]	+
Plint 2009	5	200	2	201	47.4%	0.02 [-0.01, 0.04]	+
Total (95% CI)		559		508	100.0%	0.01 [-0.01, 0.03]	•
Total events	22		14				
Heterogeneity: Tau ² =	= 0.00; Chi	i ^z = 1.2	3, df = 7 ((P = 0.9	9); I^z = 0 9	6	
Test for overall effect:				•			-0.5 -0.25 0 0.25 0. Favours systemic Favours placebo

Tremor/jitteriness – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Connett 1994	7	18	5	15	25.4%	1.26 [0.31, 5.13]	
Connett 1994	2	19	2	18	11.9%	0.94 [0.12, 7.31]	
Goebel 2000	1	24	0	24	3.3%	7.39 [0.15, 372.38]	
Kuyudu 2004	0	23	0	11		Not estimable	
Kuyudu 2004	0	23	0	12		Not estimable	
Lin 1991	3	52	1	28	11.4%	1.58 [0.19, 12.83]	
Plint 2009	4	200	4	199	25.6%	0.99 [0.25, 4.03]	
Plint 2009	5	200	2	201	22.4%	2.40 [0.54, 10.68]	
Total (95% CI)		559		508	100.0%	1.44 [0.71, 2.92]	•
Total events	22		14				
Heterogeneity: Chi ² =	= 1.59, df =	= 5 (P =	0.90); I² :	= 0%			
Test for overall effect	: Z = 1.01	(P = 0.3	31)				0.002 0.1 1 10 50 Favours systemic Favours placebo

Tremor/jitteriness (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.49.1 Single Dose							
Connett 1994	7	18	5	15	0.3%	0.06 [-0.27, 0.38]	
Connett 1994	2	19	2	18	0.8%	-0.01 [-0.21, 0.19]	
Kuyudu 2004	0	23	0	11	1.9%	0.00 [-0.13, 0.13]	
Kuyudu 2004	0	23	0	12	2.2%	0.00 [-0.12, 0.12]	
Subtotal (95% Cl)		83		56	5.2%	0.00 [-0.08, 0.08]	
Total events	9		7				
Heterogeneity: Tau² = Test for overall effect			•	P = 0.9	8); I² = 0%	6	
1.49.2 Multi-Dose							
Goebel 2000	1	24	0	24	2.7%	0.04 [-0.07, 0.15]	
Lin 1991	3	52	1	28	3.6%	0.02 [-0.07, 0.12]	 -
Plint 2009	4	200	4	199	41.1%	-0.00 [-0.03, 0.03]	+
Plint 2009	5	200	2	201	47.4%	0.02 [-0.01, 0.04]	+
Subtotal (95% CI)		476		452	94.8%	0.01 [-0.01, 0.03]	*
Heterogeneity: Tau² = Test for overall effect			•	P = 0.7	8); I² = 09	ó	
Total (95% CI)		559		508	100.0%	0.01 [-0.01, 0.03]	+
Total events	22		14				
Heterogeneity: Tau ² =	= 0.00; Ch	i = 1.23	3, df = 7 (P = 0.9	9); I² = 0 9	6 -	-0.2 -0.1 0 0.1 0.2
Test for overall effect	: Z = 1.01	(P = 0.3)	1)				Favours systemic Favours placebo
Test for subgroup dif	ferences:	Chi² = I	0.03, df=	1 (P =	0.86), I ^z =	0%	
remor/jitterines	ss (by d	ose) -	- Peto				
	Syste	mic	Place	ebo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.50.1 Single Dose							
Connett 1994	7	18	5	15	25.4%	1.26 [0.31, 5.13]	
Connett 1994	2						
Κυγυου 2004	0					Not estimable	
Kuyucu 2004	Ō					Not estimable	
Subtotal (95% CI)	Ŭ	83		56			-
Total events	9		7				T

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); l² = 0% Test for overall effect: Z = 0.24 (P = 0.81)

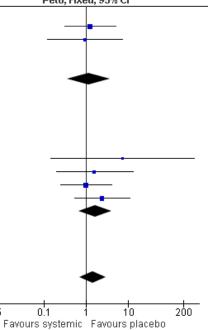
Test for overall effect: Z = 1.01 (P = 0.31)

Test for overall effect. $\Sigma = 0.24$ (P

1.50.2 Multi-Dose

Goebel 2000	1	24	0	24	3.3%	7.39 [0.15, 372.38]
Lin 1991	3	52	1	28	11.4%	1.58 [0.19, 12.83]
Plint 2009	4	200	4	199	25.6%	0.99 [0.25, 4.03]
Plint 2009	5	200	2	201	22.4%	2.40 [0.54, 10.68]
Subtotal (95% CI)		476		452	62.7%	1.65 [0.67, 4.02]
Total events	13		7			
Heterogeneity: Chi ² = 1.3	1,df=	3 (P = 0.	.73); I² = 0	1%		
Test for overall effect: Z =	1.09 (P = 0.27))			
Total (95% CI)		559		508	100.0%	1.44 [0.71, 2.92]
Total events	22		14			
Heterogeneity: Chi ² = 1.5	9, df =	5 (P = 0.	.90); I ² = 0	1%		

Test for subgroup differences: $Chi^2 = 0.23$, df = 1 (P = 0.63), $I^2 = 0\%$



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Tremor/jitteriness (by condition)

Study or Subgroup	Systen		Placel		Mojaht	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
1.51.1 Asthma	Events	TULAI	Events	TULAI	weight	M-H, Kanuolii, 95% Ci	Wi-H, Rahuolii, 95% Ci
	_	4.0	-				
Connett 1994	7	18	5	15	0.3%	0.06 [-0.27, 0.38]	
Connett 1994	2	19	2	18	0.8%	-0.01 [-0.21, 0.19]	
Subtotal (95% CI)		37		33	1.1%	0.01 [-0.16, 0.18]	
Total events	9		7				
Heterogeneity: Tau ² =				P = 0.7	3); I² = 0%		
Test for overall effect:	: Z = 0.12 (P = 0.9	90)				
1.51.2 Bronchiolitis							
Goebel 2000	1	24	0	24	2.7%	0.04 [-0.07, 0.15]	
	0	24	0	11			
Kuyucu 2004	-		-		1.9%	0.00 [-0.13, 0.13]	
Kuyucu 2004	0	23	0	12	2.2%	0.00 [-0.12, 0.12]	
Plint 2009	4	200	4	199	41.1%	-0.00 [-0.03, 0.03]	
Plint 2009	5	200	2	201	47.4%	0.02 [-0.01, 0.04]	—
Subtotal (95% CI)		470		447	95.4%	0.01 [-0.01, 0.03]	₹
Total events	10		6				
Heterogeneity: Tau ² =				P = 0.9	1); I² = 0%	D	
Test for overall effect:	Z = 0.93 (P = 0.3	35)				
1.51.3 Wheeze							
Lin 1991	3	52	1	28	3.6%	0.02 [-0.07, 0.12]	.
Subtotal (95% CI)	5	52		28	3.6%	0.02 [-0.07, 0.12]	
Subtordi (SS a Si)		52		20	0.074	0.02 [-0.01, 0.12]	
Total quanta	2						
Total events	3 anliaghta		1				
Heterogeneity: Not ap	oplicable						
	oplicable	P = 0.6					
Heterogeneity: Not ap	oplicable	P = 0.6 559		508	100.0%	0.01 [-0.01, 0.03]	•
Heterogeneity: Not ap Test for overall effect:	oplicable			508	100.0%	0.01 [-0.01, 0.03]	•
Heterogeneity: Not a; Test for overall effect: Total (95% CI) Total events	oplicable : Z = 0.46 (22	559	i4) 14				
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² =	oplicable : Z = 0.46 (22 = 0.00; Chi	559 ² = 1.23	34) 14 3, df = 7 (1				-0.2 -0.1 0 0.1 0.2
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² =	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%		Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place
Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	22 = 0.00; Chi 2 = 1.01 (559 ² = 1.23 P = 0.3)4) 14 3, df = 7 (1 31)	P = 0.9	9); I² = 0%	5 – 0%	Favours systemic Favours place

Tremor/jitteriness (by condition) - Peto

Study or Subgroup	Syster Events		Place		Moinht	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.52.1 Asthma	Events	TULAI	Events	TULAI	weight	Peto, Fixeu, 95% Ci	Peto, Fixed, 95% Ci
Connett 1994	7	18	5	15	25.4%	1.26 [0.31, 5.13]	
Connett 1994	2	19	2	18	11.9%	0.94 [0.12, 7.31]	
Subtotal (95% CI)	-	37	-	33		1.15 [0.36, 3.66]	-
Total events	9		7				
Heterogeneity: Chi ² =	-	1 (P =		= 0%			
Test for overall effect	•		<i></i>	• • •			
1.52.2 Bronchiolitis							
Goebel 2000	1	24	0	24	3.3%	7.39 [0.15, 372.38]	
Kuyucu 2004	O	23	Ő	11	//	Not estimable	
Kuyucu 2004	Ŭ	23	Ő	12		Not estimable	
Plint 2009	4	200	4	199	25.6%	0.99 [0.25, 4.03]	_
Plint 2009	5	200	2	201	22.4%	2.40 [0.54, 10.68]	
Subtotal (95% CI)	-	470	-	447	51.3%	1.66 [0.62, 4.46]	
Total events	10		6				
Heterogeneity: Chi ² =	= 1.31. df =	2 (P =	0.52); l ² :	= 0%			
Test for overall effect							
1.52.3 Wheeze							
Lin 1991	3	52	1	28	11.4%	1.58 [0.19, 12.83]	
Subtotal (95% Cl)		52		28	11.4%	1.58 [0.19, 12.83]	
Total events	3		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.43 ((P = 0.6	67)				
Total (95% Cl)		559		508	100.0%	1.44 [0.71, 2.92]	•
Total events	22		14				
Heterogeneity: Chi ² =	= 1.59, df =	5 (P =	0.90); l ² :	= 0%			0.002 0.1 1 10 50
Test for overall effect	t: Z = 1.01 ((P = 0.3	31)				Favours systemic Favours placebo
Test for subaroup dif	fferences:	Chi²=	0.23, df=	2 (P =	0.89), i ² =	: 0%	
ehaviour chang	e						
	Systen	nic	Place	00		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	1	359	1	361	70.0%	0.00 [-0.01, 0.01]] 📕
Csonka 2003	3	113	2	117	11.0%	0.01 [-0.03, 0.05]]
Klassen 1998	0	64	0	65	16.5%	0.00 [-0.03, 0.03]	ı — + —

Behaviour change

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	1	359	1	361	70.0%	0.00 [-0.01, 0.01]	
Csonka 2003	3	113	2	117	11.0%	0.01 [-0.03, 0.05]	+ •
Klassen 1998	0	64	0	65	16.5%	0.00 [-0.03, 0.03]	+
Lin 1991	3	52	0	28	2.6%	0.06 [-0.02, 0.14]	
Total (95% CI)		588		571	100.0%	0.00 [-0.01, 0.02]	•
Total events	7		3				
Heterogeneity: Tau ² =	= 0.00; Chi	i ^z = 3.7	2, df = 3 (P = 0.2	9); I^z = 19	1%	
Test for overall effect:	Z= 0.37 ((P = 0.7	'1)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo

Behaviour change – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	1	359	1	361	20.9%	1.01 [0.06, 16.11]	
Csonka 2003	3	113	2	117	51.3%	1.56 [0.27, 9.13]	
Klassen 1998	0	64	0	65		Not estimable	
Lin 1991	3	52	0	28	27.8%	4.85 [0.44, 53.60]	
Total (95% CI)		588		571	100.0%	1.95 [0.55, 6.92]	-
Total events	7		3				
Heterogeneity: Chi ² =	0.83, df=	2 (P =	0.66); I² =	= 0%			
Test for overall effect:	: Z = 1.03 ((P = 0.3	30)				0.002 0.1 1 10 500 Favours systemic Favours placebo

Behaviour change (by dose)

Study or Subgroup	Syster Events		Evente	Total	Moinht	Risk Difference M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.55.1 Single-dose	LYGING	Total	LYGING	Total	meight	W-H, Nahuoth, 55% G	Mini, Nandom, 55% Ci
Biornson 2004	1	359	1	361	70.0%	0.00 [-0.01, 0.01]	•
Klassen 1998	n	64	O	65	16.5%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)	-	423	, i	426	86.4%	0.00 [-0.01, 0.01]	
Total events	1		1				
Heterogeneity: Tau ²	= 0.00; Ch	i ^z = 0.00	D, df = 1 (l	P = 1.0	0); I ² = 09	, b	
Test for overall effec	t: Z = 0.00 ((P = 1.0	0)				
1.55.2 Multi-dose							
Csonka 2003	3	113	2	117	11.0%	0.01 [-0.03, 0.05]	
Lin 1991	3	52	ñ	28	2.6%	0.06 [-0.02, 0.14]	
Subtotal (95% CI)	5	165	0	145	13.6%	0.02 [-0.02, 0.06]	
Total events	6		2				
Heterogeneity: Tau ²	= 0.00; Ch	r= 1.1∶	3, df = 1 (l	P = 0.2	9); I² = 11	%	
Test for overall effec	:t: Z = 0.98 ((P = 0.3	(2)				
Total (95% CI)		588		571	100.0%	0.00 [-0.01, 0.02]	
· ·	7	588	3	571	100.0 %	0.00 [-0.01, 0.02]	+
Total events			-				+
Total (95% CI) Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch	r = 3.73	2, df = 3 (l				-0.1 -0.05 0 0.05 0.1
Total events Heterogeneity: Tau ²	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo
Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	
Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	
Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	
Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	
Total events Heterogeneity: Tau ² Test for overall effec	= 0.00; Ch :t: Z = 0.37 (i ^z = 3.7) (P = 0.7	2, df = 3 (l '1)	P = 0.2	9); i² = 19	% -	

Behaviour change (by dose) - Peto

	Systen	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.56.1 Single-dose							
Bjornson 2004	1	359	1	361	20.9%	1.01 [0.06, 16.11]	+
Klassen 1998	0	64	0	65		Not estimable	
Subtotal (95% CI)		423		426	20.9%	1.01 [0.06, 16.11]	
Total events	1		1				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.00 (P = 1.0)0)				
1.56.2 Multi-dose							
Csonka 2003	3	113	2	117	51.3%	1.56 [0.27, 9.13]	
Lin 1991	3	52	0	28	27.8%	4.85 [0.44, 53.60]	
Subtotal (95% CI)		165		145	79.1%	2.32 [0.56, 9.64]	
Total events	6		2				
Heterogeneity: Chi ² = I	0.56, df =	1 (P =	0.46); l ² =	= 0%			
Test for overall effect: J	Z=1.16 (P = 0.2	?5)				
Total (05% CI)		588		574	400.0%	4 05 10 55 6 021	
Total (95% CI)	_	299	_	571	100.0%	1.95 [0.55, 6.92]	
Total events	7		3				
Heterogeneity: Chi ² = I	•			= 0%			0.002 0.1 1 10 50
Test for overall effect: .	,						Favours systemic Favours placebo
Test for subgroup diffe	erences: (Chi ≃ =∣	0.28, df =	1 (P =	0.60), l² =	0%	

Behaviour change (by condition)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.57.1 Croup							
Bjornson 2004	1	359	1	361	70.0%	0.00 [-0.01, 0.01]	
Klassen 1998	0	64	0	65	16.5%	0.00 [-0.03, 0.03]	_ + _
Subtotal (95% CI)		423		426	86.4%	0.00 [-0.01, 0.01]	♦
Total events	1		1				
Heterogeneity: Tau ² = Test for overall effect	•			P = 1.0	0); I² = 09	6	
1.57.2 Wheeze							
Csonka 2003	3	113	2	117	11.0%	0.01 [-0.03, 0.05]	
Lin 1991	3	52	0	28	2.6%	0.06 [-0.02, 0.14]	
Subtotal (95% CI)		165		145	13.6%	0.02 [-0.02, 0.06]	-
Total events	6		2				
Heterogeneity: Tau ² = Test for overall effect	•			P = 0.2	9); I² = 11	%	
Total (95% CI)		588		571	100.0%	0.00 [-0.01, 0.02]	+
Total events	7		3				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 3.73	2, df = 3 (P = 0.2	9); I² = 19	I% —	-0.1 -0.05 0 0.05 0.1
Test for overall effect	Z = 0.37 (P = 0.7	71)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo
Test for subgroup dif	ferences:	Chi ^z = I	0.93, df=	1 (P =	0.33), I ^z =	: 0%	r avours systemme. Favours placebo

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	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.58.1 Croup							
Bjornson 2004	1	359	1	361	20.9%	1.01 [0.06, 16.11]	+
Klassen 1998	0	64	0	65		Not estimable	
Subtotal (95% CI)		423		426	20.9%	1.01 [0.06, 16.11]	
Total events	1		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.00 (P = 1.0	10)				
1.58.2 Wheeze							
Csonka 2003	3	113	2	117	51.3%	1.56 [0.27, 9.13]	
Lin 1991	3	52	0	28	27.8%	4.85 [0.44, 53.60]	
Subtotal (95% CI)		165		145	79.1%	2.32 [0.56, 9.64]	
Total events	6		2				
Heterogeneity: Chi ² :	= 0.56, df =	1 (P =	0.46); l² =	:0%			
Test for overall effect	t: Z = 1.16 (P = 0.2	?5)				
Total (95% Cl)		588		571	100.0%	1.95 [0.55, 6.92]	
Total events	7		3				

Headache

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Connett 1994	0	18	1	15	27.8%	-0.07 [-0.23, 0.09]	
Connett 1994	0	19	0	18	72.2%	0.00 [-0.10, 0.10]	
Total (95% CI)		37		33	100.0%	-0.02 [-0.10, 0.07]	
Total events	0		1				
Heterogeneity: Tau² =	•		•	(P = 0.4	5); I² = 09	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z= 0.43	(P = 0.6	67)				Favours systemic Favours placebo

Headache – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Connett 1994	0	18	1	15	100.0%	0.11 [0.00, 5.68]	
Connett 1994	0	19	0	18		Not estimable	
Total (95% Cl)		37		33	100.0%	0.11 [0.00, 5.68]	
Total events	0		1				
Heterogeneity: Not a	pplicable						0.002 0.1 1 10 500
Test for overall effect	: Z = 1.10	(P = 0.2	27)				Favours systemic Favours placebo

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SYSTEMIC vs. PLACEBO – Dermatologic

Integument

Study or Subgroup	Systen Events		Placel		Weight	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% Cl
Bjornson 2004	2	359	0	361	83.2%	0.01 [-0.00, 0.01]	
Csonka 2003	2	113	0	117	8.5%	0.02 [-0.01, 0.05]	—
Klassen 1998	0	64	0	65	8.3%	0.00 [-0.03, 0.03]	_ _
	-		-				
Total (95% CI)		536		543	100.0%	0.01 [-0.00, 0.01]	•
Total events	4		0		D. 17. 0.00		
Heterogeneity: Tau ² = Test for overall effect:				· = 0.6	5); i= 0%)	-0.2 -0.1 0 0.1 0.2
restion overall ellect.	Z = 1.41 (i	r – 0.1	0)				Favours systemic Favours placebo
ntegument – Pet	:0						
0							
	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	2	359	0	361	50.1%	7.45 [0.47, 119.36]	
Csonka 2003	2	113	0	117		7.72 [0.48, 124.29]	
Klassen 1998	0	64	0	65		Not estimable	
Total (95% CI)		536		542	100.0%	7.59 [1.07, 54.01]	
	4	500	0	343	100.0%	7.59[1.07, 54.01]	
Total events Heterogeneity: Chi ² =	•	1 /D -	-	- ೧ೲ			+ · · · · · · · · · · · · · · · · · · ·
Test for overall effect	•			- 070			0.005 0.1 i 10 2
Testion overall effect.	. 2 - 2.02 ((i = 0.0	54)				Favours systemic Favours placebo
ntegument (by d	ose)						
	Systen		Placel			Risk Difference	Risk Difference
Study or Subgroup	Systen				Weight	Risk Difference M-H, Random, 95% Cl	
Study or Subgroup 1.71.1 Single dose	Systen Events	Total	Events	Total		M-H, Random, 95% CI	
Study or Subgroup 1.71.1 Single dose Bjornson 2004	Systen Events 2	Total 359	Events 0	Total 361	83.2%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01]	
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998	Systen Events	Total 359 64	Events	Total 361 65	83.2% 8.3%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI)	System Events 2 0	Total 359	Events 0 0	Total 361	83.2%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events	Systen Events 2 0 2	359 64 423	Events 0 0	361 65 426	83.2% 8.3% 91.5%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI)	System Events 2 0 2 0.00; Chi	Total 359 64 423 ² = 0.13	Events 0 0 8, df = 1 (1	361 65 426	83.2% 8.3% 91.5%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	System Events 2 0 2 0.00; Chi	Total 359 64 423 ² = 0.13	Events 0 0 8, df = 1 (1	361 65 426	83.2% 8.3% 91.5%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect:	System Events 2 0 2 0.00; Chi	Total 359 64 423 ² = 0.13	Events 0 0 8, df = 1 (1	361 65 426	83.2% 8.3% 91.5%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01]	M-H, Random, 95% Cl
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose	System Events 2 0 2 0.00; Chi Z = 1.11 (Total 359 64 423 °= 0.13 P = 0.2	0 0 8, df = 1 (1 7)	Total 361 65 426 P = 0.7	83.2% 8.3% 91.5% 2); I ^z = 0%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events	System <u>Events</u> 2 0 2 0.00; Chi ² Z = 1.11 (1 2 2 2	Total 359 64 423 ² = 0.13 P = 0.2 113	0 0 8, df = 1 (1 7)	Total 361 65 426 P = 0.7: 117	83.2% 8.3% 9 1.5% 2); I ² = 0% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events Heterogeneity: Not ap	System <u>Events</u> 2 0 2 0.00; Chi ⁷ Z = 1.11 (1 2 2 pplicable	Total 359 64 423 °= 0.13 P = 0.2 113 113	Events 0 0 3, df = 1 (1 7) 0 0	Total 361 65 426 P = 0.7: 117	83.2% 8.3% 9 1.5% 2); I ² = 0% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events	System <u>Events</u> 2 0 2 0.00; Chi ⁷ Z = 1.11 (1 2 2 pplicable	Total 359 64 423 °= 0.13 P = 0.2 113 113	Events 0 0 3, df = 1 (1 7) 0 0	Total 361 65 426 P = 0.7: 117	83.2% 8.3% 9 1.5% 2); I ² = 0% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events Heterogeneity: Not ap	System <u>Events</u> 2 0 2 0.00; Chi ⁷ Z = 1.11 (1 2 2 pplicable	Total 359 64 423 °= 0.13 P = 0.2 113 113	Events 0 0 3, df = 1 (1 7) 0 0	Total 361 65 426 P = 0.7: 117 117	83.2% 8.3% 9 1.5% 2); I ² = 0% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	System <u>Events</u> 2 0 2 0.00; Chi ⁷ Z = 1.11 (1 2 2 pplicable	Total 359 64 423 ² = 0.13 P = 0.2 113 113 P = 0.2	Events 0 0 3, df = 1 (1 7) 0 0	Total 361 65 426 P = 0.7: 117 117	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI)	System Events 2 0 2 0.00; Chi ² Z = 1.11 (l 2 pplicable Z = 1.18 (l 4	Total 359 64 423 ² = 0.13 P = 0.2 113 113 P = 0.2 536	Events 0 0 3, df = 1 (1 7) 0 4) 0	Total 361 65 426 P = 0.7: 117 117 543	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5%	<u>M-H, Random, 95% CI</u> 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect:	System Events 2 0 0.00; Chi ² Z = 1.11 (2 2 pplicable Z = 1.18 (4 0.00; Chi ² Z = 1.41 (Total 359 64 423 2 = 0.13 P = 0.2 113 113 P = 0.2 536 2 = 0.87 P = 0.2	Events 0 0 3, df = 1 (1 7) 0 0 4) 7, df = 2 (1 6)	Total 361 65 426 P = 0.7: 117 117 543 P = 0.6:	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5% 100.0% 5); I ² = 0%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05] 0.01 [-0.00, 0.01]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: Total (95% CI) Total events Heterogeneity: Tau ² =	System Events 2 0 0.00; Chi ² Z = 1.11 (2 2 pplicable Z = 1.18 (4 0.00; Chi ² Z = 1.41 (Total 359 64 423 2 = 0.13 P = 0.2 113 113 P = 0.2 536 2 = 0.87 P = 0.2	Events 0 0 3, df = 1 (1 7) 0 0 4) 7, df = 2 (1 6)	Total 361 65 426 P = 0.7: 117 117 543 P = 0.6:	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5% 100.0% 5); I ² = 0%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05] 0.01 [-0.00, 0.01]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect:	System Events 2 0 0.00; Chi ² Z = 1.11 (2 2 pplicable Z = 1.18 (4 0.00; Chi ² Z = 1.41 (Total 359 64 423 2 = 0.13 P = 0.2 113 113 P = 0.2 536 2 = 0.87 P = 0.2	Events 0 0 3, df = 1 (1 7) 0 0 4) 7, df = 2 (1 6)	Total 361 65 426 P = 0.7: 117 117 543 P = 0.6:	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5% 100.0% 5); I ² = 0%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05] 0.01 [-0.00, 0.01]	M-H, Random, 95% CI
Study or Subgroup 1.71.1 Single dose Bjornson 2004 Klassen 1998 Subtotal (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect: 1.71.2 Multi-dose Csonka 2003 Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: Total (95% Cl) Total events Heterogeneity: Tau ² = Test for overall effect:	System Events 2 0 0.00; Chi ² Z = 1.11 (2 2 pplicable Z = 1.18 (4 0.00; Chi ² Z = 1.41 (Total 359 64 423 2 = 0.13 P = 0.2 113 113 P = 0.2 536 2 = 0.87 P = 0.2	Events 0 0 3, df = 1 (1 7) 0 0 4) 7, df = 2 (1 6)	Total 361 65 426 P = 0.7: 117 117 543 P = 0.6:	83.2% 8.3% 91.5% 2); I ² = 0% 8.5% 8.5% 100.0% 5); I ² = 0%	M-H, Random, 95% Cl 0.01 [-0.00, 0.01] 0.00 [-0.03, 0.03] 0.01 [-0.00, 0.01] 0.02 [-0.01, 0.05] 0.02 [-0.01, 0.05] 0.01 [-0.00, 0.01]	M-H, Random, 95% CI

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Integument	by dose) – Peto
incegament	

	System		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.72.1 Single dose							
Bjornson 2004	2	359	0	361	50.1%	7.45 [0.47, 119.36]	
Klassen 1998	0	64	0	65		Not estimable	
Subtotal (95% CI)		423		426	50.1%	7.45 [0.47, 119.36]	
Total events	2		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z=1.42 (ł	P = 0.1	6)				
1.72.2 Multi-dose							
Csonka 2003	2	113	0	117	49.9%	7.72 [0.48, 124.29]	
Subtotal (95% CI)		113		117	49.9%	7.72 [0.48, 124.29]	
Total events	2		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z=1.44 (ł	P = 0.1	5)				
Total (95% CI)		536		543	100.0%	7.59 [1.07, 54.01]	
Total events	4		0				
Heterogeneity: Chi ² =	= 0.00, df =	1 (P =	0.99); i ² =	= 0%			
Test for overall effect	: Z = 2.02 (/	P = 0.0)4)				
Test for subgroup dif	, fferences: (Chi ^z = I	0.00, df=	1 (P =	0.99), l ² =	0%	Favours systemic Favours placebo
ntegument (by c	conditior	1)					
		,					
	System	ic	Placeb	00		Risk Difference	Risk Difference

Integument (by condition)

Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.73.1 Croup							
Bjornson 2004	2	359	0	361	83.2%	0.01 [-0.00, 0.01]	
Klassen 1998	0	64	0	65	8.3%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		423		426	91.5%	0.01 [-0.00, 0.01]	•
Total events	2		0				
Heterogeneity: Tau ² =	0.00; Ch	i² = 0.1	3, df = 1 (P = 0.7	2); I² = 09	6	
Test for overall effect:	Z=1.11	(P = 0.2	?7)				
1.73.2 Wheeze							
Csonka 2003	2	113	0	117	8.5%	0.02 [-0.01, 0.05]	+
Subtotal (95% CI)		113		117	8.5%	0.02 [-0.01, 0.05]	◆
Total events	2		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z=1.18	(P = 0.2	24)				
Total (95% CI)		536		543	100.0%	0.01 [-0.00, 0.01]	•
	4		0				
Total events					5); I² = 09		

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4	Integument (by c	ondition) – P	eto			
5		Systemic	Placebo		Peto Odds Ratio	Peto Odds Ratio
6	Study or Subgroup 1.74.1 Croup	Events Total	Events Tota	l Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
7	Bjornson 2004	2 359	0 361	50.1%	7.45 [0.47, 119.36]	
8 9	Klassen 1998 Subtotal (05% CI)	0 64 423	0 65 420		Not estimable 7.45 [0.47, 119.36]	
10	Subtotal (95% CI) Total events	2 423	0	50.1%	7.45 [0.47, 119.50]	
11	Heterogeneity: Not a					
12	Test for overall effect	: Z = 1.42 (P = 0.1	6)			
13	1.74.2 Wheeze					_
14 15	Csonka 2003 Subtotal (95% Cl)	2 113 113	0 113 117		7.72 [0.48, 124.29] 7.72 [0.48, 124.29]	
16	Total events	2	0			
17	Heterogeneity: Not ap		<i>E</i> \			
18	Test for overall effect	. Z = 1.44 (P = 0.1	5)			
19	Total (95% CI)	536		3 100.0%	7.59 [1.07, 54.01]	
20 21	Total events Heterogeneity: Chi² =	4 :0.00.df=1.(P=	0 0.99): I ² = 0%			+
21	Test for overall effect	Z = 2.02 (P = 0.0	14)			0.005 0.1 1 10 200 Favours systemic Favours placebo
23	Test for subgroup dif	ferences: Chi ^z = I	0.00, df = 1 (P :	= 0.99), I ^z =	: 0%	
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SYSTEMIC vs. PLACEBO – Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Bjornson 2004	1	359	0	361	51.3%	0.00 [-0.00, 0.01]	•
Eden 1967	0	25	0	25	0.5%	0.00 [-0.07, 0.07]	
Plint 2009	0	200	0	199	31.7%	0.00 [-0.01, 0.01]	+
Plint 2009	1	200	0	201	16.0%	0.01 [-0.01, 0.02]	+
Tagarro 2014	3	48	1	32	0.4%	0.03 [-0.06, 0.12]	
Total (95% CI)		832		818	100.0%	0.00 [-0.00, 0.01]	•
Total events	5		1				
Heterogeneity: Tau ² =	= 0.00; Chi	r= 1.0°	6				
Test for overall effect:							-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Fluid & electrolyte abnormalities – Peto

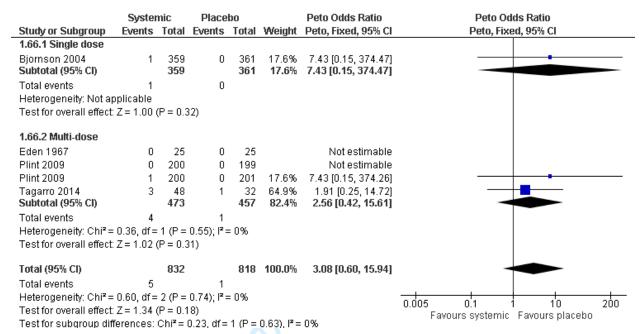
	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]	
Eden 1967	0	25	0	25		Not estimable	
Plint 2009	0	200	0	199		Not estimable	
Plint 2009	1	200	0	201	17.6%	7.43 [0.15, 374.26]	
Tagarro 2014	3	48	1	32	64.9%	1.91 [0.25, 14.72]	
Total (95% CI)		832		818	100.0%	3.08 [0.60, 15.94]	-
Total events	5		1				
Heterogeneity: Chi ² =	0.60, df=	2 (P =	0.74); l² =	= 0%			
Test for overall effect:							0.002 0.1 1 10 500 Favours systemic Favours placebo

Fluid & electrolyte abnormalities (by dose)

	Systen	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.65.1 Single dose							
Bjornson 2004	1	359	0	361	51.3%	0.00 [-0.00, 0.01]	+ −
Subtotal (95% CI)		359		361	51.3%	0.00 [-0.00, 0.01]	*
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.71 ((P = 0.4	8)				
1.65.2 Multi-dose							
Eden 1967	0	25	0	25	0.5%	0.00 [-0.07, 0.07]	
Plint 2009	0	200	0	199	31.7%	0.00 [-0.01, 0.01]	_ + _
Plint 2009	1	200	0	201	16.0%	0.01 [-0.01, 0.02]	
Tagarro 2014	3	48	1	32	0.4%	0.03 [-0.06, 0.12]	
Subtotal (95% CI)		473		457	48.7%	0.00 [-0.01, 0.01]	◆
Total events	4		1				
Heterogeneity: Tau ^z =	0.00; Chi	r = 1.2	5, df = 3 (P = 0.7	4); I ² = 09	, 0	
Test for overall effect:	Z=0.47 ((P = 0.6	64)				
Fotal (95% CI)		832		818	100.0%	0.00 [-0.00, 0.01]	•
Total events	5		1				
Heterogeneity: Tau ² =	0.00; Chi	r= 1.03	7, df = 4 (P = 0.9	0); I ² = 09	6	
Test for overall effect:	Z=0.84 ((P = 0.4	iO)				-0.1 -0.05 Ó 0.05 0.1 Favours systemic Favours placebo
Test for subgroup dif	erences: i	Chi ² = I	0.03 df=	1 (P =	087) P=	0%	Favours systemic Favours placebo

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Fluid & electrolyte abnormalities (by dose) – Peto



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Fluid & electrolyte abnormalities (by condition)

Church a contraction	Syster		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	lotal	Events	lotal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.67.1 Bronchiolitis							
Plint 2009	0	200	0	199	31.7%	0.00 [-0.01, 0.01]	+
Plint 2009	1	200	0	201	16.0%	0.01 [-0.01, 0.02]	
Tagarro 2014	3	48	1	32	0.4%	0.03 [-0.06, 0.12]	
Subtotal (95% CI)		448		432	48.1%	0.00 [-0.01, 0.01]	♦
Total events	4		1				
Heterogeneity: Tau ² =	: 0.00; Chi	i ^z = 1.3	3, df = 2 (P = 0.5	1); I² = 0 9	6	
Test for overall effect:	Z= 0.47 ((P = 0.6	(4)				
1.67.2 Croup							
Bjornson 2004	1	359	0	361	51.3%	0.00 [-0.00, 0.01]	•
Eden 1967	0	25	0	25	0.5%	0.00 [-0.07, 0.07]	
Subtotal (95% CI)		384		386	51.9%	0.00 [-0.00, 0.01]	•
Total events	1		0				
Heterogeneity: Tau ² =	: 0.00; Chi	≈ = 0.0	1.df=1(P = 0.9	3); I² = 0 9	6	
Test for overall effect:	Z= 0.71 ((P = 0.4	18)				
Total (95% Cl)		832		818	100.0%	0.00 [-0.00, 0.01]	•
Total events	5		1			- / -	
Heterogeneity: Tau ² =	: 0.00: Chi	² = 1.0	7. df = 4 (P = 0.9	0); I² = 0 9	6	+
Test for overall effect:					-71	-	-0.2 -0.1 0 0.1
							Favours systemic Favours placebo

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Fluid & electroly	te abnor	malit	ies (by	cond	lition) -	Peto	
Study or Subgroup	Systen Events		Placeb Events		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.68.1 Bronchiolitis							
Plint 2009 Plint 2009	0	200 200	0 0	199 201	17.00	Not estimable	
Tagarro 2014	1 3	200 48	1	32	17.6% 64.9%	7.43 [0.15, 374.26]	
Subtotal (95% CI)		448		432		2.56 [0.42, 15.61]	
Total events	4		1				
Heterogeneity: Chi ² =				0%			
Test for overall effect	: Z = 1.02 (I	P = 0.3	1)				
1.68.2 Croup							
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]	
Eden 1967	0	25	0	25	47.09	Not estimable	
Subtotal (95% CI)	4	384		386	17.6%	7.43 [0.15, 374.47]	
Total events Heterogeneity: Not a	1 pplicable		0				
Test for overall effect		P = 0.3	2)				
				_			
Total (95% CI)	_	832		818	100.0%	3.08 [0.60, 15.94]	
Total events Heterogeneity: Chi² =	- 16 080-	2 (P -	1 – ≊וינו 77	n %.			++
Test for overall effect				0.70			0.002 0.1 1 10 500
Test for subgroup di				1 (P =	0.63), I ² =	: 0%	Favours systemic Favours placebo
				- (V		
							Supplement 6 - Page 35 of 71
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SYSTEMIC vs. PLACEBO – Cardiovascular

Arrhythmia

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Daugbjerg 1993	0	31	0	27	100.0%	0.00 [-0.07, 0.07]	
Total (95% CI)		31		27	100.0%	0.00 [-0.07, 0.07]	
Total events	0		0				
Heterogeneity: Not ap Test for overall effect:		(P = 1.0)0)				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Arrhythmia - Peto

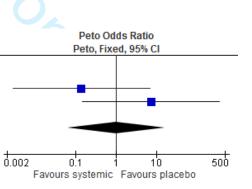
	Syster		Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Daugbjerg 1993	0	31	0	27		Not estimable	
Total (95% CI)		31		27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5 20
Test for overall effect:	Not appli	cable					Favours systemic Favours placebo

Hypertension

Syster	nic	Place	bo		Risk Difference	Risk Difference
Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
0	22	0	19	0.4%	0.00 [-0.09, 0.09]	
0	305	0	295	68.9%	0.00 [-0.01, 0.01]	–
0	200	1	199	15.3%	-0.01 [-0.02, 0.01]	
1	200	0	201	15.5%	0.01 [-0.01, 0.02]	- - -
	727		714	100.0%	0.00 [-0.01, 0.01]	•
1		1				
0.00; Ch	i ^z = 1.00	2, df = 3 (P = 0.8	0); I ² = 09	6 -	
Z = 0.00	(P = 1.0)0)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo
	Events 0 0 1 1 0.00; Ch	0 22 0 305 0 200 1 200 727 1 0.00; Chi ² = 1.0:	Events Total Events 0 22 0 0 305 0 0 200 1 1 200 0 727 1 1 1	Events Total Events Total 0 22 0 19 0 305 0 295 0 200 1 199 1 200 0 201 727 714 1 1 1 0.00; Chi ² = 1.02, df = 3 (P = 0.8) 0 1	Events Total Events Total Weight 0 22 0 19 0.4% 0 305 0 295 68.9% 0 200 1 199 15.3% 1 200 0 201 15.5% 727 714 100.0% 1 1 0.00; Chi ² = 1.02, df = 3 (P = 0.80); l ² = 09	Events Total Events Total Weight M-H, Random, 95% Cl 0 22 0 19 0.4% 0.00 [-0.09, 0.09] 0 305 0 295 68.9% 0.00 [-0.01, 0.01] 0 200 1 199 15.3% -0.01 [-0.02, 0.01] 1 200 0 201 15.5% 0.01 [-0.01, 0.02] 727 714 100.0% 0.00 [-0.01, 0.01] 1 1 1 0.00; Chi ² = 1.02, df = 3 (P = 0.80); l ² = 0% -

Hypertension – Peto

		Syster	nic	Place	bo		Peto Odds Ratio
_	Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl
	Buckingham 2002	0	22	0	19		Not estimable
	Corneli 2007	0	305	0	295		Not estimable
	Plint 2009	0	200	1	199	50.0%	0.13 [0.00, 6.79]
	Plint 2009	1	200	0	201	50.0%	7.43 [0.15, 374.26]
	Total (95% CI)		727		714	100.0%	1.00 [0.06, 15.99]
	Total events	1		1			
	Heterogeneity: Chi ² =	2.01, df=	1 (P =	0.16); I ^z =	= 50%		
	Test for overall effect:	Z = 0.00	(P = 1.0	0)			



Hypertension (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.79.1 Single Dose							
Corneli 2007	0	305	0	295	68.9%	0.00 [-0.01, 0.01]	
Subtotal (95% CI)		305		295	68.9%	0.00 [-0.01, 0.01]	•
Total events	0		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.00 (P = 1.0	0)				
1.79.2 Multi-Dose							
		22	0	4.0	0.400	0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	
Buckingham 2002 Plint 2009	0	200	1	19	0.4%	0.00 [-0.09, 0.09]	
Plint 2009	1	200	י ח	199 201	15.3% 15.5%	-0.01 [-0.02, 0.01] 0.01 [-0.01, 0.02]	
Subtotal (95% CI)	1	422	U	419	31.1%	0.00 [-0.01, 0.02]	▲
Total events	1		1				Ĭ
Heterogeneity: Tau ² =	= 0.00: Chi	² = 1.02	2. df = 2 (P = 0.6	0); I² = 0%	6	
Test for overall effect:	•		•		-71		
Total (95% CI)		727		714	100.0%	0.00 [-0.01, 0.01]	•
Total events	1		1				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 1.00	2, df = 3 (l	P = 0.8	0); I ^z = 0%	6 –	-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 0.00 (P = 1.0	0)				Favours systemic Favours placebo
Test for subaroup dif	ferences:	Chi ^z = (0.00, df=	1 (P =	1.00), I²=	0%	
lypertension (by	dose) -	Petc)				

Hypertension (by dose) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
1.81.1 Single Dose							
Corneli 2007 Subtotal (95% CI)	0	305 305	0	295 295		Not estimable Not estimable	
Total events	0	505	0	235		Notestimable	
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
1.81.2 Multi-Dose							
Buckingham 2002	0	22	0	19		Not estimable	
Plint 2009	0	200	1	199	50.0%	0.13 (0.00, 6.79)	
Plint 2009	1	200	0	201	50.0%	7.43 [0.15, 374.26]	
Subtotal (95% CI)		422		419	100.0%	1.00 [0.06, 15.99]	
Total events	1		1				
Heterogeneity: Chi ² =	2.01, df=	1 (P =	0.16); I ^z =	: 50%			
Test for overall effect:	Z = 0.00 ((P = 1.0	10)				
Total (95% CI)		727		714	100.0%	1.00 [0.06, 15.99]	
Total events	1		1				
Heterogeneity: Chi ² =	2.01, df=	1 (P =	0.16); I ^z =	: 50%			0.002 0.1 1 10 50
Test for overall effect:	Z = 0.00 ((P = 1.0	0)				Favours systemic Favours placebo
Test for subgroup diffe	erences:	Not app	olicable				r avours systemic T avours placebo

Congestive heart failure

Study or Subgroup	Syster Events		Place Events		Weight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
Eden 1967	0	25	0	25	100.0%	0.00 [-0.07, 0.07]	
Total (95% CI)		25		25	100.0%	0.00 [-0.07, 0.07]	
Total events Heterogeneity: Not ap			0				
Test for overall effect:	Z = 0.00 ((P = 1.0)0)				Favours systemic Favours placebo

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Study or Subgroup	Syster Events		Placel		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
Eden 1967	0	25	0	25	Weight	Not estimable	Peto, 11, 60, 35 / 61
Total (95% CI)		25		25		Not estimable	
Total events Heterogeneity: Not a	0 Innlicable		0				+ + + + + + + + + + + + + + + + + + +
Test for overall effec		icable					0.05 0.2 1 5 Favours systemic Favours placebo
							Supplement 6 - Page 3

SYSTEMIC vs. PLACEBO – General

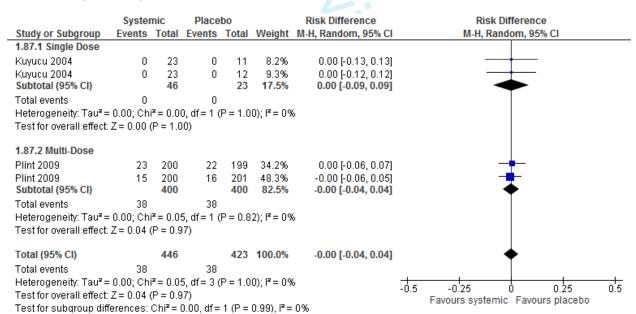
General complaints

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Kuyucu 2004	0	23	0	11	8.2%	0.00 [-0.13, 0.13]	
Kuyucu 2004	0	23	0	12	9.3%	0.00 [-0.12, 0.12]	
Plint 2009	23	200	22	199	34.2%	0.00 [-0.06, 0.07]	· -+-
Plint 2009	15	200	16	201	48.3%	-0.00 [-0.06, 0.05]	i - ₽ -
Total (95% CI)		446		423	100.0%	-0.00 [-0.04, 0.04]	↓ ♦
Total events	38		38				
Heterogeneity: Tau ² =	= 0.00; Chi	i ^z = 0.0:	5, df = 3 (P = 1.0	0); I² = 09	6	
Test for overall effect:							-0.5 -0.25 0 0.25 0.5 Favours systemic Favours placebo

General complaints - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
Kuyucu 2004	0	23	0	11		Not estimable	
Kuyucu 2004	0	23	0	12		Not estimable	
Plint 2009	23	200	22	199	58.3%	1.05 [0.56, 1.94]	
Plint 2009	15	200	16	201	41.7%	0.94 [0.45, 1.95]	
Total (95% CI)		446		423	100.0%	1.00 [0.62, 1.60]	+
Total events	38		38				
Heterogeneity: Chi ² =	0.05, df=	1 (P =	0.82); l ² =	= 0%			0.05 0.2 1 5 20
Test for overall effect:	Z = 0.00 ((P = 1.0	10)				Favours systemic Favours placebo

General complaints (by dose)



General complaints (by dose) - Peto

Study or Subgroup		nic Total	Placel		Woight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.89.1 Single Dose Kuyucu 2004 Kuyucu 2004	0	23 23	0	11 12	Trongine	Not estimable Not estimable	
Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect:		46 able	0	23		Not estimable	
1.89.2 Multi-Dose							
Plint 2009 Plint 2009 Subtotal (95% CI)	23 15	200 200 400	22 16	199 201 400	58.3% 41.7% 100.0%	1.05 (0.56, 1.94) 0.94 (0.45, 1.95) 1.00 (0.62, 1.60)	
Total events Heterogeneity: Chi ² = Test for overall effect: .				:0%			
Total (95% CI)		446		423	100.0%	1.00 [0.62, 1.60]	•
Total events Heterogeneity: Chi ² = 1 Test for overall effect : Test for subgroup diffe	Z = 0.00 (I	P = 1.0	10)	:0%		-	0.1 0.2 0.5 1 2 5 10 Favours systemic Favours placebo
Testion subgroup unit	erences. r	vorapi	JIICADIE				

SYSTEMIC vs. PLACEBO – Immune System

Immunosuppression

	Syster	nic	Placebo			Risk Difference	Risk Difference		
Study or Subgroup	Events Total		Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl		
Connolly 1969	0	47	0	48	100.0%	0.00 [-0.04, 0.04]			
Total (95% CI)		47		48	100.0%	0.00 [-0.04, 0.04]	+		
Total events	0		0						
Heterogeneity: Not ap Test for overall effect:	u Not applicable effect: Z = 0.00 (P = 1.0		10)				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo		

Immunosuppression – Peto

	Syster		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events		Events		Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Connolly 1969	0	47	0	48		Not estimable	
Total (95% CI)		47		48		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	oplicable						0.05 0.2 1 5
Test for overall effect	Not appli	cable					Favours systemic Favours placebo
							Tavours systemic Tavours placebo

INHALED vs. PLACEBO – Infection & Respiratory

Severe infections

	Inhal	ed	Placebo			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Ducharme 2009	2	62	4	67	100.0%	-0.03 [-0.10, 0.04]	
Total (95% CI)		62		67	100.0%	-0.03 [-0.10, 0.04]	
Total events	2		4				
Heterogeneity: Not ap	oplicable						-0.2 -0.1 0 0.1 0.2
Test for overall effect	Z = 0.75 ((P = 0.4	5)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Severe infections – Peto

	Inhaled					Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Ducharme 2009	2	62	4	67	100.0%	0.54 [0.11, 2.77]	
Total (95% CI)		62		67	100.0%	0.54 [0.11, 2.77]	
Total events	2		4				
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.4	46)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

Systemic infections

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events Total		Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Daugbjerg 1993	0	29	0	27	84.6%	0.00 [-0.07, 0.07]	—— — ——
Ducharme 2009	18	62	20	67	15.4%	-0.01 [-0.17, 0.15]	
Total (95% CI)		91		94	100.0%	-0.00 [-0.06, 0.06]	-
Total events	18		20				
Heterogeneity: Tau ² =	: 0.00; Chi	i² = 0.0	3, df = 1 ((P = 0.8	7); I ² = 09	6	
Test for overall effect:	Z=0.04 ((P = 0.9	97)				Favours inhaled Favours placebo

Systemic infections – Peto

			Place	Placebo vents Total W		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup			Events			Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
Daugbjerg 1993	0	29	0	27		Not estimable	
Ducharme 2009	18	62	20	67	100.0%	0.96 [0.45, 2.05]	
Total (95% CI)		91		94	100.0%	0.96 [0.45, 2.05]	-
Total events	18		20				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.10	(P = 0.9	32)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

Lung/trachea

	Inhaled		Place	bo		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl		
Ducharme 2009	13	62	10	67	100.0%	0.06 [-0.07, 0.19]			
Total (95% CI)		62		67	100.0%	0.06 [-0.07, 0.19]	•		
Total events	13		10						
Heterogeneity: Not ap	plicable								
Test for overall effect: .	Z = 0.89 ((P = 0.3	37)				-1 -0.5 0 0.5 1 Favours inhaled Favours placebo		

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Lung/trachea – Peto

	Inhaled Placebo		Inhaled Placebo Peto Odds Ratio				Peto Odds Ratio Peto, Fixed, 95% Cl			
Study or Subgroup	Events	Total Events Total Weight Peto, Fixed, 95% Cl								
Ducharme 2009	13	62	10	67	100.0%	1.51 [0.61, 3.70]		_		
Total (95% CI)		62		67	100.0%	1.51 [0.61, 3.70]				
Total events	13		10							
Heterogeneity: Not ap Test for overall effect:	•	(P = 0.3	37)				L.01	0.1 Favours inhaled	1 10 Favours place	100 bo

URT

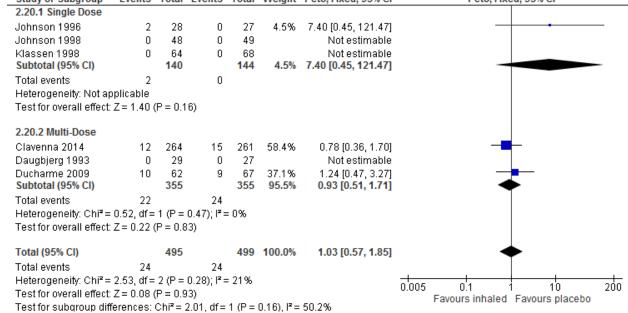
	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]	
Daugbjerg 1993	0	29	0	27	7.7%	0.00 [-0.07, 0.07]	
Ducharme 2009	10	62	9	67	2.3%	0.03 [-0.10, 0.15]	
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	_ + _
Klassen 1998	0	64	0	68	40.7%	0.00 [-0.03, 0.03]	
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	
Total events	24		24				
Heterogeneity: Tau ² =	0.00; Chi	² = 2.13	2, df = 5 (P = 0.8	3); I ² = 09	6	
Test for overall effect:	Z=0.04 ((P = 0.9	97)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

URT – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
Clavenna 2014	12	264	15	261	58.4%	0.78 [0.36, 1.70]	
Daugbjerg 1993	0	29	0	27		Not estimable	
Ducharme 2009	10	62	9	67	37.1%	1.24 [0.47, 3.27]	_
Johnson 1996	2	28	0	27	4.5%	7.40 [0.45, 121.47]	
Johnson 1998	0	48	0	49		Not estimable	
Klassen 1998	0	64	0	68		Not estimable	
Total (95% CI)		495		499	100.0%	1.03 [0.57, 1.85]	+
Total events	24		24				
Heterogeneity: Chi ² =	2.53, df =	2 (P =	0.28); l ² =	= 21%			
Test for overall effect	Z = 0.08	(P = 0.9	33)				0.01 0.1 1 10 10 Favours inhaled Favours placebo

URT (by dose)

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.19.1 Single Dose							
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	+
Klassen 1998	0	64	0	68	40.7%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		140		144	65.7%	0.00 [-0.02, 0.03]	•
Total events	2		0				
Heterogeneity: Tau ² =	•			P = 0.3	1); I² = 14	%	
Test for overall effect:	Z=0.28 ((P = 0.7	8)				
2.19.2 Multi-Dose							
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]	
Daugbjerg 1993	0	29	0	27	7.7%	0.00 [-0.07, 0.07]	
Ducharme 2009	10	62	9	67	2.3%	0.03 [-0.10, 0.15]	
Subtotal (95% CI)		355		355	34.3%	-0.01 [-0.04, 0.03]	•
Total events	22		24				
Heterogeneity: Tau ² =	: 0.00; Chi	i ² = 0.40	3, df = 2 (P = 0.8	1); I² = 09	6	
Test for overall effect:	Z = 0.41 ((P = 0.6	8)				
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	•
Total events	24		24				
Heterogeneity: Tau ² =	: 0.00; Chi	i ^z = 2.10	2, df = 5 (P = 0.8	3); l² = 09	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.04 ((P = 0.9	7)				Favours inhaled Favours placebo
Test for subgroup diff	ferences:	Chi ^z = (0.25, df =	1 (P =	0. <u>62), I^z =</u>	0%	ravours initialed i ravours placebo
JRT (by dose) – P	eto						
	Inhaled Placebo					Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Tota	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
2.20.1 Single Dose							
Johnson 1996	2	28	0	27	4.5%	7.40 [0.45, 121.47]	
Johnson 1998	0		0			Not estimable	
14 1000	-		-				



URT (by condition)

Ctudu or Cubaroup	Inhaled		Placebo		Woight	Risk Difference	Risk Difference
Study or Subgroup 2.21.1 Croup	Events	I otal E	vents	otal	weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	<u>+</u>
Klassen 1998 Subtotal (95% CI)	0	64 140	0	68 144	40.7% 65.7%	0.00 [-0.03, 0.03] 0.00 [-0.02, 0.03]	—
Total events	2		0				Ť
Heterogeneity: Tau² = Test for overall effect:				= 0.31	1); I² = 149	Хо	
2.21.2 Wheeze							
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]	_ +
Daugbjerg 1993	0	29 60	0	27	7.7%	0.00 [-0.07, 0.07]	
Ducharme 2009 Subtotal (95% CI)	10	62 355	9	67 355	2.3% 34.3%	0.03 [-0.10, 0.15] -0.01 [-0.04, 0.03]	•
Total events	22		24	-			
Heterogeneity: Tau² = Test for overall effect:	-			= 0.81	1); I ^z = 0%		
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	
Total events	24		24	_			
Heterogeneity: Tau² = Test for overall effect:				= 0.83	3); I² = 0%		-0.2 -0.1 0 0.1
Test for subgroup diff	•			(P = (0.62), I ² =	0%	Favours inhaled Favours placebo
Study or Subgroup 2.22.1 Croup						Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Johnson 1996 Johnson 1998	2 0	28 48	0 0	27 49	4.5%	7.40 [0.45, 121.47] Not estimable	
Klassen 1998	0 0	64	Ő	68		Not estimable	
Subtotal (95% CI)		140	_	144	4.5%	7.40 [0.45, 121.47]	
Total avante	2 Inlicable		0				
Total events Heterogeneity: Not ar		P = 0.16	i)				
Heterogeneity: Not ap Test for overall effect:	Z=1.40 ()				FA 142		_
Heterogeneity: Not ar Test for overall effect: 2.22.2 Wheeze				001			
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014	12	264 29	15 0	261 27		0.78 [0.36, 1.70] Not estimable	-
Heterogeneity: Not ar Test for overall effect: 2.22.2 Wheeze		264 29 62	15 0 9	261 27 67		Not estimable 1.24 [0.47, 3.27]	
Heterogeneity: Not ap Test for overall effect: Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI)	12 0 10	29	0 9	27	37.1%	Not estimable	-
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events	12 0 10 22	29 62 355	0 9 24	27 67 355	37.1%	Not estimable 1.24 [0.47, 3.27]	-
Heterogeneity: Not ap Test for overall effect: Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI)	12 0 10 22 0.52, df=	29 62 355 1 (P = 0	0 9 24 1.47); I ² =	27 67 355	37.1%	Not estimable 1.24 [0.47, 3.27]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect:	12 0 10 22 0.52, df=	29 62 355 1 (P = 0 P = 0.83	0 9 24 1.47); I ² =	27 67 355 0%	37.1% 95.5%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	12 0 10 22 0.52, df=	29 62 355 1 (P = 0	0 9 24 1.47); I ² =	27 67 355	37.1% 95.5%	Not estimable 1.24 [0.47, 3.27]	•
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi ² =	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df=	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0	0 9 (.47); I ² = 3) 24 (.28); I ² =	27 67 355 0% 499	37.1% 95.5%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total events Heterogeneity: Chi ² = Test for overall effect:	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df= Z = 0.08 (f	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0 P = 0.93	0 9 (.47); l ² =)) 24 (.28); l ² =))	27 67 355 0% 499 21%	37.1% 95.5% 100.0%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	0.05 0.2 1 5 Favours inhaled Favours placebo
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi ² =	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df= Z = 0.08 (f	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0 P = 0.93	0 9 (.47); l ² =)) 24 (.28); l ² =))	27 67 355 0% 499 21%	37.1% 95.5% 100.0%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total events Heterogeneity: Chi ² = Test for overall effect:	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df= Z = 0.08 (f	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0 P = 0.93	0 9 (.47); l ² =)) 24 (.28); l ² =))	27 67 355 0% 499 21%	37.1% 95.5% 100.0%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total events Heterogeneity: Chi ² = Test for overall effect:	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df= Z = 0.08 (f	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0 P = 0.93	0 9 (.47); l ² =)) 24 (.28); l ² =))	27 67 355 0% 499 21%	37.1% 95.5% 100.0%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total events Heterogeneity: Chi ² = Test for overall effect:	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df= Z = 0.08 (f	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0 P = 0.93	0 9 (.47); l ² =)) 24 (.28); l ² =))	27 67 355 0% 499 21%	37.1% 95.5% 100.0%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	
Heterogeneity: Not ap Test for overall effect: 2.22.2 Wheeze Clavenna 2014 Daugbjerg 1993 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² = Test for overall effect: Total (95% CI) Total events Heterogeneity: Chi ² =	12 0 10 22 0.52, df= Z = 0.22 (f 24 2.53, df=	29 62 355 1 (P = 0 P = 0.83 495 2 (P = 0	0 9 (.47); I ² = 3) 24 (.28); I ² =	27 67 355 0% 499	37.1% 95.5%	Not estimable 1.24 [0.47, 3.27] 0.93 [0.51, 1.71] 1.03 [0.57, 1.85]	

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
2.22.1 Croup							
Johnson 1996	2	28	0	27	4.5%	7.40 [0.45, 121.47]	
Johnson 1998	0	48	0	49		Not estimable	
Klassen 1998	0	64	0	68		Not estimable	
Subtotal (95% CI)		140		144	4.5%	7.40 [0.45, 121.47]	
Total events	2		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 1.40 (ł	P = 0.1	6)				
2.22.2 Wheeze							
Clavenna 2014	12	264	15	261	58.4%	0.78 [0.36, 1.70]	
Daugbjerg 1993	0	29	0	27		Not estimable	
Ducharme 2009	10	62	9	67	37.1%	1.24 [0.47, 3.27]	
Subtotal (95% CI)		355		355	95.5%	0.93 [0.51, 1.71]	-
Total events	22		24				
Heterogeneity: Chi ² =	: 0.52, df =	1 (P =	0.47); l² =	= 0%			
Test for overall effect	: Z = 0.22 (P = 0.8	33)				
Total (95% CI)		495		499	100.0%	1.03 [0.57, 1.85]	-
Total events	24		24				
Heterogeneity: Chi ² =	: 2.53, df =	2 (P =	0.28); l² =	= 21%			0.05 0.2 1 5 2
Test for overall effect	: Z = 0.08 (f	P = 0.9	93)				Favours inhaled Favours placebo
Test for subgroup dif	ferences: (Chi ≃ = :	2.01, df=	1 (P =	0.16), I ^z =	: 50.2%	avoid imaca Tavoid placebo

Voice complaints

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Clavenna 2014	34	264	34	261	35.8%	-0.00 [-0.06, 0.06]	-+-
Daugbjerg 1993	0	29	0	27	33.6%	0.00 [-0.07, 0.07]	_ + _
Svedmyr 1995	2	22	0	22	18.9%	0.09 [-0.05, 0.23]	
Svedmyr 1999	2	28	9	27	11.8%	-0.26 [-0.46, -0.06]	
Total (95% CI)		343		337	100.0%	-0.01 [-0.10, 0.07]	-
Total events	38		43				
Heterogeneity: Tau ² =	: 0.00; Ch	i ² = 8.43	2, df = 3 (P = 0.0	4); $l^2 = 64^{\circ}$	%	
Test for overall effect:	Z = 0.34	(P = 0.7	'3)				-0.5 -0.25 Ó 0.25 0.5 Favours inhaled Favours placebo

Voice complaints – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
Clavenna 2014	34	264	34	261	84.5%	0.99 [0.59, 1.64]	
Daugbjerg 1993	0	29	0	27		Not estimable	
Svedmyr 1995	2	22	0	22	2.8%	7.75 [0.47, 128.03]	
Svedmyr 1999	2	28	9	27	12.8%	0.20 [0.05, 0.74]	
Total (95% CI)		343		337	100.0%	0.85 [0.53, 1.36]	-
Total events	38		43				
Heterogeneity: Chi ² =	7.39, df =	2 (P =	0.02); l ² =	: 73%			
Test for overall effect:	Z=0.67 ((P = 0.5	i0)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

Voice complaints (by condition)

22 0 28 9 50 9 1i [≠] = 9.80, df = 1 (P (P = 0.69)	Total Weight 22 18.9% 27 11.8% 49 30.7% = 0.002); I² = 9 261 35.8% 27 33.6%	-0.26 [-0.46, -0.06] -0.08 [-0.46, 0.31] 30% -0.00 [-0.06, 0.06]	Risk Difference M-H, Random, 95% Cl
22 0 28 9 50 9 ii [#] = 9.80, df = 1 (P (P = 0.69) 264 34	22 18.9% 27 11.8% 49 30.7% = 0.002); ² = 9 261 35.8% 27 33.6%	0.09 [-0.05, 0.23] -0.26 [-0.46, -0.06] - 0.08 [-0.46, 0.31] 30% -0.00 [-0.06, 0.06]	M-H, Random, 95% Cl
28 9 50 9 1i [#] = 9.80, df = 1 (P (P = 0.69) 264 34	27 11.8% 49 30.7% = 0.002); ² = 9 261 35.8% 27 33.6%	-0.26 [-0.46, -0.06] -0.08 [-0.46, 0.31] 30% -0.00 [-0.06, 0.06]	
28 9 50 9 1i [#] = 9.80, df = 1 (P (P = 0.69) 264 34	27 11.8% 49 30.7% = 0.002); ² = 9 261 35.8% 27 33.6%	-0.26 [-0.46, -0.06] -0.08 [-0.46, 0.31] 30% -0.00 [-0.06, 0.06]	
50 9 9i ^a = 9.80, df = 1 (P (P = 0.69) 264 34	 49 30.7% = 0.002); l² = 9 261 35.8% 27 33.6% 	-0.08 [-0.46, 0.31] 30% -0.00 [-0.06, 0.06]	
9 hi [#] = 9.80, df = 1 (P (P = 0.69) 264 34	= 0.002); l² = 9 261 35.8% 27 33.6%	-0.00 [-0.06, 0.06]	-
ni [≈] = 9.80, df = 1 (P (P = 0.69) 264 34	261 35.8% 27 33.6%	-0.00 [-0.06, 0.06]	-
(P = 0.69) 264 34	261 35.8% 27 33.6%	-0.00 [-0.06, 0.06]	-
	27 33.6%		+
	27 33.6%		‡
29 0		0.00 [-0.07, 0.07]	
293	288 69.3%	-0.00 [-0.04, 0.04]	•
34			
hi ² = 0.00, df = 1 (P (P = 0.97)	= 0.97); l² = 09	%	
343	337 100.0%	-0.01 [-0.10, 0.07]	-
	= 0.04); l² = 64	4%	-0.5 -0.25 0 0.25 0.5 Favours inhaled Favours placebo
(ni	P = 0.97) 343 43 ² = 8.42, df = 3 (P P = 0.73)	P = 0.97) 343 337 100.0% 43 ² = 8.42, df = 3 (P = 0.04); I ² = 64 P = 0.73)	P = 0.97) 343 337 100.0% -0.01 [-0.10, 0.07] 43 ² = 8.42, df = 3 (P = 0.04); ² = 64%

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4	Voice complaints	(by cond	altion	i) - Peto	0			
5		Inhale	d	Placel	oo		Peto Odds Ratio	Peto Odds Ratio
6	Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
7	2.26.1 Asthma Svedmyr 1995	2	22	0	22	2.8%	7.75 [0.47, 128.03]	
8	Svedmyr 1999	2	28	9	27	12.8%	0.20 [0.05, 0.74]	
9	Subtotal (95% CI)		50		49	15.5%	0.39 [0.12, 1.26]	
10 11	Total events Heterogeneity: Chi² =	4 536 df -	1 (P – 1	9 - ⊆ו ינר ח	91%			
12	Test for overall effect:				01.00			
13	2.26.2 Wheeze							
14	Clavenna 2014	34	264	34	261	84.5%	0.99 [0.59, 1.64]	_ _ _
15	Daugbjerg 1993	0	204	0	201	04.570	Not estimable	
16	Subtotal (95% CI)		293		288	84.5%	0.99 [0.59, 1.64]	•
17	Total events Heterogeneity: Not ap	34 Inlicable		34				
18	Test for overall effect:		^o = 0.9	6)				
19				,	0.07	400.04		
20 21	Total (95% CI) Total events	38	343	43	337	100.0%	0.85 [0.53, 1.36]	-
21	Heterogeneity: Chi ² =		2 (P = (73%			
23	Test for overall effect:	Z = 0.67 (i	^o = 0.5	0)				0.01 0.1 1 10 100 Favours inhaled Favours placebo
24	Test for subgroup diff	erences: (≎hi² = 2	2.04. df =	1 (P =	0.15), I ² =	: 50.9%	
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INHALED vs. PLACEBO – GI

GI bleeding

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Johnson 1998	0	48	0	49	100.0%	0.00 [-0.04, 0.04]	
Total (95% CI)		48		49	100.0%	0.00 [-0.04, 0.04]	+
Total events	0		0				
Heterogeneity: Not ap Test for overall effect:	•	(P = 1.0)0)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

GI bleeding – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Johnson 1998	0	48	0	49		Not estimable	
Total (95% CI)		48		49		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	: Not appli	cable					0.1 0.2 0.5 1 2 5 10 Favours inhaled Favours placebo

Vomiting

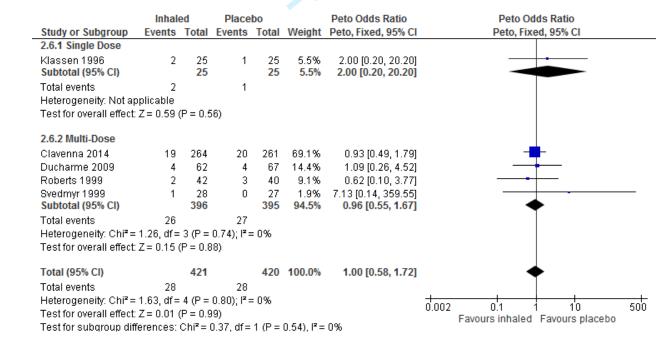
	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Clavenna 2014	19	264	20	261	55.0%	-0.00 [-0.05, 0.04]	
Ducharme 2009	4	62	4	67	15.9%	0.00 [-0.08, 0.09]	
Klassen 1996	2	25	1	25	6.4%	0.04 [-0.09, 0.17]	
Roberts 1999	2	42	3	40	10.2%	-0.03 [-0.13, 0.08]	
Svedmyr 1999	1	28	0	27	12.4%	0.04 [-0.06, 0.13]	
Total (95% CI)		421		420	100.0%	0.00 [-0.03, 0.04]	+
Total events	28		28				
Heterogeneity: Tau ² =	0.00; Ch	i ^z = 1.23	3, df = 4 (P = 0.8	7); I ² = 09	6 -	
Test for overall effect:	Z = 0.14	(P = 0.8	9)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Vomiting – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
Clavenna 2014	19	264	20	261	69.1%	0.93 [0.49, 1.79]	-#-
Ducharme 2009	4	62	4	67	14.4%	1.09 [0.26, 4.52]	+
Klassen 1996	2	25	1	25	5.5%	2.00 [0.20, 20.20]	-
Roberts 1999	2	42	3	40	9.1%	0.62 [0.10, 3.77]	
Svedmyr 1999	1	28	0	27	1.9%	7.13 [0.14, 359.55]	
Total (95% CI)		421		420	100.0%	1.00 [0.58, 1.72]	◆
Total events	28		28				
Heterogeneity: Chi ² =	1.63, df=	4 (P =					
Test for overall effect:	Z = 0.01 ((P = 0.9	99)				0.005 0.1 1 10 200 Favours inhaled Favours placebo

Vomiting (by dose)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
2.5.1 Single Dose							
Klassen 1996	2	25	1	25	6.4%	0.04 [-0.09, 0.17]	
Subtotal (95% CI)		25		25	6.4%	0.04 [-0.09, 0.17]	
Total events	2		1				
Heterogeneity: Not ap	oplicable						
Test for overall effect	Z=0.60 ((P = 0.5	5)				
2.5.2 Multi-Dose							
Clavenna 2014	19	264	20	261	55.0%	-0.00 [-0.05, 0.04]	
Ducharme 2009	4	62	4	67	15.9%	0.00 [-0.08, 0.09]	
Roberts 1999	2	42	3	40	10.2%	-0.03 [-0.13, 0.08]	
Svedmyr 1999	1	28	0	27	12.4%	0.04 [-0.06, 0.13]	•
Subtotal (95% CI)		396		395	93.6%	-0.00 [-0.03, 0.03]	•
Total events	26		27				
Heterogeneity: Tau ² =	= 0.00; Chi	= 0.89	9, df = 3 (P = 0.8	3); I² = 09	6	
Test for overall effect	Z=0.01 ((P = 0.9	99)				
Total (95% CI)		421		420	100.0%	0.00 [-0.03, 0.04]	+
Total events	28		28				
Heterogeneity: Tau ² =	= 0.00; Chi	² = 1.23	3, df = 4 (P = 0.8	7); l² = 09	6 -	-0.2 -0.1 0 0.1 0.2
Test for overall effect	Z=0.14 ((P = 0.8)	39)				Favours inhaled Favours placebo
Test for subgroup dif	ferences:	Chi² = I	0.34, df=	1 (P =	0.56), I ^z =	0%	
omiting (by dos	e) – Pet	0					



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Vomiting (by condition)

Study or Subgroup	Inhaled Events Total	Placebo Events Total	Weight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
2.7.1 Asthma Svedmyr 1999 Subtotal (95% Cl)	1 28 28		12.4% 12.4%	0.04 [-0.06, 0.13] 0.04 [-0.06, 0.13]	
Total events Heterogeneity: Not ap Test for overall effect:		0 46)			
2.7.2 Croup					
Klassen 1996 Roberts 1999	2 25 2 42		6.4% 10.2%	0.04 [-0.09, 0.17] -0.03 [-0.13, 0.08]	•
Subtotal (95% CI)	67	65		-0.00 [-0.08, 0.08]	
Total events Heterogeneity: Tau² = Test for overall effect:			3); I² = 0%	6	
2.7.3 Wheeze					
Clavenna 2014	19 264		55.0%	-0.00 [-0.05, 0.04]	_ _
Ducharme 2009 Subtotal (95% CI)	4 62 326		15.9% 70.9%	0.00 [-0.08, 0.09] - 0.00 [-0.04, 0.04]	
Total events Heterogeneity: Tau ² = Test for overall effect:	23 = 0.00; Chi² = 0.0	24)4, df = 1 (P = 0.8		- / -	
Total (95% CI)	421		100.0%	0.00 [-0.03, 0.04]	
Total events	28	28			Ť
Heterogeneity: Tau ² =			(7); I² = 09	6 ·	-0.2 -0.1 0 0.1 0.2
Test for overall effect: Test for subgroup diff			0.76), I ² =	0%	Favours inhaled Favours placebo
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Vomiting (by condition) - Peto

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	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
2.8.1 Asthma							
Svedmyr 1999	1	28	0	27	1.9%	7.13 [0.14, 359.55]	
Subtotal (95% CI)		28		27	1.9%	7.13 [0.14, 359.55]	
Total events	1		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.98 ((P = 0.3	33)				
2.8.2 Croup							
Klassen 1996	2	25	1	25	5.5%	2.00 [0.20, 20.20]	•
Roberts 1999	2	42	3	40	9.1%	0.62 [0.10, 3.77]	
Subtotal (95% CI)		67		65	14.6%	0.97 [0.23, 4.00]	
Total events	4		4				
Heterogeneity: Chi ² =	= 0.61, df =	: 1 (P =	0.43); l ² =	= 0%			
Test for overall effect	t: Z = 0.04	(P = 0.9	96)				
2.8.3 Wheeze							
Clavenna 2014	19	264	20	261	69.1%	0.93 [0.49, 1.79]	
Ducharme 2009	4	62	4	67	14.4%	1.09 [0.26, 4.52]	_
Subtotal (95% CI)		326		328	83.5%	0.96 [0.53, 1.74]	◆
Total events	23		24				
Heterogeneity: Chi ² =	= 0.04, df =	: 1 (P =	0.85); I ^z =	= 0%			
Test for overall effect	t: Z = 0.14	(P = 0.8	39)				
Total (95% CI)		421		420	100.0%	1.00 [0.58, 1.72]	▲
Total events	28		28				
Heterogeneity: Chi ² =	= 1.63. df =	4 (P =	0.80); l ² =	= 0%			
Test for overall effect							0.001 0.1 i 10 10
Test for subgroup dif		`	· ·	2 (P =	0.61), I ^z =	0%	Favours inhaled Favours placebo
				•			
Diarrhea							
	Inhale	ed	Placeb	0		Risk Difference	Risk Difference

Diarrhea

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Clavenna 2014	27	264	35	261	72.7%	-0.03 [-0.09, 0.02]	
Ducharme 2009	14	62	11	67	27.3%	0.06 [-0.08, 0.20]	
Total (95% CI)		326		328	100.0%	-0.01 [-0.09, 0.08]	
Total events	41		46				
Heterogeneity: Tau² = Test for overall effect: .				P = 0.2	1); I² = 37	%	-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Diarrhea – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio		Peto	Odds Ratio)	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl		Peto,	Fixed, 95%	CI	
Clavenna 2014	27	264	35	261	73.0%	0.74 [0.43, 1.25]		-			
Ducharme 2009	14	62	11	67	27.0%	1.48 [0.62, 3.53]			+		
Total (95% CI)		326		328	100.0%	0.89 [0.57, 1.40]			◆		
Total events	41		46								
Heterogeneity: Chi ² =	1.79, df=	1 (P =	0.18); l² :	= 44%			0.01	<mark> </mark>		10	100
Test for overall effect:	Z = 0.51	(P = 0.6	61)				0.01	Favours inhal	ed Favour:		

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INHALED vs. PLACEBO – CNS & Behaviour

Behaviour change

		d	Placeb			Dial Difference	Dick Difference
Study or Subaroup	Inhale				Woight	Risk Difference	Risk Difference M-H, Random, 95% Cl
Study or Subgroup					-	M-H, Random, 95% Cl	M-H, Rahuolii, 95% Ci
Klassen 1998 Debeste 1999	0 5	64 42	1 6	68	79.5% 5.9%	-0.01 [-0.06, 0.03]	
Roberts 1999	5	42 28	0	40		-0.03 [-0.18, 0.12]	
Svedmyr 1999	I	28	U	27	14.6%	0.04 [-0.06, 0.13]	
Total (95% CI)		134		135	100.0%	-0.01 [-0.04, 0.03]	-
Total events	6		7				
Heterogeneity: Tau² =				P = 0.6	0); I² = 0%)	-0.2 -0.1 0 0.1 0.2
Test for overall effect	:Z=0.45 (F	P = 0.6	5)				Favours inhaled Favours placebo
Behaviour change	e – Peto						
	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup					Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Klassen 1998	0	64	1	68		0.14 [0.00, 7.25]	
Roberts 1999	5	42	6	40		0.77 [0.22, 2.72]	
Svedmyr 1999	1	28	0	27			
Total (95% CI)		134		135	100.0%	0.81 [0.26, 2.54]	-
Total events	6		7				
Heterogeneity: Chi ² =	= 1.94, df =	2 (P =	0.38); l² =	:0%			0.005 0.1 1 10 200
Test for overall effect	H 7 - 0 27 /						0.000 0.1 1 10 200
. setter ereran eneer	L Z = 0.37 (P = 0.7	(1)				Favours inhaled Favours placebo
. serier ereran elleer	L. Z = 0.37 (P = 0.7	(1)				Favours inhaled Favours placebo
	·		(1)				Favours inhaled Favours placebo
Behaviour change	·		(1)				Favours inhaled Favours placebo
	e (by do	se)	-	10		Risk Difference	
Behaviour chang	e (by do: Inhale	se) d	Placeb		Weight	Risk Difference M-H. Random, 95% Cl	Risk Difference
Behaviour chang Study or Subgroup	e (by do: Inhale	se) d	Placeb		Weight	Risk Difference M-H, Random, 95% CI	
Behaviour chang Study or Subgroup 2.29.1 Single Dose	e (by do: Inhale	se) d Total	Placeb	Total		M-H, Random, 95% CI	Risk Difference
Behaviour chang Study or Subgroup	e (by do: Inhale Events	se) d	Placeb Events		Weight 79.5% 79.5%		Risk Difference
Behaviour change Study or Subgroup 2.29.1 Single Dose Klassen 1998	e (by do: Inhale Events	se) d <u>Total</u> 64	Placeb Events	Total 68	79.5%	M-H, Random, 95% Cl	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events	e (by do: Inhale Events 0	se) d <u>Total</u> 64	Placeb Events 1	Total 68	79.5%	M-H, Random, 95% Cl	Risk Difference
Study or Subgroup 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI)	e (by dos Inhale Events 0 0 pplicable	se) d <u>Total</u> 64 64	Placeb Events 1	Total 68	79.5%	M-H, Random, 95% Cl	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect	e (by dos Inhale Events 0 0 pplicable	se) d <u>Total</u> 64 64	Placeb Events 1	Total 68	79.5%	M-H, Random, 95% Cl	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect 2.29.2 Multi-Dose	e (by dos Inhale Events 0 0 pplicable : Z = 0.71 (F	se) d <u>Total</u> 64 64	Placeb Events 1 1 8)	68 68 68	79.5% 79.5%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03]	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect 2.29.2 Multi-Dose Roberts 1999	e (by dos Inhale Events 0 0 pplicable : Z = 0.71 (F	se) d Total 64 64 64 9 = 0.4 42	Placeb Events 1 1 8)	Total 68 68 68	79.5% 79.5% 5.9%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12]	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect 2.29.2 Multi-Dose Roberts 1999 Svedmyr 1999	e (by dos Inhale Events 0 0 pplicable : Z = 0.71 (F	se) d <u>Total</u> 64 64	Placeb Events 1 1 8)	Total 68 68 68 40 27	79.5% 79.5% 5.9% 14.6%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12] 0.04 [-0.06, 0.13]	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect 2.29.2 Multi-Dose Roberts 1999 Svedmyr 1999 Subtotal (95% CI)	e (by dos Inhale Events 0 0 pplicable : Z = 0.71 (F 5 1	se) d Total 64 64 64 9 = 0.4 42 28	Placeb Events 1 1 8) 6 0	Total 68 68 68	79.5% 79.5% 5.9%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12]	Risk Difference
Behaviour change 2.29.1 Single Dose Klassen 1998 Subtotal (95% Cl) Total events Heterogeneity: Not ar Test for overall effect 2.29.2 Multi-Dose Roberts 1999 Svedmyr 1999 Subtotal (95% Cl) Total events	e (by dos Inhale Events 0 0 pplicable : Z = 0.71 (F 5 1	se) d Total 64 64 64 9 = 0.4 42 28 70	Placeb <u>Events</u> 1 1 8) 6 0 6	Total 68 68 68 40 27 67	79.5% 79.5% 5.9% 14.6% 20.5%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12] 0.04 [-0.06, 0.13] 0.02 [-0.06, 0.10]	Risk Difference
Behaviour change <u>Study or Subgroup</u> 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not aj Test for overall effect 2.29.2 Multi-Dose Roberts 1999 Svedmyr 1999 Subtotal (95% CI)	e (by dos Inhale Events 0 0 0 0 0 0 0 0 0 0 0 0 0	se) d Total 64 64 64 64 64 64 64 64 64 64	Placeb <u>Events</u> 1 1 8) 6 0 6 1, df = 1 (F	Total 68 68 68 40 27 67	79.5% 79.5% 5.9% 14.6% 20.5%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12] 0.04 [-0.06, 0.13] 0.02 [-0.06, 0.10]	Risk Difference
Behaviour change 2.29.1 Single Dose Klassen 1998 Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect 2.29.2 Multi-Dose Roberts 1999 Svedmyr 1999 Subtotal (95% CI) Total events Heterogeneity: Tau ² =	e (by dos Inhale Events 0 0 0 0 0 0 0 0 0 0 0 0 0	se) d Total 64 64 64 64 64 64 64 64 64 64	Placeb <u>Events</u> 1 1 8) 6 0 6 1, df = 1 (F	Total 68 68 40 27 67 9 = 0.3	79.5% 79.5% 5.9% 14.6% 20.5%	M-H, Random, 95% CI -0.01 [-0.06, 0.03] -0.01 [-0.06, 0.03] -0.03 [-0.18, 0.12] 0.04 [-0.06, 0.13] 0.02 [-0.06, 0.10]	Risk Difference

Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); l² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Chi ² = 0.47, df = 1 (P = 0.49), l ² = 0%

Total events

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0.1

Ó

Favours inhaled Favours placebo

0.2

-0.2

-0.1

59

1								
2								
3	Pohoviour change	(by do	co)	Doto				
4	Behaviour change	(by uo	se) –	Pelo				
5		Inhale	he	Place	ho		Peto Odds Ratio	Peto Odds Ratio
6	Study or Subgroup					Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
	2.30.1 Single Dose							
7	Klassen 1998	0	64	1	68	8.6%	0.14 [0.00, 7.25]	
8	Subtotal (95% CI)	Ū	64		68	8.6%	0.14 [0.00, 7.25]	
9	Total events	0		1				
10	Heterogeneity: Not ap	plicable						
11	Test for overall effect:		(P = 0.3	(3)				
12								
13	2.30.2 Multi-Dose							
14	Roberts 1999	5	42	6	40	82.8%	0.77 [0.22, 2.72]	
	Svedmyr 1999	1	28	0	27	8.6%	7.13 [0.14, 359.55]	
15	Subtotal (95% CI)		70	_	67	91.4%	0.95 [0.28, 3.15]	
16	Total events	6	4 (7)	6	44.00			
17	Heterogeneity: Chi ² =				= 11%			
18	Test for overall effect:	Z = 0.09 (,F = 0.8	(3)				
19	Total (95% CI)		134		135	100.0%	0.81 [0.26, 2.54]	
20	Total events	6		7			0.01 [0.20, 2.0.]	
21	Heterogeneity: Chi ² =		2 (P =		:0%			
22	Test for overall effect:							0.005 0.1 1 10 200
23	Test for subgroup diff				1 (P =	0.37), I ^z =	:0%	Favours inhaled Favours placebo
24	Behaviour change	(by coi	nditic	on)				
25								
26		Inhale		Placeb			Risk Difference	Risk Difference
27	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
28	2.31.1 Asthma			_				
29	Svedmyr 1999	1	28 28	0	27 27	14.6%	0.04 [-0.06, 0.13]	
30	Subtotal (95% CI)	4	20		21	14.6%	0.04 [-0.06, 0.13]	
31	Total events Heterogeneity: Not ap	1 Nicoblo		0				
	Test for overall effect: 2		P = 0.4	6)				
32		2-0.14()	- 0.4	.,				
33	2.31.2 Croup							
34	Klassen 1998	0	64	1	68	79.5%	-0.01 [-0.06, 0.03]	
35	Roberts 1999	5	42	6	40	5.9%	-0.03 [-0.18, 0.12]	
36	Subtotal (95% CI)		106		108	85.4%	-0.02 [-0.05, 0.02]	-
37	Total events	5		7				
38	Heterogeneity: Tau ² =				P = 0.74	l); l² = 0%		
39	Test for overall effect: 2	2 = 0.80 ()	P = 0.4	3)				
40	Total (95% CI)		134		135	100.0%	-0.01 [-0.04, 0.03]	-
41	Total events	6	101	7		1001070		
	Heterogeneity: Tau ² =	-	² = 1.03		2 = 0.60)): I 2 = 0%		
42	Test for overall effect: J							-0.2 -0.1 0 0.1 0.2
43	Test for subgroup diffe	, erences: (Chi z = 0	98, df = 1	1 (P = 0).32), I ² = I	0%	Favours inhaled Favours placebo
44								
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58								Supplement 6 - Page 53 of 71
50								

Behaviour change (by condition) – Peto

	Inhaled	Placebo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup 2.32.1 Asthma	Events Total	Events Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Svedmyr 1999	1 28	0 27	8.6%	7.13 [0.14, 359.55]	
Subtotal (95% CI)	28	27	8.6%	7.13 [0.14, 359.55]	
Total events	1	0			
Heterogeneity: Not ap Test for overall effect:		33)			
2.32.2 Croup					
Klassen 1998 Roberts 1999	0 64 5 42	1 68 6 40	8.6% 82.8%	0.14 [0.00, 7.25] 0.77 [0.22, 2.72]	
Subtotal (95% CI)	5 42 106	6 40 108		0.66 [0.22, 2.72]	
Total events Heterogeneity: Chi² =					
Test for overall effect: Total (95% CI)	2 = 0.69 (P = 0.4		100.0%	0.81 [0.26, 2.54]	
Total events	6	7	100.070	0.01 [0.20, 2.04]	
Heterogeneity: Chi ² =	1.94, df = 2 (P =	0.38); I² = 0%			0.002 0.1 1 10 500
Test for overall effect:			0.000 13	00.4%	Favours inhaled Favours placebo
Test for subgroup diff	erences: Chi r =	1.30, df = 1 (P =	0.25), 1*=	: 23.1%	
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					Supplement o - Page 54 Of

INHALED vs. PLACEBO – Dermatologic

Burn

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Klassen 1994	0	27	1	27	100.0%	-0.04 [-0.13, 0.06]	
Total (95% CI)		27		27	100.0%	-0.04 [-0.13, 0.06]	
Total events	0		1				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z=0.75	(P = 0.4)	5)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Burn – Peto

	Inhal	ho	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup			Events		Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Klassen 1994	0	27	1	27	100.0%	0.14 [0.00, 6.82]	
Total (95% CI)		27		27	100.0%	0.14 [0.00, 6.82]	
Total events	0		1				
Heterogeneity: Not ap Test for overall effect	•	(P = 0.3	32)				0.002 0.1 1 10 500 Favours inhaled Favours placebo

Integument

			_	-			
	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Clavenna 2014	19	264	22	261	33.6%	-0.01 [-0.06, 0.03]	
Ducharme 2009	5	62	2	67	12.6%	0.05 [-0.03, 0.13]	
Klassen 1998	0	64	1	68	41.5%	-0.01 [-0.06, 0.03]	
Roberts 1999	0	42	2	40	12.3%	-0.05 [-0.13, 0.03]	
Total (95% CI)		432		436	100.0%	-0.01 [-0.04, 0.02]	•
Total events	24		27				
Heterogeneity: Tau ² =	0.00; Chi	i ² = 3.3	6, df = 3 (P = 0.3	4); $l^2 = 11$	%	
Test for overall effect:			•				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Integument – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Clavenna 2014	19	264	22	261	79.7%	0.84 [0.45, 1.59]	
Ducharme 2009	5	62	2	67	14.0%	2.67 [0.58, 12.19]	
Klassen 1998	0	64	1	68	2.1%	0.14 [0.00, 7.25]	•
Roberts 1999	0	42	2	40	4.2%	0.13 [0.01, 2.04]	
Total (95% CI)		432		436	100.0%	0.88 [0.50, 1.56]	+
Total events	24		27				
Heterogeneity: Chi ² =	4.76, df=	3 (P =	0.19); l ^a :	= 37%			
Test for overall effect:	Z=0.43	(P = 0.6	67)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

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Favours inhaled Favours placebo

Integument (by dose)

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
2.41.1 Single							
Klassen 1998	0	64	1	68	41.5%	-0.01 [-0.06, 0.03]	
Subtotal (95% CI)		64		68	41.5%	-0.01 [-0.06, 0.03]	•
Total events	0		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.71	(P = 0.4	18)				
2.41.2 Multi-dose							
Clavenna 2014	19	264	22	261	33.6%	-0.01 [-0.06, 0.03]	+
Ducharme 2009	5	62	2	67	12.6%	0.05 [-0.03, 0.13]	+ - -
Roberts 1999	0	42	2	40	12.3%	-0.05 [-0.13, 0.03]	-+
Subtotal (95% CI)		368		368	58.5%	-0.01 [-0.05, 0.04]	•
Total events	24		26				
Heterogeneity: Tau ² :	= 0.00; Ch	i ^z = 3.23	2, df = 2 (P = 0.2	0); I^z = 38	%	
Test for overall effect	: Z = 0.22	(P = 0.8	32)				
Total (95% CI)		432		436	100.0%	-0.01 [-0.04, 0.02]	•
Total events	24		27				
Heterogeneity: Tau ² :	= 0.00; Ch	i ^z = 3.30	6, df = 3 (P = 0.3	4); l ² = 11	%	
Test for overall effect	:Z=0.68)	(P = 0.5	50)				
Test for subgroup dif	fferences:	Chi² = I	0.08. df=	1 (P =	0.78), I ² =	0%	Favours inhaled Favours placebo
ntegument (by c	dose) – I	Peto					
	Inha	led	Place	ebo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Tota	l Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.42.1 Single							
Klassen 1998	Ο	64	1	68	21%	0.14 (0.00, 7.25)	←

Integument (by dose) – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
2.42.1 Single							
Klassen 1998	0	64	1	68	2.1%	0.14 [0.00, 7.25]	· · · ·
Subtotal (95% CI)		64		68	2.1%	0.14 [0.00, 7.25]	
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.97 ((P = 0.3	(3)				
2.42.2 Multi-dose							
Clavenna 2014	19	264	22	261	79.7%	0.84 [0.45, 1.59]	
Ducharme 2009	5	62	2	67	14.0%	2.67 [0.58, 12.19]	
Roberts 1999	0	42	2	40	4.2%	0.13 [0.01, 2.04]	• • • • • • • • • • • • • • • • • • •
Subtotal (95% CI)		368		368	97.9%	0.92 [0.52, 1.63]	•
Total events	24		26				
Heterogeneity: Chi ² =	3.92, df=	2 (P =	0.14); I ^z =	:49%			
Test for overall effect:	Z = 0.30 ((P = 0.7	'7)				
Total (95% CI)		432		436	100.0%	0.88 [0.50, 1.56]	-
Total events	24		27				
Heterogeneity: Chi ² =	4.76, df=	3 (P =	0.19); l ² =	: 37%			0.01 0.1 1 10 100
Test for overall effect: .	Z = 0.43 ((P = 0.6	(7)				Favours inhaled Favours placebo
Test for subgroup diffe	erences:	Chi ^z = I	0.84, df=	1 (P =	0.36), I ^z =	0%	r avours minarea i r avours pracebo

Integument (by condition)

	Inhaled	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events Tot	al Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.44.1 Croup						
Klassen 1998	0 (64 1	68	41.5%	-0.01 [-0.06, 0.03]	
Roberts 1999	0 4	42 2	40	12.3%	-0.05 [-0.13, 0.03]	
Subtotal (95% CI)	10	06	108	53.8%	-0.02 [-0.06, 0.01]	
Total events	0	3				
Heterogeneity: Tau ² =	= 0.00; Chi ² = ().71. df = 1 (P = 0.4	$0); I^2 = 0\%$		
Test for overall effect						
		, ,				
2.44.2 Wheeze						
Clavenna 2014	19 20	64 22	261	33.6%	-0.01 [-0.06, 0.03]	
Ducharme 2009	5 (62 2	67	12.6%	0.05 [-0.03, 0.13]	
Subtotal (95% CI)	3	26	328	46.2%	0.01 [-0.05, 0.07]	
Total events	24	24				
Heterogeneity: Tau ² =	= 0.00; Chi ^z = 1	.86, df = 1 (P = 0.1	7); l ² = 46	%	
Test for overall effect	Z = 0.35 (P =	0.72)				
Total (95% CI)	4:	32	436	100.0%	-0.01 [-0.04, 0.02]	-
Total events	24	27				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 3	8.36, df = 3 (P = 0.3	(4); l ² = 11	%	
Test for overall effect	Z = 0.68 (P =	0.50)				-0.1 -0.05 0 0.05 0
Test for subgroup dif	•	•	1 (P =	0.36) IF=	0%	Favours inhaled Favours placeb

Integument (by condition) – Peto

04	Inhaled	-	Placel			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events I	lotal	Events	lotal	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
2.46.1 Croup Klassen 1998	0	64	4	68	2.400	044000 7051	
Roberts 1999	U N	64 42	1	08 40	2.1% 4.2%	0.14 [0.00, 7.25] 0.13 [0.01, 2.04]	
Subtotal (95% CI)	· · ·	106	2	108	4.2 % 6.3%	0.13 [0.01, 2.04]	
					01070	0110 [0101] 1121]	
Total events	0		3				
	0 0 00 df=1	1 (P = 1	3 - ≊= 1 0 0 0	: 0%			
Heterogeneity: Chi ² =	: 0.00, df = 1		0.96); l ² =	:0%			
Heterogeneity: Chi ² =	: 0.00, df = 1		0.96); l ² =	:0%			
Heterogeneity: Chi² = Test for overall effect	: 0.00, df = 1		0.96); l ² =	: 0%			
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze	: 0.00, df = 1 : Z = 1.75 (P		0.96); l ² =	: 0% 261	79.7%	0.84 (0.45, 1.59)	-
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014	: 0.00, df = 1 : Z = 1.75 (P 19 5	P = 0.0 264 62	0.96); I ² = 18)	261 67	14.0%	0.84 [0.45, 1.59] 2.67 [0.58, 12.19]	-
Total events Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014 Ducharme 2009 Subtotal (95% CI)	: 0.00, df = 1 : Z = 1.75 (P 19 5	P = 0.0 264	0.96); I ² = 18) 22	261		• • •	- -
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014 Ducharme 2009	: 0.00, df = 1 : Z = 1.75 (P 19 5	P = 0.0 264 62	0.96); I ² = 18) 22	261 67	14.0%	2.67 [0.58, 12.19]	• •
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	: 0.00, df = 1 : Z = 1.75 (P 19 5 24 : 1.88, df = 1	P = 0.0 264 62 326 1 (P = 1	0.96); I ² = (8) 22 2 24 0.17); I ² =	261 67 328	14.0%	2.67 [0.58, 12.19]	•
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014 Ducharme 2009 Subtotal (95% CI) Total events Heterogeneity: Chi ² =	: 0.00, df = 1 : Z = 1.75 (P 19 5 24 : 1.88, df = 1	P = 0.0 264 62 326 1 (P = 1	0.96); I ² = (8) 22 2 24 0.17); I ² =	261 67 328	14.0%	2.67 [0.58, 12.19]	- ■
Heterogeneity: Chi ² = Test for overall effect 2.46.2 Wheeze Clavenna 2014 Ducharme 2009 Subtotal (95% CI)	: 0.00, df = 1 : Z = 1.75 (P 19 5 24 : 1.88, df = 1 : Z = 0.01 (P	P = 0.0 264 62 326 1 (P = 1	0.96); I ² = (8) 22 2 24 0.17); I ² =	261 67 328 : 47%	14.0%	2.67 [0.58, 12.19]	•

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INHALED vs. PLACEBO – Endocrine/Metabolic & Musculoskeletal

Growth - change from baseline, cm

	In	haled		Pla	icebo)		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bacharier 2008	7.8	1.75	96	7.5	1.9	47	68.3%	0.30 [-0.35, 0.95]	
Ducharme 2009	6.23	2.62	58	6.56	2.9	62	31.7%	-0.33 [-1.32, 0.66]	
Total (95% CI)			154			109	100.0%	0.10 [-0.47, 0.67]	+
Heterogeneity: Tau ² : Test for overall effect			•	= 1 (P =	0.30)	; ² = 99	%	-	-4 -2 0 2 4 Favours inhaled Favours placebo

Adrenal suppression

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
Hedlin 1999	5	6	4	10	100.0%	0.43 [0.01, 0.86]	
Total (95% CI)		6		10	100.0%	0.43 [0.01, 0.86]	
Total events	5		4				
Heterogeneity: Not a Test for overall effect		(P = 0.0)5)			-	-0.5 -0.25 0 0.25 0.5 Favours inhaled Favours placebo

Adrenal suppression - Peto

restior overall ellect.	Z = 2.00 (F -	- 0.0:	5)				Favours inhaled Favours placebo
drenal suppress	ion - Peto)					
Study or Subgroup	Inhaled Events T		Place Events		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
Hedlin 1999	5	6	4		100.0%	5.21 [0.72, 37.57]	
Total (95% CI)		6		10	100.0%	5.21 [0.72, 37.57]	
Total events	5		4				
Heterogeneity: Not ap							
Test for overall effect:	Z=1.64 (P	= 0.1	0)				Favours inhaled Favours placebo

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INHALED vs. PLACEBO – Cardiovascular

Arrhythmia

arriy china							
	Inhale		Placel			Risk Difference	Risk Difference
Study or Subgroup						M-H, Random, 95% Cl	M-H, Random, 95% Cl
Daugbjerg 1993	0	29	0	27	100.0%	0.00 [-0.07, 0.07]	
Total (95% CI)		29		27	100.0%	0.00 [-0.07, 0.07]	
Total events	0		0				
Heterogeneity: Not ap							-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.00 (F	° = 1.0	0)				Favours inhaled Favours placebo
rrhythmia – Pet	0						
	Inhale		Place			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events		Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Daugbjerg 1993	0	29	0	27		Not estimable	
Total (95% CI)		29		27		Not estimable	
Total events	0		0				
Heterogeneity: Not a							0.5 0.7 1 1.5 2
Test for overall effect	Not applie	cable					Favours inhaled Favours placebo

DEXAMETHASONE vs. OTHER STEROID – GI

Vomiting

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aljebab 2017	0	33	5	89	14.7%	-0.06 [-0.12, 0.01]	
Aljebab 2017	1	53	10	80	11.5%	-0.11 [-0.19, -0.02]	_ -
Altamimi 2006	0	56	2	54	15.5%	-0.04 [-0.10, 0.02]	
Cronin 2016	0	123	14	122	16.0%	-0.11 [-0.17, -0.06]	
Fifoot 2007	2	65	1	34	13.4%	0.00 [-0.07, 0.07]	_ + _
Garbutt 2013	3	46	7	41	5.7%	-0.11 [-0.24, 0.03]	
Paniagua 2017	6	287	12	290	23.2%	-0.02 [-0.05, 0.01]	-
Total (95% CI)		663		710	100.0%	-0.06 [-0.09, -0.02]	•
Total events	12		51				
Heterogeneity: Tau ² =	= 0.00; Chi ² =	14.42, d	f=6(P=0).03); I ² :	= 58%		
Test for overall effect	: Z = 2.97 (P =	0.003)					-0.5 -0.25 0 0.25 0.5 Favours dexamethasone Favours other steroid

Vomiting – Peto

Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
0	33	5	89	6.6%	0.24 [0.03, 1.80]	
1	53	10	80	16.9%	0.25 [0.07, 0.88]	
0	56	2	54	3.4%	0.13 [0.01, 2.07]	
0	123	14	122	22.9%	0.12 [0.04, 0.35]	_
2	65	1	34	4.6%	1.05 [0.09, 11.63]	
3	46	7	41	15.4%	0.36 [0.10, 1.33]	
6	287	12	290	30.2%	0.51 [0.20, 1.30]	
	663		710	100.0%	0.29 [0.17, 0.48]	◆
12		51				
5.57, df = 6 (P = 0.47); I ² = 0%				0.002 0.1 1 10 500
Z= 4.73 (P <	0.00001	1)				Favours dexamethasone Favours other steroid
ose)						
/						
	Events 0 1 0 2 3 6 6 12 5.57, df = 6 (0 33 1 53 0 56 0 123 2 65 3 46 6 287 663 12 5.57, df = 6 (P = 0.47 Z = 4.73 (P < 0.0000	Events Total Events 0 33 5 1 53 10 0 56 2 0 123 14 2 65 1 3 46 7 6 287 12 663 12 51 5.57, df = 6 (P = 0.47); IP = 0% Z = 4.73 (P < 0.00001)	Events Total Events Total 0 33 5 89 1 53 10 80 0 56 2 54 0 123 14 122 2 65 1 34 3 46 7 41 6 287 12 290 663 710 12 51 5.57, df = 6 (P = 0.47); P = 0% Z = 4.73 (P < 0.00001)	Events Total Events Total Weight 0 33 5 89 6.6% 1 53 10 80 16.9% 0 56 2 54 3.4% 0 123 14 122 22.9% 2 65 1 34 4.6% 3 46 7 41 15.4% 6 287 12 290 30.2% 663 710 100.0% 12 51 5.57, df = 6 (P = 0.47); P = 0% Z = 4.73 (P < 0.00001)	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$

Vomiting (by dose)

	Dexametha	sone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
3.4.1 Single-dose							
Aljebab 2017	0	33	5	89	14.7%	-0.06 [-0.12, 0.01]	
Aljebab 2017	1	53	10	80	11.5%	-0.11 [-0.19, -0.02]	
Altamimi 2006	0	56	2	54	15.5%	-0.04 [-0.10, 0.02]	
Cronin 2016	0	123	14	122	16.0%	-0.11 [-0.17, -0.06]	
Fifoot 2007	2	65	1	34	13.4%	0.00 [-0.07, 0.07]	+
Garbutt 2013	3	46	7	41	5.7%	-0.11 [-0.24, 0.03]	
Subtotal (95% CI)		376		420	76.8%	-0.07 [-0.11, -0.02]	◆
Total events	6		39				
Test for overall effect 3.4.2 Multi-dose	: Z= 3.16 (P=	0.002)					
Paniagua 2017	6	287	12	290	23.2%	-0.02 [-0.05, 0.01]	-
Subtotal (95% CI)		287		290	23.2%	-0.02 [-0.05, 0.01]	•
Total events Heterogeneity: Not a Test for overall effect	• •	0.16)	12				
Total (95% CI)		663		710	100.0%	-0.06 [-0.09, -0.02]	◆
Total events	12		51				
Heterogeneity: Tau ² :	= 0.00; Chi ² = 1	14.42, d	f= 6 (P = 0	0.03); I ≊∶	= 58%		-1 -0.5 0 0.5
Test for overall effect	: Z = 2.97 (P =	0.003)					-1 -0.5 U 0.5 Favours dexamethasone Favours other steroid
Test for subgroup dif	fferences: Chi ^a	² = 3.18,	df = 1 (P =	= 0.07),	l ^z = 68.6%		

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Vomiting (by dose) - Peto

s Total 0 33 1 53 0 56 0 123 2 65 3 46 376 6 5 (P < 0.62 (P < 0.0000	10 2 14 1 7 39 (); I ² = 0%	Total 89 80 54 122 34 41 420	Weight 6.6% 16.9% 3.4% 22.9% 4.6% 15.4% 69.8%	Peto, Fixed, 95% Cl 0.24 [0.03, 1.80] 0.25 [0.07, 0.88] 0.13 [0.01, 2.07] 0.12 [0.04, 0.35] 1.05 [0.09, 11.63] 0.36 [0.10, 1.33] 0.23 [0.12, 0.42]	Peto, Fixed, 95% Cl
1 53 0 56 0 123 2 65 3 46 376 6 5 (P = 0.62	10 2 14 1 7 39 (); I ² = 0%	80 54 122 34 41	16.9% 3.4% 22.9% 4.6% 15.4%	0.25 [0.07, 0.88] 0.13 [0.01, 2.07] 0.12 [0.04, 0.35] 1.05 [0.09, 11.63] 0.36 [0.10, 1.33]	
1 53 0 56 0 123 2 65 3 46 376 6 5 (P = 0.62	10 2 14 1 7 39 (); I ² = 0%	80 54 122 34 41	16.9% 3.4% 22.9% 4.6% 15.4%	0.25 [0.07, 0.88] 0.13 [0.01, 2.07] 0.12 [0.04, 0.35] 1.05 [0.09, 11.63] 0.36 [0.10, 1.33]	
0 56 0 123 2 65 3 46 376 6 5 (P = 0.62	2 14 1 7 39 1); I ² = 0%	54 122 34 41	3.4% 22.9% 4.6% 15.4%	0.13 [0.01, 2.07] 0.12 [0.04, 0.35] 1.05 [0.09, 11.63] 0.36 [0.10, 1.33]	
0 123 2 65 3 46 376 6 5 (P = 0.62	14 1 7 39 (); I ² = 0%	122 34 41	22.9% 4.6% 15.4%	0.12 [0.04, 0.35] 1.05 [0.09, 11.63] 0.36 [0.10, 1.33]	
2 65 3 46 376 6 5 (P = 0.62	1 7 39 !); I² = 0%	34 41	4.6% 15.4%	1.05 [0.09, 11.63] 0.36 [0.10, 1.33]	•
3 46 376 6 :5 (P = 0.62	, 7 39 2); I ² = 0%	41	15.4%	0.36 [0.10, 1.33]	•
376 6 : 5 (P = 0.62	39 (); I² = 0%				•
5 (P = 0.62	!); I ² = 0%				
287 6	12 12	290 290	30.2% 30.2 %	0.51 [0.20, 1.30] 0.51 [0.20, 1.30]	-
(P = 0.16)					
663		710	100.0%	0.29 [0.17, 0.48]	•
- 6 (P = 0.47 (P ≺ 0.0000	1)	= <u>0</u> .16), I	r = 50.5%		0.002 0.1 1 10 Favours dexamethasone Favours other steroid
	287 6 (P = 0.16) 663 2 = 6 (P = 0.47 (P < 0.0000	287 6 12 (P = 0.16) 663 2 51 = 6 (P = 0.47); I ² = 0% (P < 0.00001) : Chi ² = 2.02, df = 1 (P =	287 290 6 12 (P = 0.16) 663 710 2 51 6 (P = 0.47); $ ^{P} = 0\%$ (P < 0.00001)	287 290 30.2% 6 12 (P = 0.16) 663 710 100.0% 2 51 = 6 (P = 0.47); ² = 0% (P < 0.00001)	287 290 30.2% 0.51 [0.20, 1.30] 6 12 (P = 0.16) 663 710 100.0% 0.29 [0.17, 0.48] 2 51 = 6 (P = 0.47); ² = 0% (P < 0.00001) : Chi ² = 2.02, df = 1 (P = 0.16), ² = 50.5%

Vomiting (by condition)

omiting (by co	,,						
	Dexamethas		Other St			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.5.1 Asthma							
Altamimi 2006	0	56	2	54	15.5%	-0.04 [-0.10, 0.02]	
Cronin 2016	0	123	14	122	16.0%	-0.11 [-0.17, -0.06]	_ - _
Paniagua 2017 Subtotal (95% CI)	6	287 466	12	290 466	23.2% 54.7%	-0.02 [-0.05, 0.01] - 0.05 [-0.11, 0.00]	-
Total events	6		28				
Heterogeneity: Tau ² = I	0.00: Chi ² = 8.	74. df:		01): I ^z =	77%		
Test for overall effect: 2			- (
3.5.2 Croup							
Fifoot 2007	2	65	1	34	13.4%	0.00 [-0.07, 0.07]	
Garbutt 2013	3	46	7	41	5.7%	-0.11 [-0.24, 0.03]	
Subtotal (95% CI)		111		75	19.0%	-0.04 [-0.16, 0.08]	
Total events	5		8				
Heterogeneity: Tau ² = I	0.01; Chi ^z = 2.	75, df:	= 1 (P = 0.1	10); I² =	64%		
Test for overall effect: 2	Z = 0.65 (P = 0	.52)					
3.5.3 Other conditions	1						
Aljebab 2017	0	33	5	89	14.7%	-0.06 [-0.12, 0.01]	
Aljebab 2017	1	53	10	80	11.5%	-0.11 [-0.19, -0.02]	
Subtotal (95% CI)		86		169	26.2%	-0.08 [-0.13, -0.02]	-
Total events	1		15				
Heterogeneity: Tau ² = I			= 1 (P = 0.	31); I ² =	3%		
Test for overall effect: 2	Z = 2.90 (P = 0	.004)					
Total (95% CI)		663		710	100.0%	-0.06 [-0.09, -0.02]	•
Total events	12		51				

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Vomiting (by condition) – Peto

	Dexameth	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.7.1 Asthma							
Altamimi 2006	0	56	2	54	3.4%	0.13 [0.01, 2.07]	
Cronin 2016	0	123	14	122	22.9%	0.12 [0.04, 0.35]	
Paniagua 2017 Subtotal (95% CI)	6	287 466	12	290 466	30.2% <mark>56.5%</mark>	0.51 [0.20, 1.30] 0.26 [0.13, 0.52]	•
Total events	6		28				
Heterogeneity: Chi² = Test for overall effect							
3.7.2 Croup							
Fifoot 2007	2	65	1	34	4.6%	1.05 [0.09, 11.63]	
Garbutt 2013	3	46	7	41	15.4%	0.36 [0.10, 1.33]	
Subtotal (95% CI)		111		75	20.0%	0.46 [0.14, 1.45]	
Fotal events	5		8				
Heterogeneity: Chi² = Test for overall effect); I² = 0%				
3.7.3 Other conditio	ns						
Aljebab 2017	0	33	5	89	6.6%	0.24 [0.03, 1.80]	
Aljebab 2017	1	53	10	80	16.9%	0.25 [0.07, 0.88]	
Subtotal (95% CI)		86		169	23.4%	0.25 [0.09, 0.72]	◆
Fotal events	1		15				
Heterogeneity: Chi ² =	= 0.00, df = 1 (P = 0.98); I ^z = 0%				
Test for overall effect	: Z = 2.57 (P =	0.01)					
Total (95% CI)		663		710	100.0%	0.29 [0.17, 0.48]	◆
Total events	12		51				
Heterogeneity: Chi² =	= 5.57, df = 6 (P = 0.47); I ^z = 0%				
Test for overall effect	: Z = 4.73 (P •	0.0000	1)				0.005 0.1 i 10 200 Favours dexamethasone Favours other steroid

Abdominal pain

	Dexameth	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Aljebab 2017	8	33	21	89	11.9%	0.01 [-0.16, 0.18]	
Aljebab 2017	10	53	17	80	18.1%	-0.02 [-0.16, 0.11]	
Altamimi 2006	2	56	3	54	56.9%	-0.02 [-0.10, 0.06]	
Garbutt 2013	9	46	7	41	13.1%	0.02 [-0.14, 0.19]	
Total (95% CI)		188		264	100.0%	-0.01 [-0.07, 0.05]	
Total events	29		48				
Heterogeneity: Tau ² =	= 0.00; Chi ² =	0.35, df:	= 3 (P = 0.	95); l² =	0%	-	-0.2 -0.1 0 0.1 0.2
Test for overall effect	Z = 0.38 (P =	: 0.70)					Favours dexamethasone Favours other steroid
bdominal pair	n – Peto						
a a a a a a a a a a a a a a a a a a a							

Abdominal pain – Peto

	Dexametha	sone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aljebab 2017	8	33	21	89	31.2%	1.04 [0.41, 2.64]	_
Aljebab 2017	10	53	17	80	36.9%	0.86 [0.37, 2.04]	
Altamimi 2006	2	56	3	54	8.5%	0.64 [0.11, 3.79]	
Garbutt 2013	9	46	7	41	23.4%	1.18 [0.40, 3.47]	
Total (95% CI)		188		264	100.0%	0.96 [0.57, 1.61]	-
Total events	29		48				
Heterogeneity: Chi ² =	0.43, df = 3 (F	^o = 0.93)); I ^z = 0%				
Test for overall effect	Z = 0.16 (P =	0.87)					0.1 0.2 0.5 1 2 5 10 Favours dexamethasone Favours other steroid

Abdominal pain (by condition)

	Events	sone	Other St Events		Woight	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
Study or Subgroup 3.10.1 Asthma	Events	TOLAI	Events	Total	weight	M-H, Kalluolli, 95% Cl	W-H, Random, 95% CI
	-		-				
Altamimi 2006	2	56 56	3	54 54	56.9%	-0.02 [-0.10, 0.06]	
Subtotal (95% CI)	-	00		54	56.9%	-0.02 [-0.10, 0.06]	–
Total events	2		3				
Heterogeneity: Not a							
Test for overall effect	t: Z = 0.50 (P =	0.62)					
3.10.2 Croup							
Garbutt 2013	9	46	7	41	13.1%	0.02 [-0.14, 0.19]	
Subtotal (95% CI)		46		41	13.1%	0.02 [-0.14, 0.19]	-
Total events	9		7				
Heterogeneity: Not a	pplicable						
Test for overall effect	t: Z = 0.30 (P =	0.76)					
3.10.3 Other condition	ons						
	ons 8	33	21	89	11.9%	0.01 (-0.16, 0.18)	
Aljebab 2017		33 53	21 17	89 80	11.9% 18.1%	0.01 [-0.16, 0.18] -0.02 [-0.16, 0.11]	
Aljebab 2017 Aljebab 2017	8					0.01 [-0.16, 0.18] -0.02 [-0.16, 0.11] - 0.01 [-0.12, 0.10]	
3.10.3 Other condition Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events	8	53		80	18.1%	-0.02 [-0.16, 0.11]	
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events	8 10 18	53 <mark>86</mark>	17 38	80 169	18.1% 30.0%	-0.02 [-0.16, 0.11]	
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² :	8 10 18 = 0.00; Chi ² = 1	53 86).07, df=	17 38	80 169	18.1% 30.0%	-0.02 [-0.16, 0.11]	•
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² :	8 10 18 = 0.00; Chi ² = 1	53 86).07, df=	17 38	80 169	18.1% 30.0%	-0.02 [-0.16, 0.11]	•
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events	8 10 18 = 0.00; Chi ² = 1	53 86).07, df=	17 38	80 169 79); I ² =	18.1% 30.0%	-0.02 [-0.16, 0.11]	•
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² : Test for overall effect	8 10 18 = 0.00; Chi ² = 1	53 86 0.07, df= 0.83)	17 38	80 169 79); I ² =	18.1% 30.0% 0%	-0.02 [-0.16, 0.11] -0.01 [-0.12, 0.10]	•
Aljebab 2017 Aljebab 2017 Subtotal (95% CI) Total events Heterogeneity: Tau ² Test for overall effect Total (95% CI)	8 10 18 = 0.00; Chi ² = 1 t: Z = 0.22 (P = 29	53 86 0.07, df= 0.83) 188	17 38 = 1 (P = 0. 48	80 169 79); I ² = 264	18.1% 30.0% 0% 100.0%	-0.02 [-0.16, 0.11] -0.01 [-0.12, 0.10]	

Abdominal pain (by condition) – Peto

Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
3.10.1 Asthma						,	
Altamimi 2006 Subtotal (95% Cl)	2	56 56	3	54 54	8.5% 8.5 %	0.64 [0.11, 3.79] 0.64 [0.11, 3.79]	
Total events	2		3				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.50 (P =	0.62)					
3.10.2 Croup							
Garbutt 2013 Subtotal (95% CI)	9	46 46	7	41 41	23.4% 23.4%	1.18 [0.40, 3.47] 1.18 [0.40, 3.47]	
Total events Heterogeneity: Not a Test for overall effect	• •	0.77)	7				
3.10.3 Other condition	ons						
Aljebab 2017	8	33	21	89	31.2%	1.04 [0.41, 2.64]	_
Aljebab 2017	10	53	17	80	36.9%	0.86 [0.37, 2.04]	
Subtotal (95% CI)		86		169	68.1%	0.94 [0.50, 1.77]	
	18		38				
Total events	- 0 00 df = 1 //	P = 0.78); I² = 0%				
Total events Heterogeneity: Chi ² = Test for overall effect		0.85)					
Heterogeneity: Chi ² =		0.85) 188		264	100.0%	0.96 [0.57, 1.61]	
Heterogeneity: Chi² = Test for overall effect			48	264	100.0 %	0.96 [0.57, 1.61]	-
Heterogeneity: Chi ² = Test for overall effect Total (95% Cl)	: Z = 0.19 (P = 29	188		264	100.0%	0.96 [0.57, 1.61]	

DEXAMETHASONE vs. OTHER STEROID – CNS & Behaviour

Tremor/jitteriness

	Dexameth	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Garbutt 2013	1	46	0	41	100.0%	0.02 [-0.04, 0.08]	
Total (95% CI)		46		41	100.0%	0.02 [-0.04, 0.08]	
Total events	1		0				
Heterogeneity: Not aj Test for overall effect		= 0.48)					-0.1 -0.05 0 0.05 0.1 Favours dexamethasone Favours other steroid

Tremor/jitteriness – Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
Garbutt 2013	1	46	0	41	100.0%	6.63 [0.13, 336.21]	
Total (95% CI)		46		41	100.0%	6.63 [0.13, 336.21]	
Total events	1		0				
Heterogeneity: Not ap	pplicable						
Test for overall effect	: Z = 0.94 (P =	0.35)					0.002 0.1 1 10 500 Favours dexamethasone Favours other steroid

Behaviour change

Dexamethasone Other Steroid Risk Difference Risk Difference Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Garbutt 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Image: Comparison of the start of the s						
Garbutt 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Gries 2000 10 14 14 16 34.6% -0.16 [-0.45, 0.13] Total (95% Cl) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); I ² = 0% -0.2 -0.1 0 0.1		Dexamethasone	Other Steroid		Risk Difference	Risk Difference
Gries 2000 10 14 16 34.6% -0.16 [-0.45, 0.13] Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); I ² = 0% -0.2 -0.1 0 0.1	idy or Subgroup	Events Total	Events Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); l ² = 0% -0.2 -0.1 0 0.1	rbutt 2013	25 46	24 41	65.4%	-0.04 [-0.25, 0.17]	
Total events 35 38 Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); l ² = 0% Tect for overall effect 7 = 0.98 (P = 0.32)	es 2000	10 14	14 16	34.6%	-0.16 [-0.45, 0.13]	← ■
Heterogeneity: Tau ² = 0.00; Chi ² = 0.45, df = 1 (P = 0.50); l ² = 0% Test for versal effect 7 = 0.98 (P = 0.32) -0.2 -0.1 0 0.1	tal (95% CI)	60	57	100.0%	-0.08 [-0.25, 0.09]	
Test for overall effect: 7 = 0.06 (P = 0.33)	tal events	35	38			
Tect for overall effect: 7 – 0.06 (P – 0.22)	terogeneity: Tau ² =	0.00; Chi ² = 0.45, df	= 1 (P = 0.50); I ² =	0%		-0.2 -0.1 0 0.1 0.2
	st for overall effect:	Z = 0.96 (P = 0.33)				Favours dexamethasone Favours other steroid

Behaviour change – Peto

	Dexametha	asone	Other St	teroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
Garbutt 2013	25	46	24	41	81.4%	0.85 [0.36, 1.97]	
Gries 2000	10	14	14	16	18.6%	0.38 [0.06, 2.21]	
Fotal (95% CI)		60		57	100.0%	0.73 [0.34, 1.56]	-
Fotal events	35		38				
Heterogeneity: Chi ^z :	= 0.65, df = 1 (P = 0.42); I ^z = 0%				0.005 0.1 1 10 200
Test for overall effect	t: Z = 0.82 (P =	0.41)					0.005 0.1 1 10 200 Favours dexamethasone Favours other steroid

3.16.1 Asthma 0 14 16 3.46% -0.16 [-0.45, 0.13] Subtotal (95% CI) 14 16 3.46% -0.16 [-0.45, 0.13] Total events 10 14 16 3.46% -0.16 [-0.45, 0.13] Total events 10 14 16 3.46% -0.16 [-0.45, 0.13] Gatult 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Gatult 2013 25 24 16 57 100.0% -0.08 [-0.25, 0.09] Total events 25 24 16 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 -0.51, P= 0.% -0.5 Favours dexamethasone Favours of Test for overall effect Z = 0.36 (P = 0.33) 10 Peto Odds Ratio Peto Odds Ratio Peto Odds Ratio Study or Subgroup Events Total Events Total Events Total Events Total events 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] 0.00 [.0.2, 0.1] Total events 25 24 14 <	04 da - 0 da	Dexamethas		Other Ste		101-1-1-4	Risk Difference	Risk Difference
Subtotal (95% C) 14 16 34.6% $-0.16 [0.45, 0.13]$ Total events 10 14 Heterogeneity. Not applicable Total (95% C) 26 46 24 41 65.4% $-0.04 [0.25, 0.17]$ Total events 25 24 Heterogeneity. Total polyticable Total (95% C) 60 57 100.0% $-0.08 [-0.25, 0.09]$ Total events 35 38 Heterogeneity. Tat' = 0.00; Chi ² = 0.45, df = 1 (P = 0.51), P = 0%. Behaviour change (by condition) – Peto Behaviour change (by condition) – Peto Dexamethasone Other Steroid Peto Ages, 197 Total events 10 14 16 18.6% $0.38 [0.06, 2.21]$ Subtotal (95% C) 60 57 100.0% $0.38 [0.06, 2.21]$ Subtotal (95% C) 10 14 14 16 18.6% $0.38 [0.06, 2.21]$ Subtotal (95% C) 60 57 100.0% $0.38 [0.06, 2.21]$ Subtotal (95% C) 10 10 14 14 16 18.6% $0.38 [0.06, 2.21]$ Subtotal (95% C) 10 10 14 14 16 18.6% $0.38 [0.06, 2.21]$ Subtotal (95% C) 60 57 100.0% $0.73 [0.34, 1.56]$ Total events 25 24 Heterogeneity. Not applicable Test for overall effect Z = 0.39 (P = 0.20) 319.2 Croup Gabut 2013 25 46 24 41 81.4% $0.85 [0.36, 1.97]$ Total events 25 24 Heterogeneity. Chi = 0.65, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.65, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.65, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.65, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.85, df = 1 (P = 0.42), P = 0%. Heterogeneity. Chi = 0.02, Chi = 2.02, df = 1 (P = 0.15), P = 51%. Heterogeneity. Tat' = 0.00, Chi = 2.02, df = 1 (P = 0.15), P = 51%. Heterogeneity. Tat' = 0.00, Chi = 2.02, df = 1 (P = 0.15), P = 51%. Heterogeneity. Chi = 0.02, Chi = 2.02, df = 1 (P = 0.15), P = 51%.	Study or Subgroup 3.16.1 Asthma	Events	lotal	Events	lotal	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Total events 10 14 Heterogeneity: Not applicable Test for overall effect Z = 1.10 (P = 0.27) 3.16.2 Croup Garcut 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Garcut 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Total events 25 24 Heterogeneity: Not applicable Test for overall effect Z = 0.8 (D); Ch ² = 0.89) Total eVents 35 38 Heterogeneity: Tau ⁺ = 0.00; Ch ² = 0.43, df = 1 (P = 0.50); P = 0% Test for overall effect Z = 0.8 (D); Ch ² = 0.33, df = 1 (P = 0.51); P = 0% Behaviour change (by condition) – Peto Behaviour change (by condition) – Peto Behaviour bit 2 = 0.8 (D); Ch ² = 0.43, df = 1 (P = 0.51); P = 0% Behaviour change (by condition) – Peto Betavents 10 14 14 16 16.8% 0.38 (0.06, 2.21] Total events 10 14 Heterogeneity: Not applicable Test for overall effect Z = 0.8 (D); Ch ² = 0.28) 3.19.1 Astima Gries 2000 25 46 24 41 81.4% 0.85 (0.36, 1.97] Total events 25 24 Heterogeneity: Not applicable Test for overall effect Z = 0.10 (Ch ² = 0.28) 3.19.2 Croup Garcut 2013 25 46 24 41 81.4% 0.85 (0.36, 1.97] Total events 25 24 Heterogeneity: Not applicable Test for overall effect Z = 0.30 (Ch ² = 0.43); F= 0% Heterogeneity: Not applicable Test for overall effect Z = 0.36; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.30 (Ch ² = 0.43) Total events 25 24 Heterogeneity: Not applicable Test for overall effect Z = 0.35; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.35; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.30; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.30; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.30; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.30; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for overall effect Z = 0.00; ch ² = 2.02; df = 1 (P = 0.42); P = 0% Heterogeneity: Not applicable Test for		10		14				
Test for overall effect $Z = 1.10$ ($P = 0.27$) 3.16.2 Croup Garbut 2013 25 46 24 41 65.4% -0.04 [0.25, 0.17] Total events 25 24 Heterogeneity. Not applicable Test for overall effect $Z = 0.39$ ($P = 0.69$) Total events 35 38 Heterogeneity. Tau ⁺ = 0.00; Ch ⁺ = 0.43, df = 1 ($P = 0.50$); $P = 0\%$. Test for overall effect $Z = 0.69$ Characteristic of the start of the st		10	14	14	10	J4.0%	-0.10 [-0.45, 0.15]	
3.16.2 Croup 9arbul 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Total events 25 24 Heterogeneity: Not applicable Test for overall effect Z = 0.39 (P = 0.69) Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 -38 Heterogeneity: Tau ² = 0.00; Ch ² = 0.45, df = 1 (P = 0.50); P = 0%. Test for overall effect Z = 0.96 (P = 0.33) Test for overall effect Z = 0.93 (df = 0.50); P = 0%. Behaviour change (by condition) – Peto Behaviour change (by condition) – Peto Behaviour (hange (by condition) – Peto Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] Total events 25 24 Heterogeneity, Not applicable Test for overall effect Z = 0.39 (P = 0.70) Total (95% CI) 56 46 24 41 81.4% 0.85 [0.36, 1.97] Total (95% CI) 60 57 100.0% 0.73 [0.34, 1.56] Total events 7 4 (Hander) 95% CI H-Hange (b) Chi 20.20, df = 1 (P = 0.42); P = 0% Heterogeneity, Chi = 0.65, df = 1 (P = 0.42); P = 0% Heterogeneity Chi = 0.65, df = 1 (P = 0.42); P = 0% Heterogeneity Chi = 0.05, df = 1 (P = 0.42); P = 0% Heterogeneity Chi = 0.05, df = 1 (P = 0.42); P = 0% Heterogeneity Chi = 0.00; Chi = 2.02, df = 1 (P = 0.16); P = 51% -0.2 -0.1 0 0 0 0 0 0 0 0 0 0	Heterogeneity: Not a	applicable						
Garbuit 2013 25 46 24 41 65.4% -0.04 [-0.25, 0.17] Subtotal (95% CI) 25 24 Heterogeneity, Not applicable Test for overall effect Z = 0.39 (P = 0.69) Total events 35 38 Heterogeneity, Not applicable 7 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Heterogeneity, Taut = 0.05, ChiP = 0.43, df = 1 (P = 0.51), P = 0% Favours dexamethasone Favours dexamethasone Behaviour change (by condition) - Peto Dexamethasone Other Steroid Peto Odds Ratio Study or Subgroup Events Total Events Total Events Total Events Study or Subgroup Events Total Events Total Events 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 1.97] Total events <td< td=""><td>Test for overall effec</td><td>:t: Z = 1.10 (P = 0</td><td>1.27)</td><td></td><td></td><td></td><td></td><td></td></td<>	Test for overall effec	:t: Z = 1.10 (P = 0	1.27)					
Subtotal (95% CI) 46 41 65.4% -0.04 [-0.25, 0.17] Total events 25 24 Heterogeneity: Not applicable 7 100.0% -0.08 [-0.25, 0.09] Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 -0.08 [-0.25, 0.09] Test for overall effect Z = 0.80 (FP = 0.43, df = 1 (P = 0.50); P = 0% -0.08 [-0.25, 0.09] -1 Test for subgroup differences: ChiP = 0.43, df = 1 (P = 0.51); P = 0% -0.08 [-0.25, 0.09] -1 Behaviour change (by condition) - Peto -0.5 -0.5 Favours dexamethasone Study or Subgroup Events Total Weight Peto, Fixed, 95% CI Ories 2000 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI) 10 14 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% CI)								_
Heterogeneity: Not applicable Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 38 Heterogeneity: Tau"= 0.00; Ch"= 0.45, df= 1 (P = 0.51); P = 0% Test for verail effect Z = 0.86 (P = 0.33) Test for verail effect Z = 0.86 (P = 0.33) Test for verail effect Z = 0.86 (P = 0.33) Test for verail effect Z = 0.87 (P = 0.51); P = 0% Behaviour change (by condition) – Peto Dexamethasone Other Steroid Peto Odds Ratio Dexamethasone Other Steroid Peto Odds Ratio Dexamethasone Other Steroid Peto Odds Ratio Other Steroid Peto Odds Ratio Other Steroid Peto, Fixed, 95% CI Other Steroid Peto, Fixed, 95% CI Peto, Fixed, 95% CI Other Steroid Peto, Fixed, 95% CI Other Steroid Other Steroid Peto, Fixed, 95% CI Sterior overail effect Z = 0.39 (P		25		24				
Test for overall effect $Z = 0.39$ (P = 0.69) Total (95% CI) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Test for overall effect $Z = 0.96$ (P = 0.33) Test for overall effect $Z = 0.96$ (P = 0.33) Test for subgroup differences: Chi ^P = 0.43, df = 1 (P = 0.51), P = 0% Behaviour change (by condition) – Peto Behaviour change (by condition) – Peto Study or Subgroup $\frac{\text{Events}}{\text{Total}} \frac{\text{Events}}{\text{Total}} \frac{\text{Total}}{\text{Events}} \frac{\text{Peto Odds Ratio}}{\text{Total}} \frac{\text{Peto Odds Ratio}}{\text{Peto Odds Ratio}} \frac{\text{Peto Odds Ratio}}{\text{Peto, Fixed, 95% CI}} \frac{\text{Peto Odds Ratio}}{\text{Peto Odds Ratio}} \frac{\text{Peto Odds Ratio}}{\text{Peto Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Ratio}}{\text{Ratio} \frac{\text{Peto Ratio}}{\text{Ratio} \frac{\text{Ratio}}{\text{Ratio} \frac{\text{Ratio}}{\text{Ratio} \frac{\text{Ratio}}{\text{Ratio} \frac{\text{Ratio}}{$	Total events			24				
Total (95% Cl) 60 57 100.0% -0.08 [-0.25, 0.09] Total events 35 38 Heterogeneity: Tau" = 0.00, Chi" = 0.43, df = 1 (P = 0.50), P = 0% -0.5 0 Test for overall effect Z = 0.80 (P = 0.33) Test for overall effect Z = 0.80 (P = 0.43), df = 1 (P = 0.51), P = 0% Peto Odds Ratio Behaviour change (by condition) – Peto Dexamethasone Other Steroid Peto Adds Ratio Peto Odds Ratio Study or Subgroup Events Total Events Total Peto Adds Ratio Peto Odds Ratio Study or Subgroup Events Total Events Total Peto, Fixed, 95% Cl Peto Adds Ratio Study or Subgroup Events Total Verify 0.38 [0.06, 2.21] Image: Component of the Steroid Peto, Fixed, 95% Cl Oarbuit 2013 25 46 24 41 81.4% 0.85 [0.36, 1.97] Subtotal (95% Cl) 60 57 100.0% 0.73 [0.34, 1.56] Image: Component of the Steroid I			1.69)					
Total events 35 38 Heterogeneity: Tau ² = 0.00; Ch ² = 0.45, df = 1 (P = 0.50); P = 0% -0.5 Test for overall effect Z = 0.00; Ch ² = 0.43, df = 1 (P = 0.51); P = 0% Peto Odds Ratio Behaviour change (by condition) – Peto Dexamethasone Other Steroid Peto Odds Ratio Total Events Total Events Total Weight Peto, Fixed, 95% CL Peto Odds Ratio Other Steroid Peto Odd								
Heterogeneity: Tau" = 0.01; Chi" = 0.45, df = 1 (P = 0.50); P = 0% Test for overall effect: Z = 0.96 (P = 0.33) Test for subgroup differences: Chi" = 0.43, df = 1 (P = 0.51), P = 0% Behaviour change (by condition) – Peto Dexamethasone Other Steroid Peto Odds Ratio Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% Cl 3.19.1 Asthma Gries 2000 10 14 14 16 18.6% 0.38 (0.06, 2.21) Subtotal (95% Cl) 14 16 18.6% 0.38 (0.06, 2.21) Total events 10 14 Heterogeneity: Not applicable Test for overall effect: Z = 1.08 (P = 0.28) 3.19.2 Croup Garbut 2013 25 46 24 41 81.4% 0.85 (0.36, 1.97] Subtotal (95% Cl) 60 57 100.0% 0.73 [0.34, 1.56] Total events 25 24 Heterogeneity: Not applicable Test for overall effect: Z = 0.39 (P = 0.70) Total (95% Cl) 60 57 100.0% 0.73 [0.34, 1.56] Total events 35 (P = 0.42); P = 0% Headache Events Total Events Total Events Total Weight M-H, Random, 95% Cl Altamimi 2006 0 56 0 54 71.8% 0.00 [0.03, 0.03] Garbut 2013 7 46 4 41 28.2% 0.05 [0.08, 0.11] Total (95% Cl) 102 95 100.0% 0.02 [-0.08, 0.11] Total events 7 = 0.05; Chi" = 0.02; gift = (P = 0.16); P = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Gri = 1 (P = 0.16); P = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Gri = 1 (P = 0.16); P = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Gri = 1 (P = 0.16); P = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 2.00; Gri = 1 (P = 0.16); P = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; Chi" = 51% Total events 7 = 0.00; Chi" = 2.00; Chi" = 2.00; C		35	60	38	57	100.0%	-0.08 [-0.25, 0.09]	
Test for overall effect $Z = 0.36$ (P = 0.33) Test for subgroup differences: Chi ^P = 0.43, df = 1 (P = 0.51), P = 0% Behaviour change (by condition) – Peto Study or Subgroup Events Total Veight Peto, Fixed, 95% Cl Peto, Fixed, 95% Cl Study or Subgroup 10 14 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% Cl) 10 14 16 18.6% 0.38 [0.06, 2.21] Subtotal (95% Cl) 14 16 18.6% 0.38 [0.06, 1.97] Subtotal (95% Cl) 25 46 24 41 81.4% 0.85 [0.36, 1.97] Subtotal (95% Cl) 46 41 81.4% 0.85 [0.36, 1.97] Subtotal (95% Cl) 60 57 100.0% 0.73 [0.34, 1.56] Total events 25 24 Heterogeneity: Not applicable Test for overall effect $Z = 0.39$ (P = 0.42); P = 0% Headache Study or Subgroup Events Total Veight MH, Random, 95% Cl M-H, Ra	Heterogeneity: Tau²	= 0.00; Chi ² = 0.			i0); I 2 =	0%		-1 -0.5 0
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Test for overall effect: $Z = 0.39$ (P = 0.70) Total (95% CI) 60 57 100.0% 0.73 [0.34, 1.56] Total events 35 38 Heterogeneity: Chi ² = 0.65, df = 1 (P = 0.42); $ ^2 = 0\%$ Test for overall effect: $Z = 0.82$ (P = 0.41) Test for subgroup differences: Chi ² = 0.65, df = 1 (P = 0.42), $ ^2 = 0\%$ Headache Risk Difference Study or Subgroup Dexamethasone Other Steroid Risk Difference Altamimi 2006 0 56 0.00 [-0.03, 0.03] Garbut 2013 7 4 Total (95% CI) 102 95 100.0% 0.02 [-0.08, 0.11] Total (95% CI) 102 95 100.0% 0.02 [-0.08, 0.11] Total (95% CI) 102 95 100.0% 0.02 [-0.08, 0.11] Total (95% CI) 102 95 100.0% 0.02 [-0.1 0.00 <				24				
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Heterogeneity: $Chi^2 = 0.65$, $df = 1$ (P = 0.42); $ ^2 = 0\%$ Test for overall effect: $Z = 0.82$ (P = 0.41)Test for subgroup differences: $Chi^2 = 0.65$, $df = 1$ (P = 0.42), $ ^2 = 0\%$ HeadacheDexamethasoneOther SteroidRisk DifferenceStudy or SubgroupDexamethasoneOther SteroidRisk DifferenceStudy or SubgroupDexamethasoneOther SteroidRisk DifferenceAltamimi 20060Study or SubgroupTotalWeightM-H, Random, 95% CIM-H, Random, 95% CITotal (95% CI)10295100.0%0.00; Chi ² = 2.02; df = 1 (P = 0.16); P = 51%-0.2 </td <td></td> <td>35</td> <td>00</td> <td>38</td> <td>57</td> <td>100.0%</td> <td>0.10 [0.04, 1.00]</td> <td></td>		35	00	38	57	100.0%	0.10 [0.04, 1.00]	
Test for overall effect: $Z = 0.82$ (P = 0.41)Test for subgroup differences: Chi ² = 0.65, df = 1 (P = 0.42), i ² = 0%HeadacheDexamethasoneOther SteroidRisk DifferenceStudy or SubgroupEventsTotalWeightM-H, Random, 95% CIAltamimi 20060560544Total (95% CI)10295100.0%0.02 [-0.08, 0.11]Total (95% CI)10295100.0%0.00colspan="4">100.02-0.10Total (95% CI)10295100.0%0.00colspan="4">10-0.2-0.10Colspan="4">Total Weight M-H, Random, 95% CI <th< td=""><td>Heterogeneity: Chi²</td><td>= 0.65, df = 1 (P</td><td></td><td></td><td></td><td></td><td></td><td>0.01 0.1 1</td></th<>	Heterogeneity: Chi²	= 0.65, df = 1 (P						0.01 0.1 1
Headache Study or Subgroup Chevents Total Cliverts Total Risk Difference Study or Subgroup Events Total Events Total Weight M-H, Random, 95% Cl M-H, Random, 95% Cl <td></td> <td></td> <td></td> <td>df = 1 (P =</td> <td>= 0.42).</td> <td>I² = 0%</td> <td></td> <td>Favours dexamethasone Favours ot</td>				df = 1 (P =	= 0.42).	I² = 0%		Favours dexamethasone Favours ot
Dexamethasone Study or SubgroupDexamethasone EventsOther SteroidRisk Difference M-H, Random, 95% CIRisk Difference M-H, Random, 95% CIAltamimi 200605605471.8% $0.00 [-0.03, 0.03]$ $0.05 [-0.08, 0.19]$ Garbutt 201374644128.2% $0.05 [-0.08, 0.19]$ Total (95% CI)10295100.0% $0.02 [-0.08, 0.11]$ Total events74Heterogeneity: Tau ² = 0.00; Chi ² = 2.02; df = 1 (P = 0.16); I ² = 51%-0.2-0.10								
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Altamimi 2006 0 56 0 54 71.8% 0.00 [-0.03, 0.03] Image: Cited and Ci	Headache							
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI M-H, Random, 95% CI Altamimi 2006 0 56 0 54 71.8% 0.00 [-0.03, 0.03] Image: Cited and Ci		Dexamethas	one	Other Ste	roid		Risk Difference	Risk Difference
Garbutt 2013 7 46 4 128.2% 0.05 [-0.08, 0.19] Total (95% Cl) 102 95 100.0% 0.02 [-0.08, 0.11] Total events 7 4 Heterogeneity: Tau ² = 0.00; Chi ² = 2.02; df = 1 (P = 0.16); l ² = 51% -0.2 -0.1 0 0		Events	Total	Events	Total	_	M-H, Random, 95% Cl	
Total (95% Cl) 102 95 100.0% 0.02 [-0.08, 0.11] Total events 7 4 Heterogeneity: Tau ² = 0.00; Ch ² = 2.02; df = 1 (P = 0.16); l ² = 51% -0.2 -0.1 0								- B
Total events 7 4 Heterogeneity: Tau ² = 0.00; Chi ² = 2.02, df = 1 (P = 0.16); l ² = 51% Totat for events of fact 7 = 0.22 (P = 0.74)				т				
Heterogeneity: Tau ² = 0.00; Chi ² = 2.02, df = 1 (P = 0.16); i ² = 51% -0.2 -0.1 0 C		7	102	A	95	100.0%	0.02 [-0.08, 0.11]	
Test for suproll effect 7 = 0.32 (D = 0.74) -0.2 (U = 0.74)			02, df=		6); I ² =	51%		
								Favours dexamethasone Favours ot

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Headache – Peto

	Dexametha	isone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
Altamimi 2006	0	56	0	54		Not estimable	
Garbutt 2013	7	46	4	41	100.0%	1.63 [0.46, 5.74]	
Total (95% CI)		102		95	100.0%	1.63 [0.46, 5.74]	
Total events	7		4				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.76 (P =	0.45)					0.05 0.2 1 5 20 Favours dexamethasone Favours other steroid

Headache (by condition)

	Dexametha	sone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
3.22.1 Asthma							
Altamimi 2006	0	56	0	54	71.8%	0.00 [-0.03, 0.03]	_ _
Subtotal (95% CI)		56		54	71.8%	0.00 [-0.03, 0.03]	•
Total events	0		0				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.00 (P =	1.00)					
3.22.2 Croup							
Garbutt 2013	7	46	4	41	28.2%	0.05 [-0.08, 0.19]	
Subtotal (95% CI)		46		41	28.2%	0.05 [-0.08, 0.19]	
Total events	7		4				
Heterogeneity: Not a	pplicable						
Test for overall effect	:: Z = 0.78 (P =	0.44)					
Total (95% CI)		102		95	100.0%	0.02 [-0.08, 0.11]	
Total events	7		4				
Heterogeneity: Tau ² =	= 0.00; Chi ² = 2	2.02, df=	= 1 (P = 0.	16); I ² =	51%		
Test for overall effect	: Z = 0.33 (P =	0.74)					-0.2 -0.1 0 0.1 0.2 Favours dexamethasone Favours other steroid
Test for subgroup dif	fferences: Chi²	= 0.57,	df = 1 (P =	= 0.45),	I²=0%		Favours devanieurasone Favours ourer steroid
leadache (by d	condition)) — Pe	oto				
		,					

Headache (by condition) – Peto

	Dexamethaso	ne	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events T	otal	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% CI
3.23.1 Asthma							
Altamimi 2006	0	56	0	54		Not estimable	
Subtotal (95% CI)		56		54		Not estimable	
Total events	0		0				
Heterogeneity: Not app	olicable						
Test for overall effect: №	Not applicable						
3.23.2 Croup							
Garbutt 2013	7	46	4	41	100.0%	1.63 [0.46, 5.74]	
Subtotal (95% CI)		46		41	100.0%	1.63 [0.46, 5.74]	
Total events	7		4				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.76 (P = 0.4	5)					
Total (95% CI)		102		95	100.0%	1.63 [0.46, 5.74]	
Total events	7		4				
Heterogeneity: Not app	olicable						
Test for overall effect: 2	Z = 0.76 (P = 0.4	5)					0.05 0.2 1 5 20 Favours dexamethasone Favours other steroid
Test for subgroup diffe	erences: Not app	plicat	ole				Favours devanteurasone Favours outer steroid

DEXAMETHASONE vs. OTHER STEROID – Dermatologic

Phlebitis

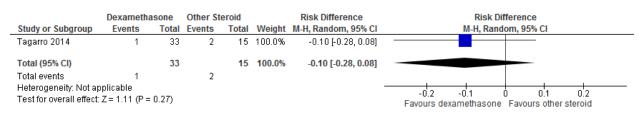
	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Gries 2000	0	15	0	17	100.0%	0.00 [-0.11, 0.11]	
Total (95% CI)		15		17	100.0%	0.00 [-0.11, 0.11]	
Total events	0		0				
Heterogeneity: Not a Test for overall effect	•	1.00)					-0.2 -0.1 0 0.1 0.2 Favours dexamethasone Favours other steroid

Phlebitis – Peto

	Dexametha	asone	Other St	teroid		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events		Events		Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl	
Gries 2000	0	15	0	17		Not estimable		
Total (95% CI)		15		17		Not estimable		
Total events	0		0					
Heterogeneity: Not ap							0.05 0.2 1 5	
Test for overall effect:	Not applicab	le					Favours dexamethasone Favours other ster	bid
			-					

DEXAMETHASONE vs. OTHER STEROID - Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities



Fluid & electrolyte abnormalities – Peto

Study or Subgroup	Dexametha Events		Other St Events		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
Tagarro 2014	1	33	2		100.0%	0.18 [0.01, 2.17]	
- Fotal (95% CI)		33			100.0%		
otal (95% CI) otal events	1	22	2	10	100.0%	0.18 [0.01, 2.17]	
leterogeneity: Not ap	plicable		-				
est for overall effect:	Z = 1.35 (P =	: 0.18)					Favours dexamethasone Favours other steroid
			-				
							Supplement 6 - Page 68 of

DEXAMETHASONE vs. OTHER STEROID – Cardiovascular

Arrhythmia

	Dexamethe	asone	Other St	eroid		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events Total Weight M-H, Random, 95% Cl		M-H, Random, 95% Cl	M-H, Random, 95% CI			
Altamimi 2006	0	56	0	54	100.0%	0.00 [-0.03, 0.03]	—		
Total (95% CI)		56		54	100.0%	0.00 [-0.03, 0.03]			
Total events	0		0						
Heterogeneity: Not ap	oplicable						-1 -0.5 0 0.5		
Test for overall effect	Z = 0.00 (P =	: 1.00)					-1 -0.5 0 0.5 Favours dexamethasone Favours other steroid		

Arrhythmia – Peto

	Dexametha	isone	Other St	teroid		Peto Odds Ratio	Peto	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto,	Fixed, 95% Cl	
Altamimi 2006	0	56	0	54		Not estimable			
Total (95% CI)		56		54		Not estimable			
Total events	0		0						
Heterogeneity: Not a	pplicable								100
Test for overall effect	Not applicab	le					0.01 0.1 Favours dexamethaso	1 10 ne Favours other ste	100 eroid

Hypertension

Hypertension							
	Dexameth	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
Gries 2000	0	15	0	17	100.0%	0.00 [-0.11, 0.11]	
Total (95% CI)		15		17	100.0%	0.00 [-0.11, 0.11]	•
Total events Heterogeneity: Not ap Test for overall effect:	•	= 1.00)	0				-1 -0.5 0 0.5 Favours dexamethasone Favours other steroid
lypertension –	Peto						

Hypertension – Peto

	Dexametha	sone	Other St	eroid		Peto Odds Ratio	Peto O	dds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fix	ed, 95% Cl	
Gries 2000	0	15	0	17		Not estimable			
Total (95% CI)		15		17		Not estimable			
Total events	0		0						
Heterogeneity: Not app	olicable						0.01 0.1	1 10	100
Test for overall effect: N	Not applicab	le					Favours dexamethasone		100

DEXAMETHASONE vs. OTHER STEROID – General

General complaints

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Altamimi 2006	0	56	1	54	79.5%	-0.02 [-0.07, 0.03]	
Garbutt 2013	3	46	2	41	20.5%	0.02 [-0.08, 0.11]	
Total (95% CI)		102		95	100.0%	-0.01 [-0.06, 0.03]	
Total events	3		3				
Heterogeneity: Tau ² = Test for overall effect		•	= 1 (P = 0.	47); I² =	0%	-	-0.1 -0.05 0 0.05 0.1 Favours dexamethasone Favours other steroid

General complaints – Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	I Peto, Fixed, 95% CI
Altamimi 2006	0	56	1	54	17.4%	0.13 [0.00, 6.58]	
Garbutt 2013	3	46	2	41	82.6%	1.35 [0.22, 8.15]	1
Total (95% CI)		102		95	100.0%	0.90 [0.18, 4.61]	
Total events	3		3				
Heterogeneity: Chi ² =	1.13, df = 1 (l	P = 0.29); I ² = 11%				
Test for overall effect	Z = 0.13 (P =	0.90)					0.002 0.1 1 10 500 Favours dexamethasone Favours other steroid

General complaints (by condition)

Study or Subgroup	Dexametha Events		Other Sto Events		Moinht	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
3.6.1 Asthma	LVCIII	TUtal	LVCIILO	TULAI	weight	M-n, Nandom, 55% Cr	Mi-ri, Nandolfi, 95% Ci
Altamimi 2006	0	56	1	54	78.7%	-0.02 [-0.07, 0.03]	
Subtotal (95% Cl)		56		54	78.7%	-0.02 [-0.07, 0.03]	•
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.73 (P =	0.46)					
3.6.2 Croup							
Garbutt 2013	3	48	2	41	21.3%	0.01 [-0.08, 0.11]	
Subtotal (95% CI)		48		41	21.3%	0.01 [-0.08, 0.11]	◆
Total events	3		2				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.28 (P =	0.78)					
Total (95% CI)		104		95	100.0%	-0.01 [-0.06, 0.03]	
Total events	3		3				
Heterogeneity: Tau ² =	0.00; Chi ² = (0.46. df	= 1 (P = 0.)	50); I ^z =	0%		
Test for overall effect: J			,				-1 -0.5 Ó 0.5
Test for subaroup diffe			df = 1 (P =	0.56).	²=0%		Favours dexamethasone Favours other steroid
		0.00,		5.507,			

1						
2						
3	General compla	ints (by condi	tion) – Peto)		
4 5	-	Dexamethasone	Other Steroid		Peto Odds Ratio	Peto Odds Ratio
6	Study or Subgroup			Weight	Peto, Fixed, 95% Cl	
7	3.34.1 Asthma Altamimi 2006	0 56	1 54	17.4%	0.13 (0.00, 6.58)	·
8	Subtotal (95% CI)	56	54		0.13 [0.00, 6.58]	
9	Total events Heterogeneity: Not apj	0 Dlicable	1			
10	Test for overall effect:					
11 12	3.34.2 Croup					
12	Garbutt 2013 Subtotal (95% CI)	3 48 48		82.6% 82.6 %	1.29 [0.21, 7.81] 1.29 [0.21, 7.81]	
14	Total events	3	2		• • •	
15	Heterogeneity: Not ap Test for overall effect: 2					
16	Total (95% CI)	104	05	100.0%	0.87 [0.17, 4.45]	
17	Total events	3	3	100.0 /4	0.07 [0.17, 4.45]	
18 19	Heterogeneity: Chi ^z = 1 Test for overall effect: 3		l); l² = 8%			
20	Test for subgroup diffe		df = 1 (P = 0.30),	I ² = 7.8%		Favours dexamethasone Favours other steroid
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59 60		For peer revie	ew only - htt	p://bmj	open.bmj.com	/site/about/guidelines.xhtml
00			,	. ,	, ,	

Supplement 7. Studies reporting no adverse events

Study	Condition	Comparisons - main	Study design	Study sample	AE reporting
Alansari 2013	bronchiolitis	systemic vs. placebo	RCT	200	No AE overall; 7 days follow-up revealed no side effect concerns in treatment groups.
Brunette 1988	asthma, before signs of wheeze	systemic vs. systemic	nRCT	32	No AE overall; Growth and weight gains for all children were within normal range.
Chen 2008	asthma	systemic vs. inhaled vs. inhaled	RCT, 3-arm	123	No AE overall; All 3 groups reported no adverse effects.
Chub-Uppakarn 2007	croup	systemic vs. systemic	RCT	41	No AE overall; No significant adverse reaction from dexamethasone treatment in either group.
Escobedo Chavez 1992	asthma	systemic vs. non- corticosteroid	RCT	50	No AE overall; We detected no side effects from the use of methylprednisolone in a single dose.
Fifoot 2007	croup	systemic vs. systemic vs. systemic	RCT, 3-arm	99	No AE overall; One patient in each group vomited their first dose of medication; all except one (dexamethasone 0.6mg/kg) tolerated their repeat dose; no patient suffered any adverse outcomes from receiving study steroid, either at index presentation or during the follow-up period.

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Ghirga 2002	wheeze - recurrent,	inhaled vs. no	RCT	26	No AE overall;
	early in URTI	intervention			No apparent adverse effects reported 4 years post-study.
Husby 1993	croup	inhaled vs. placebo	RCT	36	No AE overall; No side effects were reported.
Jartti 2006	wheeze - acute	systemic vs. placebo	RCT	78	No AE overall; Prednisolone treatment well tolerated; no clinically significant adverse effects occurred.
Jartti 2007	wheeze - recurrent	systemic vs. placebo	RCT	58	No AE overall; Prednisolone treatment well tolerated; no clinically significant adverse effects occurred.
Klassen 1994	croup	inhaled vs. placebo	RCT	54	One patient in placebo group had a burning sensation on the face. No adverse events noted in budesonide group.
Langton Hewer 1998	asthma	systemic vs. systemic vs. systemic	RCT, 3-arm	98	No AE overall; No side effect possibly attributable to prednisolone therapy was noted in any of th three treatment groups.
Leipzig 1979	croup	systemic vs. placebo	RCT	30	No AE overall; Observed no adverse effects or late relapses
Razi 2015	asthma	inhaled vs. placebo	RCT	100	No AE overall; No drug-related adverse effects were identified during hospitalization.
Roorda 1998	croup	inhaled vs. placebo	RCT	17	No AE overall; No side effects of treatment regimens were reported.

Saito 2017	asthma	systemic vs. inhaled	RCT	50	No AE overall; Adverse events did not occur in either group; Serum cortisol levels on the 4th day of hospitalization were 17.0mcg/dL and 10.9mcg/dL with significant suppression in the prednisolone group.
Schuh 2009	asthma	systemic vs. non- corticosteroid	RCT	130	No AE overall; No adverse effects developed in children given prednisolone after discharge.
Sparrow 2006	croup	systemic vs. systemic	RCT	133	No AE overall; No adverse events in either group.
Storr 1987	asthma	systemic vs. placebo	RCT	140	No AE overall; There were no observed side effects related to the single prednisolone dose.
Sung 1998	asthma	inhaled vs. placebo	RCT	44	No AE overall; No adverse effects in either group.
Super 1989	croup	systemic vs. placebo	RCT	33	No AE overall; Did not encounter any side effects directly attributable to dexamethasone.
Tal 1983	wheeze - acute	systemic + sal; systemic + placebo; sal + placebo; placebo	RCT, 2x2	32	No AE overall; No other side effects or complications were documented, aside from tremor (1 infant) as side effect of salbutamol.
Tamura 2008	refractory pneumonia (5 year old)	systemic	CS (#1)	1	No AE overall; No adverse events in any patients during steroid treatment.

van Woensel 1997	bronchiolitis	systemic vs. placebo	RCT	54	No AE overall; No clinically significant side effects of
					prednisolone were found.
Webb 1986	wheeze	systemic vs. placebo	RCT	38	No AE overall;
					No side effects reported by parents and none
					detected on clinical exam 3 days after
					completing 5-day treatment course.
Zhang 2003	bronchiolitis	systemic vs. standard	RCT	52	No AE overall;
		care			Potential side-effects of prednisolone not
					included as outcome measures in this study
					as short-term steroid therapy has been well
					confirmed. At time of analysis, no adverse
					events were noted in patients who received
					prednisolone.
AE: adverse events;	CS: case series; nRCT: no	on-randomised controlle	d trial; RCT: ran	domised contro	olled trial; sal: salbutamol; URTI: upper
respiratory tract inf	ection; vs: versus				

The PRISMA for Abstracts Checklist

TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	1
BACKGROUND		
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	3
METHODS		
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	3
4. Information sources:	Key databases searched and search dates.	3
5. Risk of bias:	Methods of assessing risk of bias.	3
RESULTS		
6. Included studies:	Number and type of included studies and participants and relevant characteristics of studies.	3
7. Synthesis of results:	Results for main outcomes (benefits and harms), preferably indicating the number of studies and participants for each. If meta-analysis was done, include summary measures and confidence intervals.	3
8. Description of the effect:	Direction of the effect (i.e. which group is favoured) and size of the effect in terms meaningful to clinicians and patients.	3
DISCUSSION		
9. Strengths and Limitations of evidence:	Brief summary of strengths and limitations of evidence (e.g. inconsistency, imprecision, indirectness, or risk of bias, other supporting or conflicting evidence)	3
10. Interpretation:	General interpretation of the results and important implications	3
OTHER		
11. Funding:	Primary source of funding for the review.	
12. Registration:	Registration number and registry name.	

Section/ topic (page no)	Item	PRISMA checklist item	PRISMA harms (minimum)	Recommendations for reporting harms in systematic reviews (desirable)	Check if done
Fitle Fitle (3)	1	Identify the report as a systematic review, meta-analysis, or both.	Specifically mention "harms" or other related terms, or the harm of interest in the review.		Title page, p. 1-2
Abstract Structured summary (4)	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.		Abstracts should report any analysis of harms undertaken in the review, if harms are a primary or secondary outcome.	p. 3
Introduction Rationale (5)	3	Describe the rationale for the review in the context of what is already known.		It should clearly describe in introduction or in methods section which events are considered harms and provide a clear rationale for the specific harm(s), condition(s), and patient group(s) included in the review.	p. 5
Objectives (5)	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	O	PICOS format should be specified, although in systematic reviews of harms the selection criteria for P, C, and O may be very broad (same intervention may have been used for heterogeneous indications in a diverse range of patients)	p. 6
Methods Protocol and registration (6)	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	_	No specific additional information is required for systematic reviews of harms.	p. 6;protocol reference# reported infunding source (p.
Eligibility criteria (6)	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication	_	Report how handled relevant studies (based on population and intervention) when the	22) p. 6-7;

		status) used as criteria for eligibility, giving rationale.		outcomes of interest were not reported. Report choices for specific study designs	Supplement 2 - Eligibility criteria for study inclusion
Information (7)	7	Describe all information sources (eg,	—	and length of follow-up. Report if only searched	p. 6;
sources (7)		contact with study authors to identify additional studies) in the search and date last searched.		also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If	Supplement 1- Search strategy
				and the process of obtaining it.	
Search (7)	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	_	If additional searches were used specifically to identify adverse events, authors should present the full search process so it can be replicated.	Supplement 1 - Search strategy
Study selection (8)	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable	_	If only included studies reporting on adverse	p. 7; Supplement 2 -
	10	included in the meta-analysis).		defined if screening was based on adverse event reporting in title/abstract or full text. If no harms reported in the text, report if any attempt was made to retrieve relevant data from authors.	Eligibility criteria for study inclusion
Data collection process (9)	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	- 0	No specific additional information is required for systematic reviews of harms.	p. 7-8
Data items (9)	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.		Report the definition of the harm and seriousness used by each included study (if applicable). Report if multiple events occurred in the same individuals, if this information is available. Consider if the harm may be related to factors associated with participants (eg, age, sex, use of medications) or provider (eg, years of practice, level of	p. 7-8
	sources (7) Search (7) Study selection (8) Data collection process (9)	sources (7) Search (7) 8 Study 9 selection (8) 9 Data collection process (9) 10	giving rationale.Information sources (7)7Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.Search (7)8Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.Study selection (8)9State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).Data collection process (9)10Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and	giving rationale. Information sources (7) 7 Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. Search (7) 8 Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. Study selection (8) 9 State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). Data collection process (9) 10 Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. Data items (9) 11 List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and	giving rationale.were not propried.Information sources (7)7Describe all information sources (eg. databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.—Report if only searched for published data, or orbuits and heap how and heap how and to all process of obtaining it.Search (7)8Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.—If additional searches were used specifical with study searches obtaining it.Study selection (8)9State the process for selecting studies included in the meta-analysis).——Data collection process (9)10Describe method of data extraction from reports (eg. ploted forms, independently, in duplicate) and any process for obtaining and confirming data from investigators.—Data collection process (9)11List and define all variables for which data were sought (eg. PICOS, funding sources) and any assumptions and simplifications made.—Report the definition of the harm and seriouses used by action law serious used by action law simplifications made.Data collection process (9)11List and define all variables for which data were sought (eg. PICOS, funding sources) and any assumptions and simplifications made.—Report the definition of the harm and seriouses used by action law and so sociated with participant (eg., ge., ser, use of metications) or provider (eg., years of or provider (eg., years of or provider (eg., years of or provider (eg., years of

1 2						
3 4 5 6 7 8 9 10 11 12 13					training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details regarding the specific methods used to capture harms (active/passive and timing of adverse event).	
14 15 16 17 18	Risk of bias in individual studies (10)	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.		The risk of bias assessment should be considered separately for outcomes of benefit and harms.	p. 8
19 20 21 22	Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	_	No specific additional information is required for systematic reviews of harms.	p. 8-9
23 24 25 26 27	Synthesis of results (11)	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I ²) for each meta- analysis.	Specify how zero events were handled, if relevant.		р. 8-9
28 29 30 31 32 33 34 35 36	Risk of bias across studies (11)	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	elien	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	p. 9
37 38 39 40 41 42 43 44 45 46 47 48 49	Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	- 0	Sensitivity analyses may be affected by different definitions, grading, and attribution of adverse events, as adverse events are typically infrequent or reported using heterogeneous classifications. Report the number of participants and studies included in each subgroup.	p. 9
50 51 52 53 54 55 56 57 58 59	Results Study selection (13)	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	_	If a review addresses both efficacy and harms, display a flow diagram specific for each (efficacy and harm).	p. 9; Figure 1 - PRISMA study flow selection
60			For peer review only - http://bmjop	pen.bmj.com/site/about/	guidelines.xhtml	

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2						
 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 	Study characteristics (14)	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period.	Add additional characteristics to: "P" (population) patient risk factors that were considered as possibly affecting the risk of the harm outcome. "I" (intervention) professional expertise/skills if relevant (for example if the intervention is a procedure). "T" (time) timing of all harms assessments and the length of follow-up.	p. 9; Supplement 3 - Characteristics of included studies
18 19	Risk of bias	19	Present data on risk of bias of each	_	Consider the possible	p. 9;
20	within studies		study and, if available, any outcome		sources of biases that	-
21	(15)		level assessment (see item 12).		could affect the specific harm under	Supplement 4 - Methodological
22					consideration within the	quality of included
23 24					review. Sample	studies
25					selection, dropouts and measurement of adverse	
26					events should be	
27 28					evaluated separately from the outcomes of	
29					benefit as described in	
30					item 12, above.	
	Results of individual	20	For all outcomes considered (benefits or harms), present, for each study: (a)	-	Report the actual numbers of adverse	p. 10;
32 33	studies (16)		simple summary data for each		events in each study,	Supplement 3 -
34			intervention group (b) effect estimates		separately for each	Characteristics of
35			and confidence intervals, ideally with a forest plot.		intervention.	included studies
36 37	Synthesis of	21	Present results of each meta-analysis	Describe any	If included data from	p. 10-15;
38	results (17)		done, including confidence intervals	assessment of possible	unpublished sources,	
39			and measures of consistency.	causality.	report clearly the data source and the impact	Table 2 - Number of studies and
40					of these studies to the	participants
41 42					final systematic review.	reporting adverse
43						events;
44						Figures 2-4 -
45 46						Forest plots of
47						adverse events;
48						Supplement 5 -
49 50						Effect estimates
50						for all adverse events with
52						subgroups;
53 54						Supplement 6 –
55						Forest plots of
56						adverse events;
57						
58 59						
60			For peer review only - http://bmjop	en.bmj.com/site/about/	guidelines.xhtml	

1 2 3 4 5 6 7	Risk of bias	22	Present results of any assessment of		No specific additional	Supplement 7 - Studies reporting no adverse events p. 9;
8 9 10 11 12 13	across studies (18)		risk of bias across studies (see item 15).		information is required for systematic reviews of harms. See item 15 above.	Table 1 - Summary of methodological quality assessments
14 15 16 17 18 19 20 21 22		23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression (see item 16)).	_	No specific additional information is required for systematic reviews of harms.	 p. 10; Supplement 5 - Effect estimates for all adverse events with subgroups; Supplement 6 - Environment 6 - Enviro
22 23 24	D' '					Forest plots of adverse events
25 26 27 28 29	Discussion Summary of evidence (18)	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	_	No specific additional information is required for systematic reviews of harms.	p. 15-17
30 31 32 33 34 35 36	Limitations (18)	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	1.02	Recognise possible limitations of meta- analysis for rare adverse events (ie, quality and quantity of data), issues noted previously related to collection and reporting.	p. 18-19
 37 38 39 40 41 42 43 44 45 46 47 	Conclusions (19) Funding	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	- 0	State conclusions in coherence with the review findings. When adverse events were not identified we caution against the conclusion that the intervention is "safe," when, in reality, its safety remains unknown.	p. 19-20
48 49 50 51 52	Funding (19)	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	_	No specific additional information is required for systematic reviews of harms.	p. 22
52 53 54 55 56 57 58						