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Safety of Corticosteroids in Young Children with Acute Respiratory Conditions: A Systematic Review & 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; I^2=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.

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 guidelines[14]) corticosteroids for up to 14 days for an acute respiratory condition in an inpatient or outpatient setting. See Supplement 2 for detailed eligibility criteria.

Given the lack of standardized terminology for safety, we gathered information on all potentially drug-related harm outcomes[15] 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.

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 I^2 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 (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.

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 complaints[42] (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 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; I^2=0%). These studies focused on asthma (n=3),[26, 40, 79] croup (n=2),[48, 51] or both (n=1);[24] all compared

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] hives[66] and burning sensation[67] (estimated pORs 0.88 and 0.14, respectively). No events of phlebitis were reported comparing *dexamethasone to another corticosteroid.*[56]

Endocrine/metabolic & Musculoskeletal Systems

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; I^2=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 asthma[57] (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 wheeze[28] (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 wheeze[44] 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 RCT[88] 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 RCT[70] 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 RCT[28] 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 wheeze[44] reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT[57] 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 illness[91] 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 patients[60] 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 arrhythmia[42] and congestive heart failure[46] (*systemic or inhaled corticosteroid versus placebo*); and arrhythmia[26] or hypertension[56] (*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 dizziness[51] 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

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.

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; I^2=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

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

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.

Tables

Table 1. 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

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Supplement 2 - Eligibility criteria for study inclusion
Supplement 3 - Characteristics of included studies
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Supplement 4 - Methodological quality of included studies
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Supplement 5 - Effect estimates for all adverse events with subgroups
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  f. Cardiovascular system
  g. General adverse events/ other symptoms
  h. Immune system & oncology
Supplement 6 - Studies reporting no adverse events

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conducted screening, quality assessments, and data extraction. AW and BV conducted data analysis. RMF, AW, BV, SA, ACP, ASS, BHR, DWJ, DA, TPK, and LH contributed to interpretation of results. All of the authors approved the final version of this report.

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Data sharing statement: Dr. Hartling had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Data for this systematic review are available from the corresponding author upon reasonable request.

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

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 infection	2	792
	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

	4)	Restlessness	3	297
	5)	New sleep problems	3	408
	6)	Emotional distress due to nebulizer mask	1	82
	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 & Musculoskeletal	**Fluid and electrolyte abnormalities**		**7**	**1849**
	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).

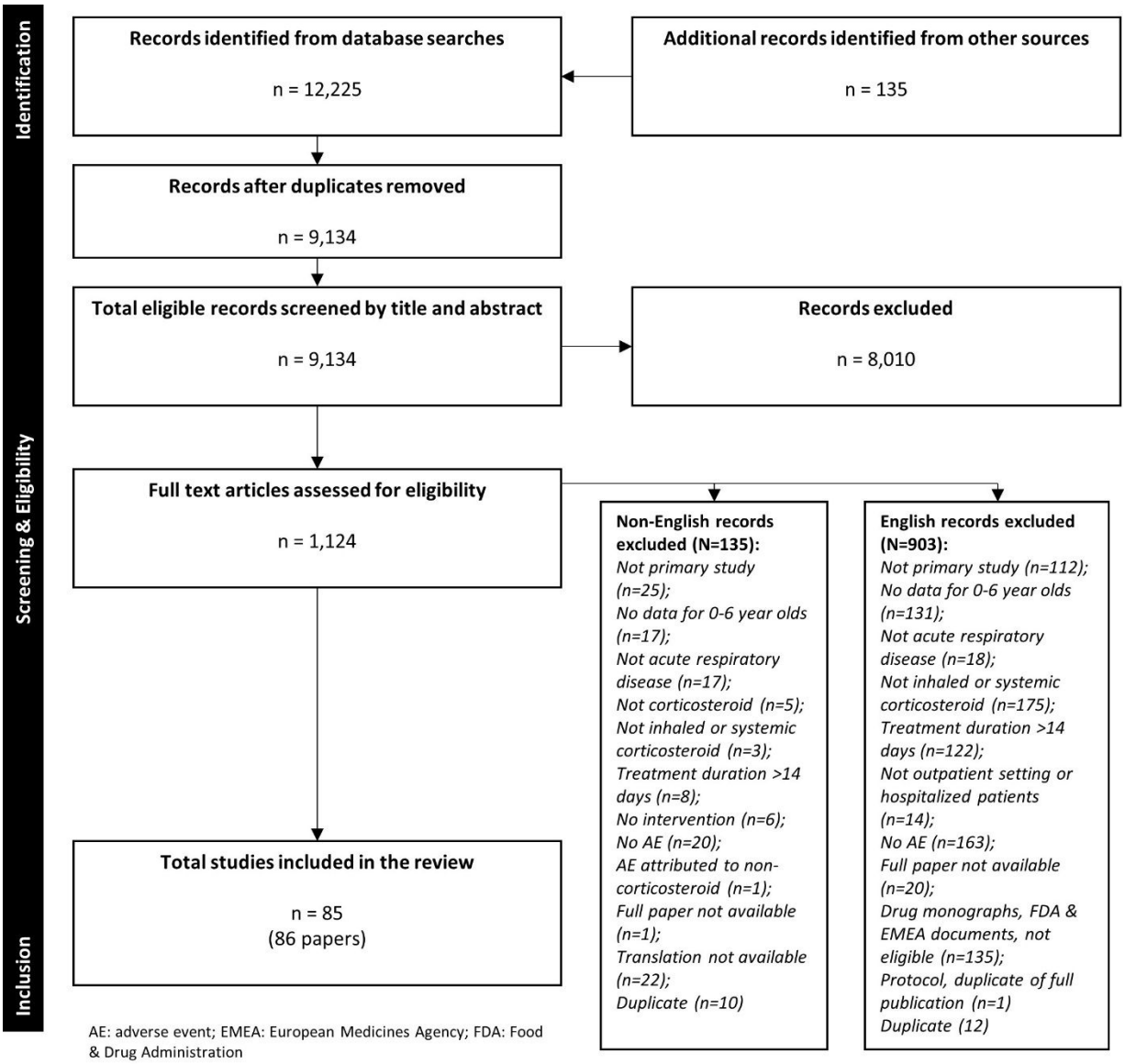

Figure 1. PRISMA study flow selection

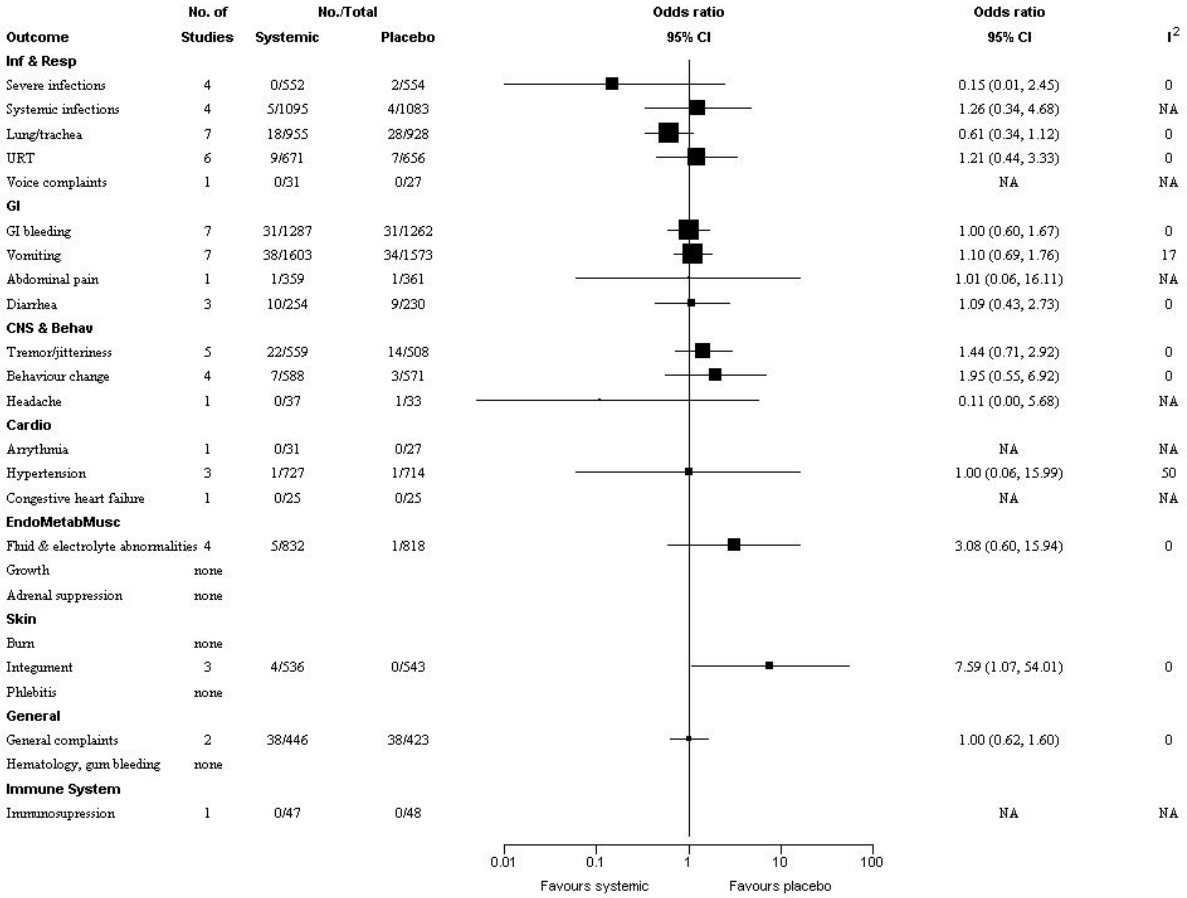

Figure 2. Forest plot of adverse events – systemic versus placebo

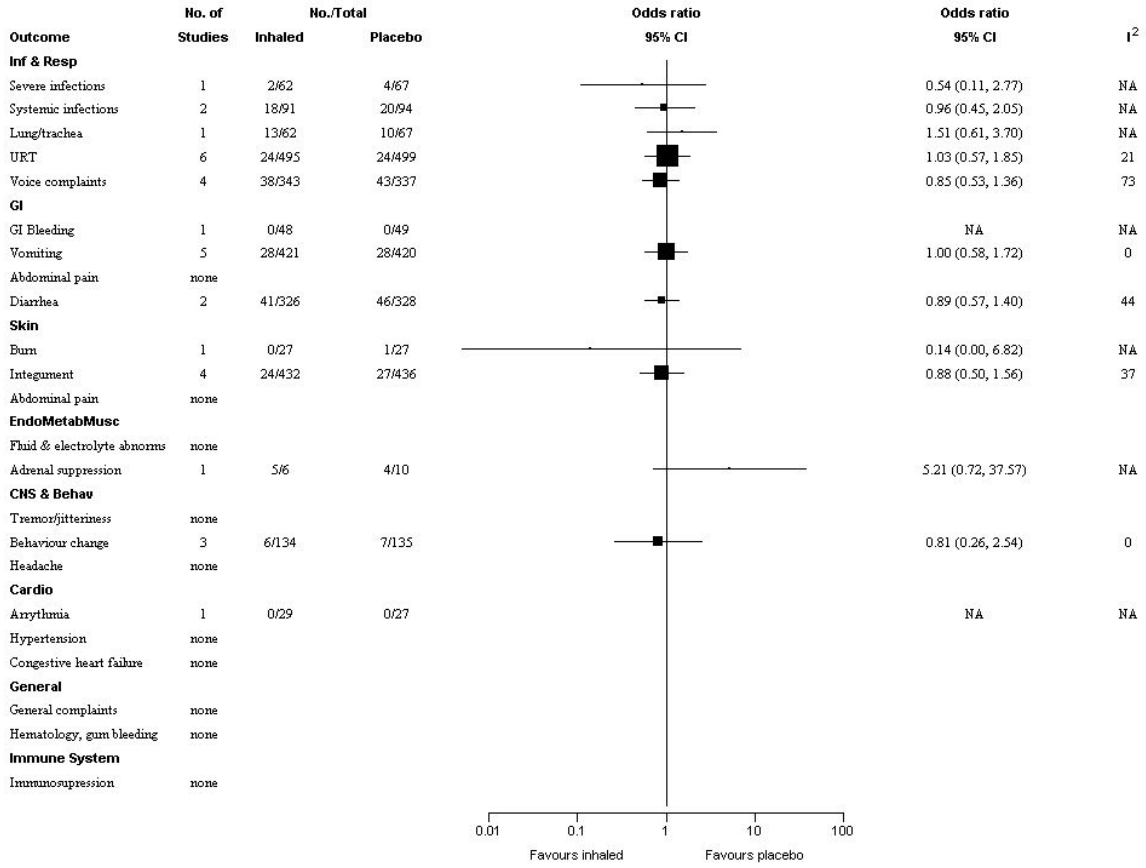

Figure 3. Forest plot of adverse events – inhaled versus placebo

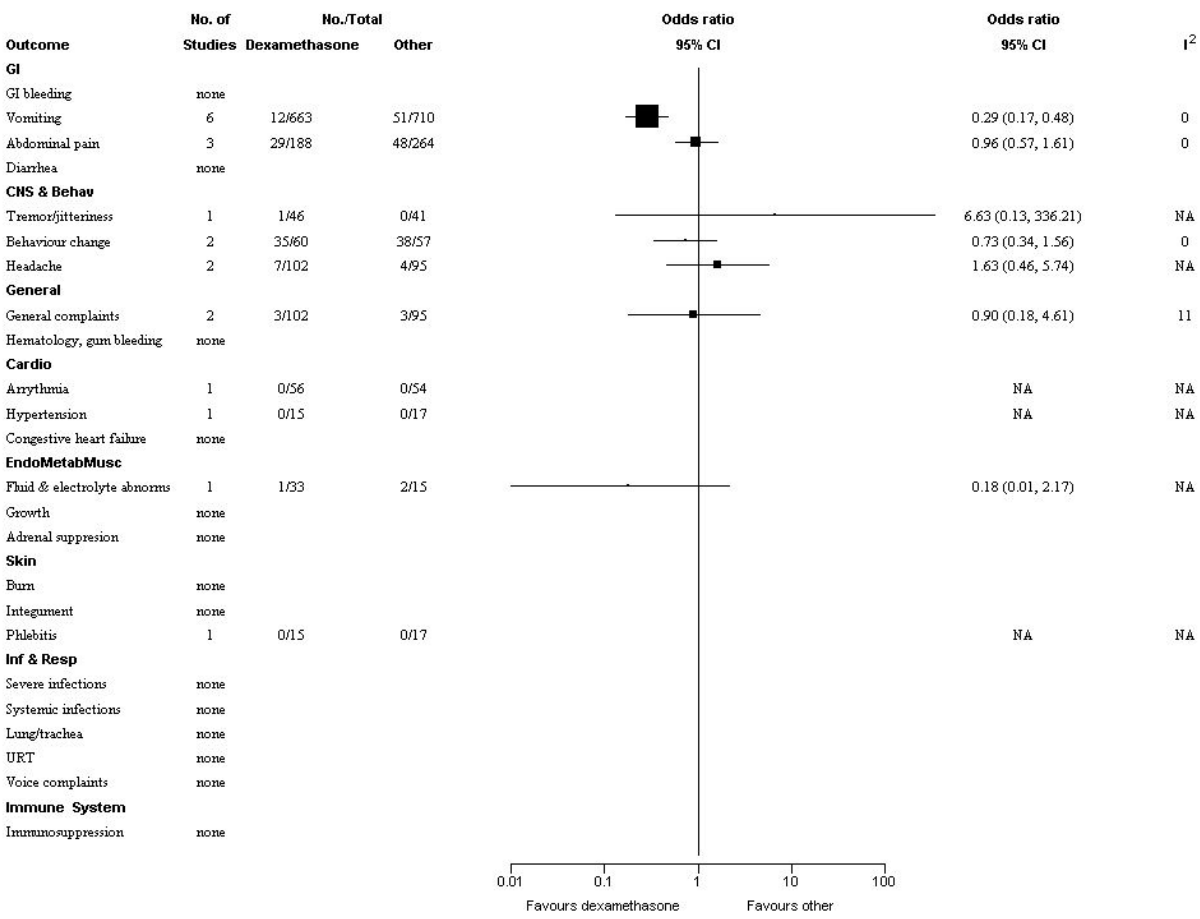

Figure 4. Forest plot of adverse events – dexamethasone versus other

Supplement 1. Search strategy

Database for original search: Ovid Medline(R) 1946 to September Week 1 2014
Databases for update searches: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date original search conducted: 14 September 2014
Date first update search conducted: 24 February 2016
Date second update search conducted: 31 July 2017
Strategy:

1. Adrenal Cortex Hormones/
2. Anti-Inflammatory Agents/
3. Beclomethasone/
4. Budesonide/
5. exp Glucocorticoids/
6. exp Hydroxycorticosteroids/
7. Pregnenediones/
8. Triamcinolone Acetonide/
9. adrenal cortex hormone*.tw,nm.
10. advair*.tw,nm.
11. alvesco*.tw,nm.
12. azmacort*.tw,nm.
13. becl?met*.tw,nm.
14. beclazone*.tw,nm.
15. beclo?ort*.tw,nm.
16. beclovent*.tw,nm.
17. beconase*.tw,nm.
18. becotide*.tw,nm.
19. betamet?asone*.tw,nm.
20. betnesol*.tw,nm.
21. budesonide*.tw,nm.
22. ciclesonide*.tw,nm.
23. clobetasol*.tw,nm.
24. cortiso*.tw,nm.
25. cortodoxone*.tw,nm.
26. corticosteroid*.tw,nm.
27. decadron*.tw,nm.
28. depo medrone*.tw,nm.
29. desoximet?asone*.tw,nm.
30. dexamethasone*.tw,nm.
31. deflazacort*.tw,nm.
32. diflucortolone*.tw,nm.
33. flixotide*.tw,nm.
34. flumethasone*.tw,nm.

35. flunisolide*.tw,nm.
36. fluocino*.tw,nm.
37. fluocortolone*.tw,nm.
38. fluorometholone*.tw,nm.
39. flurandrenolone*.tw,nm.
40. fluticasone*.tw,nm.
41. glucocortico*.tw,nm.
42. hydrocortisone*.tw,nm.
43. hydroxycorticostero*.tw,nm.
44. hydrocortone*.tw,nm.
45. hydroxypregnenolone*.tw,nm.
46. kenacort*.tw,nm.
47. kenalog*.tw,nm.
48. medrone*.tw,nm.
49. methylprednisolone*.tw,nm.
50. mometasone furoate*.tw,nm.
51. nasonex*.tw,nm.
52. paramethasone*.tw,nm.
53. predniso*.tw,nm.
54. pregnenolone*.tw,nm.
55. pulmicort*.tw,nm.
56. qvar*.tw,nm.
57. rhinocort*.tw,nm.
58. seretide*.tw,nm.
59. solu cortef*.tw,nm.
60. symbicort*.tw,nm.
61. tetrahydrocortisol*.tw,nm.
62. triamcinolone*.tw,nm.
63. tricort*.tw,nm.
64. vanceril*.tw,nm.
65. or/1-64
66. Acute Disease/ and (asthma* or pneumonia* or wheez*).mp.
67. exp Asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
68. Bronchial Hyperreactivity/
69. Bronchial Spasm/
70. exp Bronchiolitis/
71. Croup/
72. exp Dyspnea/
73. Emergencies/ and (asthma* or pneumonia* or wheez*).mp.
74. Emergency Medical Services/ and (asthma* or pneumonia* or wheez*).mp.
75. Emergency Services, Hospital/ and (asthma* or pneumonia* or wheez*).mp.
76. exp Pharyngitis/
77. exp Pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
78. exp Respiratory Syncytial Viruses/

79. exp Respiratory Syncytial Virus Infections/
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/
122. case control.tw.

123. (case adj (report* or study or studies or series)).tw.
124. cohort analy*.tw.
125. (cohort adj (study or studies)).tw.
126. cross sectional.tw.
127. (follow up adj (study or studies)).tw.
128. longitudinal.tw.
129. (observational adj (study or studies)).tw.
130. retrospective.tw.
131. or/117-130
132. 116 or 131
133. exp animals/ not humans.sh.
134. 132 not 133
135. 107 and 134
136. (comment or editorial or letter or meta analysis or review).pt.
137. 135 not 136
138. remove duplicates from 137

Database for original search: Ovid Medline(R) In-Process & Other Non-Indexed Citations, September 12, 2014
Date original search conducted: 14 September 2014
Strategy:

1. adrenal cortex hormone*.tw,nm.
2. advair*.tw,nm.
3. alvesco*.tw,nm.
4. azmacort*.tw,nm.
5. becl?met*.tw,nm.
6. beclazone*.tw,nm.
7. beclo?ort*.tw,nm.
8. beclovent*.tw,nm.
9. beconase*.tw,nm.
10. becotide*.tw,nm.
11. betamet?asone*.tw,nm.
12. betnesol*.tw,nm.
13. budesonide*.tw,nm.
14. ciclesonide*.tw,nm.
15. clobetasol*.tw,nm.
16. cortiso*.tw,nm.
17. cortodoxone*.tw,nm.
18. corticosteroid*.tw,nm.
19. decadron*.tw,nm.
20. depo medrone*.tw,nm.
21. desoximet?asone*.tw,nm.
22. dexamethasone*.tw,nm.

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.
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.

67. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
68. (nasosinusit* or rhinosinusit*).tw.
69. pharyngitis*.tw.
70. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
71. rhinit*.tw.
72. sinusit*.tw.
73. tonsillitis*.tw.
74. or/58-73
75. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).tw.
76. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).tw.
77. or/75,76
78. and/57,74,77
79. randomi?ed.tw.
80. placebo.tw.
81. randomly.tw.
82. trial.tw.
83. groups.tw.
84. or/79-83
85. case control.tw.
86. (case adj (report* or study or studies or series)).tw.
87. cohort analy*.tw.
88. (cohort adj (study or studies)).tw.
89. cross sectional.tw.
90. (follow up adj (study or studies)).tw.
91. longitudinal.tw.
92. (observational adj (study or studies)).tw.
93. retrospective.tw.
94. or/85-93
95. 84 or 94
96. 78 and 95
97. (comment* or editorial* or letter*).mp.
98. 96 not 97
99. remove duplicates from 98

Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library
Date original search conducted: 14 September 2014
Date first update search conducted: 24 February 2016
Date second update search conducted: 31 July 2017
Strategy:

1. [mh ^ “Adrenal Cortex Hormones”]
2. [mh ^ “Anti-Inflammatory Agents”]
3. [mh ^ Beclomethasone]
4. [mh ^ Budesonide]

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

49. methylprednisolone*:ti,ab,kw
50. mometasone next furoate*:ti,ab,kw
51. nasonex*:ti,ab,kw
52. paramethasone*:ti,ab,kw
53. predniso*:ti,ab,kw
54. pregnenolone*:ti,ab,kw
55. pulmicort*:ti,ab,kw
56. qvar*:ti,ab,kw
57. rhinocort*:ti,ab,kw
58. seretide*:ti,ab,kw
59. solu next cortef*:ti,ab,kw
60. symbicort*:ti,ab,kw
61. tetrahydrocortisol*:ti,ab,kw
62. triamcinolone*:ti,ab,kw
63. tricort*:ti,ab,kw
64. vanceril*:ti,ab,kw
65. {OR #1-#64}
66. [mh ^ “Acute Disease”] and (asthma* or pneumonia* or wheez*)
67. [mh Asthma] and (acute* or emergenc* or exacerbation* or severe*)
68. [mh “Bronchial Hyperreactivity”]
69. [mh “Bronchial Spasm”]
70. [mh Bronchiolitis]
71. [mh ^ Croup]
72. [mh Dyspnea]
73. [mh ^ Emergencies] and (asthma* or pneumonia* or wheez*)
74. [mh ^ “Emergency Medical Services”] and (asthma* or pneumonia* or wheez*)
75. [mh ^ “Emergency Services, Hospital”] and (asthma* or pneumonia* or wheez*)
76. [mh Pharyngitis]
77. [mh Pneumonia] and (acute* or emergenc* or exacerbation* or severe*)
78. [mh “Respiratory Syncytial Viruses”]
79. [mh “Respiratory Syncytial Virus Infections”]
80. [mh Rhinitis]
81. [mh Sinusitis]
82. [mh ^ “Status Asthmaticus”]
83. [mh ^ “Respiratory Sounds”] and (acute* or emergenc* or exacerbation* or severe*)
84. ((acute* or emergenc* or exacerbation* or severe*) near/5 (asthma* or pneumonia* or wheez*)):ti,ab,kw
85. (breath* near/2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)):ti,ab,kw
86. (bronch* near/3 (constrict* or spas*)):ti,ab,kw
87. bronchiolitis*:ti,ab,kw
88. bronchoconstrict*:ti,ab,kw
89. bronchospasm*:ti,ab,kw
90. croup*:ti,ab,kw
91. dyspne*:ti,ab,kw

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}
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.

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

66. acute disease/ and (asthma* or pneumonia* or wheez*).mp.
67. exp asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
68. exp breathing disorder/ and (acute* or emergenc* or exacerbation* or severe*).mp.
69. bronchospasm/
70. bronchus hyperreactivity/
71. exp bronchiolitis/
72. croup/
73. exp dyspnea/
74. emergency/ and (asthma* or pneumonia* or wheez*).mp.
75. emergency health service/ and (asthma* or pneumonia* or wheez*).mp.
76. exp emergency treatment/ and (asthma* or pneumonia* or wheez*).mp.
77. emergency ward/ and (asthma* or pneumonia* or wheez*).mp.
78. exp pharyngitis/
79. exp pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
80. Respiratory syncytial pneumovirus/
81. respiratory syncytial virus infection/
82. exp rhinitis/
83. exp sinusitis/
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
108. crossover procedure/
109. double blind procedure/

110. randomized controlled trial/
110. single blind procedure/
111. allocat*.tw.
112. assign*.tw.
113. cross over*.tw.
114. crossover*.tw.
115. doubl* adj blind*.tw.
116. factorial*.tw.
117. placebo*.tw.
118. random*.tw.
119. singl* adj blind*.tw.
120. volunteer*.tw.
121. or/108-120
122. exp case control study/
123. case report/
124. case study/
125. cross-sectional study/
126. cohort analysis/
127. case control.tw.
128. (case adj (report* or study or studies or series)).tw.
129. cohort analy*.tw.
130. (cohort adj (study or studies)).tw.
131. cross sectional.tw.
132. (follow up adj (study or studies)).tw.
133. longitudinal.tw.
134. (observational adj (study or studies)).tw.
135. retrospective.tw.
136. or/122-135
137. 121 or 136
138. animals/ not (animals/ and humans/)
139. 137 not 138
140. 107 and 139
141. (editorial or journal editorial or journal letter or journal note or letter or review).pt.
142. 140 not 141
143. limit 142 to embase

Database: Drugs@FDA
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Date original search conducted: 5 September 2014
Strategy:

Searched Drugs@FDA for drug name keywords:
1. beclametasone dipropionate
2. budesonide

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: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php
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=WC0b01ac058001d124
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

Supplement 2. Eligibility criteria for study inclusion

INCLUSION/EXCLUSION FORM

Reviewer ID:	**Date: / /2015**	**Record ID:**

Criteria	**Yes**	**No**	**UC**
1. PUBLICATION TYPE			
a. Primary research (RCTs, cohort studies, case control studies, case reports, and case series)	☐	☐	☐
Exclude: • Systematic reviews, letters to editor, commentaries			
2. Population			
a. Children ≤6 years of age, where age subgroups data is available:	☐	☐	☐
Unclear: • If aggregate/subgroup data include but are not limited to age ≤6 years			
Exclude: • If data is reported in aggregate with older ages			
3. CONDITION			
a. Children with acute respiratory disease (any of the following):	☐	☐	☐
• Bronchiolitis			
• Croup			
• Acute wheeze/asthma			
• Acute uncomplicated pneumonia (no abscess, effusion, etc)			
• Pharyngitis/tonsillitis			
• Peritonsillar abcess			
• Acute sinusitis			
• Respiratory syncytial virus/ rhinovirus/other viruses			
• Respiratory distress due to foreign bodies			
• PFAPA syndrome			
Exclude:			
• patients in NICU, PICU			
• respiratory distress syndrome (newborn)			
• allergic rhinitis			
• animal studies			
4. Intervention			

a. 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
- Mometasone furoate
- Prednisolone
- Prednisone
- Triamcinolone acetonide
- combination therapies (e.g. ICS + short-acting beta-agonists)

Exclude

- topical (non-systemic) corticosteroid therapy

* inhaled (moderate- to high-dose) corticosteroids, following GINA guidelines for low doses for children 5 years and younger (see Box 6-6 below).

5. Comparator group (where relevant)

a. Any comparison, including non-pharmacologic interventions which may act similarly to a placebo ☐ ☐ ☐

6. OUTCOME

Adverse drug reaction, side effect, adverse effects/events, adverse reactions ☐ ☐ ☐

7. Setting

Focus is on outpatient 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

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 p. 3
c. Characteristics of included studies p. 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, 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	
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 (1964-2017)**
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

Supplement 3b. Summary characteristics of included studies – comparisons

Number of treatment groups	Comparison	No. of studies (no. of patients)	No. of studies 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 + placebo vs. sal dose2 + placebo	1 (70)	1 (70)
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal + placebo	1 (69)	1 (69)
	Systemic CS + non-CS vs. systemic CS + placebo vs. non-CS + placebo vs. placebo + placebo	1 (800)	1 (800)
	Systemic CS + sal vs. systemic CS + placebo vs. sal + placebo vs. placebo	1 (32)	0
Non-comparative (case reports/series)	Systemic CS	5 (5)	0
	Mode of administration NR	2 (3)	0

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

Supplement 3c. Characteristics of included studies

Author, year Country Funding source	Study design Setting No. of centres	Respiratory condition Age (range)	Comparators, no. of participants	Co-interventions; Maintenance CS	Time points for assessments; FU	Outcomes related to adverse events
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 medications; FU 72h post-discharge	The most frequently reported adverse effects were fine tremors (17 cases) and palpitations (11 cases). None of the reported adverse effects was serious, and none was significantly different between the two groups.
Alansari 2013 Qatar Non-industry funded	RCT Pediatric emergency unit 1	Bronchiolitis <=18mo	1) Dexamethasone 1.0mg first day, then 0.6mg for 4d (oral) + sal, 5d total (neb), n=102 2) 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	Daily telephone surveillance (7 days) revealed no particular side effect concerns in either treatment group.
Aljebab 2017 Saudi Arabia & UK Unfunded	Cohort, 3-arm Pediatric ED of hospital	Asthma/croup, palatability & tolerability	SA 1) Dexamethasone 0.5mg/5mL elixir (oral), n=33	NR Most patients in prednisolone groups had	After each dose (within 10min) & daily on D1-D5	In SA and the UK, dexamethasone had the highest palatability

	(SA & UK) 2	2-10y (SA); 2-16y (UK)	2) Prednisolone base 5.0mg tablets (oral), n=52 3) Prednisolone sodium phosphate 15.0mg/mL syrup (oral), n=37 UK 1) Dexamethasone 2.0mg/5mL elixir (oral), n=53 2) Prednisolone base 5.0mg tablet (oral), n=38 3) Prednisolone sodium phosphate 5.0mg soluble tablets (oral), n=42	received oral steroids previously; however, most patients and none had received oral steroids previously in the SA & UK dexamethasone groups, respectively		scores and prednisolone base tablets had the lowest. Palatability scores improved for all formulations of prednisolone with each subsequent daily dose. In SA, prednisolone base tablets were associated with more nausea (24 vs. 7 patients) and vomiting (5 vs. 0 patients) than sodium phosphate syrup. In the UK, vomiting occurred more frequently with prednisolone base (8 patients) than sodium phosphate soluble tablets (2 patients) (p=0.041).

						In both centres, dexamethasone was associated with less side effects. Vomiting (1 vs. 0 patients), nausea (7 vs. 3 patients), and abdominal pain (10 vs. 8 patients) occurred more with dexamethasone sodium phosphate solution than dexamethasone elixir.
Alshehr 2005 Saudi Arabia Funding NR	RCT Emergency rooms & outpatient 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	Two patients developed bronchopneumonia 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 dexamethasone). No adverse events were

						noted in the group B patients. No patient had a clinical deterioration, either in the emergency room or after discharge and no child had gastrointestinal bleeding or bacterial infection.
Altamimi 2006 Canada Non-industry & industry funded	RCT Pediatric hospital 1	Asthma 2-16y	1) Dexamethasone 0.6mg/kg (max 18mg), single dose (oral), n=67 2) Prednisolone 1.0mg/kg (max 30mg) twice daily (oral), n=67	Salbutamol No CS in preceding 2wk	2d & 5d post-discharge & every week to a maximum of 3wk	Two subjects in the prednisolone group dropped out because of repeated vomiting. Side effects (table 5), n: Abdominal pain (2 dex vs. 3 pred); Vomiting (0 dex vs. 1 pred); Headache (0 dex vs. 0 pred); Palpitation (0 dex vs. 0 pred); Excessive urination (0 dex vs. 1 pred)
Bacharier 2008 USA	RCT, 3-arm	At least 2 wheeze episodes	1) Montelukast 4.0mg once daily (oral) +	Albuterol, prednisolone & other non-	Clinic visits 4wk after randomizati	The 3 groups did not differ significantly in

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

						treatment group.
Bjornson 2004 Canada Non-industry & industry funded	RCT Pediatric ED 4	Croup mean 35+/-23 mo	1) Dexamethasone 0.6mg, max. 20.0mg, single dose (oral), n=359 2) Placebo solution, single dose (oral), n=361	Mist, antibiotics & nebulized epinephrine or beta-agonists No CS in preceding 2wk	D1, D2, D3, D7 & D21 after day of treatment; FU interview with parent on D7 and chart and administrative database review	Among the 720 patients, there were no cases of gastrointestinal bleeding, complicated varicella, or bacterial tracheitis. There were 7 cases of pneumonia (3 in the dexamethasone group). All these cases were managed on an outpatient basis, without significant sequelae. Repeated short courses of oral corticosteroids are not associated with long-term negative effects on bone metabolism, bone density or adrenal function. There were no serious adverse events attributable

						to therapy in any children in our study. However, the study was not sufficiently powered to exclude the possibility of rare adverse events. Supplementary 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 gastroenteritis (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);

						RSV infection (1 vs. 0); Uncomplicated varicella (0 vs. 1); Urinary tract infection (0 vs. 1); Irritability (1 vs. 1); Eye discharge (1 vs. 0); Sinusitis (0 vs. 1); Bleeding from ear (0 vs. 1); Nasal discharge (1 vs. 0)
Brunette 1988 Canada Funding NR	NRCT Hospital 1	Asthma <6y	1) Theophylline 8.0mg/kg every 6-8h (oral) + metaproterenol 0.3-0.7 mg/kg every 6-8h (oral)+ prednisone 1.0mg/kg/day for 7-14d (oral), n=16 2) Theophylline 8.0mg/kg every 6-8h (oral) + metaproterenol 0.3-0.7mg/kg every 6-8h for 7-14d (oral), n=16 Multiple courses over 1yr	None NR	Monthly or every second month, depending on severity of disease; Growth (mean height gain in cm/yr and height as percentile of normal distribution) assessed (assessment method NR) at the end of each of two 1-yr periods	No side effect was observed in a particular case which received longer duration of corticosteroid (high cumulative corticosteroid dose). Growth and weight gains for all children were within the normal range during the two periods.

Buckingham 2002 USA Non-industry funded	RCT Pediatric hospital 2	RSV (bronchiolitis) <24mo	1) Dexamethasone 0.5mg/kg/dose every 12h for 4d (IV), n=22 2) Placebo saline every 12h for 4d (IV), n=19	Other treatment (not specified) No CS in preceding 3wk	Enrolment & daily until discharge; FU 30d after enrolment	Serious adverse events occurred in 2 patients in the dexamethasone group. One infant developed progressive respiratory failure that did not improve with high-frequency oscillatory ventilation or extracorporeal membrane oxygenation; support was withdrawn, and this infant died on study day 38. Another subject developed pneumothorax, which resolved following placement of a pigtail thoracotomy catheter, on study day 7. Neither adverse event was judged to be related to administration of the study

						drug. No patients in either group had microscopic or gross gastrointestinal bleeding, and no patients required antihypertensive therapy during the study.
Bulow 1999 Denmark Non-industry funded	RCT Pediatric hospital 3	RSV (bronchiolitis) 0-2y	1) Prednisolone 5.0mg/ml at dose of 2mg/kg/day, first dose at enrolment and for 4d (oral), or methylprednisolone 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	A total of 11 patients (7 in the prednisolone group and 4 in the placebo group) did not 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 Pediatric & 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,

			50.0mg/day) for 5d (oral), n=100			two parents reported that their child had 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 China Funding NR	RCT, 3-arm Pediatric outpatient, hospital ward, or ED 1	Asthma 1-14y	1) Budesonide 0.5mg (neb) + sal + ipratropium; 1-6yo (n=32); 6-14yo (n=21) 2) Budesonide 0.2-0.4mg (neb) + sal + ipratropium; 1-6yo (n=25); 6-14yo (n=16) 3) Dexamethasone 2.0mg (<2yo), 4.0mg (2-6yo) (IV); 1-6yo (n=15); 6-14yo (n=14)	NR No CS within 48h	0.5h before & post-treatment & 5d post-treatment	All three groups of children showed no adverse effects.
Chub-Appakarn 2007 Thailand Funding NR	RCT Pediatric hospital ward 1	Croup 6mo-5y	1) Dexamethasone 0.5ml/kg of 0.15 mg/kg, single dose (IV), n=20 2) Dexamethasone 0.5 ml/kg of	Epinephrine, mist, antibiotics & oxygen No CS in preceding 2wk	0, 1h, 2h, 3h, 4h, 6h, 8h, 10h & 12h post-treatment	There was no significant adverse reaction from dexamethasone treatment in either group.

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

						hospitalizatio n for adenoidectom y and tonsillectomy in the placebo group. Neither adverse event was drug related.
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	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 throughout the study period,

						though there was a trend towards decreasing tachypnoea in all four groups.
Connolly 1969 Ireland Funding NR	RCT Hospital 1	RSV Bronchiolitis 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 the course of the disease in severely ill children. There were no deaths.
Corneli 2007 USA Non-industry & industry funded	RCT ED 20	Bronchiolitis 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 gastrointestinal bleeding, hypertension, or complicated varicella. Vomiting within 20 min after administratio

						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 an 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 the PRED group (5.7%) vomited within 30 minutes of the dose of steroid on day 1 in the ED compared with none in the DEX group (absolute difference -5.7%; 95%CI -9.9% to -1.54%). Seven patients vomited after the prednisolone dose on day 2, and 6 vomited after the dose on day 3. A total of 14 patients

						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 Pediatric ED 1	Viral respiratory 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 NR	Diary recordings twice daily for 14d; examination 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 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 1993 Denmark Non-industry & industry funded	RCT, 4-arm Pediatric department 5	First or recurrent wheeze 0-18mo	1) Prednisolone 4.0-6.0mg/kg on admission; D2-3=1.6-2.6mg/kg (oral) + terbutaline 0.12-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb), n=31 2) Placebo solution (oral) + budesonide 0.5mg every 4h until discharge or for 5d (neb) + 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 4) Placebo solution (oral) + placebo (neb) + placebo saline (neb), n=27	NR No CS preceding study	Daily for 5d or until discharge	No side effects were observed, specifically no hoarseness, oral candidiasis or continued fever, in any of the groups. No significant tachycardia was found in the treatment groups compared with placebo.
Dawson 1993 Australia Industry funded	RCT Hospital 1	Asthma <6.5y	1) Prednisolone 1.0mg/kg tablets, every 24h for 5d (oral), n=25 2) Prednisolone 1.0mg/kg solution, every	None NR	D1 to D5	Twenty-one of the children taking the solution took it easily on day 3, compared to two in the

			24h for 5d (oral), n=26			tablet group 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. 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 to cause vomiting (on all five days), abdominal pain frequency (days 2-5), nausea (days 2-5) or mood change (days 2-5). As a result of persistent vomiting, the parents of two children receiving tablets stopped treatment prematurely.
Ducharme 2009 Canada Non-industry & industry funded	RCT Hospital 5	>=3 wheeze episodes in lifetime, onset of URTI 1-6y	1)Fluticasone propionate 250mcg (3 doses twice daily at start of URTI) until 48h elapsed without symptoms, for max. 10d (MDI), n=62 2) Placebo (3 doses twice daily at start of URTI until 48h elapsed without symptoms (MDI), n=67 Multiple courses over 6-12mo	Albuterol, nasal saline irrigation No more than 1 dose of CS in preceding 6mo or 2 doses in preceding 12mo	Monthly telephone contacts and a medical visit every 4mo; Growth assessed using an upright stadiometer at baseline, every month, and at the end of follow-up (6-12mo);	Thirteen serious adverse events (4 in fluticasone group and 9 in placebo) occurred in 13 children during the study period - namely, pneumonia, seizure, admission to an intensive care unit, burn, respiratory syncytial virus infection, atelectasis,

					Basal cortisol assessed using an immunoassay system, with or without corticotropin 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); Gastroenteritis (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);

						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

						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 performed.
Eboriadou 2010 Greece Funding NR	RCT, 3-arm Pediatric ED 1	Croup 6mo-5y	1) L-epinephrine 5.0ml (1 of 1:1000mg/ml), 5-10min (neb), n=25	Oxygen No CS in preceding 24h	Before treatment & at 15min, 20min, 60min, 90min &	The L-epinephrine group was the only group with side effects of

			2) Dexamethasone 0.6mg/kg (max. 8mg), single dose (IM), n=193) Beclomethasone dipropionate 200mcg (MDI), n=20		120min post-treatment; patients asked to return if relapse in next 24h	treatment. Tremor and tachycardia were observed in 4 children from Group A, who had received LE and were resolved after 2 hours, when the action of LE wear off.
Eden 1967 USA Industry funded	RCT Hospital 1	Croup 8mo-5y	1) Dexamethasone 0.10mg/kg at 0.1cc/kg/dose every 6h for 48h, total daily 0.40mg (IM), n=25 2) Control preparation 0.1cc/kg/dose every 6h for 48h (IM), n=25	Oxygen, humidity & tetracycline NR	Every 6h for total 48h	No untoward effects were noted. There were no episodes of congestive heart failure or sodium retention.
Escobedo Chavez 1992 Mexico Industry funded	RCT Hospital ED 1	Asthma 1mo-14y	1) Methylprednisolone 3.0mg/kg, single dose (IM) + placebo 4.5ml + sal 0.5ml every 4h (neb), n=25 2) Aminophylline 5.0mg/kg every 6h (IV) + sal 70 mcg/kg every 8h + oxygen (neb), n=25	Saline, salbutamol & oxygen No CS in preceding 15d	Baseline & discharge	We detected no side effects with the use of methylprednisolone in a single dose or any treatment failures that merited the use of methylxanthines or additional steroid doses.
Fifoot 2007 Australia	RCT, 3-arm	Croup 6mo-6y	1) Prednisolone 0.2ml/kg of 1.0mg/kg, single	Antipyretics or nebulized adrenaline	Baseline & hourly up	No patient suffered any adverse

Non-industry funded	Pediatric ED 1		dose (oral), 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	to 4h post-treatment; FU 1wk by telephone following index visit	outcomes 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) tolerated second dose.
Fitzgerald 1996 Canada Industry funded	RCT Pediatric 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	Six patients in each treatment group reported adverse events. These included vomiting, an erythematous rash, diarrhea, wakefulness, excessively active behavior, wheezing, and a nosebleed. These were minor and did not result in withdrawal from the study or require

						specific treatment.
Francis 1997 Australia Funding NR	RCT (trial registry data) Acute care setting 4	Asthma ≤48mo	1) Fluticasone propionate 1.0mg twice daily (neb) + placebo tablets once daily (oral) for 7d, n=37 2) Prednisolone (dose NR) daily for 7d (oral), n=19	NR No CS treatment for >7d in preceding 4wk	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); Asthma (1 vs. 2); Hoarseness/dysphonia (0 vs. 2); Serious adverse events - on-therapy: Subjects with non-fatal SAEs (2 vs. 0): Ketonuria, glycosuria and hyperglycaemia (1 vs. 0);

						Subjects with fatal SAEs (0 vs. 0)
Garbutt 2013 USA Non-industry funded	RCT Primary care office 10	Croup 1-8y	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	Acetaminophen & ibuprofen No CS preceding current croup episode	FU interviews at D1 to D4 & D11; FU chart review within 28d of index visit	No serious adverse events occurred. Study groups did not differ in reporting side effects from the study medications (24% dexamethasone, 26% prednisolone, P = 1.0; Table 4). The most common side effects identified with specific questioning were mood changes (57%), sleep problems (36%), stomach pain (19%), and headache (13%). Table 4 adverse events, n (dex vs. pred): A side effect at D11 (11/45 vs. 10/39); Mood changes (25 vs. 24);

						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 2002 Italy Funding NR	NRCT NR, "ambulatory infants" 1	Wheeze - early URTI before signs of wheeze 7-12mo	1) Beclomethasone 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 NR	Twice daily	At this writing, four years after the study was completed, no apparent adverse effects were reported. Plasma cortisol measured in four patients receiving at least 2 treatment periods of 5 days a month was normal.
Gill 2017 Canada Funding NR	Cohort Pediatric hospital ED 1	Croup >2y (mean 4.7y vs. 4.8y)	1) 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 dexamethasone 0.6mg/kg for croup is not associated with decreased endogenous glucocorticoid

			or antibiotics), n=5			levels in 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 symptoms resolved by 7 days. The other, also a 3-year-old boy, returned to the ED 4 days after dexamethasone administration for unilateral facial swelling. Serologic testing for paramyxovirus (mumps) was negative, and he was given a diagnosis of viral parotitis. His symptoms resolved by 7

						days. Four participants visited their primary care physician within 7 days of dexamethasone administration. 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 deaths.
Goebel 2000 USA Funding NR	RCT Pediatric ED or children's clinic 2	Bronchiolitis ≤23mo	1) Prednisone 2.0mg/kg/day for 5d (oral) + albuterol 0.3mg/kg/day (or 0.15mg/kg/dose (neb)) for 5d (oral), n=24	NR NR	Clinical scores on D0, D2, D3 & D6; FU when convalescence completed	One patient in the prednisolone group was observed by his caretakers to be "jittery" at times after enrollment.

			2) Placebo solution (oral) + albuterol 0.3mg/kg/day (or 0.15mg/kg/dose (neb)) for 5d (oral), n=24			This resolved after a decrease in the albuterol dose. No evidence of treatment complications was observed in any of the other patients.
Grant 1996 USA Non-industry funded	Cohort Primary care clinic & teaching hospital ED 1	Asthma 2-14y	1) Prednisone 2.0mg/kg (max. 60mg/day), single dose intermittent for 6mo (oral), n=86 2) Placebo (NR), n=86 Multiple courses over 1yr	Bronchodilators as needed NR	NR	Ninety-four episodes of acute infection occurred in 50 subjects and 222 episodes of symptoms of infection occurred in 62 subjects (table 1 episodes of infection, number of doses, and association between doses and frequency of infection). No difference was observed in the mean number of doses of prednisone received by those with the infection compared with those

						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 pharyngitis, pneumonia, and urinary tract infection; eight (73%) episodes of chickenpox; eight (57%) episodes of skin infections; and 14 (88%) episodes of ringworm.
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/creatinine assessed by radioimmunoassay (standard methods) on D14	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

						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/creatinine value for the IM Dex group was lower than that for the

						PO Pred group, but this difference was not statistically significant.
Hedlin 1999[1] Sweden Funding NR	RCT Pediatric hospital 1	Asthma – first sign of URTI 1-3y	1) Budesonide 400mcg, 4 times daily for 3d then twice daily for 7d (MDI), n=9 2) Placebo, 4 times daily for 3 days then twice daily for 7d (MDI), n=11 Multiple courses over 1yr, or max. 6 treatments *subgroup of children from Svedmyr 1999 with therapeutic failure from budesonide given 3d course (6.0mg, 4.0mg, and 2.0mg on respective days) of oral betamethasone	Beta-agonists and/or theophylline NR	D10 & D13; Routine height measurements (assessment method NR) were taken (timing of assessments NR); Serum cortisol (on D8-10 of second course of study medication, morning of day after third dose, and at 12-14d after therapy) and urinary cortisol/creatinine (in the night after third dose of betamethasone and at 12-14d after therapy)	There were no significant differences between pretreatment and post-treatment serum cortisol, osteocalcin, ICTP and urine cortisol/creatinine ratio in the groups, (the comparison was made in the children who had assessments before and after budesonide/placebo) nor were there any significant differences between the active and placebo treated groups. It was, however, noteworthy that the urine cortisol/creatinine ratio decreased in

					assessed by radioimmunoassay	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 betamethasone have pronounced systemic effects, whereas 10d of high doses of budesonide do not produce significant systemic effects.
Husby 1993 Denmark Funding NR	RCT Pediatric 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.

			doses 30min apart (neb), n=16			
Inglis 1993 USA Funding NR	Case report, 2 Hospital	Croup 18mo; 14mo	Case 1) Prednisolone 1.0mg/kg, twice daily for 4d (NR) Case 2) Dexamethasone 0.3mg/kg, 3 doses in 24h (NR)	Case 1: racemic epinephrine, acyclovir sodium Case 2: amoxicillin/clavulanate potassium, cefuroxime sodium	NR	Case 1: Twenty days into illness, airway endoscopy revealed shallow mucosal ulcerations of patient's glottis and subglottis, but a normal appearing tracheobronchial tree. Cultures were positive for HSV-1, Staphylococcus aureus and a-hemolytic streptococcus; Case 2: On day 11 of illness, airway endoscopy revealed severe subglottic edema and ulceration, purulent tracheal secretions, but normal tracheal mucosa. A tracheal aspirate

						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 postoperatively and was started on a regimen of nafcillin sodium and dexamethasone sodium phosphate, 1.5mg/kg per day. She was extubated after 48 hours and the dexamethasone therapy was discontinued. Her stridor gradually resolved

						spontaneously over the next 7 days without further intervention.
Jan 2000 Taiwan Funding NR	Non-RCT Pediatric hospital clinic 1	Asthma NR	1) Group A: Methylprednisolone 1.0mg/kg/6h (IV) for 1d, n=NR 2) Group B: Methylprednisolone 1.0mg/kg/6h (IV) for 2d, n=NR 3) Group C: Methylprednisolone 1.0mg/kg/6h (IV) for 3d, n=NR	NR NR	D1 to D3	An acute effect of glucocorticoid therapy on the suppression of osteoblasts was biochemically revealed by the finding of reduced serum osteocalcin levels; this suggests that early change in serum osteocalcin may be a useful indicator for patients at high risk of bone loss. Levels of serum osteocalcin progressively declined with increasing duration of GC therapy, with tendency toward a decrease of serum phosphate.

						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 +/- 1.5
Jartti 2006 Finland Non-industry and industry funded	RCT Pediatric 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 hospitalization, 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 Pediatric 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 hospitalization, 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 differences in the

Non-industry and industry funded	University hospital 1	rhinovirus-induced 3-23mo (mean 13.2mo vs. 12.2mo)	2mg/kg/d in 2 divided doses for 3d (max. 60.0mg/day), n=34 2) Placebo, n=40 Multiple courses over 1yr	No previous systemic or inhaled CS treatment	12mo post-discharge	incidence of adverse events between the prednisolone and placebo groups (results not shown). No clinically significant adverse events were reported.
Johnson 1996 Canada Non-industry funded	RCT Pediatric ED 1	Croup mean 15mo vs. 17mo	1) Dexamethasone 10.0mg (4ml) - 10.0mg (<8kg), 15.0mg (8-12kg) or 20.0mg (>12kg), 10min (neb), n=28 2) Control, saline (4ml), 10min (neb), n=27	Humidified oxygen No CS in preceding 2wk	Baseline, 2h & 4h post-treatment	Two patients with neutropenia treated with dexamethasone had a clinical course consistent with bacterial tracheitis.
Johnson 1998 Canada Industry funded	RCT Pediatric ED 2	Croup 3mo-9y	1) Budesonide 4.0mg for 20min (neb), n=48 2) Dexamethasone 0.6mg/kg, single dose (IM), n=47 3)Placebo suspension, single dose for 20min (neb), n=49	Racemic epinephrine & mist therapy No CS in preceding 4wk	Study entry & hourly for 5h post-treatment until discharge; FU 72h post-discharge	No child had gastrointestinal bleeding or bacterial tracheitis.
Klassen 1994 Canada Non-industry funded	RCT Pediatric ED 1	Croup 3mo-5y	1) Budesonide 2.0mg (4ml), single dose (neb), n=27 2) Placebo saline 0.9%	Racemic epinephrine or dexamethasone, or oxygen tent	Baseline & hourly for 4h; FU at 1wk	No adverse events were noted in the budesonide group. No patient in that

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

			3) Budesonide 2.0mg (4ml) (neb) + dexamethasone 0.6mg/kg (oral), n=64			reported this condition at the 1-week follow-up. Parents of 1 patient treated with dexamethasone reported hives, and parents of 1 patient treated with dexamethasone reported violent behavior. Parents of 1 patient who had received budesonide and dexamethasone reported their child to be more hyperactive than usual.
Kuyucu 2004 Turkey Funding NR	RCT Pediatric outpatient clinic and ED 1	Bronchiolitis 2-21mo	1) Epinephrine 3ml of 1:1000 solution for 10min (neb) + dexamethasone 0.6mg/kg, single dose (IM), n=23 2) Sal 0.15mg/kg of 1mg/ml solution added to 0.9% saline for 10min (neb) + dexamethasone 0.6mg/kg, single dose (IM), n=23	NR No CS in preceding 2wk	Baseline, 30min, 60min, 90min & 120min, then 24h, 5d; FU by regular hospital visits in subsequent 2mo	No side-effects such as pallor, vomiting or tremor were encountered in the patients.

			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 China Funding NR	RCT Hospital pediatric inpatient ward 1	Asthma 1-5y	1) Budesonide 0.05mg/kg every 12h (neb), n=9 2) Dexamethasone 0.1mg/kg every 8h (neb), n=9 Multiple courses over 8-19mo	Terbutaline (as needed) 0.25mg/kg every 6h to a max. of 5.0mg NR	On admission, at discharge & at follow-up; Growth (mean height) assessed (assessment method NR) at baseline and approximately 8-19mo after randomization; Adrenal suppression assessed from blood pressure (systolic	The measures of blood pressure (systolic and diastolic), blood glucose and serum potassium revealed no significant changes between admission and discharge in either group of patients (Table 3). Thus, there were no adverse effects in these patients. Table 4 also shows that there were no significant differences in

					and diastolic) and blood glucose at baseline and approximately 8-19mo after randomization	total height growth, mean rate of height increase, systolic or diastolic blood pressure, or blood glucose between the treatment groups.
Langton Hewer 1998 UK Funding NR	RCT Hospital 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	Bronchodilators (nebulized) No CS in preceding 14d	Baseline, 0h, 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 possibly attributable to prednisolone therapy was noted in any of the three treatment groups. Three children in prednisolone 2.0mg group were withdrawn because of vomiting, a diagnosis of pneumonia or the parents

						withdrew consent.
Lee 2001 Taiwan Funding NR	Case report Pediatric clinic of hospital 1	Asthma 5y	1) Terbutaline solution (loading dose: 5.0mg/kg/dose, maintaining dose: 0.6mg/kg/h); Methylprednisolone (BW 21kg, 2.0mg/kg/dose, 40.0mg every 6h) (IV), and; Procaterol 12.5mcg twice daily (oral)	NR	D1 to D3	On day 3 of admission the patient was found to have major behaviour changes and hyperventilation. She started screaming unreasonably, gazing forward and sometimes upward and became panic. She had visual hallucinations and delusion.
Leer 1969 USA Industry funded	RCT Hospital 5	Bronchiolitis <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	There were no detrimental corticosteroid effects in any of the patients. The corticosteroid neither increased the incidence of staphylococcal or other bacterial pneumonias nor masked superinfections.
Lehmann 2008 Germany Funding NR	Case report Pediatric	Asthma 2y	1) Prednisolone-21-hydrogen	None 3wk washout period (but	Post skin prick test	Patient had been on well-tolerated long-term

	Allergology Clinic 1		succinate (PSH) 50.0mg (IV) 2) Prednisone (100.0mg, suppository) 3) Betamethasone (dose NR, oral) 4) Dexamethasone (dose NR, IV)	under long-term maintenance therapy of daily 100mcg fluticasone propionate (inhaled) and intermittent prednisone suppositories		therapy of 100mcg inhaled fluticasone dipropionate daily for frequently recurring episodes of asthmatic exacerbations, with intermittent prednisone suppositories for acute bronchopulmonary obstruction with no occurrence of adverse events and no other glucocorticoid preparations. Patient was admitted to department due to severe bronchospasm (neither bronchodilators nor rectally administered prednisone provided symptom relief) and given 50mg of prednisolone-21-hydrogen succinate intravenously.

						Within a few minutes the boy developed generalized urticaria, facial angio-oedema, nausea and severe dyspnea requiring nasal oxygen supplementation. Medication was interrupted and symptoms spontaneously 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, betamethasone or dexamethasone. An oral provocation test with betamethasone and a

						titrated intravenous dexamethasone challenge test were tolerated without any complications.
Leipzig 1979 USA Funding NR	RCT Hospital 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 Hospital 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/dose 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.

			(procaterol hydrochloride) 1.25mcg/kg/dose on admission, then twice daily (oral) 3) Group C: No hydrocortisone or procaterol (n=28)			
Lucas-Bouwman 2001 Netherlands Funding NR	RCT Hospital 1	Asthma 3mo-8y (mean 2y)	1) Prednisolone 1.0mg/kg tablets, twice daily for 5d (oral), n=NR 2) Prednisolone 1.0mg/kg solution, twice daily for 5d (oral), n=NR	Bronchodilators (inhaled) NR	6d to 8d after index visit	Vomiting was observed in 23% of patients using crushed tablets, and in none of the patients on oral solution.
Nahum 2009 Israel Funding NR	Case series (n=3, 1 case relevant) Pediatric ED 1	Asthma 5y	1) Methylprednisolone 2.0mg/kg for 2d (IV)	NR	D1 & D2; FU 3mo post-discharge	He presented with wheezing, received an intravenous bolus of methylprednisolone sodium succinate (2mg/kg), and immediately developed restlessness and facial rash which resolved spontaneously. On the following day, he received again the same medication and

						immediately developed respiratory distress and cyanosis with oxygen desaturation of 89%. He recovered with oxygen supplementation and was treated afterward with oral betamethasone sodium phosphate without adverse events.
Paniagua 2016 Spain Funding NR	RCT (conference abstract) Pediatric ED 1	Asthma >12mo	1) Dexamethasone, NR, 2 doses (oral), n=287 2) Prednisone/prednisolone, NR, 5d (NR), n=290	NR NR	NR; FU at 7d & 15d post-ED visit	No differences were found regarding vomits (2.1% vs 4.1%).
Panickar 2009 UK Non-industry funded	RCT Pediatric 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. In one child in the prednisolone group, parents attributed excess

						vomiting to the study drug and discontinued the medication after discharge from hospital.
Panigada 2014 Italy Funding NR	Case report Pediatric Pulmonary and Allergy Unit 1	Progressive shortness of breath, subsequent diagnosis of inflammatory myofibroblastic tumor cell proliferation 5y	Albuterol (inhaled) + prednisone 1.0mg/kg (28.70kg) (oral), n=1	NR 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 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.

						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,

						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 the neoplasm was carried out.
Plint 2009 Canada Non-industry and industry funded	RCT Pediatric ED 8	Bronchiolitis 6wk-12mo	1) Epinephrine 3ml 1:1000, 2 doses 30min apart (neb) + dexamethasone 1.0mg/kg (max 10mg) in ED plus 5 once-daily 0.6mg/kg/dose, total 6d (oral), n=200 2) Epinephrine 3ml 1:1000, 2 doses 30min apart (neb) + placebo, total 6d (oral), n=199	Bronchodilators (albuterol, epinephrine) & antibiotics No CS in preceding 2wk	Baseline to 30min, 60min, 120min & 240min; FU daily until D7, then every 2d until D14 & every 3d until D22	Adverse events were uncommon (see Supplementary Appendix). Pallor was reported in 76 infants (9.5%), tremor in 15 (1.9%), and vomiting in 14 (1.8%), with no significant differences among the groups. One hospitalized

			3) Placebo 2 doses 30min apart (neb) + dexamethasone 1.0mg/kg (max 10mg), total 6d (oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201			infant in group 2 and one in group 3 had mild, transient hypertension, which resolved rapidly. Supplementary table: side effects and adverse 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 vs. 4 vs. 5 vs. 3); Varicella (0 in 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 vs. 0)
Razi 2015 Turkey Funding NR	RCT Hospital 1	Asthma 7-72mo	1) Budesonide 1.0mg/2ml, 2 doses for up to 5d, n=50 2) Sterile saline 2ml, 2 doses for up to 5d, n=50	Standard care: methylprednisolone 1.0mg/kg/day, for up to 5d (IV) + sal 0.15mg/kg every 4h +	Every 4h until discharge	No drug-related adverse effects were identified during hospitalization.

				ipratropium bromide 250mcg every 6h NR		
Roberts 1999 Australia Industry funded	RCT Women's and Childrens Hospital 1	Croup 6mo-8y	1) Budesonide 2.0mg (4ml) for 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	NR No CS in preceding 4wk	Baseline, 2h, 6h & 12h after first dose, then 12-hourly up to 48h if in hospital; FU by telephone 1d & 3d post-discharge	The adverse effects in both groups were attributable to either manifestations of the disease state or the mode of drug administration (Table 3). Four patients (3 placebo, 1 budesonide) experienced an exacerbation in symptoms to the point of causing interventional treatment mode outside of the protocol nebulised adrenaline). These exacerbations occurred shortly after beginning nebulisation and were apparently induced due to distress

						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. 1)

Roorda 1998 Netherlands Funding NR	RCT Hospital NR	Croup 4-52mo	1) Fluticasone propionate 1000mcg, 2 divided doses 30min apart (MDI), n=9 2) Placebo (NR), n=8	NR No CS in preceding 48h	Admission, 30min, 2h, 6h, 12h & 24h	No side effects of the treatment regimens were reported during the 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 had occult blood in their stools; two were in the dexamethasone group. No episodes of gross haematochezia were observed.
Sadowitz 2012 USA Funding NR	Case series (n=4, 1 case relevant) ED 1	Pharyngitis 3y	Dexamethasone 10.0mg single dose (oral?) + acetaminophen + amoxicillin, n=1	NR NR	NR	The patient was given a 10-mg dose of dexamethasone in addition to acetaminophen and 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 sore throat, now with an

						inability to tolerate oral fluids. Pertinent physical examination findings included pulse rate of 166 beats per minutes; oral temperature of 40.3 degrees C; dry, erythematous mucous 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 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

						dexamethasone administration before the diagnosis of ALL and in the absence of a pretreatment CBC count following the guidelines for high-risk leukemia established by the Children's Oncology Group. Induction therapy include IV daunorubicin, decadron, asparaginase, and vincristine. The patient's initial course of treatment was complicated by a ruptured duodenal ulcer with peritonitis and osteonecrosis. The patient survived these complications and achieved remission and continues on maintenance

						chemotherapy at this time.
Saito 2017 Japan Funding NR	RCT Pediatric department of hospital 1	Asthma <3y	1) Budesonide 1.0mg/dose, twice daily (neb), n=30 2) Prednisolone 0.5mg/kg, 3 times daily (IV), n=20	At admission, received hydrocortisone (IV) & one inhalation of procaterol; LTRA for wheezing episodes NR	Daily; Serum cortisol assessed (assessment method NR) on admission and D4 of hospitalization	Serum cortisol levels in the BIS and PSL groups at the time of admission were 15.0mcg/dL and 17.2mcg/dL (p>0.05), respectively. However, serum levels on the fourth day of hospitalization were 17.0mcg/dL and 10.9mcg/dL, with significant suppression in the PSL group. Adverse events did not occur in either group.
Schuh 2008 Canada Non-industry funded	RCT Pediatric ED 1	Bronchiolitis 8wk-23mo	1) Dexamethasone 1.0mg/kg in ED + 4 doses 0.15mg/kg starting 24h later, total 5d (oral), n=61 2) Dexamethasone 1.0mg in ED + 4 doses placebo syrup starting	Albuterol Baseline reports 3 patients with prior inhaled ICS	Baseline, D4 & D6 (home visits); FU by telephone on D28	The mean blood pressure increased from 96.1+/-8.8 mmHg to 99.5+/-14.8 mmHg in the single-dose group and from 96.4+/-7.9 mmHg to 103+/-

			24h later, total 5d (oral), n=64			16.8mmHg in the multiple dose group. Bag urine was obtained on day 6 visit in 47 study infants and tested positive for glucose in 1 child belonging to the multiple-dose group.
Schuh 2009 Canada Industry funded	RCT Pediatric 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/prednisolone 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	In the montelukast group, adverse effects developed in 3 patients. One patient experienced facial swelling of unknown etiology at 96 hours, another patient had vomiting and diarrhea at 72 hours, and the third patient complained of abdominal and leg pains on day 4. None of these patients required treatment for these events,

						and the relationship between montelukast and the ‘‘event’’ is questionable. No adverse effects developed in the children given prednisolone after discharge.
Siomou 2003 Greece Industry funded	Case control, 3-arm Pediatric hospital 1	Bronchiolitis, viral wheezing, or croup 2mo-10y	1) Hydrocortisone 10.0mg/kg/day for 3d (NR), n=28 2) Methylprednisolone 2.0mg/kg for 3 days (NR), n=21 3) Control, 3d, n=51	NR Never/no CS in last 2mo	Baseline, 2 days after CS administration & 12d after end of therapy	In summary, short-term IV corticosteroid administration to children suffering from acute respiratory diseases led to partial but reversible inhibition of bone formation markers, especially detectable in the >1-year-old children, without affecting the bone resorption markers. The fall in the serum phosphate levels and decrease in

						the maximum renal phosphate reabsorption decrease in the maximum renal phosphate reabsorption were significant but transient.
Sparrow 2006 Australia Funding NR	RCT Pediatric ED 1	Croup mean 37mo (28.8) vs. 45mo (31.6)	1) 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	Adrenaline No CS preceding study	Enrolment, 30min post-treatment, hourly for next 4h & every 4h until discharge; FU 7d-10d post-discharge	No adverse events were noted in either group.
Stafford 1998 Australia Industry and non-industry funded	NRCT Pediatric hospital or ED 1	Asthma/croup 1-12y	1) Prednisolone 5.0mg/ml solution (oral), n=8 2) PredMix 5.0mg/ml solution (oral), n=46 3) Dexamethasone 5.0mg/ml (oral), n=80	NR NR	Daily	No significant differences were found regarding the incidence of nausea, vomiting and abdominal pain, or any of the objective parameters tested.
Storr 1987 UK Non-industry & industry funded	RCT Pediatric 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	Salbutamol 5.0mg in 2ml saline (neb), on admission & 3 times or more daily when indicated	Admission, 4h, 12h, 24h & 36h	Prednisolone has a bitter aftertaste. Most children disliked the drink. 2 children in each group vomited

			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.
Sumboonnanonda 1997 Thailand Funding NR	RCT Pediatric 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 pediatric 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 childrenn'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 dexamethasone-treated patients in the main study, including one with a culture-positive influenza A viral infection, laryngotracheitis progressed to pneumonia.

						The other patient was the one who received a second injection of dexamethasone. At the time of his second injection, he had roentgenographic evidence of pneumonia. We did not encounter any side effects directly attributable to dexamethasone.
Sussman 1964 USA Non-industry funded	RCT Hospital NR	Bronchiolitis 1-25mo; Laryngitis 15mo-10y	1) Dexamethasone 0.1mg in divided daily dose every 6h: D1-9=0.2ml/lb/day; D10-11=0.1ml/lb/day; D12-13=0.05ml/lb/day; D14=0.02ml/lb/day (IM), n=31 2) Sodium chloride 0.15mEq/ml for 14d (IM), n=26	Oxygen, penicillin & streptomycin NR	Daily	Adverse reactions to steroid therapy were not noted on clinical examination and superinfections, bacterial or viral dissemination, were not encountered.

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

			1yr, or max. 6 treatments			became 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 reporting 4 episodes in the budesonide group. This difference was statistically significant (p = 0.024). Figure 4 – bar chart of adverse events (counts, only

						once per treatment period), including vomiting, otitis, hoarseness, sore throat, conjunctivitis, croup, stomach ache, diarrhea, agitation, sleep disturbances, and aggressiveness.
Tagarro 2014 Spain Non-industry funded	Cohort University hospital 1	Bronchiolitis 0-6mo	1) Dexamethasone 1.0mg single dose, or for 6d, or 1.0mg on first day plus 0.6mg for 5d, 6d total (likely oral), n=33 2) Prednisone 1.0-2.0mg for 5d (likely oral), n=15 3) No steroids, dose/duration NR, n=32	Adrenaline & salbutamol NR	NR	No significant adverse effects attributable to steroids or bronchodilators were found in the clinical records, apart from hyperglycemia. Hyperglycemia was found in 4 out of 23 patients tested (17%). Two of them had received PRD, one of them DXM and one no steroids.
Tal 1983 Israel	RCT Hospital	Acute wheeze 1-12mo	1) Dexamethasone 0.3mg/kg	Oral/IV fluid & humidified oxygen	Admission, 3h after first IM	One infant developed a remarkable

Non-industry funded	1		(4mg/ml) on admission + 0.1 mg/kg every 8h (IM), n=8 2) a) Sal solution 2.5mg (0.5ml), on admission & every 6h (neb); b) Sal syrup, 0.15mg/kg, 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 saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8	NR	dose & each morning (8am) until discharge	tremor as a side effect of salbutamol. No other side effects or complications of the treatment were documented.
Tamura 2008 Japan Funding NR	Case series Medical center, inpatient	Refractory mycoplasma pneumonia	Methylprednisolone 30.0mg/kg once daily for 3d (IV), n=1	NR NR	NR	All cases: There were no adverse events in any patients during steroid

	1	5y (n=6, range 3y-9y)				treatment; Case patient 1: On the 10th clinical day, we initiated methylprednisolone pulse therapy once 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.
Teeratakulpisarn 2007 Thailand	RCT Pediatric outpati	Bronchiolitis 4wk-24mo	1) Dexamethasone 0.6mg/kg, single dose (IM), n=89	Epinephrine, salbutamol, IV fluids, antimicrobial	Baseline & every 6h until study endpoint (resolution	Soon after study endpoint, but before being discharged,

Non-industry funded	ent or ED 2		2) Saline solution 0.6mg/kg, single dose (IM), n=85	drugs & oxygen No CS in preceding 2wk	of respiratory distress); FU at 2wk intervals for at least 1mo	systemic CS was prescribed to seven children (four in the dexamethasone group) because of re-wheezing. None of the children received theophylline or ribavirin. Three children (two in the dexamethasone group) developed occult blood in stools. Six children (three in the dexamethasone group) had subsequent diarrhea. Three children (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): Occult blood in stools (2 vs. 1); Pneumonia (0 vs. 0); Diarrhea (3 vs. 3)
van Woensel 1997 Netherlands Non-industry funded	RCT Hospital 1	Bronchiolitis <2y	1) Prednisolone powder 1.0mg/kg/day in 2 divided doses for 7d (oral), n=27 2) Placebo in 2 divided doses for 7d (oral), n=27	Oxygen, bronchodilators, or antibiotics No CS in preceding 2mo	Baseline & daily for 7d	In the present study no clinically significant side effects of prednisolone were found.
Webb 1986 UK Non-industry funded	RCT, crossover "unit", outpatient 1	Persistent wheeze <18mo	1) Prednisolone 1.0mg/kg, twice daily for 5d (oral), n=NR (total patients in study = 38) 2) Placebo, twice daily for 5d (oral), n=18 crossed over Multiple courses; 38 children completed a total of 56 treatment courses	Bronchodilator & antibiotics NR	Daily for 5d & clinical exam 3d after treatment course (D8)	There were no side effects reported by the parents and none was detected on clinical examination at the time of review three days after completing the five day course of treatment.
Zhang 2003 Brazil	RCT Pediatric	Bronchiolitis <12mo	1) Prednisolone 1.0mg (oral) + standard care	IV hydrocortisone in first 24h	Enrolment, 1mo, 3mo, 6mo &	The potential side-effects of prednisolone

Non-industry funded	hospital ward 1		for 5d (NR), n=28 2) Standard care (oxygen, fluid replacement, nebulised fenoterol) for 5d (NR), n=24	after hospitalization No CS in preceding 4wk	12mo after discharge	were not included as outcome measures in this study as the safety of short-term 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 received prednisolone.

[1]Hedlin 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

Supplement 4 Methodological quality of included studies

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

Supplement 4a. Summary of methodological quality assessments

McHarm* 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 reason(s) for not specifying them given?	Yes	10 (12)
	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 the harms?	Yes	20 (24)
	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)
	No	76 (89)
	Unsure	3 (4)
11) Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Yes	80 (94)
	No	2 (2)
	Unsure	3 (4)
12) Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Yes	24 (28)
	No	61 (72)

	Unsure	0
13) Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Yes	16 (19)
	No	69 (81)
	Unsure	0
14) Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	43 (51)
	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 scale[1]

[2] sum of percentages may not total 100 due to rounding

Supplement 4b. Methodological quality assessments of included studies

Study (year)	Harms pre-defined	Serious AE defined	Severe AE defined	Deaths specified	Mode of collection		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 specified	AE in each arm specified	# and type of AE specified	Type of analysis
					ACTIVE	PASSIVE									
Alangari (2014)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Alansari (2013)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N
Aljebab (2017)	Y	N	N	N	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y
Alshehr (2005)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Altamimi (2006)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	N
Bacharier (2008)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N
Bisgaard (2006)	Y	N	N	N	Y	N	N	N	Y	N	N	Y	Y	U	Y
Bjornson (2004)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Brunette (1988)	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	Y
Buckingham (2002)	N	N	N	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Bulow (1999)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
Chang (2008)	N	N	N	N	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Chen (2008)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Chub-Appakarn (2007)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Clavenna (2014)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	N
Connett (1994)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Connolly (1969)	N	N	N	Y	Y	N	N	N	Y	N	Y	N	N	Y	N
Corneli (2007)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N
Cronin (2016)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N
Csonka (2003)	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N

Daugbjerg (1993)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
Dawson (1993)	N	N	N	N	Y	Y	Y	Y	Y	U	Y	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	Y	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	Y	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]	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Husby (1993)	N	N	N	N	U	N	Y	N	Y	N	Y	N	N	N	N
Inglis (1993)	N	N	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	N
Jan (2000)	N	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N	N
Jartti (2006)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Jartti (2007)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Jartti (2015)	N	N	N	N	N	N	N	N	N	N	U	Y	N	N	N
Johnson (1996)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Johnson (1998)	N	N	N	N	N	N	N	N	N	N	U	N	N	Y	N
Klassen (1994)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Klassen (1996)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Klassen (1998)	N	N	N	N	Y	Y	Y	Y	U	N	Y	Y	N	Y	N
Kuyucu (2004)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Lai (2005)	N	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N	Y

Langton-Hewer (1998)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Lee (2001)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Leer (1969)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
Lehmann (2008)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Leipzig (1979)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Lin (1991)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Lucas-Bouwman (2001)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	N
Nahum (2009)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Paniagua (2017)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
Panickar (2009)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	N
Panigada (2014)	N	N	N	N	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Plint (2009)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Razi (2015)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Roberts (1999)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Roorda (1998)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Roosevelt (1996)	N	N	N	N	Y	N	Y	Y	N	Y	N	N	Y	N	
Sadowitz (2012)	N	N	N	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	N
Saito (2017)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N
Schuh (2008)	N	N	N	N	Y	N	Y	Y	Y	Y	Y	N	N	N	N
Schuh (2009)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	N
Siomou (2003)	Y	N	N	N	Y	N	N	N	Y	U	Y	N	N	N	N
Sparrow (2006)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Stafford (1998)	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	N
Storr (1987)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Sumboonnanonda (1997)	N	N	N	N	Y	N	N	N	Y	N	Y	N	N	Y	N
Sung (1998)	N	N	N	N	Y	Y	Y	Y	N	N	Y	N	N	N	N
Super (1989)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N

Sussman (1964)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
Svedmyr (1995)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
Svedmyr (1999)[1]	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Tagarro (2014)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Tal (1983)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N
Tamura (2008)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N
Teeratakulpisarn (2007)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
van Woensel (1997)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N
Webb (1986)	N	N	N	N	Y	Y	N	N	Y	N	Y	N	N	N	N
Zhang (2003)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	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

REFERENCES

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.

Supplement 5 Effect estimates for all adverse events with subgroups

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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).

Supplement 6a. Infection & respiratory system

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Severe infections, overall	Systemic vs. placebo		4	0/552	2/554	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
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)	NA
	Systemic vs. placebo	Multi-dose	3	0/193	1/193	0.00 (-0.01, 0.01)	0	0.17 (0.00, 8.79)	NA
Severe infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/179	0/175	0.00 (-0.01, 0.01)	0	NA	NA
	Systemic vs. placebo	Croup	2	0/373	2/379	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
Severe infections, overall	Inhaled vs. placebo		1	2/62	4/67	-0.03 (-0.10, 0.04)	NA	0.54 (0.11, 2.77)	NA
Systemic infections, overall	Systemic vs. placebo		4	5/1095	4/1083	0.00 (0.00, 0.00)	0	1.26 (0.34, 4.68)	NA
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)	NA
	Systemic vs. placebo	Multi-dose	2	0/431	0/427	0.00 (-0.01, 0.01)	0	NA	NA
Systemic infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/705	0/695	0.00 (0.00, 0.00)	0	NA	NA
	Systemic vs. placebo	Croup	1	5/359	4/361	0.00 (-0.01, 0.02)	NA	1.26 (0.34, 4.68)	NA
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA

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, 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, 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

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

Supplement 6b. Gastro-intestinal tract

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)	I^2 (%)	Peto OR (95% CI)	I^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, 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)	NA

	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)	NA
	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)	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

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
Diarrhea, overall	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03, 0.04)	0	1.09 (0.43, 2.73)	0
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
	Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
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
	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	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

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

Supplement 6c. CNS & behavior effects

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
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
	Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
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
		Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
		Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
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
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
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
	Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
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
	Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	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

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
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
	Dexamethasone 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	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
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

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

Supplement 6d. Dermatologic conditions

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
Integument, overall	Systemic vs. placebo		3	4/536	0/543	0.01 (0.00, 0.01)	0	7.59 (1.07, 54.01)	0
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
	Systemic vs. placebo	Multi-dose	1	2/133	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
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
	Systemic vs. placebo	Wheeze	1	2/113	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
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
	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. 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

Supplement 6e. Endocrine/metabolic & musculoskeletal systems

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)	I^2 (%)	Peto OR (95% CI)	I^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	1	1/359	0/361	0.00 (0.00, 0.01)	NA	7.43 (0.15, 374.47)	NA
	Systemic vs. placebo	Multi-dose	3	4/473	1/457	0.00 (-0.01, 0.01)	0	2.56 (0.42, 15.61)	0
Fluid & electrolyte abnormalities, by condition	Systemic vs. placebo	Bronchiolitis	2	4/448	1/432	0.00 (-0.01, 0.01)	0	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, bronchiolitis	1	1/33	2/15	-0.10 (-0.28, 0.08)	NA	0.18 (0.01, 2.17)	NA
Adrenal suppression, overall	Inhaled vs. placebo	Multi-dose, asthma	1	5/6	4/10	0.43 (0.01, 0.86)	NA	5.21 (0.72, 37.57)	NA

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	Subgroup	No. of studies	Comparison 1 – total no. of patients	Comparison 2 – total no. of patients	Mean Difference (95% CI)	I^2 (%)
Linear growth	Inhaled vs. placebo	Multi-dose, wheeze	2	154	109	0.10 (-0.47, 0.67)	9

CI: confidence interval; no.: number; vs.: versus

Supplement 6f. Cardiovascular system

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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 difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus

Supplement 6g. General adverse events/ other symptoms

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, 0.09)	0	NA	NA
	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. other steroid		2	3/102	3/95	-0.01 (-0.06, 0.03)	0	0.90 (0.18, 4.61)	11
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
	Dexamethasone vs. other steroid	Croup	1	3/46	2/41	0.01 (-0.08, 0.11)	NA	1.29 (0.21, 7.81)	NA

[1] Two studies reported pallor

[2] One study reported excessive urination; one study reported dizziness

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

Supplement 6h. Immune system & oncology

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Immunosuppression, overall	Systemic vs. placebo		1	0/47	0/48	0.00 (-0.04, 0.04)	NA	NA	NA

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

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.

Ghirga 2002	wheeze - recurrent, early in URTI	inhaled vs. no intervention	RCT	26	No AE overall; 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 the 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 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; CS: case series; nRCT: non-randomised controlled trial; RCT: randomised controlled trial; sal: salbutamol; URTI: upper respiratory tract infection; vs: versus

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).	—	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	p. 5-6;

		status) used as criteria for eligibility, giving rationale.		outcomes of interest were not reported. Report choices for specific study designs and length of follow-up.	Supplement 2 - Eligibility criteria for study inclusion
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.	—	Report if only searched for published data, or also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it.	p. 5; Supplement 1- Search strategy
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, included in the meta-analysis).	—	If only included studies reporting on adverse events of interest, 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.	p. 6; Supplement 2 - 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.	—	No specific additional information is required for systematic reviews of harms.	p. 6-7
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

				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).	
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
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.		p. 7-8
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).	—	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
Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	—	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
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

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
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
Results of individual studies (16)	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.	—	Report the actual numbers of adverse events in each study, separately for each intervention.	p. 8; Supplement 3 - Characteristics of included studies
Synthesis of results (17)	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Describe any assessment of possible causality.	If included data from unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	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

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
	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. 8; Supplement 5 - Effect estimates for all adverse events with subgroups
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. 14-16
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).	—	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. 16-18
Conclusions (19)	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	—	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. 18
Funding					
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. 20

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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 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; I^2=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)

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 guidelines[14]) 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 outcomes[15] 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.

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 I^2 statistic was presented to quantify the magnitude of statistical heterogeneity between studies; while the I^2 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 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

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 complaints[43] (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; I^2=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]

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

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] hives[67] and burning sensation[68] (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; I^2=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 asthma[58] (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 wheeze[29] (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 wheeze[45]

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 RCT[89] 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[57] 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 RCT[71] 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 RCT[29] 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 wheeze[45] reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT[58] 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 illness[92] 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 patients[61] 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

110 children did not report events for arrhythmia[43] and congestive heart failure[47] (*systemic or inhaled corticosteroid versus placebo*); and arrhythmia[27] or hypertension[57] (*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 dizziness[52] 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.

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; I^2=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 (GRADE[118]) 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.

Tables

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
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

c. CNS & behaviour effects
d. Dermatologic conditions
e. Endocrine/ metabolic & musculoskeletal system
f. Cardiovascular system

Dexamethasone vs. Other steroid

a. Gastro-intestinal tract
b. CNS & behaviour effects
c. Dermatologic conditions
d. Endocrine/ metabolic & musculoskeletal system
e. Cardiovascular system
f. General adverse events/ other symptoms

Supplement 7 - Studies reporting no adverse events

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Table 1. Summary of methodological quality assessments

McHarm* 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 reason(s) for not specifying them given?	Yes	10 (12)
	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 the harms?	Yes	20 (24)
	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)
	No	76 (89)
	Unsure	3 (4)
11) Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?	Yes	80 (94)
	No	2 (2)
	Unsure	3 (4)
12) Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?	Yes	24 (28)
	No	61 (72)
	Unsure	0
13) Was the TOTAL NUMBER of participants affected by harms specified for each study arm?	Yes	16 (19)
	No	69 (81)
	Unsure	0
14) Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?	Yes	43 (51)
	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 scale[1]

[2] sum of percentages may not total 100 due to rounding

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

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 infection	2	792
	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

	4)	Restlessness	3	297
	5)	New sleep problems	3	408
	6)	Emotional distress due to nebulizer mask	1	82
	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 & Musculoskeletal	**Fluid and electrolyte abnormalities**		**7**	**1849**
	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).

Identification

Records identified from database searches

n = 12,225

Additional records identified from other sources

n = 135

Screening & Eligibility

Records after duplicates removed

n = 9,134

Total eligible records screened by title and abstract

n = 9,134

Records excluded

n = 8,010

Full text articles assessed for eligibility

n = 1,124

Non-English records excluded (N=135):
Not primary study (n=25);
No data for 0-6 year olds (n=17);
Not acute respiratory disease (n=17);
Not corticosteroid (n=5);
Not inhaled or systemic corticosteroid (n=3);
Treatment duration >14 days (n=8);
No intervention (n=6);
No AE (n=20);
AE attributed to non-corticosteroid (n=1);
Full paper not available (n=1);
Translation not available (n=22);
Duplicate (n=10)

English records excluded (N=903):
Not primary study (n=112);
No data for 0-6 year olds (n=131);
Not acute respiratory disease (n=18);
Not inhaled or systemic corticosteroid (n=175);
Treatment duration >14 days (n=122);
Not outpatient setting or hospitalized patients (n=14);
No AE (n=163);
Full paper not available (n=20);
Drug monographs, FDA & EMEA documents, not eligible (n=135);
Protocol, duplicate of full publication (n=1)
Duplicate (12)

Inclusion

Total studies included in the review

n = 85
(86 papers)

AE: adverse event; EMEA: European Medicines Agency; FDA: Food & Drug Administration

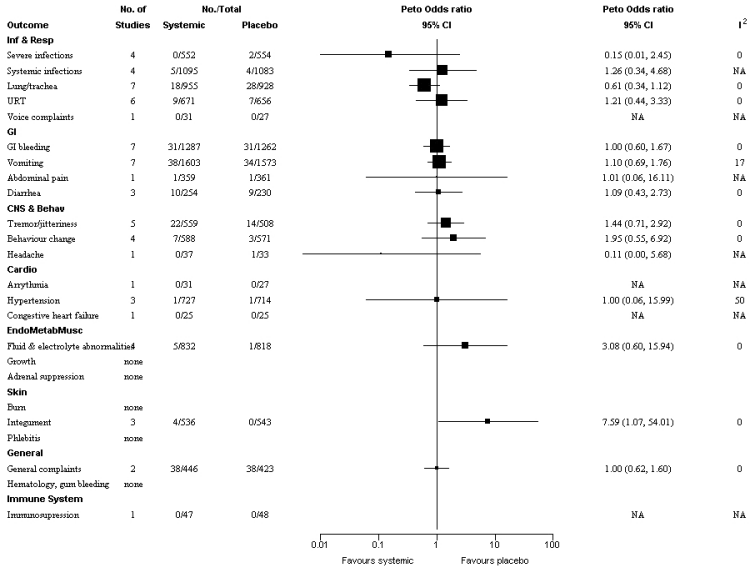

Figure 2. Forest plot of adverse events - systemic vs. placebo

101x101mm (300 x 300 DPI)

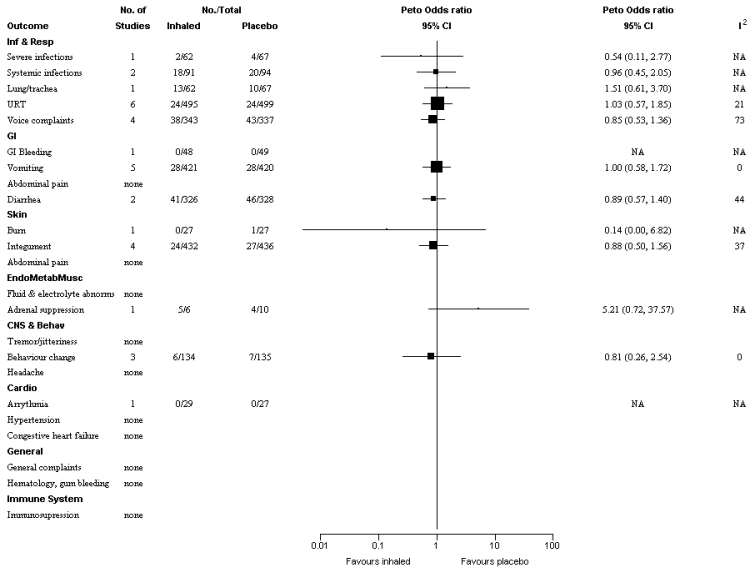

Figure 3. Forest plot of adverse events - inhaled vs. placebo

101x101mm (300 x 300 DPI)

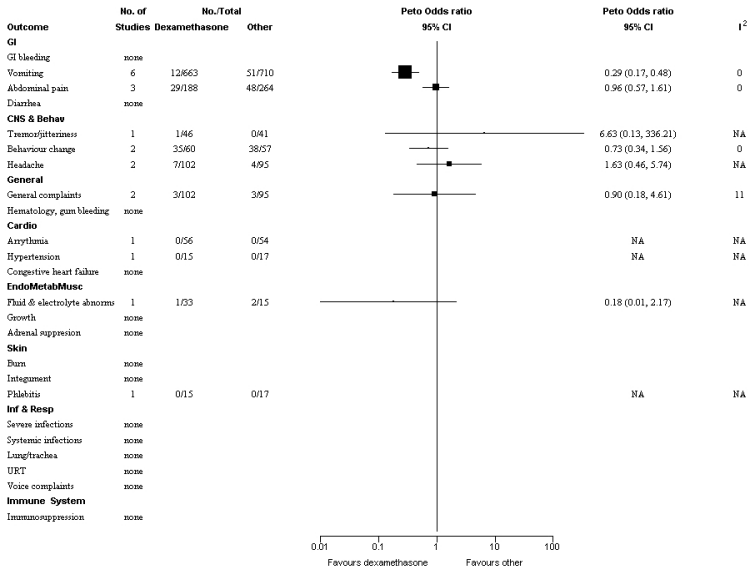

Figure 4. Forest plot of adverse events - dexamethasone vs. other

101x101mm (300 x 300 DPI)

Supplement 1. Search strategy

Database for original search: Ovid Medline(R) 1946 to September Week 1 2014
Databases for update searches: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Date original search conducted: 14 September 2014
Date first update search conducted: 24 February 2016
Date second update search conducted: 31 July 2017
Strategy:

1. Adrenal Cortex Hormones/
2. Anti-Inflammatory Agents/
3. Beclomethasone/
4. Budesonide/
5. exp Glucocorticoids/
6. exp Hydroxycorticosteroids/
7. Pregnenediones/
8. Triamcinolone Acetonide/
9. adrenal cortex hormone*.tw,nm.
10. advair*.tw,nm.
11. alvesco*.tw,nm.
12. azmacort*.tw,nm.
13. becl?met*.tw,nm.
14. beclazone*.tw,nm.
15. beclo?ort*.tw,nm.
16. beclovent*.tw,nm.
17. beconase*.tw,nm.
18. becotide*.tw,nm.
19. betamet?asone*.tw,nm.
20. betnesol*.tw,nm.
21. budesonide*.tw,nm.
22. ciclesonide*.tw,nm.
23. clobetasol*.tw,nm.
24. cortiso*.tw,nm.
25. cortodoxone*.tw,nm.
26. corticosteroid*.tw,nm.
27. decadron*.tw,nm.
28. depo medrone*.tw,nm.
29. desoximet?asone*.tw,nm.
30. dexamethasone*.tw,nm.
31. deflazacort*.tw,nm.
32. diflucortolone*.tw,nm.
33. flixotide*.tw,nm.
34. flumethasone*.tw,nm.

35. flunisolide*.tw,nm.
36. fluocino*.tw,nm.
37. fluocortolone*.tw,nm.
38. fluorometholone*.tw,nm.
39. flurandrenolone*.tw,nm.
40. fluticasone*.tw,nm.
41. glucocortico*.tw,nm.
42. hydrocortisone*.tw,nm.
43. hydroxycorticostero*.tw,nm.
44. hydrocortone*.tw,nm.
45. hydroxypregnenolone*.tw,nm.
46. kenacort*.tw,nm.
47. kenalog*.tw,nm.
48. medrone*.tw,nm.
49. methylprednisolone*.tw,nm.
50. mometasone furoate*.tw,nm.
51. nasonex*.tw,nm.
52. paramethasone*.tw,nm.
53. predniso*.tw,nm.
54. pregnenolone*.tw,nm.
55. pulmicort*.tw,nm.
56. qvar*.tw,nm.
57. rhinocort*.tw,nm.
58. seretide*.tw,nm.
59. solu cortef*.tw,nm.
60. symbicort*.tw,nm.
61. tetrahydrocortisol*.tw,nm.
62. triamcinolone*.tw,nm.
63. tricort*.tw,nm.
64. vanceril*.tw,nm.
65. or/1-64
66. Acute Disease/ and (asthma* or pneumonia* or wheez*).mp.
67. exp Asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
68. Bronchial Hyperreactivity/
69. Bronchial Spasm/
70. exp Bronchiolitis/
71. Croup/
72. exp Dyspnea/
73. Emergencies/ and (asthma* or pneumonia* or wheez*).mp.
74. Emergency Medical Services/ and (asthma* or pneumonia* or wheez*).mp.
75. Emergency Services, Hospital/ and (asthma* or pneumonia* or wheez*).mp.
76. exp Pharyngitis/
77. exp Pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
78. exp Respiratory Syncytial Viruses/

79. exp Respiratory Syncytial Virus Infections/
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/
122. case control.tw.

123. (case adj (report* or study or studies or series)).tw.
124. cohort analy*.tw.
125. (cohort adj (study or studies)).tw.
126. cross sectional.tw.
127. (follow up adj (study or studies)).tw.
128. longitudinal.tw.
129. (observational adj (study or studies)).tw.
130. retrospective.tw.
131. or/117-130
132. 116 or 131
133. exp animals/ not humans.sh.
134. 132 not 133
135. 107 and 134
136. (comment or editorial or letter or meta analysis or review).pt.
137. 135 not 136
138. remove duplicates from 137

Database for original search: Ovid Medline(R) In-Process & Other Non-Indexed Citations, September 12, 2014
Date original search conducted: 14 September 2014
Strategy:

1. adrenal cortex hormone*.tw,nm.
2. advair*.tw,nm.
3. alvesco*.tw,nm.
4. azmacort*.tw,nm.
5. becl?met*.tw,nm.
6. beclazone*.tw,nm.
7. beclo?ort*.tw,nm.
8. beclovent*.tw,nm.
9. beconase*.tw,nm.
10. becotide*.tw,nm.
11. betamet?asone*.tw,nm.
12. betnesol*.tw,nm.
13. budesonide*.tw,nm.
14. ciclesonide*.tw,nm.
15. clobetasol*.tw,nm.
16. cortiso*.tw,nm.
17. cortodoxone*.tw,nm.
18. corticosteroid*.tw,nm.
19. decadron*.tw,nm.
20. depo medrone*.tw,nm.
21. desoximet?asone*.tw,nm.
22. dexamethasone*.tw,nm.

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.
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.

67. ((naso pharynx or nasopharynx or para nasal or paranasal or sinus*) adj3 (infect* or inflam*)).tw.
68. (nasosinusit* or rhinosinusit*).tw.
69. pharyngitis*.tw.
70. (respiratory adj2 (attack* or infect* or inflam* or virus*)).tw.
71. rhinit*.tw.
72. sinusit*.tw.
73. tonsillitis*.tw.
74. or/58-73
75. (baby* or babies or child* or infant* or infancy or neonat* or newborn*).tw.
76. (boy* or girl* or paediatric* or peadiatric* or pediatric* or prepubescen*).tw.
77. or/75,76
78. and/57,74,77
79. randomi?ed.tw.
80. placebo.tw.
81. randomly.tw.
82. trial.tw.
83. groups.tw.
84. or/79-83
85. case control.tw.
86. (case adj (report* or study or studies or series)).tw.
87. cohort analy*.tw.
88. (cohort adj (study or studies)).tw.
89. cross sectional.tw.
90. (follow up adj (study or studies)).tw.
91. longitudinal.tw.
92. (observational adj (study or studies)).tw.
93. retrospective.tw.
94. or/85-93
95. 84 or 94
96. 78 and 95
97. (comment* or editorial* or letter*).mp.
98. 96 not 97
99. remove duplicates from 98

Database: Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley Cochrane Library
Date original search conducted: 14 September 2014
Date first update search conducted: 24 February 2016
Date second update search conducted: 31 July 2017
Strategy:

1. [mh ^ “Adrenal Cortex Hormones”]
2. [mh ^ “Anti-Inflammatory Agents”]
3. [mh ^ Beclomethasone]
4. [mh ^ Budesonide]

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

49. methylprednisolone*:ti,ab,kw
50. mometasone next furoate*:ti,ab,kw
51. nasonex*:ti,ab,kw
52. paramethasone*:ti,ab,kw
53. predniso*:ti,ab,kw
54. pregnenolone*:ti,ab,kw
55. pulmicort*:ti,ab,kw
56. qvar*:ti,ab,kw
57. rhinocort*:ti,ab,kw
58. seretide*:ti,ab,kw
59. solu next cortef*:ti,ab,kw
60. symbicort*:ti,ab,kw
61. tetrahydrocortisol*:ti,ab,kw
62. triamcinolone*:ti,ab,kw
63. tricort*:ti,ab,kw
64. vanceril*:ti,ab,kw
65. {OR #1-#64}
66. [mh ^ “Acute Disease”] and (asthma* or pneumonia* or wheez*)
67. [mh Asthma] and (acute* or emergenc* or exacerbation* or severe*)
68. [mh “Bronchial Hyperreactivity”]
69. [mh “Bronchial Spasm”]
70. [mh Bronchiolitis]
71. [mh ^ Croup]
72. [mh Dyspnea]
73. [mh ^ Emergencies] and (asthma* or pneumonia* or wheez*)
74. [mh ^ “Emergency Medical Services”] and (asthma* or pneumonia* or wheez*)
75. [mh ^ “Emergency Services, Hospital”] and (asthma* or pneumonia* or wheez*)
76. [mh Pharyngitis]
77. [mh Pneumonia] and (acute* or emergenc* or exacerbation* or severe*)
78. [mh “Respiratory Syncytial Viruses”]
79. [mh “Respiratory Syncytial Virus Infections”]
80. [mh Rhinitis]
81. [mh Sinusitis]
82. [mh ^ “Status Asthmaticus”]
83. [mh ^ “Respiratory Sounds”] and (acute* or emergenc* or exacerbation* or severe*)
84. ((acute* or emergenc* or exacerbation* or severe*) near/5 (asthma* or pneumonia* or wheez*)):ti,ab,kw
85. (breath* near/2 (difficult* or gasp* or hard* or labo?r* or shallow* or short*)):ti,ab,kw
86. (bronch* near/3 (constrict* or spas*)):ti,ab,kw
87. bronchiolitis*:ti,ab,kw
88. bronchoconstrict*:ti,ab,kw
89. bronchospasm*:ti,ab,kw
90. croup*:ti,ab,kw
91. dyspne*:ti,ab,kw

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}
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.

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

66. acute disease/ and (asthma* or pneumonia* or wheez*).mp.
67. exp asthma/ and (acute* or emergenc* or exacerbation* or severe*).mp.
68. exp breathing disorder/ and (acute* or emergenc* or exacerbation* or severe*).mp.
69. bronchospasm/
70. bronchus hyperreactivity/
71. exp bronchiolitis/
72. croup/
73. exp dyspnea/
74. emergency/ and (asthma* or pneumonia* or wheez*).mp.
75. emergency health service/ and (asthma* or pneumonia* or wheez*).mp.
76. exp emergency treatment/ and (asthma* or pneumonia* or wheez*).mp.
77. emergency ward/ and (asthma* or pneumonia* or wheez*).mp.
78. exp pharyngitis/
79. exp pneumonia/ and (acute* or emergenc* or exacerbation* or severe*).mp.
80. Respiratory syncytial pneumovirus/
81. respiratory syncytial virus infection/
82. exp rhinitis/
83. exp sinusitis/
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
108. crossover procedure/
109. double blind procedure/

110. randomized controlled trial/
110. single blind procedure/
111. allocat*.tw.
112. assign*.tw.
113. cross over*.tw.
114. crossover*.tw.
115. doubl* adj blind*.tw.
116. factorial*.tw.
117. placebo*.tw.
118. random*.tw.
119. singl* adj blind*.tw.
120. volunteer*.tw.
121. or/108-120
122. exp case control study/
123. case report/
124. case study/
125. cross-sectional study/
126. cohort analysis/
127. case control.tw.
128. (case adj (report* or study or studies or series)).tw.
129. cohort analy*.tw.
130. (cohort adj (study or studies)).tw.
131. cross sectional.tw.
132. (follow up adj (study or studies)).tw.
133. longitudinal.tw.
134. (observational adj (study or studies)).tw.
135. retrospective.tw.
136. or/122-135
137. 121 or 136
138. animals/ not (animals/ and humans/)
139. 137 not 138
140. 107 and 139
141. (editorial or journal editorial or journal letter or journal note or letter or review).pt.
142. 140 not 141
143. limit 142 to embase

Database: Drugs@FDA
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Date original search conducted: 5 September 2014
Strategy:

Searched Drugs@FDA for drug name keywords:
1. beclametasone dipropionate
2. budesonide

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: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/databasdon/index-eng.php
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=WC0b01ac058001d124
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

Supplement 2. Eligibility criteria for study inclusion

INCLUSION/EXCLUSION FORM

Reviewer ID:	**Date: / /2015**	**Record ID:**

Criteria	**Yes**	**No**	**UC**
1. PUBLICATION TYPE			
a. Primary research (RCTs, cohort studies, case control studies, case reports, and case series)	☐	☐	☐
Exclude: • Systematic reviews, letters to editor, commentaries			
2. Population			
a. Children ≤6 years of age, where age subgroups data is available:	☐	☐	☐
Unclear: • If aggregate/subgroup data include but are not limited to age ≤6 years			
Exclude: • If data is reported in aggregate with older ages			
3. CONDITION			
a. Children with acute respiratory disease (any of the following):	☐	☐	☐
• Bronchiolitis			
• Croup			
• Acute wheeze/asthma			
• Acute uncomplicated pneumonia (no abscess, effusion, etc)			
• Pharyngitis/tonsillitis			
• Peritonsillar abcess			
• Acute sinusitis			
• Respiratory syncytial virus/ rhinovirus/other viruses			
• Respiratory distress due to foreign bodies			
• PFAPA syndrome			
Exclude:			
• patients in NICU, PICU			
• respiratory distress syndrome (newborn)			
• allergic rhinitis			
• animal studies			
4. Intervention			

a. 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
- Mometasone furoate
- Prednisolone
- Prednisone
- Triamcinolone acetonide
- combination therapies (e.g. ICS + short-acting beta-agonists)

Exclude

- topical (non-systemic) corticosteroid therapy

* inhaled (moderate- to high-dose) corticosteroids, following GINA guidelines for low doses for children 5 years and younger (see Box 6-6 below).

5. Comparator group (where relevant)

a. Any comparison, including non-pharmacologic interventions which may act similarly to a placebo ☐ ☐ ☐

6. OUTCOME

Adverse drug reaction, side effect, adverse effects/events, adverse reactions ☐ ☐ ☐

7. Setting

Focus is on outpatient 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

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 p. 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	

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 (1964-2017)**
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

Supplement 3b. Summary characteristics of included studies – comparisons

Number of treatment groups	Comparison	No. of studies (no. of patients)	No. of studies 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 + placebo vs. placebo	1 (114)	1 (114)
	Systemic CS + sal dose1 vs. systemic CS + sal dose2 vs. sal dose1 + placebo vs. sal dose2 + placebo	1 (70)	1 (70)
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal + placebo	1 (69)	1 (69)
	Systemic CS + non-CS vs. systemic CS + placebo vs. non-CS + placebo vs. placebo + placebo	1 (800)	1 (800)
	Systemic CS + sal vs. systemic CS + placebo vs. sal + placebo vs. placebo	1 (32)	0
	Systemic CS	5 (5)	0

Non-comparative (case reports/series)	Mode of administration NR	2 (3)	0

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

Supplement 3c. Characteristics of included studies

Author, year Country Funding source	Study design Setting No. of centres	Respiratory condition Age (range)	Comparators, no. of participants	Co-interventions; Maintenance CS	Time points for assessments; FU	Outcomes related to adverse events
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 medications; FU 72h post-discharge	The most frequently reported adverse effects were fine tremors (17 cases) and palpitations (11 cases). None of the reported adverse effects was serious, and none was significantly different between the two groups.
Alansari 2013 Qatar Non-industry funded	RCT Pediatric emergency unit 1	Bronchiolitis <=18mo	1) Dexamethasone 1.0mg first day, then 0.6mg for 4d (oral) + sal, 5d total (neb), n=102 2) 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	Daily telephone surveillance (7 days) revealed no particular side effect concerns in either treatment group.
Aljebab 2017 Saudi Arabia & UK Unfunded	Cohort, 3-arm Pediatric ED of hospital (SA & UK)	Asthma/croup, 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, dexamethasone had the highest palatability scores and

	2		2) Prednisolone base 5.0mg tablets (oral), n=52 3) Prednisolone sodium phosphate 15.0mg/mL syrup (oral), n=37 UK 1) Dexamethasone 2.0mg/5mL elixir (oral), n=53 2) Prednisolone base 5.0mg tablet (oral), n=38 3) Prednisolone sodium phosphate 5.0mg soluble tablets (oral), n=42	however, most patients and none had received oral steroids previously in the SA & UK dexamethasone groups, respectively		prednisolone base tablets had the lowest. Palatability scores improved for all formulations of prednisolone with each subsequent daily dose. In SA, prednisolone base tablets were associated with more nausea (24 vs. 7 patients) and vomiting (5 vs. 0 patients) than sodium phosphate syrup. In the UK, vomiting occurred more frequently with prednisolone base (8 patients) than sodium phosphate soluble tablets (2 patients) (p=0.041).

						In both centres, dexamethasone was associated with less side effects. Vomiting (1 vs. 0 patients), nausea (7 vs. 3 patients), and abdominal pain (10 vs. 8 patients) occurred more with dexamethasone sodium phosphate solution than dexamethasone elixir.
Alshehr 2005 Saudi Arabia Funding NR	RCT Emergency rooms & outpatient 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	Two patients developed bronchopneumonia 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 dexamethasone). No adverse events were

						noted in the group B patients. No patient had a clinical deterioration, either in the emergency room or after discharge and no child had gastrointestinal bleeding or bacterial infection.
Altamimi 2006 Canada Non-industry & industry funded	RCT Pediatric hospital 1	Asthma 2-16y	1) Dexamethasone 0.6mg/kg (max 18mg), single dose (oral), n=67 2) Prednisolone 1.0mg/kg (max 30mg) twice daily (oral), n=67	Salbutamol No CS in preceding 2wk	2d & 5d post-discharge & every week to a maximum of 3wk	Two subjects in the prednisolone group dropped out because of repeated vomiting. Side effects (table 5), n: Abdominal pain (2 dex vs. 3 pred); Vomiting (0 dex vs. 1 pred); Headache (0 dex vs. 0 pred); Palpitation (0 dex vs. 0 pred); Excessive urination (0 dex vs. 1 pred)
Bacharier 2008 USA	RCT, 3-arm	At least 2 wheeze	1) Montelukast 4.0mg once daily (oral) +	Albuterol, prednisolone &	Clinic visits 4wk after randomizati	The 3 groups did not differ significantly in

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

						treatment group.
Bjornson 2004 Canada Non-industry & industry funded	RCT Pediatric ED 4	Croup mean 35+/-23 mo	1) Dexamethasone 0.6mg, max. 20.0mg, single dose (oral), n=359 2) Placebo solution, single dose (oral), n=361	Mist, antibiotics & nebulized epinephrine or beta-agonists No CS in preceding 2wk	D1, D2, D3, D7 & D21 after day of treatment; FU interview with parent on D7 and chart and administrative database review	Among the 720 patients, there were no cases of gastrointestinal bleeding, complicated varicella, or bacterial tracheitis. There were 7 cases of pneumonia (3 in the dexamethasone group). All these cases were managed on an outpatient basis, without significant sequelae. Repeated short courses of oral corticosteroids are not associated with long-term negative effects on bone metabolism, bone density or adrenal function. There were no serious adverse events attributable

						to therapy in any children in our study. However, the study was not sufficiently powered to exclude the possibility of rare adverse events. Supplementary 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 gastroenteritis (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);

						RSV infection (1 vs. 0); Uncomplicated varicella (0 vs. 1); Urinary tract infection (0 vs. 1); Irritability (1 vs. 1); Eye discharge (1 vs. 0); Sinusitis (0 vs. 1); Bleeding from ear (0 vs. 1); Nasal discharge (1 vs. 0)
Brunette 1988 Canada Funding NR	NRCT Hospital 1	Asthma <6y	1) Theophylline 8.0mg/kg every 6-8h (oral) + metaproterenol 0.3-0.7 mg/kg every 6-8h (oral)+ prednisone 1.0mg/kg/day for 7-14d (oral), n=16 2) Theophylline 8.0mg/kg every 6-8h (oral) + metaproterenol 0.3-0.7mg/kg every 6-8h for 7-14d (oral), n=16 Multiple courses over 1yr	None NR	Monthly or every second month, depending on severity of disease; Growth (mean height gain in cm/yr and height as percentile of normal distribution) assessed (assessment method NR) at the end of each of two 1-yr periods	No side effect was observed in a particular case which received longer duration of corticosteroid (high cumulative corticosteroid dose). Growth and weight gains for all children were within the normal range during the two periods.

Buckingham 2002 USA Non-industry funded	RCT Pediatric hospital 2	RSV (bronchiolitis) <24mo	1) Dexamethasone 0.5mg/kg/dose every 12h for 4d (IV), n=22 2) Placebo saline every 12h for 4d (IV), n=19	Other treatment (not specified) No CS in preceding 3wk	Enrolment & daily until discharge; FU 30d after enrolment	Serious adverse events occurred in 2 patients in the dexamethasone group. One infant developed progressive respiratory failure that did not improve with high-frequency oscillatory ventilation or extracorporeal membrane oxygenation; support was withdrawn, and this infant died on study day 38. Another subject developed pneumothorax, which resolved following placement of a pigtail thoracotomy catheter, on study day 7. Neither adverse event was judged to be related to administration of the study

						drug. No patients in either group had microscopic or gross gastrointestinal bleeding, and no patients required antihypertensive therapy during the study.
Bulow 1999 Denmark Non-industry funded	RCT Pediatric hospital 3	RSV (bronchiolitis) 0-2y	1) Prednisolone 5.0mg/ml at dose of 2mg/kg/day, first dose at enrolment and for 4d (oral), or methylprednisolone 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	A total of 11 patients (7 in the prednisolone group and 4 in the placebo group) did not 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 Pediatric & 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,

			50.0mg/day) for 5d (oral), n=100			two parents reported that their child had 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 China Funding NR	RCT, 3-arm Pediatric outpatient, hospital ward, or ED 1	Asthma 1-14y	1) Budesonide 0.5mg (neb) + sal + ipratropium; 1-6yo (n=32); 6-14yo (n=21) 2) Budesonide 0.2-0.4mg (neb) + sal + ipratropium; 1-6yo (n=25); 6-14yo (n=16) 3) Dexamethasone 2.0mg (<2yo), 4.0mg (2-6yo) (IV); 1-6yo (n=15); 6-14yo (n=14)	NR No CS within 48h	0.5h before & post-treatment & 5d post-treatment	All three groups of children showed no adverse effects.
Chub-Appakarn 2007 Thailand Funding NR	RCT Pediatric hospital ward 1	Croup 6mo-5y	1) Dexamethasone 0.5ml/kg of 0.15 mg/kg, single dose (IV), n=20 2) Dexamethasone 0.5 ml/kg of	Epinephrine, mist, antibiotics & oxygen No CS in preceding 2wk	0, 1h, 2h, 3h, 4h, 6h, 8h, 10h & 12h post-treatment	There was no significant adverse reaction from dexamethasone treatment in either group.

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

						hospitalization for adenoidectomy and tonsillectomy in the placebo group. Neither adverse event was drug related.
Connett 1994 UK Non-industry funded	RCT, factorial Hospital 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 nebulization & at treatment completion	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 throughout the study period,

						though there was a trend towards decreasing tachypnoea in all four groups.
Connolly 1969 Ireland Funding NR	RCT Hospital 1	RSV Bronchiolitis 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 the course of the disease in severely ill children. There were no deaths.
Corneli 2007 USA Non-industry & industry funded	RCT ED 20	Bronchiolitis 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 gastrointestinal bleeding, hypertension, or complicated varicella. Vomiting within 20 min after administratio

						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 an 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 the PRED group (5.7%) vomited within 30 minutes of the dose of steroid on day 1 in the ED compared with none in the DEX group (absolute difference -5.7%; 95%CI -9.9% to -1.54%). Seven patients vomited after the prednisolone dose on day 2, and 6 vomited after the dose on day 3. A total of 14 patients

						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 Pediatric ED 1	Viral respiratory 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 NR	Diary recordings twice daily for 14d; examination 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 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 1993 Denmark Non-industry & industry funded	RCT, 4-arm Pediatric department 5	First or recurrent wheeze 0-18mo	1) Prednisolone 4.0-6.0mg/kg on admission; D2-3=1.6-2.6mg/kg (oral) + terbutaline 0.12-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb), n=31 2) Placebo solution (oral) + budesonide 0.5mg every 4h until discharge or for 5d (neb) + 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 4) Placebo solution (oral) + placebo (neb) + placebo saline (neb), n=27	NR No CS preceding study	Daily for 5d or until discharge	No side effects were observed, specifically no hoarseness, oral candidiasis or continued fever, in any of the groups. No significant tachycardia was found in the treatment groups compared with placebo.
Dawson 1993 Australia Industry funded	RCT Hospital 1	Asthma <6.5y	1) Prednisolone 1.0mg/kg tablets, every 24h for 5d (oral), n=25 2) Prednisolone 1.0mg/kg solution, every	None NR	D1 to D5	Twenty-one of the children taking the solution took it easily on day 3, compared to two in the

			24h for 5d (oral), n=26			tablet group 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. 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 to cause vomiting (on all five days), abdominal pain frequency (days 2-5), nausea (days 2-5) or mood change (days 2-5). As a result of persistent vomiting, the parents of two children receiving tablets stopped treatment prematurely.
Ducharme 2009 Canada Non-industry & industry funded	RCT Hospital 5	>=3 wheeze episodes in lifetime, onset of URTI 1-6y	1)Fluticasone propionate 250mcg (3 doses twice daily at start of URTI) until 48h elapsed without symptoms, for max. 10d (MDI), n=62 2) Placebo (3 doses twice daily at start of URTI until 48h elapsed without symptoms (MDI), n=67 Multiple courses over 6-12mo	Albuterol, nasal saline irrigation No more than 1 dose of CS in preceding 6mo or 2 doses in preceding 12mo	Monthly telephone contacts and a medical visit every 4mo; Growth assessed using an upright stadiometer at baseline, every month, and at the end of follow-up (6-12mo);	Thirteen serious adverse events (4 in fluticasone group and 9 in placebo) occurred in 13 children during the study period - namely, pneumonia, seizure, admission to an intensive care unit, burn, respiratory syncytial virus infection, atelectasis,

					Basal cortisol assessed using an immunoassay system, with or without corticotropin 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); Gastroenteritis (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);

						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

						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 performed.
Eboriadou 2010 Greece Funding NR	RCT, 3-arm Pediatric ED 1	Croup 6mo-5y	1) L-epinephrine 5.0ml (1 of 1:1000mg/ml), 5-10min (neb), n=25	Oxygen No CS in preceding 24h	Before treatment & at 15min, 20min, 60min, 90min &	The L-epinephrine group was the only group with side effects of

			2) Dexamethasone 0.6mg/kg (max. 8mg), single dose (IM), n=19 3) Beclomethasone dipropionate 200mcg (MDI), n=20		120min post-treatment; patients asked to return if relapse in next 24h	treatment. Tremor and tachycardia were observed in 4 children from Group A, who had received LE and were resolved after 2 hours, when the action of LE wear off.
Eden 1967 USA Industry funded	RCT Hospital 1	Croup 8mo-5y	1) Dexamethasone 0.10mg/kg at 0.1cc/kg/dose every 6h for 48h, total daily 0.40mg (IM), n=25 2) Control preparation 0.1cc/kg/dose every 6h for 48h (IM), n=25	Oxygen, humidity & tetracycline NR	Every 6h for total 48h	No untoward effects were noted. There were no episodes of congestive heart failure or sodium retention.
Escobedo Chavez 1992 Mexico Industry funded	RCT Hospital ED 1	Asthma 1mo-14y	1) Methylprednisolone 3.0mg/kg, single dose (IM) + placebo 4.5ml + sal 0.5ml every 4h (neb), n=25 2) Aminophylline 5.0mg/kg every 6h (IV) + sal 70 mcg/kg every 8h + oxygen (neb), n=25	Saline, salbutamol & oxygen No CS in preceding 15d	Baseline & discharge	We detected no side effects with the use of methylprednisolone in a single dose or any treatment failures that merited the use of methylxanthines or additional steroid doses.
Fifoot 2007 Australia	RCT, 3-arm	Croup 6mo-6y	1) Prednisolone 0.2ml/kg of 1.0mg/kg, single	Antipyretics or nebulized adrenaline	Baseline & hourly up	No patient suffered any adverse

Non-industry funded	Pediatric ED 1		dose (oral), 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	to 4h post-treatment; FU 1wk by telephone following index visit	outcomes 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) tolerated second dose.
Fitzgerald 1996 Canada Industry funded	RCT Pediatric 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	Six patients in each treatment group reported adverse events. These included vomiting, an erythematous rash, diarrhea, wakefulness, excessively active behavior, wheezing, and a nosebleed. These were minor and did not result in withdrawal from the study or require

						specific treatment.
Francis 1997 Australia Funding NR	RCT (trial registry data) Acute care setting 4	Asthma ≤48mo	1) Fluticasone propionate 1.0mg twice daily (neb) + placebo tablets once daily (oral) for 7d, n=37 2) Prednisolone (dose NR) daily for 7d (oral), n=19	NR No CS treatment for >7d in preceding 4wk	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); Asthma (1 vs. 2); Hoarseness/dysphonia (0 vs. 2); Serious adverse events - on-therapy: Subjects with non-fatal SAEs (2 vs. 0): Ketonuria, glycosuria and hyperglycaemia (1 vs. 0);

						Subjects with fatal SAEs (0 vs. 0)
Garbutt 2013 USA Non-industry funded	RCT Primary care office 10	Croup 1-8y	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	Acetaminophen & ibuprofen No CS preceding current croup episode	FU interviews at D1 to D4 & D11; FU chart review within 28d of index visit	No serious adverse events occurred. Study groups did not differ in reporting side effects from the study medications (24% dexamethasone, 26% prednisolone, P = 1.0; Table 4). The most common side effects identified with specific questioning were mood changes (57%), sleep problems (36%), stomach pain (19%), and headache (13%). Table 4 adverse events, n (dex vs. pred): A side effect at D11 (11/45 vs. 10/39); Mood changes (25 vs. 24);

						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 2002 Italy Funding NR	NRCT NR, "ambulatory infants" 1	Wheeze - early URTI before signs of wheeze 7-12mo	1) Beclomethasone 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 NR	Twice daily	At this writing, four years after the study was completed, no apparent adverse effects were reported. Plasma cortisol measured in four patients receiving at least 2 treatment periods of 5 days a month was normal.
Gill 2017 Canada Funding NR	Cohort Pediatric hospital ED 1	Croup >2y (mean 4.7y vs. 4.8y)	1) 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 dexamethasone 0.6mg/kg for croup is not associated with decreased endogenous glucocorticoid

			or antibiotics), n=5			levels in 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 symptoms resolved by 7 days. The other, also a 3-year-old boy, returned to the ED 4 days after dexamethasone administration for unilateral facial swelling. Serologic testing for paramyxovirus (mumps) was negative, and he was given a diagnosis of viral parotitis. His symptoms resolved by 7

						days. Four participants visited their primary care physician within 7 days of dexamethasone administration. 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 deaths.
Goebel 2000 USA Funding NR	RCT Pediatric ED or children's clinic 2	Bronchiolitis ≤23mo	1) Prednisone 2.0mg/kg/day for 5d (oral) + albuterol 0.3mg/kg/day (or 0.15mg/kg/dose (neb)) for 5d (oral), n=24	NR NR	Clinical scores on D0, D2, D3 & D6; FU when convalescence completed	One patient in the prednisolone group was observed by his caretakers to be "jittery" at times after enrollment.

			2) Placebo solution (oral) + albuterol 0.3mg/kg/day (or 0.15mg/kg/dose (neb)) for 5d (oral), n=24			This resolved after a decrease in the albuterol dose. No evidence of treatment complications was observed in any of the other patients.
Grant 1996 USA Non-industry funded	Cohort Primary care clinic & teaching hospital ED 1	Asthma 2-14y	1) Prednisone 2.0mg/kg (max. 60mg/day), single dose intermittent for 6mo (oral), n=86 2) Placebo (NR), n=86 Multiple courses over 1yr	Bronchodilators as needed NR	NR	Ninety-four episodes of acute infection occurred in 50 subjects and 222 episodes of symptoms of infection occurred in 62 subjects (table 1 episodes of infection, number of doses, and association between doses and frequency of infection). No difference was observed in the mean number of doses of prednisone received by those with the infection compared with those

						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 pharyngitis, pneumonia, and urinary tract infection; eight (73%) episodes of chickenpox; eight (57%) episodes of skin infections; and 14 (88%) episodes of ringworm.
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/creatinine assessed by radioimmunoassay (standard methods) on D14	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

						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/creatinine value for the IM Dex group was lower than that for the

						PO Pred group, but this difference was not statistically significant.
Hedlin 1999[1] Sweden Funding NR	RCT Pediatric hospital 1	Asthma – first sign of URTI 1-3y	1) Budesonide 400mcg, 4 times daily for 3d then twice daily for 7d (MDI), n=9 2) Placebo, 4 times daily for 3 days then twice daily for 7d (MDI), n=11 Multiple courses over 1yr, or max. 6 treatments *subgroup of children from Svedmyr 1999 with therapeutic failure from budesonide given 3d course (6.0mg, 4.0mg, and 2.0mg on respective days) of oral betamethasone	Beta-agonists and/or theophylline NR	D10 & D13; Routine height measurements (assessment method NR) were taken (timing of assessments NR); Serum cortisol (on D8-10 of second course of study medication, morning of day after third dose, and at 12-14d after therapy) and urinary cortisol/creatinine (in the night after third dose of betamethasone and at 12-14d after therapy)	There were no significant differences between pretreatment and post-treatment serum cortisol, osteocalcin, ICTP and urine cortisol/creatinine ratio in the groups, (the comparison was made in the children who had assessments before and after budesonide/placebo) nor were there any significant differences between the active and placebo treated groups. It was, however, noteworthy that the urine cortisol/creatinine ratio decreased in

					assessed by radioimmunoassay	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 betamethasone have pronounced systemic effects, whereas 10d of high doses of budesonide do not produce significant systemic effects.
Husby 1993 Denmark Funding NR	RCT Pediatric 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.

			doses 30min apart (neb), n=16			
Inglis 1993 USA Funding NR	Case report, 2 Hospital	Croup 18mo; 14mo	Case 1) Prednisolone 1.0mg/kg, twice daily for 4d (NR) Case 2) Dexamethasone 0.3mg/kg, 3 doses in 24h (NR)	Case 1: racemic epinephrine, acyclovir sodium Case 2: amoxicillin/clavulanate potassium, cefuroxime sodium	NR	Case 1: Twenty days into illness, airway endoscopy revealed shallow mucosal ulcerations of patient's glottis and subglottis, but a normal appearing tracheobronchial tree. Cultures were positive for HSV-1, Staphylococcus aureus and a-hemolytic streptococcus; Case 2: On day 11 of illness, airway endoscopy revealed severe subglottic edema and ulceration, purulent tracheal secretions, but normal tracheal mucosa. A tracheal aspirate

						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 postoperatively and was started on a regimen of nafcillin sodium and dexamethasone sodium phosphate, 1.5mg/kg per day. She was extubated after 48 hours and the dexamethasone therapy was discontinued. Her stridor gradually resolved

						spontaneously over the next 7 days without further intervention.
Jan 2000 Taiwan Funding NR	Non-RCT Pediatric hospital clinic 1	Asthma NR	1) Group A: Methylprednisolone 1.0mg/kg/6h (IV) for 1d, n=NR 2) Group B: Methylprednisolone 1.0mg/kg/6h (IV) for 2d, n=NR 3) Group C: Methylprednisolone 1.0mg/kg/6h (IV) for 3d, n=NR	NR NR	D1 to D3	An acute effect of glucocorticoid therapy on the suppression of osteoblasts was biochemically revealed by the finding of reduced serum osteocalcin levels; this suggests that early change in serum osteocalcin may be a useful indicator for patients at high risk of bone loss. Levels of serum osteocalcin progressively declined with increasing duration of GC therapy, with tendency toward a decrease of serum phosphate.

						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 +/- 1.5
Jartti 2006 Finland Non-industry and industry funded	RCT Pediatric 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 hospitalization, 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 Pediatric 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 hospitalization, 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 differences in the

Non-industry and industry funded	University hospital 1	rhinovirus-induced 3-23mo (mean 13.2mo vs. 12.2mo)	2mg/kg/d in 2 divided doses for 3d (max. 60.0mg/day), n=34 2) Placebo, n=40 Multiple courses over 1yr	No previous systemic or inhaled CS treatment	12mo post-discharge	incidence of adverse events between the prednisolone and placebo groups (results not shown). No clinically significant adverse events were reported.
Johnson 1996 Canada Non-industry funded	RCT Pediatric ED 1	Croup mean 15mo vs. 17mo	1) Dexamethasone 10.0mg (4ml) - 10.0mg (<8kg), 15.0mg (8-12kg) or 20.0mg (>12kg), 10min (neb), n=28 2) Control, saline (4ml), 10min (neb), n=27	Humidified oxygen No CS in preceding 2wk	Baseline, 2h & 4h post-treatment	Two patients with neutropenia treated with dexamethasone had a clinical course consistent with bacterial tracheitis.
Johnson 1998 Canada Industry funded	RCT Pediatric ED 2	Croup 3mo-9y	1) Budesonide 4.0mg for 20min (neb), n=48 2) Dexamethasone 0.6mg/kg, single dose (IM), n=47 3)Placebo suspension, single dose for 20min (neb), n=49	Racemic epinephrine & mist therapy No CS in preceding 4wk	Study entry & hourly for 5h post-treatment until discharge; FU 72h post-discharge	No child had gastrointestinal bleeding or bacterial tracheitis.
Klassen 1994 Canada Non-industry funded	RCT Pediatric ED 1	Croup 3mo-5y	1) Budesonide 2.0mg (4ml), single dose (neb), n=27 2) Placebo saline 0.9%	Racemic epinephrine or dexamethasone, or oxygen tent	Baseline & hourly for 4h; FU at 1wk	No adverse events were noted in the budesonide group. No patient in that

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

			3) Budesonide 2.0mg (4ml) (neb) + dexamethasone 0.6mg/kg (oral), n=64			reported this condition at the 1-week follow-up. Parents of 1 patient treated with dexamethasone reported hives, and parents of 1 patient treated with dexamethasone reported violent behavior. Parents of 1 patient who had received budesonide and dexamethasone reported their child to be more hyperactive than usual.
Kuyucu 2004 Turkey Funding NR	RCT Pediatric outpatient clinic and ED 1	Bronchiolitis 2-21mo	1) Epinephrine 3ml of 1:1000 solution for 10min (neb) + dexamethasone 0.6mg/kg, single dose (IM), n=23 2) Sal 0.15mg/kg of 1mg/ml solution added to 0.9% saline for 10min (neb) + dexamethasone 0.6mg/kg, single dose (IM), n=23	NR No CS in preceding 2wk	Baseline, 30min, 60min, 90min & 120min, then 24h, 5d; FU by regular hospital visits in subsequent 2mo	No side-effects such as pallor, vomiting or tremor were encountered in the patients.

			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 China Funding NR	RCT Hospital pediatric inpatient ward 1	Asthma 1-5y	1) Budesonide 0.05mg/kg every 12h (neb), n=9 2) Dexamethasone 0.1mg/kg every 8h (neb), n=9 Multiple courses over 8-19mo	Terbutaline (as needed) 0.25mg/kg every 6h to a max. of 5.0mg NR	On admission, at discharge & at follow-up; Growth (mean height) assessed (assessment method NR) at baseline and approximately 8-19mo after randomization; Adrenal suppression assessed from blood pressure (systolic	The measures of blood pressure (systolic and diastolic), blood glucose and serum potassium revealed no significant changes between admission and discharge in either group of patients (Table 3). Thus, there were no adverse effects in these patients. Table 4 also shows that there were no significant differences in

					and diastolic) and blood glucose at baseline and approximately 8-19mo after randomization	total height growth, mean rate of height increase, systolic or diastolic blood pressure, or blood glucose between the treatment groups.
Langton Hewer 1998 UK Funding NR	RCT Hospital 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	Bronchodilators (nebulized) No CS in preceding 14d	Baseline, 0h, 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 possibly attributable to prednisolone therapy was noted in any of the three treatment groups. Three children in prednisolone 2.0mg group were withdrawn because of vomiting, a diagnosis of pneumonia or the parents

						withdrew consent.
Lee 2001 Taiwan Funding NR	Case report Pediatric clinic of hospital 1	Asthma 5y	1) Terbutaline solution (loading dose: 5.0mg/kg/dose, maintaining dose: 0.6mg/kg/h); Methylprednisolone (BW 21kg, 2.0mg/kg/dose, 40.0mg every 6h) (IV), and; Procaterol 12.5mcg twice daily (oral)	NR	D1 to D3	On day 3 of admission the patient was found to have major behaviour changes and hyperventilation. She started screaming unreasonably, gazing forward and sometimes upward and became panic. She had visual hallucinations and delusion.
Leer 1969 USA Industry funded	RCT Hospital 5	Bronchiolitis <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	There were no detrimental corticosteroid effects in any of the patients. The corticosteroid neither increased the incidence of staphylococcal or other bacterial pneumonias nor masked superinfections.
Lehmann 2008 Germany Funding NR	Case report Pediatric	Asthma 2y	1) Prednisolone-21-hydrogen	None 3wk washout period (but under	Post skin prick test	Patient had been on well-tolerated long-term

	Allergology Clinic 1		succinate (PSH) 50.0mg (IV) 2) Prednisone (100.0mg, suppository) 3) Betamethasone (dose NR, oral) 4) Dexamethasone (dose NR, IV)	long-term maintenance therapy of daily 100mcg fluticasone propionate (inhaled) and intermittent prednisone suppositories		therapy of 100mcg inhaled fluticasone dipropionate daily for frequently recurring episodes of asthmatic exacerbations, with intermittent prednisone suppositories for acute bronchopulmonary obstruction with no occurrence of adverse events and no other glucocorticoid preparations. Patient was admitted to department due to severe bronchospasm (neither bronchodilators nor rectally administered prednisone provided symptom relief) and given 50mg of prednisolone-21-hydrogen succinate intravenously.

						Within a few minutes the boy developed generalized urticaria, facial angio-oedema, nausea and severe dyspnea requiring nasal oxygen supplementation. Medication was interrupted and symptoms spontaneously 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, betamethasone or dexamethasone. An oral provocation test with betamethasone and a

						titrated intravenous dexamethasone challenge test were tolerated without any complications.
Leipzig 1979 USA Funding NR	RCT Hospital 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 Hospital 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/dose 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.

			(procaterol hydrochloride) 1.25mcg/kg/dose on admission, then twice daily (oral) 3) Group C: No hydrocortisone or procaterol (n=28)			
Lucas-Bouwman 2001 Netherlands Funding NR	RCT Hospital 1	Asthma 3mo-8y (mean 2y)	1) Prednisolone 1.0mg/kg tablets, twice daily for 5d (oral), n=NR 2) Prednisolone 1.0mg/kg solution, twice daily for 5d (oral), n=NR	Bronchodilators (inhaled) NR	6d to 8d after index visit	Vomiting was observed in 23% of patients using crushed tablets, and in none of the patients on oral solution.
Nahum 2009 Israel Funding NR	Case series (n=3, 1 case relevant) Pediatric ED 1	Asthma 5y	1) Methylprednisolone 2.0mg/kg for 2d (IV)	NR	D1 & D2; FU 3mo post-discharge	He presented with wheezing, received an intravenous bolus of methylprednisolone sodium succinate (2mg/kg), and immediately developed restlessness and facial rash which resolved spontaneously. On the following day, he received again the same medication and

						immediately developed respiratory distress and cyanosis with oxygen desaturation of 89%. He recovered with oxygen supplementation and was treated afterward with oral betamethasone sodium phosphate without adverse events.
Paniagua 2016 Spain Funding NR	RCT (conference abstract) Pediatric ED 1	Asthma >12mo	1) Dexamethasone, NR, 2 doses (oral), n=287 2) Prednisone/prednisolone, NR, 5d (NR), n=290	NR NR	NR; FU at 7d & 15d post-ED visit	No differences were found regarding vomits (2.1% vs 4.1%).
Panickar 2009 UK Non-industry funded	RCT Pediatric 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. In one child in the prednisolone group, parents attributed excess

						vomiting to the study drug and discontinued the medication after discharge from hospital.
Panigada 2014 Italy Funding NR	Case report Pediatric Pulmonary and Allergy Unit 1	Progressive shortness of breath, subsequent diagnosis of inflammatory myofibroblastic tumor cell proliferation 5y	Albuterol (inhaled) + prednisone 1.0mg/kg (28.70kg) (oral), n=1	NR 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 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.

						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,

						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 the neoplasm was carried out.
Plint 2009 Canada Non-industry and industry funded	RCT Pediatric ED 8	Bronchiolitis 6wk-12mo	1) Epinephrine 3ml 1:1000, 2 doses 30min apart (neb) + dexamethasone 1.0mg/kg (max 10mg) in ED plus 5 once-daily 0.6mg/kg/dose, total 6d (oral), n=200 2) Epinephrine 3ml 1:1000, 2 doses 30min apart (neb) + placebo, total 6d (oral), n=199	Bronchodilators (albuterol, epinephrine) & antibiotics No CS in preceding 2wk	Baseline to 30min, 60min, 120min & 240min; FU daily until D7, then every 2d until D14 & every 3d until D22	Adverse events were uncommon (see Supplementary Appendix). Pallor was reported in 76 infants (9.5%), tremor in 15 (1.9%), and vomiting in 14 (1.8%), with no significant differences among the groups. One hospitalized

			3) Placebo 2 doses 30min apart (neb) + dexamethasone 1.0mg/kg (max 10mg), total 6d (oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201			infant in group 2 and one in group 3 had mild, transient hypertension, which resolved rapidly. Supplementary table: side effects and adverse 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 vs. 4 vs. 5 vs. 3); Varicella (0 in 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 vs. 0)
Razi 2015 Turkey Funding NR	RCT Hospital 1	Asthma 7-72mo	1) Budesonide 1.0mg/2ml, 2 doses for up to 5d, n=50 2) Sterile saline 2ml, 2 doses for up to 5d, n=50	Standard care: methylprednisolone 1.0mg/kg/day, for up to 5d (IV) + sal 0.15mg/kg every 4h + ipratropium bromide 250mcg every 6h	Every 4h until discharge	No drug-related adverse effects were identified during hospitalization.

				NR		
Roberts 1999 Australia Industry funded	RCT Women's and Childre n's Hospita l 1	Croup 6mo-8y	1) Budesonide 2.0mg (4ml) for 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	NR No CS in preceding 4wk	Baseline, 2h, 6h & 12h after first dose, then 12-hourly up to 48h if in hospital; FU by telephone 1d & 3d post-discharge	The adverse effects in both groups were attributable to either manifestation s of the disease state or the mode of drug administratio n (Table 3). Four patients (3 placebo, 1 budesonide) experienced an exacerbation in symptoms to the point of causing interventional treatment mode outside of the protocol nebulised adrenaline). These exacerbations occurred shortly after beginning nebulisation and were apparently induced due to distress 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. 1)
Roorda 1998 Netherlands Funding NR	RCT Hospital NR	Croup 4-52mo	1) Fluticasone propionate 1000mcg, 2 divided doses	NR No CS in preceding 48h	Admission, 30min, 2h, 6h, 12h & 24h	No side effects of the treatment regimens were reported

			30min apart (MDI), n=9 2) Placebo (NR), n=8			during the 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 had occult blood in their stools; two were in the dexamethasone group. No episodes of gross haematochezia were observed.
Sadowitz 2012 USA Funding NR	Case series (n=4, 1 case relevant) ED 1	Pharyngitis 3y	Dexamethasone 10.0mg single dose (oral?) + acetaminophen + amoxicillin, n=1	NR NR	NR	The patient was given a 10-mg dose of dexamethasone in addition to acetaminophen and 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 sore throat, now with an inability to tolerate oral fluids. Pertinent

						physical examination findings included pulse rate of 166 beats per minutes; oral temperature of 40.3 degrees C; dry, erythematous mucous 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

						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 dexamethasone administration before the

						diagnosis of ALL and in the absence of a pretreatment CBC count following the guidelines for high-risk leukemia established by the Children's Oncology Group. Induction therapy include IV daunorubicin, decadron, asparaginase, and vincristine. The patient's initial course of treatment was complicated by a ruptured duodenal ulcer with peritonitis and osteonecrosis. The patient survived these complications and achieved remission and continues on maintenance chemotherapy at this time.
Saito 2017 Japan Funding NR	RCT Pediatric	Asthma <3y	1) Budesonide 1.0mg/dose,	At admission, received hydrocortisone (IV)	Daily;	Serum cortisol levels in the BIS and PSL

	depart ment of hospital 1		twice daily (neb), n=30 2) Prednisolone 0.5mg/kg, 3 times daily (IV), n=20	& one inhalation of procaterol; LTRA for wheezing episodes NR	Serum cortisol assessed (assessmen t method NR) on admission and D4 of hospitalizati on	groups at the time of admission were 15.0mcg/dL and 17.2mcg/dL (p>0.05), respectively. However, serum levels on the fourth day of hospitalizatio n were 17.0mcg/dL and 10.9mcg/dL, with significant suppression in the PSL group. Adverse events did not occur in either group.
Schuh 2008 Canada Non-industry funded	RCT Pediatri c ED 1	Bronchiolitis 8wk-23mo	1) Dexamethasone 1.0mg/kg in ED + 4 doses 0.15mg/kg starting 24h later, total 5d (oral), n=61 2) Dexamethasone 1.0mg in ED + 4 doses placebo syrup starting 24h later, total 5d (oral), n=64	Albuterol Baseline reports 3 patients with prior inhaled ICS	Baseline, D4 & D6 (home visits); FU by telephone on D28	The mean blood pressure increased from 96.1+/-8.8 mmHg to 99.5+/-14.8 mmHg in the single-dose group and from 96.4+/-7.9 mmHg to 103+/-16.8mmHg in the multiple dose group. Bag urine was obtained on

						day 6 visit in 47 study infants and tested positive for glucose in 1 child belonging to the multiple-dose group.
Schuh 2009 Canada Industry funded	RCT Pediatric 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/prednisolone 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	In the montelukast group, adverse effects developed in 3 patients. One patient experienced facial swelling of unknown etiology at 96 hours, another patient had vomiting and diarrhea at 72 hours, and the third patient complained of abdominal and leg pains on day 4. None of these patients required treatment for these events, and the relationship between montelukast and the

						‘‘event’’ is questionable. No adverse effects developed in the children given prednisolone after discharge.
Siomou 2003 Greece Industry funded	Case control, 3-arm Pediatric hospital 1	Bronchiolitis, viral wheezing, or croup 2mo-10y	1) Hydrocortisone 10.0mg/kg/day for 3d (NR), n=28 2) Methylprednisolone 2.0mg/kg for 3 days (NR), n=21 3) Control, 3d, n=51	NR Never/no CS in last 2mo	Baseline, 2 days after CS administration & 12d after end of therapy	In summary, short-term IV corticosteroid administration to children suffering from acute respiratory diseases led to partial but reversible inhibition of bone formation markers, especially detectable in the >1-year-old children, without affecting the bone resorption markers. The fall in the serum phosphate levels and decrease in the maximum renal phosphate reabsorption decrease in

						the maximum renal phosphate reabsorption were significant but transient.
Sparrow 2006 Australia Funding NR	RCT Pediatric ED 1	Croup mean 37mo (28.8) vs. 45mo (31.6)	1) 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	Adrenaline No CS preceding study	Enrolment, 30min post-treatment, hourly for next 4h & every 4h until discharge; FU 7d-10d post-discharge	No adverse events were noted in either group.
Stafford 1998 Australia Industry and non-industry funded	NRCT Pediatric hospital or ED 1	Asthma/croup 1-12y	1) Prednisolone 5.0mg/ml solution (oral), n=8 2) PredMix 5.0mg/ml solution (oral), n=46 3) Dexamethasone 5.0mg/ml (oral), n=80	NR NR	Daily	No significant differences were found regarding the incidence of nausea, vomiting and abdominal pain, or any of the objective parameters tested.
Storr 1987 UK Non-industry & industry funded	RCT Pediatric 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.

			single dose (oral), n=73			There were no observed side-effects related to the single prednisolone dose.
Sumboonnanonda 1997 Thailand Funding NR	RCT Pediatric 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 pediatric 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 children'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 dexamethasone-treated patients in the main study, including one with a culture-positive influenza A viral infection, laryngotracheitis progressed to pneumonia. The other patient was the one who received a second

						injection of dexamethasone. At the time of his second injection, he had roentgenographic evidence of pneumonia. We did not encounter any side effects directly attributable to dexamethasone.
Sussman 1964 USA Non-industry funded	RCT Hospital NR	Bronchiolitis 1-25mo; Laryngitis 15mo-10y	1) Dexamethasone 0.1mg in divided daily dose every 6h: D1-9=0.2ml/lb/day; D10-11=0.1ml/lb/day; D12-13=0.05ml/lb/day; D14=0.02ml/lb/day (IM), n=31 2) Sodium chloride 0.15mEq/ml for 14d (IM), n=26	Oxygen, penicillin & streptomycin NR	Daily	Adverse reactions to steroid therapy were not noted on clinical examination and superinfections, bacterial or viral dissemination, were not encountered.
Svedmyr 1995 Sweden Funding NR	RCT, crossover NR	Asthma 3-10y	1) Budesonide 0.2mg 4 times daily for first 3d, 0.2mg 3 times daily for next 3d and 0.2mg twice	Maintenance bronchodilators permitted No CS in preceding month	NR	Ten adverse events were reported in the budesonide group and

			daily for last 3d (neb), n=NR (all groups=26) 2) Placebo (NR), n=NR (all groups=26) Multiple courses; 17 children completed one paired (Grp 1&2) treatment; 15 children completed 4 paired treatments			nine in the placebo group. There were two cases of dysphonia in the budesonide group. The other events were correlated more to the children's URTI such as headache, diarrhoea, epistaxis or sore throat. There were no significant differences between the two groups.
Svedmyr 1999[1] Sweden Funding NR	RCT Pediatric hospital 4	Asthma – first sign of URTI 1-3y	1) Budesonide 400mcg, 4 times daily for 3d then twice daily for 7d (MDI), n=28 2) Placebo, 4 times daily for 3d then twice daily for 7d (MDI), n=27 Multiple courses over 1yr, or max. 6 treatments	Beta-agonists and/or theophylline No CS in preceding 2mo	Daily for 10d	In the budesonide group a 24-month-old girl discontinued treatment during the first treatment period because of a suspected side effect. The child became 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 reporting 4 episodes in the budesonide group. This difference was statistically significant (p = 0.024). Figure 4 – bar chart of adverse events (counts, only once per treatment period), including vomiting, otitis,

						hoarseness, sore throat, conjunctivitis, croup, stomach ache, diarrhea, agitation, sleep disturbances, and aggressiveness.
Tagarro 2014 Spain Non-industry funded	Cohort University hospital 1	Bronchiolitis 0-6mo	1) Dexamethasone 1.0mg single dose, or for 6d, or 1.0mg on first day plus 0.6mg for 5d, 6d total (likely oral), n=33 2) Prednisone 1.0-2.0mg for 5d (likely oral), n=15 3) No steroids, dose/duration NR, n=32	Adrenaline & salbutamol NR	NR	No significant adverse effects attributable to steroids or bronchodilators were found in the clinical records, apart from hyperglycemia. Hyperglycemia was found in 4 out of 23 patients tested (17%). Two of them had received PRD, one of them DXM and one no steroids.
Tal 1983 Israel Non-industry funded	RCT Hospital 1	Acute wheeze 1-12mo	1) Dexamethasone 0.3mg/kg (4mg/ml) on admission + 0.1 mg/kg every 8h (IM), n=8 2) a) Sal solution 2.5mg (0.5ml),	Oral/IV fluid & humidified oxygen NR	Admission, 3h after first IM dose & each morning (8am) until discharge	One infant developed a remarkable tremor as a side effect of salbutamol. No other side effects or complications

			on admission & every 6h (neb); b) Sal syrup, 0.15mg/kg, 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 saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8			of the treatment were documented.
Tamura 2008 Japan Funding NR	Case series Medical center, inpatient 1	Refractory mycoplasma pneumonia 5y (n=6, range 3y-9y)	Methylprednisolone 30.0mg/kg once daily for 3d (IV), n=1	NR NR	NR	All cases: There were no adverse events in any patients during steroid treatment; Case patient 1: On the 10th clinical day, we initiated methylprednis

						olone pulse therapy once 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.
Teeratakul pisarn 2007 Thailand Non-industry funded	RCT Pediatric outpatient or ED 2	Bronchiolitis 4wk-24mo	1) Dexamethasone 0.6mg/kg, single dose (IM), n=89 2) Saline solution 0.6mg/kg, single dose (IM), n=85	Epinephrine, salbutamol, IV fluids, antimicrobial drugs & oxygen No CS in preceding 2wk	Baseline & every 6h until study endpoint (resolution of respiratory distress); FU at 2wk intervals for	Soon after study endpoint, but before being discharged, systemic CS was prescribed to seven children (four in the dexamethaso

					at least 1mo	ne group) because of re-wheezing. None of the children received theophylline or ribavirin. Three children (two in the dexamethasone group) developed occult blood in stools. Six children (three in the dexamethasone group) had subsequent diarrhea. Three children (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):

						Occult blood in stools (2 vs. 1); Pneumonia (0 vs. 0); Diarrhea (3 vs. 3)
van Woensel 1997 Netherlands Non-industry funded	RCT Hospital 1	Bronchiolitis <2y	1) Prednisolone powder 1.0mg/kg/day in 2 divided doses for 7d (oral), n=27 2) Placebo in 2 divided doses for 7d (oral), n=27	Oxygen, bronchodilators, or antibiotics No CS in preceding 2mo	Baseline & daily for 7d	In the present study no clinically significant side effects of prednisolone were found.
Webb 1986 UK Non-industry funded	RCT, crossover "unit", outpatient 1	Persistent wheeze <18mo	1) Prednisolone 1.0mg/kg, twice daily for 5d (oral), n=NR (total patients in study = 38) 2) Placebo, twice daily for 5d (oral), n=18 crossed over Multiple courses; 38 children completed a total of 56 treatment courses	Bronchodilator & antibiotics NR	Daily for 5d & clinical exam 3d after treatment course (D8)	There were no side effects reported by the parents and none was detected on clinical examination at the time of review three days after completing the five day course of treatment.
Zhang 2003 Brazil Non-industry funded	RCT Pediatric hospital ward 1	Bronchiolitis <12mo	1) Prednisolone 1.0mg (oral) + standard care for 5d (NR), n=28 2) Standard care (oxygen, fluid replacement, nebulised	IV hydrocortisone in first 24h after hospitalization No CS in preceding 4wk	Enrolment, 1mo, 3mo, 6mo & 12mo after discharge	The potential side-effects of prednisolone were not included as outcome measures in this study as the safety of

			fenoterol) for 5d (NR), n=24			short-term 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 received prednisolone.

[1]Hedlin 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

Supplement 4. Methodological quality assessments of included studies

Study (year)	Harms pre-defined	Serious AE defined	Severe AE defined	Deaths specified	Mode of collection		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 specified	AE in each arm specified	No. and type of AE specified	Type of analysis
					ACTIVE	PASSIVE									
Alangari (2014)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Alansari (2013)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N
Aljebab (2017)	Y	N	N	N	Y	Y	Y	Y	Y	U	Y	Y	N	Y	Y
Alshehr (2005)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Altamimi (2006)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	Y	N
Bacharier (2008)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	N	N
Bisgaard (2006)	Y	N	N	N	Y	N	N	N	Y	N	N	Y	Y	U	Y
Bjornson (2004)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Brunette (1988)	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	Y
Buckingham (2002)	N	N	N	Y	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Bulow (1999)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
Chang (2008)	N	N	N	N	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Chen (2008)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Chub-Appakarn (2007)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Clavenna (2014)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	N	N
Connett (1994)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Connolly (1969)	N	N	N	Y	Y	N	N	N	Y	N	Y	N	N	Y	N
Corneli (2007)	N	N	N	N	Y	N	Y	Y	Y	N	Y	Y	N	N	N

Cronin (2016)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	Y	N	Y	N
Csonka (2003)	N	N	N	N	N	N	N	N	N	N	Y	Y	Y	Y	N
Daugbjerg (1993)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
Dawson (1993)	N	N	N	N	Y	Y	Y	Y	Y	U	Y	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	Y	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	Y	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]	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Husby (1993)	N	N	N	N	U	N	Y	N	Y	N	Y	N	N	N	N
Inglis (1993)	N	N	N	Y	Y	Y	N	N	Y	N	Y	Y	Y	Y	N
Jan (2000)	N	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N	N
Jartti (2006)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Jartti (2007)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Jartti (2015)	N	N	N	N	N	N	N	N	N	N	U	Y	N	N	N
Johnson (1996)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Johnson (1998)	N	N	N	N	N	N	N	N	N	N	U	N	N	Y	N
Klassen (1994)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Klassen (1996)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Klassen (1998)	N	N	N	N	Y	Y	Y	Y	U	N	Y	Y	N	Y	N

Kuyucu (2004)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Lai (2005)	N	N	N	N	Y	N	N	N	Y	Y	Y	N	N	N	Y
Langton-Hewer (1998)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Lee (2001)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Leer (1969)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	Y	N
Lehmann (2008)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Leipzig (1979)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Lin (1991)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Lucas-Bouwman (2001)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	N
Nahum (2009)	N	N	N	Y	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Paniagua (2017)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
Panickar (2009)	N	N	N	N	Y	Y	Y	Y	Y	N	Y	N	N	Y	N
Panigada (2014)	N	N	N	N	Y	N	N	N	Y	N	Y	Y	Y	Y	N
Plint (2009)	N	N	N	N	Y	N	Y	Y	N	Y	N	N	Y	N	
Razi (2015)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Roberts (1999)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Roorda (1998)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Roosevelt (1996)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
Sadowitz (2012)	N	N	N	N	Y	Y	N	N	Y	N	Y	Y	Y	Y	N
Saito (2017)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N
Schuh (2008)	N	N	N	N	Y	N	Y	Y	Y	Y	Y	N	N	N	N
Schuh (2009)	N	N	N	N	N	N	N	N	N	N	Y	Y	N	Y	N
Siomou (2003)	Y	N	N	N	Y	N	N	N	Y	U	Y	N	N	N	N
Sparrow (2006)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Stafford (1998)	Y	N	N	N	Y	N	N	N	Y	Y	Y	N	N	Y	N
Storr (1987)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Sumboonnanonda (1997)	N	N	N	N	Y	N	N	N	Y	N	Y	N	N	Y	N

Sung (1998)	N	N	N	N	Y	Y	Y	Y	N	N	Y	N	N	N	N
Super (1989)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Sussman (1964)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	Y	N
Svedmyr (1995)	N	N	N	N	N	N	N	N	N	N	Y	N	Y	N	N
Svedmyr (1999)[1]	N	N	N	N	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y
Tagarro (2014)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Y	N
Tal (1983)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N
Tamura (2008)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N
Teeratakulpisarn (2007)	N	N	N	N	Y	N	Y	Y	Y	N	Y	N	N	Y	N
van Woensel (1997)	N	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N
Webb (1986)	N	N	N	N	Y	Y	N	N	Y	N	Y	N	N	N	N
Zhang (2003)	N	N	N	N	Y	N	N	N	N	N	Y	N	N	N	N

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

N: no; No.: number; U: unsure; Y: yes

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Supplement 5 Effect estimates for all adverse events with subgroups

a. Infection & respiratory system p. 2-4
b. Gastro-intestinal tract p. 5-7
c. CNS & behaviour effects p. 8-9
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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).

Supplement 5a. Infection & respiratory system

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Severe infections, overall	Systemic vs. placebo		4	0/552	2/554	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
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)	NA
	Systemic vs. placebo	Multi-dose	3	0/193	1/193	0.00 (-0.01, 0.01)	0	0.17 (0.00, 8.79)	NA
Severe infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/179	0/175	0.00 (-0.01, 0.01)	0	NA	NA
	Systemic vs. placebo	Croup	2	0/373	2/379	0.00 (-0.01, 0.00)	0	0.15 (0.01, 2.45)	0
Severe infections, overall	Inhaled vs. placebo		1	2/62	4/67	-0.03 (-0.10, 0.04)	NA	0.54 (0.11, 2.77)	NA
Systemic infections, overall	Systemic vs. placebo		4	5/1095	4/1083	0.00 (0.00, 0.00)	0	1.26 (0.34, 4.68)	NA
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)	NA
	Systemic vs. placebo	Multi-dose	2	0/431	0/427	0.00 (-0.01, 0.01)	0	NA	NA
Systemic infections, by condition	Systemic vs. placebo	Bronchiolitis	2	0/705	0/695	0.00 (0.00, 0.00)	0	NA	NA
	Systemic vs. placebo	Croup	1	5/359	4/361	0.00 (-0.01, 0.02)	NA	1.26 (0.34, 4.68)	NA
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.07)	NA	NA	NA

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, 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, 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 (-0.46, 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

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

Supplement 5b. Gastro-intestinal tract

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)	I^2 (%)	Peto OR (95% CI)	I^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, 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)	NA

	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)	NA
	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)	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	-0.07 (-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)	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

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
Diarrhea, overall	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03, 0.04)	0	1.09 (0.43, 2.73)	0
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
	Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03, 0.05)	0	1.16 (0.38, 3.54)	0
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
	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	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

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

Supplement 5c. CNS & behavior effects

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
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
	Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
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
		Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
		Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
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
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
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
	Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
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
	Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	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

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
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
	Dexamethasone 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	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
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

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

Supplement 5d. Dermatologic conditions

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
Integument, overall	Systemic vs. placebo		3	4/536	0/543	0.01 (0.00, 0.01)	0	7.59 (1.07, 54.01)	0
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
	Systemic vs. placebo	Multi-dose	1	2/133	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
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
	Systemic vs. placebo	Wheeze	1	2/113	0/117	0.02 (-0.01, 0.05)	NA	7.72 (0.48, 124.29)	NA
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
	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. 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

Supplement 5e. Endocrine/metabolic & musculoskeletal systems

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)	I^2 (%)	Peto OR (95% CI)	I^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	1	1/359	0/361	0.00 (0.00, 0.01)	NA	7.43 (0.15, 374.47)	NA
	Systemic vs. placebo	Multi-dose	3	4/473	1/457	0.00 (-0.01, 0.01)	0	2.56 (0.42, 15.61)	0
Fluid & electrolyte abnormalities, by condition	Systemic vs. placebo	Bronchiolitis	2	4/448	1/432	0.00 (-0.01, 0.01)	0	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, bronchiolitis	1	1/33	2/15	-0.10 (-0.28, 0.08)	NA	0.18 (0.01, 2.17)	NA
Adrenal suppression, overall	Inhaled vs. placebo	Multi-dose, asthma	1	5/6	4/10	0.43 (0.01, 0.86)	NA	5.21 (0.72, 37.57)	NA

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	Subgroup	No. of studies	Comparison 1 – total no. of patients	Comparison 2 – total no. of patients	Mean Difference (95% CI)	I^2 (%)
Linear growth	Inhaled vs. placebo	Multi-dose, wheeze	2	154	109	0.10 (-0.47, 0.67)	9

CI: confidence interval; no.: number; vs.: versus

Supplement 5f. Cardiovascular system

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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 difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: versus

Supplement 5g. General adverse events/ other symptoms

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
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
General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, 0.09)	0	NA	NA
	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. other steroid		2	3/102	3/95	-0.01 (-0.06, 0.03)	0	0.90 (0.18, 4.61)	11
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
	Dexamethasone vs. other steroid	Croup	1	3/46	2/41	0.01 (-0.08, 0.11)	NA	1.29 (0.21, 7.81)	NA

[1] Two studies reported pallor

[2] One study reported excessive urination; one study reported dizziness

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

Supplement 5h. Immune system & oncology

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)	I^2 (%)	Peto OR (95% CI)	I^2 (%)
Immunosuppression, overall	Systemic vs. placebo		1	0/47	0/48	0.00 (-0.04, 0.04)	NA	NA	NA

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

Supplement 6 **Forest plots of adverse events**

Systemic vs. Placebo
a. Infection & respiratory system p. 2-12
b. Gastro-intestinal tract p. 13-22
c. CNS & behaviour effects p. 23-29
d. Dermatologic conditions p. 30-32
e. Endocrine/ metabolic & musculoskeletal systems p. 33-35
f. Cardiovascular system p. 36-38
g. General adverse events/ other symptoms p. 39-40
h. Immune system & oncology p. 41
Inhaled vs. Placebo
a. Infection & respiratory system p. 42-47
b. Gastro-intestinal tract p. 48-51
c. CNS & behaviour effects p. 52-54
d. Dermatologic conditions p. 55-57
e. Endocrine/ metabolic & musculoskeletal systems p. 58
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Dexamethasone vs. Other steroid
a. Gastro-intestinal tract p. 60-63
b. CNS & behaviour effects p. 64-66
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d. Endocrine/ metabolic & musculoskeletal systems p. 68
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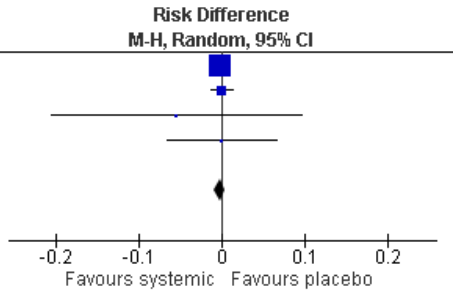
SYSTEMIC vs. PLACEBO – Infection & Respiratory

Severe infections

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]**
Total events	0		2			

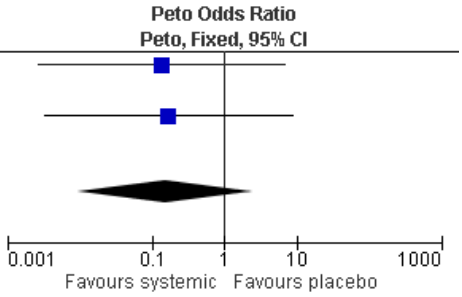
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)



Severe infections – Peto

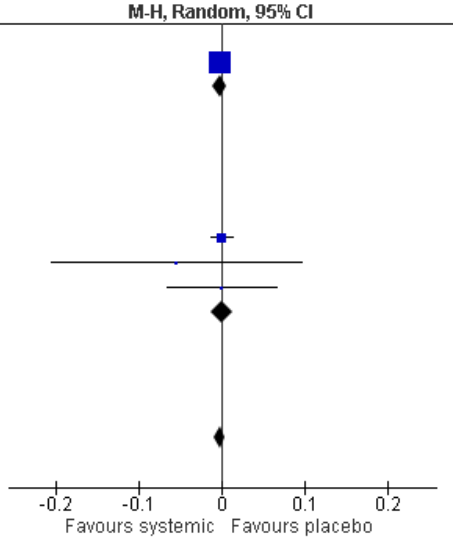
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjornson 2004	0	359	1	361	50.4%	0.14 [0.00, 6.86]
Leer 1969	0	148	0	149		Not estimable
Sumboonnanonda 1997	0	14	1	18	49.6%	0.17 [0.00, 8.79]
Sussman 1964	0	31	0	26		Not estimable
Total (95% CI)		**552**		**554**	**100.0%**	**0.15 [0.01, 2.45]**
Total events	0		2			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)



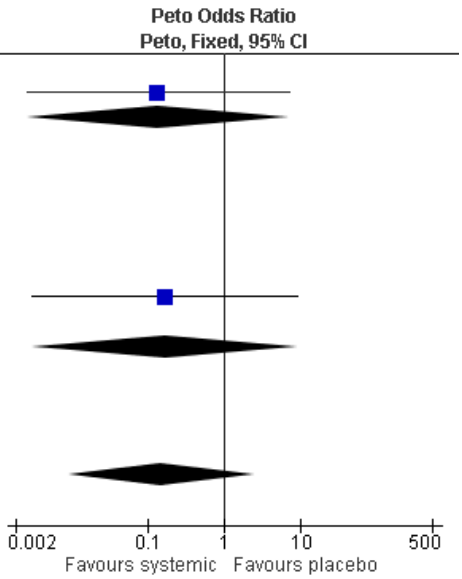
Severe infections (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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 applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
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: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Total (95% CI)		**552**		**554**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.76), I² = 0%						



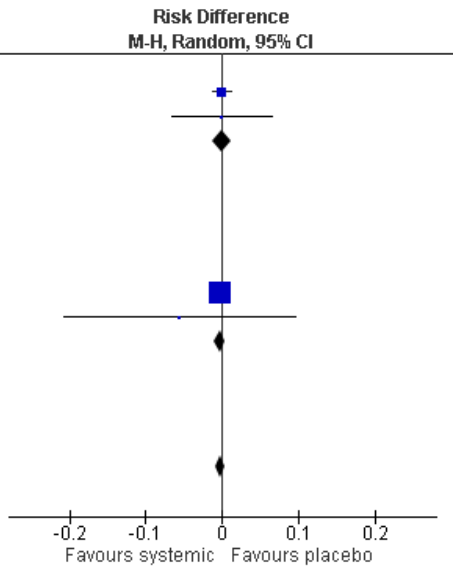
Severe infections (by dose) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable						
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% CI)		**193**		**193**	**49.6%**	**0.17 [0.00, 8.79]**
Total events	0		1			
Heterogeneity: Not applicable						
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: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.94), I² = 0%						



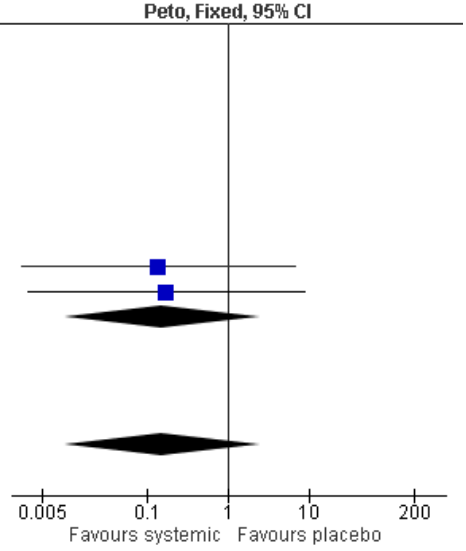
Severe infections (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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% CI)		**179**		**175**	**26.2%**	**0.00 [-0.01, 0.01]**
Total events	0		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
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% CI)		**373**		**379**	**73.8%**	**-0.00 [-0.01, 0.00]**
Total events	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						
Total (95% CI)		**552**		**554**	**100.0%**	**-0.00 [-0.01, 0.00]**
Total events	0		2			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



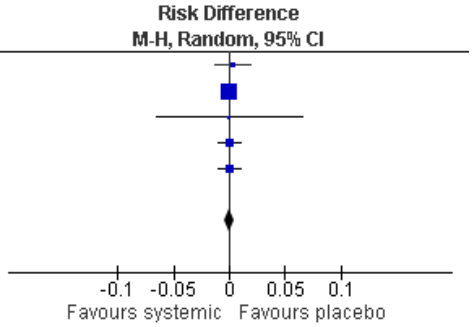
Severe infections (by condition) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.26.1 Bronchiolitis						
Leer 1969	0	148	0	149		Not estimable
Sussman 1964	0	31	0	26		Not estimable
Subtotal (95% CI)		**179**		**175**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
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% CI)		**373**		**379**	**100.0%**	**0.15 [0.01, 2.45]**
Total events	0		2			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.94); I² = 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: Chi² = 0.01, df = 1 (P = 0.94); I² = 0%						
Test for overall effect: Z = 1.33 (P = 0.18)						
Test for subgroup differences: Not applicable						



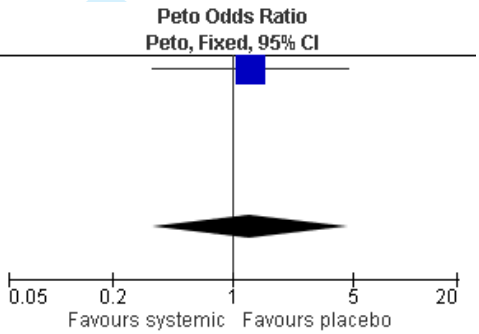
Systemic infections

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]**
Total events	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						



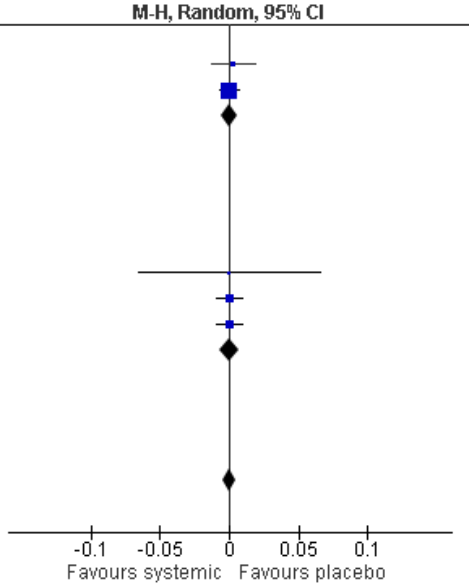
Systemic infections – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						



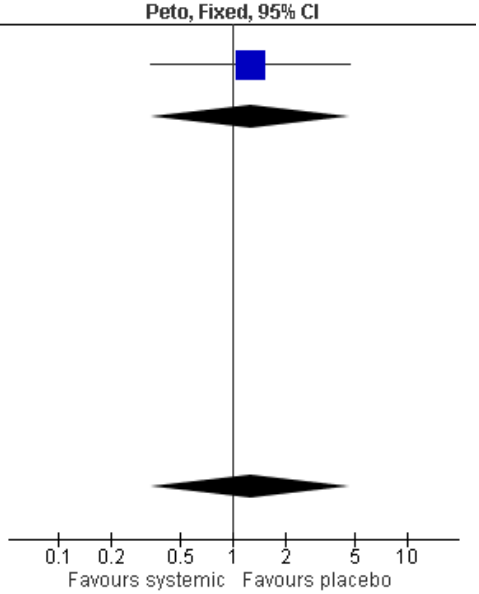
Systemic infections (by dose)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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% CI)		**664**		**656**	**56.2%**	**0.00 [-0.01, 0.01]**
Total events	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.90)						
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% CI)		**431**		**427**	**43.8%**	**0.00 [-0.01, 0.01]**
Total events	0		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1095**		**1083**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%						



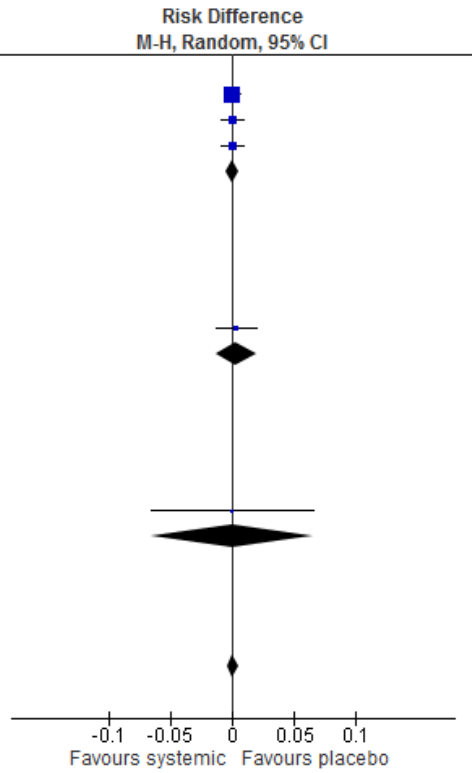
Systemic infections (by dose) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.30.1 Single dose						
Bjornson 2004	5	359	4	361	100.0%	1.26 [0.34, 4.68]
Corneli 2007	0	305	0	295		Not estimable
Subtotal (95% CI)		**664**		**656**	**100.0%**	**1.26 [0.34, 4.68]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
1.30.2 Multi-dose						
Daugbjerg 1993	0	31	0	27		Not estimable
Plint 2009	0	200	0	199		Not estimable
Plint 2009	0	200	0	201		Not estimable
Subtotal (95% CI)		**431**		**427**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1095**		**1083**	**100.0%**	**1.26 [0.34, 4.68]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



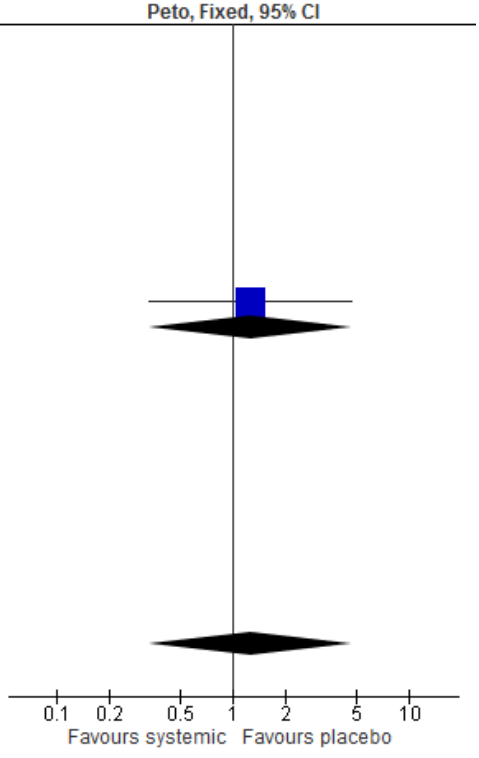
Systemic infections (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]
Subtotal (95% CI)		**705**		**695**	**91.7%**	**0.00 [-0.00, 0.00]**
Total events	0		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 2 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
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 applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1095**		**1083**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	5		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 4 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
Test for subgroup differences: Chi² = 0.11, df = 2 (P = 0.95), I² = 0%						



Systemic infections (by condition) – Peto

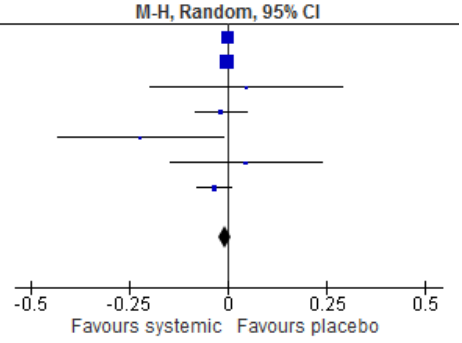
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.32.1 Bronchiolitis						
Corneli 2007	0	305	0	295		Not estimable
Plint 2009	0	200	0	199		Not estimable
Plint 2009	0	200	0	201		Not estimable
Subtotal (95% CI)		**705**		**695**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
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 applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
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 applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1095**		**1083**	**100.0%**	**1.26 [0.34, 4.68]**
Total events	5		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



Lung/trachea

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

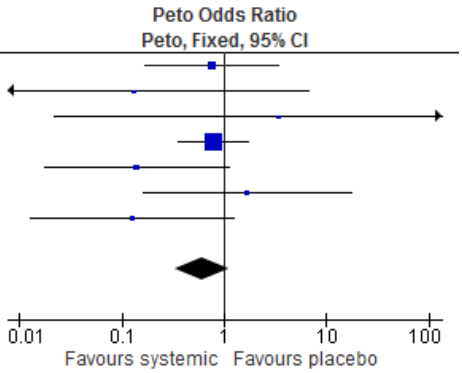
Heterogeneity: Tau² = 0.00; Chi² = 9.51, df = 6 (P = 0.15); I² = 37%
Test for overall effect: Z = 0.99 (P = 0.32)



Lung/trachea – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio 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: Chi² = 6.02, df = 6 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.59 (P = 0.11)



Lung/trachea (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

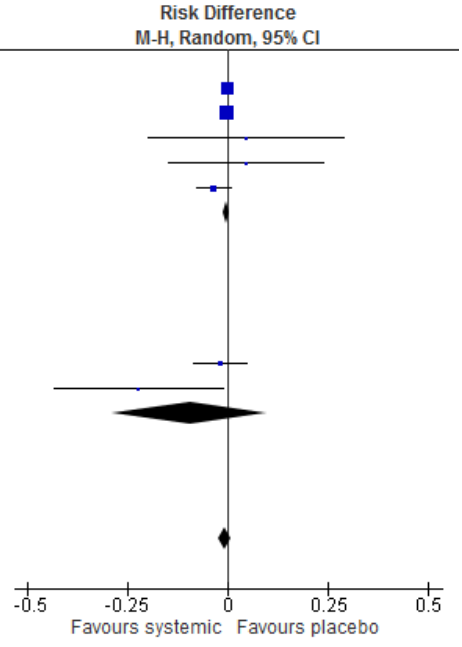
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 4 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)

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]
Subtotal (95% CI)		**162**		**167**	**5.6%**	**-0.09 [-0.29, 0.10]**
Total events	12		19			

Heterogeneity: Tau² = 0.01; Chi² = 3.22, df = 1 (P = 0.07); I² = 69%
Test for overall effect: Z = 0.97 (P = 0.33)

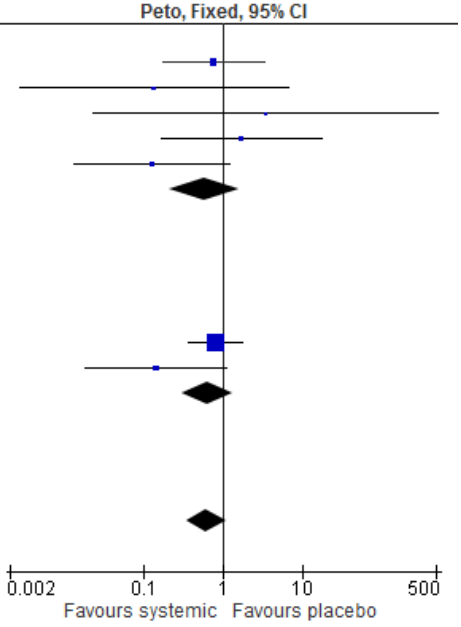
Total (95% CI)		**955**		**928**	**100.0%**	**-0.01 [-0.02, 0.01]**
Total events	18		28			

Heterogeneity: Tau² = 0.00; Chi² = 9.51, df = 6 (P = 0.15); I² = 37%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Chi² = 0.86, df = 1 (P = 0.35), I² = 0%



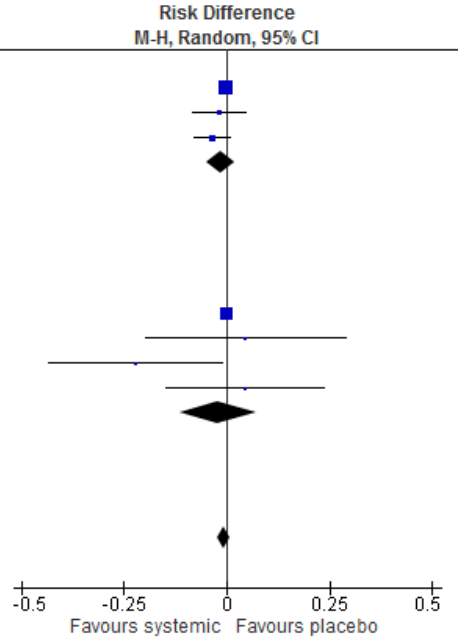
Lung/trachea (by dose) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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: Chi² = 3.67, df = 4 (P = 0.45); I² = 0%						
Test for overall effect: Z = 1.05 (P = 0.29)						
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: Chi² = 2.33, df = 1 (P = 0.13); I² = 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		28			
Heterogeneity: Chi² = 6.02, df = 6 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



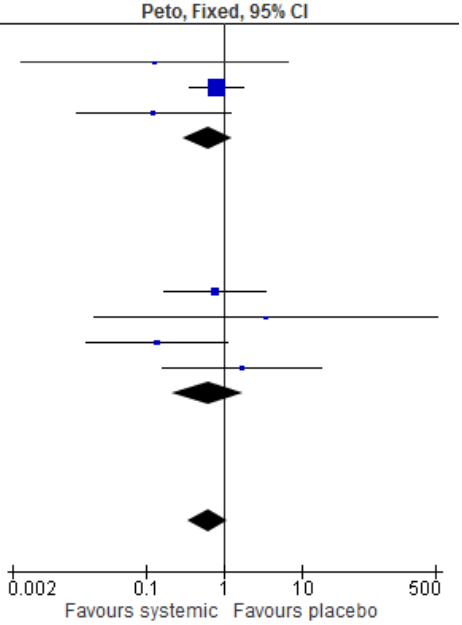
Lung/trachea (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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: Tau² = 0.00; Chi² = 5.18, df = 2 (P = 0.07); I² = 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: Tau² = 0.00; Chi² = 5.01, 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: Tau² = 0.00; Chi² = 9.51, df = 6 (P = 0.15); I² = 37%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						



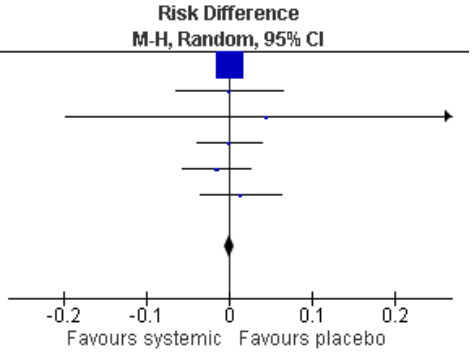
Lung/trachea (by condition) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.38.1 Bronchiolitis						
Corneli 2007	0	305	1	295	2.4%	0.13 [0.00, 6.60]
Leer 1969	12	148	15	149	58.0%	0.79 [0.36, 1.74]
Teeratakulpisarn 2007	0	89	3	85	7.0%	0.13 [0.01, 1.23]
Subtotal (95% CI)		**542**		**529**	**67.3%**	**0.61 [0.29, 1.28]**
Total events	12		19			
Heterogeneity: Chi² = 2.84, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 1.31 (P = 0.19)						
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	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]
Subtotal (95% CI)		**413**		**399**	**32.7%**	**0.61 [0.21, 1.76]**
Total events	6		9			
Heterogeneity: Chi² = 3.18, df = 3 (P = 0.37); I² = 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: Chi² = 6.02, df = 6 (P = 0.42); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



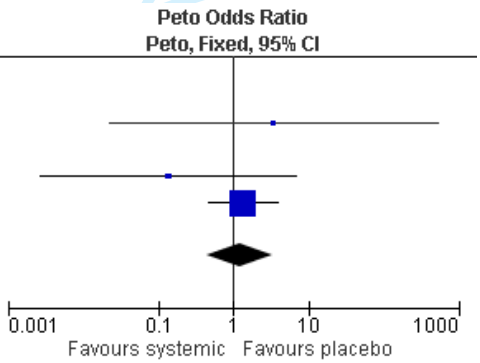
URT

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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% CI)		**671**		**656**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	9		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						



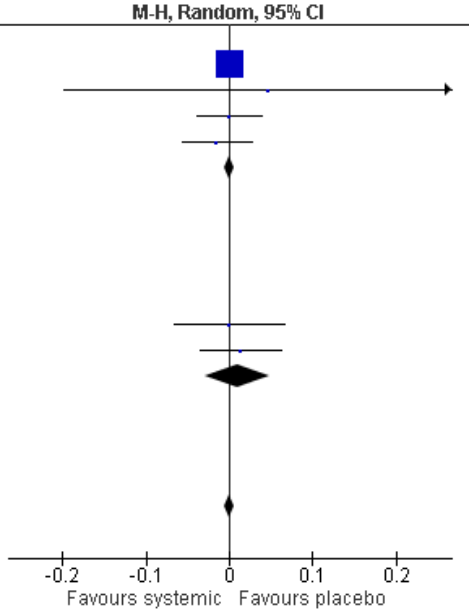
URT – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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: Chi² = 1.39, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						



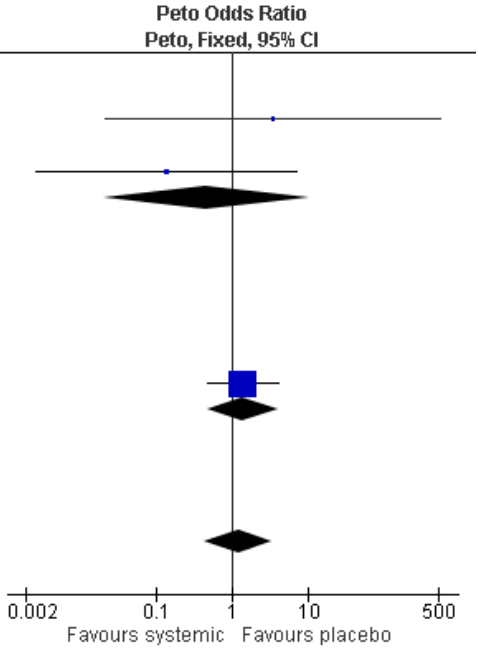
URT (by dose)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.41.1 Single Dose						
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% CI)		**492**		**480**	**98.1%**	**-0.00 [-0.01, 0.01]**
Total events	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.80, df = 3 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
1.41.2 Multi-Dose						
Daugbjerg 1993	0	31	0	27	0.7%	0.00 [-0.07, 0.07]
Leer 1969	8	148	6	149	1.2%	0.01 [-0.03, 0.06]
Subtotal (95% CI)		**179**		**176**	**1.9%**	**0.01 [-0.03, 0.05]**
Total events	8		6			
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Total (95% CI)		**671**		**656**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	9		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.65, df = 5 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: Chi² = 0.21, df = 1 (P = 0.65), I² = 0%						



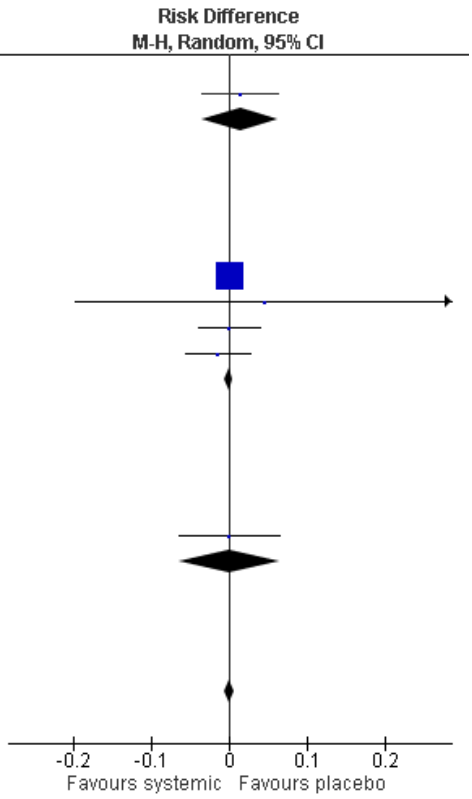
URT (by dose) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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% CI)		**492**		**480**	**10.7%**	**0.46 [0.02, 10.18]**
Total events	1		1			
Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
1.42.2 Multi-Dose						
Daugbjerg 1993	0	31	0	27		Not estimable
Leer 1969	8	148	6	149	89.3%	1.36 [0.47, 3.96]
Subtotal (95% CI)		**179**		**176**	**89.3%**	**1.36 [0.47, 3.96]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
Total (95% CI)		**671**		**656**	**100.0%**	**1.21 [0.44, 3.33]**
Total events	9		7			
Heterogeneity: Chi² = 1.39, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



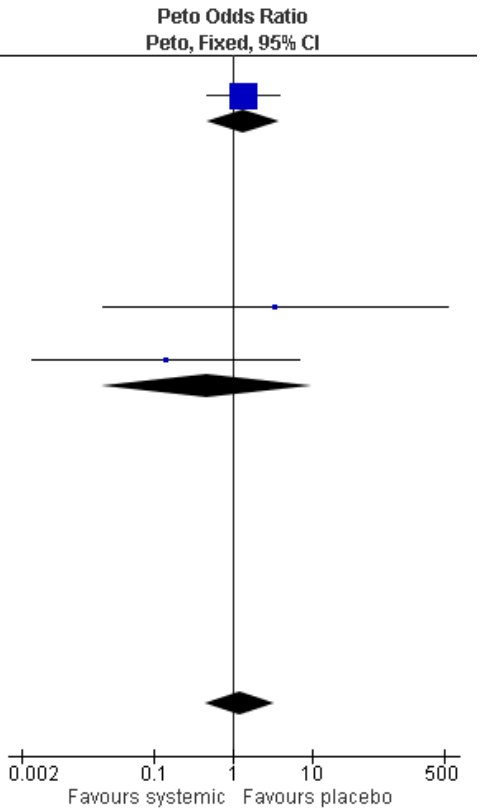
URT (by condition)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.43.1 Bronchiolitis						
Leer 1969	8	148	6	149	1.2%	0.01 [-0.03, 0.06]
Subtotal (95% CI)		**148**		**149**	**1.2%**	**0.01 [-0.03, 0.06]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.43.2 Croup						
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% CI)		**492**		**480**	**98.1%**	**-0.00 [-0.01, 0.01]**
Total events	1		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.80$, df = 3 (P = 0.85); $I^2 = 0\%$						
Test for overall effect: Z = 0.08 (P = 0.93)						
1.43.3 Wheeze						
Daugbjerg 1993	0	31	0	27	0.7%	0.00 [-0.07, 0.07]
Subtotal (95% CI)		**31**		**27**	**0.7%**	**0.00 [-0.07, 0.07]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**671**		**656**	**100.0%**	**-0.00 [-0.01, 0.01]**
Total events	9		7			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.65$, df = 5 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 0.02 (P = 0.98)						
Test for subgroup differences: $Chi^2 = 0.32$, df = 2 (P = 0.85), $I^2 = 0\%$						



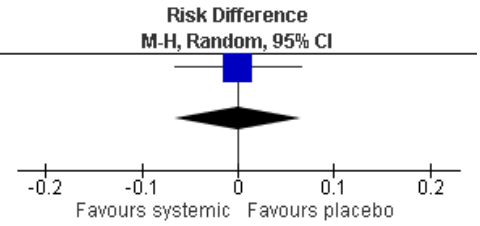
URT (by condition) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.44.1 Bronchiolitis						
Leer 1969	8	148	6	149	89.3%	1.36 [0.47, 3.96]
Subtotal (95% CI)		**148**		**149**	**89.3%**	**1.36 [0.47, 3.96]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
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]**
Total events	1		1			
Heterogeneity: Chi² = 0.97, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
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 applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**671**		**656**	**100.0%**	**1.21 [0.44, 3.33]**
Total events	9		7			
Heterogeneity: Chi² = 1.39, df = 2 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 0.42, df = 1 (P = 0.52), I² = 0%						



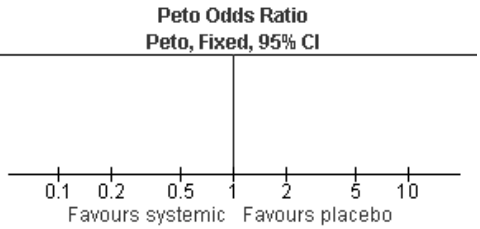
Voice complaints

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



Voice complaints – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Daugbjerg 1993	0	31	0	27		Not estimable
Total (95% CI)		**31**		**27**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

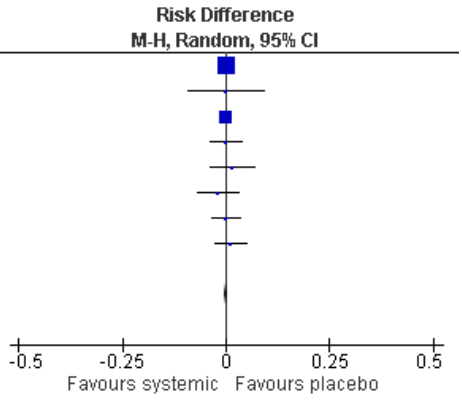


SYSTEMIC vs. PLACEBO – GI

GI bleeding

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

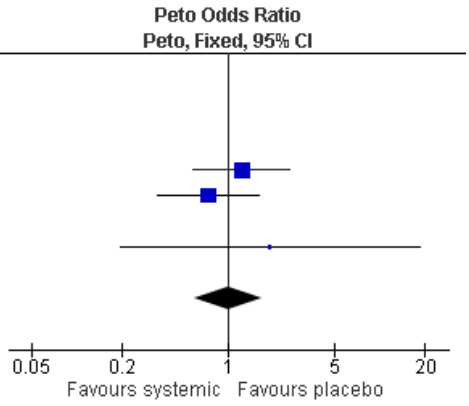
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 7 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



GI bleeding – Peto

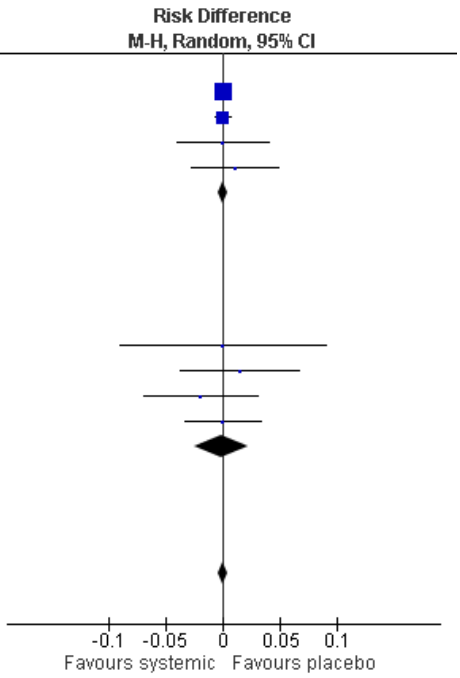
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjornson 2004	0	359	0	361		Not estimable
Buckingham 2002	0	22	0	19		Not estimable
Corneli 2007	0	305	0	295		Not estimable
Johnson 1998	0	47	0	49		Not estimable
Plint 2009	17	200	14	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]
Total (95% CI)		**1287**		**1262**	**100.0%**	**1.00 [0.60, 1.67]**
Total events	31		31			

Heterogeneity: Chi² = 1.18, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



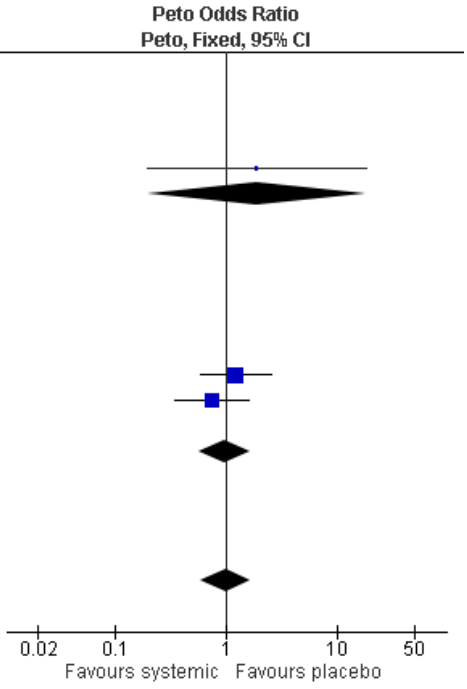
GI bleeding (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.3.1 Single Dose						
Bjornson 2004	0	359	0	361	56.0%	0.00 [-0.01, 0.01]
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]
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: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 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; Chi² = 0.88, df = 3 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Total (95% CI)		**1287**		**1262**	**100.0%**	**0.00 [-0.00, 0.00]**
Total events	31		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 7 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.90), I² = 0%						

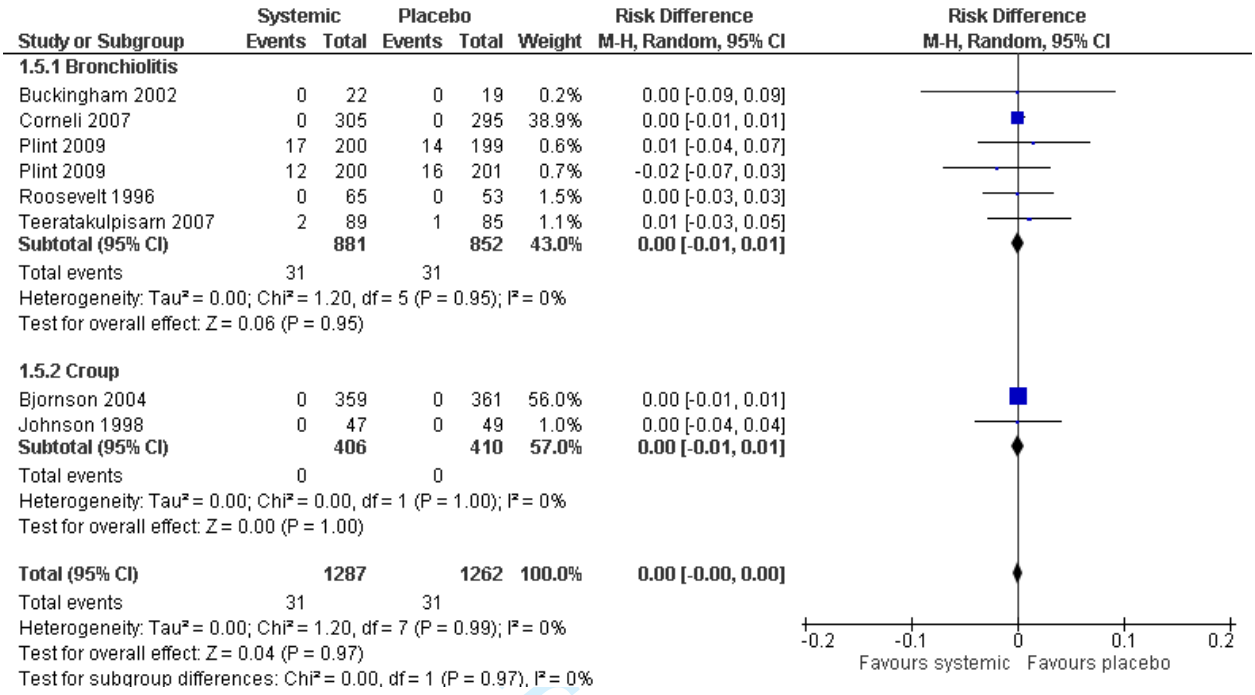


GI bleeding (by dose) – Peto

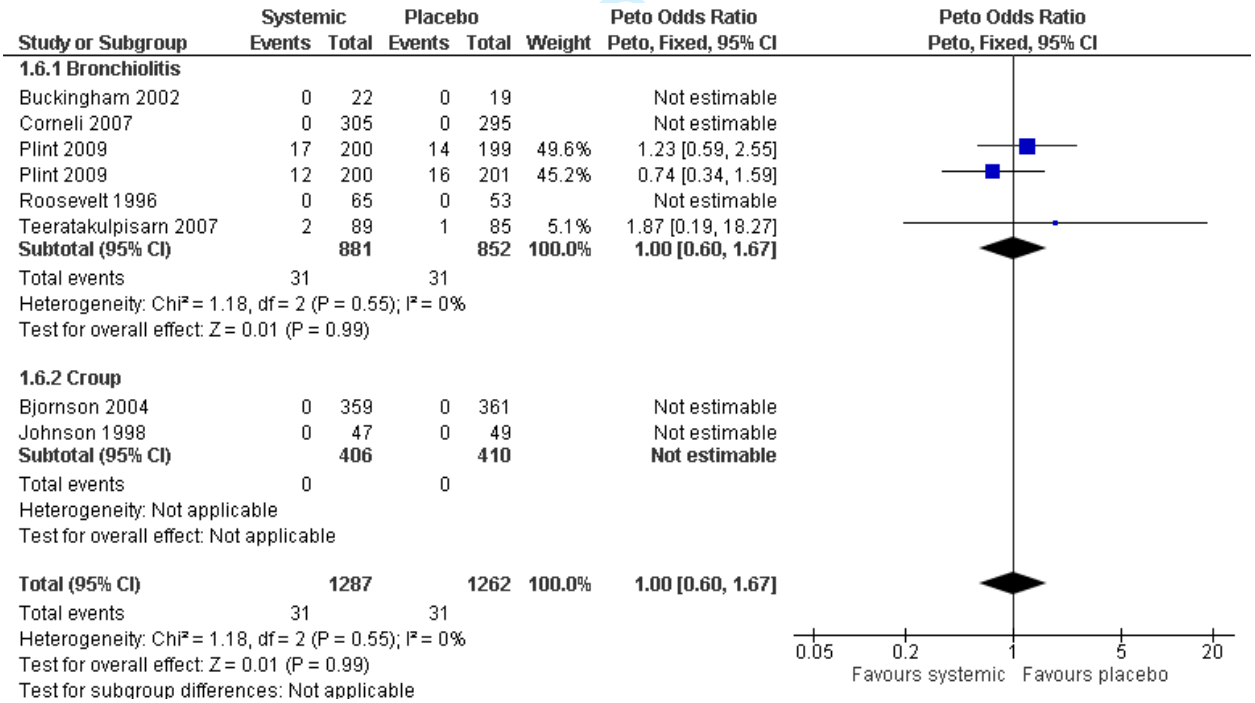
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.4.1 Single Dose						
Bjornson 2004	0	359	0	361		Not estimable
Corneli 2007	0	305	0	295		Not estimable
Johnson 1998	0	47	0	49		Not estimable
Teeratakulpisarn 2007	2	89	1	85	5.1%	1.87 [0.19, 18.27]
Subtotal (95% CI)		**800**		**790**	**5.1%**	**1.87 [0.19, 18.27]**
Total events	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
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: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
Total (95% CI)		**1287**		**1262**	**100.0%**	**1.00 [0.60, 1.67]**
Total events	31		31			
Heterogeneity: Chi² = 1.18, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.01 (P = 0.99)						
Test for subgroup differences: Chi² = 0.31, df = 1 (P = 0.58), I² = 0%						



GI bleeding (by condition)



GI bleeding (by condition) - Peto

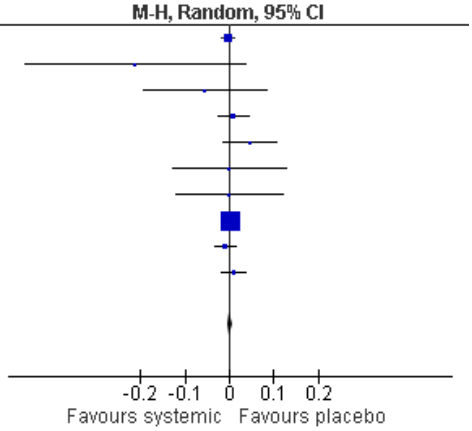


Vomiting

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]
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: Tau² = 0.00; Chi² = 7.45, df = 9 (P = 0.59); I² = 0%

Test for overall effect: Z = 0.51 (P = 0.61)

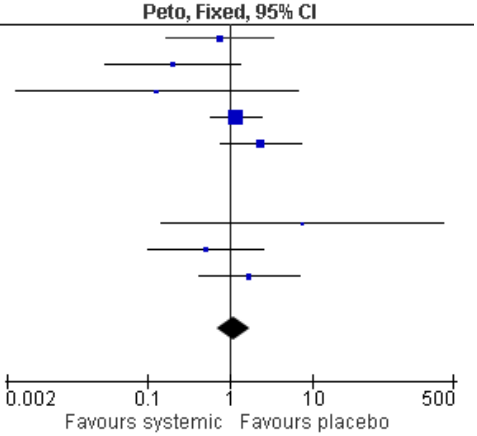


Vomiting – Peto

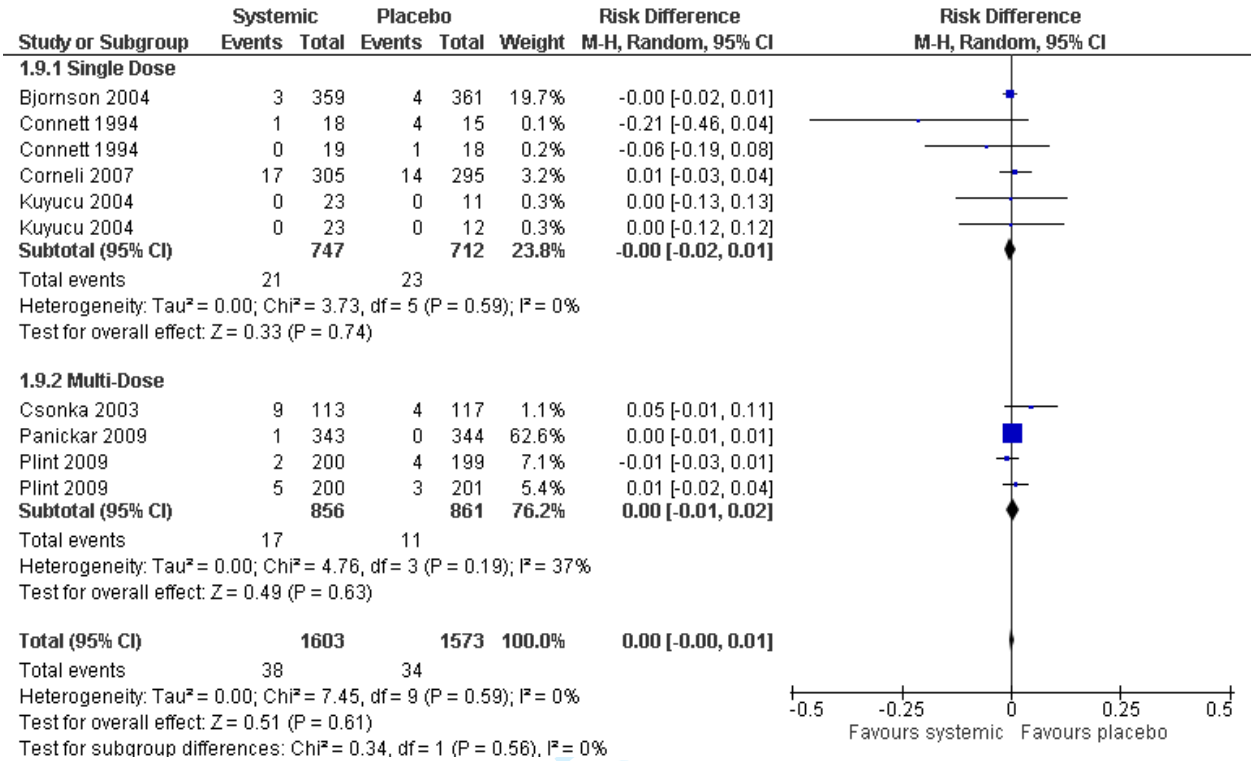
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjornson 2004	3	359	4	361	10.1%	0.75 [0.17, 3.34]
Connett 1994	1	18	4	15	6.3%	0.20 [0.03, 1.34]
Connett 1994	0	19	1	18	1.5%	0.13 [0.00, 6.46]
Corneli 2007	17	305	14	295	42.8%	1.18 [0.57, 2.44]
Csonka 2003	9	113	4	117	17.9%	2.34 [0.76, 7.14]
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% CI)		**1603**		**1573**	**100.0%**	**1.10 [0.69, 1.76]**
Total events	38		34			

Heterogeneity: Chi² = 8.43, df = 7 (P = 0.30); I² = 17%

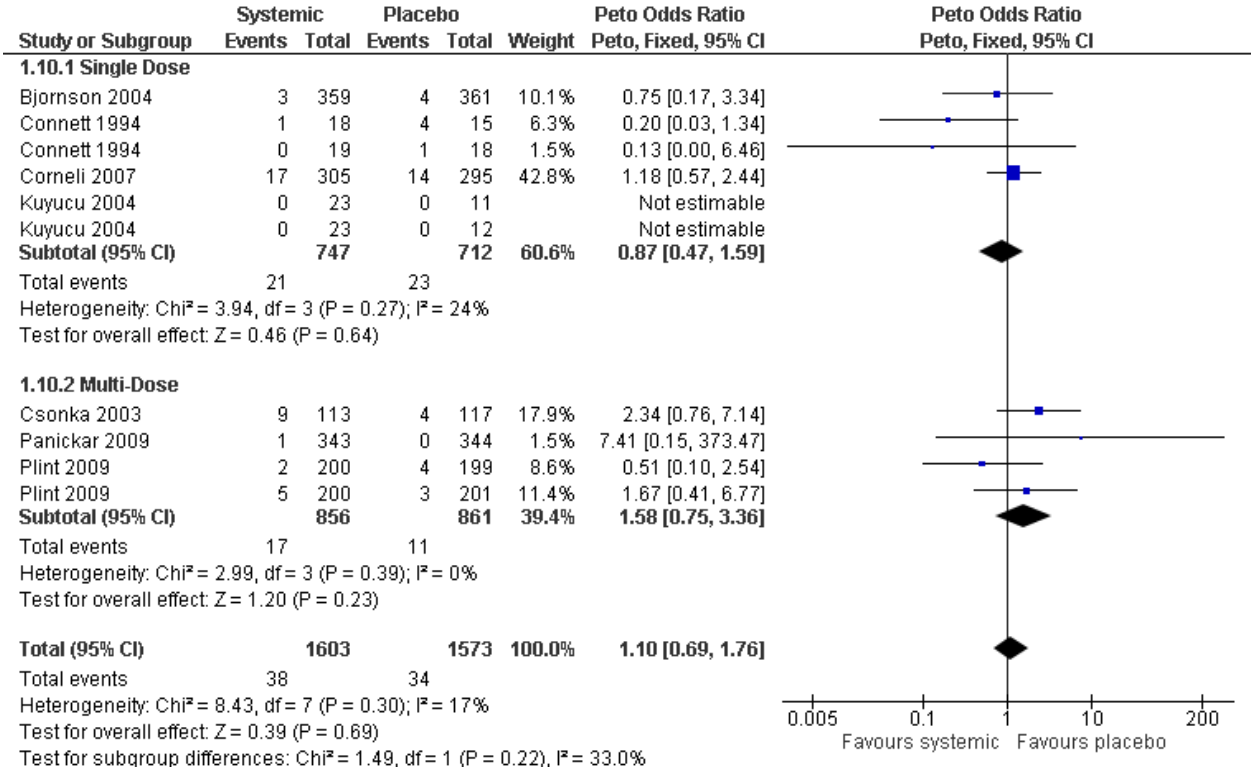
Test for overall effect: Z = 0.39 (P = 0.69)



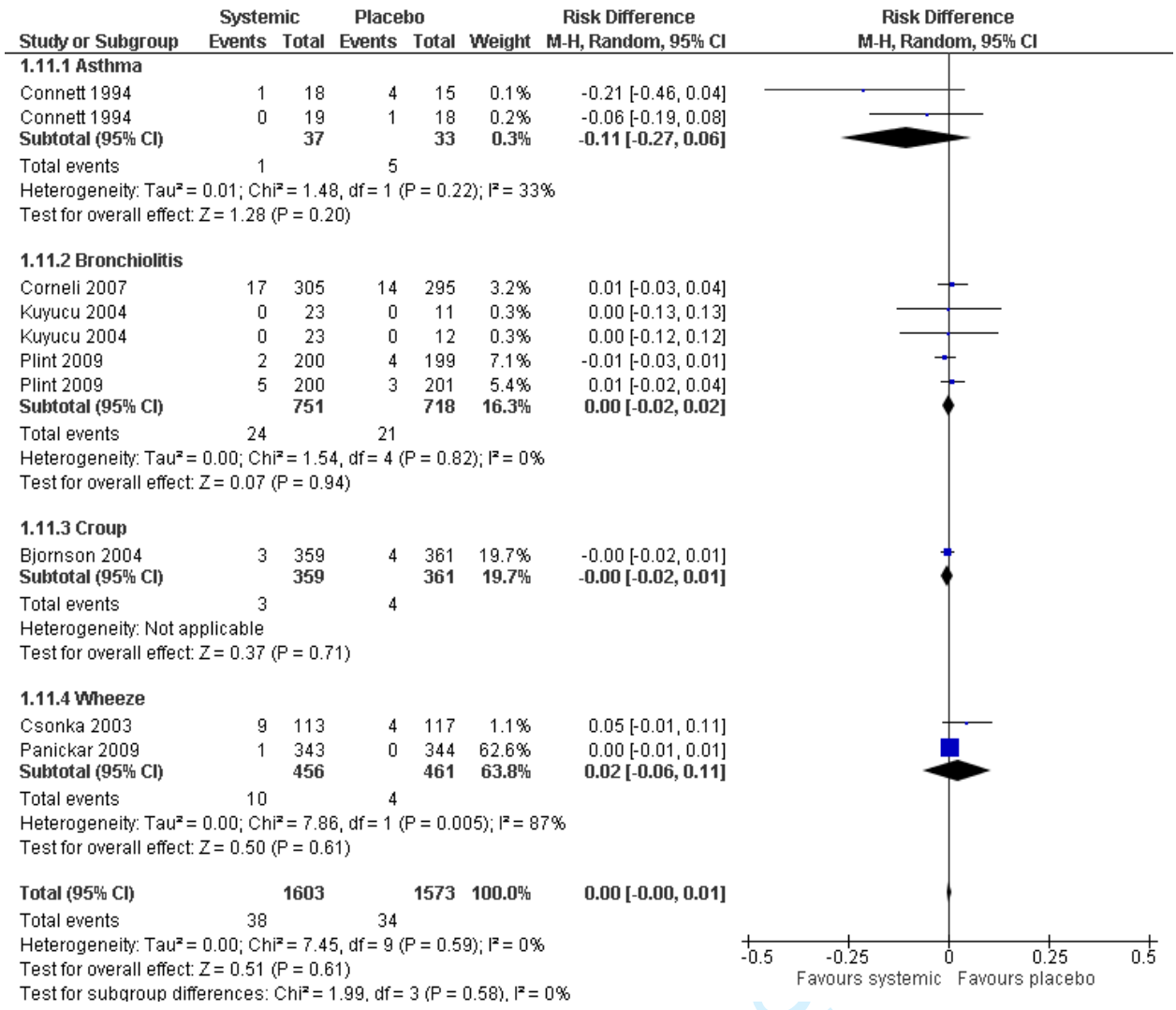
Vomiting (by dose)



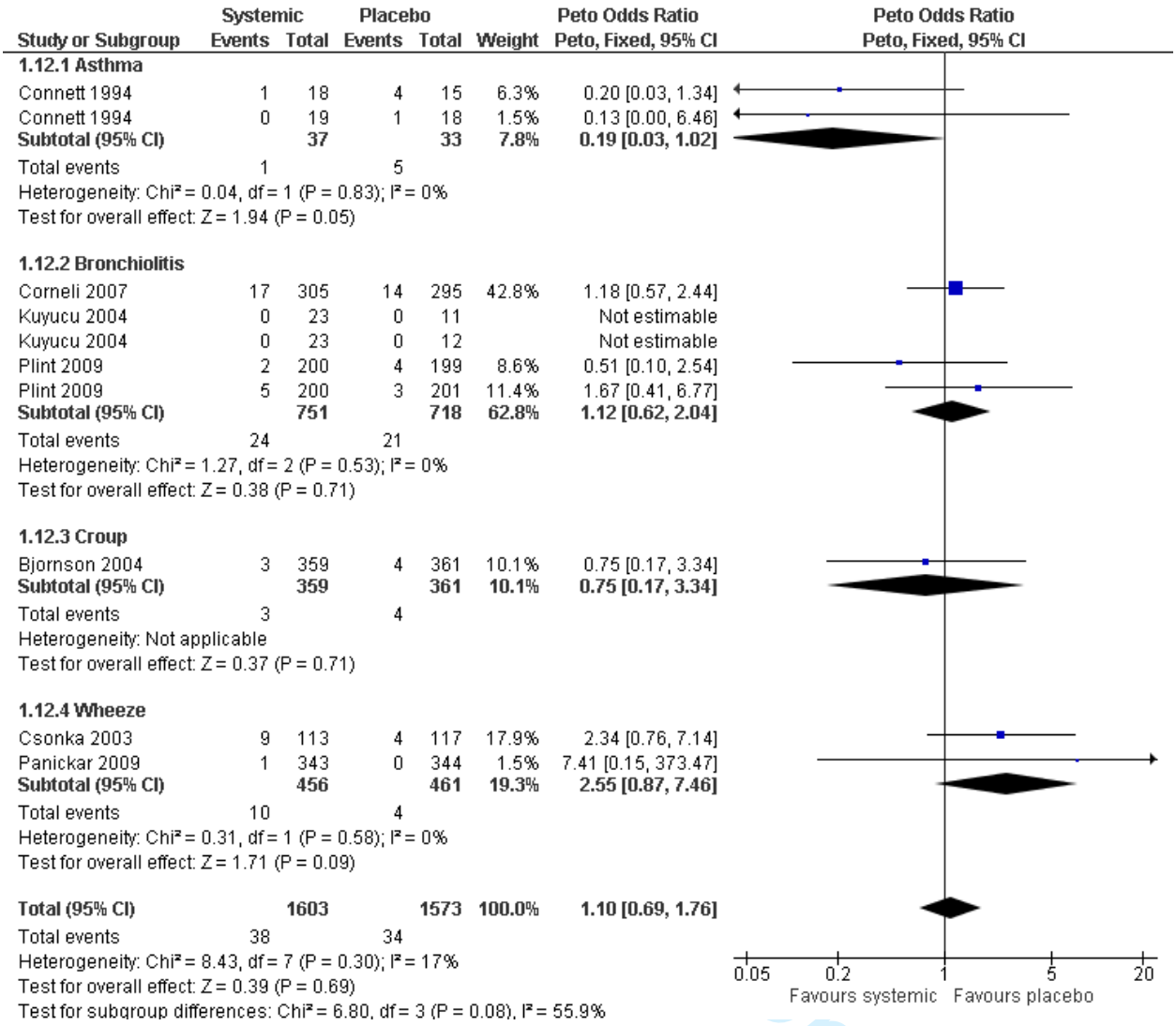
Vomiting (by dose) – Peto



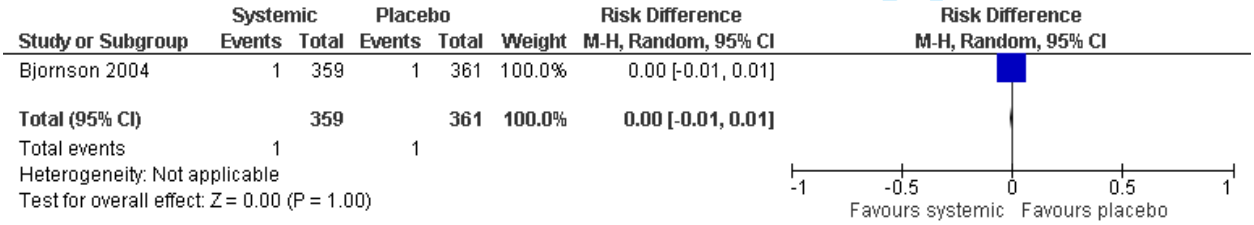
Vomiting (by condition)



Vomiting (by condition) – Peto



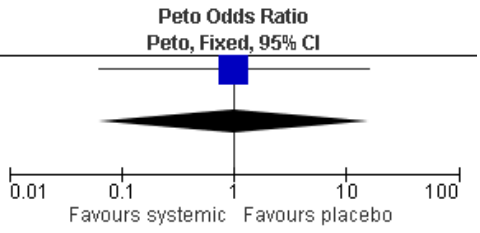
Abdominal pain



Abdominal pain – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

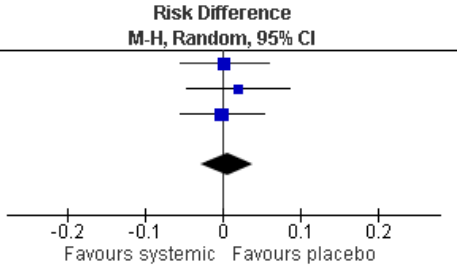
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Diarrhea

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

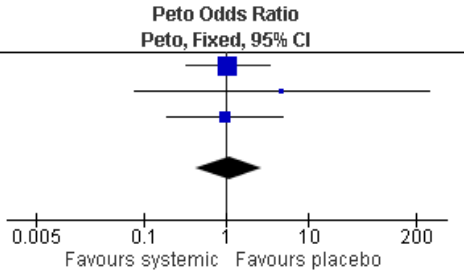
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)



Diarrhea – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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: Chi² = 0.51, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.18 (P = 0.86)



Diarrhea (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.17.1 Single Dose						
Teeratakulpisarn 2007	3	89	3	85	38.7%	-0.00 [-0.06, 0.05]
Subtotal (95% CI)		**89**		**85**	**38.7%**	**-0.00 [-0.06, 0.05]**
Total events	3		3			

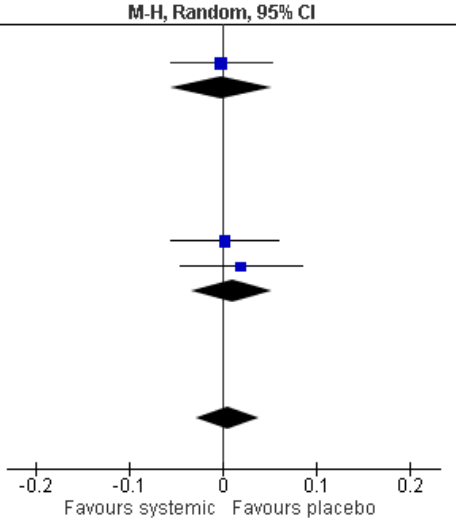
Heterogeneity: Not applicable
Test for overall effect: Z = 0.06 (P = 0.95)

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% CI)		**165**		**145**	**61.3%**	**0.01 [-0.03, 0.05]**
Total events	7		6			

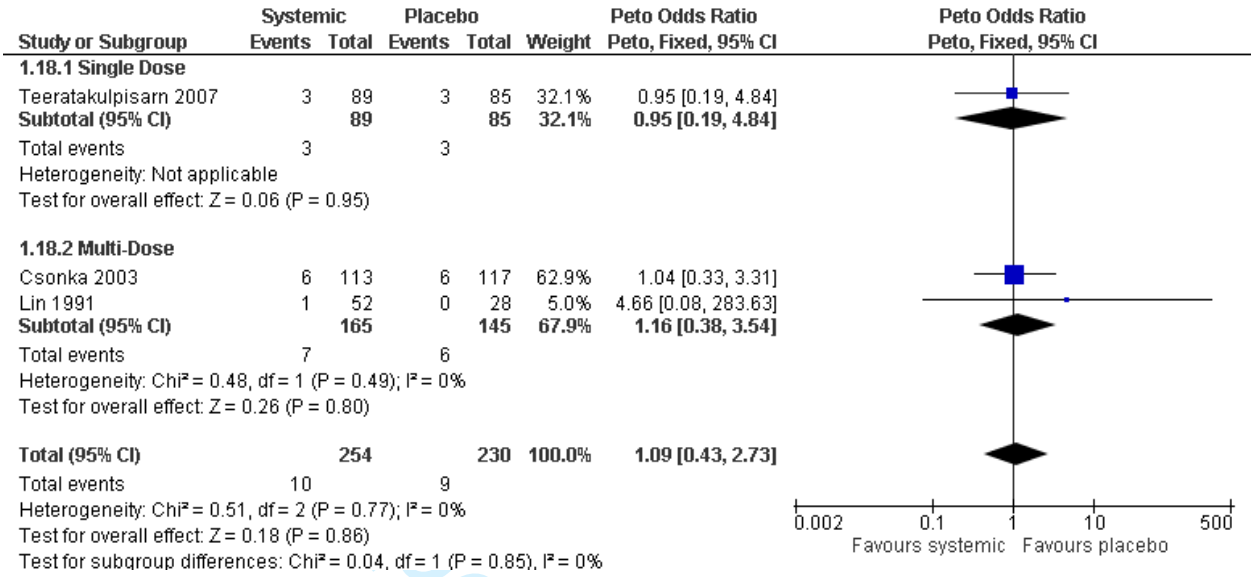
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.67)

Total (95% CI)		**254**		**230**	**100.0%**	**0.01 [-0.03, 0.04]**
Total events	10		9			

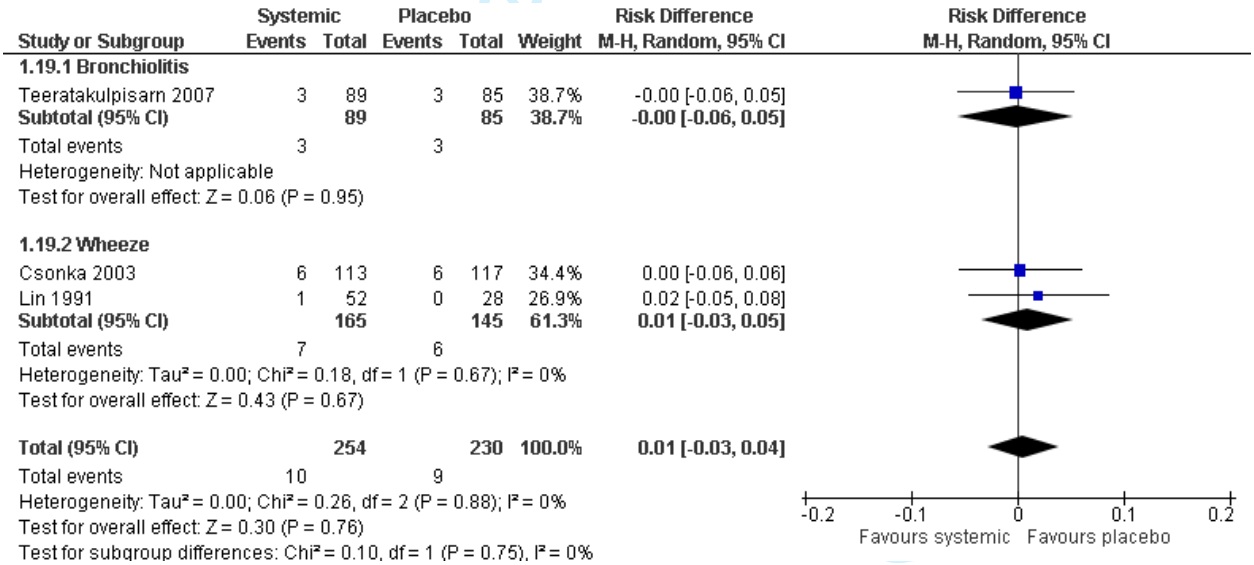
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%



Diarrhea (by dose) – Peto

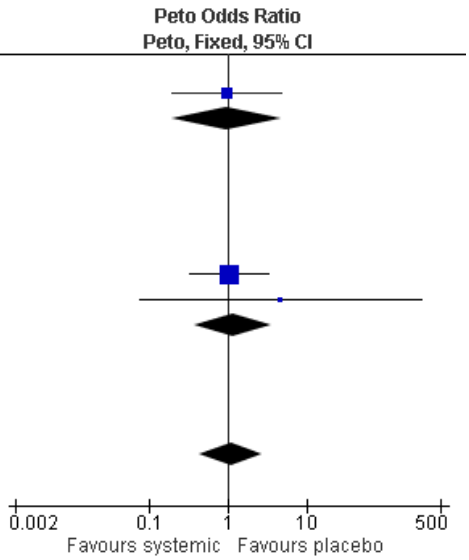


Diarrhea (by condition)



Diarrhea (by condition) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
1.20.2 Wheeze						
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: Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**254**		**230**	**100.0%**	**1.09 [0.43, 2.73]**
Total events	10		9			
Heterogeneity: Chi² = 0.51, df = 2 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: Chi² = 0.04, df = 1 (P = 0.85), I² = 0%						

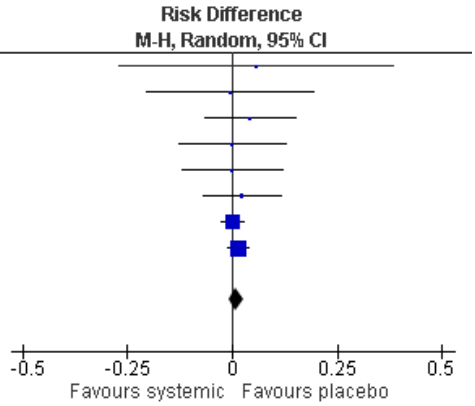


SYSTEMIC vs. PLACEBO – CNS & Behaviour

Tremor/jitteriness

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]
Kuyucu 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			

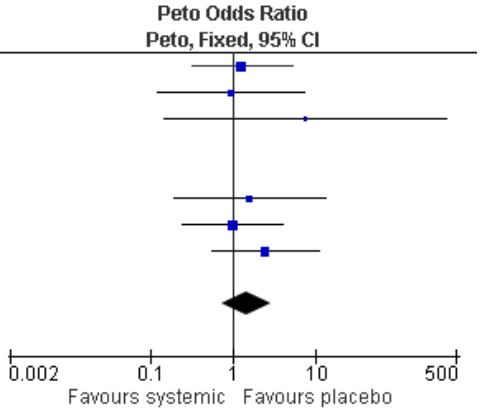
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 7 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



Tremor/jitteriness – Peto

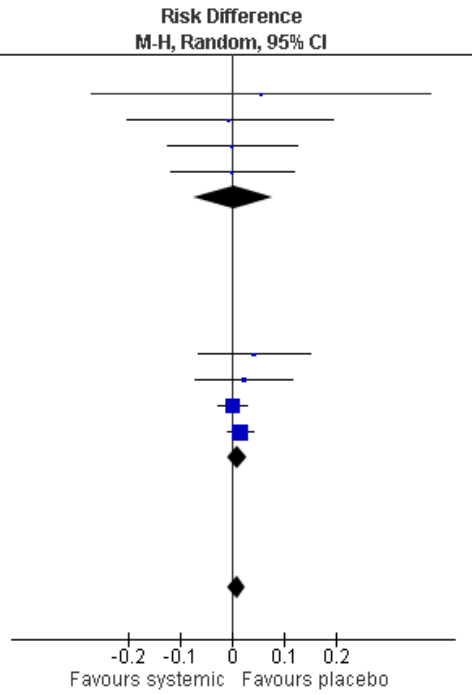
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Connett 1994	7	18	5	15	25.4%	1.26 [0.31, 5.13]
Connett 1994	2	19	2	18	11.9%	0.94 [0.12, 7.31]
Goebel 2000	1	24	0	24	3.3%	7.39 [0.15, 372.38]
Kuyucu 2004	0	23	0	11		Not estimable
Kuyucu 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: Chi² = 1.59, df = 5 (P = 0.90); I² = 0%
Test for overall effect: Z = 1.01 (P = 0.31)



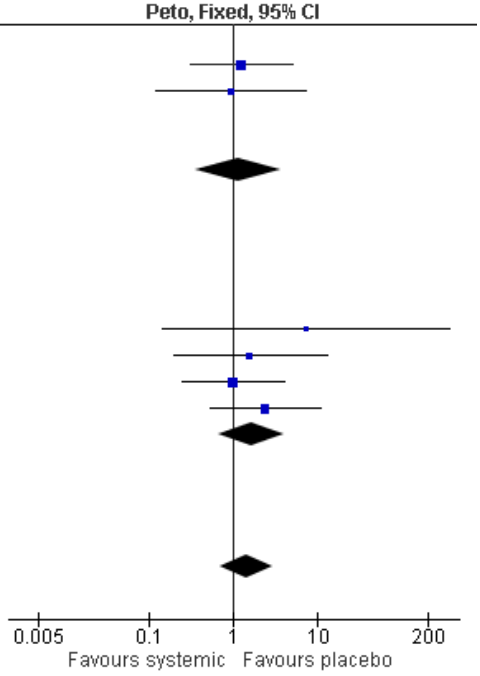
Tremor/jitteriness (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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]
Kuyucu 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]
Subtotal (95% CI)		**83**		**56**	**5.2%**	**0.00 [-0.08, 0.08]**
Total events	9		7			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.96)						
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]**
Total events	13		7			
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 3 (P = 0.78); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.31)						
Total (95% CI)		**559**		**508**	**100.0%**	**0.01 [-0.01, 0.03]**
Total events	22		14			
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 7 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%						



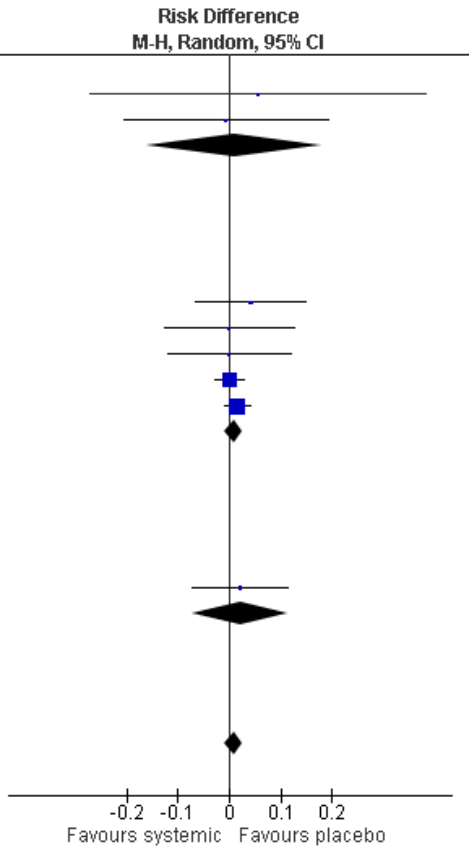
Tremor/jitteriness (by dose) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.50.1 Single Dose						
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]
Kuyucu 2004	0	23	0	11		Not estimable
Kuyucu 2004	0	23	0	12		Not estimable
Subtotal (95% CI)		**83**		**56**	**37.3%**	**1.15 [0.36, 3.66]**
Total events	9		7			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
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: Chi² = 1.31, df = 3 (P = 0.73); I² = 0%						
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: Chi² = 1.59, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						



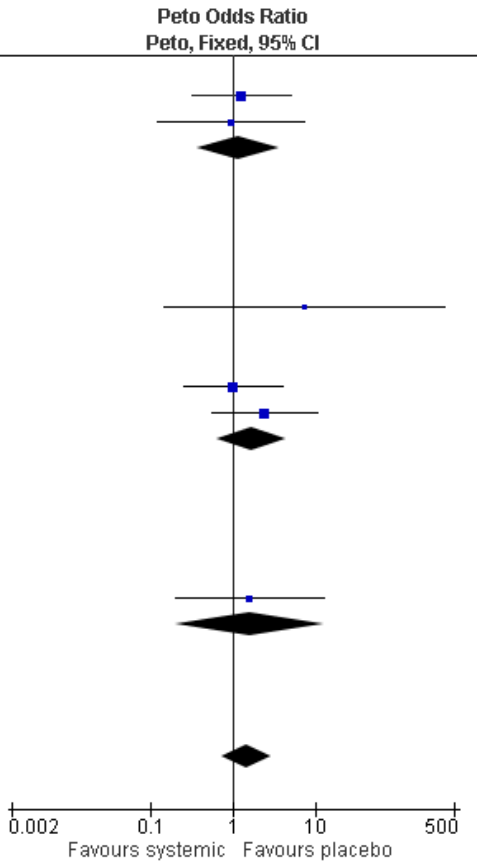
Tremor/jitteriness (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.51.1 Asthma						
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: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
1.51.2 Bronchiolitis						
Goebel 2000	1	24	0	24	2.7%	0.04 [-0.07, 0.15]
Kuyucu 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]
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: Tau² = 0.00; Chi² = 1.03, df = 4 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.51.3 Wheeze						
Lin 1991	3	52	1	28	3.6%	0.02 [-0.07, 0.12]
Subtotal (95% CI)		**52**		**28**	**3.6%**	**0.02 [-0.07, 0.12]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**559**		**508**	**100.0%**	**0.01 [-0.01, 0.03]**
Total events	22		14			
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 7 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.08, df = 2 (P = 0.96), I² = 0%						



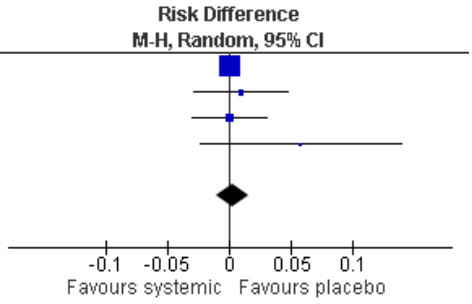
Tremor/jitteriness (by condition) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.52.1 Asthma						
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**	**37.3%**	**1.15 [0.36, 3.66]**
Total events	9		7			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
1.52.2 Bronchiolitis						
Goebel 2000	1	24	0	24	3.3%	7.39 [0.15, 372.38]
Kuyucu 2004	0	23	0	11		Not estimable
Kuyucu 2004	0	23	0	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: Chi² = 1.31, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.52.3 Wheeze						
Lin 1991	3	52	1	28	11.4%	1.58 [0.19, 12.83]
Subtotal (95% CI)		**52**		**28**	**11.4%**	**1.58 [0.19, 12.83]**
Total events	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
Total (95% CI)		**559**		**508**	**100.0%**	**1.44 [0.71, 2.92]**
Total events	22		14			
Heterogeneity: Chi² = 1.59, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Chi² = 0.23, df = 2 (P = 0.89), I² = 0%						



Behaviour change

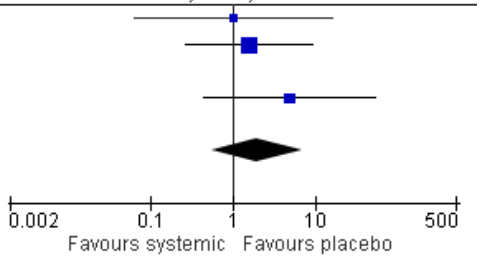
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Bjornson 2004	1	359	1	361	70.0%	0.00 [-0.01, 0.01]
Csonka 2003	3	113	2	117	11.0%	0.01 [-0.03, 0.05]
Klassen 1998	0	64	0	65	16.5%	0.00 [-0.03, 0.03]
Lin 1991	3	52	0	28	2.6%	0.06 [-0.02, 0.14]
Total (95% CI)		**588**		**571**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	7		3			
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 3 (P = 0.29); I² = 19%						
Test for overall effect: Z = 0.37 (P = 0.71)						



Behaviour change – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)



Behaviour change (by dose)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
1.55.1 Single-dose						
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			

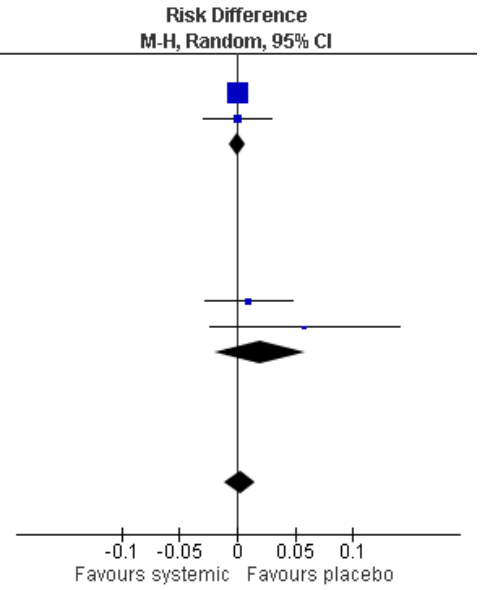
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

1.55.2 Multi-dose						
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: Tau² = 0.00; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 0.98 (P = 0.32)

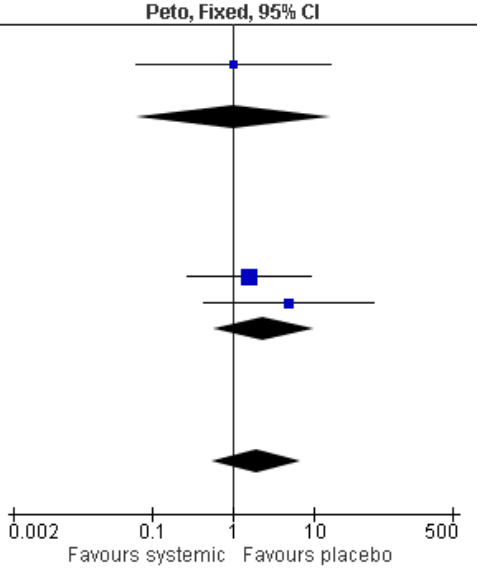
Total (95% CI)		**588**		**571**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	7		3			

Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 3 (P = 0.29); I² = 19%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33), I² = 0%



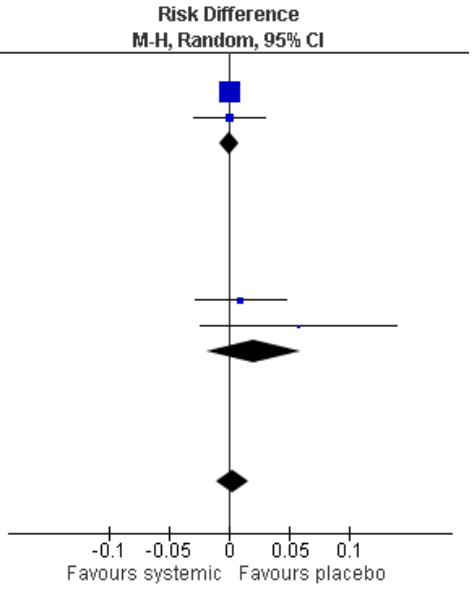
Behaviour change (by dose) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
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: Chi² = 0.56, df = 1 (P = 0.46); I² = 0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Total (95% CI)		**588**		**571**	**100.0%**	**1.95 [0.55, 6.92]**
Total events	7		3			
Heterogeneity: Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%						



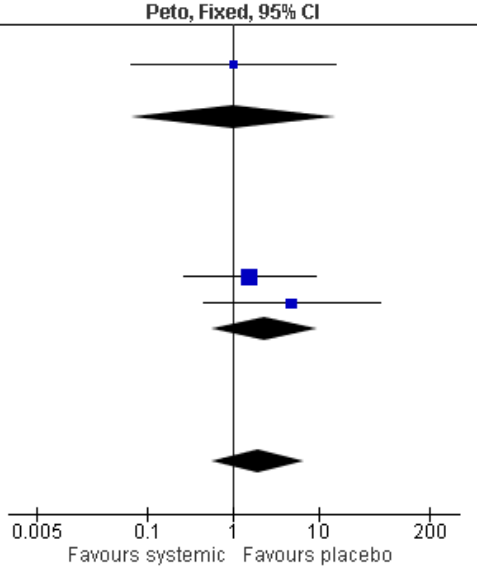
Behaviour change (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
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: Tau² = 0.00; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%						
Test for overall effect: Z = 0.98 (P = 0.32)						
Total (95% CI)		**588**		**571**	**100.0%**	**0.00 [-0.01, 0.02]**
Total events	7		3			
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 3 (P = 0.29); I² = 19%						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: Chi² = 0.93, df = 1 (P = 0.33), I² = 0%						



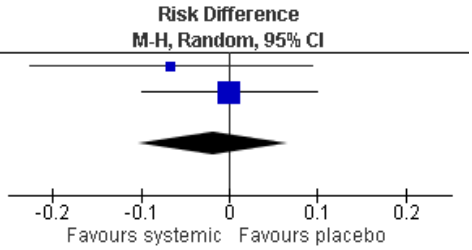
Behaviour change (by condition) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 1.16 (P = 0.25)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 1.03 (P = 0.30)						
Test for subgroup differences: $Chi^2 = 0.28$, df = 1 (P = 0.60), $I^2 = 0\%$						



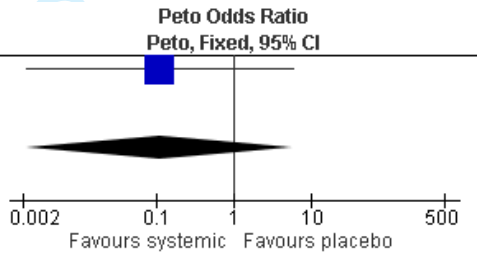
Headache

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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: $Tau^2 = 0.00$; $Chi^2 = 0.57$, df = 1 (P = 0.45); $I^2 = 0\%$						
Test for overall effect: Z = 0.43 (P = 0.67)						



Headache – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Connett 1994	0	18	1	15	100.0%	0.11 [0.00, 5.68]
Connett 1994	0	19	0	18		Not estimable
Total (95% CI)		**37**		**33**	**100.0%**	**0.11 [0.00, 5.68]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						

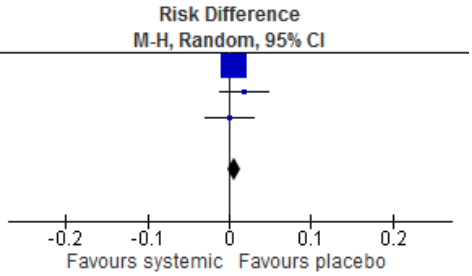


SYSTEMIC vs. PLACEBO – Dermatologic

Integument

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

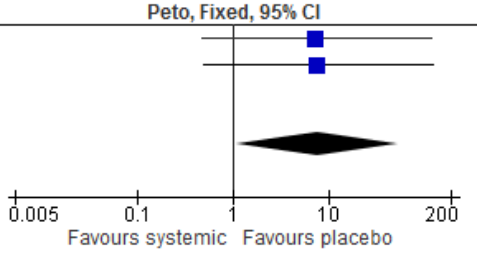
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)



Integument – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjornson 2004	2	359	0	361	50.1%	7.45 [0.47, 119.36]
Csonka 2003	2	113	0	117	49.9%	7.72 [0.48, 124.29]
Klassen 1998	0	64	0	65		Not estimable
Total (95% CI)		**536**		**543**	**100.0%**	**7.59 [1.07, 54.01]**
Total events	4		0			

Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)



Integument (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.71.1 Single dose						
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			

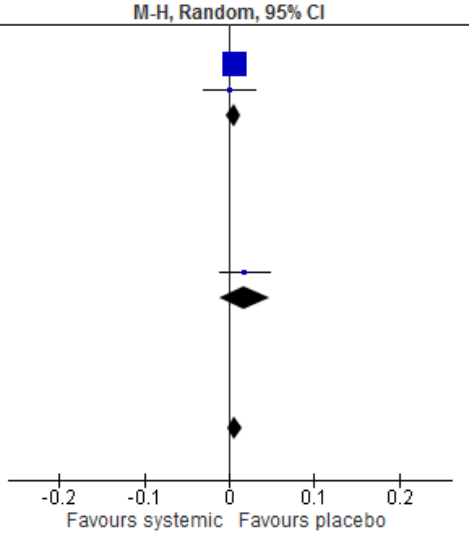
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)

1.71.2 Multi-dose						
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 applicable
Test for overall effect: Z = 1.18 (P = 0.24)

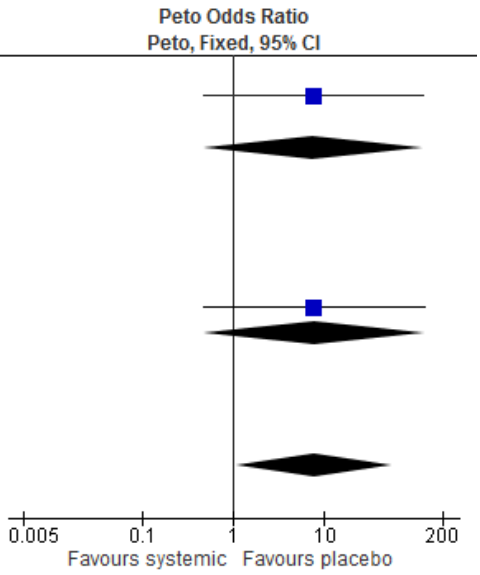
Total (95% CI)		**536**		**543**	**100.0%**	**0.01 [-0.00, 0.01]**
Total events	4		0			

Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%



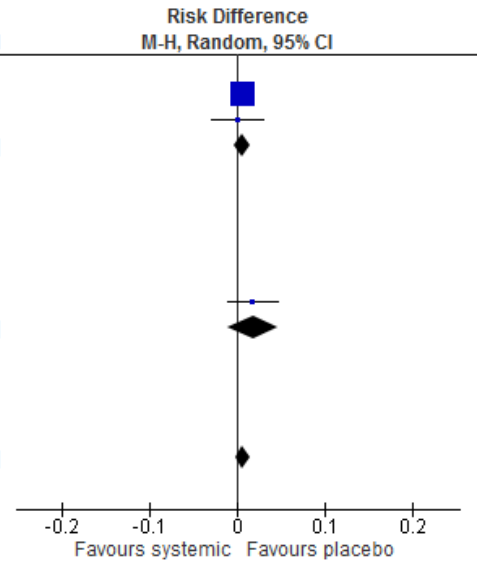
Integument (by dose) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
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 applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**536**		**543**	**100.0%**	**7.59 [1.07, 54.01]**
Total events	4		0			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						



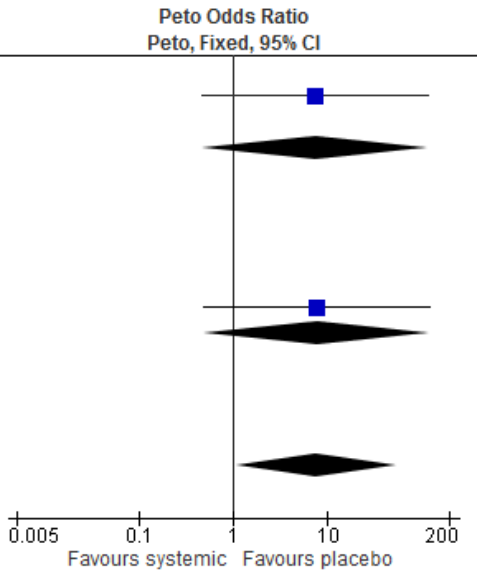
Integument (by condition)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%						
Test for overall effect: Z = 1.11 (P = 0.27)						
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 applicable						
Test for overall effect: Z = 1.18 (P = 0.24)						
Total (95% CI)		**536**		**543**	**100.0%**	**0.01 [-0.00, 0.01]**
Total events	4		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.41 (P = 0.16)						
Test for subgroup differences: Chi² = 0.65, df = 1 (P = 0.42), I² = 0%						



Integument (by condition) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.74.1 Croup						
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 applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
1.74.2 Wheeze						
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 applicable						
Test for overall effect: Z = 1.44 (P = 0.15)						
Total (95% CI)		**536**		**543**	**100.0%**	**7.59 [1.07, 54.01]**
Total events	4		0			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.02 (P = 0.04)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%						

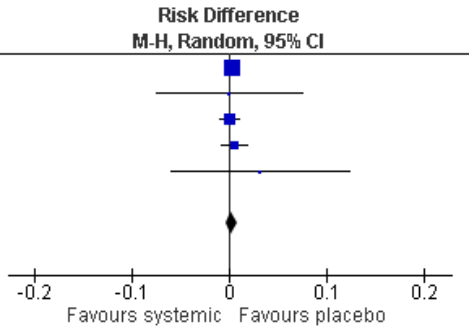


SYSTEMIC vs. PLACEBO – Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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			

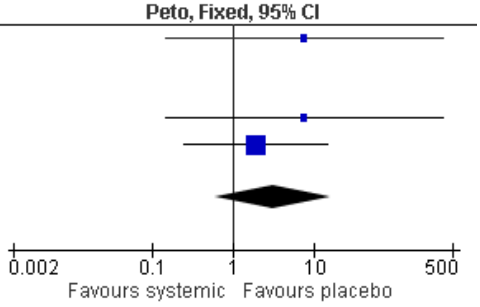
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 4 (P = 0.90); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)



Fluid & electrolyte abnormalities – Peto

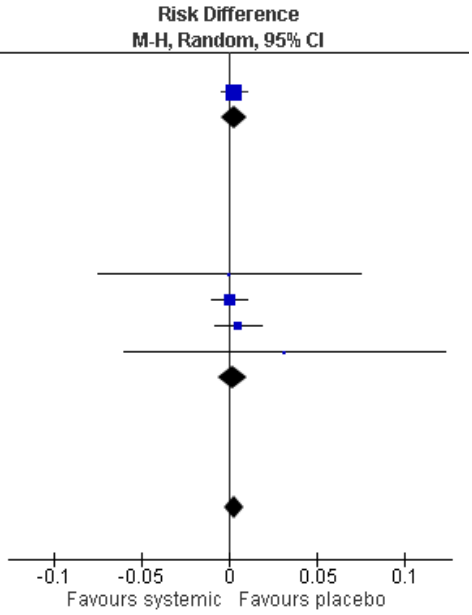
Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]
Eden 1967	0	25	0	25		Not estimable
Plint 2009	0	200	0	199		Not estimable
Plint 2009	1	200	0	201	17.6%	7.43 [0.15, 374.26]
Tagarro 2014	3	48	1	32	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: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.34 (P = 0.18)



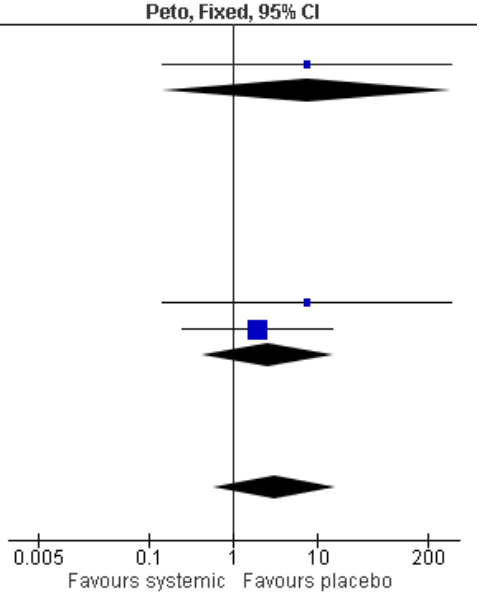
Fluid & electrolyte abnormalities (by dose)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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 applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
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: Tau² = 0.00; Chi² = 1.25, df = 3 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Total (95% CI)		**832**		**818**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	5		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 4 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



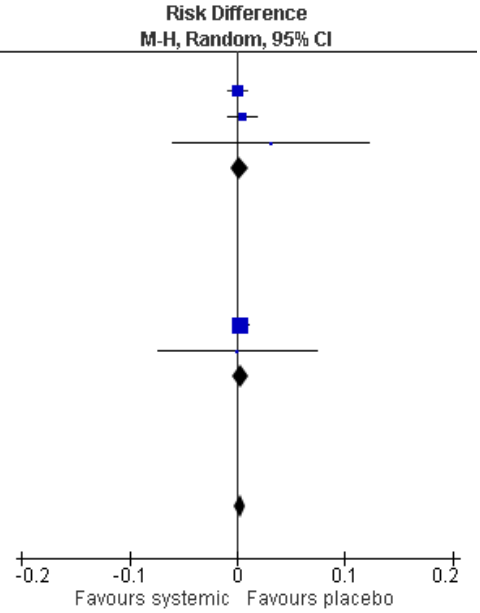
Fluid & electrolyte abnormalities (by dose) – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.66.1 Single dose						
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]
Subtotal (95% CI)		**359**		**361**	**17.6%**	**7.43 [0.15, 374.47]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
1.66.2 Multi-dose						
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]
Subtotal (95% CI)		**473**		**457**	**82.4%**	**2.56 [0.42, 15.61]**
Total events	4		1			
Heterogeneity: $Chi^2 = 0.36$, df = 1 (P = 0.55); $I^2 = 0\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: $Chi^2 = 0.23$, df = 1 (P = 0.63), $I^2 = 0\%$						



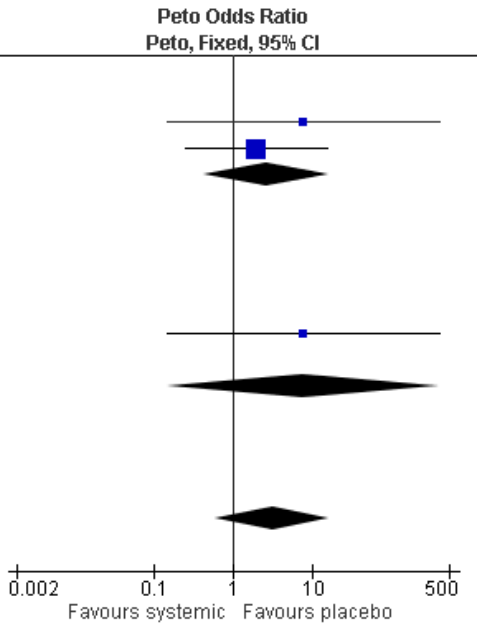
Fluid & electrolyte abnormalities (by condition)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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: $Tau^2 = 0.00$; $Chi^2 = 1.33$, df = 2 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 0.47 (P = 0.64)						
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: $Tau^2 = 0.00$; $Chi^2 = 0.01$, df = 1 (P = 0.93); $I^2 = 0\%$						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**832**		**818**	**100.0%**	**0.00 [-0.00, 0.01]**
Total events	5		1			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.07$, df = 4 (P = 0.90); $I^2 = 0\%$						
Test for overall effect: Z = 0.84 (P = 0.40)						
Test for subgroup differences: $Chi^2 = 0.02$, df = 1 (P = 0.88), $I^2 = 0\%$						



Fluid & electrolyte abnormalities (by condition) - Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.68.1 Bronchiolitis						
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]
Subtotal (95% CI)		**448**		**432**	**82.4%**	**2.56 [0.42, 15.61]**
Total events	4		1			
Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.68.2 Croup						
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]
Eden 1967	0	25	0	25		Not estimable
Subtotal (95% CI)		**384**		**386**	**17.6%**	**7.43 [0.15, 374.47]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**832**		**818**	**100.0%**	**3.08 [0.60, 15.94]**
Total events	5		1			
Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
Test for subgroup differences: Chi² = 0.23, df = 1 (P = 0.63), I² = 0%						

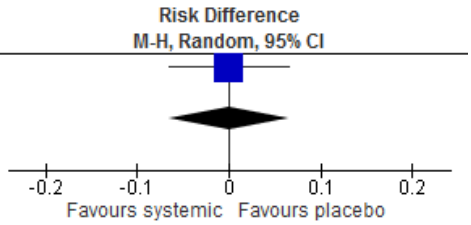


SYSTEMIC vs. PLACEBO – Cardiovascular

Arrhythmia

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

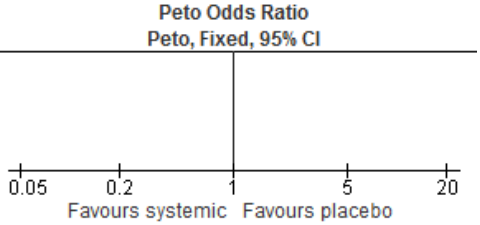
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Arrhythmia - Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Daugbjerg 1993	0	31	0	27		Not estimable
Total (95% CI)		**31**		**27**		**Not estimable**
Total events	0		0			

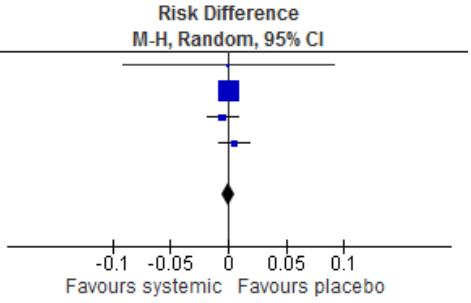
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Hypertension

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
Buckingham 2002	0	22	0	19	0.4%	0.00 [-0.09, 0.09]
Corneli 2007	0	305	0	295	68.9%	0.00 [-0.01, 0.01]
Plint 2009	0	200	1	199	15.3%	-0.01 [-0.02, 0.01]
Plint 2009	1	200	0	201	15.5%	0.01 [-0.01, 0.02]
Total (95% CI)		**727**		**714**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	1		1			

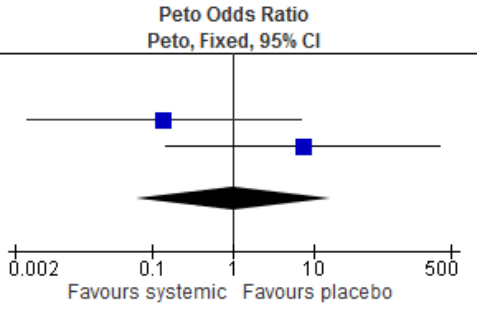
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



Hypertension – Peto

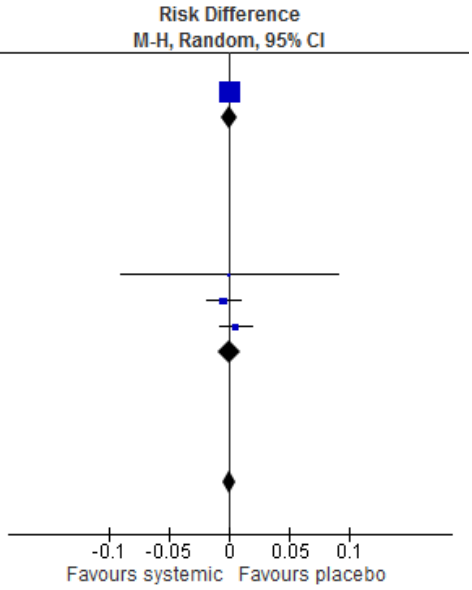
Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Buckingham 2002	0	22	0	19		Not estimable
Corneli 2007	0	305	0	295		Not estimable
Plint 2009	0	200	1	199	50.0%	0.13 [0.00, 6.79]
Plint 2009	1	200	0	201	50.0%	7.43 [0.15, 374.26]
Total (95% CI)		**727**		**714**	**100.0%**	**1.00 [0.06, 15.99]**
Total events	1		1			

Heterogeneity: Chi² = 2.01, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 0.00 (P = 1.00)



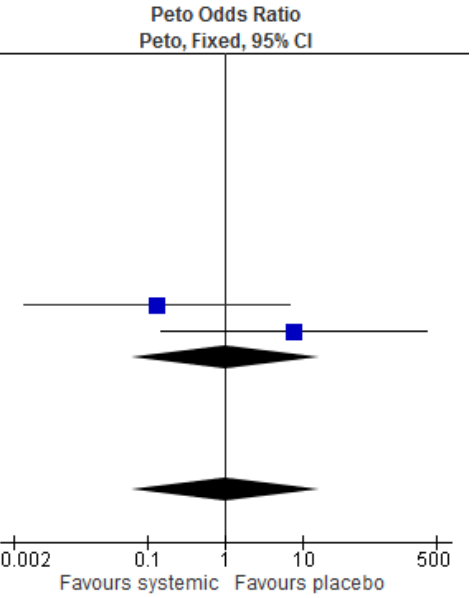
Hypertension (by dose)

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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 applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.79.2 Multi-Dose						
Buckingham 2002	0	22	0	19	0.4%	0.00 [-0.09, 0.09]
Plint 2009	0	200	1	199	15.3%	-0.01 [-0.02, 0.01]
Plint 2009	1	200	0	201	15.5%	0.01 [-0.01, 0.02]
Subtotal (95% CI)		**422**		**419**	**31.1%**	**0.00 [-0.01, 0.01]**
Total events	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 2 (P = 0.60); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**727**		**714**	**100.0%**	**0.00 [-0.01, 0.01]**
Total events	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 1.02, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



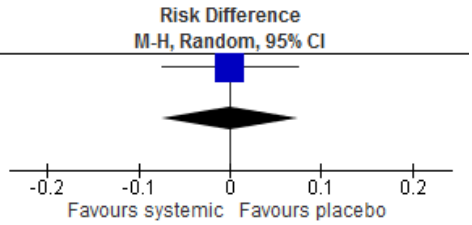
Hypertension (by dose) - Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.81.1 Single Dose						
Corneli 2007	0	305	0	295		Not estimable
Subtotal (95% CI)		**305**		**295**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
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: Chi² = 2.01, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**727**		**714**	**100.0%**	**1.00 [0.06, 15.99]**
Total events	1		1			
Heterogeneity: Chi² = 2.01, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						



Congestive heart failure

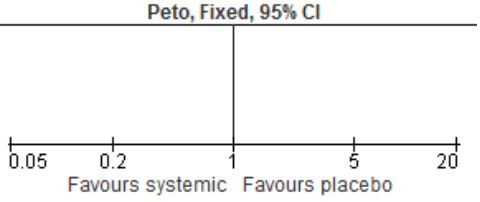
Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
Eden 1967	0	25	0	25	100.0%	0.00 [-0.07, 0.07]
Total (95% CI)		**25**		**25**	**100.0%**	**0.00 [-0.07, 0.07]**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						



Congestive heart failure - Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Eden 1967	0	25	0	25		Not estimable
Total (95% CI)		**25**		**25**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

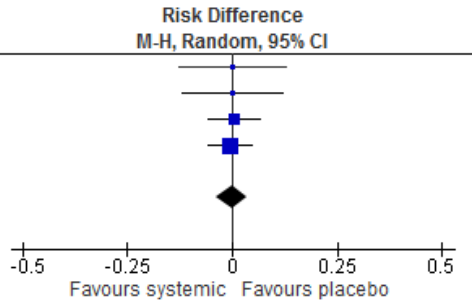


SYSTEMIC vs. PLACEBO – General

General complaints

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference 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]
Total (95% CI)		**446**		**423**	**100.0%**	**-0.00 [-0.04, 0.04]**
Total events	38		38			

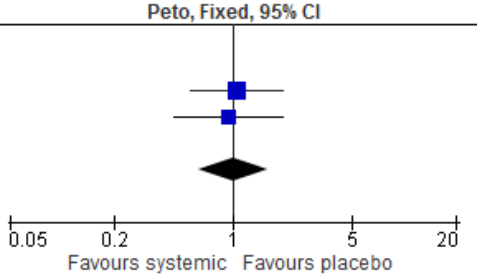
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



General complaints – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio 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: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)



General complaints (by dose)

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
1.87.1 Single Dose						
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]
Subtotal (95% CI)		**46**		**23**	**17.5%**	**0.00 [-0.09, 0.09]**
Total events	0		0			

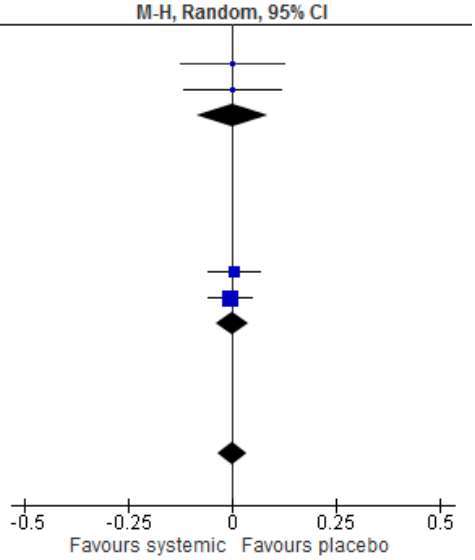
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)

1.87.2 Multi-Dose						
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]
Subtotal (95% CI)		**400**		**400**	**82.5%**	**-0.00 [-0.04, 0.04]**
Total events	38		38			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)

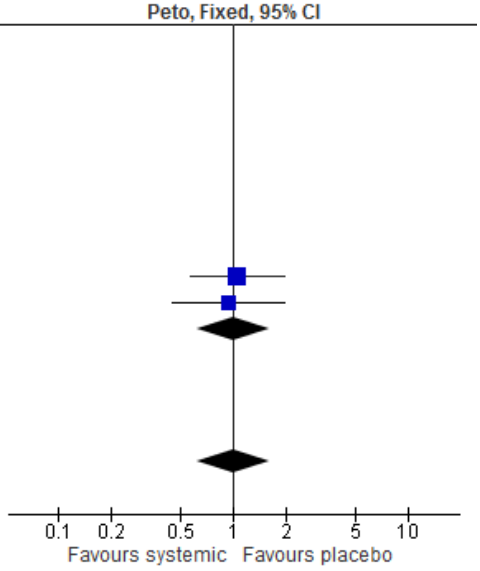
Total (95% CI)		**446**		**423**	**100.0%**	**-0.00 [-0.04, 0.04]**
Total events	38		38			

Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 3 (P = 1.00); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%



General complaints (by dose) – Peto

Study or Subgroup	Systemic Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.89.1 Single Dose						
Kuyucu 2004	0	23	0	11		Not estimable
Kuyucu 2004	0	23	0	12		Not estimable
Subtotal (95% CI)		**46**		**23**		**Not estimable**
Total events	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.89.2 Multi-Dose						
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]
Subtotal (95% CI)		**400**		**400**	**100.0%**	**1.00 [0.62, 1.60]**
Total events	38		38			
Heterogeneity: $Chi^2 = 0.05$, df = 1 (P = 0.82); $I^2 = 0\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Not applicable						

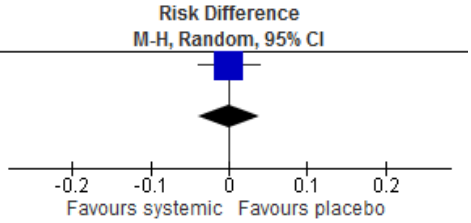


SYSTEMIC vs. PLACEBO – Immune System

Immunosuppression

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

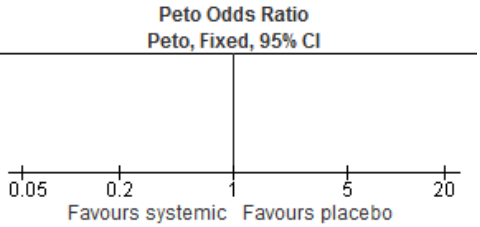
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Immunosuppression – Peto

Study or Subgroup	Systemic Events	Systemic Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Connolly 1969	0	47	0	48		Not estimable
Total (95% CI)		**47**		**48**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

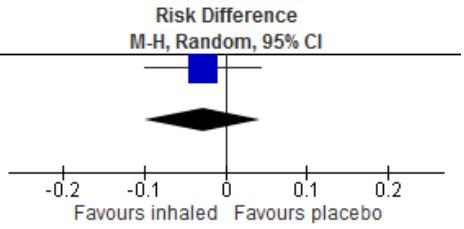


INHALED vs. PLACEBO – Infection & Respiratory

Severe infections

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

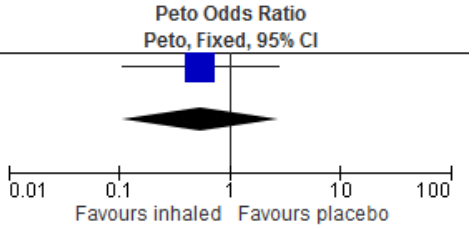
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



Severe infections – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

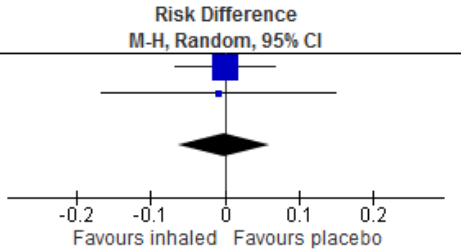
Heterogeneity: Not applicable
Test for overall effect: Z = 0.74 (P = 0.46)



Systemic infections

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

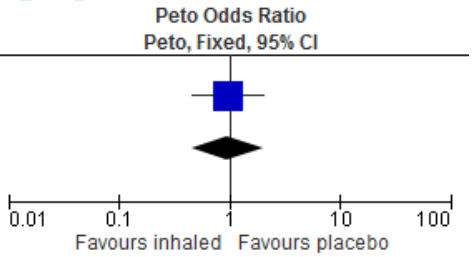
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



Systemic infections – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio 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			

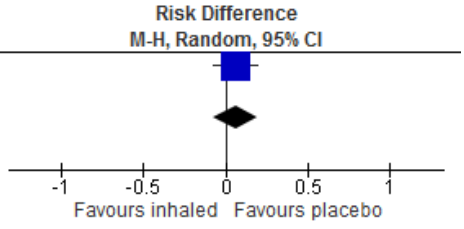
Heterogeneity: Not applicable
Test for overall effect: Z = 0.10 (P = 0.92)



Lung/trachea

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

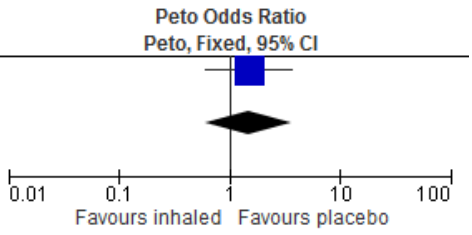
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)



Lung/trachea – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

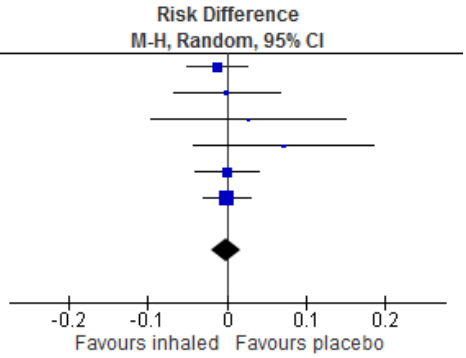
Heterogeneity: Not applicable
Test for overall effect: Z = 0.89 (P = 0.37)



URT

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference 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			

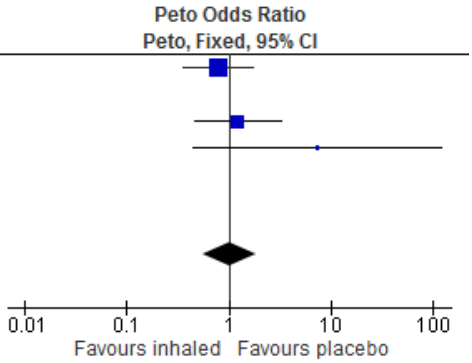
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 5 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



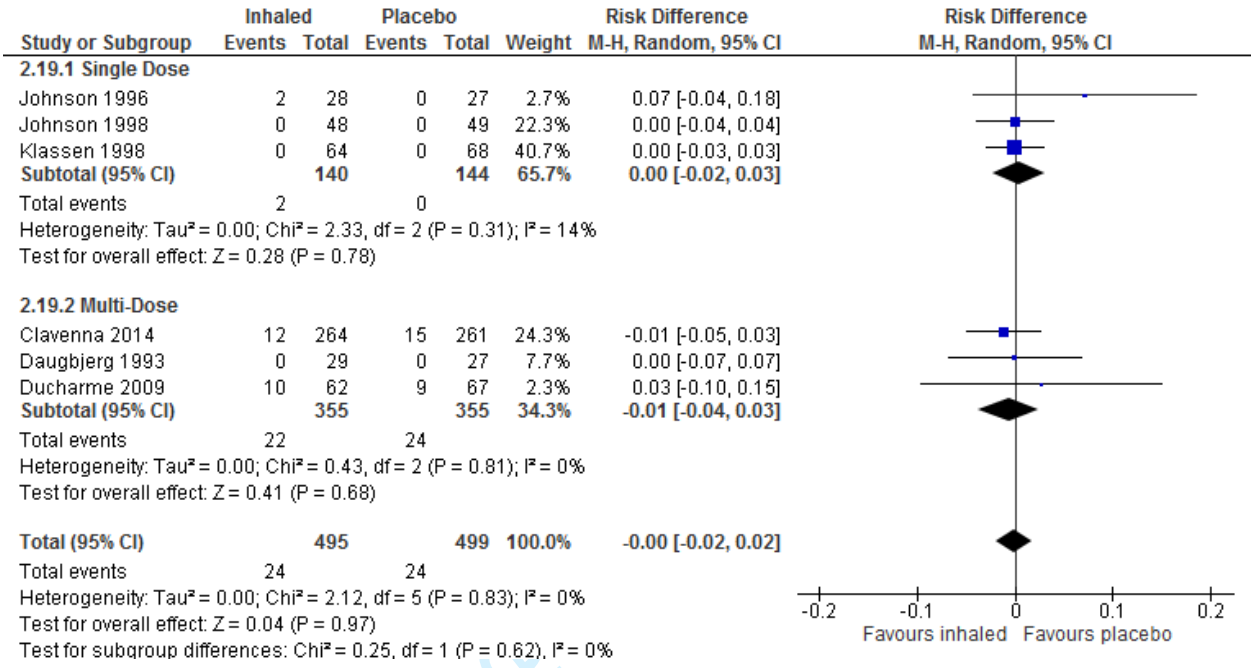
URT – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

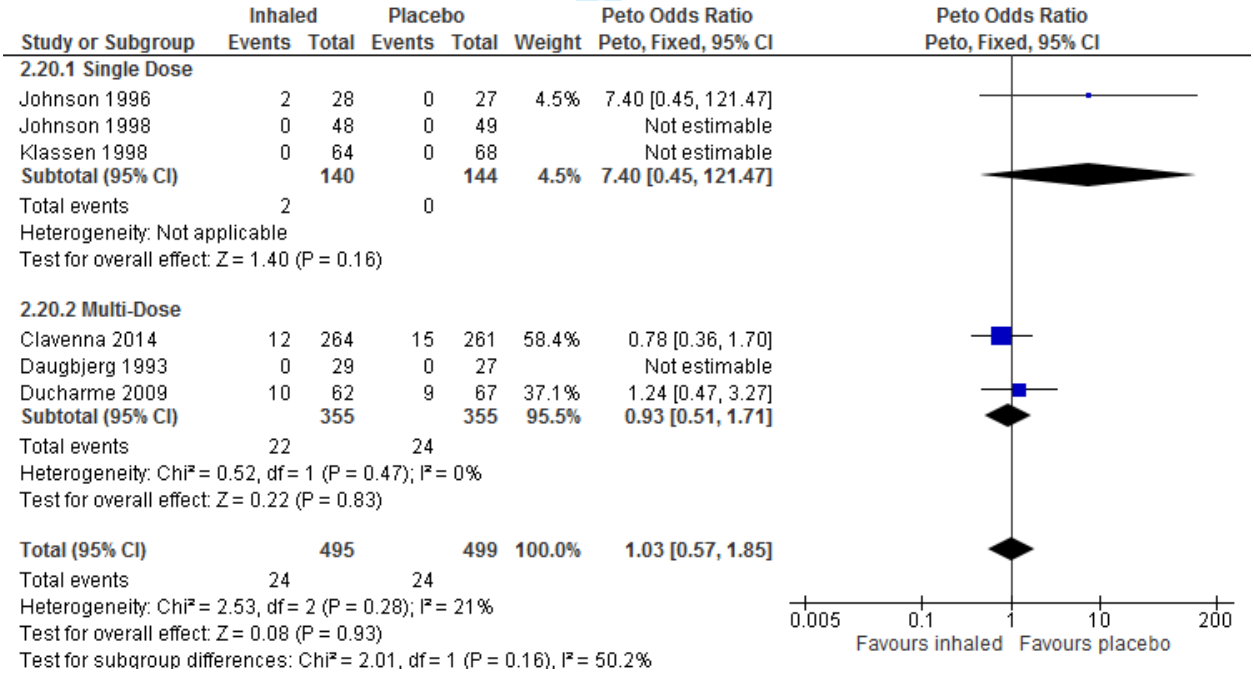
Heterogeneity: Chi² = 2.53, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 0.08 (P = 0.93)



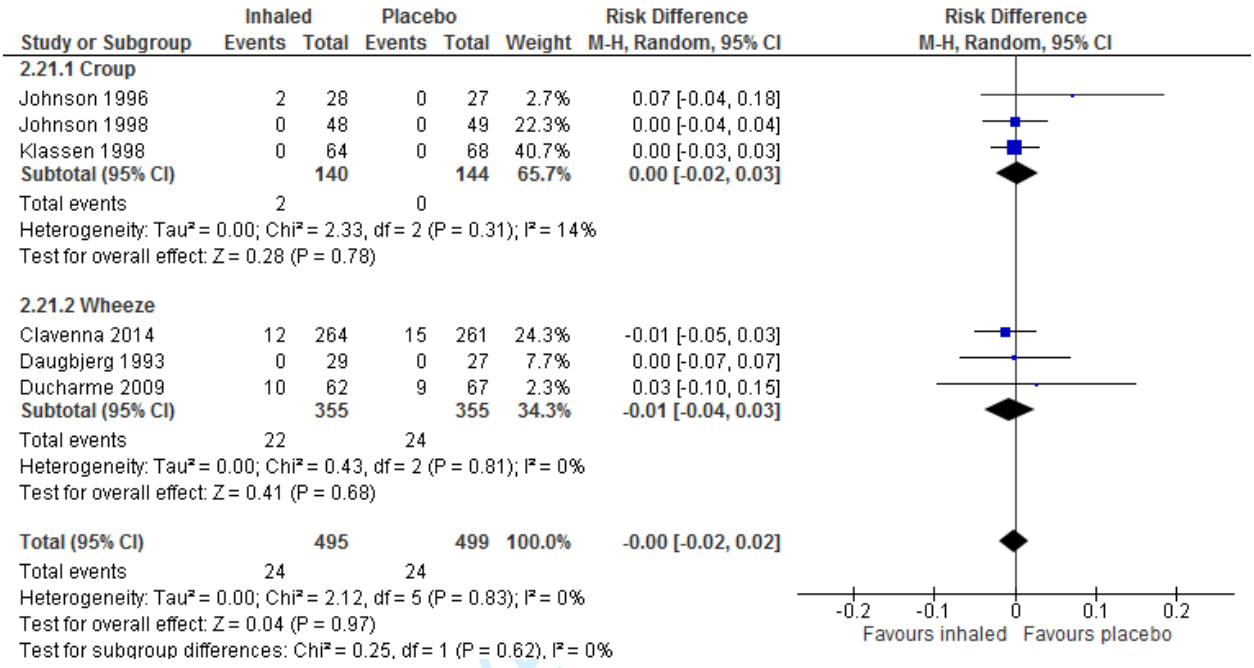
URT (by dose)



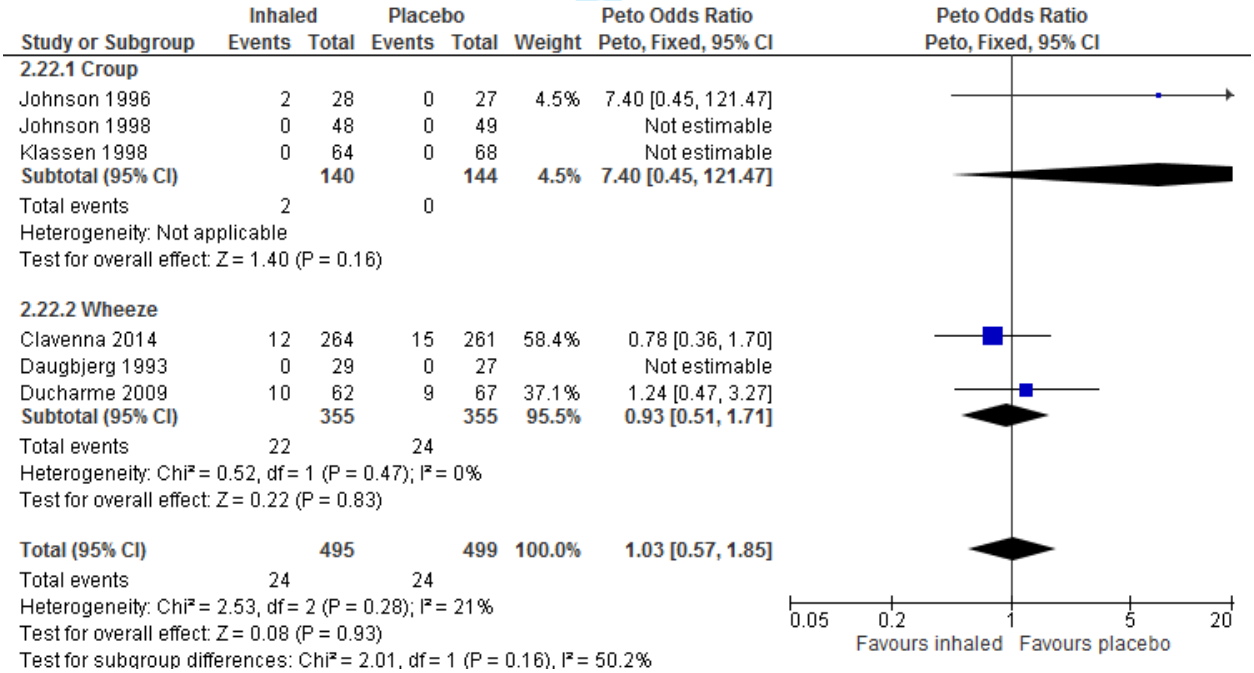
URT (by dose) – Peto



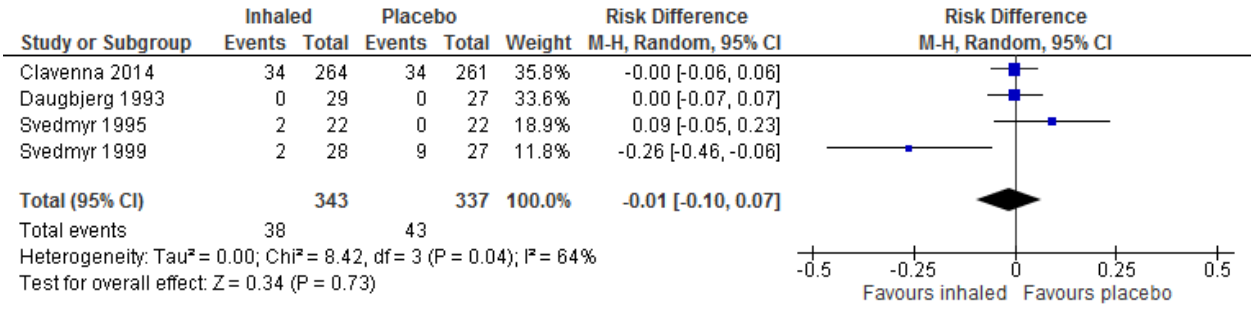
URT (by condition)



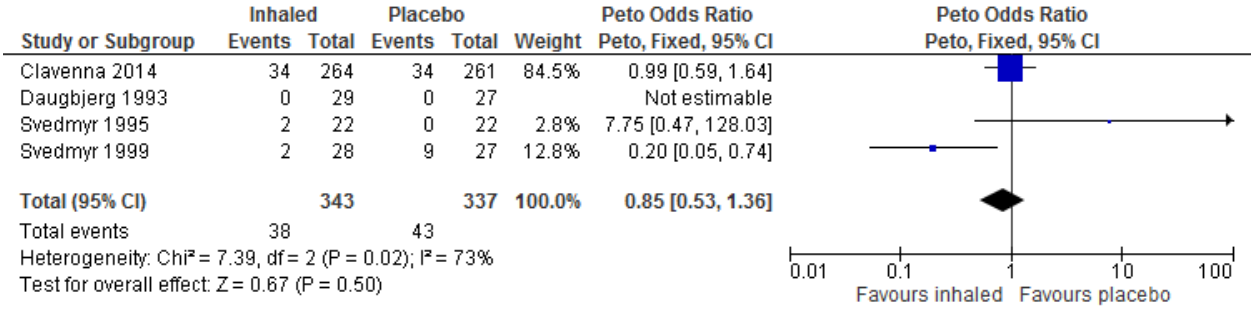
URT (by condition) – Peto



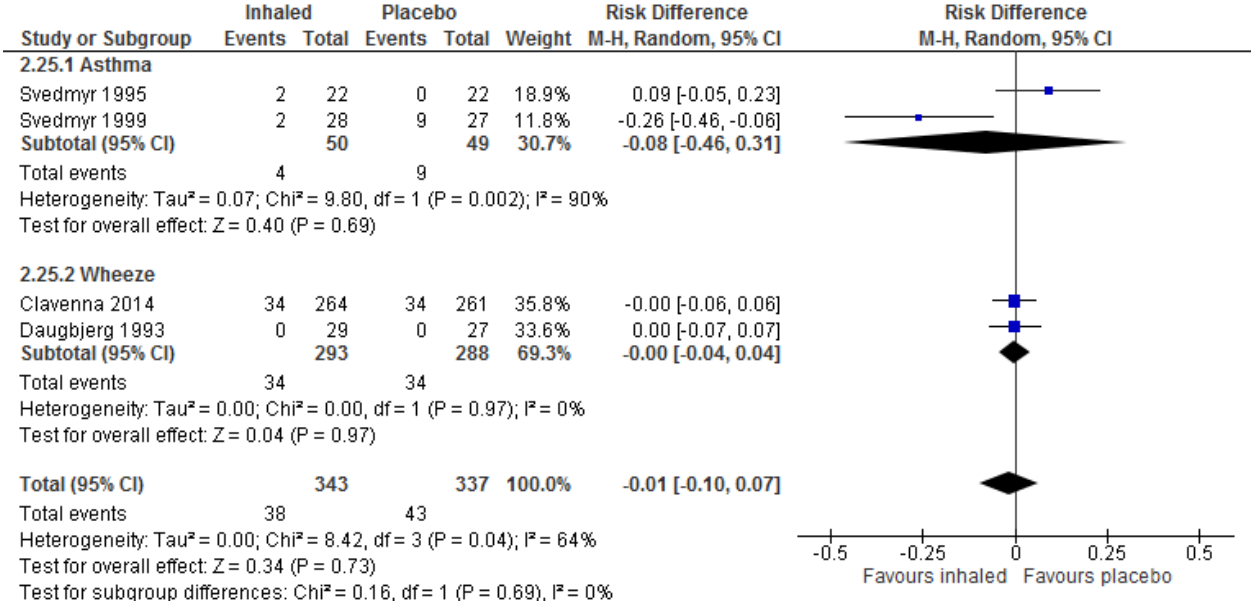
Voice complaints



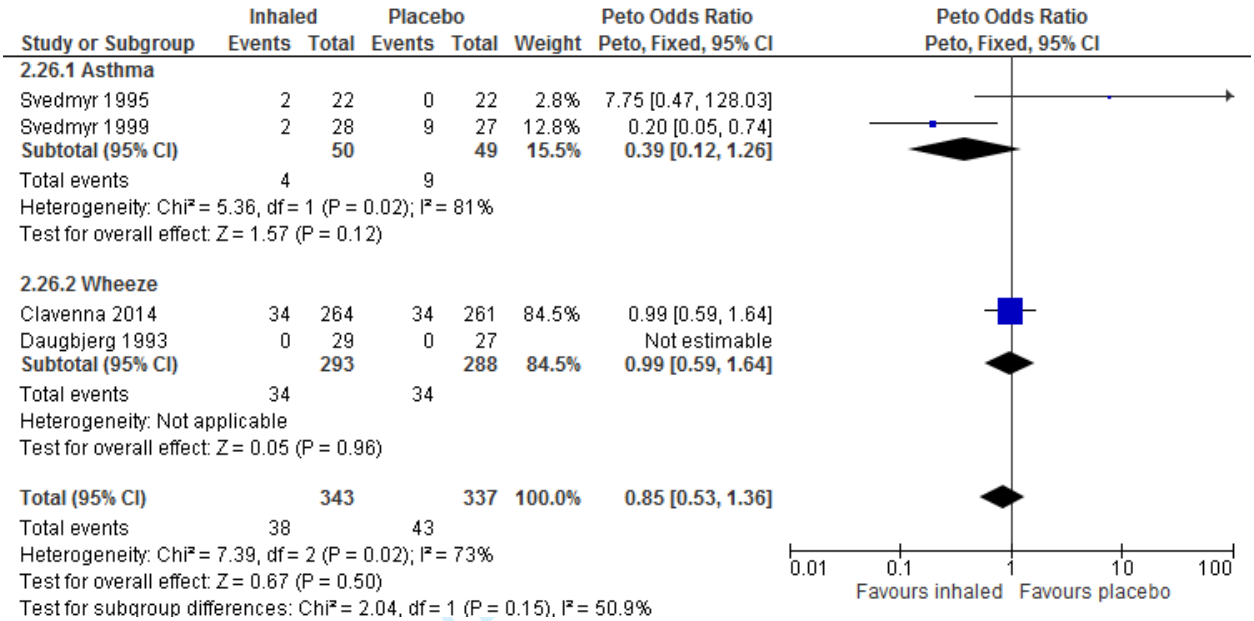
Voice complaints – Peto



Voice complaints (by condition)



Voice complaints (by condition) - Peto

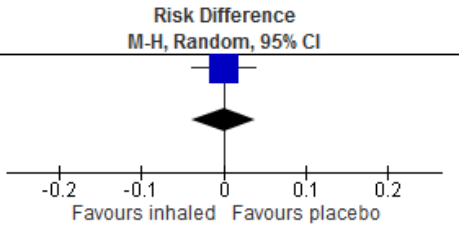


INHALED vs. PLACEBO – GI

GI bleeding

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference 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			

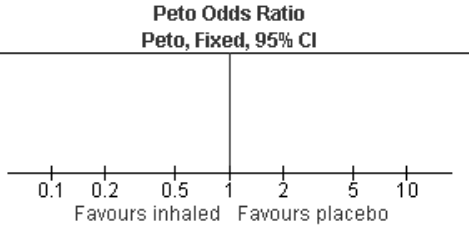
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



GI bleeding – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Johnson 1998	0	48	0	49		Not estimable
Total (95% CI)		**48**		**49**		**Not estimable**
Total events	0		0			

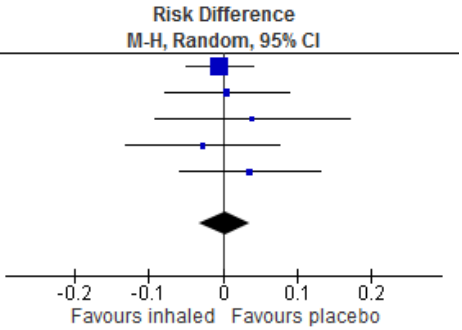
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Vomiting

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference 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			

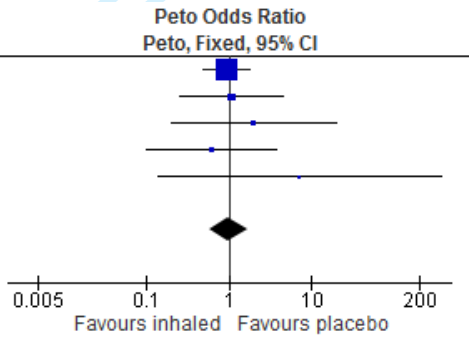
Heterogeneity: Tau² = 0.00; Chi² = 1.23, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.14 (P = 0.89)



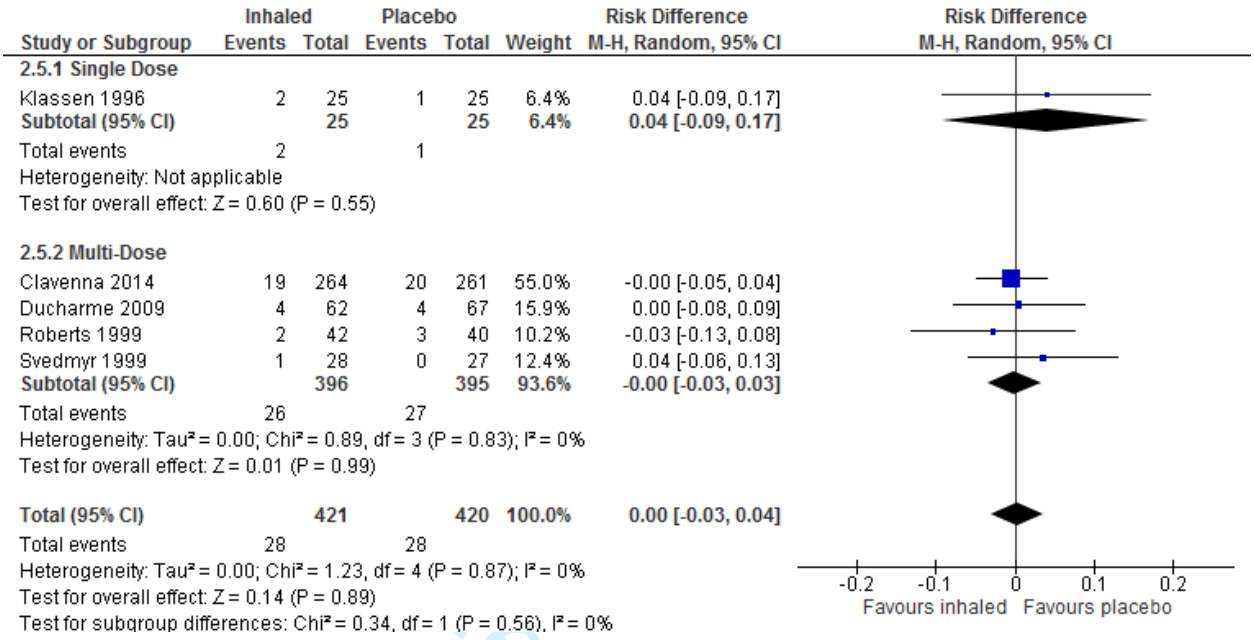
Vomiting – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio 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			

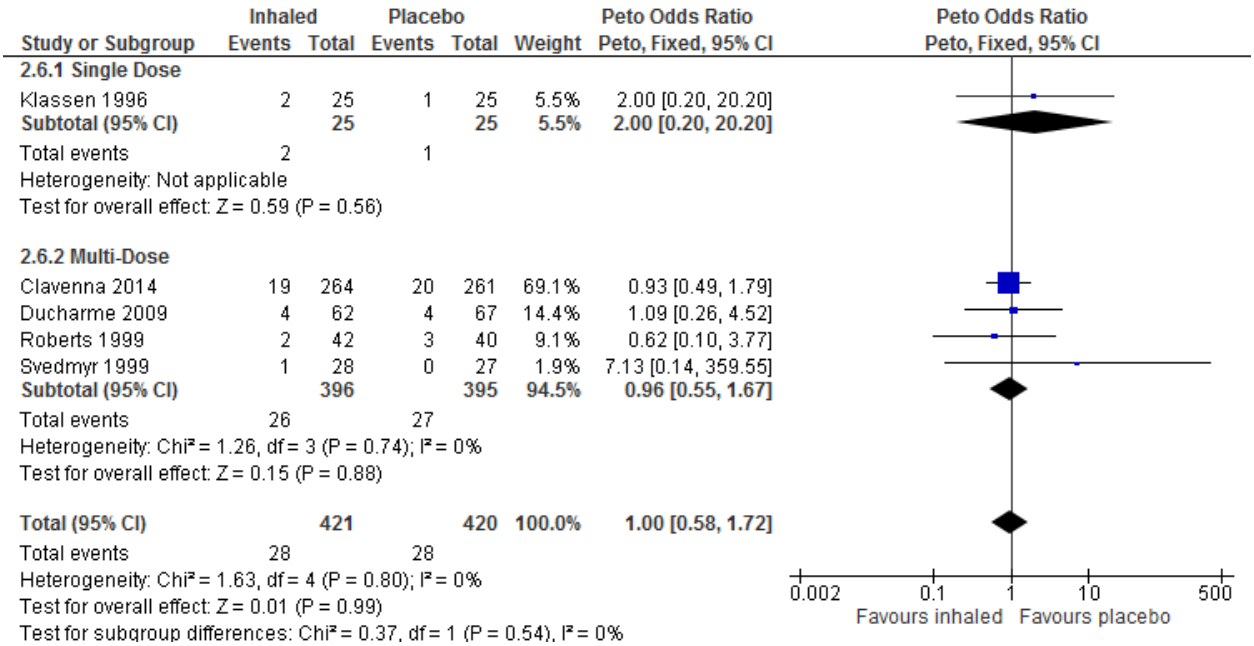
Heterogeneity: Chi² = 1.63, df = 4 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.01 (P = 0.99)



Vomiting (by dose)

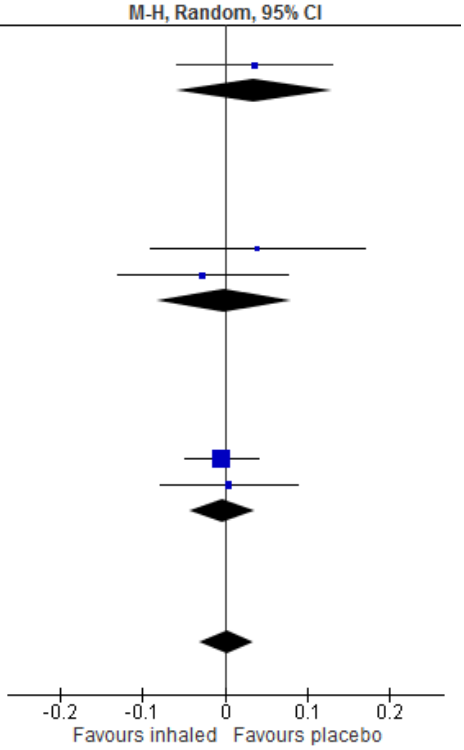


Vomiting (by dose) – Peto

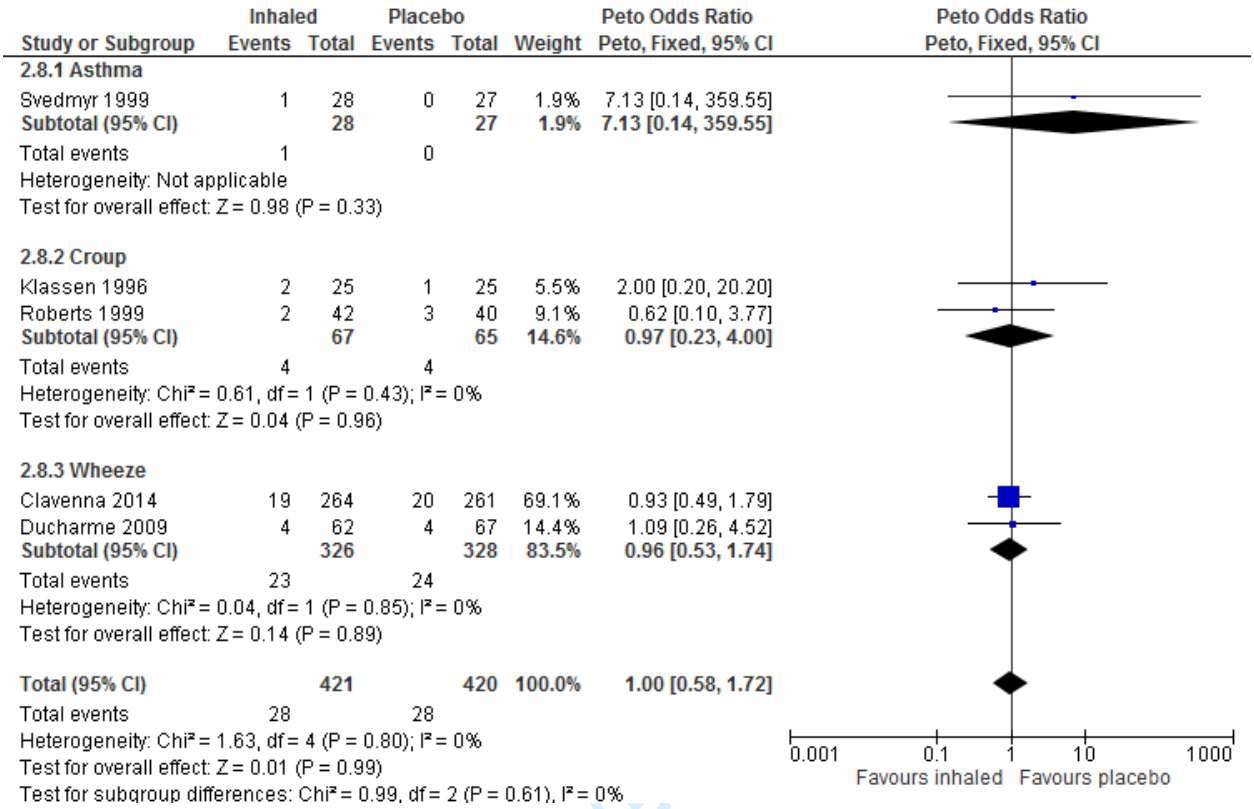


Vomiting (by condition)

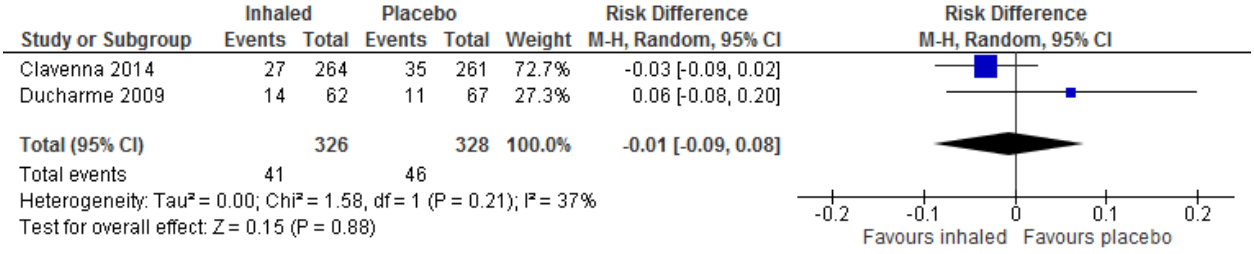
Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
2.7.1 Asthma						
Svedmyr 1999	1	28	0	27	12.4%	0.04 [-0.06, 0.13]
Subtotal (95% CI)		**28**		**27**	**12.4%**	**0.04 [-0.06, 0.13]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.7.2 Croup						
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]
Subtotal (95% CI)		**67**		**65**	**16.7%**	**-0.00 [-0.08, 0.08]**
Total events	4		4			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.62$, df = 1 (P = 0.43); $I^2 = 0\%$						
Test for overall effect: Z = 0.03 (P = 0.97)						
2.7.3 Wheeze						
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]
Subtotal (95% CI)		**326**		**328**	**70.9%**	**-0.00 [-0.04, 0.04]**
Total events	23		24			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**421**		**420**	**100.0%**	**0.00 [-0.03, 0.04]**
Total events	28		28			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.23$, df = 4 (P = 0.87); $I^2 = 0\%$						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: $Chi^2 = 0.55$, df = 2 (P = 0.76), $I^2 = 0\%$						



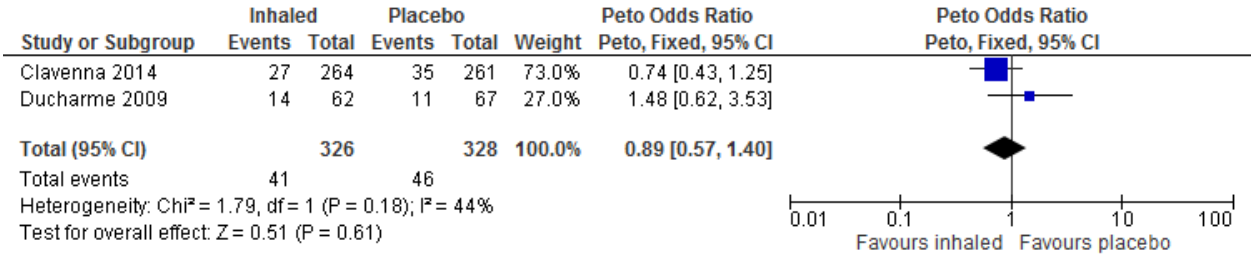
Vomiting (by condition) - Peto



Diarrhea

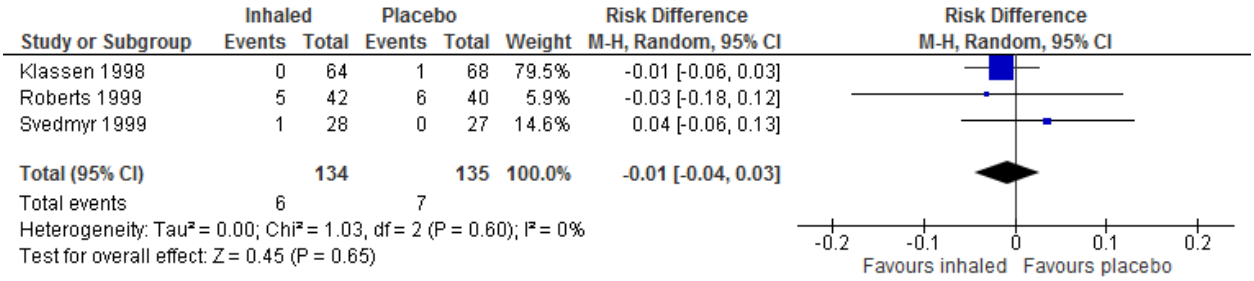


Diarrhea – Peto

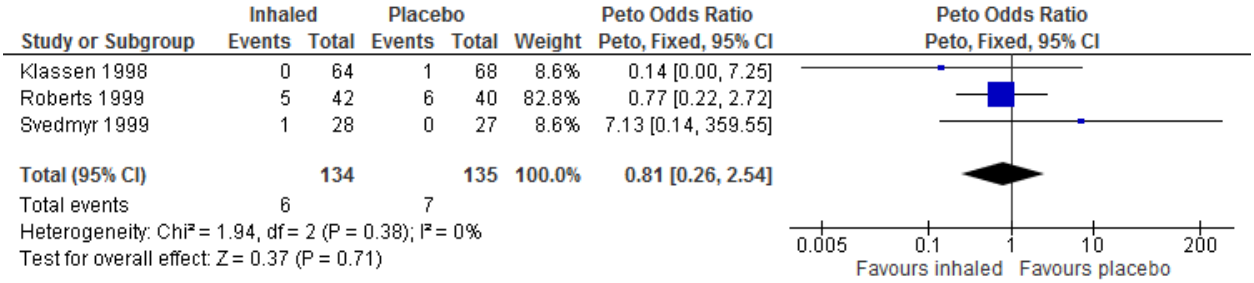


INHALED vs. PLACEBO – CNS & Behaviour

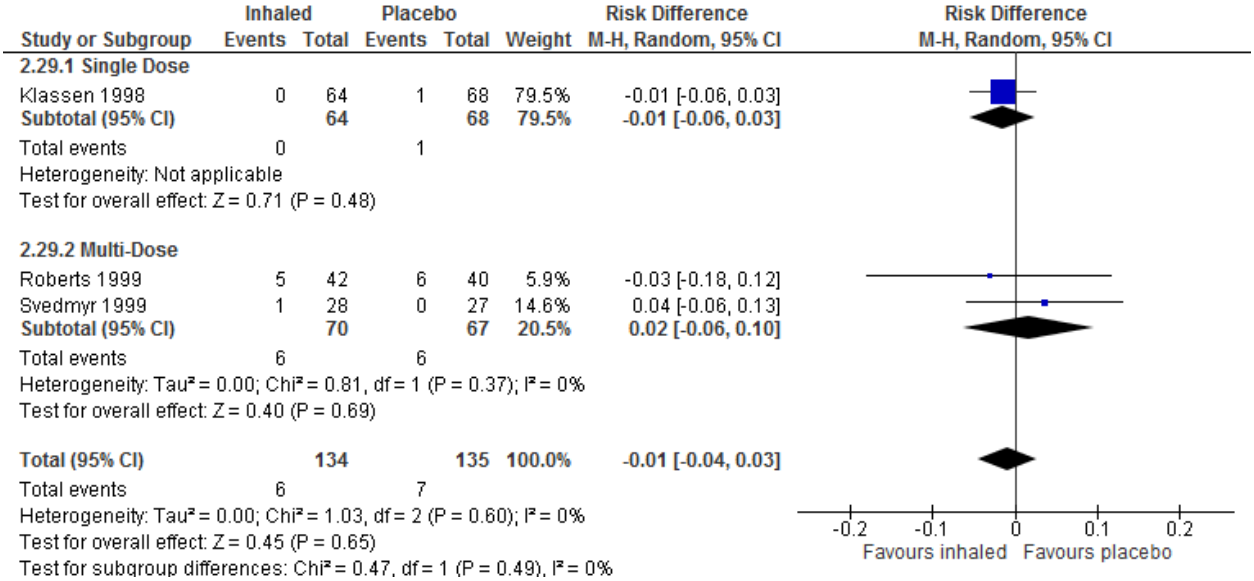
Behaviour change



Behaviour change – Peto

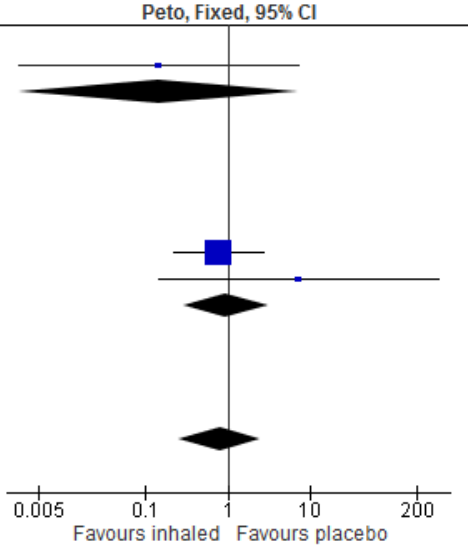


Behaviour change (by dose)



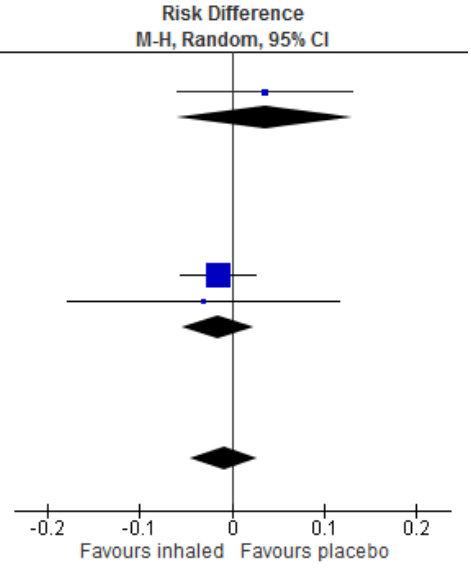
Behaviour change (by dose) – Peto

Study or Subgroup	Inhaled Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.30.1 Single Dose						
Klassen 1998	0	64	1	68	8.6%	0.14 [0.00, 7.25]
Subtotal (95% CI)		**64**		**68**	**8.6%**	**0.14 [0.00, 7.25]**
Total events	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
2.30.2 Multi-Dose						
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]
Subtotal (95% CI)		**70**		**67**	**91.4%**	**0.95 [0.28, 3.15]**
Total events	6		6			
Heterogeneity: $Chi^2 = 1.12$, df = 1 (P = 0.29); $I^2 = 11\%$						
Test for overall effect: Z = 0.09 (P = 0.93)						
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); $I^2 = 0\%$						
Test for overall effect: Z = 0.37 (P = 0.71)						
Test for subgroup differences: $Chi^2 = 0.81$, df = 1 (P = 0.37), $I^2 = 0\%$						

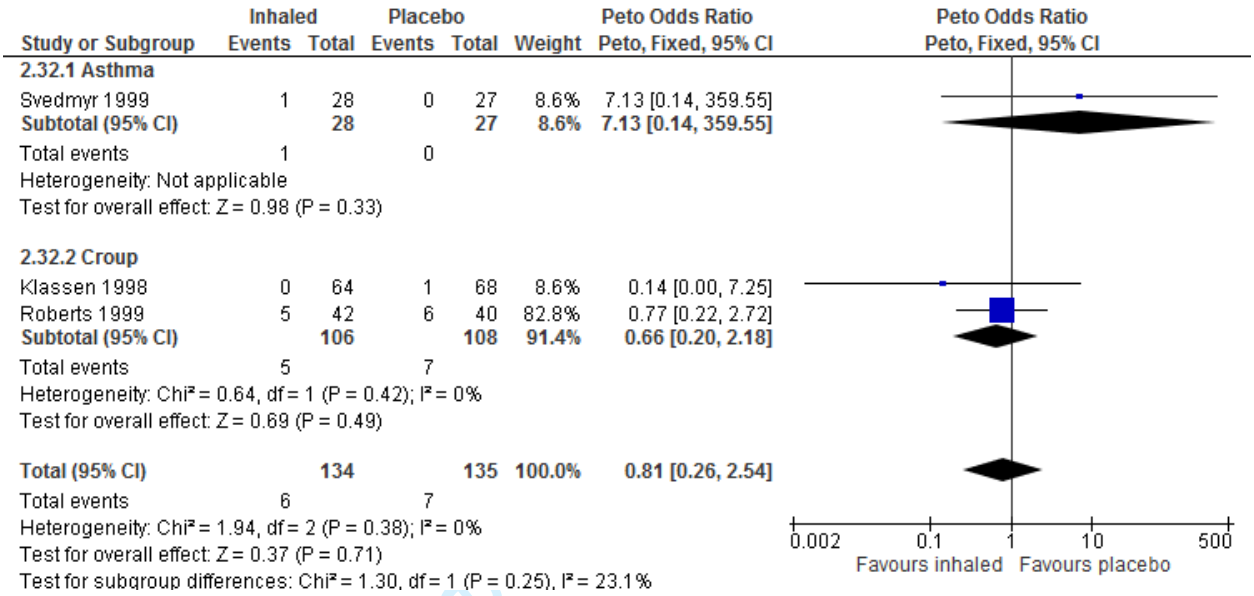


Behaviour change (by condition)

Study or Subgroup	Inhaled Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
2.31.1 Asthma						
Svedmyr 1999	1	28	0	27	14.6%	0.04 [-0.06, 0.13]
Subtotal (95% CI)		**28**		**27**	**14.6%**	**0.04 [-0.06, 0.13]**
Total events	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
2.31.2 Croup						
Klassen 1998	0	64	1	68	79.5%	-0.01 [-0.06, 0.03]
Roberts 1999	5	42	6	40	5.9%	-0.03 [-0.18, 0.12]
Subtotal (95% CI)		**106**		**108**	**85.4%**	**-0.02 [-0.05, 0.02]**
Total events	5		7			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.11$, df = 1 (P = 0.74); $I^2 = 0\%$						
Test for overall effect: Z = 0.80 (P = 0.43)						
Total (95% CI)		**134**		**135**	**100.0%**	**-0.01 [-0.04, 0.03]**
Total events	6		7			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.03$, df = 2 (P = 0.60); $I^2 = 0\%$						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: $Chi^2 = 0.98$, df = 1 (P = 0.32), $I^2 = 0\%$						



Behaviour change (by condition) – Peto

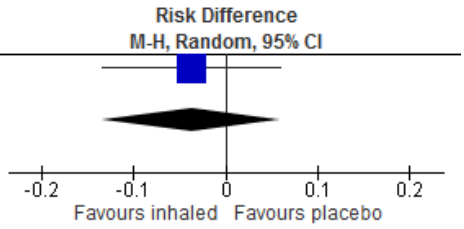


INHALED vs. PLACEBO – Dermatologic

Burn

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

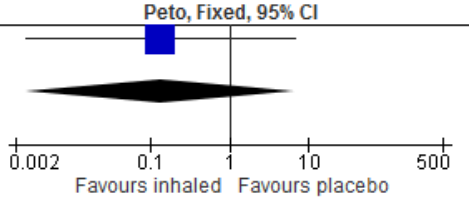
Heterogeneity: Not applicable
Test for overall effect: Z = 0.75 (P = 0.45)



Burn – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

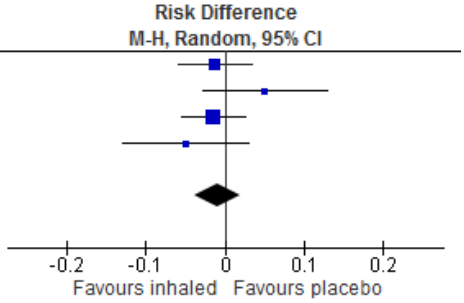
Heterogeneity: Not applicable
Test for overall effect: Z = 1.00 (P = 0.32)



Integument

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

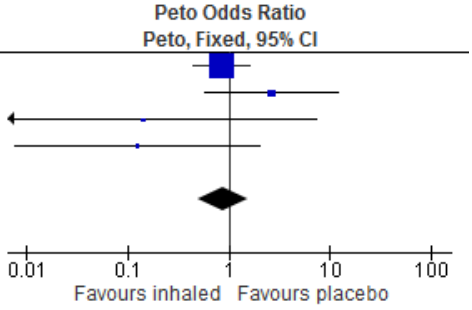
Heterogeneity: Tau² = 0.00; Chi² = 3.36, df = 3 (P = 0.34); I² = 11%
Test for overall effect: Z = 0.68 (P = 0.50)



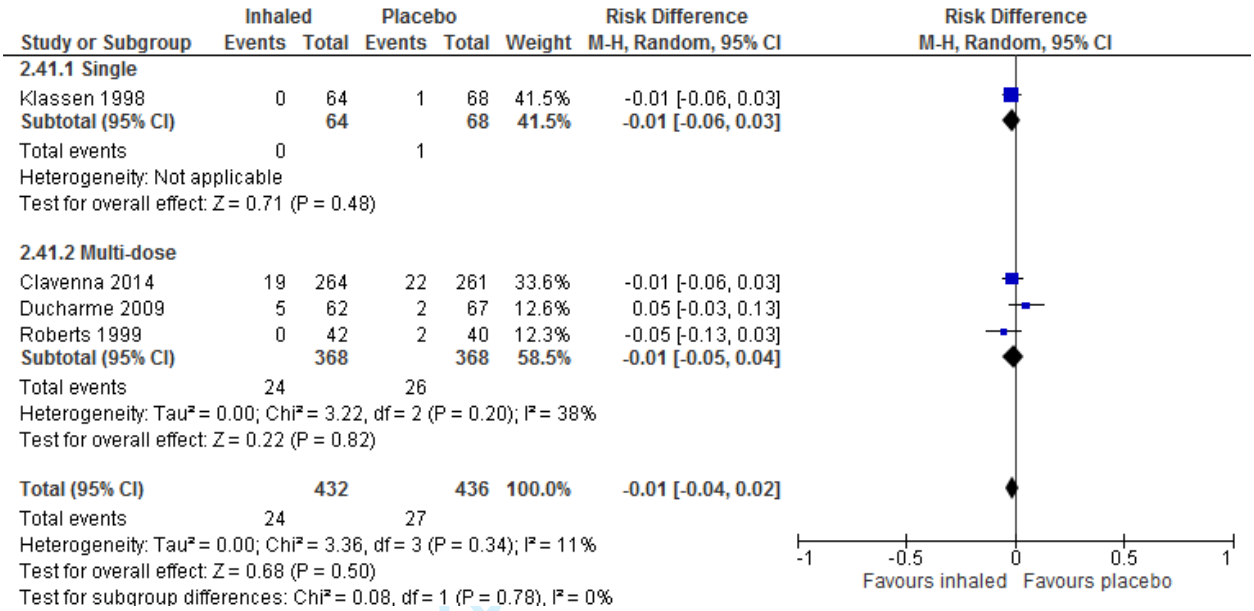
Integument – Peto

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

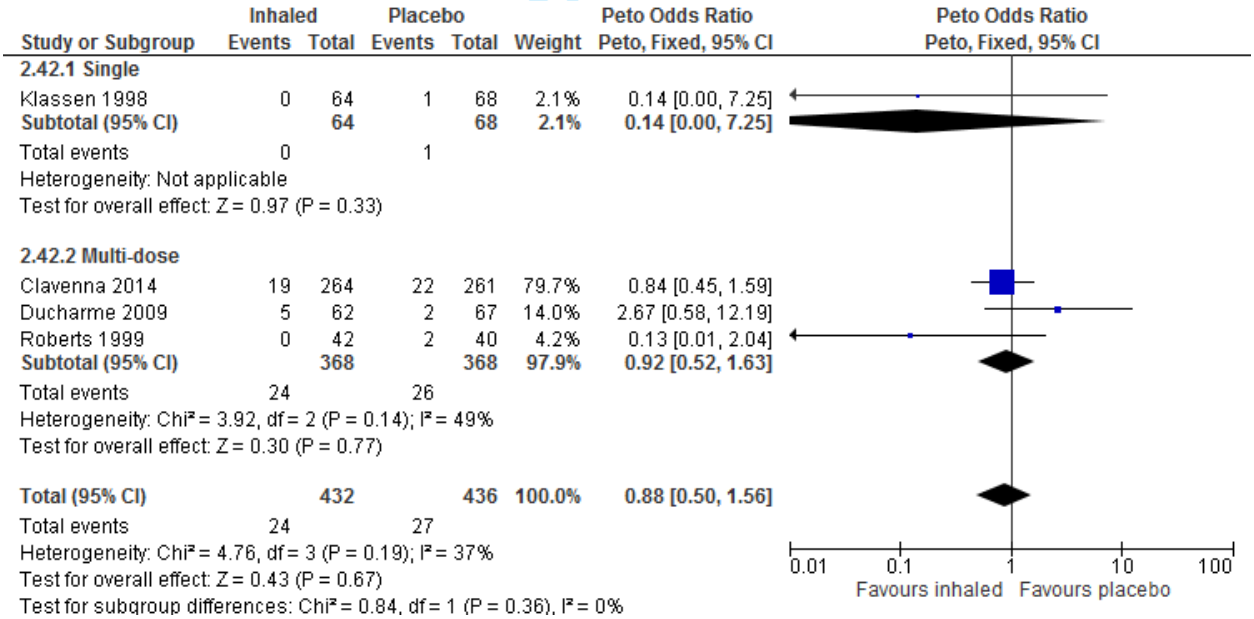
Heterogeneity: Chi² = 4.76, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 0.43 (P = 0.67)



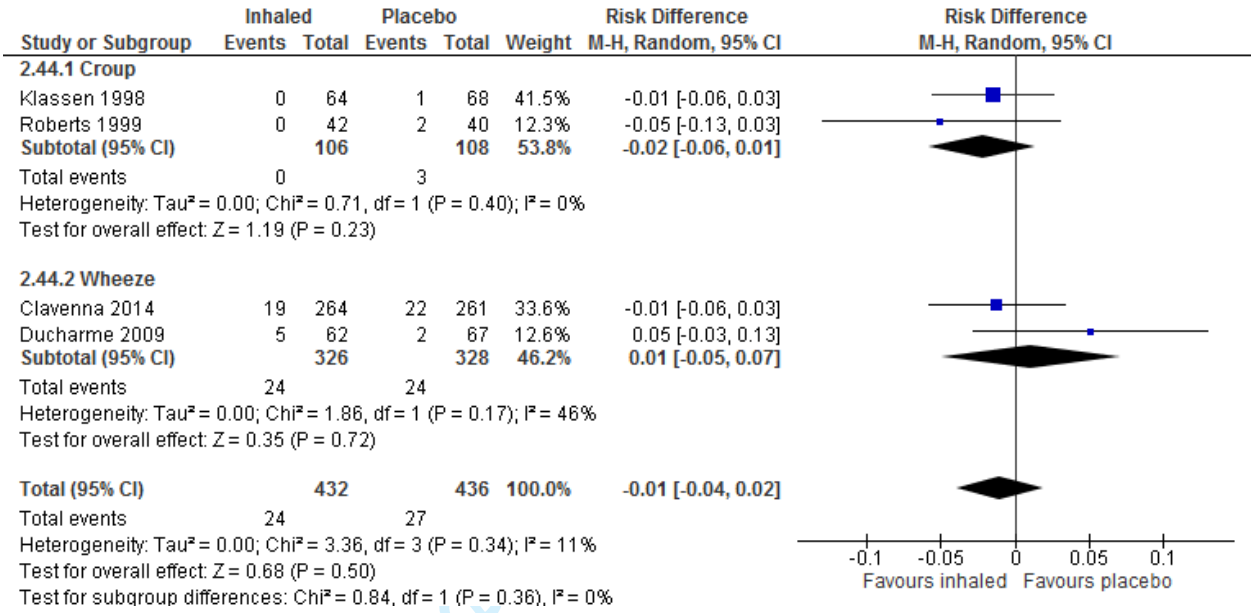
Integument (by dose)



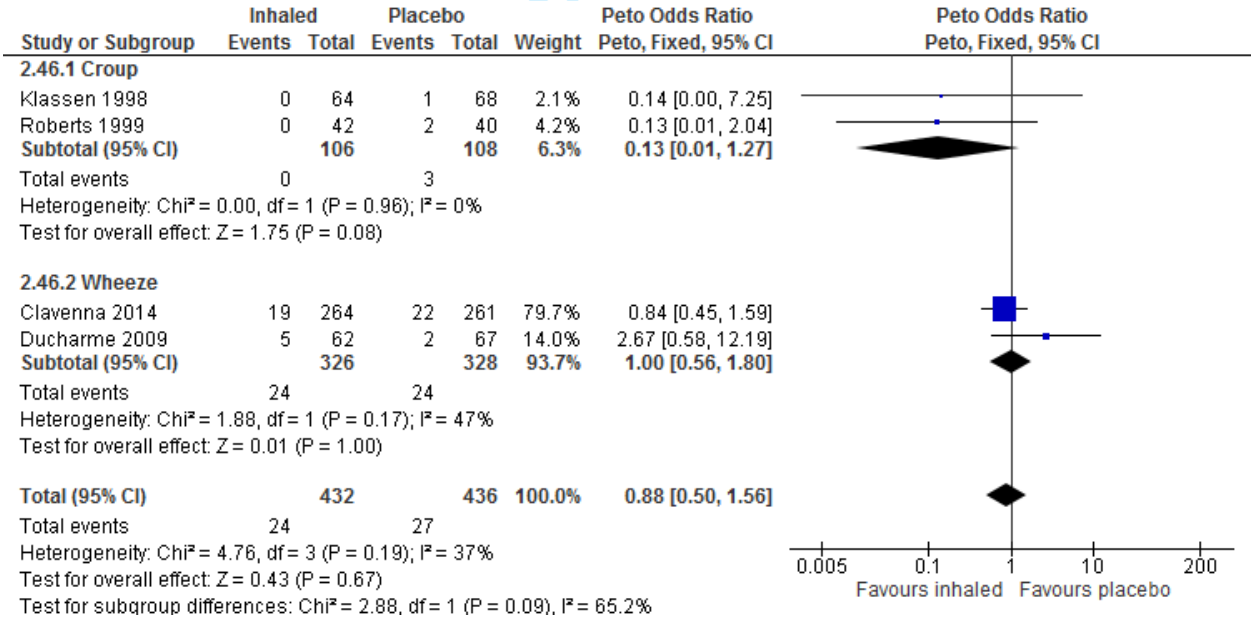
Integument (by dose) – Peto



Integument (by condition)



Integument (by condition) – Peto

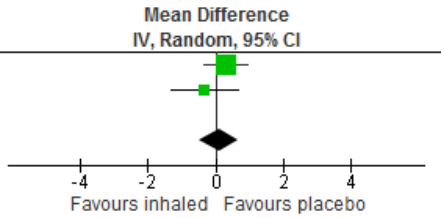


INHALED vs. PLACEBO – Endocrine/Metabolic & Musculoskeletal

Growth – change from baseline, cm

Study or Subgroup	Inhaled Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference 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]**

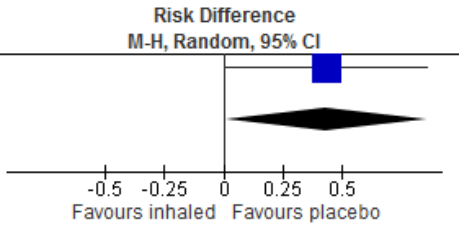
Heterogeneity: Tau² = 0.02; Chi² = 1.09, df = 1 (P = 0.30); I² = 9%
Test for overall effect: Z = 0.34 (P = 0.73)



Adrenal suppression

Study or Subgroup	Inhaled Events	Total	Placebo Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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			

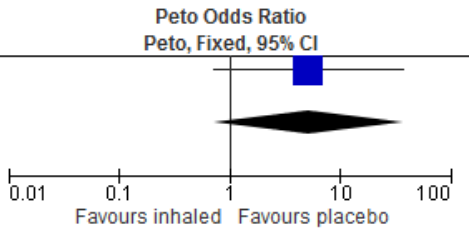
Heterogeneity: Not applicable
Test for overall effect: Z = 2.00 (P = 0.05)



Adrenal suppression - Peto

Study or Subgroup	Inhaled Events	Total	Placebo Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hedlin 1999	5	6	4	10	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 applicable
Test for overall effect: Z = 1.64 (P = 0.10)

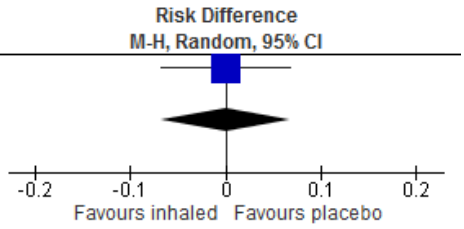


INHALED vs. PLACEBO – Cardiovascular

Arrhythmia

Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Risk Difference M-H, Random, 95% CI
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			

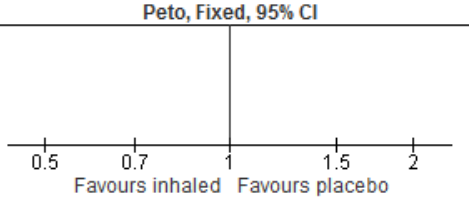
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Arrhythmia – Peto

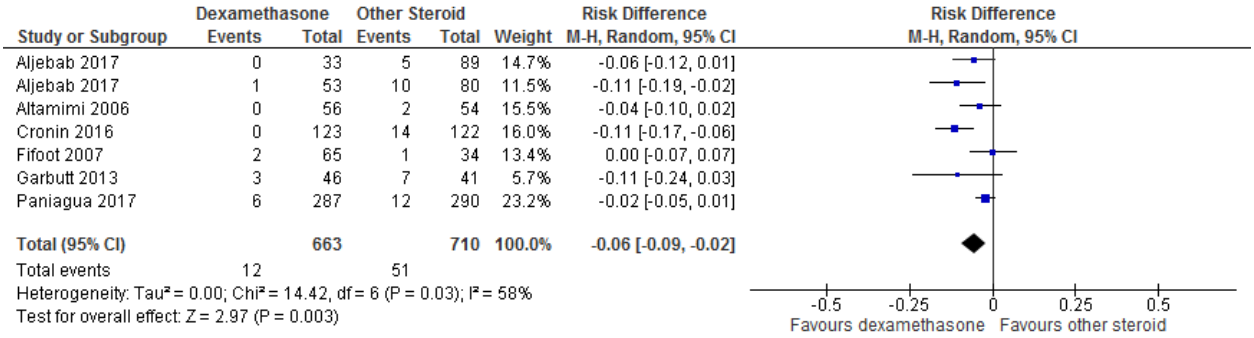
Study or Subgroup	Inhaled Events	Inhaled Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Daugbjerg 1993	0	29	0	27		Not estimable
Total (95% CI)		**29**		**27**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

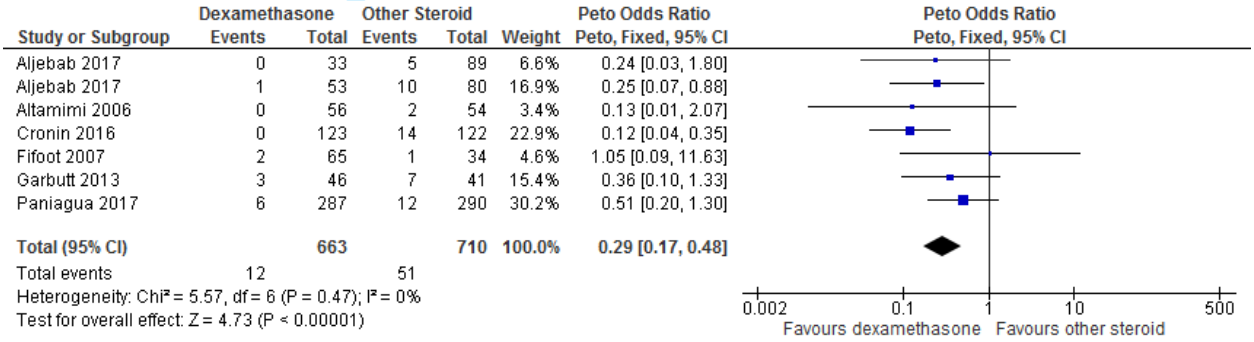


DEXAMETHASONE vs. OTHER STEROID – GI

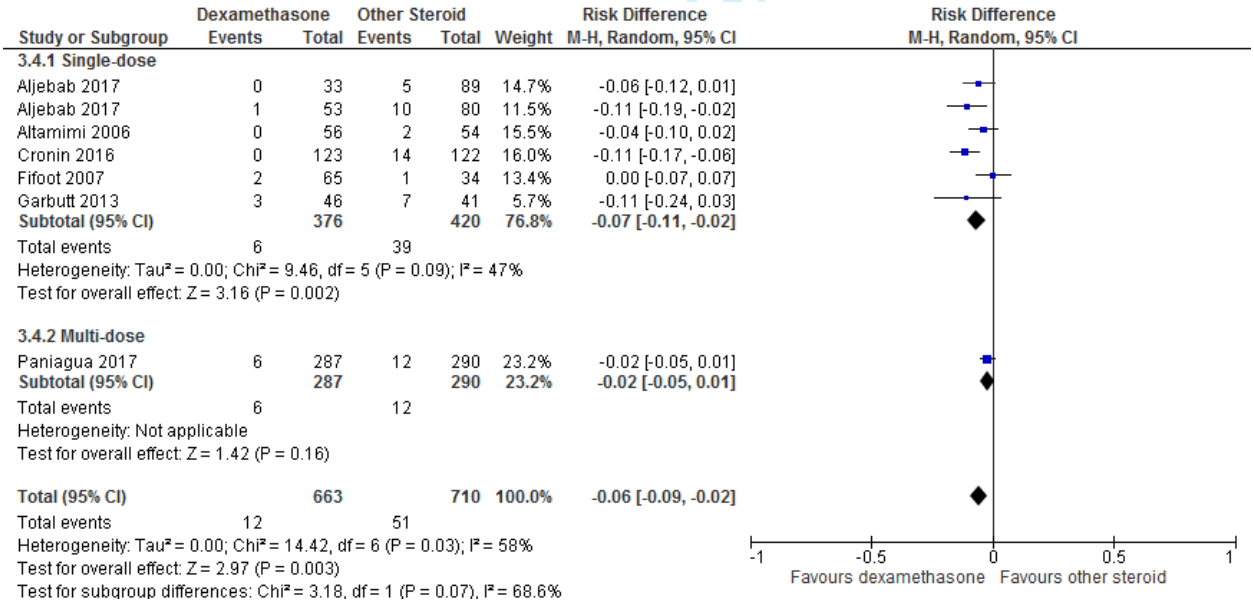
Vomiting



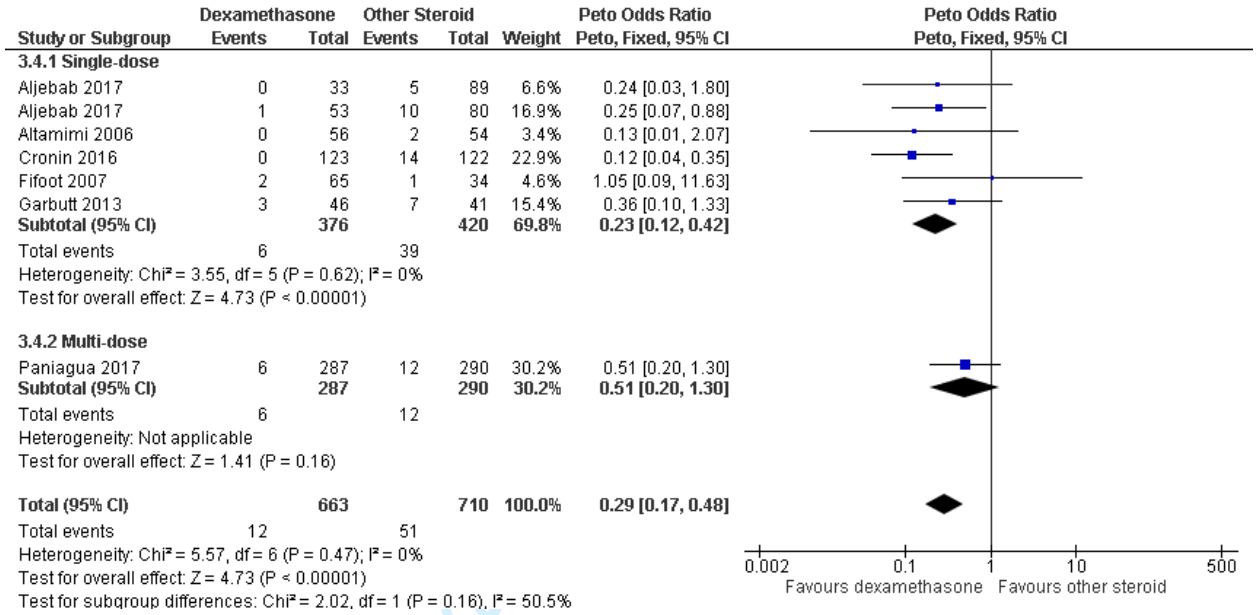
Vomiting – Peto



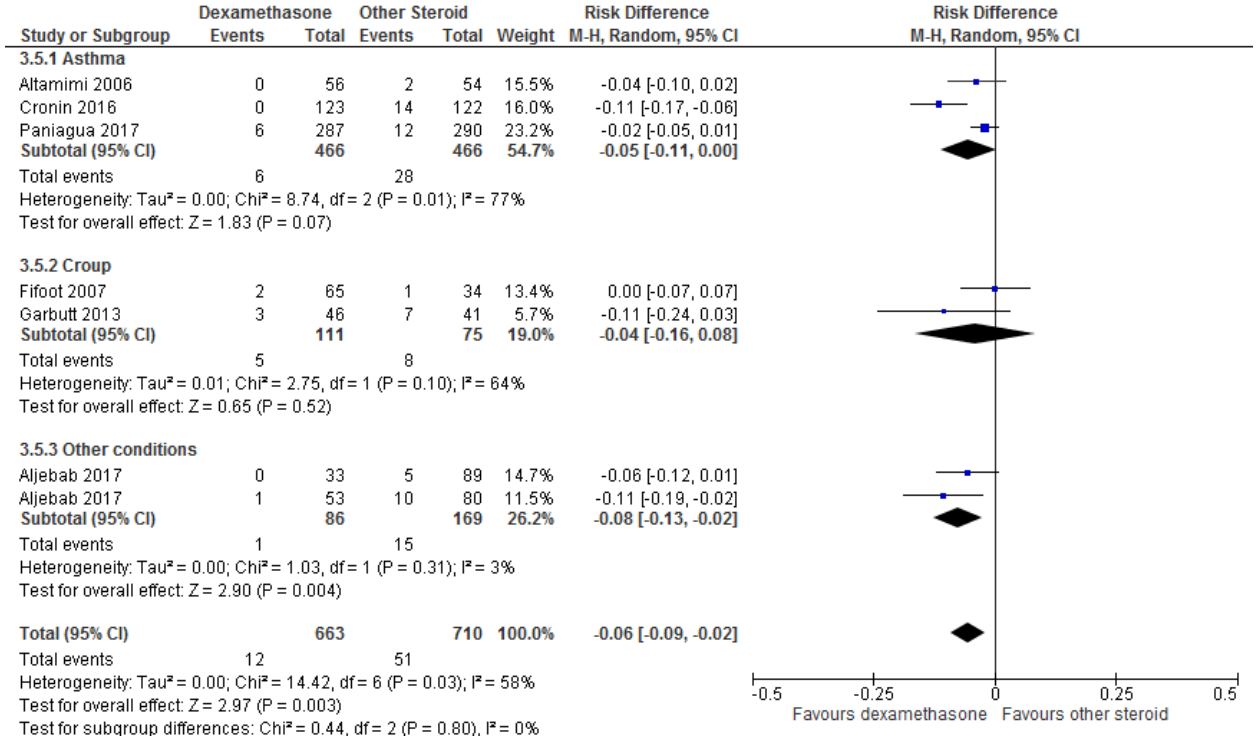
Vomiting (by dose)



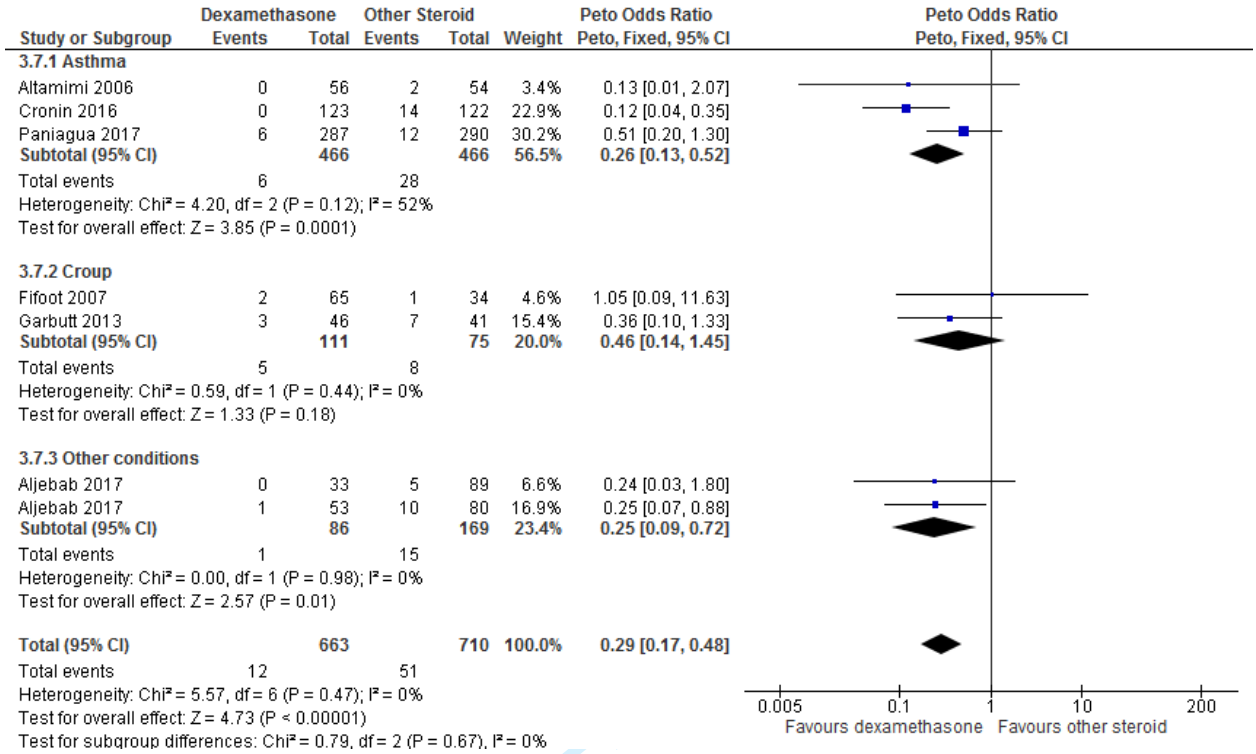
Vomiting (by dose) – Peto



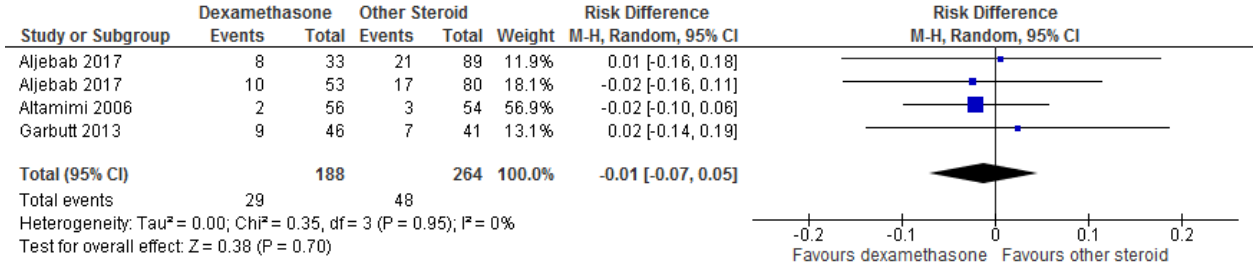
Vomiting (by condition)



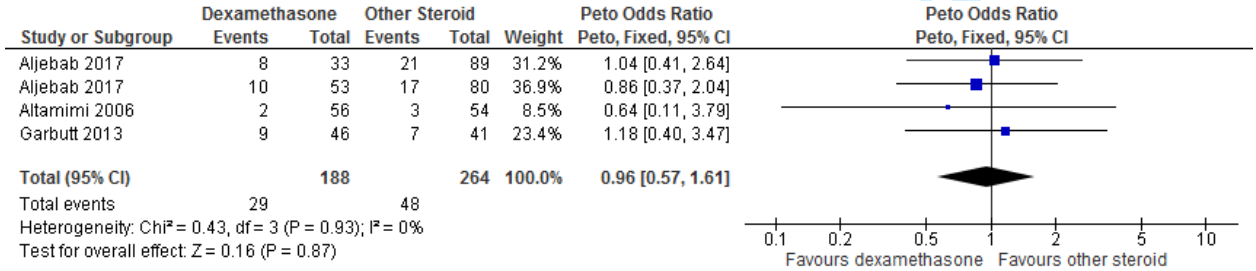
Vomiting (by condition) – Peto



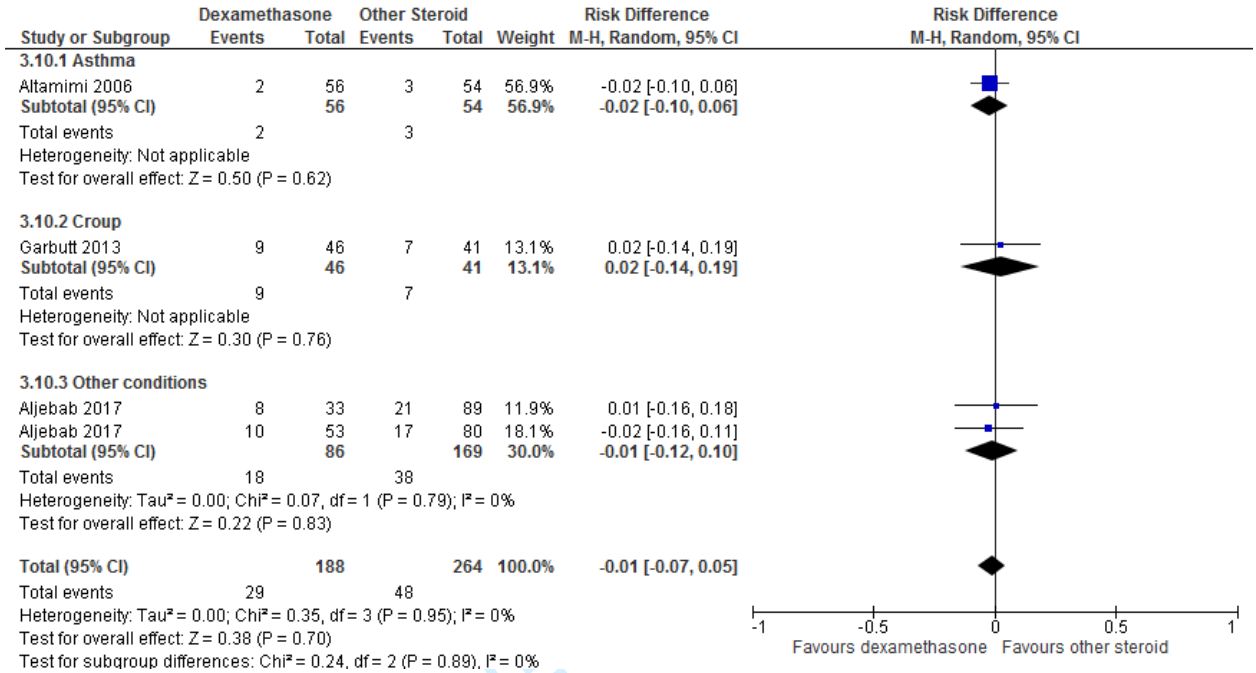
Abdominal pain



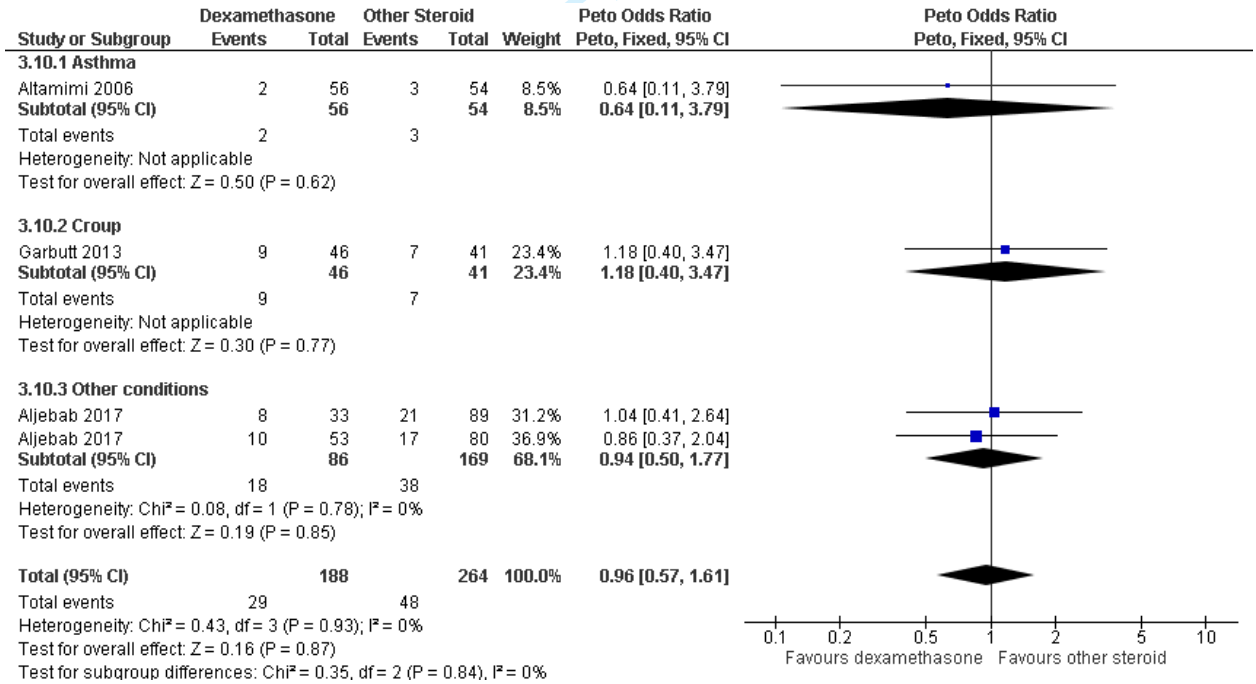
Abdominal pain – Peto



Abdominal pain (by condition)



Abdominal pain (by condition) – Peto

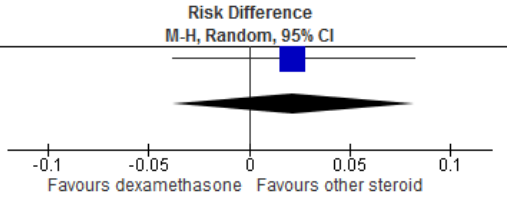


DEXAMETHASONE vs. OTHER STEROID – CNS & Behaviour

Tremor/jitteriness

Study or Subgroup	Dexamethasone Events	Total	Other Steroid Events	Total	Weight	Risk Difference 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			

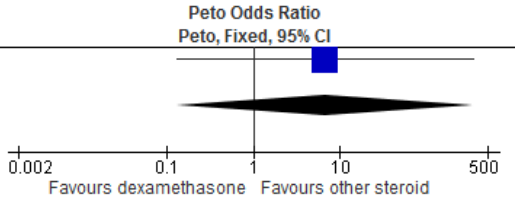
Heterogeneity: Not applicable
Test for overall effect: Z = 0.71 (P = 0.48)



Tremor/jitteriness – Peto

Study or Subgroup	Dexamethasone Events	Total	Other Steroid Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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			

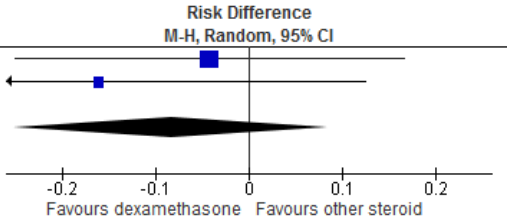
Heterogeneity: Not applicable
Test for overall effect: Z = 0.94 (P = 0.35)



Behaviour change

Study or Subgroup	Dexamethasone Events	Total	Other Steroid Events	Total	Weight	Risk Difference M-H, Random, 95% CI
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% CI)		**60**		**57**	**100.0%**	**-0.08 [-0.25, 0.09]**
Total events	35		38			

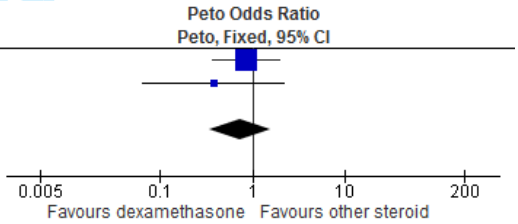
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 1 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.96 (P = 0.33)



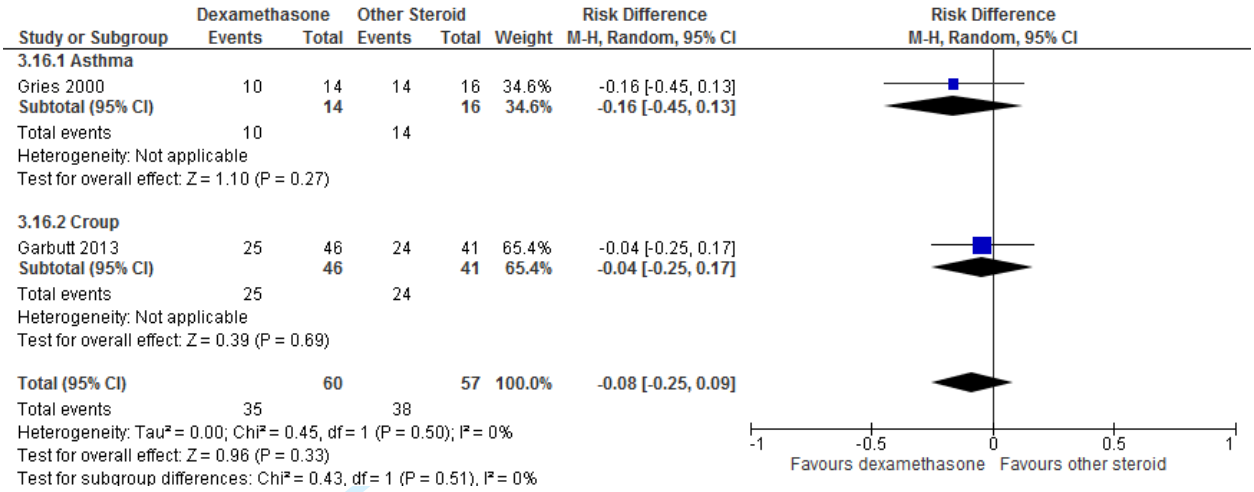
Behaviour change – Peto

Study or Subgroup	Dexamethasone Events	Total	Other Steroid Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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]
Total (95% CI)		**60**		**57**	**100.0%**	**0.73 [0.34, 1.56]**
Total events	35		38			

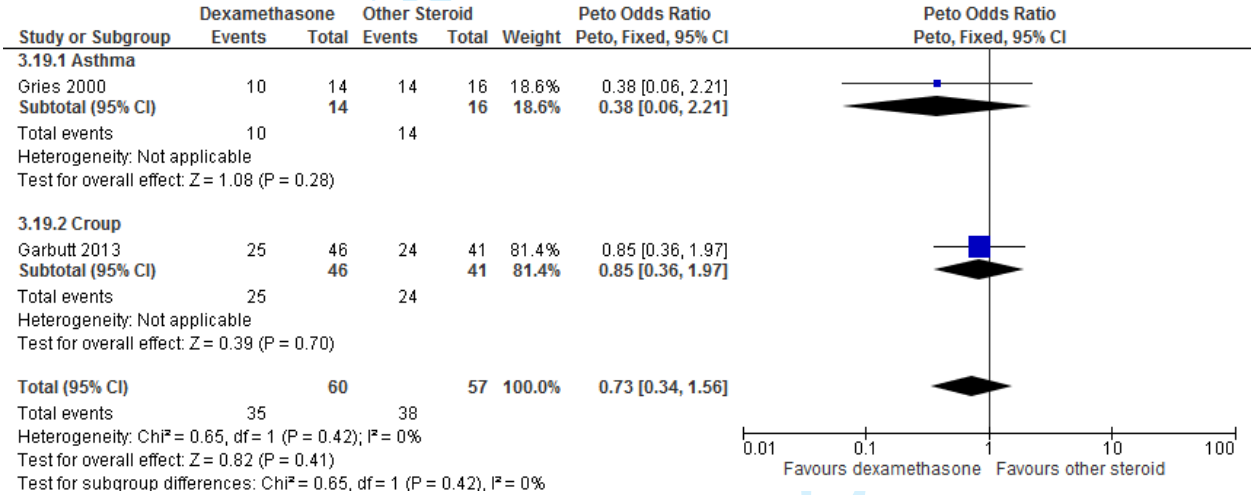
Heterogeneity: Chi² = 0.65, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 0.82 (P = 0.41)



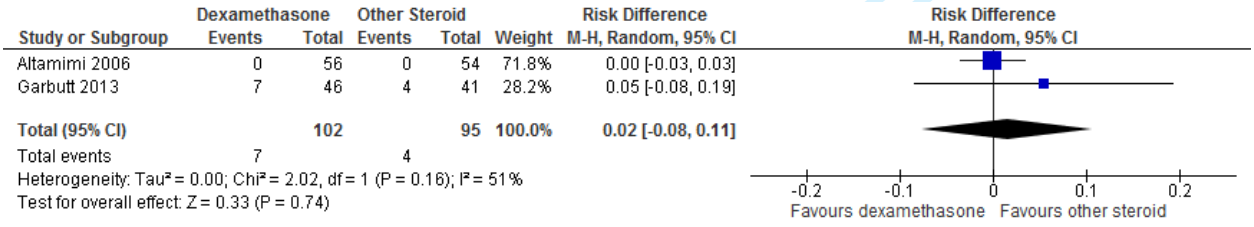
Behaviour change (by condition)



Behaviour change (by condition) – Peto



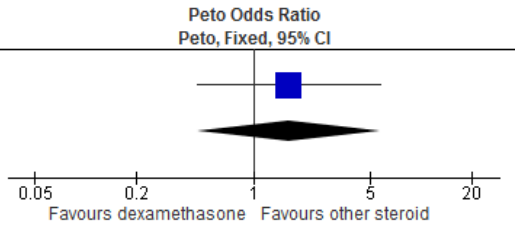
Headache



Headache – Peto

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
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 applicable
Test for overall effect: Z = 0.76 (P = 0.45)



Headache (by condition)

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Risk Difference M-H, Random, 95% CI
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			

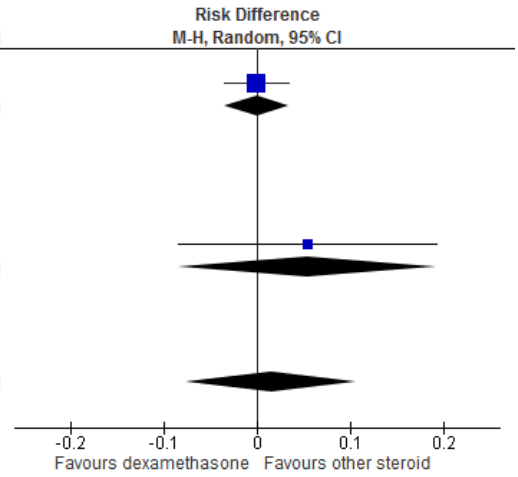
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

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 applicable
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: $Tau^2 = 0.00$; $Chi^2 = 2.02$, df = 1 (P = 0.16); $I^2 = 51\%$
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: $Chi^2 = 0.57$, df = 1 (P = 0.45), $I^2 = 0\%$



Headache (by condition) – Peto

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Peto Odds Ratio 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			

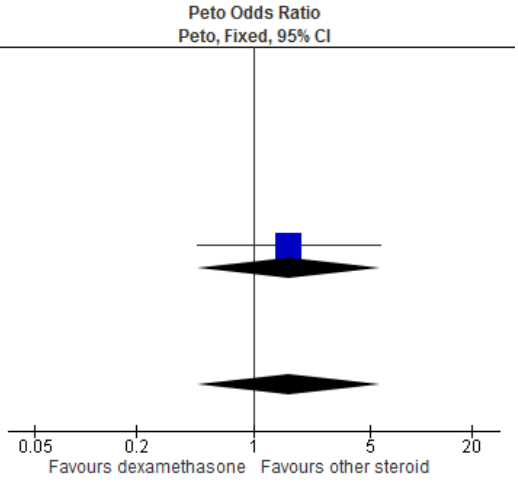
Heterogeneity: Not applicable
Test for overall effect: Not applicable

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 applicable
Test for overall effect: Z = 0.76 (P = 0.45)

Total (95% CI)		**102**		**95**	**100.0%**	**1.63 [0.46, 5.74]**
Total events	7		4			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)
Test for subgroup differences: Not applicable

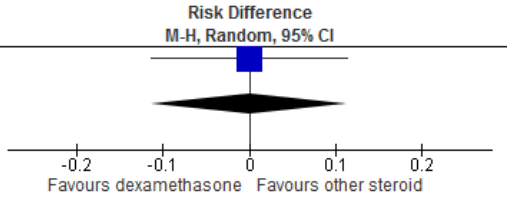


DEXAMETHASONE vs. OTHER STEROID – Dermatologic

Phlebitis

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Risk Difference 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	0		0			

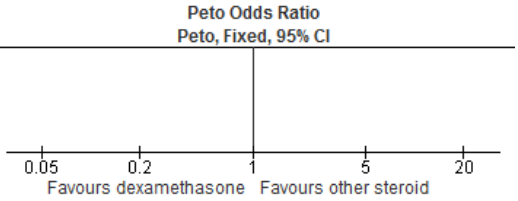
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Phlebitis – Peto

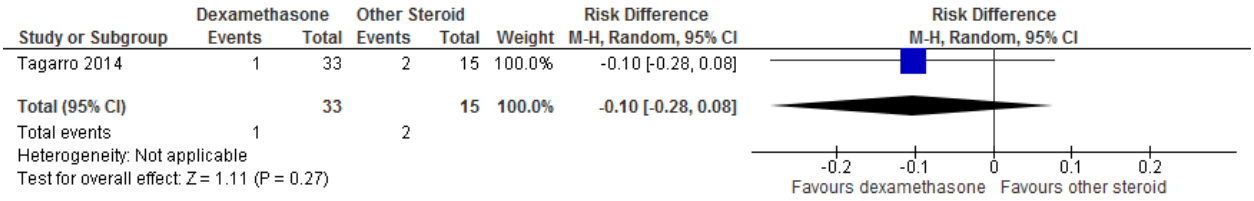
Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gries 2000	0	15	0	17		Not estimable
Total (95% CI)		**15**		**17**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

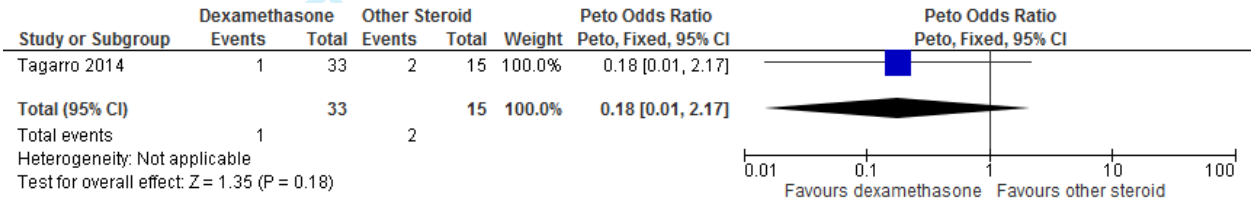


DEXAMETHASONE vs. OTHER STEROID – Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities



Fluid & electrolyte abnormalities – Peto

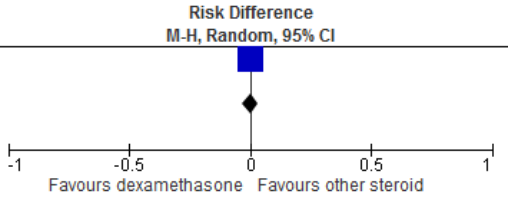


DEXAMETHASONE vs. OTHER STEROID – Cardiovascular

Arrhythmia

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Risk Difference 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			

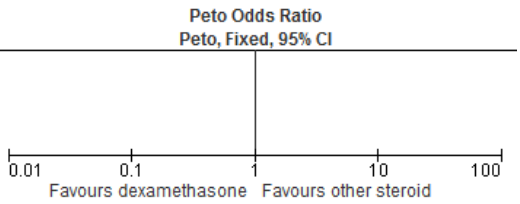
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Arrhythmia – Peto

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Altamimi 2006	0	56	0	54		Not estimable
Total (95% CI)		**56**		**54**		**Not estimable**
Total events	0		0			

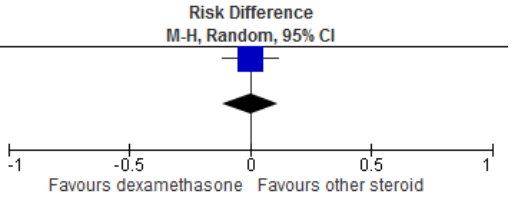
Heterogeneity: Not applicable
Test for overall effect: Not applicable



Hypertension

Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Risk Difference 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	0		0			

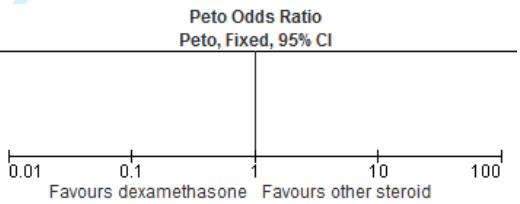
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)



Hypertension – Peto

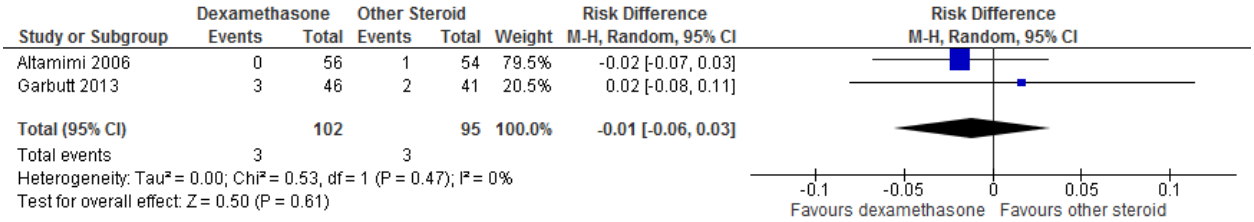
Study or Subgroup	Dexamethasone Events	Dexamethasone Total	Other Steroid Events	Other Steroid Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gries 2000	0	15	0	17		Not estimable
Total (95% CI)		**15**		**17**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

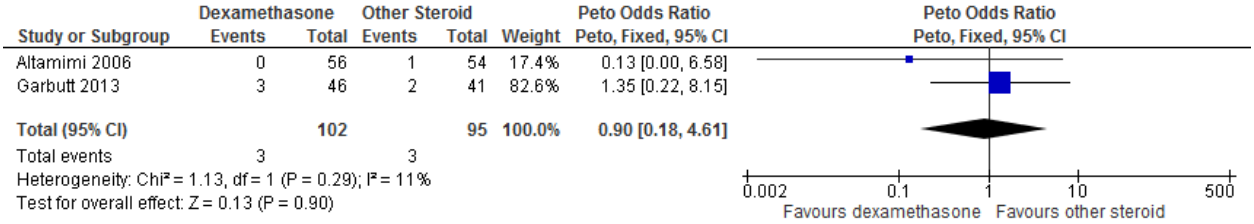


DEXAMETHASONE vs. OTHER STEROID – General

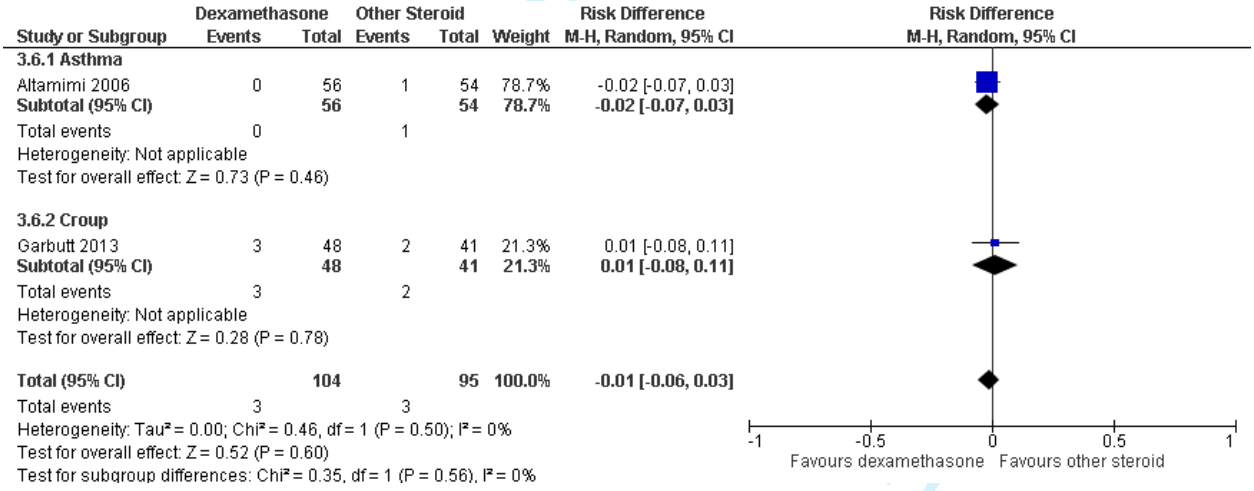
General complaints



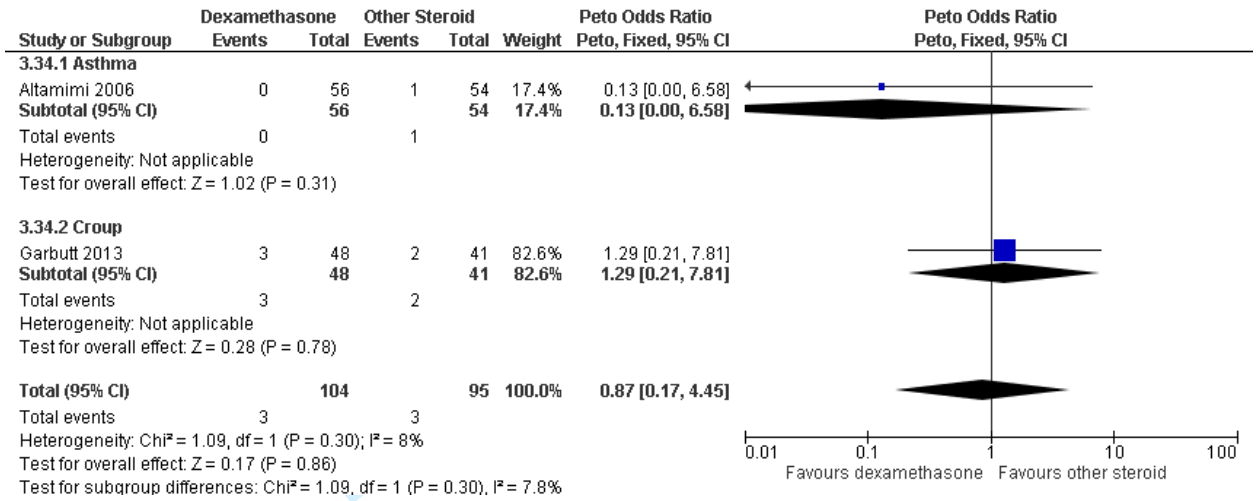
General complaints – Peto



General complaints (by condition)



General complaints (by condition) – Peto



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.

Ghirga 2002	wheeze - recurrent, early in URTI	inhaled vs. no intervention	RCT	26	No AE overall; 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 the 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 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; CS: case series; nRCT: non-randomised controlled trial; RCT: randomised controlled trial; sal: salbutamol; URTI: upper respiratory tract infection; 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
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. 5
Objectives (5)	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	—	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 in funding source (p. 22)
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	p. 6-7;

		status) used as criteria for eligibility, giving rationale.		outcomes of interest were not reported. Report choices for specific study designs and length of follow-up.	Supplement 2 - Eligibility criteria for study inclusion
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.	—	Report if only searched for published data, or also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it.	p. 6; Supplement 1- Search strategy
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, included in the meta-analysis).	—	If only included studies reporting on adverse events of interest, 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.	p. 7; Supplement 2 - 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.	—	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

				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).	
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
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
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.		p. 8-9
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).	—	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
Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	—	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
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

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
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. 9; Supplement 4 - Methodological quality of included studies
Results of individual studies (16)	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.	—	Report the actual numbers of adverse events in each study, separately for each intervention.	p. 10; Supplement 3 - Characteristics of included studies
Synthesis of results (17)	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Describe any assessment of possible causality.	If included data from unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	p. 10-15; Table 2 - 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 – Forest plots of adverse events;

					Supplement 7 - Studies reporting no adverse events p. 9;
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.	Table 1 - Summary of methodological quality assessments p. 10;
	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.	Supplement 5 - Effect estimates for all adverse events with subgroups; Supplement 6 – Forest plots of adverse events
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
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).	—	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
Conclusions (19)	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	—	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
Funding					
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