

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (http://bmjopen.bmj.com).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	BMJ Open
	<u>'</u>
Manuscript ID	bmjopen-2018-028511
Article Type:	Research
Date Submitted by the Author:	11-Dec-2018
Complete List of Authors:	Fernandes, Ricardo; Hospital de Santa Maria, Pediatrics; Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Instituto de Medicina Molecular, University of Lisbon Wingert, Aireen; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence Vandermeer, Ben; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Featherstone, Robin; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Ali, Samina; University of Alberta, Pediatrics; Women & Children's Health Research Institute, Pediatrics, University of Alberta Plint, AMy; University of Ottawa, Stang, Antonia; University of Calgary, Pediatrics, Emergency Medicine, Community Health Sciences Rowe, Brian; University of Alberta, Emergency Medicine; University of Alberta, School of Public Health Johnson, David; University of Calgary Cumming School of Medicine, Pediatrics, Emergency Medicine, and Physiology and Pharmacology Allain, Dominic; University of Alberta, Pediatrics, Faculty of Medicine & Dentistry Klassen, Terry; Manitoba Institute of Child Health & Associate Dean of Academic, Faculty of Medicine, University of Manitoba Hartling, Lisa; University of Alberta, Pediatrics; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence
Keywords:	corticosteroids, Asthma < THORACIC MEDICINE, bronchiolitis, croup, PAEDIATRICS, safety

SCHOLARONE™ Manuscripts

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

Ricardo M. Fernandes, Aireen Wingert, Ben Vandermeer, Robin Featherstone, Samina Ali, Amy C. Plint, Antonia S. Stang, Brian H. Rowe, David W. Johnson, Dominic Allain, Terry P. Klassen, Lisa Hartling

Ricardo M. Fernandes, Department of Pediatrics, Hospital de Santa Maria, Lisbon, Portugal; Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Instituto de Medicina Molecular, University of Lisbon, Lisbon, Portugal

Aireen Wingert, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Ben Vandermeer, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Robin Featherstone, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Samina Ali, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada; Women & Children's Health Research Institute, Department of Pediatrics, University of Alberta, 5-083 Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Amy C. Plint, Department of Pediatrics, University of Ottawa, Children's Hospital of Eastern Ontario 401 Smyth Road, Ottawa, Ontario, Canada

Antonia S. Stang, Departments of Pediatrics, Emergency Medicine, Community Health Sciences, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada

Brian H. Rowe, Department of Emergency Medicine, University of Alberta, 8440 – 112 Street NW, Edmonton, Alberta, Canada; School of Public Health, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

David W. Johnson, Departments of Pediatrics, Emergency Medicine, and Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada

Dominic Allain, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Terry P. Klassen, Manitoba Institute of Child Health, University of Winnipeg, Children's Hospital of Research Institute of Manitoba 513 – 715 McDermot Avenue, Winnipeg, Manitoba, Canada

Lisa Hartling, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada; Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Corresponding author: Dr. Lisa Hartling, 11405 - 87 Avenue, Edmonton, Alberta, T6G 1C9, Canada; phone: 780-492-6124; e-mail: hartling@ualberta.ca; ords

Manuscript = 3654 words

ABSTRACT (300 words)

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

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

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

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

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

Strengths and limitations of this study:

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

INTRODUCTION

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

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

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

METHODS

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

Literature search

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

Eligibility criteria

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

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

Study selection

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

Data extraction

One reviewer extracted data using a structured form, with verification by a second reviewer.

Data were extracted on study characteristics (design features), patient characteristics (age, sex, baseline characteristics), respiratory conditions, interventions (type, dose, duration, route of administration, timing, co-interventions, rescue medications), outcomes (types and timing), care setting, funding sources, and results.

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

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

Five studies reported on adrenal function/suppression, with few children contributing data for this outcome. 44, 56, 57, 70, 88 The RCT of high-dose inhaled fluticasone propionate versus placebo (99 children with data)⁴⁴ found no significant differences between groups in basal cortisol (baseline and 12 months). Another RCT in asthma reported no differences in serum cortisol and urinary cortisol/creatinine after 10 days of inhaled budesonide or placebo (16 children with data). A subgroup who received oral betamethasone (n=9) showed significant changes from baseline after three days, but no differences at 12 to 14 days. 57 Two studies included comparisons between different corticosteroids. One RCT⁸⁸ in acute asthma compared IV prednisolone (n=20) with nebulized budesonide (n=30) and found significant levels of suppressed serum cortisol in the prednisolone group, albeit not considered pathologic by the study authors. Although another RCT⁵⁶ comparing intramuscular (IM) dexamethasone with oral prednisone for asthma (n=32) found lower median urinary cortisol/creatinine in the former group at day 14, there was no statistically significant difference. An RCT⁷⁰ comparing IV dexamethasone (n=9) with inhaled budesonide (n=9) found no significant differences between groups from baseline for blood pressure and blood glucose measurements.

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

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

Cardiovascular System

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

General AEs/Other Symptoms

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

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

Immune System & Oncology

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

DISCUSSION

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

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

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. While the estimated increased pOR for rash and hives was close to statistical significance, no other differences were found in systemic or severe infections as well as immunosuppression.

This review did not ascertain a clear safety advantage between systemic or inhaled corticosteroids compared with placebo. When comparing between different systemic corticosteroids, evidence favored oral dexamethasone over oral prednisone for vomiting (pOR 0.029; 95% CI 0.17 to 0.48; I²=0%). Differences in palatability and tolerability between corticosteroids are well known to parents, healthcare providers and researchers, and can influence adherence to medication in children. 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.

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.

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.

The provided estimates are separated as a significant increase in rates of sepsis, venous thromboembolism and fracture.

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. 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

- 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
- Supplement 4 Methodological quality of included studies
 - a. Summary of methodological quality assessments
 - b. 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 - Studies reporting no adverse events

Acknowledgments: We gratefully acknowledge the following individuals for their contributions: Megan Nuspl, Sanjaya Dhakal and Pritam Chordiya for assisting with screening, initial data extraction and verification, and article retrieval; Marc Parsons for assisting with data extraction and verification, and quality assessment; and, Jack Yeung, Marta Oleszczuk and Igor Pravdivyi for assistance with translations. MN, SD, PC and MP received remuneration for their work from a Canadian Institutes of Health Research (CIHR) grant (funding reference number KRS134306). JY, MO and IP did not receive remuneration for the translation work. None of the acknowledged individuals have industry affiliations, or any conflicts of interest to declare.

Contributors: RMF, AW, BV, SA, ACP, ASS, BHR, DWJ, DA, TPK, and LH critically reviewed and contributed to drafts of the report. RF conducted the literature searches. AW

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.

Funding: This study was funded by a Knowledge Synthesis Grant from CIHR (funding reference number KRS134306). The funder had no role in the design of the study, the collection, analysis or interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Competing interests: All authors declare funding from CIHR for the submitted work. LH was funded in part by a New Investigator Salary Award from the CIHR; ASP is supported by a Tier II University of Ottawa Research Chair Award; BHR was supported by a Tier I Canada Research Chair in Evidence-based Emergency Medicine from CIHR. The remaining authors have no financial relationships relevant to this manuscript to disclose. DWJ, TPK and ASP are also authors on some of the included studies. The other authors have no conflicts of interest to declare.

Provenance and peer review: Not commissioned; externally peer-reviewed.

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.

REFERENCES

- 1. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012;185(1):12-23.
- 2. Johnson D. Croup. BMJ Clin Evid 2009.
- 3. Russell KF, Liang Y, O'Gorman K, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev* 2011;1(CD001955).
- 4. Adams NP, Bestall JC, Jones P, et al. Fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008;4(CD003534).
- 5. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367(10):904-912.
- 6. van Staa T, Cooper C, Leufkens H, et al. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18(5):913-918.
- 7. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: A systematic review with meta-analysis. *Pediatrics* 2009;123(3):e519-525.
- 8. Zhang L, Axelsson I, Chung M, et al. Dose response of inhaled corticosteroids in children with persistent asthma: A systematic review. *Pediatrics* 2011;127(1):129-138.
- 9. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: Framework for a structured approach. *BMC Med Res Methodol* 2007;7(1):1-9.
- 10. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: A network metaanalysis and cochrane overview. *Cochrane Database Syst Rev* 2011;2(CD008794).
- 11. Higgins J, Green S. (editors). The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed. January 12, 2018.
- 12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 2009;62(10):1006-1012.

13. Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: Improving harms reporting in systematic reviews. *BMJ* 2016;352:i157.

- 14. Global Initiative for Asthma. Global strategy for asthma management and prevention. http://www.ginasthma.org. Accessed: January 12, 2018.
- 15. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: A clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140(10):795-801.
- 16. Tugwell P, Judd MG, Fries JF, et al. Powering our way to the elusive side effect: A composite outcome 'basket' of predefined designated endpoints in each organ system should be included in all controlled trials. *J Clin Epidemiol* 2005;58(8):785-790.
- 17. Chou R, Aronson N, Atkins DL, et al. Assessing harms when comparing medication interventions. In: Agency for Healthcare Research and Quality (US). Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD; 2008.
- 18. Higgins JPT, Green S (editors). The Cochrane Handbook for Systematic Reviews of Interventions. Section 9.5.2: Identifying and measuring heterogeneity. www.cochrane-handbook.org. Accessed: January 24, 2018.
- 19. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-634.
- 20. Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- 21. TS Inc. TIBCO Spotfire S+ Workbench, Version 3.4 [statistical software]. 1996.
- 22. Alangari AA, Malhis N, Mubasher M, et al. Budesonide nebulization added to systemic prednisolone in the treatment of acute asthma in children: A double-blind, randomized, controlled trial. *Chest* 2014;145(4):772-778.
- 23. Alansari KS, Sakran M, Davidson BL, et al. Oral dexamethasone for bronchiolitis: A randomized trial. *Pediatrics* 2013;132(4):e810-816.
- 24. Aljebab F, Alanazi M, Choonara I, et al. Observational study on the palatability and tolerability of oral prednisolone and oral dexamethasone in children in Saudi Arabia and the UK. *Arch Dis Child* 2017;103(1):83-88.

- 25. Alshehr M, Almegamsi T, Hammdi A. Efficacy of a small dose of oral dexamethasone in croup. *Biomed Res* 2005;16(1):65-72.
- 26. Altamimi S, Robertson G, Jastaniah, W, et al. Single-dose oral dexamethasone in the emergency management of children with exacerbations of mild to moderate asthma. *Pediatr Emerg Care* 2006;22(12):786-793.
- 27. Bacharier LB, Phillips BR, Zeiger RS, et al; Childhood Asthma Research and Education Network. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122(6):1127-1135.e8.
- 28. Bisgaard H, Hermansen MN, Loland L, et al. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998-2005.
- 29. Bjornson CL, Klassen, TP, Williamson J, et al; Pediatric Emergency Research Canada Network. A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med* 2004;351(13):1306-1313.
- 30. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: Prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81(5):624-629.
- 31. Buckingham SC, Jafri HS, Bush AJ, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: Effects on RSV quantity and clinical outcome. *J Infect Dis* 2002;185(9):1222-1228.
- 32. Bülow SM, Nir M, Levin E, et al. Prednisolone treatment of respiratory syncytial virus infection: A randomized controlled trial of 147 infants. *Pediatrics* 1999;104(6):e77.
- 33. Chang AB, Clark R, Sloots TP, et al. A 5- versus 3-day course of oral corticosteroids for children with asthma exacerbations who are not hospitalised: A randomised controlled trial. *Med J Aust* 2008;189(6):306-310.
- 34. Chen ZG, Li M, Chen H, et al. Efficacy of pulmicort suspension plus salbutamol and ipratropium bromide for management of acute asthma exacerbation in children: A comparative study. *J South Med Univ* 2008;28(3):470-472.

35. Chub-Uppakarn S. Sangsupawanich P. A randomized comparison of dexamethasone 0.15 mg/kg versus 0.6 mg/kg for the treatment of moderate to severe croup. *Int J Pediatr Otorhinolaryngol* 2007;71(3):473-477.

- 36. Clavenna A, Sequi M, Cartabia M, et al. Effectiveness of nebulized beclomethasone in preventing viral wheezing: An RCT. *Pediatrics* 2014;133(3):e505-512.
- 37. Connett GJ, Warde C, Wooler E, et al. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70(3):170-173.
- 38. Connolly JH, Field CMB, Glasgow JFT, et al. A double blind trial of prednisolone in epidemic bronchiolitis due to respiratory syncytial virus. *Acta Paediatr Scand* 1969;58(2):116-120.
- 39. Corneli HM, Zorc JJ, Mahajan P, et al; Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;357(4):331-339.
- 40. Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. *Ann Emerg Med* 2016;67(5):593-601.
- 41. Csonka P, Kaila M, Laippala P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: A randomized, placebo-controlled trial. *J Pediatr* 2003;143(6):725-730.
- 42. Daugbjerg P, Brenøe E, Forchhammer H, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr* 1993;82(6-7):547-551.
- 43. Dawson KP, Sharpe C. A comparison of the acceptability of prednisolone tablets and prednisolone sodium phosphate solution in childhood acute asthma. *Aust J Hosp Pharm* 1993;23(5):320-323.
- 44. Ducharme FM, Lemire C, Noya FJD, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360(4):339-353.
- 45. Eboriadou M, Chryssanthopoulou D, Stamoulis P, et al. The effectiveness of local corticosteroids therapy in the management of mild to moderate viral croup. *Minerva Pediatr* 2010;62(1):23-28.

- 46. Eden AN, Kaufman A, Yu R. Corticosteroids and croup. Controlled double-blind study. *JAMA* 1967;200(5):403-404.
- 47. Escobedo Chavez E, Garcia Muniz LO, Thompson Chagoyan O, et al. Steroids and inhalation therapy in the management of acute asthma in children. *Curr Ther Res Clin Exp* 1992;52(1):7-12.
- 48. Fifoot AA, Ting JYS. Comparison between single-dose oral prednisolone and oral dexamethasone in the treatment of croup: A randomized, double-blinded clinical trial. *Emerg Med Australas* 2007;19(1):51-58.
- 49. Fitzgerald D, Mellis C, Johnson M, et al. Nebulized budesonide is as effective as nebulized adrenaline in moderately severe croup. *Pediatrics* 1996;97(5):722-725.
- 50. Francis P, Geelhoed G, Harris MA, et al. Effect of nebulised fluticasone propionate 1 mg twice daily compared with oral prednisolone in pre-school children aged 48 months or less with an acute exacerbation of asthma [abstract]. *Eur Respir J* 1997(Suppl 25):275s.
- 51. Garbutt JMC, Bridget C, Sterkel R, et al. The comparative effectiveness of prednisolone and dexamethasone for children with croup: A community-based randomized trial. *Clin Pediatr (Phila)* 2013;52(11):1014-1021.
- 52. Ghirga G, Ghirga P, Fagioli S, et al. Intermittent treatment with high dose nebulized beclomethasone for recurrent wheezing in infants due to upper respiratory tract infection. *Minerva Pediatr* 2002;54(3):217-220.
- 53. Gill N, Sirizzotti N, Johnson D, et al. Endogenous glucocorticoid response to single-dose dexamethasone for croup in children: A pharmacodynamic study. *Pediatr Emerg Care* 2017;11.
- 54. Goebel J, Estrada B, Quinonez J, et al. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr (Phila)* 2000;39(4):213-220.
- 55. Grant CC, Duggan AK, Santosham M, et al. Oral prednisone as a risk factor for infections in children with asthma. *Arch Pediatr Adolesc Med* 1996;150(1):58-63.
- 56. Gries DM, Moffitt DR, Pulos E, et al. A single dose of intramuscularly administered dexamethasone acetate is as effective as oral prednisone to treat asthma exacerbations in young children. *J Pediatr* 2000;136(3):298-303.

57. Hedlin G, Svedmyr J, Ryden AC. Systemic effects of a short course of betamethasone compared with high-dose inhaled budesonide in early childhood asthma. *Acta Paediatr* 1999;88(1):48-51.

- 58. Husby S, Agertoft L, Mortensen S, et al. Treatment of croup with nebulised steroid (budesonide): A double blind, placebo controlled study. *Arch Dis Child* 1993;68(3):352-325.
- 59. Inglis AF. Herpes simplex virus infection. A rare cause of prolonged croup. *Arch Otolaryngol Head Neck Surg* 1993;119(5):551-552.
- 60. Jan JS, Wu WF. Acute effect of glucocorticoid treatment on serum osteocalcin levels in asthmatic children. *J Microbiol Immunol Infect* 2000;33(1):25-28.
- 61. Jartti T, Nieminen R, Vuorinen T, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. *J Allergy Clin Immunol* 2015;135(3):691-698.
- 62. Jartti T, Lehtinen Pasi, Timo V, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;25(6):482-488.
- 63. Jartti T, Lehtinen P, Vanto T, et al. Efficacy of prednisolone in children hospitalized for recurrent wheezing. *Pediatr Allergy Immunol* 2007;18(4):326-334.
- 64. Johnson DW, Jacobson S, Edney PC, et al. A comparison of nebulized budesonide, intramuscular dexamethasone, and placebo for moderately severe croup. *N Engl J Med* 1998;339(8):498-503.
- 65. Johnson DW, Schuh S, Koren G, et al. Outpatient treatment of croup with nebulized dexamethasone. *Arch Pediatr Adolesc Med* 1996;150(4):349-355.
- 66. Klassen TP, Craig WR, Moher D, et al. Nebulized budesonide and oral dexamethasone for treatment of croup: A randomized controlled trial. *JAMA* 1998;279(20):1629-1632.
- 67. Klassen TP, Feldman ME, Watters LK, et al. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994;331(5):285-289.

- 68. Klassen TP, Watters LK, Feldman ME, et al. The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996;97(4):463-466.
- 69. Kuyucu S, Unal S, Kuyucu N, et al. Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis. *Pediatr Int* 2004;46(5):539-544.
- 70. Lai ST, Hua YM, Lai YS, et al. Comparison of nebulized budesonide with intravenous dexamethasone in the treatment of young children hospitalized with acute asthma. *J Med Sci* 2005;25(5):223-228.
- 71. Langton Hewer S, Hobbs J, Reid F, et al. Prednisolone in acute childhood asthma: Clinical responses to three dosages. *Respir Med* 1998;92(3):541-546.
- 72. Lee KM, Lin YZ, Huang FY. Steroid-induced acute psychosis in a child with asthma: Report of one case. *Acta Paediatr Taiwan* 2001;42(3):169-171.
- 73. Leer JA, Green JL, Heimlich EM, et al. A controlled, collaborative study in 297 infants and children. *Am J Dis Child* 1969;117(5):495-503.
- 74. Lehmann S, Ott H. Glucocorticoid hypersensitivity as a rare but potentially fatal side effect of paediatric asthma treatment: A case report. *J Med Case Rep* 2008;2:186.
- 75. Leipzig B, Oski FA, Cummings CW, et al. A prospective randomized study to determine the efficacy of steroids in treatment of croup. *J Pediatr* 1979;94(2):194-196.
- 76. Lin YZ, Hsieh KH, Chen W, et al. Clinical trial of corticosteroid and beta-2 bronchodilator in acute wheezing infants. *Acta Paed Sin* 1991;32(6):333-340.
- 77. Lucas-Bouwman ME, Roorda RJ, Jansman FGA, et al. Crushed prednisolone tablets or oral solution for acute asthma? *Arch Dis Child* 2001;84(4):347-348.
- 78. Nahum A, Garty BZ, Marcus N, et al. Severe hypersensitivity reactions to corticosteroids in children. *Pediatr Emerg Care* 2009;25(5):339-341.
- 79. Paniagua N, Munoz N, Lopez R, et al. Randomized trial of two doses of oral dexamethasone versus prednisone/prednisolone for children with acute asthma exacerbations in pediatric emergency department. *Eur J Pediatr* Conference: 6th Congress of the European Academy of Paediatric Societies Switzerland 2016;175(11):1480.

80. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360(4):329-338.

- 81. Panigada S, Sacco O, Girosi D, et al. Corticosteroids may favor proliferation of thoracic inflammatory myofibroblastic tumors. *Pediatr Pulmonol* 2014;49(3):E109-E111.
- 82. Plint AC, Johnson DW, Patel H, et al; Pediatric Emergency Research Canada. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009;360(20):2079-2089.
- 83. Razi CH, Akelma AZ, Harmanci K, et al. The addition of inhaled budesonide to standard therapy shortens the length of stay in hospital for asthmatic preschool children: A randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2015;166(4):297-303.
- 84. Roberts GW, Master VV, Staugas RE, et al. Repeated dose inhaled budesonide versus placebo in the treatment of croup. *J Paediatr Child Health* 1999;35(2):170-174.
- 85. Roorda RJ, Walhof CM. Effects of inhaled fluticasone propionate administered with metered dose inhaler and spacer in mild to moderate croup: A negative preliminary report. *Pediatr Pulmonol* 1998;25(2):114-117.
- 86. Roosevelt G, Sheehan K, Grupp-Phelan J, et al. Dexamethasone in bronchiolitis: A randomised controlled trial. *Lancet* 1996;348(9023):292-295.
- 87. Sadowitz PD, Page NE, Crowley K. Adverse effects of steroid therapy in children with pharyngitis with unsuspected malignancy. *Pediatr Emerg Care* 2012;28(8):807-809.
- 88. Saito M, Kikuchi Y, Kawarai Lefor A, et al. High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age. *Eur Ann Allergy Clin Immunol* 2017;49(1):22-27.
- 89. Schuh S, Coates AL, Dick P, et al. A single versus multiple doses of dexamethasone in infants wheezing for the first time. *Pediatr Pulmonol* 2008;43(9):844-850.
- 90. Schuh S, Willan AR, Stephens D, et al. Can montelukast shorten prednisolone therapy in children with mild to moderate acute asthma? A randomized controlled trial. *J Pediatr* 2009;155(6):795-800.

- 91. Siomou E, Challa A, Tzoufi M, et al. Biochemical markers of bone metabolism in infants and children under intravenous corticosteroid therapy. *Calcif Tissue Int* 2003;73(4):319-325.
- 92. Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: A randomised equivalence trial. *Arch Dis Child* 2006;91(7):580-583.
- 93. Stafford L, Hope ME, Janney EP, et al. Comparison of paediatric steroid mixtures. *Australian Journal of Hospital Pharmacy* 1998;28(4):246-249.
- 94. Storr J, Barry BE, Barrell E, et al. Effect of a single oral dose of prednisolone in acute childhood asthma. *Lancet* 1987;1(8538):879-882.
- 95. Sumboonnanonda A, Suwanjutha S, Sirinavin S. Randomized controlled trial of dexamethasone in infectious croup. *J Med Assoc Thai* 1997;80(4):262-265.
- 96. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. *Acad Emerg Med* 1998;5(3):209-213.
- 97. Super DM, Cartelli NA, Brooks LJ, et al. A prospective randomized double-blind study to evaluate the effect of dexamethasone in acute laryngotracheitis. *J Pediatr* 1989;115(2):323-329.
- 98. Sussman S, Grossman M, Magoffin R, et al. Dexamethasone (16 alpha methyl, 9 alpha fluoroprednisolone) in obstructive respiratory tract infections in children. *Pediatrics* 1964;34(6):851-855.
- 99. Svedmyr J, Nyberg E, Åsbrink-Nilsson E, et al. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995;84(8):884-888.
- 100. Svedmyr J, Nyberg E, Thunqvist P, et al. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999;88(1):42-47.
- 101. Tagarro A, Pérez L, Quintero VM, et al. Dexamethasone does not reduce length of hospitalization or recurrent wheezing 1 year after early bronchiolitis. *Minerva Pediatr* 2014;66(2):131-140.
- 102. Tal A, Bavailski C, Yohai D, et al. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;71(1):13-18.

103. Tamura A, Matsubara K, Tanaka T, et al. Methylprednisolone pulse therapy for refractory mycoplasma pneumoniae pneumonia in children. *J Infect* 2008;57(3):223-228.

- 104. Teeratakulpisarn J, Limwattananon C, Tanupattarachai S, et al. Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: A randomized, double-blind, placebo-controlled trial. *Pediatr Pulmonol* 2007;42(5):433-439.
- 105. van Woensel JBM, Wolfs TFW, van Aalderen WMC, et al. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997;52(7):634-637.
- 106. Webb MSC, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986;61(1):15-19.
- 107. Zhang L, Ferruzzi E, Bonfanti T, et al. Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis. *J Paediatr Child Health* 2003;39(7):548-551.
- 108. Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: A prospective longitudinal assessment in the childhood asthma management program (CAMP) study. *Pediatrics* 2008;122(1):e53-e61.
- 109. Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: Effects on bone mineral density and growth. *Lancet Respir Med* 2014;2(6):487-496.
- 110. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of long-course oral corticosteroids in children. *PLoS ONE* 2017;12(1):e0170259.
- 111. Vatti RR, Ali F, Teuber S, et al. Hypersensitivity reactions to corticosteroids. *Clinic Rev Allerg Immunol* 2014;47(1):26-37.
- 112. Rieder M. Size and taste matters: Recent progress in the development of age-appropriate medicines for children. *Pharm Med* 2018;32(1):21-30.
- 113. Beigelman A, Durrani S, Guilbert TW. Should a preschool child with acute episodic wheeze be treated with oral corticosteroids? A pro/con debate. *J Allergy Clin Immunol Pract* 2016;4(1):27-35.

- 114. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. Arch Dis Child 2016;101(4):365-370.
- 115. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the united states: Population based cohort study. BMJ 2017;357;j1415.
- 116. Hartling L, Ali S, Dryden DM, et al. How safe are common analgesics for the treatment of acute pain for children? A systematic review. Pain Res Manag 2016;5346819.

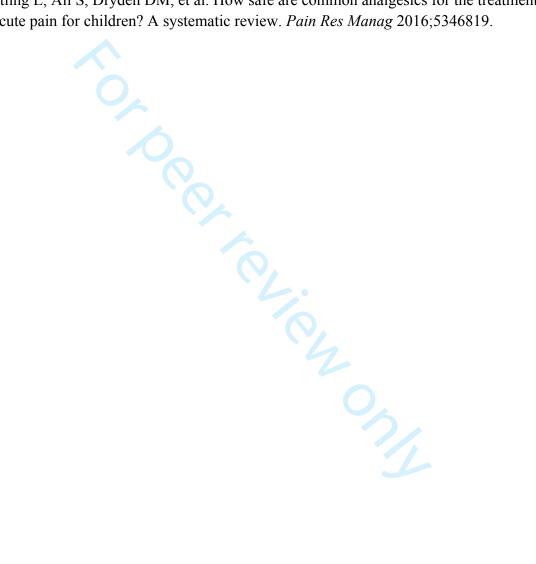


Table 5. Number of studies and participants reporting adverse events*

Organ system	AE - category	AE – specific	No. of studies	No. of
I., C 4° 0				participants
Infection &	Severe infections		5	1235
Respiratory	1)	Samaia	1	32
	1)	Sepsis		354
	2)	Superinfection	2	
	3)	UTI	1	720
	4)	Streptococcal infection	1 7	129
	Systemic infections		5	1635
	1)	Fever	3	963
	2)	Common	2	792
		viral/bacterial/fungal		
	2)	infection		1.4.40
	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	- Cittery	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	1	82
	7)	nebulizer mask	1	1
	7)	Psychosis	1	1
D (1 1 1	Headache		3	291
Dermatological	Burn		1	198
•	Integument	11.	10	1954
	1)	Hives	2	199
	2)	Rash	8	1954
	3)	Eczema	1	129
	4)	Eye irritation	2	211
	5)	Tongue irritation	1	82
	6)	Positive wheal	1	1
	7)	Bleeding from ear	1	720
	Phlebitis		1	32
Endocrine/Metabolic	Fluid and electrolyte		7	1849
& Musculoskeletal	abnormalities			
	1)	Hyperkalemia	1	800
	2)	Hyperglycemia	3	154
	3)	Glycosuria	1	125
	4)	Sodium retention	1	50
	5)	Dehydration	1	720
	Growth		6	731
	Adrenal suppression		5	249
	Bone health		5	579
Cardiovascular	Arrhythmia) ,	3	312
	1)	Tachycardia	2	178
	2)	Palpitations	1	134
	Hypertension		5	1491
	Congestive heart failure		1	50
General	General complaints		5	1146
	1)	Dizziness	1	87
	2)	Pallor	2	869
	3)	Excessive urination	1	134
	4)	Normal tooth eruption	1	56
	Hematology, gum bleeding		1	1
Immune System & Oncology	Immunosuppression		4	147
	1)	Immunosuppression	3	146
	2)	Tumor cell proliferation	1	1

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

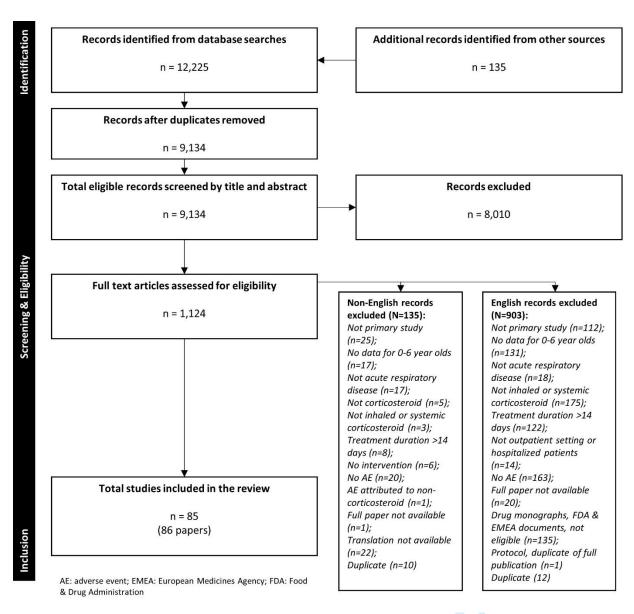


Figure 1. PRISMA study flow selection



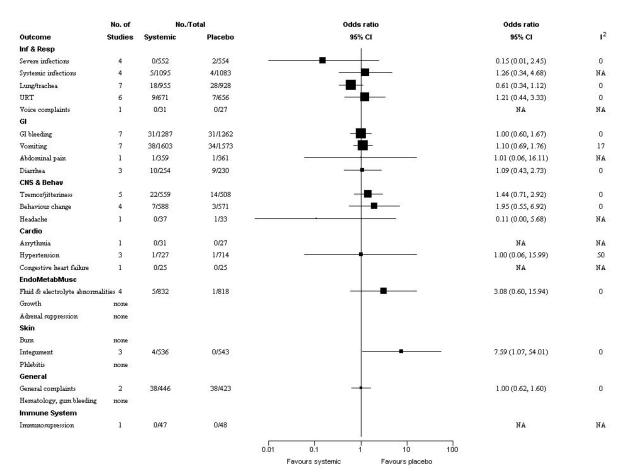


Figure 2. Forest plot of adverse events – systemic versus placebo

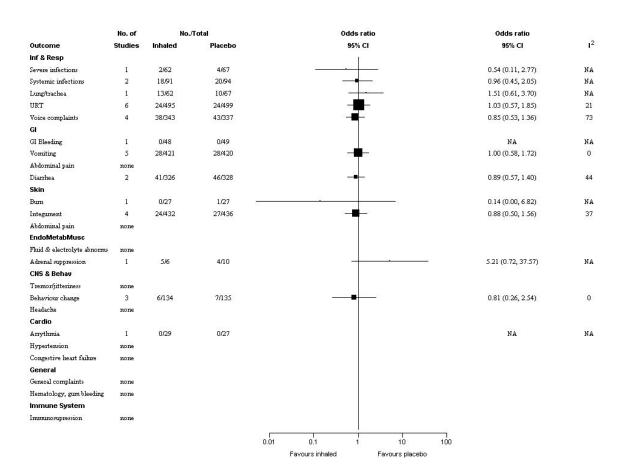


Figure 3. Forest plot of adverse events – inhaled versus placebo

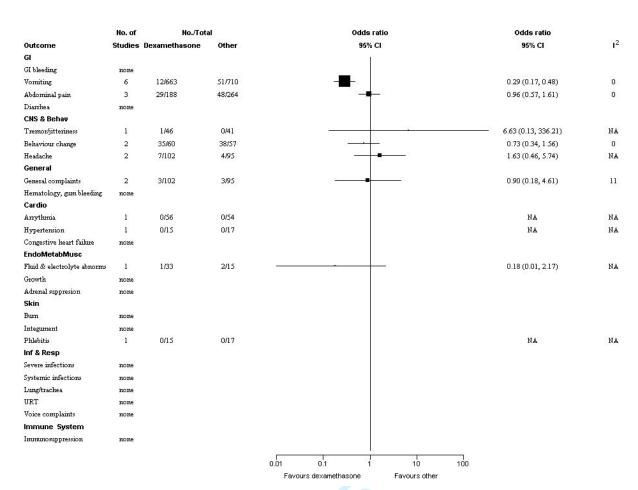


Figure 4. Forest plot of adverse events – dexamethasone versus other

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

2 3

4 5

6

7 8

9

10

11

12 13

14 15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

```
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.

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22 23

24 25

26

27

28 29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

60

```
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.
- beclovent*.tw,nm.
 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.

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43 44

45

46

47

48 49

50 51

52

53 54

55

56 57 58

59

60

```
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 pediatric* 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]

1

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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
- 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

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53

54 55

56 57 58

59

60

91. dyspne*: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
```

```
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

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25 26

27

28

29 30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

60

- 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.

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

```
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.
```

89. bronchospasm*.tw.90. croup*.tw.

88. bronchoconstrict*.tw.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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/

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45 46

47

48 49

50

51 52

53

54 55

56 57 58

59

60

```
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

2

4

5

6

7 8 9

10

11 12

13 14

15

16

17 18

19 20

21

22

23

24 25

26

27 28

29 30 31

32

33

34

35

36 37

38 39

40

41 42

43

44

45

46

47

48 49

50

51

52 53 54

59

60

- 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=WC0b 01ac058001d124

Date original search conducted: 9, 10 September 2014

Strategy:

Searched EMA reports for drug name keywords:

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

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

Supplement 2. Eligibility criteria for study inclusion

INCLUSION/EXCLUSION FORM

Revie				
Cuitoui		Vaa	N.a	110
Criteria		Yes	No	UC
	BLICATION TYPE			
	Primary research (RCTs, cohort studies, case control studies, case reports, and cas	e 📙		
series)				
Exclud				
•	Systematic reviews, letters to editor, commentaries			
2 Pon	ulation			
a.	Children ≤6 years of age, where age subgroups data is available:			
Unclea	3r.			
Officiea	If aggregate/subgroup data include but are not limited to age ≤6 years			
Exclud				
•	If data is reported in aggregate with older ages			
	ii data is reported iii aggregate with older ages			
3. CON	NOITION			
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			
Exclud	۵۰			
•	patients in NICU, PICU			
•	respiratory distress syndrome (newborn)			
•	allergic rhinitis			
•	animal studies			
•	anima stadies			
4. Inte	rvention			

a. All inhaled* and systemic (IV, IM, oral) corticosteroids used for ≤14 days per	r 🗌	
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		
topical (non systemic) controsterola therapy		
* inhaled (moderate- to high-dose) corticosteroids, following GINA guidelines for lo	w	
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 sin	nilarly 🔲	
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
 b. Summary characteristics of included studies - comparisons
 c. Characteristics of included studies
 p. 3
 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,	2, each (21)
Turkey	
Brazil, Germany, Mexico, Qatar	1, each (5)
SA & UK	1 (1)
Study designs	
RCT (all)	68 (80)
2-arm	52 (61)
3-arm	7 (8)
4-arm non-factorial	1 (1)
factorial 4 x4	4 (5)
crossover	2 (2)
trial registry	1 (1)
conference abstract	1 (1)
Non-RCT	5 (6)
Cohort	4 (5)
Case control	1 (1)
Case series	4 (5)
Case report	3 (4)
Number of centres	
Single centre	56 (66)
Multi-centre	24 (28)
Unclear/NR	5 (6)
Setting	
Inpatient	41 (48)
Outpatient	22 (26)
Inpatient & outpatient	21 (25)
NR	1 (1)

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 studies
		(no. o∰patients)	contributing
		on 1	data
		Au	(no. of patients)
2-arms	Systemic CS vs. placebo/no intervention/standard care	26 (41 6 6)	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 (23 7)	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)3	1 (80)
4-arms	Systemic CS vs. inhaled CS vs. non-CS vs. placebo	1 (114)	1 (114)
	Systemic CS + sal dose1 vs. systemic CS + sal dose2 vs. sal dose1 +	1 (70)g	1 (70)
	placebo vs. sal dose2 + placebo	Ap	
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal +	1 (69)	1 (69)
	placebo	7, 2	
	Systemic CS + non-CS vs. systemic CS + placebo vs. non-CS + placebo vs.	1 (800)	1 (800)
	placebo + placebo	by	
	Systemic CS + sal vs. systemic CS + placebo vs. sal + placebo vs. placebo	1 (32)မြ	0
Non-comparative (case	Systemic CS	5 (5) 👯	0
reports/series)	Mode of administration NR	2 (3) 호	0

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

Supplement 3c. Characteristics of included studies

Author,	Study	Respirato	Comparators,	Co-	Time points	Outcomes
_	design	l -	no. of		for	related to
year	_	ry condition		interventions;		
Country	Setting		participants	Maintenance	assessment	adverse
Funding	No. of	Age		CS	s;	events
source	centres	(range)			FU	
A la:	DCT	A -+ l	1) David a a sui dia	Callantanaal	Danalina at	Th
Alangari	RCT	Asthma	1) Budesonide	Salbutamol,	Baseline, at	The most
2014	ED	2-12y	500mcg/dose, 3	ipratropium &	1h, 2h, 3h	frequently
Saudi	1		doses 20min	prednisolone	and 4h	reported
Arabia			apart (neb),	No CC in	from the	adverse
Non-			n=458	No CS in	start of	effects were
industry			2) Placebo	preceding 7d	medication	fine tremors
funded			saline, 3 doses		S;	(17 cases) and
			20min apart		FU 72h	palpitations
			(neb), n=448		post-	(11 cases).
					discharge	None of the
						reported
						adverse
						effects was
						serious, and
			\sim			none was
						significantly different
						between the
				\bigcirc .		two groups.
Alansari	RCT	Bronchiol	1)	Epinephrine,	At study	Daily
2013	Pediatri	itis	Dexamethasone	oxygen &	entry, then	telephone
Qatar	C	<=18mo	1.0mg first day,	hydration	assessed if	surveillance (7
Non-	emerge	V-101110	then 0.6mg for	Hydration	ready for	days)
industry	ncy unit		4d (oral) + sal,	No CS in	discharge	revealed no
funded	1		5d total (neb),	preceding 48h	at 12h, 18h,	particular side
ranaca	-		n=102	preceding for	24h, 36h &	effect
			2) Placebo (oral)		48h;	concerns in
			+ sal, 5d total		FU by	either
			(neb), n=98		telephone	treatment
			()		1wk post-	group.
					discharge	9. 5 % P.
Aljebab	Cohort,	Asthma/c	SA	NR	After each	In SA and the
2017	3-arm	roup,	1)		dose	UK,
Saudi	Pediatri	palatabili	Dexamethasone	Most patients	(within	dexamethaso
Arabia &	c ED of	ty &	0.5mg/5mL	in	10min) &	ne had the
UK	hospital	tolerabilit	elixir (oral),	prednisolone	daily on D1-	highest
Unfunded		у	n=33	groups had	D5	palatability

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

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

	T					noted in the
						group B
						- '
						patients. No
						patient had a
						clinical
						deterioration,
						either in the
						emergency
						room or after
						discharge and
						no child had
						gastrointestin
						al bleeding or
						bacterial
						infection.
Altamimi	RCT	Asthma	1)	Salbutamol	2d & 5d	Two subjects
2006	Pediatri	2-16y	Dexamethasone		post-	in the
Canada	С	,	0.6mg/kg (max	No CS in	discharge &	prednisolone
Non-	hospital		18mg), single	preceding 2wk	every week	group
industry &	1		dose (oral),		to a	dropped out
industry	_		n=67		maximum	because of
funded			2) Prednisolone		of 3wk	repeated
Turiaca			1.0mg/kg (max		OI SWK	vomiting. Side
			30mg) twice			effects (table
			daily (oral),			5), n:
			n=67	\mathcal{O}_{\star}		Abdominal
			11-07	4		
						pain (2 dex vs.
						3 pred);
						Vomiting (0
					5	dex vs. 1
						pred);
				•		Headache (0
						dex vs. 0
						pred);
						Palpitation (0
						dex vs. 0
						pred);
						Excessive
						urination (0
						dex vs. 1
						pred)
Bacharier	RCT, 3-	At least 2	1) Montelukast	Albuterol,	Clinic visits	The 3 groups
2008	arm	wheeze	4.0mg once	prednisolone	4wk after	did not differ
USA		episodes	daily (oral) +	& other non-	randomizati	significantly in
33/1		chisoacs	daily (oral) i		Tanaomizati	Significantly iii

	1	1	T	T	1	
Non-	Clinical	in last	placebo ICS	asthma	on, then	several other
industry &	center	year	twice daily for	medications	every 8wk;	outcomes
industry	5	12-59mo	7d (neb), n=95		FU by	assessed over
funded			2) Budesonide	No more than	phone 2wk	the 1-year
			1.0mg twice	6 courses of	after	trial, including
			daily (neb) +	CS in past year	randomizati	oral
			placebo LTRA		on,	corticosteroid
			once daily (neb),		followed by	use, health
			n=96		calls 4wk	care use,
			3) conventional		after each	linear growth,
			therapy +		scheduled	quality of life,
			placebo		clinic visit	and
			(systemic +			frequencies of
			inhaled), n=47		Linear	adverse
					growth in	events.
			Multiple		height or	
			courses over 1yr		length	
					(assessmen	
					t method	
					NR) from	
			A		baseline to	
					study end	
					(12mo)	
Bisgaard	RCT	Wheeze	1) Budesonide	NR	Height &	Safety, as
2006	Clinical	1mo	400mcg/day for		bone	evaluated by
Denmark	researc		2wk (MDI),	NR	mineral	height and
Non-	h unit		n=149		density	bone mineral
industry &	1		2) Placebo once		measured	density, were
industry	_		daily for 2wk		using	not affected
funded			(MDI), n=145		Harpenden	by treatment;
10.110.00			(2.,,		stadiometry	the height at
			Multiple	•	at 3yrs of	three years of
			courses over		age	age measured
			3yrs		uge	by
			3413			stadiometry
						and bone
						mineral
						density
						measured by
						ultrasonograp
						hy at the
						phalanx were
						unaffected by
						unamected by

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



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

Buckingha	RCT	RSV	1)	Other	Enrolment	Serious
m 2002	Pediatri	(bronchio	Dexamethasone	treatment		adverse
USA		litis)			& daily until	events
	C	· ·	0.5mg/kg/dose	(not specified)	discharge;	
Non-	hospital 2	<24mo	every 12h for 4d	No CC in	FU 30d	occurred in 2
industry	2		(IV), n=22	No CS in	after	patients in the
funded			2) Placebo	preceding 3wk	enrolment	dexamethaso
			saline every 12h			ne group. One
			for 4d (IV), n=19			infant
						developed
						progressive
						respiratory
						failure that
						did not
						improve with
						high-
						frequency
						oscillatory
		· ·				ventilation or
						extracorporea
						I membrane
						oxygenation;
			\sim			support was withdrawn,
						and this infant
						died on study
				\bigcirc		day 38.
						Another
						subject
						developed
						pneumothora
						x, which
				•		resolved
						following
						placement of
						a pigtail
						thoracotomy
						catheter, on
						study day 7.
						Neither
						adverse event
						was judged to
						be related to
						administratio
						n of the study
	<u>I</u>	l		<u> </u>		

Bulow 1999 Denmark Non- industry funded	RCT Pediatri c hospital 3	RSV (bronchio litis) 0-2y	1) Prednisolone 5.0mg/ml at dose of 2mg/kg/day, first dose at enrolment and for 4d (oral), or methylprednisol one for patients with IV line (40.0mg/ml at dose of 1.5mg/kg/day) for 5d (IV), n=73 2) quinine hydrochloride (or saline for	Beta-2- agonist, antibiotics, oxygen & hydration No CS in preceding month	Enrolment & 5d; FU 1mo & at 1y	drug. No patients in either group had microscopic or gross gastrointestin al bleeding, and no patients required antihypertensi ve therapy during the study. 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.
			patients with IV line) for 5d (IV), n=74			cases.
Chang 2008 Australia Non- industry & industry funded	RCT Pediatri c & general ED 3	Asthma 2-15y	1) Prednisolone 1.0mg/kg (max. 50.0mg/day) for 3d + placebo solution for 2d (oral), n=101 2) Prednisolone 1.0mg/kg (max.	NR No maintenance CS or CS preceding presentation	24h, 48h, D5, D7, D10, D14 & D28	There were five recorded adverse events, with no significant difference between groups. In the 3-day group,

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

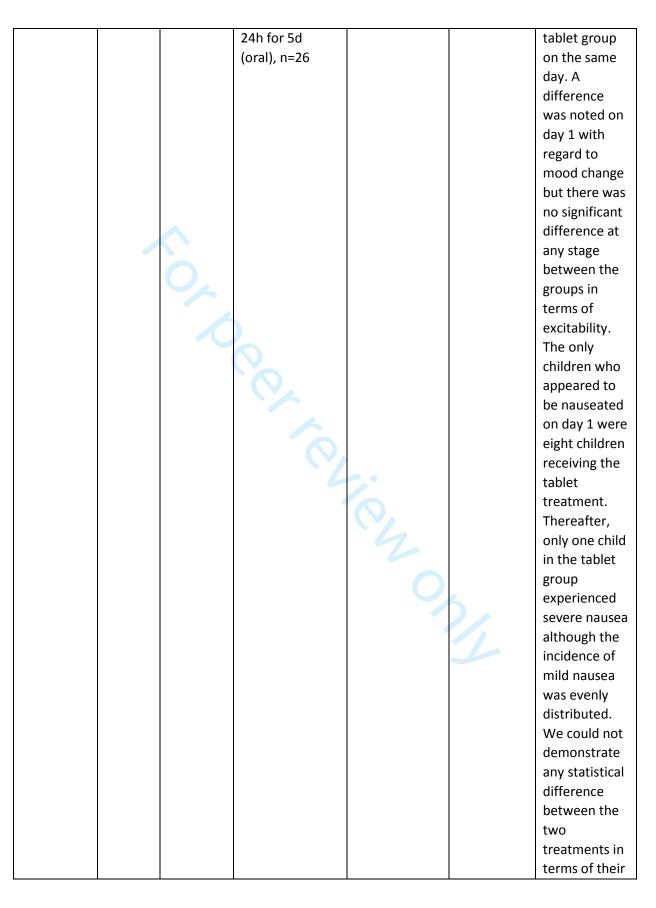
	1	T	0.6		T	<u> </u>
			0.6mg/kg, single			
			dose (IV), n=21			
Clavenna	RCT	Wheeze	1)	Paracetamol,	Entry visit,	No
2014	Family	1-5y	Beclomethason	nasal saline	D11 (or	differences
Italy	pediatri		e 400mcg (1ml)	irrigation &	prior if	were found in
Non-	c health		twice daily for	antibiotics	requested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

	l	<u> </u>		<u> </u>	<u> </u>	Alaman de alle
						though there
						was a trend
						towards
						decreasing
						tachypnoea in
						all four
						groups.
Connolly	RCT	RSV	1) Prednisolone	Ampicillin,	FU 1mo &	There was no
1969	Hospita	Bronchiol	D1=15.0mg;	oxygen	1y	evidence in
Ireland	1	itis	D2-3=10.0mg;			this trial that
Funding NR	1	0-2y	D4-5=5.0mg;	NR		prednisolone
			D6-7=2.5mg			treatment of
			(NR, likely IV),			the patients
			n=47			affected the
			2) Placebo (NR,			antibody
			likely IV), n=48			response. In
			, "			the dosage
						used in this
						trial,
						prednisolone
			4			had no
						beneficial or
			(V)			harmful
						effects on the
						course of the
			•	\sim		disease in
						severely ill children.
						There were
	207		4)		1	no deaths.
Corneli	RCT	Bronchiol	1)	Not specified	Baseline, 1h	There were
2007	ED	itis	Dexamethasone		& 4 h;	few adverse
USA	20	2-12mo	1.0mg/kg (max.	No CS in	FU at 7-10d	events. No
Non-			12mg), single	preceding 14d	by	infant had
industry &			dose (oral),		telephone	gastrointestin
industry			n=305			al bleeding,
funded			2) Placebo			hypertension,
			solution			or
			1.0ml/kg (max.			complicated
			12ml), NR (oral),			varicella.
			n=295			Vomiting
						within 20 min
						after
						administratio
<u> </u>	<u>I</u>	l .	<u> </u>	<u> </u>		

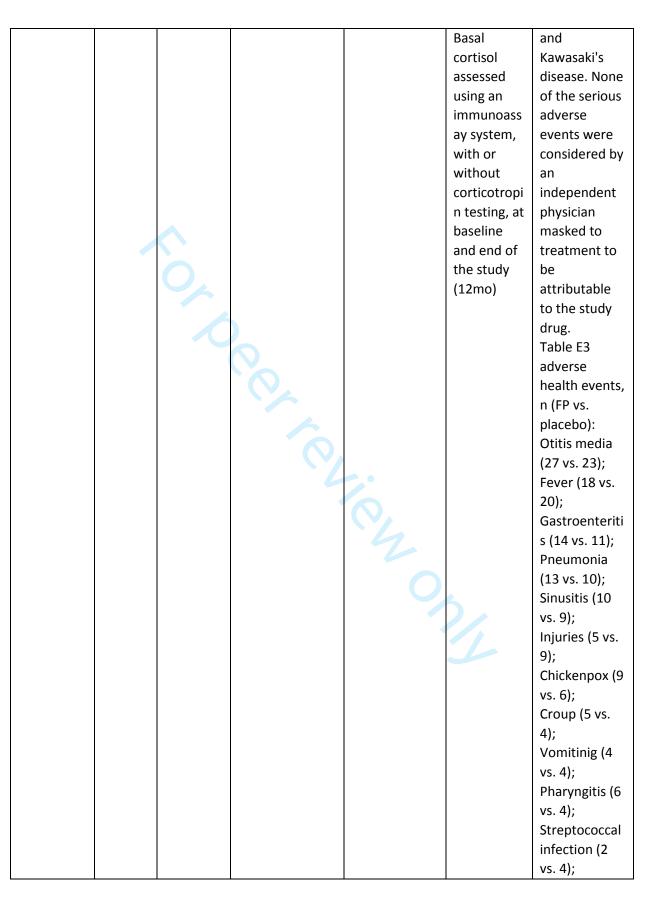
						n of study
						medication
						(5.5% in dex; 4.7% in
						placebo). Pneumonia
						was diagnosed in
						three infants;
						two were in
						the placebo
						group, and an
						empyema
		U 2				developed in
						one of these
						two infants.
Cronin	RCT	Asthma	1)	Regular	Baseline &	Seven
2016	Tertiary	2-16y	Dexamethasone	inhaled	D4 for	patients in the
Ireland	hospital	,	0.3mg/kg (max.	bronchodilato	primary	PRED group
Non-	ED		12.0mg) single	rs prior to	outcome;	(5.7%)
industry	1		dose, n=123	enrolment in	14d period	vomited
funded			2) Prednisolone	trial	for adverse	within 30
			1.0mg/kg per		events	minutes of
			day, once daily	No IV or oral		the dose of
			(max. 40.0mg)	CS in previous		steroid on day
			for 3d, n=122	4wk		1 in the ED
				7		compared
						with none in
						the DEX group
					5	(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

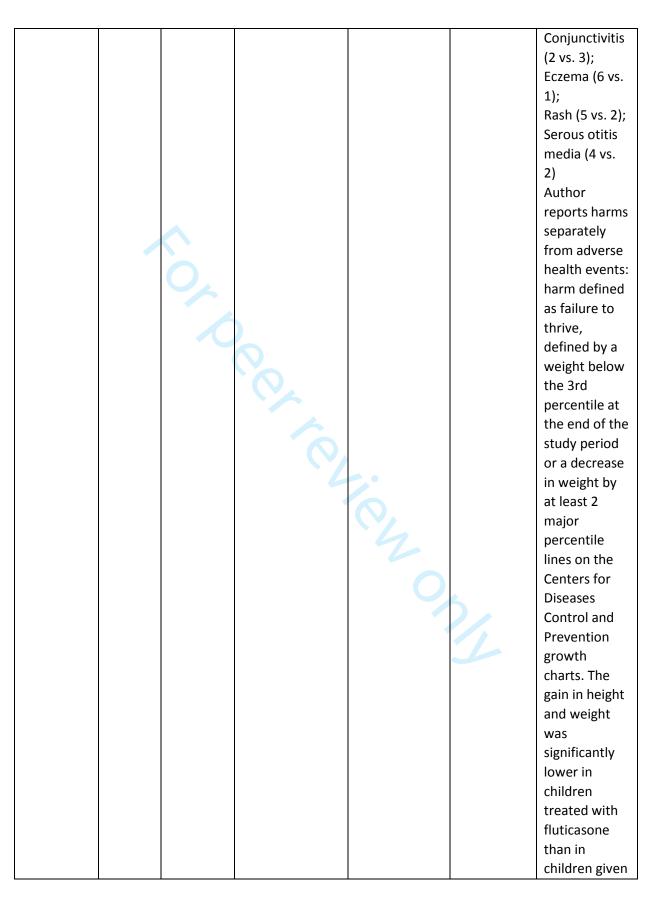
						vomited after
						at least 1 dose
						of
						prednisolone.
						No other
						adverse
						events
						attributable
						to the study
						medications
						were noted.
Csonka	RCT	Viral	1) Prednisolone	NR	Diary	Fifteen
2003	Pediatri	respirator	2.0mg/kg in ED		recordings	children (4 in
Finland	c ED	У	followed by	NR	twice daily	the placebo
Non-	1	infection-	2.0mg/kg/day		for 14d;	group and 11
industry		induced	for 3d (oral),		examinatio	in the
funded		lower	n=113		n by	prednisolone
		airway	2) Placebo		physician	group)
		disease	10.0mL fructose		14d-21d	discontinued
		6-35mo	in water (in ED)		post-ED	the study
			followed by		visit	medication
			subsequent			because of
			doses for 3d,			perceived side
			n=117			effects. The
						reported
				4		reactions
						were mild and
						resolved
						without
					5	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.

Dawson RCT Asthmatical Dawson RCT Dawson Dawson RCT Dawson Da	Daugbjerg	RCT, 4-	First or	1) Prednisolone	NR	Daily for 5d	No side
Denmark Non- industry & depart ment funded Denmark Non- industry & depart ment funded Solution (oral) + budesonide					INIX	l -	
Non- industry & depart industry funded Solution (oral) + terbutaline on 1.2-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb) + terbutaline on 1.2-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb) + terbutaline on 1.2-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb) + terbutaline on 1.2-0.2mg/kg (4ml) every 4h until discharge or for 5d, n=29 3) Placebo solution (oral) + placebo (neb) + terbutaline on 1.2-0.2mg/kg (4ml) every 4h until discharge or for 5d, n=29 3) Placebo solution (oral) + placebo (neb) + terbutaline on 1.2-0.2mg/kg every 4h until discharge or for 5d (neb) n=27 4) Placebo solution (oral) + placebo (neb) + placeb		-			No CS		
industry & industry & ment funded S						uisciiaige	•
industry funded S			0-181110				
funded 5	,			_ ·	Study		· ·
Australia Part Australia I Australia	•						
Dawson RCT Asthma O.12-0.2mg/kg every 4h until discharge or for 5d (neb) + placebo (neb), n=27 4) Placebo solution (oral) + placebo (neb), n=27 4) Placebo solution (oral) + placebo (neb) + terbutaline O.12-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb) + terbutaline O.12-0.2mg/kg (4ml) every 4h until discharge or for 5d (neb) + terbutaline O.12-0.2mg/kg every 4h until discharge or for 5d (neb) + placebo (neb) + terbutaline O.12-0.2mg/kg every 4h until discharge or for 5d (neb) + placebo (neb) + placebo (neb) + placebo (neb) + placebo solution (oral) + placebo solution took it easily on day 3, compared to	funded	5					
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) + 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 4) Placebo solution (oral) + placebo saline (neb), n=27 4) Placebo solution (oral) + placebo saline (neb), n=27 4) Placebo solution (oral) + placeb				` ' '			
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 solution				_			-
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				I			
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, 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 solution (oral) + placebo solution (oral) + placebo saline (neb), n=27 Hospita Australia Industry							_
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 soline (neb), n=27 Dawson 1993 Hospita Australia Industry Indu							•
Dawson Part Asthma Placebo (neb) + placebo (ne				· · ·			
Dawson RCT Asthma 1) Prednisolone (neb), n=27 Dawson Boy Hospita 46.5y 1.0mg/kg Australia Industry 1 Industry 2 Industry 2 Industry 3 Industry 4 Industry 4 Industry 4 Industry 5 Industry 6 Industry 7 Industry 8 Industry 8 Industry 8 Industry 9 Industry							the treatment
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 Dawson RCT Asthma 1) Prednisolone (neb), n=27 Dawson Hospita <6.5y 1.0mg/kg Australia I tablets, every NR Industry 1 24h for 5d (oral), n=25							groups
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 solution (oral) + placebo solution (oral) + placebo saline (neb), n=27 4) Placebo solution (oral) + placebo saline (neb), n=27 None Dawson 1993 Hospita 46.5y 1.0mg/kg Australia I I tablets, every Industry I I orally n=25 2) Prednisolone 1.0mg/kg solution, every Industry I I orally n=25 2) Prednisolone 1.0mg/kg solution, every I I orally n=25 I I orally n=1 I I orall				_			-
Dawson RCT Asthma (neb), n=27 Hospital Hospital Australia I Hospital Industry 1 Industry 2 Industry 3 Industry 4 Industry 4 Industry 5 Industry 6 Industry 6 Industry 6 Industry 6 Industry 7 Industry 7 Industry 8 Industry 8 Industry 9 Industry				or for 5d (neb) +			with placebo.
Compared to				terbutaline			
Dawson RCT Asthma 1) Prednisolone (neb), n=27 Hospita Hospita I tablets, every Industry 1 Dawson Industry				0.12-0.2mg/kg			
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 solution (oral) + placebo saline (neb), n=27 Dawson 1993 Hospita Hospita Hospita I Industry I I Industry I I I I I I I I I I I I I I I I I I I				(4ml) every 4h			
Dawson 1993 Hospita 46.5y 1.0mg/kg Australia I 24h for 5d Industry 1 1 24h for 5d Industry 1 1 24h for 5d Industry 1 1 20 2 1.0mg/kg Industry 1 1 2 24h for 5d Industry 1 1.0mg/kg Industry 1 1.0mg/kg Industry 1 2.0mg/kg Industry 2 2.0mg/kg Industry 3 2.0mg/kg Industry 4 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3				until discharge			
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 solution (or				or for 5d, n=29			
Dawson RCT Asthma 1) Prednisolone (neb), n=27 Hospita I Lomg/kg Australia I Lomg/kg Industry 1 Industry 24h for 5d (oral), n=25 Industry 2) Prednisolone (oral), n=25 Industry 2) Prednisolone (oral), n=25 Industry 2) Prednisolone (oral), n=25 Industry 3, compared to				3) Placebo			
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 Dawson 1993 Hospita Australia I Industry 1 1 24h for 5d (oral), n=25 (oral), n=25 2) Prednisolone 1.0mg/kg solution, every Hospita 10 10 10 10 10 10 10 10 10 10 10 10 10				solution (oral) +			
Dawson RCT Asthma 1) Prednisolone (neb), n=27 Hospita I Lablets, every 10 NR RCT Asthma 1) Prednisolone (neb) + placebs, every 10 NR Australia I Lablets, every 10 Lablets,				placebo (neb) +			
every 4h until discharge or for 5d (neb), n=27 4) Placebo solution (oral) + placebo saline (neb), n=27 Dawson 1993 Hospita				terbutaline			
discharge or for 5d (neb), n=27 4) Placebo solution (oral) + placebo (neb) + placebo saline (neb), n=27 Dawson 1993 Hospita				0.12-0.2mg/kg	4		
Dawson 1993 Australia Industry funded BCT Asthma I) Prednisolone tablets, every funded Coral), n=25 2) Prednisolone 1.0mg/kg solution, every Solution (oral) + placebo solution (oral) + placebo (neb) + placebo saline (neb), n=27 None D1 to D5 Twenty-one of the children taking the solution took it easily on day 3, compared to				every 4h until			
Dawson 1993 Australia Industry funded BCT Asthma I) Prednisolone tablets, every funded Coral), n=25 2) Prednisolone 1.0mg/kg solution, every Std (neb), n=27 None D1 to D5 Twenty-one of the children taking the solution took it easily on day 3, compared to				discharge or for			
Solution (oral) + placebo (neb) + placebo saline (neb), n=27 Dawson 1993 Hospita						4	
Solution (oral) + placebo (neb) + placebo saline (neb), n=27 Dawson 1993 Hospita							
placebo (neb) + placebo saline (neb), n=27 Dawson RCT Asthma 1) Prednisolone None D1 to D5 Twenty-one of the children tablets, every 1 tablets, every 24h for 5d (oral), n=25				·			
Dawson RCT Asthma 1) Prednisolone None D1 to D5 Twenty-one of the Australia I tablets, every 1 taking the funded (oral), n=25 (orall), n=25 (ora				I			
Dawson RCT Asthma 1) Prednisolone None D1 to D5 Twenty-one of the Australia I tablets, every Industry 1 (oral), n=25 (orall),				·			
Dawson RCT Asthma 1) Prednisolone None D1 to D5 Twenty-one of the Australia I tablets, every 1 taking the funded Coral), n=25				·			
1993 Hospita <6.5y 1.0mg/kg	Dawson	RCT	Asthma		None	D1 to D5	Twenty-one
Australia I tablets, every 1 24h for 5d taking the solution took it easily on day 3, solution, every 2 tablets, every 1 tablets, every 2 tablets, every 3 tablets, every 4 tablets, every 4 tablets, every 5 tablets, every 5 tablets, every 6 tablets, every 7 tablets, every 8 tablets, every 8 tablets, every 8 tablets, every 9 table						30 23	-
Industry 1 24h for 5d (oral), n=25 solution took it easily on day 3, solution, every taking the solution took			,	J. J.	NR		
funded (oral), n=25 2) Prednisolone 1.0mg/kg day 3, solution, every compared to		1					
2) Prednisolone 1.0mg/kg solution, every it easily on day 3, compared to		-					_
1.0mg/kg day 3, solution, every compared to	7anaca						
solution, every compared to				-			-
							-
two in the				Solution, every			-
		<u> </u>			<u> </u>		two iii tile



		1	<u> </u>	T	T	
						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	RCT	>=3	1)Fluticasone	Albuterol,	Monthly	Thirteen
2009	Hospita	wheeze	propionate	nasal saline	telephone	serious
Canada	1	episodes	250mcg (3	irrigation	contacts	adverse
Non-	5	in	doses twice		and a	events (4 in
industry &		lifetime,	daily at start of	No more than	medical	fluticasone
industry		onset of	URTI) until 48h	1 dose of CS in	visit every	group and 9 in
funded		URTI	elapsed without	preceding	4mo;	placebo)
		1-6y	symptoms, for	6mo or 2		occurred in 13
			max. 10d (MDI),	doses in	Growth	children
			n=62	preceding	assessed	during the
			2) Placebo (3	12mo	using an	study period -
			doses twice		upright	namely,
			daily at start of		stadiomete	pneumonia,
			URTI until 48h		r at	seizure,
			elapsed without		baseline,	admission to
			symptoms		every	an intensive
			(MDI), n=67		month, and	care unit,
					at the end	burn,
			Multiple		of follow-	respiratory
			courses over 6-		up (6-	syncytial virus
			12mo		12mo);	infection,
						atelectasis,
						atelectasis,





Γ	I	1	1	1		alasali. Ol
						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
				$\langle \cdot \rangle$		density, bone
						mineral
						content, or
						bone age; low
						values for
						these and
						cortisol were
						normal when
						repeated or
						when
						corticotropin
						testing was
et	DCT C	C	4)	0	D . C .	performed.
	RCT, 3-	Croup	1) L-epinephrine	Oxygen	Before	The L-
2010	arm	6mo-5y	5.0ml (1 of	N 00:	treatment	epinephrine
Greece	Pediatri		1:1000mg/ml),	No CS in	& at 15min,	group was the
Funding NR	c ED		5-10min (neb),	preceding 24h	20min,	only group
	1		n=25		60min,	with side
					90min &	effects of

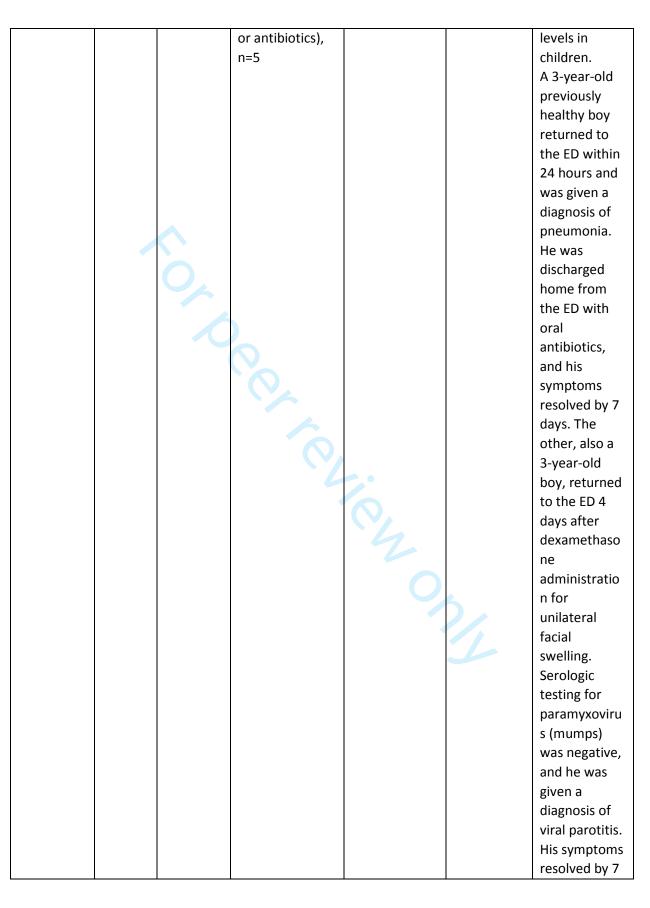
			2)		120min	troatmont
			2)		120min	treatment.
			Dexamethasone		post-	Tremor and
			0.6mg/kg (max.		treatment;	tachycardia
			8mg), single		patients	were
			dose (IM), n=19		asked to	observed in 4
			3)		return if	children from
			Beclomethason		relapse in	Group A, who
			e dipropionate		next 24h	had received
			200mcg (MDI),			LE and were
			n=20			resolved after
						2 hours, when
						the action of
						LE wear off.
Eden 1967	RCT	Croup	1)	Oxygen,	Every 6h for	No untoward
USA	Hospita	8mo-5y	Dexamethasone	humidity &	total 48h	effects were
Industry	1		0.10mg/kg at	tetracycline		noted. There
funded	1		0.1cc/kg/dose	,		were no
			every 6h for	NR		episodes of
			48h, total daily			congestive
			0.40mg (IM),			heart failure
			n=25			or sodium
			2) Control			retention.
			preparation			reterrition.
			0.1cc/kg/dose			
			every 6h for 48h			
			(IM), n=25	\sim		
Escobedo	RCT	Asthma	1)	Saline,	Baseline &	We detected
Chavez	Hospita	1mo-14y	Methylprednisol	salbutamol &	discharge	no side
1992	I ED	11110-14y	one 3.0mg/kg,		uiscriarge	effects with
Mexico			single dose (IM)	oxygen		the use of
	1			No CC in		
Industry			+ placebo 4.5ml	No CS in		methylprednis
funded			+ sal 0.5ml	preceding 15d		olone in a
			every 4h (neb),			single dose or
			n=25			any treatment
			2)			failures that
			Aminophylline			merited the
			5.0mg/kg every			use of
			6h (IV) + sal 70			methylxanthin
			mcg/kg every 8h			es or
			+ oxygen (neb),			additional
			n=25			steroid doses.
Fifoot 2007	RCT, 3-	Croup	1) Prednisolone	Antipyretics or	Baseline &	No patient
Australia	arm	6mo-6y	0.2ml/kg of	nebulized	hourly up	suffered any
			1.0mg/kg, single	adrenaline		adverse

Nan	Da diatai	T	da / ()		+ - 4l+	
Non-	Pediatri		dose (oral),		to 4h post-	outcomes
industry	c ED		n=34	No CS in	treatment;	from receiving
funded	1		2)	preceding wk	FU 1wk by	study steroid,
			Dexamethasone		telephone	either at
			0.2ml/kg of		following	index
			0.15mg/kg,		index visit	presentation
			single dose			or during the
			(oral), n=34			follow-up
			3)			period. One
			Dexamethasone			patient from
			0.2ml/kg of			each group
			0.6mg/kg, single			vomited their
			dose (oral),			first dose of
			n=31			medication,
						all except one
						(dex
						0.6mg/kg)
						tolerated
						second dose.
Fitzgerald	RCT	Croup	1) Budesonide	Additional	Baseline,	Six patients in
1996	Pediatri	6mo-6y	2.0mg (4ml) for	medications	30min,	each
Canada	c ED	,	5min (neb),	permitted 2h	60min,	treatment
Industry	3		n=35	after study	90min,	group
funded			2) Adrenaline		120min,	reported
			4.0mg (4ml) for	No CS in	12h & 24h	adverse
			5min (neb),	preceding 4wk	post-	events. These
			n=31		treatment	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

	I	<u> </u>		I	1	: : ::
						specific
						treatment.
Francis	RCT	Asthma	1) Fluticasone	NR	D1 to D7	Most frequent
1997	(trial	≤48mo	propionate			adverse
Australia	registry		1.0mg twice	No CS		events – on-
Funding NR	data)		daily (neb) +	treatment for		therapy, n (FP
	Acute		placebo tablets	>7d in		vs. pred):
	care		once daily (oral)	preceding 4wk		Nausea &
	setting		for 7d, n=37			vomiting (7
	4		2) Prednisolone			vs. 1);
			(dose NR) daily			Diarrhoea (3
			for 7d (oral),			vs. 0);
			n=19			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);
				4		Asthma (1 vs.
						2);
						Hoarseness/d
					4	ysphonia (0
						vs. 2);
						Serious
						adverse
						events - on-
						therapy:
						Subjects with
						non-fatal SAEs
						(2 vs. 0):
						Ketonuria,
						glycosuria and
						hyperglycaem
						ia (1 vs. 0);
	<u> </u>	<u> </u>	<u> </u>	<u> </u>	<u> </u>	(1 00.0),

					<u> </u>	Subjects with
						fatal SAEs (0
						•
Caulantt	DCT	Carrie	4)	A t :	FILE	vs. 0)
Garbutt	RCT	Croup	1)	Acetaminophe	FU	No serious
2013	Primary	1-8y	Dexamethasone	n & ibuprofen	interviews	adverse
USA	care		0.6mg/kg (max.	No CC	at D1 to D4	events
Non-	office		18mg), single	No CS	& D11;	occurred.
industry funded	10		dose, followed	preceding	FU chart	Study groups did not differ
Tunded			by placebo for	current croup	review within 28d	
			2d, 2 doses total	episode	of index	in reporting side effects
			(oral), n=46 2) Prednisolone		visit	from the
			2.0mg/kg/d		VISIC	study
			(max. 60mg/d)			medications
			for 3d (oral),			(24%
			n=41			dexamethaso
			11-41			ne, 26%
						prednisolone,
						P = 1.0; Table
						4). The most
						common side
						effects
						identified
						with specific
						questioning
						were mood
				1		changes
						(57%), sleep
						problems
					4	(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);

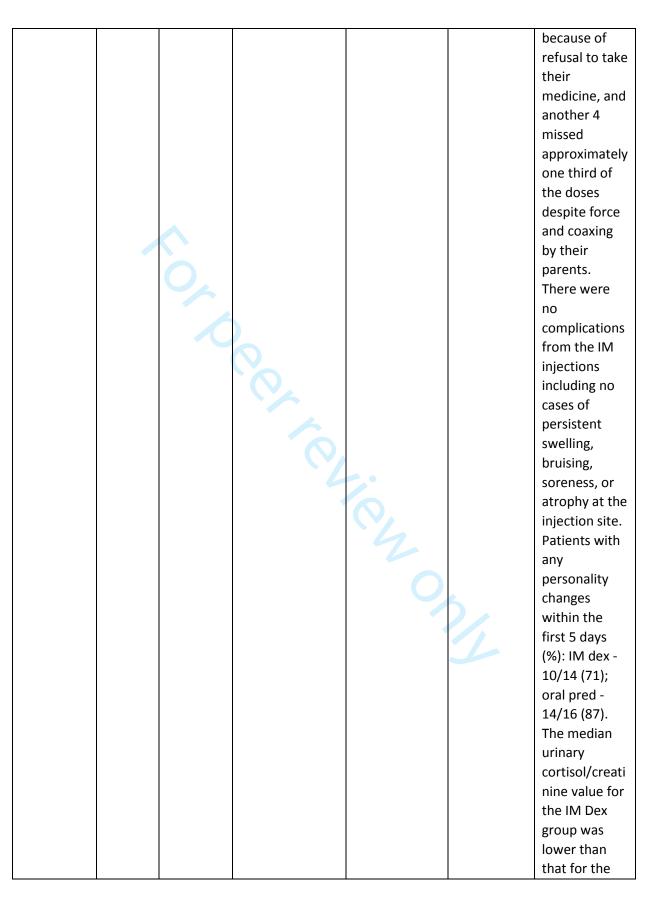
Chinas	NDCT			ND		New sleep problems (18 vs. 13); Stomach pain (9 vs. 7); Headache (7 vs. 4); Vomiting (3 vs. 7); Nausea (3 vs. 4); Dizziness (3 vs. 2); Tremor (1 vs. 0)
Ghirga 2002	NRCT NR,	Wheeze - early	1) Beclomethason	NR	Twice daily	At this writing, four
Italy	"ambul	URTI	e 400mcg 3	NR		years after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



Goebel	RCT	Bronchiol	1) Prednisone	NR	Clinical	days. Four participants visited their primary care physician within 7 days of dexamethaso ne administratio n. One patient was healthy, another was given a diagnosis of otitis media and treated with oral antibiotics, and two patients who had persistent coughs were prescribed salbutamol. None of the participants were admitted to hospital, and there were no serious adverse events or deaths. One patient in interest of the participant of the particip
2000	Pediatri	itis	2.0mg/kg/day	ND	scores on	the
USA Funding NR	c ED or childre	≤23mo	for 5d (oral) + albuterol	NR	D0, D2, D3 & D6;	prednisolone group was
i dildilig ivit	n's		0.3mg/kg/day		FU when	observed by
	clinic		(or		convalesce	his caretakers
	2		0.15mg/kg/dose		nce	to be "jittery"
	_		(neb)) for 5d		completed	at times after
					completed	
			(oral), n=24			enrollment.

	T	ı			I	
			2) Placebo			This resolved
			solution (oral) +			after a
			albuterol			decrease in
			0.3mg/kg/day			the albuterol
			(or			dose. No
			0.15mg/kg/dose			evidence of
			(neb)) for 5d			treatment
			(oral), n=24			complications
			(//			was observed
						in any of the
						other
						patients.
Grant 1996	Cohort	Asthma	1) Prednisone	Bronchodilato	NR	Ninety-four
USA	Primary	2-14y	2.0mg/kg (max.	rs as needed	INIX	episodes of
	•	Z-14y		is as fieeded		· .
Non-	care		60mg/day),	NB		acute
industry	clinic &		single dose	NR		infection
funded	teachin		intermittent for			occurred in 50
	g	,	6mo (oral),			subjects and
	hospital		n=86			222 episodes
	ED		2) Placebo (NR),			of symptoms
	1		n=86			of infection
						occurred in 62
			Multiple			subjects
			courses over 1yr			(table 1
						episodes of
						infection,
				4		number of
						doses, and
						association
					4	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
						WILLI LIIOSE

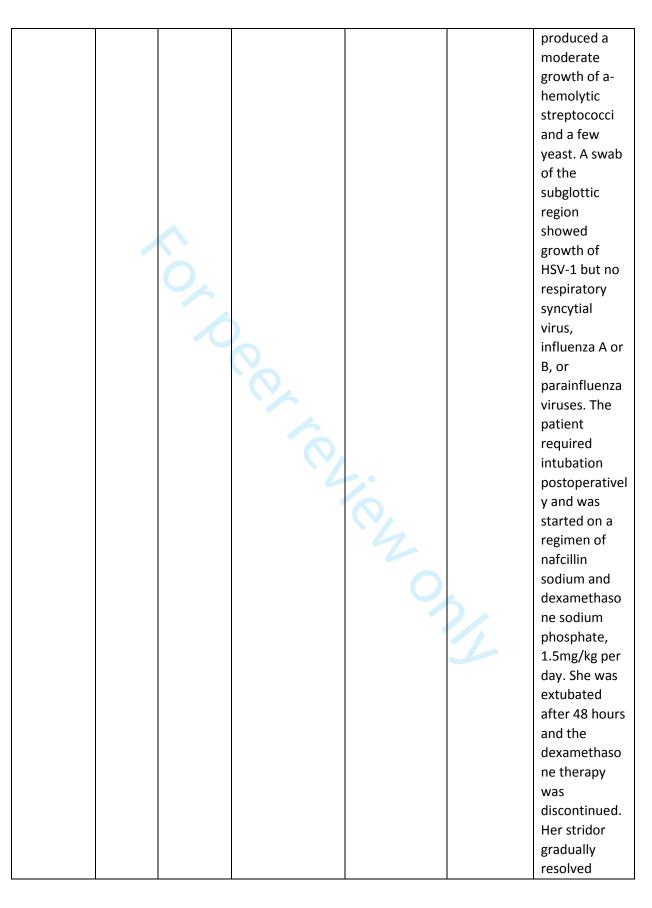
,				1		
						without the
						infection. No
						correlation
						was observed
						between the
						number of
						doses of
						prednisone
						received and
						the number of
						episodes of
						-
						each
						infection. This
						included all
						episodes of
						otitis media,
						streptococcal
						pharyngitis,
						pneumonia,
						and urinary
						tract
						infection;
						eight (73%)
						episodes of
						chickenpox;
						eight (57%)
						episodes of
						skin
						infections;
						and 14 (88%)
						episodes of
0 1 2000	DCT	A - 1 l	4)	Alle Level	D2 DE D7	ringworm.
Gries 2000	RCT	Asthma	1)	Albuterol	D3, D5, D7,	Ten of the 17
USA	Tertiary	6mo-7y	Dexamethasone		D14 & D28;	children who
Funding NR	care		1.7mg/kg/dose	No CS in		received PO
	center		single dose, (IV),	preceding 2wk	Urinary	Pred took the
	1		n=15		cortisol/cre	prednisone
			2) Prednisolone		atinine	without much
			2.2mg/kg/dose,		assessed by	difficulty.
			twice daily for		radioimmu	However, 3
			5d (oral), n=17		noassay	children
					(standard	missed more
					methods)	than 75% of
					on D14	their doses
<u> </u>		<u> </u>	<u> </u>		<u> </u>	



	T .	T	T		Ī	
						PO Pred
						group, but
						this difference
						was not
						statistically
						significant.
Hedlin	RCT	Asthma –	1) Budesonide	Beta-agonists	D10 & D13;	There were
1999¹	Pediatri	first sign	400mcg, 4 times	and/or		no significant
Sweden	С	of URTI	daily for 3d then	theophylline	Routine	differences
Funding NR	hospital	1-3y	twice daily for		height	between
	1		7d (MDI), n=9	NR	measureme	pretreatment
			2) Placebo, 4		nts	and post-
			times daily for 3		(assessmen	treatment
			days then twice		t method	serum
			daily for 7d		NR) were	cortisol,
			(MDI), n=11		taken	osteocalcin,
					(timing of	ICTP and urine
			Multiple		assessment	cortisol/creati
			courses over		s NR);	nine ratio in
			1yr, or max. 6			the groups,
			treatments		Serum	(the
					cortisol (on	comparison
			*subgroup of		D8-10 of	was made in
			children from		second	the children
			Svedmyr 1999		course of	who had
			with		study	assessments
			therapeutic	4	medication,	before and
			failure from		morning of	after
			budesonide		day after	budesonide/p
			given 3d course		third dose,	lacebo) nor
			(6.0mg, 4.0mg,		and at 12-	were there
			and 2.0mg on		14d after	any significant
			respective days)		therapy)	differences
			of oral		and urinary	between the
			betamethasone		cortisol/cre	active and
					atinine (in	placebo
					the night	treated
					after third	groups. It
					dose of	was, however,
					betamethas	noteworthy
					one and at	that the urine
					12-14d	cortisol/creati
					after	nine ratio
					therapy)	decreased in
	l	I.	<u> </u>		11	

				<u> </u>		Г /С ala:1.ala.
					assessed by	5/6 children
					radioimmu	studied in the
					noassay	active group
						and in 4/10 in
						the placebo
						group.
						Neither this
						change nor
						the difference
						was
						statistically
						significant.
						PIIINP
						decreased
						after both
						budesonide
						and placebo
		\				treatment
						periods (p<
						0.05). Short
						courses of
						oral
						betamethaso
						ne have
						pronounced
						systemic
						effects,
						whereas 10d
						of high doses
						of budesonide
						do not
						produce
						significant
						systemic
Lluch:	DCT	Cro	1) Dudaas: da	Antihintin	Doceline 0	effects.
Husby	RCT	Croup	1) Budesonide	Antibiotics	Baseline &	No side
1993	Pediatri	3mo-4.9y	1000mcg (2ml	N = CC	2h post-	effects were
Denmark	C		500mcg/ml),	No CS	treatment	reported.
Funding NR	hospital		two doses	preceding		
	1		30min apart	study		
			(neb), n=20			
			2) Placebo			
			saline 0.9%			
			(2ml), two			
	<u> </u>					

			doses 30min			
			apart (neb), n=16			
Inglis 1993 USA Funding NR	Case report, 2 Hospita I	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/cla vulanate 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 tracheobronc hial tree. Cultures were positive for HSV-1, Staphylococcu s 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



	1	T		Г	Т	Г
						spontaneousl
						y over the
						next 7 days
						without
						further
						intervention.
Jan 2000	Non-	Asthma	1) Group A:	NR	D1 to D3	An acute
Taiwan	RCT	NR	Methylprednisol			effect of
Funding NR	Pediatri		one	NR		glucocorticoid
	С		1.0mg/kg/6h			therapy on
	hospital		(IV) for 1d,			the
	clinic		n=NR			suppression
	1		2) Group B:			of osteoblasts
			, Methylprednisol			was
			one			biochemically
			1.0mg/kg/6h			revealed by
			(IV) for 2d,			the finding of
			n=NR			reduced
			3) Group C:			serum
			Methylprednisol			osteocalcin
			one			levels; this
			1.0mg/kg/6h			suggests that
			(IV) for 3d,			
			n=NR			early change in serum
			II-INK			osteocalcin
				\bigcirc		
				4		may be a useful
						indicator for
						patients at
					5	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.

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

			T		T	
Non-	Univers	rhinoviru	2mg/kg/d in 2	No previous	12mo post-	incidence of
industry	ity	s-induced	divided doses	systemic or	discharge	adverse
and	hospital	3-23mo	for 3d (max.	inhaled CS		events
industry	1	(mean	60.0mg/day),	treatment		between the
funded		13.2mo	n=34			prednisolone
		vs.	2) Placebo, n=40			and placebo
		12.2mo)				groups
			Multiple			(results not
			courses over 1yr			shown). No
			·			clinically
						significant
						adverse
						events were
						reported.
Johnson	RCT	Croup	1)	Humidified	Baseline, 2h	Two patients
1996	Pediatri	mean	Dexamethasone	oxygen	& 4h post-	with
Canada	c ED	15mo vs.	10.0mg (4ml) -	OXYGEN	treatment	neutropenia
Non-	1	17mo	10.0mg (4111)	No CS in	treatment	treated with
industry	1	171110	15.0mg (8-12kg)	preceding 2wk		dexamethaso
funded			or 20.0mg	preceding 2wk		ne had a
Turided						clinical course
			(>12kg), 10min			
			(neb), n=28			consistent
			2) Control,			with bacterial
			saline (4ml),			tracheitis.
			10min (neb),	\bigcirc		
Laboraco	DCT	Constant	n=27	Danasanta	Charles and a	Nia alattal la al
Johnson	RCT	Croup	1) Budesonide	Racemic	Study entry	No child had
1998	Pediatri	3mo-9y	4.0mg for 20min	epinephrine &	& hourly	gastrointestin
Canada	c ED		(neb), n=48	mist therapy	for 5h post-	al bleeding or
Industry	2		2)		treatment	bacterial
funded			Dexamethasone	No CS in	until	tracheitis.
			0.6mg/kg, single	preceding 4wk	discharge;	
			dose (IM), n=47		FU 72h	
			3)Placebo		post-	
			suspension,		discharge	
			single dose for			
			20min (neb),			
			n=49			
Klassen	RCT	Croup	1) Budesonide	Racemic	Baseline &	No adverse
1994	Pediatri	3mo-5y	2.0mg (4ml),	epinephrine	hourly for	events were
Canada	c ED		single dose	or	4h;	noted in the
Non-	1		(neb), n=27	dexamethaso	FU at 1wk	budesonide
industry			2) Placebo	ne, or oxygen		group. No
funded			saline 0.9%	tent		patient in that

			(4ml) single		<u> </u>	aroup bad
			(4ml), single			group had
			dose (neb),	No CS in		clinical
			n=27	preceding 2wk		deterioration,
						either in the
						emergency
						department
						or after
						discharge.
						One patient in
						the placebo
						group had a
						burning
						sensation on
						the face.
Klassen	RCT	Croup	1)	Racemic	Baseline &	Two patients
1996	Pediatri	3m-5y	Dexamethasone	epinephrine &	hourly for	in the
Canada	c ED		0.6mg/kg (oral)	croup tent	4h;	budesonide
Non-	1		+ budesonide	0.00p coc	FU 1wk	group and 1
industry	_		2.0mg (4ml)	No CS in	TO IWK	patient in the
funded			(neb), n=25	preceding 2		placebo group
Turiaca			2)	weeks		vomited their
			Dexamethasone	WEEKS		initial doses of
						dexamethaso
			0.6mg/kg (oral)			
			+ placebo saline			ne within
			0.9% (4ml)			30min and
			(neb), n=25			required
						readministrati
						on of
						dexamethaso
					6	ne, which was
						subsequently
						tolerated in
						all 3 patients.
Klassen	RCT	Croup	1) Budesonide	Epinephrine,	Baseline &	All parents
1998	Pediatri	3mo-5y	2.0mg (4ml)	supplemental	hourly for	were asked
Canada	c ED		(neb) + placebo	glucocorticoid	4h;	about the
Non-	2		syrup (oral),	s & mist	FU 1wk	presence of
industry			n=65	therapy	post-	oral thrush
funded			2)		enrolment	and only 1
			Dexamethasone	No CS in		parent whose
			0.6mg/kg (oral)	preceding 2wk		child was in
			+ placebo saline	-		the
			4ml (neb), n=69			budesonide
			, , ,			group
	l					0.000

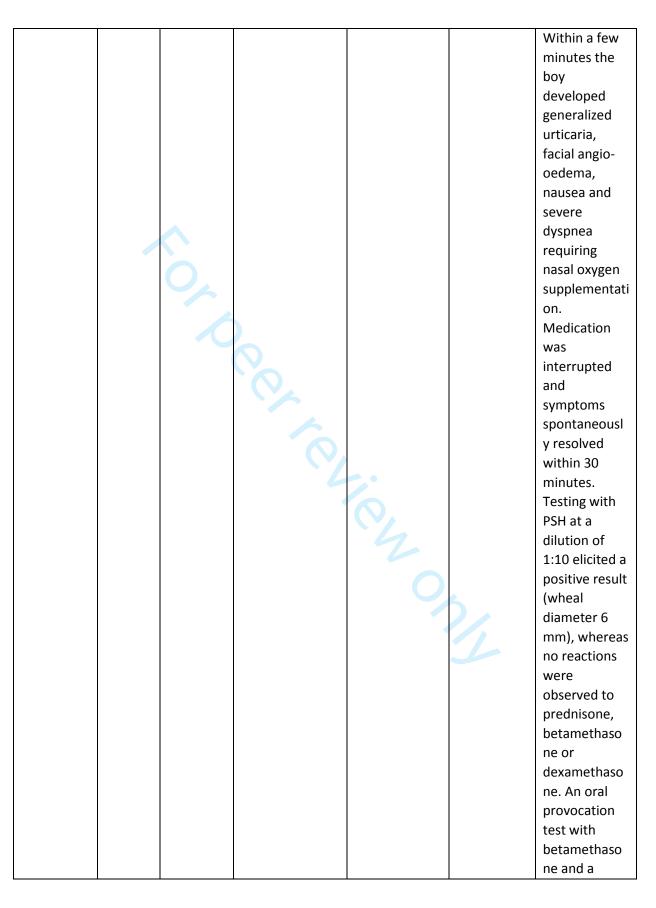
	T		T .	Г	Γ	
			3) Budesonide			reported this
			2.0mg (4ml)			condition at
			(neb) +			the 1-week
			dexamethasone			follow-up.
			0.6mg/kg (oral),			Parents of 1
			n=64			patient
						treated with
						dexamethaso
						ne reported
						hives, and
						parents of 1
						patient
						treated with
						dexamethaso
						ne reported
						violent
						behavior.
						Parents of 1
						patient who
						had received
						budesonide
						and
						dexamethaso
						ne reported
						their child to
						be more
						hyperactive
						than usual.
Kuyucu	RCT	Bronchiol	1) Epinephrine	NR	Baseline,	No side-
2004	Pediatri	itis	3ml of 1:1000		30min,	effects such
Turkey	С	2-21mo	solution for	No CS in	60min,	as pallor,
Funding NR	outpati		10min (neb) +	preceding 2wk	90min &	vomiting or
	ent		dexamethasone		120min,	tremor were
	clinic		0.6mg/kg, single		then 24h,	encountered
	and ED		dose (IM), n=23		5d;	in the
	1		2) Sal		FU by	patients.
			0.15mg/kg of		regular	·
			1mg/ml solution		hospital	
			added to 0.9%		visits in	
			saline for 10min		subsequent	
			(neb) +		2mo	
			dexamethasone			
			0.6mg/kg, single			
			dose (IM), n=23			
		<u> </u>	4550 (1111), 11-25			

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

					and	total height
					diastolic)	growth, mean
					and blood	rate of height
					glucose at	increase,
					baseline	systolic or
					and	diastolic
					approximat	blood
					ely 8-19mo	pressure, or
					after	blood glucose
					randomizati	between the
					on	treatment
					011	groups.
Langton	RCT	Asthma	1) Prednisolone	Bronchodilato	Baseline,	No serious
Hewer	Hospita	1-15y	0.5mg/kg/day	rs (nebulized)	0h, 12h,	short-term
1998	I	1-134	until discharge	13 (Hebulizeu)	24h, 36h,	side-effects
UK	1		(max.	No CS in	48h, 60h &	were noted
Funding NR	1		60.0mg/day)	preceding 14d	72h;	but
I unumg mix			(oral), n=35	preceding 140	FU 2wks	hyperactivity
			2) Prednisolone		post-	related to
			1.0mg/kg/day		enrollment	nebulized B2
			until discharge		emonnent	agonist
						_
			(max. 60.0mg/day)			therapy was seen. No side-
			(oral), n=33			effect possibly
			3) Prednisolone			attributable
			2.0mg/kg/day	\bigcirc		to
			until discharge			prednisolone therapy was
			(max. 60.0mg/day)			noted in any
			(oral), n=30			of the three
			(Orai), 11-30		5	
						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	Case	Asthma	1) Torbutalina	NR	D1 to D3	
Taiwan			1) Terbutaline solution	INIT	D1 (0 D3	On day 3 of admission the
	report	5y				
Funding NR	Pediatri		(loading dose:			patient was
	c clinic		5.0mg/kg/dose,			found to have
	of		maintaining			major
	hospital		dose:			behaviour
	1		0.6mg/kg/h);			changes and
			Methylprednisol			hyperventilati
			one (BW 21kg,			on. She
			2.0mg/kg/dose,			started
			40.0mg every			screaming
			6h) (IV), and;			unreasonably,
			Procaterol			gazing
			12.5mcg twice			forward and
			daily (oral)			sometimes
						upward and
			` ().			became panic.
						She had visual
						hallucinations
						and delusion.
Leer 1969	RCT	Bronchiol	1)	Mist, oxygen,	Clinical	There were
USA	Hospita	itis	Betamethasone,	parenteral	signs every	no
Industry	I	<30mo	1.0mg/5lb first	fluids &	6h	detrimental
funded	5	1301110	dose and	antibiotics	0	corticosteroid
Tarraca			0.5mg/5lb every	difficiences		effects in any
			12h (total	NR		of the
			3.5mg/5lb (6	INIX		patients. The
			doses) for 72h)			corticosteroid
			(IM/IV), n=148	•		neither
			2) Aqueous			increased the
			vehicle, 5cc			incidence of
			every 12h for			staphylococca
			72h for total 6			I or other
			doses (IM/IV),			bacterial
			n=149			pneumonias
						nor masked
						superinfection
						S.
Lehmann	Case	Asthma	1)	None	Post skin	Patient had
2008	1 .	1 2	Dradnicalana		prick test	been on well-
	report	2y	Prednisolone-		prick test	been on wen
Germany	report Pediatri	2 y	21-hydrogen	3wk washout	prick test	tolerated

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

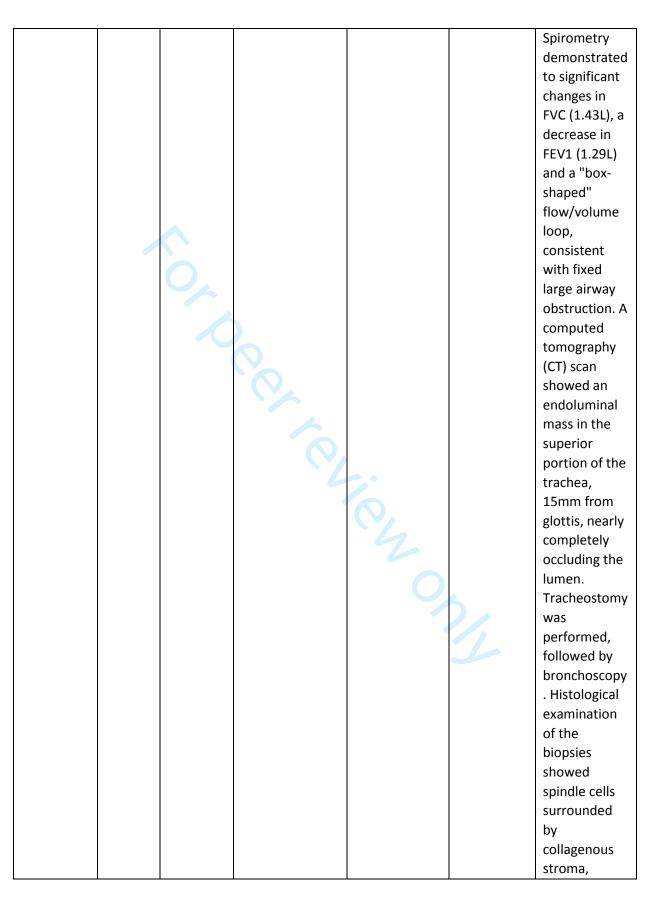


						titrated intravenous dexamethaso ne challenge test were tolerated without any complications.
Leipzig 1979	RCT Hospita	Croup 8mo-5y	1) Dexamethasone	Vaponephrine , mist tent	Baseline, 12h & 24h	We observed no adverse
USA	1		0.3mg/kg	therapy &		effects or late
Funding NR	2		(4mg/ml) 2	racemic	NR	relapses.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

Lucas- Bouwman 2001 Netherland s	RCT Hospita I	Asthma 3mo-8y (mean 2y)	(procaterol hydrochloride) 1.25mcg/kg/dos e on admission, then twice daily (oral) 3) Group C: No hydrocortisone or procaterol (n=28) 1) Prednisolone 1.0mg/kg tablets, twice daily for 5d (oral), n=NR	Bronchodilato rs (inhaled) NR	6d to 8d after index visit	Vomiting was observed in 23% of patients using crushed
Funding NR			2) Prednisolone 1.0mg/kg solution, twice daily for 5d (oral), n=NR			tablets, and in none of the patients on oral solution.
Nahum 2009 Israel Funding NR	Case series (n=3, 1 case relevan t) Pediatri c ED 1	Asthma 5y	1) Methylprednisol one 2.0mg/kg for 2d (IV)	NR	D1 & D2; FU 3mo post- discharge	He presented with wheezing, received an intravenous bolus of methylprednis olone sodium succinate (2mg/kg), and immediately developed restlessness and facial rash which resolved spontaneousl y. 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 supplementati on and was treated afterward with oral betamethaso ne sodium
Paniagua 2016 Spain Funding NR	RCT (confer ence abstrac t) Pediatri c ED	Asthma >12mo	1) Dexamethasone , NR, 2 doses (oral), n=287 2) Prednisone/pre dnisolone, 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 Pediatri c ED 3	Wheeze 10-60mo	1) Prednisolone 10.0mg/day (10ml) once daily for 10- 24mo old (oral); 20.0mg/day (10ml) once daily for >24mo old (oral), for 5d, n=343 2) Placebo solution (10ml) once daily for 5d (oral), n=344	Albuterol, oxygen & antibiotics NR	4h, 12h & 24h after albuterol & daily post-discharge; FU by phone 1mo post-discharge	No clinically significant adverse events were reported to the patient safety committee. In one child in the prednisolone group, parents attributed excess

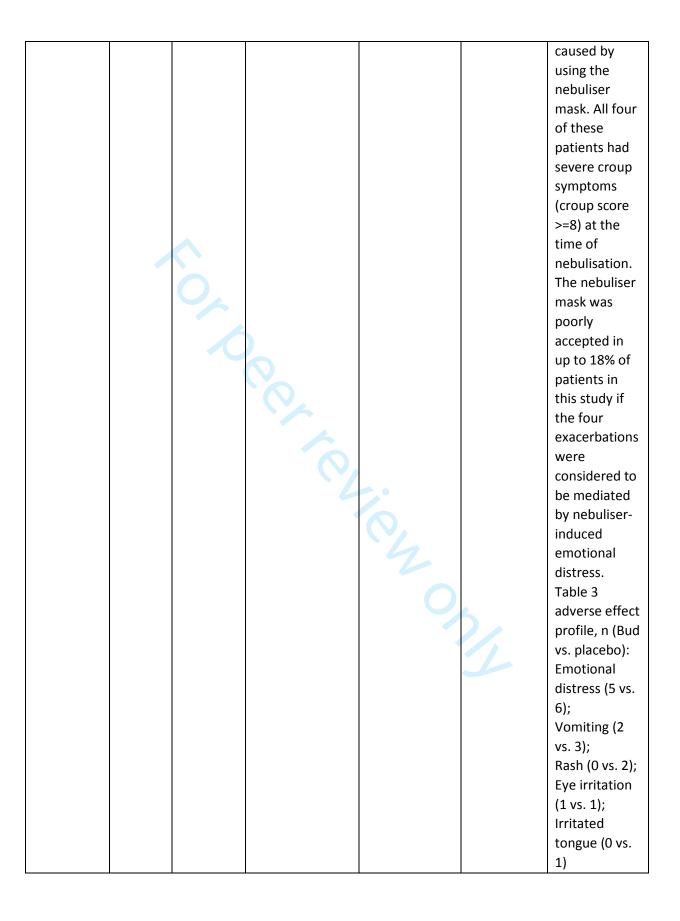
		ı			T	· · · · · · · · · · · · · · · · · · ·
						vomiting to
						the study
						drug and
						discontinued
						the
						medication
						after
						discharge
						from hospital.
Panigada	Case	Progressi	Albuterol	NR	NR	The child was
2014		_	(inhaled) +	INIX	INIX	sent home on
	report Pediatri	ve shortness		NR		inhaled
Italy			prednisone	INK		
Funding NR	C	of breath,	1.0mg/kg			albuterol and
	Pulmon	subseque	(28.70kg) (oral),			prednisone to
	ary and	nt	n=1			be tapered
	Allergy	diagnosis				and
	Unit	of				discontinued
	1	inflamma				after 7-10
		tory				days. Fifteen
		myofibro				days after first
		blastic				presentation,
		tumor				1 day after
		cell				the
		proliferat				discontinuatio
		ion				n of
		5y		9		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.



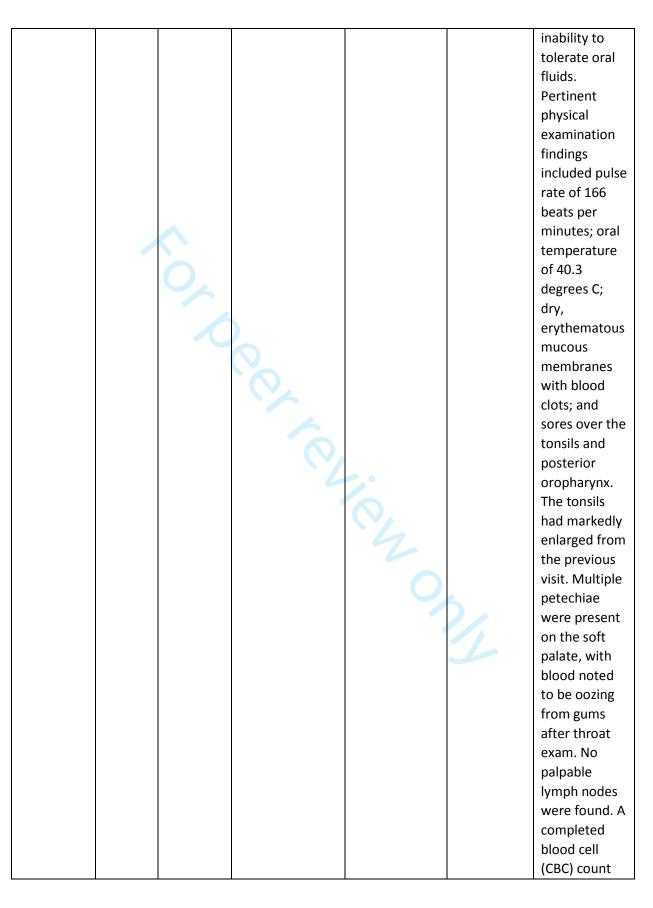
	1	T	T	T	T	T
						displaying
						strong
						positivity for
						vimentin,
						focal positivity
						for a-smooth
						muscle actin,
						and weak
						positivity for
						clusterin. No
						desmin, ALK,
						S100, CD21,
						and CD 23
						expression
						was detected.
						A diagnosis of
						IMT of the
						trachea was
						performed
						and a
						complete
						surgical
						resection of
						the neoplasm
			•			was carried
						out.
Plint 2009	RCT	Bronchiol	1) Epinephrine	Bronchodilato	Baseline to	Adverse
Canada	Pediatri	itis	3ml 1:1000, 2	rs (albuterol,	30min,	events were
Non-	c ED	6wk-	doses 30min	epinephrine)	60min,	uncommon
industry	8	12mo	apart (neb) +	& antibiotics	120min &	(see
and			dexamethasone		240min;	Supplementar
industry			1.0mg/kg (max	No CS in	FU daily	y Appendix).
funded			10mg) in ED	preceding 2wk	until D7,	Pallor was
			plus 5 once-		then every	reported in 76
			daily		2d until	infants (9.5%),
			0.6mg/kg/dose,		D14 &	tremor in 15
			total 6d (oral),		every 3d	(1.9%), and
			n=200		until D22	vomiting in 14
			2) Epinephrine			(1.8%), with
			3ml 1:1000, 2			no significant
			doses 30min			differences
			apart (neb) +			among the
			placebo, total			groups. One
			6d (oral), n=199			hospitalized

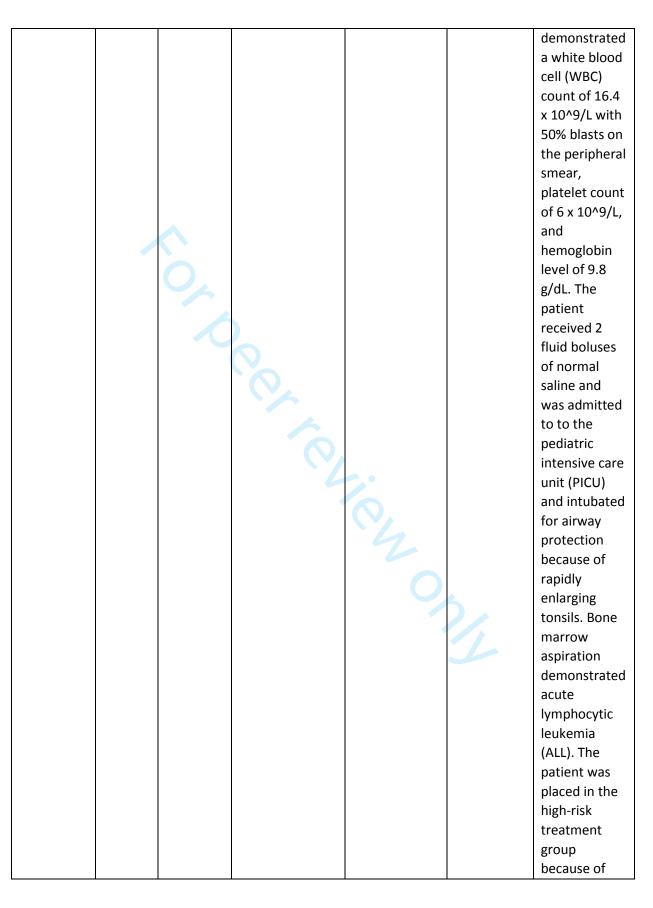
	T		Г.	Г		T .
			3) Placebo 2			infant in
			doses 30min			group 2 and
			apart (neb) +			one in group 3
			dexamethasone			had mild,
			1.0mg/kg (max			transient
			10mg), total 6d			hypertension,
			(oral), n=200			which
			4) Placebo 2			resolved
			doses 30min			rapidly.
			apart (neb) +			Supplementar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

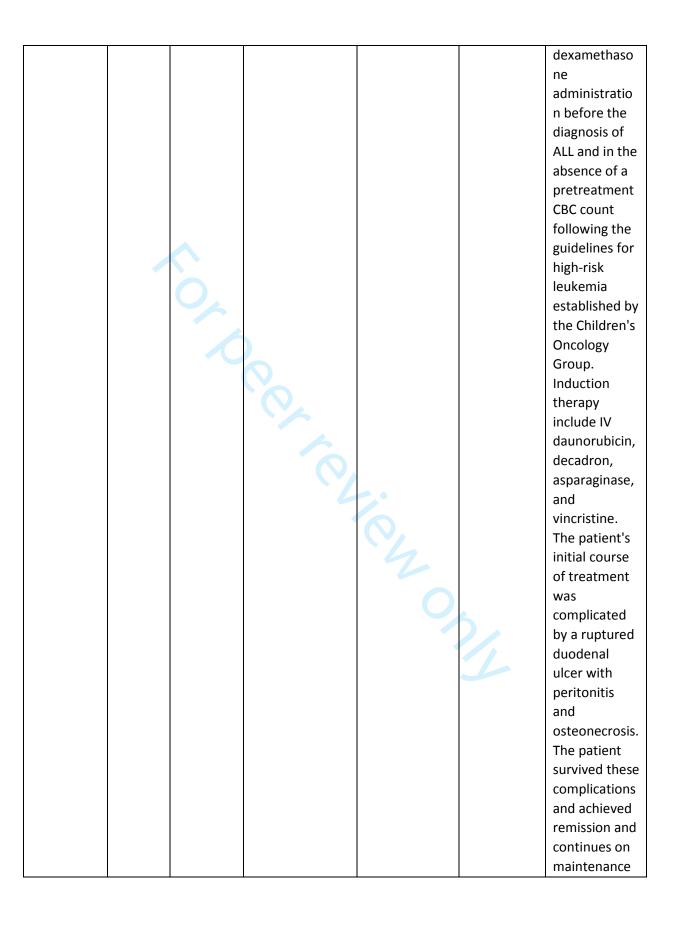
				T	,	,
				ipratropium		
				bromide		
				250mcg every		
				6h		
				NR		
Roberts	RCT	Croup	1) Budesonide	NR	Baseline,	The adverse
1999	Women	6mo-8y	2.0mg (4ml) for		2h, 6h &	effects in both
Australia	's and		10min each	No CS in	12h after	groups were
Industry	Childre		dose, every 12h	preceding 4wk	first dose,	attributable
funded	n's		(max. 4 doses)	, , , , , ,	then 12-	to either
ranaca	Hospita		(neb), n=42		hourly up	manifestation
	I		2) Placebo for		to 48h if in	s of the
	1		10min each		hospital;	disease state
	1				-	or the mode
			dose, every 12h		FU by	
			(max. 4 doses)		telephone	of drug
			(neb), n=40		1d & 3d	administratio
		,			post-	n (Table 3).
					discharge	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



Roorda 1998 Netherland s Funding NR	RCT Hospita I 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	Bronchiol itis <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, bronchodilato rs & tribavirin NR	Admission & every 12h; FU 1wk post- discharge	Three patients had occult blood in their stools; two were in the dexamethaso ne group. No episodes of gross haematochezi a were
Sadowitz 2012 USA Funding NR	Case series (n=4, 1 case relevan t) ED 1	Pharyngit is 3y	Dexamethasone 10.0mg single dose (oral?) + acetaminophen + amoxicillin, n=1	NR NR	NR	observed. The patient was given a 10-mg dose of dexamethaso ne in addition to acetaminophe n 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







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

		,		1	1	,
			24h later, total			16.8mmHg in
			5d (oral), n=64			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	RCT	Asthma	1) Montelukast	Albuterol &	48h & D8	In the
Canada	Pediatri	>=2y	1.0mg/kg:	fluticasone		montelukast
Industry	c ED		2-5y=4.0mg;			group,
funded	1		6-14y=5.0mg;	>1 single dose		adverse
			and,	or oral		effects
			15-17y=10.0mg	prednisolone		developed in
			at 24h, 48h,	or >250mcg		3 patients.
			72h, 96h & 120h	per day of		One patient
			(oral), n=67	inhaled		experienced
			2)	fluticasone		facial swelling
			Prednisone/pre	within 72h		of unknown
			dnisolone			etiology at 96
			1.0mg/kg: 2-			hours,
			5y=4.0mg;			another
			6-14y=5.0mg;			patient had
			and 15-			vomiting and
			17y=10.0mg at			diarrhea at 72
			24h, 48h, 72h,			hours, and
			96h & 120h			the third
			(oral), n=63			patient
			(5141), 11-05			complained of
						abdominal
						and leg pains
						on day 4.
						None of these
						patients
						required
						treatment for
						these events,

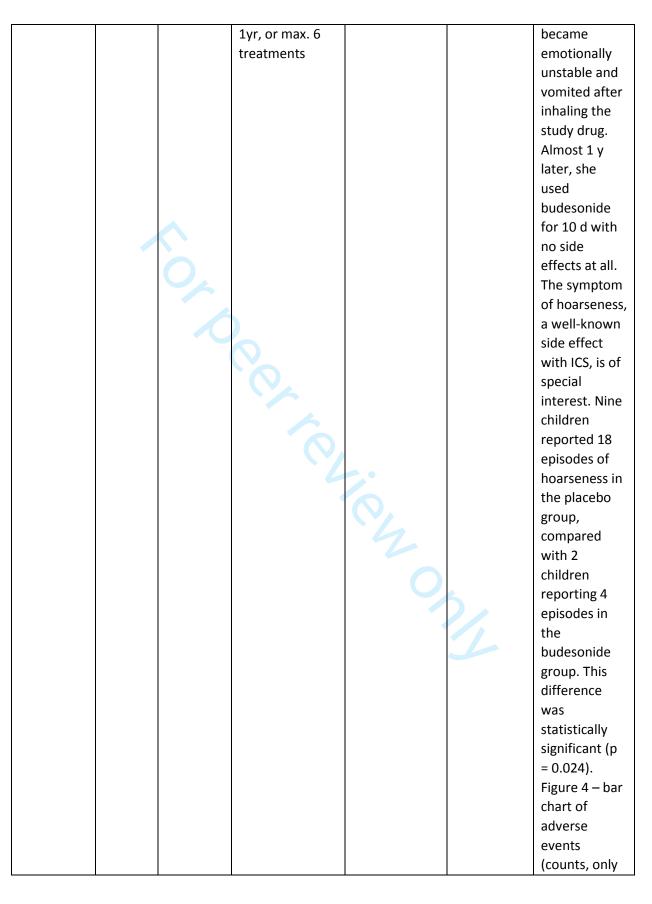
						and the
						relationship
						between
						montelukast
						and the
						"event" is
						questionable.
						No adverse
						effects
						developed in
						the children
						given
						prednisolone
						after
						discharge.
Siomou	Case	Bronchiol	1)	NR	Baseline, 2	In summary,
2003	control,	itis, viral	Hydrocortisone		days after	short-term IV
Greece	3-arm	wheezing	10.0mg/kg/day	Never/no CS	cs	corticosteroid
Industry	Pediatri	, or croup	for 3d (NR),	in last 2mo	administrati	administratio
funded	С	2mo-10y	n=28		on & 12d	n to children
	hospital		2)		after end of	suffering from
	1		Methylprednisol		therapy	acute
			one 2.0mg/kg			respiratory
			for 3 days (NR),			diseases led
			n=21			to partial but
			3) Control, 3d,			reversible
			n=51	1		inhibition of
						bone
						formation
					4	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

Sparrow 2006 Australia Funding NR	RCT Pediatri c 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),	Adrenaline No CS preceding study	Enrolment, 30min post- treatment, hourly for next 4h & every 4h until discharge; FU 7d-10d post-	the maximum renal phosphate reabsorption decrease in the maximum renal phosphate reabsorption were significant but transient. No adverse events were noted in either group.
Stafford 1998 Australia Industry and non- industry funded	NRCT Pediatri c hospital or ED 1	Asthma/c roup 1-12y	n=65 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	discharge 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 Pediatri c hospital 1	Asthma NR (mean 5y)	1) Prednisolone 30.0mg (<5yo), otherwise 60.0mg, max. dose 3.0mg/kg (range 1.0- 3.0mg/kg) single dose (oral), n=67	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

	ī	1	T	Г	ı	
			2) Placebo	No CS in		almost
			solution	preceding 48h		immediately
			identical to			and were
			treatment,			consequently
			single dose			excluded.
			(oral), n=73			There were
						no observed
						side-effects
						related to the
						single
						prednisolone
						dose.
Sumboonn	RCT	Croup	1)	Aerosolized	Admission,	Complications
anonda	Pediatri	<5y	Dexamethasone	adrenaline,	24h & 48h;	included
1997	C	\Jy	0.5mg/kg/d, 3d	antibiotics, IV	FU 3wks	pneumonia in
Thailand	_		<u> </u>	fluid & cool		·
	hospital		(IM/IV), n=14		post-	4 controls, Acinetobacter
Funding NR	1		2) Control, n=18	mist	discharge	
						sepsis in 1
				NR		control and
						bacterial
						tracheitis in 1
						cases.
Sung 1998	RCT	Asthma	1) Budesonide	Salbutamol	Baseline,	No adverse
Canada	Tertiary	>6mo or	4000mcg (4ml),	0.15mg/kg	discharge &	effects were
Non-	pediatri	<18y	single dose	every 30min	7d to 10d	noted in
industry	С		(neb), n=24	for 3 doses,	post-	either group.
funded	hospital		2) Placebo,	then hourly	treatment	
	1		single dose	for 4 doses		
			(neb), n=20			
Super 1989	RCT	Croup	1)	Mist, racemic	Baseline,	In two
USA	General	NR (mean	Dexamethasone	epinephrine,	30min, and	dexamethaso
Funding NR	hospital	16mo)	0.6mg/kg, single	oxygen &	every 12h	ne-treated
	or	,	dose (IM), n=16	antibiotics	until	patients in the
	childre		2) Placebo		discharge	main study,
	n's		saline, single			including one
			Janne, Jingre			_
	hospital		dose (IM) n=13			l with a
	hospital		dose (IM), n=13			with a
	hospital 2		dose (IM), n=13			culture-
	-		dose (IM), n=13			culture- positive
	-		dose (IM), n=13			culture- positive influenza A
	-		dose (IM), n=13			culture- positive influenza A viral infection,
	-		dose (IM), n=13			culture- positive influenza A viral infection, laryngotrachei
	-		dose (IM), n=13			culture- positive influenza A viral infection, laryngotrachei tis progressed
	-		dose (IM), n=13			culture- positive influenza A viral infection, laryngotrachei

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

Cuadrour	DCT	Asthma	1) Dudosopido	Maintananca	ND	Top adverse
Svedmyr	RCT,		1) Budesonide	Maintenance	NR	Ten adverse
1995	crossov	3-10y	0.2mg 4 times	bronchodilato		events were
Sweden	er		daily for first 3d,	rs permitted		reported in
Funding NR	NR		0.2mg 3 times			the
			daily for next 3d	No CS in		budesonide
			and 0.2mg twice	preceding		group and
			daily for last 3d	month		nine in the
			(neb), n=NR (all			placebo
			groups=26)			group. There
			2) Placebo (NR),			were two
			n=NR (all			cases of
			groups=26)			dysphonia in
			,			the
			Multiple			budesonide
			courses;			group. The
			17 children			other events
			completed one			were
			paired (Grp			correlated
			1&2) treatment;			more to the
			15 children			children's
						URTI such as
			completed 4			
			paired			headache,
			treatments			diarrhoea,
						epistaxis or
						sore throat.
						There were
						no significant
						differences
						between the
					4	two groups.
Svedmyr	RCT	Asthma –	1) Budesonide	Beta-agonists	Daily for	In the
1999¹	Pediatri	first sign	400mcg, 4 times	and/or	10 d	budesonide
Sweden	С	of URTI	daily for 3d then	theophylline		group a 24-
Funding NR	hospital	1-3y	twice daily for			month-old girl
	4		7d (MDI), n=28	No CS in		discontinued
			2) Placebo, 4	preceding		treatment
			times daily for	2mo		during the
			3d then twice			first
			daily for 7d			treatment
			(MDI), n=27			period
			(, , ,			because of a
			Multiple			suspected
			courses over			side effect.
			COUISCS OVEI			The child
					<u> </u>	THE CHILL



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

Non- industry funded Amission + 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 (IM); 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 every 8h (oral), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (uming next 3d (IM), n=8 Methylprednisol one 30.0mg/kg one daily for 3d (IV), n=1 maintain patients during steroid			1	/A / !!	<u> </u>	1 0	· · · · · · · · · · · · · · · · · · ·
funded mg/kg every 8h (IM), n=8 2) a) Sal solution 2.5mg (0.5ml), on admission & every 6h (heb); b) Sal syrup,		1					
(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 (real), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg every 8h (IM)	-				NR		
Z) 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); b) Sal syrup, 0.15mg/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 Tamura 2008 Series Japan Medical Medical mycoplas Medical ry one daily for 3d (IV), n=1 inpatie pneumon Zimg (0.5ml) NR NR NR NR All cases: There were no adverse events in any patients	funded					_	
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); al 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 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission admiss				` '			
on admission & every 6h (neb); b) Sal syrup,				2) a) Sal solution		discharge	effects or
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 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg on admission then 0.025ml/kg				2.5mg (0.5ml),			complications
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 Tamura 2008 Series Vy One 30.0mg/kg Japan Medical Medical mycoplas				on admission &			of the
O.15mg/kg, every 8h (oral); and, c) Placebo saline (IM), n=8 3) Dexamethasone O.3mg/kg (4mg/ml) on admission + O.1mg/kg every 8h (IM); a) Sal solution 2.5mg (0.5ml), on admission & every 6h (neb); and, b) Sal syrup, O.15mg/kg, every 8h (oral), n=8 4) Placebo saline O.075ml/kg on admission, then O.025ml/kg every 8h during next 3d (IM), n=8 Tamura Zoos series Japan Medical Funding NR center, ma inpatie manual patients O.15mg/kg, every 8h during next 3d (IM), n=8 Methylprednisol NR NR NR All cases: There were no adverse events in any patients				every 6h (neb);			treatment
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 Tamura Case very 8h during next 3d (IM), n=8 Tamura Cose series y once 30.0mg/kg once daily for surprise o				b) Sal syrup,			were
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 Tamura 2008 series Japan Medical mycoplas Funding NR center, inpatie mycuplas once daily for 3d (IV), n=1 Refractor one 30.0mg/kg NR All cases: There were no adverse events in any patients				0.15mg/kg,			documented.
c) Placebo saline (IM), n=8 3) Dexamethasone 0.3mg/kg (4mg/ml) on admission + 0.1mg/kg every 8h (IMI); 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 Tamura 2008 Series y one 30.0mg/kg Japan Medical mycoplas myco				every 8h (oral);			
(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 Tamura 2008 Series Vy Medical Funding NR Medical Funding NR Medical Funding NR Funding NR (IM), n=8 Refractor y Medical mycoplas once daily for one 30.0mg/kg NR NR All cases: There were no adverse events in any patients				and,			
Tamura 2008 Tamura 2008 Tamura 2008 Tending NR Center, inpatie Medical Funding NR Admission 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 Methylprednisol one 30.0mg/kg NR NR NR All cases: There were no adverse events in any patients				c) Placebo saline			
Tamura 2008 Tamura 2008 Tamura 2008 Tending NR Center, inpatie Medical Funding NR Admission 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 Methylprednisol one 30.0mg/kg NR NR NR All cases: There were no adverse events in any patients				(IM), n=8			
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 Tamura 2008 series Japan Medical Funding NR mycoplas Genter, inpatie Dexamethasone 0.3mg/kg (4mg/ml) on admission + 0.1mg/kg (9.5ml), 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 All cases: There were no adverse events in any patients							
Tamura Case aseries 2008 series 2008 series 2008 series 40 Medical Funding NR center, inpatie with a manual cases and manual center, inpatie with a manual cases and manual cases (4mg/ml) on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 Tamura case series y one 30.0mg/kg NR NR NR NR All cases: There were no adverse events in any patients				•			
Tamura Case series 2008 series 2008 series 3 Medical Funding NR center, inpatie with a mycoplas and madmission will mark and mycoplas for my				0.3mg/kg			
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 Tamura 2008 series Japan Medical Funding NR center, inpatie mycoplas pneumon 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 All cases: There were no adverse events in any patients							
Refractor very 8h during next 3d (IM), n=8 Tamura 2008 series Japan Medical Funding NR Very 6 (Sal solution 2.5mg (0.5ml), on admission & every 8h (IM); and, b) Sal syrup, 0.15mg/kg, every 8h (IM); 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 Tamura 2008 series y Methylprednisol one 30.0mg/kg once daily for 3d (IV), n=1 pneumon NR (IV), n=1 NR (IV), n=1 pneumon NR (I							
Refractor very 8h during next 3d (IM), n=8 Tamura 2008 series Japan Medical Funding NR Very 6 (Sal solution 2.5mg (0.5ml), on admission & every 8h (IM); and, b) Sal syrup, 0.15mg/kg, every 8h (IM); 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 Tamura 2008 series y Methylprednisol one 30.0mg/kg once daily for 3d (IV), n=1 pneumon NR (IV), n=1 NR (IV), n=1 pneumon NR (I				0.1mg/kg every			
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 Tamura 2008 Japan Medical mycoplas once daily for Japan Funding NR Medical mycoplas center, ma inpatie pneumon a) Sal solution 2.5mg (0.5ml), on admission & every 6h (neb); and, b) Sal syrup, 0.15mg/kg, every 8h (oral), n=8 NR All cases: There were no adverse events in any patients				V= = -			
Tamura 2008 series y Medical Funding NR Medical Funding NR Medical Funding NR Center, inpatie pneumon PS Sal Syrup, 0.25mg (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 NR All cases: There were no adverse events in any patients							
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 Tamura Case Refractor young one 30.0mg/kg Japan Medical Funding NR center, inpatie pneumon NR NR NR NR All cases: There were no adverse events in any patients							
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 Tamura 2008 Japan Medical Funding NR Center, inpatie every 6h (neb); and, b) Sal syrup, 0.15mg/kg, every 8h (oral), n=8 NR NR NR All cases: There were no adverse events in any patients				<u> </u>			
Tamura Case series Japan Medical Funding NR Funding NR Funding NR Funding NR Funding NR And 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 Wethylprednisol one 30.0mg/kg one 30.0mg/kg NR NR NR All cases: There were no adverse events in any patients							
Tamura 2008 Japan Medical Medical Funding NR Funding NR In the overy 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 All cases: There were no adverse events in any patients					(V)		
Tamura 2008 Japan Medical Medical Funding NR Funding NR In the overy 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 All cases: There were no adverse events in any patients				· ·	1		
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 Tamura 2008 Japan Funding NR Medical Medica							
Tamura 2008 Series Japan Medical Funding NR Funding NR Methylare n=8 4) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 NR NR All cases: There were no adverse events in any patients							
A) Placebo saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 Tamura Case Refractor y one 30.0mg/kg Japan Medical Funding NR Center, inpatie Pneumon A) Placebo saline 0.075ml/kg on admission, then NR NR NR All cases: There were no adverse events in any patients							
Saline 0.075ml/kg on admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 Tamura Case Series y One 30.0mg/kg Japan Funding NR Center, inpatie Punding NR Saline 0.075ml/kg on Admission, then NR NR NR NR All cases: There were NR NR NR Punding NR N							
Tamura Case Refractor y one 30.0mg/kg Japan Medical Funding NR Funding NR pneumon				· ·	•		
admission, then 0.025ml/kg every 8h during next 3d (IM), n=8 Tamura Case Refractor One 30.0mg/kg Japan Medical Medica							
Tamura Case Refractor Methylprednisol NR NR All cases: 2008 series y one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, inpatie pneumon one of the severy 8h during next 3d (IM), n=1							
every 8h during next 3d (IM), n=8 Tamura Case Refractor Methylprednisol one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, ma inpatie pneumon inpatie pneumon every 8h during next 3d (IV), n=1 events in any patients				· ·			
Tamura Case Refractor Methylprednisol NR NR All cases: 2008 series y one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, ma inpatie pneumon inpatie pneumon next 3d (IM), n=1							
Tamura Case Refractor Methylprednisol NR NR All cases: 2008 series y one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, ma inpatie pneumon inpatie new new new new new new new new new ne				,			
Tamura Case Refractor Methylprednisol NR NR All cases: 2008 series y one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, ma inpatie pneumon inpatie pneumon NR NR NR All cases: NR NR NR NR ONE NR							
2008 series y one 30.0mg/kg Japan Medical mycoplas once daily for Funding NR center, inpatie pneumon pneumon one 30.0mg/kg NR There were no adverse events in any patients	Tamura	Case	Dofractor		ND	ND	All cases:
Japan Medical mycoplas once daily for Funding NR center, inpatie pneumon inpatie no adverse patients NR no adverse events in any patients					INL	INL	
Funding NR center, ma 3d (IV), n=1 events in any patients			-		ND		
inpatie pneumon patients	-			•	INK		
	Funding NR			30 (IV), N=1			-
nt la during steroid		-	-				
		nt	ıa				auring steroid

		Г	Г			
	1	5y (n=6,				treatment;
		range 3y-				Case patient
		9y)				1: On the 10th
						clinical day,
						we initiated
						methylprednis
						olone pulse
						therapy once
						daily for 3
						days. Six
						hours after
						the initiation
						of steroid
		O ,				therapy, she
						became
						afebrile. On
						the next day,
						dyspnea was
						resolved.
						Chest
						radiograph on
						that day
						showed
						dramatic
						improvement.
				$\langle \mathcal{O}_{\star} \rangle$		Five days
				1		after the
						initiation of
						steroid
						therapy,
						laboratory
						findings were
						normalized.
						She was
						discharged on
						the 17th day
						of admission
						without
						sequelae.
Teeratakul	RCT	Bronchiol	1)	Epinephrine,	Baseline &	Soon after
pisarn 2007	Pediatri	itis	Dexamethasone	salbutamol, IV	every 6h	study
Thailand	С	4wk-	0.6mg/kg, single	fluids,	until study	endpoint, but
-	outpati	24mo	dose (IM), n=89	antimicrobial	endpoint	before being
			,		(resolution	discharged,
		1	1		,. 5551461011	

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

						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 Netherland s Non- industry funded	RCT Hospita I 1	Bronchiol itis <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, bronchodilato rs, 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	RCT,	Persisten	1) Prednisolone	Bronchodilato	Daily for 5d	There were
UK	crossov	t wheeze	1.0mg/kg, twice	r & antibiotics	& clinical	no side
Non- industry	er "unit",	<18mo	daily for 5d (oral), n=NR	NR	exam 3d after	effects reported by
funded	outpati		(total patients in		treatment	the parents
	ent		study = 38)		course (D8)	and none was
	1		2) Placebo, twice daily for		5	detected on clinical
			5d (oral), n=18	•		examination
			crossed over			at the time of
			Multiple			review three days after
			courses;			completing
			38 children			the five day
			completed a total of 56			course of
			total of 56 treatment			treatment.
			courses			
Zhang 2003	RCT	Bronchiol	1) Prednisolone	IV	Enrolment,	The potential
Brazil	Pediatri	itis	1.0mg (oral) +	hydrocortison	1mo, 3mo,	side-effects of
	С	<12mo	standard care	e in first 24h	6mo &	prednisolone

Г	1	1				
Non-	hospital		for 5d (NR),	after	12mo after	were not
industry	ward		n=28	hospitalization	discharge	included as
funded	1		2) Standard care			outcome
			(oxygen, fluid	No CS in		measures in
			replacement,	preceding 4wk		this study as
			nebulised			the safety of
			fenoterol) for			short-term
			5d (NR), n=24			steroid
						therapy has
						been well
						confirmed. 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.
LL - 411: - 4000 -		000	scociated publicati	C - 1 - 100	20	D.O.T.

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

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

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

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

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

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

² sum of percentages may not total 100 due to rounding

1136/bmjopen-2018-0

Supplement 4b. Methodologica	Il quality assessments of	included studies
------------------------------	---------------------------	------------------

	efined	AE defined	efined	ified	Mode of co	ollection	ed AE	ckground	uency of	ed for AE		28511 on 1	and ow-up	arm	of AE	ysis
Study (year)	Harms pre-defined	Serious AE d	Severe AE defined	Deaths specified	ACTIVE	PASSIVE	Who collected AE	Training/ background of assessors	Timing/ frequency AE collection	Checklist used for		on 1 August 2019.	Withdrawal and losses to follow-up	AE in each a specified	# and type o specified	Type of analysis
Alangari (2014)	N	N	N	N	N	N	N	N	N	N	Υ	~	N	N	N	N
Alansari (2013)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	0	Υ	N	N	N
Aljebab (2017)	Υ	N	N	N	Υ	Υ	Υ	Υ	Υ	U	Υ	Φl	Υ	N	Υ	Υ
Alshehr (2005)	N	N	N	N	N	N	N	N	N	N	Υ	Ο.	N	N	Υ	N
Altamimi (2006)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	\rightarrow	Υ	N	Υ	N
Bacharier (2008)	N	N	N	N	N	N	N	N	N	N		٠.	Υ	N	N	N
Bisgaard (2006)	Υ	N	N	N	Υ	N	N	N	Υ	N		3	Υ	Υ	U	Υ
Bjornson (2004)	N	N	N	N	Υ	N	Υ	Υ	Υ	N		Φ.	N	N	Υ	N
Brunette (1988)	Υ	N	N	N	Υ	N	N	N	Υ	Υ	Υ	\sim	N	N	Υ	Υ
Buckingham (2002)	N	N	N	Υ	Υ	N	Υ	Υ	Υ	N	Υ	mj.com,	N	N	Υ	N
Bulow (1999)	N	N	N	N	N	N	N	N	N	N	Υ	on	N	Υ	N	N
Chang (2008)	N	N	N	N	Υ	N	N	N	Υ	N	Υ	Apr	Υ	Υ	Υ	N
Chen (2008)	N	N	N	N	N	N	N	N	N	N	Υ	117	N	Ν	Ν	N
Chub-Appakarn (2007)	N	N	N	N	N	N	N	N	N	Z	Υ		N	Z	Z	N
Clavenna (2014)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	N	Υ	by g	Υ	N	N	N
Connett (1994)	N	N	N	N	N	N	N	N	N	N	Υ		N	N	Υ	N
Connolly (1969)	N	N	N	Υ	Υ	N	N	N	Υ	N	Υ	. Prote	N	N	Υ	N
Corneli (2007)	N	N	N	N	Υ	N	Υ	Υ	Υ	N		\circ	Υ	N	N	N
Cronin (2016)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	N		_	Υ	N	Υ	N
Csonka (2003)	N	N	N	N	N	N	N	N	N	N	Υ	by co	Υ	Υ	Υ	N

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	

Page 133 of 158 BMJ Open 80 bm															
											136/bmjopen-20				
Daugbjerg (1993)	N	N	N	N	N	N	N	N	N	N	Υ 😤	N	Υ	Υ	N
Dawson (1993)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	U	γ 8-0285 Υ	N	N	N	N
Ducharme (2009)	Υ	Υ	N	N	Υ	N	Υ	Υ	Υ	N	γ 3		Υ	Υ	Υ
Eboriadou (2010)	N	N	N	N	Υ	N	N	N	N	N	Λ ¬	N	N	U	N
Eden (1967)	N	N	N	Υ	N	N	N	N	N	N			N	U	N
Escobedo Chavez											August 2019. L				
(1992)	N	N	N	N	N	N	N	N	N	N	Y 201	N	N	N	N
Fifoot (2007)	N	N	N	N	N	N	N	N	N	N	γ .	Υ	N	N	N
Fitzgerald (1996)	N	N	N	N	U	U	N	N	Υ	N	ΥŞ	Υ	N	N	Υ
Francis (1997)	N	Υ	N	N	N	N	N	N	N	N	U oaded	Υ	Υ	N	N
Garbutt (2013)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Y ed	N	N	N	N
Ghirga (2002)	N	N	N	N	N	N	N	N	N	N	Y fro	N	N	N	N
Gill (2017)	N	N	N	Υ	Υ	N	N	N	Υ	N	Y	N	N	Υ	Υ
Goebel (2000)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	N S	N	N	Υ	N
Grant (1996)	N	N	N	N	Υ	Υ	N	N	Υ	N	Y j	N	N	N	Υ
Gries (2000)	N	N	N	N	Υ	N	Y	Υ	Υ	N	Y g	N	N	Υ	Υ
Hedlin (1999) ¹	N	N	N	N	Υ	N	Υ	N	Υ	Υ	Υġ	N	Υ	Υ	Υ
Husby (1993)	N	N	N	N	U	N	Υ	N	Υ	N	Y 8		N	N	N
Inglis (1993)	N	N	N	Υ	Υ	Υ	N	N	Υ	N	γ	Υ	Υ	Υ	N
Jan (2000)	N	N	N	N	Υ	N	N	N	Υ	Υ	Y A	N	N	N	N
Jartti (2006)	N	N	N	N	N	N	N	N	N	N	Y E	N	N	N	N
Jartti (2007)	N	N	N	N	N	N	N	N	N	N	Υ ,5	N	N	N	N
Jartti (2015)	N	N	N	N	N	N	N	N	N	N	U 202,	Υ	N	N	N
Johnson (1996)	N	N	N	N	N	N	N	N	N	N	Y by		N	Υ	N
Johnson (1998)	N	N	N	N	N	N	N	N	N	N	U y		N	Υ	N
Klassen (1994)	N	N	N	N	N	N	N	N	N	N	Y	N	N	Υ	N
Klassen (1996)	N	N	N	N	N	N	N	N	N	N	Y of	N	N	Υ	N
Klassen (1998)	N	N	N	N	Υ	Υ	Υ	Υ	U	N	Y rotected by	Υ	N	Υ	N
Kuyucu (2004)	N	N	N	N	N	N	N	N	N	N	Υğ	N	N	N	N
Lai (2005)	N	N	N	N	Υ	N	N	N	Υ	Υ	Υ 8	N	N	N	Υ
		•	•								Y copyriq		•		

1	
2	
3	
4	
5	
6	
7	
8	
9	
	0
1	1
1	2
1	3
1	4
1	5
1	6
1	7
1	, 8
	9
	0
	1
2	
2	3
2	4
2	5
2	6
2	7
2	, 8
_	U

						BMJ	Open				1.136/billJopen-20			Pa	age 134 of 15
1 2															
Langton-Hewer											Y 2020-0-2020-				
(1998)	N	N	N	N	N	N	N	N	N	N	Υ 200	N	N	Υ	N
Lee (2001)	Ν	N	N	Υ	Υ	N	N	N	Υ	N			Υ	Υ	N
7 Leer (1969)	N	N	N	N	N	N	N	N	N	N	Y	4 1 4	Υ	Υ	N
Lehmann (2008)	Z	N	N	Υ	Υ	N	Z	N	Υ	Ν	Y August	Y	Υ	Υ	N
Leipzig (1979)	Z	N	N	N	N	N	Ν	N	N	Ν) >	N	N	N	N
I1 Lin (1991)	N	N	N	N	N	N	N	N	N	N	Υ	N	N	Υ	N
Lucas-Bouwman												7		,,	
14 (2001)	N	N	N	N	N	N	N	N	N	N	Υ	Y	N	Υ	N
Nahum (2009)	N	N	N	Υ	Υ	N	N	N	Y	N	Y Gaded	Y	Υ	Υ	N
Paniagua (2017)	N	N	N	N	Y	N	N	N	N	N			N	Υ	N
18 Fallickai (2009)	N	N	N	N	Υ	Y	Υ	Υ	Υ	N	Υ 5		N	Υ	N
19 Panigada (2014)	N	N	N	N	Υ	N	N	N	Υ	N	Υ	-	Υ	Υ	N
20 Plint (2009)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ		N	Υ	N
Razi (2015)	N	N	N	N	N	N	N	N	N	N	Υ	•	N	N	N
Roberts (1999)	N	N	N	N	N	N	N	N	N	N	Υ		N	Υ	N
24 Roorda (1998)	N	N	N	N	N	N	N	N	N	N	Υ	N	N	N	N
Roosevelt (1996)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Ϋ́	N	N	Υ	N
Sadowitz (2012)	N	N	N	N	Υ	Υ	N	N	Υ	N	Υ		Υ	Υ	N
Saito (2017)	N	N	N	N	Υ	N	N	N	N	N	Υ		N	N	N
29 Schuh (2008)	N	N	N	N	Υ	N	Υ	Υ	Υ	Υ	Y		N	N	N
Schuh (2009)	N	N	N	N	N	N	N	N	N	N	Υ		N	Υ	N
Siomou (2003)	Υ	N	N	N	Υ	N	Ν	N	Υ	٦	Y Y	N	N	N	N
Sparrow (2006)	N	N	N	N	N	N	N	N	N	N	Υ	N	N	N	N
34 Stafford (1998)	Υ	N	N	N	Υ	N	N	N	Υ	Υ	γ	N N	N	Υ	N
Storr (1987)	N	N	N	N	N	N	N	N	N	N			N	N	N
Sumboonnanonda											Y Y				
Storr (1987) Sumboonnanonda (1997) Sung (1998)	Ν	N	N	N	Υ	N	N	N	Υ	N	\ \	N	N	Υ	N
	N	N	N	N	Υ	Υ	Υ	Υ	N	N	Υ	N	N	N	N
Super (1989)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N

1
2
3
4
5
6
_

3	
4	-
5	
6	•
7	•
8	}
9)
1	0
1	1
1	2
1	3
1	4
1	5
1	6

1	C
1	1
1	2
1	3
1	4
1	5
1	6
1	7
1	8
1	ç

45 46 47

-	_
1	4
1	5
1	6
1	6 7 8
1	8
1	9
2	0
2	1
	2
_	
2	3
2	4
2	5
2	6
2	7
2	8
_	۰
2	9
3	0
3	1
3	2
3	3
3	4
3	5
3	
3	6 7
3	8
`	_
3	9
4	0
4	1
4	2
4	3

											Ë	5			
Sussman (1964)	N	N	N	N	Υ	N	N	N	N	N	γ	N	N	Υ	N
Svedmyr (1995)	N	N	N	N	N	N	N	N	N	N	γ δ	N	Υ	N	N
Svedmyr (1999) ¹	N	N	N	N	Υ	N	Υ	N	Υ	Υ	Υ	N	Υ	Υ	Υ
Tagarro (2014)	N	N	N	N	N	N	N	N	N	N	Υ	I INI	N	Υ	N
Tal (1983)	N	N	N	Υ	N	N	N	N	N	N	Υ	N	N	N	N
Tamura (2008)	N	N	N	N	Υ	N	N	N	N	N	Y USI	N	N	N	N
Teeratakulpisarn											20				
(2007)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Ϋ́	N	N	Υ	N
van Woensel											WOW				
(1997)	N	N	N	Υ	N	N	N	N	N	N	Y	N	N	N	N
Webb (1986)	N	N	N	N	Υ	Υ	N	N	Υ	N	Υ	N	N	N	N
Zhang (2003)	N	N	N	N	Υ	N	N	N	N	N	Υ	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 Heathcare Research and eathcare Research and
on April 17, 2024 by guest. Protected by copyright. Quality. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD; 2008.

Supplement 5 Effect estimates for all adverse events with subgroups

			-2018-028511 on 1 August 2019. Downloadec	
Supplement 5	Effect estimates for all adverse events with subgroups		8- 02	
	a. Infection & respiratory system	p. 2-4	285	
	b. Gastro-intestinal tract	p. 5-7	11 0	
	c. CNS & behaviour effects	p. 8-9	n 1	
	d. Dermatologic conditions	p. 10	≥	
	e. Endocrine/ metabolic & musculoskeletal systems	p. 11	snô	
	f. Cardiovascular system	p. 12	t 20	
	g. General adverse events/ other symptoms	p. 13	19.	
	h. Immune system & oncology	p. 14	Do	
			<i>w</i> nlc	
The tables below report result	to of moto analysis for advance avents, arganized by argan sy	rt om c	Sade	
-	ts of meta-analyses for adverse events, organized by organ sy			
	ed for studies with more than one treatment arm, using risk o		=	
	ies that reported at least one event in at least one treatment			
study level data were conduc	comparison, without subgroup analysis. When data was avail	dition (o a bronchi	olitic)	
study-level data were conduc	comparison, without subgroup analysis. When data was avail ted for dose (single versus multi-dose) and for respiratory con	aition (e.g., bronch	olitis). <u>3</u>	
			per	
			1. bn	
			ာj. cc	
			om/	
			on .	
			Apri	
			117	
			, , 20	
			024	
			by (
			nes	
			%. ⊞	
			Prote	
			ecte	
			ä. o	
			у сс	
			уруг	
			ed by copyri ggupplement 5 - Page 1 of 14	
	Farmanum and Law Object of the Control of the Contr	/austalalta a substitut		
	For peer review only - http://bmjopen.bmj.com/site/abou	/guidelines.xhtml		

1136/bmjopen-2018-028511 on 1 August 2019. Downloaded

137 of 158 Supplement 62 Info	ction & respiratory sy	stam	В	MJ Open		1136/bmjopen-2018-0285 RD			
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) (95% CI)	l ² (%)	Peto OR (95% CI)	l 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.	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, 0.1)	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, 5 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, 0.81)	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, 0.87)	NA	NA	NA

				BMJ Open		1136/bmjopen-20		Pag	ge 138
Systemic infections, overall	Inhaled vs. placebo	Multi-dose, wheeze	2	18/91	20/94	0.00 (-0.06, 0.66)	0	0.96 (0.45, 2.05)	NA
Lung/trachea, overall	Systemic vs. placebo		7	18/955	28/928	-0.01 (-0.02, ====================================	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. p 0)	0	0.57 (0.20, 1.62)	0
	Systemic vs. placebo	Multi-dose	2	12/162	19/167	-0.09 (-0.29, 8 0.10) 9	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, Own of 0.02)	61	0.61 (0.29, 1.28)	30
	Systemic vs. placebo	Croup	4	6/413	9/399	0.02) no	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, 0.39)	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, 0.91)	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. 0 7)	NA	NA	NA
URT, overall	Inhaled vs. placebo		6	24/495	24/499	0.00 (-0.02, 0.92)	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, 0.83)	14	7.40 (0.45, 121.47)	NA
	Inhaled vs. placebo	Multi-dose	3	22/355	24/355	-0.01 (-0.04, db by 0.03)	0	0.93 (0.51, 1.71)	0

						Ó			
URT, by condition	Inhaled vs. placebo	Croup	3	2/140	0/144	0.00 (-0.02, 0.83)	14	7.40 (0.45,	NA
)285		121.47)	
	Inhaled vs. placebo	Wheeze	3	22/355	24/355	-0.01 (-0.04, = 0.03)	0	0.93 (0.51, 1.71)	0
	·					0.03)		,	
oice complaints, overall	Systemic vs.		1	0/31	0/27	0.00 (-0.07, 0.27)	NA	NA	NA
	placebo					subir			
/oice complaints, overall	Inhaled vs. placebo	All multi-	4	38/343	43/337	-0.01 (-0.10,	64	0.85 (0.53, 1.36)	73
		dose				0.07) 9			
oice complaints, by	Inhaled vs. placebo	Asthma	2	4/50	9/49	-0.08 (-0.046, ₽	90	0.39 (0.12, 1.26)	81
ondition						0.31) ≦			
	Inhaled vs. placebo	Wheeze	2	34/293	34/288	0.00 (-0.04, 0.04) to odds ratio; URT mom http://bmjopen.bmj.com/ on April 17, 2024 by gue:	0	0.99 (0.59, 1.64)	NA
RD: risk difference:		NA not applic	able/estir	mable; no.: num	ber; Peto OR: Pe	to odds ratio; URT jpp	er res		
vs.: versus				,	,	O O		, , , , , , , , , , , , , , , , , , , ,	
vs versus						3			
						ottp			
						<u>ă</u>			
						jop			
						en.			
						.bm			
						<u>ئ.</u> م.ن			
						ğ			
						or			
						→			
						Pr <u>i</u>			
						17			
						, 20			
)24			
						by			
						, G L			
						Jes			
						<u>:+</u>			
						Pro			
						ote			
						cte			
						g t			
						y			
						00 P			
						ÿri			
						Şupp	leme	nt 5 - Page 4 of 14	
	_							nt 5 - Page 4 of 14	
	For pe	er review only	- http://bn	njopen.bmj.com/	site/about/guidel	ines.xhtml			

				ВМЈ О	pen		1136/bmjopen-20		Page 140 of 1		
	Supplement 6b Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 - no. of patients	Comparison 2 - no. of patients	-2018-0285 RD CI → on 1 Au	l² (%)	Peto OR (95% CI)	l ² (%)	
0 1 2 3		5			with events/total no. of patients	with events/total no. of patients	August 2019. Dow				
4 5	Bleeding, overall	Systemic vs. placebo	Cinala dasa	7	31/1287	31/1262	0.00 (0.00, \$00)	0	1.00 (0.60, 1.67)	0	
6 7 8	Bleeding, by dose	Systemic vs. placebo Systemic vs. placebo	Single dose Multi-dose	3	2/800 29/487	1/790 30/472	0.00 (0.00, & 00) 0.00 (-0.02, a 0.02)	0	1.87 (0.19, 18.27) 0.96 (0.57, 1.64)	NA 0	
9 0 1	Bleeding, by condition	Systemic vs. placebo	Bronchiolitis	5	31/881	31/852	0.00 (-0.01, http://o.01)	0	1.00 (0.60, 1.67)	0	
2		Systemic vs. placebo	Croup	2	0/406	0/410	0.00 (-0.01, 3) 0.01) <u>9</u>	0	NA	NA	
4 5 6	Bleeding, overall	Inhaled vs. placebo	Single dose, croup	1	0/48	0/49	0.00 (-0.04, 5 0.04)	NA	NA	NA	
7	Vomiting, overall	Systemic vs. placebo		7	38/1603	34/1573	0.00 (0.00, है.01)	0	1.10 (0.69, 1.76)	17	
8	Vomiting, by dose	Systemic vs. placebo	Single dose	4	21/747	23/712	0.00 (-0.02,5 0.01) =:	0	0.87 (0.47, 1.59)	24	
0		Systemic vs. placebo	Multi-dose	3	17/856	11/861	0.00 (-0.01, ⁷ , 0.02) ²⁰	37	1.58 (0.75, 3.36)	0	
2 3 4	Vomiting, by condition	Systemic vs. placebo	Asthma	1	1/37	5/33	-0.11 (-0.27 ද් 0.06) ල	33	0.19 (0.03, 1.02)	0	
5 6 7		Systemic vs. placebo	Bronchiolitis	3	24/751	21/718	0.00 (-0.02, \$\frac{\text{P}}{2}\$	0	1.12 (0.62, 2.04)	0	
/ 8 9		Systemic vs. placebo	Croup	1	3/359	4/361	0.00 (-0.02, ref 0.01)	NA	0.75 (0.17, 3.34)	NA	

•	
2	
3	
4	
5	
6	
7	
8	
9	
10	
12	
13	
14	
15	
16)
17	
	,
19	
20	
21	
22	
23	
24	
25	
26	,
27	,
28	;
)
30)
31	
32	
33	
34	
35	
36	
20	,
37	
38	
)
40)
41	
42	
43	

44

age 141 of 158			BM.	l Open		1136/bmjopen-20			
						open-20			
	Systemic vs. placebo	Wheeze	2	10/456	4/461	0.02 (-0.06, ⁸ / ₆) 0.11) ⁸ / ₈	87	2.55 (0.87, 7.46)	0
Vomiting, overall	Inhaled vs. placebo		5	28/421	28/420	0.00 (-0.03,	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, Auguston 0.17)	NA	2.00 (0.20, 20.20)	NA
	Inhaled vs. placebo	Multi-dose	4	26/396	27/395	0.00 (-0.03,8 0.03) .9	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 0.13)	NA	7.13 (0.14, 359.55)	NA
	Inhaled vs. placebo	Croup	2	4/67	4/65	0.00 (-0.08,de 0.08)	0	0.97 (0.23, 4.00)	0
	Inhaled vs. placebo	Wheeze	2	23/326	24/328	0.00 (-0.04,3 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 ⁹ / ₅ -0.05)	47	0.23 (0.12, 0.42)	0
	Dexamethasone vs. other steroid	Multi-dose	1	6/287	12/290	-0.02 (-0.058- 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 (-0.16,7 0.08)	64	0.46 (0.14, 1.45)	0
	Dexamethasone vs. other steroid	Other conditions	1	1/86	15/169	-0.08 (-0.13g- 0.02) 9	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,st 0.01)	NA	1.01 (0.06, 16.11)	NA
Abdominal pain, overall	Dexamethasone vs. other steroid		3	29/188	48/264	-0.01 (-0.07g	0	0.96 (0.57, 1.61)	0

17	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	

_	Abdominal pain by	Dovamothasana vs. other	Acthma	1	2/56	2/54	0.03 (0.10%	NA	0.64/0.11.2.70\	NIA
	Abdominal pain, by condition	Dexamethasone vs. other	Asthma	1	2/30	3/54	-0.02 (-0.10% 0.06)	INA	0.64 (0.11, 3.79)	NA
1	JOHUILIOH	steroid	Croun	1	0/46	7/41	. 0	NI A	1 10 (0 40 2 47)	NI A
			Croup	1	9/46	7/41	0.02 (-0.14,	NA	1.18 (0.40, 3.47)	NA
-			Othor	1	10/06	20/160	0.13)	0	0.04/0.50.4.77\	
			Other	1	18/86	38/169	-0.01 (-0.12≱	0	0.94 (0.50, 1.77)	0
0 _			conditions	_	/	- /	0.10) gg			_
1 [Diarrhea, overall	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03,8	0	1.09 (0.43, 2.73)	0
2							0.04) 9			
-	Diarrhea, by dose	Systemic vs. placebo	Single dose	1	3/89	3/85	0.00 (-0.06,5	NA	0.95 (0.19, 4.84)	NA
4 5 —							0.05) $\frac{50}{0.01}$ 0.01 (-0.03, $\frac{50}{0.00}$			
6		Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03,a	0	1.16 (0.38, 3.54)	0
7							0.05)			
8 [Diarrhea, by condition	Systemic vs. placebo	Bronchiolitis	1	3/89	3/85	0.00 (-0.06,ਤ	NA	0.95 (0.19, 4.84)	NA
9							0.05)			
0		Systemic vs. placebo	Wheeze	2	7/165	6/145	0.01 (-0.03,	0	1.16 (0.38, 3.54)	0
1 2		, , , , , , , , , , , , , , , , , , , ,				,	0.05)			
	Diarrhea, overall	Inhaled vs. placebo	Multi-dose,	2	41/326	46/328	-0.01 (-0.09	37	0.89 (0.57, 1.40)	44
4	oreran	minared voi pracede	wheeze	_	11,020	10,320	0.08)		0.03 (0.07) 21.10)	
5 🗀	RD: risk differer	nce; CI: confidence interval; NA: r		stimahle:	no : number: P	eto OR: Peto oc	<u> </u>	<u> </u>		
6	ND. Hok differen	ice, ci. comidence meerval, iv.	iot applicable, c	Juliane,	io namber, i	cto on reto oc	₽	,		
7							on			
8 9							Apr			
0							117			
1							on April 17, 2024 by guest.			
2)24			
3							by			
4							gue			
5 6							št.			
7							Protected			
8							le ct			
9							ed F			
0							у с			
1							о́ру			
2 3							21. 11.	ament	5 - Page 7 of 14	
ر 4							i x ubbı	ement	J - rage / UI 14	
5		For peer rev	view only - http://	bmjopen.b	mj.com/site/ab	out/guidelines.x	html			
6										
7										

Pag	ge 143 of 158				BMJ Open		1136/DM			
1 2 3	Supplement 6c. CN	IS & behavior effects					RD (280)			
4 5 6 7 8 9 10 11	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	(95% CI) - on 1 August 2019.		Peto OR (95% CI)	l ² (%)
13 14	Tremor/jitteriness, overall	Systemic vs. placebo		5	22/559	14/508	0.01 (-0.01, 0.03)	0	1.44 (0.71, 2.92)	0
15 16 17	Tremor/jitteriness, by dose	Systemic vs. placebo	Single dose	2	9/83	7/56	0.00 (-0.08, 0.08)	0	1.15 (0.36, 3.66)	0
18 19		Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
20 21 22	Tremor/jitteriness, by condition	Systemic vs. placebo	Asthma	1	9/37	7/33	0.01 (-0.16, 0.18)	0	1.15 (0.36, 3.66)	0
23			Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
24			Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
25 26 27	Tremor/jitteriness, overall	Dexamethasone vs. other steroid	Single dose, croup	1	1/46	0/41	0.02 (-0.04, 0.08)	NA	6.63 (0.13, 336.21)	NA
28 29	Behaviour change, overall	Systemic vs. placebo		4	7/588	3/571	0.00 (-0.01, 0.02)	19	1.95 (0.55, 6.92)	0
30 31	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
32 33 34		Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06)		2.32 (0.56, 9.64)	0
35 36	Behaviour change, by condition	Systemic vs. placebo	Croup	2	1/423	1/426	0.00 (-0.01, 0.01)	. 0	1.01 (0.06, 16.11)	NA
37 38 39		Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06)	11	2.32 (0.56, 9.64)	0
40 41	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

1136/bmjopen-20

1	3
1	4
1	5
1	6
1	7
1	8
1	9
2	0
2	1
2	2
2	
	4
_	5
	6
	7
	, 8
	9
_	0
	1
3	2
3	3
3	4
3	5
3	6
3	7
3	8
3	9
4	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	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06, 0.13)	NA	7.13 (0.14, 359.55)	NA
,	condition							on 1		
}		Inhaled vs. placebo	Croup	2	5/106	7/108	-0.02 (-0.05, 0.02)	≥ 0	0.66 (0.20, 2.18)	0
n	Behaviour change, overall	Dexamethasone	All single	2	35/60	38/57	-0.08 (-0.25, 0.09)	ous 0	0.73 (0.34, 1.56)	0
1		vs. other steroid	dose					t 20		
2	Behaviour change, by	Dexamethasone	Asthma	1	10/14	14/16	-0.16 (-0.45, 0.13)	9 NA	0.38 (0.06, 2.21)	NA
3	condition	vs. other steroid						Do		
4		Dexamethasone	Croup	1	25/46	24/41	-0.04 (-0.25, 0.17)	NA	0.85 (0.36, 1.97)	NA
5		vs. other steroid						ade		
7	Headache, overall	Systemic vs.	Single dose,	1	0/37	1/33	-0.02 (-0.10, 0.07)	ŭ ⇒ 0	0.11 (0.00, 5.68)	NA
8		placebo	asthma					om		
9	Headache, overall	Dexamethasone	All single	2	7/102	4/95	0.02 (-0.08, 0.11)	51	1.63 (0.46, 5.74)	NA
0		vs. other steroid	dose					://bi		
2	Headache, by condition	Dexamethasone	Asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	NA	NA	NA
3	•	vs. other steroid						oen.		
4			Croup	1	7/46	4/41	0.05 (-0.08, 0.19)	NA	1.63 (0.46, 5.74)	NA
5	RD: risk difference;	CI: confidence interva	ıl; NA: not appli	cable/estir	mable; no.: num	ber; Peto OR: F	eto odds ratio; vs.:	ersus	1	
6 7							:	™ o		
8								n ≥		
9							クケ	<u> </u>		
0								17.		
1 2								202		
3								4 b		
4							Q	<u> </u>		
5								est.		
6								Pro		
7 8)tec	ent 5 - Page 9 of 14	
9								te d		
0								by c		
1							-	XQDX		
2							Q). O	ont C Dogo O of 14	
3 4								anhhieme	ent 5 - Page 9 Of 14	
_		For	neer review only	- http://bm	ionen bmi com/	site/about/quide				

e 145 of 158				BMJ Open		1136/bmj			
Supplement 6d. Do	ermatologic conditions					1136/bmjopen-2018-028511 on RD (95% CI)			
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	1 August 2019.	l ² (%)	Peto OR (95% CI)	l 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
<u> </u>	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, 0.018	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) eg	NA	NA	NA
RD: risk difference;	CI: confidence interval	; NA: not applic	able/estim	able; no.: numk	per; Peto OR: Pe	otected by copyri		nt 5 - Page 10 of 14	

No.

of

studies

4

1

3

2

2

1

RD: risk difference; CI: confidence interval; NA: not applicable/estimable; no.: number; Peto OR: Peto odds ratio; vs.: $\sqrt[q]{e}$ ersus

Comparison

1 - no. of

patients

with

events/total

no. of

patients

5/832

1/359

4/473

4/448

1/384

1/33

5/6

Comparison

2 - no. of

patients

with

events/total

no. of

patients

1/818

0/361

1/457

1/432

0/386

2/15

4/10

No. of

studies

Comparison

1 – total

no. of

patients

(%)

NA

0

NA

NA

NA

Peto OR

(95% CI)

3.08 (0.60, 15.94)

7.43 (0.15, 374.47)

2.56 (0.42, 15.61)

2.56 (0.42, 15.61)

7.43 (0.15, 374,47)

0.18 (0.01, 2.17)

5.21 (0.72, 37.57)

l²

(%)

136/bmjopen-2018-028511

on 1 August 2019

(%)

0

NA

NA

Mean

Difference

(95% CI)

0.10 (-0.47, 0.67) 9

RD

(95% CI)

0.00 (0.00, 0.01

0.00 (0.00, 0.0省

 $0.00 (-0.01, 0.0\frac{9}{3})$

0.00 (-0.01, 0.03)

0.00 (0.00, 0.0

-0.10 (-0.28, 0.98)

0.43 (0.01, 0.86)

Comparison ?

2 – total

no. of

patients

5

Adverse event

abnormalities, overall

Fluid & electrolyte

13 Fluid & electrolyte

44

45 46 47

42 43

abnormalities, by dose P Fluid & electrolyte abnormalities, by condition

23 Fluid & electrolyte abnormalities, overall Adrenal suppression, overall

4		(
2	•	
2	•	8
2		
3		
3		
3		•
3		:
3		
3		ı
3		
3		

Linear growth	Inhaled vs. placebo	Multi-dose, wheeze	2	154	109	Pic
Cl: confidence interval; no.: numb	oer; vs.: versus					tected b
						~

Subgroup

Adverse event

Supplement 6e. Endocrine/metabolic & musculoskeletal systems

Subgroup

Single dose

Multi-dose

Croup

Bronchiolitis

Multi-dose,

bronchiolitis

Multi-dose,

asthma

Comparison 1

vs. Comparison 2

Comparison 1

VS.

Comparison 2

Systemic vs. placebo

Dexamethasone vs.

Inhaled vs. placebo

other steroid

15-16 17, 18 19 20-21 22, 23 24 25-26 27, 28 29

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	028511 on 1 August 2019. RD (95% CI)	l ² (%)	Peto OR (95% CI)	1 ² (%)
3 A	rrhythmia, overall	Systemic vs. placebo	Multi-dose, wheeze	1	0/31	0/27	0.00 (-0.07, 0.0)	NA	NA	NA
A A	rrhythmia, overall	Inhaled vs. placebo	Multi-dose, wheeze	1	0/29	0/27	0.00 (-0.07, 0.02)	NA	NA	NA
3 A	rrhythmia, overall	Dexamethasone vs. other steroid	Multi-dose, asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	NA	NA	NA
Н	lypertension, overall	Systemic vs. placebo	All bronchiolitis	3	1/727	1/714	0.00 (-0.01, 0.03)	0	1.00 (0.06, 15.99)	50
3 H	lypertension, by dose	Systemic vs. placebo	Single dose	1	0/305	0/295	0.00 (-0.01, 0.01)	NA	NA	NA
4		Systemic vs. placebo	Multi-dose	2	1/422	1/419	0.00 (-0.01, 0.03)	0	1.00 (0.06, 15.99)	50
Р 5 7	lypertension, overall	Dexamethasone vs. other steroid	Single dose, asthma	1	0/15	0/17	0.00 (-0.11, 0.13)	NA	NA	NA
_	ongestive heart failure, verall	Systemic vs. placebo	Multi-dose, croup	1	0/25	0/25	0.00 (-0.07, 0.07)	NA	NA	NA
) 1 2 3 3 4 4 5 5 7 7 7 8 9 9 9	RD: risk difference;	CI: confidence interval;	NA: not applicab	ole/estimak	ole; no.: numbe	r; Peto OR: Peto	2024 by guest. Protected by copyri		5 - Page 12 of 14	
		For pe	er review only - h	ttn·//hmion	en hmi com/site	/ahout/auidelin	es yhtml			

 Supplement 6g. General adverse events/ other symptoms

+ 5	Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	285 RD	l ²	Peto OR	l ²
5		vs.		of	1 – no. of	2 – no. of	(95% CI∓	(%)	(95% CI)	(%)
7		Comparison 2		studies	patients	patients	on 1			
3					with	with	ΑL			
9					events/total	events/total	ıgus			
1 U 1 1					no. of	no. of	st 20			
11 12					patients	patients	019.			
13	General complaints ¹ , overall	Systemic vs. placebo	All	2	38/446	38/423	0.00 (-0.04, 100)	0	1.00 (0.62, 1.60)	0
14			bronchiolitis				wnlo			
15 16	General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, (209)	0	NA	NA
17		Systemic vs. placebo	Multi-dose	1	38/400	38/400	0.00 (-0.04, 0.04)	0	1.00 (0.62, 1.60)	0
18	General complaints ² , overall	Dexamethasone vs.		2	3/102	3/95	-0.01 (-0.06, \$\frac{1}{9}.03)	0	0.90 (0.18, 4.61)	11
19		other steroid					http			
20	General complaints, by	Dexamethasone vs.	Asthma	1	0/56	1/54	-0.02 (-0.07, 9.03)	NA	0.13 (0.00, 6.58)	NA
∠ i 22	condition	other steroid		16			mjol			
23		Dexamethasone vs.	Croup	1	3/46	2/41	0.01 (-0.08, 👺11)	NA	1.29 (0.21, 7.81)	NA
24		other steroid					.bmj			
25	1									

¹Two studies reported pallor
²One 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.: gersus

19 of 158			ВМЈ С	Open		1136/bmjopen-2018-0			
Supplement 6h. Immui	ne system & oncology					en-2018-C			
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	285 1 on 1 August 2019. RD (95%	l ² (%)	Peto OR (95% CI)	l ² (%)
mmunosuppression, overall	Systemic vs. placebo confidence interval; NA:		1	0/47	0/48	0.00 (-0.04, 👺 04)	NA	NA	NA
						dds ratio; vs.: dds ratio; vs.: population on April 17, 2024 by guest. Protected by copyright S.	ent 5 -	Page 14 of 14	
	For peer re	view only - http:/	//bmjopen.	bmj.com/site/ab	out/guidelines.x	html			

Supplement 6. Studies reporting no adverse events

		E	BMJ Open		AE reporting
Supplement 6. Study	dies reporting no adverse Condition	events Comparisons - main	Study	Study	, , ,
Alansari 2013	bronchiolitis	systemic vs. placebo	design RCT	sample 200	No AE overall; 7 days follow-upgevealed no side effect concerns in treatment groups.
Brunette 1988	asthma, before signs of wheeze	systemic vs. systemic	nRCT	32	No AE overall; Of 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 reatment in either group.
Escobedo Chavez 1992	asthma	systemic vs. non- corticosteroid	RCT	50	No AE overall;
Fifoot 2007	croup	systemic vs. systemic vs. systemic	RCT, 3-arm	99	No AE overall; One patient in exh group vomited their first dose of medication; all except one (dexamethasone 0.6mg/kg) tolerated their repeat dose; on patient suffered any adverse outcomes from receiving story steroid, either at index presentation or during the follow-up period.

Ghirga 2002	wheeze - recurrent,	inhaled vs. no	RCT	26	No AE overall;
	early in URTI	intervention			No apparent adverse effects reported 4 years
					post-study. $\frac{3}{2}$
Husby 1993	croup	inhaled vs. placebo	RCT	36	No AE overall;
					No side effects ware reported.
Jartti 2006	wheeze - acute	systemic vs. placebo	RCT	78	No AE overall; 8
					Prednisolone trestment well tolerated; no
		h			clinically significant adverse effects occurred.
Jartti 2007	wheeze - recurrent	systemic vs. placebo	RCT	58	No AE overall;
		100			Prednisolone treatment well tolerated; no
		CO.			clinically significant adverse effects occurred.
Klassen 1994	croup	inhaled vs. placebo	RCT	54	One patient in pacebo group had a burning
					sensation on the acce. No adverse events
			0//		noted in budesopide group.
Langton Hewer 1998	asthma	systemic vs. systemic	RCT, 3-arm	98	No AE overall;
		vs. systemic		11	No side effect possibly attributable to
					prednisolone the apy was noted in any of the
					three treatment groups.
					pr <u>il</u>
Leipzig 1979	croup	systemic vs. placebo	RCT	30	No AE overall; 1/7
					Observed no adverse effects or late relapses.
Razi 2015	asthma	inhaled vs. placebo	RCT	100	No AE overall;
					No drug-related dverse effects were
					identified during nospitalization.
Roorda 1998	croup	inhaled vs. placebo	RCT	17	No AE overall; ਰੇ
					No side effects of treatment regimens were
					reported. ♥

		E	BMJ Open		P 1136/bmjopen-20
Saito 2017	asthma	systemic vs. inhaled	RCT	50	No AE overall; Adverse events and 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; $\frac{80}{100}$ No adverse effects developed in children given prednisologie after discharge.
Sparrow 2006	croup	systemic vs. systemic	RCT	133	No AE overall; ခြို့ No adverse evenus in either group.
Storr 1987	asthma	systemic vs. placebo	RCT	140	No AE overall; There were no observed side effects related to the single pregnisolone dose.
Sung 1998	asthma	inhaled vs. placebo	RCT	44	No AE overall;
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, asige from tremor (1 infant) as side effect of saleutamol.
Tamura 2008	refractory pneumonia (5 year old)	systemic	CS (#1)	1	No AE overall;

van Woensel 1997	bronchiolitis	systemic vs. placebo	RCT	54	No AE overall;
					No clinically sign act and 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 clinial exam 3 days after
					completing 5-da reatment course.
Zhang 2003	bronchiolitis	systemic vs. standard	RCT	52	No AE overall; 👂
		care			Potential side-efects of prednisolone not
					included as outcome measures in this study
					as short-term steroid therapy has been well
					confirmed. At tinge of analysis, no adverse
					events were noted in patients who received
					prednisolone.
					<u>j</u>

AE: adverse events; CS: case series; nRCT: non-randomised controlled trial; RCT: randomised controlled trial; sal: salbitamol; URTI: upper n.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

respiratory tract infection; vs: versus

찣

Section/ topic (page no)	Item	PRISMA checklist item	PRISMA harms (minimum)	Recommendations for reporting harms in systematic reviews (desirable)	Check if done
Title 0 Title (3) 1 2 3 4	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
5 Abstract 6 Structured 7 summary (4) 8 9 1 1 2 3 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) 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
6 Objectives (5) 7 8 9 1 1 2 8 4 6	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 4 criteria (6) 5 6 7	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;

1 2							BMJ
3 4 5 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	Open: first put
8 9	Information sources (7)	7	Describe all information sources (eg, databases with dates of coverage,	_	Report if only searched for published data, or	p. 5;	olished
10 11 12 13 14 15 16 17 18			contact with study authors to identify additional studies) in the search and date last searched.		also sought data from unpublished sources, from authors, drug manufacturers and regulatory agencies. If includes unpublished data, provide the source and the process of obtaining it.	Supplement 1- Search strategy	l as 10.1136/bmjopen-2018
19	Search (7)	8	Present full electronic search strategy for at least one database, including	_	If additional searches were used specifically	Supplement 1 - Search strategy	3-028
20 21 22 23 24			any limits used, such that it could be repeated.		to identify adverse events, authors should present the full search process so it can be replicated.	Source States	511 on 1 Augu
25 26	Study selection (8)	9	State the process for selecting studies (ie, screening, eligibility, included in	_	If only included studies reporting on adverse	p. 6;	st 20
27 28 29 30 31 32 33 34 35 36	Data	10	systematic review, and, if applicable, included in the meta-analysis). Describe method of data extraction	2	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. No specific additional	Supplement 2 - Eligibility criteria for study inclusion p. 6-7	19. Downloaded from http://bmj
37 38 39 40	collection process (9)	10	from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.		information is required for systematic reviews of harms.	μ. 0-7	pen.bmj.cc
41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56	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	BMJ Open: first published as 10.1136/bmjopen-2018-028511 on 1 August 2019. Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copy

1 2 3 4 5 6 7 8 9 10 11 12 13					training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details regarding the specific methods used to capture harms (active/passive and timing of adverse event).	
14 15 16 17 18 19	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
20 21 22	Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	_	No specific additional information is required for systematic reviews of harms.	p. 7-8
23 24 25 26 27	Synthesis of results (11)	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I ²) for each metaanalysis.	Specify how zero events were handled, if relevant.		p. 7-8
28 29 30 31 32 33 34 35 36	Risk of bias across studies (11)	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	6-10-1 10-1	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	p. 7
37 38 39 40 41 42 43 44 45 46 47 48 49	Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.		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
50 51 52 53 54 55 56 57 58	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

60

1 2 3 4 5 6 7 8 9	Study characteristics (14)	18
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28	Risk of bias within studies (15)	19
29 30 31 32 33 34	Results of individual studies (16)	20
35 36 37 38 39 40 41	Synthesis of results (17)	21
42 43 44 45 46 47 48 49 50 51 52 53 54 55 56		
56 57 58 59		

For each study, present characteristics for which data were extracted (eg. study size, PICOS, follow-up period) and provide the citations.

Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).

For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.

Present results of each meta-analysis done, including confidence intervals and measures of consistency.

Define each harm addressed, how it was ascertained (eg, patient report, active search), and over what time period.

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. 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. Report the actual numbers of adverse events in each study, separately for each intervention.

Add additional

characteristics to: "P"

(population) patient risk

If included data from unpublished sources. report clearly the data source and the impact of these studies to the

final systematic review.

p. 8;

Supplement 3 -Characteristics of included studies

p. 8;

Supplement 4 -Methodological quality of included studies

p. 8;

Supplement 3 -Characteristics of included studies

p. 8-14;

Table 1 - Number of studies and participants reporting adverse events;

Figures 2-4 -Forest plots of adverse events:

Supplement 5 -Effect estimates for all adverse events with subgroups;

Supplement 6 -Studies reporting no adverse events

Describe any

causality.

assessment of possible

							BM
2 3 1 5 7	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	lJ Open: first publi
3 9 10 11 12 13 14		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.	studies p. 8; Supplement 5 - Effect estimates for all adverse events with subgroups	shed as 10.1136/bmjop
6 7 8 9	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	pen-2018-02851
21 22 23 24 25 26 27 28	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	1 on 1 August 2019. Dc
29 30 31 32 33 34 35 36 37	Conclusions (19)	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	- 2 2	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	BMJ Open: first published as 10.1136/bmjopen-2018-028511 on 1 August 2019. Downloaded from http://bmjopen.
39 10 11 12 13	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	bmj.com/ on /
14 15 16 17 18 19 10 10 10 10 10 10 10 10 10 10 10 10 10							en.bmj.com/ on April 17, 2024 by guest. Protected by copyright.

BMJ Open

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

Journal:	BMJ Open
Manuscript ID	bmjopen-2018-028511.R1
Article Type:	Research
Date Submitted by the Author:	24-Jun-2019
Complete List of Authors:	Fernandes, Ricardo; Hospital de Santa Maria, Pediatrics; Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Instituto de Medicina Molecular, University of Lisbon Wingert, Aireen; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence Vandermeer, Ben; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Featherstone, Robin; University of Alberta Faculty of Medicine & Dentistry, Alberta Research Centre for Health Evidence Ali, Samina; University of Alberta, Pediatrics; Women & Children's Health Research Institute, Pediatrics, University of Alberta Plint, AMy; University of Ottawa, Stang, Antonia; University of Calgary, Pediatrics, Emergency Medicine, Community Health Sciences Rowe, Brian; University of Alberta, Emergency Medicine; University of Alberta, School of Public Health Johnson, David; University of Calgary Cumming School of Medicine, Pediatrics, Emergency Medicine, and Physiology and Pharmacology Allain, Dominic; University of Alberta, Pediatrics, Faculty of Medicine & Dentistry Klassen, Terry; Manitoba Institute of Child Health & Associate Dean of Academic, Faculty of Medicine, University of Manitoba Hartling, Lisa; University of Alberta, Pediatrics; University of Alberta Faculty of Medicine and Dentistry, Alberta Research Centre for Health Evidence
Primary Subject Heading :	Paediatrics
Secondary Subject Heading:	Respiratory medicine
Keywords:	corticosteroids, Asthma < THORACIC MEDICINE, bronchiolitis, croup, PAEDIATRICS, safety

SCHOLARONE™ Manuscripts

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

Ricardo M. Fernandes, Aireen Wingert, Ben Vandermeer, Robin Featherstone, Samina Ali, Amy C. Plint, Antonia S. Stang, Brian H. Rowe, David W. Johnson, Dominic Allain, Terry P. Klassen, Lisa Hartling

Ricardo M. Fernandes, Department of Pediatrics, Hospital de Santa Maria, Lisbon, Portugal; Laboratory of Clinical Pharmacology and Therapeutics, Faculty of Medicine, Instituto de Medicina Molecular, University of Lisbon, Lisbon, Portugal

Aireen Wingert, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Ben Vandermeer, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Robin Featherstone, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Samina Ali, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada; Women & Children's Health Research Institute, Department of Pediatrics, University of Alberta, 5-083 Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Amy C. Plint, Department of Pediatrics, University of Ottawa, Children's Hospital of Eastern Ontario 401 Smyth Road, Ottawa, Ontario, Canada

Antonia S. Stang, Departments of Pediatrics, Emergency Medicine, Community Health Sciences, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada

Brian H. Rowe, Department of Emergency Medicine, University of Alberta, 8440 – 112 Street NW, Edmonton, Alberta, Canada; School of Public Health, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

David W. Johnson, Departments of Pediatrics, Emergency Medicine, and Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, 2500 University Drive NW, Calgary, Alberta, Canada

Dominic Allain, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Terry P. Klassen, Manitoba Institute of Child Health, University of Winnipeg, Children's Hospital of Research Institute of Manitoba 513 – 715 McDermot Avenue, Winnipeg, Manitoba, Canada

Lisa Hartling, Alberta Research Centre for Health Evidence, Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada; Department of Pediatrics, Faculty of Medicine & Dentistry, University of Alberta, Edmonton Clinic Health Academy 11405 – 87 Avenue, Edmonton, Alberta, Canada

Corresponding author: Dr. Lisa Hartling, 11405 - 87 Avenue, Edmonton, Alberta, T6G 1C9, Canada; phone: 780-492-6124; e-mail: hartling@ualberta.ca; ords

Manuscript = 3819 words

ABSTRACT (300 words)

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

Design Systematic review of primary studies.

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

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

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

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

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

Strengths and limitations of this study:

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



INTRODUCTION

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

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

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

METHODS

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

Patient and Public Involvement

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

Literature search

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

Eligibility criteria

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

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

Study selection

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

Data extraction

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. Studies that reported at least one event in at least one treatment arm were included in the analysis of pORs and all comparative studies were used for analysis of

RD. One AE (growth) was reported as a continuous outcome and data were pooled using a DerSimonian Laird inverse variance random effects method as a mean difference (MD; in cm). The I² statistic was presented to quantify the magnitude of statistical heterogeneity between studies; while the I² has the potential to be misinterpreted, it is the standard in the field and we chose to present the statistic for informational purposes. 19 Subgroup analyses from study-level data were conducted for respiratory condition and dose (single versus multi-dose) using Cochran's Q (α=0.05) to detect statistical heterogeneity. Studies contributing no numerical data for analysis (e.g., single arm studies, studies that reported no AEs overall) are summarized in Supplement 3. Assessment of small-study bias (for meta-analyses with at least eight studies) was planned using the funnel plot and Egger's test; 20 however, this was not conducted due to inadequate number of studies for each outcome. Analyses were conducted using Review Manager Version 5.3 (Cochrane Collaboration). 21 Graphs were constructed using TIBCO 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; I²=0%). These studies focused on asthma (n=3),^{27, 41, 80} croup (n=2),^{49, 52} or both (n=1);²⁵ all compared oral dexamethasone with oral prednisone. No statistically significant difference was found for abdominal pain between *dexamethasone and another corticosteroid*.^{25, 27, 52}

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; I²=9%). Five studies reported measurements of growth (height and weight) ranging from one to three years of follow-up, which could not be pooled due to heterogeneous interventions, comparators, or outcome measurements.^{29, 31, 45, 58, 71} Three studies included data on inhaled corticosteroid versus placebo. One RCT on asthma⁵⁸ (n=20) comparing budesonide and placebo found no signs of growth retardation by height measurements at 12 months or after up to six treatments. An RCT of episodic wheeze²⁹ (n=294) found height at three years of age was unaffected in children receiving budesonide or placebo. One RCT of inhaled fluticasone propionate at very high doses (1500 mcg daily during upper respiratory infections) versus placebo in recurrent wheeze⁴⁵

reported additional outcome data on height that was not pooled in the meta-analysis mentioned above. There was a smaller mean change in height *z* score in the corticosteroid group over one year (MD –0.24; 95% CI -0.40 to -0.08; adjusted results). 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'. 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); 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).

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

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

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

Cardiovascular System

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

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

General AEs/ Other Symptoms

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

Immune System & Oncology

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

DISCUSSION

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

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. 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. On 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. Further, results from individual studies reporting transient differences in bone and adrenal biomarkers are of unclear clinical relevance, particularly for previously healthy children and single use. This calls for caution and monitoring of linear growth, particularly when use of high-dose inhaled or systemic corticosteroid is recurrent.

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

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

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

Strengths and limitations

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

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

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

CONCLUSION

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

Tables

1

2

4

5

6 7 8

9

10 11

12

13

14 15 16

17

18 19

20

21

22 23

24

25

26 27

28

29

30

31 32

33

34 35

36

37

38

39 40

41

42

43 44

45

46

47 48

49

50

51 52

53

54

55 56 57

58 59

60

- 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

Acknowledgments: We gratefully acknowledge the following individuals for their contributions: Megan Nuspl, Sanjaya Dhakal and Pritam Chordiya for assisting with screening, initial data extraction and verification, and article retrieval; Marc Parsons for assisting with data extraction and verification, and quality assessment; and, Jack Yeung, Marta Oleszczuk and Igor Pravdivyi for assistance with translations. MN, SD, PC and MP received remuneration for their work from a Canadian Institutes of Health Research (CIHR) grant (funding reference number KRS134306). JY, MO and IP did not receive remuneration for the translation work. None of the acknowledged individuals have industry affiliations, or any conflicts of interest to declare.

Contributors: RMF, AW, BV, SA, ACP, ASS, BHR, DWJ, DA, TPK, and LH critically reviewed and contributed to drafts of the report. RF conducted the literature searches. AW conducted screening, quality assessments, and data extraction. AW and BV conducted data synthesis/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.

Funding: This study was funded by a Knowledge Synthesis Grant from CIHR (funding reference number KRS134306). The funder had no role in the design of the study, the collection, analysis or interpretation of data, the writing of the report, or the decision to submit the paper for publication.

Competing interests: All authors declare funding from CIHR for the submitted work. LH was funded in part by a New Investigator Salary Award from the CIHR; ASP is supported by a Tier II University of Ottawa Research Chair Award; BHR was supported by a Tier I Canada Research Chair in Evidence-based Emergency Medicine from CIHR. The remaining authors have no financial relationships relevant to this manuscript to disclose. DWJ, TPK and ASP are also authors on some of the included studies. The other authors have no conflicts of interest to declare.

Provenance and peer review: Not commissioned; externally peer-reviewed.

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 (using published data) are available from the corresponding author upon reasonable request.



REFERENCES

- 1. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med* 2012;185(1):12-23.
- 2. Johnson D. Croup. BMJ Clin Evid 2009.
- 3. Russell KF, Liang Y, O'Gorman K, et al. Glucocorticoids for croup. *Cochrane Database Syst Rev* 2011;1(CD001955).
- 4. Adams NP, Bestall JC, Jones P, et al. Fluticasone at different doses for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2008;4(CD003534).
- 5. Kelly HW, Sternberg AL, Lescher R, et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367(10):904-912.
- 6. van Staa T, Cooper C, Leufkens H, et al. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18(5):913-918.
- 7. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: A systematic review with meta-analysis. *Pediatrics* 2009;123(3):e519-525.
- 8. Zhang L, Axelsson I, Chung M, et al. Dose response of inhaled corticosteroids in children with persistent asthma: A systematic review. *Pediatrics* 2011;127(1):129-138.
- 9. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: Framework for a structured approach. *BMC Med Res Methodol* 2007;7(1):1-9.
- 10. Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: A network metaanalysis and cochrane overview. *Cochrane Database Syst Rev* 2011;2(CD008794).
- 11. Higgins J, Green S. (editors). The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org (accessed 12 January 2018).
- 12. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *J Clin Epidemiol* 2009;62(10):1006-1012.

13. Zorzela L, Loke YK, Ioannidis JP, et al. PRISMA harms checklist: Improving harms reporting in systematic reviews. *BMJ* 2016;352:i157.

- 14. Global Initiative for Asthma. Global strategy for asthma management and prevention. http://www.ginasthma.org (accessed 12 January 2018).
- 15. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: A clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004;140(10):795-801.
- 16. Tugwell P, Judd MG, Fries JF, et al. Powering our way to the elusive side effect: A composite outcome 'basket' of predefined designated endpoints in each organ system should be included in all controlled trials. *J Clin Epidemiol* 2005;58(8):785-790.
- 17. Chou R, Aronson N, Atkins DL, et al. Assessing harms when comparing medication interventions. In: Agency for Healthcare Research and Quality (US). Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD; 2008.
- 18. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26(1):53-77.
- 19. Hedges LV. Comment on 'Misunderstandings about Q and "Cochran's Q Test" in meta analysis'. *Stat Med* 2016;35(4):496-497.
- 20. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315(7109):629-634.
- 21. Review Manager (RevMan) [computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.
- 22. TS Inc. TIBCO Spotfire S+ Workbench, Version 3.4 [statistical software]. 1996.
- 23. Alangari AA, Malhis N, Mubasher M, et al. Budesonide nebulization added to systemic prednisolone in the treatment of acute asthma in children: A double-blind, randomized, controlled trial. *Chest* 2014;145(4):772-778.
- 24. Alansari KS, Sakran M, Davidson BL, et al. Oral dexamethasone for bronchiolitis: A randomized trial. *Pediatrics* 2013;132(4):e810-816.

- 25. Aljebab F, Alanazi M, Choonara I, et al. Observational study on the palatability and tolerability of oral prednisolone and oral dexamethasone in children in Saudi Arabia and the UK. *Arch Dis Child* 2017;103(1):83-88.
- 26. Alshehr M, Almegamsi T, Hammdi A. Efficacy of a small dose of oral dexamethasone in croup. *Biomed Res* 2005;16(1):65-72.
- 27. Altamimi S, Robertson G, Jastaniah, W, et al. Single-dose oral dexamethasone in the emergency management of children with exacerbations of mild to moderate asthma. *Pediatr Emerg Care* 2006;22(12):786-793.
- 28. Bacharier LB, Phillips BR, Zeiger RS, et al; Childhood Asthma Research and Education Network. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122(6):1127-1135.e8.
- 29. Bisgaard H, Hermansen MN, Loland L, et al. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354(19):1998-2005.
- 30. Bjornson CL, Klassen, TP, Williamson J, et al; Pediatric Emergency Research Canada Network. A randomized trial of a single dose of oral dexamethasone for mild croup. *N Engl J Med* 2004;351(13):1306-1313.
- 31. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: Prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81(5):624-629.
- 32. Buckingham SC, Jafri HS, Bush AJ, et al. A randomized, double-blind, placebo-controlled trial of dexamethasone in severe respiratory syncytial virus (RSV) infection: Effects on RSV quantity and clinical outcome. *J Infect Dis* 2002;185(9):1222-1228.
- 33. Bülow SM, Nir M, Levin E, et al. Prednisolone treatment of respiratory syncytial virus infection: A randomized controlled trial of 147 infants. *Pediatrics* 1999;104(6):e77.
- 34. Chang AB, Clark R, Sloots TP, et al. A 5- versus 3-day course of oral corticosteroids for children with asthma exacerbations who are not hospitalised: A randomised controlled trial. *Med J Aust* 2008;189(6):306-310.

35. Chen ZG, Li M, Chen H, et al. Efficacy of pulmicort suspension plus salbutamol and ipratropium bromide for management of acute asthma exacerbation in children: A comparative study. *J South Med Univ* 2008;28(3):470-472.

- 36. Chub-Uppakarn S. Sangsupawanich P. A randomized comparison of dexamethasone 0.15 mg/kg versus 0.6 mg/kg for the treatment of moderate to severe croup. *Int J Pediatr Otorhinolaryngol* 2007;71(3):473-477.
- 37. Clavenna A, Sequi M, Cartabia M, et al. Effectiveness of nebulized beclomethasone in preventing viral wheezing: An RCT. *Pediatrics* 2014;133(3):e505-512.
- 38. Connett GJ, Warde C, Wooler E, et al. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70(3):170-173.
- 39. Connolly JH, Field CMB, Glasgow JFT, et al. A double blind trial of prednisolone in epidemic bronchiolitis due to respiratory syncytial virus. *Acta Paediatr Scand* 1969;58(2):116-120.
- 40. Corneli HM, Zorc JJ, Mahajan P, et al; Bronchiolitis Study Group of the Pediatric Emergency Care Applied Research Network. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;357(4):331-339.
- 41. Cronin JJ, McCoy S, Kennedy U, et al. A randomized trial of single-dose oral dexamethasone versus multidose prednisolone for acute exacerbations of asthma in children who attend the emergency department. *Ann Emerg Med* 2016;67(5):593-601.
- 42. Csonka P, Kaila M, Laippala P, et al. Oral prednisolone in the acute management of children age 6 to 35 months with viral respiratory infection-induced lower airway disease: A randomized, placebo-controlled trial. *J Pediatr* 2003;143(6):725-730.
- 43. Daugbjerg P, Brenøe E, Forchhammer H, et al. A comparison between nebulized terbutaline, nebulized corticosteroid and systemic corticosteroid for acute wheezing in children up to 18 months of age. *Acta Paediatr* 1993;82(6-7):547-551.
- 44. Dawson KP, Sharpe C. A comparison of the acceptability of prednisolone tablets and prednisolone sodium phosphate solution in childhood acute asthma. *Aust J Hosp Pharm* 1993;23(5):320-323.
- 45. Ducharme FM, Lemire C, Noya FJD, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360(4):339-353.

- 46. Eboriadou M, Chryssanthopoulou D, Stamoulis P, et al. The effectiveness of local corticosteroids therapy in the management of mild to moderate viral croup. *Minerva Pediatr* 2010;62(1):23-28.
- 47. Eden AN, Kaufman A, Yu R. Corticosteroids and croup. Controlled double-blind study. *JAMA* 1967;200(5):403-404.
- 48. Escobedo Chavez E, Garcia Muniz LO, Thompson Chagoyan O, et al. Steroids and inhalation therapy in the management of acute asthma in children. *Curr Ther Res Clin Exp* 1992;52(1):7-12.
- 49. Fifoot AA, Ting JYS. Comparison between single-dose oral prednisolone and oral dexamethasone in the treatment of croup: A randomized, double-blinded clinical trial. *Emerg Med Australas* 2007;19(1):51-58.
- 50. Fitzgerald D, Mellis C, Johnson M, et al. Nebulized budesonide is as effective as nebulized adrenaline in moderately severe croup. *Pediatrics* 1996;97(5):722-725.
- 51. Francis P, Geelhoed G, Harris MA, et al. Effect of nebulised fluticasone propionate 1 mg twice daily compared with oral prednisolone in pre-school children aged 48 months or less with an acute exacerbation of asthma [abstract]. *Eur Respir J* 1997(Suppl 25):275s.
- 52. Garbutt JMC, Bridget C, Sterkel R, et al. The comparative effectiveness of prednisolone and dexamethasone for children with croup: A community-based randomized trial. *Clin Pediatr (Phila)* 2013;52(11):1014-1021.
- 53. Ghirga G, Ghirga P, Fagioli S, et al. Intermittent treatment with high dose nebulized beclomethasone for recurrent wheezing in infants due to upper respiratory tract infection. *Minerva Pediatr* 2002;54(3):217-220.
- 54. Gill N, Sirizzotti N, Johnson D, et al. Endogenous glucocorticoid response to single-dose dexamethasone for croup in children: A pharmacodynamic study. *Pediatr Emerg Care* 2017;11.
- 55. Goebel J, Estrada B, Quinonez J, et al. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr (Phila)* 2000;39(4):213-220.
- 56. Grant CC, Duggan AK, Santosham M, et al. Oral prednisone as a risk factor for infections in children with asthma. *Arch Pediatr Adolesc Med* 1996;150(1):58-63.

- 57. Gries DM, Moffitt DR, Pulos E, et al. A single dose of intramuscularly administered dexamethasone acetate is as effective as oral prednisone to treat asthma exacerbations in young children. *J Pediatr* 2000;136(3):298-303.
- 58. Hedlin G, Svedmyr J, Ryden AC. Systemic effects of a short course of betamethasone compared with high-dose inhaled budesonide in early childhood asthma. *Acta Paediatr* 1999;88(1):48-51.
- 59. Husby S, Agertoft L, Mortensen S, et al. Treatment of croup with nebulised steroid (budesonide): A double blind, placebo controlled study. *Arch Dis Child* 1993;68(3):352-325.
- 60. Inglis AF. Herpes simplex virus infection. A rare cause of prolonged croup. *Arch Otolaryngol Head Neck Surg* 1993;119(5):551-552.
- 61. Jan JS, Wu WF. Acute effect of glucocorticoid treatment on serum osteocalcin levels in asthmatic children. *J Microbiol Immunol Infect* 2000;33(1):25-28.
- 62. Jartti T, Nieminen R, Vuorinen T, et al. Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode. *J Allergy Clin Immunol* 2015;135(3):691-698.
- 63. Jartti T, Lehtinen Pasi, Timo V, et al. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;25(6):482-488.
- 64. Jartti T, Lehtinen P, Vanto T, et al. Efficacy of prednisolone in children hospitalized for recurrent wheezing. *Pediatr Allergy Immunol* 2007;18(4):326-334.
- 65. Johnson DW, Jacobson S, Edney PC, et al. A comparison of nebulized budesonide, intramuscular dexamethasone, and placebo for moderately severe croup. *N Engl J Med* 1998;339(8):498-503.
- 66. Johnson DW, Schuh S, Koren G, et al. Outpatient treatment of croup with nebulized dexamethasone. *Arch Pediatr Adolesc Med* 1996;150(4):349-355.
- 67. Klassen TP, Craig WR, Moher D, et al. Nebulized budesonide and oral dexamethasone for treatment of croup: A randomized controlled trial. *JAMA* 1998;279(20):1629-1632.

- 68. Klassen TP, Feldman ME, Watters LK, et al. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994;331(5):285-289.
- 69. Klassen TP, Watters LK, Feldman ME, et al. The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996;97(4):463-466.
- 70. Kuyucu S, Unal S, Kuyucu N, et al. Additive effects of dexamethasone in nebulized salbutamol or L-epinephrine treated infants with acute bronchiolitis. *Pediatr Int* 2004;46(5):539-544.
- 71. Lai ST, Hua YM, Lai YS, et al. Comparison of nebulized budesonide with intravenous dexamethasone in the treatment of young children hospitalized with acute asthma. *J Med Sci* 2005;25(5):223-228.
- 72. Langton Hewer S, Hobbs J, Reid F, et al. Prednisolone in acute childhood asthma: Clinical responses to three dosages. *Respir Med* 1998;92(3):541-546.
- 73. Lee KM, Lin YZ, Huang FY. Steroid-induced acute psychosis in a child with asthma: Report of one case. *Acta Paediatr Taiwan* 2001;42(3):169-171.
- 74. Leer JA, Green JL, Heimlich EM, et al. A controlled, collaborative study in 297 infants and children. *Am J Dis Child* 1969;117(5):495-503.
- 75. Lehmann S, Ott H. Glucocorticoid hypersensitivity as a rare but potentially fatal side effect of paediatric asthma treatment: A case report. *J Med Case Rep* 2008;2:186.
- 76. Leipzig B, Oski FA, Cummings CW, et al. A prospective randomized study to determine the efficacy of steroids in treatment of croup. *J Pediatr* 1979;94(2):194-196.
- 77. Lin YZ, Hsieh KH, Chen W, et al. Clinical trial of corticosteroid and beta-2 bronchodilator in acute wheezing infants. *Acta Paed Sin* 1991;32(6):333-340.
- 78. Lucas-Bouwman ME, Roorda RJ, Jansman FGA, et al. Crushed prednisolone tablets or oral solution for acute asthma? *Arch Dis Child* 2001;84(4):347-348.
- 79. Nahum A, Garty BZ, Marcus N, et al. Severe hypersensitivity reactions to corticosteroids in children. *Pediatr Emerg Care* 2009;25(5):339-341.
- 80. Paniagua N, Munoz N, Lopez R, et al. Randomized trial of two doses of oral dexamethasone versus prednisone/prednisolone for children with acute asthma exacerbations in pediatric

emergency department. *Eur J Pediatr* Conference: 6th Congress of the European Academy of Paediatric Societies Switzerland 2016;175(11):1480.

- 81. Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360(4):329-338.
- 82. Panigada S, Sacco O, Girosi D, et al. Corticosteroids may favor proliferation of thoracic inflammatory myofibroblastic tumors. *Pediatr Pulmonol* 2014;49(3):E109-E111.
- 83. Plint AC, Johnson DW, Patel H, et al; Pediatric Emergency Research Canada. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009;360(20):2079-2089.
- 84. Razi CH, Akelma AZ, Harmanci K, et al. The addition of inhaled budesonide to standard therapy shortens the length of stay in hospital for asthmatic preschool children: A randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol* 2015;166(4):297-303.
- 85. Roberts GW, Master VV, Staugas RE, et al. Repeated dose inhaled budesonide versus placebo in the treatment of croup. *J Paediatr Child Health* 1999;35(2):170-174.
- 86. Roorda RJ, Walhof CM. Effects of inhaled fluticasone propionate administered with metered dose inhaler and spacer in mild to moderate croup: A negative preliminary report. *Pediatr Pulmonol* 1998;25(2):114-117.
- 87. Roosevelt G, Sheehan K, Grupp-Phelan J, et al. Dexamethasone in bronchiolitis: A randomised controlled trial. *Lancet* 1996;348(9023):292-295.
- 88. Sadowitz PD, Page NE, Crowley K. Adverse effects of steroid therapy in children with pharyngitis with unsuspected malignancy. *Pediatr Emerg Care* 2012;28(8):807-809.
- 89. Saito M, Kikuchi Y, Kawarai Lefor A, et al. High-dose nebulized budesonide is effective for mild asthma exacerbations in children under 3 years of age. *Eur Ann Allergy Clin Immunol* 2017;49(1):22-27.
- 90. Schuh S, Coates AL, Dick P, et al. A single versus multiple doses of dexamethasone in infants wheezing for the first time. *Pediatr Pulmonol* 2008;43(9):844-850.

- 91. Schuh S, Willan AR, Stephens D, et al. Can montelukast shorten prednisolone therapy in children with mild to moderate acute asthma? A randomized controlled trial. *J Pediatr* 2009;155(6):795-800.
- 92. Siomou E, Challa A, Tzoufi M, et al. Biochemical markers of bone metabolism in infants and children under intravenous corticosteroid therapy. *Calcif Tissue Int* 2003;73(4):319-325.
- 93. Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: A randomised equivalence trial. *Arch Dis Child* 2006;91(7):580-583.
- 94. Stafford L, Hope ME, Janney EP, et al. Comparison of paediatric steroid mixtures. *Australian Journal of Hospital Pharmacy* 1998;28(4):246-249.
- 95. Storr J, Barry BE, Barrell E, et al. Effect of a single oral dose of prednisolone in acute childhood asthma. *Lancet* 1987;1(8538):879-882.
- 96. Sumboonnanonda A, Suwanjutha S, Sirinavin S. Randomized controlled trial of dexamethasone in infectious croup. *J Med Assoc Thai* 1997;80(4):262-265.
- 97. Sung L, Osmond MH, Klassen TP. Randomized, controlled trial of inhaled budesonide as an adjunct to oral prednisone in acute asthma. *Acad Emerg Med* 1998;5(3):209-213.
- 98. Super DM, Cartelli NA, Brooks LJ, et al. A prospective randomized double-blind study to evaluate the effect of dexamethasone in acute laryngotracheitis. *J Pediatr* 1989;115(2):323-329.
- 99. Sussman S, Grossman M, Magoffin R, et al. Dexamethasone (16 alpha methyl, 9 alpha fluoroprednisolone) in obstructive respiratory tract infections in children. *Pediatrics* 1964;34(6):851-855.
- 100. Svedmyr J, Nyberg E, Åsbrink-Nilsson E, et al. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995;84(8):884-888.
- 101. Svedmyr J, Nyberg E, Thunqvist P, et al. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr* 1999;88(1):42-47.

102. Tagarro A, Pérez L, Quintero VM, et al. Dexamethasone does not reduce length of hospitalization or recurrent wheezing 1 year after early bronchiolitis. *Minerva Pediatr* 2014;66(2):131-140.

- 103. Tal A, Bavailski C, Yohai D, et al. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;71(1):13-18.
- 104. Tamura A, Matsubara K, Tanaka T, et al. Methylprednisolone pulse therapy for refractory mycoplasma pneumoniae pneumonia in children. *J Infect* 2008;57(3):223-228.
- 105. Teeratakulpisarn J, Limwattananon C, Tanupattarachai S, et al. Efficacy of dexamethasone injection for acute bronchiolitis in hospitalized children: A randomized, double-blind, placebo-controlled trial. *Pediatr Pulmonol* 2007;42(5):433-439.
- 106. van Woensel JBM, Wolfs TFW, van Aalderen WMC, et al. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997;52(7):634-637.
- 107. Webb MSC, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986;61(1):15-19.
- 108. Zhang L, Ferruzzi E, Bonfanti T, et al. Long and short-term effect of prednisolone in hospitalized infants with acute bronchiolitis. *J Paediatr Child Health* 2003;39(7):548-551.
- 109. Kelly HW, Van Natta ML, Covar RA, et al. Effect of long-term corticosteroid use on bone mineral density in children: A prospective longitudinal assessment in the childhood asthma management program (CAMP) study. *Pediatrics* 2008;122(1):e53-e61.
- 110. Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: Effects on bone mineral density and growth. *Lancet Respir Med* 2014;2(6):487-496.
- 111. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of long-course oral corticosteroids in children. *PLoS ONE* 2017;12(1):e0170259.
- 112. Vatti RR, Ali F, Teuber S, et al. Hypersensitivity reactions to corticosteroids. *Clinic Rev Allerg Immunol* 2014;47(1):26-37.
- 113. Rieder M. Size and taste matters: Recent progress in the development of age-appropriate medicines for children. *Pharm Med* 2018;32(1):21-30.

- 114. Beigelman A, Durrani S, Guilbert TW. Should a preschool child with acute episodic wheeze be treated with oral corticosteroids? A pro/con debate. *J Allergy Clin Immunol Pract* 2016;4(1):27-35.
- 115. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child* 2016;101(4):365-370.
- 116. Waljee AK, Rogers MA, Lin P, et al. Short term use of oral corticosteroids and related harms among adults in the united states: Population based cohort study. *BMJ* 2017;357;j1415.
- 117. Hartling L, Ali S, Dryden DM, et al. How safe are common analgesics for the treatment of acute pain for children? A systematic review. *Pain Res Manag* 2016;5346819.
- 118. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336(7650):924-926.

Table 1. Summary of methodological quality assessments

McHarm* criteria			No. of studies (%²)	
1)	Were the harms PRE-DEFINED using standardized or precise definitions?		6 (7)	
-,	were the marins i KE-DEI IIVED using standardized of precise definitions?	Yes	79 (93)	
		Unsure	0	
2)	Were SERIOUS events precisely defined?	Yes	2 (2)	
_,	The second processing accounts	No	83 (98)	
		Unsure	0	
3)	Were SEVERE events precisely defined?	Yes	0	
		No	85 (100)	
		Unsure	0	
4)	Were the number of DEATHS in each study group specified OR were the	Yes	10 (12)	
	reason(s) for not specifying them given?	No	75 (88)	
		Unsure	0	
5)	Was the mode of harms collection specified as ACTIVE?	Yes	46 (54)	
		No	37 (44)	
		Unsure	2 (2)	
6)	Was the mode of harms collection specified as PASSIVE?	Yes	11 (13)	
		No	73 (86)	
		Unsure	1(1)	
7)	Did the study specify WHO collected the harms?	Yes	22 (26)	
		No	63 (74)	
		Unsure	0	
8)	Did the study specify the TRAINING or BACKGROUND of who ascertained the	Yes	20 (24)	
	harms?	No	65 (76)	
		Unsure	0	
9)	Did the study specify the TIMING and FREQUENCY of collection of the harms?	Yes	39 (46)	
	7	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	Yes	80 (94)	
	or a selected SAMPLE?	No	2 (2)	
		Unsure	3 (4)	
12)	Was the NUMBER of participants that withdrew or were lost to follow-up	Yes	24 (28)	
	specified for each study group?	No	61 (72)	
		Unsure	0	
13)	Was the TOTAL NUMBER of participants affected by harms specified for each 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?		10 (12)	
		No	75 (88)	
		Unsure	0	

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

² sum of percentages may not total 100 due to rounding

1. Chou R, Aronson N, Atkins DL. Assessing harms when comparing medication interventions. In: editors. Methods guide for effectiveness and comparative effectiveness reviews. Rockville, MD: Agency for Healthcare Research and Quality (US); 2008. p.



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

Organ system	AE - category	AE – specific	No. of studies	No. of
I., C 4° 0	Samuel Sa			participants
Infection &	Severe infections		5	1235
Respiratory	1)	Samaia	1	32
	1)	Sepsis		354
	2)	Superinfection	2	
	3)	UTI	1	720
	4)	Streptococcal infection	1 7	129
	Systemic infections		5	1635
	1)	Fever	3	963
	2)	Common	2	792
		viral/bacterial/fungal		
	2)	infection		1.4.40
	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	- Cittery	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	1	82
		nebulizer mask	*	02
	7)	Psychosis	1	1
	Headache	1 sychosis	3	291
Dermatological	Burn		1	198
Dermatorogrear	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	Breeding from ear	1	32
Endocrine/Metabolic	Fluid and electrolyte		7	1849
& Musculoskeletal	abnormalities		'	1017
- Triusculositeietui	1)	Hyperkalemia	1	800
	2)	Hyperglycemia	3	154
	3)	Glycosuria	1	125
	4)	Sodium retention	1	50
	5)	Dehydration	1	720
	Growth	Denjuranon	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
oncology .	1)	Immunosuppression	3	146
	2)	Tumor cell proliferation	1	1

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

BM Open Records identified from database searches Additional records identified from othensput0esf 234 n = 12,225n = 135**Records after duplicates removed** n = 9,134Total eligible records screened by title and abstract Records excluded n = 9.134n = 8,010Full text articles assessed for eligibility Non-English records **English records excluded** n = 1,124excluded (N=135): (N=903): Not primary study Not primary study (n=112); No data for 0-6 year olds (n=25);No data for 0-6 year olds (n=131);(n=17);*Not acute respiratory* Not acute respiratory disease (n=18); disease (n=17); Not inhaled or systemic Not corticosteroid (n=5); corticosteroid (n=175); Not inhaled or systemic Treatment duration >14 corticosteroid (n=3); days (n=122); Treatment duration >14 Not outpatient setting or days (n=8); hospitalized patients No intervention (n=6); (n=14);No AE (n=20); No AE (n=163); Total studies included in the review Full paper not available AE attributed to noncorticosteroid (n=1): (n=20): Full paper not available Drug monographs, FDA & n = 85(n=1): EMEA documents, not (86 papers) Translation not available eliqible (n=135); (n=22);Protocol, duplicate of full For peer review only - http://bmjopen.bmj.com/site/about/guidelines.x
AE: adverse event; EMEA: European Medicines Agency; FDA: Food
& Drug Administration publication (n=1) htm Duplicate (12) & Drug Administration

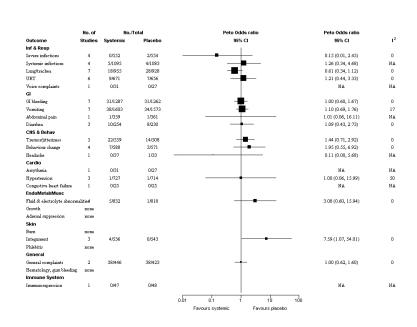


Figure 2. Forest plot of adverse events - systemic vs. placebo $101 \times 101 \text{mm} \ (300 \times 300 \ \text{DPI})$

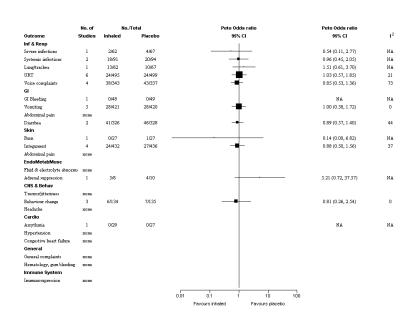


Figure 3. Forest plot of adverse events - inhaled vs. placebo $101 \times 101 \text{mm}$ (300 \times 300 DPI)

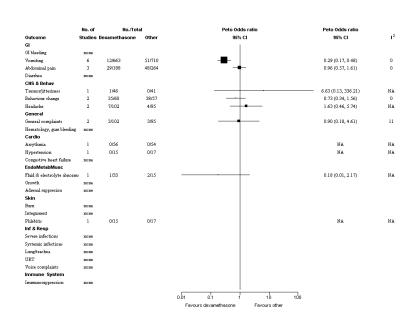


Figure 4. Forest plot of adverse events - dexamethasone vs. other $101 x 101 mm \; (300 \; x \; 300 \; DPI)$

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

2 3

4 5

6

7 8

9

10

11

12 13

14 15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 1. Adrenal Cortex Hormones/
- 2. Anti-Inflammatory Agents/
- 3. Beclomethasone/
- 4. Budesonide/
- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

```
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/

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22 23

24 25

26

27

28 29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

60

```
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.
- beclovent*.tw,nm.
 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.

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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.

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43 44

45

46

47

48 49

50 51

52

53 54

55

56 57 58

59

60

```
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 pediatric* 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]

1

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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
- 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

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53

54 55

56 57 58

59

```
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

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25 26

27

28

29 30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

60

- 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.

2

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41 42

43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

```
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/

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18

19 20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45

46

47

48 49

50

51

52

53 54

55

56 57 58

59

- 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/

2 3

4

5

6

7 8

9

10

11

12

13 14

15

16

17

18 19

20

21

22

23

24 25

26

27

28

29

30 31

32

33

34

35

36 37

38

39

40

41

42 43

44

45 46

47

48 49

50

51 52

53

54 55

56 57 58

59

60

```
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

2

4

5

6

7 8 9

10

11 12

13 14

15

16

17 18

19 20

21

22

23

24 25

26

27 28

29 30 31

32

33

34

35

36 37

38 39

40

41 42

43

44

45

46

47

48 49

50

51

52 53 54

59

60

- 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=WC0b 01ac058001d124

Date original search conducted: 9, 10 September 2014

Strategy:

Searched EMA reports for drug name keywords:

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

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

Supplement 2. Eligibility criteria for study inclusion

INCLUSION/EXCLUSION FORM

Revie	wer ID:	Date:	/	/2015	Record ID:			
Criteria						Yes	No	UC
1. PUB	LICATION TYPE							
a. P	rimary research (RCTs, coh	ort studie	s, case	control stu	dies, case reports, and case			
series)								
Exclude								
•	Systematic reviews, letter	rs to edito	r, com	mentaries				
2. Popi	ulation							
	Children ≤6 years of age,	where age	suhøi	rouns data is	s available:			$\overline{\Box}$
ű.	emaren zo years or age,	Where age	, Jubbi	oups dutu i	d valiable.	ш	ш	Ш
Unclea	r:							
•	If aggregate/subgroup da	ta include	but a	re not limite	d to age ≤6 years			
Exclude					0 ,			
•	If data is reported in aggr	egate witl	n older	ages				
	, 33							
3. CON	IDITION			1/2	•			
a.	Children with acute respin	ratory dise	ease (a	ny of the fo	llowing):			
•	Bronchiolitis							
•	Croup							
•	Acute wheeze/asthma							
•	Acute uncomplicated pne	umonia (r	no abs	cess, effusio	n, etc)			
•	Pharyngitis/tonsillitis							
•	Peritonsillar abcess							
•	Acute sinusitis							
•	Respiratory syncytial virus	s/ rhinovii	rus/oth	ner viruses				
•	Respiratory distress due t	o foreign	bodies	5				
•	PFAPA syndrome							
Exclude	e:							
•	patients in NICU, PICU							
•	respiratory distress syndr	ome (new	born)					
•	allergic rhinitis	- (,					
•	animal studies							
4. Inte	rvention							

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	e		
•	topical (non-systemic) corticosteroid therapy		
	ed (moderate- to high-dose) corticosteroids, following GINA guidelines for low		
doses f	for children 5 years and younger (see Box 6-6 below).		
5. Com	parator group (where relevant)		
a. A	ny comparison, including non-pharmacologic interventions which may act similarly		
to a			
pl	acebo		
6. OUT	COME		
Advers	e drug reaction, side effect, adverse effects/events, adverse reactions		
7. Sett	ing		
Focus i	s on outpatient settings (e.g. ambulatory, ED), and hospitalised patients		
Exclude	e		
•	patients in NICU, PICU		
Comr	nents:		
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
 b. Summary characteristics of included studies - comparisons
 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,	2, each (21)
Turkey	
Brazil, Germany, Mexico, Qatar	1, each (5)
SA & UK	1 (1)
Study designs	
RCT (all)	68 (80)
2-arm	52 (61)
3-arm	7 (8)
4-arm non-factorial	1 (1)
factorial 4 x4	4 (5)
crossover	2 (2)
trial registry	1 (1)
conference abstract	1 (1)
Non-RCT	5 (6)
Cohort	4 (5)
Case control	1 (1)
Case series	4 (5)
Case report	3 (4)
Number of centres	
Single centre	56 (66)
Multi-centre	24 (28)
Unclear/NR	5 (6)
Setting	
Inpatient	41 (48)
Outpatient	22 (26)
Inpatient & outpatient	21 (25)
NR	1 (1)
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

¹sum of percentages may not total 100 due to rounding

	BMJ Open	1136/bmjopen-2018	Pag
Number of treatment groups	Comparison Comparison	No. of tudies (no. of patients)	No. of studies contributing data (no. of patients)
2-arms	Systemic CS vs. placebo/no intervention/standard care	26 (41 8 66)	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)ရှိ	1 (50)
	Inhaled CS vs. placebo/no intervention	14 (23 <u>६</u> 7)	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	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 (1983)	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) <u>></u>	1 (80)
4-arms	Systemic CS + terb vs. inhaled CS + terb + placebo vs. non-CS + terb + placebo vs. placebo	1 (114年	1 (114)
	Systemic CS + sal dose1 vs. systemic CS + sal dose2 vs. sal dose1 + placebo vs. sal dose2 + placebo	1 (70)24 b	1 (70)
	Systemic CS + non-CS vs. systemic CS + sal vs. non-CS + placebo vs. sal + placebo	1 (69)guest	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) (32)	0
	Systemic CS	5 (5) §	0

Non-comparative (case	Mode of administration NR	2 (3) %	0		
reports/series)			285			
CS: corticosteroid; no.: number; NR: not reported; sal: salbutamol; terb: terbutaline; vs.: versus						

Supplement 3c. Characteristics of included studies

Author,	Study	Respiratory	Comparators,	Co-interventions;	Time points	Outcomes
year	design	condition	no. of	Maintenance CS	for	related to
Country	Setting	Age (range)	participants		assessment	adverse
Funding	No. of				s;	events
source	centres				FU	
Alangari	RCT	Asthma	1) Budesonide	Salbutamol,	Baseline, at	The most
2014	ED	2-12y	500mcg/dose, 3	ipratropium &	1h, 2h, 3h	frequently
Saudi	1		doses 20min	prednisolone	and 4h	reported
Arabia			apart (neb),		from the	adverse
Non-			n=458	No CS in preceding	start of	effects were
industry			2) Placebo	7d	medication	fine tremors
funded			saline, 3 doses		s;	(17 cases) and
			20min apart		FU 72h	palpitations
			(neb), n=448		post-	(11 cases).
					discharge	None of the
						reported
						adverse
						effects was
						serious, and
						none was
				A		significantly
						different
						between the
01	DCT	B lette Pitte	4)	5	A	two groups.
Alansari	RCT	Bronchiolitis	1)	Epinephrine,	At study	Daily
2013	Pediatri	<=18mo	Dexamethasone	oxygen & hydration	entry, then	telephone
Qatar	C		1.0mg first day,	No CC in proceeding	assessed if	surveillance (7
Non-	emerge		then 0.6mg for 4d (oral) + sal,	No CS in preceding 48h	ready for discharge	days) revealed no
industry funded	ncy unit		5d total (neb),	4011	at 12h, 18h,	particular side
Turided			n=102		24h, 36h &	effect
			2) Placebo (oral)		48h;	concerns in
			+ sal, 5d total		FU by	either
			(neb), n=98		telephone	treatment
			(1.65), 11 36		1wk post-	group.
					discharge	8.000
Aljebab	Cohort,	Asthma/cro	SA	NR	After each	In SA and the
2017	3-arm	up,	1)		dose	UK,
Saudi	Pediatri	palatability	Dexamethasone	Most patients in	(within	dexamethaso
Arabia &	c ED of	&	0.5mg/5mL	prednisolone	10min) &	ne had the
UK	hospital	tolerability	elixir (oral),	groups had	daily on D1-	highest
Unfunded	(SA &	2-10y (SA);	n=33	received oral	D5	palatability
	UK)	2-16y (UK)		steroids previously;		scores and

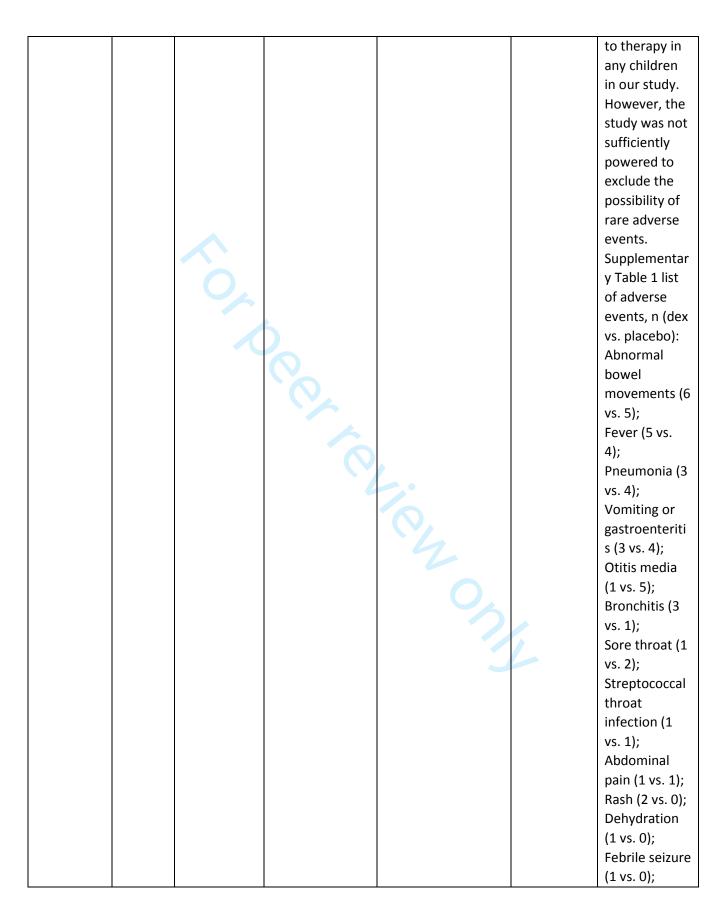
Ι_	T	T	г.	
2		2) Prednisolone	however, most	prednisolone
		base 5.0mg	patients and none	base tablets
		tablets (oral),	had received oral	had the
		n=52	steroids previously	lowest.
		3) Prednisolone	in the SA & UK	Palatability
		sodium	dexamethasone	scores
		phosphate	groups,	improved for
		15.0mg/mL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

						In both
						centres,
						dexamethaso
						ne 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
						dexamethaso
						ne sodium
						phosphate
						solution than
						dexamethaso
						ne elixir.
Alshehr	RCT	Croup	1)	Mist therapy,	12h & 24h	Two patients
2005	Emerge	3mo-9y	Dexamethasone	racemic	after	developed
Saudi	ncy		0.6mg/kg, single	epinephrine,	treatment	bronchopneu
Arabia	rooms		dose (oral),	oxygen &	& change in	monia on
Funding NR	&		n=36	antibiotics	total croup	second day of
	outpati		2)		scores per	admission as
	ent		Dexamethasone	No CS in preceding	12h	confirmed by
	clinics		0.15mg/kg,	4wk	intervals	chest x-ray
	3		single dose		within &	and one
			(oral), n=36		between	patient had
					study	bacterial
					groups	tracheitis. All
						these three
						patients were
						in group A
						(0.6 mg/kg
						dexamethaso
						ne). 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
						gastrointestin
						al bleeding or
						bacterial
Alta va iva i	RCT	A atlanta	41)	Callantanal	2d & 5d	infection.
Altamimi 2006	Pediatri	Asthma 2-16y	1) Dexamethasone	Salbutamol	post-	Two subjects in the
Canada	C	2-10y	0.6mg/kg (max	No CS in preceding	discharge &	prednisolone
Non-	hospital		18mg), single	2wk	every week	group
industry &	1		dose (oral),		to a	dropped out
industry			n=67		maximum	because of
funded			2) Prednisolone		of 3wk	repeated
			1.0mg/kg (max	>		vomiting. Side
			30mg) twice			effects (table
			daily (oral),			5), n:
			n=67			Abdominal
				4		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
	207 2		4) 24			pred)
Bacharier	RCT, 3-	At least 2	1) Montelukast	Albuterol,	Clinic visits	The 3 groups
2008	arm	wheeze	4.0mg once	prednisolone &	4wk after	did not differ
USA			daily (oral) +		randomizati	significantly in

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

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



	I	T				DO111 6 11
						RSV infection
						(1 vs. 0);
						Uncomplicate
						d varicella (0
						vs. 1);
						Urinary tract
						infection (0
						vs. 1);
						Irritability (1
						vs. 1);
						Eye discharge
						(1 vs. 0);
		O_{λ}				Sinusitis (0 vs. 1);
						Bleeding from
						ear (0 vs. 1);
						Nasal
						discharge (1
						vs. 0)
Brunette	NRCT	Asthma	1) Theophylline	None	Monthly or	No side effect
1988	Hospita	<6y	8.0mg/kg every		every	was observed
Canada	1	,	6-8h (oral) +	NR	second	in a particular
Funding NR	1		metaproterenol	>	month,	case which
			0.3-0.7 mg/kg		depending	received
			every 6-8h		on severity	longer
			(oral)+		of disease;	duration of
			prednisone			corticosteroid
			1.0mg/kg/day		Growth	(high
			for 7-14d (oral),		(mean	cumulative
			n=16		height gain	corticosteroid
			2) Theophylline		in cm/yr	dose).
			8.0mg/kg every		and height	Growth and
			6-8h (oral) +		as	weight gains
			metaproterenol		percentile	for all children
			0.3-0.7mg/kg		of normal	were within
			every 6-8h for		distribution	the normal
			7-14d (oral),) assessed	range during
			n=16		(assessmen	the two
					t method	periods.
			Multiple		NR) at the	
			courses over 1yr		end of each	
					of two 1-yr	
					periods	

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

Dulance	DCT		4) Duadria lana			drug. No patients in either group had microscopic or gross gastrointestin al bleeding, and no patients required antihypertensi ve therapy during the study.
Bulow 1999 Denmark Non- industry funded	RCT Pediatri c hospital 3	RSV (bronchioliti s) 0-2y	1) Prednisolone 5.0mg/ml at dose of 2mg/kg/day, first dose at enrolment and for 4d (oral), or methylprednisol one for patients with IV line (40.0mg/ml at dose of 1.5mg/kg/day) for 5d (IV), n=73 2) quinine hydrochloride (or saline for patients with IV line) for 5d (IV), n=74	Beta-2-agonist, antibiotics, oxygen & hydration No CS in preceding month	Enrolment & 5d; FU 1mo & at 1y	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 Pediatri c & general ED 3	Asthma 2-15y	1) Prednisolone 1.0mg/kg (max. 50.0mg/day) for 3d + placebo solution for 2d (oral), n=101 2) Prednisolone 1.0mg/kg (max.	NR No maintenance CS or CS preceding presentation	24h, 48h, D5, D7, D10, D14 & D28	There were five recorded adverse events, with no significant difference between groups. In the 3-day group,

	I	T		T	T	T
			50.0mg/day) for			two parents
			5d (oral), n=100			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	RCT, 3-	Asthma	1) Budesonide	NR	0.5h before	All three
China	arm	1-14y	0.5mg (neb) +		& post-	groups of
Funding NR	Pediatri	,	sal +	No CS within 48h	treatment	children
	C		ipratropium; 1-		& 5d post-	showed no
	outpati		6yo (n=32); 6-		treatment	adverse
	ent,		14yo (n=21)			effects.
	hospital		2) Budesonide			
	ward,		0.2-0.4mg (neb)			
	or ED		+ sal +			
	1		ipratropium; 1-			
	_		6yo (n=25); 6-	1		
			14yo (n=16)			
			3)			
			Dexamethasone			
			2.0mg (<2yo),			
			4.0mg (2-6yo)			
			(IV); 1-6yo			
			(n=15); 6-14yo			
			(n=14)			
Chub-	RCT	Croup	1)	Epinephrine, mist,	0, 1h, 2h,	There was no
Appakarn	Pediatri	6mo-5y	Dexamethasone	antibiotics &	3h, 4h, 6h,	significant
2007	C	Citio 3y	0.5ml/kg of 0.15	oxygen	8h, 10h &	adverse
Thailand	hospital		mg/kg, single	18C11	12h post-	reaction from
Funding NR	ward		dose (IV), n=20	No CS in preceding	treatment	dexamethaso
I dildilig ivit	waru 1		2)	2wk	deadifieff	ne treatment
	*		Dexamethasone	∠ v v I \		in either
			0.5 ml/kg of			
			וט אַא אָוווו כ.ט			group.

			0.6mg/kg, single dose (IV), n=21			
Clavenna	RCT	Wheeze	1)	Daracotomol	Entra dicit	No
2014			Beclomethason	Paracetamol, nasal	Entry visit, D11 (or	differences
	Family pediatri	1-5y	e 400mcg (1ml)	saline irrigation & antibiotics	prior if	were found in
Italy Non-	c health			antibiotics	•	the incidence
	units		twice daily for	No CS in proceeding	requested	of adverse
industry &			10d (neb), n=264	No CS in preceding	by parents)	
industry funded	9		2) Placebo twice	month	& daily	events reported by
Turided			_ ·		diary	parents at the
			daily for 10d		symptom	end of the
			(neb), n=261		recording during 10d	
					treatment	therapy. Table 4 AEs
		O .			treatment	
						reported by parents, n
						(beclo vs.
						placebo):
						Any AEs (97
						vs. 98)
						Hoarseness
						(34 vs. 34); Diarrhea (27
			\sim			vs. 35);
						Skin rash (19
						vs. 22);
				$^{\circ}$ \bigcirc ,		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
						beclomethaso
						ne group and
						I ue group and

						hospitalizatio n for adenoidectom
						y and
						tonsillectomy
						in the placebo
						group.
						Neither
						adverse event
						was drug
Connett	RCT,	Asthma	1) Prednisolone	NR	On arrival,	related. Tremor and
1994	factoria	>18mo	2.0mg/kg single	IVIX	after	hyperactivity
UK	I	7101110	dose (oral) + sal	No CS in preceding	nebulizatio	were more
Non-	Hospita		0.15mg/kg	2wk	n & at	commonly
industry	1 '		every 30min for		treatment	reported in
funded	1		3h (max. 5.0mg)		completion	those children
			(neb), n=18			receiving the
			2) Prednisolone			more
			2.0mg/kg single			intensive
			dose (oral) + sal			nebuliser
			5.0mg every 1-			regimen but
			4h as needed			symptoms
			(neb), n=19			were mild and
			3) Placebo			self-limiting in
			single dose	4		most
			(oral) + sal			instances.
			0.15mg/kg every 30min for			Vomiting was more a
			3h (neb), n=15	O ,		feature of
			4) Placebo			disease
			single dose			severity than
			(oral) plus sal			any particular
			5.0mg every 1-			treatment
			4h as needed			group. There
			(neb), n=18			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	RCT	RSV	1) Prednisolone	Ampicillin, oxygen	FU 1mo &	There was no
1969	Hospita	Bronchiolitis	D1=15.0mg;		1y	evidence in
Ireland	1	0-2y	D2-3=10.0mg;	NR		this trial that
Funding NR	1		D4-5=5.0mg;			prednisolone
			D6-7=2.5mg			treatment of
			(NR, likely IV),			the patients
			n=47			affected the
			2) Placebo (NR,			antibody
			likely IV), n=48			response. In
			,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,			the dosage
						used in this
						trial,
						prednisolone
						had no
			\sim			beneficial or
						harmful
						effects on the
						course of the
						disease in
						severely ill
						children.
						There were
						no deaths.
Corneli	RCT	Bronchiolitis	1)	Not specified	Baseline, 1h	There were
2007	ED	2-12mo	Dexamethasone		& 4 h;	few adverse
USA	20		1.0mg/kg (max.	No CS in preceding	FU at 7-10d	events. No
Non-			12mg), single	14d	by	infant had
industry &			dose (oral),		telephone	gastrointestin
industry			n=305			al bleeding,
funded			2) Placebo			hypertension,
lanaca			solution			or
			1.0ml/kg (max.			complicated
			= '			varicella.
			12ml), NR (oral),			
			n=295			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
			5			two infants.
Cronin	RCT	Asthma	1)	Regular inhaled	Baseline &	Seven
2016	Tertiary	2-16y	Dexamethasone	bronchodilators	D4 for	patients in the
Ireland	hospital		0.3mg/kg (max.	prior to enrolment	primary	PRED group
Non-	ED		12.0mg) single	in trial	outcome;	(5.7%)
industry	1		dose, n=123		14d period	vomited
funded			2) Prednisolone	No IV or oral CS in	for adverse	within 30
			1.0mg/kg per	previous 4wk	events	minutes of
			day, once daily			the dose of
			(max. 40.0mg)	1 0.		steroid on day
			for 3d, n=122			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

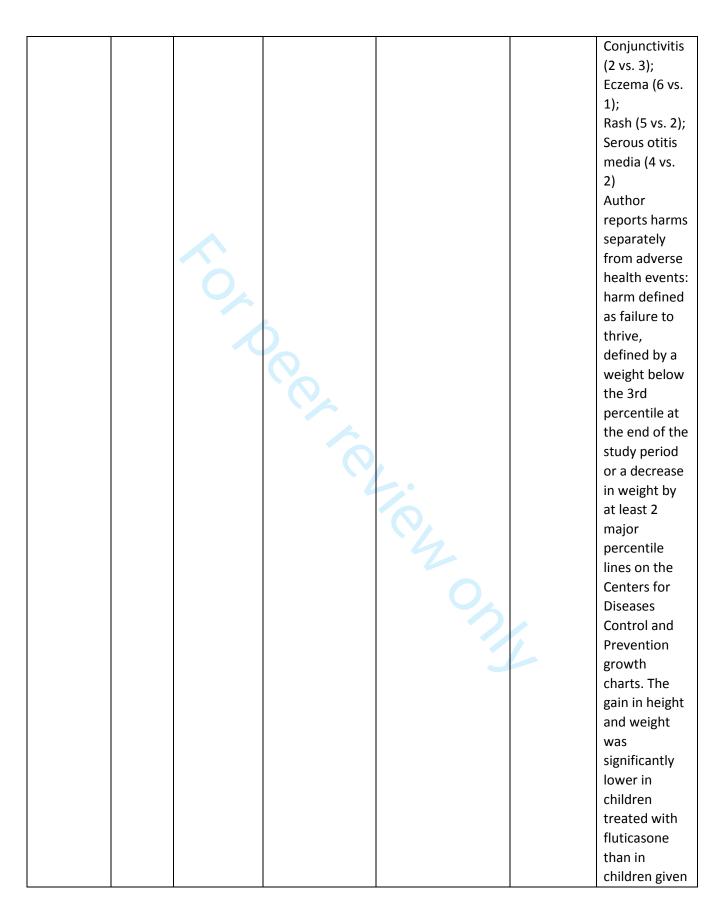
						vomited after
						at least 1 dose of
						prednisolone.
						No other
						adverse
						events
						attributable
						to the study
						medications
						were noted.
Csonka	RCT	Viral	1) Prednisolone	NR	Diary	Fifteen
2003	Pediatri	respiratory	2.0mg/kg in ED		recordings	children (4 in
Finland	c ED	infection-	followed by	NR	twice daily	the placebo
Non-	1	induced	2.0mg/kg/day		for 14d;	group and 11
industry		lower	for 3d (oral),		examinatio	in the
funded		airway	n=113		n by	prednisolone
		disease	2) Placebo		physician	group)
		6-35mo	10.0mL fructose		14d-21d	discontinued
			in water (in ED)		post-ED	the study
			followed by		visit	medication
			subsequent			because of
			doses for 3d,			perceived side
			n=117			effects. The
				92		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	RCT, 4-	First or	1) Prednisolone	NR	Daily for 5d	No side
1993			I	INK	or until	effects were
	arm	recurrent	4.0-6.0mg/kg on	No CC managina		
Denmark	Pediatri	wheeze	admission; D2-	No CS preceding	discharge	observed,
Non-	C	0-18mo	3=1.6-2.6mg/kg	study		specifically no
industry &	depart		(oral) +			hoarseness,
industry	ment		terbutaline			oral
funded	5		0.12-0.2mg/kg			candidiasis or
			(4ml) every 4h			continued
			until discharge			fever, in any
			or for 5d (neb),			of the groups.
			n=31			No significant
			2) Placebo			tachycardia
			solution (oral) +			was found in
			budesonide			the treatment
			0.5mg every 4h			groups
			until discharge			compared
			or for 5d (neb) +			with placebo.
			terbutaline			
			0.12-0.2mg/kg			
			(4ml) every 4h			
			until discharge			
			or for 5d, n=29			
			3) Placebo			
			solution (oral) +			
			placebo (neb) +			
			terbutaline			
			0.12-0.2mg/kg			
			every 4h until			
			discharge or for			
			5d (neb), n=27			
			4) Placebo			
			solution (oral) +			
			placebo (neb) +			
			placebo saline			
			(neb), n=27			
Dawson	RCT	Asthma	1) Prednisolone	None	D1 to D5	Twenty-one
1993	Hospita	<6.5y	1.0mg/kg			of the
Australia	T		tablets, every	NR		children
Industry	1		24h for 5d			taking the
funded			(oral), n=25			solution took
			2) Prednisolone			it easily on
			1.0mg/kg			day 3,
			solution, every			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
(oral), n=26	day. A difference was noted on
	difference was noted on
	was noted on
	day 1 with
	uay 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

	1	T	T			,
						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	RCT	>=3 wheeze	1)Fluticasone	Albuterol, nasal	Monthly	Thirteen
2009	Hospita	episodes in	propionate	saline irrigation	telephone	serious
Canada	1	lifetime,	250mcg (3		contacts	adverse
Non-	5	onset of	doses twice	No more than 1	and a	events (4 in
industry &		URTI	daily at start of	dose of CS in	medical	fluticasone
industry		1-6y	URTI) until 48h	preceding 6mo or 2	visit every	group and 9 in
funded			elapsed without	doses in preceding	4mo;	placebo)
			symptoms, for	12mo		occurred in 13
			max. 10d (MDI),		Growth	children
			n=62		assessed	during the
			2) Placebo (3		using an	study period -
			doses twice		upright	namely,
			daily at start of		stadiomete	pneumonia,
			URTI until 48h		r at	seizure,
			elapsed without		baseline,	admission to
			symptoms		every	an intensive
			(MDI), n=67		month, and	care unit,
					at the end	burn,
			Multiple		of follow-	respiratory
			courses over 6-		up (6-	syncytial virus
i i	1	Ĩ	ì	İ	• •	
			12mo		12mo);	infection,

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



	placebo, with a difference between the groups of 5
	between the groups of 5
	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.
	The L-
2010 arm 6mo-5y 5.0ml (1 of treatment	epinephrine
	group was the
Funding NR c ED 5-10min (neb), 24h 20min,	only group
1 n=25 60min,	with side
90min &	effects of

	I	<u> </u>	۵۱			I
			2)		120min	treatment.
			Dexamethasone		post-	Tremor and
			0.6mg/kg (max.		treatment;	tachycardia
			8mg), single		patients	were
			dose (IM), n=19		asked to	observed in 4
			3)		return if	children from
			Beclomethason		relapse in	Group A, who
			e dipropionate		next 24h	had received
			200mcg (MDI),			LE and were
			n=20			resolved after
						2 hours, when
						the action of
						LE wear off.
Eden 1967	RCT	Croup	1)	Oxygen, humidity &	Every 6h for	No untoward
USA	Hospita	8mo-5y	Dexamethasone	tetracycline	total 48h	effects were
Industry	ı	Billo-3y	0.10mg/kg at	tetracycline	totai 4811	noted. There
funded			0.1cc/kg/dose	NR		were no
landed	1		every 6h for	INIX		
						episodes of
			48h, total daily			congestive
			0.40mg (IM),			heart failure
			n=25			or sodium
			2) Control	•		retention.
			preparation			
			0.1cc/kg/dose			
			every 6h for 48h			
			(IM), n=25			
Escobedo	RCT	Asthma	1)	Saline, salbutamol	Baseline &	We detected
Chavez	Hospita	1mo-14y	Methylprednisol	& oxygen	discharge	no side
1992	I ED		one 3.0mg/kg,			effects with
Mexico	1		single dose (IM)	No CS in preceding		the use of
Industry			+ placebo 4.5ml	15d		methylprednis
funded			+ sal 0.5ml			olone in a
			every 4h (neb),			single dose or
			n=25			any treatment
			2)			failures that
			Aminophylline			merited the
			5.0mg/kg every			use of
			6h (IV) + sal 70			methylxanthin
			mcg/kg every 8h			es or
			+ oxygen (neb),			additional
			n=25			steroid doses.
Fifoot 2007	RCT, 3-	Croup	1) Prednisolone	Antipyretics or	Baseline &	No patient
Australia	arm	6mo-6y	0.2ml/kg of	nebulized	hourly up	suffered any
		,	1.0mg/kg, single	adrenaline	' '	adverse
	<u> </u>	<u> </u>	- 3,, 5		<u> </u>	

Non-	Pediatri		dose (oral),		to 4h post-	outcomes
industry	c ED		n=34	No CS in preceding	treatment;	from receiving
funded	1		2)	wk	FU 1wk by	study steroid,
			Dexamethasone		telephone	either at
			0.2ml/kg of		following	index
			0.15mg/kg,		index visit	presentation
			single dose			or during the
			(oral), n=34			follow-up
			3)			period. One
			Dexamethasone			patient from
			0.2ml/kg of			each group
			0.6mg/kg, single			vomited their
			dose (oral),			first dose of
l			n=31			medication,
						all except one
						(dex
						0.6mg/kg)
						tolerated
						second dose.
Fitzgerald	RCT	Croup	1) Budesonide	Additional	Baseline,	Six patients in
1996	Pediatri	6mo-6y	2.0mg (4ml) for	medications	30min,	each
Canada	c ED		5min (neb),	permitted 2h after	60min,	treatment
Industry	3		n=35	study	90min,	group
funded			2) Adrenaline		120min,	reported
			4.0mg (4ml) for	No CS in preceding	12h & 24h	adverse
			5min (neb),	4wk	post-	events. These
			n=31	4	treatment	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

		I			1	
						specific
						treatment.
Francis	RCT	Asthma	1) Fluticasone	NR	D1 to D7	Most frequent
1997	(trial	≤48mo	propionate			adverse
Australia	registry		1.0mg twice	No CS treatment		events – on-
Funding NR	data)		daily (neb) +	for >7d in		therapy, n (FP
	Acute		placebo tablets	preceding 4wk		vs. pred):
	care		once daily (oral)			Nausea &
	setting		for 7d, n=37			vomiting (7
	4		2) Prednisolone			vs. 1);
			(dose NR) daily			Diarrhoea (3
			for 7d (oral),			vs. 0);
			n=19			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/d
						ysphonia (0
						vs. 2);
						Serious
						adverse
						events - on-
						therapy:
						Subjects with
						non-fatal SAEs
						(2 vs. 0):
						Ketonuria,
						glycosuria and
						hyperglycaem
						ia (1 vs. 0);

						Subjects with fatal SAEs (0 vs. 0)
Garbutt	RCT	Croup	1)	Acetaminophen &	FU	No serious
2013	Primary	1-8y	Dexamethasone	ibuprofen	interviews	adverse
USA	care	,	0.6mg/kg (max.	'	at D1 to D4	events
Non-	office		18mg), single	No CS preceding	& D11;	occurred.
industry	10		dose, followed	current croup	FU chart	Study groups
funded			by placebo for	episode	review	did not differ
			2d, 2 doses total	•	within 28d	in reporting
			(oral), n=46		of index	side effects
			2) Prednisolone		visit	from the
			2.0mg/kg/d			study
			(max. 60mg/d)			medications
			for 3d (oral),			(24%
			n=41			dexamethaso
						ne, 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);
						V3. 10/35), Mood
						changes (25
						vs. 24);

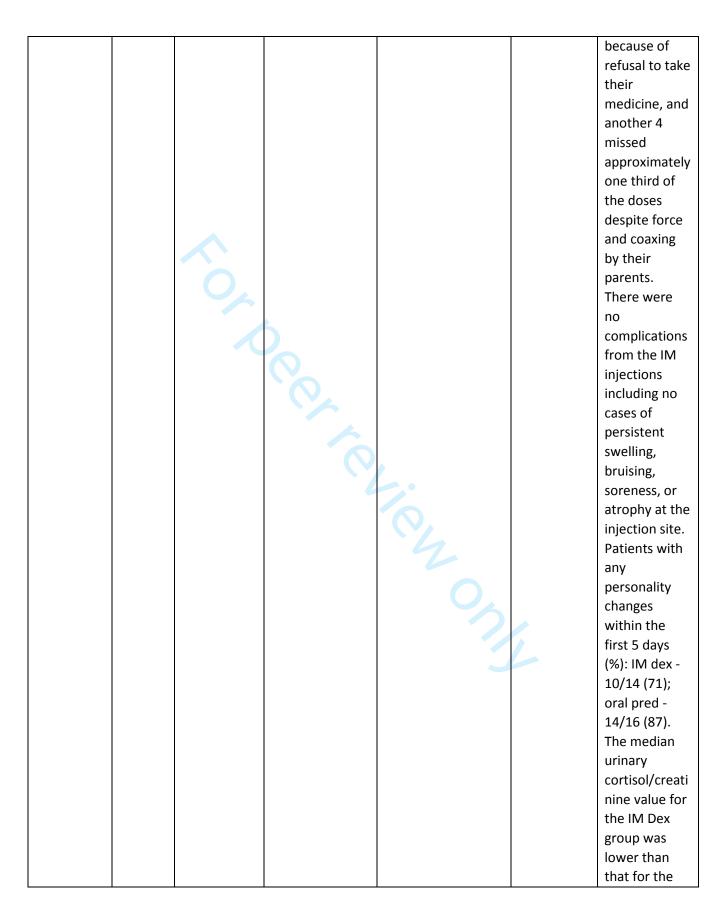
						New sleep problems (18 vs. 13); Stomach pain (9 vs. 7); Headache (7 vs. 4); Vomiting (3 vs. 7); Nausea (3 vs. 4); Dizziness (3 vs. 2); Tremor (1 vs. 0)
Ghirga 2002	NRCT NR,	Wheeze - early URTI	1) Beclomethason	NR	Twice daily	At this writing, four
Italy	"ambul	before signs	e 400mcg 3	NR		years after
Funding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

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

USA c ED or Funding NR childre n's clinic 2 (or 2 (neb)) for 5d (oral), n=24 scores on the D0, D2, D3 prednisolone scores on the D0, D2, D3 prednisolone prednisolone scores on the D0, D2, D3 prednisolone prednisolone & D6; group was prednisolone & D6; group was convalesce his caretakers nce to be "jittery" at times after enrollment.	Goebel	RCT	Bronchiolitis	1) Prednisone	NR	Clinical	days. Four participants visited their primary care physician within 7 days of dexamethaso ne administratio n. One patient was healthy, another was given a diagnosis of otitis media and treated with oral antibiotics, and two patients who had persistent coughs were prescribed salbutamol. None of the participants were admitted to hospital, and there were no serious adverse events or deaths. One patient in
Funding NR childre n's 0.3mg/kg/day (or convalesce to be "jittery" (neb)) for 5d & D6; group was proup was observed by convalesce to be "jittery" completed at times after	2000	Pediatri	≤23mo	2.0mg/kg/day		scores on	the
n's clinic (or convalesce his caretakers 2 (neb)) for 5d FU when observed by convalesce his caretakers completed at times after					ואול		•
clinic 2 (or convalesce his caretakers nce to be "jittery" (neb)) for 5d completed at times after	Fulluling INK						- '
2 0.15mg/kg/dose nce to be "jittery" completed at times after							=
(neb)) for 5d completed at times after							
		_					

	1	T	T .	Т		T
			2) Placebo			This resolved
			solution (oral) +			after a
			albuterol			decrease in
			0.3mg/kg/day			the albuterol
			(or			dose. No
			0.15mg/kg/dose			evidence of
			(neb)) for 5d			treatment
			(oral), n=24			complications
						was observed
						in any of the
						other
						patients.
Grant 1996	Cohort	Asthma	1) Prednisone	Bronchodilators as	NR	Ninety-four
USA	Primary	2-14y	2.0mg/kg (max.	needed		episodes of
Non-	care	,	60mg/day),	necaca		acute
industry	clinic &		single dose	NR		infection
funded	teachin		intermittent for	IVIX		occurred in 50
Turided			6mo (oral),			subjects and
	g					-
	hospital		n=86			222 episodes
	ED		2) Placebo (NR),			of symptoms
	1		n=86			of infection
			()	A		occurred in 62
			Multiple			subjects
			courses over 1yr			(table 1
						episodes of
				7		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
						WILLI LIIUSE

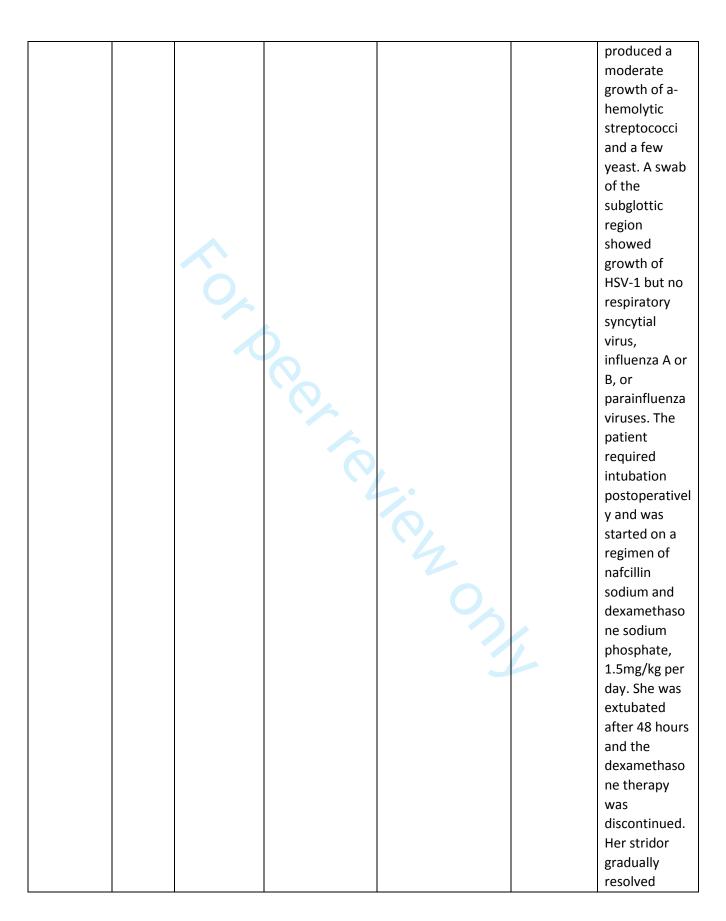
						without the infection. No
						correlation
						was observed
						between the
						number of
						doses of
						prednisone
						received and
						the number of
						episodes of
						each
						infection. This
						included all
						episodes of
			5			otitis media,
						streptococcal
			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



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

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

			doses 30min			
			apart (neb),			
			n=16			
Inglis 1993	Case	Croup	Case 1)	Case 1: racemic	NR	Case 1:
USA	report,	18mo;	Prednisolone	epinephrine,		Twenty days
Funding NR	2	14mo	1.0mg/kg, twice	acyclovir sodium		into illness,
	Hospita		daily for 4d (NR)	Case 2:		airway
	I		Case 2)	amoxicillin/clavulan		endoscopy
	'		Dexamethasone	ate potassium,		revealed
			0.3mg/kg, 3	cefuroxime sodium		shallow
			doses in 24h	ceruroxime sociam		mucosal
			(NR)			ulcerations of
			(INK)			
						patient's
						glottis and
						subglottis, but
						a normal
						appearing
						tracheobronc
			,0			hial tree.
						Cultures were
						positive for
				A		HSV-1,
						Staphylococcu
						s 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
	<u> </u>	I	<u> </u>			'



						spontaneousl y over the next 7 days without
						further
lan 2000	Non	Asthma	1) Croup A.	ND	D1 to D2	intervention.
Jan 2000 Taiwan Funding NR	Non- RCT Pediatri c hospital clinic 1	Asthma	1) Group A: Methylprednisol one 1.0mg/kg/6h (IV) for 1d, n=NR 2) Group B: Methylprednisol one 1.0mg/kg/6h (IV) for 2d, n=NR 3) Group C: Methylprednisol one 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

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

	_	T			ī	
Non-	Univers	rhinovirus-	2mg/kg/d in 2	No previous	12mo post-	incidence of
industry	ity	induced	divided doses	systemic or inhaled	discharge	adverse
and	hospital	3-23mo	for 3d (max.	CS treatment		events
industry	1	(mean	60.0mg/day),			between the
funded		13.2mo vs.	n=34			prednisolone
		12.2mo)	2) Placebo, n=40			and placebo
						groups
			Multiple			(results not
			courses over 1yr			shown). No
						clinically
						significant
						adverse
						events were
						reported.
Johnson	RCT	Croup	1)	Humidified oxygen	Baseline, 2h	Two patients
1996	Pediatri	mean 15mo	Dexamethasone	,,,	& 4h post-	with
Canada	c ED	vs. 17mo	10.0mg (4ml) -	No CS in preceding	treatment	neutropenia
Non-	1		10.0mg (<8kg),	2wk		treated with
industry			15.0mg (8-12kg)			dexamethaso
funded			or 20.0mg			ne had a
10.110.00			(>12kg), 10min			clinical course
			(neb), n=28			consistent
			2) Control,			with bacterial
			saline (4ml),			tracheitis.
			10min (neb),			tracricitis.
			n=27			
Johnson	RCT	Croup	1) Budesonide	Racemic	Study entry	No child had
1998	Pediatri	3mo-9y	4.0mg for 20min	epinephrine & mist	& hourly	gastrointestin
Canada	c ED	35 37	(neb), n=48	therapy	for 5h post-	al bleeding or
Industry	2		2)	therapy	treatment	bacterial
funded	-		Dexamethasone	No CS in preceding	until	tracheitis.
Tanaca			0.6mg/kg, single	4wk	discharge;	tracricitis.
			dose (IM), n=47		FU 72h	
			3)Placebo		post-	
			suspension,		discharge	
			single dose for		aiscriaige	
			20min (neb),			
			n=49			
Klassen	RCT	Croup	1) Budesonide	Racemic	Baseline &	No adverse
1994	Pediatri	3mo-5y	2.0mg (4ml),	epinephrine or	hourly for	events were
Canada	c ED	Jillo Jy	single dose	dexamethasone, or	4h;	noted in the
Non-	1		(neb), n=27	oxygen tent	FU at 1wk	budesonide
industry	1		2) Placebo	ONYBEILIEIT	1 O at 1WK	group. No
funded			saline 0.9%			• .
Turided			Sallile 0.9%			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 Pediatri c 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 dexamethaso ne within 30min and required readministrati on of dexamethaso ne, which was subsequently tolerated in all 3 patients.
Klassen 1998 Canada Non- industry funded	RCT Pediatri c 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

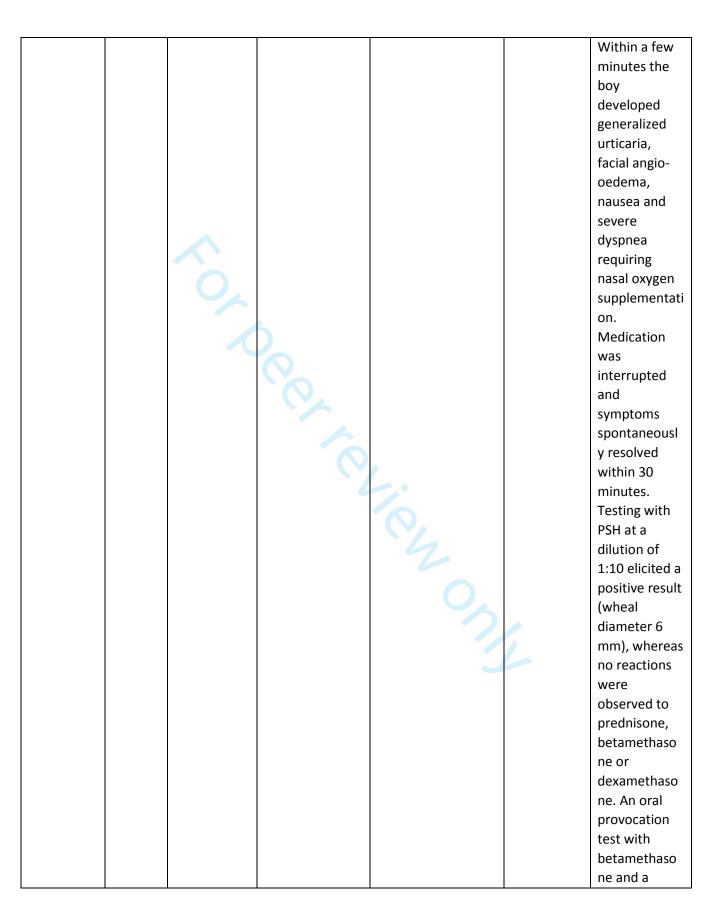
			3) Budesonide			reported this
			2.0mg (4ml)			condition at
			(neb) +			the 1-week
			dexamethasone			follow-up.
			0.6mg/kg (oral),			Parents of 1
			n=64			patient
						treated with
						dexamethaso
						ne reported
						-
						hives, and
						parents of 1
						patient
						treated with
	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

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

	1	T	1		T	
					and	total height
					diastolic)	growth, mean
					and blood	rate of height
					glucose at	increase,
					baseline	systolic or
					and	diastolic
					approximat	blood
					ely 8-19mo	pressure, or
					after	blood glucose
					randomizati	between the
					on	treatment
						groups.
Langton	RCT	Asthma	1) Prednisolone	Bronchodilators	Baseline,	No serious
Hewer	Hospita	1-15y	0.5mg/kg/day	(nebulized)	0h, 12h,	short-term
1998	1		until discharge		24h, 36h,	side-effects
UK	1		(max.	No CS in preceding	48h, 60h &	were noted
Funding NR			60.0mg/day)	14d	72h;	but
			(oral), n=35		FU 2wks	hyperactivity
			2) Prednisolone		post-	related to
			1.0mg/kg/day		enrollment	nebulized B2
			until discharge			agonist
			(max.			therapy was
			60.0mg/day)	>		seen. No side-
			(oral), n=33			effect possibly
			3) Prednisolone			attributable
			2.0mg/kg/day	4		to
			until discharge	1		prednisolone
			(max.			therapy was
			60.0mg/day)			noted in any
			(oral), n=30			of the three
						treatment
						groups.
						Three children
						in
						prednisolone
						2.0mg group
						were
						withdrawn
						because of
						vomiting, a
						diagnosis of
						pneumonia or
						the parents
	1	l .	l	<u> </u>	l	'

						withdrew
						consent.
Lee 2001 Taiwan Funding NR	Case report Pediatri c clinic of hospital 1	Asthma 5y	1) Terbutaline solution (loading dose: 5.0mg/kg/dose, maintaining dose: 0.6mg/kg/h); Methylprednisol one (BW 21kg, 2.0mg/kg/dose, 40.0mg every 6h) (IV), and; Procaterol 12.5mcg twice daily (oral)	NR	D1 to D3	consent. On day 3 of admission the patient was found to have major behaviour changes and hyperventilati on. She started screaming unreasonably, gazing forward and sometimes upward and became panic. She had visual hallucinations and delusion.
Leer 1969 USA Industry funded	RCT Hospita I 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 staphylococca I or other bacterial pneumonias nor masked superinfection
Lehmann 2008 Germany Funding NR	Case report Pediatri c	Asthma 2y	1) Prednisolone- 21-hydrogen	None 3wk washout period (but under	Post skin prick test	Patient had been on well- tolerated long-term

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

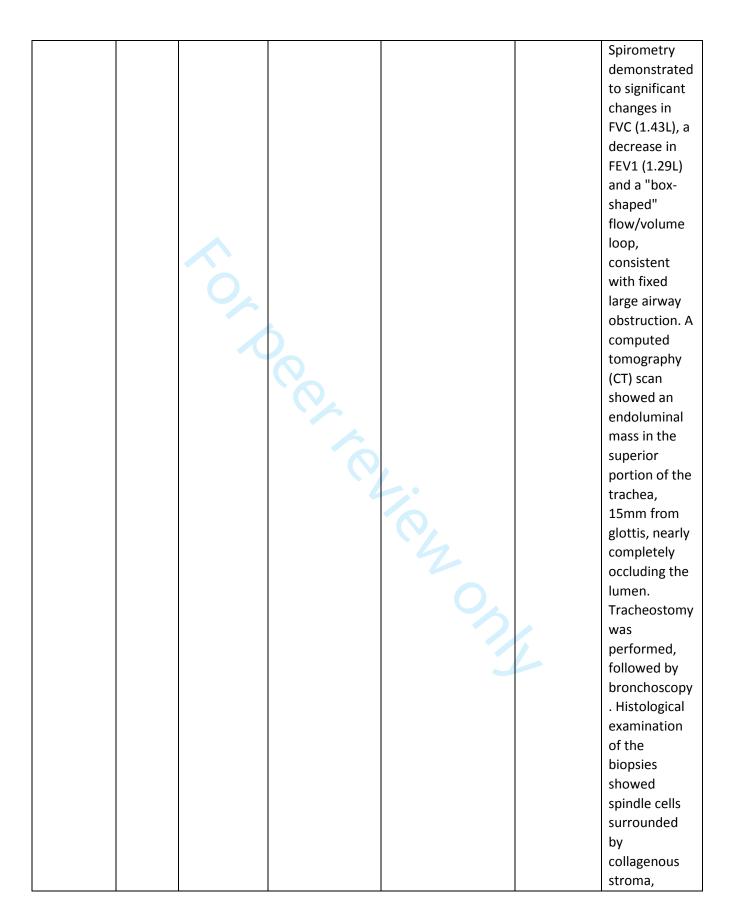


						titrated
						intravenous
						dexamethaso
						ne challenge
						test were
						tolerated
						without any
						complications.
Leipzig	RCT	Croup	1)	Vaponephrine, mist	Baseline,	We observed
1979	Hospita	8mo-5y	Dexamethasone	tent therapy &	12h & 24h	no adverse
USA	I	Billo-3y	0.3mg/kg	racemic	1211 & 2411	effects or late
Funding NR	2		(4mg/ml) 2	epinephrine	NR	relapses.
Fulluling NK	2		doses 2h apart	ершершше	INIX	relapses.
			(IM), n=16	NR		
				INK		
			2) Placebo			
			saline, two			
			doses 2h apart			
			(IM), n=14			
Lin 1991	NRCT	Acute	1) Group A:	IV fluid, oxygen &	Daily for 5d	Regarding
Taiwan	Hospita	wheeze	<12mo old	antibiotics		side effects,
Funding NR		<36mo	(n=29):			two patients
	1		hydrocortisone	NR		in Group B
			5.0mg/kg			and one
			loading dose			patient each
			(IV) plus	(().		in Groups A
			2.5mg/kg/dose			and C had
			every 6h for 3d			tremor. One
			+ meptin liquid			patient in
			(procaterol			Group A had
			hydrochloride)			irritability,
			1.25mcg/kg/dos			and another
			e on admission,			had diarrhea.
			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			

Vomiting was
lex observed in
23% of
patients using
crushed
tablets, and in
none of the
patients on
oral solution.
; He presented
with
wheezing,
e received an
intravenous
bolus of
methylprednis
olone sodium
succinate
(2mg/kg), and
immediately
developed
restlessness
and facial rash
which
resolved
spontaneousl
y. On the
following day,
he received
again the
same
medication
and

		T				ina na a ali - t - t
						immediately
						developed
						respiratory
						distress and
						cyanosis with
						oxygen
						desaturation
						of 89%. He
						recovered
						with oxygen
						supplementati
						on and was
						treated
						afterward
						with oral
						betamethaso
						ne sodium
						phosphate
						without
						adverse
						events.
Paniagua	RCT	Asthma	1)	NR	NR;	No
2016	(confer	>12mo	Dexamethasone	>	FU at 7d &	differences
Spain	ence		, NR, 2 doses	NR	15d post-	were found
Funding NR	abstrac		(oral), n=287		ED visit	regarding
	t)		2)			vomits (2.1%
	Pediatri		Prednisone/pre			vs 4.1%).
	c ED		dnisolone, NR,			
	1		5d (NR), n=290			
Panickar	RCT	Wheeze	1) Prednisolone	Albuterol, oxygen &	4h, 12h &	No clinically
2009	Pediatri	10-60mo	10.0mg/day	antibiotics	24h after	significant
UK	c ED		(10ml) once		albuterol &	adverse
Non-	3		daily for 10-	NR	daily post-	events were
industry			24mo old (oral);		discharge;	reported to
funded			20.0mg/day		FU by	the patient
			(10ml) once		phone 1mo	safety
			daily for >24mo		post-	committee. In
			old (oral), for		discharge	one child in
			5d, n=343			the
			2) Placebo			prednisolone
			solution (10ml)			group,
			once daily for			parents
			5d (oral), n=344			attributed
			. (= =:,, :: = : :			excess
	l .	l		<u> </u>		2,0003

				MD	MD	vomiting to the study drug and discontinued the medication after discharge from hospital.
Panigada 2014 Italy Funding NR	Case report Pediatri c Pulmon ary and Allergy Unit 1	Progressive shortness of breath, subsequent diagnosis of inflammator y myofibrobla stic 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 discontinuatio n of prednisone, the boy was readmitted because of progressive shortness of breath. He had moderate-to-severe dyspnoea, inspiratory, and expiratory wheezes: SaO2 was 97% in room air, RR 39 breaths/min.



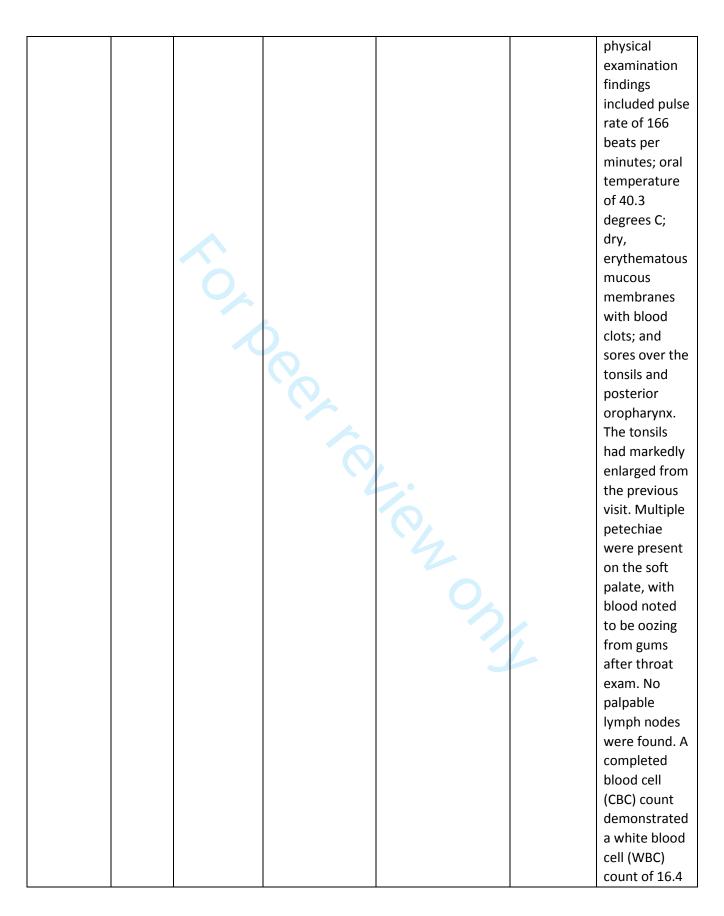
						displaying
						strong
						positivity for
						vimentin,
						focal positivity
						for a-smooth
						muscle actin,
						and weak
						positivity for
						clusterin. No
						desmin, ALK,
						S100, CD21,
						and CD 23
						expression
						was detected.
						A diagnosis of
						IMT of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

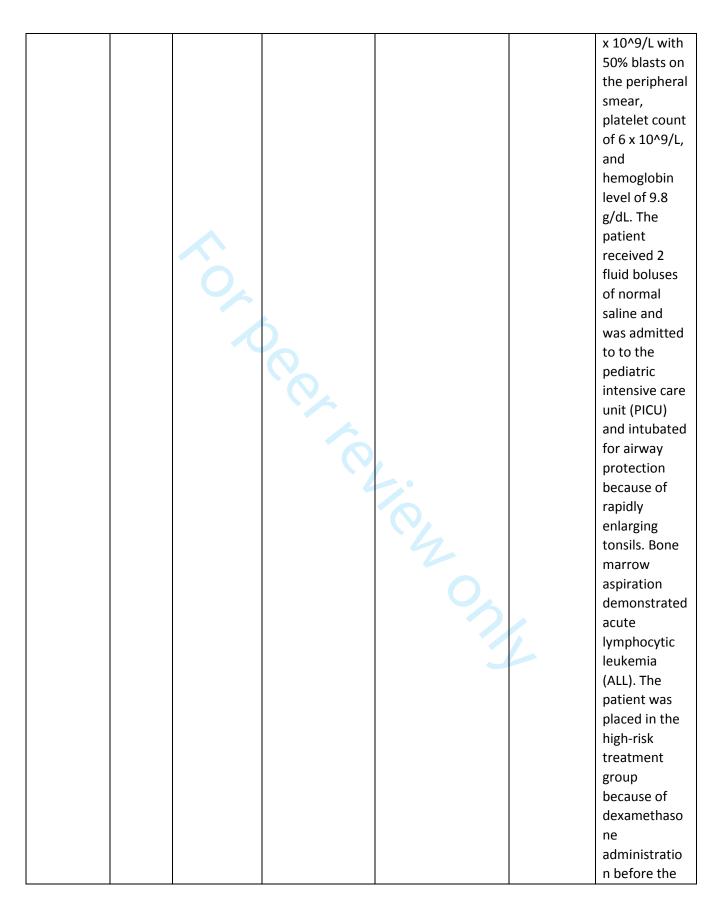
apart (neb) + dexamethasone 1.0mg/kg (max 10mg), total 6d (oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 apart (neb) + Placebo solution (max 12ml), adverse events, n (Epi + Dex vs. Epi vs. Dax 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 (Art vs. 14 vs.
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 Pex 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
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 Pex 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
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 1.0mg/kg (max 12ml), total 6d (oral), n=201 1.0mg/kg (max 12ml) + Placebo solution (max 12ml), total 6d (oral), n=201 1.0mg/kg (max 12ml) + Placebo solution (max 12ml), 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
10mg), total 6d (oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 Pexor Sepi 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
(oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 events, n (Epi + Dex vs. Epi vs. Dex vs. Placebo): Tremor (4 vs. 4 vs. 5 vs. 2); Pallor (23 vs. 22 vs. 15 vs. 16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
(oral), n=200 4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 events, n (Epi + Dex vs. Epi vs. Dex vs. Placebo): Tremor (4 vs. 4 vs. 5 vs. 2); Pallor (23 vs. 22 vs. 15 vs. 16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
4) Placebo 2 doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 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
doses 30min apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 rapidly. Supplementar y 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
apart (neb) + Placebo solution (max 12ml), total 6d (oral), n=201 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
Placebo solution (max 12ml), total 6d (oral), n=201 Placebo solution (max 12ml), total 6d (oral), n=201 Placebo solution 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
(max 12ml), total 6d (oral), n=201 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
total 6d (oral), n=201 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
n=201 events, n (Epi + Dex vs. Epi vs. Dex vs. Placebo): Tremor (4 vs. 4 vs. 5 vs. 2); Pallor (23 vs. 22 vs. 15 vs. 16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
+ 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
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
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
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
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
Pallor (23 vs. 22 vs. 15 vs. 16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
22 vs. 15 vs. 16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
16); Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
Vomiting (2 vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
vs. 4 vs. 5 vs. 3); Varicella (0 in all groups); Dark stools
3); Varicella (0 in all groups); Dark stools
Varicella (0 in all groups); Dark stools
all groups); Dark stools
Dark stools
(47.00.44.00
(17 vs. 14 vs.
12 vs. 16);
Hypertension
(0 vs. 1 vs. 1
(\$\sigma\$.1\sigma\$.1\vs.0);
Hyperkalemia
(0 vs. 0 vs. 1
(0 vs. 0 vs. 1 vs. 0)
Razi 2015 RCT Asthma 1) Budesonide Standard care: Every 4h No drug-
Turkey Hospita 7-72mo 1.0mg/2ml, 2 methylprednisolon until related
Funding NR I I.omg/2111, 2 Intertry preditisoion drith Terated doses for up to e 1.0mg/kg/day, for discharge adverse
2) Sterile saline 0.15mg/kg every 4h identified
2ml, 2 doses for + ipratropium during
up to 5d, n=50 bromide 250mcg hospitalizatio
every 6h n.

			<u> </u>		T	
				NR		
Roberts	RCT	Croup	1) Budesonide	NR	Baseline,	The adverse
1999	Women	6mo-8y	2.0mg (4ml) for		2h, 6h &	effects in both
Australia	's and		10min each	No CS in preceding	12h after	groups were
Industry	Childre		dose, every 12h	4wk	first dose,	attributable
funded	n's		(max. 4 doses)		then 12-	to either
	Hospita		(neb), n=42		hourly up	manifestation
	1		2) Placebo for		to 48h if in	s of the
	1		10min each		hospital;	disease state
			dose, every 12h		FU by	or the mode
			(max. 4 doses)		telephone	of drug
			(neb), n=40		1d & 3d	administratio
					post-	n (Table 3).
					discharge	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
			4	•		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	RCT	Croup	1) Fluticasone	NR	Admission,	No side
1998	Hospita	4-52mo	propionate		30min, 2h,	effects of the
Netherland	I		1000mcg, 2	No CS in preceding	6h, 12h &	treatment
S	NR		divided doses	48h	24h	regimens
Funding NR						were reported
		· _			·	

			30min apart			during the
			(MDI), n=9			study.
			2) Placebo (NR),			
			n=8			
Roosevelt	RCT	Bronchiolitis	1)	Antibiotics,	Admission	Three
1996	ED	<12mo	Dexamethasone	bronchodilators &	& every	patients had
USA	1		1.0mg/kg every	tribavirin	12h;	occult blood
Non-			24h for max. 3		FU 1wk	in their stools;
industry			doses (IM),	NR	post-	two were in
funded			n=65		discharge	the
			2) Placebo			dexamethaso
			saline, every			ne group. No
			24h for max. 3			episodes of
			doses (IM),			gross
			n=53			haematochezi
						a were
						observed.
Sadowitz	Case	Pharyngitis	Dexamethasone	NR	NR	The patient
2012	series	Зу	10.0mg single			was given a
USA	(n=4, 1		dose (oral?) +	NR		10-mg dose of
Funding NR	case		acetaminophen			dexamethaso
	relevan		+ amoxicillin,			ne in addition
	t)		n=1	>		to
	ED					acetaminophe
	1					n and
						amoxicillin;
						she was able
				9		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





A	liagnosis of
	ALL and in the
al	bsence of a
p p	pretreatment
	CBC count
fc	ollowing the
gu gu	guidelines for
hi hi	nigh-risk
le le	eukemia
e e	established by
th	he Children's
0	Oncology
G G	Group.
In In	nduction
tt	herapy
in	nclude IV
d	launorubicin,
de de	decadron,
as	isparaginase,
aı	ind
vi	vincristine.
TI	he patient's
in	nitial course
O ⁴	of treatment
w w	vas
	complicated
	y a ruptured
	luodenal
	ılcer with
	peritonitis
	ind
	osteonecrosis.
	he patient
	urvived these
	complications
	and achieved
	emission and
	continues on
	maintenance
	chemotherap
	at this time.
	Serum cortisol
' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' ' '	evels in the
Funding NR c hydrocortisone (IV) B	BIS and PSL

	depart		twice daily	& one inhalation of	Serum	groups at the
	ment of		·			
			(neb), n=30	procaterol; LTRA	cortisol	time of
	hospital		2) Prednisolone	for wheezing	assessed	admission
	1		0.5mg/kg, 3	episodes	(assessmen	were
			times daily (IV),		t method	15.0mcg/dL
			n=20	NR	NR) on	and
					admission	17.2mcg/dL
					and D4 of	(p>0.05),
					hospitalizati	respectively.
					on	However,
						serum levels
						on the fourth
						day of
						hospitalizatio
						n were
						17.0mcg/dL
						and
						10.9mcg/dL,
			`O			with
						significant
						suppression in
						the PSL group.
						Adverse
						events did not
						occur in either
						group.
Schuh 2008	RCT	Bronchiolitis	1)	Albuterol	Baseline,	The mean
Canada	Pediatri	8wk-23mo	Dexamethasone		D4 & D6	blood
Non-	c ED		1.0mg/kg in ED	Baseline reports 3	(home	pressure
industry	1		+ 4 doses	patients with prior	visits);	increased
funded			0.15mg/kg	inhaled ICS	FU by	from 96.1+/-
			starting 24h		telephone	8.8 mmHg to
			later, total 5d		on D28	99.5+/-14.8
			(oral), n=61		0220	mmHg in the
			2)			single-dose
			Dexamethasone			group and
			1.0mg in ED + 4			from 96.4+/-
			doses placebo			7.9 mmHg to
			syrup starting			103+/-
			24h later, total			16.8mmHg in
			5d (oral), n=64			the multiple
			50 (Orai), 11-04			dose group.
						Bag urine was
						obtained on

Schuh 2009	RCT	Asthma	1) Mantalukast	Albuterol &	48h & D8	day 6 visit in 47 study infants and tested positive for glucose in 1 child belonging to the multiple- dose group. In the
Canada Industry funded	Pediatri c ED 1	>=2y	1) Montelukast 1.0mg/kg: 2-5y=4.0mg; 6-14y=5.0mg; and, 15-17y=10.0mg at 24h, 48h, 72h, 96h & 120h (oral), n=67 2) Prednisone/pre dnisolone 1.0mg/kg: 2- 5y=4.0mg; 6-14y=5.0mg; and 15- 17y=10.0mg at 24h, 48h, 72h, 96h & 120h (oral), n=63	fluticasone >1 single dose or oral prednisolone or >250mcg per day of inhaled	TOTI & DO	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

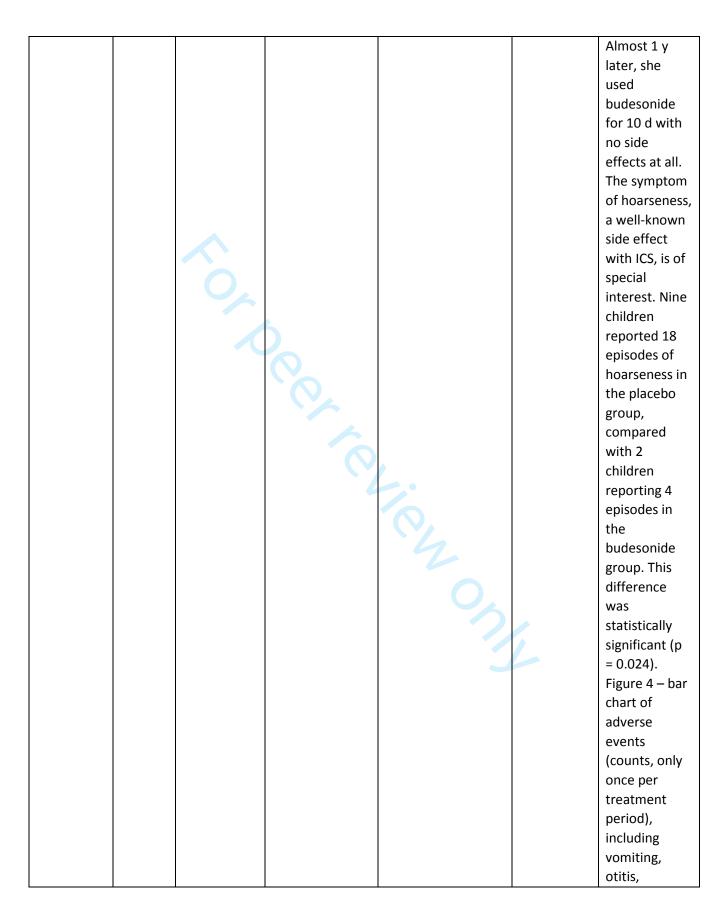
						,
						"event" is
						questionable.
						No adverse
						effects
						developed in
						the children
						given
						prednisolone
						after
						discharge.
Siomou	Case	Bronchiolitis	1)	NR	Baseline, 2	In summary,
2003	control,	, viral	Hydrocortisone		days after	short-term IV
Greece	3-arm	wheezing,	10.0mg/kg/day	Never/no CS in last	cs	corticosteroid
Industry	Pediatri	or croup	for 3d (NR),	2mo	administrati	administratio
funded	С	2mo-10y	n=28		on & 12d	n to children
	hospital		2)		after end of	suffering from
	1		Methylprednisol		therapy	acute
			one 2.0mg/kg		.,	respiratory
			for 3 days (NR),			diseases led
			n=21			to partial but
			3) Control, 3d,			reversible
			n=51			inhibition of
			01			bone
						formation
						markers,
				2		especially
				1		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
				<u> </u>		accicase iii

Sparrow	RCT	Croup	1)	Adrenaline	Enrolment,	the maximum renal phosphate reabsorption were significant but transient. No adverse
2006	Pediatri	mean 37mo	Dexamethasone		30min post-	events were
Australia	c ED 1	(28.8) vs.	0.2ml/kg of 0.15	No CS preceding	treatment,	noted in
Funding NR		45mo (31.6)	mg/kg, single dose (oral),	study	hourly for next 4h &	either group.
			n=68		every 4h	
			2) Prednisolone		until	
			0.2ml/kg of		discharge;	
			1.0mg/kg, single		FU 7d-10d	
			dose (oral), n=65		post- discharge	
Stafford	NRCT	Asthma/cro	1) Prednisolone	NR	Daily	No significant
1998	Pediatri	up	5.0mg/ml		- 5,	differences
Australia	С	1-12y	solution (oral),	NR		were found
Industry	hospital		n=8	A		regarding the
and non-	or ED		2) PredMix			incidence of
industry funded	1		5.0mg/ml solution (oral),			nausea,
Tunueu			n=46			vomiting and abdominal
			3)	4		pain, or any of
			Dexamethasone			the objective
			5.0mg/ml (oral),			parameters
			n=80		A -	tested.
Storr 1987	RCT	Asthma	1) Prednisolone	Salbutamol 5.0mg	Admission,	Prednisolone
UK Non-	Pediatri c	NR (mean 5y)	30.0mg (<5yo), otherwise	in 2ml saline (neb), on admission & 3	4h, 12h, 24h & 36h	has a bitter aftertaste.
industry &	hospital	341	60.0mg, max.	times or more daily	2411 & 3011	Most children
industry	1		dose 3.0mg/kg	when indicated		disliked the
funded			(range 1.0-			drink. 2
			3.0mg/kg) single	No CS in preceding		children in
			dose (oral),	48h		each group
			n=67			vomited almost
			2) Placebo solution			immediately
			identical to			and were
			treatment,			consequently
						excluded.

			single dose			There were
			(oral), n=73			no observed
						side-effects
						related to the
						single
						prednisolone
						dose.
Sumboonn	RCT	Croup	1)	Aerosolized	Admission,	Complications
anonda	Pediatri	<5y	Dexamethasone	adrenaline,	24h & 48h;	included
1997	С		0.5mg/kg/d, 3d	antibiotics, IV fluid	FU 3wks	pneumonia in
Thailand	hospital		(IM/IV), n=14	& cool mist	post-	4 controls,
Funding NR	1		2) Control, n=18		discharge	Acinetobacter
			,	NR		sepsis in 1
						control and
						bacterial
			5			tracheitis in 1
						cases.
Sung 1998	RCT	Asthma	1) Budesonide	Salbutamol	Baseline,	No adverse
Canada	Tertiary	>6mo or	4000mcg (4ml),	0.15mg/kg every	discharge &	effects were
Non-	pediatri	<18y	single dose	30min for 3 doses,	7d to 10d	noted in
		<10y	_			
industry	C		(neb), n=24	then hourly for 4	post-	either group.
funded	hospital		2) Placebo,	doses	treatment	
	1		single dose			
6 4000	D.O.T.		(neb), n=20		5 I	
Super 1989	RCT	Croup	1)	Mist, racemic	Baseline,	In two
USA	General	NR (mean	Dexamethasone	epinephrine,	30min, and	dexamethaso
Funding NR	hospital	16mo)	0.6mg/kg, single	oxygen &	every 12h	ne-treated
	or		dose (IM), n=16	antibiotics	until	patients in the
	childre		2) Placebo		discharge	main study,
	n's		saline, single			including one
	hospital		dose (IM), n=13			with a
	2					culture-
						positive
						influenza A
						viral infection,
						laryngotrachei
						tis progressed
						to
						pneumonia.
						The other
						patient was
						the one who
						received a
						second
						5555114

in his room poor poor poor poor poor poor poor	oneumonia. We did not encounter any ide effects lirectly ettributable
e e	encounter any
si	ide effects
d	lirectly
l af	ittributable
to	О
d d	lexamethaso
	ie.
Sussman RCT Bronchiolitis 1) Oxygen, penicillin & Daily A	Adverse
	eactions to
USA I Laryngitis 0.1mg in divided st	teroid
Non- NR 15mo-10y daily dose every NR th	herapy were
industry 6h:	not noted on
funded D1-	linical
9=0.2ml/lb/day; e.	examination
D10-	ınd
11=0.1ml/lb/da su	uperinfection
y; s,	, bacterial or
	riral
13=0.05ml/lb/d d	lissemination
ay;	were not
	ncountered.
day (IM), n=31	
2) Sodium	
chloride	
0.15mEq/ml for	
14d (IM), n=26	
	en adverse
	events were
	eported in
	he
	oudesonide
	roup and

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



						hoarseness, sore throat, conjunctivitis, croup, stomach ache, diarrhea, agitation, sleep disturbances, and aggressivenes s.
Tagarro	Cohort	Bronchiolitis	1)	Adrenaline &	NR	No significant
2014	Univers 	0-6mo	Dexamethasone	salbutamol		adverse
Spain Non-	ity hospital		1.0mg single dose, or for 6d,	NR		effects attributable
industry	1		or 1.0mg on	IVIX		to steroids or
funded			first day plus			bronchodilato
			0.6mg for 5d, 6d			rs were found
			total (likely			in the clinical
			oral), n=33			records, apart
			2) Prednisone			from
			1.0-2.0mg for			hyperglycemi
			5d (likely oral), — n=15			a. Hyperglycemi
			3) No steroids,	7		a was found
			dose/duration	1		in 4 out of 23
			NR, n=32			patients
						tested (17%).
						Two of them
						had received
						PRD, one of
						them DXM and one no
						steroids.
Tal 1983	RCT	Acute	1)	Oral/IV fluid &	Admission,	One infant
Israel	Hospita	wheeze	, Dexamethasone	humidified oxygen	3h after	developed a
Non-	1	1-12mo	0.3mg/kg		first IM	remarkable
industry	1		(4mg/ml) on	NR	dose &	tremor as a
funded			admission + 0.1		each	side effect of
			mg/kg every 8h		morning	salbutamol.
			(IM), n=8		(8am) until	No other side
			2) a) Sal solution		discharge	effects or
			2.5mg (0.5ml),			complications

	1					-
			on admission &			of the
			every 6h (neb);			treatment
			b) Sal syrup,			were
			0.15mg/kg,			documented.
			every 8h (oral);			
			and,			
			c) Placebo saline			
			(IM), n=8			
			3)			
			Dexamethasone			
			0.3mg/kg			
			(4mg/ml) on			
			admission +			
			0.1mg/kg every			
			8h (IM);			
			a) Sal solution			
			2.5mg (0.5ml),			
			on admission &			
			every 6h (neb);			
			and,			
			b) Sal syrup,			
			0.15mg/kg,			
			every 8h (oral),			
			n=8			
			4) Placebo	7		
			saline			
			0.075ml/kg on			
			admission, then			
			0.025ml/kg			
			every 8h during			
			next 3d (IM),			
			n=8			
Tamura	Case	Refractory	Methylprednisol	NR	NR	All cases:
2008	series	mycoplasma	one 30.0mg/kg			There were
Japan	Medical	pneumonia	once daily for	NR		no adverse
Funding NR	center,	5y (n=6,	3d (IV), n=1			events in any
3 3	inpatie	range 3y-9y)				patients
	nt					during steroid
	1					treatment;
	_					Case patient
						1: On the 10th
						clinical day,
						we initiated
						methylprednis

		I	T	T		<u>, </u>
						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
			\bigcirc			dramatic
						improvement.
						Five days
						after the
						initiation of
			\sim			steroid
						therapy,
						laboratory
						findings were
						normalized.
						She was
						discharged on
						the 17th day
						of admission
						without
						sequelae.
Teeratakul	RCT	Bronchiolitis	1)	Epinephrine,	Baseline &	Soon after
pisarn 2007	Pediatri	4wk-24mo	Dexamethasone	salbutamol, IV	every 6h	study
Thailand	С		0.6mg/kg, single	fluids, antimicrobial	until study	endpoint, but
Non-	outpati		dose (IM), n=89	drugs & oxygen	endpoint	before being
industry	ent or		2) Saline		(resolution	discharged,
funded	ED		solution	No CS in preceding	of	systemic CS
	2		0.6mg/kg, single	2wk	respiratory	was
			dose (IM), n=85		distress);	prescribed to
					FU at 2wk	seven children
					intervals for	(four in the
						dexamethaso
		<u>I</u>		I .		

		at least	ne group)
		1mo	because of re-
		11110	wheezing.
			None of the
			children
			received
			theophylline or ribavirin.
			Three children
			(two in the
			dexamethaso
			ne group)
			developed
			occult blood
			in stools. Six
			children
			(three in the
			dexamethaso
			ne group) had
			subsequent
			diarrhea.
			Three children
			(all in the
			placebo
			group) had
			subsequent
	1		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):

van Woensel 1997 Netherland s Non- industry funded	RCT Hospita I	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 1) Prednisolone	Oxygen, bronchodilators, or antibiotics No CS in preceding 2mo	Baseline & daily for 7d	Occult blood in stools (2 vs. 1); Pneumonia (0 vs. 0); Diarrhea (3 vs. 3) In the present study no clinically significant side effects of prednisolone were found.
Webb 1986 UK Non- industry funded	RCT, crossov er "unit", outpati ent 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 Pediatri c 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

1		Т	
	fenoterol) for		short-term
	5d (NR), n=24		steroid
			therapy has
			been well
			confirmed. At
			the time of
			analysis of the
			data, all 52
			patients'
			hospital
			records were
			reviewed and
			no adverse
			event was
			noted in the
			patients who
			received
			prednisolone.

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

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

1	
2	
3	
4	
5	

44

45 46 47

35 36

37

38 39 Connett (1994)

Connolly (1969)

Corneli (2007)

Ν

Ν

Ν

Ν

Ν

Ν

Ν

Ν

Ν

N

ag	ge 137 of 234 Suppleme	ent 4. Me	thodolog	ical qualit	y assessn	nents of incl		l Open					1136/kmionon 2018 (
						Mode of co			d of	fAE		200	pecified	fied	pecified	
0 1 2 3 4 5	Study (year)	Harms pre-defined	Serious AE defined	Severe AE defined	Deaths specified	ACTIVE	PASSIVE	Who collected AE	Training/ background assessors	Timing/ frequency of collection	Checklist used for AE	Encompass all AE		AE in each arm specified	No. and type of AE specified	Type of analysis
6	Alangari (2014)	N	N	N	N	N	N	N	N	N	N	Υ	N	N	N	N
/ ጸ	Alansari (2013)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	Ϋ́	N	N	N
9	Aljebab (2017)	Υ	N	N	N	Υ	Υ	Υ	Υ	Υ	U	Υ	Y	N	Υ	Υ
0	Alshehr (2005)	N	N	N	N	N	N	N	N	N	N	Υ	11	N	Υ	N
1 ว	Altamimi (2006)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	\	N	Υ	N
3	Bacharier (2008)	N	N	N	N	N	N	N	N	N	N	Υ	<u> </u>	N	N	N
4	Bisgaard (2006)	Υ	N	N	N	Υ	N	N	N	Υ	N	N .	<u> </u>	Υ	U	Υ
5	Bjornson (2004)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	2	N	Υ	N
7	Brunette (1988)	Υ	N	N	N	Υ	N	N	N	Υ	Υ	Υ	N	N	Υ	Υ
8	Buckingham											Y	>			
9	(2002)	N	N	N	Υ	Υ	N	Υ	Υ	Υ	N			N	Υ	N
1	Bulow (1999)	N	N	N	N	N	N	N	N	N	N	Υ 5	7 N	Υ	N	N
2	Chang (2008)	N	N	N	N	Υ	N	N	N	Υ	N	+) Y	Υ	Υ	N
3	Chen (2008)	N	N	N	N	N	N	N	N	N	N	y	N	N	N	N
4	Chub-Appakarn											y y				
6	(2007)	N	N	N	N	N	N	N	N	N	N			N	N	N
7	Clavenna (2014)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	N	Υ	Y	N	N	N

Ν

Ν

Ν

Ν

Υ

Ν

Ν

Υ

Ν

Υ

Υ

Ν

Ν

Ν

Υ

Υ

Ν

Ν

Ν

Υ

Υ

	1	
	2	
	3	
•	4	
	5	
	6	
	7	
	8	
	9	
	- 1	
	-	
	1 1	
	1	
	1	
	1	
	1	
	1	
	1	
	1 1 1	
	2	
	2	
	2	
	2	
	2	
	2	
	2	
	า	

1							ВМЈ	Open				i i sazai iljopei i-zo			Pa	age 138 of 23
2 3	Cronin (2016)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	N			N	Υ	N
4 5	Csonka (2003)	N	N	N	N	N	N	N	N	N	N	Υ ο	Υ	Υ	Υ	N
6	Daugbjerg (1993)	N	N	N	N	N	N	N	N	N	N	Υ =	N	Υ	Υ	N
7	Dawson (1993)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	U	Υ =	N	N	N	N
8 9	Ducharme (2009)	Υ	Υ	N	N	Υ	N	Υ	Υ	Υ	N	Υ	Y	Υ	Υ	Υ
10	Eboriadou (2010)	N	N	N	N	Υ	N	N	N	N	N	Υ	N	N	U	N
11	Eden (1967)	N	N	N	Υ	N	N	N	N	N	N	Υ	N	N	U	N
12 13 14	Escobedo Chavez (1992)	N	N	N	N	N	N	N	N	N	N	Υ Κ	N	N	N	N
15	Fifoot (2007)	N	N	N	N	N	N	N	N	N	N			N	N	N
16	Fitzgerald (1996)	N	N	N	N	U	U	N	N	Υ	N	Y 0	Υ	N	N	Υ
17 18	Francis (1997)	N	Υ	N	N	N	N	N	N	N	N	U Ē	Υ	Υ	N	N
19	Garbutt (2013)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	N	N	N	N
20	Ghirga (2002)	N	N	N	N	N	N	Ν	Ν	N	N	Υ	N	N	Ν	N
21	Gill (2017)	N	N	N	Υ	Υ	N	N	N	Υ	N	Y	N	Ν	Υ	Υ
22 23	Goebel (2000)	N	N	N	N	Υ	N	Υ	Y	Υ	N	N G	N	N	Υ	N
24	Grant (1996)	N	N	N	N	Υ	Υ	N	N	Υ	N	Υ	N	N	Ν	Υ
25	Gries (2000)	N	N	N	N	Υ	Ν	Υ	Y	Υ	N	Y	N	N	Υ	Υ
26 27	Hedlin (1999) ¹	N	N	N	N	Υ	N	Υ	N	Υ	Υ	Υ	IN	Υ	Υ	Υ
28	Husby (1993)	N	N	N	N	U	N	Υ	N	Υ	N	Υ 🗦	N	N	N	N
29	Inglis (1993)	N	N	N	Υ	Υ	Υ	N	N	Υ	N	Υ =	Y	Υ	Υ	N
30 31	Jan (2000)	N	N	N	N	Υ	N	N	N	Υ	Υ	Υ ,	N	N	N	N
32	Jartti (2006)	N	N	N	N	N	N	N	N	N	N	Υ (N	N	N	N
33	Jartti (2007)	N	N	N	N	N	N	N	N	N	N	Ϋ́	N	N	N	N
34	Jartti (2015)	N	N	N	N	N	N	N	N	N	N	U g	Y	N	N	N
35 36	Johnson (1996)	N	N	N	N	N	N	N	N	N	N	_	-1	N	Υ	N
37	Johnson (1998)	N	N	N	N	N	N	N	N	N	N	U g	N N N	N	Υ	N
38	Klassen (1994)	N	N	N	N	N	N	N	N	N	N	γ ξ	N	N	Υ	N
39 40	Klassen (1996)	N	N	N	N	N	N	N	N	N	N	Υ 5	N	N	Υ	N
41	Klassen (1998)	N	N	N	N	Υ	Υ	Υ	Υ	U	N	Υ 2	Υ	N	Υ	N

2
3
3 4
4
5
7
, 8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

ge 139 of 234						BMJ	Open				136/bn				
											1136/bmJopen-20				
Kuyucu (2004)	N	N	N	N	N	N	N	N	N	N	Υ	N	N	N	N
Lai (2005)	N	N	N	N	Υ	N	N	N	Υ	Υ	γ %-0285 Υ 85	N	N	N	Υ
Langton-Hewer											1				
(1998)	N	N	N	N	N	N	N	N	N	N	Y on 1	N	N	Υ	N
Lee (2001)	N	N	N	Υ	Υ	N	N	N	Υ	N	Y Au	Y	Υ	Υ	N
Leer (1969)	N	N	N	N	Ν	N	N	N	Ν	N	Y August		Υ	Υ	N
Lehmann (2008)	N	N	N	Υ	Υ	N	N	N	Υ	N	Y 201	Y	Υ	Υ	N
Leipzig (1979)	N	N	N	N	N	N	N	N	N	N	γ	N	N	N	N
Lin (1991)	N	N	N	N	N	N	N	N	N	N	Ϋ́	N	N	Υ	N
Lucas-Bouwman					4						mloaded Y				
(2001)	N	N	N	N	N	N	N	N	N	N	Y dea	Υ	N	Υ	N
Nahum (2009)	N	N	N	Υ	Υ	N	N	N	Υ	N	Y fo	Y	Υ	Υ	N
Paniagua (2017)	N	N	N	N	Υ	N	N	N	N	N	Υ 📑	N	N	Υ	N
Panickar (2009)	N	N	N	N	Υ	Υ	Υ	Υ	Υ	N	Υ	N	N	Υ	N
Panigada (2014)	N	N	N	N	Υ	N	N	N	Υ	N	Y jij		Υ	Υ	N
Plint (2009)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ 💆	N	N	Υ	N
Razi (2015)	N	N	N	N	N	N	N	N	N	N	Υg	N	N	N	N
Roberts (1999)	N	N	N	N	N	N	N	N	N	N	Υ ο	N	N	Υ	N
Roorda (1998)	N	N	N	N	N	N	N	N	N	N	Υ		N	N	N
Roosevelt (1996)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ		N	Υ	N
Sadowitz (2012)	N	N	N	N	Υ	Υ	N	N	Υ	N	Y P	. Y	Υ	Υ	N
Saito (2017)	N	N	N	N	Υ	N	N	N	N	N	Υ ,	N	N	N	N
Schuh (2008)	N	N	N	N	Υ	N	Υ	Υ	Υ	Υ	Υ 202	N	N	N	N
Schuh (2009)	N	N	N	N	N	N	N	N	N	N	Y by		N	Υ	N
Siomou (2003)	Υ	N	N	N	Υ	N	N	N	Υ	U			N	N	N
Sparrow (2006) Stafford (1998)	N	N	N	N	N	N	N	N	N	N	Y guest.	N	N	N	N
Stafford (1998)	Υ	N	N	N	Υ	N	N	N	Υ	Υ	Y 70	N	N	Υ	N
Storr (1987)	N	N	N	N	N	N	N	N	N	N	Y rotected by co	. N	N	N	N
Sumboonnanonda											ā ō				
(1997)	N	N	N	N	Υ	N	N	N	Υ	N	Υg	N	N	Υ	N

Page 140 of 234

												2			
Sung (1998)	N	N	N	N	Υ	Υ	Υ	Υ	N	N	γ ?	° N	N	N	N
Super (1989)	N	N	N	N	N	N	N	N	N	N	Υ δ	N N	N	N	N
Sussman (1964)	N	N	N	N	Υ	N	N	N	N	N	Υ	N	N	Υ	N
Svedmyr (1995)	N	N	N	N	N	N	N	N	N	N		N	Υ	N	N
Svedmyr (1999) ¹	N	N	N	N	Υ	N	Υ	N	Υ	Υ	γ 2	N	Υ	Υ	Υ
Tagarro (2014)	N	N	N	N	N	N	N	N	N	N		N	N	Υ	N
Tal (1983)	N	N	N	Υ	N	N	N	N	N	N	Υ	N	N	N	N
Tamura (2008)	N	N	N	N	Υ	N	N	N	N	N	Υ	N	N	N	N
Teeratakulpisarn											ČW.				
(2007)	N	N	N	N	Υ	N	Υ	Υ	Υ	N	Υ	N	N	Υ	N
van Woensel											a	2			
(1997)	N	N	N	Υ	N	N	N	N	N	N	Υ 5	N	N	N	N
Webb (1986)	N	N	N	N	Υ	Υ	N	N	Υ	N		N	N	N	N
Zhang (2003)	N	N	N	N	Υ	N	N	N	N	N	Υ	N	N	N	N
¹ Hedlin 1	.999 and :	Svedmyr	1999 are a	ssociated	publication	s; the two p	apers are	assessed	as one stu	ıdy	0111	3			

REFERENCES

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

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.

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.

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

			-2018-028511 on 1 August 2019. Downloadec	
Supplement 5	Effect estimates for all adverse events with subgroups		8- ₀₂	
	a. Infection & respiratory system	p. 2-4	285	
	b. Gastro-intestinal tract	p. 5-7	11 0	
	c. CNS & behaviour effects	p. 8-9	n 1	
	d. Dermatologic conditions	p. 10	≥	
	e. Endocrine/ metabolic & musculoskeletal systems	p. 11	gus	
	f. Cardiovascular system	p. 12	1 20	
	g. General adverse events/ other symptoms	p. 13	19.	
	h. Immune system & oncology	p. 14	Do	
			v nic	
The tables below report result	tr of moto analysis for advorce events, organized by organ sy	stams	bade	
-	ts of meta-analyses for adverse events, organized by organ sy		_	
	ed for studies with more than one treatment arm, using risk of the treatment arm, at least one treatment		<u> </u>	
	ies that reported at least one event in at least one treatment			
study level data were conduc	comparison, without subgroup analysis. When data was avail	abie, subgroup anai	olitic)	
study-level data were conduc	comparison, without subgroup analysis. When data was avail ted for dose (single versus multi-dose) and for respiratory con	dition (e.g., bronch	olitis). <u>3</u>	
			per	
			1. bn	
			ာj. cc	
			om/	
			on .	
			А Рлі	
			117	
			20	
			224	
			by g	
			nes	
			; ; □	
			rote	
			ecte	
			<u>σ</u> . ত	
			y cc	
			руг	
			ed by copyri Supplement 5 - Page 1 of 14	
	For peer review only - http://bmjopen.bmj.com/site/abou	t/guidalinas vhtred	• • •	
	roi peer review only - http://bmjopen.bmj.com/site/abou	./guideiines.xntml		

1136/bmjopen-2018-028511 on 1 August 2019. Downloaded

Supplement 52 Info	ction & respiratory sy	stom	В	MJ Open		1136/bmjopen-2018-0285 RD		Paç	ge 142 (
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) on 1 August 20	l ² (%)	Peto OR (95% CI)	l 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, <u>5</u> 0.04) <u>8</u>	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, 0.81)	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. 0 2)	NA	1.26 (0.34, 4.68)	NA
	Systemic vs. placebo	Wheeze	1	0/31	0/27	0.00 (-0.07, 0.17)	NA	NA	NA

						20 [,]			
Systemic infections, overall	Inhaled vs. placebo	Multi-dose, wheeze	2	18/91	20/94	0.00 (-0.06, 0.86)	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, 0.20)	0	0.57 (0.20, 1.62)	0
	Systemic vs. placebo	Multi-dose	2	12/162	19/167	-0.09 (-0.29, % 0.10) 9	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, Own 0.02)	61	0.61 (0.29, 1.28)	30
	Systemic vs. placebo	Croup	4	6/413	9/399	-0.02 (-0.12, ab 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, 0.39)	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, 0.91)	0	0.46 (0.02, 10.18)	0
	Systemic vs. placebo	Multi-dose	2	8/179	6/176	0.01 (-0.03, 0.95)	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. 0 7)	NA	NA	NA
URT, overall	Inhaled vs. placebo		6	24/495	24/499	0.00 (-0.02, 0.\)\(\bar{\bar{9}}{2}\)	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, 0.83)	14	7.40 (0.45, 121.47)	NA
	Inhaled vs. placebo	Multi-dose	3	22/355	24/355	-0.01 (-0.04, dd by 0.03)	0	0.93 (0.51, 1.71)	0

Voice complaints, overall Voice complaints, overall Voice complaints, by condition RD: risk difference; oversus	Inhaled vs. placebo Inhaled vs. placebo Systemic vs. placebo Inhaled vs. placebo Inhaled vs. placebo Inhaled vs. placebo Cl: confidence interval;	Croup Wheeze All multidose Asthma	3 3 1 4 2	2/140 22/355 0/31 38/343 4/50	0/144 24/355 0/27 43/337	0.00 (-0.02, 0.83) -0.01 (-0.04, 14 0.03) 0.00 (-0.07, 0.87) -0.01 (-0.10, 8)	14 0 NA 64	7.40 (0.45, 121.47) 0.93 (0.51, 1.71) NA	0 NA
Voice complaints, overall Voice complaints, by condition RD: risk difference;	Systemic vs. placebo Inhaled vs. placebo Inhaled vs. placebo Inhaled vs. placebo	All multi- dose Asthma	1 4 2	0/31 38/343	0/27	-0.01 (-0.04, $\stackrel{\rightarrow}{\rightarrow}$ 0.03) $\stackrel{\rightarrow}{\rightarrow}$ 0.00 (-0.07, 0.27)	NA	0.93 (0.51, 1.71) NA	NA
/oice complaints, overall /oice complaints, by condition RD: risk difference;	Inhaled vs. placebo Inhaled vs. placebo Inhaled vs. placebo	dose Asthma	2	38/343	·	0.00 (-0.07, 0.27)			
/oice complaints, by condition RD: risk difference;	Inhaled vs. placebo Inhaled vs. placebo	dose Asthma	2		43/337	-0.01 (-0.10, 🖔	64		_
ondition RD: risk difference;	Inhaled vs. placebo			4/50		0.07)		0.85 (0.53, 1.36)	73
	· ·	Wheeze			9/49	-0.08 (-0.46, Own Co.31)	90	0.39 (0.12, 1.26)	81
	CI: confidence interval;	VVIICEZE	2	34/293	34/288	0.00 (-0.04, 0.84)	0	0.99 (0.59, 1.64)	N/
					site/about/guideli	0.00 (-0.04, 0.00 pp. o odds ratio; URT mipper of odds ratio; URT mipper odd ratio; URT mipp	lemer	nt 5 - Page 4 of 14	

1	
2	
3	
4	

age 145 of 234			ВМЈ О	pen		1136/bmjopen-2018-028514 on 1 August 2019. RD % 95			
Supplement 5b	o. Gastro-intestinal tract					018-0			
Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	RD 85	l ²	Peto OR	l ²
	vs.		of	1 –	2 –	(95% CI)	(%)	(95% CI)	(%)
	Comparison 2		studies	no. of	no. of	on 1			
				patients	patients	Au			
				with	with	gus			
				events/total	events/total	20:			
2				no. of	no. of	19. [
3			_	patients	patients	0			
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, 8.00)	0	1.87 (0.19, 18.27)	NA
3	Systemic vs. placebo	Multi-dose	3	29/487	30/472	0.00 (-0.02, c fr) 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 (-0.01,5 0.01)	0	NA	NA
Bleeding, overall	Inhaled vs. placebo	Single dose,	1	0/48	0/49	0.00 (-0.04,	NA	NA	NA
	·	croup				0.04)			
Vomiting, overall	Systemic vs. placebo		7	38/1603	34/1573	0.00 (0.00, 6.01)	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, 5 0.01) 51	0	0.87 (0.47, 1.59)	24
	Systemic vs. placebo	Multi-dose	3	17/856	11/861	0.00 (-0.01,7 0.02) 8	37	1.58 (0.75, 3.36)	0
Vomiting, by condition	Systemic vs. placebo	Asthma	1	1/37	5/33	-0.11 (-0.27 _ළ 0.06) ල	33	0.19 (0.03, 1.02)	0
	Systemic vs. placebo	Bronchiolitis	3	24/751	21/718	0.00 (-0.02, ES 0.02) P	0	1.12 (0.62, 2.04)	0
3	Systemic vs. placebo	Croup	1	3/359	4/361	0.00 (-0.02, 0 0.01)	NA	0.75 (0.17, 3.34)	NA

1	
2	
3	
4	
5	
6	
7	
8	
9	
1	0
	1
1	2
1	3
1	4
1	5
1	6
1	7
1	
1	
2	0
2	1
2	1
2	1 2
2 2 2	1 2
2	1 2 3 4
2 2 2 2	1 2 3 4 5 6
2 2 2 2	1 2 3 4 5 6
2 2 2 2 2 2	1 2 3 4 5 6 7
2 2 2 2 2 2 2	1 2 3 4 5 6 7 8
2 2 2 2 2 2 2 2	1 2 3 4 5 6 7 8 9
2 2 2 2 2 2 2 3	1234567890
2 2 2 2 2 2 3 3	12345678901
2 2 2 2 2 2 2 3	123456789012
2 2 2 2 2 2 3 3 3	123456789012
2 2 2 2 2 2 3 3 3 3	12345678901234
2 2 2 2 2 2 3 3 3 3 3	123456789012345
2 2 2 2 2 2 3 3 3 3 3 3 3 3	1234567890123456
2 2 2 2 2 2 3 3 3 3 3 3 3 3	12345678901234567
2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3	123456789012345678
2 2 2 2 2 2 2 3 3 3 3 3 3 3 3 3 3 3	123456789012345678

		Systemic vs. placebo	Wheeze	2	10/456	4/461	0.02 (-0.06, [∞]	87	2.55 (0.87, 7.46)	0
,							0.11) 8			
	Vomiting, overall	Inhaled vs. placebo		5	28/421	28/420	0.00 (-0.03, $\stackrel{\rightharpoonup}{\rightarrow}$ 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
0		Inhaled vs. placebo	Multi-dose	4	26/396	27/395	0.00 (-0.03,22 0.03)	0	0.96 (0.55, 1.67)	0
2 3 4	Vomiting, by condition	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06,0 0.13)	NA	7.13 (0.14, 359.55)	NA
5 6 7		Inhaled vs. placebo	Croup	2	4/67	4/65	0.00 (-0.08, a 0.08)	0	0.97 (0.23, 4.00)	0
8 9		Inhaled vs. placebo	Wheeze	2	23/326	24/328	0.00 (-0.04,3	0	0.96 (0.53, 1.74)	0
0 1 2	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
3	Vomiting, by dose	Dexamethasone vs. other steroid	Single dose	5	6/376	39/420	-0.07 (-0.11 ⁸ / ₂ -0.02)	47	0.23 (0.12, 0.42)	0
5 6 7		Dexamethasone vs. other steroid	Multi-dose	1	6/287	12/290	-0.02 (-0.058- 0.01)	NA	0.51 (0.20, 1.30)	NA
8 9	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
0		Dexamethasone vs. other steroid	Croup	2	5/111	8/75	-0.04 (-0.16,7 0.08) %	64	0.46 (0.14, 1.45)	0
2 3 4		Dexamethasone vs. other steroid	Other conditions	1	1/86	15/169	-0.08 (-0.13ද්දි 0.02) පු	3	0.25 (0.09, 0.72)	0
5 6	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
/ 8 9	Abdominal pain, overall	Dexamethasone vs. other steroid		3	29/188	48/264	-0.01 (-0.07g) 0.05)	0	0.96 (0.57, 1.61)	0

Abdominal pain, by	Dexamethasone vs. other	Asthma	1	2/56	3/54	-0.02 (-0.10	NA	0.64 (0.11, 3.79)	NA
condition	steroid	Astiiiia	1	2/30	3/54	0.06)	INA	0.64 (0.11, 3.79)	INA
Condition	steroid	Constant	1	0/46	7/44	, 01	- NA	1 10 (0 10 2 17)	- NIA
		Croup	1	9/46	7/41	0.02 (-0.14, $\stackrel{\rightharpoonup}{\rightarrow}$	NA	1.18 (0.40, 3.47)	NA
		0.1		10/06	20/462	0.19)	 	0.04/0.00 4.00	
		Other	1	18/86	38/169	-0.01 (-0.12≱ 0.10)	0	0.94 (0.50, 1.77)	0
		conditions				0.10) 👼			
Diarrhea, overall	Systemic vs. placebo		3	10/254	9/230	0.01 (-0.03,8	0	1.09 (0.43, 2.73)	0
						0.04)			
Diarrhea, by dose	Systemic vs. placebo	Single dose	1	3/89	3/85	0.00 (-0.06,5	NA	0.95 (0.19, 4.84)	NA
						0.05) 흥			
	Systemic vs. placebo	Multi-dose	2	7/165	6/145	0.01 (-0.03,	0	1.16 (0.38, 3.54)	0
						0.05)			
Diarrhea, by condition	Systemic vs. placebo	Bronchiolitis	1	3/89	3/85	0.00 (-0.06,3	NA	0.95 (0.19, 4.84)	NA
						0.05)			
	Systemic vs. placebo	Wheeze	2	7/165	6/145	0.01 (-0.03,	0	1.16 (0.38, 3.54)	0
			1			0.05)			
Diarrhea, overall	Inhaled vs. placebo	Multi-dose,	2	41/326	46/328	-0.01 (-0.09	37	0.89 (0.57, 1.40)	44
·	· ·	wheeze				0.08)			
RD: risk differe	ence; CI: confidence interval; NA:	not applicable/e	estimable:	no.: number:	Peto OR: Peto	odds ratio: vs.: Rers	us		
	,		•			, ø			
						on /			
						⊅ pri			
						117			
						, 20			
						24			
						by (
						gue			
						9 .			
						rot			
						ecte			
						9d			
						ر ک			
						ору			
						ri. Shini	olement	5 - Page 7 of 14	
						iπη	t	5 1 46c 7 01 1 4	
	For neer re	eview only - http://	/bmiopen l	omi.com/site/a	about/auidelines	s.xhtml			

1136/bmjopen-201

					BMJ Open		i i sazurii juperi-zo io	100 (Fac: 100)	Pag	e 148 of 2
	Supplement 5c. CN	S & behavior effects)	,	
	Adverse event	Comparison 1 vs. Comparison 2	Subgroup	No. of studies	Comparison 1 – no. of patients with	Comparison 2 – no. of patients with	(95% CI)	I ² (%)	Peto OR (95% CI)	I ² (%)
0 1 2		<i>(</i>			events/total no. of patients	events/total no. of patients	August 2019.	5		
4	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
5	remor/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
8 9		Systemic vs. placebo	Multi-dose	3	13/476	7/452	0.01 (-0.01, 0.03)	0	1.65 (0.67, 4.02)	0
11	Fremor/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
3			Bronchiolitis	3	10/470	6/447	0.01 (-0.01, 0.03)	0	1.66 (0.62, 4.46)	0
4			Wheeze	1	3/52	1/28	0.02 (-0.07, 0.12)	NA	1.58 (0.19, 12.83)	NA
5 7 6	Fremor/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
8 E	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
0 1 2	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
3 4		Systemic vs. placebo	Multi-dose	2	6/165	2/145	0.02 (-0.02, 0.06) g	-	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
/ 8 9		Systemic vs. placebo	Wheeze	2	6/165	2/145	0.02 (-0.02, 0.06) वि	11	2.32 (0.56, 9.64)	0
0 [Behaviour change, overall	Inhaled vs. placebo		3	6/134	7/135	-0.01 (-0.04, 0.03)	0	0.81 (0.26, 2.54)	0

1
2
3
4
5

2	
3	
4	
5	
6	
7	
8	
9	
1	0
1	1
1	2
1	
1	
1	5
1	6
1	7
	8
	9
	0
2	1
	2
	3
2	4

23
24
25
26
27
28
29
30
31
32
33
34
35
36

}	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
ŀ ;		Inhaled vs. placebo	Multi-dose	2	6/70	6/67	0.02 (-0.06, 0.10)	0	0.95 (0.28, 3.15)	11
5	Behaviour change, by	Inhaled vs. placebo	Asthma	1	1/28	0/27	0.04 (-0.06, 0.13)	1 NA	7.13 (0.14, 359.55)	NA
7	condition							on 1		
3		Inhaled vs. placebo	Croup	2	5/106	7/108	-0.02 (-0.05, 0.02)	<u></u> 0	0.66 (0.20, 2.18)	0
0	Behaviour change, overall	Dexamethasone	All single	2	35/60	38/57	-0.08 (-0.25, 0.09)	o	0.73 (0.34, 1.56)	0
1		vs. other steroid	dose					t 20		
2	Behaviour change, by	Dexamethasone	Asthma	1	10/14	14/16	-0.16 (-0.45, 0.13)	19. NA	0.38 (0.06, 2.21)	NA
3	condition	vs. other steroid						Dov		
4 5		Dexamethasone	Croup	1	25/46	24/41	-0.04 (-0.25, 0.17)) NA	0.85 (0.36, 1.97)	NA
6		vs. other steroid						ade		
7	Headache, overall	Systemic vs.	Single dose,	1	0/37	1/33	-0.02 (-0.10, 0.07)	d fr 0	0.11 (0.00, 5.68)	NA
8		placebo	asthma					m		
9	Headache, overall	Dexamethasone	All single	2	7/102	4/95	0.02 (-0.08, 0.11)	5 1	1.63 (0.46, 5.74)	NA
21		vs. other steroid	dose					//bn		
2	Headache, by condition	Dexamethasone	Asthma	1	0/56	0/54	0.00 (-0.03, 0.03)	형 NA	NA	NA
23		vs. other steroid						en.		
4			Croup	1	7/46	4/41	0.05 (-0.08, 0.19)	<u>ă</u> NA	1.63 (0.46, 5.74)	NA
25 26	RD: risk difference;	CI: confidence interva	ıl; NA: not applic	cable/estin	nable; no.: num	ber; Peto OR: P	eto odds ratio; vs.:	gersus		
27								or or		
8								Αp		
9								<u>→</u>		
1								7, 2		
2								024		
3								by		
4								gue		
5								st. F		
7								rot		
8								ecte	ent 5 - Page 9 of 14	
9								ğ. Ö		
.0 .1								у Со		
2								Ďугі.		
3								Suppleme	ent 5 - Page 9 of 14	
4		For	peer review only	http://bm	ionon hmi com/	sito/about/auida	lings whem!			
.5		FOr	peer review only	- umb://pm	Jopen.billJ.com/s	site/about/gulde	HITCS.XIIUIII			

				BMJ Open		1136/bm	Page 150		
Supplement 5d. De	ermatologic conditions					1136/bmjopen-2018-028511 on RD (95% CI)			
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	1 August 2019.	l ² (%)	Peto OR (95% CI)	l ² (%)
Burn, overall	Inhaled vs. placebo	Single dose, croup	1	0/27	1/27	-0.04 (-0.13, 0.06P	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, 0.018	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 applic	cable/estim	able; no.: numl	per; Peto OR: Pe	otected by copyri		nt 5 - Page 10 of 14	

Supplement 5e. Endocrine/metabolic & musculoskeletal systems

Adverse event	Comparison 1	Subgroup	No.	Comparison	Comparison	285 RD	l ²	Peto OR	l ²
6	vs.		of	1 – no. of	2 – no. of	(95% CI) =	(%)	(95% CI)	(%)
7	Comparison 2		studies	patients	patients	on 1			
8				with	with	Au			
9				events/total	events/total	snbn			
1 1				no. of	no. of	it 20			
1 <u>2</u>				patients	patients	19.			
13 Fluid & electrolyte	Systemic vs. placebo		4	5/832	1/818	0.00 (0.00, 0.01)	0	3.08 (0.60, 15.94)	0
1 abnormalities, overall						vnlo			
Fluid & electrolyte	Systemic vs. placebo	Single dose	1	1/359	0/361	0.00 (0.00, 0.01)	NA	7.43 (0.15, 374.47)	NA
$\frac{1}{17}$ abnormalities, by dose						ed fr			
18	Systemic vs. placebo	Multi-dose	3	4/473	1/457	0.00 (-0.01, 0.0)	0	2.56 (0.42, 15.61)	0
¹⁹ Fluid & electrolyte	Systemic vs. placebo	Bronchiolitis	2	4/448	1/432	0.00 (-0.01, 0.03)	0	2.56 (0.42, 15.61)	0
$\frac{20}{3}$ abnormalities, by condition)://b			
22	Systemic vs. placebo	Croup	2	1/384	0/386	0.00 (0.00, 0.0🕏	0	7.43 (0.15, 374.47)	NA
23 Fluid & electrolyte	Dexamethasone vs.	Multi-dose,	1	1/33	2/15	-0.10 (-0.28, 0.98)	NA	0.18 (0.01, 2.17)	NA
²⁴ abnormalities, overall	other steroid	bronchiolitis				.bmj			
Adrenal suppression, overall	Inhaled vs. placebo	Multi-dose,	1	5/6	4/10	0.43 (0.01, 0.86)	NA	5.21 (0.72, 37.57)	NA
20 27		asthma				m/ o			

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 for no. of patients	Difference	l 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

No.

of

studies

1

3

1

2

Comparison

1 - no. of

patients

with

events/total

no. of

patients

0/31

0/29

0/56

1/727

0/305

1/422

0/15

0/25

Comparison

2 - no. of

patients

with

events/total

no. of

patients

0/27

0/27

0/54

1/714

0/295

1/419

0/17

0/25

(%)

NA

NA

NA

50

NA

50

NA

NA

Peto OR

(95% CI)

2 3

Supplement 5f. Cardiovascular system

Comparison 1

vs.

Comparison 2

Systemic vs. placebo

Inhaled vs. placebo

Dexamethasone vs.

Systemic vs. placebo

Systemic vs. placebo

Systemic vs. placebo

Dexamethasone vs.

Systemic vs. placebo

other steroid

other steroid

Subgroup

Multi-dose,

Multi-dose,

Multi-dose,

bronchiolitis

Single dose

Multi-dose

Single dose,

Multi-dose,

asthma

croup

wheeze

wheeze

asthma

ΑII

Adverse event

9 10 11 13 Arrhythmia, overall 14 Arrhythmia, overall Arrhythmia, overall Hypertension, overall 21 Hypertension, by dose 24 Hypertension, overall 26 27 Congestive heart failure, 29 overall

> 46 47

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

1136/bmjopen-2018-0<mark>28511 on 1 August 2019</mark>

(%)

NA

1.00 (0.06, 15.99)

1.00 (0.06, 15.99)

RD

(95% CI)

0.00 (-0.07, 0.0割

0.00 (-0.07, 0.0割

0.00 (-0.03, 0.03)

0.00 (-0.01, 0.03)

0.00 (-0.01, 0.01)

0.00 (-0.01, 0.03)

0.00 (-0.11, 0.12)

0.00 (-0.07, 0.07)

Supplement 5g. General adverse events/ other symptoms

5	Adverse event	Comparison 1	Subgroup	No. of	Comparison	Comparison	RD ²⁸ (95% CI I ²	l² (%)	Peto OR (95% CI)	2 (9/)
5		vs. Comparison 2		studies	1 – no. of patients	2 – no. of patients	(95% CI P	(%)	(95% CI)	(%)
8		Companison 2		studies	with	with	1 1 1			
9					events/total	events/total	∖ugı			
10					no. of	no. of	ıst 2			
11 12					patients	patients	2019.			
13	General complaints ¹ , overall	Systemic vs. placebo	All	2	38/446	38/423	0.00 (-0.04, 0,04)	0	1.00 (0.62, 1.60)	0
14			bronchiolitis				wnlo			
15 16	General complaints, by dose	Systemic vs. placebo	Single dose	1	0/46	0/23	0.00 (-0.09, (209)	0	NA	NA
17		Systemic vs. placebo	Multi-dose	1	38/400	38/400	0.00 (-0.04, 0,04)	0	1.00 (0.62, 1.60)	0
18	General complaints ² , overall	Dexamethasone vs.		2	3/102	3/95	-0.01 (-0.06, \$\frac{1}{9}.03)	0	0.90 (0.18, 4.61)	11
19		other steroid					http			
20 21	General complaints, by	Dexamethasone vs.	Asthma	1	0/56	1/54	-0.02 (-0.07, 3.03)	NA	0.13 (0.00, 6.58)	NA
22	condition	other steroid		′ (mjop			
23		Dexamethasone vs.	Croup	1	3/46	2/41	0.01 (-0.08, 👺11)	NA	1.29 (0.21, 7.81)	NA
24		other steroid			10.		.bmj			

¹Two studies reported pallor
²One 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.: gersus

		1136/bmjopen-2018-		Pa	age 154 of 234						
Supplement 5h. Immu	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	0285 T on 1 August 2019. (95% CT)	l ² (%)	Peto OR (95% CI)	l ² (%)		
Immunosuppression, overall	Systemic vs. placebo confidence interval; NA:		1	0/47	0/48	0.00 (-0.04, 👰 04)	NA	NA	NA		
		view only - http:/					ent 5 -	Page 14 of 14			

ipplement 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
	f. Cardiovascular system	p. 59
	Dexamethasone vs. Other steroid	
	a. Gastro-intestinal tract	p. 60-63
	b. CNS & behaviour effects	p. 64-66
	c. Dermatologic conditions	p. 67
	d. Endocrine/ metabolic & musculoskeletal systems	p. 68
	e. Cardiovascular system	p. 69
	f. General adverse events/ other symptoms	p. 70-71
	f. General adverse events/ other symptoms	

SYSTEMIC vs. PLACEBO - Infection & Respiratory

Severe infections

Systemic		mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² = 0.00	$; Chi^2 = 0.$.75, df=		-0.2 -0.1 0 0.1 0.2			
Test for overall effect: Z = 0).64 (P = 0	0.52)					Favours systemic Favours placebo

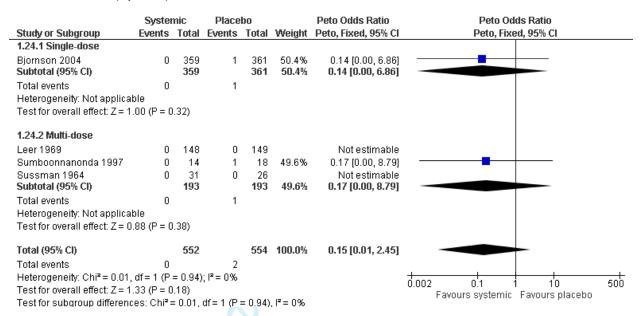
Severe infections – Peto

	Syster	mic	Place	bo		Peto Odds Ratio		Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixe	ed, 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: Chi ² = 0.01	df=1 (P	= 0.94)	; I² = 0%				0.004		<u> </u>	4000
Test for overall effect: Z = 1	.33 (P = 0).18)					0.001	0.1 Favours systemic	1 10 Favours placebo	1000

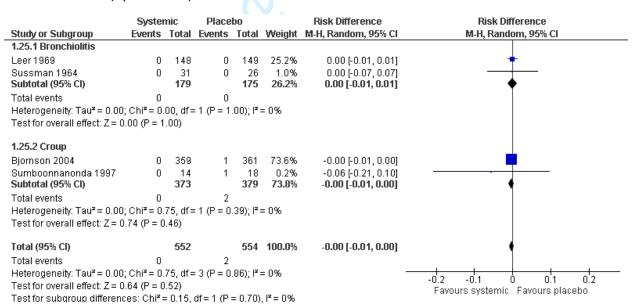
Severe infections (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 applical	ble						
Test for overall effect: Z = 0	.71 (P = 0	1.48)					
1.23.2 Multi-dose							
Leer 1969	0	148	0	149	25.2%	0.00 [-0.01, 0.01]	+
Sumboonnanonda 1997	0	14	1	18	0.2%	-0.06 [-0.21, 0.10]	
Sussman 1964	0	31	0	26	1.0%	0.00 [-0.07, 0.07]	-
Subtotal (95% CI)		193		193	26.4%	-0.00 [-0.01, 0.01]	•
Total events	0		1				
Heterogeneity: Tau ^z = 0.00;	$Chi^2 = 0.$	92, df=	= 2 (P = 0)	.63); l²:	= 0%		
Test for overall effect: Z = 0	.06 (P = 0	1.95)					
Total (95% CI)		552		554	100.0%	-0.00 [-0.01, 0.00]	•
Total events	0		2				
Heterogeneity: Tau ² = 0.00;	$Chi^2 = 0.$	75, df=	3 (P = 0)	.86); l²:	= 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z = 0	.64 (P = 0)	1.52)					-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo
Test for subgroup differenc	es: Chi ^z :	= 0.10,	df=1 (P:	= 0.76)	$I^2 = 0\%$		i avouro oyotennic i Favouro piacebo

Severe infections (by dose) – Peto



Severe infections (by condition)



Severe infections (by condition) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 applica	able						
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: Chi ² = 0.01	, df = 1 (P	= 0.94)); I² = 0%				
Test for overall effect: Z = 1	1.33 (P = 0	1.18)					
Total (95% CI)		552		554	100.0%	0.15 [0.01, 2.45]	
Total events	0		2				
Heterogeneity: Chi ² = 0.01	, df = 1 (P	= 0.94)); I² = 0%				0.005 0.1 1 10 200
Test for overall effect: Z = 1	1.33 (P = 0	1.18)					Favours systemic Favours placebo
Test for subgroup differen	ces: Not a	pplicat	ole				i avoui o systeinit. Favoui o piacebo

Systemic infections

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Ch	$i^2 = 0.2$	1, df = 4 (P = 1.0	$0); I^2 = 09$	₆ –	1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
Test for overall effect	Z= 0.10	(P = 0.9)	32)	-			-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo

Systemic infections – Peto

	Syster	nic	Place	bo		Peto Odds Ratio		Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl		Peto, Fixe	d, 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 ap	plicable						0.05	n'2 1	 	20
Test for overall effect:	Z = 0.34	(P = 0.7)	'3)				0.05	Favours systemic	Favours placebo	20

Systemic infections (by dose)

	Syster	nic	Place	Placebo		Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Ch	$i^2 = 0.2$	4, df = 1 (P = 0.6	i2); I² = 09	6			
Test for overall effect:	Z = 0.13	(P = 0.9)	30)						
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: Tau ^z =	0.00; Ch	$i^2 = 0.0$	0, df = 2 (P = 1.0	$ 0\rangle; ^2 = 09$	6			
Test for overall effect:	Z = 0.00	(P = 1.0)	00)						
Total (95% CI)		1095		1083	100.0%	0.00 [-0.00, 0.00]	•		
Total events	5		4						
Heterogeneity: Tau² =	0.00; Ch	i² = 0.2	1, df = 4 (P = 1.0	6 -	-0.1 -0.05 0 0.05 0.1			
Test for overall effect:	Z = 0.10	(P = 0.9)	92)				-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo		
Test for subaroup diff	i avouro systemmo i ravouro pracebo								

Systemic infections (by dose) – Peto

•		-					
	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap	plicable						
Test for overall effect:	Z = 0.34	(P = 0.7)	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 ap	plicable						
Test for overall effect:	Not appli	cable					
Total (95% CI)		1095		1083	100.0%	1.26 [0.34, 4.68]	
, ,	_	1095		1003	100.0%	1.20 [0.34, 4.06]	
Total events	5		4				
Heterogeneity: Not ap		a .	100		0.1 0.2 0.5 1 2 5 10		
Test for overall effect:			•				Favours systemic Favours placebo
Test for subgroup diff	rerences:	Not ap	plicable				

Systemic infections (by condition)

	Syster	nic	Placebo		Risk Difference		Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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]	<u>†</u>
Subtotal (95% CI)		705		695	91.7%	0.00 [-0.00, 0.00]	†
Total events	0		0				
Heterogeneity: Tau² =				P = 1.0	$0); I^2 = 09$	6	
Test for overall effect: .	Z = 0.00	(P = 1.0)	00)				
1.31.2 Croup							
Biornson 2004	5	359	4	361	7.8%	0.00 [-0.01, 0.02]	+
Subtotal (95% CI)		359		361	7.8%	0.00 [-0.01, 0.02]	*
Total events	5		4				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.34	(P = 0.7)	'3)				
1.31.3 Wheeze							
Daugbjerg 1993	0	31	0	27	0.5%	0.00 [-0.07, 0.07]	
Subtotal (95% CI)		31		27	0.5%	0.00 [-0.07, 0.07]	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.00	(P = 1.0)	00)				
Total (95% CI)		1095		1083	100.0%	0.00 [-0.00, 0.00]	•
Total events	5		4				
Heterogeneity: Tau ² =	0.00; Ch	i² = 0.2	1, df = 4 (P = 1.0	$0); I^2 = 09$	6	-0.1 -0.05 0 0.05 0.1
Test for overall effect: .	Z = 0.10	(P = 0.9)	92)	-			-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo
Test for subaroup diffe	erences:	Chi²=	0.11, df=	2 (P =	0.95), l ² =	: 0%	ravours systemic ravours pracedo

Systemic infections (by condition) – Peto

		Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
	Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
-	1.32.1 Bronchiolitis							
	Corneli 2007	0	305	0	295		Not estimable	
	Plint 2009	0	200	0	199		Not estimable	
	Plint 2009	0	200	0	201		Not estimable	
	Subtotal (95% CI)		705		695		Not estimable	
	Total events	0		0				
	Heterogeneity: Not ap							
	Test for overall effect:	Not appli	cable					
	1.32.2 Croup							
	Bjornson 2004	5	359	4	361	100.0%	1.26 [0.34, 4.68]	
	Subtotal (95% CI)	3	359	4	361	100.0%	1.26 [0.34, 4.68]	
	Total events	5	000	4		1001070	1120 [010 1, 1100]	
	Heterogeneity: Not ap	-		4				
	Test for overall effect:		(P = 0.7	'3)				
	TOOLIOT OFFICIAL CHOOLS	2 - 0.04	(i — 0.1	٥,				
	1.32.3 Wheeze							
	Daugbjerg 1993	0	31	0	27		Not estimable	
	Subtotal (95% CI)		31		27		Not estimable	
	Total events	0		0				
	Heterogeneity: Not ap	plicable						
	Test for overall effect:	Not appli	cable					
	Total (95% CI)		1095		1083	100.0%	1.26 [0.34, 4.68]	
	Total events	5		4				
	Heterogeneity: Not ap	_		7				
	Test for overall effect:		(P = 0.7	'3)				0.1_0.2 0.5 1 2 5 10
	Test for subgroup diffe		•					Favours systemic Favours placebo

Supplement 6 - Page 6 of 71

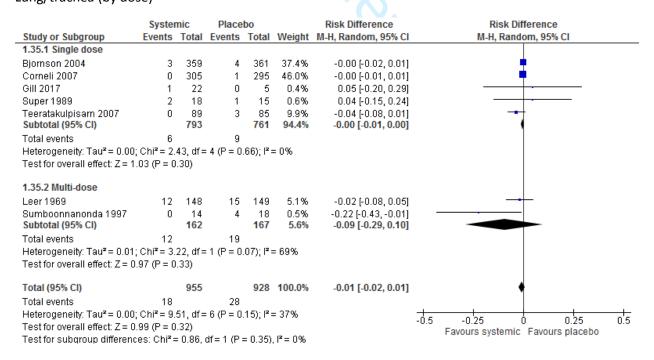
Lung/trachea

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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: Tau ² = 0.00	i; Chi² = 9.	51, df=	6 (P = 0.	.15); l²:	= 37%		-0.5 -0.25 0 0.25 0.5
Test for overall effect: Z = 0).99 (P = 0	.32)					-0.5 -0.25 0 0.25 0.5 Favours systemic Favours placebo

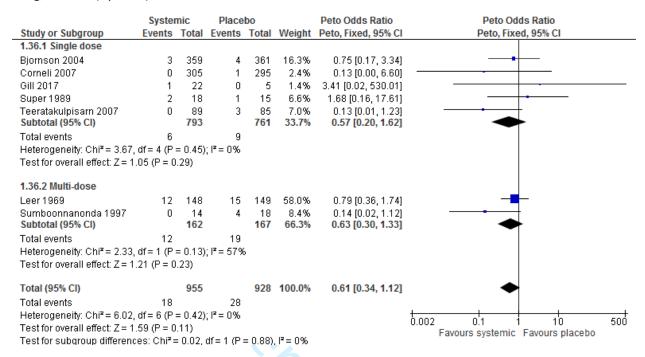
Lung/trachea – Peto

	Syster	mic	Place	bo		Peto Odds Ratio		Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI	
Bjornson 2004	3	359	4	361	16.3%	0.75 [0.17, 3.34]			
Corneli 2007	0	305	1	295	2.4%	0.13 [0.00, 6.60]	←		
Gill 2017	1	22	0	5	1.4%	3.41 [0.02, 530.01]	-		→
Leer 1969	12	148	15	149	58.0%	0.79 [0.36, 1.74]			
Sumboonnanonda 1997	0	14	4	18	8.4%	0.14 [0.02, 1.12]	_	-	
Super 1989	2	18	1	15	6.6%	1.68 [0.16, 17.61]			
Teeratakulpisarn 2007	0	89	3	85	7.0%	0.13 [0.01, 1.23]		•	
Total (95% CI)		955		928	100.0%	0.61 [0.34, 1.12]		•	
Total events	18		28						
Heterogeneity: Chi ² = 6.02	df = 6 (P	= 0.42)	; I² = 0%				+	- 1 10	400
Test for overall effect: $Z = 1$.59 (P = 0	.11)					0.01	0.1 1 10 Favours systemic Favours placebo	100

Lung/trachea (by dose)



Lung/trachea (by dose) - Peto



Lung/trachea (by condition)

	Syster	mic	Place	bo		Risk Difference	Risk Difference			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² = 0.00; Chi ² = 5.18, df = 2 (P = 0.07); i ² = 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;	Chi ² = 5.	01, df=	3 (P = 0	.17); l³ :	= 40%					
Test for overall effect: $Z = 0$			•							
	·									
Total (95% CI)		955		928	100.0%	-0.01 [-0.02, 0.01]	. ♦			
Total events	18		28							
Heterogeneity: Tau ² = 0.00;	Chi ² = 9.	51, df=	6 (P = 0	.15); l³ :	= 37%		-0.5 -0.25 0 0.25 0.5			
Test for overall effect: $Z = 0$			•							
Test for subgroup difference	•		df = 1 (P :	= 0.91)	. I² = 0%		Favours systemic Favours placebo			
	Total and and an									

Lung/trachea (by condition) – Peto

	Syster	mic	Place	Placebo Peto Odds R		Peto Odds Ratio	Peto Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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,	Heterogeneity: Chi ^z = 2.84, df = 2 (P = 0.24); i ^z = 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: Chi ² = 3.18,	df = 3 (P	= 0.37)	$ 1^2 = 6\% $							
Test for overall effect: $Z = 0$.	.91 (P = 0	.36)								
Total (95% CI)		955		928	100.0%	0.61 [0.34, 1.12]	•			
Total events	18		28							
Heterogeneity: Chi²= 6.02, df= 6 (P = 0.42); I²= 0% 0.002 0.1 10 500										
Test for overall effect: Z = 1.59 (P = 0.11) Favours systemic Favours placebo										
Test for subgroup differences: Chi²= 0.00, df=1 (P=1.00), l²= 0%										

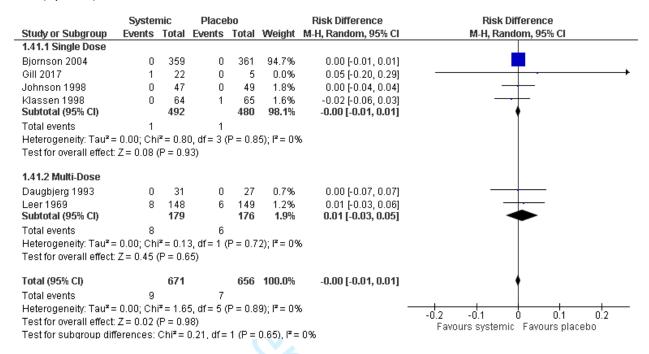
URT

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 = Test for overall effect				P = 0.8	9); I² = 09	%	-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

URT - Peto

	Systemic Place		ebo		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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]	<u> </u>
Leer 1969	8	148	6	149	89.3%	1.36 [0.47, 3.96]	-
Total (95% CI)		671		656	100.0%	1.21 [0.44, 3.33]	•
Total events	9		7				
Heterogeneity: Chi ^z =	1.39, df=	2 (P =	0.50); l ^z :	0.001 0.1 1 10 1000			
Test for overall effect:	Z= 0.37	(P = 0.7)	1)				Favours systemic Favours placebo

URT (by dose)



URT (by dose) – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
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);	= 0%			
Test for overall effect:	Z = 0.49	(P = 0.6)	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 ap	plicable						
Test for overall effect:	Z = 0.56	(P = 0.6)	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); l² =	= 0%			0.002 0.1 1 10 500
Test for overall effect:	Z = 0.37	(P = 0.7)	71)				Favours systemic Favours placebo
Test for subgroup diff	ferences:	Chi²=	0.42, df=	1 (P=	0.52), l²=	: 0%	r avours systemme - Favours praceso

URT (by condition)

Ct. t C. t	Syster		Place		184-1-14	Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	rotai	vveignt	M-H, Random, 95% CI	M-H, Random, 95% CI
1.43.1 Bronchiolitis		440		4.40	4.00/	0.04 (0.00 0.00)	
Leer 1969 Subtotal (95% CI)	8	148 148	6	149 149	1.2% 1.2 %	0.01 [-0.03, 0.06] 0.01 [-0.03, 0.06]	
		140		149	1.270	0.01 [-0.03, 0.00]	
Total events	8 aldaaila		6				
Heterogeneity: Not ap Test for overall effect:		/D = 0.4	:0\				
restror overall ellect.	Z= 0.50 ((F = 0.0	10)				
1.43.2 Croup							
Bjornson 2004	0	359	0	361	94.7%	0.00 [-0.01, 0.01]	
Gill 2017	1	22	Ö	5	0.0%	0.05 [-0.20, 0.29]	
Johnson 1998	Ċ	47	0	49	1.8%	0.00 [-0.04, 0.04]	
Klassen 1998	Ö	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 =		i²= 0.8	0. df = 3 (P = 0.8	5): I² = 09	6	
Test for overall effect:					-,,		
			,				
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 ap							
Test for overall effect:	Z = 0.00	(P = 1.0)0)				
Total (95% CI)		671		656	100.0%	-0.00 [-0.01, 0.01]	•
Total events	9		7				
Heterogeneity: Tau²=	_	i² = 1 6		P = 0.8	9): P= 09	γ ₀	
Test for overall effect:					0,,. 0,	*	-0.2 -0.1 0 0.1 0.2
Test for subgroup diff		•		2 (P =	0.85), l ² =	: 0%	Favours systemic Favours placebo
			,				
						: 0%	

URT (by condition) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
1.44.1 Bronchiolitis							<u>_</u>
Leer 1969 Subtotal (95% CI)	8	148 148	6	149 149	89.3% 89.3 %	1.36 [0.47, 3.96] 1.36 [0.47, 3.96]	-
Total events	8		6				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.56 ((P = 0.5)	58)				
1.44.2 Croup	_		_				
Bjornson 2004	0	359	0	361		Not estimable	
Gill 2017	1	22	0	5	4.0%	3.41 [0.02, 530.01]	-
Johnson 1998	0	47	0	49	0.70	Not estimable	
Klassen 1998 Subtotal (95% CI)	0	64 492	1	65 480	6.7% 10.7 %	0.14 [0.00, 6.93] 0.46 [0.02, 10.18]	
Total events	- 1	432	- 1	400	10.7 /8	0.40 [0.02, 10.10]	
Heterogeneity: Chi ^z =	0 07 df=	1 /P =	n 22\-i≥-	- 0%			
Test for overall effect:	•	,		- 0 70			
restror overall effect.	2-0.43	, - 0.0	,2,				
1.44.3 Wheeze							
Daugbjerg 1993	0	31	0	27		Not estimable	
Subtotal (95% CI)		31		27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Not appli	cable					
Total (95% CI)		671		656	100.0%	1.21 [0.44, 3.33]	_
Total events	9	071	7	030	100.078	1.21 [0.44, 5.55]	
Heterogeneity: Chi ² =	_	2/0-	'	- 006			
Test for overall effect:		•		- 070			0.002 0.1 1 10 500
Test for subgroup diffi		•		1 (P -	0.62) 12-	n%.	Favours systemic Favours placebo
restror sundroub ann	erences.	CIII —	0.42, ui –	1 (1 -	0.52), 1 -	0.20	

Voice complaints

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ap	•	(D. 4.)	200				-0.2 -0.1 0 0.1 0.2
Test for overall effect:	∠= 0.00	(P = 1.0	10)				Favours systemic Favours placebo

Voice complaints – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Daugbjerg 1993	0	31	0	27		Not estimable	
Total (95% CI)		31		27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap Test for overall effect:	•	cable					0.1 0.2 0.5 2 5 10 Favours systemic Favours placebo

SYSTEMIC vs. PLACEBO - GI

GI bleeding

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 = 0.0	0; Chi²=	1.20, d	f= 7 (P=	0.99);	P= 0%	+	5 -0.25 0 0.25 0.5
Test for overall effect: Z=	0.04 (P =	0.97)				-U.	Favours systemic Favours placebo

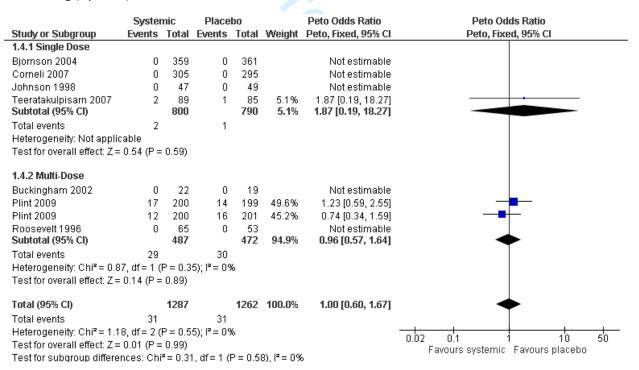
GI bleeding – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% 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: Chi ² = 1.1	8, df = 2 (P = 0.5	5); $I^2 = 0.9$	%			0.05 0.2 1 5 20
Test for overall effect: Z=	0.01 (P =	0.99)					Favours systemic Favours placebo
							r avours systemme in avours pracess

GI bleeding (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 Subtotal (95% CI)	2	89 800	1	85 790	1.1% 97.0 %	0.01 [-0.03, 0.05] 0.00 [-0.00, 0.00]	
Total events	2		1				
Heterogeneity: Tau ² = 0.0	_	0.54. d	f=3(P=	0.91):	l² = 0%		
Test for overall effect: Z=	•			,			
1.3.2 Multi-Dose							
				4.0	0.000	0.001.000.000	
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: Tau ² = 0.0			f=3 (P=	0.83);	l ² = 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: Tau ² = 0.0	00; Chi²=	1.20, d	f= 7 (P=	0.99);	l² = 0%	_	1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
Test for overall effect: Z=	0.04 (P =	0.97)	•				-0.1 -0.05 0 0.05 0.1
Test for subgroup differe	nces: Chi	$^{2} = 0.03$	2, df = 1 (P = 0.9	$0), I^2 = 09$	6	Favours systemic Favours placebo

GI bleeding (by dose) - Peto



GI bleeding (by condition)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.5.1 Bronchiolitis							
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]	•
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]	
Subtotal (95% CI)		881		852	43.0%	0.00 [-0.01, 0.01]	•
Total events	31		31				
Heterogeneity: Tau² = 0.0	00; Chi²=	1.20, d	f= 5 (P =	0.95);	I²=0%		
Test for overall effect: Z =	: 0.06 (P =	0.95)					
4500							
1.5.2 Croup							<u>_</u>
Bjornson 2004	0	359	0	361	56.0%	0.00 [-0.01, 0.01]	<u> </u>
Johnson 1998	0	47	0	49	1.0%	0.00 [-0.04, 0.04]	
Subtotal (95% CI)		406		410	57.0%	0.00 [-0.01, 0.01]	†
Total events	0		0				
Heterogeneity: Tau² = 0.0	•		f=1 (P=	1.00);	I²=0%		
Test for overall effect: Z =	: 0.00 (P =	1.00)					
Total (95% CI)		1287		1262	100.0%	0.00 [-0.00, 0.00]	•
Total events	31		31				
Heterogeneity: Tau ² = 0.0	00; Chi²=	1.20, d	f=7 (P=	0.99);	l² = 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z=	•		`				
Test for subgroup differe	nces: Chi	= 0.00	0, df = 1 (l	P = 0.9	7), $I^2 = 0.9$	6	Favours systemic Favours placebo

GI bleeding (by condition) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
1.6.1 Bronchiolitis							
Buckingham 2002	0	22	0	19		Not estimable	
Corneli 2007	0	305	0	295		Not estimable	
Plint 2009	17	200	14	199	49.6%	1.23 [0.59, 2.55]	-
Plint 2009	12	200	16	201	45.2%	0.74 [0.34, 1.59]	
Roosevelt 1996	0	65	0	53		Not estimable	
Teeratakulpisarn 2007 Subtotal (95% CI)	2	89 881	1	85 852	5.1% 100.0%	1.87 [0.19, 18.27] 1.00 [0.60, 1.67]	
Total events	31	001	31	032	100.070	1.00 [0.00, 1.07]	
Heterogeneity: Chi ² = 1.1		0 - 0 6		v.			
Test for overall effect: Z=			0),1 - 01	ю.			
restion overall effect. Z =	0.01 (F =	0.55)					
1.6.2 Croup							
Bjornson 2004	0	359	0	361		Not estimable	
Johnson 1998	0	47	0	49		Not estimable	
Subtotal (95% CI)		406		410		Not estimable	
Total events	0		0				
Heterogeneity: Not applic	able						
Test for overall effect: No	t applicab	le					
							1
Total (95% CI)		1287		1262	100.0%	1.00 [0.60, 1.67]	•
Total events	31		31				
Heterogeneity: Chi² = 1.1	8, df = 2 (P = 0.5	5); I² = 09	%			0.05 0.2 1 5 20
Test for overall effect: Z=	0.01 (P =	0.99)					Favours systemic Favours placebo
Test for subgroup differe	nces: Not	applic	able				r areard dysterrite in around processo

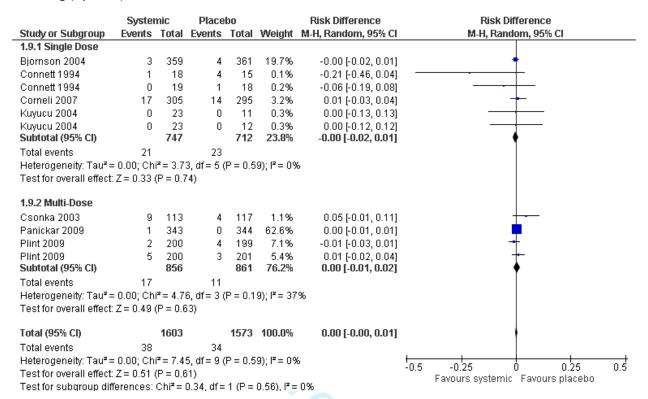
Vomiting

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Ch	$i^2 = 7.4$	5, df = 9 (P = 0.5	9); I² = 09	6 -	
Test for overall effect:	Z = 0.51	(P = 0.6)	31)				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo
							i avodio oyoteiiiic i avodio piacebo

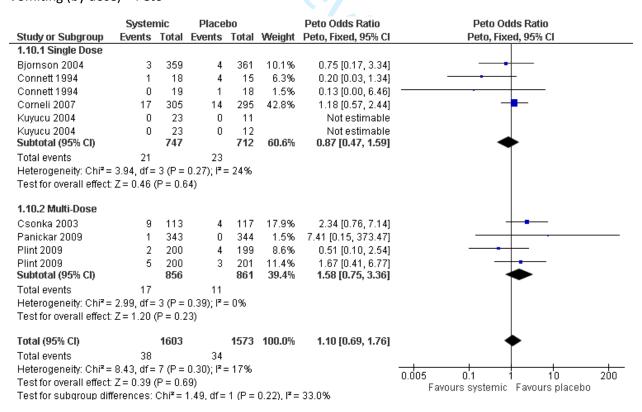
Vomiting – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% 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				

Vomiting (by dose)



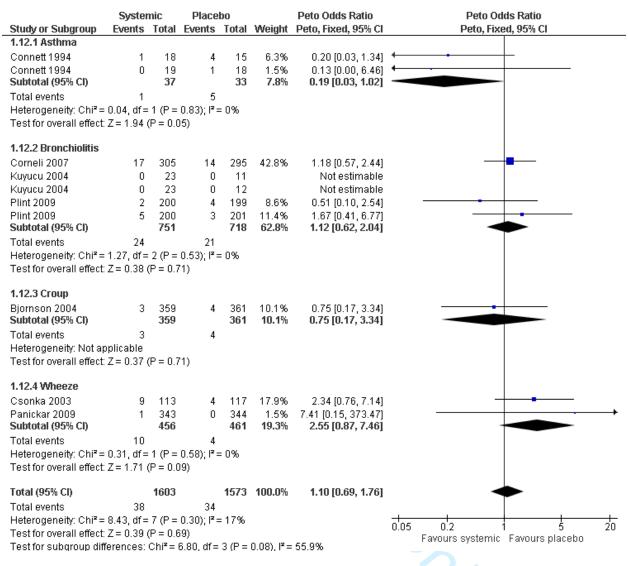
Vomiting (by dose) - Peto



Vomiting (by condition)

	Systen		Place			Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% CI
1.11.1 Asthma							
Connett 1994	1	18	4	15	0.1%	-0.21 [-0.46, 0.04]	-
Connett 1994	0	19	1	18	0.2%	-0.06 [-0.19, 0.08]	
Subtotal (95% CI)		37		33	0.3%	-0.11 [-0.27, 0.06]	
Total events	1		5				
Heterogeneity: Tau² =	0.01; Chi	z = 1.48	8, df = 1 (P = 0.2	2); $I^2 = 33$	1%	
Test for overall effect:	Z = 1.28 (P = 0.2	20)				
1.11.2 Bronchiolitis							
Corneli 2007	17	305	14	295	3.2%	0.01 [-0.03, 0.04]	<u>†</u>
Kuyucu 2004	0	23	0	11	0.3%	0.00 [-0.13, 0.13]	
Kuyucu 2004	0	23	0	12	0.3%	0.00 [-0.12, 0.12]	
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]	<u>†</u>
Subtotal (95% CI)		751		718	16.3%	0.00 [-0.02, 0.02]	†
Total events	24		21				
Heterogeneity: Tau² =				P = 0.8	2); $I^2 = 09$	6	
Test for overall effect:	Z = 0.07 (P = 0.9	34)				
1.11.3 Croup							
Biornson 2004	2	250		204	19.7%	0.001.000.0041	1
Subtotal (95% CI)	3	359 359	4	361 361	19.7%	-0.00 [-0.02, 0.01] - 0.00 [-0.02, 0.01]	I .
	3	333	4	301	15.17.10	-0.00 [-0.02, 0.0 1]	Ĭ
Total events Heterogeneity: Not ap	_		4				
Test for overall effect:	•	D = 0.7	743				
restion overall ellect.	Z-0.37 (,F = 0.7	1)				
1.11.4 Wheeze							
Csonka 2003	9	113	4	117	1.1%	0.05 [-0.01, 0.11]	
Panickar 2009	1	343	Ö	344	62.6%	0.00 [-0.01, 0.01]	<u> </u>
Subtotal (95% CI)		456	·	461	63.8%	0.02 [-0.06, 0.11]	-
Total events	10		4				
Heterogeneity: Tau ² =		2 = 7.81		P = 0.0	05): I ² = 8	17%	
Test for overall effect:					00,,. 0		
	(,				
Total (95% CI)		1603		1573	100.0%	0.00 [-0.00, 0.01]	
Total events	38		34				
Heterogeneity: Tau ^z =	0.00; Chi	$^{2} = 7.49$	5, df = 9 (P = 0.5	9); I² = 09	6	-0.5 -0.25 0 0.25 0.5
Test for overall effect:					.,		-0.5 -0.25 0 0.25 0.5
Test for subgroup diff	erences:	Chi²=	1.99, df=	3 (P =	0.58), ==	: 0%	Favours systemic Favours placebo

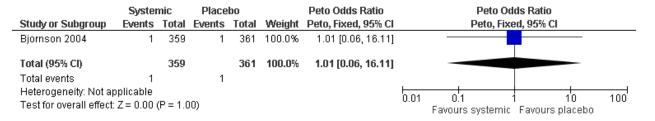
Vomiting (by condition) – Peto



Abdominal pain

	Syster	mic	Place	ho		Risk Difference		Rie	k Difference		
Study or Subgroup	Events		Events		Weight	M-H, Random, 95% CI			andom, 95%	_	
Bjornson 2004	1	359	1	361	100.0%	0.00 [-0.01, 0.01]					
Total (95% CI)		359		361	100.0%	0.00 [-0.01, 0.01]					
Total events	1		1								
Heterogeneity: Not a	•						-1	-0.5	 	0.5	
Test for overall effect	Z = 0.00	(P = 1.0)	00)				'	Favours syste	mic Favou		'

Abdominal pain - Peto



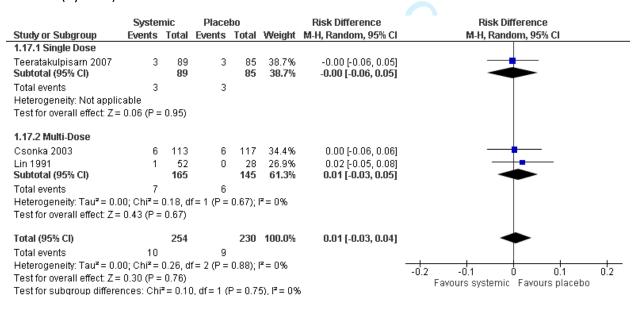
Diarrhea

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 = 0.0	00; Chi²=	0.26, d	f= 2 (P =	0.88);	l² = 0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z=	= 0.30 (P =	0.76)					Favours systemic Favours placebo

Diarrhea - Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 = 0.5	51, df = 2 (P = 0.7	7); $I^2 = 09$	6			0.005
Test for overall effect: Z =	= 0.18 (P =	0.86)					0.005 0.1 1 10 200 Favours systemic Favours placebo

Diarrhea (by dose)



Diarrhea (by dose) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
1.18.1 Single Dose							
Teeratakulpisarn 2007 Subtotal (95% CI)	3	89 89	3	85 85	32.1% 32.1 %	0.95 [0.19, 4.84] 0.95 [0.19, 4.84]	
Total events	3		3				
Heterogeneity: Not applic	cable						
Test for overall effect: Z =	0.06 (P =	0.95)					
1.18.2 Multi-Dose							
Csonka 2003	6	113	6	117	62.9%	1.04 [0.33, 3.31]	
Lin 1991	1	52	0	28	5.0%	4.66 [0.08, 283.63]	
Subtotal (95% CI)		165		145	67.9%	1.16 [0.38, 3.54]	*
Total events	7		6				
Heterogeneity: Chi² = 0.4	l8, df = 1 (P = 0.4	9); I² = 09	6			
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 = 0.5	51, df = 2 (P = 0.7	7); I² = 09	6			0.002 0.1 1 10 500
Test for overall effect: Z=	0.18 (P =	0.86)					0.002 0.1 1 10 500 Favours systemic Favours placebo
Test for subgroup differe	nces: Chi	z = 0.04	1, df = 1 (l	P = 0.8	5), I² = 0%	5	i avodio oyoteiilic T avodio piacebo

Diarrhea (by condition)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.19.1 Bronchiolitis							
Teeratakulpisarn 2007 Subtotal (95% CI)	3	89 89	3	85 85	38.7% 38.7 %	-0.00 [-0.06, 0.05] - 0.00 [-0.06, 0.05]	
Total events	3		3				
Heterogeneity: Not applic	able						
Test for overall effect: Z=	0.06 (P =	0.95)					
1.19.2 Wheeze							
Csonka 2003	6	113	6	117	34.4%	0.00 [-0.06, 0.06]	
Lin 1991	1	52	0	28	26.9%	0.02 [-0.05, 0.08]	
Subtotal (95% CI)		165		145	61.3%	0.01 [-0.03, 0.05]	-
Total events	7		6				
Heterogeneity: Tau² = 0.0	00; Chi²=	0.18, ď	f=1 (P=	0.67);	l² = 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 = 0.0	00; Chi²=	0.26, d	f= 2 (P =	0.88);	l²=0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect: Z=	0.30 (P =	0.76)					Favours systemic Favours placebo
Test for subgroup differe	nces: Chi	$^2 = 0.10$), df = 1 (l	P = 0.7	5), I² = 0%	6	

Diarrhea (by condition) – Peto

Study or Subgroup	Syster		Place!		Weinht	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
1.20.1 Bronchiolitis	LIOIRO	Total	LIOINO	Total	- I O I GIN	T Oto, Tillou, CO II OI	1 oto, i mod, o o o
Teeratakulpisarn 2007 Subtotal (95% CI)	3	89 89	3	85 85	32.1% 32.1 %	0.95 [0.19, 4.84] 0.95 [0.19, 4.84]	*
Total events	3		3				
Heterogeneity: Not applic			_				
Test for overall effect: Z=		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: Chi ² = 0.4	8. df = 1 (l	P = 0.4	9): I² = 09	6			
Test for overall effect: Z=			<i>'</i> '				
	•	,					
Total (95% CI)		254		230	100.0%	1.09 [0.43, 2.73]	*
Total events	10		9				
Heterogeneity: Chi² = 0.5	51, df = 2 (P = 0.7	7); $I^2 = 09$	6			0.002 0.1 1 10 500
Test for overall effect: Z =							Favours systemic Favours placebo
Test for subgroup differe	nces: Chi	z = 0.04	I_{i} df = 1 (F	P = 0.89	5), I² = 0%		ravouis systelliic Favouis placebo

SYSTEMIC vs. PLACEBO - CNS & Behaviour

Tremor/jitteriness

	Syster	nic	Placel	bo		Risk Difference	Risk Difference	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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]	<u></u>	
Total (95% CI)		559		508	100.0%	0.01 [-0.01, 0.03]	•	
Total events	22		14					
Heterogeneity: Tau² =	0.00; Ch	i²=1.2	3, df = 7 (P = 0.9	9); I² = 09	6	-0.5 -0.25 0 0.25 0.5	-
Test for overall effect:	Z = 1.01	(P = 0.3)	81)				Favours systemic Favours placebo	J

Tremor/jitteriness – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% 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: Chi ² =	: 1.59, df=	5 (P=	0.90);	= 0%			1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1
Test for overall effect	Z = 1.01	(P = 0.3)	31)				0.002 0.1 1 10 500 Favours systemic Favours placebo

Tremor/jitteriness (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Ch	i² = 0.1	7, df = 3 (P = 0.9	8); I² = 09	6	
Test for overall effect:	Z = 0.06	(P = 0.9)	36)				
1.49.2 Multi-Dose							
					0.70/	0041007.045	
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]	T
Subtotal (95% CI)		476		452	94.8%	0.01 [-0.01, 0.03]	*
Total events	13		7				
Heterogeneity: Tau² =				P = 0.7	'8); I² = 09	6	
Test for overall effect:	Z = 1.03	(P = 0.3)	31)				
Total (95% CI)		559		508	100.0%	0.01 [-0.01, 0.03]	•
Total events	22		14				
Heterogeneity: Tau ² =	0.00; Ch	i² = 1.2	3, df = 7 (P = 0.9	9); i² = 09	₆ —	
Test for overall effect:							-0.2 -0.1 0 0.1 0.2
Test for subgroup diff				1 (P =	0.86), l ^z =	: 0%	Favours systemic Favours placebo

Tremor/jitteriness (by dose) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
1.50.1 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);	= 0%			
Test for overall effect:	Z = 0.24	(P = 0.8)	31)				
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);	= 0%			
Test for overall effect:	Z=1.09	(P = 0.2)	27)				
Total (95% CI)		559		508	100.0%	1.44 [0.71, 2.92]	*
Total events	22		14				
Heterogeneity: Chi ² =	1.59, df=	5 (P =	0.90);	- 0%			0.005 0.1 1 10 200
Test for overall effect:	Z = 1.01	(P = 0.3)	31)				0.005 0.1 1 10 200 Favours systemic Favours placebo
Test for subgroup diff	erences:	Chi²=	0.23, df=	1 (P=	0.63), $I^2 =$: 0%	ravours systemme in ravours placebo

Tremor/jitteriness (by condition)

Study or Subgroup	Syster		Place		Moinht	Risk Difference M-H, Random, 95% Cl	Risk Difference M-H, Random, 95% Cl
1.51.1 Asthma	Events	TULAI	Events	TULAI	vveigni	W-ri, Random, 95% Ci	Wi-ri, Random, 95% Ci
	7	4.0	-	4.5	0.20	0.001.0.27.0.201	
Connett 1994	7	18	5	15	0.3%	0.06 [-0.27, 0.38]	
Connett 1994 Subtotal (95% CI)	2	19 37	2	18 33	0.8% 1.1 %	-0.01 [-0.21, 0.19] 0.01 [-0.16, 0.18]	
Total events	9		7				
Heterogeneity: Tau² =				P = 0.7	$(3); I^2 = 09$	%	
Test for overall effect:	Z = 0.12 (P = 0.9	0)				
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]	<u> </u>
Plint 2009	5	200	2	201	47.4%	0.02 [-0.01, 0.04]	+
Subtotal (95% CI)	·	470	_	447	95.4%	0.01 [-0.01, 0.03]	•
Total events	10		6				
Heterogeneity: Tau ² =		² = 1.00	-	P = 0.9	11): P= 09	%	
Test for overall effect:				. 0.0	.,,,	~	
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 ap	plicable						
Test for overall effect:	Z = 0.46 (P = 0.6	4)				
Total (95% CI)		559		508	100.0%	0.01 [-0.01, 0.03]	•
Total events	22		14				
Heterogeneity: Tau ² =	0.00; Chi	² = 1.20	3. df = 7 (P = 0.9	9); i² = 09	%	
Test for overall effect:	Z = 1.01 (P = 0.3	1)				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo
Test for subgroup diffe	erences:	Chi² = (0.08, df=	2 (P =	0.96), $I^2 =$: 0%	ravours systemme ravours pracepo
			•	-	• •		

Tremor/jitteriness (by condition) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.52.1 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); l² :	= 0%			
Test for overall effect:	Z = 0.24	(P = 0.8)	31)				
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); l² =	= 0%			
Test for overall effect:	Z=1.01	(P = 0.3)	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 ap	plicable						
Test for overall effect:	Z = 0.43	(P = 0.6)	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); l² =	= 0%			0.002 0.1 1 10 500
Test for overall effect:	Z = 1.01	(P = 0.3)	31)				Favours systemic Favours placebo
Test for subgroup diff	erences:	Chi ^z =	0.23, df=	2 (P =	0.89), $I^2 =$: 0%	i arodio oyotoiille ii arodio piacebo

Behaviour change

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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: Tau ² =	0.00; Ch	i² = 3.7	2, df = 3 (P = 0.2	$(9); I^2 = 19$	ı% —	1, 1, 1, 1, 1, 1,
Test for overall effect:					••		-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo

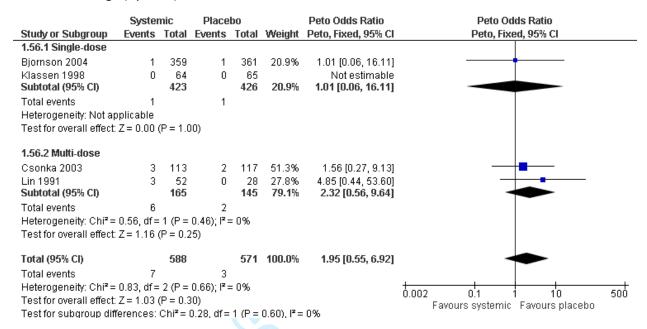
Behaviour change – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bjornson 2004	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);	= 0%			0.002 0.1 1 10 500
Test for overall effect:	Z=1.03	(P = 0.3)	30)				Favours systemic Favours placebo

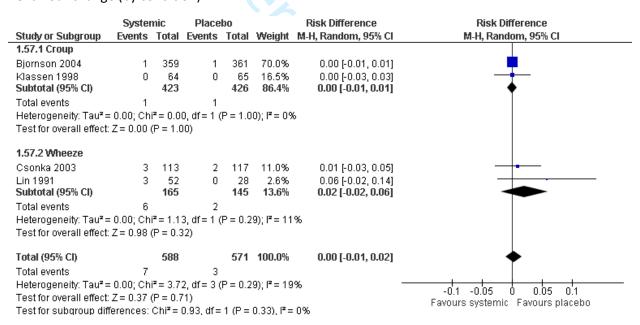
Behaviour change (by dose)

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 :				P = 1.0	$ 0\rangle; 2 = 09$	%	
Test for overall effect	Z = 0.00	(P = 1.0)	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 :				P = 0.2	(9); I² = 11	%	
Test for overall effect	Z = 0.98	(P = 0.3)	32)				
Total (95% CI)		588		571	100.0%	0.00 [-0.01, 0.02]	+
Total events	7		3				
Heterogeneity: Tau² :				P = 0.2	!9);	3%	-0.1 -0.05 0 0.05 0.1
Test for overall effect							Favours systemic Favours placebo
Test for subgroup dif	ferences:	Chi ^z =	0.93, df=	1 (P =	0.33), ==	: 0%	

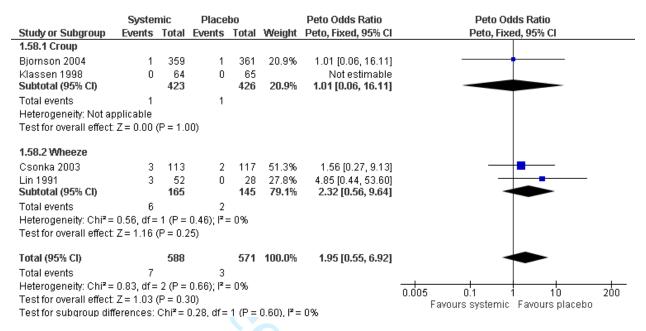
Behaviour change (by dose) - Peto



Behaviour change (by condition)



Behaviour change (by condition) – Peto



Headache

	Syster	mic	Place	ebo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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; Ch	$i^2 = 0.5$	7, df = 1	(P = 0.4)	$(5); I^2 = 09$	%	
Test for overall effect							-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placeho

Headache – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% Cl	Peto, Fixed, 95% 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 a Test for overall effect		(P = 0.2	27)				0.002 0.1 1 10 500 Favours systemic Favours placebo

SYSTEMIC vs. PLACEBO – Dermatologic

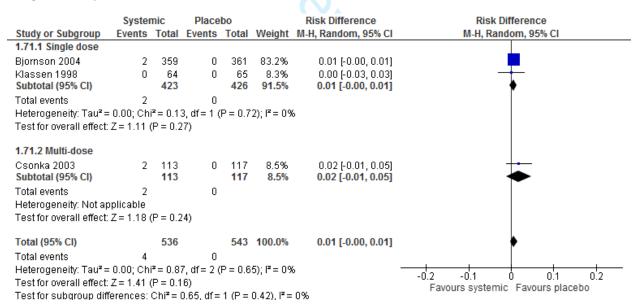
Integument

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 = Test for overall effect				P = 0.6	(5); I² = 09	6	-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Integument – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bjornson 2004	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: Chi ^z = Test for overall effect:	•	,		= 0%			0.005 0.1 10 200 Favours systemic Favours placebo

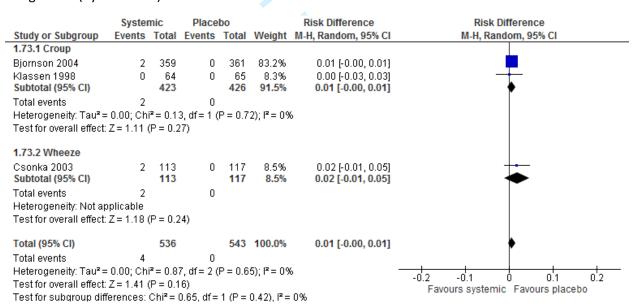
Integument (by dose)



Integument (by dose) – Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% 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 ap	plicable						
Test for overall effect:	Z = 1.42	(P = 0.1)	6)				
1.72.2 Multi-dose							
Csonka 2003	2	113	0	117	49.9%	7.72 [0.48, 124.29]	
Subtotal (95% CI)	_	113		117	49.9%	7.72 [0.48, 124.29]	
Total events	2		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.44	(P = 0.1)	5)				
Total (95% CI)		536		543	100.0%	7.59 [1.07, 54.01]	
Total events	4		0				
Heterogeneity: Chi ² =		1 (P =	_	= 0%			
Test for overall effect:		•		- /-			0.005 0.1 1 10 200
Test for subgroup diffe		•		1 (P=	0.99), I ^z =	0%	Favours systemic Favours placebo

Integument (by condition)



Integument (by condition) - Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup					Weight	Peto, Fixed, 95% CI	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 ap	•						
Test for overall effect:	Z=1.42 ((P = 0.1	16)				
1.74.2 Wheeze							
Csonka 2003	2	113	0	117	49.9%	7.72 [0.48, 124.29]	
Subtotal (95% CI)		113		117		7.72 [0.48, 124.29]	
Total events	2		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.44	(P = 0.1)	15)				
Total (95% CI)		536		543	100.0%	7.59 [1.07, 54.01]	
Total events	4	000	0	010	1001070	1100 [1101, 01101]	
Heterogeneity: Chi ² =		1 (P =		= 0%			+ + + + + + + + + + + + + + + + + + + +
Test for overall effect:							0.005 0.1 1 10 200
Test for subgroup diff				1 (P =	0.99), i ²=	0%	Favours systemic Favours placebo

SYSTEMIC vs. PLACEBO - Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities

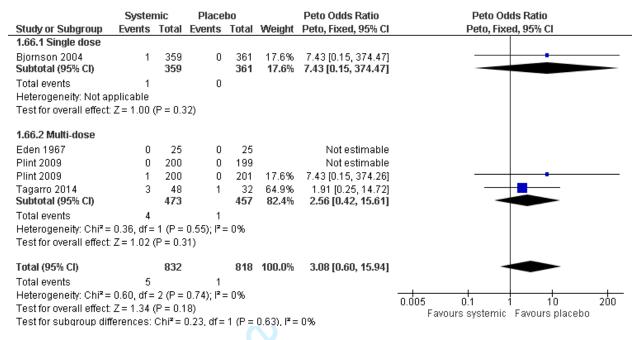
	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Bjornson 2004	1	359	0	361	51.3%	0.00 [-0.00, 0.01]	•
Eden 1967	0	25	0	25	0.5%	0.00 [-0.07, 0.07]	
Plint 2009	0	200	0	199	31.7%	0.00 [-0.01, 0.01]	+
Plint 2009	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; Ch	i² = 1.0	7, df = 4 (P = 0.9	0); I² = 09	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.84	(P = 0.4)	10)				Favours systemic Favours placebo

Fluid & electrolyte abnormalities – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Bjornson 2004	1	359	0	361	17.6%	7.43 [0.15, 374.47]	-
Eden 1967	0	25	0	25		Not estimable	
Plint 2009	0	200	0	199		Not estimable	
Plint 2009	1	200	0	201	17.6%	7.43 [0.15, 374.26]	-
Tagarro 2014	3	48	1	32	64.9%	1.91 [0.25, 14.72]	- •
Total (95% CI)		832		818	100.0%	3.08 [0.60, 15.94]	
Total events	5		1				
Heterogeneity: Chi ² =	0.60, df=	2 (P =	0.74); l² :	= 0%			t
Test for overall effect	Z=1.34	(P = 0.1)	8)				0.002 0.1 1 10 500 Favours systemic Favours placebo

Fluid & electrolyte abnormalities (by dose)

	Syste	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.65.1 Single dose							
Bjornson 2004 Subtotal (95% CI)	1	359 359	0	361 361	51.3% 51.3 %	0.00 [-0.00, 0.01] 0.00 [-0.00, 0.01]	‡
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.71	(P = 0.4)	18)				
1.65.2 Multi-dose							
Eden 1967	0	25	0	25	0.5%	0.00 [-0.07, 0.07]	
Plint 2009	Ō	200	Ō	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; Ch	i² = 1.2	5, df = 3 (P = 0.7	$(4); I^2 = 09$	6	
Test for overall effect:	Z = 0.47	(P = 0.8)	64)				
Total (95% CI)		832		818	100.0%	0.00 [-0.00, 0.01]	•
Total events	5	OOL	1	0.0	1001011	0.00 [-0.00, 0.0 1]	ľ
Heterogeneity: Tau ² =	-	i² = 1 ∩	7 df = 4 (p = n q	n): P= 09	6	
Test for overall effect:				0.5	0,,1 - 0,	•	-0.10.05 0_ 0.05 0.1
Test for subgroup diff		`		1 (P =	0.87). $I^2 =$: 0%	Favours systemic Favours placebo



Fluid & electrolyte abnormalities (by condition)

	Syster	nic	Place	bo		Risk Difference	Risk Difference				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ^z = 0.00; Chi ^z = 1.33, df = 2 (P = 0.51); i ^z = 0%											
Test for overall effect:	Z = 0.47	(P = 0.8)	34)								
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: Tau² =				P = 0.9	$ 3\rangle; ^2 = 09$	%					
Test for overall effect:	Z = 0.71	(P = 0.4)	18)								
T 4 1405TH ON					400.00		<u> </u>				
Total (95% CI)		832		818	100.0%	0.00 [-0.00, 0.01]	,				
Total events	5		1								
Heterogeneity: Tau² =				P = 0.9	i0); i² = 09	6	-0.2 -0.1 0 0.1 0.2				
Test for overall effect:		•	,				Favours systemic Favours placebo				
Test for subgroup diffe	erences:	Chi ² =	0.02, df=	1 (P=	0.88), $I^2 =$: 0%					

Fluid & electrolyte abnormalities (by condition) - Peto

Study or Subgroup	Syster Events		Place Events		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
1.68.1 Bronchiolitis							
Plint 2009 Plint 2009	0 1	200 200	0	199 201	17.6%	Not estimable 7.43 [0.15, 374.26]	
Tagarro 2014 Subtotal (95% CI)	3	48 448	1	32 432	64.9% 82. 4%	1.91 [0.25, 14.72] 2.56 [0.42, 15.61]	
Total events	4		1				
Heterogeneity: Chi² = 1 Test for overall effect: 2		-		= 0%			
1.68.2 Croup			_				
Bjornson 2004 Eden 1967	1 0	359 25	0	361 25	17.6%	7.43 [0.15, 374.47] Not estimable	
Subtotal (95% CI)	U	384	U	386	17.6%	7.43 [0.15, 374.47]	
Total events	1		0				
Heterogeneity: Not app							
Test for overall effect: 2	Z = 1.00 ((P = 0.3)	32)				
Total (95% CI)		832		818	100.0%	3.08 [0.60, 15.94]	
Total events	5		1				
Heterogeneity: Chi²=1				= 0%			0.002 0.1 1 10 50
Test for overall effect:				4.00		00/	Favours systemic Favours placebo
Test for subgroup diffe	erences:	Cni*=	U.23, at =	1 (P=	U.63), I*=	: U%	

SYSTEMIC vs. PLACEBO – Cardiovascular

Arrhythmia

	Systemic Placebo			Risk Difference	Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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)							-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Arrhythmia - Peto

	Syster	Systemic Placebo			Peto Odds Ratio		Peto Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixe	ed, 95% CI	
Daugbjerg 1993	0	31	0	27		Not estimable				
Total (95% CI)		31		27		Not estimable				
Total events	0		0							
Heterogeneity: Not applicable							0.05	02	<u> </u>	
Test for overall effect: Not applicable							0.00	Favours systemic	Favours placebo	20

Hypertension

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
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: Tau ² =	= 0.00; Ch	$i^2 = 1.03$	6 ·	1 1 1 1 1 1 1			
Test for overall effect	Z = 0.00	(P = 1.0)	-0.1 -0.05 0 0.05 0.1 Favours systemic Favours placebo				

Hypertension - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odd	Is Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixe	d, 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: Chi ^z =	2.01, df=	1 (P =	0.16);	= 50%			0.002 0.1 1	10 5	
Test for overall effect:	Z = 0.00	(P = 1.0)	10)				Favours systemic		JU

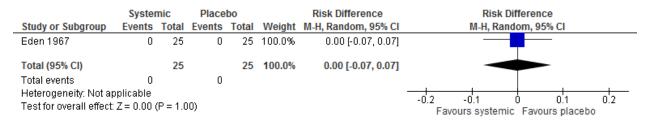
Hypertension (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.79.1 Single Dose							
Corneli 2007 Subtotal (95% CI)	0	305 305	0	295 295	68.9% 68.9%	0.00 [-0.01, 0.01] 0.00 [-0.01, 0.01]	₹
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.00 (P = 1.0	10)				
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: Tau ² =	0.00; Chi	z = 1.00	2, df = 2 (P = 0.6	$0); I^2 = 09$	6	
Test for overall effect:	Z = 0.00 (P = 1.0	10)				
Total (95% CI)		727		714	100.0%	0.00 [-0.01, 0.01]	•
Total events	1		1				
Heterogeneity: Tau ² =	0.00; Chi	z = 1.00	2. df = 3 (P = 0.8	0); $I^2 = 0.9$	6 -	
Test for overall effect:							-0.1 -0.05 0 0.05 0.1
Test for subgroup diffe				1 (P=	1.00), l²=	0%	Favours systemic Favours placebo

Hypertension (by dose) - Peto

	Syster	nic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap	•						
Test for overall effect:	Not appli	cable					
1.81.2 Multi-Dose							
Buckingham 2002	0	22	0	19		Not estimable	
Plint 2009	0	200	1	199	50.0%	0.13 [0.00, 6.79]	
Plint 2009	1	200	0	201	50.0%	7.43 [0.15, 374.26]	
Subtotal (95% CI)		422		419	100.0%	1.00 [0.06, 15.99]	
Total events	1		1				
Heterogeneity: Chi ^z =	2.01, df=	1 (P=	0.16);	50%			
Test for overall effect:	Z = 0.00 ((P = 1.0)	10)				
Total (95% CI)		727		714	100.0%	1.00 [0.06, 15.99]	
Total events	1		1				
Heterogeneity: Chi ² =	2.01. df=	1 (P =	0.16): I ² =	: 50%			-1
Test for overall effect:	•	•					0.002 0.1 1 10 500
Test for subgroup diffe		•	•				Favours systemic Favours placebo

Congestive heart failure



Congestive heart failure - Peto

	Systemic Placebo			Peto Odds Ratio		Peto Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixe	ed, 95% CI	
Eden 1967	0	25	0	25		Not estimable				
Total (95% CI)		25		25		Not estimable				
Total events	0		0							
Heterogeneity: Not ap	Heterogeneity: Not applicable						0.05	0.2	<u> </u>	20
Test for overall effect:	Not appli	cable					0.03	Favours systemic	Favours placebo	20



SYSTEMIC vs. PLACEBO – General

General complaints

	Syster	mic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	: 0.00; Ch	$i^2 = 0.09$	5, df = 3 (P = 1.0	$0); I^2 = 09$	6	15 025 0 025 05
Test for overall effect:	Z = 0.04	(P = 0.9)	17)				-0.5 -0.25 0 0.25 0.5 Favours systemic Favours placebo

General complaints – Peto

	Syster	mic	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Kuyucu 2004	0	23	0	11		Not estimable	
Kuyucu 2004	0	23	0	12		Not estimable	
Plint 2009	23	200	22	199	58.3%	1.05 [0.56, 1.94]	- •
Plint 2009	15	200	16	201	41.7%	0.94 [0.45, 1.95]	
Total (95% CI)		446		423	100.0%	1.00 [0.62, 1.60]	•
Total events	38		38				
Heterogeneity: Chi ² =	0.05, df =	1 (P=	0.82); l² =	= 0%			105 00
Test for overall effect:	Z = 0.00	(P = 1.0)	10)				0.05 0.2 1 5 20 Favours systemic Favours placebo

General complaints (by dose)

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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: Tau ² =	: 0.00; Chi	$f^2 = 0.01$	O, df=1(P = 1.0	$0); I^2 = 09$	6	
Test for overall effect:	Z = 0.00 (P = 1.0	10)				
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: Tau ² =	: 0.00; Chi	$r^2 = 0.09$	5, df = 1 (P = 0.8	2); $I^2 = 0.9$	6	
Test for overall effect:	Z = 0.04 (P = 0.9	97)				
Total (95% CI)		446		423	100.0%	-0.00 [-0.04, 0.04]	•
Total events	38		38				
Heterogeneity: Tau ² =	: 0.00; Chi	$i^2 = 0.09$	5, df = 3 (P = 1.0	0); I² = 09	6	-0.5 -0.25 0 0.25 0.5
Test for overall effect:	Z = 0.04 (P = 0.9	97)				Favours systemic Favours placebo
Test for subgroup diff	ferences:	Chi²=1	0.00, df=	1 (P=	0.99), $I^2 =$: 0%	r avours systemic i avours praceso

General complaints (by dose) – Peto

Study on Sub-resur	System		Place		187-:	Peto Odds Ratio	Peto Odds Ratio
1.89.1 Single Dose	Events	rotai	Events	rotai	vveignt	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Kuyucu 2004	0	23	0	11		Not estimable	
Kuyucu 2004 Subtotal (95% CI)	0	23 46	0	12 23		Not estimable Not estimable	
Total events	0		0				
Heterogeneity: Not ap Test for overall effect:		cable					
1.89.2 Multi-Dose							
Plint 2009	23	200	22	199	58.3%	1.05 [0.56, 1.94]	
Plint 2009 Subtotal (95% CI)	15	200 400	16	201 400	41.7% 100.0%	0.94 [0.45, 1.95] 1.00 [0.62, 1.60]	
Total events	38		38				
Heterogeneity: Chi² = Test for overall effect:				: 0%			
Total (95% CI)		446		423	100.0%	1.00 [0.62, 1.60]	•
Total events	38		38				
Heterogeneity: Chi²=				- 0%			0.1 0.2 0.5 1 2 5 10
Test for overall effect:							Favours systemic Favours placebo
Test for subgroup diff	erences: I	Not ap	olicable				

SYSTEMIC vs. PLACEBO – Immune System

Immunosuppression

	Syster	nic	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ap Test for overall effect:	•	P = 1.0	10)				-0.2 -0.1 0 0.1 0.2 Favours systemic Favours placebo

Immunosuppression – Peto

Study or Subgroup	Syster Events		Place Events		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
Connolly 1969	0	47	0			Not estimable	
Total (95% CI)		47		48		Not estimable	
Total events	0 oldcoile		0				
Heterogeneity: Not ap Test for overall effect:		cable					0.05 0.2 1 5 20 Favours systemic Favours placebo

INHALED vs. PLACEBO – Infection & Respiratory

Severe infections

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ap	plicable						-02 -01 0 01 02
Test for overall effect:	Z = 0.75 ((P = 0.4)	15)				Favours inhaled Favours placebo

Severe infections - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 a Test for overall effect	•	(P = 0.4	16)				0.01 0.1 10 100 Favours inhaled Favours placebo

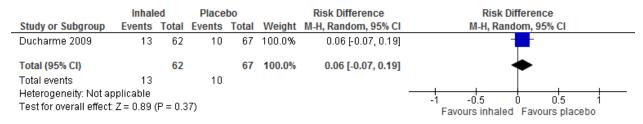
Systemic infections

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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: Tau ² =	= 0.00; Chi	$i^2 = 0.0$	3, df = 1	P = 0.8	7); $I^2 = 09$	6	
Test for overall effect	Z = 0.04	P = 0.9	37)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Systemic infections - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Daugbjerg 1993	0	29	0	27		Not estimable	<u></u>
Ducharme 2009	18	62	20	67	100.0%	0.96 [0.45, 2.05]	-
Total (95% CI)		91		94	100.0%	0.96 [0.45, 2.05]	•
Total events	18		20				
Heterogeneity: Not ap Test for overall effect:		(P = 0.9	32)				0.01 0.1 10 100 Favours inhaled Favours placebo

Lung/trachea



Lung/trachea - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap Test for overall effect:		(P = 0.3	37)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

URT

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]	
Daugbjerg 1993	0	29	0	27	7.7%	0.00 [-0.07, 0.07]	
Ducharme 2009	10	62	9	67	2.3%	0.03 [-0.10, 0.15]	- ·
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	-
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	-
Klassen 1998	0	64	0	68	40.7%	0.00 [-0.03, 0.03]	+
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	+
Total events	24		24				
Heterogeneity: Tau ² =	0.00; Ch	i² = 2.1:	2, df = 5 (P = 0.8	3); $I^2 = 0.9$	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.04	(P = 0.9)	7)				Favours inhaled Favours placebo

URT – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% 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: Chi ² =	= 2.53, df=	2 (P =	0.28); l² =	= 21%			204 24 40 40
Test for overall effect	:: Z = 0.08	(P = 0.9)	33)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

URT (by dose)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.19.1 Single Dose							
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	-
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	
Klassen 1998	0	64	0	68	40.7%	0.00 [-0.03, 0.03]	
Subtotal (95% CI)		140		144	65.7%	0.00 [-0.02, 0.03]	•
Total events	2		0				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 2.33$	3, df = 2 (P = 0.3	1); $I^2 = 14$	%	
Test for overall effect:	Z = 0.28 ((P = 0.7)	78)				
2.19.2 Multi-Dose							
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]	
Daugbjerg 1993	0	29	0	27	7.7%	0.00 [-0.07, 0.07]	
Ducharme 2009	10	62	9	67	2.3%	0.03 [-0.10, 0.15]	
Subtotal (95% CI)		355		355	34.3%	-0.01 [-0.04, 0.03]	•
Total events	22		24				
Heterogeneity: Tau ² =	0.00; Chi	$i^2 = 0.43$	3, df = 2 (P = 0.8	1); $I^2 = 09$	6	
Test for overall effect:	Z = 0.41	(P = 0.6)	88)				
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	•
Total events	24		24				
Heterogeneity: Tau ² =	0.00; Chi	$i^2 = 2.13$	2, df = 5 (P = 0.8	3); $I^2 = 0.9$	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:							
Test for subgroup diffe		•	,	1 (P =	0.62), $I^2 =$	0%	Favours inhaled Favours placebo

URT (by dose) – Peto

	Inhaled		Placebo		Peto Odds Ratio		Peto Odds Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI			
2.20.1 Single Dose										
Johnson 1996	2	28	0	27	4.5%	7.40 [0.45, 121.47]				
Johnson 1998	0	48	0	49		Not estimable				
Klassen 1998	0	64	0	68		Not estimable				
Subtotal (95% CI)		140		144	4.5%	7.40 [0.45, 121.47]				
Total events	2		0							
Heterogeneity: Not ap	plicable									
Test for overall effect:	Z = 1.40	(P = 0.1)	6)							
2.20.2 Multi-Dose										
Clavenna 2014	12	264	15	261	58.4%	0.78 [0.36, 1.70]	-			
Daugbjerg 1993	0	29	0	27		Not estimable				
Ducharme 2009	10	62	9	67	37.1%	1.24 [0.47, 3.27]				
Subtotal (95% CI)		355		355	95.5%	0.93 [0.51, 1.71]	•			
Total events	22		24							
Heterogeneity: Chi ^z = 0.52, df = 1 (P = 0.47); l ^z = 0%										
Test for overall effect:	Z = 0.22	(P = 0.8)	3)							
							1			
Total (95% CI)		495		499	100.0%	1.03 [0.57, 1.85]	•			
Total events	24		24							
Heterogeneity: Chi ² = 2.53, df = 2 (P = 0.28); i ² = 21% 0.005 0.1 1 10 200										
Test for overall effect:	Z = 0.08	(P = 0.9)	3)				Favours inhaled Favours placebo			
Test for subgroup differences: Chi ² = 2.01, df = 1 (P = 0.16), i ² = 50.2%										

URT (by condition)

	Inhaled		Placebo		Risk Difference		Risk Difference		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI		
2.21.1 Croup									
Johnson 1996	2	28	0	27	2.7%	0.07 [-0.04, 0.18]	 		
Johnson 1998	0	48	0	49	22.3%	0.00 [-0.04, 0.04]	-		
Klassen 1998	0	64	0	68	40.7%	0.00 [-0.03, 0.03]	- -		
Subtotal (95% CI)		140		144	65.7%	0.00 [-0.02, 0.03]	•		
Total events	2		0						
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 2.33$	3, df = 2 (P = 0.3	1); $I^2 = 14$	%			
Test for overall effect:	Z = 0.28 ((P = 0.7)	'8)						
2.21.2 Wheeze									
Clavenna 2014	12	264	15	261	24.3%	-0.01 [-0.05, 0.03]			
Daugbjerg 1993	0	29	0	27	7.7%	0.00 [-0.07, 0.07]	- + -		
Ducharme 2009	10	62	9	67	2.3%	0.03 [-0.10, 0.15]			
Subtotal (95% CI)		355		355	34.3%	-0.01 [-0.04, 0.03]	•		
Total events	22		24						
Heterogeneity: Tau² = 0.00; Chi² = 0.43, df = 2 (P = 0.81); l² = 0%									
Test for overall effect:	Z = 0.41 ((P = 0.6)	8)						
							1		
Total (95% CI)		495		499	100.0%	-0.00 [-0.02, 0.02]	•		
Total events	24		24						
Heterogeneity: Tau ² = 0.00; Chi ² = 2.12, df = 5 (P = 0.83); I^2 = 0% -0.2 -0.1 0 0.1 0.2									
Test for overall effect:	Z = 0.04 ((P = 0.9)	97)				Favours inhaled Favours placebo		
Test for subgroup differences: Chi² = 0.25, df = 1 (P = 0.62), l² = 0%									

URT (by condition) – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio		Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
2.22.1 Croup								
Johnson 1996	2	28	0	27	4.5%	7.40 [0.45, 121.47]		
Johnson 1998	0	48	0	49		Not estimable		
Klassen 1998	0	64	0	68		Not estimable		
Subtotal (95% CI)		140		144	4.5%	7.40 [0.45, 121.47]		
Total events	2		0					
Heterogeneity: Not ap	plicable							
Test for overall effect:	Z = 1.40 ((P = 0.1)	6)					
2.22.2 Wheeze								
Clavenna 2014	12	264	15	261	58.4%	0.78 [0.36, 1.70]		
Daugbjerg 1993	0	29	0	27		Not estimable		
Ducharme 2009	10	62	9	67	37.1%	1.24 [0.47, 3.27]		
Subtotal (95% CI)		355		355	95.5%	0.93 [0.51, 1.71]		-
Total events	22		24					
Heterogeneity: Chi²=	0.52, df =	1 (P =	0.47); l² =	= 0%				
Test for overall effect:	Z = 0.22 ((P = 0.8)	33)					
Total (95% CI)		495		499	100.0%	1.03 [0.57, 1.85]		-
Total events	24		24					
Heterogeneity: Chi²=	2.53, df=	2 (P =	0.28); l²=	= 21%			0.05	0.2 1 5 20
Test for overall effect:	Z = 0.08 ((P = 0.9)	33)				0.05	Favours inhaled Favours placebo
Test for subgroup diff	erences:	Chi²=	2.01, df=	1 (P=	0.16), l²=	50.2%		1 avours minared 1 avours pracedo

Voice complaints

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

Voice complaints – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio		Peto Odds Rat	io	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixed, 95%	CI	
Clavenna 2014	34	264	34	261	84.5%	0.99 [0.59, 1.64]		-		
Daugbjerg 1993	0	29	0	27		Not estimable				
Svedmyr 1995	2	22	0	22	2.8%	7.75 [0.47, 128.03]		-		→
Svedmyr 1999	2	28	9	27	12.8%	0.20 [0.05, 0.74]				
Total (95% CI)		343		337	100.0%	0.85 [0.53, 1.36]		•		
Total events	38		43							
Heterogeneity: Chi²=	7.39, df=	2 (P =	0.02); l² =	= 73%			 	1 1	10	100
Test for overall effect:	Z = 0.67	(P = 0.5)	50)				0.01 0. Favou	ı ırs inhaled Favou	10 rs placebo	100

Voice complaints (by condition)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.25.1 Asthma							
Svedmyr 1995	2	22	0	22	18.9%	0.09 [-0.05, 0.23]	 •
Svedmyr 1999	2	28	9	27	11.8%	-0.26 [-0.46, -0.06]	
Subtotal (95% CI)		50		49	30.7%	-0.08 [-0.46, 0.31]	
Total events	4		9				
Heterogeneity: Tau² =	0.07; Chi	$i^2 = 9.81$	0, df=1 (P = 0.0	02); $I^z = 9$	0%	
Test for overall effect:	Z = 0.40 ((P = 0.6)	9)				
2.25.2 Wheeze							
Clavenna 2014	34	264	34	261	35.8%	-0.00 [-0.06, 0.06]	-
Daugbjerg 1993	0	29	0	27	33.6%	0.00 [-0.07, 0.07]	- -
Subtotal (95% CI)		293		288	69.3%	-0.00 [-0.04, 0.04]	*
Total events	34		34				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 0.01$	0, df=1 (P = 0.9	7); $I^2 = 09$	6	
Test for overall effect:	Z = 0.04 ((P = 0.9)	97)				
Total (95% CI)		343		337	100.0%	-0.01 [-0.10, 0.07]	•
Total events	38		43				
Heterogeneity: Tau ^z =	0.00; Chi	$i^2 = 8.43$	2, df = 3 (P = 0.0	4); $I^2 = 64$	%	-0.5 -0.25 0 0.25 0.5
Test for overall effect:	Z = 0.34 (P = 0.7	'3)				-0.5 -0.25 0 0.25 0.5 Favours inhaled Favours placebo
Test for subgroup diff	oroneoe:	Chi≅ – I	0 1 G AF —	1 /D =	0.607.13=	.000	ravours illiaieu Tavours placebo

Voice complaints (by condition) - Peto

	Inhaled	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events To	tal Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.26.1 Asthma						
Svedmyr 1995	2	22 0	22	2.8%	7.75 [0.47, 128.03]	- · · · · · · · · · · · · · · · · · ·
Svedmyr 1999		28 9	27	12.8%	0.20 [0.05, 0.74]	
Subtotal (95% CI)		50	49	15.5%	0.39 [0.12, 1.26]	
Total events	4	9				
Heterogeneity: Chi ² =			= 81%			
Test for overall effect:	Z= 1.57 (P=	0.12)				
2.26.2 Wheeze						
Clavenna 2014	34 2	64 34	261	84.5%	0.99 [0.59, 1.64]	-
Daugbjerg 1993	0	29 0	27		Not estimable	Ţ
Subtotal (95% CI)	2	93	288	84.5%	0.99 [0.59, 1.64]	•
Total events	34	34				
Heterogeneity: Not ap						
Test for overall effect:	Z = 0.05 (P =	0.96)				
Total (95% CI)	3	43	337	100.0%	0.85 [0.53, 1.36]	•
Total events	38	43				
Heterogeneity: Chi²=	7.39, df = 2 (F	o = 0.02); l ^a :	= 73%			0.01 0.1 1 10 100
Test for overall effect:	Z = 0.67 (P =	0.50)				Favours inhaled Favours placebo
Test for subgroup diff	erences: Chi	² = 2.04, df=	1 (P=	0.15), $I^2 =$	50.9%	Tavouro minarca Tavouro piacobo

INHALED vs. PLACEBO - GI

GI bleeding

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 a Test for overall effec		(P = 1.0	10)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

GI bleeding – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap	oplicable						01 02 05 1 2 5 10
Test for overall effect	Not appli	cable					Favours inhaled Favours placebo

Vomiting

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

Vomiting - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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); l² =	= 0%			0.005 0.1 1 10 200
Test for overall effect:	Z = 0.01 (P = 0.9	19)				0.005 0.1 1 10 200 Favours inhaled Favours placebo

Vomiting (by dose)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.5.1 Single Dose							
Klassen 1996	2	25	1	25	6.4%	0.04 [-0.09, 0.17]	-
Subtotal (95% CI)		25		25	6.4%	0.04 [-0.09, 0.17]	
Total events	2		1				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.60 (P = 0.5	5)				
2 F 2 Multi Daga							
2.5.2 Multi-Dose							_
Clavenna 2014	19	264	20	261	55.0%	-0.00 [-0.05, 0.04]	
Ducharme 2009	4	62	4	67	15.9%	0.00 [-0.08, 0.09]	
Roberts 1999	2	42	3	40	10.2%	-0.03 [-0.13, 0.08]	
Svedmyr 1999	1	28	0	27	12.4%	0.04 [-0.06, 0.13]	
Subtotal (95% CI)		396		395	93.6%	-0.00 [-0.03, 0.03]	•
Total events	26		27				
Heterogeneity: Tau² =	0.00; Chi	$^{2} = 0.89$	9, df = 3 (P = 0.8	3); $I^2 = 0.9$	6	
Test for overall effect:	Z = 0.01 (P = 0.9	19)				
T / 1/05*/ OB					400.00		
Total (95% CI)		421		420	100.0%	0.00 [-0.03, 0.04]	—
Total events	28		28				
Heterogeneity: Tau² =	0.00; Chi	$^{2} = 1.23$	3, df = 4 (P = 0.8	7); $I^2 = 09$	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z = 0.14 (P = 0.8	(9)				Favours inhaled Favours placebo
Test for subgroup diff	erences: (Chi²= I	D.34, df=	1 <u>(</u> P =	0.56), $I^2 =$: 0%	r areare minarea i avento piacebe

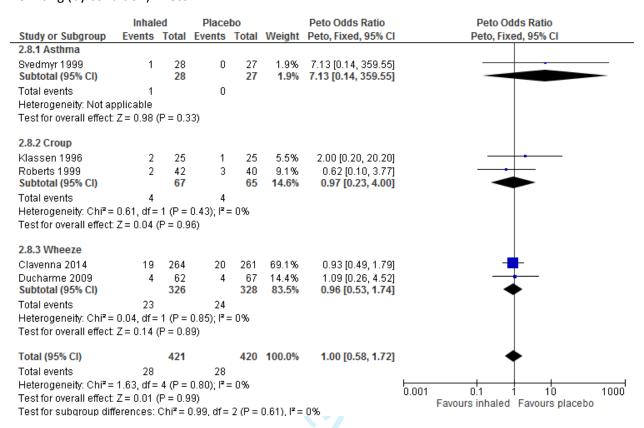
Vomiting (by dose) - Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.6.1 Single Dose							
Klassen 1996	2	25	1	25	5.5%	2.00 [0.20, 20.20]	
Subtotal (95% CI)		25		25	5.5%	2.00 [0.20, 20.20]	
Total events	2		1				
Heterogeneity: Not ap	•						
Test for overall effect:	Z = 0.59	(P = 0.6)	56)				
2.6.2 Multi-Dose							
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]	
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]	
Subtotal (95% CI)		396		395	94.5%	0.96 [0.55, 1.67]	•
Total events	26		27				
Heterogeneity: Chi²=		,		= 0%			
Test for overall effect:	Z = 0.15	(P = 0.8)	38)				
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); l² =	= 0%			0.002 0.1 1 10 500
Test for overall effect:	Z = 0.01	(P = 0.9)	99)				Favours inhaled Favours placebo
Test for subgroup diffi	erences:	Chi ² =	0.37. df=	1(P =	0.54), $I^2 =$	0%	r around minarca. I avourd pracebo

Vomiting (by condition)

Study or Subarraya	Inhale		Placel		Majaht	Risk Difference	Risk Difference
Study or Subgroup 2.7.1 Asthma	Events	Total	Events	TOTAL	vveignt	M-H, Random, 95% CI	M-H, Random, 95% CI
			_				
Svedmyr 1999 Subtotal (95% CI)	1	28 28	0	27 27	12.4% 12.4%	0.04 [-0.06, 0.13] 0.04 [-0.06, 0.1 3]	
Total events	1		0				
Heterogeneity: Not ap	oplicable						
Test for overall effect:	Z = 0.74 (P = 0.4	6)				
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: Tau² =		z = 0.60		P = N 4	3): I² = 0%	6	
Test for overall effect:				- 0.4	0/11 - 0 /	•	
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: Tau² =	= 0.00; Chi	$^{2} = 0.04$	I, df = 1 (l	P = 0.8	4); $I^2 = 0\%$	6	
Test for overall effect:	Z= 0.13 (P = 0.9	0)				
Total (95% CI)		421		420	100.0%	0.00 [-0.03, 0.04]	*
Total events	28		28				
Heterogeneity: Tau² =				P = 0.8	7); I² = 0%	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect:			•				Favours inhaled Favours placebo
Test for subgroup dif	ferences: (Chi²=0).55, df=	2 (P =	0.76), I ^z =	0%	

Vomiting (by condition) - Peto



Diarrhea

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Clavenna 2014	27	264	35	261	72.7%	-0.03 [-0.09, 0.02]	
Ducharme 2009	14	62	11	67	27.3%	0.06 [-0.08, 0.20]	-
Total (95% CI)		326		328	100.0%	-0.01 [-0.09, 0.08]	
Total events	41		46				
Heterogeneity: Tau ² =	= 0.00; Ch	i² = 1.5	8, df = 1 (P = 0.2	1); $I^2 = 37$	'%	
Test for overall effect							-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Diarrhea - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio		Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI	
Clavenna 2014	27	264	35	261	73.0%	0.74 [0.43, 1.25]			
Ducharme 2009	14	62	11	67	27.0%	1.48 [0.62, 3.53]		 -	
Total (95% CI)		326		328	100.0%	0.89 [0.57, 1.40]		•	
Total events	41		46						
Heterogeneity: Chi²=		,		= 44%			0.01	01 1 10 1	100
Test for overall effect	Z = 0.51 ((P = 0.6)	61)				0.01	Favours inhaled Favours placebo	

INHALED vs. PLACEBO - CNS & Behaviour

Behaviour change

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
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]	
Svedmyr 1999	1	28	0	27	14.6%	0.04 [-0.06, 0.13]	
Total (95% CI)		134		135	100.0%	-0.01 [-0.04, 0.03]	•
Total events	6		7				
Heterogeneity: Tau² = Test for overall effect:				P = 0.6	0); I² = 09	6	-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Behaviour change – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Klassen 1998	0	64	1	68	8.6%	0.14 [0.00, 7.25]	<u> </u>
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]	-
Total (95% CI)		134		135	100.0%	0.81 [0.26, 2.54]	-
Total events	6		7				
Heterogeneity: Chi²=	1.94, df=	2 (P =	0.38); l² =	= 0%			0.005 0.1 1 10 200
Test for overall effect:	Z = 0.37	(P = 0.7)	71)				Favours inhaled Favours placebo

Behaviour change (by dose)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.29.1 Single Dose							
Klassen 1998	0	64	1	68	79.5%	-0.01 [-0.06, 0.03]	
Subtotal (95% CI)		64		68	79.5%	-0.01 [-0.06, 0.03]	•
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect: .	Z = 0.71 ((P = 0.4)	18)				
2.29.2 Multi-Dose							
Roberts 1999	5	42	6	40	5.9%	-0.03 [-0.18, 0.12]	
Svedmyr 1999	1	28	0	27	14.6%	0.04 [-0.06, 0.13]	
Subtotal (95% CI)		70		67	20.5%	0.02 [-0.06, 0.10]	
Fotal events	6		6				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 0.8$	1, df = 1 (P = 0.3	7); $I^2 = 09$	6	
Test for overall effect: .	Z = 0.40 ((P = 0.8)	69)				
Total (95% CI)		134		135	100.0%	-0.01 [-0.04, 0.03]	•
Fotal events	6		7				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 1.03$	3, df = 2 (P = 0.6	$0); I^2 = 09$	6	-0.2 -0.1 0 0.1 0.2
Test for overall effect: .	Z = 0.45 ((P = 0.8)		-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo			
Test for subgroup diffe	erences:	Chi ^z = I	0.47, df=	1 (P=	0.49), $I^2 =$	0%	r avours minated Pavours placebo

Behaviour change (by dose) – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.30.1 Single Dose							
Klassen 1998 Subtotal (95% CI)	0	64 64	1	68 68	8.6% 8.6%	0.14 [0.00, 7.25] 0.14 [0.00, 7.25]	
Total events	0		1				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z= 0.97 ((P = 0.3)	33)				
2.30.2 Multi-Dose							
Roberts 1999	5	42	6	40	82.8%	0.77 [0.22, 2.72]	—
Svedmyr 1999 Subtotal (95% CI)	1	28 70	0	27 67	8.6% 91.4%	7.13 [0.14, 359.55] 0.95 [0.28, 3.15]	
Total events	6		6				T
Heterogeneity: Chi²=	1.12, df=	1 (P=	0.29); l² =	= 11%			
Test for overall effect:	Z = 0.09 ((P = 0.9)	33)				
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 =					
Test for overall effect:	Z = 0.37 ((P = 0.7)		0.005 0.1 1 10 200 Favours inhaled Favours placebo			
Test for subgroup diffe	erences:	Chi²=1	0.81, df=	1 (P=	0.37), $I^2 =$	0%	ravours illitated ravours placebo

Behaviour change (by condition)

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 a	pplicable						
Test for overall effect	t: Z = 0.74	(P = 0.4)	16)				
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: Tau²:	= 0.00; Ch	$i^2 = 0.1$	1, df = 1 (P = 0.7	4); $I^2 = 09$	6	
Test for overall effect	t: Z = 0.80	(P = 0.4)	13)				
Total (95% CI)		134		135	100.0%	-0.01 [-0.04, 0.03]	•
Total events	6		7				
Heterogeneity: Tau ² :	= 0.00; Ch	$i^2 = 1.03$	3, df = 2 (P = 0.6	$0); I^2 = 09$	6	
Test for overall effect	t: Z = 0.45	(P = 0.8)	35)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo
Test for subgroup di	fferences:	Chi ^z = I	0.98, df=	1 (P=	0.32), $I^2 =$: 0%	i avours illitateu i avours placebo

Behaviour change (by condition) – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.32.1 Asthma							
Svedmyr 1999	1	28	0	27	8.6%	7.13 [0.14, 359.55]	-
Subtotal (95% CI)		28		27	8.6%	7.13 [0.14, 359.55]	
Total events	1		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 0.98 ((P = 0.3)	33)				
2.32.2 Croup							
Klassen 1998	0	64	1	68	8.6%	0.14 [0.00, 7.25]	-
Roberts 1999	5	42	6	40	82.8%	0.77 [0.22, 2.72]	
Subtotal (95% CI)		106		108	91.4%	0.66 [0.20, 2.18]	-
Total events	5		7				
Heterogeneity: Chi²=	0.64, df=	1 (P=	0.42);	= 0%			
Test for overall effect:	Z = 0.69	(P = 0.4)	19)				
Total (95% CI)		134		135	100.0%	0.81 [0.26, 2.54]	•
Total events	6		7				
Heterogeneity: Chi²=	1.94, df=	2 (P=	0.002 0.1 1 10 500				
Test for overall effect:	Z = 0.37 (P = 0.7	0.002 0.1 1 10 500 Favours inhaled Favours placebo				
Test for subgroup diffe	erences:	Chi²=	i avouis iiiilaieu Pavouis piacebo				

INHALED vs. PLACEBO – Dermatologic

Burn

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 ap Test for overall effect:	•	(P = 0.4	15)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Burn - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap Test for overall effect	•	(P = 0.3	32)				0.002 0.1 1 10 500 Favours inhaled Favours placebo

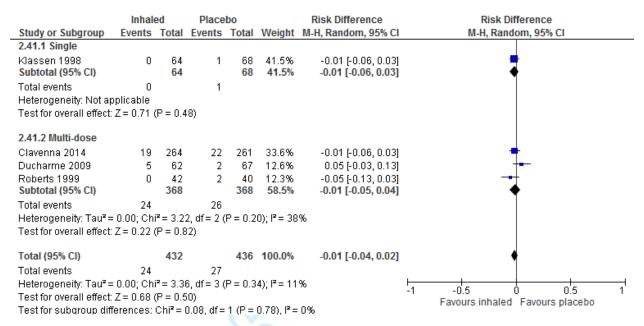
Integument

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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: Tau ² =	0.00; Chi	$i^2 = 3.31$	6, df = 3 (P = 0.3	4); $I^2 = 11$	%	
Test for overall effect:	Z = 0.68 ((P = 0.5)	0)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

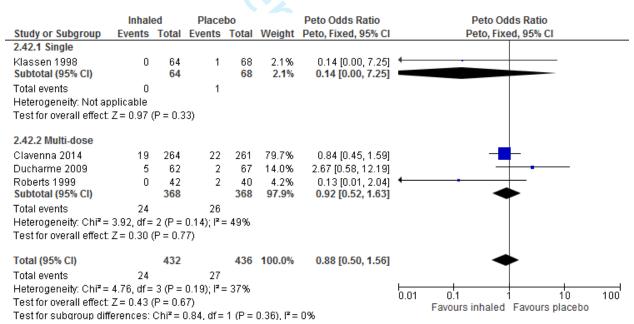
Integument – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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: Chi ² =	4.76, df=	3 (P=	0.19);	= 37%			
Test for overall effect:	Z= 0.43	(P = 0.6	67)				0.01 0.1 1 10 100 Favours inhaled Favours placebo

Integument (by dose)



Integument (by dose) - Peto



Integument (by condition)

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
2.44.1 Croup							
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]	•
Subtotal (95% CI)		106		108	53.8%	-0.02 [-0.06, 0.01]	
Total events	0		3				
Heterogeneity: Tau² =	0.00; Chi	$i^2 = 0.7^\circ$	1, df = 1 (P = 0.4	$0); I^2 = 0\%$	6	
Test for overall effect:	Z = 1.19 ((P = 0.2)	(3)				
2.44.2 Wheeze							
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]	•
Subtotal (95% CI)		326		328	46.2%	0.01 [-0.05, 0.07]	
Total events	24		24				
Heterogeneity: Tau² =	0.00; Chi	i² = 1.81	8, df = 1 (P = 0.1	7); $I^2 = 46$	%	
Test for overall effect:	Z = 0.35 ((P = 0.7)	'2)				
Total (95% CI)		432		436	100.0%	-0.01 [-0.04, 0.02]	
Total events	24		27				
Heterogeneity: Tau² =	0.00; Chi	i² = 3.31	6, df = 3 (P = 0.3	4); $I^2 = 11$	%	-0.1 -0.05 0 0.05 0.1
Test for overall effect:	Z = 0.68 ((P = 0.5)	i0)				Favours inhaled Favours placebo
Test for subgroup diffe	erences:	Chi ² =1	D.84, df=	1 (P =	0.36), $I^2 =$	0%	r drodio minaroa i r drodio pidocoo

Integument (by condition) – Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
2.46.1 Croup							
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]	
Subtotal (95% CI)		106		108	6.3%	0.13 [0.01, 1.27]	
Total events	0		3				
Heterogeneity: Chi²=	0.00, df =	1 (P=	0.96); l² =	- 0%			
Test for overall effect:	Z = 1.75 ((P = 0.0)	18)				
2.46.2 Wheeze							
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]	 -
Subtotal (95% CI)		326		328	93.7%	1.00 [0.56, 1.80]	•
Total events	24		24				
Heterogeneity: Chi²=	1.88, df=	1 (P=	0.17);	47%			
Test for overall effect:	Z = 0.01	(P = 1.0)	10)				
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);	37%			0.005 0.1 1 10 200
Test for overall effect:	Z = 0.43 ((P = 0.8)	67)				Favours inhaled Favours placebo
Test for subgroup diff	ferences:	Chi² = :	2.88. df =	1 (P =	0.09), $I^2 =$	65.2%	ravours initiated in avours placebo

INHALED vs. PLACEBO - Endocrine/Metabolic & Musculoskeletal

Growth – change from baseline, cm

	In	haled		Pla	aceb	0		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bacharier 2008	7.8	1.75	96	7.5	1.9	47	68.3%	0.30 [-0.35, 0.95]	-
Ducharme 2009	6.23	2.62	58	6.56	2.9	62	31.7%	-0.33 [-1.32, 0.66]	
Total (95% CI)			154			109	100.0%	0.10 [-0.47, 0.67]	*
Heterogeneity: Tau² = Test for overall effect:				= 1 (P =	0.30)); I = 9'	%		-4 -2 0 2 4 Favours inhaled Favours placebo

Adrenal suppression

	Inhal	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	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 a Test for overall effect	•	(P = 0.0)5)				-0.5 -0.25 0 0.25 0.5 Favours inhaled Favours placebo

Adrenal suppression - Peto

	Inhale	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	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 ap	plicable						0.01 0.1 1 10 100
Test for overall effect: .	Z=1.64 (P = 0.1	0)				0.01 0.1 1 10 100 Favours inhaled Favours placebo
							r avours minareu i avours praceso

INHALED vs. PLACEBO – Cardiovascular

Arrhythmia

	Inhale	ed	Place	bo		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ap Test for overall effect:	•	(P = 1.0	10)				-0.2 -0.1 0 0.1 0.2 Favours inhaled Favours placebo

Arrhythmia – Peto

	Inhal	ed	Place	bo		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Daugbjerg 1993	0	29	0	27		Not estimable	
,,							
Total (95% CI)		29		27		Not estimable	
Total events	0		0				
Heterogeneity: Not ap	plicable						
Test for overall effect:		cable					0.5 0.7 1 1.5 2
							Favours inhaled Favours placebo

DEXAMETHASONE vs. OTHER STEROID - GI

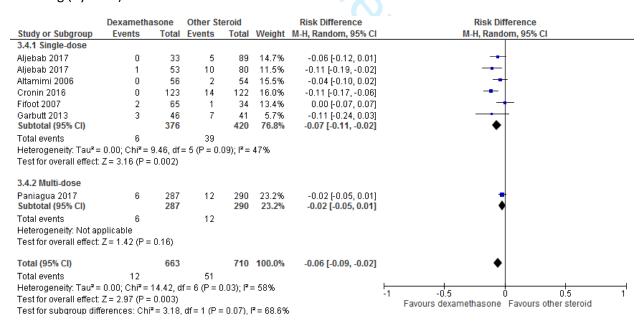
Vomiting

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

Vomiting – Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Aljebab 2017	0	33	5	89	6.6%	0.24 [0.03, 1.80]		
Aljebab 2017	1	53	10	80	16.9%	0.25 [0.07, 0.88]		
Altamimi 2006	0	56	2	54	3.4%	0.13 [0.01, 2.07]		
Cronin 2016	0	123	14	122	22.9%	0.12 [0.04, 0.35]		
Fifoot 2007	2	65	1	34	4.6%	1.05 [0.09, 11.63]		
Garbutt 2013	3	46	7	41	15.4%	0.36 [0.10, 1.33]		
Paniagua 2017	6	287	12	290	30.2%	0.51 [0.20, 1.30]		
Total (95% CI)		663		710	100.0%	0.29 [0.17, 0.48]	•	
Total events	12		51					
Heterogeneity: Chi²=	5.57, df = 6 (P = 0.47); I² = 0%				0.002 0.1 1 10	500
Test for overall effect:	Z= 4.73 (P =	0.0000	1)				Favours dexamethasone Favours other steroid	500

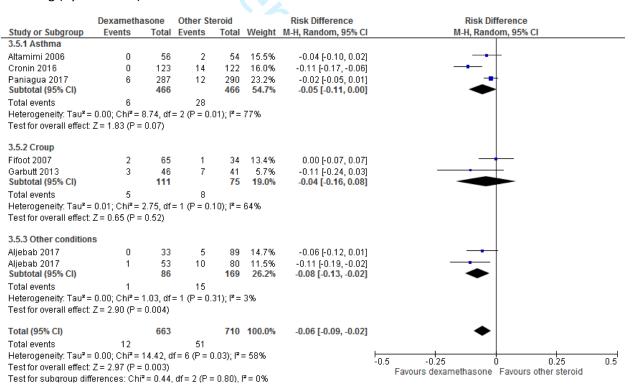
Vomiting (by dose)



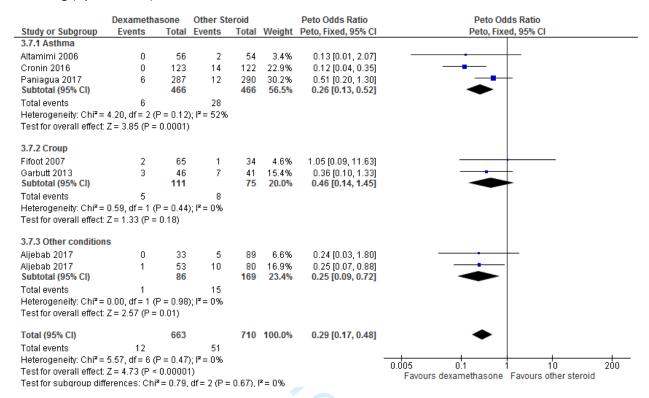
Vomiting (by dose) – Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
3.4.1 Single-dose							
Aljebab 2017	0	33	5	89	6.6%	0.24 [0.03, 1.80]	
Aljebab 2017	1	53	10	80	16.9%	0.25 [0.07, 0.88]	
Altamimi 2006	0	56	2	54	3.4%	0.13 [0.01, 2.07]	
Cronin 2016	0	123	14	122	22.9%	0.12 [0.04, 0.35]	
Fifoot 2007	2	65	1	34	4.6%	1.05 [0.09, 11.63]	
Garbutt 2013	3	46	7	41	15.4%	0.36 [0.10, 1.33]	
Subtotal (95% CI)		376		420	69.8%	0.23 [0.12, 0.42]	•
Total events	6		39				
Heterogeneity: Chi²=	3.55, df = 5 (P = 0.62); $I^2 = 0\%$				
Test for overall effect	$Z = 4.73 (P \le$	0.0000	1)				
3.4.2 Multi-dose							
Paniagua 2017	6	287	12	290	30.2%	0.51 [0.20, 1.30]	
Subtotal (95% CI)		287		290	30.2%	0.51 [0.20, 1.30]	→
Total events	6		12				
Heterogeneity: Not ap	pplicable						
Test for overall effect	Z = 1.41 (P =	0.16)					
							•
Total (95% CI)		663		710	100.0%	0.29 [0.17, 0.48]	•
Total events	12		51				
Heterogeneity: Chi²=	: 5.57, df = 6 (P = 0.47); I² = 0%				0.002 0.1 1 10 500
Test for overall effect	Z = 4.73 (P ≤	0.0000	1)				Favours dexamethasone Favours other steroid
Test for subgroup dif	ferences: Chi	$^{2} = 2.02$	df = 1 (P =	0.16),	r = 50.5%	6	Tarouro dovarriouracerio il divodro otrici oterora

Vomiting (by condition)



Vomiting (by condition) - Peto



Abdominal pain

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Aljebab 2017	8	33	21	89	11.9%	0.01 [-0.16, 0.18]	
Aljebab 2017	10	53	17	80	18.1%	-0.02 [-0.16, 0.11]	
Altamimi 2006	2	56	3	54	56.9%	-0.02 [-0.10, 0.06]	
Garbutt 2013	9	46	7	41	13.1%	0.02 [-0.14, 0.19]	-
Total (95% CI)		188		264	100.0%	-0.01 [-0.07, 0.05]	
Total events	29		48				
Heterogeneity: Tau² =	= 0.00; Chi ² =	0.35, df:	= 3 (P = 0.	95); l² =	0%	•	-0.2 -0.1 0 0.1 0.2
Test for overall effect	Z= 0.38 (P=	0.70)					Favours dexamethasone Favours other steroid
Abdominal pair	n – Peto						
	_						

Abdominal pain - Peto

	Dexameth	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Aljebab 2017	8	33	21	89	31.2%	1.04 [0.41, 2.64]	
Aljebab 2017	10	53	17	80	36.9%	0.86 [0.37, 2.04]	
Altamimi 2006	2	56	3	54	8.5%	0.64 [0.11, 3.79]	
Garbutt 2013	9	46	7	41	23.4%	1.18 [0.40, 3.47]	
Total (95% CI)		188		264	100.0%	0.96 [0.57, 1.61]	
Total events	29		48				
Heterogeneity: Chi ² =	= 0.43, df = 3 (P = 0.93); I² = 0%				01 02 05 1 2 5 10
Test for overall effect	:: Z = 0.16 (P =	0.87)					0.1 0.2 0.5 1 2 5 10 Favours dexamethasone Favours other steroid

Abdominal pain (by condition)

	Dexameth	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.10.1 Asthma							
Altamimi 2006	2	56	3	54	56.9%	-0.02 [-0.10, 0.06]	_
Subtotal (95% CI)		56		54	56.9%	-0.02 [-0.10, 0.06]	•
Total events	2		3				
Heterogeneity: Not a							
Test for overall effect	: Z = 0.50 (P =	: 0.62)					
3.10.2 Croup							
Garbutt 2013	9	46	7	41	13.1%	0.02 [-0.14, 0.19]	
Subtotal (95% CI)		46		41	13.1%	0.02 [-0.14, 0.19]	•
Total events	9		7				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.30 (P =	0.76)					
3.10.3 Other condition	ons						
Aljebab 2017	8	33	21	89	11.9%	0.01 [-0.16, 0.18]	
Aljebab 2017	10	53	17	80	18.1%	-0.02 [-0.16, 0.11]	
Subtotal (95% CI)		86		169	30.0%	-0.01 [-0.12, 0.10]	•
Total events	18		38				
Heterogeneity: Tau ² :	= 0.00; Chi ² =	0.07, df:	= 1 (P = 0.	79); l² =	0%		
Test for overall effect	: Z = 0.22 (P =	0.83)					
Total (95% CI)		188		264	100.0%	-0.01 [-0.07, 0.05]	•
Total events	29		48				
Heterogeneity: Tau ² :	= 0.00; Chi² =	0.35, df	= 3 (P = 0.	95); l² =	0%		-1 -0.5 0 0.5 1
Test for overall effect	Z = 0.38 (P =	0.70)					-1 -0.5 U 0.5 1 Favours dexamethasone Favours other steroid
Test for subgroup dif	ferences: Chi	i² = 0.24.	df = 2 (P =	0.89).	l² = 0%		Favours devantemensone Favours office steroid

Abdominal pain (by condition) - Peto

·			•				
	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
3.10.1 Asthma							
Altamimi 2006	2	56	3	54	8.5%	0.64 [0.11, 3.79]	•
Subtotal (95% CI)		56		54	8.5%	0.64 [0.11, 3.79]	
Total events	2		3				
Heterogeneity: Not ap	pplicable						
Test for overall effect	Z = 0.50 (P =	0.62)					
3.10.2 Croup							
Garbutt 2013	9	46	7	41	23.4%	1.18 [0.40, 3.47]	
Subtotal (95% CI)		46		41	23.4%	1.18 [0.40, 3.47]	
Total events	9		7				
Heterogeneity: Not ap	pplicable						
Test for overall effect	Z = 0.30 (P =	0.77)					
3.10.3 Other condition	ons						
Aljebab 2017	8	33	21	89	31.2%	1.04 [0.41, 2.64]	
Aljebab 2017	10	53	17	80	36.9%	0.86 [0.37, 2.04]	
Subtotal (95% CI)		86		169	68.1%	0.94 [0.50, 1.77]	-
otal events	18		38				
Heterogeneity: Chi²=	0.08, df = 1 (P = 0.78); I² = 0%				
Test for overall effect	: Z= 0.19 (P=	0.85)					
Total (95% CI)		188		264	100.0%	0.96 [0.57, 1.61]	-
Total events	29		48				
Heterogeneity: Chi²=	0.43, df = 3 (P = 0.93); I² = 0%				0.1 0.2 0.5 1 2 5 10
Γest for overall effect	Z = 0.16 (P =	0.87)					Favours dexamethasone Favours other steroid
Test for subgroup dif	ferences: Chi	$i^2 = 0.35$,	df = 2 (P =	0.84),	l² = 0%		1 avous accumousone 1 avous other steroid

DEXAMETHASONE vs. OTHER STEROID – CNS & Behaviour

Tremor/jitteriness

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
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 a Test for overall effect		0.48)					-0.1 -0.05 0 0.05 0.1 Favours dexamethasone Favours other steroid

Tremor/jitteriness - Peto

	Dexameth	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	CI 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 ap Test for overall effect		= 0.35)					0.002 0.1 10 500 Favours dexamethasone Favours other steroid

Behaviour change

	Dexametha	sone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
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: Tau ² =	0.00; Chi ² = 1	0.45, df	= 1 (P = 0.	50); l² =	0%		-0.2 -0.1 0 0.1 0.2
Test for overall effect:	Z=0.96 (P=	0.33)					Favours dexamethasone Favours other steroid

Behaviour change - Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
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: Chi ² =	0.65, df = 1 (P = 0.42); I² = 0%				0.005 0.1 1 10 20	<u>—</u>
Test for overall effect	: Z = 0.82 (P =	0.41)					0.005 0.1 1 10 20 Favours dexamethasone Favours other steroid	00

Behaviour change (by condition)

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.16.1 Asthma							
Gries 2000	10	14	14	16	34.6%	-0.16 [-0.45, 0.13]	
Subtotal (95% CI)		14		16	34.6%	-0.16 [-0.45, 0.13]	
Total events	10		14				
Heterogeneity: Not ap	pplicable						
Test for overall effect	Z = 1.10 (P =	0.27)					
3.16.2 Croup							
Garbutt 2013	25	46	24	41	65.4%	-0.04 [-0.25, 0.17]	
Subtotal (95% CI)		46		41	65.4%	-0.04 [-0.25, 0.17]	
Total events	25		24				
Heterogeneity: Not ap	pplicable						
Test for overall effect	Z = 0.39 (P =	0.69)					
Total (95% CI)		60		57	100.0%	-0.08 [-0.25, 0.09]	
Total events	35		38				
Heterogeneity: Tau² =	= 0.00; Chi² =	0.45, df	= 1 (P = 0.	50); l²=	0%		-1 -0.5 0 0.5 1
Test for overall effect	: Z = 0.96 (P =	0.33)					Favours dexamethasone Favours other steroid
Test for subgroup dif	ferences: Chi	$^{2} = 0.43$	df = 1 (P =	= 0.51), I	² =0%		

Behaviour change (by condition) – Peto

	Dexameth	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
3.19.1 Asthma							
Gries 2000	10	14	14	16	18.6%	0.38 [0.06, 2.21]	-
Subtotal (95% CI)		14		16	18.6%	0.38 [0.06, 2.21]	
Total events	10		14				
Heterogeneity: Not as	oplicable						
Test for overall effect	Z=1.08 (P=	0.28)					
3.19.2 Croup							
Garbutt 2013	25	46	24	41	81.4%	0.85 [0.36, 1.97]	
Subtotal (95% CI)		46		41	81.4%	0.85 [0.36, 1.97]	-
Total events	25		24				
Heterogeneity: Not ap	oplicable						
Test for overall effect	Z= 0.39 (P=	0.70)					
Total (95% CI)		60		57	100.0%	0.73 [0.34, 1.56]	•
Total events	35		38				
Heterogeneity: Chi²=	0.65, df = 1 (P = 0.42); I² = 0%				0.01 0.1 1 10 100
Test for overall effect:	Z = 0.82 (P =	0.41)					Favours dexamethasone Favours other steroid
Test for subgroup dif	ferences: Chi	$i^2 = 0.65$,	df = 1 (P =	= 0.42),	l² = 0%		Tavouro devamentacióne i avouro otrier steroid

Headache

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Altamimi 2006	0	56	0	54	71.8%	0.00 [-0.03, 0.03]	-
Garbutt 2013	7	46	4	41	28.2%	0.05 [-0.08, 0.19]	-
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); l² =	51%		
Test for overall effect	Z = 0.33 (P =	0.74)					-0.2 -0.1 0 0.1 0.2 Favours dexamethasone Favours other steroid

Headache - Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
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 as	pplicable						0.05 0.2 1 5 20
Test for overall effect:	: Z= 0.76 (P=	0.45)					Favours dexamethasone Favours other steroid

Headache (by condition)

	Dexametha	sone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.22.1 Asthma							
Altamimi 2006	0	56	0	54	71.8%	0.00 [-0.03, 0.03]	<u>+</u>
Subtotal (95% CI)		56		54	71.8%	0.00 [-0.03, 0.03]	_
Total events	0		0				
Heterogeneity: Not ap	oplicable						
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 ap	plicable						
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 = 0.1	16); l² =	51%	_	
Test for overall effect:			•				-0.2 -0.1 0 0.1 0.2
Test for subgroup diff	,		df = 1 (P =	0.45).	$I^2 = 0\%$		Favours dexamethasone Favours other steroid

Headache (by condition) - Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
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 as	oplicable						
Test for overall effect:	: Not applicab	le					
2 22 2 Crown							
3.23.2 Croup	_						
Garbutt 2013	7	46		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 as	•						
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 as	oplicable						
Test for overall effect:		0.45)					0.05 0.2 1 5 20
Test for subgroup diff	,		ble				Favours dexamethasone Favours other steroid

DEXAMETHASONE vs. OTHER STEROID – Dermatologic

Phlebitis

	Dexametha	asone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% 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 ap	pplicable						-0.2 -0.1 0 0.1 0.2
Test for overall effect	Z = 0.00 (P =	1.00)					Favours dexamethasone Favours other steroid

Phlebitis - Peto

	Dexametha	asone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Fries 2000	0	15	0	17		Not estimable	
otal (95% CI)		15		17		Not estimable	
otal events	0		0				
Heterogeneity: Not ap							0.05 0.2 1 5 3
est for overall effect	: Not applicab	le					Favours dexamethasone Favours other steroid
							Favours dexametriasone Favours other steroid

DEXAMETHASONE vs. OTHER STEROID - Endocrine/Metabolic & Musculoskeletal

Fluid & electrolyte abnormalities

	Dexametha	isone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Tagarro 2014	1	33	2	15	100.0%	-0.10 [-0.28, 0.08]	
Total (95% CI)		33		15	100.0%	-0.10 [-0.28, 0.08]	
Total events	1		2				
Heterogeneity: Not a Test for overall effect		0.27)					-0.2 -0.1 0 0.1 0.2 Favours dexamethasone Favours other steroid

Fluid & electrolyte abnormalities - Peto

	Dexameth		Other St			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup Tagarro 2014	Events 1	33	Events 2		100.0%	Peto, Fixed, 95% CI 0.18 [0.01, 2.17]	Peto, Fixed, 95% CI
	'						_
Total (95% CI)		33		15	100.0%	0.18 [0.01, 2.17]	
Fotal events Heterogeneity: Not ap	1 Indicable		2				
Test for overall effect:		= 0.18)					0.01 0.1 1 10 100
	(,					Favours dexamethasone Favours other steroid

DEXAMETHASONE vs. OTHER STEROID – Cardiovascular

Arrhythmia

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

Arrhythmia – Peto

	Dexameth	asone	Other St	teroid		Peto Odds Ratio	Peto Od	ds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixe	ed, 95% CI	
Altamimi 2006	0	56	0	54		Not estimable			
Total (95% CI)		56		54		Not estimable			
Total events	0		0						
Heterogeneity: Not ap Test for overall effect:		ole					0.01 0.1 Favours dexamethasone	10 Favours other steroid	100

Hypertension

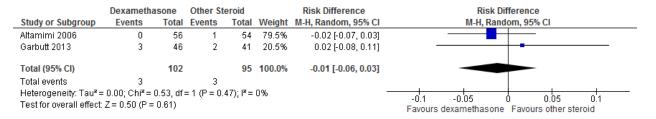
	Dexametha	asone	Other St	eroid		Risk Difference		F	Risk Difference	е	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H	, Random, 959	% CI	
Gries 2000	0	15	0	17	100.0%	0.00 [-0.11, 0.11]			-		
Total (95% CI)		15		17	100.0%	0.00 [-0.11, 0.11]			•		
Total events	0		0								
Heterogeneity: Not ap Test for overall effect		1.00)					-1 F	-0.5 Favours dexameth:	0 asone Favour	0.5 rs other steroid	1

Hypertension – Peto

	Dexametha	sone	Other St	eroid		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Gries 2000	0	15	0	17		Not estimable		
Total (95% CI)		15		17		Not estimable		
Total events	0		0					
Heterogeneity: Not ap Test for overall effect:	•	le					0.01 0.1 1 Favours dexamethasone Favours other	10 100 r steroid

DEXAMETHASONE vs. OTHER STEROID – General

General complaints



General complaints – Peto

	Dexametha	sone	Other Ste	eroid		Peto Odds Ratio	Peto Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	
Altamimi 2006	0	56	1	54	17.4%	0.13 [0.00, 6.58]		
Garbutt 2013	3	46	2	41	82.6%	1.35 [0.22, 8.15]		
Total (95% CI)		102		95	100.0%	0.90 [0.18, 4.61]		
Total events	3		3					
Heterogeneity: Chi ^z = Test for overall effect:); I² = 11%				0.002 0.1 10 50 Favours dexamethasone Favours other steroid) <u>o</u>

General complaints (by condition)

	Dexametha	sone	Other St	eroid		Risk Difference	Risk Difference
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
3.6.1 Asthma							
Altamimi 2006	0	56	1	54	78.7%	-0.02 [-0.07, 0.03]	· ·
Subtotal (95% CI)		56		54	78.7%	-0.02 [-0.07, 0.03]	•
Total events	0		1				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z= 0.73 (P=	0.46)					
3.6.2 Croup							
Garbutt 2013	3	48	2	41	21.3%	0.01 [-0.08, 0.11]	-
Subtotal (95% CI)		48		41	21.3%	0.01 [-0.08, 0.11]	◆
Total events	3		2				
Heterogeneity: Not a	pplicable						
Test for overall effect	: Z = 0.28 (P =	0.78)					
Total (95% CI)		104		95	100.0%	-0.01 [-0.06, 0.03]	•
Total events	3		3				
Heterogeneity: Tau² :	= 0.00; Chi² = I	0.46, df	= 1 (P = 0.	50); l² =	0%		-1 -0.5 0 0.5 1
Test for overall effect	: Z= 0.52 (P=	0.60)					Favours dexamethasone Favours other steroid
Test for subgroup dif	fferences: Chi ^a	2 = 0.35,	df=1 (P=	0.56),	l² = 0%		1 avours devanientasone avours oniet stetota

General complaints (by condition) – Peto

Study or Subgroup	Dexamethasone Events Tota	Other Sto		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
3.34.1 Asthma Altamimi 2006 Subtotal (95% CI)	0 5 50		54 5 4	17.4% 17.4 %	0.13 [0.00, 6.58]	
Total events Heterogeneity: Not ap	0	1	34	17.470	0.13 [0.00, 6.58]	
Test for overall effect:	Z = 1.02 (P = 0.31)					
3.34.2 Croup Garbutt 2013	3 4		41	82.6%	1.29 [0.21, 7.81]	
Subtotal (95% CI) Total events Heterogeneity: Not ap	4: 3 onlicable	2	41	82.6%	1.29 [0.21, 7.81]	
Test for overall effect:						
Total (95% CI) Total events	10- 3	4 3	95	100.0%	0.87 [0.17, 4.45]	
Heterogeneity: Chi²= Test for overall effect:	1.09, df = 1 (P = 0.3 Z = 0.17 (P = 0.86)	10); I² = 8%				0.01 0.1 1 10 100 Favours dexamethasone Favours other steroid
Test for subgroup diff	ferences: Chi² = 1.0					

Supplement 7. Studies reporting no adverse events

		E	BMJ Open		AE reporting
Supplement 7. Stu	dies reporting no adverse	Comparisons - main	Study design	Study sample	AE reporting 65
Alansari 2013	bronchiolitis	systemic vs. placebo	RCT	200	No AE overall; ≧ 7 days follow-upgevealed no side effect concerns in treatment groups.
Brunette 1988	asthma, before signs of wheeze	systemic vs. systemic	nRCT	32	No AE overall; O 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;
Chub-Uppakarn 2007	croup	systemic vs. systemic	RCT	41	No AE overall; No significant adverse reaction from dexamethasone reatment in either group.
Escobedo Chavez 1992	asthma	systemic vs. non- corticosteroid	RCT	50	No AE overall;
Fifoot 2007	croup	systemic vs. systemic vs. systemic	RCT, 3-arm	99	No AE overall; One patient in exh group vomited their first dose of medication; all except one (dexamethasone 0.6mg/kg) tolerated their repeat dose; on patient suffered any adverse outcomes from receiving story steroid, either at index presentation or during the follow-up period.

34		E	BMJ Open		136/bmjopen-20
Ghirga 2002	wheeze - recurrent, early in URTI	inhaled vs. no intervention	RCT	26	No AE overall; 80 No apparent adverse effects reported 4 years post-study.
Husby 1993	croup	inhaled vs. placebo	RCT	36	No AE overall; $\stackrel{\hookrightarrow}{\rightarrow}$ No side effects were reported.
Jartti 2006	wheeze - acute	systemic vs. placebo	RCT	78	No AE overall; S Prednisolone trestment well tolerated; no clinically significant adverse effects occurred.
Jartti 2007	wheeze - recurrent	systemic vs. placebo	RCT	58	No AE overall; Some 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 budesopide group.
Langton Hewer 1998	asthma	systemic vs. systemic vs. systemic	RCT, 3-arm	98	No AE overall; No side effect possibly attributable to prednisolone the apy was noted in any of the three treatment proups.
Leipzig 1979	croup	systemic vs. placebo	RCT	30	No AE overall; 7 Observed no adverse effects or late relapses.
Razi 2015	asthma	inhaled vs. placebo	RCT	100	No AE overall; $\begin{tabular}{c} $\not \xi \\ No drug-related & dverse effects were identified during hospitalization. \begin{tabular}{c} $ $
Roorda 1998	croup	inhaled vs. placebo	RCT	17	No AE overall; 중 No side effects of treatment regimens were reported. 방

			BMJ Open		Pc 1136/bmjopen-20
Saito 2017	asthma	systemic vs. inhaled	RCT	50	No AE overall; Adverse events and 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; On AE overall; No adverse effects developed in children given prednisologie after discharge.
Sparrow 2006	croup	systemic vs. systemic	RCT	133	No AE overall; ခြို့ No adverse evengs in either group.
Storr 1987	asthma	systemic vs. placebo	RCT	140	No AE overall; There were no observed side effects related to the single pregnisolone dose.
Sung 1998	asthma	inhaled vs. placebo	RCT	44	No AE overall;
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, asige from tremor (1 infant) as side effect of saleutamol.
Tamura 2008	refractory pneumonia (5 year old)	systemic	CS (#1)	1	No AE overall; No adverse evens in any patients during steroid treatment.

van Woensel 1997	bronchiolitis	systemic vs. placebo	RCT	54	No AE overall; Representation of the control of the
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-da 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.

ben.bmj.com/ on April 17, 2024 by guest. Protected by copyright. AE: adverse events; CS: case series; nRCT: non-randomised controlled trial; RCT: randomised controlled trial; sal: salbitamol; URTI: upper respiratory tract infection; vs: versus

The PRISMA for Abstracts Checklist

	BMJ Open Boy Dope	Paç
The PRISMA for Abstracts Che	BMJ Open BMJ Open ecklist	
TITLE	CHECKLIST ITEM	REPORTED ON PAGE #
1. Title:	Identify the report as a systematic review, meta-analysis, or both.	1
BACKGROUND	st 20	
2. Objectives:	The research question including components such as participants, interventions, comparators, and outcomes.	3
METHODS	ownic	
3. Eligibility criteria:	Study and report characteristics used as criteria for inclusion.	3
4. Information sources:		3
5. Risk of bias:	Key databases searched and search dates. Methods of assessing risk of bias.	3
RESULTS	//bmj	
6. Included studies:	Number and type of included studies and participants and relevant characteristics of sudies.	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 megningful to clinicians and patients.	3
DISCUSSION	ii 17,	
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	t. Pro	
11. Funding:	Primary source of funding for the review.	
12. Registration:	Registration number and registry name.	

1 2 3 4 5 6 7 8	
9 10 11 12 13 14 15	,
16 17 18 19 20 21 22 23	
24 25 26 27 28 29 30 31 32	
33 34 35 36 37 38 39 40 41 42 43 44	,
45 46 47 48 49 50 51 52	
53 54 55 56 57 58 59 60	

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.
Eligibility criteria (6)	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication	_	Report how handled relevant studies (based on population and intervention) when the	22) p. 6-7;

1							BMJ Open: first published as 10.1136/bmJopen-2018-028511 on 1 August 2019.
2							ر
3			status) used as criteria for eligibility,		outcomes of interest	Supplement 2 -	ğ
4			giving rationale.		were not reported.	Eligibility criteria	ž
5					Report choices for	for study inclusion	=
6					specific study designs	,	St
7					and length of follow-up.		ŭ
8	Information	7	Describe all information sources (eg,		Report if only searched	p. 6;	S
9	sources (7)	,	databases with dates of coverage,		for published data, or	p. 0,	he
	sources (7)		contact with study authors to identify		also sought data from	Supplement 1-	a
10			additional studies) in the search and				S
11					unpublished sources,	Search strategy	ē
12			date last searched.		from authors, drug		
13					manufacturers and		6
14					regulatory agencies. If		3
15					includes unpublished		뎡
16					data, provide the source		ěn
17					and the process of		<u>'</u>
18					obtaining it.		18
19	Search (7)	8	Present full electronic search strategy	_	If additional searches	Supplement 1 -	Ö
20			for at least one database, including		were used specifically	Search strategy	382
21			any limits used, such that it could be		to identify adverse		1
			repeated.		events, authors should		9
22					present the full search		
23					process so it can be		Ą
24					replicated.		ū
25	Study	9	State the process for selecting studies		If only included studies	p. 7;	St
26	selection (8)		(ie, screening, eligibility, included in		reporting on adverse	1 ,	201
27	(-)		systematic review, and, if applicable,		events of interest,	Supplement 2 -	9
28			included in the meta-analysis).		defined if screening was	Eligibility criteria	D
29			morauda m viid mata anarysis).		based on adverse event	for study inclusion	₹
30					reporting in	ioi stady inclusion	헔
31					title/abstract or full text.		ge
32					If no harms reported in		ă
33					the text, report if any		<u>S</u>
					attempt was made to		크
34					retrieve relevant data		₹
35							Š
36	D-4-	10	Describe mode de Calaba comunica		from authors.	7.0	ĭ
37	Data	10	Describe method of data extraction	_	No specific additional	p. 7-8	용
38	collection		from reports (eg, piloted forms,		information is required		9
39	process (9)		independently, in duplicate) and any		for systematic reviews		b
40			processes for obtaining and		of harms.		٦
41			confirming data from investigators.			- 0	Ö
42	Data items (9)	11	List and define all variables for which	_	Report the definition of	p. 7-8	0
43			data were sought (eg, PICOS, funding		the harm and		Ď
44			sources) and any assumptions and		seriousness used by		þŗ
45			simplifications made.		each included study (if		=
					applicable). Report if		7,
46					multiple events		202
47					occurred in the same		24
48					individuals, if this		Ş
49					information is available.		ù
50					Consider if the harm		est
51					may be related to		τ
52					factors associated with		ō
53					participants (eg, age,		ect
54					sex, use of medications)		ed
55					or provider (eg, years of		à
56					practice, level of		Downloaded from http://bmjopen.bmj.com/ on April 17, 2024 by guest. Protected by copyright.
57					r,		ğΥ
58							rigi
58							;÷

1 2 3 4 5 6 7 8 9 10 11 12 13					training). Specify if information was extracted and how it was used in subsequent results. Specify if extracted details regarding the specific methods used to capture harms (active/passive and timing of adverse event).	
14 15 16 17 18 19	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
20 21 22	Summary measures (11)	13	State the principal summary measures (eg, risk ratio, difference in means).	_	No specific additional information is required for systematic reviews of harms.	p. 8-9
23 24 25 26 27	Synthesis of results (11)	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I ²) for each metaanalysis.	Specify how zero events were handled, if relevant.		p. 8-9
28 29 30 31 32 33 34 35 36	Risk of bias across studies (11)	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	62: 	Present the extent of missing information (studies without harms outcomes), any factors that may account for their absence, and whether these reasons may be related to the results.	p. 9
37 38 39 40 41 42 43 44 45 46 47 48 49	Additional analyses (12)	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.		Sensitivity analyses may be affected by different definitions, grading, and attribution of adverse events, as adverse events are typically infrequent or reported using heterogeneous classifications. Report the number of participants and studies included in each subgroup.	p. 9
50 51 52 53 54 55 56 57 58	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

59

60

1						
2 3 4 5 6 7 8 9 10 11 12 13 14 15		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)	p. 9; Supp Char inclu
16 17					timing of all harms assessments and the	
17 18 19 20 21 22 23 24 25 26 27 28 29	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).	_	length of follow-up. 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 honefit as described in	p. 9; Supp Meth quali studio
30					benefit as described in item 12, above.	
31 32 33 34 35	. ,	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	704	Report the actual numbers of adverse events in each study, separately for each intervention.	p. 10 Supp Chara inclu
36 37	Synthesis of	21	a forest plot. Present results of each meta-analysis	Describe any	If included data from	p. 10
38 39 40 41 42 43 44 45			done, including confidence intervals and measures of consistency.	assessment of possible causality.	unpublished sources, report clearly the data source and the impact of these studies to the final systematic review.	Table of stupartic report event
46						Fores
47 48 49 50 51 52						Supp Effect for all event subgr
53 54 55 56 57 58						Supp Fores adver

plement 3 aracteristics of luded studies

plement 4 thodological lity of included dies

0;

plement 3 aracteristics of luded studies

0-15;

ole 2 - Number studies and ticipants orting adverse nts;

ures 2-4 est plots of erse events;

plement 5 ect estimates all adverse nts with groups;

plement 6 – est plots of erse events;

2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23	Risk of bias across studies (18)	22	Present results of any assessment of risk of bias across studies (see item 15). 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. See item 15 above. No specific additional information is required for systematic reviews of harms.	Supplement 7 - Studies reporting no adverse events p. 9; Table 1 - Summary of methodological quality assessments p. 10; Supplement 5 - Effect estimates for all adverse events with subgroups; Supplement 6 - Forest plots of
24 25 26 27 28 29	Discussion Summary of evidence (18)	24	Summarise the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	_	No specific additional information is required for systematic reviews of harms.	p. 15-17
30 31 32 33 34 35 36	Limitations (18)	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	1.52	Recognise possible limitations of meta- analysis for rare adverse events (ie, quality and quantity of data), issues noted previously related to collection and reporting.	p. 18-19
37 38 39 40 41 42 43 44 45 46 47	Conclusions (19)	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	- 0	State conclusions in coherence with the review findings. When adverse events were not identified we caution against the conclusion that the intervention is "safe," when, in reality, its safety remains unknown.	p. 19-20
48 49 50 51 52	Funding (19)	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	_	No specific additional information is required for systematic reviews of harms.	p. 22