BMJ Open

# Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis

Ricardo M Fernandes,[1,2] Aireen Wingert,[3] Ben Vandermeer,[3] Robin Featherstone,[3] Samina Ali,[4,5] Amy C Plint,[6] Antonia S Stang,[7] Brian H Rowe,[8,9] David W Johnson,[10] Dominic Allain,[4] Terry P Klassen,[11] Lisa Hartling[3,4]

**To cite:** Fernandes RM, Wingert A, Vandermeer B, *et al*. Safety of corticosteroids in young children with acute respiratory conditions: a systematic review and meta-analysis. *BMJ Open* 2019;**9**:e028511. doi:10.1136/bmjopen-2018-028511

► Prepublication history and additional material for this paper are available online. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2018-028511).

Received 11 December 2018
Revised 24 June 2019
Accepted 3 July 2019



For numbered affiliations see end of article.

**Correspondence to**
Lisa Hartling;
hartling@ualberta.ca

## ABSTRACT

**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 categorisation model by organ systems. Meta-analyses used Peto ORs (pORs) and DerSimonian Laird inverse variance method utilising Mantel-Haenszel Q statistic, with 95% CI. Subgroup analyses were conducted for respiratory condition and dose.

**Results** Eighty-five studies (11 505 children) were included; 68 were randomised trials. Methodological quality was poor overall due to lack of assessment and inadequate reporting of AEs. Meta-analysis (six studies; n=1373) found fewer cases of vomiting comparing oral dexamethasone with prednisone (pOR 0.29, 95% CI 0.17 to 0.48; $I^2$=0%). The mean difference in change-from-baseline height after one year between inhaled corticosteroid and placebo was 0.10 cm (two studies, n=268; 95% CI −0.47 to 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 (AEs) captured across organ systems.
- Inconsistent definitions, assessments and reporting of AEs.
- Extensive variation in corticosteroid formulations and dosages within and between studies.
- Did not examine long-term corticosteroid use (>14 days).

## INTRODUCTION

Corticosteroids are the cornerstone of treatment for many common paediatric 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-term and long-term adverse events (AEs), 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 randomised controlled trials (RCTs). These reviews also focused on a specific underlying condition, disease severity, or particular corticosteroid, and mostly for longer-term administration (eg, 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 optimise management of young children who seek care due to acute respiratory illness.

The goal of this study was to synthesise evidence regarding the safety of short course corticosteroid use in young children (<6 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 online supplementary file 1.

### Eligibility criteria

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

Given the lack of standardised terminology for safety, we gathered information on all potentially drug-related harm outcomes[15] from studies including, but not limited to: adverse drug reactions, adverse drug events, medication errors, side effects and potential adverse drug events. For consistency, these outcomes are referred to in the manuscript as 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, cointerventions, rescue medications), outcomes (types and timing), care setting, funding sources and results.

AEs were extracted as reported by study authors and categorised using a published model based on organ systems (see Results section).[16] A panel of clinicians with specialties in paediatrics, 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 utilising the Mantel-Haenszel Q statistic. Binary data were also pooled using the Peto ORs (pORs) fixed-effects method.[18] Studies that reported at least one event in at least one treatment arm were included in the analysis of pORs and all comparative studies were used for analysis of RD. One AE (growth) was reported as a continuous outcome and data were pooled using a DerSimonian Laird inverse variance random effects method as a mean difference (MD; in cm). The $I^2$ statistic was presented to quantify the magnitude of statistical heterogeneity between studies; while the $I^2$ has the potential to be misinterpreted, it is the standard in the field and we chose to present the statistic for

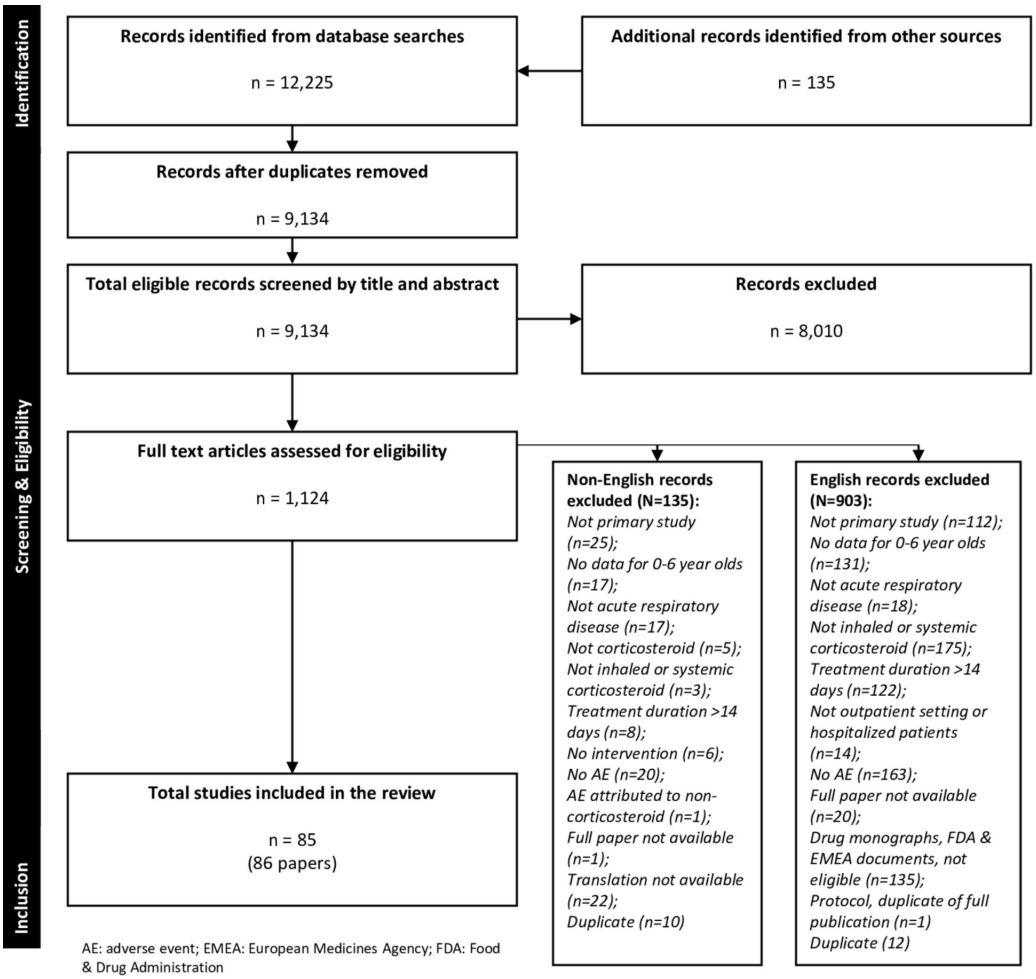


**Figure 1** PRISMA study flow selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

informational purposes.[19] Subgroup analyses from study-level data were conducted for respiratory condition and dose (single vs multidose) using Cochran's Q ($\alpha$=0.05) to detect statistical heterogeneity. Studies contributing no numerical data for analysis (eg, single arm studies, studies that reported no AEs overall) are summarised in online supplementary file 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 V.5.3 (Cochrane Collaboration).[21] Graphs were constructed using TIBCO Spotfire S+Workbench V.3.4.[22]

## RESULTS

Database and grey literature searches yielded 9134 records. Eighty-six papers (85 studies)[23–108] involving 11 505 participants were included (figure 1). Characteristics of the included studies are in online supplementary file 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; online supplementary file 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 online supplementary file 5, with effect estimates and 95% CIs. Forest plots from meta-analyses are in online supplementary file 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 summarised in online supplementary file 7.

#### Infections and respiratory system

The number of studies contributing to each meta-analysis ranged from one to seven (range 58–2178 children).

**Table 1** Summary of methodological quality assessments

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

*Methodological quality of publications/studies as assessed by the McHarm scale.[17]
†Sum of percentages may not total 100 due to rounding.

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

| Organ system | AE—category | AE—specific | No of studies | No of participants |
|---|---|---|---|---|
| Infection and respiratory GI | Severe infections | | 5 | 1235 |
| | (1) | Sepsis | 1 | 32 |
| | (2) | Superinfection | 2 | 354 |
| | (3) | UTI | 1 | 720 |
| | (4) | Streptococcal infection | 1 | 129 |
| | Systemic infections | | 5 | 1635 |
| | (1) | Fever | 3 | 963 |
| | (2) | Common viral/bacterial/fungal infection | 2 | 792 |
| | (3) | Varicella | 3 | 1449 |
| | Lung/trachea | | 10 | 2053 |
| | (1) | Empyema | 1 | 600 |
| | (2) | Pneumonia | 8 | 2051 |
| | (3) | Respiratory distress | 2 | 2 |
| | Upper respiratory tract | | 14 | 2457 |
| | (1) | Bacterial tracheitis | 5 | 1023 |
| | (2) | Sinusitis | 2 | 849 |
| | (3) | Croup | 2 | 131 |
| | (4) | Viral parotitis | 1 | 27 |
| | (5) | Pharyngitis | 1 | 129 |
| | (6) | Persistent cough | 1 | 27 |
| | (7) | Oral thrush | 3 | 837 |
| | (8) | Otitis media | 4 | 1173 |
| | (9) | Ear, nose, throat infection | 3 | 862 |
| | (10) | Nasal discharge | 1 | 720 |
| | (11) | Eye discharge | 1 | 720 |
| | Voice complaints | | 5 | 794 |
| | GI 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 |
| | Diarrhoea | | 8 | 1346 |
| | (1) | Diarrhoea | 7 | 1217 |
| | (2) | Gastroenteritis | 1 | 129 |
| CNS and behaviour | Tremor/jitteriness | | 8 | 1274 |
| | (1) | Tremor | 7 | 1226 |
| | (2) | Jittery | 1 | 48 |
| | Behaviour change | | 14 | 2078 |
| | (1) | Violent behaviour | 1 | 198 |
| | (2) | Mood change | 7 | 1430 |
| | (3) | Hyperactivity | 2 | 268 |
| | (4) | Restlessness | 3 | 297 |
| | (5) | New sleep problems | 3 | 408 |
| | (6) | Emotional distress due to nebulizer mask | 1 | 82 |
| | (7) | Psychosis | 1 | 1 |
| | Headache | | 3 | 291 |

Continued

**Table 2** Continued

| Organ system | AE—category | AE—specific | No of studies | No of participants |
|---|---|---|---|---|
| Dermatological | Burn | | 1 | 198 |
| | Integument | | 10 | 1954 |
| | (1) | Hives | 2 | 199 |
| | (2) | Rash | 8 | 1954 |
| | (3) | Eczema | 1 | 129 |
| | (4) | Eye irritation | 2 | 211 |
| | (5) | Tongue irritation | 1 | 82 |
| | (6) | Positive weal | 1 | 1 |
| | (7) | Bleeding from ear | 1 | 720 |
| | Phlebitis | | 1 | 32 |
| Endocrine/metabolic and musculoskeletal | Fluid and electrolyte abnormalities | | 7 | 1849 |
| | (1) | Hyperkalemia | 1 | 800 |
| | (2) | Hyperglycemia | 3 | 154 |
| | (3) | Glycosuria | 1 | 125 |
| | (4) | Sodium retention | 1 | 50 |
| | (5) | Dehydration | 1 | 720 |
| | Growth | | 6 | 731 |
| | Adrenal suppression | | 5 | 249 |
| | Bone health | | 5 | 579 |
| Cardiovascular | Arrhythmia | | 3 | 312 |
| | (1) | Tachycardia | 2 | 178 |
| | (2) | Palpitations | 1 | 134 |
| | Hypertension | | 5 | 1491 |
| | Congestive heart failure | | 1 | 50 |
| General | General complaints | | 5 | 1146 |
| | (1) | Dizziness | 1 | 87 |
| | (2) | Pallor | 2 | 869 |
| | (3) | Excessive urination | 1 | 134 |
| | (4) | Normal tooth eruption | 1 | 56 |
| | Haematology, gum bleeding | | 1 | 1 |
| Immune system and oncology | Immunosuppression | | 4 | 147 |
| | (1) | Immunosuppression | 3 | 146 |
| | (2) | Tumour cell proliferation | 1 | 1 |

*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 (ie, infection and respiratory).
AE, adverse event; CNS, central nervous system; GI, gastrointestinal; URT, upper respiratory tract.

There were no statistically significant differences between: (1) *systemic corticosteroid compared with 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 (2) *inhaled corticosteroid compared with 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.

### Gastrointestinal tract

The number of studies contributing to each meta-analysis ranged from one to seven (range 97–3176 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for gastrointestinal (GI) bleeding,[30 32 40 65 83 87 105] vomiting,[30 38 40 42 70 81 83] abdominal pain[30] or diarrhoea[42 77 105] and (2) *inhaled corticosteroid and placebo* for GI bleeding,[65] vomiting[37 45 69 85 101] or diarrhoea.[37 45] Estimated pORs for both comparisons ranged from 0.89 to 1.10.

Meta-analysis of six studies (1373 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 vs 51/710 cases; pOR 0.29, 95% CI 0.17 to 0.48; $I^2$=0%). These studies focused on asthma (n=3),[27 41 80] croup (n=2)[49 52] or both (n=1)[25]; all compared oral dexamethasone with oral prednisone. No statistically significant difference was found for abdominal pain between *dexamethasone and another corticosteroid*.[25 27 52]

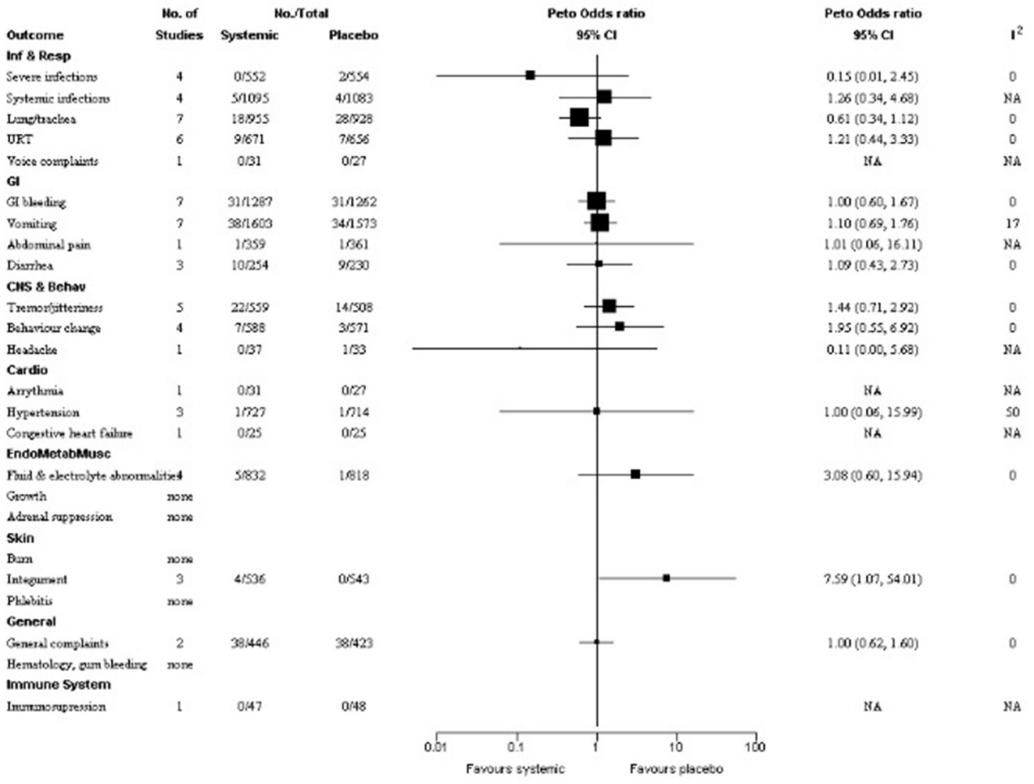


**Figure 2** Forest plot of adverse events—systemic versus placebo.

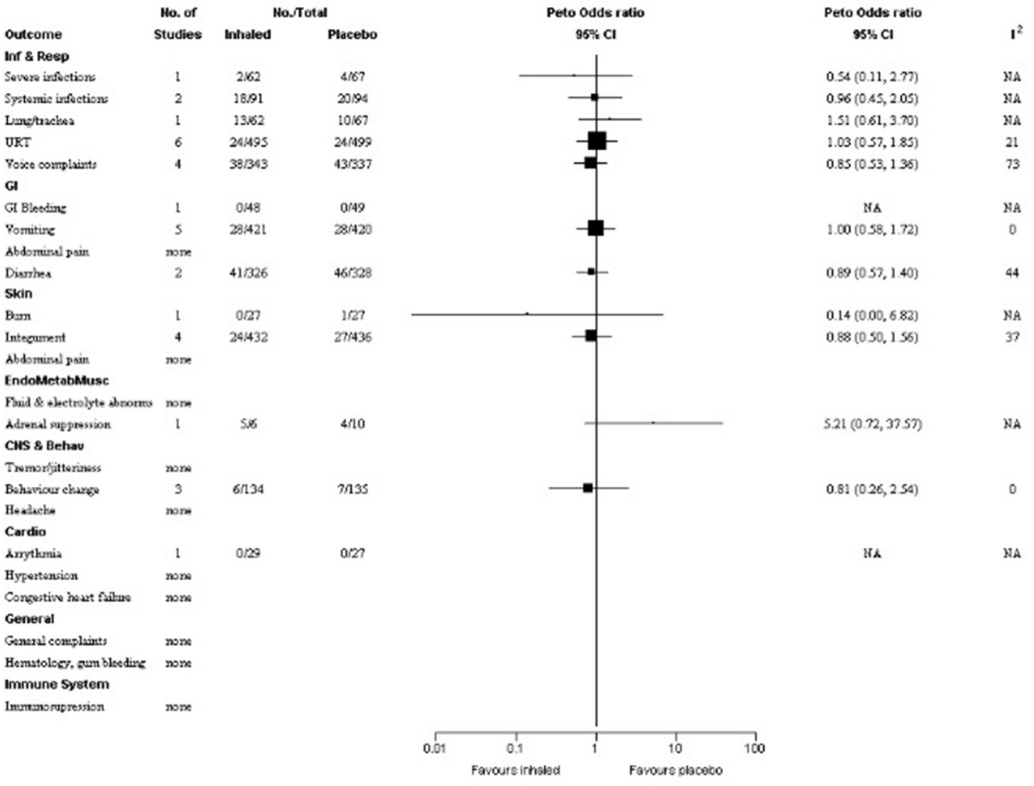


**Figure 3** Forest plot of adverse events—inhaled versus placebo.

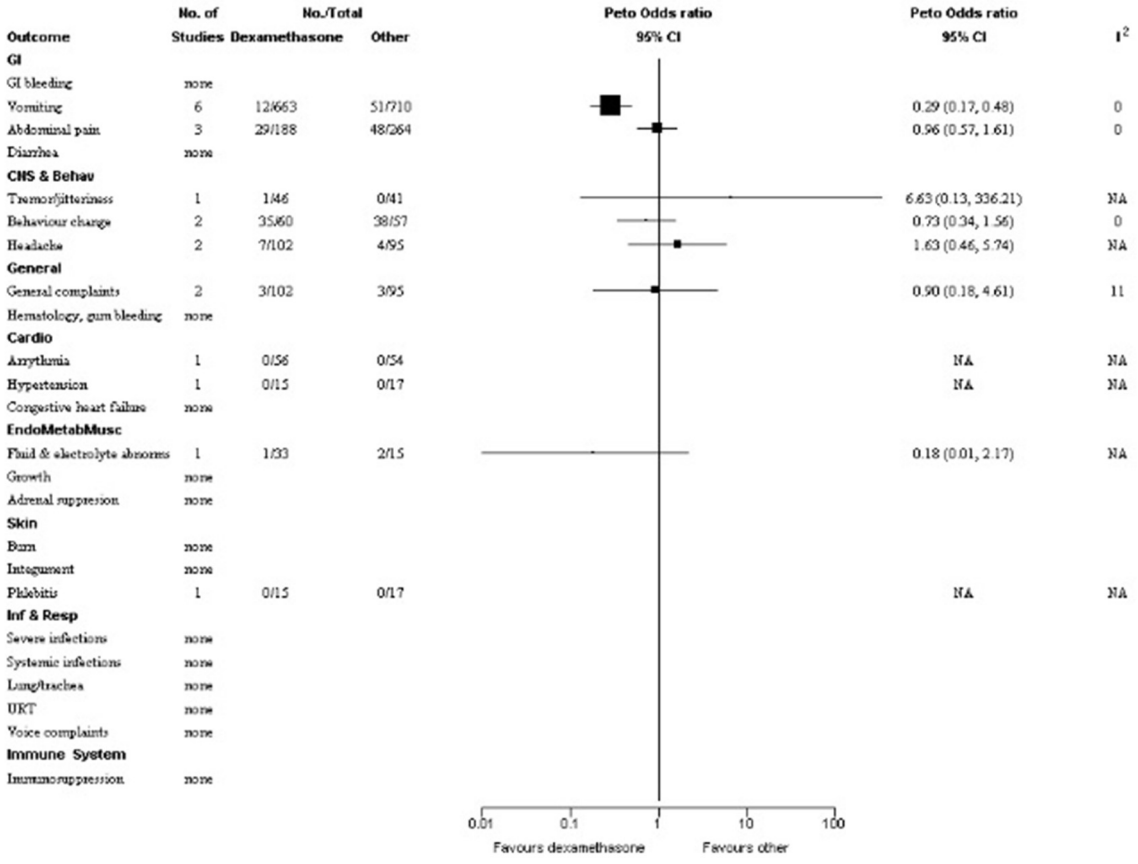


**Figure 4** Forest plot of adverse events—dexamethasone versus other.

### CNS and behaviour effects

The number of studies for each meta-analysis ranged from one to five (range 70–1159 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 32–1079 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for rash and hives,[30 42 67] albeit with an estimated pOR of 7.59 (4/536 vs 0/543; 95% CI 1.07 to 54.01) and (2) *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 and musculoskeletal systems

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

Pooled data for linear growth between *inhaled corticosteroid and placebo* included two studies (n=263) using recurrent doses for acute wheeze with follow-up at one year.[28 45] The estimated change-from-baseline height was small (MD 0.10 cm; 95% CI −0.47 to 0.67; $I^2$=9%). Five studies reported measurements of growth (height and weight) ranging from one to three years of follow-up, which could not be pooled due to heterogeneous interventions, comparators or outcome measurements.[29 31 45 58 71] Three studies included data on inhaled corticosteroid versus placebo. One RCT on asthma[58] (n=20) comparing budesonide and placebo found no signs of growth retardation by height measurements at 12 months or after up to six treatments. An RCT of episodic wheeze[29] (n=294) found height at three years of age was unaffected in children receiving budesonide or placebo. One RCT of inhaled fluticasone propionate at very high doses (1500 µg per day during upper respiratory infections) versus placebo in recurrent wheeze[45] reported additional outcome data on height that was not pooled in the meta-analysis mentioned above. There was a smaller mean change in height z score in the corticosteroid group over one year (MD −0.24; 95% CI −0.40 to −0.08; adjusted results).[45] Furthermore, mean weight was significantly lower at one-year follow-up in the fluticasone group (n=62) versus placebo (n=67); two children given

fluticasone and one given placebo met criteria for 'failure to thrive'.[45] Finally, two small trials did not report group differences for other comparisons: total and mean height growth (at 8–19 months) for intravenous dexamethasone versus inhaled budesonide in asthma (n=18)[71]; weight and height gains at 2 years for theophylline and metaproterenol with or without systemic prednisone on prevention of wheeze during upper respiratory infections in asthma (n=32).[31]

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

Five studies reported on bone health biomarkers, three of which compared inhaled corticosteroids and placebo; no pooled analyses were performed.[29 45 58 61 92] One RCT[29] compared inhaled budesonide (n=294) with placebo in episodic wheeze and found no effect on bone mineral density over three years. The RCT comparing high-dose inhaled fluticasone propionate with placebo (n=59 children with data) in viral wheeze[45] reported no statistically significant differences between groups in lumbar bone mineral density, bone mineral content or bone age at 12 months. A small RCT[58] comparing inhaled budesonide with placebo (n=20) in asthma found transient decreased levels of bone and collagen markers post-treatment and in a subset of children who received oral betamethasone, with no difference between groups. A study of patients with acute respiratory illness[92] compared hydrocortisone (n=28), methylprednisone (n=21) and controls (n=51) and found decreased levels of osteocalcin and alkaline phosphatase in younger children 2 days post-treatment; these effects were reversed 12 days after treatment. A non-randomised controlled trial of 36 asthma patients[61] compared intravenous methylprednisolone of three different durations and found that all had decreasing levels of serum osteocalcin that correlated with increasing duration of treatment.

### Cardiovascular system

No significant differences were found between *systemic corticosteroid and placebo* in three bronchiolitis studies reporting hypertension (estimated pOR 1).[32 40 83] Single studies with up to 110 children did not report events for arrhythmia[43] and congestive heart failure[47] (*systemic or inhaled corticosteroid* vs *placebo*); and arrhythmia[27] or hypertension[57] (*dexamethasone with another corticosteroid*).

### General AEs/other symptoms

Meta-analyses included a total of two studies (range 197–869 children). There were no statistically significant differences between: (1) *systemic corticosteroid and placebo* for pallor[70 83] and (2) *dexamethasone and another corticosteroid* for dizziness[52] or excessive urination.[27] No study comparing *inhaled corticosteroid with placebo* reported general AEs.

### Immune system and oncology

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

## DISCUSSION

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

A common concern when using corticosteroids in young children is effect on growth. Results from a single, small trial (n=129) of recurrent high-dose inhaled fluticasone propionate in wheezing preschoolers were heterogeneous across outcome measures, but suggested a small significant risk of growth suppression.[45] Observational data have also suggested that multiple corticosteroid bursts can increase the risk of growth suppression, fractures, bone mineral accretion and osteopenia in children with underlying respiratory disease.[5 6 109] Conversely, a pooled analysis using change-from-baseline linear growth did not find significant differences, although the other included study used a substantially lower equivalent dose of inhaled corticosteroid.[110] Further, results from individual studies reporting transient differences in bone

and adrenal biomarkers are of unclear clinical relevance, particularly for previously healthy children and single use. This calls for caution and monitoring of linear growth, particularly when use of high-dose inhaled or systemic corticosteroid is recurrent.

We found no other statistically significant differences between systemic or inhaled corticosteroid and placebo, or between dexamethasone and other systemic corticosteroid, including subgroup analyses by respiratory condition or dose, for AEs across organ systems. Due to small sample sizes and low number of events, these results should be interpreted with caution. While we found increased pORs when comparing systemic corticosteroids for behavioural outcomes such as tremor/jitteriness and behaviour change, there were wide CIs 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 behavioural 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 favoured oral dexamethasone over oral prednisone for vomiting (pOR 0.029; 95% CI 0.17 to 0.48; $I^2$=0%). Differences in palatability and tolerability between corticosteroids are well known to parents, healthcare providers and researchers, and can influence adherence to medication in children.[113] Further, different specific formulations of corticosteroid (eg, prednisolone tablets vs 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 vs multiple) for these outcomes. Due to extensive variation in dosing within and across studies, we were unable to analyse 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 minimise 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 synthesise 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-study and post-study conduct. Common nomenclature (eg, www.meddra.org) and standardised 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) among 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[118] approach.

## CONCLUSION

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

**Author affiliations**
[1]Pediatrics, Hospital de Santa Maria, Lisbon, Portugal
[2]Faculty of Medicine, Instituto de Medicina Molecular, University of Lisbon, Laboratory of Clinical Pharmacology and Therapeutics, Lisbon, Portugal
[3]Alberta Research Centre for Health Evidence, Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[4]Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[5]Women & Children's Health Research Institute, Pediatrics, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[6]Pediatrics, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[7]Pediatrics, Emergency Medicine, and Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[8]Emergency Medicine, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada
[9]School of Public Health, University of Alberta, Edmonton, Alberta, Canada
[10]Pediatrics, Emergency Medicine, and Physiology and Pharmacology, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada
[11]Manitoba Institute of Child Health, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

**Acknowledgements** 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.

**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. ACP 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 ACP are also authors on some of the included studies.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** LH 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;185:12–23.
2. Johnson D. Croup. *BMJ Clin Evid* 2009;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:CD003534.
5. Kelly HW, Sternberg AL, Lescher R, *et al*. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;367:904–12.
6. van Staa TP, Cooper C, Leufkens HG, *et al*. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res* 2003;18:913–8.
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:e519–e525.
8. Zhang L, Axelsson I, Chung M, *et al*. Dose response of inhaled corticosteroids in children with persistent asthma: a systematic review. *Pediatrics* 2011;127:129–38.
9. Loke YK, Price D, Herxheimer A. Systematic reviews of adverse effects: framework for a structured approach. *BMC Med Res Methodol* 2007;7:1–9.
10. Singh JA, Wells GA, Christensen R, *et al*. Adverse effects of biologics: a network meta-analysis and Cochrane overview. *Cochrane Database Syst Rev* 2011;2:CD008794.
11. Higgins J, Green S. The Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration. 2011 www.cochrane-handbook.org
12. Moher D, Liberati A, Tetzlaff J, *et al*. PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol* 2009;62:1006–12.
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 Jan 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;140:795–801.
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;58:785–90.
17. Chou R, Aronson N, Atkins DL, *et al*. Assessing harms when comparing medication interventions. *Methods guide for effectiveness and comparative effectiveness reviews*. Rockville, MD: Agency for Healthcare Research and Quality (US), 2008.
18. Bradburn MJ, Deeks JJ, Berlin JA, *et al*. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Stat Med* 2007;26:53–77.

19. Hedges LV. Comment on 'Misunderstandings about Q and "Cochran's Q Test" in meta analysis'. *Stat Med* 2016;35:496–7.
20. Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
21. The Cochrane Collaboration. *Review Manager (RevMan) [computer program]. Version 5.3*. Copenhagen: The Nordic Cochrane Centre, 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;145:772–8.
24. Alansari K, Sakran M, Davidson BL, *et al*. Oral dexamethasone for bronchiolitis: a randomized trial. *Pediatrics* 2013;132:e810–e816.
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* 2018;103:83–8.
26. Alshehr M, Almegamsi T, Hammdi A. Efficacy of a small dose of oral dexamethasone in croup. *Biomed Res* 2005;16:65–72.
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;22:786–93.
28. Bacharier LB, Phillips BR, Zeiger RS, *et al*. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127–35.
29. Bisgaard H, Hermansen MN, Loland L, *et al*. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;354:1998–2005.
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;351:1306–13.
31. Brunette MG, Lands L, Thibodeau LP. Childhood asthma: prevention of attacks with short-term corticosteroid treatment of upper respiratory tract infection. *Pediatrics* 1988;81:624–9.
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;185:1222–8.
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: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;189:306–10.
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]. *Nan Fang Yi Ke Da Xue Xue Bao* 2008;28:470–2.
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;71:473–7.
37. Clavenna A, Sequi M, Cartabia M, *et al*. Effectiveness of nebulized beclomethasone in preventing viral wheezing: an RCT. *Pediatrics* 2014;133:e505–12.
38. Connett GJ, Warde C, Wooler E, *et al*. Prednisolone and salbutamol in the hospital treatment of acute asthma. *Arch Dis Child* 1994;70:170–3.
39. Connolly JH, Field CM, Glasgow JF, *et al*. A double blind trial of prednisolone in epidemic bronchiolitis due to respiratory syncytial virus. *Acta Paediatr Scand* 1969;58:116–20.
40. Corneli HM, Zorc JJ, Mahajan P, *et al*. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007;357:331–9.
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;67:593–601.
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;143:725–30.
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;82:547–51.
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;23:320–3.
45. Ducharme FM, Lemire C, Noya FJ, *et al*. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360:339–53.
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;62:23–8.
47. Eden AN, Kaufman A, Yu R. Corticosteroids and croup. Controlled double-blind study. *JAMA* 1967;200:403–4.
48. Escobedo Chavez E, Garcia Munīz LO, Thompson Chagoyan O, *et al*. Steroids and inhalation therapy in the management of acute asthma in children. *Current Therapeutic Research* 1992;52:7–12.
49. Fifoot AA, Ting JY. Comparison between single-dose oral prednisolone and oral dexamethasone in the treatment of croup: a randomized, double-blinded clinical trial. *Emerg Med Australas* 2007;19:51–8.
50. Fitzgerald D, Mellis C, Johnson M, *et al*. Nebulized budesonide is as effective as nebulized adrenaline in moderately severe croup. *Pediatrics* 1996;97:722–5.
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* 2013;52:1014–21.
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;54:217–20.
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;11:1.
55. Goebel J, Estrada B, Quinonez J, *et al*. Prednisolone plus albuterol versus albuterol alone in mild to moderate bronchiolitis. *Clin Pediatr* 2000;39:213–20.
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;150:58–63.
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;136:298–303.
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;88:48–51.
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;68:352–5.
60. Inglis AF. Herpes simplex virus infection. A rare cause of prolonged croup. *Arch Otolaryngol Head Neck Surg* 1993;119:551–2.
61. Jan JS, Wu WF. Acute effect of glucocorticoid treatment on serum osteocalcin levels in asthmatic children. *J Microbiol Immunol Infect* 2000;33:25–8.
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;135:691–8.
63. Jartti T, Lehtinen P, Vanto T, *et al*. Evaluation of the efficacy of prednisolone in early wheezing induced by rhinovirus or respiratory syncytial virus. *Pediatr Infect Dis J* 2006;25:482–8.
64. Jartti T, Lehtinen P, Vanto T, *et al*. Efficacy of prednisolone in children hospitalized for recurrent wheezing. *Pediatr Allergy Immunol* 2007;18:326–34.
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;339:498–503.
66. Johnson DW, Schuh S, Koren G, *et al*. Outpatient treatment of croup with nebulized dexamethasone. *Arch Pediatr Adolesc Med* 1996;150:349–55.
67. Klassen TP, Craig WR, Moher D, *et al*. Nebulized budesonide and oral dexamethasone for treatment of croup: a randomized controlled trial. *JAMA* 1998;279:1629–32.
68. Klassen TP, Feldman ME, Watters LK, *et al*. Nebulized budesonide for children with mild-to-moderate croup. *N Engl J Med* 1994;331:285–9.

69. Klassen TP, Watters LK, Feldman ME, *et al*. The efficacy of nebulized budesonide in dexamethasone-treated outpatients with croup. *Pediatrics* 1996;97:463–6.
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;46:539–44.
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;25:223–8.
72. Langton Hewer S, Hobbs J, Reid F, *et al*. Prednisolone in acute childhood asthma: clinical responses to three dosages. *Respir Med* 1998;92:541–6.
73. Lee KM, Lin YZ, Huang FY. Steroid-induced acute psychosis in a child with asthma: report of one case. *Acta Paediatr Taiwan* 2001;42:169–71.
74. Leer JA, Green JL, Heimlich EM, *et al*. A controlled, collaborative study in 297 infants and children. *Am J Dis Child* 1969;117:495–503.
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;94:194–6.
77. Lin YZ, Hsieh KH, Chen W, *et al*. Clinical trial of corticosteroid and beta-2 bronchodilator in acute wheezing infants. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi* 1991;32:333–40.
78. Lucas-Bouwman ME, Roorda RJ, Jansman FG, *et al*. Crushed prednisolone tablets or oral solution for acute asthma? *Arch Dis Child* 2001;84:347–8.
79. Nahum A, Garty BZ, Marcus N, *et al*. Severe hypersensitivity reactions to corticosteroids in children. *Pediatr Emerg Care* 2009;25:339–41.
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;175:1480.
81. Panickar J, Lakhanpaul M, Lambert PC, *et al*. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med* 2009;360:329–38.
82. Panigada S, Sacco O, Girosi D, *et al*. Corticosteroids may favor proliferation of thoracic inflammatory myofibroblastic tumors. *Pediatr Pulmonol* 2014;49:E109–E111.
83. Plint AC, Johnson DW, Patel H, *et al*. Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 2009;360:2079–89.
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;166:297–303.
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;35:170–4.
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;25:114–7.
87. Roosevelt G, Sheehan K, Grupp-Phelan J, *et al*. Dexamethasone in bronchiolitis: a randomised controlled trial. *Lancet* 1996;348:292–5.
88. Sadowitz PD, Page NE, Crowley K. Adverse effects of steroid therapy in children with pharyngitis with unsuspected malignancy. *Pediatr Emerg Care* 2012;28:807–9.
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;49:22–7.
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;43:844–50.
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;155:795–800.
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;73:319–25.
93. Sparrow A, Geelhoed G. Prednisolone versus dexamethasone in croup: a randomised equivalence trial. *Arch Dis Child* 2006;91:580–3.
94. Stafford L, Hope ME, Janney EP, *et al*. Comparison of paediatric steroid mixtures. *The Australian Journal of Hospital Pharmacy* 1998;28:246–9.
95. Storr J, Barrell E, Barry W, *et al*. Effect of a single oral dose of prednisolone in acute childhood asthma. *Lancet* 1987;1:879–82.
96. Sumboonnanonda A, Suwanjutha S, Sirinavin S. Randomized controlled trial of dexamethasone in infectious croup. *J Med Assoc Thai* 1997;80:262–5.
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;5:209–13.
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;115:323–9.
99. Sussman S, Grossman M, Magoffin R, *et al*. Dexamethasone (16-alpha-methyl, 9-alpha-fluoroprednisolone) in obstructive respiratory tract infections in children. a controlled study. *Pediatrics* 1964;34:851–5.
100. Svedmyr J, Nyberg E, Asbrink-Nilsson E, *et al*. Intermittent treatment with inhaled steroids for deterioration of asthma due to upper respiratory tract infections. *Acta Paediatr* 1995;84:884–8.
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;88:42–7.
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;66:131–40.
103. Tal A, Bavilski C, Yohai D, *et al*. Dexamethasone and salbutamol in the treatment of acute wheezing in infants. *Pediatrics* 1983;71:13–18.
104. Tamura A, Matsubara K, Tanaka T, *et al*. Methylprednisolone pulse therapy for refractory Mycoplasma pneumoniae pneumonia in children. *J Infect* 2008;57:223–8.
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;42:433–9.
106. van Woensel JB, Wolfs TF, van Aalderen WM, *et al*. Randomised double blind placebo controlled trial of prednisolone in children admitted to hospital with respiratory syncytial virus bronchiolitis. *Thorax* 1997;52:634–7.
107. Webb MS, Henry RL, Milner AD. Oral corticosteroids for wheezing attacks under 18 months. *Arch Dis Child* 1986;61:15–19.
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;39:548–51.
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:e53–e61.
110. Fuhlbrigge AL, Kelly HW. Inhaled corticosteroids in children: effects on bone mineral density and growth. *Lancet Respir Med* 2014;2:487–96.
111. Aljebab F, Choonara I, Conroy S. Systematic Review of the Toxicity of Long-Course Oral Corticosteroids in Children. *PLoS One* 2017;12:e0170259.
112. Vatti RR, Ali F, Teuber S, *et al*. Hypersensitivity reactions to corticosteroids. *Clin Rev Allergy Immunol* 2014;47:26–37.
113. Rieder M. Size and taste matters: recent progress in the development of age-appropriate medicines for children. *Pharmaceut Med* 2018;32:21–30.
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;4:27–35.
115. Aljebab F, Choonara I, Conroy S. Systematic review of the toxicity of short-course oral corticosteroids in children. *Arch Dis Child* 2016;101:365–70.
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;2016:1–15.
118. Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.