Inhaled Corticosteroids and Respiratory Infections in Children With Asthma: A Meta-analysis

Cristine Cazeiro, BSN,[a] Cristina Silva, MD,[b] Susana Mayer,[b] Vanessa Mariany, MD,[b] Claire Elizabeth Wainwright, MBBS, MD,[c] Linjie Zhang, MD, PhD[a,b,d]

abstract

CONTEXT: Inhaled corticosteroids (ICS) are associated with an increased risk of pneumonia in adult patients with chronic obstructive pulmonary disease.

OBJECTIVE: To assess the association between ICS use and risk of pneumonia and other respiratory infections in children with asthma.

DATA SOURCES: We searched PubMed from inception until May 2015. We also searched clinicaltrials.gov and databases of pharmaceutical manufacturers.

STUDY SELECTION: We selected randomized trials that compared ICS with placebo for at least 4 weeks in children with asthma.

DATA EXTRACTION: We included 39 trials, of which 31 trials with 11 615 patients contributed data to meta-analyses.

RESULTS: The incidence of pneumonia was 0.58% (44/7465) in the ICS group and 1.51% (63/4150) in the placebo group. The meta-analysis of 9 trials that revealed at least 1 event of pneumonia revealed a reduced risk of pneumonia in patients taking ICS (risk ratio [RR]: 0.65; 95% confidence interval [CI]: 0.44 to 0.94). Using risk difference as effect measure, the meta-analysis including all 31 trials revealed no significant difference in the risk of pneumonia between the ICS and placebo groups (risk difference: −0.1%; 95% CI: −0.3% to 0.2%). No significant association was found between ICS and risk of pharyngitis (RR: 1.01; 95% CI: 0.87 to 1.18), otitis media (RR: 1.07; 95% CI: 0.83 to 1.37), and sinusitis (RR: 0.89; 95% CI: 0.76 to 1.05).

LIMITATIONS: Lack of clearly defined criteria for respiratory infections and possible publication bias.

CONCLUSIONS: Regular use of ICS may not increase the risk of pneumonia or other respiratory infections in children with asthma.

[a]Postgraduate Program in Public Health, [d]Postgraduate Program in Health Science, and [b]Faculty of Medicine, Federal University of Rio Grande, Rio Grande, Brazil; and [c]Department of Respiratory and Sleep Medicine, Lady Cilento Children's Hospital and School of Medicine, The University of Queensland, Brisbane, Australia

Ms Cazeiro conceptualized and designed the study, participated in trial selection, quality assessment, data collection, data analysis and interpretation, and drafted the protocol and the review article; Dr Silva, Ms Mayer, and Dr Mariany provided input for study conception and design, participated in trial selection, quality assessment and data collection, and critically revised the manuscript; Dr Wainwright provided input for study conception and design and critically revised the manuscript; Dr Zhang contributed to study conception and design, participated in trial selection, quality assessment, data collection, data analysis and interpretation, and critically revised the review protocol and the manuscript; and all authors approved the final manuscript as submitted.

DOI: 10.1542/peds.2016-3271

To cite: Cazeiro C, Silva C, Mayer S, et al. Inhaled Corticosteroids and Respiratory Infections in Children With Asthma: A Meta-analysis. *Pediatrics.* 2017;139(3):e20163271

Inhaled corticosteroids (ICS) are widely used in the treatment of asthma and chronic obstructive pulmonary disease.[1,2] They are generally considered safe and well tolerated in both adults and children.[3,4] However, recent studies have raised concerns about increased risk of pneumonia related to regular use of ICS in adult patients with chronic obstructive pulmonary disease.[5–7] There have been few studies assessing the association between ICS and risk of pneumonia in patients with asthma.

The retrospective analysis of individual patient data from 26 AstraZeneca-sponsored randomized trials revealed a reduced risk of pneumonia in patients (4 to 78 years) with asthma treated with budesonide.[8] A recent meta-analysis of 10 randomized trials also revealed a protective effect of ICS against pneumonia in patients with asthma.[9] However, caution should be taken in interpreting the results of this review. Firstly, "pneumonia" and "pneumonitis" were used as the search terms. Such search strategy might exclude a considerable number of relevant studies given that pneumonia is not a well-established adverse event of ICS and is less likely to be used as keyword or subject heading in clinical trials. Secondly, the authors limited literature search to adults, but the largest trial that contributed with 83.1% of the weight included patients aged 5 to 66 years of age. No separate data were available for pediatric patients.

One recent study revealed an increased risk of oropharyngeal colonization by *Streptococcus pneumoniae* in children with asthma regularly taking ICS.[10] An increased microbial burden in the oropharyngeal area may lead to a higher risk of respiratory infections, especially infections of neighborhood sites such as pharyngitis, otitis media, and sinusitis. Up until now, no study has assessed the possible link between use of ICS and the risk of other respiratory infections besides pneumonia in patients with asthma. Thus, we conducted this systematic review and meta-analysis of randomized trials to assess the association between regular use of ICS and risk of pneumonia, as well as other respiratory infections, in children with asthma. We also investigated the potential effect modifiers, such as drug molecules, daily doses, delivery devices, duration of treatment, and patient's age.

METHODS

We followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[11] for writing this systematic review. The review protocol was registered on PROSPERO (the International Prospective Register of Systemic Reviews, CRD42015020656).[12] There are 2 differences between the previously registered protocol and this review: "triamcinolone" was added in addition as a search term, and 5 posthoc subgroup analyses and 2 posthoc sensitivity analyses were also added.

Search Strategy

We searched PubMed from inception until May 2015 to identify clinical trials. The search strategy was as follows: asthma AND ("inhaled corticosteroid" OR "inhaled steroid" OR beclomethasone OR budesonide OR ciclesonide OR flunisolide OR fluticasone OR mometasone OR triamcinolone). There was no restriction on language of publication. We also identified systematic reviews of randomized trials that compared ICS with placebo, by searching PubMed and the Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information, which contains Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Literatura Latino-Americana e do Caribe em Ciencias da Saude (LILACS), Scientific Electronic Library OnLine (SciELO), the Cochrane Library, and more than 20 other databases.[13] Reference lists of primary studies and systematic reviews were screened for additional relevant trials. We also conducted searches on clinicaltrials.gov and the databases of 2 main pharmaceutical manufacturers of ICS (GSK and AstraZeneca) to identify unpublished trials and to obtain unpublished safety data of the trials.

Study Selection

To be included in this review, studies had to meet all of the following criteria: (1) study design: randomized controlled trials; (2) participants: children up to 18 years old with diagnosis of asthma; (3) interventions and comparisons: daily use of ICS, delivered by any type of inhalation device for at least 4 weeks, compared with placebo delivered by the same type of device; (4) outcome measures: at least 1 of respiratory infections reported as adverse event. For this review, we defined "clinically diagnosed pneumonia, with or without radiological confirmation" as the primary outcome. The secondary outcomes included other respiratory infections, such as pharyngitis, otitis media, sinusitis, bronchitis, bronchiolitis, and influenza.

We excluded cross-over trials, trials that compared ICS to other interventions without placebo, trials that used ICS plus other drugs, and trials that included children but in which pediatric patient data were not identifiable.

Four review authors (CC, CS, SM, VM), divided into 2 groups, independently assessed the titles and abstracts of all citations identified by the searches. We obtained the full articles when they appeared to meet the inclusion criteria or there were insufficient data in the title and abstract to make

a clear decision for their inclusion. The definitive inclusion of trials was made after reviewing the full-text articles. Any disagreements about study selection were resolved by discussion and, where necessary, a senior reviewer (LZ) was consulted.

Data Extraction and Management

Data from the included trials were extracted independently by 4 review authors (CC, CS, SM, VM) and cross-checked. A standardized data extraction form was used to extract the following data: (1) study characteristics: year of publication, country, and setting of study; (2) methods: study design, methods of random sequence generation, allocation concealment and blinding, description of withdrawal, and adherence to treatment; (3) participants: sample size, age, sex, and inclusion and exclusion criteria; (4) interventions: corticosteroid molecule, daily dose, interval of administration, duration of treatment, drug delivery device, and cointerventions; (5) outcomes: we extracted the number of participants affected and the total number of participants in each treatment arm. For trials that examined multiple doses of ICS, we combined the active treatment groups. Intention-to-treat (ITT) data sets were used whenever available. Given that it is likely that outcomes for which no events occur in either arm may not be mentioned in reports of many randomized trials, we considered no events of pneumonia in both arms if the trial had revealed at least 1 respiratory infection event but not explicitly reported pneumonia. We obtained additional or unpublished safety data through Clinical Trial Register (clinicaltrials.gov) and databases of pharmaceutical manufacturers. When there was inconsistency between unpublished data and data from published articles, we used only unpublished data from above-mentioned databases because they generally provide more detailed and accurate information about drug adverse events.

Assessment of Risk of Bias in Included Studies

Four reviewers (CC, CS, SM, VM) independently assessed the risk of bias in included trials by examining the 6 key domains according to the recommendations of the Cochrane Collaboration[14]: (1) allocation sequence generation, (2) concealment of allocation, (3) blinding of participants and investigators, (4) incomplete outcome data, (5) selective outcome reporting, and (6) other sources of bias. We graded each potential source of bias as yes, no, or unclear, relating to whether the potential for bias was low, high, or unknown.

Any disagreements about assessment of risk of bias were resolved by discussion and, where necessary, a senior reviewer (LZ) was consulted.

Data Synthesis and Statistical Analysis

We performed meta-analyses for quantitative data synthesis. The risk ratios (RRs) and 95% confidence intervals (CIs) were used to estimate the risk of adverse events associated with ICS. We used the random-effects model for pooling RRs and 95% CIs, assuming that the patients and interventions in clinical trials would have differed in ways that could have impacted on the results, and therefore the trials would not share a common effect size.[14] For trials with no events in 1 arm, 0.5 was added to each of the 4 cell counts of 2-by-2 tables. Trials with no events in both arms were not included in the pooled analysis. Given that many outcomes are rare events, we also undertook meta-analyses by using Peto's odds ratios (ORs) as effect size measure. For the primary outcome pneumonia, we also used risk difference (RD) as effect size measure because RD method appears to have advantage over relative statistics (RR, OR) in that the RD is defined as zero when no events occur in either arm.[14] Such trials are therefore included in the pooled analysis.

We assessed heterogeneity in results between trials by using the Cochrane Q test ($P < .1$ considered significant) and the I^2 statistic.[15]

We conducted posthoc subgroup analyses on the basis of the type of drugs, type of delivery devices (metered-dose inhaler, dry powder inhaler, nebulizer), duration of treatment (≥6 months, <6 months), patient's age (<4 years, 4 to 18 years), and data source (published data, unpublished data). The χ^2 test was used for subgroup comparison. To assess dose–response effects of ICS, we conducted a meta-analysis including only trials that compared directly 2 or more daily doses. We conducted 2 posthoc sensitivity analyses, excluding the trials in which adverse events were not collected by systematic assessment and the trials that contributed more than 50% of the weight to the meta-analysis. All meta-analyses were performed by using Stata version 11.0 (Stata Corp, College Station, TX).

RESULTS

Literature Search and Study Selection

The search strategy identified 2756 unique records from PubMed. After screening the titles and abstracts, we retrieved 227 potentially relevant full-text articles for further evaluation. One hundred fifty-four articles were excluded for reasons shown in Fig 1. We identified 7 unpublished trials from clinicaltrials.gov. Twelve additional trials were found by checking the reference lists of 9 systematic review articles. Thus, a total of 92 randomized trials comparing ICS with placebo in children with asthma were selected. Thirty-seven trials did not reveal

safety data, and 16 trials did not reveal respiratory infections as adverse events. Thirty-nine trials[16–54] involving 13 595 (8945 ICS-treated, 4650 placebo) children with persistent asthma were therefore included in the review. Thirty-one trials[16–46] involving 11 615 participants (7465 ICS-treated, 4150 placebo) contributed data to the meta-analyses.

Study Characteristics and Risk of Bias

Table 1 summarizes the characteristics of the 39 included trials. Thirty-two were published trials,[16–39,47–54] but unpublished safety data were obtained through clinicaltrials.gov and databases of pharmaceutical manufacturers in 7 trials.[16,20,23,26,27,30,39] Seven were unpublished trials identified through clinicaltrials.gov.[40–46] All 39 studies were randomized, double-blind, placebo-controlled trials. Thirty-five[16–20,22–35,37–46] were multicenter trials. Only 6 trials[16–18,35–37] were designed to assess the safety of ICS, whereas the remaining 33 trials aimed mainly to assess the efficacy of ICS. All but 4 trials[24,28,48,50] were industry funded. Five ICS (beclomethasone, budesonide, ciclesonide, fluticasone, and mometasone) given at low or medium daily doses were used. Duration of intervention varied from 4 weeks to 3 years. Adverse events were collected by systematic assessment in 29 trials,[16,18,20,22–25,29–39,41–43,45–47,50–54] but none of the trials explicitly defined the criteria for diagnosis of pneumonia and other respiratory infections. All 39 trials were stated as randomized; however, only 9 published trials[18,20,28,29,31,33,35,50,51] described the methods for random sequence generation and 2[28,35] described the methods for allocation concealment (Supplemental Table 4). The risk of performance and detection bias was low in all 39 trials because matching placebos were used for blinding. The risk of attrition bias was also low

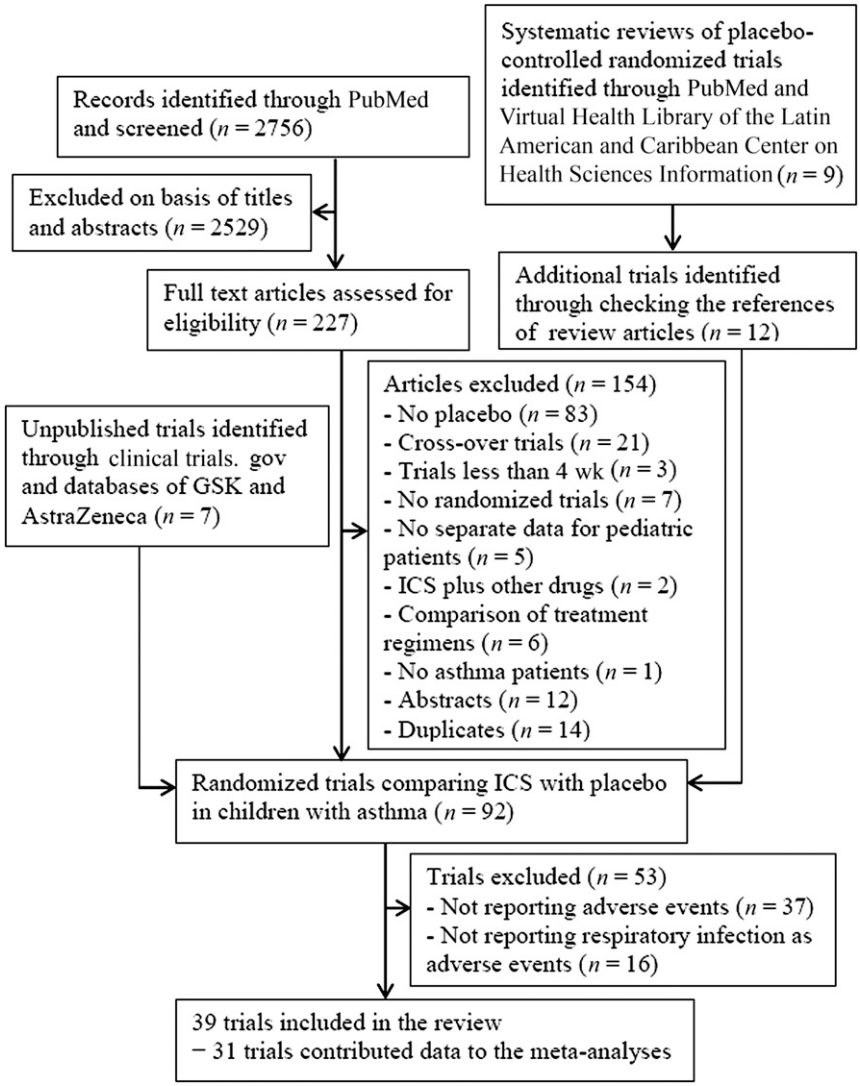

FIGURE 1
Flow diagram of study selection.

as ITT or quasi-ITT population was used for calculating rate of adverse events in all 31 trials that contributed data to the meta-analyses. Given that respiratory infections are not well-established adverse events of ICS, underreporting of some respiratory infection outcomes might occur. We rated the risk of outcome reporting bias as high in the 3 trials[21,28,35] because only 1 type of respiratory infection was reported.

Use of ICS and Risk of Pneumonia

Nine trials[23,27,30,38,40,41,43,44,46] involving a total of 4617 participants (2684 ICS-treated, 1933 placebo) revealed at least 1 event of pneumonia. The meta-analysis of 9 trials revealed that ICS significantly reduced the risk of pneumonia compared with placebo (RR: 0.65, 95% CI: 0.44 to 0.94, $P = .02$, $I^2 = 0\%$; Peto's OR: 0.63, 95% CI: 0.43 to 0.93, $P = .02$, $I^2 = 22.1\%$; Table 2). Posthoc subgroup analyses did not reveal significant effects of drug molecules, delivery devices, treatment duration, patient's age, and data source on the size of risk of pneumonia related to ICS (Table 3). The posthoc sensitivity analysis excluding 1 trial[38] that contributed more than 50% of the weight revealed no significant

TABLE 1 Characteristics of Included Trials

Study ID, Country, Sponsor	Participants	Study Design	Intervention and Control	Primary Outcome	Adverse Event Outcomes	
					RTI Reported	Systematic Data Collection
Allen et al 1998,[16] USA, GSK	Patients aged 4 to 11 y with persistent asthma (ATS criteria)	52-wk, multicenter, RDBPCT (FLD-220 trial)	Fluticasone 100, 200 μg/d, DPI (n = 219) Placebo, DPI (n = 106)	Growth velocity, height	Yes	Yes
Baker et al 1999,[47] USA, AstraZeneca	Patients aged 6 mo to 11 y with moderate persistent asthma	12-wk, multicenter, RDBPCT	Budesonide 0.25, 0.5, 1.0 mg/d, nebulizer (n = 386); Placebo, nebulizer (n = 95)	Symptom score	No	Yes
Becker et al 2006,[17] USA, Canada, Hong Kong, South Africa, 7 countries in Latin America, Merck	Boys (6.4 to 9.4 y) and girls (6.4 to 8.4 y) at Tanner stage I with mild persistent asthma (GINA criteria)	56-wk, multicenter, RDBPCT	Beclomethasone 400 μg/d, MDI (n = 119); Placebo, MDI (n = 121)	Growth velocity, height	Yes	Unclear
Berger et al 2005,[18] USA, AstraZeneca	Infants aged 6 to 12 mo with mild to moderate persistent asthma or recurrent wheeze	12-wk, multicenter, RDBPCT	Budesonide 0.5, 1.0 mg/d, nebulizer (n = 92); Placebo, nebulizer (n = 49)	Adrenal function	Yes	Yes
Berger et al 2006,[19] USA, Schering-Plough	Children 4 to 11 y with persistent asthma	12-wk, multicenter, RDBPCT	Mometasone 100, 200 μg/d, DPI (n = 197); Placebo, DPI (n = 99)	FEV_1	Yes	Unclear
Carlsen et al 2005,[20] Australia, Canada, Germany, Greece, Italy, Latvia, Lithuania, Norway, UK, GSK	Children aged 12 to 47 mo with recurrent/ persistent asthma symptoms	12-wk, multicenter, RDBPCT (FAS30007 trial)	Fluticasone 200 μg/d, MDI (n = 79); Placebo, MDI (n = 81)	Symptom-free	Yes	Yes
Connett et al 1993,[48] UK	Children aged 1 to 3 y with persistent asthma symptoms	12-wk, unicenter, RDBPCT	Budesonide 200 μg/d, MDI (n = 20); Placebo, MDI (n = 20)	Symptom score	No	Unclear
de Blic et al 1996,[21] France, AstraZeneca	Infants aged 6 to 30 mo with severe asthma	12-wk, unicenter, RDBPCT	Budesonide 2 mg/d, nebulizer (n = 20); Placebo, nebulizer (n = 18)	Asthma exacerbations	Yes	Unclear
FLTA2007 trial 2005,[40] USA, GSK	Children aged 4 to 11 y with chronic asthma (ATS criteria)	12-wk, multicenter, RDBPCT	Fluticasone 100 μg/d, DPI (n = 179); Placebo, DPI (n = 83)	FEV_1, PEF	Yes	Unclear
FMS30059 trial 2005,[46] USA, Puerto Rico, Chile, GSK	Children aged 6 to 23 mo with asthma	12-wk, multicenter, RDBPCT	Fluticasone 100, 200 μg/d, MDI (n = 142) ; Placebo, MDI (n = 69)	PEF	Yes	Yes
Gelfand et al 2006,[22] USA, Aventis	Children aged 4 to 11 y with persistent asthma (NIH criteria)	12-wk, multicenter, RDBPCT	Ciclesonide 40, 80, 160 μg/d, MDI (n = 768); Placebo, MDI (n = 257)	FEV_1	Yes	Yes
Hofstra et al 2000,[49] The Netherlands, GSK	Children aged 6 to 14 y with asthma	6-wk, multicenter, RDBPCT	Fluticasone 200, 500 μg/d, MDI (n = 25) Placebo, MDI (n = 12)	Lung function measurements	No	Unclear
Jónasson et al 1998,[50] Norway	Patients aged 7 to 16 y with mild asthma	12-wk, unicenter, RDBPCT	Budesonide 100, 200 μg/d, DPI (n = 123); Placebo, DPI (n = 40)	Lung function measurements	No	Yes
Katz et al 1998,[23] Finland, France, Hong Kong, Israel, Italy, Portugal, Singapore, Spain, United Arab Emirates, GSK	Patients aged 1 to 5 y with persistent asthma	12-wk, multicenter, RDBPCT (FLIT85 trial)	Fluticasone 100, 200 μg/d, DPI (n = 171) Placebo, DPI (n = 92)	PEF	Yes	Yes

TABLE 1 Continued

Study ID, Country, Sponsor	Participants	Study Design	Intervention and Control	Primary Outcome	Adverse Event Outcomes	
					RTI Reported	Systematic Data Collection
Kerwin et al 2008,[51] Indonesia, Philippines, Thailand, Singapore, USA, AstraZeneca	Patients 6 to 17 y with mild asthma	12-wk, multicenter, RDBPCT	Budesonide 180, 200, 720, 800 μg/d, DPI (n = 410); Placebo, DPI (n = 106)	FEV_1	No	Yes
Kooi et al 2008,[24] The Netherlands	Children aged 2 to 5 y with asthmalike symptoms	6-mo, multicenter, RDBPCT	Fluticasone 200 μg/d, MDI (n = 25); Placebo, MDI (n = 20)	Symptom score	Yes	Yes
LaForce et al 2000,[25] USA, GSK	Children aged 4 to 11 y with persistent asthma	12-wk, multicenter, RDBPCT	Fluticasone 200 μg/d, DPI (n = 164); Placebo, DPI (n = 78)	FEV_1, PEF	Yes	Yes
Levy et al 2006,[26] USA, GSK	Children aged 4 to 11 y with ≥ 6-mo history of asthma requiring pharmacotherapy	12-wk, multicenter, RDBPCT (FAP30010 trial)	Fluticasone 200 μg/d, MDI (n = 160); Placebo, MDI (n = 81)	PEF	Yes	Unclear
MacKenzie et al 1993,[27] Austria, Belgium, Finland, Germany, Greece, Ireland, Israel, Italy, the Netherlands, Norway, South Africa, UK, GSK	Children aged 6 to 12 y with asthma	4-wk, multicenter, RDBPCT (FLIP20 trial)	Fluticasone 100 μg/d, DPI (n = 128); Placebo, DPI (n = 130)	Symptom score	Yes	Unclear
Martinez et al 2011,[28] USA	Patients aged 5 to 18 y with mild persistent asthma (US NAEPP criteria)	44-wk, multicenter, RDBPCT (NCT00394329 trial)	Beclomethasone 100 μg/d, MDI (n = 72); Placebo, MDI (n = 74)	PEF	Yes	Unclear
Nayak et al 2002,[29] USA, 3M Pharmaceuticals	Children aged 5 to 12 y with moderate symptomatic asthma	12-wk, multicenter, RDBPCT	Beclomethasone 100, 200 μg/d, MDI (n = 237); Placebo, MDI (n = 116)	FEV_1	Yes	Yes
NCT00163293 trial 2012,[41] Canada, Hungary, South Africa, Takeda	Children aged 4 to 11 y with mild persistent asthma.	12-mo, multicenter, RDBPCT	Ciclesonide 200, 400 μg/d, MDI (n = 155); Placebo, MDI (n = 85)	Asthma exacerbations	Yes	Yes
NCT00392288 trial 2012,[42] USA, Hungary, Mexico, Poland, Russian Federation, South Africa, Nycomed, Sanofi	Children aged 4 to <12 y with persistent asthma	12-wk, multicenter, RDBPCT	Ciclesonide 100, 200 μg/d, MDI (n = 349); Placebo, MDI (n = 172)	FEV_1	Yes	Yes
NCT00569192 trial 2013,[43] India, Allergan	Children aged 12 mo to 8 y with mild to moderate persistent asthma (NIH criteria)	12-wk, multicenter, RDBPCT	Budesonide 0.27, 0.50 mg/d, nebulizer (n = 246); Placebo, nebulizer (n = 110)	Symptom score	Yes	Yes
NCT00920959 trial, 2013,[44] USA, 11 centers in Latin America, GSK	Children were aged between 4 and 11 y with asthma	12-wk, multicenter, RDBPCT	Fluticasone 100 μg/d, DPI (n = 304); Placebo, DPI (n = 300)	PEF	Yes	Unclear
NCT01136382 trial 2014,[45] USA, Bulgaria, Hungary, Latvia, Poland, Romania, Slovakia, South Africa, AstraZeneca	Children aged 6 to <12 y with asthma	6-wk, multicenter, RDBPCT	Budesonide 400 μg/d, MDI (n = 152); Placebo, MDI (n = 152)	PEF	Yes	Yes
Peden et al 1998,[30] USA, GSK	Children aged 4 to 11 y with persistent asthma (ATS criteria)	12-wk, multicenter, RDBPCT (FLTA2006 trial)	Fluticasone 100, 200 μg/d, DPI (n = 351) Placebo, DPI (n = 86)	FEV_1, PEF	Yes	Yes

TABLE 1 Continued

Study ID, Country, Sponsor	Participants	Study Design	Intervention and Control	Primary Outcome	Adverse Event Outcomes	
					RTI Reported	Systematic Data Collection
Pedersen et al 2010,[31] Bulgaria, Germany, Hungary, Poland, Romania, Russia, South Africa, Spain, Ukraine, Nycomed	Children aged 6 to 11 y with persistent asthma	12-wk, multicenter, RDBPCT (RAINBOW trial)	Ciclesonide 50, 100, 200 μg/d, MDI (n = 930); Placebo, MDI (n = 150)	PEF	Yes	Yes
Qaqundah et al 2006,[32] Argentina, Chile, USA, GSK	Children aged 1 to <4 y with asthma	12-wk, multicenter, RDBPCT	Fluticasone 200 μg/d, MDI (n = 239); Placebo, MDI (n = 120)	Symptom score	Yes	Yes
Schokker et al 2008,[33] The Netherland, GSK and Stichting Astmabestrijding	Children 1 to 5 y with asthmalike symptoms	6-mo, multicenter, RDBPCT (ASTERISK trial)	Fluticasone 200 μg/d, MDI (n = 48); Placebo, MDI (n = 48)	Symptom score	Yes	Yes
Shapiro et al 1998,[52] USA, AstraZeneca	Children aged 6 to 18 y with moderate to severe persistent asthma	12-wk, multicenter, RDBPCT	Budesonide 100, 200, 400 μg/d, DPI (n = 301); Placebo, DPI (n = 103)	PEF, FEV_1	No	Yes
Shapiro et al 1998,[53] USA, AstraZeneca	Children aged 4 to 8 y with persistent asthma (NHI criteria)	12-wk, multicenter, RDBPCT	Budesonide 0.5, 1.0, 2.0 mg/d, nebulizer (n = 134); Placebo, nebulizer (n = 44)	Symptom score	No	Yes
Shapiro et al 2001,[34] USA, AstraZeneca	Children aged 6 to 17 y with persistent asthma (ATS criteria)	12-wk, multicenter, RDBPCT	Budesonide 200, 400 μg/d, DPI (n = 183); Placebo, DPI (n = 91)	FEV_1	Yes	Yes
Silverman et al 2006,[38] UK and other 31 countries throughout the world, AstraZeneca	Children aged 5 to 10 y with mild persistent asthma	3-y, multicenter, RDBPCT (START trial)	Budesonide 200 μg/d, DPI (n = 1004); Placebo, DPI (n = 977)	Severe asthma-related event	Yes	Yes
Simons 1997,[54] Canada, GSK	Children aged 6 to 14 y with asthma	1-y, multicenter, RDBPCT	Beclomethasone 400 μg/d, DPI (n = 81); Placebo, DPI (n = 80)	Airway responsiveness	No	Yes
Skoner et al 2008,[35] Argentina, Chile, USA, Venezuela, Sanofi-aventis, Altana Pharma US, Nycomed	Children aged 5 to 18 y with mild persistent asthma	1-y, multicenter, RDBPCT	Ciclesonide 50, 100 μg/d, MDI (n = 440); Placebo, MDI (n = 221)	Growth velocity	Yes	Yes
Skoner et al 2010,[36] USA, Schering-Plough	Children aged 6 to 11 y with mild asthma	4-wk, unicenter, RDBPCT	Mometasone 200, 400, 800 μg/d, DPI (n = 38); Placebo, DPI (n = 12)	Plasma cortisol	Yes	Yes
Skoner et al 2011,[37] USA, Merck	Children aged 4 to 9 y with mild persistent asthma	52-wk, multicenter, RDBPCT	Mometasone 100, 200 μg/d, DPI (n = 142); Placebo, DPI (n = 45)	Growth velocity	Yes	Yes
Wasserman et al 2006,[39] USA, GSK	Children aged 2 to 4 y with asthma requiring regular maintenance therapy	12-wk, multicenter, RDBPCT (FMS30058 trial)	Fluticasone 100, 200 μg/d, MDI (n = 219); Placebo, MDI (n = 113)	Symptom score	Yes	Yes

ATS, American Thoracic Society; DPI, dry powder inhaler; FEV_1, forced expiratory volume in the first second; GINA, global initiative for asthma; MDI, metered-dose inhaler; NAEPP, National Asthma Education and Prevention Program; NIH, National Institutes of Health; PEF, peak expiratory flow; RDBPCT, randomized double-blind placebo controlled trial; RTI, respiratory tract infection.

TABLE 2 Risk of Pneumonia Associated With Use of ICS in Children With Asthma

Study ID	Participants Affected/ Participants Randomly Assigned		Treatment Effect (95% CI)		
	ICS	Placebo	RR	Peto's OR	RD
Allen et al 1998[16]	0/219	0/106	UC	UC	0 (−0.01 to 0.01)
Becker et al 2006[17]	0/119	0/121	UC	UC	0 (−0.02 to 0.02)
Berger et al 2005[18]	0/92	0/49	UC	UC	0 (−0.03 to 0.03)
Berger et al 2006[19]	0/197	0/99	UC	UC	0 (−0.02 to 0.02)
Carlsen et al 2005[20]	0/79	0/81	UC	UC	0 (−0.02 to 0.02)
de Blic et al 1996[21]	0/20	0/18	UC	UC	0 (−0.09 to 0.09)
FLTA2007 2005[40]	0/179	2/83	0.09 (0.01 to 1.92)	0.04 (0.002 to 0.83)	−0.024 (−0.06 to 0.01)
FMS30059 2005[46]	2/142	0/69	2.45 (0.12 to 50.29)	4.45 (0.23 to 85.99)	0.01 (−0.02 to 0.04)
Gelfand et al 2006[22]	0/764	0/254	UC	UC	0 (−0.01 to 0.01)
Katz et al 1998[23]	1/172	0/93	1.63 (0.07 to 39.62)	4.67 (0.08 to 283.50)	0.01 (−0.01 to 0.03)
Kooi et al 2008[24]	0/25	0/20	UC	UC	0 (−0.08 to 0.08)
LaForce et al 2000[25]	0/164	0/78	UC	UC	0 (−0.02 to 0.02)
Levy et al 2006[26]	0/160	0/81	UC	UC	0 (−0.02 to 0.02)
Mackenzie et al 1993[27]	0/128	3/130	0.15 (0.01 to 2.78)	0.14 (0.01 to 1.31)	−0.02 (−0.05 to 0.01)
Martinez et al 2011[28]	0/143	0/74	UC	UC	0 (−0.02 to 0.02)
NCT00163293 2012[41]	1/155	0/84	1.64 (0.07 to 39.69)	4.67 (0.07 to 283.50)	0.01 (−0.02 to 0.03)
NCT00392288 2012[42]	0/174	0/172	UC	UC	0 (−0.01 to 0.01)
NCT00569192 2013[43]	1/249	0/111	1.34 (0.06 to 32.74)	4.25 (0.06 to 295.90)	0.004 (−0.01 to 0.02)
NCT00920959 2013[44]	0/304	1/300	0.33 (0.01 to 8.04)	0.13 (0.003 to 6.73)	−0.003 (−0.01 to 0.01)
NCT01136382 2014[45]	0/152	0/152	UC	UC	0 (−0.01 to 0.01)
Nayak et al 2002[29]	0/237	0116	UC	UC	0 (−0.01 to 0.01)
Peden et al 1998[30]	1/351	0/86	0.74 (0.03 to 18.05)	3.48 (0.03 to 480.40)	0.003 (−0.01 to 0.02)
Pedersen et al 2010[31]	0/927	0/146	UC	UC	0 (−0.01 to 0.01)
Qaqundah et al 2006[32]	0/239	0/120	UC	UC	0 (−0.01 to 0.01)
Schokker et al 2008[33]	0/48	0/48	UC	UC	0 (−0.04 to 0.04)
Shapiro et al 2001[34]	0/183	0/91	UC	UC	0 (−0.02 to 0.02)
Silverman et al 2006[38]	38/1004	57/977	0.65 (0.43 to 0.97)	0.64 (0.43 to 0.96)	−0.02 (−0.04 to −0.00)
Skoner et al 2008[35]	0/440	0/221	UC	UC	0 (−0.01 to 0.01)
Skoner et al 2010[36]	0/38	0/12	UC	UC	0 (−0.11 to 0.11)
Skoner et al 2011[37]	0/142	0/45	UC	UC	0 (−0.03 to 0.03)
Wasserman et al 2006[39]	0/219	0/113	UC	UC	0 (−0.01 to 0.01)
All trials combined	44/7465	63/4150	0.65 (0.44 to 0.94)	0.63 (0.43 to 0.93)	−0.001 (−0.003 to 0.002)

UC, unable to calculate using RR and Peto's OR because no events in either group.

association between use of ICS and risk of pneumonia (RR: 0.62, 95% CI: 0.21 to 1.86, $P = .39$, $I^2 = 0\%$; Peto's OR: 0.57, 95% CI: 0.17 to 1.89, $P = .36$, $I^2 = 31.6\%$). In another posthoc sensitivity analysis, excluding 3 trials[27,40,44] in which adverse events were not collected by systematic assessment did not significantly change the results.

Using RD as effect estimate, we conducted the meta-analysis including all 31 trials that revealed at least 1 respiratory infection event. Twenty-three trials[16–22,24–26,28,29,31–37,39,42,45,46] did not explicitly reveal pneumonia as adverse events, and we considered no events of pneumonia in both treatment arms. Thus, 44 patients in the corticosteroid group (44/7465, 0.58%) and 63 patients in the placebo group (63/4150, 1.51%) had pneumonia as adverse events. The summary RD between the corticosteroid and placebo groups was –0.1% (95% CI: –0.3% to 0.2%, $P = .72$, $I^2 = 0\%$; Table 2). The posthoc sensitivity analysis excluding 8 trials[17,19,21,26–28,40,44] in which adverse events were not collected by systematic assessment yielded the similar results.

Use of ICS and Risk of Other Respiratory Infections

Figure 2 reveals the results of meta-analyses of secondary outcomes—other respiratory infections. No significant association was found between use of ICS and risk of pharyngitis (23 trials,[16,18–20,22,23,26,27,29,31,33–42,44–46] RR: 1.01, 95% CI: 0.87 to 1.18, $I^2 = 19\%$), otitis media (17 trials,[16,18–20,23,26,27,30,32,33,37–41,44,46] RR: 1.07, 95% CI: 0.83 to 1.37, $I^2 = 34.2\%$), sinusitis (15 trials,[16,18,22,25,26,29,30,34,37–41,44,46] RR: 0.89, 95% CI: 0.76 to 1.05, $I^2 = 0\%$), bronchitis (9 trials,[16,23,27,28,32,37–39,46] RR: 0.89, 95% CI: 0.75 to 1.05, $I^2 = 0\%$), and influenza (4 trials,[16,23,41,45] RR: 1.12, 95% CI: 0.65 to 1.93, $I^2 = 0\%$). Posthoc subgroup analyses did not reveal significant effects of drug molecules, delivery devices, treatment duration, patient's age, and data source on the treatment effect size of ICS (Table 3).

Use of ICS and Risk of Respiratory Infections: Dose–Response Relationship

Seventeen trials[16,18,19,22,23,29–31,34–37,39,41–43,46] in which 2 or more daily doses of ICS were compared had contributed data to the

TABLE 3 Risk of Respiratory Infections Associated With Use of ICS in Children With Asthma: Subgroup Analyses

Subgroups	Pneumonia		Bronchitis		Otitis media		Sinusitis		Pharyngitis		Upper Respiratory Infection	
	RR (95% CI)	Trial, *n*	RR (95% CI)	Trial, *n*	RR (95% CI)	Trial, *n*	RR (95% CI)	Trial, *n*	RR (95% CI)	Trial, *n*	RR (95% CI)	Trial, *n*
Type of ICS	*P* = .71*		*P* = .94		*P* = .80		*P* = .61		*P* = .11		*P* = .65	
Beclomethasone	—	0	1.56 (0.06 to 37.89)	1	—	0	1.96 (0.22 to 17.32)	1	0.83 (0.43 to 1.59)	1	1.09 (0.73 to 1.64)	1
Fluticasone	0.43 (0.11 to 1.71)	5	0.88 (0.74 to 1.04)	6	1.12 (0.76 to 1.64)	12	0.84 (0.65 to 1.08)	7	1.42 (1.01 to 1.84)	10	1.09 (0.93 to 1.27)	13
Budesonide	0.66 (0.44 to 0.97)	3	1.14 (0.45 to 2.90)	1	1.08 (0.86 to 1.34)	2	0.96 (0.56 to 1.65)	3	0.93 (0.82 to 1.06)	4	0.87 (0.60 to 1.27)	5
Mometasone	—	0	0.90 (0.27 to 3.02)	1	0.72 (0.11 to 4.76)	2	1.45 (0.66 to 3.18)	2	0.92 (0.61 to 1.40)	3	0.90 (0.69 to 1.18)	2
Ciclesonide	1.64 (0.07 to 39.69)	1	—	0	2.17 (0.47 to 9.98)	1	1.08 (0.68 to 1.72)	2	0.83 (0.56 to 1.22)	5	0.94 (0.61 to 1.44)	4
Type of devices	*P* = .52		*P* = .92		*P* = .21		*P* = .69		*P* = .61		*P* = .87	
MDI	2.02 (0.23 to 18.41)	2	0.86 (0.45 to 1.63)	4	1.57 (0.94 to 2.60)	7	0.97 (0.59 to 1.61)	6	0.91 (0.67 to 1.22)	12	1.00 (0.83 to 1.21)	13
DPI	0.62 (0.42 to 0.91)	6	0.89 (0.75 to 1.06)	5	0.92 (0.63 to 1.36)	9	0.86 (0.72 to 1.03)	8	1.00 (0.89 to 1.12)	10	1.02 (0.88 to 1.20)	9
Nebulizer	1.34 (0.06 to 32.74)	1	—	0	0.93 (0.61 to 1.43)	1	1.33 (0.44 to 4.03)	1	1.86 (0.40 to 8.63)	1	0.87 (0.50 to 1.53)	3
Duration of treatment	*P* = .75		*P* = .85		*P* = .54		*P* = .32		*P* = .72		*P* = .93	
<6 mo	0.54 (0.17 to 1.76)	7	0.84 (0.47 to 1.48)	5	1.00 (0.66 to 1.52)	12	0.79 (0.63 to 1.06)	4	0.98 (0.76 to 1.27)	18	1.01 (0.87 to 1.17)	21
≥6 mo	0.66 (0.44 to 0.98)	2	0.89 (0.75 to 1.06)	4	1.16 (0.93 to 1.44)	5	1.20 (0.89 to 1.61)	11	1.04 (0.85 to 1.26)	5	1.00 (0.84 to 1.20)	4
Patient's age	*P* = .38		*P* = .87		*P* = .97		*P* = .60		*P* = .25		*P* = .66	
<4 y	2.45 (0.12 to 50.29)	1	0.84 (0.43 to 1.61)	3	1.04 (0.78 to 1.39)	5	1.06 (0.57 to 1.97)	3	1.68 (0.70 to 3.97)	5	1.08 (0.78 to 1.49)	5
4 to 18 y	0.63 (0.43 to 0.92)	8	0.89 (0.75 to 1.06)	6	1.05 (0.73 to 1.52)	12	0.89 (0.74 to 1.07)	12	1.00 (0.85 to 1.15)	18	1.00 (0.88 to 1.12)	20
Data source	*P* = .94		*P* = .84		*P* = .66		*P* = .84		*P* = .51		*P* = .74	
Published	0.64 (0.43 to 0.95)	4	0.89 (0.74 to 1.08)	4	1.15 (0.78 to 1.69)	6	0.94 (0.76 to 1.16)	7	0.94 (0.84 to 1.06)	11	0.99 (0.82 to 1.19)	11
Unpublished	0.68 (0.17 to 2.78)	5	0.85 (0.57 to 1.26)	5	1.01 (0.68 to 1.50)	10	0.90 (0.62 to 1.29)	8	1.07 (0.74 to 1.51)	12	1.03 (0.89 to 1.19)	14

DPI, dry powder inhaler; MDI, metered-dose inhaler. —, no data.

* *P* value for subgroup comparison using χ^2 test.

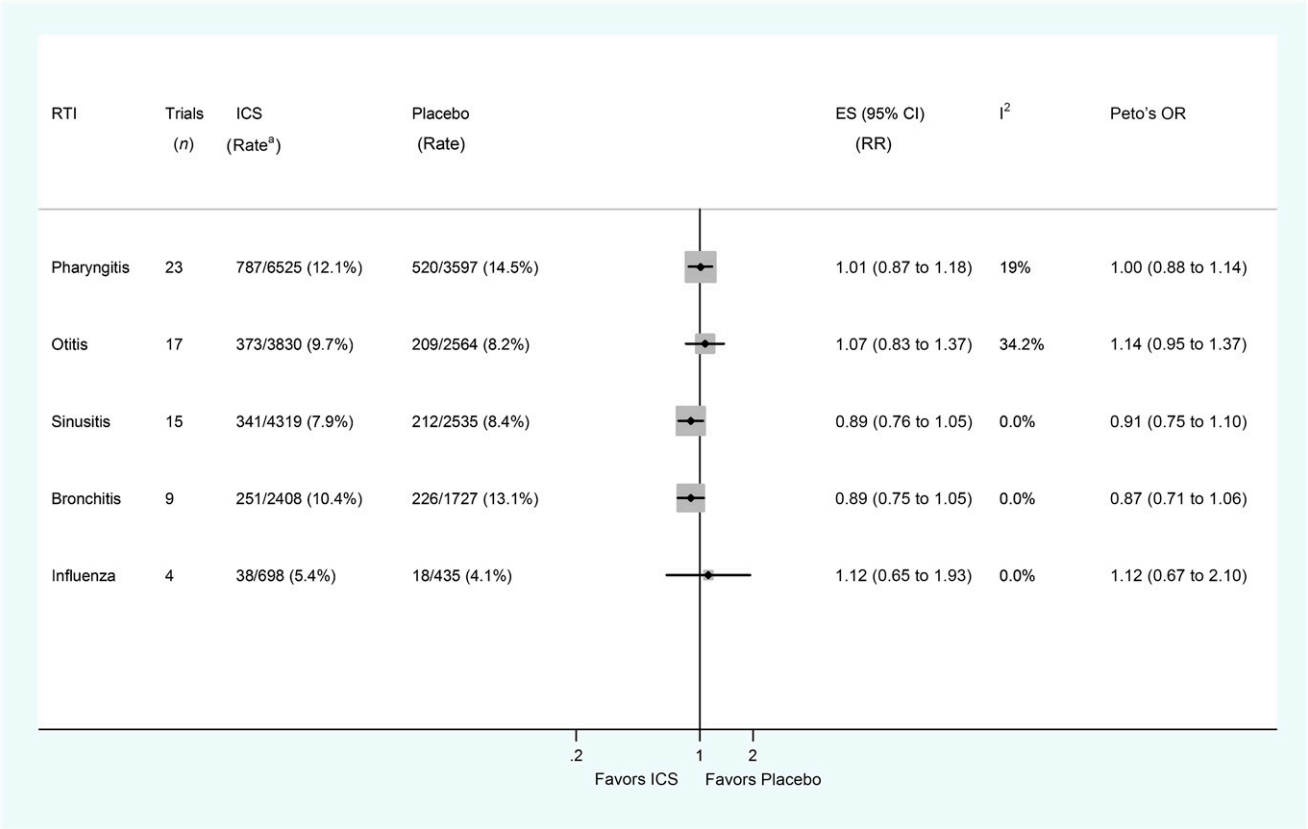

FIGURE 2
Use of ICS and risk of other respiratory infections. RR > 1 favors placebo, suggesting a higher risk of respiratory infections in the ICS group. Weights are from random effects analysis. ES, effect size; RTI, respiratory tract infection. [a] Rate: cases/participants at risk.

meta-analyses. Five trials[16,23,30,39,46] used fluticasone (100 vs 200 µg/day), 3 trials[18,34,43] used budesonide (200 to 500 vs 400 to 1000 µg/day), 1 trial[29] used beclomethasone (100 vs 200 µg/day), 3 trials[19,36,37] used mometasone (100 vs 200 µg/day), and 5 trials[22,31,35,41,42] used ciclesonide (50 to 100 vs 100 to 200 µg/day). Three trials compared 3 daily doses, of which 2 trials[22,31] used ciclesonide (50, 100, and 200 µg/day), and 1 trial[36] used mometasone (200, 400, and 800 µg/day). In these 3 trials, we combined 2 higher doses into a single group. The meta-analyses did not reveal a significant dose–response relationship between ICS and risk of respiratory infections (Fig 3). Moreover, an inverse relationship was observed between dose of ICS and risk of otitis media, that is, higher dose of ICS was significantly associated with lower risk of otitis media (9 trials, RR: 0.73, 95% CI: 0.57 to 0.93, I^2 = 0%).

DISCUSSION

This systematic review and meta-analysis of randomized trials suggests that regular use of ICS is unlikely to increase the risk of pneumonia or other respiratory infections in children with asthma. Drug molecules, daily doses, delivery devices, treatment duration, and patient's age appear to have no significant impact on the size of risk of respiratory infections related to use of ICS.

In this review, we used 2 data sets and 3 different effect size measures (RR, Peto's OR, and RD) to estimate the risk of pneumonia due to ICS. The first data set includes only 9 trials that revealed at least 1 event of pneumonia. The meta-analysis of 9 trials using RR as effect measure reveals that use of ICS could result in a 35% reduction in the risk of pneumonia when compared with placebo. The meta-analysis using Peto's OR as effect measure yields a similar result. These results are consistent with those found in a meta-analysis[9] of 10 trials in which the majority of participants were adults with asthma. However, caution should be taken when interpreting these results. Firstly, meta-analysis may overestimate the incidence of pneumonia if excluding the trials in which no events of pneumonia were reported in either arm. Secondly, 1 trial[38] contributed with 89% of the weight to the meta-analysis and the results were no longer statistically significant when this trial was excluded in the sensitivity analysis. However, exclusion

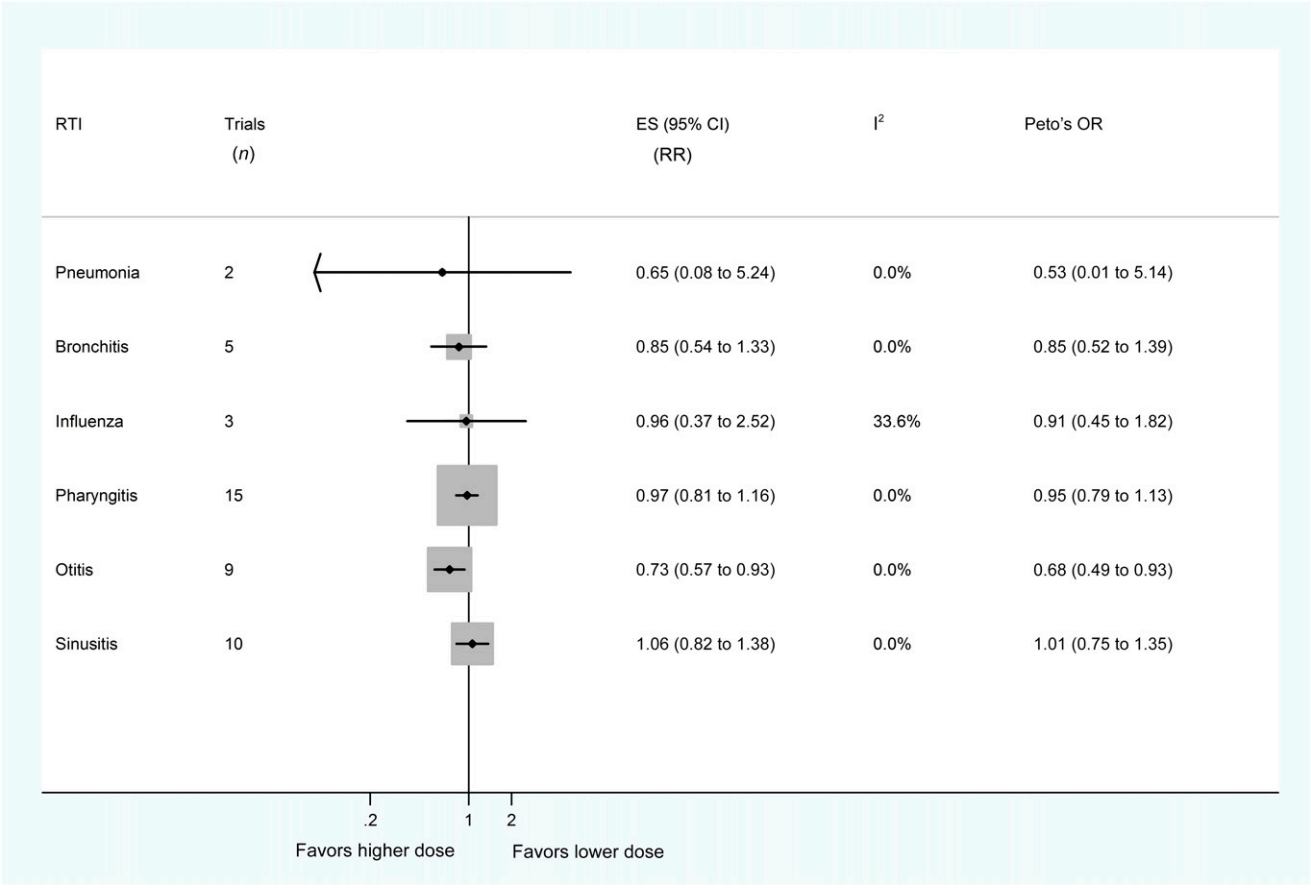

FIGURE 3
Use of ICS and risk of respiratory infections: dose–response relationship. RR > 1 favors lower doses, suggesting a greater risk of respiratory infections in subgroup higher doses. Weights are from random effects analysis. ES, effect size; RTI, respiratory tract infection.

of this trial changed the upper limit of 95% CI from 0.94 to 1.86, suggesting a potential increase of risk of pneumonia on the basis of the results of smaller trials. Thirdly, asthma exacerbations could be easily misclassified as pneumonia given the lack of clearly defined criteria for pneumonia in the trials and similar clinical manifestations between pneumonia and asthma exacerbation.

The second data set consists of all 31 trials that revealed at least 1 respiratory infection event, even if pneumonia was not explicitly mentioned. Using RD as effect measure, the meta-analysis of 31 trials reveals no significant association between use of ICS and risk of pneumonia in children with asthma. In this database, we considered no events in both arms if pneumonia had not been explicitly reported. The rationale for this strategy is that no events of pneumonia in either treatment arm were likely not to be mentioned in the trial reports because the majority of trials were designed to assess the efficacy of ICS and pneumonia was rarely considered an a priori safety end point.

On the other hand, if the trial revealed at least 1 respiratory infection event, it is unlikely that pneumonia, a more severe respiratory infection, could be ignored. Taking all together, we believe that the meta-analysis on the basis of second data set may provide more accurate estimates, suggesting no significant association between use of ICS and risk of pneumonia in children with asthma. We recognize that the method used for dealing with possibly no events in both arms is not yet validated, but no other better method is currently available.

ICS may affect local immunity and microbial community in the respiratory tract.[55] One cross-sectional study demonstrates that children with asthma regularly taking ICS are almost 4 times more likely to have oropharyngeal colonization by *S pneumoniae* than those not taking such drugs when adjusted for potential confounders.[10] It could be expected that children with an increased microbial burden in the oropharyngeal area may be at higher risk for respiratory infections, not only pneumonia but also other respiratory infections. However, this systematic review does not find a significantly increased risk

of other respiratory infections such as pharyngitis, otitis media, sinusitis, bronchitis, and influenza in children with asthma taking ICS. These findings suggest that impaired local immunity and increased oropharyngeal bacterial colonization related to use of ICS may not be associated with an increased risk of respiratory infections in children with asthma.

We also explored other potential effect modifiers through subgroup analyses, and we did not find significant impact of drug molecules, delivery devices, treatment duration, and patient's age on the effect size of ICS.

The meta-analysis of 17 trials that compared different doses of ICS does not reveal a dose–response relationship between ICS and risk of respiratory infections in children with asthma. However, only low to medium doses of ICS were used in the trials.

Most of the included trials did not describe the methods for random sequence generation and allocation concealment. This may raise a concern about the potential selection bias. However, these potential biases may have no significant impact on the trial results given that the baseline characteristics were similar between treatment groups in all included trials. Underreporting of adverse events of treatment is common in clinical trials. This inherent methodological shortcoming of primary trials is the main limitation of all systematic review of safety data. It may underestimate the rate of adverse events; however, the risk estimation could not be substantially affected because underreporting may occur equally in both treatment arms. To minimize outcome reporting bias, we obtained additional data for 7 published trials through clinicaltrials.gov. Another inherent methodological shortcoming of primary trials is lack of clearly defined criteria for diagnosis of respiratory infections and this should be considered as the other main limitation of this review. Publication bias is always a concern in meta-analysis and there is no standard method for detecting it.[56] To minimize the potential publication bias, we have attempted to identify the maximum number as possible of published and unpublished trials through the following strategies: building an effective search strategy by using only 2 types of search terms (asthma and inhaled corticosteroids); checking the references of retrieved articles including systematic reviews to find additional relevant trials; searching clinicaltrials.gov and the databases of GSK and AstraZeneca to identify unpublished trials. Moreover, the subgroup analysis on the basis of data source did not find significant difference in the results between published and unpublished data, suggesting that the potential publication bias might not substantially affect the results of the review. Given that this review did not include trials that used ICS plus other drugs, caution should be taken when extrapolating the findings of this review to patients taking ICS plus long-acting β_2 agonist or other drugs. Children aged 12 to 16 through 18 years might be underrepresented because only 6 trials of this review included children in this age group. Some posthoc subgroup analyses and meta-analysis of dose–response might be underpowered to detect an effect. Use of antibiotic and oral steroids may have acted as a potential confounder because patients taking placebo were more likely to receive these medications than those taking ICS due to poorer asthma control. Unfortunately, there was no available data from the trials to assess the effect of potential confounding.

The quality of evidence provided by this systematic review could be graded only as low for primary outcome (pneumonia) and moderate for secondary outcomes (other respiratory infections), according to the Grading of Recommendations, Assessment, Development and Evaluations[57] criteria (Supplemental Table 5). Further prospective studies examining the safety of ICS in children with asthma including well-defined pneumonia and other respiratory infections as a priori outcomes are still needed.

CONCLUSIONS

The evidence provided by this systematic review suggests that regular use of ICS is unlikely to increase the risk of pneumonia or other respiratory infections in children with asthma. These data add to the already considerable body of evidence suggesting a good safety profile of ICS in children with asthma.

ABBREVIATIONS

CI: confidence interval
ICS: inhaled corticosteroids
ITT: intention-to-treat
OR: odds ratio
RD: risk difference
RR: risk ratio

Accepted for publication Dec 2, 2016

Address correspondence to Linjie Zhang, MD, PhD, Associate Professor, Faculty of Medicine, Federal University of Rio Grande, Rua Visconde de Paranagua 102, Centro, Rio Grande-RS, Brazil. E-mail: lzhang@furg.br

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: Dr Wainwright declared the following relationships/conditions/circumstances that may present a potential conflict of interest: income on a per patient basis derived from pharmaceutical studies (Vertex Pharmaceuticals, Inc; Boehringer Ingelheim; and Ablynx NV); epidemiological research support from GlaxoSmithKline (analysis of bronchoalveolar lavage [BAL] fluid from children with respiratory disorders, 2010–2012); research grant from Novo Nordisk Pharmaceuticals P/L- CF-IDEA Study, 2012–2013; and honorarium and travel reimbursement from Vertex Pharmaceuticals, Inc, Gilead Sciences, Inc, Medscape, and Novartis Pharmaceuticals; the other authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Wilkie M, Finch S, Schembri S. Inhaled corticosteroids for chronic obstructive pulmonary disease–the shifting treatment paradigm. *COPD*. 2015;12(5):582–590
2. Thomson NC, Spears M. Inhaled corticosteroids for asthma: on-demand or continuous use. *Expert Rev Respir Med*. 2013;7(6):687–699
3. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids. New developments. *Am J Respir Crit Care Med*. 1998; 157(3 pt 2):S1–S53
4. Allen DB. Safety of inhaled corticosteroids in children. *Pediatr Pulmonol*. 2002;33(3):208–220
5. Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;3(3):CD010115
6. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169(3):219–229
7. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(20):2407–2416
8. O'Byrne PM, Pedersen S, Carlsson LG, et al. Risks of pneumonia in patients with asthma taking inhaled corticosteroids. *Am J Respir Crit Care Med*. 2011;183(5):589–595
9. Bansal V, Mangi MA, Johnson MM, Festic E. Inhaled corticosteroids and incident pneumonia in patients with asthma: Systematic review and meta-analysis. *Acta Med Acad*. 2015;44(2):135–158
10. Zhang L, Prietsch SO, Mendes AP, et al. Inhaled corticosteroids increase the risk of oropharyngeal colonization by Streptococcus pneumoniae in children with asthma. *Respirology*. 2013;18(2):272–277
11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700
12. Zhang L, Cazeiro C, Silva C, Mayer S, Mariany V. Inhaled corticosteroids and risk of pneumonia in children with asthma. PROSPERO 2015: CRD42015020656. Available at: www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015020656
13. Virtual Health Library of the Latin American and Caribbean Center on Health Sciences Information (BIREME). Available at: http://bvsalud.org. Accessed May 25, 2015
14. Higgins JPT, Green S, eds. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available at: www.handbook.cochrane.org. Accessed May 10, 2015
15. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560
16. Allen DB, Bronsky EA, LaForce CF, et al; Fluticasone Propionate Asthma Study Group. Growth in asthmatic children treated with fluticasone propionate. *J Pediatr*. 1998; 132(3 pt 1):472–477
17. Becker AB, Kuznetsova O, Vermeulen J, et al; Pediatric Montelukast Linear Growth Study Group. Linear growth in prepubertal asthmatic children treated with montelukast, beclomethasone, or placebo: a 56-week randomized double-blind study. *Ann Allergy Asthma Immunol*. 2006;96(6):800–807
18. Berger WE, Qaqundah PY, Blake K, et al. Safety of budesonide inhalation suspension in infants aged six to twelve months with mild to moderate persistent asthma or recurrent wheeze. *J Pediatr*. 2005;146(1):91–95
19. Berger WE, Milgrom H, Chervinsky P, et al. Effects of treatment with mometasone furoate dry powder inhaler in children with persistent asthma. *Ann Allergy Asthma Immunol*. 2006;97(5):672–680
20. Carlsen KC, Stick S, Kamin W, Cirule I, Hughes S, Wixon C. The efficacy and safety of fluticasone propionate in very young children with persistent asthma symptoms. *Respir Med*. 2005;99(11):1393–1402
21. de Blic J, Delacourt C, Le Bourgeois M, et al. Efficacy of nebulized budesonide in treatment of severe infantile asthma: a double-blind study. *J Allergy Clin Immunol*. 1996;98(1):14–20
22. Gelfand EW, Georgitis JW, Noonan M, Ruff ME. Once-daily ciclesonide in children: efficacy and safety in asthma. *J Pediatr*. 2006;148(3):377–383
23. Katz Y, Lebas FX, Medley HV, Robson R; Fluticasone Propionate Study Group. Fluticasone propionate 50 micrograms BID versus 100 micrograms BID in the treatment of children with persistent asthma. *Clin Ther*. 1998;20(3):424–437
24. Kooi EM, Schokker S, Marike Boezen H, et al. Fluticasone or montelukast for preschool children with asthma-like symptoms: Randomized controlled trial. *Pulm Pharmacol Ther*. 2008;21(5):798–804
25. LaForce CF, Pearlman DS, Ruff ME, et al. Efficacy and safety of dry powder fluticasone propionate in children with persistent asthma. *Ann Allergy Asthma Immunol*. 2000;85(5):407–415

26. Levy AL, Given JT, Weinstein SF, et al. Efficacy and safety of fluticasone propionate hydrofluoroalkane inhalation aerosol in four-to eleven-year-old children with asthma: a randomized, double-blinded, placebo-controlled study. *Pediatr Asthma Allergy Immunol*. 2006;19(2):106–117

27. MacKenzie CA, Weinberg EG, Tabachnik E, Taylor M, Havnen J, Crescenzi K. A placebo controlled trial of fluticasone propionate in asthmatic children. *Eur J Pediatr*. 1993;152(10):856–860

28. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377(9766):650–657

29. Nayak A, Lanier R, Weinstein S, Stampone P, Welch M. Efficacy and safety of beclomethasone dipropionate extrafine aerosol in childhood asthma: a 12-week, randomized, double-blind, placebo-controlled study. *Chest*. 2002;122(6):1956–1965

30. Peden DB, Berger WE, Noonan MJ, et al. Inhaled fluticasone propionate delivered by means of two different multidose powder inhalers is effective and safe in a large pediatric population with persistent asthma. *J Allergy Clin Immunol*. 1998;102(1):32–38

31. Pedersen S, Potter P, Dachev S, et al. Efficacy and safety of three ciclesonide doses vs placebo in children with asthma: the RAINBOW study. *Respir Med*. 2010;104(11):1618–1628

32. Qaqundah PY, Sugerman RW, Ceruti E, et al. Efficacy and safety of fluticasone propionate hydrofluoroalkane inhalation aerosol in pre-school-age children with asthma: a randomized, double-blind, placebo-controlled study. *J Pediatr*. 2006;149(5):663–670

33. Schokker S, Kooi EM, de Vries TW, et al. Inhaled corticosteroids for recurrent respiratory symptoms in preschool children in general practice: randomized controlled trial. *Pulm Pharmacol Ther*. 2008;21(1):88–97

34. Shapiro GG, Mendelson LM, Pearlman DS. Once-daily budesonide inhalation powder (Pulmicort Turbuhaler) maintains pulmonary function and symptoms of asthmatic children previously receiving inhaled corticosteroids. *Ann Allergy Asthma Immunol*. 2001;86(6):633–640

35. Skoner DP, Maspero J, Banerji D; Ciclesonide Pediatric Growth Study Group. Assessment of the long-term safety of inhaled ciclesonide on growth in children with asthma. *Pediatrics*. 2008;121(1). Available at: www.pediatrics.org/cgi/content/full/121/1/e1

36. Skoner DP, Gentile DA, Angelini B. Effect of therapeutic doses of mometasone furoate on cortisol levels in children with mild asthma. *Allergy Asthma Proc*. 2010;31(1):10–19

37. Skoner DP, Meltzer EO, Milgrom H, Stryszak P, Teper A, Staudinger H. Effects of inhaled mometasone furoate on growth velocity and adrenal function: a placebo-controlled trial in children 4-9 years old with mild persistent asthma. *J Asthma*. 2011;48(8):848–859

38. Silverman M, Sheffer AL, Díaz PV, Lindberg B. Safety and tolerability of inhaled budesonide in children in the Steroid Treatment As Regular Therapy in early asthma (START) trial. *Pediatr Allergy Immunol*. 2006;17(suppl 17):14–20

39. Wasserman RL, Baker JW, Kim KT, et al. Efficacy and safety of inhaled fluticasone propionate chlorofluorocarbon in 2- to 4-year-old patients with asthma: results of a double-blind, placebo-controlled study. *Ann Allergy Asthma Immunol*. 2006;96(6):808–818

40. FLTA2007 trial. 2005. Available at: https://gsk.sylogent.com/files/1327.pdf. Accessed January 10, 2015

41. NCT00163293 trial. 2012. Available at: https://clinicaltrials.gov/ct2/show/NCT00163293. Accessed January 10, 2015

42. NCT00392288 trial. 2012. Available at: https://clinicaltrials.gov/ct2/show/NCT00392288. Accessed January 10, 2015

43. NCT00569192 trial. 2013. Available at: https://clinicaltrials.gov/ct2/show/NCT00569192. Accessed January 10, 2015

44. NCT00920959 trial. 2013. Available at: https://gsk.sylogent.com/files/23658.pdf. Accessed January 10, 2015

45. NCT01136382 trial. 2014. Available at: https://clinicaltrials.gov/ct2/show/NCT01136382. Accessed January 10, 2015

46. FMS30059 trial. 2005. Available at: www.gsk-clinicalstudyregister.com/files2/gsk-fms30059-clinical-study-report-redact.pdf. Accessed January 10, 2015

47. Baker JW, Mellon M, Wald J, Welch M, Cruz-Rivera M, Walton-Bowen K. A multiple-dosing, placebo-controlled study of budesonide inhalation suspension given once or twice daily for treatment of persistent asthma in young children and infants. *Pediatrics*. 1999;103(2):414–421

48. Connett GJ, Warde C, Wooler E, Lenney W. Use of budesonide in severe asthmatics aged 1-3 years. *Arch Dis Child*. 1993;69(3):351–355

49. Hofstra WB, Neijens HJ, Duiverman EJ, et al. Dose-responses over time to inhaled fluticasone propionate treatment of exercise- and methacholine-induced bronchoconstriction in children with asthma. *Pediatr Pulmonol*. 2000;29(6):415–423

50. Jónasson G, Carlsen KH, Blomqvist P. Clinical efficacy of low-dose inhaled budesonide once or twice daily in children with mild asthma not previously treated with steroids. *Eur Respir J*. 1998;12(5):1099–1104

51. Kerwin EM, Pearlman DS, de Guia T, et al. Evaluation of efficacy and safety of budesonide delivered via two dry powder inhalers. *Curr Med Res Opin*. 2008;24(5):1497–1510

52. Shapiro G, Mendelson L, Kraemer MJ, Cruz-Rivera M, Walton-Bowen K, Smith JA. Efficacy and safety of budesonide inhalation suspension (Pulmicort Respules) in young children with inhaled steroid-dependent, persistent asthma. *J Allergy Clin Immunol*. 1998;102(5):789–796

53. Shapiro G, Bronsky EA, LaForce CF, et al. Dose-related efficacy of budesonide administered via a dry powder inhaler in the treatment of children with moderate to severe persistent asthma. *J Pediatr*. 1998;132(6):976–982

54. Simons FE; Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med*. 1997;337(23):1659–1665

55. Fukushima C, Matsuse H, Saeki S, et al. Salivary IgA and oral candidiasis in asthmatic patients treated with inhaled corticosteroid. *J Asthma*. 2005;42(7):601–604

56. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *JAMA*. 2006;295(6):676–680

57. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013;66(2):151–157

Inhaled Corticosteroids and Respiratory Infections in Children With Asthma: A Meta-analysis

Cristine Cazeiro, Cristina Silva, Susana Mayer, Vanessa Mariany, Claire Elizabeth Wainwright and Linjie Zhang

Pediatrics; originally published online February 24, 2017;
DOI: 10.1542/peds.2016-3271

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Inhaled Corticosteroids and Respiratory Infections in Children With Asthma: A Meta-analysis

Cristine Cazeiro, Cristina Silva, Susana Mayer, Vanessa Mariany, Claire Elizabeth Wainwright and Linjie Zhang

Pediatrics; originally published online February 24, 2017;
DOI: 10.1542/peds.2016-3271