Asthma and the Risk of Invasive Pneumococcal Disease: A Meta-analysis

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abstract

CONTEXT: Invasive pneumococcal disease (IPD) and pneumonia are a leading cause of morbidity and mortality throughout the world, and asthma is the most common chronic disease of childhood.

OBJECTIVE: To evaluate the risk of IPD or pneumonia among children with asthma after the introduction of pneumococcal conjugate vaccines (PCVs).

DATA SOURCES: Four electronic databases were searched.

STUDY SELECTION: We selected all cohorts or case-control studies of IPD and pneumonia in populations who already received PCV (largely 7-valent pneumococcal conjugate vaccine), but not 23-valent pneumococcal polysaccharide, in which authors reported data for children with asthma and in which healthy controls were included, without language restriction.

DATA EXTRACTION: Two reviewers independently reviewed all studies. Primary outcomes were occurrence of IPD and pneumonia. Secondary outcomes included mortality, hospital admissions, hospital length of stay, ICU admission, respiratory support, costs, and additional medication use.

RESULTS: Five studies met inclusion criteria; of those, 3 retrospective cohorts ($\sim$26 million person-years) and 1 case-control study ($N = 3294$ children) qualified for the meta-analysis. Children with asthma had 90% higher odds of IPD than healthy controls (odds ratio = 1.90; 95% confidence interval = 1.63–2.11; $I^2 = 1.7\%$). Pneumonia was also more frequent among children with asthma than among controls, and 1 study reported that pneumonia-associated costs increased by asthma severity.

LIMITATIONS: None of the identified studies had information of asthma therapy or compliance.

CONCLUSIONS: Despite PCV vaccination, children with asthma continue to have a higher risk of IPD than children without asthma. Further research is needed to assess the need for supplemental 23-valent pneumococcal polysaccharide vaccination in children with asthma, regardless of their use of oral steroids.

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Streptococcus pneumoniae is still one of the most frequent causes of invasive disease, such as sepsis and meningitis, and a frequent cause of bacterial pneumonia, acute otitis media, and rhinosinusitis.[1] Although these diseases can occur in both healthy children and those with chronic underlying diseases, their incidence and severity are significantly higher in those with chronic underlying disease.[2]

Invasive pneumococcal disease (IPD) is a leading cause of morbidity and mortality throughout the world. In 2000, before the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), an estimated 14.5 million episodes of IPD occurred among children <5 years of age, resulting in an estimated 826 000 deaths (11% of all deaths in that age group).[3] Pneumococcal conjugate vaccine (PCV) PCV7 was introduced in the United States in 2000, and 13-valent pneumococcal conjugate vaccine (PCV13) replaced it in 2010. Current guidelines from the US Centers for Disease Control and Prevention (CDC)[4] and the American Academy of Pediatrics (AAP)[5] recommend 4 doses of PCV13 (at 2, 4, 6, and 12–15 months of age) and a dose of the 23-valent pneumococcal polysaccharide vaccine (PPSV23) at 2 years of age for children with conditions considered high risk for IPD or as soon as possible after a diagnosis of chronic illness is made after the age of 2 years. High-risk conditions include cerebrospinal fluid leak or cochlear implants; diabetes; HIV infection or immunodeficiencies (congenital, acquired, or secondary to medications); anatomic or functional asplenia; sickle cell and other hemoglobinopathies; neoplasms; and chronic diseases including chronic heart, lung, kidney, or liver diseases. Currently, PPSV23 vaccination is recommended for patients with asthma only if they are treated with high-dose oral corticosteroid therapy.[4,5]

Asthma is the most common chronic disease of childhood.[6] It affects >6.5 million children in the United States alone,[7] with millions more around the world, and its prevalence steadily increased from the 1980s to at least the 2000s.[7] In a previous study in which authors reported increased risk of IPD in children with asthma and adults involved a period of time (1995–2002) in which most children would not have received PCV,[8] and a systematic review of IPD in asthma included only 1 pediatric study in the PCV era.[9] Here, we aim to evaluate current evidence on the risk of IPD in children with asthma after the introduction of PCV.

METHODS

Search and Selection Criteria

We searched 4 electronic databases (Medline, the Cochrane Collaboration clinical trials register, Latin American and Caribbean Health Sciences Literature, and Cumulative Index to Nursing and Allied Health Literature) up to October 2018. The search was conducted by using the following keywords: "(((pneumococcal infections) OR (invasive pneumococcal disease) OR (pneumococcal pneumonia)) AND ((asthma OR wheezing)))," as well as the corresponding Medical Subject Headings terms, restricted to children (birth to 18 years of age). We also searched the references of included publications as well as other nonbibliographic data sources such as pharmaceutical industry Web sites.

The inclusion criteria were (1) cohorts or case-control studies including children with and without asthma; (2) assessment of IPD (defined as the isolation of *S pneumoniae* from a normally sterile fluid [eg, blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone or joint fluid by any laboratory diagnosis test]) with association of morbidity or mortality; (3) in

populations who have already received PCV7, 10-valent pneumococcal conjugate vaccine, or PCV13, but not PPSV23; with (4) no language restriction. The exclusion criteria were (1) no specific data for children with asthma reported in the population analysis, (2) IPD morbidity or mortality description in children with asthma but in the absence of a control group, and (3) reviews, letters, abstracts, or articles lacking sufficient information in English for data synthesis or analysis. The primary outcomes were the occurrence of IPD, defined as above, and pneumococcal pneumonia. Secondary outcomes, if available, were hospital admissions, mortality, length of hospital stay, admission to the ICU, need for invasive respiratory support, additional medication use (ie, in addition to the patient's baseline), all-cause pneumonia, and costs associated with disease.

Data Abstraction and Assessment of Risk of Bias

Titles, abstracts, and citations were independently analyzed by 2 independent investigators (J.A.C.-R. and E.F.), and any disagreements were resolved by consensus after discussion. The reviewers independently assessed the full text of all studies for inclusion on the basis of the criteria for population intervention, study design, and outcomes. After obtaining full reports from potentially relevant studies, they independently reassessed eligibility. If the information was incomplete, we attempted to contact the authors. The risk of bias from including certain studies was assessed according to the Newcastle-Ottawa Scale.[10,11]

Data Analysis

When feasible, we calculated pooled odds ratios (ORs) with 95% confidence intervals (CIs). Heterogeneity was assessed by using the I^2 test (≤25% absence of bias; 26%–39% unimportant; 40%–60% moderate; 60%–100% substantial

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bias).[12] To address the variability across studies for each outcome of interest, a fixed-effects meta-analysis was used when low heterogeneity was present ($I^2 < 40\%$), and a random-effects meta-analysis was performed when high heterogeneity was detected ($I^2 \geq 40\%$). Meta-analyses were performed by using Stata version 14.0 (Stata Corp, College Station, TX) or Review Manager 5.3 software (2014; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

A total of 125 studies were initially identified in the databases and other sources (Fig 1). After excluding duplicates, we reviewed 123 abstracts; 112 studies were excluded because they did not meet inclusion criteria. Eleven full-text articles were evaluated, and 5 of them[13-17] fulfilled

the inclusion criteria for the qualitative synthesis, of which 4[13-16] also fulfilled criteria for the quantitative synthesis or meta-analysis (Table 1). The other 6 studies were excluded because they were performed before introduction of PCV7 (n = 3),[8,18,19] they provided no specific data by asthma status (n = 1),[20] or they included no pediatric data (n = 2).[21,22]

The 5 identified studies were published from 2010 to 2016. One study was a case-control analysis of children with and without IPD[13] and included 3294 children (45 with asthma; 782 with IPD and 2512 in the control group), 3 were retrospective cohorts,[14-16] and the fifth study was a retrospective study of microbiology laboratory reports from 586 IPD cases from 2001 to 2007.[17] The latter study was not included for the quantitative synthesis. In none of the

studies did the authors report separately the fluid site from which the pneumococcal infection was isolated.

Among the 4 studies included for the quantitative synthesis or meta-analysis (Table 1), 3 were conducted in the United States,[13,14,16] and 1 was conducted in Korea.[15] Pelton et al[14] and Weycker et al[16] reported on the same cohort, with a total of 26.5 million person-years of follow-up, including 1.23 million person-years in children with asthma. In the third retrospective cohort,[15] the authors reported 398 IPD cases among 935 106 participants (467 294 with asthma) in 2010 and 428 IPD cases among 952 295 participants (482 155 with asthma) in 2011, but it was unclear whether the populations at risk were different for each of the 2 years. Pilishvili et al[13] defined IPD on the basis of isolation of *Pneumococcus* from a normally sterile site in an active bacterial core surveillance program, and asthma was defined by questionnaires. Pelton et al[14] and Weycker et al[16] defined IPD and asthma by using *International Classification of Diseases, Ninth Revision* (ICD-9), codes, whereas Kwak et al[15] used *International Classification of Diseases, 10th Revision*, codes.

Pilishvili et al[13] included children <6 years of age, and Pelton et al[14] reported separate estimates for children <5 and 5 to 17 years of age; in contrast, Kwak et al[15] and Weycker et al[16] reported estimates for children <18 years old. Pilishvili et al[13] included children of an age group for which PCV7 was recommended and adjusted their analyses by receipt of ≥1 dose of PCV7, Pelton stated that study data were collected during a period when 89% of children <2 years old had received 3 PCV7 doses, and Kwak et al[15] only mention that children not receiving oral steroids and children with asthma >6 years old were excluded from receiving PCV13 and PPSV23. A
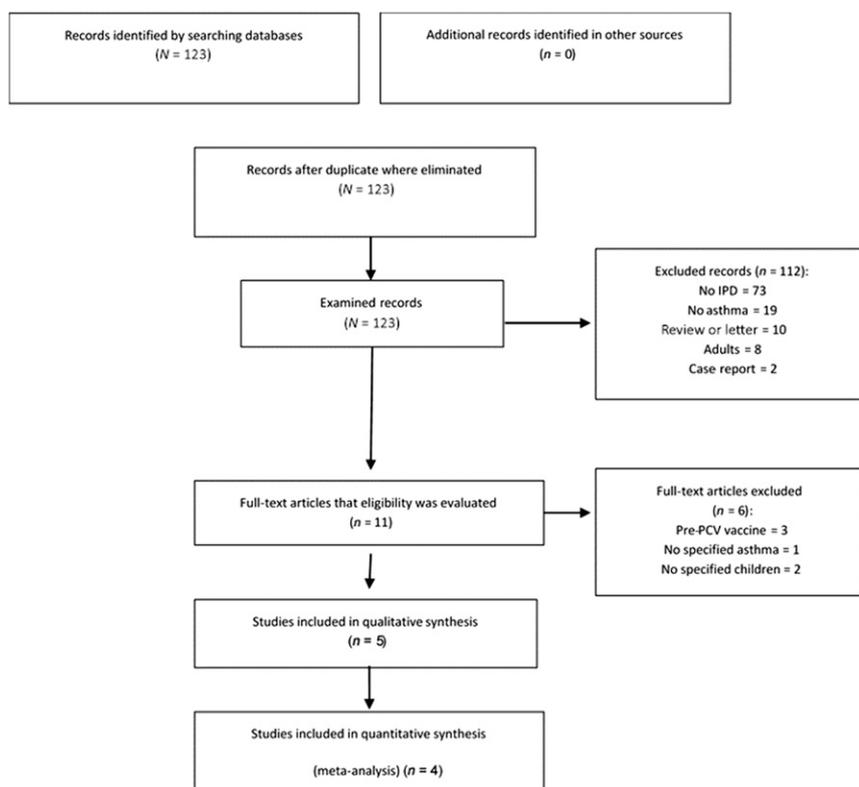

FIGURE 1
Flowchart of study selection. Two studies were reviewed but not included in the meta-analysis: Weycker et al[16] (used data from the same cohort as Pelton et al[14]) and Hsu et al[17] (insufficient data available).

TABLE 1 Summary of Studies Included in the Qualitative Summary and Quantitative Analysis

Author (Year)	Country (Region)	Study Design	Included Participants	Outcomes	Main Results, Notes, and Funding
Pilishvili et al[13] (2010)	United States (select counties in 8 US states)	CC	Children 3–59 mo old with IPD versus children without IPD of the same age living in same area. IPD defined on the basis of culture data from an active bacteria core surveillance system (2001–2004). Asthma was defined by report during questionnaires.	IPD	IPD = 27% with asthma; CG = 18% with asthma
			IPD cases: $n = 782$		Risk of IPD (asthma compared to the CG): aOR = 1.8 (95% CI = 1.5–2.2); $P < .001$
			CG: $n = 2512$		Multivariable model (controlling for multiple comorbidities): aOR = 1.5 (1.1–2.1)
					Funding: CDC, National Vaccine Program
Pelton et al[14] (2014)[a]	United States (claims data covering providers in several states)	RC	Children <18 y of age with high-risk and at-risk conditions for IPD versus children without risk conditions in 3 integrated health care claims database (2007–2010). Children <5 y old: 6 million person-years. Children 5–17 y old: 20.5 million person-years; IPD and asthma defined by using the ICD-9.	IPD, pneumococcal pneumonia, all-cause pneumonia	RR for IPD among children with asthma: Age <5 y: aRR 1.6 (1.0–2.4) Age 5–17 y: aRR 2.1 (1.4–3.2) RR for pneumococcal pneumonia among children with asthma: Age <5 y: aRR 3.5 (3.0–4.0) Age 5–17 y: aRR 2.8 (2.6–3.1) Funding: Pfizer, Inc
Kwak et al[15] (2015)	Korea (whole-country database)	RC	Retrospective population-based cohort using Korean Health Insurance Review and Assessment database (2010–2011) 2010: 398 of 935 106 subjects had IPD. 2011: 428 of 952 295 subjects had IPD. IPD and asthma were defined by using the ICD-10.	IPD	In children 0–18 y of age, odds of asthma among IPD cases: In 2010: aOR = 2.08 (1.25–3.45) In 2011: aOR = 3.26 (1.74–6.11) Unclear whether the risk pool overlapped between 2010 and 2011; also, ~50% of subjects in each year had asthma, suggesting a matched CC design, but it was not stated in the methods Funding: Pfizer Korea Ltd
Weycker et al[16] (2016)[a]	United States (claims data covering providers in several states)	RC	Review of 3 integrated health care claims repositories (2007–2010) Children <18 y old: 26.5 million person-years; IPD and asthma defined by using ICD-9	IPD, all-cause pneumonia	In children <18 y: aRR of IPD among children with asthma: 1.5 (1.1–2.0); aRR of pneumonia among children with asthma: 2.9 (2.9–3.0) Funding: Pfizer, Inc

aRR, adjusted risk rate; CC, case-control; CG, control group; ICD-10, *International Classification of Diseases, 10th Revision*; RC, retrospective cohort.
[a] Pelton et al[14] and Weycker et al[16] reported on the same cohort.

description of study quality assessment is presented in Table 2. Pilishvili et al[13] was funded by the CDC and the National Vaccine Program Office, Pelton et al[14] and Weycker et al[16] were funded by Pfizer, Inc, and Kwak et al[15] were funded by Pfizer Korea, Ltd.

Primary Outcomes

Authors of all 5 studies reported IPD.[13–17] Pilishvili et al[13] reported that 27% of patients with IPD had asthma compared with 18% of patients in the control group, for an adjusted odds ratio (aOR) of 1.8 (95% CI = 1.50–2.22). Pelton et al[14] reported IPD rates (per 100 000) of 11.6 for children <5 years of age with asthma (compared to 7.3 for healthy children) and 2.3 for children 5 to 17 years old with asthma (compared to 1.1 for healthy children); the adjusted rate ratios (RRs) were 1.6 (1.0–2.4) and 2.1 (1.4–3.2) for each age group, respectively. Kwak et al[15] reported aORs of 2.08 (1.25–3.45) in 2010 and 3.26 (1.74–6.11) in 2011 for IPD among children with asthma versus children without asthma. Weycker et al[16] reported an IPD rate of 3.7 per 100 000 for children with asthma (compared to 2.5 for healthy controls), with an adjusted RR of 1.5 (1.1–2.0).

The meta-analysis (Fig 2) of IPD revealed a pooled estimate of 1.90 (1.63–2.11) using a fixed-effects model and 1.90 (1.63–2.21) using a random-effects model. There was low heterogeneity ($I^2 = 1.7\%$; $P = .40$)

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TABLE 2 Study Quality Assessment

Newcastle-Ottawa Scale for Cohort Studies	Pelton et al[14] 2014	Kwak et al[15] 2015	Weycker et al[16] 2016	Pilishvili et al[13] 2010	Hsu et al[17] 2011
A Selection					
Exposed representative of the community	Adequate	Adequate	Adequate	Adequate	Adequate
Nonexposed selected from the same community	Adequate	Unclear or not reported	Adequate	Adequate	Unclear or not reported
Exposure ascertained by secure records or structured interview	Adequate	Adequate	Adequate	Adequate	Adequate
Demonstration that outcome of interest was not present at study start	Adequate	Adequate	Adequate	Adequate	Adequate
B Comparability					
Study controlled for most important factor(s)	Inadequate	Adequate	Unclear or not reported	Inadequate	Inadequate
Study controlled for other factor(s)	Inadequate	Inadequate	Inadequate	Adequate	Inadequate
C Outcome					
Independent blind assessment or using record linkage	Adequate	Adequate	Adequate	Adequate	Adequate
Follow-up long enough for outcome to occur	Adequate	Adequate	Adequate	Adequate	Adequate
Subjects lost to follow-up unlikely to introduce bias	Unclear or not reported	Adequate	Unclear or not reported	Inadequate	Inadequate

among studies. The studies by Pelton et al[14] and Weycker et al[16] were reported on the same cohort. Only estimates reported by Pelton et al[14] were included in the pooled analysis because they reported data on preschoolers and schoolchildren separately. In a sensitivity analysis including data from Weycker et al[16] instead, the pooled estimate remained virtually unchanged (OR 1.86 [1.48–2.35]). Hsu et al[17] was not included in the meta-analysis of IPD because they only reported data on pneumonia.

Authors in some of the included studies performed subgroup analyses. Pilishvili et al[13] evaluated the risk of IPD from serotypes not covered by PCV7 and reported an aOR of 1.5 (1.1–2.1) for children with asthma compared with children in a control group. Pelton et al[14] evaluated the risk of IPD by asthma severity and reported adjusted RRs of 0.9 (0.3–2.4), 1.4 (0.8–2.6), and 6.6 (3.0–14.8) for mild, moderate, and severe asthma, respectively, among children <5 years of age. For children 5 to 17 years old, the adjusted RRs were 1.7 (0.8–3.4) for mild asthma and 2.6 (1.5–4.3) for moderate asthma (severe asthma was not analyzed in that age group).[14]

Authors of 3 studies also reported on the risk of pneumococcal or all-cause pneumonia in children with asthma.[14,16,17] Among children <5 years of age, Pelton et al[14] reported adjusted RRs of 3.5 (3.0–4.0) for pneumococcal pneumonia and of 3.0 (3.0–3.0) for all-cause pneumonia. For children ages 5 to 17 years, the RRs were 2.8 (2.6–3.1) and 3.5 (3.4–3.5), respectively.[14] Using data from the same cohort, Weycker et al[16] reported an adjusted RR of 2.9 (2.9–3.0) for all-cause pneumonia in children with asthma <18 years of age. Hsu et al[17] reported that a higher proportion of children with asthma had pneumococcal pneumonia
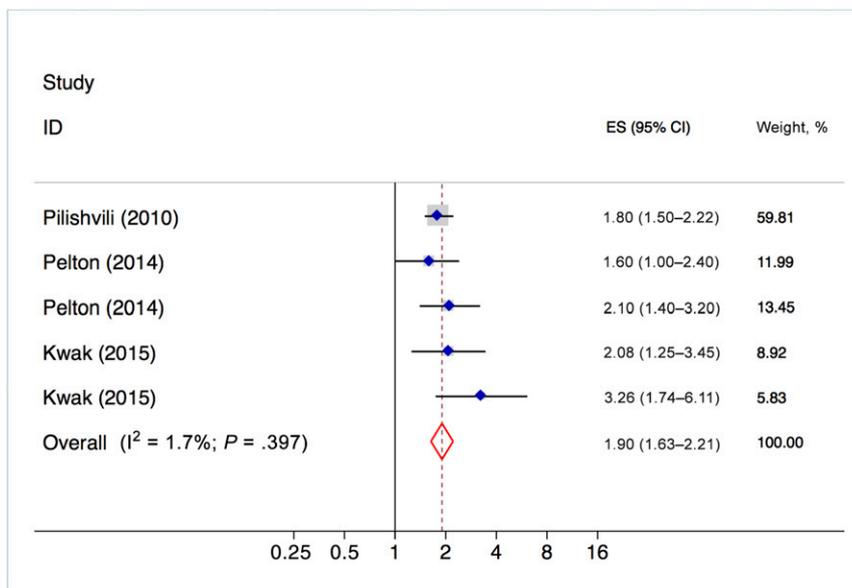

FIGURE 2
Meta-analysis of IPD in children with asthma compared with children without known risk factors. Please note that Pelton includes 2 different age groups (<5 years and 5–17 years), and Kwak et al[15] included estimates for 2 years (2010 and 2011); thus, the studies have 2 separate entries in the analysis. ES, effect estimate for the OR. ID, identification.

compared with children with no known risk factors (65% vs 31%; *P* < .05); of note, that study included only children with asthma who were not receiving corticosteroids. As mentioned before, Pelton et al[14] and Weycker et al[16] reported on the same population; thus, a meta-analysis was not performed.

Secondary Outcomes

In none of the included studies did authors report data on asthma for hospital admission, mortality, length of hospital stay, ICU admission, invasive respiratory support, or additional medication use. Weycker et al[16] reported on costs associated with IPD and all-cause pneumonia. Estimated costs (per 100 000 person-years) for IPD were $100 020 for children with mild asthma, $172 002 for moderate asthma, and $638 452 for severe asthma (compared with $72 581 for healthy controls), with cost ratios of 1.4 (0.1–3.9), 2.4 (0.6–5.0), and 8.9 (0.0–33.9), respectively. For all-cause pneumonia, estimated costs per 100 000 person-years for mild, moderate, and severe asthma were $7.5, $14.6, and $46.8 million, respectively (compared with $1.7 million for healthy controls), and the respective cost ratios were 4.3 (3.8–4.9), 8.4 (7.7–9.1), and 26.8 (22.5–31.3).

DISCUSSION

This review reveals that children with asthma are at a higher risk of IPD and pneumonia than children without asthma, even after the introduction of PCV. For the first time, this meta-analysis reveals 90% increased odds of IPD among children with asthma in populations vaccinated with PCV7, 10-valent pneumococcal conjugate vaccine, and/or PCV13 but not PPSV23. If confirmed, these findings will bear clinical and public health importance because the CDC[7] and AAP[5] guidelines currently recommend the polysaccharide vaccine (PPSV23) after 2 years of age

for children with asthma only "if treated with prolonged high-dose oral corticosteroids." However, it is important to note that the pooled analysis was based on a small number of studies; thus, there is not sufficient evidence at this time to make any clinical or policy recommendations.

The reported results have biologically plausible explanations. In a case-control study, children with asthma receiving inhaled corticosteroid (ICS) therapy for at least 30 days (mean duration 8.6 months) had significantly higher prevalence of oropharyngeal colonization by *S pneumoniae* than those not being treated with ICS (adjusted prevalence ratio of 3.75 [1.72–8.18]).[23] ICS deposition in the oropharynx may inhibit mucosal immune response and partially contribute to the risk of oropharyngeal candidiasis, a well-known local adverse event of ICS,[24] and one could hypothesize that the same may be true of *S pneumoniae*. Thus, a higher carrier rate of *S pneumoniae* in the oropharynx, along with the impaired airway clearance that may be present in asthma, could potentially increase the risk of pneumococcal diseases such as pneumonia or IPD. Furthermore, *S pneumoniae* colonization may be common in all school-aged children and adolescents with asthma, regardless of the severity of the disease and the administration of PCV7 in the first years of life.[25] A recent quasi-cohort study[26] that included 152 412 patients with asthma aged 12 to 35 years (of whom 1928 had pneumonia during follow-up) revealed an increased risk of pneumonia associated with current use of ICSs (RR: 1.83 [1.57–2.14]) for an excess risk of 1.44 cases per 1000 person-years (rate difference [RD]: 1.44 [1.03–1.87]). There was an excess pneumonia risk with low doses (RD: 1.60 [1.06–2.45]), moderate doses (RD: 1.53 [1.12–2.08]), and high doses (RD:

1.96 [1.64–2.34]) of ICSs, and this increased risk was present for both budesonide and fluticasone. That study was done between 1990 and 2007 in Canada, where the PCV7 for children was implemented in 2001.[26] Serotypes ^{19}F, 4, and 9V (all contained in PCV7) were the most frequently identified serotypes in vaccinated subjects, highlighting the limited protection against colonization provided by PCV7 and the issue of persistent colonization by the pneumococcal serotypes included in the vaccine, which could leave children with asthma at risk for infection.

Children with atopic conditions other than asthma may also have an impaired response to *S pneumoniae*.[27] Among children ages 3 to 8 years, only 18% of those with eczema showed adequate antibody responses to PPSV23, compared with 57% of those without eczema (OR: 0.2 [0.05–0.84]; *P* = .03). On the other hand, however, Quezada et al[28] recently reported that children with well-controlled asthma without a history of recurrent respiratory infections had pneumococcal antibody levels and percentages of serotype-specific protection to *S pneumoniae* comparable to those of healthy children. Rose et al[29] enrolled preschoolers (2–5 years of age) with mild to moderate asthma to undergo sequential immunization with 1 dose of PCV7 followed by a single dose of PPSV23, with half of them randomly assigned to receiving PPSV23 8 weeks after PCV and the other half to a 10-month interval. They reported that although both sequential pneumococcal vaccine regimens were safe and immunogenic, immunogenicity was higher when the booster was given after 10 months compared to 8 weeks. Thus, limitations in serum antibody response may contribute to the increased rates of IPD among children with asthma.

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Finally, a Canadian study designed to estimate the number needed to vaccinate (NNV) to prevent 1 case of IPD revealed for PPSV23 in children with asthma is higher than for healthy children and comparable to that of other high-risk conditions.[30] The NNV for PPSV23 ranged from 905 to 1023 for healthy children, 581 to 677 for low-risk asthma, and 318 to 371 for high-risk asthma. On the basis of this finding, they concluded that it was warranted to add asthma to the list of high-risk conditions recommended for pneumococcal vaccination. Our results further highlight that the recommendation to administer PPSV23 to children with asthma should be regardless of asthma severity or chronic use of oral steroids.

This systematic review and meta-analysis have several limitations. First, there was a small number of studies available in the literature, with differences in design, study population, and reporting methodology. Given the small number of studies, we could not perform a formal assessment of publication bias. None of the identified studies had information of asthma therapy or compliance. None of our secondary outcomes were reported in the available studies. Given the small number of studies with information

about pneumococcal pneumonia (most of them defined by *International Classification of Diseases* codes), we were not able to perform a quantitative analysis. Although in their study, Weycker et al[16] reported markedly increased costs of treating all-cause pneumonia in children with asthma, there was no analysis on pneumococcal pneumonia, and the cost ratios for IPD were nonsignificant. Finally, 3 of 4 studies that reported funding were supported by pharmaceutical companies, and only 1 was funded by the CDC; although we cannot make any assertions to this regard on the basis of the available data, it will be important that future studies continue to be transparent about the role of the funding source in the study design, execution, interpretation, and publication.

CONCLUSIONS

Our review and meta-analysis revealed that children with asthma who received PCV as part of their regular immunization schedules still have 90% higher odds of IPD than children without asthma. Pneumococcal and all-cause pneumonia were also significantly more frequent in children with

asthma. If further confirmed in large, independent studies, these findings would suggest that children with asthma >2 years of age should receive PPSV23 after their regular PCV vaccination schedule irrespective of the use of high-dose oral steroids indicated in the current CDC and AAP guidelines.

ABBREVIATIONS

AAP: American Academy of Pediatrics
aOR: adjusted odds ratio
CDC: Centers for Disease Control and Prevention
CI: confidence interval
ICD-9: *International Classification of Diseases, Ninth Revision*
ICS: inhaled corticosteroid
IPD: invasive pneumococcal disease
NNV: number needed to vaccinate
OR: odds ratio
PCV: pneumococcal conjugate vaccine
PCV7: 7-valent pneumococcal conjugate vaccine
PCV13: 13-valent pneumococcal conjugate vaccine
PPSV23: 23-valent pneumococcal polysaccharide vaccine
RD: rate difference
RR: rate ratio

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