



Risk of invasive pneumococcal disease in children and adults with asthma: A systematic review



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ABSTRACT

Background: The Advisory Committee on Immunization Practices (ACIP) recommended the inclusion of asthma as a high-risk condition that should warrant pneumococcal vaccination, but the National Advisory Committee on Immunization (NACI) in Canada has not yet done so. We aimed to determine the risk of invasive pneumococcal disease (IPD) in patients with asthma.

Methods: We searched Ovid Medline, EMBASE, Classic EMBASE, PubMed and Cochrane for articles published between January 1990 and February 2013, using the MeSH terms pneumococcal infections/or invasive pneumococcal disease and asthma. Google Scholar was used to retrieve articles citing the seminal article by Talbot et al. Articles were included if they were population-based studies that evaluated the relationship between IPD and asthma. Two authors independently assessed all titles and abstracts. All potentially relevant articles were retrieved as full text and assessed for inclusion.

Results: The combined searches yielded 376 articles, which were reviewed by title and abstract. At this stage, 330 articles were excluded; 40 articles were excluded at the full article review stage – leaving 6 articles. Two additional articles were found through Google Scholar. The evidence reviewed consistently showed a positive association between asthma and risk of IPD. However, the magnitude of this effect was heterogeneous with adjusted odds ratios ranging from 6.7 (95% CI 1.6–27.3) in adults >18 years to 1.7 (95% CI 0.99–3.0) in individuals aged 2–49 with low-risk asthma.

Conclusion: The positive association between asthma and risk of IPD supports the addition of asthma as a high-risk condition warranting pneumococcal vaccination. Data on vaccine effectiveness in this population is needed.

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1. Introduction

Streptococcus pneumoniae (pneumococcus) is the causative agent of invasive pneumococcal disease (IPD), which includes bacteremia, meningitis, and/or pneumonia with bacteremia. Fifteen of the ninety-two pneumococcus serotypes account for a major cause of IPD-related morbidity and mortality worldwide [1]. It is known that young children, the elderly and those with certain underlying medical conditions, like severe asthma, are at increased risk of IPD [2]. As such, the Canadian National Advisory Committee on Immunizations (NACI) has recommended that adults with asthma associated with chronic obstructive pulmonary

disease (COPD), emphysema, or those who need prolonged systemic corticosteroid receive one dose of the 23-valent pneumococcal polysaccharide vaccine (PPV23). Children aged 2 years and over with asthma requiring prolonged systemic corticosteroid should receive one dose of pneumococcal conjugate vaccine (13-valent) if not previously vaccinated, followed by PPV23 [3].

Recent studies reported a positive association between asthma (regardless of severity) and IPD [4–9]. Currently in Canada, there is no recommendation to vaccinate asthmatics in general. A risk-based approach to pneumococcal vaccination using PPV23 could prevent substantial morbidity in the entire asthmatic population. Recent statistics show that as of 2011, there were 1,785,173 asthmatics in Canada between the ages of 20 and 64, representing close to 10% of the Canadian population in this age group [10]. Given the recent data and the prevalence of asthma in Canada, we aimed to conduct a systematic review of the literature to determine if asthma significantly increases risk of IPD, providing support for a vaccination policy to prevent IPD for asthmatics in Canada.

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2. Methods

2.1. Search strategy

In collaboration with a research librarian, we searched the following four electronic databases: Ovid Medline, EMBASE (1966–2013 Week 7), Classic EMBASE (1947–2013 February), PubMed and Cochrane for articles published between January 1990 and February 2013. For Medline searches, we used the MeSH Headings: pneumococcal infections/OR invasive pneumococcal disease AND asthma OR asthma/. Analogous terms were used to conduct the EMBASE, PubMed and Cochrane searches. [Appendix A](#) details the full search strategy. We also hand-searched Google Scholar for articles citing the Talbot et al. study [4], as this is the seminal study where asthma was described as a risk factor for IPD.

2.2. Inclusion and exclusion criteria

Articles were included if they were population-based studies that evaluated the relationship between asthma and IPD and, either exclusively (i.e. studies that evaluated only asthma as a risk factor for IPD) or inclusively (i.e. studies that evaluated the relationship between asthma, among other factors, and IPD). Only studies published between January 1990 and February 2013 in either French or English were included. Articles were excluded if they presented secondary data, were policy recommendations, or did not evaluate asthma as a risk factor for IPD; however, references from these articles were perused.

2.3. Assessment of studies

Two authors (CB and CQ) independently assessed all titles and abstracts identified by the search strategy described above. All potentially relevant articles, chosen by consensus between the two authors, were retrieved as full text and assessed by CB and CQ for inclusion. All included studies were given a quality ranking by CB based on the ranking devised by Harris et al. [11] and adapted by NACI. This quality schedule scores across three dimensions labeled as “good”, “fair”, and “poor” based on the number of flaws present in study design methodology. It was concluded that a meta-analysis of the selected studies was not justifiable as included studies differed greatly in their definition of IPD, asthma, and outcome measures.

3. Results

3.1. Search results

The combined searches yielded 376 articles, which were reviewed by title and abstract. During this process, 330 articles were excluded either because they were not published between 1990 and 2013 or did not explicitly discuss the relationship between asthma and IPD. As such, 46 articles remained for full-text review. We excluded 40 articles that did not fulfill inclusion criteria ([Fig. 1](#)). Eight articles were kept after full-text review; six articles [4–9] from the database search and two articles [12,13] that were missed by our database search but identified from Google Scholar ([Table 1](#)). Of the included studies there were: six case-control studies [4,5,7,8,12,13], a retrospective population-based surveillance study [9] and a prospective population-based surveillance study [6]. Three of the six studies evaluated risk of IPD in asthmatic children (<18 years old [9], <17 years old [13], 3–59 months old [8]); three studies only included adult participants (>18 years old) [7,12,6], and two studies included both adults and children [4,5]. It should be noted here that the study by Juhn et al. [5] was included because it met inclusion criteria (it was published in 2008); however, this study uses data from before the inclusion period outlined

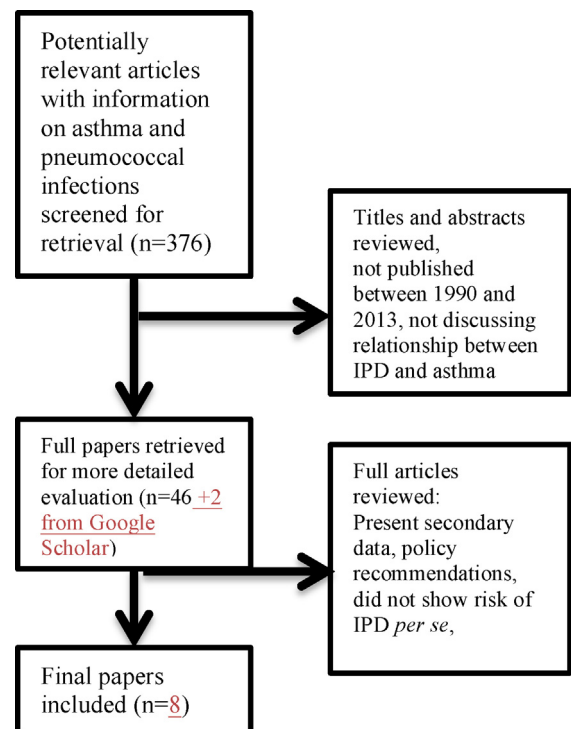


Fig. 1. Description of search and inclusion/exclusion process.

in our protocol. It was included in our analysis regardless of the potential differences in asthma treatment because the data in this article is relevant to our study question and the study methodology is valid.

3.2. Quality assessment

Case-control studies and surveillance studies were evaluated based on the ascertainment and selection of cases and controls, the unbiased treatment of cases and controls with respect to inclusion/exclusion criteria and diagnostic testing procedures, and on the attention to potential confounding variables [11]. No included studies received a quality assessment score of “poor”. Six studies [4,7–9,6] received a grade of “good”. Two studies [5,12] received a grade of “fair”.

4. Retrieved studies

4.1. Pediatric studies

Pilishvili et al. [8] conducted a population- and lab-based case-control study with a population of 3924 U.S. children aged 3–59 months. Cases were identified through routine Active Bacterial Core (ABC) surveillance of IPD in California, Colorado, Georgia, Minnesota, New York, Oregon, Tennessee and Connecticut. Three controls were matched to each case on the basis of age and mother’s residence zip code at time of birth. Health care providers, “from whom children reportedly received routine medical care and immunizations” [8], ascertained information on underlying illnesses, including asthma status, for all study participants. This study found that IPD case patients with non-PCV7 type IPDs were more likely than controls to have asthma (OR 1.5; 95% CI 1.1–2.1).

Hsu et al. [9] conducted a retrospective population-based study to determine the underlying conditions predisposing Massachusetts’ children aged <18 years old to IPD in the “PCV-7 vaccine era” between October 1, 2001 and September 30, 2007. Cases were ascertained using microbiology laboratory reports. Cases classified

Table 1
Studies included.

Authors	Study design	Study population	Outcome measures	Quality
Flory et al. [6]	Prospective population-based surveillance study of bacteremic pneumococcal pneumonia (BPP) (<i>n</i> = 609) • 30 min structured telephone interview data for those who could be contacted after their hospitalization; proxy if necessary • Annual incidence of disease based on Poisson distribution; census data used for pop-denominator values	Adults in 43 of 46 acute care hospitals in the 5-county region surrounding Philadelphia, in Southeastern Pennsylvania • March 31 2002–April 1 2004 • Case definition: adults ≥ 18 with at least one blood culture drawn within 48 h of hospital admission with growth of <i>S. pneumoniae</i> ; clinical diagnosis of pneumonia provided by treating physician, residence in 1 of 5 counties and confirmation in their lab that the bacterial isolate was <i>S. pneumoniae</i>	• Asthma present in 25% of cases • “For individuals with a history of asthma, the incidence was 21.1 (95% CI 16.7–26.6) cases per 100,000 person years compared to 8.8 (95% CI 7.9–9.8) for individuals without a history of asthma” “In terms of clinical risk factors, our study confirms... the association between pneumococcal disease and specific comorbidities, including asthma, diabetes, and cancer”	Good
Hjuler et al. [13]	Population-based case–control study (<i>n</i> = 17 028; 60 cases and 282 controls with asthma) • 10 age- and gender-matched controls per case	Children (aged 0–17 years old) with IPD between 1977 and 2005 in Denmark that were singleton births • IPD defined as isolation of <i>S. pneumoniae</i> from a normally sterile site • IPD and asthma status ascertained by linking 4 Danish national data sources	Adjusted IPD rate ratio 1.1 (95% CI 0.7–1.6) in asthmatic children compared to control children without asthma on record	Good
Hsu et al. [9]	Retrospective population-based surveillance study • Standardized case report forms → interview primary care providers – demographics and clinical info	Children (<18 years) with IPD between October 2001 and September 2007 from Massachusetts • Classified as high risk (HR) IPD: sickle cell anemia, asplenia or splenic dysfunction, HIV, cochlear implants • Classified as probable HR: congenital immune deficiency, immunosuppressive treatment or radiotherapy, transplant, chronic heart and lung disease (including asthma if high dose oral steroids); chronic renal failure, CSF leak, diabetes, prematurity. History of hay fever or infantile eczema or cough, dyspnea, and wheezing regularly on exposure to an antigen; Pulmonary function tests showing 1 FEV1 or FVC < 70% predicted and another with $\geq 20\%$ improvement to an FEV1 of >70% predicted or methacholine challenge test showing $\geq 20\%$ decrease in FEV1; favorable clinical response to bronchodilator	• 578 of 586 cases enrolled. • 95 (16%) HR/PHR; 20 (3%) asthma without corticosteroid. Mean age 5.6 years • After adjustment for age and study year, HR/PHR more likely to be hospitalized (OR 2.75; 1.44–5.24) • Similar clinical presentation with or without HR • Asthma: increased likelihood of presenting with pneumonia (65 vs. 31% if NKR <i>p</i> < 0.05)	Good
Juhn et al. [5]	Population-based retrospective case–control/cumulative-incidence case–control study (<i>n</i> = 3941) • Medical chart review • Case to control ratio 2:1, matched by gender and birthday	Residents of Rochester Minnesota who had SPD between 1964 and 1983 • Cases of SPD defined as: sepsis, BSI, meningitis, PNC infections, pneumonia, empyema • Asthma status ascertained from previous study (using structured logarithm and predetermined criteria for asthma)	Including children and adults: OR 2.4, 95% CI 0.9–6.6 Including >18 years only: fully adjusted (smoking, ethnicity, high-risk conditions, educational status): OR 6.7, 95% CI 1.6–27.3 “SPD associated with a prior history of asthma in adults, suggesting that asthma increased risk for SPD”	Fair (SPD, including non-bacteremic pneumococcal pneumonia outcome rather than IPD)
Klemets et al. [7]	Nationwide Finnish registry- and population-based case–control study (<i>n</i> = 14,067; 1282 cases, 12,785 controls) • 10 selected age-, sex- and health-district matched controls	Individuals aged 18–49 years during 1995–2002 • High-risk asthma (HRA): record in the HILMO of asthma requiring ≥ 1 hospitalization in the past 12 months • Low-risk asthma (LRA): entitlement to prescription drug benefits and no hospitalization for asthma in the past 12 months	• IPD associated with both LRA: mOR 2.3 (95% CI 2.1–3.6) and HRA: mOR 12.3 (95% CI 5.4–28.0) “Results of our national, population-based study indicate that LRA is also an independent factor moderately increasing the risk for IPD among adults 18–49 years of age”	Good

Table 1 (Continued)

Authors	Study design	Study population	Outcome measures	Quality
Pilishvili et al. [8]	Population- and lab-based case-control study, $n = 3294$ (cases: 782, controls: 2512) • IPD from Active Bacterial Core surveillance-CDC surveillance program • Telephone interviews of parents or guardians using standardized questionnaire. Underlying illnesses (including asthma) collected from HC providers • Matched median of 3 controls: case by age and zip code	Children aged 3–59 months residing in certain counties in California, Colorado, Georgia, Minnesota, NY, Oregon, Tennessee and Connecticut between 2001 and 2004 • IPD case: isolation of <i>Pneumococcus</i> from a normally sterile site (blood, CSF, pleural fluid) or a surveillance area resident	• N: 1267 IPD – 1121 eligible Multivariable log reg: (1 + PCV7) • Vaccinated: underlying HR condition: OR 23.9 (9.5–60.4) - Daycare 1.1 (0.6–2.2) • Unvaccinated: underlying HR: 4.1 (2.4–7.2) - Daycare 2.0 (1.3–3.0) - Black 3.5 (1.9–6.6) • Risk for non-PCV7: underlying medical illness only significant in household without smoker (3.3; 2.2–5.1) - Daycare both Black and White asthma (1.5; 1.1–2.1)	Good
Talbot et al. [4]	Nested matched case-control study ($n = 6985$; 635 cases, 6350 controls) • IPD from ABC-CDC surveillance program in Tennessee • 10 age-matched controls without IPD randomly selected from the same population as cases • Adjusted for sex, race, high-risk co-existing conditions	Individuals aged 2–49 years participating in Tennessee Medicare – state-based capitated managed health care program (TennCare) for more than one year during study period (1995–2002) • IPD “defined as isolation of <i>S. pneumoniae</i> from a normally sterile site • Between 1995 and 2002 – 635 episodes from TennCare - Ascertainment of asthma: 1 of: 1. 1 or + hospital or Emergency department visit with dx code for asthma 2. 2 or + Rx B-agonist 3. 1 or + Rx inhaled corticosteroid, long-acting B-agonist, inhaled anti-inflammatory agents, LKT-modifying drug • High-risk asthma: 1 or + hospitalization or ED visit AND Rx of PO steroids OR Rx of 3+ B-agonist - Controls: 10 age-matched	• Any asthma: OR 2.4 (95% CI 1.9–3.1) • High-risk asthma: OR 2.6 (95% CI 2.0–3.5) • Low-risk asthma: OR 1.7 (95% CI 0.99–3.0) • No coexisting HR conditions OR 2.4 (95% CI 1.7–3.4) • Coexisting HR: 2.3 (1.3–4.1) - Age 2–4 (2.3; 1.4–4.0); 5–17 (4.0; 1.5–10.7); 18–49 (2.4; 1.8–3.3) • Incidence: Asthma: 6.1/10 000 - No asthma: 2.0/10 000 • High-risk asthma: 6.9 - Low-risk asthma: 3.9 • In those without HR condition: High-risk: 4.2 - Low-risk: 2.3 - No asthma: 1.2 “Through the linkage of two large, population based databases in Tennessee, we identified an increase by more than a factor of two in the risk of invasive pneumococcal disease among persons with asthma, even after adjustment for other risk factors for the disease”	Good
Watt et al. [12]	Matched case control study ($n = 417$; 8 cases and 19 controls with asthma) • Age-, gender-, neighborhood-matched controls • Asthma status ascertained from medical records	Enrolled adult (≥ 18 years old) members of a Navajo tribe in the US with IPD between December 1999 and February 2002 • IPD defined as isolation of <i>S. pneumoniae</i> from a normally sterile site • Cases identified through the Center for American Indian Health surveillance system	Odds of having asthma were 1.3 (95% CI 0.6–2.9) times higher in asthmatics compared to non-asthmatics	Fair (small sample size)

as “high-risk” for IPD included, among others, children with chronic pulmonary disease, which included asthmatics treated with high dose oral corticosteroids. Children with asthma not receiving corticosteroid therapy were evaluated separately. High-risk children with asthma receiving oral corticosteroid therapy represented 3% of the 578 cases that had sufficient information about underlying diseases. Hsu et al. found that 65% of children with asthma presented

with pneumonia compared to only 31% of children with no known risk factors ($P < 0.05$). Moreover, after adjusting for age and study year, children classified as “high risk” (including conditions such as asplenia and HIV) had 2.17 times the odds (95% CI 1.44–5.24) of being hospitalized for IPD compared to children classified as “probable high risk” (conditions including asthma with oral steroids and congenital immune deficiencies).

Hjuler et al. [13] conducted a case–control study with a population of Danish children aged 0–17 years aiming to quantify the risk of IPD in a wide range of chronic diseases, including asthma ($n = 17,028$; 60 cases and 282 controls with asthma). Cases of IPD between January 1977 and May 2005 were selected from the Danish Streptococcus Database. Ten age- and gender-matched population controls were randomly sampled per case from the Danish Civil Registration System. Ascertainment of chronic diseases (including asthma status) was obtained from the National registry of patients. Risk ratios were adjusted for hospital contacts for any reason within the last 3–30 days. This study found an IPD rate ratio (adjusted for the number of hospital contacts) of 1.1 (95% CI 0.7–1.6) in asthmatic children compared to control children without asthma on record.

4.2. Adult studies

Flory et al. [6] conducted a prospective population-based surveillance study to evaluate the association between bacteremic pneumococcal pneumonia (BPP), asthma and other socioeconomic risk factors. Specifically, 43 of 46 acute care hospitals in the 5-county region surrounding Philadelphia between March 31, 2002 and April 1, 2004 participated in the study. Cases were eligible if they were 18 years or older “with at least one blood culture within 48 h of hospital admission positive for *S. pneumoniae*; a clinical diagnosis of pneumonia provided by the treating physician; residence in one of the five counties; and laboratory confirmation of *S. pneumoniae*” [6]. Each case underwent a 30-min structured interview. The annual incidence of BPP was calculated using annual census data as a denominator value and Poisson distribution for confidence intervals. Of the 281 subjects with BPP that completed the telephone interview, 25% had been diagnosed with asthma. The reported incidence of BPP was 21.1 (95% CI 16.7–26.6) cases per 100,000 person years for individuals with a history of asthma compared to 8.8 (95% CI 7.9–9.8) for individuals without a history of asthma.

Klemets et al. [7] conducted a nationwide registry- and population-based case–control study in order to establish the risk of IPD among adults with asthma in Finland. Cases of IPD, defined as the isolation of *S. pneumoniae* from blood or cerebrospinal fluid, were ascertained from national population-based laboratory surveillance during 1995–2002. First cases of IPD among adults aged 18–49 were evaluated to reduce confounding due to smoking and related lung disease as well as to minimize misclassification of asthma as COPD. Ten controls randomly selected from the National Population Information System were matched to each case based on age, sex and health district of residence. Patients and controls with asthma were defined in this study as “persons who had been granted a prescription drug benefit for asthma or COPD by the [Finnish National Social Insurance Institution], or who had a record of hospitalization for these conditions during 12 months before the reference date in the [National Hospital Discharge Register] database” [7]. More specifically, the Finnish National Social Insurance institution uses the following criteria to determine a patient's eligibility for prescription drug benefit: a physician's certificate verifying the diagnosis as well as the severity of illness using lung function tests (such as spirometry) as well as the need for prescription medications for at least 6 months. Asthma status, requiring ≥ 1 hospitalization in the past 12 months, was defined as high risk if the patient had been hospitalized at least once with an ICD-coded primary diagnosis for asthma in the past 23 months and defined as low risk when the patient was entitled to prescription drug benefit during the 12 months before the reference date. Asthma status was ascertained by linking the case–control study base to four other national population-based healthcare registries. Overall, Klemets et al. reported that patients with IPD were more likely than controls to have low-risk asthma (matched OR 2.3 [95% CI 2.1–3.6]) and high-risk asthma (matched OR 12.3 [95% CI 5.4–28.0]). The results

from this study support the notion asthma – both low and high risk – is an independent risk factor for IPD in adults aged 18–49 years.

Watt et al. [12] conducted a matched case–control study of Navajo adults (>18 years old) in the US to identify risk factors for IPD ($n = 417$; 8 cases and 19 controls with asthma). Study participants were identified through prospective, population-based active laboratory surveillance (date of *S. pneumoniae* culture between December 1999 and February 2002) and asthma status was ascertained from medical record data. Controls were matched to cases based on age, gender, and neighborhood. Asthma status was ascertained through a structured interview. A matched univariate analysis was used to identify possible risk factors for IPD in this population. This study found that the odds of having IPD were 1.3 (95% CI 0.6–2.9) times higher in asthmatics compared to non-asthmatics.

4.3. Pediatric and adult studies

Juhn et al. [5] conducted a population-based retrospective case–control study evaluating whether asthma status was associated with serious pneumococcal disease (SPD). They reviewed medical records of 3941 residents of Rochester, Minnesota between 1964 and 1983 to ascertain SPD, asthma status and identified potential cases of IPD. Cases of SPD were then confirmed by medical records review and defined as individuals with an isolation of *S. pneumoniae* from a normally sterile site or pneumococcal pneumonia requiring all of the following three criteria: (1) a physician's diagnosis of pneumonia, (2) identification of pneumococcus from sputum Gram stain or in culture, and (3) pneumonia documented by means of chest radiography. Exposure ascertainment (i.e. asthma status) was obtained by merging SPD case and control data with data collected from a previous study. Two controls were matched to every case by gender and birthday. Using a conditional logistic regression model for matched analysis, the authors showed that SPD was associated with a prior history of asthma (OR 2.4; 95% CI 0.9–6.6) among all age groups as well as for adults (OR 6.7; 95% CI 1.6–27.3), controlling for high-risk conditions for IPD and smoking exposure. Results from this study suggest that asthma increases risk for serious pneumococcal disease.

Talbot et al. [4] examined the association between asthma and IPD by conducting a nested matched case–control study of 6985 residents of Tennessee aged 2–49 during the study period 1995–2002. Data from the Active Bacterial Core Surveillance (ABC) was used to identify eligible study participants with IPD. Once identified, ABC data was linked to administrative data from the Tennessee Medicare (TennCare) program. Ten age-matched controls without IPD were randomly matched to each case from the same population. Asthma status was ascertained by screening inpatient and outpatient claims for all participants for a diagnosis of asthma based on the ICD-9-CM code (section 493). Participants with asthma were classified as either high risk (“a history of one or more hospitalizations or visits to an emergency department for asthma or who were given a prescription for a course of corticosteroids as rescue therapy or a long-term course of oral corticosteroids (120 days or more) of prescriptions for three or more β -agonist medications during the year before the index date”) [4] or low-risk (all other participants with asthma). After adjusting results for sex, race, and high-risk co-existing conditions, the authors showed that any diagnosis of asthma was associated with an increased risk of IPD (OR 2.4; 95% CI 1.9–3.1). This positive association persisted when results were stratified by asthma severity: patients with a classification of high-risk asthma had 2.4 times the odds of IPD compared to controls (95% CI 1.9–3.1) while patients with a classification of low risk asthma had 1.7 times the odds of IPD (95% CI 0.99–3.0). It should be noted that while misclassification of asthma status in this study was possible, such misclassification would have been non-differential for cases and controls, biasing the study results

toward the null and potentially underestimating risk of IPD in asthmatics.

5. Discussion

The U.S. Advisory Committee on Immunization Practices (ACIP) recommended the inclusion of asthma as a high-risk condition that should warrant pneumococcal vaccination. Currently in Canada, NACI has not yet made analogous recommendations. As such, this systematic review aimed to answer the question of whether asthmatics are at an increased risk for IPD in order to provide an evidence framework for Canadian pneumococcal vaccination recommendations.

5.1. Interpretation

The eight studies reviewed suggest that adults and children with IPD are more likely to have asthma. A meta-analysis was not conducted given the heterogeneity in the definitions of pneumococcal diseases (some used IPD only, others also included pneumococcal pneumonia without bacteremia), asthma and the differences in study populations. Critical appraisal of the eight included studies demonstrated a few minor quality flaws – none of which threatened the validity of any included studies, but which are important to mention nonetheless. First, the study by Juhn et al. [5] included pneumococcal pneumonias in their outcomes, not only IPD; 108/174 (62%) of cases had pneumococcal pneumonia, and the remaining 38% had IPD, the condition of interest. The inclusion of pneumococcal pneumonia in the analysis may overestimate the relationship between asthma and IPD should asthma be a risk factor for pneumococcal pneumonias. For this reason, this study was the only study to receive a quality rating of “fair”. The study by Watt et al. [12] was also given a quality rating of “fair” due to the small number of cases and controls with asthma and correspondingly diminished power to detect a statistically significant association between asthma and IPD. Second, although misclassification of asthma status was possible in the study by Talbot et al. [4], it was likely non-differential between cases and controls. Therefore, results may slightly underestimate the actual association. Furthermore, study participants in this study were enrolled in the TennCare program, and were thus generally of low socioeconomic status. This is problematic for generalizability to other socioeconomic strata. Third, the study by Flory et al. [6] excluded patients with bacterial meningitis (identification of *S. pneumoniae* in the CSF). Although a component of the IPD definition is missing, we do not expect this to affect the internal validity of the study; given the pathophysiology of bacterial meningitis, asthma is less likely to be a risk factor for isolated meningitis without bacteremia [14]. Finally, the study by Hsu et al. [9] does not establish asthma as a risk factor for IPD per se; it merely establishes that asthmatic children present with IPD more often than children with no known underlying risk, and presents a p -value <0.05 to support this claim. While the problems associated with using p -values to determine statistical significance are known and have been thoroughly discussed in the literature [15,16], we feel that this study nonetheless provides support for the consideration of asthma as a risk factor for IPD.

The confounders most adjusted for were age [9,6], other high-risk conditions for IPD [4,5,7], education [5,6] and race/ethnicity

[4–6]. Other confounders adjusted for included annual income (which could serve as a proxy for socioeconomic status) [6], study year [9], smoking exposure [4], sex [4], prolonged use of corticosteroids [4], and the number of hospital contacts [13]. Two studies [4,7] stratified risk of IPD in asthmatics by asthma severity, and only one study [8] presented ORs for risk of IPD in asthmatics by pneumococcal vaccination status. Importantly, while HIV status was taken into account in four of the eight included studies [4,7–9], undiagnosed HIV infection was a potential confounding factor that remained uncontrolled for in all six included studies. We, however, do not expect that a large proportion of HIV-positive individuals at high risk for IPD (i.e. immunosuppressed) would remain undiagnosed. The study by Klemets et al. addressed this issue by stating that “the prevalence of HIV infection and the proportion of IPD cases who have HIV is very low” [7] and therefore did not pose a threat of residual confounding in their study.

Overall, the evidence reviewed consistently showed a positive association between asthma and risk of IPD. The data was consistent and showed a dose response in several studies. Adjusted ORs for invasive pneumococcal disease ranged from 1.3 [12] to 6.7 [5] in people with asthma than people without asthma. This slight variation in results may be in part due to variations in host, agent and environment – i.e. factors such as socioeconomic status, vaccination status, immune status and asthma severity, but also in definitions used.

While some efficacy data on PPV23 exists [17], currently no data exists on the effectiveness of PPV23 in patients with asthma aged less than 60 years. The Public Health Agency of Canada estimates that PPV23 efficacy against IPD is between 50% and 80% in the elderly and in patients with certain conditions (diabetes mellitus, anatomic or physiologic asplenia, congestive heart failure and COPD) [18]. A low-quality study by Jung et al. [19] suggested that pneumococcal vaccines and/or pneumococcal carriage may be less immunogenic in patients with asthma compared to patients with no asthma. As such, studies evaluating the effectiveness of PPV23 in asthmatics patients are a necessary corollary to this study when evaluating the feasibility of implementing pneumococcal vaccination in this population [5].

5.2. Limitations and strengths

Our study has two major limitations. First, our search strategy was limited to published studies. Given that many small or negative studies go unreported, a publication bias may exist. Second, while our search was comprehensive, there is potential bias surrounding the exclusion of non-English and non-French studies.

Our study has several integral strengths. First, the search strategy is reproducible and comprehensive. Broad inclusion and exclusion criteria allowed us to capture a larger number of studies for evaluation. Second, positive association between asthma and IPD was found despite the fact that the included studies focused on different populations in the U.S. as well as on segments of the Finnish and Danish populations. As such, the fact that no Canadian studies were available for inclusion in this study might not be of great concern.

In sum, these results provide a strong foundation for policy-makers to recommend pneumococcal vaccination for all diagnosed asthmatics.

Appendix A. Search strategy

Search: IPD and asthma Database: MEDLINE 1. exp Pneumococcal Infections/or invasive pneumococcal disease.mp. 2. asthma.mp. or exp Asthma/ 3. 1 and 2 Filtered: published between January 1, 1990 and December 31, 2013	Search: IPD and asthma Database: EMBASE + Classic EMBASE 1. invasive pneumococcal disease.mp. or exp pneumococcal infection/ 2. exp moderate persistent asthma/or asthma.mp. or exp extrinsic asthma/or exp nocturnal asthma/or exp severe persistent asthma/or exp exercise induced asthma/or exp occupational asthma/or exp mild intermittent asthma/or exp asthma/or exp allergic asthma/or exp intrinsic asthma/or exp mild persistent asthma/ 3. 1 and 2 Filtered: published between January 1, 1990 and December 31, 2013	Search: IPD and asthma Database: PubMed (asthma[Text Word] OR "asthma"[MeSH Terms]) AND ((invasive pneumococcal disease[Text Word] OR invasive pneumococcal diseases[Text Word]) OR (invasive pneumococcal infection[Text Word] OR invasive pneumococcal infections[Text Word]) OR "pneumococcal infections"[MeSH Terms] OR IPD[tw]) Filtered: published between January 1, 1990 and December 31, 2013	Search: IPD and asthma Database: Cochrane invasive pneumococcal disease asthma
Number of articles: 79	Number of articles: 199	Number of articles: 98	Number of articles: 0

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