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Increased Risk of Serious Pneumococcal Disease in Patients with Atopic Conditions Other Than Asthma

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Abstract

Background—We reported an increased risk of serious pneumococcal disease (SPD) among patients with asthma. It is not known whether this is true for patients with other atopic conditions.

Objective—To determine the relationship between atopic conditions other than asthma and SPD.

Methods—The study subjects were Rochester, Minnesota residents who developed SPD between 1964 and 1983 and their two gender- and age-matched controls. We used a population-based computer-linked medical diagnosis system to identify all individuals with potential SPD. All records

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were reviewed using explicit predetermined criteria for SPD. All individuals with atopic conditions were identified by the physician diagnoses including atopic dermatitis or eczema, allergic rhinitis, and hay fever documented in medical records. The associations between these atopic conditions and SPD were assessed using conditional logistic regression.

Results—A total of 3,941 records were reviewed and we identified 174 SPD cases. Of these 174 cases, 50.6% were male and 94.3% were Caucasians. Twenty-six (14.9%) of the SPD cases and 29 (8.3%) of the controls had atopy. Atopic conditions other than asthma were associated with an increased risk of SPD (OR:2.13, 95% CI: 1.04-4.35, p=0.04) after adjusting for smoking status, prior high-risk conditions for SPD, educational status, and ethnicity.

Conclusions—Like asthma, other atopic conditions, particularly atopic dermatitis, are also associated with an increased risk of SPD. There may be a common immunogenetic mechanism underlying increased risk of SPD among individuals with either asthma or other atopic conditions. Our study findings need to be further studied.

Clinical Implications—In addition to asthma, atopic conditions other than asthma are also associated with an increased risk of serious pneumococcal infections. Clinicians need to be more cognizant about our study findings.

Capsule Summary—Atopic conditions other than asthma are associated with an increased risk of serious pneumococcal disease(SPD). There may be common immunogenetic mechanisms underlying increased risk of SPD among individuals with either asthma or other atopic conditions.

Keywords

Atopic dermatitis; allergic rhinitis; serious pneumococcal disease; epidemiology; risk; pneumococcal pneumonia; and Rochester Epidemiology Project

Introduction

Streptococcus pneumoniae presents a global threat of morbidity and mortality among children and adults. One million children younger than 5 years of age die from pneumonia and invasive pneumococcal disease (IPD) globally each year.[1] In the US, the annual number of fatal pneumococcal infections is 40,000.[2] *S. pneumoniae* is responsible for six million otitis media per year; nasopharyngeal colonization among 20-50% of population as a prelude of IPD, 100,000 cases of pneumonia; 60,000 cases of sepsis per year; and 3,300 cases of meningitis per year in the US. The case-fatality rate was 10% for all reported cases (1,556 deaths/15,544 cases). Case-fatality rates increased from 1.4% among persons younger than two years to 20.6% among persons aged 80 years or older.[3]

For the causes of IPD, the Advisory Committee on Immunization Practices (ACIP)-recommended pneumococcal vaccine-eligible conditions accounted for only 50.6% of IPD but still a large proportion of IPD cases occur among people without high-risk conditions for IPD.[3] Talbot et al. and Juhn et al. independently reported that patients with asthma were at a significantly increased risk of IPD.[4, 5] According to the results of these studies, the population attributable risk percent for asthma was 11-17%. The ACIP has recently issued a new recommendation that all adult asthmatics (19-64 years) receive a single dose of 23-valent pneumococcal vaccine (PPV-23) to prevent IPD.[6]

Atopic conditions other than asthma such as atopic dermatitis or eczema, allergic rhinitis, or hay fever, share the similar underlying immunological mechanisms with asthma, i.e., T-helper 2 cells (Th2)-predominant immune milieu[7-10] and individuals with atopic dermatitis have been reported to have poor humoral and cell-mediated immune responses as well as innate immunity.[11-15] At present, despite the shared immunologic mechanism among asthma and other atopic

conditions, little is known about whether patients with atopic conditions other than asthma are associated with the risk of serious pneumococcal disease (SPD). No population-based study has been conducted to examine the relationship between atopic conditions other than asthma and SPD. To determine whether individuals with atopic dermatitis and/or allergic rhinitis have an increased risk of developing SPD defined as IPD and/or pneumococcal pneumonia, we conducted a population-based case-control study among the residents of Rochester, Minnesota, between 1964 and 1983.

Methods

The study was approved by both the Institutional Review Boards at Mayo Clinic and Olmsted Medical Center. This is a population-based retrospective case-control study designed to assess if there is a higher prevalence of atopic conditions other than asthma prior to January 1, 1984 among the Rochester residents who developed SPD between 1964 and 1983, a primarily pre-pneumococcal vaccine era, compared to controls. SPD cases were identified through reviewing 3,941 medical records and atopic dermatitis and/or allergic rhinitis were ascertained by using documentation of the physician diagnosis of atopic dermatitis or eczema, allergic rhinitis and/or hay fever in medical records.

Study setting and population

The study setting and population were previously described.[5] Rochester, Minnesota is an excellent setting to conduct a retrospective case-control study such as this because medical care is virtually self-contained within the community and the Rochester Epidemiology Project provides information on all Rochester residents who had received medical care from two primary medical centers in Rochester, MN. The medical records for each site contain all inpatient and outpatient data. All diagnostic information has been indexed since 1935 using Berkson codes even before ICD codes were available.[16] The incidence rate of asthma in Rochester was 238 per 100,000, which is comparable to those in other communities such as Tecumseh, Michigan (250/100,000).[17]

Ascertainment of serious pneumococcal disease (SPD) cases

We reported the details for ascertainment of SPD cases previously.[5] Briefly, a total of 85 different medical index search codes (Berkson codes and ICD codes) were used to identify potential SPD cases and each potential case was then confirmed by medical records review. We reviewed medical records of all 3,941 persons and identified 174 SPD cases between 1964 and 1983. Case definition of SPD included isolation of *S. pneumoniae* from a normally sterile site (such as blood or cerebrospinal fluid), and/or pneumococcal pneumonia requiring all three of the following criteria, 1) a physician diagnosis of pneumonia, 2) the isolation of pneumococcus from sputum gram-stain or culture, and 3) the documented pneumonia by chest radiograph. We defined the index date of onset of the SPD as the date of documented isolation of *S. pneumoniae*.

Selection of controls

Selection of controls was previously described.[5] A list of potential controls was generated from the Rochester Epidemiology Project computerized database (almost 95% of community members) and the index date for controls was defined as the index date of SPD for the corresponding matched case. Two gender- and age-matched control individuals who had never developed SPD were randomly selected from the community. We applied the same eligibility and exclusion criteria of SPD cases to controls.

Exposure ascertainment (i.e., atopy conditions other than asthma)

After we identified SPD cases and their age- and gender-matched controls, atopic conditions were ascertained by the presence of physician diagnoses of atopic dermatitis or eczema, allergic rhinitis, and/or hay fever in medical records. To identify the physician diagnoses of these atopic conditions, we conducted a comprehensive medical record review. The category of the physician diagnoses of atopic conditions in verbatim included atopic dermatitis, eczema, allergic rhinitis, or hay fever documented in the entire medical records of individual subjects (i.e., prevalent cases of atopic conditions prior to 1964 and the incident cases of atopic dermatitis between 1964 and 1983).

Other variables

During data abstraction from medical records, we collected information including; sociodemographic variables (age, gender, ethnicity, and educational status), high-risk conditions for SPD (based on ACIP-recommended pneumococcal vaccine-eligible conditions) prior to the index date of SPD, smoking status at the time of index, pneumococcal vaccination status based on medical records during the study period, and antibiotics use within 7 days prior to the index date of SPD.

Data analysis

Data analysis for the association between atopic conditions other than asthma and SPD followed that for the association between asthma and SPD as previously reported.[5] Briefly, conditional logistic regression for matched analysis was used to determine whether atopic conditions other than asthma were associated with the risk of SPD adjusting for pertinent covariates or confounders. Associations were summarized using the odds ratios (OR) and corresponding 95% confidence intervals (CI) derived from the estimated parameters in the conditional logistic models. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. The analysis was conducted using the entire study cohort, and separately by age group (<18, ≥18 years of age). Analyses were performed using the SAS version 9.1 software package (SAS Institute, Inc.; Cary, NC).

Results

Study subjects

The details of sociodemographic and clinical characteristics of study subjects are summarized in Table 1. We reviewed a total of 3,941 records and identified 174 SPD cases. Of these confirmed 174 SPD cases, 16% (n=28), 22% (n=38), and 62% (n=108) had SPD, SPD with pneumococcal pneumonia, and pneumococcal pneumonia, respectively. Of the SPD cases, the age at index date was 57.0±26.5 years old, 50.6% were male, and 94.3% were Caucasians. Only 21 cases (12%) were younger than 18 years. Fifty one SPD cases (29.3%) and 18 controls (5.2%) had at least one high-risk condition for SPD prior to the index date of SPD. Twelve SPD cases (11 for 14-valent pneumococcal vaccine and 1 for 23-valent pneumococcal vaccines) had received a pneumococcal vaccine prior to the index date whereas none of controls had received a pneumococcal vaccine. Of these 12 SPD cases, seven (58%) had pneumococcal vaccine-eligible conditions prior to the index date whereas five (42%) did not have any pneumococcal vaccine-eligible conditions prior to the index date.

Atopic conditions and SPD

The results are summarized in Table 2. Twenty-six (14.9%) of the SPD cases and 29 (8.3%) of the controls had atopic conditions other than asthma. In analysis with all subjects, the unadjusted odds ratio for SPD in association with atopic dermatitis, eczema, allergic rhinitis and/or hay fever was 1.98 (95%CI: 1.11-3.55, p=0.02), i.e., patients with these atopic

conditions had almost two-times higher odds of SPD, compared to controls. In adult subjects, SPD was associated with atopic conditions (unadjusted OR: 1.89, 95%CI: 1.02-3.49, p=0.04). Other than atopic conditions, ethnicity, smoking exposure, prior high-risk conditions for SPD, and educational status were significantly associated with the risk of SPD in univariate analyses based on the entire cohort. We adjusted the association between atopic conditions and SPD for these variables. In analysis with all subjects, atopic conditions were still associated with the risk of SPD (adjusted OR: 2.13, 95% CI: 1.04-4.35, p=0.04) adjusting for smoking status, prior high-risk conditions for SPD, educational status, and ethnicity. However, in analysis with only adult subjects, the adjusted odds ratio for atopic conditions was not significant (adjusted OR: 1.83, 95%CI: 0.85-3.92, p=0.12) adjusting for the same covariates. We performed both matched conditional logistic and unmatched logistic regression and we found similar results. We assessed the association between individual atopic condition (atopic dermatitis vs. allergic rhinitis) and SPD in all subjects. Adjusting for ethnicity, smoking exposure, prior high-risk conditions for SPD, and educational status, atopic dermatitis was associated with the risk of SPD (adjusted OR: 2.45, 95% CI: 1.07-5.65, p=0.04) whereas allergic rhinitis or hay fever did not reach statistical significance despite a similarly increased risk for SPD (adjusted OR: 1.99, 95% CI: 0.71-5.58, p=0.19) due to a small sample size. Thus, each individual atopic condition, particularly atopic dermatitis, may a risk factor for SPD.

The role of asthma and other atopic conditions in SPD

As previously reported, asthma was associated with the risk of SPD and is associated with atopic conditions. In our study, six of 55 patients (11%) with a history of atopic condtions had asthma, compared to 18 asthmatics among 467 subjects (4%) without atopic conditions (p=0.031). Thus, we adjusted the association between atopic conditions and SPD for asthma status in addition to the above mentioned covariates (i.e., ethnicity, educational status, smoking exposure, and prior high-risk condition for SPD). Atopic conditions were still associated with the risk of SPD (adjusted OR: 2.07, 95%CI: 1.01-4.25, p=0.048) among all subjects. However, in analysis with only adult subjects, atopy was not significantly associated with SPD after adjusting for ethnicity, educational status, smoking exposure, prior high-risk condition for SPD, and asthma status (adjusted OR:1.82, 95%CI: 0.83-3.99, p=0.14). On the other hand, in the same model with only adult subjects, asthma was strongly associated with the risk of SPD (adjusted OR: 6.79, 95%CI: 1.47-31.30, p=0.01) adjusting for ethnicity, educational status, smoking exposure, prior high-risk condition for SPD, and atopic dermatitis and/or allergic rhinitis which is virtually the same as the effect size for asthma in association with the risk of SPD we previously reported.

Discussion

In all subjects of our study, individuals with atopic conditions other than asthma were at an increased risk of developing SPD (adjusted OR: 2.13, 95%CI: 1.04- 4.35, p=0.04), compared to those without such conditions adjusting for smoking status, prior high-risk conditions for SPD, educational status, and ethnicity. These findings were still significant after adjusting for asthma status (OR: 2.07, 95%CI: 1.01-4.25, p=0.048) and thus, the impact of atopic dermatitis/ allergic rhinitis on the risk of SPD in all subjects is likely to be independent of asthma status. The population attributable risk percent for atopic conditions in all subjects was up to 10% suggesting 10% of the disease burden of SPD can be attributable to atopic conditions at a population level. The results on adult subjects only showed that the direction of the association between the risk of SPD and atopic conditions was consistent but they did not reach statistical significance primarily due to a smaller sample size. Overall, our study results suggest that atopic conditions other than asthma may contribute to a risk of SPD independent of asthma but in adult subjects, asthma status is still a major risk factor for SPD independent of atopic conditions. At present, no previous studies on the relationship between atopic conditions other

than asthma and SPD are available to compare with our study results and, thus, our study results are subject to be further studied. However, we believe our study findings are noteworthy given the significant burden of pneumococcal disease and the high prevalence of atopic conditions other than asthma, e.g., 10-19% of atopic dermatitis and 26-33% of allergic rhinitis in the US.[18-20]

The potential mechanisms underlying the increased risk of SPD among patients with asthma or other atopic conditions remain to be determined. The study results may imply that atopic conditions other than asthma themselves may potentially pose a risk for SPD. Although asthma is still a major risk factor for SPD, the results suggest a possibility that certain immunologic factors shared by atopic conditions in general may contribute to the risks of SPD in addition to factors unique to bronchial asthma at either airway structure or immunogenetic levels. Patients with allergic rhinitis or atopic dermatitis may have certain features observed in asthma such as airway hyperresponsiveness [21, 22] but significant airway inflammation or airway remodeling observed in bronchial asthma is unlikely in those with atopic conditions without asthma.[23] Thus, immunogenetic mechanisms instead of alteration in airway architecture may play a more important role for increased risk of SPD in patients with atopic conditions without asthma. As a pneumococcal infection-specific mechanism, polymeric immunoglobulin receptor (PIgR),[24] a receptor for pneumococcal cholin binding protein A (CbpA) that causes transcytosis of pneumococci across epithelial cells, has been suggested given the increased expression of this receptor by IL-4, a T-helper 2 cell (Th2) cytokine,[25] that is often up-regulated in patients with atopic conditions. A previous study based on a mouse model reported that mice with allergic sensitization through intransal challenge with ovalbumin increased risk of pneumococcal colonization and colony count of pneumococci in sinus cavity. [26] As an alternative mechanism, Arkwright et al compared antibody response to pneumococcal polysaccharide vaccine (PPV-23) between children with and without eczema aged 3-8 years. [27] They found that 17% of children with eczema responded to PPV-23, compared to 57% of children without eczema (OR:0.2, 95%CI: 0.05-0.84, p=0.03). The literature suggests that individuals with atopic dermatitis may have impaired innate and adaptive immunity against various microbial organisms.[11, 13-15, 28-30]

The main strength of this study was a population-based study design, which was conducted in a study setting with a self-contained health care environment and unified medical record system for research. Another strength of this study included a study population during a primarily pre-pneumococcal vaccine era. Also, our study has the inherent limitations of retrospective studies. A broad category of codes to identify SPD was applied in this study but it is still possible to miss SPD cases. The physician diagnoses of atopic conditions ascertained by medical record review might not be entirely accurate but this limitation is subject to a non-differential misclassification bias. If it occurred, it is likely to support the null hypothesis. Also, we had limited statistical power in assessing the impact of atopic conditions on SPD in adult subjects. Although data abstractors were not blinded to case and control status, they were not aware of the study hypothesis during the data collection and ascertained exposure status using the specific physician diagnosis of atopic conditions. Also, we did not include socioeconomic measures other than educational status and clinical variables reflecting nutritional status. We included educational levels of parents for measuring socioeconomic status of children whereas adults had their own educational levels. However, there was no a significant interaction between age and educational levels. Finally, given the predominantly Caucasian population of the study, one needs to be cautious when generalize the findings to other study settings.

In conclusion, individuals with atopic conditions, particularly atopic dermatitis, are at an increased risk of SPD. Our study findings need to be confirmed at other study settings. There may be a common immunogenetic mechanism underlying increased risk of SPD among individuals with either asthma or other atopic conditions, which deserve further investigation.

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References

1. CDC. Prevention of pneumococcal disease: Recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR 1997;46:1–24.
2. Obaro S, Adegbola R. The pneumococcus: carriage, disease and conjugate vaccines. J Med Microbiol 2002;51:98–104. [PubMed: 11863272]
3. Robinson KA, Baughman W, Rothrock G, Barrett NL, Pass M, Lexau C, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: Opportunities for prevention in the conjugate vaccine era. Jama 2001;285:1729–35. [PubMed: 11277827]
4. Talbot T, Hartert TV, Arbogast PG, Mitchel E, Schaffner K, Craig AS, Griffin MR. Asthma as a Risk Factor for Invasive Pneumococcal Disease. New England Journal of Medicine 2005;352:2082–90. [PubMed: 15901861]
5. Juhn YJ, Kita H, Yawn BP, Boyce TG, Yoo KH, McGree ME, et al. Increased risk of serious pneumococcal disease in patients with asthma. Journal of Allergy and Clinical Immunology 2008;122:719–23. [PubMed: 18790525]
6. The Advisory Committee on Immunization Practices. ACIP Provisional Recommendations for Use of Pneumococcal Vaccines. Center for Disease Control and Prevention (CDC); 2008.
7. Nurse B, Puterman A, Haus M, Berman D, Weinberg E, Potter P. PBMC's from both atopic asthmatic and nonatopic children show a TH2 cytokine response to house dust mite allergen. The Journal of Allergy & Clinical Immunology 2000;106:84–91. [PubMed: 10887310]
8. Kimura M, Tsuruta S, Yoshida T. Unique profile of IL-4 and IFN-gamma production by peripheral blood mononuclear cells in infants with atopic dermatitis. Journal of Allergy & Clinical Immunology 1998;102:238–44. [PubMed: 9723667]
9. Kimura M, Tsuruta S, Yoshida T. Correlation of house dust mite-specific lymphocyte proliferation with IL-5 production, eosinophilia, and the severity of symptoms in infants with atopic dermatitis. Journal of Allergy & Clinical Immunology 1998;101:84–9. [PubMed: 9449505]
10. Ohashi Y, Nakai Y, Kakinoki Y, Ohno Y, Tanaka A, Masamoto T, et al. Immunotherapy affects the seasonal increase in specific IgE and interleukin-4 in serum of patients with seasonal allergic rhinitis. Scandinavian Journal of Immunology 1997;46:67–77. [PubMed: 9246210]
11. Beck LA, Latchney LR, Zaccaro D, Reese J, Schneider L, Gallo R, et al. Biomarkers of Disease Severity and Th2 Polarity are Predictors of Risk for Eczema Herpeticum. Journal of Allergy and Clinical Immunology 2008;121:S37–S.
12. Grove DI, R J, Forbes IJ. Humoral and cellular immunity in atopic eczema. British Journal of Dermatology 1975;92:611–8. [PubMed: 1101939]
13. Kim BE, Leung DY, Streib JE, Boguniewicz M, Hamid QA, Howell MD. Macrophage inflammatory protein 3alpha deficiency in atopic dermatitis skin and role in innate immune response to vaccinia virus. Journal of Allergy & Clinical Immunology 2007;119:457–63. [PubMed: 17141855]
14. Kisich K, Carspecken C, Fieve S, Boguniewicz M, Leung D. Defective killing of Staphylococcus aureus in atopic dermatitis is associated with reduced mobilization of human B-defensin-3. Journal of Allergy and Clinical Immunology 2008;122:62–8. [PubMed: 18538383]
15. Schneider LC, Weinberg A, Boguniewicz M, Zaccaro D, Taylor P, Borras-Coughlin I, et al. Abnormal Immune Response to Varicella Vaccine in Subjects with Atopic Dermatitis Compared to Non-atopic controls. Journal of Allergy and Clinical Immunology 2008;121:S272–S3.

16. Kurland LT, Molgaard CA. The patient record in epidemiology. Scientific American 1981;245:54–63. [PubMed: 7027437]
17. Broder I, Higgins MW, Mathews KP, Keller JB. Epidemiology of asthma and allergic rhinitis in a total community, Tecumseh, Michigan. IV. Natural history. Journal of Allergy & Clinical Immunology 1974;54:100–10. [PubMed: 4851886]
18. Hanifin JM, Reed ML. Eczema Prevalence and Impact Working G. A population-based survey of eczema prevalence in the United States. Dermatitis 2007;18:82–91. [PubMed: 17498413]
19. Nathan R, Meltzer E, Derebery J, Stang P, Corrao M, Allen G, et al. Prevalence of Nasal Symptoms in the United States: Findings from the Burden of Allergic Rhinitis in America Survey. Journal of Allergy and Clinical Immunology 2008;121:S208–S9.
20. Gordon B, Blaiss M, Meltzer E, Mahr T, Boyle J. Prevalence of Seasonal and Perennial Allergic Rhinitis in Children and Adults. The Journal of Allergy and Clinical Immunology 2008;121:S209.
21. Choi SH, Yoo Y, Yu J, Rhee CS, Min YG, Koh YY. Bronchial hyperresponsiveness in young children with allergic rhinitis and its risk factors. Allergy 2007;62:1051–6. [PubMed: 17686108]
22. Kyllonen H, Malmberg P, Remitz A, Rytila P, Metso T, Helenius I, et al. Respiratory symptoms, bronchial hyper-responsiveness, and eosinophilic airway inflammation in patients with moderate-to-severe atopic dermatitis. Clinical & Experimental Allergy 2006;36:192–7. [PubMed: 16433856]
23. Bradley BL, Azzawi M, Jacobson M, Assoufi B, Collins JV, Irani AM, et al. Eosinophils, T-lymphocytes, mast cells, neutrophils, and macrophages in bronchial biopsy specimens from atopic subjects with asthma: comparison with biopsy specimens from atopic subjects without asthma and normal control subjects and relationship to bronchial hyperresponsiveness. Journal of Allergy & Clinical Immunology 1991;88:661–74. [PubMed: 1918731]
24. Luo R, Mann B, Lewis WS, Rowe A, Heath R, Stewart ML, et al. Solution structure of choline binding protein A, the major adhesin of Streptococcus pneumoniae. Embo J 2005;24:34–43. [PubMed: 15616594]
25. Kaetzel CS. The polymeric immunoglobulin receptor: bridging innate and adaptive immune responses at mucosal surfaces. Immunol Rev 2005;206:83–99. [PubMed: 16048543]
26. Blair C, Nelson M, Thompson K, Boonlayangoor S, Haney L, Gabr U, et al. Allergic inflammation enhances bacterial sinusitis in mice. Journal of Allergy & Clinical Immunology 2001;108:424–9. [PubMed: 11544463]
27. Arkwright P, Moran P, Haeney M, Ewing C, David T. Atopic Eczema is associated with delayed maturation of the antibody response to pneumococcal vaccine. Clin Exp Immunology 2000;122:16–9.
28. Howell MD, Gallo RL, Boguniewicz M, Jones JF, Wong C, Streib JE, et al. Cytokine milieu of atopic dermatitis skin subverts the innate immune response to vaccinia virus. Immunity 2006;24:341–8. see comment. [PubMed: 16546102]
29. Howell MD, Kim BE, Gao P, Grant AV, Boguniewicz M, Debenedetto A, et al. Cytokine modulation of atopic dermatitis filaggrin skin expression. Journal of Allergy & Clinical Immunology 2007;120:150–5. [PubMed: 17512043]
30. Grove DI, B T, Wellby ML, Ford RM, Forbes IJ. Humoral and cellular immunity in asthma. Journal of Allergy & Clinical Immunology 1975;55:152–63. [PubMed: 1089697]
31. American Academy of Pediatrics. Red Book 2006. Elk Grove Village, IL: American Academy of Pediatrics; 2006.
32. Barnighausen T, Hosegood V, Timaeus IM, Newell ML. The socioeconomic determinants of HIV incidence: evidence from a longitudinal, population-based study in rural South Africa. AIDS 2007;21:S29–38. [PubMed: 18040162]
33. West P. Inequalities? Social class differentials in health in British Youth. Social Science & Medicine 1988;27:291–6. [PubMed: 3175713]

Abbreviations

IPD	Invasive Pneumococcal Disease
SPD	Serious Pneumococcal Disease

95%CI	95% confidence interval
ACIP	Advisory Committee on Immunization Practices
PCV-7	heptavalent pneumococcal conjugate vaccine
PPV-23	23-valent pneumococcal polysaccharide vaccine
ICD	International Classification of Disease
OR	Odds Ratio

Table 1

Demographic and clinical characteristics of cases with serious pneumococcal diseases and their age- and gender-matched corresponding controls

	Case (N=174)	Control (N=348)
Age at index date (years)		
Mean (SD)	57.0 (26.5)	57.0 (26.4)
Median	65.1	65.1
Atopic conditions		
Allergic rhinitis(or hay fever)	6 (3.5%)	13 (3.7%)
Atopic dermatitis	16 (9.2%)	13 (3.7%)
Both	4 (2.3%)	3 (0.9%)
No	148 (85.1%)	319 (91.7%)
Asthma		
Yes	11 (6.3%)	13 (3.7%)
No	163 (93.7%)	335 (96.3%)
Gender		
Male	88 (50.6%)	176 (50.6%)
Female	86 (49.4%)	172 (49.4%)
Ethnicity		
Caucasian	164 (94.3%)	340 (97.7%)
Asian	2 (1.1%)	0 (0.0%)
Hispanic/Latino	1 (0.6%)	1 (0.3%)
African American	0 (0%)	1 (0.3%)
Unknown	7 (4.0%)	6 (1.7%)
Educational status*		
< High school education	35 (20.1%)	61 (17.5%)
High school graduate	32 (18.4%)	79 (22.7%)
Some college education	11 (6.3%)	49 (14.1%)
College graduate	20 (11.5%)	44 (12.6%)
Unknown	76 (43.7%)	115 (33.0%)
Tobacco smoke exposure at index date		
No	54 (31.0%)	181 (52.0%)
Active	54 (31.0%)	62 (17.8%)
Passive	15 (8.6%)	15 (4.3%)
Unknown	51 (29.3%)	90 (25.9%)
Vaccination before index date		
No vaccination	162 (93.1%)	348 (100%)
14V only	11 (6.3%)	0 (0.0%)
23V only	1 (0.6%)	0 (0.0%)
Antibiotic use within 7 days of index date		
No	164 (94.3%)	346 (99.4%)
Yes	9 (5.2%)	2 (0.6%)
Unknown	1 (0.6%)	0 (0.0%)

	Case (N=174)	Control (N=348)
High-risk conditions† for SPD before the index date of SPD		
Any condition	51 (29.3%)	18 (5.2%)
Cardiac disease	12 (15.6%)	5 (20.8%)
Chronic pulmonary disease	1 (1.3%)	0
Neurosurgical trauma/procedure	1 (1.3%)	0
Chronic renal insufficiency	5 (6.5%)	1 (4.2%)
Immunosuppressive therapy††	9 (11.7%)	0
Diabetes mellitus - Type I	8 (10.4%)	7 (29.2%)
Diabetes mellitus - Type II	3 (3.9%)	3 (12.5%)
Alcohol abuse	4 (5.2%)	1 (4.2%)
COPD‡ in absence of asthma	24 (31%)	4 (16.6%)
Rheumatoid arthritis	3 (3.9%)	3 (12.5%)
Hepatic disease	3 (3.9%)	0
Long-term corticosteroid use/high-dose steroid use at index date#	4 (5.2%)	0

*For children, parents' educational status was used;

†High-risk conditions are based on the ACIP-recommended pneumococcal vaccine eligible conditions and these conditions are not mutually exclusive because subjects can have more than one condition;

††defined as immunosuppressive drug intake for malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplantation prior to index date;

‡chronic obstructive lung disease;

#defined by the definition of the Red Book.[31]

Table 2

The association between atopic conditions other than asthma and serious pneumococcal disease

Subjects	**All subjects**	
Variables	Unadjusted OR for SPD with 95%CI, p-value	Adjusted OR for SPD with 95%CI, p-value
Atopic conditions		
No	Referent	Referent
Yes	1.98 (1.11- 3.55), p=0.02	2.13 (1.04- 4.35), p=0.04
Ethnicity		
Caucasian	Referent	Referent
Non-Caucasian	2.50 (0.99- 6.33), p=0.05	3.88 (1.34- 11.27), p=0.01
Tobacco smoke exposure at index date		
Active	Referent	Referent
Passive	1.76 (0.60- 5.13), p=0.30	1.80 (0.52- 6.19), p=0.35
Non-smokers	0.31 (0.18- 0.52), p<.001	0.28 (0.15- 0.51), p<.001
High-risk conditions (prior to index date)		
No	Referent	Referent
Yes	7.31 (3.96- 13.47), p<.001	8.27 (4.19- 16.31), p<.001
Educational status †		
<High school education	Referent	Referent
High school graduate	0.69 (0.38- 1.25), p=0.22	0.85 (0.42- 1.75), p=0.66
Some college education	0.33 (0.14- 0.76), p=0.01	0.31 (0.12- 0.78), p=0.01
College graduate	0.70 (0.35- 1.41), p=0.32	0.85 (0.37- 1.96), p=0.70

† For children, parents' educational status was used. [32, 33]