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Increased Risk of Serious Pneumococcal Disease in Patients with Asthma

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Abstract

Background—Individuals with asthma have been reported to be at increased risk of invasive pneumococcal disease. These findings need to be confirmed in a different population-based study setting.

Objective—We assessed whether serious pneumoccocal disease (SPD) defined as an invasive pneumococcal disease (IPD) and/or pneumococcal pneumonia was associated with asthma status.

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The study investigators have nothing to disclose that poses a conflict of interest.

Key Messages

Due to the potentially increased risk of serious pneumococcal diseases in adult asthmatics, asthma should be included as an indication for pneumococcal vaccination. The underlying mechanisms need to be studied.

Methods—This is a retrospective case-control study using criteria-based methods for ascertaining SPD as well as asthma. Subjects were residents of Rochester, Minnesota who developed SPD between 1964 and 1983 (the primarily pre-pneumococcal vaccine era) and their age- and gender-matched controls, using 1:2 matching. Potential cases and controls were identified using the Rochester Epidemiology project database and confirmed by medical record reviews. All cases and controls were merged with the database comprising the entire Rochester residents with and without asthma between 1964 and 1983.

Results—A total of 3,941 records of potential SPD cases were reviewed and we identified 174 cases of SPD, 51% male and 94% Caucasians. SPD was associated with a history of asthma among all ages (odds ratio: 2.4, 95%CI: 0.9 – 6.6, p=0.09) and among adults (odds ratio: 6.7, 95%CI: 1.6 – 27.3, p=0.01), controlling for high-risk conditions for IPD and smoking exposure. The population-attributable risk percent was 17% in the adult population.

Conclusion—Adults with asthma may be at increased risk of developing SPD.

Keywords

Asthma; invasive pneumococcal disease; epidemiology; risk; microbial infection; pneumococcal pneumonia; adults; Rochester Epidemiology Project

Introduction

Asthma affects almost 30 million Americans and 300 million people worldwide.[1–3] The prevalence of asthma has increased over the past two decades in both children and adults.[4, 5] Indeed, these same trends have been seen in Rochester, Minnesota. The annual age-and gender-adjusted incidence of asthma rose from 183 per 100, 000 in 1964 to 284 per 100, 000 in 1983.[6] In this study, we assessed whether asthma is associated with an increased risk of developing serious pneumococcal disease (SPD) defined as invasive pneumococcal disease and/or pneumococcal pneumonia.

Prior to the introduction of hepavalent pneumococcal conjugate vaccine (PCV7), patients aged 2–64 years who developed invasive pneumococcal diseases (n=3,469) were assessed for underlying conditions. Of these patients, only 50.6% (n=1,755) had at least one condition that was a known indication for either the pneumococcal polysaccharide or conjugate vaccine.[7] At present, asthma is not a pneumococcal vaccine-eligible condition and to what extent asthmatic patients contribute to the burden of serious pneumococcal disease at a population-level has not been known. To address this question, recently, Talbot et al. reported that having a diagnosis of asthma is associated with an increased risk of IPD, (OR: 2.4, 95%CI: 1.9–3.1).[8] The study population included only those receiving Medicaid insurance and the relationship between asthma and serious pneumococcal disease needs to be confirmed in another study population.

We conducted a population-based case-control study using a cohort in whom those with asthma status have been previously defined and uses information from the primarily pre-pneumococcal vaccine era, 1964–1983.

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 of 3941 records from a Rochester, Minnesota US population, 1964 through 1983, designed to assess if there is a higher incidence of serious pneumococcal disease among persons with asthma. Among the 3941 study participants, the diagnosis of asthma had been previously determined as a part of another study, using a structured algorithm and predetermined criteria for asthma.

Study population and setting

All study subjects are residents of Rochester, Minnesota, which is located in southeast Minnesota. The Olmsted County and Rochester populations are similar to the U.S. Caucasian population, with the exception of a higher proportion of the working population employed in the health care industry.[9–11] In 1980, the Rochester population was 60,541 (97% white). Rochester, Minnesota is an excellent setting to conduct a retrospective case-control study because medical care is virtually self-contained within the community and the Rochester Epidemiology Projects provides information on people attending medical care in all health care sites in Rochester. 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.[12] 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).[13]

Study subjects: Case ascertainment (serious pneumococcal disease)

Because all cases of SPD were confirmed by medical record review, we used very broad criteria to identify potential subjects. This allowed us to increase both sensitivity and specificity in identifying SPD cases. Our broad criteria for potential SPD cases included the diagnostic categories of: sepsis, bacteremia, meningitis, leptomeningitis, pneumococcal infections, diplococcal infections, lobar pneumonia, acute pneumonia, pneumococcal pneumonia, pneumococcal bacteremia, diplococcal pneumonia, osteomyelitis, pleuritis, pleurisy, pleural effusion, empyema, peritonitis, septic arthritis, shock (bacteremic), septic shock, streptococcal septicemia, and streptococcal bateremia. A total of 85 different medical index search codes (Berkson codes and ICD codes) were used to identify potential SPD cases. Each potential case was then confirmed by medical records review. Case definition of SPD included isolation of *S. pneumoniae* from a normally sterile site (such as blood or cerebrospinal fluid), 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 SPD as the date of documented isolation of *S. pneumoniae*.

Selection of controls

This study was designed as a cumulative-incidence case-control study in which cases were selected at the end of the study period and controls were selected from among individuals who at the end of the study period had not developed SPD. Therefore, controls were not at risk of becoming cases in the study. Controls were randomly selected from gender- and birthday-matched individuals who did not develop SPD by the end of the study period. Additional criteria for controls were as follows: 1) must be residents of Rochester, MN between 1964 and 1983; 2) must have research authorization for medical record review; and 3) had the same (i.e., within one year) clinic registration year as their matched case. Two controls were matched for each case with regard to gender and birthday (within two months for younger than 18 years of age, and within one year for older than 18 years of age). A list of potential controls were generated from the Rochester Epidemiology computerized database and the index date for controls was defined as the index date of SPD for the corresponding matched case. Therefore, because SPD cases and their matched controls had similar clinic registration date (starting point) and same index date (end point) by selecting controls at the end of the study period, we ensured that cases and controls had a similar length of follow-up with regard to disease and exposure status.

Exposure ascertainment (asthma status)

Once we identified confirmed SPD cases and their controls, we used the previously collected data on asthma to ascertain the asthma status among the confirmed SPD cases and controls. Data abstractors of this present study were not blinded to the asthma status, but they were not

aware of the study hypothesis at the time of data abstraction. The asthma status of all children and adults of Rochester, Minnesota, had been determined for a previous study during the period 1964 to 1983 (n=2,499).[6] Briefly, all potential asthma cases were identified using the medical diagnostic list within the Rochester Epidemiology Project and then the person's medical records were reviewed to confirm asthma using the pre-specified criteria. Diagnostic categories have been linked across the many updates of the diagnostic indices including revisions of the International Classifications of Diseases (ICD) e.g.ICD-7, ICD-8 and ICD-9. From the 18,000 potential asthma cases, 2,499 patients met the criteria for asthma.

To determine the relationship between SPD and asthma status, we merged SPD case and control data with the previously confirmed database for asthma using unique identifiers such as clinic registration number, names, and birthday. We were also able to address the temporal relationship between asthma and SPD since the previous study included the incidence dates for asthma in all confirmed asthma cases,[14]

Other variables

During medical record abstraction, we collected information including; sociodemographic variables (age, gender, ethnicity, and educational status), high-risk conditions for IPD (based on ACIP-recommended pneumococcal vaccine-eligible conditions) before and after the index date, smoking status at the time of index date (either active or passive smoking exposure to any number of cigarettes, cigar, and pipe a day by patient self or household members within one month of index date, if smoking exposure was documented in medical records both before and after index date, we included it as smoking exposure), 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

We calculated the age- and gender-adjusted annual incidence of IPD and SPD per 100, 000 using the year 2000 US population for adjustment for age and gender. A conditional logistic regression for matched analysis was used to determine whether the risk of SPD was associated with asthma status. We conducted data analysis using the entire group of subjects and stratified analysis by age focusing on adult subjects due to a small sample size of pediatric subjects. We also assessed the relationship between other variables and the risk of SPD. For any potential interaction between asthma and other variables in relation to risk of SPD, we used stratified analysis and tested the statistical significance of the interaction term using a regression model. The full model included variables associated with risk of SPD that meet an entry criteria (p-value less than 0.2) based on univariate analysis.[15] The odds ratio for a history of asthma was calculated, with 95% confidence interval, and tested for significance using a two-sided test, alpha = 0.05. In addition to these primary analyses, we calculated the population attributable risk percent (PAR%) of asthma on SPD. PAR% was calculated by using the following formula, P(OR-1)/[1+P(OR-1)], where P is the prevalence of asthma in the population and OR is matched odds ratio.[16]

Results

Study subjects

The characteristics of the subjects and the relationship between individual risk factors and SPD are summarized in Table 1. We identified 174 confirmed SPD cases of which 16% (n=28), 22% (n=38), and 62% (n=108) had IPD, IPD with pneumococcal pneumonia, and pneumococcal pneumonia, respectively. Of the 174 SPD cases, 51% were male and 94% were Caucasian. The median and mean age at the index date of SPD were 65 and 57 years, respectively. Only 21 cases (12%) were younger than 18 years. We confirmed that none of the

controls had SPD. The overall age- and gender- adjusted annual incidence of SPD was 13.1 (11.1–15.1) per 100,000 and the age- and gender-adjusted annual incidence of SPD in adults was 12.2 (10.2–14.1) per 100,000 during the study period. The age- and gender- adjusted annual incidence of IPD alone was 4.7 (3.5–5.9) per 100, 000. 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 whereas 5 (42%) did not have any pneumococcal vaccine-eligible conditions.

Asthma and serious pneumococcal disease

The results of the relationship between asthma and SPD are summarized in Table 2. Of the 13 controls, eight had definite asthma (62%) and five had probable asthma. Of the 11 cases, six (55%) had definite asthma and five had probable asthma. Our previous study showed that most probable asthma cases became definite asthma over time.[17] SPD was positively associated with a history of asthma status among adults. In children, the unadjusted odds ratio was not increased and not significant [0.40 (95%CI: 0.05–3.42, p=0.40)] with a very wide confidence interval due to our small number of SPD cases. The rest of our analyses focused on adults.

Because adult subjects with SPD were more likely to be smokers and to have high-risk conditions before the index date of SPD (Table 2) we performed a multivariate analysis to account for these factors. The adjusted odds ratio for asthma was 6.7 (95%CI: 1.6–27.3, p=0.01) up from the 2.9 unadjusted odds ratio. Further adjustment for educational status and ethnicity of subjects did not change the odds ratio (OR: 6.7, 95%CI: 1.5–29.5, p=0.01). Of the adult subjects, 47 of 153 SPD cases (31%) and 18 of 306 controls (5.9%) had at least one high-risk condition for IPD prior to the index date of SPD. Because of a possibility that some high-risk conditions for IPD such as immune deficiency can be subclinical before the index date of SPD, we adjusted odds ratio for high-risk conditions for IPD before and after (i.e., ever) index date and smoking status. The results remained significant (OR: 4.37, 95%CI: 1.06–18.08, p=0.04) based on a matched logistic regresion. We performed both matched conditional logistic and unmatched logistic regression for the association between asthma and SPD and we did not find a significant difference.

The population attributable risk percent in adults using an asthma prevalence in control (3.7%) ranged from 7% (using the unadjusted odds ratio of 2.9) to 17.4% (using the adjusted odds ratio of 6.7).

The significant increase in the effect size after adjustment suggested a potential for negative confounding with or without interaction between asthma and smoking exposure status and/or high-risk conditions for IPD. Therefore, among the adults only, we assessed the odds ratios after stratification of the subjects by smoking exposure status and high-risk conditions for SPD separately. We found a potential effect modification on the risk of SPD by smoking exposure status (unadjusted OR for asthma status among smokers was 5.8, p=0.11 and that among non-smokers was 2.0, p=0.24). However, the interaction term was not statistically significant (p=0.41). The effect of asthma status on the risk of SPD appeared also to change by the presence (vs. absence) of high-risk conditions for IPD (unadjusted OR for asthma status among the subjects with high-risk conditions was 1.2, p=0.86 and that among those without high-risk conditions was 2.9, p=0.04). However, the interaction term in a multivariate model was not statistically significant (p=0.52).

Discussion

In our study, SPD was associated with a prior history of asthma in adults, suggesting that asthma increased risk for SPD. Our study results are consistent with the study findings reported by Talbot et al. They reported an adjusted odds ratio for asthma status of 2.4 (95%CI: 1.9–3.1) which is comparable with our adjusted odds ratio (OR:2.4, 95%CI: 0.9—6.6, p=0.09) for all subjects. The effect size for adult subjects in our study was still elevated and significant after adjustment for smoking exposure, high-risk conditions for IPD, educational status, and ethnicity, although the confidence interval was relatively wide. Also, in our study, we adjusted the results for high-risk conditions for IPD prior to the index date and separately for high-risk conditions for IPD before and after the index date but the risk estimates remained high and statistically significant. However, results from the two studies must be compared cautiously since we assessed SPD while Talbot et al. included only IPD. In addition, Talbot's study population was Medicaid recipients and included larger numbers of children but ours was an entire community population. At any rate, our study confirms an increased risk of SPD among adults with asthma.

The population attributable risk percent (PAR%) for asthma in adults of our study was up to 17% and the PAR% in adults of the study by Talbot et al based on the provided data is estimated to be 11% whereas the PAR% for all combined ACIP vaccine-eligible conditions in adults was 24%. These data suggest that asthma status alone increases the burden of serious pneumococcal disease disproportionately at a population level. The results of these two studies plus the known high case-fatality of IPD (10–20%),[7, 18] suggest that asthma should be included as a pneumococcal vaccine-eligible condition for children and adults. However, in the prevention of SPD through pneumococcal vaccinations, it is important to determine whether patients with asthma have normal antibody response to pneumococcal vaccines because this is currently unknown.[19–21]

In our study, the crude odds ratio for the association between asthma and SPD was smaller than both the adjusted odds ratios suggesting a potential negative confounding effect by smoking status and the high-risk condition for IPD. In addition, the stratum-specific odds ratios by smoking status or the high-risk conditions for IPD appeared to be different from each other suggesting a potential effect modification although interaction terms in the models were not statistically significant. The possible effect-modifying roles of smoking exposure and the high-risk conditions for IPD need to be assessed in a larger study with greater statistical power.

An unexpected finding was a relatively lower incidence of IPD (4.7 per 100, 000) than expected considering that our study was conducted in the primarily pre-pneumococcal vaccine era. Our incidence rates of IPD were lower than those in Atlanta (9.5 per 100, 000) and Baltimore (7.6 per 100, 000) in 1995 surveillance data among non-African-American population.[22] Tsigrelis et al examined the incidence of IPD in our community between 1999 and 2006 and reported that the incidence of IPD in our community was 11.7 per 100, 000 in 1999 and 5.4 per 100, 0000 in 2003.[23] Therefore, the incidence rate of IPD in our study appears to be relatively lower than those reported in other communities. The difference may be due to differences in community demographics such as greater ethnic and socio-economic diversity in the larger cities and potential missing cases for SPD from our study. Also, our limited sample of children (12% of all SPD cases) did not allow us to draw a meaningful conclusion for children from this study.

Busse suggests that mechanical (e.g., epithelial lining or mucus secretion), immunological (humoral or cell-mediated immunity), and phagocytic functions are important defense mechanisms in the airways to protect the host from microbial infections.[24] Other researchers

have published information suggesting differences in innate and acquired immunity between asthmatic and non-asthmatic subjects.[19, 21, 25–31]

All retrospective studies have inherent limitations including failure to identify all SPD cases based on diagnostic codes. Although we did include a very broad range of codes to identify IPD, it is still possible to miss IPD cases resulting in a lower estimate of IPD incidence. The retrospective medical record-based ascertainment of asthma might have its own limitation and data abstractors were not blinded to the asthma status when they determined case and control status. However, data abstractors had no specific knowledge of our study hypotheses. Also, independent ascertainment of asthma status by predetermined criteria not physician diagnosis alone and the specific and objective criteria for SPD minimized performance (observation) bias. Some variables such as tobacco smoke or educational status were not available for all subjects but missing variables are likely to occur in random and is subject to a non-differential misclassification bias. Thus, it is unlikely to change the current study results substantially. In our study, we were not able to assess the influence of asthma severity on the risk of SPD. Although we had limited statistical power (54% power to detect the effect size of 2.4 reported by Talbot et al), we did find a positive result in adults due to a larger proportion of SPD cases and higher prevalence of asthma in adult SPD cases. The findings of this study may not be generalizable to other settings with different ethnic compositions because Rochester, Minnesota had a predominantly Caucasian population during the study period. However, our results are similar to those of Talbot et al, which came from a Medicaid population in the more racially diverse State of Tennessee.

In conclusion, adults with asthma may be at increased risk of invasive pneumococcal disease and/or pneumococcal pneumonia. The mechanisms underlying this increased risk of SPD among individuals with asthma requires further study. In the meantime, consideration should be given to including asthma as an indication for pneumococcal vaccination in adults.

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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
PAR%	population attributable risk percent

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Table 1

Socio-demographic and clinical characteristics of cases with serious pneumococcal disease and their birthday- and gender-matched corresponding controls

	Control (N=348)	Case (N=174)
Age at case's index date (years)		
Mean (SD)	57.0 (26.4)	57.0 (26.5)
Median	65.1	65.1
Asthma		
Yes	13 (3.7%)	11 (6.3%)
No	335 (96.3%)	163 (93.7)
History of atopy		
Yes	45 (12.9%)	30 (17.2%)
No	303 (87.1%)	144 (82.8%)
Gender		
Male	176 (50.6%)	88 (50.6%)
Female	172 (49.4%)	86 (49.4%)
Ethnicity		
Hispanic/Latino	1 (0.3%)	1 (0.6%)
Asian	0 (0.0%)	2 (1.1%)
Black/African American	1 (0.3%)	0 (0%)
Caucasian	340 (97.7%)	164 (94.3%)
Unknown	6 (1.7%)	7 (4.0%)
Educational status*		
< High school	61 (17.5%)	35 (20.1%)
High school graduate	79 (22.7%)	32 (18.4%)
Some college	49 (14.1%)	11 (6.3%)
College graduate	44 (12.6%)	20 (11.5%)
Unknown	115 (33.0%)	76 (43.7%)
Vaccination before index date		
No vaccination	348 (100%)	162 (93.1%)
14V only		11 (6.3%)
23V only		1 (0.6%)
Pre-index date antibiotic use		
No	346 (99.4%)	164 (94.3%)
Yes	2 (0.6%)	9 (5.2%)
Unknown	0 (0.0%)	1 (0.6%)
Tobacco smoke exposure at index date		
No	181 (52.0%)	54 (31.0%)
Active	62 (17.8%)	54 (31.0%)
Passive	15 (4.3%)	15 (8.6%)
Unknown	90 (25.9%)	51 (29.3%)
High-risk conditions for IPD before the index date of SPD**		

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

*For children, parents' educational status was used;

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

†serious pneumococcal disease;

††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.[32]

Table 2

Risk factors for serious pneumococcal disease for all subjects (both adults and children, n=522) and adult subjects (≥18 years of age, n=459)

Subjects	All subjects		Adult subjects only	
Variables	**Unadjusted OR for SPD with 95%CI, p-value**	**Adjusted OR for SPD with 95%CI, p-value**	**Unadjusted OR for SPD with 95%CI, p-value**	**Adjusted OR for SPD with 95%CI, p-value**
Asthma status				
No	Referent	Referent	Referent	Referent
Yes	1.79 (0.76, 4.18), p=0.18	2.40 (0.88, 6.56), p=0.09	2.91 (1.04, 8.13), p=0.04	6.70 (1.64, 27.30), p=0.01
Ethnicity				
Caucasian	Referent	Referent	Referent	Referent
Non-Caucasian	2.50 (0.99, 6.33), p=0.05	3.98 (1.37, 11.59), p=0.01	1.33 (0.38, 4.73), p=0.66	3.18 (0.73, 13.86), p=0.12
Tobacco smoke exposure at index date				
Active	Referent	Referent	Referent	Referent
Passive	1.76 (0.60, 5.13), p=0.30	1.70 (0.51, 5.80), p=0.39	2.15 (0.69, 6.70), p=0.22	2.25 (0.61, 8.35), p=0.22
Non-smokers	0.31 (0.18, 0.52), p<0.001	0.27 (0.15, 0.48), p<0.001	0.26 (0.15, 0.45), p<0.001	0.22 (0.11, 0.42), p<0.001
High-risk conditions (prior to index date)				
No	Referent	Referent	Referent	Referent
Yes	7.31 (3.96, 13.47), p<0.001	8.17 (4.19, 15.0), p<0.001	6.69 (3.61, 12.42), p<0.001	8.3 (4.04, 16.88), p<0.001
Educational status †				
<high school education	Referent	Referent	Referent	Referent
High school graduate	0.69 (0.38, 1.25), p=0.22	0.83 (0.40, 1.70), p=0.61	0.68 (0.36, 1.26), p=0.22	0.84 (0.40, 1.70), p=0.61
Some college education	0.33 (0.14, 0.76), p=0.01	0.91 (0.40, 2.06), p=0.82	0.30 (0.12, 0.71), p=0.01	0.31 (0.13, 0.83), p=0.02
College graduate	0.70 (0.35, 1.41), p=0.32	1.36 (0.69, 2.70), p=0.37	0.66 (0.32, 1.36), p=0.26	0.88 (0.37, 2.08), p=0.82

The full model included all variables listed in this table using an entry criteria of p-value of less than 0.2 (i.e., asthma status was adjusted for ethnicity, tobacco smoke status, high risk condition, and educational status); SPD; serious pneumococcal disease (i.e., invasive pneumococcal disease and/or pneumococcal pneumonia);

† For children, parents' educational status was used