Editors' choice article

Increased risk of serious pneumococcal disease in patients with asthma

Young J. Juhn, MD, MPH,[a] Hirohito Kita, MD,[a] Barbara P. Yawn, MD, MSc,[b] Thomas G. Boyce, MD, MPH,[a] Kwang H. Yoo, MD, PhD,[a,c] Michaela E. McGree, BS,[d] Amy L. Weaver, MS,[d] Peter Wollan, PhD,[b] and Robert M. Jacobson, MD[a] *Rochester, Minn, and Seoul, South Korea*

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

Objective: We assessed whether serious pneumococcal disease (SPD), defined as an IPD, pneumococcal pneumonia, or both, was associated with asthma status.

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 had SPD between 1964 and 1983 (the primarily pre–pneumococcal vaccine era) and their age- and sex-matched control subjects using 1:2 matching. Potential cases and control subjects were identified by using the Rochester Epidemiology project database and confirmed by medical record reviews. All cases and control subjects were merged with the database comprising the entire pool of Rochester residents with and without asthma between 1964 and 1983.

Results: A total of 3941 records of potential patients with SPD were reviewed, and we identified 174 cases of SPD (51% male subjects and 94% white subjects). SPD was associated with a history of asthma among all ages (odds ratio, 2.4; 95% CI, 0.9-6.6; $P = .09$) and among adults (odds ratio, 6.7; 95% CI, 1.6-27.3; $P = .01$), controlling for high-risk conditions for IPD and smoking exposure. The population-attributable risk percentage was 17% in the adult population.

Conclusion: Adults with asthma might be at increased risk of SPD. (J Allergy Clin Immunol 2008;122:719-23.)

Key words: *Asthma, invasive pneumococcal disease, epidemiology, risk, microbial infection, pneumococcal pneumonia, adults, Rochester Epidemiology Project*

Asthma affects almost 30 million Americans and 300 million persons worldwide.[1-3] The prevalence of asthma has increased over the past 2 decades in both children and adults.[4,5] Indeed, these same trends have been seen in Rochester, Minnesota. The annual age- and sex-adjusted incidence of asthma increased 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 serious pneumococcal disease (SPD), which was defined as invasive pneumococcal disease (IPD), pneumococcal pneumonia, or both.

Before the introduction of heptavalent pneumococcal conjugate vaccine, patients aged 2 to 64 years who had IPDs (n = 3469) were assessed for underlying conditions. Of these patients, only 50.6% (n = 1755) had at least 1 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 SPD at a population level has not been known. To address this question, recently, Talbot et al[8] reported that having a diagnosis of asthma is associated with an increased risk of IPD (odds ratio [OR], 2.4; 95% CI, 1.9-3.1). The study population included only those receiving Medicaid insurance, and the relationship between asthma and SPD 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 that uses information from the primarily pre–pneumococcal vaccine era (ie, 1964-1983).

METHODS

The study was approved by the Institutional Review Boards of both Mayo Clinic and Olmsted Medical Center. This is a population-based, retrospective case-control study of 3941 records from a Rochester, Minnesota, population from 1964 through 1983 designed to assess whether there is a higher incidence of SPD among persons with asthma. Among the 3941 study participants, the diagnosis of asthma had been previously determined as part of another study by 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

From [a]the Departments of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester; [b]the Department of Research, Olmsted Medical Center, Rochester; [c]the Department of Internal Medicine, Kunkook University School of Medicine, Seoul; and [d]the Department of Health Sciences Research, Mayo Clinic, Rochester.

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Reprint requests: Young J. Juhn, MD, MPH, Division of Community Pediatric and Adolescent Medicine, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905. E-mail: juhn.young@mayo.edu.

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Abbreviations used
ICD: International Classification of Diseases
IPD: Invasive pneumococcal disease
OR: Odds ratio
PAR%: Population attributable risk percentage
SPD: Serious pneumococcal disease

similar to the US white 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 persons 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 by using Berkson codes, even before International Classification of Diseases (ICD) codes were available.[12] The incidence rate of asthma in Rochester was 238 per 100,000, which is comparable with rates in other communities, such as Tecumseh, Michigan (250/100,000).[13]

Study subjects: Case ascertainment (SPD)

Because all cases of SPD were confirmed by means of medical record review, we used very broad criteria to identify potential subjects. This allowed us to increase both the sensitivity and specificity in identifying cases of SPD. Our broad criteria for potential cases of SPD 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 bacteremia. A total of 85 different medical index search codes (Berkson codes and ICD codes) were used to identify potential cases of SPD. Each potential case was then confirmed by means of medical records review. Case definition of SPD included isolation of *Streptococcus pneumoniae* from a normally sterile site (eg, blood or cerebrospinal fluid) or pneumococcal pneumonia requiring all 3 of the following criteria: (1) a physician's diagnosis of pneumonia, (2) the isolation of pneumococcus from sputum Gram stain or culture, and (3) pneumonia documented by means of chest radiography. We defined the index date of onset of SPD as the date of documented isolation of *S pneumoniae*.

Selection of control subjects

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

Exposure ascertainment (asthma status)

Once we identified cases and their control subjects, we used the previously collected data on asthma to ascertain the asthma status among the subjects with confirmed cases of SPD and control subjects. Data abstractors of this study were not blinded to 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 in Rochester, Minnesota, had been determined for a previous study during the period 1964 to 1983 (n = 2499).[6] Briefly, all potential cases of asthma were identified by using the medical diagnostic list within the Rochester Epidemiology Project, and then each person's medical records were reviewed to confirm asthma by using the prespecified criteria. Diagnostic categories have been linked across the many updates of the diagnostic indices, including revisions of the ICD (eg, ICD-7, ICD-8, and ICD-9). From the 18,000 potential asthma cases, 2499 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 by using unique identifiers, such as clinic registration numbers, names, and birthdays. We were also able to address the temporal relationship between asthma and SPD because the previous study included the incidence dates for asthma in all confirmed cases of asthma.[14]

Other variables

During medical record abstraction, we collected information, including sociodemographic variables (age, sex, ethnicity, and educational status), high-risk conditions for IPD (based on Advisory Committee on Immunization Practices–recommended pneumococcal vaccine–eligible conditions) before and after the index date, smoking status at the time of the index date (either active or passive smoking exposure to any number of cigarettes, cigars, or pipes a day by patient or household members within 1 month of index date; if smoking exposure was documented in medical records both before and after the index date, we included it as smoking exposure), pneumococcal vaccination status based on medical records during the study period, and antibiotic use within 7 days before the index date of SPD.

Data analysis

We calculated the age- and sex-adjusted annual incidence of IPD and SPD per 100,000 by using the year 2000 US population for adjustment for age and sex. 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 by using the entire group of subjects and stratified analysis by age, focusing on adult subjects because of the 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 the risk of SPD, we used stratified analysis and tested the statistical significance of the interaction term by using a regression model. The full model included variables associated with risk of SPD that meet an entry criterion ($P < .2$) based on univariate analysis.[15] The OR for a history of asthma was calculated with the 95% CI and tested for significance by using a 2-sided test ($\alpha = .05$). In addition to these primary analyses, we calculated the population-attributable risk percentage (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 the matched OR.[16]

RESULTS

Study subjects

The characteristics of the subjects and the relationship between individual risk factors and SPD are summarized in Table I. 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 subjects with SPD, 51% were male, and 94% were white. The median and mean ages at the index date of SPD were 65 and 57 years, respectively. Only 21 (12%) cases were younger than 18

TABLE I. Sociodemographic and clinical characteristics of cases with SPD and their birthday- and sex-matched corresponding control subjects

	Control (n = 348)	Case (n = 174)
Age at case's index date (y)		
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%)
Sex		
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%)
White	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%)
Preindex 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		
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 Advisory Committee on Immunization Practices–recommended pneumococcal vaccine–eligible conditions, and these conditions were not mutually exclusive because subjects could have more than 1 condition.
‡Defined as immunosuppressive drug intake for malignant neoplasms, leukemias, lymphomas, Hodgkin disease, and solid organ transplantation before the index date.
§Defined by the definition of the Red Book.[17]

years. We confirmed that none of the control subjects had SPD. The overall age- and sex-adjusted annual incidence of SPD was 13.1 (95% CI, 11.1-15.1) per 100,000, and the age- and sex-adjusted annual incidence of SPD in adults was 12.2 (95% CI, 10.2-14.1) per 100,000 during the study period. The age- and sex-adjusted annual incidence of IPD alone was 4.7 (95% CI, 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 before the index date, whereas none of the control subjects had received a pneumococcal vaccine. Of these 12 SPD cases, 7 (58%) had pneumococcal vaccine–eligible conditions, whereas 5 (42%) did not have any pneumococcal vaccine–eligible conditions.

Asthma and SPD

The results of the relationship between asthma and SPD are summarized in Table II.[17] Of the 13 control subjects, 8 (62%) had definite asthma, and 5 had probable asthma. Of the 11 cases, 6 (55%) had definite asthma, and 5 had probable asthma. Our previous study showed that most cases of probable asthma became definite asthma over time.[18] SPD was positively associated with a history of asthma status among adults. In children, the unadjusted OR was not increased and not significant (OR, 0.40; 95% CI, 0.05-3.42; $P = .40$), with a very wide CI because of 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 II), we performed a multivariate analysis to account for these factors. The adjusted OR for asthma was 6.7 (95% CI, 1.6-27.3; $P = .01$), which was up from the unadjusted OR of 2.9. Further adjustment for educational status and ethnicity of subjects did not change the OR (OR, 6.7; 95% CI, 1.5-29.5; $P = .01$). Of the adult subjects, 47 (31%) of 153 SPD cases and 18 (5.9%) of 306 control subjects had at least 1 high-risk condition for IPD before 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 the OR for high-risk conditions for IPD before and after (ie, ever) the index date and smoking status. The results remained significant (OR, 4.37; 95% CI, 1.06-18.08; $P = .04$) based on a matched logistic regression. We performed both matched conditional logistic and unmatched logistic regression for the association between asthma and SPD and did not find a significant difference.

The PAR% in adults using asthma prevalence in control subjects (3.7%) ranged from 7% (using the unadjusted OR of 2.9) to 17.4% (using the adjusted OR 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, high-risk conditions for IPD, or both. Therefore among the adults only, we assessed the ORs 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; the unadjusted OR for asthma status among smokers was 5.8 ($P = .11$), and that among nonsmokers was 2.0 ($P = .24$). However, the interaction term was not statistically significant ($P = .41$). The effect of asthma status on the risk of SPD appeared also to change based on the presence (vs absence) of high-risk conditions for IPD; the unadjusted OR for asthma status among the subjects with high-risk conditions was

TABLE II. Risk factors for SPD for all subjects (both adults and children, n = 522) and adult subjects (≥18 years of age, n = 459)

Variables	All subjects		Adult subjects only	
	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), .18	2.40 (0.88-6.56), .09	2.91 (1.04-8.13), .04	6.70 (1.64-27.30), .01
Ethnicity				
White	Referent	Referent	Referent	Referent
Nonwhite	2.50 (0.99-6.33), .05	3.98 (1.37-11.59), .01	1.33 (0.38-4.73), .66	3.18 (0.73-13.86), .12
Tobacco smoke exposure at the index date				
Active	Referent	Referent	Referent	Referent
Passive	1.76 (0.60-5.13), .30	1.70 (0.51-5.80), .39	2.15 (0.69-6.70), .22	2.25 (0.61-8.35), .22
Nonsmokers	0.31 (0.18-0.52), .001	0.27 (0.15-0.48), .001	0.26 (0.150-0.45), .001	0.22 (0.11-0.42), .001
High-risk conditions (before the index date)				
No	Referent	Referent	Referent	Referent
Yes	7.31 (3.96-13.47), .001	8.17 (4.19-15.0), .001	6.69 (3.61-12.42), .001	8.3 (4.04-16.88), .001
Educational status*				
<High school	Referent	Referent	Referent	Referent
High school graduate	0.69 (0.38-1.25), .22	0.83 (0.40-1.70), .61	0.68 (0.36-1.26), .22	0.84 (0.40-1.70), .61
Some college	0.33 (0.14-0.76), .01	0.91 (0.40-2.06), .82	0.30 (0.12-0.71), .01	0.31 (0.13-0.83), .02
College graduate	0.70 (0.35-1.41), .32	1.36 (0.69-2.70), .37	0.66 (0.32-1.36), .26	0.88 (0.37-2.08), .82

The full model included all variables listed in this table using an entry criteria of a *P* value of less than .2 (ie, asthma status was adjusted for ethnicity, tobacco smoke status, high-risk condition, and educational status).

*For children, parents' educational status was used.

1.2 ($P = .86$), and that among those without high-risk conditions was 2.9 ($P = .04$). However, the interaction term in a multivariate model was not statistically significant ($P = .52$).

DISCUSSION

In our study SPD was associated with a prior history of asthma in adults, suggesting that asthma increased the risk for SPD. Our study results are consistent with the study findings reported by Talbot et al.[8] They reported an adjusted OR for asthma status of 2.4 (95% CI, 1.9-3.1), which is comparable with our adjusted OR (OR, 2.4; 95% CI, 0.9-6.6; $P = .09$) for all subjects. The effect size for adult subjects in our study was still increased and significant after adjustment for smoking exposure, high-risk conditions for IPD, educational status, and ethnicity, although the CI was relatively wide. Also, in our study we adjusted the results for high-risk conditions for IPD before 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 2 studies must be compared cautiously because we assessed SPD whereas Talbot et al[8] included only IPD. In addition, the Talbot et al study population comprised 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 PAR% for asthma in adults of our study was up to 17%, and the PAR% in adults of the study by Talbot et al[8] based on the provided data is estimated to be 11%, whereas the PAR% for all combined Advisory Committee on Immunization Practices vaccine–eligible conditions in adults was 24%. These data suggest that asthma status alone increases the burden of SPD disproportionately at a population level. The results of these 2 studies plus the known high case fatality of IPD (10%-to 20%),[7,19] suggests 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.[20-22]

In our study the crude OR for the association between asthma and SPD was smaller than both the adjusted ORs, suggesting a potential negative confounding effect by smoking status and the high-risk condition for IPD. In addition, the stratum-specific ORs 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 (4.7/100,000) 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 (9.5/100,000) and Baltimore (7.6/100,000) in 1995 surveillance data among the non–African American population.[23] Tsigrelis et al[24] 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. Therefore the incidence rate of IPD in our study appears to be relatively lower than those reported in other communities. The difference might be due to differences in community demographics, such as greater ethnic and socioeconomic 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[25] suggests that mechanical (eg, epithelial lining or mucus secretion), immunologic (humoral or cell-mediated immunity), and phagocytic functions are important defense mechanisms in the airways to protect the host from microbial infections. Other researchers have published information suggesting differences in innate and acquired immunity between asthmatic and nonasthmatic subjects.[20,22,26-32]

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 limitations, 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 means of predetermined criteria and 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 randomly and are subject to a nondifferential 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[8]), we did find a positive result in adults caused by a larger proportion of SPD cases and higher prevalence of asthma in adult SPD cases. The findings of this study might not be generalizable to other settings with different ethnic compositions because Rochester, Minnesota, had a predominantly white population during the study period. However, our results are similar to those of Talbot et al,[8] which came from a Medicaid population in the more racially diverse state of Tennessee.

In conclusion, adults with asthma might be at increased risk of IPD, pneumococcal pneumonia, or both. 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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Key message

- **Because of the potentially increased risk of SPD in adult asthmatic subjects, asthma should be included as an indication for pneumococcal vaccination. The underlying mechanisms need to be studied.**

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