

ORIGINAL ARTICLE

# Asthma as a Risk Factor for Invasive Pneumococcal Disease

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## ABSTRACT

### BACKGROUND

The risk of invasive pneumococcal disease among persons with asthma is unknown.

### METHODS

We conducted a nested case-control study to examine the association between asthma and invasive pneumococcal disease. The study population included persons 2 to 49 years of age who were enrolled in Tennessee's Medicaid program (TennCare) for more than one year during the study period (1995 through 2002) and who resided in counties participating in a prospective laboratory-based program of surveillance for invasive pneumococcal disease. For each subject with invasive pneumococcal disease, 10 age-matched controls without invasive pneumococcal disease were randomly selected from the same population. TennCare files were queried to identify the presence of coexisting conditions that confer a high risk of pneumococcal disease. For the purpose of our study, asthma was defined by documentation of one or more inpatient or emergency-department diagnoses of asthma, two outpatient diagnoses, or the use of asthma-related medications. High-risk asthma was defined as asthma requiring admission to a hospital or a visit to an emergency department, the use of rescue therapy or long-term use of oral corticosteroids, or the dispensing of three or more prescriptions for  $\beta$ -agonists within the year before enrollment in the study.

### RESULTS

A total of 635 persons with invasive pneumococcal disease and 6350 controls were identified, of whom 114 (18.0 percent) and 516 (8.1 percent), respectively, had asthma. Persons with asthma had an increased risk of invasive pneumococcal disease (adjusted odds ratio, 2.4; 95 percent confidence interval, 1.9 to 3.1) as compared with controls. Among those without coexisting conditions, the annual incidence of invasive pneumococcal disease was 4.2 episodes per 10,000 persons with high-risk asthma and 2.3 episodes per 10,000 persons with low-risk asthma, as compared with 1.2 episodes per 10,000 persons without asthma.

### CONCLUSIONS

Asthma is an independent risk factor for invasive pneumococcal disease. The risk among persons with asthma was at least double that among controls.

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**S**TREPTOCOCCUS PNEUMONIAE IS THE cause of substantial morbidity and mortality in the United States, particularly among people who are at high risk for pneumococcal infection.<sup>1</sup> Among those at risk, pneumococcal vaccination has been shown to prevent invasive disease from this ubiquitous pathogen.<sup>1,2</sup> The identification and confirmation of other groups at risk as potential candidates for vaccination are key steps in the prevention of invasive pneumococcal disease.

Unlike the known increase in the risk of invasive pneumococcal disease among persons with other chronic obstructive pulmonary diseases (COPDs) (e.g., emphysema and chronic bronchitis),<sup>1</sup> the risk among persons with asthma is unknown. Guidelines for pneumococcal vaccination specifically exclude persons with asthma,<sup>1,2</sup> and guidelines for the management of asthma do not include pneumococcal vaccination as a strategy to prevent infectious complications.<sup>3,4</sup> An estimated 7 percent of the U.S. population has asthma. As the prevalence of this disease steadily increases,<sup>5-7</sup> clarification of the role of asthma in the epidemiology of invasive pneumococcal disease becomes more important. We examined the association between asthma and invasive pneumococcal disease by conducting a nested case-control study with the use of data from two large, population-based databases. After performing the analysis of this association, we conducted a cohort analysis to ascertain the incidence of invasive pneumococcal disease among persons with and those without asthma who were enrolled in Tennessee's Medicaid program (TennCare).

## METHODS

### ASCERTAINMENT OF EPISODES OF INVASIVE PNEUMOCOCCAL DISEASE

Surveillance for episodes of invasive pneumococcal disease has been conducted in five urban counties in Tennessee as a part of the Active Bacterial Core surveillance (ABCs) network of the Centers for Disease Control and Prevention (CDC)<sup>8</sup> since January 1, 1995. In August 1999, six more counties were added to the Tennessee ABCs network, increasing the surveillance population to more than 2.8 million persons.<sup>9</sup> Invasive pneumococcal disease was defined as the isolation of *S. pneumoniae* from a normally sterile site (e.g., blood, cerebrospinal fluid, pleural fluid, peritoneal fluid, pericardial fluid, surgical aspirate, bone, or joint fluid). Each episode was identified through prospective active surveil-

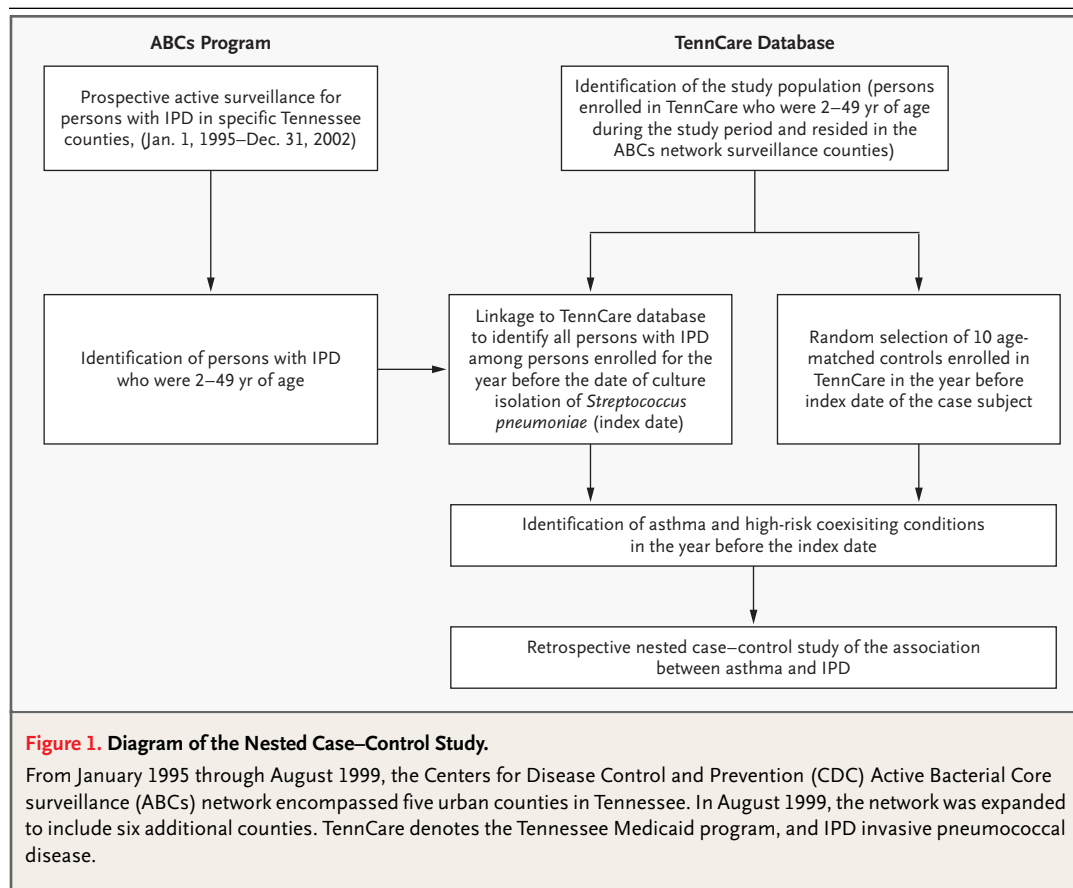
lance, as described previously.<sup>8,10,11</sup> Through the ABCs network, serotyping of pneumococcal isolates from persons with invasive pneumococcal disease identified after 1997 was performed.<sup>8,12</sup> Serotypes included in the 7-valent pneumococcal conjugate vaccine (PCV) were designated as PCV serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Serotypes included in the 23-valent pneumococcal polysaccharide vaccine (PPV) were designated as PPV serotypes (PCV serotypes plus 1, 2, 3, 5, 7F, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F). Serotypes not included in either vaccine were considered nonvaccine serotypes. The study was approved by the institutional review boards of Vanderbilt University and the Tennessee Department of Health.

### STUDY POPULATION

In 1994 in Tennessee, TennCare replaced the federal Medicaid program. TennCare is a state-based capitated managed health care program covering state residents who were eligible for Medicaid benefits and those who were uninsured or uninsurable.<sup>13</sup> Administrative data from the TennCare system are contained in several computerized files: an enrollment file serves as the central registry of those enrolled, a pharmacy file consists of all outpatient and nursing-home prescription records, an inpatient file contains hospitalization records, and an outpatient file consists of encounter records for visits to emergency departments, hospital outpatient visits, and physician visits. Diagnoses in these files are coded according to the *International Classification of Diseases, 9th Revision, Clinical Modification*, (ICD-9-CM).<sup>14</sup>

We conducted a nested case-control study using the study population of TennCare recipients 2 to 49 years of age who had been enrolled in TennCare for at least one year and who lived in a county included in the ABCs program. The population was a dynamic cohort, because people entered it when they met age and eligibility requirements for enrollment and they left it when they reached 50 years of age, when their enrollment ended, when they died, or when invasive pneumococcal disease developed.

ABCs data on cases of invasive pneumococcal disease from January 1, 1995, through December 31, 2002, were linked to TennCare enrollment data with the use of patient-specific identifiers (Fig. 1).<sup>15</sup> Subjects with invasive pneumococcal disease were those between the ages of 2 and 49 years in whom invasive pneumococcal disease had been detected by the ABCs and who had been enrolled in TennCare



for at least one year before the index date, defined as the date of isolation of *S. pneumoniae*. The previous year of TennCare eligibility was required to classify cases according to the presence or absence of asthma and other coexisting conditions before an episode of invasive pneumococcal disease. To reduce confounding from tobacco-related lung disease, the upper age limit of 49 years was chosen. Children less than two years of age were not included, because asthma is difficult to diagnose with certainty in very young children. Among subjects with multiple episodes of invasive pneumococcal disease, only the first episode to occur after the subject had been enrolled in TennCare for at least one year was included.

For each subject with an episode of invasive pneumococcal disease, 10 controls were randomly selected from the study population of eligible persons enrolled in TennCare. Controls were matched to case subjects according to age ( $\pm 1$  month) and the index date of the case subject. Eligible controls met the criteria for age and enrollment according

to the case subject's index date and lived in an ABCs county on the index date. For case subjects with an index date between January 1995 and August 1999, eligible controls resided in 1 of the original 5 surveillance counties, whereas eligible control subjects for case subjects with an index date after August 1999 resided in 1 of the 11 surveillance counties. In addition, eligible controls had no history of pneumococcal disease on the basis of ICD-9-CM coded diagnoses in TennCare claims during the year before the index date. For each case subject, all eligible controls were assigned a random number; these numbers were then put into order, and the first 10 were selected as the controls. Controls were assigned the same index date as their respective case subject. Selected controls became ineligible as controls for other case subjects.

#### ASCERTAINMENT OF ASTHMA

The presence or absence of asthma was determined by screening inpatient and outpatient claims of each case subject for a diagnosis of asthma accord-

ing to the ICD-9-CM code (section 493). With the use of a previously validated definition,<sup>16,17</sup> case subjects and controls were classified as having asthma if any of the following criteria were met in the year before the index date: one or more hospitalizations or visits to an emergency department resulting in a diagnostic code for asthma, two or more outpatient physician visits resulting in a diagnostic code for asthma, two or more prescriptions for any short-acting  $\beta$ -agonist medication (albuterol, isoproterenol, metaproterenol, pirbuterol, bitolterol, terbutaline, or levalbuterol), or one or more prescriptions for a medication for chronic asthma (inhaled corticosteroid, long-acting  $\beta$ -agonist, other inhaled antiinflammatory agents such as nedocromil or cromolyn, or a leukotriene-modifying drug, such as montelukast, zafirlukast, or zileuton) during the eligibility period. Subjects with asthma who had 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) or prescriptions for three or more  $\beta$ -agonist medications during the year before the index date were classified as having high-risk asthma. All other subjects with asthma were classified as having low-risk asthma.

#### IDENTIFICATION OF COEXISTING CONDITIONS

To identify coexisting conditions associated with an increased risk of invasive pneumococcal disease, TennCare claims from the year before the index date for case subjects and controls were reviewed for condition-specific diagnoses according to ICD-9-CM codes and for prescribed medications (described in detail in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). High-risk coexisting conditions were defined by the documentation of one or more discharges from a hospital or emergency department with a condition-specific coded diagnosis, two or more outpatient visits with a condition-specific coded diagnosis, or a recorded prescription for condition-specific medications. The high-risk conditions that were examined were infection with the human immunodeficiency virus (HIV), sickle cell disease, diabetes mellitus, cardiac disease, renal disease, hepatic disease including cirrhosis, obstructive pulmonary disease in the absence of asthma, cancer or immunosuppression due to illness or use of medication (including oral corticosteroids), alcohol

abuse, and tobacco use. Long-term use of corticosteroids was defined as receipt of prescriptions for oral corticosteroids to be taken for 120 days or more during the year before the index date.

#### STATISTICAL ANALYSIS

The primary objective of the study was to examine the association between asthma and invasive pneumococcal disease. For the nested case-control study, we used conditional logistic-regression analysis to assess the relationship between asthma and the risk of invasive pneumococcal disease, with adjustment for potential confounding factors, including sex, race as determined by TennCare, prolonged use of oral corticosteroids, and the presence of coexisting conditions that confer a high risk of pneumococcal disease.

After the case-control analysis had been completed, a cohort analysis was conducted to determine annual incidence rates of invasive pneumococcal disease among eligible persons enrolled in TennCare who had asthma and eligible enrolled persons who did not have asthma. The numerators for the unadjusted rates were all cases of invasive pneumococcal disease that had been included in the case-control study. The person-years in the denominator were estimated as the number of persons in the study population on July 1 of each study year. The annual incidence rates of invasive pneumococcal disease among persons with asthma and those without asthma were then determined according to the number of cases of invasive pneumococcal disease among persons with asthma and those without asthma per year, divided by the total number of eligible persons enrolled in TennCare on July 1 of each year who had asthma and who did not have asthma (defined according to the study definition of asthma during the previous year). A similar calculation was performed to ascertain the annual incidence of invasive pneumococcal disease among persons with high-risk coexisting conditions and those without high-risk coexisting conditions. The analyses were conducted with the use of Stata software (version 7.0) and SAS software (version 8.2).

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## RESULTS

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Of a total of 4581 episodes of invasive pneumococcal disease in the surveillance counties between 1995 and 2002, 1695 episodes (37.0 percent) occurred in persons 2 to 49 years of age. Of these, 635 episodes (37.5 percent) occurred in persons who

had been enrolled in TennCare for at least one year before the index date and who were designated as case subjects. For each case subject, 10 age-matched control subjects (for a total of 6350) were selected. The mean age of the case subjects and age-matched controls was 28.5 years (Table 1). Subjects with invasive pneumococcal disease were significantly more likely than controls to be male and black. Asthma was identified in 114 case subjects (18.0 percent) and 516 controls (8.1 percent) (Table 1). Among subjects with invasive pneumococcal disease, there was also a greater prevalence of coexisting conditions that are associated with an increased risk of pneumococcal disease.

Among controls with asthma, during the year before the index date, 8.5 percent had been hospitalized and 18.4 percent had had at least one visit to an emergency department for asthma. Use of corticosteroids as rescue therapy during the year before the index date occurred among 41.5 percent of the

control subjects, and 1.4 percent had received oral corticosteroid therapy for more than 120 days during that year. Case subjects with asthma were more likely than controls with asthma to have high-risk asthma (83.3 percent vs. 74.2 percent), to have been hospitalized for asthma within the previous year (24.6 percent vs. 8.5 percent), and to have received long-term oral corticosteroid therapy (7.9 percent vs. 1.4 percent).

After adjustment for sex, race, and high-risk coexisting conditions, asthma was significantly associated with an increase by more than a factor of two in the risk of invasive pneumococcal disease (adjusted odds ratio, 2.4; 95 percent confidence interval, 1.9 to 3.1) (Table 2). These findings were consistent in analyses stratified according to the severity of asthma, the presence or absence of high-risk coexisting conditions, and age (2 to 4 years, 5 to 17 years, and 18 to 49 years).

From 1995 through 2002, the average annual incidence of invasive pneumococcal disease among persons enrolled in TennCare who were 2 to 49 years of age was 6.1 episodes (range, 4.2 to 8.5) per 10,000 persons with asthma, as compared with 2.0 episodes (range, 1.5 to 2.2) per 10,000 persons without asthma. The annual incidence of invasive pneumococcal disease among persons with high-risk asthma was 6.9 episodes (range, 2.8 to 10.0) per 10,000 and among those with low-risk asthma was 3.9 episodes (range, 1.7 to 7.3) per 10,000 (Fig. 2). When only persons who did not have other high-risk coexisting conditions were included in the analysis, the annual incidence of the disease remained higher among those with asthma (4.2 episodes per 10,000 persons with high-risk asthma and 2.3 episodes per 10,000 persons with low-risk asthma) than among those without asthma (1.2 episodes per 10,000). Thus, the excess incidence of invasive pneumococcal disease among persons with asthma among those without coexisting conditions was one to three episodes per 10,000 persons per year.

Serotype analysis was performed on 313 (75.4 percent) of the 415 pneumococcal isolates from subjects with asthma and invasive pneumococcal disease that occurred after 1997, the year serotyping was first available through the ABCs program. Of these isolates, 178 (56.9 percent) were among the seven serotypes included in the pneumococcal conjugate vaccine and an additional 91 (29.1 percent) were serotypes found only in the 23-valent polysaccharide vaccine.

**Table 1. Baseline Characteristics of Subjects with Invasive Pneumococcal Disease and Control Subjects Enrolled in the Tennessee Medicaid Program, 1995 through 2002.\***

Characteristic	Case Subjects (N=635)	Controls (N=6350)
Age — yr	28.5±16.4	28.5±16.4
Sex — no. (%)		
Female	295 (46.5)	3916 (61.7)
Male	340 (53.5)	2434 (38.3)
Race or ethnic group — no. (%)†		
White	187 (29.4)	2585 (40.7)
Black	395 (62.2)	3427 (54.0)
Hispanic	1 (0.2)	43 (0.7)
Other	52 (8.2)	295 (4.6)
Asthma — no. (%)	114 (18.0)	516 (8.1)
High-risk coexisting conditions — no. (%)		
HIV infection	101 (15.9)	59 (0.9)
Cancer or immunosuppression	70 (11.0)	120 (1.9)
Alcohol abuse	57 (9.0)	126 (2.0)
Cardiac disease	51 (8.0)	167 (2.6)
Chronic renal or hepatic disease	51 (8.0)	52 (0.8)
Diabetes mellitus	43 (6.8)	297 (4.7)
COPD in the absence of asthma	31 (4.9)	134 (2.1)
Tobacco use	21 (3.3)	91 (1.4)
Sickle cell disease	18 (2.8)	11 (0.2)

\* Plus-minus values are means ±SD. Subjects were 2 to 49 years of age. HIV denotes human immunodeficiency virus, and COPD chronic obstructive pulmonary disease.

† Race was determined by TennCare.

**Table 2. Association between the Presence of Asthma and the Risk of Invasive Pneumococcal Disease.**

Variable	Case Subjects (N=635)	Controls (N=6350)	Adjusted Odds Ratio for Invasive Pneumococcal Disease (95% CI)*
	<i>no./total no. (%)</i>		
Any asthma	114/635 (18.0)	516/6350 (8.1)	2.4 (1.9–3.1)
High-risk asthma	95/635 (15.0)	383/6350 (6.0)	2.6 (2.0–3.5)
Low-risk asthma	19/635 (3.0)	133/6350 (2.1)	1.7 (0.99–3.0)
Coexisting conditions that confer a high risk of invasive pneumococcal disease†			
Absent	51/347 (14.7)	410/5542 (7.4)	2.4 (1.7–3.4)
Present	63/288 (21.9)	106/808 (13.1)	2.3 (1.3–4.1)
Age†			
2–4 yr	26/122 (21.3)	116/1220 (9.5)	2.3 (1.4–4.0)
5–17 yr	11/62 (17.7)	34/620 (5.5)	4.0 (1.5–10.7)
18–49 yr	77/451 (17.1)	366/4510 (8.1)	2.4 (1.8–3.3)

\* Conditional logistic regression was used to control for male sex, black race, and the presence of infection with the human immunodeficiency virus (HIV), sickle cell disease, diabetes mellitus, cardiac disease, renal disease, hepatic disease, alcohol abuse, tobacco use, cancer or immunosuppression (in the absence of HIV infection), and chronic obstructive pulmonary disease in the absence of asthma. CI denotes confidence interval.

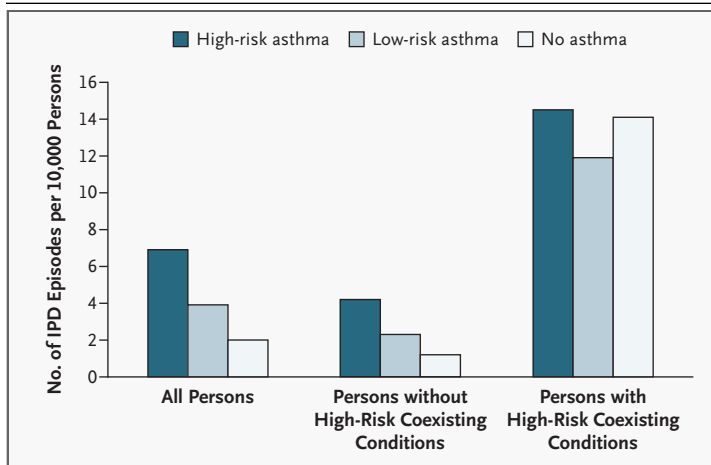
† Data are for persons with high-risk or low-risk asthma.

## DISCUSSION

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. This increased risk was present among those with and those without other coexisting conditions and among young children, adolescents, and adults. The validity of the use of the two databases to define the risk of invasive pneumococcal disease appears high, as was confirmed by the finding of well-known associations between invasive pneumococcal disease and traditional risk factors, such as infection with HIV and sickle cell disease. These data provide new insights into the role of asthma as a risk factor for invasive pneumococcal disease and firmly place asthma on the list of conditions that confer an increased risk of this disease.

In studies analyzing the causes of pneumococcal disease<sup>18</sup> or the efficacy of pneumococcal vaccines<sup>19,20</sup> and describing COPD as a risk factor for invasive pneumococcal disease, asthma usually has not been distinguished from other forms of

obstructive lung disease. Descriptions of asthma as an independent risk factor for pneumococcal disease are rare. The most recent recommendations from the CDC for vaccination against *S. pneumoniae* include chronic pulmonary disease (namely, COPD and emphysema) as a risk factor for pneumococcal disease; however, these guidelines state that “asthma has not been associated with an increased risk for pneumococcal disease, unless it occurs with chronic bronchitis, emphysema, or long-term use of systemic corticosteroids,”<sup>1</sup> and persons with asthma are explicitly excluded among those considered for vaccination.<sup>1,2</sup> Similarly, pneumococcal vaccination is not included in the most recently published guidelines for the management of asthma.<sup>3,4</sup> Few studies have delineated asthma as a potential risk factor separate from other forms of obstructive lung disease. In a case-control analysis of the risk cigarette smoking confers on the development of invasive pneumococcal disease, asthma (as distinguished from other forms of obstructive lung disease) was associated with an increase by a factor of 2.5 in the risk of the development of invasive pneumococcal disease before, but not after, adjustment for other risk factors.<sup>21</sup> Whereas in that study,



**Figure 2. Incidence of Invasive Pneumococcal Disease (IPD) among Persons 2 to 49 Years Old, According to Asthma Status and the Presence or Absence of High-Risk Coexisting Conditions.**

Coexisting conditions that were identified as conferring a high risk of invasive pneumococcal disease were infection with the human immunodeficiency virus (HIV), sickle cell disease, diabetes mellitus, cardiac disease, renal disease, hepatic disease, alcohol abuse, tobacco use, cancer or immunosuppression (in the absence of HIV infection), and chronic obstructive pulmonary disease in the absence of asthma.

patient questionnaires were used to ascertain the presence of asthma, we used previously validated criteria that incorporated diagnostic coding and the prescription of asthma-related medications — an approach that probably provided a more accurate assessment of the presence of medically treated asthma in the study population.

The increased risk of invasive pneumococcal disease among persons with asthma has biologic plausibility, because in asthma unique pathologic alterations in the airway can lead to impaired clearance of pathogenic bacteria. The respiratory epithelium and submucosal tissue of persons with asthma exhibit abnormal deposition of collagen and hyperplasia of goblet cells.<sup>22</sup> The hyperplasia leads to increased production of mucin and alterations in secreted mucus, resulting in abnormalities in viscosity and in mucociliary clearance of the airway, increased production of sputum, and airway obstruction.<sup>22</sup> The impaired clearance of airway debris can serve as a focus for localized infection that can develop into invasive bacterial infection. Furthermore, chronic inflammation of the airway among persons with asthma and those with COPD may well contribute to impaired immunity and to a predisposition to bacterial and viral infections.<sup>23-26</sup>

The incidence of invasive pneumococcal disease among persons with asthma in our study mirrored rates reported among other persons at high risk who may be considered for pneumococcal vaccination, such as persons 65 years of age or older (8.3 episodes of pneumococcal bacteremia per 10,000).<sup>27</sup> In addition, a majority (85.9 percent) of the pneumococcal serotypes associated with invasive pneumococcal disease among persons with asthma were included in the currently licensed pneumococcal vaccines, and the association between asthma and invasive pneumococcal disease was similar to that found among persons with other conditions that are targets for vaccination, such as COPD and diabetes.<sup>21,28</sup>

Consideration of vaccination is most salient for persons in the study population without other high-risk conditions for which pneumococcal vaccination is already recommended. In this population, asthma resulted in an annual excess of 1 to 3 cases of invasive pneumococcal disease per 10,000 persons. Given the young age of these subjects, they would remain at increased risk for years before becoming eligible for vaccination at 65 years of age or as a result of the development of other high-risk conditions. Thus, the cumulative excess risk over a period of 10 years may be 10 to 30 excess cases of invasive pneumococcal disease per 10,000 persons. These data suggest that pneumococcal vaccination of persons with asthma may be a worthwhile strategy to reduce the incidence of invasive pneumococcal disease in this risk group. However, further studies and more formal cost-benefit analyses are needed to change current recommendations for vaccination.

There were some limitations to our investigation. Case subjects with asthma had higher frequencies of hospitalization and the need to visit an emergency department, of high-risk asthma, and of long-term use of oral corticosteroids than did control subjects without asthma. However, the association between invasive pneumococcal disease and asthma remained after adjustment for long-term use of oral corticosteroids. In addition, ICD-9-CM coded diagnoses of tobacco use recorded in inpatient discharge files and outpatient claims are probably absent from the records for many smokers; thus, the use of diagnostic coding to determine tobacco use probably resulted in underestimation of the true prevalence of tobacco use in the study population. The TennCare database lacks other techniques to elucidate smoking status.

However, the association between asthma and invasive pneumococcal disease is unlikely to be confounded by unmeasured primary tobacco use among young children (two to five years of age), a population with minimal to no tobacco use or tobacco-related lung disease and an asthma-associated risk of invasive pneumococcal disease similar to that noted among older persons. Passive exposure to tobacco, which has also been found to increase the risk of invasive pneumococcal disease,<sup>21</sup> was not quantified in our study population. Thus, the effect of exposure to cigarette smoke on the risk of invasive pneumococcal disease cannot be ruled out by our study. Finally, the study population comprised primarily persons of low socioeconomic status enrolled in a Medicaid program and may not be generalizable to other populations. However, the incidence of invasive pneumococcal disease among persons without asthma in our study mirrored rates reported for the general population (0.3 to 1.6 episodes per 10,000 persons 2 to 49 years of age), which suggests that our findings may be applicable to a broader population.<sup>29</sup>

This investigation provided strong evidence of an association between asthma and invasive pneumococcal disease, independent of long-term use of corticosteroids and other obstructive pulmo-

nary disease, that increases among persons with high-risk asthma. This increased risk remained even among those with no other high-risk coexisting conditions. Defining this association argues for the addition of asthma to the list of conditions that increase the risk of invasive pneumococcal disease. As the incidence of asthma continues to climb in the United States,<sup>5,6</sup> the burden of invasive pneumococcal disease due to asthma is likely to increase, and discussions with regard to the feasibility and cost-effectiveness of pneumococcal vaccination among persons with asthma will need to be carefully explored.

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