Rates of Pneumococcal Disease in Adults With Chronic Medical Conditions

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**Background.** Although it is widely accepted that adults with immunocompromising conditions are at greatly increased risk of pneumococcal infection, the extent of risk among immunocompetent adults with chronic medical conditions is less certain, particularly in the current era of universal vaccination of children with pneumococcal conjugate vaccines.

**Methods.** We conducted a retrospective cohort study using data from 3 healthcare claims repositories (2006–2010) to compare rates of pneumococcal disease in immunocompetent adults with chronic medical conditions (“at-risk”) and immunocompromised adults (“high-risk”), with rates in adults without these conditions (“healthy”). Risk profiles and episodes of pneumococcal disease—all-cause pneumonia, pneumococcal pneumonia, and invasive pneumococcal disease (IPD)—were ascertained from diagnosis, procedure, and drug codes.

**Results.** Rates of all-cause pneumonia among at-risk persons aged 18–49 years, 50–64 years, and ≥65 years were 3.2 (95% confidence interval [CI], 3.1–3.2), 3.1 (95% CI, 3.1–3.1), and 3.0 (95% CI, 3.0–3.0) times the rates in age-matched healthy counterparts, respectively. We identified rheumatoid arthritis, systemic lupus erythematosus, Crohn’s disease, and neuromuscular or seizure disorders as additional at-risk conditions for pneumococcal disease. Among persons with at-risk conditions, the rate of all-cause pneumonia substantially increased with the accumulation of concurrent at-risk conditions (risk stacking): among persons 18–49 years, rate ratios increased from 2.5 (95% CI, 2.5–2.5) in those with 1 at-risk condition to 6.2 (95% CI, 6.1–6.3) in those with 2 conditions, and to 15.6 (95% CI, 15.3–16.0) in those with ≥3 conditions. Findings for pneumococcal pneumonia and IPD were similar.

**Conclusions.** Despite widespread use of pneumococcal conjugate vaccines, rates of pneumonia and IPD remain disproportionately high in adults with at-risk conditions, including those with conditions not currently included in the Advisory Committee on Immunization Practices’ guidelines for prevention and those with multiple at-risk conditions.

**Keywords.** comorbidity; pneumococcal infections; pneumonia; risk stacking; Streptococcus pneumoniae.

Streptococcus pneumoniae (pneumococcus) has long been recognized as a major cause of serious infections, especially pneumonia and meningitis. In 1983, a 23-valent polysaccharide pneumococcal vaccine (PPSV23) was licensed in the United States and subsequently recommended by the Advisory Committee on Immunization Practices (ACIP) for all persons aged ≥65 years as well as those aged ≥2 years with chronic illnesses associated with an increased risk of pneumococcal infection or complications thereof [1]. In subsequent recommendations, the ACIP divided persons with such chronic illnesses into 2 groups: immunocompetent persons and immunocompromised persons [2]. In 2010, asthma and cigarette smoking were added to the list of vaccine-eligible conditions among immunocompetent adults [3]. In 2011, the 13-valent pneumococcal conjugate vaccine (PCV13) was licensed in the United States, and the ACIP recommended in 2012 that adults aged ≥19 years...
with immunocompromising conditions, anatomic or functional asplenia, cerebrospinal fluid leaks, or cochlear implants receive PCV13 followed by PPSV23 [4]. Although it is widely accepted that adults with immunocompromising medical conditions are at greatly increased risk for pneumococcal infection, the magnitude of risk among immunocompetent adults with some of the chronic illnesses identified by the ACIP is less certain, because current estimates are based primarily on small case series or community surveys. Moreover, in the current era of universal vaccination of children with pneumococcal conjugate vaccines—with consequent disease reduction in the adult population via herd (indirect) effects—it is unclear whether the increased risks for pneumococcal infections associated with certain chronic medical conditions have persisted [5, 6].

Therefore, we analyzed recent data from 3 large healthcare claims repositories in the United States to examine rates of all-cause pneumonia, pneumococcal pneumonia, and invasive pneumococcal disease (IPD) among adults with and without 1 or more of the chronic illnesses currently listed in the ACIP guidelines as indications for pneumococcal vaccination. In addition, we examined disease rates among adults with several other conditions that might increase infection risk based on limited data from other studies, including 3 autoimmune diseases—rheumatoid arthritis, systemic lupus erythematosus (SLE), and Crohn’s disease—and neuromuscular (chiefly cerebral palsy) and seizure disorders [7–9]. Finally, we examined the impact of risk stacking among the at-risk population, by estimating disease rates within subgroups defined on the basis of the number of concurrent conditions.

**METHODS**

**Study Design**

A retrospective cohort design was used. Study cohorts were identified at the beginning of each calendar year of observation—from 2007 to 2010—and study subjects were characterized in terms of the presence of underlying medical conditions (ie, risk profile) based on information recorded at any time before January 1st of that calendar year. For each cohort, episodes of disease (ie, all-cause pneumonia, pneumococcal pneumonia, and IPD) were ascertained during the 1-year period beginning on January 1st of each corresponding year and ending on December 31st of that year (or the date of loss to follow-up, if earlier). Subjects who met criteria for inclusion in multiple calendar years contributed data to each cohort for which they were eligible.

**Data Source**

Data spanning January 1, 2006 through December 31, 2010 from 3 large integrated healthcare claims repositories were pooled for analyses. The 3 repositories—(1) Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases; (2) IMS LifeLink PharMetrics Health Plan Claims Database; and (3) Optum Research Database—include medical (ie, facility and professional-service) claims and outpatient pharmacy claims from private US health plans. Together, these 3 geographically diverse repositories capture healthcare claims information for >35 million plan members annually.

Data available from each facility and professional-service claim included dates and places of service, diagnoses (ICD-9-CM), procedures performed and services rendered (ICD-9-CM, HCPCS), and quantity of services (professional-service claims). Data available for each outpatient pharmacy claim included the drug dispensed, dispensing date, quantity dispensed, and number of days supplied. Selected demographic and eligibility information (including age and year of birth, sex, geographic region of residence, dates of plan eligibility) also were available.

Patient-identifying information was encrypted or removed from the study databases before their release to study investigators. Use of these study databases for health-services research is therefore fully compliant with the HIPAA Privacy Rule and federal guidance on Public Welfare and the Protection of Human Subjects (Public Welfare—Protection of Human Subjects; 45CFR 46 §46.101).

**Study Population**

The study population comprised adults aged ≥18 years who were enrolled in participating health plans on the first day of 1 or more calendar year(s) from 2007 to 2010. Study subjects were stratified based on their age (18–49, 50–64, and ≥65 years) and risk profile (“at-risk”, “high-risk”, and “healthy”) as of the beginning of each year.

Risk profiles were defined by the presence of medical conditions for which the ACIP currently recommends pneumococcal vaccination in adults [4], or other medical conditions that we hypothesized may increase the risk of pneumococcal disease despite not currently being recognized by the ACIP. Immunocompetent persons with ≥1 chronic medical condition identified by the ACIP, or with neuromuscular or seizure disorders, autoimmune diseases (rheumatoid arthritis, SLE, and Crohn’s disease), or chronic use of steroids (defined as receipt of ≥30 days of oral corticosteroid therapy during the past year) were classified as at-risk. Immunocompromised or immunosuppressed persons and those with a cochlear implant were classified as high-risk. At-risk and high-risk were mutually exclusive categories, and thus, for example, persons considered immunosuppressed due to cancer treatment were included in the high-risk category only, even if they also had an at-risk condition. Persons without evidence of at-risk or high-risk conditions were classified as healthy.

At-risk and high-risk medical conditions were ascertained using ICD-9-CM diagnosis codes, ICD-9-CM/HCPCS...
procedure codes, and HCPCS/NDC drug codes recorded any
time before the beginning of the corresponding study year.
Operational algorithms that were used to identify at-risk and
high-risk conditions are available in Tables S1 and S2 (online
supplement). Persons who were not continuously eligible for
comprehensive health (ie, medical and drug) benefits for at
least 1 year before January 1st of ≥1 corresponding year were
excluded from the study population.

Study Measures
Episodes of nonbacteremic all-cause pneumonia, nonbactere-
ic pneumococcal pneumonia, and IPD that occurred from
January 1st through December 31st of each study year were
identified using operational algorithms based on ICD-9-CM di-
agnosis codes and HCPCS/NDC drug codes (Table S3, online
supplement). All-cause pneumonia was included as a study
measure because S pneumoniae infection is the most common
cause of bacterial pneumonia, and pathogen-specific diagnostic
codes for pneumonia seldom appear in healthcare claims data.
Multiple episodes of pneumococcal disease that occurred dur-
ing a single study year were included as independent events if
they were separated by ≥90 days.

Statistical Analyses
Rates of pneumococcal disease episodes were estimated within
each age group by risk profile as well as individual medical con-
dition, and they were expressed per 100 000 person-years. Rate
ratios for disease episodes among persons with at-risk and high-
risk conditions, respectively—overall and by individual medical
condition—versus their age-matched healthy counterparts were
estimated using Poisson regression (SAS version 9.3). Rates of
disease and corresponding rate ratios (vs healthy counterparts)
were also calculated for at-risk persons by the number of at-risk
conditions.

RESULTS
Characteristics of the Study Population
Persons aged 18–49 years, 50–64 years, and ≥65 years contrib-
uted a total of 49.3 million, 30.6 million, and 11.7 million per-
son-years of observation, respectively. Approximately 86% of
adults aged 18–49 years had none of the selected chronic or im-
munocompromising conditions, whereas approximately 12%
had ≥1 at-risk condition (and no high-risk conditions), and
approximately 2% had a high-risk condition. The prevalence of
at-risk and high-risk conditions increased with increasing age:
approximately 25% and 6% of adults aged 50 to 64 years, and
39% and 15% of adults aged ≥65 years, had at-risk and high-
risk conditions, respectively.

Among adults aged 18–49 years, 10.0% had 1 at-risk condi-
tion, 1.2% had 2, and 0.2% had 3 or more; the most common
chronic conditions were diabetes (34% of those with ≥1 at-
risk condition), asthma (23%), and smoking (20%). In adults
50–64 years of age, 19.6% had 1 at-risk condition, 4.4% had
2, and 1.2% had 3 or more; the most common conditions
were diabetes (49%), chronic heart disease (30%), and smoking
(13%). In adults ≥65 years of age, 26.4% had 1 at-risk condition,
9.5% had 2, and 3.1% had 3 or more; the most common condi-
tions were chronic heart disease (52%), diabetes (50%), and
chronic lung disease (20%). In all 3 age groups, the most com-
mon high-risk condition was the presence of diseases associated
with immunosuppression or receipt of immunosuppressive
drugs.

Rates of Disease
The rates of all-cause pneumonia (cases per 100 000 person-
years) in the study population increased with age and risk pro-
file (Table 1). In healthy adults, the rate increased from 363 in
persons aged 18–49 years to 1874 in those aged ≥65 years. Cor-
responding rates in at-risk adults were 1147 and 5662, and in
high-risk adults corresponding rates were 2204 and 7594. Rates of pneumococcal pneumonia and IPD similarly increased
with age and risk profile (Table 2).

The rates of all-cause pneumonia were consistently higher in
at-risk and high-risk persons compared with healthy persons in
all age groups. In persons aged 18–49 years, 50–64 years, and
≥65 years with at least 1 at-risk condition, the rate of all-
cause pneumonia was 3.2 (95% confidence interval [CI], 3.1–
3.2), 3.1 (95% CI, 3.1–3.1), and 3.0 (95% CI, 3.0–3.0) times
the rate in healthy persons, respectively. In high-risk persons
in these age groups, the rate of all-cause pneumonia was 6.1
(95% CI, 6.0–6.2), 5.5 (95% CI, 5.5–5.6), and 4.1 (95% CI,
4.0–4.1) times the rate in healthy persons. Rate ratios for pneu-
 mococcal pneumonia and IPD were generally similar (Tables 1
and 2).

Notably, the rates of all-cause pneumonia among persons
with autoimmune diseases (rheumatoid arthritis, SLE, or
Crohn’s disease) were substantially greater than the rates in
healthy persons (Figure 1). Rate ratios in the 3 age groups
were 4.1 (95% CI, 4.0–4.3), 4.0 (95% CI, 3.9–4.0), and 3.5
(95% CI, 3.4–3.5), respectively. Corresponding rate ratios for
persons with neuromuscular or seizure disorders were 4.6
(4.5–4.8), 4.8 (4.7–5.0), and 4.6 (4.5–4.7).

Absolute rates of all-cause pneumonia in persons with at-risk
conditions substantially increased with the number of concur-
rent conditions, and they were progressively higher across in-
creasing age groups (Figure 2). Rates in persons with 2 at-risk
conditions were generally similar to rates in persons with high-
risk conditions, and rates in persons with ≥3 at-risk conditions
were substantially higher than rates in persons with high-risk
conditions. Because baseline disease rates were lowest among
adults aged 18–49 years, the increase in rate ratios with an in-
creasing number of at-risk conditions was most pronounced for
this age group: for all-cause pneumonia, rate ratios increased

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Table 1. Rates of All-Cause Pneumonia Among Healthy, At-Risk, and High-Risk Adults

| Risk Group                        | No. of Person-Years | All-Cause Pneumonia |
|-----------------------------------|---------------------|---------------------|
|                                   | Age 18–49 Years     | Age 50–64 Years     | Age ≥65 Years |
| Healthy                           | 42 472 513          | 20 972 935          | 5 389 930    | 363 | 3.2 (3.1–3.2) | 651 | 3.1 (3.1–3.1) | 1874 | -- |
| At-risk                           | 5 672 688           | 7 696 247           | 4 579 505    | 1147| 3.0 (2.9–3.1) | 2024| 3.1 (3.1–3.1) | 5662| 3.0 (3.0–3.0) |
| Alcoholism                        | 198 416             | 135 218             | 23 905       | 1313| 3.6 (3.5–3.8) | 3278| 5.0 (4.9–5.2) | 7400| 3.9 (3.8–4.1) |
| Asthma                            | 1 277 390           | 908 130             | 362 183      | 1389| 3.8 (3.8–3.9) | 3046| 4.7 (4.6–4.7) | 8570| 4.6 (4.5–4.6) |
| Chronic heart disease             | 769 514             | 2 314 484           | 2 363 798    | 1793| 4.9 (4.9–5.0) | 2779| 4.3 (4.2–4.3) | 7100| 3.8 (3.8–3.8) |
| Chronic liver disease             | 117 513             | 175 184             | 50 540       | 2042| 5.6 (5.4–5.9) | 3646| 5.6 (5.5–5.8) | 7742| 4.1 (4.0–4.3) |
| Chronic lung disease              | 406 388             | 844 755             | 882 061      | 3105| 8.6 (8.4–8.7) | 5618| 8.6 (8.5–8.7) | 12 379| 6.6 (6.6–6.7) |
| Chronic use of oral steroids      | 145 067             | 130 200             | 65 775       | 873 | 2.4 (2.3–2.5) | 1488| 2.3 (2.2–2.4) | 3696| 2.0 (1.9–2.1) |
| Diabetes                          | 1 913 653           | 3 807 505           | 2 267 133    | 1134| 3.1 (3.1–3.2) | 1959| 3.0 (3.0–3.0) | 5266| 2.8 (2.8–2.8) |
| Neuromuscular/seizure disorders   | 307 529             | 199 605             | 104 864      | 1677| 4.6 (4.5–4.8) | 3144| 4.8 (4.7–5.0) | 8539| 4.6 (4.5–4.7) |
| Rheumatoid arthritis/Crohn’s/lupus| 238 225             | 341 148             | 162 206      | 1491| 4.1 (4.0–4.3) | 2578| 4.0 (3.9–4.0) | 6465| 3.5 (3.4–3.5) |
| Smokers                           | 1 118 296           | 1 010 649           | 180 504      | 1188| 3.3 (3.2–3.3) | 2599| 4.0 (3.9–4.0) | 6691| 3.6 (3.5–3.6) |
| High-risk                         | 1 111 272           | 1 961 128           | 1 774 181    | 2204| 6.1 (6.0–6.2) | 3601| 5.5 (5.5–5.6) | 7594| 4.1 (4.0–4.1) |
| Chronic renal failure             | 122 921             | 233 166             | 344 160      | 4033| 11.1 (10.8–11.4) | 6375| 9.8 (9.6–10.0) | 11 873| 6.3 (6.3–6.4) |
| Cochlear implant                  | 1211                | 1306                | 1144         | 1404| 3.9 (2.4–2.6) | 1990| 3.1 (2.1–4.5) | 4544| 2.4 (1.8–3.2) |
| Congenital immunodeficiency       | 37 780              | 38 991              | 14 392       | 4312| 11.9 (11.3–12.5) | 7476| 11.5 (11.1–11.9) | 14 738| 7.9 (7.5–8.2) |
| Diseases of white blood cells     | 55 679              | 94 123              | 46 869       | 5092| 14.0 (14.1–14.6) | 7806| 12.0 (11.7–12.3) | 13 262| 7.1 (6.9–7.3) |
| Functional/anatomic asplenia      | 53 484              | 55 834              | 42 976       | 6616| 18.2 (17.7–18.9) | 10 737| 16.5 (16.1–16.9) | 15 976| 8.5 (8.3–8.7) |
| HIV                               | 109 093             | 84 091              | 7306         | 2080| 5.7 (5.5–6.0) | 2947| 4.5 (4.4–4.7) | 6461| 3.4 (3.2–3.8) |
| Immunosuppressive drugs/conditions| 840 806             | 1 654 970           | 1 523 021    | 2188| 6.0 (5.9–0.00) | 3633| 5.6 (5.5–5.6) | 7248| 3.9 (3.8–3.9) |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.
* Relative to healthy counterparts.
Table 2. Rates of Pneumococcal Pneumonia and Invasive Pneumococcal Disease Among Healthy, At-Risk, and High-Risk Adults

| Risk Group                  | No. of Person-Years | Pneumococcal Pneumonia | Invasive Pneumococcal Disease |
|-----------------------------|---------------------|-------------------------|------------------------------|
|                             | Age 18–49 Years     | Age 50–64 Years         | Age ≥65 Years                | Age 18–49 Years | Age 50–64 Years | Age ≥65 Years |
|                             | Rate per 100K        | Rate Ratios* (95% CI)   | Rate per 100K                | Rate Ratios* (95% CI) | Rate Ratios* (95% CI) | Rate Ratios* (95% CI) |
| Healthy                     | 42 472 513          | 20 972 935              | 5 389 930                    | 100K           | 100K           | 100K           |
| Alcoholism                  | 198 416             | 135 218                 | 23 905                       | 100K           | 100K           | 100K           |
| Asthma                      | 1 277 380           | 908 130                 | 362 183                      | 100K           | 100K           | 100K           |
| Chronic heart disease       | 768 514             | 2 314 484               | 2 363 796                    | 100K           | 100K           | 100K           |
| Chronic liver disease       | 117 513             | 175 184                 | 50 540                       | 100K           | 100K           | 100K           |
| Chronic lung disease        | 406 388             | 844 755                 | 882 061                      | 100K           | 100K           | 100K           |
| Chronic use of oral steroids| 145 067             | 130 200                 | 65 775                       | 100K           | 100K           | 100K           |
| Diabetes                    | 1 913 653           | 3 807 505               | 2 267 133                    | 100K           | 100K           | 100K           |
| Neuromuscular/seizure disorders | 307 529            | 199 605                 | 104 864                      | 100K           | 100K           | 100K           |
| Rheumatoid arthritis/Crohn's/scleritis | 238 225          | 341 148                 | 162 206                      | 100K           | 100K           | 100K           |
| Smokers                     | 1 118 296           | 1 010 649               | 180 504                      | 100K           | 100K           | 100K           |
| High-risk                   | 1 111 272           | 1 961 128               | 1 774 181                    | 100K           | 100K           | 100K           |
| Chronic renal failure       | 122 921             | 233 166                 | 344 160                      | 100K           | 100K           | 100K           |
| Coeliac implant             | 121 1306            | 1306 1144               | 165 111                      | 100K           | 100K           | 100K           |
| Congenital immunodeficiency | 37 780              | 38 991                  | 14 392                       | 100K           | 100K           | 100K           |
| Diseases of white blood cells | 55 679             | 94 123                  | 46 869                       | 100K           | 100K           | 100K           |
| Functional/anatomic asplenia| 53 464              | 55 834                  | 42 976                       | 100K           | 100K           | 100K           |
| HIV                         | 109 093             | 84 091                  | 7306                         | 100K           | 100K           | 100K           |
| Immunosuppressive drugs/conditions | 840 806           | 1 654 970               | 1 523 021                    | 100K           | 100K           | 100K           |

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus. * Relative to healthy counterparts.
from 2.5 (95% CI, 2.5−2.5) in those with 1 at-risk condition to 6.2 (95% CI, 6.1–6.3) in those with 2 conditions, and 15.6 (95% CI, 15.3–16.0) in those with ≥3 conditions. Results for pneumococcal pneumonia and IPD were similar.

**DISCUSSION**

Our findings, based on 3 large and geographically diverse US populations, indicate that the increased risks of pneumococcal disease associated with established risk factors have persisted in the era of widespread vaccination of children with pneumococcal conjugate vaccines. In our study, 18–49-year-olds with at-risk conditions accounted for 12% of the population but 27% of all-cause pneumonia cases; 50–64-year-olds with at-risk conditions accounted for 25% of the population but 43% of all-cause pneumonia cases; and individuals aged ≥65 years with at-risk conditions accounted for 39% of the population but 52% of all-cause pneumonia cases. Two recent large studies from the United Kingdom and United States found similar persistence of increased risk of IPD in adults with selected medical conditions, although with different relative risks in some instances [10, 11].

We observed substantially increased rates of pneumococcal disease among persons with >1 at-risk condition, and disease rates were especially high among those with ≥3 at-risk conditions—for younger adults, an all-cause pneumonia rate 15.6 times that of healthy persons. This phenomenon of “risk stacking”—whereby risk of disease increases with increasing numbers of risk factors—has been noted for other diseases, for example, osteoporotic hip fractures and cardiovascular events [12, 13]. Although only a small percentage of our study population had >1 concurrent at-risk condition, especially among the youngest age group, recent evidence from the Centers for Disease Control and Prevention (CDC) has shown that...
the percentage of older US adults (≥45 years) with 2 or more of 9 selected chronic conditions (most of which are risk factors for pneumococcal disease) increased by 5% in those aged 45–64 and by 7% in those aged ≥65 years between 1999 and 2000 and 2009 and 2010 [14]. This increase was seen in men and women and across all race and ethnicity groups examined. If this trend continues into the future, risk stacking is likely to account for an increasing proportion of cases of pneumococcal disease.

Two patterns in our results merit explanation. First, rate ratios for the 3 outcomes considered—all-cause pneumonia, pneumococcal pneumonia, and IPD—were similar. This finding is not surprising and is likely explained by 2 factors. The predominant manifestation of IPD is bacteremic pneumonia—70.4% of all cases in the United States in 2009—and the pneumococcus is the most common bacterial pathogen in all-cause pneumonia [15]. Thus, to a considerable extent, these 3 outcomes represent the same clinical entity of pneumonia caused by pneumococcal infection. Moreover, conditions that predispose to pneumonia caused by pneumococcus are probably not specific to that pathogen. For example, chronic lung disease likely increases the risk of pneumonia caused by a variety of pathogens. The second pattern we observed was that rate ratios were smaller in older persons. This important observation likely reflects a smaller contrast in disease risk between “healthy” older adults and “unhealthy” older adults due to waning immunocompetence that occurs with advancing age.

An additional finding in our study was substantially increased risks of pneumococcal disease associated with 3 relatively common autoimmune diseases (rheumatoid arthritis, SLE, and Crohn’s disease) and with neuromuscular and seizure disorders. Other investigators have also described increased risks for pneumococcal disease in persons with autoimmune disorders. A large retrospective study from the United Kingdom demonstrated that patients who were admitted to the hospital or received hospital-based care for a variety of immune-mediated
diseases, including the 3 of interest in our study, had an elevated risk for IPD [7]. In another recent large study from the United Kingdom, investigators used a case-control design (17 000 cases) to examine the risk of all-cause pneumonia associated with a variety of conditions that are not well established risk factors for pneumonia [8]. The adjusted odds ratio for the association between rheumatoid arthritis and IPD was 2.2 (95% CI, 1.7–2.8). We could not determine the extent to which our observed increased rates of disease among persons with rheumatoid arthritis, SLE, and Crohn’s disease was attributable to the disease itself versus the receipt of immunosuppressive medications used to treat these diseases due to the inability to separate out the effects of treatment versus disease severity—which could be the reason for treatment —using claims data.

We chose to examine the risk of pneumococcal disease associated with neuromuscular and seizure disorders because epilepsy has previously been identified as a risk factor for pneumonia [16, 17], and because in prior work, in which we studied the risks of pneumococcal disease in children, these disorders were found to be significant risk factors. We initially examined neuromuscular and seizure disorders in our study of children on the basis of a finding that one-third of children who died from influenza in the United States during 2003–2004 had such conditions [9]. Bhat et al [9] hypothesized that neuromuscular and seizure disorders may somehow compromise respiratory function in such a way that increases the risk of aspiration, subsequently increasing the risk of influenza complications such as pneumonia.

Our study has several limitations. First, use of operational algorithms and healthcare claims data undoubtedly resulted in misclassification of risk profiles, including both errors of omission and commission. Although it was not possible to formally evaluate the accuracy of these algorithms within the context of this study, we did evaluate the sensitivity of our study results by using alternative approaches to characterizing individual medical conditions and risk profiles, and found our findings largely unchanged. Second, the incidence of pneumococcal pneumonia and IPD in our population is lower than national estimates from the CDC [18]. However, IPD incidence in our study population followed the same general age distribution as has been reported by the CDC, and imperfect sensitivity of case ascertainment that is proportional across age groups should not impact rate ratios. Third, persons with public or no health insurance are not represented in the study databases, potentially limiting the generalizability of study results to other populations. In addition, our estimates of the percentage of the US population with 1 or more chronic medical conditions will be underestimated to the extent that the under- or uninsured population includes a larger percentage of such persons. Fourth, data used in this analysis did not permit us to identify pneumococcal serotypes causing disease in adults with at-risk or high-risk conditions. It would be of interest to know the proportion of cases among persons in various risk groups due to individual serotypes and according to whether or not they are included in the PCV7, PCV13, PP23, or no currently available pneumococcal vaccines. Finally, lack of reliable data precluded us from including information on pneumococcal vaccination status in our analyses.

These data support the observation that despite the widespread use of pneumococcal conjugate vaccines in infants and an overall decline in rates of pneumonia and IPD in children and adults, disease rates remain disproportionately high in adults with at-risk and high-risk conditions [5, 11, 19, 20]. In addition, we have identified a group of adults who are at increased risk for pneumococcal disease due to having medical conditions not currently included within the ACIP recommendations for prevention—including rheumatoid arthritis, SLE, Crohn’s disease, and neuromuscular and seizure disorders—as well as a small group of adults with ≥3 at-risk conditions whose risk of pneumococcal disease is as high as or higher than those associated with the presence of selected high-risk conditions. In combination with work done by others, our findings suggest that it may be worthwhile to consider expansion of the lists of at-risk and high-risk conditions for which adult pneumococcal vaccination is recommended.

Supplementary Data
Supplementary material is available online at Open Forum Infectious Diseases ([http://OpenForumInfectiousDiseases.oxfordjournals.org/](http://OpenForumInfectiousDiseases.oxfordjournals.org/)).

Notes

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References

1. Centers for Disease Control and Prevention (CDC). Update: pneumococcal polysaccharide vaccine usage—United States. MMWR Morb Mortal Wkly Rep 1984; 33:273–6.
2. Centers for Disease Control and Prevention (CDC). Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 1997; 46:1–24.
3. Centers for Disease Control and Prevention (CDC). Updated recommendations for prevention of invasive pneumococcal disease among adults using the 23-valent pneumococcal polysaccharide vaccine (PPSV23). MMWR Morb Mortal Wkly Rep 2010; 59:1102–6.
4. Centers for Disease Control and Prevention (CDC). Use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine for adults with immunocompromising conditions: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2012; 61:816–9.
5. Griffin MR, Zhu Y, Moore MR, et al. US hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med 2013; 369:155–63.
6. Pillishvilli T, Lexau C, Farley MM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. J Infect Dis 2010; 201:32–41.
7. Wotton CJ, Goldacre MJ. Risk of invasive pneumococcal disease in people admitted to hospital with selected immune-mediated diseases: record linkage cohort analyses. J Epidemiol Community Health 2012; 66:1177–81.
8. Vinogradova Y, Hippisley-Cox J, Coupland C. Identification of new risk factors for pneumonia: population-based case-control study. Br J Gen Pract 2009; 59:e329–38.
9. Bhat N, Wright JG, Broder KR, et al. Influenza-associated deaths among children in the United States, 2003–2004. N Engl J Med 2005; 353:2559–67.
10. van Hoek AJ, Andrews N, Waight P, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Infect 2012; 65:17–24.
11. Muhammad RD, Oza-Frank R, Elizabeth Z, et al. Epidemiology of invasive pneumococcal disease among high-risk adults since the introduction of pneumococcal conjugate vaccine for children. Clin Infect Dis 2013; 56:e59–67.
12. Cummings S, Nevitt M, Browner W, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med 1995; 332:767–73.
13. Acharjee S, Qin J, Murphy SA, et al. Distribution of traditional and novel risk factors and their relation to subsequent cardiovascular events in patients with acute coronary syndromes (from the PROVE IT-TIMI 22 trial). Am J Cardiol 2010; 105:619–23.
14. Freid VM, Bernstein AB, Bush MA. Multiple chronic conditions among adults aged 45 and over: Trends over the past 10 years. NCHS data brief, no 100. Hyattsville, MD: National Center for Health Statistics. 2012.
15. Said MA, Johnson HL, Nonyane BAS, et al. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. PLoS One. 2013; 84: e60273.
16. Schlienger RG, Fedson DS, Jick SS, et al. Statins and the risk of pneumonia: a population-based, nested case-control study. Pharmacotherapy 2007; 27:325–32.
17. Almirall J, Bolibar I, Serra-Prat M, et al. New evidence of risk factors for community-acquired pneumonia: a population-based study. Eur Respir J 2008; 31:1274–84.
18. Centers for Disease Control and Prevention. Active Bacterial Core Surveillance report, Emerging Infections Program Network, Streptococcus pneumoniae, 2012. Available at: http://www.cdc.gov/abcs/reports-findings/survreports/spneu12.html. Accessed 4 July 2013.
19. Grijalva CG, Griffin MR. Population-based impact of routine infant immunization with pneumococcal conjugate vaccine in the USA. Expert Rev Vaccines 2008; 7:83–95.
20. Yildirim I, Stevenson A, Hsu K, et al. Evolving picture of invasive pneumococcal disease in Massachusetts children: a comparison of disease in 2007–2009 with earlier periods. Pediatr Infect Dis J 2012; 31:1016–1021.