MAJOR ARTICLE

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 pneumonia*.

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

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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, nonbacteremic 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 diagnosis 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 during 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 condition, 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 contributed a total of 49.3 million, 30.6 million, and 11.7 million person-years of observation, respectively. Approximately 86% of adults aged 18–49 years had none of the selected chronic or immunocompromising 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 condition, 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 conditions were chronic heart disease (52%), diabetes (50%), and chronic lung disease (20%). In all 3 age groups, the most common 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 profile (Table 1). In healthy adults, the rate increased from 363 in persons aged 18–49 years to 1874 in those aged ≥65 years. Corresponding 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 pneumococcal 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 concurrent conditions, and they were progressively higher across increasing 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 increasing number of at-risk conditions was most pronounced for this age group: for all-cause pneumonia, rate ratios increased

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

	No. of Person-Years			All-Cause Pneumonia					
				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 per 100K	Rate Ratios* (95% CI)
Risk Group									
Healthy	42 472 513	20 972 935	5 389 930	363	–	651	–	1874	–
At-risk	5 672 688	7 696 247	4 579 505	1147	3.2 (3.1–3.2)	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	1 277 380	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	768 514	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 (5.5–5.7)	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	1 951 128	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 (2.4–6.2)	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	53 464	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

				Pneumococcal Pneumonia						Invasive Pneumococcal Disease					
	No. of Person-Years			Age 18–49 Years		Age 50–64 Years		Age ≥65 Years		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 per 100K	Rate Ratios* (95% CI)	Rate per 100K	Rate Ratios* (95% CI)	Rate per 100K	Rate Ratios* (95% CI)	Rate per 100K	Rate Ratios* (95% CI)
Risk Group															
Healthy	42 472 513	20 972 935	5 389 930	14	–	25	–	67	–	1.8	–	4.5	–	8.3	–
At-risk	5 672 688	7 696 247	4 579 505	44	3.1 (3.0–3.3)	80	3.2 (3.0–3.3)	210	3.1 (3.0–3.2)	5.6	3.0 (2.7–3.5)	12	2.7 (2.5–2.9)	23	2.8 (2.5–3.1)
Alcoholism	198 416	135 218	23 905	51	3.6 (3.0–4.4)	116	4.6 (3.9–5.4)	305	4.5 (3.6–5.7)	14.1	7.7 (5.3–11.2)	29.6	6.6 (4.8–9.1)	41.8	5.0 (2.7–9.4)
Asthma	1 277 380	908 130	362 183	52	3.7 (3.4–4.0)	124	4.9 (4.6–5.2)	398	5.9 (5.6–6.3)	4.5	2.5 (1.9–3.2)	16.7	3.8 (3.2–4.5)	34.2	4.1 (3.4–5.0)
Chronic heart disease	768 514	2 314 484	2 363 798	72	5.1 (4.6–5.5)	106	4.2 (4.0–4.4)	254	3.8 (3.6–3.9)	7.2	3.9 (3.0–5.1)	13	2.9 (2.6–3.3)	26.6	3.2 (2.8–3.6)
Chronic liver disease	117 513	175 184	50 540	90	6.4 (5.3–7.7)	148	5.8 (5.2–6.6)	287	4.3 (3.6–5.0)	18.7	10.2 (6.7–15.6)	28.5	6.4 (4.8–8.5)	53.4	6.4 (4.4–9.5)
Chronic lung disease	406 388	844 755	882 061	126	8.9 (8.1–9.7)	248	9.8 (9.3–10.3)	516	7.7 (7.3–8.0)	11.6	6.3 (4.7–8.5)	34.4	7.7 (6.8–8.8)	51.1	6.2 (5.4–7.0)
Chronic use of oral steroids	145 067	130 200	65 775	39	2.7 (2.1–3.5)	61	2.4 (1.9–3.0)	128	1.9 (1.5–2.4)	6.2	3.4 (1.8–6.5)	10	2.2 (1.3–3.9)	15.2	1.8 (1.0–3.4)
Diabetes	1 913 653	3 807 505	2 267 133	44	3.1 (2.9–3.3)	76	3.0 (2.8–3.1)	187	2.8 (2.7–2.9)	5.5	3.0 (2.4–3.7)	11.6	2.6 (2.3–2.9)	21.1	2.5 (2.2–2.9)
Neuromuscular/seizure disorders	307 529	199 605	104 864	81	5.7 (5.0–6.5)	136	5.3 (4.7–6.0)	330	4.9 (4.4–5.5)	7.2	3.9 (2.5–6.0)	21.5	4.8 (3.6–6.6)	38.1	4.6 (3.3–6.3)
Rheumatoid arthritis/ Crohn's/lupus	238 225	341 148	162 206	63	4.4 (3.8–5.2)	108	4.3 (3.8–4.7)	266	4.0 (3.6–4.4)	13	7.1 (4.9–10.1)	21.1	4.7 (3.7–6.0)	33.3	4.0 (3.0–5.3)
Smokers	1 118 296	1 010 649	180 504	42	3.0 (2.7–3.3)	111	4.4 (4.1–4.6)	264	3.9 (3.6–4.3)	6.5	3.6 (2.8–4.5)	19.2	4.3 (3.7–5.0)	34.9	4.2 (3.2–5.5)
High-risk	1 111 272	1 951 128	1 774 181	103	7.3 (6.8–7.7)	149	5.9 (5.6–6.1)	290	4.3 (4.1–4.5)	18.5	10.1 (8.7–11.8)	30.8	6.9 (6.2–7.6)	36.7	4.4 (3.9–5.0)
Chronic renal failure	122 921	233 166	344 160	197	13.9 (12.2–15.8)	285	4.2 (4.0–4.4)	438	6.5 (6.1–6.9)	26.8	14.6 (10.3–20.7)	57.9	13.0 (10.8–15.6)	50	6.0 (5.0–7.2)
Cochlear implant	1211	1306	1144	165	11.7 (2.9–46.6)	0	–	262	3.9 (1.3–12.1)	0	–	0	–	87.4	10.5 (1.5–74.8)
Congenital immunodeficiency	37 780	38 991	14 392	265	18.7 (15.3–22.8)	418	16.4 (14.1–19.2)	632	9.4 (7.6–11.6)	68.8	37.5 (25.4–55.4)	105.2	2.2 (1.5–3.4)	118.1	14.2 (8.8–23.1)
Diseases of white blood cells	55 679	94 123	46 869	237	16.7 (14.1–19.9)	339	13.3 (11.9–14.9)	565	8.4 (7.4–9.5)	52.1	28.4 (19.6–41.1)	68	15.3 (11.8–19.6)	110.9	13.3 (10.0–17.8)
Functional/anatomic asplenia	53 464	55 834	42 976	346	24.4 (21.1–28.3)	464	18.3 (16.1–20.7)	710	10.5 (9.4–11.9)	59.9	32.6 (22.9–46.4)	125.4	28.1 (22.1–35.9)	116.3	14.0 (10.5–18.7)
HIV	109 093	84 091	7306	138	9.8 (8.3–11.5)	165	6.5 (5.5–7.7)	329	4.9 (3.3–7.3)	40.3	22.0 (16.2–29.8)	54.7	12.3 (9.1–16.5)	27.4	3.3 (0.8–13.2)
Immunosuppressive drugs/conditions	840 806	1 654 970	1 523 021	100	7.1 (6.6–7.6)	148	5.8 (5.5–6.1)	278	4.1 (4.0–4.3)	15.5	8.4 (7.0–10.1)	28.9	6.5 (5.8–7.2)	36.4	4.4 (3.9–5.0)

Abbreviations: CI, confidence interval; HIV,human immunodeficiency virus.

* Relative to healthy counterparts.

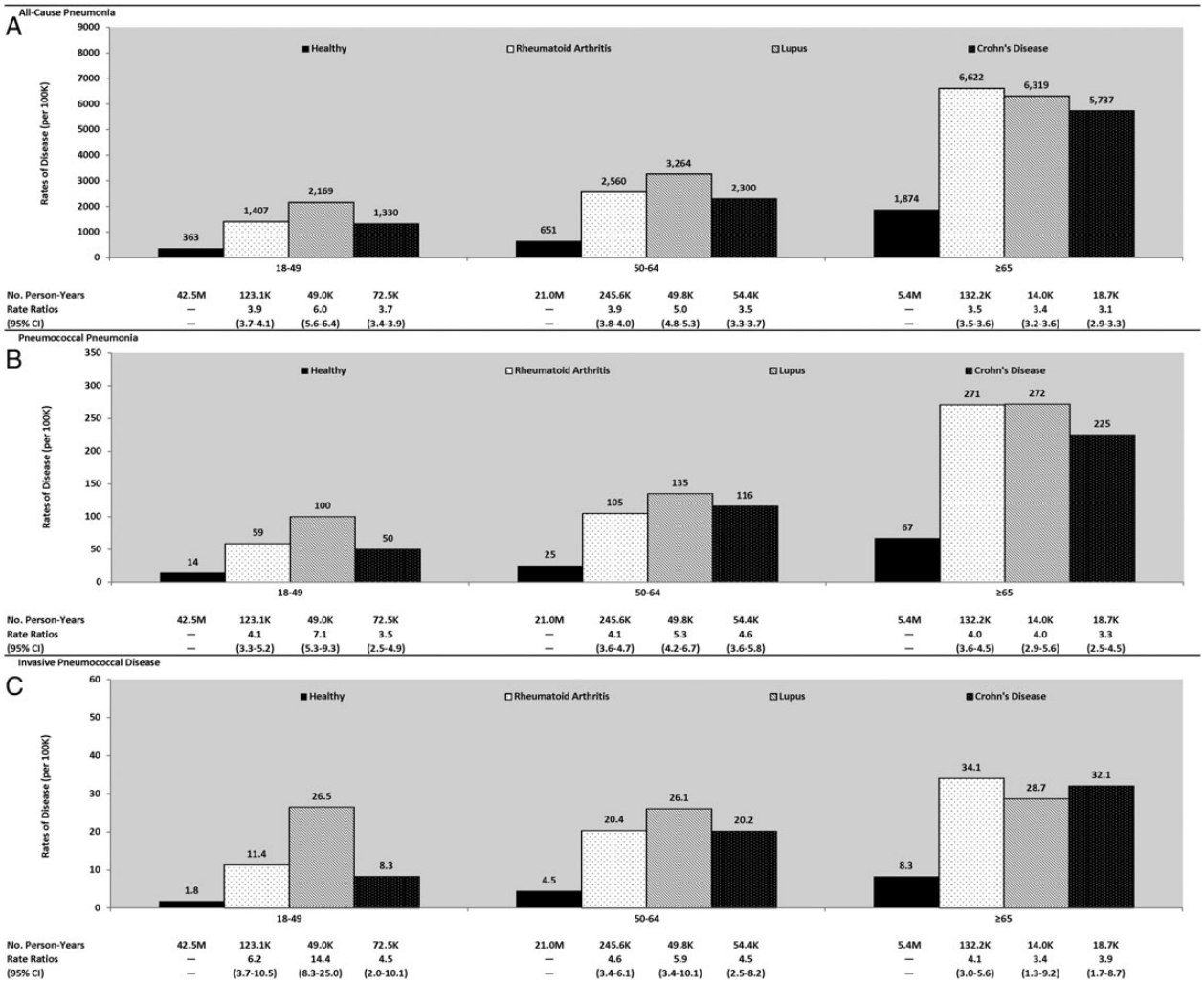

Figure 1. Rates of all-cause pneumonia, pneumococcal pneumonia, and invasive pneumococcal disease among adults with rheumatoid arthritis, lupus, or Crohn's disease versus their healthy counterparts.

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

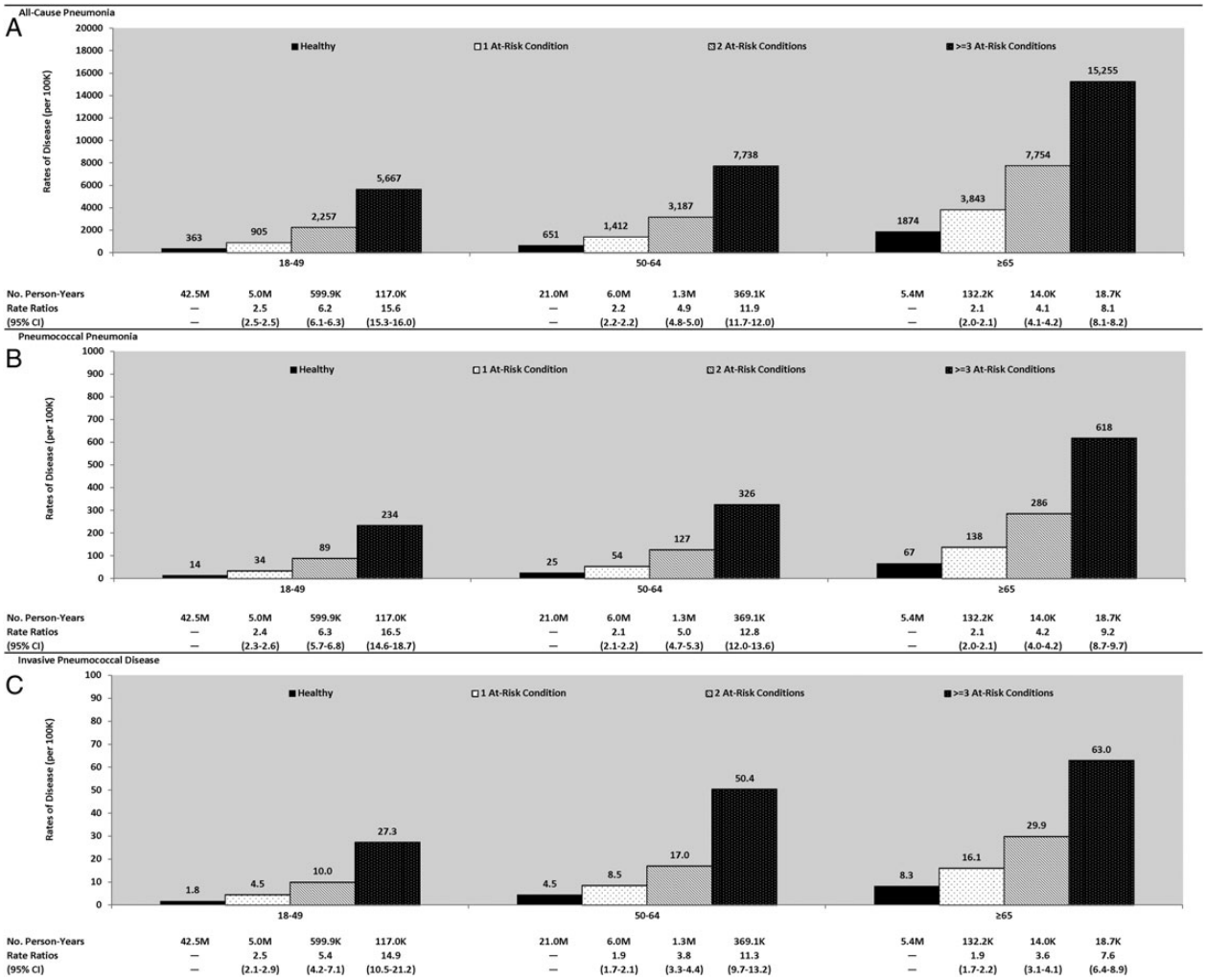

Figure 2. Rates of all-cause pneumonia, pneumococcal pneumonia, and invasive pneumococcal disease among adults with at-risk conditions by number of conditions versus their healthy counterparts

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, PPS23, 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/).

Notes

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The study sponsor, Pfizer Inc., reviewed the study research plan and study manuscript; data management, processing, and analyses were conducted by PAI; and all final analytic decisions were made by study investigators. S. I. P. confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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