Open Forum Infectious Diseases

MAJOR ARTICLE

Risk of Pneumococcal Disease in US Adults by Age and Risk Profile

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Background. Older age and certain medical conditions are known to modify the risk of pneumococcal disease among adults. We quantified the risk of pneumococcal disease among adults with and without medical conditions in the United States between 2016 and 2019.

Methods. This retrospective cohort study used administrative health claims data from Optum's de-identified Clinformatics Data Mart Database. Incidence rates of pneumococcal disease—all-cause pneumonia, invasive pneumococcal disease (IPD), and pneumococcal pneumonia—were estimated by age group, risk profile (healthy, chronic, other, and immunocompromising medical condition), and individual medical condition. Rate ratios and 95% CIs were calculated comparing adults with risk conditions with age-stratified healthy counterparts.

Results. Among adults aged 18–49 years, 50–64 years, and ≥65 years, the rates of all-cause pneumonia per 100 000 patient-years were 953, 2679, and 6930, respectively. For the 3 age groups, the rate ratios of adults with any chronic medical condition vs healthy counterparts were 2.9 (95% CI, 2.8–2.9), 3.3 (95% CI, 3.2–3.3), and 3.2 (95% CI, 3.2–3.2), while the rate ratios of adults with any immunocompromising condition vs healthy counterparts were 4.2 (95% CI, 4.1–4.3), 5.8 (95% CI, 5.7–5.9), and 5.3 (95% CI, 5.3–5.4). Similar trends were observed for IPD and pneumococcal pneumonia. Persons with other medical conditions, such as obesity, obstructive sleep apnea, and neurologic disorders, were associated with increased risk of pneumococcal disease.

Conclusions. The risk of pneumococcal disease was high among older adults and adults with certain risk conditions, particularly immunocompromising conditions.

Keywords. chronic condition; comorbidity; pneumococcal disease; pneumonia; *Streptococcus pneumoniae*.

Streptococcus pneumoniae (pneumococcus) is a leading cause of bacterial pneumonia across all ages, especially among young children and older adults. Other serious pneumococcal infections include bacteremia and meningitis. These pneumococcal infections are a substantial cause of morbidity and mortality worldwide [1, 2].

Previous research has demonstrated that pneumococcal disease is concentrated in a subset of the population with certain medical conditions [3]. For example, among US adults aged 50–64 years, 67% of invasive pneumococcal disease (IPD) episodes occurred among those with a chronic medical condition (CMC; eg, diabetes mellitus) or an immunocompromising condition (IC; eg, generalized malignancy); this subset comprises 31% of adults aged 50–64 years [3]. Further, adults who had ≥2 CMCs had similar or higher incidence rates of pneumococcal disease compared with those with an IC [4]. In addition to medical conditions, older age, due to immunosenescence and frailty, is a well-recognized risk factor for pneumococcal disease [5]. The prevalence of CMCs and ICs has been shown to increase with age, which compounds the risk of pneumococcal disease [4, 6]. In the United States from 2013 to 2015, in adults aged 18–49 years, 50–64 years, and ≥65 years, the prevalence of at least 1 CMC was 11%, 25%, and 39%, respectively. Likewise, the prevalence of at least 1 IC increased from 3% to 6% to 15% in these age groups [4].

Currently, 2 types of pneumococcal vaccines are recommended for adult use in the United States: pneumococcal polysaccharide vaccine (PPSV23) and pneumococcal conjugate vaccine (PCV20 and PCV15). Although PPSV23 has been recommended in older adults since 1983, effectiveness data of PPSV23 against nonbacteremic pneumonia are conflicting [7]. As nonbacteremic pneumonia represents the largest share of pneumonia in adults [8], considerable disease burden remains in this population. The US Centers for Disease Control and Prevention (CDC) has recommended the use of PCV13 for adults ≥19 years with ICs since 2012 and for all adults

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aged ≥65 years since 2014 based on increased disease risk [9]. In 2021, PCV20 alone and PCV15 followed by PPSV23 were recommended for all adults aged ≥65 years and adults aged 19–64 years with certain medical conditions [10].

Although there have been studies describing the incidence of pneumococcal disease in the United States, with the most recent analysis conducted from 2013 to 2015 [3, 6], we evaluated the epidemiology of pneumococcal disease following PCV13 recommendations in older adults and adults with an IC and continued routine use of PCV13 in children. In this study, we used data from a large health care claims database to determine the incidence of pneumococcal disease—all-cause pneumonia, IPD, and pneumococcal pneumonia—by age, risk profile, and individual medical condition among adults. These data can be used to establish a baseline incidence for evaluating epidemiologic changes due to higher-valency PCV recommendations and use in these populations. We also assessed the compounding effect of multiple risk conditions, referred to as "risk stacking," by analyzing disease rates among adults with more than 1 risk condition. Risk conditions included in the analysis were those known to increase the risk of pneumococcal disease and conditions that might predispose patients to disease based on limited data from other studies.

METHODS

Study Design

This was a retrospective cohort study (Figure 1*A*). The study cohort was identified using de-identified claims data from Optum's de-identified Clinformatics Data Mart Database (CDM) between January 1, 2016, and December 31, 2019. The study period was chosen to exclude the coronavirus disease 2019 (COVID-19) era and to include the time period immediately before PCV20 review/recommendation. Patients were characterized by age (18–49, 50–64, and ≥65 years) and risk profile (see below).

Data Source

The CDM is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The de-identified data include patient-level information derived from all medical and pharmacy health care services. The population included in the CDM is geographically diverse, spanning all 50 states.

Study Population

Patients who met the following criteria were included in the analysis: (1) enrollment in a participating health plan on January 1st of each calendar year from 2016 to 2019 (index date), (2) ≥18 years of age on the index date, and (3) at least 1 year of continuous enrollment before the index date of each corresponding calendar year (Figure 1*A* and *B*). Episodes of disease (ie, all-cause pneumonia, IPD, and pneumococcal pneumonia) were ascertained over a 1-year period beginning on January 1st of each calendar year and ending on the earliest of: December 31st of that year, the date of death, or the date of disenrollment. Patients who met inclusion criteria in multiple calendar years contributed to the pooled analysis. Patients were excluded from analyses if gender data were missing, if the patient had a death date before January 1st of the index year, or if the patient had overlapping pneumonia inpatient admissions.

Risk Profiles

Patients were classified into risk profiles (healthy, CMCs, ICs, and other medical conditions) based on the presence of certain medical conditions during the baseline period (ie, a minimum of 12 months before January 1st of the corresponding calendar year). CMCs and ICs were aligned with those indicated by CDC for pneumococcal vaccine recommendations (Supplementary Table 1) [10]. Other medical conditions were selected by the authors based on a literature review of conditions that may be associated with an increased risk of pneumococcal disease (Supplementary Table 1) [6, 11–16]. CMCs, ICs, and other medical conditions were ascertained using International Classification of Diseases, Ninth Revision/Tenth Revision, Clinical Modification (ICD-9/ICD-10-CM) diagnosis codes, ICD-9/ICD-10-CM/Healthcare Common Procedure Coding System procedure codes, and National Drug Code Directory drug codes (Supplementary Table 2) and were defined as follows. If an adult had 1 IC, they were counted in the category of ICs even if they had a concurrent CMC, a concurrent other medical condition, or both (Supplementary Figure 1). If an adult had 1 CMC and 1 other medical condition, they were counted in both categories. Adults without evidence of ICs, CMCs, or other medical conditions were classified as healthy.

Episode Identification

The disease episodes were identified using operational algorithms based on ICD-9-CM and ICD-10-CM diagnosis codes (Supplementary Table 2). Disease episodes separated by ≥30 days were considered independent events. For claims that included episodes separated by <30 days, they were counted as 1 episode (Figure 1*A*).

Episode Care Settings

Disease episodes from inpatient hospital admissions, emergency department visits (but not admitted to a hospital), outpatients, and others (all categories not listed previously) were included in the analysis.

Statistical Analyses

Crude disease rates were calculated by episode care setting, within each age group and by risk profile, and among adults with a CMC or an IC, by number of medical conditions.

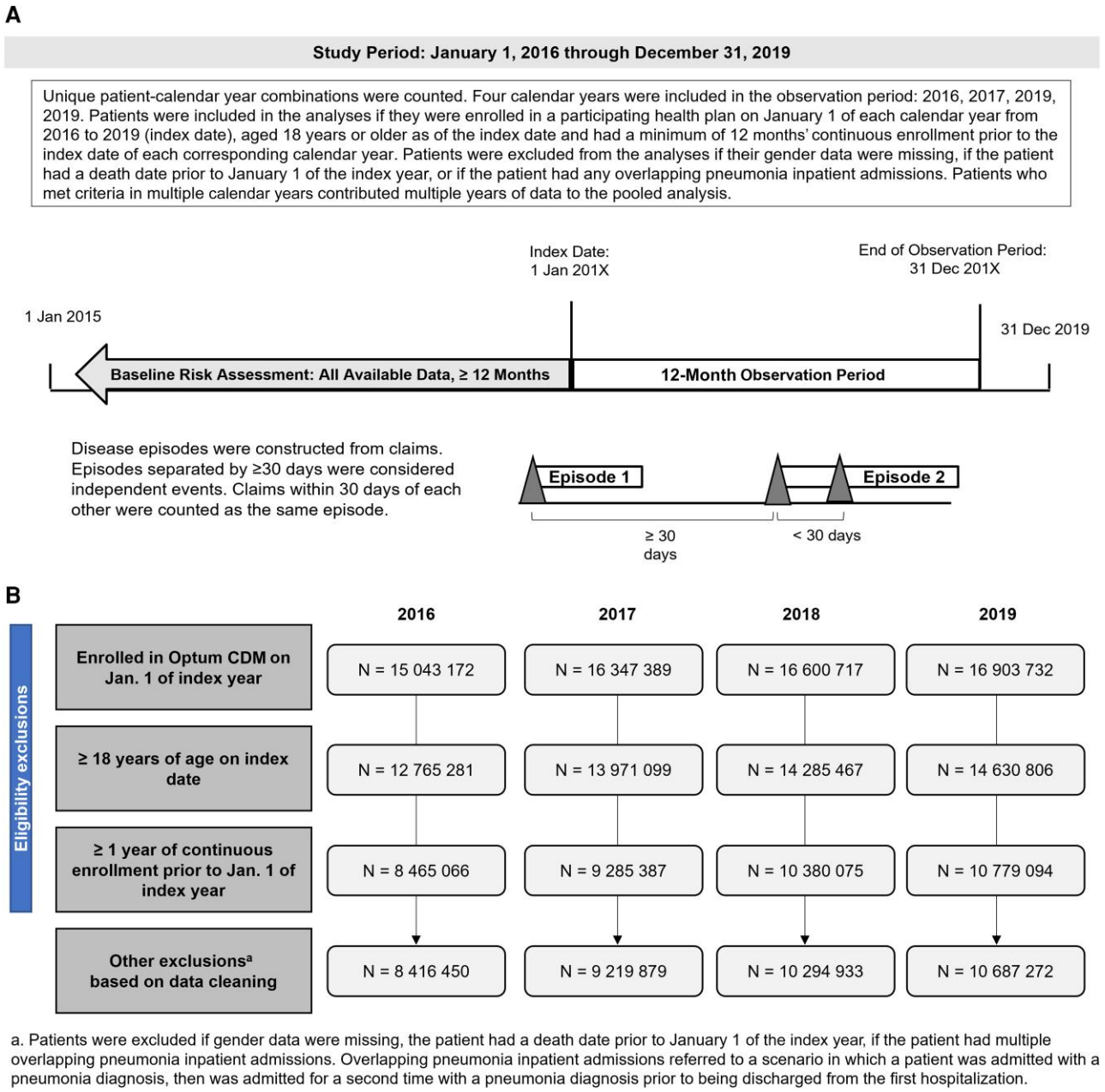

Figure 1. *A,* Study design. *B,* Patient flow chart.

Within an age group and risk profile, disease rates of persons with select individual medical conditions were also calculated. Disease rates were reported as the number of events per 100 000 person-years. To maintain patient de-identification, disease rates were only presented when there were ≥10 episodes in that group. Rate ratios and 95% confidence intervals were used to compare rates with healthy adults, using Poisson regression with robust standard errors to account for adults contributing to more than 1 calendar year. Statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

Patient Consent

This study does not include factors necessitating patient consent.

RESULTS

Study Population

Adults aged 18–49 years, 50–64 years, and ≥65 years contributed 15.2 million, 8.5 million, and 14.9 million person–calendar years of observation, respectively, to the analysis (Table 1). The prevalence of medical conditions increased with age.

Among adults aged 18–49 years, 50–64 years, and ≥65 years, respectively, approximately 13.0%, 26.3%, and 31.4% had at least 1 CMC, while 10.9%, 25.2%, and 41.6% had at least 1 IC. When the risk groups were combined, the corresponding percentages of adults with at least 1 CMC or IC in the 3 age groups were 23.9%, 51.5%, and 73.0%.

The most common CMC was asthma for adults aged 18–49 years (4.6%) and diabetes mellitus for adults aged 50–64 years (13.2%) and ≥65 years (17.0%). In all 3 age groups, the most common other medical condition was obesity (5.5% to 9.1%), and the most common IC was iatrogenic immunosuppression (9.4% to 20.1%) (Supplementary Table 3).

Disease Rates and Rate Ratios—All Care Settings

Among the study population that had a CDC-indicated medical condition for pneumococcal disease, the incidence rates of all-cause pneumonia (episodes per 100 000 person–calendar years) increased with age and risk profile (Table 2). Among healthy adults, the rate of all-cause pneumonia increased from 577 in those aged 18–49 years to 944 in those aged 50–64 years to 1983 in those aged ≥65 years. The corresponding rates in the 3 age groups among adults with at least 1 CMC were 1667, 3048, and 6328, and among adults with at least 1 IC they were 2432, 5488, and 10 549. Rates of IPD and pneumococcal pneumonia similarly increased with age and risk profile (IPD in Table 2; pneumococcal pneumonia in Supplementary Table 4). The number of episodes and person-time for each disease end point by age group and risk profile are shown in Supplementary Table 5.

The rates of all-cause pneumonia among adults with CDC-indicated medical conditions were higher than those in healthy adults in all 3 age groups (Table 2). Among adults aged 18–49 years, 50–64 years, and ≥65 years, the rate of all-cause pneumonia in those with at least 1 CMC was 2.9 (95% CI, 2.8–2.9), 3.3 (95% CI, 3.2–3.3), and 3.2 (95% CI, 3.2–3.2) times the rate in healthy adults in the same age group. In adults with at least 1 IC, the rate of all-cause pneumonia in the 3 age groups was 4.2 (95% CI, 4.1–4.3), 5.8 (95% CI, 5.7–5.9), and 5.3 (95% CI, 5.3–5.4) times the rate in healthy adults in the same age group.

The rates of all-cause pneumonia among adults with other medical conditions were also higher than the rates in healthy adults (Table 3). The rate ratios of all-cause pneumonia for adults with other medical conditions vs healthy adults ranged from 2.7 (95% CI, 2.6–2.9) to 8.7 (95% CI, 7.2–10.5) in those aged 18–49 years, from 2.9 (95% CI, 2.7–3.2) to 15.8 (95% CI, 13.2–19.0) in those aged 50–64 years, and from 2.8 (95% CI, 2.6–2.9) to 13.3 (95% CI, 7.9–22.7) in those aged ≥65 years. Notably, among adults with certain other medical conditions such as neuromuscular or seizure disorders and Down syndrome, the rate of all-cause pneumonia was higher than the rate among adults with an IC. Similar comparisons were present for IPD and pneumococcal pneumonia (IPD in Table 3; pneumococcal pneumonia in Supplementary Table 4).

Disease Rates by Care Setting

For all-cause pneumonia and pneumococcal pneumonia, the overall inpatient incidence rate was lower than the overall outpatient incidence rate among younger adults aged 18–64 years; however, these 2 rates were comparable among older adults aged ≥65 years (Supplementary Table 6). Such trends generally persisted among healthy adults and adults with a CMC; however, the inpatient incidence rates were generally higher than the outpatient incidence rates among older adults aged ≥65 years who had an IC. For IPD, compared with the outpatient incidence rates, higher inpatient incidence rates were observed for all age groups and risk profiles.

Risk Stacking

The prevalence of concurrent medical conditions increased with age (Supplementary Table 2). Among adults aged 18–49 years, 50–64 years, and ≥65 years, respectively, 2.2%, 12.8%, and 28.3% had at least 3 risk conditions.

Table 1. Study Participant Characteristics

	18–49 years		50–64 years		≥65 years	
Unique Patient–Calendar Year Combinations by Risk Profile	No.	%	No.	%	No.	%
Overall	15 235 822	100.0	8 483 080	100.0	14 899 632	100.0
At least 1 chronic medical condition/immunocompromising condition	3 647 198	23.9	4 368 786	51.5	10 876 568	73.0
At least 1 chronic medical condition[a]	1 982 512	13.0	2 231 933	26.3	4 674 059	31.4
At least 1 immunocompromising condition[b]	1 664 686	10.9	2 136 853	25.2	6 202 509	41.6
At least 1 other medical condition[a]	1 377 188	9.0	1 371 014	16.2	2 315 461	15.5
Healthy[c]	10 759 424	70.6	3 593 877	42.4	3 423 701	23.0

Abbreviation: CSF, cerebrospinal fluid.

[a]Excludes immunocompromising conditions.

[b]Includes CSF leaks and cochlear implants.

[c]Excludes chronic, other, and immunocompromising medical conditions.

Table 2. Incidence Rates and Rate Comparisons for All-Cause Pneumonia and IPD Among US Adults With CDC-Indicated Medical Conditions From 2016 to 2019

	All-Cause Pneumonia						IPD					
	18–49 years		50–64 years		≥65 years		18–49 years		50–64 years		≥65 years	
Risk Profile	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)
Overall	952.8	N/A	2678.7	N/A	6930.3	N/A	3.2	N/A	16.0	N/A	38.7	N/A
Healthy[a]	577.0	N/A	943.7	N/A	1982.8	N/A	1.3	N/A	4.1	N/A	9.8	N/A
At least 1 chronic medical condition[b]	1667.2	2.9 (2.8–2.9)	3048.3	3.3 (3.2–3.3)	6328.2	3.2 (3.2–3.2)	6.2	4.9 (3.7–6.5)	17.1	4.2 (3.4–5.2)	32.8	3.3 (2.9–3.8)
Chronic heart disease	2489.7	4.3 (4.1–4.5)	4148.3	4.4 (4.3–4.5)	8019.2	4.0 (4.0–4.1)	12.8	10.2 (6.4–16.3)	23.9	5.9 (4.6–7.5)	41.1	4.2 (3.7–4.8)
Chronic lung disease	3722.0	6.5 (6.2–6.7)	7773.1	8.2 (8.0–8.4)	13 318.8	6.7 (6.6–6.8)	14.2	11.3 (7.0–18.4)	43.3	10.7 (8.3–13.7)	70.0	7.1 (6.2–8.2)
Asthma	1791.6	3.1 (3.0–3.2)	4374.6	4.6 (4.5–4.8)	9372.2	4.7 (4.7–4.8)	5.0	4.0 (2.5–6.5)	21.6	5.3 (3.9–7.3)	41.8	4.3 (3.6–5.1)
Diabetes	1859.7	3.2 (3.1–3.3)	3052.4	3.2 (3.2–3.3)	5790.5	2.9 (2.9–3.0)	7.7	6.2 (4.3–8.9)	18.8	4.6 (3.7–5.8)	30.6	3.1 (2.7–3.6)
Alcoholism	1978.8	3.4 (3.2–3.7)	5239.5	5.6 (5.3–5.8)	9436.5	4.8 (4.6–4.9)	18.4	14.7 (8.4–25.6)	42.3	10.4 (6.6–16.5)	76.9	7.8 (6–10.3)
Chronic liver disease	2194.0	3.8 (3.6–4.0)	4010.0	4.3 (4.1–4.4)	6699.1	3.4 (3.3–3.5)	15.3	12.3 (7.3–20.7)	31.7	7.8 (5.6–10.8)	41.9	4.3 (3.3–5.6)
Smokers	1949.0	3.4 (3.3–3.5)	4472.2	4.7 (4.6–4.8)	9273.1	4.7 (4.6–4.7)	10.1	8.1 (5.7–11.4)	29.5	7.3 (5.8–9.2)	55.0	5.6 (4.8–6.5)
At least 1 immunocompromising condition	2431.7	4.2 (4.1–4.3)	5488.4	5.8 (5.7–5.9)	10 548.7	5.3 (5.3–5.4)	12.8	10.3 (8.0–13.1)	37.4	9.2 (7.5–11.3)	61.1	6.2 (5.5–7.0)
Cochlear implants	1718.3	3.0 (1.1–8.3)	3670.3	3.9 (2.1–7.2)	12 054.8	6.1 (4.3–8.6)	0	0	0	0	0	0
Congenital or acquired asplenia	5050.8	8.8 (6.7–11.4)	12 194.0	12.9 (10.5–15.9)	16 590.1	8.4 (7.4–9.4)	173.5	138.8 (31.9–603.5)	130.9	32.2 (10.2–101.1)	197.7	20.1 (9.6–42.2)
Sickle cell disease/other hemoglobinopathies	7619.0	13.2 (12.4–14.1)	14 728.7	15.6 (15–16.3)	21 249.7	10.7 (10.5–11.0)	113.7	91.0 (62.7–132.0)	202.6	49.8 (36.6–67.8)	175.7	17.9 (14.9–21.4)
HIV infection	3579.8	6.2 (5.6–6.9)	6962.3	7.4 (6.9–7.9)	11 314.2	5.7 (5.3–6.2)	75.8	60.6 (37.8–97.3)	108.9	26.8 (15.0–47.9)	105.5	10.7 (6.7–17.3)
Leukemia	11 204.4	19.4 (17.3–21.8)	14 567.4	15.4 (14.3–16.7)	19 234.3	9.7 (9.4–10.0)	247.7	198.2 (119.4–329.0)	221.3	54.4 (30.4–97.3)	196.1	20.0 (16.1–24.7)
Lymphoma	6792.8	11.8 (10.6–13.1)	11 353.1	12.0 (11.3–12.8)	16 652.8	8.4 (8.2–8.6)	128.2	102.5 (55.1–190.9)	107.6	26.4 (17.4–40.2)	163.2	16.6 (13.6–20.3)
Iatrogenic immunosuppression	2339.8	4.1 (4.0–4.1)	5510.0	5.8 (5.7–5.9)	10 917.6	5.5 (5.5–5.6)	11.9	9.5 (7.3–12.3)	36.2	8.9 (7.2–10.9)	63.6	6.5 (5.7–7.3)
Nephrotic syndrome	7836.9	13.6 (12.1–15.2)	15 895.3	16.8 (15.5–18.3)	20 002.7	10.1 (9.6–10.6)	90.2	72.1 (33.6–154.7)	99.3	24.4 (12.1–49.2)	143.1	14.6 (10.3–20.6)
Hodgkin disease	5100.4	8.8 (7.5–10.4)	10 656.1	11.3 (9.8–13.1)	19 507.9	9.8 (9.1–10.7)	56.7	45.4 (13.5–152.7)	269.4	66.2 (26.5–165.4)	203.2	20.7 (12.2–35.0)
Multiple myeloma	14 219.7	24.6 (19.0–31.9)	19 985.9	21.2 (19.4–23.1)	24 591.8	12.4 (11.9–12.9)	0	0	358.3	88.1 (57.4–135.2)	328.2	33.4 (26.0–43.0)
Chronic renal failure	9601.2	16.6 (15.8–17.5)	12 897.7	13.7 (13.4–14.0)	14 401.6	7.3 (7.2–7.3)	64.4	51.5 (35.1–75.6)	102.0	25.1 (18.5–34.0)	82.5	8.4 (7.4–9.5)
CSF leak	3515.7	6.1 (4.6–8.1)	7085.9	7.5 (6.1–9.3)	11 368.0	5.7 (4.9–6.8)	395.8	316.7 (69.6–1441.4)	139.8	34.4 (11.0–107.8)	25.2	2.6 (0.4–18.3)
Generalized malignancy	3578.9	6.2 (6.0–6.4)	6101.2	6.5 (6.3–6.6)	10 926.9	5.5 (5.5–5.6)	24.2	19.3 (13.4–27.9)	41.9	10.3 (8.2–13.0)	69.9	7.1 (6.3–8.1)
Solid organ transplant	14 265.3	24.7 (22.7–26.9)	19 517.1	20.7 (19.6–21.8)	25 761.0	13 (12.5–13.5)	184.3	147.4 (83.9–259.2)	228.3	56.1 (35.8–88.0)	220.3	22.4 (16.1–31.3)
Congenital or acquired immunodeficiencies	6454.7	11.2 (10.5–11.9)	13 787.7	14.6 (14.0–15.3)	22 393.7	11.3 (11.0–11.6)	56.1	44.9 (28.2–71.4)	121.7	29.9 (20.6–43.5)	155.7	15.8 (12.7–19.7)
Lymphatic and hematopoietic tissue malignancy	7438.2	12.9 (11.9–13.9)	12 544.5	13.3 (12.7–13.9)	18 249.2	9.2 (9.0–9.4)	130.3	104.2 (67.1–161.9)	170.8	42 (30.1–58.7)	189.9	19.3 (16.4–22.7)

Rates expressed per 100 000 person-years.

Abbreviations: CDC, Centers for Disease Control and Prevention; CSF, cerebrospinal fluid; IPD, invasive pneumococcal disease; N/A, not applicable.

[a]Excludes immunocompromising, chronic, and other medical conditions.

[b]Excludes immunocompromising conditions.

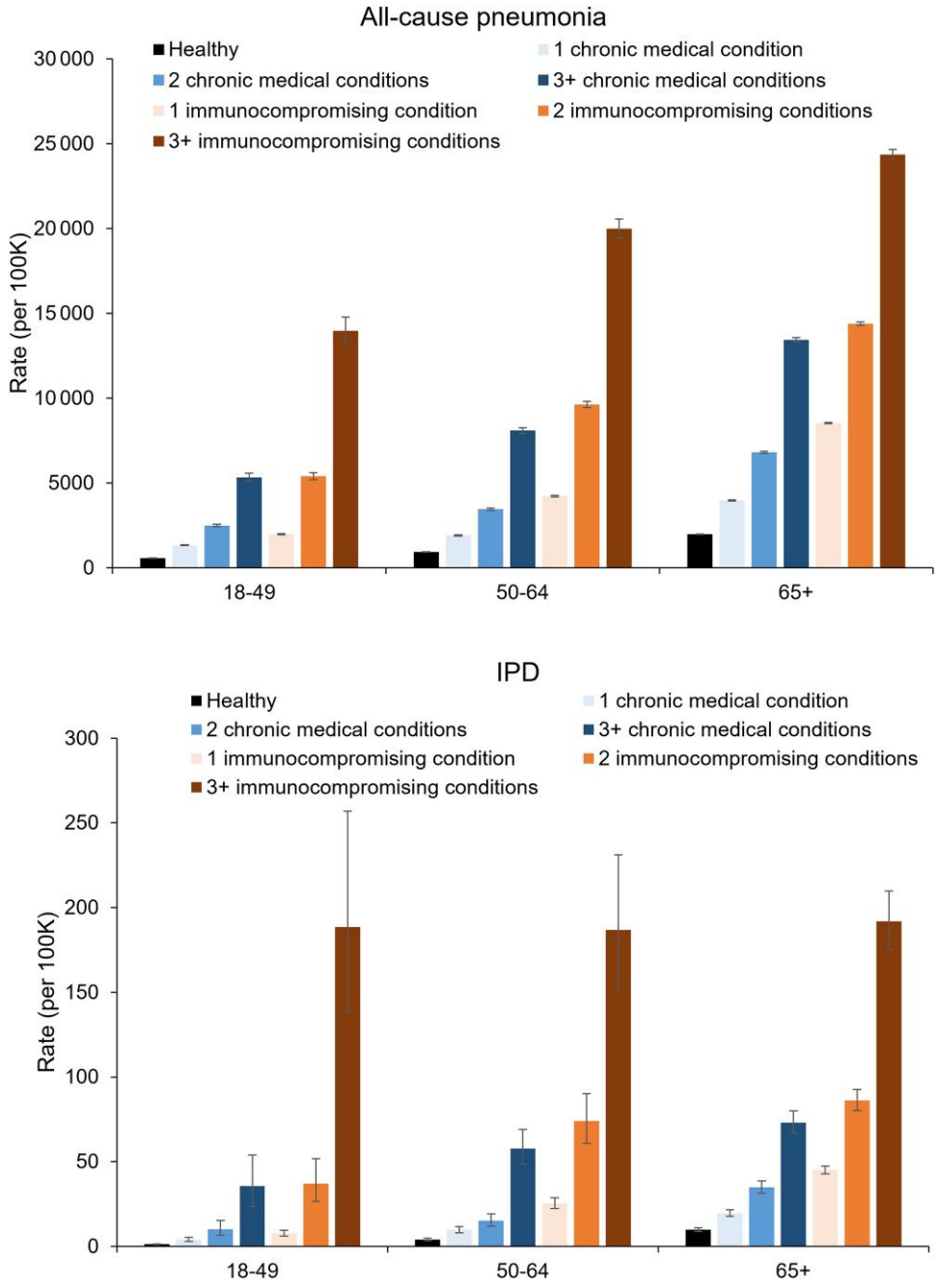

Figure 2. Rates of all-cause pneumonia and invasive pneumococcal disease among adults with chronic medical conditions or immunocompromising conditions by number of conditions. Abbreviation: IPD, invasive pneumococcal disease.

The rates of all-cause pneumonia and IPD in adults with CMCs or ICs increased with the number of concurrent conditions (Figure 2). For all-cause pneumonia, rates were generally similar between adults with 2 CMCs and adults with 1 IC across the age groups; however, rates among adults with 3 or more CMCs were higher than the rates among adults with 1 IC.

The trends noted for all-cause pneumonia and IPD were also observed for pneumococcal pneumonia (Supplementary Table 4).

DISCUSSION

In this retrospective cohort analysis using a large health care claims database, we assessed the risk of pneumococcal disease by age and risk profile among US adults between 2016 and 2019. We estimated the incidence rates for 3 disease end points, with the primary analysis conducted on all-cause pneumonia and IPD, and additional data supplemented from pneumococcal pneumonia. We chose to focus on all-cause pneumonia and

Table 3. Incidence Rates and Rate Comparisons for All-Cause Pneumonia and IPD Among US Adults With Other Medical Conditions From 2016 to 2019

	All-Cause Pneumonia						IPD					
	18–49 years		50–64 years		≥65 years		18–49 years		50–64 years		≥65 years	
Risk Profile	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)	Rate	Rate Ratio vs Healthy (95% CI)
Healthy[a]	577.0	N/A	943.7	N/A	1982.8	N/A	1.3	N/A	4.1	N/A	9.8	N/A
At least 1 chronic medical condition[b]	1667.2	2.9 (2.8–2.9)	3048.3	3.2 (3.2–3.3)	6328.2	3.2 (3.2–3.2)	6.2	4.9 (3.7–6.5)	17.1	4.2 (3.4–5.2)	32.8	3.3 (2.9–3.8)
At least 1 immunocompromising condition	2431.7	4.2 (4.1–4.3)	5488.4	5.8 (5.7–5.9)	10 548.7	5.3 (5.3–5.4)	12.8	10.3 (8.0–13.1)	37.4	9.2 (7.5–11.3)	61.1	6.2 (5.5–7.0)
At least 1 chronic medical/ immunocompromising condition	2014.7	3.5 (3.4–3.5)	4238.1	4.5 (4.4–4.6)	8718.6	4.4 (4.4–4.4)	9.2	7.3 (5.9–9.2)	27.0	6.6 (5.5–8.0)	48.9	5 (4.4–5.6)
Other medical conditions[b]	…	…	…	…	…	…	…	…	…	…	…	…
Presence of at least 1 other medical condition	1694.6	2.9 (2.9–3.0)	3100.8	3.3 (3.2–3.4)	7050.7	3.6 (3.5–3.6)	5.8	4.6 (3.4–6.4)	16.3	4 (3.2–5.0)	37.5	3.8 (3.3–4.4)
Neuromuscular or seizure disorders	2872.2	5.0 (4.7–5.3)	5766.5	6.1 (5.9–6.4)	10 885.8	5.5 (5.4–5.6)	21.5	17.2 (10.3–28.6)	33.5	8.2 (5.5–12.3)	64.8	6.6 (5.3–8.3)
Autoimmune diseases[c]	1583.7	2.7 (2.6–2.9)	3086.1	3.3 (3.1–3.4)	6694.2	3.4 (3.3–3.5)	6.8	5.5 (2.8–10.7)	15.7	3.9 (2.5–6.0)	35.2	3.6 (2.8–4.5)
Connective tissue diseases	1827.2	3.2 (2.7–3.7)	3202.5	3.4 (3.0–3.8)	6472.6	3.3 (3.1–3.5)	6.9	5.6 (0.8–39.7)	17.0	4.2 (1.3–13.1)	44.7	4.6 (2.6–7.9)
Obstructive sleep apnea	2095.1	3.6 (3.5–3.8)	3427.4	3.6 (3.5–3.7)	6687.1	3.4 (3.3–3.4)	7.1	5.7 (3.5–9.3)	16.9	4.2 (3.1–5.6)	33.7	3.4 (2.8–4.2)
Down syndrome	5017.9	8.7 (7.2–10.5)	14 943.0	15.8 (13.2–19.0)	26 454.9	13.3 (7.9–22.7)	15.2	12.1 (1.7–86.8)	191.7	47.1 (17.4–127.3)	931.4	94.8 (23.8–378.1)
Obesity	1675.5	2.9 (2.8–3.0)	3119.7	3.3 (3.2–3.4)	5755.6	2.9 (2.9–3.0)	5.1	4.0 (2.8–5.9)	16.9	4.2 (3.2–5.4)	27.9	2.8 (2.4–3.4)
Stroke	2985.4	5.2 (4.6–5.8)	5687.5	6.0 (5.7–6.3)	10 926.4	5.5 (5.4–5.6)	18.3	14.7 (4.4–49.4)	35.3	8.7 (5.4–13.9)	59.8	6.1 (5.1–7.3)
Neurologic and neurodevelopment disorders	3305.6	5.7 (5.4–6.1)	5247.4	5.6 (5.4–5.8)	10 629.0	5.4 (5.3–5.4)	22.2	17.8 (10.4–30.4)	31.9	7.8 (5.7–10.8)	57.2	5.8 (5.0–6.8)
Metabolic disorders	1833.5	3.2 (2.8–3.6)	2744.2	2.9 (2.7–3.2)	5460.2	2.8 (2.6–2.9)	2.9	2.3 (0.3–16.7)	13.1	3.2 (1.1–9.2)	26.7	2.7 (1.7–4.3)

Rates expressed per 100 000 person-years.

Abbreviations: IPD, invasive pneumococcal disease; N/A, not applicable.

[a]Excludes immunocompromising, chronic, and other medical conditions.

[b]Excludes immunocompromising conditions.

[c]Autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, and inflammatory bowel disease.

IPD for the primary analysis because all-cause pneumonia is the most common clinical manifestation of pneumococcal infections and IPD is the most specific disease end point as its coding in a claims database generally requires a confirmation from microbiology testing. Our results showed that the burden of pneumococcal disease was concentrated in adults of older age and adults who had a risk condition, and the results were generally consistent across all 3 disease end points.

Previous studies by Shea et al. and Pelton et al. also detailed the incidence rates of pneumococcal disease (pneumonia and IPD separately, as in this study) among US adults [3, 6]. Similar to the 2 other studies, our study employed a retrospective cohort design using data from health care claims databases; however, differences existed between the studies in the study periods (eg, 2006–2010 in Shea et al. vs 2016–2019 in our study), databases analyzed (eg, CDM and Truven in Pelton et al. vs CDM in our study), and ICD codes used (eg, ICD-9 in Shea et al. vs ICD-9/10 in our study). Additionally, while Pelton et al. only focused on inpatient cases, our study included disease episodes from all care settings, which allowed us to capture the additional disease burden from outpatient encounters that was not described in other studies. Although it is difficult to directly compare the disease rates between the studies due to the aforementioned differences and others, our observation that the risk of pneumococcal disease increased with age, risk profile, and number of risk conditions is consistent with the previous findings. Further, the IPD incidence rates from our analysis (3.2, 16.0, and 38.7 per 100 000 person–calendar years for age groups of 18–49, 50–64, and ≥65 years, respectively) are comparable to the rates published by the Active Bacterial Core surveillance (ABCs) report in 2019 (corresponding rates for the 3 age groups: 4.4, 15.6, and 23.6 per 100 000 population) [17]. The higher IPD rate in individuals aged ≥65 years in our study may be due to demographic differences in the catchment area between CDM and the ABCs program.

In the recently updated recommendations from the CDC, a higher-valency PCV (PCV20 or PCV15) is now routinely recommended for adults aged ≥65 and for adults aged 19–64 years with certain CMCs, such as asthma and diabetes mellitus, on the basis of elevated disease risk [10]. In support of these recommendations, our study showed that adults aged ≥65 had the highest disease rates among those who were healthy or who had a CMC or IC for nearly every condition when compared with younger adults. Our study also showed that among adults with CDC-indicated medical conditions, disease rates were higher among adults with these CMCs or ICs than the rates in the healthy counterparts. Across all age groups, the rate ratios ranged from 2.9 (95% CI, 2.8–2.9) to 24.7 (95% CI, 22.7–26.9) for all-cause pneumonia and from 3.3 (95% CI, 2.9–3.8) to 316.7 (95% CI, 69.6–1441.4) for IPD. Prior research has identified medical conditions—such as autoimmune diseases (including rheumatoid arthritis, systemic lupus erythematosus, and Crohn's disease) and neuromuscular/seizure disorders—to be associated with a higher risk of pneumococcal disease [4, 6]. In our study, we expanded the list of medical conditions of Shea et al. and Pelton et al. to include additional risk conditions (eg, obesity and stroke) (Table 3) and investigated whether these medical conditions could also confer a higher risk of disease. Our analysis showed that the rates of all-cause pneumonia in adults with other medical conditions ranged from 2.7 (95% CI, 2.6–2.9) to 15.8 (95% CI, 13.2–19.0) times the rate in healthy adults, and the corresponding rate ratios ranged from 2.3 (95% CI, 0.3–16.7) to 94.8 (95% CI, 23.8–378.1) for IPD. Thus, our study adds to an existing body of evidence that individuals with these other medical conditions are also associated with increased risk of pneumococcal disease. The list of risk conditions indicated for pneumococcal vaccines is periodically updated by the vaccine technical committees (VTCs); the identified other medical conditions may be considered by the VTCs to further reduce the burden of pneumococcal disease.

Our study has limitations. First, inherent with the use of operational algorithms, disease episodes and risk profiles may have been misclassified or incomplete. However, it is likely that this limitation had an impact on disease rates in a nondifferential manner across the age and risk groups, leaving the rate ratios largely unaffected. Second, due to the lack of information on pneumococcal serotypes, it was not possible to assess the proportion of disease caused by serotypes included in pneumococcal vaccines (eg, PCV13, PCV15, PCV20, and PPSV23) in various age and risk groups. However, vaccine effectiveness studies have shown that the preventable fraction of all-cause pneumonia in adults aged ≥65 years is between 6% and 11.4% [18–20]. Similarly, lack of data precluded us from stratifying the rates by race/ethnicity. Third, the rate ratios were not adjusted for individual-level covariates. Fourth, although the CDM data are derived from a health claims database for members of large commercial and Medicare Advantage health plans, individuals with public health insurance or no health insurance are not included in the database. Thus, results presented here may not be generalizable to other patient populations.

CONCLUSIONS

In this large observational study, we show that the risk of pneumococcal disease is high among older adults and adults with risk conditions. Our findings suggest that vaccination against respiratory pathogens including *S. pneumoniae*, among others, as well as CMC prevention, remain important strategies to prevent and reduce disease. Additionally, our study has identified individuals with other medical conditions, such as obesity, who are at increased risk of disease and could benefit from inclusion of these conditions in pneumococcal vaccine recommendations. Finally, future studies quantifying disease risk will be

needed to evaluate the impact of higher-valency pneumococcal vaccines and updated pneumococcal vaccination recommendations. Assessing disease rates in different age groups (eg, ≥50 years) and by race and geography will help focus future prevention strategies.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. L.R.G., A.Mi., L.M., A.Me., T.A., Q.Y., and E.C. are employees of Pfizer and may hold stock and/or stock options.

Author contributions. L.R.G., A.Me., and E.C. contributed to study design and concept; all authors contributed to data analysis and interpretation; L.R.G., L.M., T.A., Q.Y., and E.C. wrote the first draft of the manuscript; all authors provided critical review of the manuscript; all authors read and approved the final manuscript.

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