

Epidemiology of Pneumococcal Disease in a National Cohort of Older Adults

Haley J. Morrill · Aisling R. Caffrey ·
Eunsun Noh · Kerry L. LaPlante

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ABSTRACT

Introduction: *Streptococcus pneumoniae* is a major cause of morbidity and mortality. We sought to describe the epidemiology of non-invasive and invasive pneumococcal disease in a national Veterans Affairs population within the United States.

Methods: We conducted a retrospective study in older patients (aged ≥ 50 years) with positive pneumococcal cultures from any site between 2002 and 2011. We described outpatient and inpatient pneumococcal disease incidence per

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H. J. Morrill · A. R. Caffrey · E. Noh · K. L. LaPlante
Infectious Diseases Research Program, Veterans Affairs Medical Center, Providence, Rhode Island, USA

H. J. Morrill · A. R. Caffrey · E. Noh ·
K. L. LaPlante (✉)
Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Kingston, Rhode Island, USA
e-mail: kerrylaplante@uri.edu

K. L. LaPlante
Division of Infectious Diseases, Warren Alpert Medical School of Brown University, Providence, Rhode Island, USA

100,000 clinic visits/hospitalizations. Repeat cultures within a 30-day period were considered to represent the same episode. To describe the epidemiology of serious pneumococcal infections (bacteremia, meningitis, pneumonia), we assessed demographics, clinical characteristics, and risk factors for *S. pneumoniae*. Pneumonia was defined as a positive respiratory culture with a pneumonia diagnosis code. Bacteremia and meningitis were identified from positive cultures. Generalized linear mixed models were used to quantify changes over time.

Results: Over the study period, we identified 45,983 unique episodes of pneumococcal disease (defined by positive cultures). Incidence decreased significantly by 3.5% per year in outpatients and increased non-significantly by 0.2% per year in inpatients. In 2011, the outpatient and inpatient incidence was 2.6 and 328.1 infections per 100,000 clinic visits/hospitalizations, respectively. Among inpatients with serious infections, chronic disease risk factors for pneumococcal disease increased significantly each year, including respiratory disease (1.9% annually), diabetes (1.3%), and renal failure

(1.0%). Overall, 30.2% of inpatients with serious infections had a pneumococcal immunization in the previous 5 years. Invasive disease (37.4% versus 34.9%, $P = 0.004$) and mortality (14.0% versus 12.7%, $P = 0.045$) were higher in non-vaccinated patients compared to vaccinated patients.

Conclusions: In our national study of older adults, the baseline health status of those with serious pneumococcal infections worsened over the study period. As the population ages and the chronic disease epidemic grows, the burden of pneumococcal disease is likely to increase thus highlighting the importance of pneumococcal vaccination.

Keywords: Epidemiology; Infectious disease; Pneumococcal disease; *Streptococcus pneumoniae*; United States; Veteran

INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality in the United States (US), causing over 500,000 cases of pneumonia, over 40,000 cases of invasive pneumococcal disease, and 4,000 associated deaths annually [1, 2]. *S. pneumoniae* is differentiated by one of at least 90 different polysaccharide capsules [3]. The capsule acts as the major virulence factor protecting the pathogen from destruction by host phagocytes [3]. *S. pneumoniae* is part of the normal bacterial flora of the upper respiratory tract and is mainly found in the nasopharynx [4].

Pneumococcus causes a wide variety of invasive (such as bacteremia and meningitis) and non-invasive infections (such as pneumonia, sinusitis, and otitis media) [5, 6]. A number of patient demographics and comorbidities, including age, diabetes mellitus,

chronic lung disease, chronic liver disease, chronic cardiovascular disease, chronic renal failure, and immune deficiencies, increase one's risk of developing pneumococcal disease [7–11]. In patients with underlying medical conditions the incidence of pneumococcal infections may be as high as 176–483 per 100,000 persons, while the incidence for patients with immunocompromising conditions has been reported to be even higher from 342 to 2,031 per 100,000 persons [7, 12].

Since the introduction and widespread use of the pneumococcal conjugate vaccine in children in 2000, the incidence of invasive pneumococcal disease in the US has decreased [13–18]. Vaccinating children provides indirect protection or “herd immunity” to non-vaccinated adults, and has led to a nearly one-third decrease in the rate of invasive pneumococcal disease among adults aged 50 and older [14, 18]. Subsequent changes in the epidemiology of *S. pneumoniae* infections are not well described, particularly among high-risk patients. Therefore, we sought to describe changes in the epidemiology from 2002 to 2011 of pneumococcal disease nationally among adults aged 50 years and older in the Veterans Affairs (VA) Healthcare System, specifically disease incidence and risk factors for *S. pneumoniae* among those with serious pneumococcal infections.

METHODS

The study design and methods were reviewed and approved by the Institutional Review Board and Research and Development Committee of the Providence VA Medical Center. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Sources

The VA Healthcare System operates 151 medical centers and 827 community-based outpatient clinics throughout the US [19]. Inpatient and outpatient care is captured electronically in each VA healthcare facility through the electronic medical record system, which has been in place since 1999 [20]. We identified *S. pneumoniae* using microbiology data and merged data from multiple domains, including demographics, medical, and immunization to capture patient care [21, 22]. International Classification of Diseases, 9th Revision (ICD-9) diagnostic and procedure codes from inpatient and outpatient records were utilized to identify patient comorbidities, risk factors, and infection history [23, 24]. Immunization administration records were used to determine vaccination rates.

Patient Population and Study Design

We conducted a descriptive, retrospective study of patients age 50 years and older with microbiology cultures from any collection site positive for *S. pneumoniae* between January 1, 2002 and December 31, 2011. To assess incidence, both inpatient and outpatient cultures were included. Repeat positive *S. pneumoniae* cultures from the same patient within a 30-day period were considered to represent the same episode of infection [25]. Yearly incidence rates were calculated as the number of pneumococcal infections per 100,000 clinic visits or per 100,000 hospital admissions.

To describe the epidemiology of serious (bacteremia, meningitis, and pneumonia) *S. pneumoniae* infections, we included positive respiratory, blood, or cerebrospinal fluid cultures collected during a hospital admission.

Bacteremia and meningitis were identified from positive cultures. Pneumonia was defined as a positive respiratory culture with a corresponding ICD-9 code for pneumonia (482.40–482.42, 482.49, 482.89, 482.9, 484.8, 485–486, 510.0, 510.9, 513.0–513.1) [23, 24]. Invasive pneumococcal disease was categorized as bacteremia, meningitis, and bacteremic pneumonia; and non-invasive disease included pneumonia without bacteremia. Bacteremic pneumonia was defined by the presence of both pneumococcal pneumonia and bacteremia.

Patient Characteristics

We evaluated demographic and clinical characteristics among inpatients infected with serious *S. pneumoniae* infections [23, 24]. Diagnosed infections in the year prior to the positive pneumococcal culture, such as pneumonia and bacteremia (attributed to any organism), and Streptococcal infections (any infection type attributed to any *Streptococcus* species), were assessed. Risk factors for *S. pneumoniae* were evaluated including heart failure, chronic respiratory disease, diabetes mellitus, chronic liver disease, human immunodeficiency virus (HIV), chronic renal disease, immunodeficiency syndromes, and cancer. Pneumococcal vaccination was defined as any pneumococcal immunization administration record in the previous 1, 5, and 10 years prior to the culture collection date. As the conjugate vaccine was not recommended for use in adults until 2012, our vaccination rates reflect vaccination with 23-valent pneumococcal polysaccharide vaccine only [26]. Inpatient mortality was defined as death from any cause during the pneumococcal-related admission and 30-day mortality was defined as death from any cause within 30 days of the culture collection date.

Statistical Analysis

Descriptive statistics were calculated, including number and percent for categorical characteristics, mean and standard deviation for normally distributed continuous variables, and median and interquartile range (IQR) for non-normal variables. To assess fluctuations in incidence over time, modeled annualized change and percent change in incidence were determined with generalized linear mixed models. Additionally, generalized linear mixed models quantified the modeled annualized percent change in *S. pneumoniae* risk factors over the study period. Differences between vaccinated and non-vaccinated patients were assessed using Chi-square or Fisher's exact tests for categorical variables and the *t* test or Wilcoxon rank sum test for continuous variables as appropriate. A two-tailed *P* value of 0.05 or less was considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Over the 10-year study period, we identified 45,983 unique episodes of pneumococcal disease (defined by positive cultures; 62.9% outpatient and 37.1% inpatient). Positive cultures were obtained from the following sites: respiratory (43.0%), urine (23.2%), blood (16.9%), skin (11.8%), and other (such as nares, bone, joint, and cerebrospinal fluid; 5.2%). The median time to culture collection from admission for inpatients was 0 days (IQR 0–1 days).

From 2002 to 2011, pneumococcal disease incidence (as defined from positive cultures) decreased from 5.8 to 2.9 infections per 100,000 clinic visits for outpatients and increased from

262.3 to 328.1 infections per 100,000 hospital admissions for inpatients (Table 1). Outpatient pneumococcal disease incidence decreased significantly by 3.5% per year, while there was a non-significant 0.2% per year increase in incidence of inpatient pneumococcal disease over the study period. Outpatient incidence decreased significantly per year for patients aged 50–64 years and also for patients aged 65 years and older. Inpatient incidence decreased by 0.6% per year for patients aged 50–64 years, and increased by 0.7% per year for patients aged 65 years and older. Inpatient invasive disease incidence decreased by 1.0% per year.

There were 14,511 unique episodes of serious (bacteremia, meningitis, and pneumonia) *S. pneumoniae* infections over the study period (Table 2). Non-invasive pneumonia was the most common infection (63.4%, *n* = 9,193), followed by bacteremia (25.7%, *n* = 3,735), bacteremic pneumonia (10.5%, *n* = 1,529), bacteremia and meningitis (0.2%, *n* = 23), and meningitis alone (0.1%, *n* = 21). The overall mean age of this population was 67.7 ± 10.6 years. The majority of patients were white males from facilities in the South for all infection types. The most common treating specialty was general medicine (57.5%, *n* = 8,351), followed by intensive care (25.9%, *n* = 3,758).

Approximately 30% of patients in each infection group received the pneumococcal vaccine (Table 2). History of multiple pneumococcal infections during the study period ranged from 30% to 40% for all infection types. One-third of patients with both invasive and non-invasive pneumococcal pneumonia had a pneumonia ICD-9 diagnosis in the year prior to the positive pneumococcal culture. Overall, 11.9% of patients had an ICD-9 diagnosis for a Streptococcal infection (from

Table 1 Annual incidence of pneumococcal disease by healthcare and age group

Year	Outpatient incidence ^a			Inpatient incidence ^b				
	Total ^c	50–64 years	≥65 years	Total ^c	50–64 years	≥65 years	Serious disease ^d	Invasive disease ^e
2002	5.8	2.4	3.4	262.3	105.5	156.8	235.3	78.1
2003	6.0	2.5	3.4	288.5	116.2	172.2	254.8	97.0
2004	5.9	2.5	3.4	270.4	116.9	153.5	234.5	88.9
2005	6.0	2.7	3.3	280.6	124.7	155.9	240.0	88.6
2006	6.0	2.7	3.3	278.1	136.1	141.9	240.6	91.0
2007	5.9	2.7	3.2	277.7	135.5	142.2	230.1	87.5
2008	5.6	2.6	3.0	309.9	147.1	162.8	264.0	97.7
2009	4.9	2.2	2.7	307.4	148.7	158.7	258.5	91.6
2010	4.0	1.8	2.2	305.4	144.3	161.1	253.4	92.6
2011	2.9	1.3	1.6	328.1	154.5	173.5	264.7	94.6
Annualized percent change (%)	−3.5	−4.1	−3.1	0.2	−0.6	0.7	0.1	−1.0
<i>P</i> value	<0.001	0.001	0.003	0.846	0.391	0.533	0.888	0.454

Incidence based on all positive *Streptococcus pneumoniae* cultures from any site, unless otherwise indicated

^a Number of infections per 100,000 clinic visits

^b Number of infections per 100,000 hospital visits

^c Includes all patients aged ≥50 years

^d Includes only serious pneumococcal infections (pneumonia, bacteremia, and meningitis)

^e Includes only invasive pneumococcal disease (bacteremia, meningitis, and bacteremic pneumonia)

any *Streptococcus* species, including *S. pneumoniae*) in the previous year. Among inpatients with serious infections, 40.2% had chronic respiratory disease, 16.2% had diabetes, 16.2% had cancer, and 14.6% had heart failure. Approximately 12% of patients used tobacco, and the highest percentage of tobacco use was among those with non-invasive pneumonia (14.0%). Overall inpatient mortality and 30-day mortality rates were 13.6% and 17.9%, respectively. The highest mortality was among those with bacteremic pneumonia (inpatient mortality 29.1%; 30-day mortality 28.8%) and the lowest was among those with non-invasive pneumonia (inpatient mortality 9.5%; 30-day mortality 14.2%).

Prevalence of risk factors for *S. pneumoniae* among inpatients with serious pneumococcal infections is presented for each year of the study period in Table 3. In 2011, chronic respiratory disease (50.9%) and diabetes (22.6%) were the most common conditions in our population, while immunodeficiency disorders (0.2%) and HIV (1.8%) were the least common risk factors. The modeled annual percent change increased significantly for all risk factors assessed, except HIV and immunity disorders where the increase was non-significant. Chronic respiratory disease, diabetes, and renal failure increased by 1.9%, 1.3%, and 1.0% per year, respectively.

Table 4 compares demographics, comorbid conditions, and healthcare exposures among

Table 2 Population demographics, comorbid conditions, and healthcare exposures of hospitalized patients with serious pneumococcal infections by infection type

Variable	Total ^a (n = 14,511)	Pneumonia ^b (n = 9,193)	Bacteremic pneumonia (n = 1,529)	Bacteremia (n = 3,735)	Meningitis ^c (n = 44)	Invasive disease ^d (n = 5,318)
Age (years), mean (SD)	67.7 (10.6)	67.9 (10.3)	66.9 (10.5)	67.4 (11.2)	67.7 (10.6)	67.2 (11.0)
Male gender	14,237 (98.1)	9,042 (98.4)	1,507 (98.6)	3,637 (97.4)	41 (93.2)	5,195 (97.7)
White race	11,526 (79.4)	7,607 (82.7)	1,167 (76.3)	2,716 (72.7)	28 (63.6)	3,919 (73.7)
Region of facility						
Midwest	3,430 (23.6)	2,297 (25.0)	326 (21.3)	798 (21.4)	7 (15.9)	1,133 (21.3)
Northeast	2,206 (15.2)	1,510 (16.4)	238 (15.6)	455 (12.2)	<5	696 (13.1)
South	5,414 (37.3)	3,107 (33.8)	633 (41.4)	1,639 (43.9)	29 (65.9)	2,307 (43.4)
West	3,461 (23.9)	2,279 (24.8)	332 (21.7)	843 (22.6)	5 (11.4)	1,182 (22.2)
Treating specialty						
General medicine	8,351 (57.5)	5,375 (58.5)	654 (42.8)	2,307 (61.8)	12 (27.3)	2,976 (56.0)
Intensive care unit	3,758 (25.9)	2,167 (23.6)	654 (42.8)	910 (24.4)	22 (50.0)	1,591 (29.9)
Surgery	739 (5.1)	501 (5.4)	82 (5.4)	151 (4.0)	<5	238 (4.5)
Other	1,663 (11.5)	1,150 (12.5)	139 (9.1)	367 (9.8)	6 (13.6)	238 (4.5)
Pneumococcal immunization						
1 year prior to infection	1,274 (8.8)	831 (9.0)	120 (7.8)	318 (8.5)	<5	443 (8.3)
5 years prior to infection	4,386 (30.2)	2,855 (31.1)	435 (28.4)	1,084 (29.0)	9 (20.5)	1,531 (28.8)
10 years prior to infection	5,274 (36.3)	3,441 (37.4)	513 (33.6)	1,305 (34.9)	11 (25.0)	1,833 (34.5)
History of multiple pneumococcal infections ^e	5,279 (36.4)	3,277 (35.6)	566 (37.0)	1,421 (38.0)	13 (29.5)	2,002 (37.6)
Infection diagnosis previous year						
Pneumonia ^f	4,244 (29.2)	3,046 (33.1)	433 (28.3)	759 (20.3)	<5	1,198 (22.5)
Bacteremia ^f	551 (3.8)	160 (1.7)	137 (9.0)	250 (6.7)	<5	391 (7.4)
<i>Streptococcus</i> species infection ^g	1,726 (11.9)	1,207 (13.1)	188 (12.3)	326 (8.7)	<5	519 (9.8)
Charlson comorbidity index, median (IQR)	1 (0–3)	1 (0–2)	1 (0–3)	2 (0–3)	0 (0–2)	2 (0–3)
Comorbid conditions						
Heart failure	2,118 (14.6)	1,269 (13.8)	250 (16.4)	595 (15.9)	<5	849 (16.0)
Chronic respiratory disease	5,827 (40.2)	4,034 (43.9)	559 (36.6)	1,233 (33)	<5	1,793 (33.7)
Diabetes	2,344 (16.2)	1,287 (14)	243 (15.9)	806 (21.6)	6 (13.6)	1,057 (19.9)

Table 2 continued

Variable	Total ^a (n = 14,511)	Pneumonia ^b (n = 9,193)	Bacteremic pneumonia (n = 1,529)	Bacteremia (n = 3,735)	Meningitis ^c (n = 44)	Invasive disease ^d (n = 5,318)
Diabetes with complications	328 (2.3)	192 (2.1)	24 (1.6)	112 (3)	–	136 (2.6)
Tobacco use	1,856 (12.8)	1,283 (14.0)	149 (9.7)	422 (11.3)	<5	573 (10.8)
Alcohol abuse	1,307 (9.0)	726 (7.9)	175 (11.4)	397 (10.6)	7 (15.9)	581 (10.9)
Mild liver disease	851 (5.9)	318 (3.5)	124 (8.1)	406 (10.9)	<5	533 (10.0)
HIV/AIDS	246 (1.7)	100 (1.1)	30 (2.0)	113 (3.0)	<5	146 (2.7)
Chronic renal disease	1,233 (8.5)	570 (6.2)	169 (11.1)	493 (13.2)	–	663 (12.5)
Dialysis	397 (2.7)	135 (1.5)	103 (6.7)	157 (4.2)	<5	262 (4.9)
Transplant	79 (0.5)	32 (0.3)	10 (0.7)	36 (1.0)	<5	47 (0.9)
Immunity disorders	26 (0.2)	11 (0.1)	5 (0.3)	10 (0.3)	–	15 (0.3)
Cancer	2,355 (16.2)	1,308 (14.2)	272 (17.8)	768 (20.6)	7 (15.9)	1,047 (19.7)
Metastatic cancer	572 (3.9)	312 (3.4)	69 (4.5)	190 (5.1)	<5	260 (4.9)
Length of stay (days), median (IQR)	6 (3–13)	6 (3–12)	12 (6–25)	6 (4–12)	11 (6.5–15.5)	7 (4–15)
Inpatient mortality	1,972 (13.6)	872 (9.5)	445 (29.1)	649 (17.4)	<5	1,100 (20.7)
30-day mortality	2,596 (17.9)	1,301 (14.2)	441 (28.8)	848 (22.7)	5 (11.4)	1,295 (24.4)

Data are no. (%) of patients, unless otherwise indicated

AIDS Acquired immunodeficiency syndrome, HIV human immunodeficiency virus, IQR interquartile range, SD standard deviation

^a Includes only serious pneumococcal infections (pneumonia, bacteremia, and meningitis)

^b Includes patients with positive pneumococcal respiratory cultures and corresponding pneumonia diagnosis

^c Includes patients with positive pneumococcal cerebrospinal fluid cultures with or without positive pneumococcal blood cultures

^d Includes only invasive pneumococcal disease (bacteremia, meningitis, and bacteremic pneumonia)

^e Includes all infection types from any positive *Streptococcus pneumoniae* culture site

^f Attributed to any organism

^g Any infection type attributed to any *Streptococcus* species

patients vaccinated within 5 years of infection and those not vaccinated within 5 years of infection. A number of patient characteristics varied significantly between the two groups, including race, region of facility, and infection type. Patients with a history of multiple pneumococcal infections during the study period and patients with other infection types in the year prior were more likely to be

vaccinated. Additionally, patients with several comorbid conditions, including heart failure, diabetes, and chronic renal disease, were more likely to be vaccinated. Invasive disease was more common in non-vaccinated patients (37.4% versus 34.9%, $P = 0.004$), as was inpatient mortality (14.0% versus 12.7%, $P = 0.045$). Similar significant differences were observed when comparing vaccination

Table 3 Annual prevalence of risk factors for *Streptococcus pneumoniae* in hospitalized patients with serious pneumococcal infections

Year	Heart failure (%)	Chronic respiratory (%)	Diabetes (%)	Liver disease (%)	HIV (%)	Renal failure or dialysis (%)	Immunity disorder (%)	Cancer (%)
2002	11.1	33.1	11.3	4.6	1.2	5.6	0.0	13.0
2003	14.4	34.2	12.0	5.4	1.3	6.4	0.3	14.9
2004	12.2	35.7	12.5	4.0	1.4	5.1	0.0	15.9
2005	14.0	36.2	13.8	5.2	1.6	6.9	0.1	14.5
2006	14.1	35.4	14.3	5.9	1.7	8.6	0.4	16.3
2007	13.4	38.2	15.5	5.6	1.5	9.0	0.3	17.5
2008	13.9	41.6	18.5	7.2	3.1	11.1	0.1	16.3
2009	16.2	44.6	16.6	6.8	1.6	12.3	0.3	17.4
2010	16.7	47.6	21.9	7.7	1.7	13.5	0.2	16.9
2011	18.6	50.9	22.6	7.4	1.8	13.8	0.2	18.9
Annualized change in prevalence (%)	0.6	1.9	1.3	0.4	0.1	1.0	0.0	0.5
<i>P</i> value	0.002	<0.001	<0.001	<0.001	0.186	<0.001	0.427	<0.001

($n = 5,274$) versus non-vaccination ($n = 9,237$) in the previous 10 years (data not presented).

DISCUSSION

We assessed the burden of invasive and non-invasive pneumococcal disease in a large population of adults aged 50 years and older receiving care at outpatient and inpatient VA facilities nationally. While outpatient incidence decreased, a small, non-significant increase in pneumococcal infections was observed in the hospital setting over our 10-year study period. The decrease in outpatient incidence in our population is likely associated with routine pneumococcal conjugate vaccination in children. Previous studies have demonstrated decreasing rates of invasive and non-invasive pneumococcal disease, otitis media and pneumonia, including post-introduction of the

pneumococcal conjugate vaccine [14, 18, 27–29]. It is possible that non-vaccine serotypes were responsible for the slight increase in pneumococcal disease we observed in our inpatient population; however, serotype data were not available. In a previous multi-center observational study the annual rate of bacteremic pneumococcal disease due to vaccine serotypes declined by 29% per year; however, the rate of disease due to non-vaccine serotypes increased by 13% per year, resulting in an overall annual increase [30].

Our aging Veteran population may also explain the slight increase in inpatient pneumococcal infections we observed. Incidence increased in patients aged 65 years and older, while incidence decreased in younger patients. Elderly patients are at the highest risk for pneumococcal disease and disease incidence in these patients is up to 50 times greater than

Table 4 Population demographics, comorbid conditions, and healthcare exposures of hospitalized patients with serious pneumococcal infections by vaccination status

Variable	Not vaccinated (<i>n</i> = 10,125)	Vaccinated (<i>n</i> = 4,386)	<i>P</i> value
Age (years), mean (SD)	67.7 (10.8)	67.5 (10.1)	0.853
Male gender	9,921 (98.0)	4,316 (98.4)	0.089
White race	7,951 (78.5)	3,575 (81.5)	<0.001
Region of facility			
Midwest	2,473 (24.4)	957 (21.8)	<0.001
Northeast	1,519 (15.0)	687 (15.7)	
South	3,583 (35.4)	1,831 (41.7)	
West	2,550 (25.2)	911 (20.8)	
Treating specialty			
General medicine	5,773 (57.0)	2,578 (58.8)	0.074
Intensive care unit	2,634 (26.0)	1,124 (25.6)	
Surgery	538 (5.3)	201 (4.6)	
Other	1,180 (11.7)	483 (11.0)	
History of multiple pneumococcal infections ^a	3,180 (31.4)	2,099 (47.9)	<0.001
Infections previous year			
Pneumonia ^b	2,694 (26.6)	1,550 (35.3)	<0.001
Bacteremia ^b	350 (3.5)	201 (4.6)	0.001
<i>Streptococcus</i> species infection ^c	1,156 (11.4)	570 (13.0)	0.007
Charlson comorbidity index, median (IQR)	1 (0–3)	1 (0–3)	<0.001
Comorbid conditions			
Heart failure	1,438 (14.2)	680 (15.5)	0.041
Chronic respiratory disease	3,845 (38.0)	1,982 (45.2)	<0.001
Diabetes	1,574 (15.5)	770 (17.6)	0.003
Diabetes with complications	223 (2.2)	105 (2.4)	0.476
Tobacco use	1,256 (12.4)	600 (13.7)	0.035
Alcohol abuse	917 (9.1)	390 (8.9)	0.750
Mild liver disease	576 (5.7)	275 (6.3)	0.171
Moderate or severe liver disease	127 (1.3)	69 (1.6)	0.127
HIV/AIDS	144 (1.4)	102 (2.3)	<0.001
Chronic renal disease	823 (8.1)	410 (9.3)	0.016
Dialysis	269 (2.7)	128 (2.9)	0.375

Table 4 continued

Variable	Not vaccinated (<i>n</i> = 10,125)	Vaccinated (<i>n</i> = 4,386)	<i>P</i> value
Transplant	55 (0.5)	24 (0.6)	0.750
Immunity disorders	11 (0.1)	15 (0.3)	0.002
Cancer	1,584 (15.6)	771 (17.6)	0.004
Metastatic cancer	403 (4.0)	169 (3.9)	0.718
Length of stay (days), median (IQR)	6 (3–13)	6 (3–13)	0.768
Inpatient mortality	1,414 (14.0)	558 (12.7)	0.045
30-day mortality	1,836 (18.1)	760 (17.3)	0.245
Invasive disease	3,787 (37.4)	1,531 (34.9)	0.004
Infection type			
Pneumonia	6,338 (62.6)	2,855 (65.1)	0.049
Bacteremic pneumonia	1,094 (10.8)	435 (9.9)	
Bacteremia	2,651 (26.2)	1,084 (24.7)	
Meningitis	35 (0.4)	9 (0.2)	

Data are no. (%) of patients, unless otherwise indicated. Vaccination status based on receipt or not of a pneumococcal immunization in the 5 years prior to infection

AIDS Acquired immunodeficiency syndrome, *HIV* human immunodeficiency virus, *IQR* interquartile range, *SD* standard deviation

^a Includes all infection types from any positive *Streptococcus pneumoniae* culture site

^b Attributed to any organism

^c Any infection type attributed to any *Streptococcus* species

that of adolescents [31]. As the general population ages, the burden of pneumococcal disease is expected to dramatically increase [32]. This increase may be exacerbated in the Veteran population, which is older than the general population and is aging at a disproportionate rate compared to the general population [33–35].

Non-invasive pneumococcal pneumonia is generally not included in *S. pneumoniae* surveillance; however, *S. pneumoniae* is the most common cause of community-acquired pneumonia [1, 36–38]. Therefore, our findings may more accurately define the true burden of pneumococcal disease in the US. Rates of pneumonia directly attributable to

S. pneumoniae range from 36.1 to 500 cases per 100,000 persons per year [5, 39].

Worldwide pneumococcal pneumonia mortality rates range considerably from 6% to greater than 50% depending on disease severity and host factors, including age and the presence of comorbid conditions [40–44]. The non-invasive pneumococcal pneumonia 30-day mortality rate we observed is similar to that previously reported in a Veteran population (14.2% versus 12.8%) [45]. The pneumococcal bacteremia and meningitis mortality rates we observed also agreed with previous findings, which range from 10% to greater than 40% [46–50].

Overall, one-third of the patients in our study with serious infections had a history of pneumococcal vaccination, which is much lower than the previously reported vaccination rate of 85% for patients at VA facilities nationally in 2003 [51]. As we conducted our study in older adults and observed significant increases in risk factors for *S. pneumoniae*, it is likely that a number of these non-vaccinated patients had indications for vaccination. This is extremely concerning as non-vaccinated patients with indications for vaccination are more likely to become infected with pneumococcus than those without indications, and non-vaccinated patients are also twice as likely to die if they develop invasive pneumococcal disease [52, 53].

The sickest patients in our study were more likely to receive pneumococcal vaccination. Therefore, the vaccinated patients likely had more healthcare exposures resulting in greater opportunities to receive a pneumococcal vaccination than the non-vaccinated patients. Increased pneumococcal vaccination awareness may be needed for patients who are at risk of pneumococcal disease and have indications for vaccination but have fewer healthcare exposures. The administration of vaccination in non-traditional settings, such as pharmacies and shopping malls, may improve vaccine coverage in these patients [4].

There are several limitations to this study. Our estimation of burden of non-invasive pneumococcal disease may be an underestimate, particularly in the outpatient population, as the value of cultures is limited in the diagnosis of many non-invasive pneumococcal infections. For acute otitis media, the standard of diagnosis is with otoscopic examination not bacterial cultures. For pneumonia, sputum samples are optional in most patients as utility is limited by the

inability of many patients to produce adequate sputum samples and by poor specificity due to pneumococcal colonization of the upper airways [38]. For the inpatient population, we attempted to increase the specificity of respiratory cultures by requiring a diagnosis code for pneumonia. We did not include *S. pneumoniae* antigen detection tests to define pneumococcal disease. Pneumococcal urinary antigen tests may be adequate to diagnose pneumococcal pneumonia; however, sputum cultures are often still indicated at the point of care for sensitivity testing to confirm the appropriate antimicrobial treatment [38].

Our vaccination rates may be lower than that previously reported as we defined vaccination as documentation of pneumococcal vaccination administration in the previous 1, 5, and 10 years, while the earlier study considered vaccinated patients to be those with any prior medical documentation indicating receipt of a vaccination [51]. Patients may have received a pneumococcal vaccination outside the VA which would underestimate our vaccination rates. However, our pneumococcal vaccination rates are comparable to the national vaccination rate of 20.1% for high-risk adults aged 19–64 reported in the 2011 National Health Interview Survey [54].

Due to the retrospective nature of this study, isolates were not available and as such serotype data were not available. Data on immunosuppressant use, such as corticosteroid and chemotherapy, were not available, which are risk factors for pneumococcal disease. Additionally, there is always the potential for misclassification when relying on ICD-9 codes; however, disease coding in the VA database has been validated for a number of conditions and is determined to be of high quality [55–58]). Moreover, we identified pneumococcal infections using microbiology data rather than

ICD-9 codes. Finally, the generalizability of our study is limited to the Veteran population.

CONCLUSION

We described the epidemiology of invasive and non-invasive pneumococcal disease in a large, national population of older adults, who are at the greatest risk for pneumococcal infections. We observed a concerning trend of increasing *S. pneumoniae* risk factors among those with serious pneumococcal infections. With the aging population and the epidemic of chronic illnesses, the burden of pneumococcal disease is likely to rise. Efforts to improve vaccination rates among high-risk patients may be an important strategy to mitigate increases in pneumococcal disease, however this requires further investigation.

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