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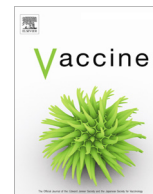
Pneumococcal epidemiology among us adults hospitalized for community-acquired pneumonia

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ABSTRACT

Background: Few studies have measured the burden of adult pneumococcal disease after the introduction of 13-valent pneumococcal conjugate vaccine (PCV13) into the US infant vaccination schedule. Further, most data regarding pneumococcal serotypes are derived from invasive pneumococcal disease (IPD), which represents only a fraction of all adult pneumococcal disease burden. Understanding which pneumococcal serotypes cause pneumonia in adults is critical for informing current immunization policy. The objective of this study was to measure the proportion of radiographically-confirmed (CXR+) community-acquired pneumonia (CAP) caused by PCV13 serotypes in hospitalized US adults.
Methods: This observational, prospective surveillance study recruited hospitalized adults aged ≥18 years from 21 acute care hospitals across 10 geographically-dispersed cities in the United States between October 2013 and September 2016. Clinical and demographic data were collected during hospitalization. Vital status was ascertained 30 days after enrollment. Pneumococcal serotypes were detected via culture from the respiratory tract and normally-sterile sites (including blood and pleural fluid). Additionally, a novel, Luminex-based serotype-specific urinary antigen detection (UAD) assay was used to detect serotypes included in PCV13.
Results: Of 15,572 enrolled participants, 12,055 eligible patients with CXR+CAP were included in the final analysis population. Mean age was 64.1 years and 52.7% were aged ≥65 years. Common comorbidities included chronic obstructive pulmonary disease (43.0%) and diabetes mellitus (28.6%). PCV13 serotypes were detected in 552/12,055 (4.6%) of all patients and 265/6347 (4.2%) of those aged ≥65 years. Among patients aged 18–64 years PCV13 serotypes were detected in 3.8–5.3% of patients depending on their risk status.
Conclusions: After implementation of a pneumococcal conjugate vaccination program in US children, and despite the herd protection observed in US adults, a persistent burden of PCV13-type CAP remains in this population.

1. Introduction

Community-acquired pneumonia (CAP) is an infection of the lung parenchyma that develops in persons outside of a health-care facility. Pneumonia and other lower respiratory tract infections cause 79% of infectious-disease-related deaths in the United States [1]. Adults aged ≥65 years have substantial morbidity and mortality related to CAP [2], and are hospitalized more frequently with the disease compared to younger populations. Comorbid conditions such as chronic respiratory disease, chronic heart disease, diabetes mellitus, and high alcohol intake place individuals at increased risk for CAP, more severe illness, and worse outcomes than otherwise healthy individuals [3–5]. In addition, adults with immunocompromising conditions such as human immunodeficiency virus (HIV) infection, chronic renal failure, leukemia, and lymphoma are at even higher risk of developing CAP [6].

Streptococcus pneumoniae is a leading cause of CAP, bacterial meningitis, and bacteremia [7–13]. Non-invasive CAP is the most common manifestation of pneumococcal disease in adults. In 2004, *S. pneumoniae* was estimated to be the etiologic agent in nearly 600,000 cases of pneumonia in US adults aged >18 years [14]. Although *S. pneumoniae* remains the most commonly identified cause of bacterial CAP, the estimated proportion of disease attributed to *S. pneumoniae* has decreased since the introduction of pneumococcal conjugate vaccines (PCV) for use in children and adults [15–17].

In 2000, a 7-valent PCV (PCV7) covering serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F was introduced into the US infant vaccination program. In 2010, PCV7 was replaced with a 13-valent PCV (PCV13) which added coverage for serotypes 1, 3, 5, 6A, 7F, and 19A. Well-documented, significant reduction of vaccine-type pneumococcal diseases has resulted from this vaccination program in the United States and in other cohorts of children around the world [18–21]. Unvaccinated children and adults have also benefited from the indirect (herd) effects of the program [22–25]. In September 2014, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) expanded their 2012 recommendation of PCV13 in adults with immunocompromising conditions [6] to include all adults aged ≥65 years [26].

The majority of data describing the prevalence of pneumococcal serotypes are limited to invasive pneumococcal disease (IPD). Culture-based diagnostic methods can only identify a very limited fraction of VT-bacteremic pneumonia and conventional urinary diagnostic testing methods (such as the Binax-NOW assay [27]) cannot identify the specific pneumococcal serotypes in patients with pneumonia [28]. Therefore, a novel, proprietary urinary antigen detection (UAD) assay was developed [29] to detect 13 serotype-specific pneumococcal antigens corresponding to the serotypes contained in PCV13 [29]. Few studies investigating pneumococcal serotype distribution in CAP utilizing the UAD have been completed since the introduction of PCV13 in adults [28]. Thus, the current burden of non-invasive CAP due to PCV13 serotypes in adults is not fully understood.

The primary objective of this study was to estimate the proportion of radiographically-confirmed (CXR+) CAP caused by *S. pneumoniae* serotypes contained in PCV13 among adults aged ≥18 years. A secondary objective was to describe the difference in detection of *S. pneumoniae* by culture, BinaxNOW, and UAD. We also report mortality related to CXR+CAP.

2. Methods

2.1. Study design and participants

Detailed methodology for this observational, prospective study of adults aged ≥18 years hospitalized with CXR+CAP has been published previously [30]. Briefly, study participants were recruited between October 2013 and September 2016 from 21 acute care hospitals across 10 cities (Akron, OH, Chicago, IL, Detroit, MI, Louisville, KY, Nashville, TN, Norfolk, VA, Houston TX, Las Vegas, NV, San Diego, CA, Worcester, MA). Each city had one hospital site involved in adult CAP patient recruitment except for Detroit, MI (n = 2), San Diego, CA (n = 3), and Louisville, KY (n = 9). Institutional Review Board approval was obtained from each individual institution. This study was conducted in accordance with applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All study participants provided informed consent prior to enrollment.

2.2. Inclusion criteria

All adults who presented to any of the study hospitals or emergency departments with suspected pneumonia were prospectively identified and screened for inclusion. Selection criteria were evaluated at the time of enrollment. To be eligible, participants had to: (1) be aged ≥18 years; (2) present to a study healthcare facility where the treating clinician clinically suspected CAP based on the presence of two or more of the following signs or symptoms: fever or hypothermia within 24 h of enrollment, chills or rigors, pleuritic chest pain, cough, sputum production, dyspnea, tachypnea, malaise, or abnormal auscultatory findings suggestive of pneumonia; (3) have a radiographic finding confirmed by a board-certified radiologist that was consistent with pneumonia obtained no more than 72 h prior to study enrollment; and (4) be able and willing to provide a urine sample.

2.3. Exclusion criteria

Participants were excluded if they had hospital-acquired pneumonia (HAP). HAP was defined as any patient who was i) transferred to a study healthcare facility after already being hospitalized for ≥48 h at any other in-patient facility, such as a community hospital, or ii) developed signs and symptoms of pneumonia after being hospitalized at a study site for ≥48 h. Patients were also excluded if they had severe chronic conditions or laboratory abnormalities that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study. Finally, patients who were previously enrolled in the study within the past 30 days were also excluded. Thus, patients could contribute >1 CAP hospitalization event to the study if a subsequent CAP hospitalization for the same patient occurred >30 days after the previous hospitalization.

2.4. Risk status definitions

Participants were classified as "high-risk" if they had any of the following immunocompromising medical conditions: chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency

syndrome (AIDS), HIV, or immunosuppressive drug therapy. Participants were classified as "at-risk" if they did not fulfill the criteria for "high-risk" (ie, were not immunocompromised) and had any of the following medical conditions or health behaviors: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse. The presence of medical conditions was determined by medical record review, and health behaviors like smoking and alcohol abuse were based on self-reported data obtained from a screening questionnaire. Participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk". These risk categories were based on CDC designations which are applied to current ACIP recommendations for pneumococcal vaccination [31–33].

2.5. Study assessments

If eligible for enrollment, participant demographic and medical history information was collected. Results of blood and respiratory cultures collected as a part of the patient's standard medical care were recorded. For participants not having blood cultures collected as standard medical care, blood was collected for culture as a study-related procedure. Urine was collected in a non-invasive manner from all patients as a study-related procedure as soon as possible following the signing of the Informed Consent. When feasible, urine was collected within 24 h after study enrollment. Only patients with a final diagnosis of CXR+CAP confirmed by a study physician were included. Hospital admission and discharge dates were also collected. Assessment of vital status occurred up to 30 days after enrollment.

2.6. Microbiological assessments

All samples collected either as part of standard of care or study-related procedure underwent bacterial culture at the local laboratory for the identification of pathogens (and antibiotic susceptibility) according to standard methodology. All *S. pneumoniae* isolates were sub-cultured and maintained at the study sites. An aliquot was also sent to a central laboratory for confirmation of *S. pneumoniae* and serotype identification. In addition to laboratory culture, both BinaxNOW and the serotype-specific *S. pneumoniae* UAD assay were performed on urine samples [30]. UAD and BinaxNOW testing of urine samples was completed at Pfizer's Vaccines Research and Development Laboratory (Pearl River, NY). Urine testing and serotyping were performed blinded to all clinical information.

2.7. UAD assay

The UAD is a validated limit assay based on defined positivity cut-off limits and can simultaneously detect the 13 different serotypes of *S. pneumoniae* that are contained in PCV13 by capturing serotype-specific polysaccharides excreted in human urine [29]. This assay has demonstrated higher sensitivity than culture or conventional urinary antigen detection and excellent specificity in a convenience sample obtained from 776 participants with CXR +CAP [34], and in a separate prospective study of adults with radiographically-confirmed pneumonia [17]. Co-detections of up to two serotypes constitute a valid result and were reported. Detection of three or more serotypes was classified as an indeterminate result [29].

2.8. Data analysis

Only patients who met study eligibility criteria, had a final diagnosis of CXR+CAP, and did not receive pneumococcal vaccine

within 30-days of study enrollment (based on patient self-report) were included in the primary analysis population. Patients who received a pneumococcal vaccine within 30 days of enrollment were excluded because a previous study suggested that recent pneumococcal vaccination could impact detection of pneumococcal serotypes in urine samples [35]. Patients with *S. pneumoniae* isolated from any microbiologic specimen, or with a positive UAD assay or BinaxNOW result were considered to have *S. pneumoniae* detected. The proportion of patients in the final analysis population where *S. pneumoniae* and PCV13 serotypes were detected was summarized using descriptive statistics. Categorical variables were described using frequencies and percentages, and continuous variables were described with means (with standard deviations), ranges, and medians (for highly skewed variables). Results were presented for the entire analysis population and were also stratified across time period (ie, epidemiological year) and four different age/risk groups that reflected current ACIP recommendations for pneumococcal vaccination [31–33] (ie, all adults aged ≥65 years and adults aged <65 years with high-risk, at-risk, or low-risk conditions as described previously). Chi-square tests were used to evaluate changes in PCV13 serotypes over time, comparing the proportion of PCV13 serotypes identified in year one to year three, for each age/risk group.

3. Results

Overall, 15,572 participants were enrolled, 12,055 of which were eligible, had CXR+CAP, and were included in the final analysis population (Table 1). Most participants (79.7%) included in the analysis were recruited from hospitals in Louisville, KY. Roughly half (52.7%, n = 6347) were aged ≥65 years, 15.5% were aged 18 to 64 years with high-risk conditions (n = 1864), 24.7% were aged 18 to 64 years with at-risk conditions (n = 2976), and 7.2% were aged 18 to 64 years without underlying chronic illness (ie, low-risk; n = 868) (Table 1). Mean age at consent was 64.1 years. Roughly half (50.5%) of the participants were female and the majority (80.0%) was white/non-Hispanic. Mean pneumonia severity index (PSI) score was 89.5, although patients aged ≥65 years had a mean score of 110.2 (Table 2). Mean hospital stay was 7.1 days (supplementary Table 1).

3.1. Chronic medical conditions and risk status

In total, 38.5% and 47.8% of all patients were considered high risk and at risk, respectively (supplementary Table 1). The most prevalent at-risk conditions were chronic obstructive pulmonary disease (43.0%), smoking (29.3%), and diabetes (28.6%), while the most prevalent high-risk conditions were chronic kidney disease (15.4%), solid tumor (15.3%), and immunosuppressant therapy (12.4%) (supplementary Table 1). Only 13.8% (1659/12,055) did not have at least one high-risk or at-risk condition.

3.2. S. pneumoniae detection

S. pneumoniae was detected in 1194/12,055 (9.9%) participants as determined by BinaxNOW, UAD, or culture. *S. pneumoniae* was detected by UAD alone in 345/12,055 (2.9%) patients, which represented 28.9% (345/1194) of all pneumococcal CAP detected. Another 122/12,055 (1.0%) cases were detected by culture alone, and 447/12,055 (3.7%) cases were detected by BinaxNOW alone (Fig. 1). Using any diagnostic method, *S. pneumoniae* was detected in 585/6347 (9.2%) of those aged ≥65 years and 609/5708 (10.7%) of those aged 18 to 64 years (supplementary Table 2). For patients aged <65 years, the prevalence of *S. pneumoniae* was 10.8%

Table 1
Analysis populations by age and risk condition, n = 15,572.

		Age/risk group				
	Unknown	≥65n (%)	18–64 high-risk n (%)	18–64 at-risk n (%)	18–64 low-risk n (%)	Total n (%)
All enrolled population[a]	559	8234 (100.0%)	2210 (100.0%)	3574 (100.0%)	995 (100.0%)	15,572 (100.0%)
Radiographically confirmed CAP		6347 (77.1%)	1864 (84.3%)	2976 (83.3%)	868 (87.2%)	12,055 (77.4%)
SP + CAP subpopulation		585 (7.1%)	201 (9.1%)	334 (9.3%)	74 (7.4%)	1194 (7.7%)
SP – CAP subpopulation		5762 (70.0%)	1663 (75.2%)	2642 (73.9%)	794 (79.8%)	10,861 (69.7%)
Excluded from CAP population[b]	559	1887 (22.9%)	346 (15.7%)	598 (16.7%)	127 (12.8%)	3517 (22.6%)
Important protocol deviations	558	863 (10.5%)	20 (0.9%)	20 (0.6%)	10 (1.0%)	1471 (9.4%)
Without final diagnosis of radiographically-confirmed CAP	551	1676 (20.4%)	280 (12.7%)	445 (12.5%)	101 (10.2%)	3053 (19.6%)
Received pneumococcal vaccine within 30 days before consent		193 (2.3%)	64 (2.9%)	168 (4.7%)	30 (3.0%)	455 (2.9%)
UAD population	22	7400 (89.9%)	2191 (99.1%)	3552 (99.4%)	984 (98.9%)	14,149 (90.9%)
UAD assay CAP subpopulation		6344 (77.0%)	1860 (84.2%)	2973 (83.2%)	866 (87.0%)	12,043 (77.3%)
Microbiology culture population	7	6741 (81.9%)	2043 (92.4%)	3223 (90.2%)	915 (92.0%)	12,929 (83.0%)
Microbiology culture CAP subpopulation		5993 (72.8%)	1775 (80.3%)	2791 (78.1%)	823 (82.7%)	11,382 (73.1%)
BinaxNOW population	22	7404 (89.9%)	2195 (99.3%)	3555 (99.5%)	986 (99.1%)	14,162 (90.9%)
BinaxNOW assay CAP subpopulation		6347 (77.1%)	1864 (84.3%)	2976 (83.3%)	868 (87.2%)	12,055 (77.4%)

Note: 'Unknown' included 13 participants from Site 1029 as the IRB did not allow further info entered into database if participants are not eligible; the remaining 'Unknown' were patients with medical history information (for risk condition) missing. High-risk = chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency syndrome (AIDS), HIV, or immunosuppressive drug therapy; at-risk = were not immunocompromised and had any of the following medical conditions: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse; low-risk = participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk".
SP+ = *Streptococcus pneumoniae* positive; SP− = *Streptococcus pneumoniae* negative; CAP = community acquired pneumonia; UAD = urinary antigen detection assay.
 [a] The count for this row is used as denominators for percentages.
 [b] Participant may be excluded for multiple reasons.

(201/1864), 11.2% (334/2976), and 8.5% (74/868), for high risk, at risk, and low risk respectively (supplementary Table 2).

3.3. PCV13 serotype detection

Overall, PCV13 serotypes were detected in 552 of 12,055 (4.6%) participants via UAD or culture (Table 3). Among those, PCV13 serotypes were detected in 42 patients (7.6%) via culture, and 547 patients (99.1%) via UAD. Of the 547 detected by UAD, 65 (11.9%) had two serotypes identified. Of the 37 patients where a PCV13 serotype was identified by both UAD and culture, the same serotype was identified in 34 patients (91.9%). The three patients with different serotypes identified between culture and UAD were: 3 (blood culture) *vs* 19A (UAD); 3 (sputum culture) *vs* 3 and 18C (UAD); and 3 (sputum culture) *vs* 5 and 9V (UAD). The five patients who had PCV13 identified only from culture were serotypes 19F (n = 2), 3 (n = 2), and 19A (n = 1).

Overall, the most common *S. pneumoniae* serotypes detected were PCV13 serotypes not covered by PCV7 (Table 3), however, a UAD was not available for non-PCV13 serotypes. These included serotypes 19A (1.3%, n = 152), 3 (1.1%, n = 130), 5 (0.6%, n = 78), 7F (0.4%, n = 54), and 6A (0.4%, n = 47) (Table 2). Serotype 1, also a PCV13 serotype not covered by PCV7, was detected at a similar frequency to the most common PCV7 serotypes (14, 18C, 19F, and 23F each 0.2%). The remaining PCV7 serotypes included serotypes 4 and 9V (each 0.1%) and serotype 6B (<0.1%, n = 6) (Table 3). Non-vaccine type *S. pneumoniae* (as determined by culture only) was identified in 1.4% (n = 173) of patients. The most common non-PCV13 serotype was 22F (0.2%, n = 28); all others occurred in <0.1% of all participants. PCV13 serotypes were detected in 265/6347 (4.2%) participants aged ≥65 years. Among patients aged 18–64 years classified as high-risk, at-risk, or low-risk, PCV13 serotypes were detected by UAD or culture in 95/1864 (5.1%), 159/2976 (5.3%), and 33/868 (3.8%), respectively.

Among all participants >18 years of age over the three-year study period (October 2013 through September 2016), the proportion caused by PCV13 serotypes decreased from 5.3% (n = 163/3076) in the first year to 4.6% (n = 247/5366) and 3.9% (n = 142/3613) in years two and three, respectively (P = .01 year one *vs* year three). This statistically-significant reduction trend was driven by reductions among adults aged ≥65 years (5.1% [76/1495] at year one *vs* 3.4% [68/2010] at year three, P = .01) and in high-risk patients aged 18–64 years (7.0% [37/530] at year one *vs* 4.0% [17/428] at year three [n = 17], P = .05) (Fig. 2). Reductions were generally seen across all PCV13 serotypes except for serotype 3, which did not decrease in prevalence over the study period. Serotype-specific evaluations, however, were limited by small sample size (supplementary Table 3). For adults aged 18–64 years with at-risk (5.3% [41/782] at year one *vs* 5.3% [50/948] at year three, P = .98) or low-risk (3.4% [9/269] at year one *vs* 3.1% [7/227] at year three, P = .87) conditions, the prevalence of PCV13 serotypes remained stable over the study period (Fig. 2).

3.4. Mortality

Deaths occurring within 30 days of enrollment were recorded, as were some deaths occurring after day 30 (due to follow-up schedule, etc.). Overall mortality was 9.0% (1081/12,055), and 514 (47.5%) of these deaths were caused by pneumonia (Table 4). Thirty-day mortality was 8.4% (1009/12,055) (Table 4). Overall mortality among patients with PCV13 serotype-positive CXR+CAP was similar to the overall study population (9.4%, 52/552), and 30 of these deaths (57.7%) were caused by pneumonia. Thirty-day mortality among those with PCV13 serotype-positive CXR +CAP was also similar (8.7%, 48/552) (Table 4).

Overall mortality among patients aged 18–64 years classified as high-risk, at-risk, and low-risk was 8.8% (164/1864), 3.0% (90/2976), and 1.6% (14/868), respectively (Table 4). As expected, higher overall mortality (12.8%, 813/6347) was seen in patients aged ≥65 years. Patients aged ≥65 years (11.9%, 754/6347) and those aged 18–64 years classified as high-risk (8.4%, 156/1864) were more likely to die within 30 days of hospitalization when compared to adults aged <65 years with at-risk (2.9%, 85/2976) or low-risk (1.6%, 14/868) conditions (Table 4).

Table 2
Demographics by age and risk conditions for those with CAP, n = 12,055.

Age/risk group					
	≥65 (N = 6347)	18–64 high-risk (N = 1864)	18–64 at-risk (N = 2976)	18–64 low-risk (N = 868)	Total (N = 12055)
Age at consent (years)					
N	6347	1864	2976	868	12,055
Mean (SD)	76.7 (8.15)	51.9 (10.34)	50.1 (11.22)	45.3 (13.17)	64.1 (16.61)
Median	76	55	53	47	65
Range	65, 103	18, 64	18, 64	18, 64	18, 103
Sex					
Female	3149 (49.6%)	934 (50.1%)	1560 (52.4%)	445 (51.3%)	6088 (50.5%)
Male	3198 (50.4%)	930 (49.9%)	1416 (47.6%)	423 (48.7%)	5967 (49.5%)
Race					
White	5551 (87.5%)	1302 (69.8%)	2138 (71.8%)	659 (75.9%)	9650 (80.0%)
Black	765 (12.1%)	541 (29.0%)	809 (27.2%)	195 (22.5%)	2310 (19.2%)
Asian	25 (0.4%)	17 (0.9%)	13 (0.4%)	7 (0.8%)	62 (0.5%)
Other	6 (0.1%)	4 (0.2%)	16 (0.5%)	7 (0.8%)	33 (0.3%)
Ethnicity					
Not Hispanic/Latino	6288 (99.1%)	1830 (98.2%)	2915 (98.0%)	828 (95.4%)	11,861 (98.4%)
Hispanic/Latino	58 (0.9%)	34 (1.8%)	60 (2.0%)	39 (4.5%)	191 (1.6%)
Missing	1 (0.0%)	0 (0%)	1 (0.0%)	1 (0.1%)	3 (0.0%)
Height (cm)					
N	6334	1860	2968	861	12,023
Mean (SD)	168.7 (11.02)	169.9 (10.91)	169.9 (10.82)	170.6 (11.29)	169.3 (10.99)
Median	168	170	170	170.18	170
Min, Max	91, 213	119, 206	116, 198.12	91, 208.3	91, 213
Weight (kg)					
N	6345	1863	2975	863	12,046
Mean (SD)	77.9 (22.41)	83.2 (26.04)	89.2 (28.79)	87.4 (28.48)	82.2 (25.62)
Median	75	79.4	84.2	83.14	78.4
Min, Max	29.6, 226.8	29.4, 226.9	30.3, 261.27	25.5, 284	25.5, 284
BMI (kg/m^2)					
N	6334	1860	2968	860	12,022
Mean (SD)	27.3 (7.52)	28.9 (8.97)	30.9 (9.73)	30.0 (9.37)	28.6 (8.61)
Median	26.175	27.35	29.26	28.535	27.17
Min, Max	11.73, 106.47	12.19, 81.33	11.11, 106.84	8.58, 91.35	8.58, 106.84
Previous enrollment in this study					
Yes	714 (11.2%)	218 (11.7%)	262 (8.8%)	29 (3.3%)	1223 (10.1%)
No	5632 (88.7%)	1644 (88.2%)	2714 (91.2%)	839 (96.7%)	10,829 (89.8%)
Unknown	1 (0.0%)	2 (0.1%)	0 (0%)	0 (0%)	3 (0.0%)
Participant resides in the surveillance area					
Yes	4895 (77.1%)	1402 (75.2%)	2352 (79.0%)	634 (73.0%)	9283 (77.0%)
No	1172 (18.5%)	372 (20.0%)	455 (15.3%)	151 (17.4%)	2150 (17.8%)
Missing	280 (4.4%)	90 (4.8%)	169 (5.7%)	83 (9.6%)	622 (5.2%)
Pneumonia Severity Index (PSI)					
N	6250	1836	2937	856	11,879
Mean (SD)	110.2 (33.85)	86.9 (41.77)	60.6 (41.86)	43.3 (38.47)	89.5 (44.70)
Median	106	88	62	50	90
Min, Max	0, 264	0, 244	0, 230	0, 173	0, 264
PSI grade					
GRADE I	22 (0.3%)	159 (8.5%)	651 (21.9%)	309 (35.6%)	1141 (9.5%)
GRADE II	560 (8.8%)	397 (21.3%)	1113 (37.4%)	348 (40.1%)	2418 (20.1%)
GRADE III	1377 (21.7%)	417 (22.4%)	530 (17.8%)	115 (13.2%)	2439 (20.2%)
GRADE IV	2764 (43.5%)	626 (33.6%)	501 (16.8%)	68 (7.8%)	3959 (32.8%)
GRADE V	1527 (24.1%)	237 (12.7%)	142 (4.8%)	16 (1.8%)	1922 (15.9%)
Missing	97 (1.5%)	28 (1.5%)	39 (1.3%)	12 (1.4%)	176 (1.5%)

Note: SD = standard deviation. High-risk = chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency syndrome (AIDS), HIV, or immunosuppressive drug therapy; at-risk = were not immuno-compromised and had any of the following medical conditions: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse; low-risk = participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk".
BMI = body mass index; PSI = pneumonia severity index.

4. Discussion

This is the largest prospective multicenter surveillance study conducted to date in the United States to estimate the burden of CAP due to PCV13 pneumococcal serotypes. Among 12,055 patients with CXR+CAP, 9.9% had *S. pneumoniae* detected—almost half of which were attributable to PCV13 serotypes (4.6%). The most commonly identified serotypes were 19A, 3, 5, 7F, and 6A, all of which are contained in PCV13 but not in PCV7. At the time of this study, however, a serotype-specific UAD assay did not exist for the other non-PCV13 serotypes. Thus, given the higher sensitivity of the UAD for detecting pneumococcal serotypes compared to BinaxNOW and traditional culture methods [17,34], this study likely underestimates the proportion of CAP due to all pneumococcus and overestimates the proportion of pneumococcal disease due to PCV13 serotypes.
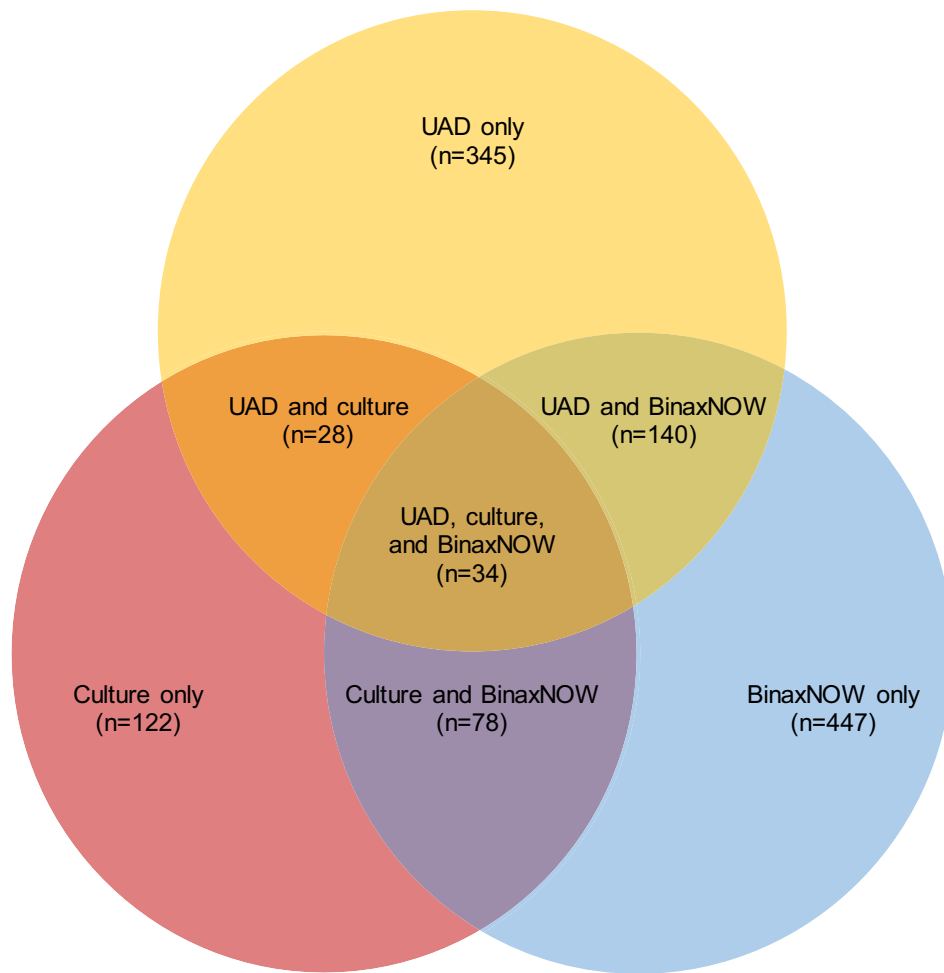
Fig. 1. *S. pneumoniae* identification by diagnostic method among all study participants with radiographically-confirmed CAP, n = 1194. UAD = proprietary serotype-specific urinary antigen detection assay. A total of 1194/12,055 (9.9%) had *S. pneumoniae* detected by any method. The UAD only detects serotypes contained in 13-valent pneumococcal conjugate vaccine.

The prevalence of *S. pneumoniae* has long been underestimated in patients diagnosed with CAP, especially non-bacteremic pneumococcal CAP, due to a lack of sensitive diagnostic assays [36]. Our study utilized traditional culture, BinaxNOW, and a serotype-specific UAD assay designed to identify PCV13 serotypes that may have been missed utilizing traditional culture or a qualitative urinary antigen test. Importantly, nearly a third of all pneumococcal CXR+CAP was detected only by UAD in our study, and UAD allowed for the detection of an additional 345 cases of *S. pneumoniae* that would have otherwise been missed using traditional detection methods only (BinaxNOW and culture).

Similar results were found in the Etiology of Pneumonia in the Community (EPIC) study, conducted between 2010 and 2012 to determine the etiology and incidence of CAP among 2488 adults in the United States [28]. The original EPIC study utilized culture and BinaxNOW urine testing, and showed that *S. pneumoniae* was detected in only 5.0% of adults with radiographically confirmed pneumonia. More recent data from a sub-study of EPIC, however, has since been published (utilizing residual urine samples) and showed that many cases of pneumococcal CAP were missed by traditional detection methods. Specifically, after utilizing the serotype-specific UAD assay, the EPIC sub-study showed, that 9.7% and 6.3% of hospitalized CAP in adults was due to *S. pneumoniae* and PCV13 serotypes, respectively [37]. This represented a near doubling of the original number of *S. pneumoniae* detections in the early EPIC publication where the UAD was not incorporated.

It should be noted that the EPIC sub-study reported data that was originally gathered from January 2010 through June 2012 [28]. These data were therefore obtained prior to the full impact of transitioning the pediatric immunization program from PCV7 to PCV13 in 2010. The data also preceded the 2014 ACIP recommendation for adults aged ≥65 years.

The prevalence of *S. pneumoniae* observed in the current study is lower than previously reported in a study by Sherwin et al. [38]. In that study, which enrolled participants between 2010 and 2011, *S. pneumoniae* and PCV13 serotypes were detected in 13.8% and 11.0% of CAP cases, respectively, using several diagnostic methods, including the same proprietary UAD assay used in the current study [29,38]. The lower rates of PCV13 serotype disease (roughly 5%) in our study is not unexpected, however, given that more years of indirect effects stemming from the pediatric PCV13 program had occurred during our study period. In addition, the more recent decline in PCV13 serotypes seen in our study may reflect the effectiveness of direct vaccination of adults aged ≥65 years.

Despite pediatric herd effects, PCV13 serotypes continue to cause CAP in adults in the United States. A small but consistent decline in PCV13 serotypes was observed over the three-year study period (5.3% in year one to 3.9% in year three), which was driven by PCV13-type reductions in the two adult populations who are recommended to receive PCV13 (i.e., adults aged ≥65 years and aged <65 years with high-risk conditions). Only immunocompromised

Table 3
Distribution of pneumococcal serotypes identified from CAP cases by UAD or culture, n = 12,055.

	Age/risk group				
	≥65 n (%)	18 to 64 high-risk n (%)	18 to 64 at-risk n (%)	18 to 64 low-risk n (%)	Total n (%)
Total population[a] (Denominator for % participants)	6347	1864	2976	868	12,055
SP + by UAD or culture	350 (5.5%)	134 (7.2%)	214 (7.2%)	49 (5.6%)	747 (6.2%)
SP + isolates not serotyped[b]	21 (0.3%)	8 (0.4%)	15 (0.5%)	3 (0.3%)	47 (0.4%)
SP + with serotypes[c]	336 (5.3%)	128 (6.9%)	202 (6.8%)	47 (5.4%)	713 (5.9%)
Serotypes covered by PCV13[c]	265 (4.2%)	95 (5.1%)	159 (5.3%)	33 (3.8%)	552 (4.6%)
Serotypes covered by PCV7	53 (0.8%)	37 (2.0%)	31 (1.0%)	3 (0.3%)	124 (1.0%)
4	8 (0.1%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	12 (0.1%)
6B	2 (0.0%)	4 (0.2%)	0 (0.0%)	0 (0.0%)	6 (0.0%)
9V	5 (0.1%)	6 (0.3%)	4 (0.1%)	0 (0.0%)	15 (0.1%)
14	11 (0.2%)	6 (0.3%)	8 (0.3%)	1 (0.1%)	26 (0.2%)
18C	6 (0.1%)	7 (0.4%)	9 (0.3%)	0 (0.0%)	22 (0.2%)
19F	10 (0.2%)	5 (0.3%)	3 (0.1%)	1 (0.1%)	19 (0.2%)
23F	12 (0.2%)	9 (0.5%)	7 (0.2%)	1 (0.1%)	29 (0.2%)
Additional 6 serotypes covered by PCV13	222 (3.5%)	69 (3.7%)	136 (4.6%)	31 (3.6%)	458 (3.8%)
1	15 (0.2%)	5 (0.3%)	4 (0.1%)	5 (0.6%)	29 (0.2%)
3	57 (0.9%)	21 (1.1%)	41 (1.4%)	11 (1.3%)	130 (1.1%)
5	36 (0.6%)	11 (0.6%)	30 (1.0%)	1 (0.1%)	78 (0.6%)
6A	29 (0.5%)	3 (0.2%)	13 (0.4%)	2 (0.2%)	47 (0.4%)
7F	24 (0.4%)	8 (0.4%)	18 (0.6%)	4 (0.5%)	54 (0.4%)
19A	73 (1.2%)	25 (1.3%)	46 (1.5%)	8 (0.9%)	152 (1.3%)
Serotypes NOT covered by PCV13[b]	77 (1.2%)	35 (1.9%)	46 (1.5%)	15 (1.7%)	173 (1.4%)
10A	1 (0.0%)	0 (0.0%)	1 (0.0%)	1 (0.1%)	3 (0.0%)
11A	9 (0.1%)	2 (0.1%)	2 (0.1%)	0 (0.0%)	13 (0.1%)
11C	0 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	1 (0.0%)
12F	3 (0.0%)	4 (0.2%)	2 (0.1%)	0 (0.0%)	9 (0.1%)
13	1 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
15A	7 (0.1%)	0 (0.0%)	2 (0.1%)	0 (0.0%)	9 (0.1%)
15B	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.2%)	3 (0.0%)
15C	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
16F	6 (0.1%)	2 (0.1%)	5 (0.2%)	0 (0.0%)	13 (0.1%)
17F	3 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (0.0%)
20	2 (0.0%)	0 (0.0%)	4 (0.1%)	2 (0.2%)	8 (0.1%)
21	3 (0.0%)	3 (0.2%)	0 (0.0%)	0 (0.0%)	6 (0.0%)
22F	10 (0.2%)	8 (0.4%)	5 (0.2%)	5 (0.6%)	28 (0.2%)
23A	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.0%)
23B	4 (0.1%)	1 (0.1%)	2 (0.1%)	0 (0.0%)	7 (0.1%)
25F	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.0%)
31	2 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	3 (0.0%)
33F	3 (0.0%)	1 (0.1%)	5 (0.2%)	0 (0.0%)	9 (0.1%)
34	2 (0.0%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	6 (0.0%)
35B	5 (0.1%)	1 (0.1%)	3 (0.1%)	0 (0.0%)	9 (0.1%)
38	1 (0.0%)	0 (0.0%)	1 (0.0%)	0 (0.0%)	2 (0.0%)
6C	8 (0.1%)	2 (0.1%)	5 (0.2%)	0 (0.0%)	15 (0.1%)
7B	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.0%)
7C	0 (0.0%)	2 (0.1%)	1 (0.0%)	0 (0.0%)	3 (0.0%)
8	3 (0.0%)	2 (0.1%)	1 (0.0%)	3 (0.3%)	9 (0.1%)
9N	3 (0.0%)	3 (0.2%)	2 (0.1%)	0 (0.0%)	8 (0.1%)
Serotypes covered by PPSV23[c]	273 (4.3%)	113 (6.1%)	169 (5.7%)	44 (5.1%)	599 (5.0%)

Note: high-risk = chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency syndrome (AIDS), HIV, or immunosuppressive drug therapy; at-risk = were not immunocompromised and had any of the following medical conditions: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse; low-risk = participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk".
UAD = urinary antigen detection assay; SP+ = *Streptococcus pneumoniae* positive; SP- = *Streptococcus pneumoniae* negative; CAP = community acquired pneumonia; PCV7 = 7-valent pneumococcal conjugate vaccine; PCV13 = 13-valent pneumococcal conjugate vaccine; PPSN23 = 23-valent pneumococcal polysaccharide vaccine.
  [a] Number of participants included in the population, with non-missing UAD/Culture results. The values in this row are used as the denominators for percentage of participants.
  [b] From culture only. Only one isolate is considered as 'Not Serotyped' if participants had none SP + isolates serotyped. The remaining isolates will NOT be considered as 'Not Serotyped' if at least one SP + isolate were serotyped.
  [c] From culture or UAD.

adults aged ≥19 years were recommended to receive PCV13 during the entire study period, and PCV13 uptake in this population is around 20–25% [39]. During the course of our study (in September 2014), ACIP recommended routine use of PCV13 for all adults aged ≥65 years, with PCV13 uptake steadily increasing in this population during the remainder of our study period [40,41]. Interestingly, in adults aged <65 years with at-risk or low-risk conditions, where PCV13 is not used, no decline in PCV13 sero-types was observed over the current study period. Given that indirect effects should affect all populations equally, this implies that (1) there may be an additional reduction in PCV13 serotypes in vaccinated adult populations and (2) PCV13-type CAP may have reached a plateau (e.g., between 5% and 6% in adults aged <65 years with at-risk conditions) in adult populations where PCV13 is not used. These findings were recently confirmed in a time-trend analysis [42], however, teasing apart the impact of adult PCV13 use
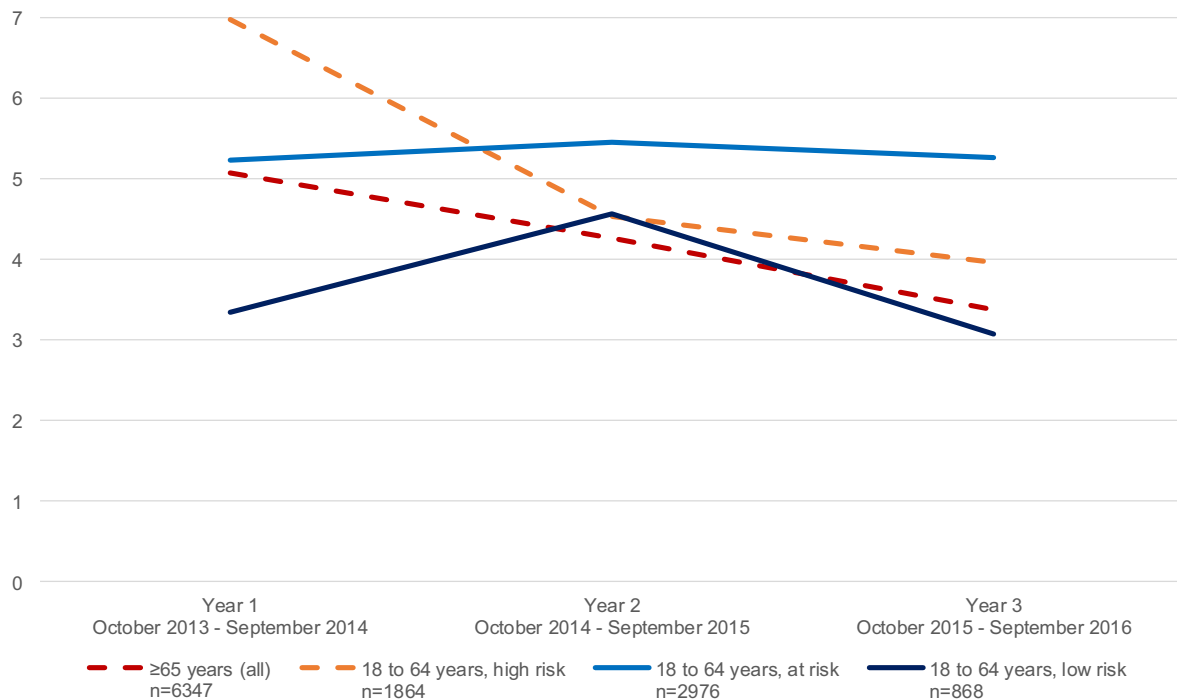
Fig. 2. Percentage of CAP caused by PCV13 serotypes over time by age/risk group among US adults, n = 12,055. CAP = community-acquired pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine. Dotted lines represent declines between year one and year three that were statistically significant at $P < .05$. High-risk = chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency syndrome (AIDS), HIV, or immunosuppressive drug therapy; at-risk = were not immunocompromised and had any of the following medical conditions: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse; low-risk = participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk".

from continued indirect effects stemming from the pediatric vaccination program remains difficult and warrants future research.

Our data describing the proportion of CAP in adults that remains PCV13-type are important when viewed in the context of the overall burden of all-cause CAP in the United States. Ramirez et al recently published a prospective, population-based study that demonstrated the incidence of CAP was roughly 700 per 100,000 among adults aged $\geq$18 years—which is higher than has been previously estimated. The authors showed that, when extrapolated to the population of the United States, this incidence rate corresponds to approximately 1.7 million total adult hospitalizations per year for CAP [43]. Based on this recently-published CAP burden [43], the roughly 4–5% of all CAP that remains PCV13-type observed in our current study translates to thousands of potentially-preventable hospitalizations in adults each year—the large majority of which occurs in adults aged $\geq$ 65 years or aged <65 years with underlying chronic medical conditions where the overall incidence rate of CAP is at least 1000–2000 per 100,000 per year [43].

Patients with underlying comorbidities are at increased risk for developing pneumonia including pneumococcal pneumonia [44] and older adults surviving CAP experience a long recovery period [45]. Ramirez et al. showed that patients who had diabetes, chronic heart failure, or chronic obstructive pulmonary disease had three to nine times higher incidence of hospitalization compared to the overall all-cause CAP population [43]. In a retrospective cohort study conducted by Shea et al, rates of pneumococcal pneumonia among at-risk adults were three times the rate in age-matched healthy counterparts [44]. Notably, patients with COPD had pneumonia rates that were eight to nine times higher compared to heathy counterparts [44]. Patients enrolled in our study had numerous underlying conditions placing them at increased risk of pneumonia. Most patients (86%) with CXR+CAP had at least one high-risk or at-risk condition, predominantly COPD (43%).

Thirty-day all-cause mortality in our population was approximately 9% in patients with CXR+CAP, similar to previous reports [43,46].

Our study has several limitations. First, most participants (80%) were from the Louisville sites. Despite having other sites from across the country to enroll patients, this high proportion of patients recruited from this one city limits the generalizability of the results. Second, study start-up was staggered, and recruitment varied considerably among sites and over time. Third, the study began approximately one year prior to the September 2014 ACIP recommendation of PCV13 for adults aged $\geq$65 years. Uptake of PCV13 in this population after the recommendation was slow and the impact of direct vaccination in this population is unclear. Fourth, detection of pneumococcal serotypes by the UAD assay is limited to detection of only the serotypes contained in the PCV13 vaccine.

Despite its limitations, our study demonstrates that despite the success of a national pediatric immunization program (since 2010 for PCV13), residual PCV13 serotype disease remains in adults. Moreover, our results suggest that this persistent disease burden has been grossly underestimated by previous studies that used only traditional pneumococcal detection methods and did not include a serotype-specific UAD. Given this remaining vaccine-type disease identified in adults, direct vaccination with PCV13 is likely beneficial in all older adults and younger adults with underlying chronic conditions. Our data support the appropriateness of current ACIP recommendations, which include routine pneumococcal vaccination in all adults aged $\geq$65 years and younger adults with high-risk medical conditions. These recommendations are rooted in the fact that, although the overall prevalence has declined, PCV13 serotype disease remains and the potential public-health benefit of continued PCV13 vaccination in the adult population remains substantial.

Table 4
Mortality and case fatality rate for those with CAP by age and risk status, n = 12,055.

Age/risk group	≥65 Years % (n/N)	18–64 High-risk % (n/N)	18–64 At-risk % (n/N)	18–64 Low-risk % (n/N)	Total % (n/N)
CAP population					
Lost to follow-up	8.3% (524/6347)	8.6% (161/1864)	14.7% (438/2976)	11.8% (102/868)	10.2% (1225/12055)
Total death[a]	12.8% (813/6347)	8.8% (164/1864)	3.0% (90/2976)	1.6% (14/868)	9.0% (1081/ 12055)
Pneumonia	48.5% (394/813)	40.9% (67/164)	48.9% (44/90)	64.3% (9/14)	47.5% (514/1081)
Unknown	36.2% (294/813)	34.8% (57/164)	31.1% (28/90)	28.6% (4/14)	35.4% (383/1081)
Other	19.3% (157/813)	37.2% (61/164)	26.7% (24/90)	7.1% (1/14)	22.5% (243/1081)
Time from hospitalization to death[b]					
n	812	163	90	14	1079
Mean (SD)	15.1 (9.29)	15.0 (8.68)	14.1 (8.68)	12.6 (6.92)	15.0 (9.12)
Median	13	14	13	11.5	13
Range	2, 55	2, 40	2, 40	4, 24	2, 55
Death within 30-day of hospitalization	11.9% (754/6347)	8.4% (156/1864)	2.9% (85/2976)	1.6% (14/868)	8.4% (1009/12055)
Death in the hospital[c]	6.3% (397/6347)	4.1% (77/1864)	1.8% (55/2976)	0.9% (8/868)	4.5% (537/12055)
PCV13 serotype CAP					
Lost to follow-up	9.1% (24/265)	15.8% (15/95)	18.9% (30/159)	9.1% (3/33)	13.0% (72/552)
Total death[a]	12.5% (33/265)	10.5% (10/95)	5.7% (9/159)	0.0% (0/33)	9.4% (52/552)
Pneumonia	57.6% (19/33)	60.0% (6/10)	55.6% (5/9)	(/0)	57.7% (30/52)
Unknown	33.3% (11/33)	20.0% (2/10)	22.2% (2/9)	(/0)	28.8% (15/52)
Other	9.1% (3/33)	40.0% (4/10)	33.3% (3/9)	(/0)	19.2% (10/52)
Time from hospitalization to death[b]					
n	33	10	9	0	52
Mean (SD)	14.8 (9.85)	9.8 (7.63)	12.2 (9.56)	()	13.4 (9.47)
Median	13	9.5	10		10
Range	2, 37	2, 28	3, 34	,	2, 37
Death within 30-day of hospitalization	11.3% (30/265)	10.5% (10/95)	5.0% (8/159)	0.0% (0/33)	8.7% (48/552)
Death in the hospital[c]	7.2% (19/265)	5.3% (5/95)	3.8% (6/159)	0.0% (0/33)	5.4% (30/552)

Note: N = number of participants included in the specified subgroup/SP status; n = number of participants died for the specified subgroup. High-risk = chronic kidney disease including end-stage renal disease (ESRD), organ transplantation, immunodeficiency, hematologic cancer/malignancy, solid tumor cancer/malignancy, acquired immunodeficiency syndrome (AIDS), HIV, or immunosuppressive drug therapy; at-risk = were not immunocompromised and had any of the following medical conditions: asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease (COPD), diabetes mellitus, current smoking, or alcohol abuse; low-risk = participants who were not categorized as "high-risk" or "at-risk" were considered "low-risk".

[a] Participants may have more than one causes of death.

[b] The 15th day was used to impute death date if death month and year are available; no imputation was used if only death year is available.

[c] Patients with death date and discharge date on the same day or died within 11 days of admission while hospitalization status was 'ongoing'. CAP = community acquired pneumonia; PCV13 = 13-valent pneumococcal conjugate vaccine.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.04.087.

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