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Expanded Analysis of 20 Pneumococcal Serotypes Associated With Radiographically Confirmed Community-acquired Pneumonia in Hospitalized US Adults

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Background. *Streptococcus pneumoniae* is a causative agent of community-acquired pneumonia (CAP). The 13-valent pneumococcal conjugate vaccine (PCV13) has significantly decreased the burden of PCV13-serotype pneumococcal disease; however, disease from nonvaccine serotypes remains substantial. A recent study documented the persistence of PCV13 serotypes among US adults hospitalized with radiographically confirmed CAP. The current analysis used a recently developed urinary antigen detection (UAD) assay (UAD2) to extend these results to additional serotypes included in an investigational PCV20 vaccine.

Methods. This prospective study enrolled adults aged ≥18 years hospitalized with radiographically confirmed CAP between October 2013 and September 2016. Presence of *S pneumoniae* was determined by blood and respiratory sample culture, BinaxNOW urine testing, and UAD. In addition to Quellung on cultured isolates when available, serotypes were identified from urine specimens using UAD1 for PCV13 serotypes and UAD2 for 7 PCV20-unique serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F) and 4 additional serotypes (2, 9N, 17F, and 20).

Results. Among 12 055 subjects with radiographically confirmed CAP, 1482 were positive for *S pneumoniae*. PCV13- and PCV20-unique serotypes were associated with 37.7% (n = 559) and 27.0% (n = 400) of cases, respectively; 288 subjects were exclusively diagnosed as positive for *S pneumoniae* by UAD2. Demographic and clinical disease characteristics were similar between subjects with CAP caused by PCV13 and PCV20-unique serotypes.

Conclusions. The current analysis using UAD2 identified a sizeable proportion of hospitalized adult CAP associated with PCV20-unique serotypes. PCV20 may therefore address the burden of CAP caused by the additional serotypes present in the vaccine.

Keywords. Pneumonia; urinary antigen detection; adult; 20-valent pneumococcal conjugate vaccine; serotypes.

Community-acquired pneumonia (CAP) is a common cause of morbidity and mortality in the United States and globally [1, 2]. In the United States, the burden of CAP is particularly pronounced among individuals ≥65 years old, for whom a recent study of CAP requiring hospitalization yielded an incidence rate of 2093 cases per 100 000 population [1]. Hospitalization rates for CAP in the same study correlated with increasing age, with 898, 1507, 2205, and 3951 hospitalizations per 100 000 population for those 60 to 64, 65 to 74, 75 to 84, and ≥85 years of age, respectively; all-cause mortality rates were 6.5% during CAP hospitalization and 30.6% within 1 year.

Vaccines are available to prevent CAP caused by *Streptococcus pneumoniae*, which contributes to 10% to 14% of confirmed US adult hospitalized CAP cases [3, 4] and is thus a significant component of CAP burden. The 13-valent pneumococcal conjugate vaccine (PCV13) is licensed for active immunization for the prevention of invasive disease caused by pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F [5].

The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices has recommended PCV13 use in all children <5 years old since 2010 [6]; this recommendation led to substantial declines in PCV13-serotype

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pneumococcal disease via both direct effects in the vaccinated pediatric population and indirect effects in other age groups [7]. Point estimates of PCV13 vaccine efficacy against nonbacteremic PCV13-serotype CAP was 45.0% in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA); a real-world evaluation estimated vaccine effectiveness of PCV13 to be 70.1% [8, 9]. However, the burden of non-PCV13 serotype disease remains substantial, representing 42% and 75% of invasive pneumococcal disease (IPD) cases in children and adults, respectively [10, 11]. Additionally, a substantial proportion of CAP is attributed to non-PCV13 serotypes [3]. Higher valent PCVs (including a PCV15 [containing serotypes in PCV13 as well as 22F and 33F] and a PCV20 [containing serotypes in PCV15 as well as 8, 10A, 11A, 12F, and 15B]) targeting some of these serotypes are currently in development and have been evaluated in adults [12, 13].

Laboratory methods are critical for assessing serotype-specific etiology of pneumococcal CAP and thus potential coverage by existing and investigational vaccines. The very small proportion of respiratory cultures available in nonbacteremic pneumococcal pneumonia cases mandates an alternative approach to determine causative serotypes [14, 15]. A urinary antigen detection (UAD) assay, termed UAD1, was previously developed for the detection of the PCV13 serotypes (ie, 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) in urine samples from patients with CAP [16]. The assay was validated against urine specimens from patients with bacteremic CAP, but has the added advantage of evaluating PCV13 serotypes in nonbacteremic CAP [16]. UAD assays can thus help monitor CAP epidemiology and support vaccine efficacy evaluations, as was done in a large study assessing PCV13 efficacy against CAP in 84 496 older adults [16, 17]. A recent observational, prospective surveillance study used the UAD1 assay to document the persistence of PCV13 serotypes among US adults hospitalized with radiographically confirmed CAP [3].

A second UAD assay, termed UAD2, has been developed for the identification of 11 additional pneumococcal serotypes beyond those evaluated by UAD1 [18]; these 11 serotypes include the 7 non-PCV13 serotypes covered by the investigational PCV20 vaccine (8, 10A, 11A, 12F, 15B, 22F, and 33F) [12] and an additional 4 serotypes (2, 9N, 17F, and 20). Collectively, UAD1 and UAD2 detect 24 pneumococcal serotypes [18]. The current analysis used UAD2 to extend the previously published study findings regarding the percentage of PCV13-serotype CAP among radiographically confirmed US adult CAP cases, as evaluated by UAD1 [3], with those serotypes included in UAD2.

METHODS

Study Design and Participants

The study design and associated methodologies have been previously reported [3, 19]. Briefly, this prospective, multicenter surveillance study enrolled adults ≥18 years old hospitalized with radiographically confirmed CAP in 10 US cities between October 2013 and September 2016. For inclusion, subjects had to present with suspected CAP based on 2 or more predefined signs or symptoms, have a radiographic finding consistent with pneumonia within 72 hours before study enrollment, be able and willing to provide a urine sample, and provide informed consent. Subjects with hospital-acquired pneumonia (ie, hospitalized for ≥48 hours before development of symptoms or transfer to study site) who had received a pneumococcal vaccine within 30 days before enrollment or who had enrolled in the study within the previous 30 days were excluded, as were subjects with severe chronic conditions or laboratory/radiographic abnormalities that could interfere with interpretation of study results, as judged by the investigator.

Subjects were classified as high risk (ie, immunocompromised) if they had chronic kidney disease, organ transplantation, immunodeficiency, hematologic or solid tumor malignancy, acquired immunodeficiency syndrome, human immunodeficiency virus, or were treated with immunosuppressive drug therapy. At-risk subjects were those without immunocompromising conditions who had asthma, congestive heart failure, liver disease, chronic obstructive pulmonary disease, diabetes mellitus, alcohol abuse, or who were currently smoking. All other subjects were classified as low risk.

Study Procedures and Assessments

Demographic information, medical history, and clinical data of consented participants were collected. Microbiologic results were recorded from blood and respiratory cultures (eg, high-quality sputum, bronchoalveolar lavage, pleural fluid, tracheal aspirate). Urine samples were collected from all participants, preferably within 24 hours of enrollment.

Blood and respiratory samples were cultured and underwent antimicrobial susceptibility testing in local laboratories according to local laboratory standard methods. Samples positive for *S pneumoniae* were subcultured at the study site and shipped at ambient temperature to the German National Reference Center for Streptococci at Aachen University for confirmatory testing. The *S pneumoniae* were recultured on sheep blood agar plates and assessed for optochin sensitivity and bile solubility. If further confirmation was required, 16s ribosomal RNA and sodA sequencing were performed. Serotyping was performed by Neufeld Quellung reaction using antisera obtained from the Staten Serum Institute in Copenhagen, Denmark.

Urine specimens were tested by BinaxNOW (a commercially available testing kit for the identification of *S pneumoniae;* Abbott Diagnostics Scarborough Inc., Scarborough, ME, USA), UAD1, and UAD2 at Pfizer's Vaccines Research and Development Laboratory (Pearl River, NY, USA) [16, 18]. The UAD assay is a limit assay that uses Luminex technology, with positivity cutoff limits (based on antigen concentrations read off a standard curve), established for each serotype using 400 control urine specimens collected from otherwise healthy adults without CAP. Using

nonparametric tolerance intervals, the assay is set to achieve at least 97% specificity for each serotype. The UAD1 assay is designed to capture 13 *S pneumoniae* serotype-specific polysaccharides excreted in human urine; the UAD2 assay is able to detect an additional 11 *S pneumoniae* serotypes.

Data Analysis

Subjects were considered positive for *S pneumoniae* if they had at least 1 positive pneumococcal test result from culture (from blood, high-quality sputum, bronchoalveolar lavage, pleural fluid, tracheal aspirate, or other specimen type), BinaxNOW, UAD1, or UAD2. The 24 UAD1/UAD2 serotypes, as determined from cultured isolates and UAD assays, were categorized into different groups for analysis including PCV13 serotypes, PCV20 serotypes, PCV20-unique serotypes (ie, serotypes included in PCV20 but not PCV13 [8, 10A, 11A, 12F, 15B, 22F, 33F]), and non-PCV20 serotypes. Percentages of subjects with radiographically confirmed CAP were analyzed descriptively within these groups and for individual serotypes. Subjects positive for multiple serotypes were included within the total for each corresponding serotype and could therefore be included in multiple groups.

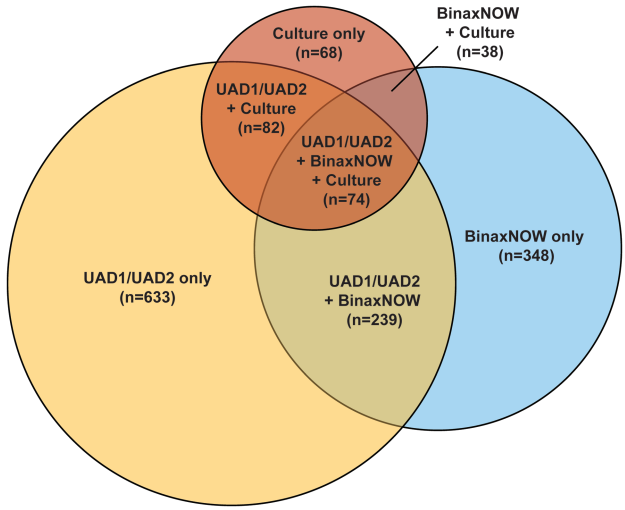

Figure 1. *Streptococcus pneumoniae* identification by diagnostic method among the 1482 positive samples. Culture specimen types included blood (n = 142), sputum (n = 116), bronchoalveolar lavage (13), pleural fluid (3), or other (n = 3). Circle areas are proportional to the number of total samples positive by the corresponding assays. Abbreviations: UAD1, urinary antigen detection assay for PCV13 serotypes; UAD2, urinary antigen detection assay for 11 non-PCV13 serotypes.

RESULTS

As detailed in the publication describing UAD1 results, of the 15 572 participants enrolled in the study, 12 055 had radiographically confirmed CAP and were included in the final analysis population; subjects without radiographically confirmed CAP were excluded from the final analysis [3]. Approximately one-half of the patients were female, and most were White/non-Hispanic. Slightly more than one-half (n = 6347; 52.7%) were ≥65 years old; of these, 43.7% were high risk, 43.8% were at risk, and 12.5% were low risk. Among the 5708 subjects aged 18 to 64 years, 32.7% were high risk, 52.1% were at risk, and 15.2% were low risk.

Among the 12 055 subjects with radiographically confirmed CAP, 12.3% (n = 1482) had a positive result for *S pneumoniae* as determined by culture, BinaxNOW, UAD1, and/or UAD2; 722 (48.7%) of these subjects were ≥65 years of age, and 760 (51.3%) were 18 to 64 years of age. *S pneumoniae* was detected by UAD1 and/or UAD2 in 69.4% (n = 1028) of these subjects, including 42.7% of subjects (n = 633) in whom *S pneumoniae* was not detected by any other method (Figure 1). A total of 288 subjects were exclusively diagnosed as positive for *S pneumoniae* by UAD2. For the remainder of subjects, *S pneumoniae* was detected by BinaxNOW alone (n = 348; 23.5%), culture alone (n = 68; 4.6%), or both BinaxNOW and culture (n = 38; 2.6%).

Among 1134 subjects positive for *S pneumoniae* by culture, UAD1, or UAD2, 1111 (9.2% of the 12 055 total cases) had serotyping information available. Among these, 559 (4.6%) were positive for the UAD1 serotypes, 516 (4.3%) for the additional UAD2 serotypes, 1001 (8.3%) for the serotypes collectively included in UAD1 and UAD2, and 64 (0.5%) for the non-UAD1/UAD2 serotypes. Of the 1001 subjects positive for UAD1 and/or UAD2 serotypes combined, 74 subjects were positive for both UAD1 and UAD2 serotypes. The serotype distribution by age (ie, younger subjects 18–64 and older subjects ≥65 years of age) and risk group among subjects with UAD1/UAD2 serotypes identified is shown in Table 1. Findings among all-risk subjects ≥50 years of age and among at-risk and high-risk subjects 18 -49 years of age are shown in Table S1. Overall, percentages of subjects with radiographically confirmed CAP caused by PCV13- or PCV20-unique serotypes were slightly higher in the younger age group (ie, 18–64 years of age) regardless of risk status (Table 1). The current analysis identified 400 subjects (3.3%) with radiographically confirmed CAP caused by the 7 PCV20-unique serotypes. Among PCV20-unique serotypes, serotype 22F was associated with the highest number of cases (n = 126; 1.1%), followed by serotype 11A (n = 97; 0.8%). The non-PCV20 serotypes included in UAD2 were collectively associated with 123 (1.0%) cases, with serotype 9N responsible for approximately one-half of these cases (n = 60; 0.5%).

The demographics, risk status, and disease characteristics of subjects with radiographically confirmed CAP caused by PCV13- and PCV20-unique serotypes are shown in Table 2. Demographic information for both groups was similar to that described previously for the overall population of subjects with radiographically confirmed CAP. In both groups, approximately one-third of subjects had ≥2 at-risk conditions. Clinical characteristics were similar between the 2 groups; these included mean Pneumonia Severity Index (PSI; PCV13 serotypes: 90.7; PCV20-unique serotypes: 85.9), most frequent PSI grade (IV; PCV13 serotypes: 32.4%; PCV20-unique serotypes: 30.3%),

Table 1. Distribution of pneumococcal serotypes detected by culture or UAD1/UAD2 by age and risk group.

	≥65 years of age, n (%)[a]			18–64 years of age, n (%)[a]				
	All-Risk	High-Risk	At-Risk/ Low-Risk	All-Risk	High-Risk	At-Risk	Low-Risk	All Subjects, n (%)[a]
Subjects with radiographically confirmed CAP	6347 (100.0)	2773 (100.0)	3574 (100.0)	5708 (100.0)	1864 (100.0)	2976 (100.0)	868 (100.0)	12,055 (100.0)
Positive for *S pneumoniae* by UAD1/UAD2 or culture	530 (8.4)	215 (7.8)	315 (8.8)	604 (10.6)	193 (10.4)	331 (11.1)	80 (9.2)	1134 (9.4)
Not serotyped and UAD1/ UAD2 negative	10 (0.2)	3 (0.1)	7 (0.2)	13 (0.2)	3 (0.2)	9 (0.3)	1 (0.1)	23 (0.2)
With serotype information	520 (8.2)	212 (7.7)	308 (8.6)	591 (10.4)	190 (10.2)	322 (10.8)	79 (9.1)	1111 (9.2)
UAD1/UAD2 serotypes[b]								
PCV13 serotypes	269 (4.2)	106 (3.8)	163 (4.6)	290 (5.1)	96 (5.2)	161 (5.4)	33 (3.8)	559 (4.6)
1	15 (0.2)	10 (0.4)	5 (0.1)	14 (0.3)	5 (0.3)	4 (0.1)	5 (0.6)	29 (0.2)
3	57 (0.9)	17 (0.6)	40 (1.1)	73 (1.3)	21 (1.1)	41 (1.4)	11 (1.3)	130 (1.1)
4	8 (0.1)	0 (0)	8 (0.2)	4 (0.1)	2 (0.1)	2 (0.1)	0 (0.0)	12 (1.0)
5	36 (0.6)	17 (0.6)	19 (0.5)	42 (0.7)	11 (0.6)	30 (1.0)	1 (0.1)	78 (0.7)
6A/6C[c]	33 (0.5)	12 (0.4)	21 (0.6)	21 (0.4)	4 (0.2)	15 (0.5)	2 (0.2)	54 (0.5)
6B	2 (0.0)	0 (0.0)	2 (0.1)	4 (0.1)	4 (0.2)	0 (0.0)	0 (0.0)	6 (0.1)
7F	24 (0.4)	6 (0.2)	18 (0.5)	30 (0.5)	8 (0.4)	18 (0.6)	4 (0.5)	54 (0.5)
9V	5 (0.1)	2 (0.1)	3 (0.1)	10 (0.2)	6 (0.3)	4 (0.1)	0 (0.0)	15 (0.1)
14	11 (0.2)	3 (0.1)	8 (0.2)	15 (0.3)	6 (0.3)	8 (0.3)	1 (0.1)	26 (0.2)
18C	6 (0.1)	4 (0.1)	2 (0.1)	16 0.3)	7 (0.4)	9 (0.3)	0 (0.0)	22 (0.2)
19A	73 (1.2)	28 (1.0)	45 (1.3)	79 (1.4)	25 (1.3)	46 (1.6)	8 (0.9)	152 (1.3)
19F	10 (0.2)	7 (0.3)	3 (0.1)	9 (0.2)	5 (0.3)	3 (0.1)	1 (0.1)	19 (0.2)
23F	12 (0.2)	6 (0.2)	6 (0.2)	17 (0.3)	9 (0.5)	7 (0.2)	1 (0.1)	29 (0.2)
PCV20 serotypes	441 (7.0)	180 (6.5)	261 (7.3)	497 (8.7)	164 (8.8)	268 (9.0)	65 (7.5)	938 (7.8)
PCV20-unique serotypes	181 (2.9)	77 (2.8)	104 (2.9)	219 (3.8)	74 (4.0)	112 (3.8)	33 (3.8)	400 (3.3)
8	11 (0.2)	3 (0.1)	8 (0.2)	25 (0.4)	3 (0.2)	17 (0.6)	5 (0.6)	36 (0.3)
10A	24 (0.4)	11 (0.4)	13 (0.4)	27 (0.5)	6 (0.3)	18 (0.6)	3 (0.4)	51 (0.4)
11A	46 (0.7)	17 (0.6)	29 (0.8)	51 (0.9)	23 (1.2)	26 (0.9)	2 (0.2)	97 (0.8)
12F	13 (0.2)	5 (0.2)	8 (0.2)	21 (0.4)	9 (0.5)	11 (0.4)	1 (0.1)	34 (0.3)
15B/15C[d]	7 (0.1)	2 (0.1)	5 (0.1)	15 (0.3)	8 (0.4)	4 (0.1)	3 (0.4)	22 (0.2)
22F	59 (0.9)	28 (1.0)	31 (0.9)	67 (1.2)	21 (1.1)	31 (1.0)	15 (1.7)	126 (1.1)
33F	24 (0.4)	12 (0.4)	12 (0.3)	16 (0.3)	4 (0.2)	8 (0.3)	4 (0.5)	40 (0.3)
Non-PCV20 serotypes	54 (0.9)	19 (0.7)	35 (1.0)	69 (1.2)	15 (0.8)	41 (1.4)	13 (1.5)	123 (1.0)
2	3 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.0)
9N	23 (0.4)	8 (0.3)	15 (0.4)	37 (0.7)	9 (0.5)	23 (0.8)	5 (0.6)	60 (0.5)
17F	15 (0.2)	2 (0.1)	13 (0.4)	15 (0.3)	4 (0.2)	9 (0.3)	2 (0.2)	30 (0.3)
20	14 (0.2)	7 (0.3)	7 (0.2)	17 (0.3)	2 (0.1)	9 (0.3)	6 (0.7)	31 (0.3)

Abbreviations: CAP, community-acquired pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; UAD1, urinary antigen detection assay for PCV13 serotypes; UAD2, urinary antigen detection assay for 11 non-PCV13 serotypes.

[a]Percentages are calculated using the total number of subjects with radiographically confirmed CAP in each column as the denominator.

[b]Subjects could be positive for more than one serotype.

[c]Serotypes 6A and 6C are identified together as 6A/6C in the UAD1 assay; in contrast, in a previously published study [3], 6A and 6C were counted as distinct serotypes.

[d]Serotypes 15B and 15C are identified together as 15B/15C in the UAD2 assay.

and mean inpatient hospitalization days (PCV13 serotypes: 6.9; PCV20-unique serotypes: 6.8), among others.

DISCUSSION

Previously presented results from this study found that 1194 of 12 055 (9.9%) US adults hospitalized with radiographically confirmed CAP were positive for *S pneumoniae* based on culture, BinaxNOW, or UAD1 [3]. Before the use of the UAD2 assay, non-PCV13 serotypes were detected for only 173 (1.4%) of the 12 055 subjects; this underestimate resulted from culture of blood and respiratory samples being the only available method for identification of these additional serotypes [3]. The addition of 288 subjects exclusively diagnosed by UAD2 dramatically increased the number of patients with radiographically confirmed CAP positive for *S pneumoniae* to 1482 (12.3%). These findings support suggestions by others that the contribution of *S pneumoniae* to nonbacteremic CAP may be larger than indicated in previous studies that were more limited in diagnostic capability [3, 4, 18, 23]. Data on IPD from the Centers for Disease Control and Prevention Active Bacterial Core surveillance in 2016 found that approximately 25% to 40% of IPD

Table 2. Demographics, Risk Status, and Disease Characteristics of Subjects With Radiographically Confirmed CAP Caused by PCV13 and PCV20-unique Serotypes

	PCV13 Serotypes,[a] n (%)	PCV20-unique Serotypes,[a] n (%)
Age, y[b]		
18–64	290 (51.9)	219 (54.8)
18–49	102 (18.2)	83 (20.8)
50–64	188 (33.6)	136 (34.0)
≥65	269 (48.1)	181 (45.3)
65–74	128 (22.9)	95 (23.8)
75–84	98 (17.5)	49 (12.3)
≥85	43 (7.7)	37 (9.3)
Sex[b]		
Female	273 (48.8)	200 (50.0)
Male	286 (51.2)	200 (50.0)
Race[b]		
White	452 (80.9)	319 (79.8)
Black	102 (18.2)	78 (19.5)
Asian	4 (0.7)	0 (0)
Other	1 (0.2)	3 (0.8)
Ethnicity[c]		
Hispanic/Latino	9 (1.6)	10 (2.5)
Non-Hispanic/non-Latino	549 (98.4)	390 (97.5)
Risk grouping[b]		
≥2 high-risk conditions with ≥1 at-risk condition(s)	44 (7.9)	34 (8.5)
≥2 high-risk conditions	9 (1.6)	5 (1.3)
≥1 high-risk condition(s) with ≥1 at-risk condition(s)	120 (21.5)	95 (23.8)
1 high-risk condition only	29 (5.2)	17 (4.3)
≥2 at-risk conditions	183 (32.7)	128 (32.0)
≥1 at-risk condition(s) only	113 (20.2)	72 (18.0)
No high-risk or at-risk conditions	61 (10.9)	49 (12.3)
PSI[d]		
Mean (SD)	90.7 (44.9)	85.9 (44.3)
Median	90	85
Minimum, maximum	0, 248	0, 217
PSI grade[d] (score)		
I	49 (8.9)	40 (10.3)
II (≤70)	103 (18.8)	90 (23.1)
III (71–90)	125 (22.8)	86 (22.1)
IV (91–130)	178 (32.4)	118 (30.3)
V (>130)	94 (17.1)	55 (14.1)
Inpatient hospitalization[e]		
General ward (medical/surgical unit)	425 (76.3)	293 (74.4)
Intensive care unit/critical care unit	108 (19.4)	79 (20.1)
Pulmonary ward	6 (1.1)	6 (1.5)
Intermediate/stepdown unit	10 (1.8)	11 (2.8)
Other	8 (1.4)	5 (1.3)
Inpatient hospitalization duration (d)[f,g]		
Mean (SD)	6.9 (4.4)	6.8 (4.5)
Median	6	6
Minimum, maximum	1, 29	1, 35
Hospitalization lasting ≥30 days[e,h]	0 (0)	3 (0.8)
Death within 30 days of enrollment[b]	48 (8.6)	26 (6.5)

Abbreviations: CAP, community-acquired pneumonia; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; PSI, Pneumonia Severity Index.

[a]Subjects could be positive for both PCV13 serotypes and PCV20-unique serotypes.

[b]PCV13 serotypes, N = 559; PCV20-unique serotypes, N = 400.

[c]PCV13 serotypes, N = 558; PCV20-unique serotypes, N = 400.

[d]PCV13 serotypes, N = 549; PCV20-unique serotypes, N = 389.

[e]PCV13 serotypes, N = 557; PCV20-unique serotypes, N = 394.

[f]PCV13 serotypes, N = 550; PCV20-unique serotypes, N = 393.

[g]Only subjects with hospital admission date and discharge date were included in the analysis. "Ongoing" inpatient stays were not included in the analysis.

[h]Subjects with "ongoing" hospitalization status were included in the analysis.

cases were due to serotypes other than those detected by UAD1/UAD2 [10]. Therefore, further expanding the coverage of UAD assays beyond the 24 serotypes already included in UAD1 and UAD2 may identify an even greater proportion of CAP caused by *S pneumoniae*.

Although 2.2% of CAP patients were positive for a PCV20-unique serotype using UAD2, this may be an underestimate of the true burden, as has been suggested for PCV13 serotypes identified by UAD1 [3]. A large database study of US Medicare beneficiaries ≥65 years of age enrolled during 2014–2017 found that PCV13 prevented 6.0% to 11.4% of all-cause CAP [21]; a similar PCV13 impact against all-cause CAP is supported by 2 additional studies from Europe, including a randomized controlled trial (CAPiTA) [22, 23]. We found that the proportion of primarily UAD1-confirmed CAP resulting from PCV13 serotypes was 4.4%. Applying a PCV13 effectiveness of 50% [9, 24] to this value suggests that vaccination should prevent 2.2% of all CAP among older US adults rather than the 6% to 11.4% from the Medicare study. UAD is a tool to assess serotype distribution, and although the UAD assays are highly sensitive against bacteremic CAP [16, 18], sensitivity against nonbacteremic CAP is unknown due to lack of a gold standard; consequently, UAD1 may have substantially underestimated the true proportion of CAP from PCV13 serotypes. Etiologically confirmed pneumococcal CAP also may underestimate the proportion of CAP preventable by PCVs because PCVs prevent pneumococcal carriage acquisition and reduce density, and pneumococcal carriage may increase the likelihood of symptomatic viral infection, including viral lower respiratory tract infections [25–27]. Last, estimates of PCV13 effectiveness against all-cause CAP could be biased; however, as indicated previously, multiple studies from Europe and the United States, including a randomized controlled trial (CAPiTA), produced similar effectiveness estimates [21–23]. Although data such as these are only available for PCV13 serotypes, it is possible these principles would also apply to the PCV20-unique serotypes resulting in an underestimate of the burden.

Importantly, non-PCV13 serotypes included in UAD2 were associated with 523 (4.3%) cases in the current analysis, highlighting the remaining burden of serotypes not currently covered by a licensed conjugate vaccine. In particular, 400 cases (3.3%) were attributed to PCV20-unique serotypes, more than one-half of which were associated with serotypes not included in PCV15; proportions were generally higher in younger subjects across risk groups.

Clinical characteristics of subjects with PCV13-serotype and PCV20-unique serotype CAP were similar across many outcomes, including disease severity and hospitalization type and length of stay. This suggests that the invasive disease potential of PCV20-unique serotypes is similar to disease caused by PCV13 serotypes, against which there is a widely used vaccine [7]. The clinical burden of PCV20-unique serotypes is supported by previous studies identifying elevated prevalence as a global cause of IPD and related deaths, increased disease severity, and frequent antibiotic resistance in connection with these serotypes [7, 11, 28–33]. In the post-PCV era, 6 of the 7 PCV20-unique serotypes (8, 10A, 12F, 15B, 22F, and 33F) have emerged as prominent nonvaccine serotypes responsible for IPD worldwide [7, 11, 28, 29]. PCV20-unique serotypes are also responsible for a substantial proportion of IPD-related deaths; 1 study in England and Wales reported that non-PCV13 serotypes including certain PCV20-unique serotypes (8, 11A, 15B, 15C, 22F, and 33F) were responsible for 73% to 92% of IPD-related deaths in children after PCV13 introduction [31].

Clinical manifestation of these serotypes can be particularly severe; 1 study showed serotypes 10A, 22F, and 33F have a high likelihood of leading to meningitis compared with other serotypes [32]. Although meningitis was not assessed in the current study, almost one-half of subjects infected with PCV20-unique serotypes had very severe PSI (grade IV/V), highlighting the serious consequences of infection with these serotypes. Recent studies have shown that common nonvaccine serotypes identified among cases with antibiotic-resistant IPD included PCV20-unique serotypes such as 11A, 15B/15C, 22F, and 33F [30, 33]. Taken together, current and previous findings suggest that a PCV20 vaccine could further reduce pneumococcal disease severity and reduce mortality caused by PCV20-unique serotypes [31, 32]. Further, PCV20 could address growing concern over antibiotic resistance of *S pneumoniae* serotypes not currently covered by a vaccine licensed for use in pediatrics [30, 33]. Overall, the findings of this study, coupled with promising immunogenicity and safety findings from early PCV20 evaluation [12], suggest that PCV20 has the potential to prevent a sizeable proportion of existing adult CAP in the United States.

As noted for the previously published results, study limitations include most subjects having come from a single geographic area; however, the demographics of this area may be representative of the United States at large [1]. Another potential limitation of this study was the staggered start-up and the variable recruitment among sites and over time [3]. The study was also limited to hospitalized patients and did not assess the burden of CAP in the outpatient setting. No viral testing was included during the UAD2 assay; therefore, another potential limitation is the lack of information on the interaction between bacteria and viruses in this setting. Additionally, determination of pneumococcal etiology in the current analysis is still limited by available laboratory methods as outlined previously; however, the inclusion of 11 additional serotypes in the UAD2 assay [18] represents a critical leap in diagnostic capability for informing CAP etiology and potential for coverage by higher valent PCVs in development. Results of the current analysis are further strengthened by the large study size.

CONCLUSIONS

Findings from the current analysis highlight the remaining high burden of US adult pneumococcal CAP requiring

hospitalization and suggest that higher valent vaccines in development could prevent a substantial proportion of disease that is caused by PCV13 and non-PCV13 serotypes. Characterization of the distribution of these serotypes among different age and risk groups and associated disease may help inform vaccination decisions at both the individual and policy levels.

Notes

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Data sharing statement. Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual deidentified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the United States and/or European Union or (2) in programs that have been terminated (ie, development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The deidentified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

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Potential conflicts of interest. R. I., L. G., S. G., R. A-P., Q. J., L. J., P. P., K. F., and M. P. are employees of Pfizer and may hold stock and/or stock options. W. H. S. has received funding for research and consulting from Merck & Co, Inc. L. O-Z. has received funding for research as well as speaking and consulting from Pfizer. R. W. has received funding for consulting and is on a data safety monitoring committee for an unrelated Pfizer study. All other authors report no potential conflicts.

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