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Noninvasive *Streptococcus pneumoniae* Serotypes Recovered from Hospitalized Adult Patients in the United States in 2009 to 2012

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This study was conducted to determine the serotype distribution and trends over time of *Streptococcus pneumoniae* strains associated with noninvasive infections among adult patients ≥18 years of age in the United States (2009 to 2012). A total of 2,927 *S. pneumoniae* isolates recovered from patients presenting with respiratory infections and obtained mainly (87.0%) from lower respiratory tract specimens (sputum) were included. The levels of the 7-valent pneumococcal conjugate vaccine (PCV7) serotypes remained stable over the 4-year study period (4.6% to 5.5%; $P = 0.953$). Overall, 13-valent pneumococcal conjugate vaccine (PCV13) serotypes were identified in 32.7% of samples, declining from 33.7% to 35.5% in 2009 to 2011 to 28.2% in 2012 ($P = 0.007$), with a significant decrease in the levels of serotypes 7F ($P = 0.013$) and 6A ($P = 0.010$). The levels of 19A remained constant (15.8% to 17.1%) during 2009 to 2011, dropping to 12.2% in 2012 ($P = 0.089$). The prevalence of serotypes associated with the 23-valent pneumococcal polysaccharide vaccine (PPSV23), but not PCV13, remained generally stable; however, the prevalence of serotypes 15B and 15C (15B/15C) increased from 2.7% to 6.3% ($P = 0.010$). The proportion of nonvaccine serotypes increased gradually during the study period ($P = 0.044$), particularly for serotype 35B (from 3.6% in 2009 to 8.2% in 2012; $P = 0.001$). Nonsusceptibility rates for penicillin (susceptible breakpoint, ≤2 μg/ml) and clindamycin against PCV7 serotypes decreased over the period. These results suggest the emergence of indirect effects following introduction of PCV13 for infants and young children; continued surveillance is needed to assess the burden of PCV13 serotypes in the adult population after the implementation of age-based recommendations in the United States.

Streptococcus pneumoniae is an important pathogen responsible for community-acquired bacterial pneumonia, bacteremia, meningitis, and otitis media and continues to be a major cause of morbidity and mortality worldwide (1). In 2000, the 7-valent pneumococcal conjugate vaccine (PCV7) was introduced into the infant immunization program in the United States, and a marked decline in the incidence of invasive pneumococcal disease (IPD) was documented among children <5 years old (2, 3). Further evidence also demonstrated a reduction of IPD among the members of the adult population following the introduction of PCV7 which has been attributed to a reduction of nasopharyngeal colonization in vaccinated children (indirect or herd effects) (3, 4). The decline in IPD among children <5 years old was accompanied by a sustained decline in the hospitalizations for pneumonia among children <2 years old through 2009; more-modest declines in hospitalizations for pneumonia among older adults were also reported (5).

In 2010, PCV13 was introduced in the United States, and emerging data for PCV13 have been consistent with earlier reports for PCV7. These emerging data have indicated rapid and significant reductions in the incidence of IPD among children <5 years old, especially in reducing diseases caused by serotypes 19A and 7F (6). In addition, these emerging reports described clear evidence of indirect effects of PCV13 in all adult age groups. Simonsen et al. (7) demonstrated significantly reduced hospital admissions caused by IPD and non-IPD in children <5 years old, as well as in members of some adult age groups 2 years after the introduction of PCV13 in the United States.

Diagnostic assays available for the detection and determination of pneumococcal serotypes in noninvasive community acquired pneumonia are limited. Therefore, information about the serotypes causing non-IPD and the dynamics associated with serotypes and infection/colonization are also limited. Studies utilizing recently developed serotype-specific urinary antigen detection technologies have suggested the persistence of vaccine serotypes causing pneumonia despite a rapid decline of the same serotypes causing IPD, suggesting that IPD data may not be an adequate surrogate for pneumonia data (8, 9). This study was conducted to determine the serotype distribution and trend over time of *S. pneumoniae* isolates (predominately sputum or lower respiratory tract) recovered from nonsterile sites among patients ≥18 years of age during 2009 to 2012.

MATERIALS AND METHODS

Clinical isolates. A total of 2,927 *S. pneumoniae* clinical isolates received during the years 2009 to 2012 surveyed as part of the SENTRY Antimicrobial Surveillance Program were included in the study. These isolates were recovered from adult patients (≥18 years of age) seen or hospitalized in 50 medical centers located in the nine U.S. Census regions (Table 1). Only medical sites contributing *S. pneumoniae* for at least three consecutive surveyed years were included. Isolates were recovered primarily (87.0%;

Received 23 January 2015 Returned for modification 24 March 2015
Accepted 23 June 2015
Accepted manuscript posted online 29 June 2015
Citation Mendes RE, Hollingsworth RC, Costello A, Jones RN, Isturiz RE, Hewlett D, Jr, Farrell DJ. 2015. Noninvasive *Streptococcus pneumoniae* serotypes recovered from hospitalized adult patients in the United States in 2009 to 2012. Antimicrob Agents Chemother 59:5595–5601. doi:10.1128/AAC.00182-15.
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doi:10.1128/AAC.00182-15
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TABLE 1 Characteristics of specimen types and subjects from whom noninvasive *S. pneumoniae* isolates were collected during 2009 to 2012 in the United States

Characteristic	No. (%) by yr				No. (%) for all yrs
	2009	2010	2011	2012	
Age (yrs)					
18–49	185 (33.7)	241 (35.0)	320 (33.9)	237 (31.8)	983 (33.6)
50–64	178 (32.4)	225 (32.7)	311 (32.9)	265 (35.5)	979 (33.4)
≥65	186 (33.9)	222 (32.3)	313 (33.2)	244 (32.7)	965 (33.0)
Census region[a] (no. of sites)					
New England (5)	88 (16.0)	99 (14.4)	155 (16.4)	105 (14.1)	447 (15.3)
Mid-Atlantic (7)	50 (9.1)	70 (10.2)	53 (5.6)	70 (9.4)	243 (8.3)
East North Central (8)	98 (17.9)	136 (19.8)	197 (20.9)	154 (20.6)	585 (20.0)
West North Central (5)	69 (12.6)	59 (8.6)	85 (9.0)	65 (8.7)	278 (9.5)
South Atlantic (6)	61 (11.1)	88 (12.8)	114 (12.1)	66 (8.8)	329 (11.2)
East South Central (5)	61 (11.1)	77 (11.2)	114 (12.1)	70 (9.4)	322 (11.0)
West South Central (4)	11 (2.0)	33 (4.8)	33 (3.5)	39 (5.2)	116 (4.0)
Mountain (4)	39 (7.1)	41 (6.0)	64 (6.8)	78 (10.5)	222 (7.6)
Pacific (6)	72 (13.1)	85 (12.4)	129 (13.7)	99 (13.3)	385 (13.2)
Specimen					
Lower respiratory tract[b]	498 (90.7)	604 (87.8)	815 (86.3)	630 (84.5)	2,547 (87.0)
Upper respiratory tract[c]	46 (8.4)	82 (11.9)	128 (13.6)	116 (15.5)	372 (12.7)
Other	5 (0.9)	2 (0.3)	1 (0.1)	0 (0.0)	8 (0.3)
All	549 (100.0)	688 (100.0)	944 (100.0)	746 (100.0)	2,927 (100.0)

[a] The New England region includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; the Mid-Atlantic region includes New Jersey, New York, and Pennsylvania; the East North Central region includes Illinois, Indiana, Michigan, Ohio, and Wisconsin; the West North Central region includes Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota; the South Atlantic region includes the District of Columbia, Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, and West Virginia; the East South Central region includes Alabama, Kentucky, Mississippi, and Tennessee; the West South Central region includes Arkansas, Louisiana, Oklahoma, and Texas; the Mountain region includes Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, and Wyoming; and the Pacific region includes Alaska, California, Hawaii, Oregon, and Washington.

[b] Most (62.8%; 1,600/2,547) of the specimens consisted of sputum.

[c] The specimens were comprised predominantly of middle ear fluid or sinus secretions.

2,547/2,927) from lower respiratory tract cultures, mostly (62.8%; 1,600/2,547) consisting of sputum cultures (Table 1). Other specimen types (13.0%; 380/2,927) were from the upper respiratory tract and were comprised predominantly of middle ear fluid or sinus secretions. Only clinically relevant isolates were included in the study.

Bacterial identification was performed by the participating microbiology laboratory and confirmed by the central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA). Confirmation of bacterial identification was performed by colony morphology analysis and biochemical algorithms. When the bacterial identification was questionable using phenotypic methods or a nontypeable serotyping result was obtained by the applied methodology, isolates were subjected to a PCR assay for further identification (10).

Antimicrobial susceptibility testing. Isolates were tested for susceptibility by broth microdilution methods, according to the recommendations of the Clinical and Laboratory Standards Institute (11). MIC results for several anti-Gram-positive-species agents were obtained using panels manufactured by Thermo Fisher Scientific (formerly Trek Diagnostics Systems/Sensititre; Cleveland, OH, USA). Validation of the MIC values was performed by concurrent testing of quality control strain *S. pneumoniae* ATCC 49619 (12). In addition, the inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. MIC interpretations were based on CLSI M100-S24 (12).

Pneumococcal serotyping. Isolates were subjected to PCR assays for amplification of the *cpsB* gene as previously described by Leung et al. (13). Amplicons were sequenced on both strands, and the nucleotide sequences were analyzed using the Lasergene software package (DNASTAR, Madison, WI). Sequences were compared to others available via Pubmed (http://www.ncbi.nlm.nih.gov/blast/). Due to sequence homology among certain serotypes, those showing nucleotide sequence similarity greater than 99% were grouped (e.g., 9V with 9A [9V/9A], 7F/7A, 11A/11D, 15A/15F, 22F/22A, and 15B/15C). All isolates determined to be of serogroup 6 by sequencing analysis were subjected to multiplex PCR assays for confirmation and discrimination between 6A/6B and 6C/6D (14). Isolates determined to be of serogroups 6A/6B and 7F/7A were serotyped by the capsular swelling method using commercially available antisera according to the instructions of the manufacturer (Statens Serum Institut, Copenhagen, Denmark).

RESULTS

Serotype distributions and trends over time. Patient age, medical site region, and specimen source distributions for the pneumococcal isolates obtained during the 4-year surveillance period are described in Table 1. The distributions of isolates per age group were very similar, and each age group contributed approximately 33% of the isolates. Most U.S. Census regions contributed between 7.6 and 13.2% of isolates, while the New England and East North Central regions contributed 15.3% and 20.0%, respectively, and the West South Central region contributed only 4.0% of isolates. The vast majority of isolates (87.0%) were recovered from lower respiratory clinical specimens (mostly sputum [54.7%]).

The serotype distribution over the study period is depicted in Table 2. Percentages described here refer to proportions of serogroups and types observed for tested isolates overall or by year. The proportion of PCV7 serotypes (approximately 5%; P =

TABLE 2 Distribution of serogroups/types of noninvasive *S. pneumoniae* collected during 2009 to 2012 in the United States

Serogroup/type(s)[a]	No. (%) by yr				No. (%) for all yrs
	2009	2010	2011	2012	
PCV7	25 (4.6)	38 (5.5)	47 (5.0)	37 (5.0)	147 (5.0)
19F	15 (2.7)	24 (3.5)	31 (3.3)	25 (3.4)	95 (3.2)
9V/9A	3 (0.5)	0 (0.0)	6 (0.6)	2 (0.3)	11 (0.4)
23F	2 (0.4)	4 (0.6)	2 (0.2)	3 (0.4)	11 (0.4)
6B	2 (0.4)	2 (0.3)	4 (0.4)	2 (0.3)	10 (0.3)
18 (18A/18B/18C/18F)	3 (0.5)	2 (0.3)	0 (0.0)	2 (0.3)	7 (0.2)
14	0 (0.0)	4 (0.6)	1 (0.1)	2 (0.3)	7 (0.2)
4	0 (0.0)	2 (0.3)	3 (0.3)	1 (0.1)	6 (0.2)
PCV13*	195 (35.5)	232 (33.7)	319 (33.8)	210 (28.2)	956 (32.7)
19A	88 (16.0)	109 (15.8)	161 (17.1)	91 (12.2)	449 (15.3)
3	50 (9.1)	60 (8.7)	84 (8.9)	64 (8.6)	258 (8.8)
7F*	21 (3.8)	22 (3.2)	24 (2.5)	13 (1.7)	80 (2.7)
6A*	11 (2.0)	3 (0.4)	3 (0.3)	5 (0.7)	22 (0.8)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPSV23-nonPCV13	134 (24.4)	172 (25.0)	229 (24.3)	197 (26.4)	732 (25.0)
11A/11D	34 (6.2)	41 (6.0)	49 (5.2)	44 (5.9)	168 (5.7)
22A/22F	31 (5.6)	36 (5.2)	49 (5.2)	35 (4.7)	151 (5.2)
15B/15C*	15 (2.7)	36 (5.2)	47 (5.0)	47 (6.3)	145 (5.0)
9N/9L	12 (2.2)	22 (3.2)	26 (2.8)	21 (2.8)	81 (2.8)
17F	14 (2.6)	11 (1.6)	15 (1.6)	11 (1.5)	51 (1.7)
10A	13 (2.4)	6 (0.9)	20 (2.1)	11 (1.5)	50 (1.7)
33F/33A/37	7 (1.3)	8 (1.2)	14 (1.5)	12 (1.6)	41 (1.4)
20	2 (0.4)	6 (0.9)	3 (0.3)	9 (1.2)	20 (0.7)
8	4 (0.7)	4 (0.6)	5 (0.5)	6 (0.8)	19 (0.6)
12F/12A/44/46	2 (0.4)	2 (0.3)	1 (0.1)	1 (0.1)	6 (0.2)
Nonvaccine*	207 (37.7)	271 (39.4)	374 (39.6)	324 (43.4)	1,176 (40.2)
6C/6D	45 (8.2)	40 (5.8)	64 (6.8)	54 (7.2)	203 (6.9)
35B*	20 (3.6)	45 (6.5)	75 (7.9)	61 (8.2)	201 (6.9)
23A	31 (5.6)	32 (4.7)	54 (5.7)	46 (6.2)	163 (5.6)
15A/15F	30 (5.5)	40 (5.8)	44 (4.7)	34 (4.6)	148 (5.1)
23B	22 (4.0)	22 (3.2)	37 (3.9)	43 (5.8)	124 (4.2)
16F	15 (2.7)	23 (3.3)	22 (2.3)	16 (2.1)	76 (2.6)
31	13 (2.4)	18 (2.6)	23 (2.4)	20 (2.7)	74 (2.5)
34	6 (1.1)	17 (2.5)	12 (1.3)	11 (1.5)	46 (1.6)
35F/47F	10 (1.8)	10 (1.5)	11 (1.2)	8 (1.1)	39 (1.3)
7C/7B/40	5 (0.9)	12 (1.7)	10 (1.1)	7 (0.9)	34 (1.2)
13	3 (0.5)	4 (0.6)	3 (0.3)	8 (1.1)	18 (0.6)
21	3 (0.5)	2 (0.3)	6 (0.6)	7 (0.9)	18 (0.6)
38/25F/25A	1 (0.2)	2 (0.3)	9 (1.0)	5 (0.7)	17 (0.6)
Other	3 (0.5)	4 (0.6)	4 (0.4)	4 (0.5)	15 (0.5)
Nontypeable	13 (2.4)	13 (1.9)	22 (2.3)	15 (2.0)	63 (2.2)
All	549 (100.0)	688 (100.0)	944 (100.0)	746 (100.0)	2,927 (100.0)

[a] Differences in serotype prevalence rates over time were assessed by calculating the *P* values by the chi-square test for trends using Epi Info, version 7.1.1.14. *, calculated *P* values were <0.05 and were considered statistically significant. "Nonvaccine" indicates those strains not present in the three vaccines available in the United States.

0.953) remained stable over time, and 19F accounted for the majority (64.6%; 95/147) of PCV7 serotypes. PCV13 serotypes declined ($P = 0.007$), and among these, a decrease in the prevalence of 7F ($P = 0.013$) and 6A (0.010) was observed from 2009 through 2012. Other PCV13 serotypes, such as 19A ($P = 0.089$), were identified less frequently in 2012 than in 2009 to 2011. According to the results of analysis of the PCV7 and PCV13 serotypes by age group, PCV7 serotypes were more commonly isolated from patients ≥65 years of age (38.8%) than from patients aged <65 years (29.9% to 31.3%; Table 3). The PCV13 serotypes were identified in similar overall proportions (32.8% to 33.9%) across the age groups. A decline in the proportion of PCV13 serotypes over time was observed among subjects ≥65 years of age (Table 3).

Those serotypes contained within the 23-valent pneumococcal polysaccharide vaccine (PPSV23), but not PCV13 (PPSV23-nonPCV13), did not change in prevalence over the 4 years (Table 2). Among PPSV23-nonPCV13 serotypes, serotypes 15B/15C increased in prevalence over time ($P = 0.010$). Interestingly, the

TABLE 3 Distribution of vaccine types of noninvasive *S. pneumoniae* isolates according to subject age group during 2009 to 2012 in the United States

Vaccine type[a] by age group (yrs)	No. (%) by yr				No. (%) for all yrs
	2009	2010	2011	2012	
PCV7	25 (4.6)	38 (5.5)	47 (5.0)	37 (5.0)	147 (5.0)
18–49	7 (28.0)	9 (23.7)	16 (34.0)	14 (37.8)	46 (31.3)
50–64	11 (44.0)	10 (26.3)	16 (34.0)	7 (18.9)	44 (29.9)
≥65	7 (28.0)	19 (50.0)	15 (31.9)	16 (43.2)	57 (38.8)
PCV13	195 (35.5)	232 (33.7)	319 (33.8)	210 (28.2)	956 (32.7)
18–49	64 (32.8)	74 (31.9)	118 (37.0)	68 (32.4)	324 (33.9)
50–64	58 (29.7)	82 (35.3)	99 (31.0)	79 (37.6)	318 (33.3)
≥65	73 (37.4)	76 (32.8)	102 (32.0)	63 (30.0)	314 (32.8)
PPSV23-nonPCV13	134 (24.4)	172 (25.0)	229 (24.3)	197 (26.4)	732 (25.0)
18–49*	53 (39.6)	65 (37.8)	75 (32.8)	59 (29.4)	252 (34.4)
50–64	45 (33.6)	49 (28.5)	77 (33.6)	75 (38.1)	246 (33.6)
≥65	36 (26.9)	58 (33.7)	77 (33.6)	63 (32.0)	234 (32.0)
Nonvaccine	207 (37.7)	271 (39.4)	374 (39.6)	324 (43.4)	1,176 (40.2)
18–49	63 (30.4)	99 (36.5)	119 (31.9)	106 (32.7)	387 (32.9)
50–64	68 (32.9)	88 (32.5)	128 (34.2)	109 (33.6)	393 (33.4)
≥65	76 (36.7)	84 (31.0)	127 (34.0)	109 (33.6)	396 (33.7)
Nontypeable	13 (2.4)	13 (1.9)	22 (2.3)	15 (2.0)	63 (2.2)
18–49	5 (38.5)	3 (23.1)	8 (36.4)	4 (26.7)	20 (31.7)
50–64*	7 (53.8)	6 (46.2)	7 (31.8)	2 (13.3)	22 (34.9)
≥65*	1 (7.7)	4 (30.8)	7 (31.8)	9 (60.0)	21 (33.3)
All	549 (100.0)	688 (100.0)	944 (100.0)	746 (100.0)	2,927 (100.0)

[a] Differences in serotype prevalence rates over time were assessed by calculating the *P* values by the chi-square test for trends using Epi Info, version 7.1.1.14. *, calculated *P* values were <0.05 and were considered statistically significant. "Nonvaccine" indicates those strains not present in the three vaccines available in the United States.

frequency of the associated PPSV23-nonPCV13 serotypes decreased steadily among the subjects in the population age group consisting of those 18 to 49 years of age from 39.6% in 2009 to 29.4% in 2012 ($P = 0.035$; Table 3). Overall, the proportion of nonvaccine serotypes (defined as those not present in the three vaccines available in the United States) increased gradually during the study period ($P = 0.044$; Table 2). An increase in the frequency of serotype 35B, which rose from 3.6% of isolates in 2009 to 8.2% in 2012 ($P = 0.001$), was particularly noticeable. Other serotypes, such as 6C/6D and 23A, also demonstrated a slight increase in proportion over the last 3 years of the study (2010 to 2012). In contrast, 15A/15F, 16F, and 35F/47F showed a small decrease in prevalence. Of note, isolates clustering within the nontypeable group remained stable overall during the period. However, the prevalence of these isolates did shift between the age groups evaluated; in 2009, 53.8% of nontypeable isolates were obtained from adults 50 to 64 years of age, and this rate had fallen by 2012 to 13.3% ($P = 0.012$). In contrast, the prevalence of the nontypeable isolates recovered from patients ≥65 years of age increased from 7.7% to 60.0% over the same period ($P = 0.009$; Table 3).

Antimicrobial susceptibility testing. All isolates were susceptible to vancomycin and linezolid (data not shown), and the overall penicillin (parenteral susceptible [nonmeningitis] breakpoint, ≤2 μg/ml) and ceftriaxone nonsusceptibility rates were 10.3% to 15.0% and 7.7% to 10.9%, respectively (Table 4). According to analysis of penicillin using the oral administration breakpoint (susceptibility breakpoint, ≤0.06 μg/ml), overall nonsusceptibility rates were between 38.3% and 46.3%, and high rates were noted for PCV7 (19F) and PCV13 (19A) and for nonvaccine (6C/6D, 23A, 15A/15F, 23B, and 35B) groups or serotypes. PPSV23-nonPCV13 serotypes, except for 15B/15C, showed lowered nonsusceptibility rates for oral penicillin.

Serotype 19A displayed high nonsusceptibility rates for all agents described in Table 4. Of note, 19F isolates demonstrated decreasing nonsusceptibility rates for penicillin (parenteral [nonmeningitis] breakpoint), ceftriaxone, clindamycin, and erythromycin, especially during the last three surveyed years (Table 4). No major additional variations were observed in the antimicrobial nonsusceptibility rates during the study period among vaccine serotypes or specific serogroups and serotypes, except for the following results (Table 4): nonsusceptibility rates for penicillin (susceptibility breakpoint for nonmeningitis disease, ≤2 μg/ml) and clindamycin decreased over the period tested against PCV7 serotypes; serotype 3 displayed increased nonsusceptibility rates for clindamycin (from 5.0% to 6.0% in 2009 to 2010 to 12.5% to 15.5% in 2011 to 2012) and erythromycin (from 6.0% to 8.3% in 2009 to 2010 to 14.1% to 14.3% in 2011 to 2012) over time; serotypes 6C/6D (from 2.2% to 5.6%) and 23B (from 0.0% to 9.3%) demonstrated a low but steady increase in the nonsusceptibility rates for clindamycin.

DISCUSSION

The results of this 4-year longitudinal study indicate stable frequencies (4.6% to 5.5%) of PCV7 serotypes among non-IPD in adults in the United States. Richter et al. (15) reported a similar prevalence range (4.2% to 5.5%) in non-IPD across all age groups

TABLE 4 Nonsusceptible rates of most common serogroups/types observed among noninvasive *S. pneumoniae* isolates collected during 2009 to 2012 in the United States

	% nonsusceptibility[a] by yr															
	Penicillin				Ceftriaxone				Clindamycin				Erythromycin			
Serogroup/type	2009	2010	2011	2012	2009	2010	2011	2012	2009	2010	2011	2012	2009	2010	2011	2012
PCV7	32.0 (52.0)	28.9 (52.6)	19.1 (55.3)	16.2 (51.4)	28.0	21.1	17.0	21.6	32.0	31.6	23.4	18.9	52.0	52.6	59.6	48.6
19F	26.7 (46.7)	33.3 (50.0)	25.8 (45.2)	20.0 (60.0)	20.0	25.0	22.6	20.0	40.0	37.5	29.0	24.0	46.7	50.0	41.9	40.0
Additional PCV13	34.9 (52.3)	33.6 (50.0)	42.6 (58.6)	35.7 (51.9)	26.7	22.8	29.2	31.4	34.9	33.2	44.8	38.1	45.6	49.6	60.2	52.4
19A	66.8 (89.8)	61.5 (86.2)	78.9 (96.3)	74.7 (91.2)	50.0	41.3	52.2	63.7	64.8	56.9	73.3	70.3	73.9	80.7	91.9	86.8
3	0.0 (0.0)	0.0 (0.0)	0.0 (2.4)	0.0 (6.2)	0.0	0.0	0.0	0.0	6.0	5.0	15.5	12.5	6.0	8.3	14.3	14.1
7F	0.0 (9.5)	0.0 (0.0)	0.0 (8.3)	0.0 (0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	7.7	4.8	0.0	8.3	7.7
PPSV23-nonPCV13	0.7 (10.4)	0.0 (8.1)	1.3 (15.7)	0.5 (13.2)	2.2	0.0	1.7	1.5	1.5	3.5	5.7	3.6	26.1	22.1	34.1	32.5
11A/11D	0.0 (8.8)	0.0 (2.4)	0.0 (8.2)	2.3 (6.8)	2.9	0.0	2.0	2.3	0.0	0.0	2.0	4.5	35.3	19.5	34.7	27.3
22A/22F	0.0 (6.5)	0.0 (0.0)	4.1 (14.3)	0.0 (2.9)	3.2	0.0	2.0	2.9	6.5	2.8	12.2	5.7	17.9	16.7	36.7	20.0
15B/15C	0.0 (33.3)	0.0 (33.3)	2.1 (44.7)	0.0 (36.2)	0.0	0.0	2.1	0.0	0.0	5.6	6.4	2.1	46.7	38.9	61.7	53.2
17F	0.0 (7.1)	0.0 (0.0)	0.0 (0.0)	0.0 (9.1)	0.0	0.0	0.0	9.1	0.0	0.0	0.0	0.0	28.6	18.2	20.0	9.1
10A	7.7 (15.4)	0.0 (0.0)	0.0 (5.0)	0.0 (0.0)	7.7	0.0	0.0	0.0	0.0	0.0	0.0	9.1	7.7	0.0	10.0	9.1
9N/9L	0.0 (0.0)	0.0 (4.5)	0.0 (7.7)	0.0 (4.8)	0.0	0.0	0.0	0.0	0.0	13.6	3.8	4.8	0.0	18.2	3.8	9.5
33F/33A/37	0.0 (0.0)	0.0 (0.0)	0.0 (7.1)	0.0 (8.3)	0.0	0.0	7.1	0.0	0.0	0.0	14.3	0.0	71.4	50.0	57.1	91.7
Nonvaccine[b]	1.9 (44.0)	0.4 (47.6)	0.5 (55.0)	0.3 (52.8)	1.9	0.0	1.6	0.9	15.5	18.1	16.9	14.5	33.3	37.6	42.9	37.0
6C/6D	0.0 (60.0)	0.0 (42.5)	0.0 (59.4)	0.0 (55.6)	0.0	0.0	3.1	0.0	2.2	2.5	3.1	5.6	53.3	40.0	56.2	50.0
23A	0.0 (45.2)	0.0 (75.0)	0.0 (70.4)	0.0 (71.7)	0.0	0.0	0.0	0.0	6.5	15.6	16.7	13.0	9.7	25.0	18.5	26.1
15A/15F	0.0 (76.7)	0.0 (97.5)	0.0 (90.9)	0.0 (88.2)	0.0	0.0	0.0	0.0	80.0	92.5	95.5	88.2	86.7	95.0	97.7	94.1
23B	0.0 (27.3)	0.0 (27.3)	2.7 (32.4)	0.0 (44.2)	0.0	0.0	2.7	0.0	0.0	4.5	5.4	9.3	13.6	4.5	27.0	11.6
35B	5.0 (80.0)	2.2 (91.1)	1.4 (95.9)	1.6 (91.8)	5.0	0.0	2.7	4.9	5.0	4.4	4.1	1.6	40.0	60.0	62.2	54.1
16F	6.7 (13.3)	0.0 (0.0)	0.0 (9.1)	0.0 (6.2)	6.7	0.0	4.5	0.0	0.0	0.0	9.1	6.2	0.0	13.0	9.1	6.2
31	7.7 (7.7)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	7.7	0.0	0.0	0.0	15.4	0.0	0.0	5.0	23.1	27.8	26.1	25.0
35F/47F	0.0 (0.0)	0.0 (10.0)	0.0 (0.0)	0.0 (0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	10.0	27.3	12.5
34	0.0 (0.0)	0.0 (0.0)	0.0 (8.3)	0.0 (9.1)	0.0	0.0	0.0	0.0	0.0	11.8	0.0	0.0	0.0	11.8	8.3	18.2
7C/7B/40	0.0 (20.0)	0.0 (0.0)	0.0 (10.0)	0.0 (0.0)	0.0	0.0	0.0	0.0	20.0	0.0	0.0	0.0	20.0	0.0	0.0	0.0
Nontypeable	0.0 (23.1)	7.7 (61.5)	0.0 (40.9)	0.0 (13.3)	0.0	0.0	0.0	0.0	15.4	30.8	13.6	0.0	23.1	53.8	40.9	33.3
All	13.3 (38.3)	11.6 (38.8)	15.0 (46.3)	10.3 (41.3)	10.7	7.7	10.9	9.7	18.9	19.8	23.5	18.0	35.7	38.1	46.6	40.1

[a] Data represent percentages of nonsusceptible isolates according to the susceptible parenteral (≤2 μg/ml) (for nonmenigitis patients) and oral (≤0.06 μg/ml) (in parentheses) penicillin breakpoints for ceftriaxone (≤1 μg/ml), clindamycin (≤0.25 μg/ml), and erythromycin (≤0.25 μg/ml) published in the CLSI M100-S24 document.
[b] "Nonvaccine" indicates those strains not present in the three vaccines available in the United States.

during a similar time period (2008 to 2011) and a prevalence of 4.8% among all age groups and specimens during 2012 to 2013 (16). These results suggest low but persistent circulation of PCV7 serotypes (mainly 19F) in all age groups, despite the documented direct effect in vaccinated children as well as indirect effects in the adult population. Of note, approximately 30% of the PCV7 serotypes were isolated from the 18-to-49 (31.3%) and 50-to-64 (29.9%) age groups, but these serotypes were slightly more common (38.8%) in patients ≥65 years of age.

The frequencies of PCV13 serotypes showed signs of decline, especially during the last surveyed year, when the observed prevalence (28.2%) was lower than the prevalence seen in 2009 through 2011 (33.7% to 35.5%). This trend was mostly driven by a decreased prevalence of 19A and 7F. The trends observed for these serotypes are similar to those recently reported by Kaplan et al. and Richter et al. for IPD in children (17) and for IPD and non-IPD in all age groups (15, 16) in the United States. Also in agreement, data recently reported from the Active Bacterial Core surveillance (ABCs) indicated dramatic reductions in the incidence of IPD in children caused by PCV13 serotypes and notable indirect effects in all adult age groups which were largely due to declines in the prevalence of serotypes 19A and 7F (18).

No change in the occurrence of serotype 3 was noted in this analysis. Similar proportions of serotype 3 causing non-IPD have been observed elsewhere among all age groups (9.3%; 2010 to 2011) (15) or among those isolates recovered from lower respiratory tract specimens in all age groups (9.9%; 2012 to 2013) (16) during the early PCV13 era in the United States. Since the introduction of PCV13 into routine childhood immunization programs globally, surveillance data for serotype 3 have demonstrated inconsistent results. Cases of serotype 3 infection are generally very few, and the direct impact of PCV13 against serotype 3 requires further observation. In addition, the indirect effects that have been observed following pediatric use of PCV13 have been few, suggesting either that more time is required for indirect effects against this serotype to develop or that direct immunization of adults may be required to prevent serotype 3 infections in older adults.

PCV13 serotypes 1 and 5 were not detected over the study period, which is in line with some studies conducted in the United

States (3, 15, 17, 19) but is in contrast to others conducted among older patients with pneumonia (8, 9, 20). However, the latter studies used serotype-specific urinary antigen detection assays and the reported differences could have been due to epidemiological circumstances (serotype 5 may occur in outbreaks) or to the use of distinct methodological approaches.

The prevalence of PPSV23-nonPCV13 serotypes remained stable (24.3% to 26.4%) during the study period, with no major variation in the frequencies of detected serotypes. However, a constant decrease in the prevalence of these serotypes was noted in the group consisting of those who were 18 to 49 years of age ($P = 0.035$). Interestingly, the prevalence of 15B/15C increased from 2.7% in the first year of the study to approximately 5.0% during the second and third year and 6.3% in 2012, which is in agreement with other studies (15, 19, 21). PPSV23 is recommended to prevent IPD among adults, and the effectiveness of this vaccine for the prevention of nonbacteremic pneumococcal pneumonia remains uncertain (22). Therefore, it was not unexpected that the prevalence of the PPSV23-specific serotypes did not change over the study period, given that the majority of these isolates were obtained from non-IPD sources. However, it is important that information on vaccination status was not collected from the adults who contributed isolates to this study (22).

Nonvaccine serotypes, mostly led by serotype 35B, increased in prevalence. Other studies have reported similar findings, regardless of specimen type or patient's age, as well as among carriage isolates (15, 16, 21). However, Kaplan et al. (17) did not show any change in the prevalence of this serotype causing IPD in children in eight hospitals in the United States. Of note, the proportion of nontypeable pneumococci isolated from adults aged 65 years and older increased over time, with a corresponding decrease in the group consisting of those who were 50 to 64 years of age. The reasons for these results are unknown. The number of nontypeable isolates is small, and additional analyses are needed to determine (i) whether these trends remain true in subsequent years and, if so, to further determine (by the classical method) (ii) the serotypes responsible for these trends.

One limitation of this study was that the incidence rates of disease caused by the pneumococcal serotypes could not be determined. However, this report provides valuable information with regard to the relative distributions of serotypes causing noninvasive lower respiratory tract infections in this population of adult patients in the United States. In summary, the prevalence of PCV7 serotypes of approximately 5% was stable throughout, while the frequency of PCV13 serotypes showed signs of decline but still consisted of 28.2% of tested isolates in 2012. The downward trend was mostly driven by a decreased prevalence of serotypes 19A and 7F. These results suggest the emergence of indirect effects of PCV13 following use of this vaccine in infants and young children in the United States. However, the persistence of PCV7 serotypes and the time taken for indirect effects to establish postimplementation in pediatric settings suggest that indirect effects alone may not be sufficient to maximize the public health impact in adults, particularly for the prevention of pneumonia. Indeed, the U.S. Advisory Committee on Immunization Practices recently issued recommendations for the use of PCV13 and PPSV23 in series in adults aged 65 years and older, recognizing the burden of pneumococcal pneumonia in older adults and the opportunity to impact this burden as indirect effects from the pediatric immunization program continue to develop (23). Continued surveillance is needed to truly assess the herd effects of PCV13 as well as to detect the emergence of possible serotype replacement.

ACKNOWLEDGMENTS

We thank the following staff members at JMI Laboratories (North Liberty, IA, USA): S. Benning, M. Castanheira, S. Costello, L. Deshpande, M. Gerst, and K. Hass. We also thank other staff members for technical support and manuscript assistance.

This study was supported by Pfizer Inc. (Collegeville, PA).

JMI Laboratories, Inc., has received research and educational grants in 2011 to 2013 from the American Proficiency Institute (API), Anacor, Astellas, AstraZeneca, Bayer, Cempra, Cerexa/Forest, Contrafect, Cubist, Daiichi, Dipexium, Enanta, Furiex, GlaxoSmithKline, Johnson & Johnson (Ortho McNeil), LegoChem Biosciences Inc., Meiji Seika Kaisha, Merck, Nabriva, Novartis, Pfizer, Rempex, Rib-X Pharmaceuticals, Seachaid, Shionogi, The Medicines Company, Theravance, Thermo Fisher, and some other corporations. Some JMI employees are advisors/consultants for Astellas, Cubist, Pfizer, Cempra, Cerexa/Forest, Johnson and Johnson (J&J), and Theravance Biopharma US, Inc. R. C. Hollingsworth, R. E. Isturiz, and D. Hewlett, Jr., are employees of, and may hold stock in, Pfizer Inc.

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