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Distributions and Annual Changes of *Streptococcus pneumoniae* Serotypes Causing Infections in Adult Patients: 8 Years of US Surveillance (2009–2016)

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Introduction

- *Streptococcus pneumoniae* remains an important pathogen responsible for community-acquired pneumonia (CAP), bacteremia, meningitis, and otitis media and continues to be a major cause of morbidity and mortality worldwide
- There are currently two vaccines that are available in the United States to prevent pneumococcal disease:
  - A 23-valent pneumococcal polysaccharide vaccine (PPV23) which has been used for more than 30 years. As PPV23 is poorly immunogenic in children <2 years of age, it is not used in the US routine infant immunization program.
    - Despite high PPV23 vaccine uptake in adults in the US, surveillance data have shown no measurable impact on invasive pneumococcal disease (IPD) caused by the serotypes in PPV23. In addition, effectiveness studies of PPV23 for preventing non-bacteremic CAP, the most common manifestation of pneumococcal disease in adults, have been conflicting.
  - A 13-valent pneumococcal conjugate vaccine (PCV13) in which capsular polysaccharides are conjugated to carrier proteins to enhance immunogenicity has been included in the US infant national immunization program since 2010. PCV13 replaced the 7-valent vaccine (PCV7) which was licensed in 2000.
- PCV13 reduces nasopharyngeal pneumococcal carriage in children resulting in decreases in pneumococcal disease in unvaccinated individuals (i.e. indirect protection due to herd effect)
- Despite PCV use in children, there was still a remaining burden of disease in US adults
  - In 2012, the US Food and Drug Administration (FDA) licensed PCV13 for all adults ≥50 years of age through Accelerated Approval Regulation [21 CFR 601.41] based on a potentially "meaningful therapeutic benefit to patients over existing treatments" (i.e., PPV23)
  - PCV13 efficacy in adults was subsequently confirmed in a large randomized controlled trial. As a result, in September 2014, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommended PCV13 use for all adults ≥65 years of age. This updated the previous 17 year old recommendation of PPV23 only, to sequential administration of PCV13 followed by PPV23.
  - According to a recent study by the CDC, which analyzed claims for vaccination submitted for reimbursement to the Centers for Medicare & Medicaid Services, by September 18, 2015, 14.8% of Medicare beneficiaries aged ≥65 years had claims for PCV13, which increased to 31.5% by September 18, 2016
- Continued monitoring of the impact of infant and adult vaccination in preventing vaccine-type pneumococcal disease at the population level is required to assess the additional impact of PCV13 use in adults in the context of PCV13 use in children
- This study was conducted to determine the prevalence and serotype distribution of *S. pneumoniae* clinical isolates recovered predominantly from non-sterile sites (mostly sputum or lower respiratory tract secretions) and associated with disease among adults (≥18 years of age) in the US from 2009 through 2016

Materials and Methods

Clinical isolates

- 6,885 *S. pneumoniae* clinical isolates recovered from adult patients (≥18 years old) seen or hospitalized in 106 US centers were included in this study
- Isolates were collected primarily (77.7%; 5,347/6,885) from lower respiratory tract specimens and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, Iowa, USA), as part of the SENTRY Antimicrobial Surveillance Program
- Participating microbiology laboratories identified bacteria and the central monitoring laboratory confirmed bacterial identification by colony morphology and biochemical algorithms
- Isolates were subjected to a PCR assay for further identification when bacterial identification was questionable after using phenotypic methods or an untypeable serotyping result was obtained by the applied methodology

Pneumococcal serotyping

- The *cpsB* gene of isolates was analyzed by PCR assays or whole genome sequencing
- Amplicons were sequenced on both strands, and the nucleotide sequences were analyzed using the Lasergene software package (DNASTAR, Madison, Wisconsin, USA)
- Sequences were compared to others available via NCBI (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/9A, 7F/7A, 11A/11D, 15A/15F, 22F/22A, 15B/15C)
- All isolates determined to be serogroup 6 by sequencing analysis were subjected to multiplex PCR assays for confirmation and discrimination between 6A/6B and 6C/6D
- Isolates determined to be serogroup 6A/6B and 7F/7A were serotyped by the capsular swelling method using commercially available antisera according to manufacturer's instructions (Statens Serum Institut, Copenhagen, Denmark)

Results

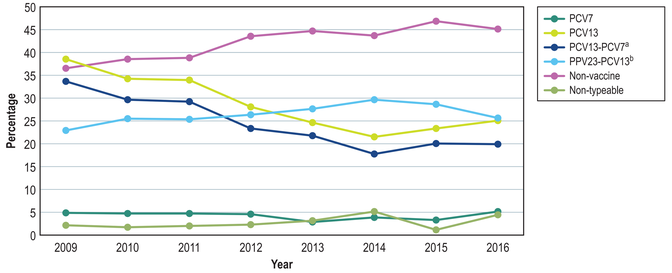
- Overall, PCV7, PCV13-PCV7 (PCV13 serotypes excluding those covered by PCV7), and PCV13 serotypes composed 4.2%, 24.3%, and 28.6% of all isolates, respectively, with serotype 19F (2.9%) predominating among PCV7-type isolates and serotypes 19A (12.1%) and 3 (9.3%) prevailing among PCV13-type isolates (Table 1)
- The prevalence of PCV7 serotypes remained stable (2.8%–5.1%) during the study period (Table 1 and Figure 1)
- PCV13 (from 38.6% in 2009 to 25.0% in 2016) and PCV13-PCV7 (from 33.6% to 19.9%) showed a consistent decreasing trend over the study period (Table 1 and Figure 1)
  - Within PCV13, prevalence of serotypes 19A, 7F, and 6A in 2016 was lower than that observed in 2009
  - Serotype 3 increased from 9.9% (2009) to 12.2% (2016; Table 1)

Table 1 Distribution of serogroups/types of *S. pneumoniae* causing infections in the US adult population during 2009–2016

Serogroup/type	Number (%) of *S. pneumoniae* serogroups/types								All years
	2009	2010	2011	2012	2013	2014	2015	2016	
PCV7	33 (4.9)	39 (4.7)	54 (4.7)	39 (4.6)	29 (2.8)	36 (3.8)	25 (3.3)	35 (5.1)	290 (4.2)
19F	19 (2.8)	24 (2.9)	34 (3.0)	27 (3.2)	17 (1.7)	26 (2.8)	22 (2.9)	29 (4.2)	198 (2.9)
9V/9A	3 (0.4)	0 (0.0)	7 (0.6)	2 (0.2)	4 (0.4)	1 (0.1)	1 (0.1)	0 (0.0)	18 (0.3)
6B	4 (0.6)	2 (0.2)	4 (0.3)	2 (0.2)	2 (0.2)	2 (0.2)	1 (0.1)	1 (0.1)	18 (0.3)
23F	3 (0.4)	4 (0.5)	3 (0.3)	3 (0.4)	2 (0.2)	1 (0.1)	0 (0.0)	3 (0.4)	19 (0.3)
4	0 (0.0)	3 (0.4)	5 (0.4)	1 (0.1)	4 (0.4)	3 (0.3)	1 (0.1)	1 (0.1)	18 (0.3)
18	3 (0.4)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	10 (0.1)
14	1 (0.1)	4 (0.5)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	9 (0.1)
PCV13	258 (38.6)	282 (34.3)	387 (33.9)	238 (28.0)	251 (24.6)	203 (21.5)	175 (23.4)	172 (25.0)	1,966 (28.6)
PCV13-PCV7[a]	225 (33.6)	243 (29.5)	333 (29.1)	199 (23.4)	222 (21.7)	167 (17.7)	150 (20.1)	137 (19.9)	1,676 (24.3)
19A	117 (17.5)	123 (14.9)	196 (17.1)	108 (12.7)	116 (11.4)	75 (8.0)	49 (6.6)	47 (6.8)	831 (12.1)
3	66 (9.9)	70 (8.5)	100 (8.7)	69 (8.1)	84 (8.2)	78 (8.3)	92 (12.3)	84 (12.2)	643 (9.3)
7F	31 (4.6)	45 (5.5)	32 (2.8)	14 (1.6)	17 (1.7)	10 (1.1)	7 (0.9)	5 (0.7)	161 (2.3)
6A	11 (1.6)	5 (0.6)	4 (0.3)	8 (0.9)	4 (0.4)	2 (0.2)	2 (0.3)	1 (0.1)	37 (0.5)
1	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.2)	0 (0.0)	0 (0.0)	4 (0.1)
5	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)
PPV23-PCV13[b]	153 (22.9)	210 (25.5)	289 (25.3)	224 (26.3)	282 (27.6)	279 (29.6)	214 (28.6)	176 (25.6)	1,827 (26.5)
11A/11D	38 (5.7)	47 (5.7)	59 (5.2)	55 (6.5)	63 (6.2)	78 (8.3)	47 (6.3)	32 (4.7)	419 (6.1)
22A/22F	33 (4.9)	48 (5.8)	67 (5.9)	41 (4.8)	61 (6.0)	50 (5.3)	40 (5.3)	40 (5.8)	380 (5.5)
15B/15C	18 (2.7)	39 (4.7)	53 (4.6)	54 (6.3)	45 (4.4)	39 (4.1)	39 (5.2)	21 (3.1)	308 (4.5)
9N/9L	15 (2.2)	23 (2.8)	33 (2.9)	22 (2.6)	33 (3.2)	28 (3.0)	33 (4.4)	24 (3.5)	211 (3.1)
10A	15 (2.2)	8 (1.0)	22 (1.9)	11 (1.3)	24 (2.4)	17 (1.8)	17 (2.3)	14 (2.0)	128 (1.9)
33F/33A	10 (1.5)	10 (1.2)	20 (1.7)	13 (1.5)	28 (2.7)	28 (3.0)	16 (2.1)	10 (1.5)	135 (2.0)
17F	16 (2.4)	13 (1.6)	18 (1.6)	11 (1.3)	15 (1.5)	15 (1.6)	8 (1.1)	11 (1.6)	107 (1.6)
8	4 (0.6)	6 (0.7)	8 (0.7)	6 (0.7)	9 (0.9)	13 (1.4)	9 (1.2)	9 (1.3)	64 (0.9)
20	2 (0.3)	9 (1.1)	6 (0.5)	10 (1.2)	4 (0.4)	11 (1.2)	4 (0.5)	7 (1.0)	53 (0.8)
12F/12A/44/46	2 (0.3)	7 (0.9)	3 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.1)	8 (1.2)	22 (0.3)
Non-vaccine	244 (36.5)	317 (38.5)	444 (38.8)	370 (43.5)	456 (44.7)	412 (43.7)	351 (46.9)	310 (45.1)	2,904 (42.2)
35B	26 (3.9)	54 (6.6)	82 (7.2)	79 (9.3)	73 (7.1)	90 (9.6)	87 (11.6)	76 (11.0)	567 (8.2)
23A	38 (5.7)	37 (4.5)	64 (5.6)	50 (5.9)	86 (8.4)	66 (7.0)	49 (6.6)	36 (5.2)	426 (6.2)
6C/6D	51 (7.6)	53 (6.4)	77 (6.7)	63 (7.4)	52 (5.1)	47 (5.0)	24 (3.2)	27 (3.9)	394 (5.7)
15A/15F	35 (5.2)	45 (5.5)	50 (4.4)	36 (4.2)	55 (5.4)	38 (4.0)	37 (4.9)	32 (4.7)	328 (4.8)
23B	25 (3.7)	28 (3.4)	43 (3.8)	46 (5.4)	42 (4.1)	57 (6.1)	50 (6.7)	45 (6.5)	336 (4.9)
16F	18 (2.7)	28 (3.4)	22 (1.9)	16 (1.9)	31 (3.0)	29 (3.1)	16 (2.1)	22 (3.2)	182 (2.6)
31	17 (2.5)	19 (2.3)	31 (2.7)	22 (2.6)	26 (2.5)	19 (2.0)	13 (1.7)	12 (1.7)	159 (2.3)
35F/47F	10 (1.5)	11 (1.3)	16 (1.4)	9 (1.1)	17 (1.7)	19 (2.0)	13 (1.7)	10 (1.5)	105 (1.5)
7C/7B/40	7 (1.0)	12 (1.5)	12 (1.0)	8 (0.9)	11 (1.1)	8 (0.8)	15 (2.0)	11 (1.6)	84 (1.2)
34	7 (1.0)	17 (2.1)	17 (1.5)	14 (1.6)	14 (1.4)	0 (0.0)	4 (0.5)	10 (1.5)	83 (1.2)
21	3 (0.4)	2 (0.2)	9 (0.8)	9 (1.1)	23 (2.3)	11 (1.2)	11 (1.5)	10 (1.5)	78 (1.1)
38/25F/25A	1 (0.1)	3 (0.4)	13 (1.1)	6 (0.7)	10 (1.0)	5 (0.5)	5 (0.7)	8 (1.2)	51 (0.7)
13	3 (0.4)	4 (0.5)	3 (0.3)	8 (0.9)	2 (0.2)	3 (0.3)	1 (0.1)	1 (0.1)	25 (0.4)
Other	3 (0.4)	4 (0.5)	5 (0.4)	4 (0.5)	14 (1.4)	20 (2.1)	26 (3.5)	10 (1.5)	86 (1.2)
Untypeable	14 (2.1)	14 (1.7)	23 (2.0)	19 (2.2)	32 (3.1)	48 (5.1)	8 (1.1)	30 (4.4)	188 (2.7)

[a] Includes PCV13 serotypes excluding those covered by PCV7
[b] Includes PPV23 serotypes excluding those covered by PCV13

Figure 1 Relative percentages of *S. pneumoniae* vaccine serotypes observed in the US adult population (≥18 years old) during 2009–2016



[a] Includes PCV13 serotypes excluding those covered by PCV7
[b] Includes PPV23 serotypes excluding those covered by PCV13

- The decline in PCV13 serotypes was observed in all age groups (18–49, 50–64, and ≥65 years), and was most pronounced among isolates from patients ≥65 years old (18.3% difference versus 13.9% and 8.5%, respectively; Table 2)
- In those ≥65 years of age, between 2014 and 2016 (i.e. the time period after the recommendation of PCV13 in this age group) prevalence of PCV13 serotypes remained stable
- Overall, a total of 26.5% and 42.2% of isolates consisted of serotypes unique to PPV23 (i.e., PPV23-non-PCV13) and non-vaccine serotypes, respectively (Table 1)
  - A consistent upward trend (from 22.9% in 2009 to 29.6% in 2014, with a decrease to 25.6% in 2016) was noted for PPV23-non-PCV13, which was driven largely by the 50–64 and ≥65 age groups (Tables 1 and 2; Figure 1)
- An increase from 36.5% in 2009 to 45.1% in 2016 for non-vaccine serotypes was observed over the study period (Table 1 and Figure 1), and this trend was present among patients from all age groups (Table 2)
  - Among non-vaccine serotypes, 35B (11.0%) was the most common in 2016, followed by 23B (6.5%), 23A (5.2%), 15A/15F (4.7%), and 6C/6D (3.9%)
  - Serotype 6C/6D showed a decreased prevalence from 7.6% in 2009 to 3.9% in 2016, whereas 35B prevalence increased during the study period from 3.9% in 2009 to 11.0% in 2016 (Table 1)

Table 2 Vaccine type distribution of non-invasive *S. pneumoniae* according to subject age group during 2009–2016 in the US

Age group	Number (% of total) of vaccine type by age group and year			
Year	PCV7	PCV13	PPV23-PCV13[a]	Non-vaccine
18–49				
2009	8 (3.7)	77 (36.0)	61 (28.5)	70 (32.7)
2010	9 (3.3)	91 (33.1)	72 (26.2)	109 (39.6)
2011	16 (4.2)	140 (36.9)	88 (23.2)	142 (37.5)
2012	14 (5.1)	78 (28.3)	70 (25.4)	121 (43.8)
2013	8 (2.5)	83 (25.5)	93 (28.6)	141 (43.4)
2014	12 (4.7)	51 (20.2)	71 (28.1)	115 (45.5)
2015	7 (3.7)	44 (23.3)	50 (26.5)	93 (49.2)
2016	6 (2.9)	46 (22.1)	62 (29.8)	88 (42.3)
50–64				
2009	13 (5.8)	82 (36.4)	51 (22.7)	85 (37.8)
2010	11 (4.0)	98 (35.8)	64 (23.4)	106 (38.7)
2011	20 (5.3)	119 (31.6)	101 (26.9)	149 (39.6)
2012	8 (2.7)	88 (30.0)	81 (27.6)	122 (41.6)
2013	13 (3.7)	90 (25.4)	96 (27.1)	161 (45.5)
2014	13 (4.0)	75 (22.8)	96 (29.2)	148 (45.0)
2015	15 (5.2)	68 (23.4)	89 (30.6)	130 (44.7)
2016	7 (3.0)	65 (27.9)	63 (27.0)	91 (39.1)
≥65				
2009	12 (5.2)	99 (43.0)	41 (17.8)	89 (38.7)
2010	19 (6.9)	93 (33.9)	74 (27.0)	102 (37.2)
2011	18 (4.6)	128 (33.0)	100 (25.8)	153 (39.4)
2012	17 (6.0)	72 (25.5)	73 (25.9)	127 (45.0)
2013	8 (2.3)	78 (22.8)	93 (27.2)	154 (45.0)
2014	11 (3.1)	77 (21.4)	112 (31.1)	149 (41.4)
2015	3 (1.1)	63 (23.5)	75 (28.0)	128 (47.8)
2016	22 (8.9)	61 (24.7)	51 (20.6)	131 (53.0)

[a] Includes PPV23 serotypes excluding those covered by PCV13

Conclusions

- PCV7 serotypes causing lower respiratory tract infections in the US adult population showed low, but persistent, prevalence (2.8%–5.1%) during the study period
- The yearly prevalence of PCV13 serotypes showed signs of decline, which was primarily driven by decreases in serotypes 19A and 7F, whereas serotype 3 increased during the study period
- PCV13 serotypes did not decline between 2014 and 2016 in those ≥65 years of age, the age group for whom the vaccine is recommended, presumably due to low vaccine uptake. Thus the impact of adult vaccination has yet to be realized.
- Clear trends for increased prevalence over time were documented for the serotypes which are unique to PPV23 and non-vaccine serotypes across all age groups
- Continued surveillance will remain important for monitoring the impact of adult immunization programs in the US

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