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Serotype Distributions and Analysis of Susceptibility Profiles of *Streptococcus pneumoniae* Causing Infections in Adult Patients in the United States (2009–2013)

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ABSTRACT

Background: A pneumococcal polysaccharide vaccine has been used for adults since 1997. A conjugate vaccine (PCV13) had been recommended since 2014. The serotype (ST) distribution and susceptibility profiles of pneumococci causing infections in adult patients in the United States before PCV13 introduction in adults (2009–2013) were evaluated.

Methods: 4,491 *S. pneumoniae* originated from patients (≥18 years old) seen/hospitalized in 87 US centers. Isolates were recovered primarily (79.0%; 3,549/4,491) from lower respiratory tract specimens. Serotyping was performed by *cpsB* sequencing, multiplex PCR and/or Quellung. Susceptibility testing applied CLSI methods.

Results: PCV7 ST (4.6%–4.9%) remained stable during 2009–2012, decreasing to 2.9% in 2013. 19F (62.4%, all years) represented the majority of PCV7 pneumococci with rates of 2.8%, 2.9%, 3.0%, and 3.2% in 2009, 2010, 2011, and 2012, respectively, and declined to 1.7% in 2013. Overall, PCV13 comprised 31.5% of ST, declining from 38.6% in 2009 to 24.7% in 2013. Rates of 19A (15.0%–17.5%) remained consistent during 2009–2011 and declined to 12.7% and 11.5% in 2012 and 2013, respectively. ST 6A decreased to 0.2% in 2013, whereas ST 7F increased from 4.6% to 5.5% during 2009 and 2010 before decreasing in the following years to 1.8%. ST 3 showed consistent rates (8.1%–9.9%) over time. The proportion of non-PCV ST increased during the study period, as did the serotypes that are unique to PPV23. Among non-PCV, 23A (8.6%) was the most common ST in 2013, followed by 35B (7.3%), 11A/11D (6.3%), 22F/22A (6.1%), 15A/15F (5.5%) and 6C/6D (4.8%). The latter showed a decreased prevalence from 7.6% in 2009 to 4.8% in 2013, whereas 35B and 15B/15C rates increased during the four initial years but had lower rates in 2013. Overall, susceptibility rates for penicillin (MIC, ≤2 µg/ml; +3.0%) and tetracycline (+10.1%) increased during 2009–2010 and 2012–2013 periods.

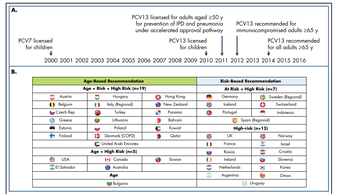
Conclusion: Nine years after its pediatric introduction, PCV7 rates in adults were stable four consecutive years before decreasing in 2013. PCV13 rates declined over time, mostly due to decreasing rates of 19A, 6A and 7F, consistent with an indirect effect. Continued surveillance is needed to constantly assess the dynamic changes of ST affecting this older US population.

BACKGROUND

- *Streptococcus pneumoniae* is an important adult pathogen responsible for community-acquired pneumonia.
- A 7-valent pneumococcal conjugate vaccine (PCV7; Prevnar/Prevenar, Wyeth Lederle Vaccines) containing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F was licensed in the United States (US) in 2000 for use in children **(Figure 1)**. A 13-valent vaccine (PCV13; Prevnar 13/Prevenar 13, Wyeth/Pfizer Vaccines) containing all of the polysaccharide antigens common to PCV7 along with serotypes 1, 3, 7F, 3, 6A, and 19A was approved for use in children in 2010 **(Figure 1)**.
- Beyond the effect of PCV13 in vaccinated age groups, there is a documented reduction in nasopharyngeal pneumococcal carriage, which results in decreases in pneumococcal disease in unvaccinated individuals (ie, indirect protection due to herd effect; **Figure 2**).[1-3]
- Despite the use of these vaccines in children, there remains a burden of disease in adults owing to the PCV7 and PCV13 serotypes.[4]
  - In 2011, the US Food and Drug Administration (FDA) approved PCV13 for use in adults ≥50 years of age under the FDA's accelerated approval pathway, which grants early approval to products that provide meaningful therapeutic benefit over existing treatments for serious illnesses.[5]
- The FDA defined the meaningful therapeutic benefit of PCV13 over existing treatment—23-valent plain polysaccharide vaccine (PPV23)—as protection from nonbacteremic pneumococcal pneumonia or nonbacteremic pneumococcal pneumonia combined with protection from invasive pneumococcal disease (IPD).
- The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (ACIP) recommended routine use of PCV13 for adults ≥65 years of age in 2014. This recommendation has had a significant effect on adult uptake of PCV13 **(Figure 3)**.[5]
- 45 countries have made age-based or risk-based recommendations for the use of PCV13 in adults **(Figure 1)**.
- It is important to monitor the effect and magnitude of vaccination on IPD and non-IPD among adults.[6] In addition, surveillance for antimicrobial resistance and distribution of serotypes in *S. pneumoniae* is of paramount relevance.

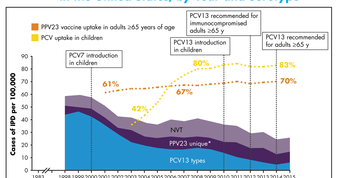
BACKGROUND (con't)

Figure 1. (A) History of PCV Licensure by the FDA in the United States; (B) Worldwide Recommendations for Use of PCV13 in Adults as of August 2016



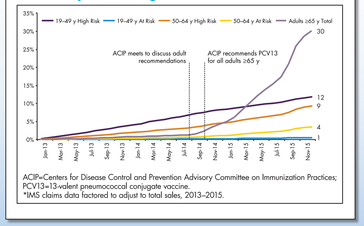
FDA=US Food and Drug Administration; IPD=invasive pneumococcal disease; PCV=pneumococcal conjugate vaccine; PCV7=7-valent pneumococcal conjugate vaccine; PCV13=13-valent pneumococcal conjugate vaccine.

Figure 2. Incidence of IPD in Adults ≥65 Years of Age in the United States, by Year and Serotype



IPD=invasive pneumococcal disease; NVT=nonvaccine types; PCV=pneumococcal conjugate vaccine; PCV7=7-valent pneumococcal conjugate vaccine; PCV13=13-valent pneumococcal conjugate vaccine; PPV23=23-valent pneumococcal polysaccharide vaccine.
*Serotypes contained in PPV23 and not PCV13 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F)
Source data for incidence and vaccination rates can be found at http://www.cdc.gov/abcs/reports-findings/survereports/spneu-types.html; http://www.cdc.gov/brfss/brfsprevalence; http://www.cdc.gov/nchs/data/hus/hus15.pdf#066; and http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5634a2.htm#tab1

Figure 3. Estimated PCV13 Cumulative Uptake in Adults by Risk and Age*



ACIP=Centers for Disease Control and Prevention Advisory Committee on Immunization Practices; PCV13=13-valent pneumococcal conjugate vaccine.
*IMS claims data factored to adjust to total sales, 2013–2015.

OBJECTIVES

- To determine the prevalence and serotype distribution of *S. pneumoniae* clinical isolates recovered predominantly from nonsterile sites (mostly sputum or lower respiratory tract secretions) among adult patients (≥18 years of age) in the United States from 2009 to 2013 (ie, the years immediately before the ACIP recommendation for PCV13 use in adults)
- To assess the antimicrobial susceptibility profiles during this time period

MATERIALS AND METHODS

Clinical Isolates

- 4491 *S. pneumoniae* clinical isolates recovered from adult patients (≥18 years old) seen as outpatients or hospitalized in 87 US centers with symptoms of respiratory infections were included.
- Isolates were collected primarily (79.0%; 3549/4491) from lower respiratory tract specimens and submitted to a central monitoring laboratory (JMI Laboratories, North Liberty, IA, USA), as part of the SENTRY Antimicrobial Surveillance Program.
- Bacterial identification was performed by the participating microbiology laboratory and confirmed by the central monitoring laboratory.
- Confirmation of bacterial identification was performed by colony morphology and biochemical algorithms.
- When the bacterial identification was questionable using phenotypic methods or an untypeable serotyping result was obtained by the applied methodology, isolates were subjected to a polymerase chain reaction (PCR) assay for further identification.

Antimicrobial Susceptibility Testing

- Isolates were tested for susceptibility by broth microdilution methods according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI).[7]
- Validation of the minimal inhibitory concentration (MIC) values was performed by concurrent testing of the quality control strain *S. pneumoniae* American Type Culture Collection 49619.[8]
- Inoculum density was monitored by colony counts to ensure an adequate number of cells for each testing event. MIC interpretations were based on the CLSI breakpoint criteria.[8]

Pneumococcal Serotyping

- Isolates were subjected to PCR assays for amplification of the *cpsB* gene.
- Amplicons were sequenced on both strands, and the nucleotide sequences were analyzed using the Lasergene software package (DNASTAR, Madison, WI, USA).
- Sequences were compared with others available via PubMed (http://www.ncbi.nlm.nih.gov/blast/). Because of sequence homology among certain serotypes, those showing nucleotide sequence similarity greater than 99% were grouped (ie, 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-nonPCV7, and PCV13 serotypes accounted for 4.3%, 27.1%, and 31.5% of all isolates, respectively, with serotypes 19F (2.7%) predominating among PCV7-type isolates and serotypes 19A (14.7%) and 3 (8.6%) prevailing among PCV13-type isolates **(Table 1)**.
- Rates for PCV7 serotypes remained stable (4.6%–4.9%) during 2009–2012, declining in 2013 (2.9%). A similar trend was observed for serotype 19F, with rates of 2.8%–3.2% during the first 4 surveillance years and 1.7% in 2013 **(Table 1)**.
- There was a consistent decreasing trend over the study period for PCV13 (from 38.6% to 24.7%) and PCV13-nonPCV7 (from 33.6% to 21.8%, **Table 1**). Within PCV13, serotypes 19A, 3, 7F, and 6A showed declining trends.
- Overall, a total of 25.8% of isolates consisted of serotypes that are unique to PPV23, with a consistent upward trend (from 22.9% to 28.2%) during the surveillance period **(Table 1)**.
- Among the non-PCV13 serotypes, 23A (8.6%) was the most common in 2013, followed by 35B (7.3%), 11A/11D (6.3%), 22F/22A (6.1%), 15A/15F (5.5%), and 6C/6D (4.8%), which showed a decreased prevalence, from 7.6% in 2009 to 4.8% in 2013. The rates for 35B and 15B/15C increased during the 4 initial years but had lower rates in 2013 **(Table 1)**.
- **Figure 4** shows the proportion of isolates associated with PCV13 serotypes, serotypes that are unique to PPV23, and nonvaccine types by age group (18–64 and ≥65 years). Consistent with the observations for the entire cohort, the prevalence of PCV13 serotypes in each age group began to decrease after the introduction of PCV13 in children, whereas the serotypes that are unique to PPV23 increased, as did nonvaccine types.
- Overall, susceptibility rates increased slightly for penicillin (MIC, ≤2 µg/mL; +3.0%) and tetracycline (+10.1%) and decreased slightly for erythromycin (–5.1%) between the 2009–2010 and 2012–2013 periods. Other antimicrobial agents showed similar overall susceptibility rates between study periods **(Table 2)**.

Table 1. Distribution of Serogroups/types of *S. pneumoniae* Causing Infections in the US Adult Population From 2009 to 2013

Serogroup/type	Year, n(%)					All Years (n=4491)
	2009 (n=669)	2010 (n=823)	2011 (n=1143)	2012 (n=851)	2013 (n=1005)	
PCV7	33 (4.9)	39 (4.7)	54 (4.7)	39 (4.6)	29 (2.9)	194 (4.3)
19F	19 (2.8)	24 (2.9)	34 (3.0)	27 (3.2)	17 (1.7)	121 (2.7)
9V/9A	3 (0.5)	0 (0.0)	7 (0.6)	2 (0.2)	4 (0.4)	16 (0.4)
23F	3 (0.5)	4 (0.5)	3 (0.3)	3 (0.4)	2 (0.2)	15 (0.3)
6B	4 (0.6)	2 (0.2)	4 (0.4)	2 (0.2)	2 (0.2)	14 (0.3)
4	0 (0)	3 (0.4)	5 (0.4)	1 (0.1)	4 (0.4)	13 (0.3)
14	1 (0.2)	4 (0.5)	1 (0.1)	2 (0.2)	0 (0.0)	8 (0.2)
18 (18A/18B/18C/18F)	3 (0.5)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	7 (0.2)
PCV13	258 (38.6)	282 (34.3)	387 (33.9)	238 (28.0)	248 (24.7)	1413 (31.5)
PCV13-PCV7	225 (33.6)	243 (29.5)	333 (29.1)	199 (23.4)	219 (21.8)	1219 (27.1)
19A	117 (17.5)	123 (15.0)	196 (17.2)	108 (12.7)	116 (11.5)	660 (14.7)
3	66 (9.9)	70 (8.5)	100 (8.8)	69 (8.1)	82 (8.2)	387 (8.6)
7F	31 (4.6)	45 (5.5)	32 (2.8)	14 (1.7)	18 (1.8)	140 (3.1)
6A	11 (1.6)	5 (0.6)	4 (0.4)	8 (0.9)	2 (0.2)	30 (0.7)
1	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	2 (<0.1)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PPV23 unique	153 (22.9)	210 (25.5)	289 (25.3)	224 (26.3)	284 (28.2)	1160 (25.8)
11A/11D	38 (5.7)	47 (5.7)	59 (5.2)	55 (6.5)	63 (6.3)	262 (5.8)
22F/22A	33 (4.9)	48 (5.8)	67 (5.9)	41 (4.8)	61 (6.1)	250 (5.6)
15B/15C	18 (2.7)	39 (4.7)	53 (4.6)	54 (6.4)	45 (4.5)	209 (4.7)
9N/9L	15 (2.2)	23 (2.8)	33 (2.9)	22 (2.6)	33 (3.3)	126 (2.8)
33F/33A/37	10 (1.5)	10 (1.2)	20 (1.8)	13 (1.5)	31 (3.1)	84 (1.9)
10A	15 (2.2)	8 (1.0)	22 (1.9)	11 (1.3)	23 (2.3)	79 (1.8)
17F	16 (2.4)	13 (1.6)	18 (1.6)	11 (1.3)	15 (1.5)	73 (1.6)
8	4 (0.6)	6 (0.7)	8 (0.7)	6 (0.7)	9 (0.9)	33 (0.7)
20	2 (0.3)	9 (1.1)	6 (0.5)	10 (1.2)	4 (0.4)	31 (0.7)
12F/12A/44/46	2 (0.3)	7 (0.9)	3 (0.3)	1 (0.1)	0 (0.0)	13 (0.3)
Nonvaccine	224 (36.5)	317 (38.5)	444 (38.8)	370 (43.5)	447 (44.5)	1,822 (40.6)
35B	26 (3.9)	54 (6.6)	82 (7.2)	79 (9.3)	73 (7.3)	314 (7.0)
6C/6D	51 (7.6)	53 (6.4)	77 (6.7)	63 (7.4)	48 (4.8)	292 (6.5)
23A	38 (5.7)	37 (4.5)	64 (5.6)	50 (5.9)	86 (8.6)	275 (6.1)
15A/15F	35 (5.2)	45 (5.5)	50 (4.4)	36 (4.2)	55 (5.5)	221 (4.9)
23B	25 (3.7)	28 (3.4)	43 (3.8)	46 (5.4)	42 (4.2)	184 (4.1)
16F	18 (2.7)	28 (3.4)	22 (1.9)	16 (1.9)	31 (3.1)	115 (2.6)
31	17 (2.5)	19 (2.3)	31 (2.7)	22 (2.6)	25 (2.5)	114 (2.5)
34	7 (1.1)	17 (2.1)	17 (1.5)	14 (1.7)	17 (1.7)	72 (1.6)
35F/47F	10 (1.5)	11 (1.3)	16 (1.4)	9 (1.1)	17 (1.7)	63 (1.4)
7C/7B/40	7 (1.1)	12 (1.5)	12 (1.1)	8 (0.9)	11 (1.1)	50 (1.1)
21	3 (0.5)	2 (0.2)	9 (0.8)	9 (1.1)	23 (2.3)	46 (1.0)
38/25F/25A	1 (0.2)	3 (0.4)	13 (1.1)	6 (0.7)	6 (0.6)	29 (0.7)
Other	3 (0.4)	4 (0.5)	5 (0.4)	4 (0.5)	11 (1.0)	27 (0.6)
13	3 (0.5)	4 (0.5)	3 (0.3)	8 (1.0)	2 (0.2)	20 (0.5)
Nontypeable	14 (2.1)	14 (1.7)	23 (2.0)	19 (2.2)	26 (2.6)	96 (2.1)

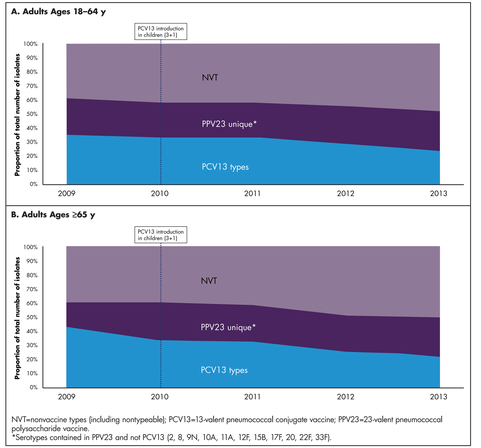
PCV7=7-valent pneumococcal conjugate vaccine; PCV13=13-valent pneumococcal conjugate vaccine; PPV23=23-valent pneumococcal polysaccharide vaccine.

Table 2. Antimicrobial Activity Against *S. pneumoniae* Isolates Collected During the 2009–2010 and 2012–2013 Periods in the United States

Antimicrobial Agent	MIC, µg/mL			% Susceptible/ Intermediate/ Resistant*
	MIC_{50}	MIC_{90}	Range	
2009–2010 (n=1492)				
Penicillin†	≤0.03	4	≤0.03–>4	87.7, 10.9, 1.5
A/C‡	≤1	8	≤1–>8	85.7, 2.7, 11.5
Ceftriaxone§	≤0.25	1	≤0.25–8	90.7, 7.5, 1.8
Erythromycin	≤0.25	>2	≤0.25–>2	62.8, 0.6, 36.6
Clindamycin	≤0.25	>1	≤0.25–>1	81.0, 0.3, 18.6
Levofloxacin	1	1	≤0.5–>4	98.8, 0.0, 1.2
Tetracycline	≤2	>8	≤2–>8	67.4, 0.0, 32.6
TMP-SMX	≤0.5	>2	≤0.5–>2	69.6, 7.0, 23.4
Linezolid	1	1	≤0.12–4	99.9, NA, NA
Vancomycin	≤1	≤1	≤1–≤1	100.0, NA, NA
2012–2013 (n=1856)				
Penicillin	≤0.06	2	≤0.06–8	90.7, 8.3, 1.0
A/C	≤1	4	≤1–>8	86.8, 3.4, 9.8
Ceftriaxone	≤0.06	1	≤0.06–8	91.1, 8.1, 0.8
Erythromycin	≤0.12	>16	≤0.12–>16	57.1, 0.8, 42.2
Clindamycin	≤0.25	>2	≤0.25–>2	81.7, 0.8, 17.6
Levofloxacin	1	1	0.25–>4	98.8, 0.2, 1.0
Tetracycline	0.25	32	≤0.03–>32	77.5, 0.2, 22.3
TMP-SMX	≤0.5	>4	≤0.5–>4	68.2, 12.3, 19.5
Linezolid	1	1	≤0.12–2	100.0, NA, NA
Vancomycin	0.25	0.5	≤0.12–0.5	100.0, NA, NA

A/C=amoxicillin-clavulanate; TMP-SMX=trimethoprim-sulfamethoxazole; CLSI=Clinical and Laboratory Standards Institute; MIC=minimal inhibitory concentration; MIC_{50}=MIC value at which 50% of isolates are inhibited; MIC_{90}=MIC value at which 90% of isolates are inhibited; NA=not available.
*Breakpoint criteria were those from CLSI 2016.
†Parenteral nonmeningitidis (≤2 µg/mL for susceptible; 4 µg/mL for intermediate; and ≥8 µg/mL for resistant).
‡Nonmeningitidis (≤2/1 µg/mL for susceptible; 4/2 µg/mL for intermediate; and ≥8/4 µg/mL for resistant).
§Nonmeningitidis (≤1 µg/mL for susceptible; 2 µg/mL for intermediate; and ≥4 µg/mL for resistant).

Figure 4. Proportion of Isolates by Vaccine Serotype



NVT=nonvaccine types (including nontypeable); PCV13=13-valent pneumococcal conjugate vaccine; PPV23=23-valent pneumococcal polysaccharide vaccine.
*Serotypes contained in PPV23 and not PCV13 (2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F).

DISCUSSION

- **Despite PPV23 use in adults for 3 decades with approximately 60%–70% vaccination coverage over the last decade, PCV7 use in children since 2000, PCV13 use in children since 2010, and significant herd effects for IPD in children and adults, there remains a significant burden in respiratory cultures of adults presenting for respiratory infections.**
- **The circulation of PCV7 and PCV13 serotypes in this population could be addressed by direct vaccination of adults with PCV13.**
- **With the ability to prevent nasopharyngeal carriage, vaccination of adults with PCVs may change the transmission dynamics in the adult population.**
- **Continued surveillance remains important for monitoring the impact of pediatric and adult immunization programs in the US adult population.**

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ACKNOWLEDGMENTS

The research and publication process was supported by Pfizer Inc, Collegeville, PA, USA.