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Yearly Trends of Antimicrobial Nonsusceptibility among *Streptococcus pneumoniae* Serotypes Causing Infections in Adult Patients in the United States (2009–2015)

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Introduction

- *Streptococcus pneumoniae* is a gram-positive encapsulated diplococcus that is a significant cause of disease associated with mortality and morbidity in children and adults
- Pneumococcal conjugate vaccines (PCVs) containing 7 (PCV7), 10 (PCV10), and 13 (PCV13) pneumococcal polysaccharide antigens were developed and introduced in several countries
  - As of December of 2016, a total of 138 countries have introduced PCVs into their infant national immunization program (NIP) (96 with PCV13, 33 with PCV10, and 8 with both PCV10 and PCV13)
- Implementing and using PCVs in children has led to substantial incidence rate reductions of vaccine type invasive pneumococcal disease (IPD) among vaccinated children. Reductions in vaccine type disease have also been observed in nonvaccinated persons through indirect effects
- PCV7 reduced disease incidence by vaccine-type antimicrobial nonsusceptible strains throughout the 2000s
  - Some of these emerging strains were derived from vaccine types that had changed their capsule by recombination
- Introducing PCV13 in the United States in 2010 also changed the epidemiology of *S. pneumoniae* serotypes, and the impact on the antimicrobial susceptibility profiles are not yet very well understood
- This study describes the yearly trends in antimicrobial nonsusceptibility rates in pneumococci during 2009–2015 causing infections in adult patients (≥18 years) in the United States

Materials and Methods

Clinical isolates

- A total of 6,177 *S. pneumoniae* clinical isolates recovered from adult patients (≥18 years old) seen/hospitalized in 91 US centers were included in this study
- Isolates were collected primarily (78.3%; 4,852/6,197) 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 when an untypeable serotyping result was obtained by the applied methodology

Antimicrobial susceptibility testing

- Isolates were susceptibility tested by broth microdilution following guidelines from the Clinical and Laboratory Standards Institute (CLSI) M07-A10 document
- Quality assurance was performed by concurrently testing CLSI-recommended quality-control (QC) reference strains (*S. pneumoniae* ATCC 49169)
  - All QC results were within published acceptable ranges
- Breakpoint criteria were those from CLSI (2017)

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 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 (eg, 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, susceptibility rates for penicillin (parenteral), ceftriaxone, amoxicillin-clavulanate, and clindamycin increased during the period (Figure 1)
  - Isolates included in the study remained susceptible to levofloxacin (98.0%–99.2%), vancomycin (100.0%), linezolid (99.9%–100.0%), and tigecycline (99.8%–100.0%)
  - Susceptibility rates for tetracycline remained generally more consistent during 2009–2015
- PCV7 serotypes showed a reduction in the nonsusceptibility rates for penicillin G (parenteral, nonmeningitis; from 32.0% in 2009 to 16.0% in 2015) and ceftriaxone (from 28.0% to 12.0%), as did PCV13 serotypes (from 34.9% to 16.0% and from 26.7% to 8.6%, respectively) (Table 1)
- Overall, nonsusceptibility rates for ceftriaxone, clindamycin, and erythromycin obtained against serotype 19F decreased (Tables 1 and 2), while trends for penicillin nonsusceptibility against this serotype were not observed
- Nonsusceptibility rates obtained for penicillin, ceftriaxone, clindamycin, and erythromycin against serotype 19A tended to increase between 2009 and 2011–2012 and decreased in the following years (2013–2015) (Tables 1 and 2)
- The erythromycin nonsusceptibility rate (91.9%) against 19A peaked in 2011 and decreased in the following years; however, the erythromycin nonsusceptibility rate noted in 2015 (79.6%) remained higher than that of 2009 (73.9%)
- Although nonsusceptibility rates for penicillin (49.0% or 73.5%), ceftriaxone (24.5%), and clindamycin (51.0%) obtained against serotype 19A in 2015 were lower than those rates of 2009, generally 19A remained the less susceptible serotype (Tables 1 and 2)
- Nonsusceptibility rates for clindamycin and erythromycin against serotype 3 increased to 19.6% and 23.9%, respectively, in 2015 (Table 2)
- The 23-valent polysaccharide vaccine (PPV23) serotypes, excluding PCV13 serotypes (i.e. the 11 serotypes that are unique to PPV23), showed stable nonsusceptibility rates throughout the study (Tables 1 and 2)

Figure 1 Susceptibility rates for antimicrobial agents tested against *S. pneumoniae* causing infections in adult patients during 2009–2015 in the US

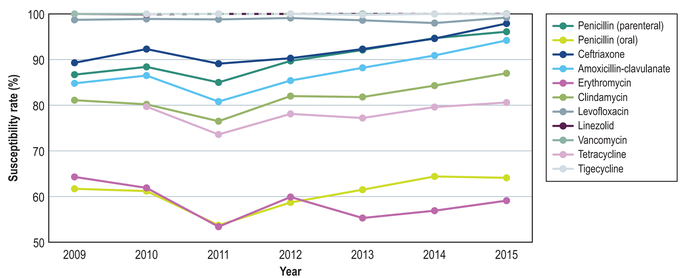

Table 1 Penicillin and ceftriaxone nonsusceptible rates against the most common serogroups/types observed among *S. pneumoniae* collected during 2009–2015 in the US

Serogroup/type	Percent of nonsusceptibility[a] by year														
	Penicillin							Ceftriaxone							
	2009	2010	2011	2012	2013	2014	2015	2009	2010	2011	2012	2013	2014	2015
PCV7	32.0 (52.0)	28.9 (52.6)	19.1 (55.3)	16.2 (51.4)	10.3 (44.8)	17.6 (41.2)	16.0 (36.0)	28.0	21.1	17.0	21.6	10.3	8.8	12.0
19F	26.7 (46.7)	33.3 (50.0)	25.8 (45.2)	20.0 (60.0)	11.8 (41.2)	23.1 (34.6)	18.2 (36.4)	20.0	25.0	22.6	20.0	11.8	7.7	13.6
PCV13	34.9 (52.3)	33.6 (50.0)	42.6 (58.6)	35.7 (51.9)	30.6 (47.2)	24.3 (38.1)	16.0 (28.6)	26.7	22.8	29.2	31.4	28.2	21.7	8.6
19A	66.8 (89.8)	61.5 (86.2)	78.9 (96.3)	74.7 (91.2)	62.9 (82.8)	58.8 (82.4)	49.0 (73.5)	50.0	41.3	52.2	63.7	57.8	54.4	24.5
3	0.0 (0.0)	0.0 (0.0)	0.0 (2.4)	0.0 (6.2)	0.0 (6.0)	0.0 (1.4)	0.0 (5.4)	0.0	0.0	0.0	0.0	1.2	0.0	0.0
7F	0.0 (9.5)	0.0 (0.0)	0.0 (8.3)	0.0 (0.0)	0.0 (5.6)	0.0 (0.0)	0.0 (0.0)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
PPV23-non-PCV13	0.7 (10.4)	0.0 (8.1)	1.3 (15.7)	0.5 (13.2)	0.4 (12.4)	0.0 (9.8)	0.0 (15.0)	2.2	0.0	1.7	1.5	1.1	0.8	0.0
11A/11D	0.0 (8.8)	0.0 (2.4)	0.0 (8.2)	2.3 (6.8)	0.0 (11.1)	0.0 (6.8)	0.0 (12.8)	2.9	0.0	2.0	2.3	3.2	1.4	0.0
22A/22F	0.0 (6.5)	0.0 (0.0)	4.1 (14.3)	0.0 (2.9)	0.0 (4.9)	0.0 (4.2)	0.0 (2.5)	3.2	0.0	2.0	2.9	0.0	0.0	0.0
15B/15C	0.0 (33.3)	0.0 (33.3)	2.1 (44.7)	0.0 (36.2)	2.2 (44.4)	0.0 (35.9)	0.0 (43.6)	0.0	0.0	2.1	0.0	2.2	2.6	0.0
17F	0.0 (7.1)	0.0 (0.0)	0.0 (0.0)	0.0 (9.1)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0	0.0	0.0	9.1	0.0	0.0	0.0
10A	7.7 (15.4)	0.0 (0.0)	0.0 (5.0)	0.0 (0.0)	0.0 (0.0)	0.0 (17.6)	0.0 (0.0)	7.7	0.0	0.0	0.0	0.0	0.0	0.0
9N/9L	0.0 (0.0)	0.0 (4.5)	0.0 (7.7)	0.0 (4.8)	0.0 (9.1)	0.0 (3.7)	0.0 (9.1)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
33F/33A/37	0.0 (0.0)	0.0 (0.0)	0.0 (7.1)	0.0 (8.3)	0.0 (7.1)	0.0 (3.7)	0.0 (18.8)	0.0	0.0	7.1	0.0	0.0	0.0	0.0
Nonvaccine[b]	1.9 (44.0)	0.4 (47.6)	0.5 (55.0)	0.3 (52.8)	0.7 (49.6)	0.3 (51.8)	0.3 (52.9)	1.9	0.0	1.6	0.9	1.1	1.0	0.3
6C/6D	0.0 (60.0)	0.0 (42.5)	0.0 (59.4)	0.0 (55.6)	0.0 (38.5)	0.0 (39.1)	0.0 (75.0)	0.0	0.0	3.1	0.0	0.0	2.2	0.0
23A	0.0 (45.2)	0.0 (75.0)	0.0 (70.4)	0.0 (71.7)	0.0 (69.8)	0.0 (67.2)	0.0 (61.2)	0.0	0.0	0.0	0.0	0.0	0.0	2.0
15A/15F	0.0 (76.7)	0.0 (97.5)	0.0 (90.9)	0.0 (88.2)	0.0 (83.6)	0.0 (84.2)	0.0 (73.0)	0.0	0.0	0.0	0.0	3.6	0.0	0.0
23B	0.0 (27.3)	0.0 (27.3)	2.7 (32.4)	0.0 (44.2)	2.4 (42.9)	1.9 (48.1)	0.0 (48.0)	0.0	0.0	2.7	0.0	0.0	3.8	0.0
35B	5.0 (80.0)	2.2 (91.1)	1.4 (95.9)	1.6 (91.8)	2.7 (97.3)	0.0 (94.3)	1.1 (85.1)	5.0	0.0	2.7	4.9	2.7	1.1	0.0
16F	6.7 (13.3)	0.0 (0.0)	0.0 (9.1)	0.0 (6.2)	0.0 (12.9)	0.0 (13.8)	0.0 (6.2)	6.7	0.0	4.5	0.0	3.2	0.0	0.0
31	7.7 (7.7)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (7.7)	0.0 (0.0)	0.0 (15.4)	7.7	0.0	0.0	0.0	0.0	0.0	0.0
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	0.0	0.0	0.0	0.0
34	0.0 (0.0)	0.0 (0.0)	0.0 (8.3)	0.0 (9.1)	NA	0.0 (7.1)	0.0 (25.0)	0.0	0.0	0.0	0.0	0.0	NA	0.0
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)	0.0 (0.0)	0.0	0.0	0.0	0.0	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 (41.9)	0.0 (34.8)	0.0 (12.5)	0.0	0.0	0.0	0.0	0.0	2.2	0.0
All	13.3 (38.3)	11.6 (38.8)	15.0 (46.3)	10.3 (41.3)	7.9 (38.5)	5.3 (35.6)	3.9 (35.9)	10.7	7.7	10.9	9.7	7.7	5.4	2.1

[a] Percentage of nonsusceptible isolates according to the susceptible parenteral (≤2 µg/mL; for non-meningitis) and oral (≤0.06 µg/mL; between parentheses) penicillin and ceftriaxone (≤1 µg/mL) breakpoints published in the CLSI M100-S27 document. NA, isolates not detected
[b] Nonvaccine was defined as those not present in the 3 vaccines available in the US

- Overall, nonvaccine serotypes showed stable nonsusceptibility rates for penicillin G (parenteral, nonmeningitis), ceftriaxone, and clindamycin. An overall increasing trend for nonsusceptibility to erythromycin was noted among nonvaccine strains (from 33.3% in 2009 to 45.0% in 2015; Table 3)
  - The nonsusceptibility rates for penicillin against nonvaccine strains increased over time when applying the oral breakpoint, remaining at 52.9% in 2015 (Table 1)
  - Overall, the nonsusceptibility rates for oral penicillin peaked in 2010 against 15A/F and 23A serotypes, and decreased in the following years (Table 1); however, rates against 15A/F and 23A serotypes remained elevated (73.0% and 61.2%, respectively) in 2015
  - While nonsusceptibility rates for oral penicillin against serotype 6C/D (38.5%–75.0%) or 35B (80.0%–97.3%) varied over time, these rates increased against serotype 23B (from 27.3% to 48.0%)
  - Clindamycin nonsusceptibility rate (95.5%) against serotype 15A/F was highest in 2011 and continued to decrease to 59.5% in 2015 (Table 2)
  - Increasing nonsusceptibility rates for erythromycin were obtained against serotype 35B (from 40.0% in 2009 to 71.3% in 2015)

Table 2 Clindamycin and erythromycin nonsusceptible rates against the most common serogroups/types observed among nonvinvasive *S. pneumoniae* collected during 2009–2015 in the US

Serogroup/type	Percent of nonsusceptibility[a] by year													
	Clindamycin							Erythromycin						
	2009	2010	2011	2012	2013	2014	2015	2009	2010	2011	2012	2013	2014	2015
PCV7	32.0	31.6	23.4	18.9	27.6	26.5	20.0	52.0	52.6	59.6	48.6	60.7	50.0	36.0
19F	40.0	37.5	29.0	24.0	29.4	30.8	22.7	46.7	50.0	41.9	40.0	62.5	46.2	36.4
PCV13	34.9	33.2	44.8	38.1	36.5	35.4	27.4	45.6	49.6	60.2	52.4	51.4	49.7	40.0
19A	64.8	56.9	73.3	70.3	69.8	70.6	51.0	73.9	80.7	91.9	86.8	86.2	85.3	79.6
3	6.0	5.0	15.5	12.5	2.4	13.7	19.6	6.0	8.3	14.3	14.1	7.1	21.9	23.9
7F	0.0	0.0	0.0	7.7	5.6	0.0	0.0	4.8	0.0	8.3	7.7	11.1	20.0	0.0
PPV23-non-PCV13	1.5	3.5	5.7	3.6	3.9	3.4	3.3	26.1	22.1	34.1	32.5	40.7	35.2	35.0
11A/11D	0.0	0.0	2.0	4.5	3.2	4.1	2.1	35.3	19.5	34.7	27.3	42.9	43.8	38.3
22A/22F	6.5	2.8	12.2	5.7	6.6	0.0	0.0	17.9	16.7	36.7	20.0	29.5	16.7	25.0
15B/15C	0.0	5.6	6.4	2.1	6.7	10.3	7.7	46.7	38.9	61.7	53.2	67.4	48.7	51.3
17F	0.0	0.0	0.0	0.0	0.0	0.0	0.0	28.6	18.2	20.0	9.1	33.3	15.4	25.0
10A	0.0	0.0	0.0	9.1	0.0	0.0	5.9	7.7	0.0	10.0	9.1	33.3	41.2	23.5
9N/9L	0.0	13.6	3.8	4.8	0.0	3.7	6.1	0.0	18.2	3.8	9.5	9.1	14.8	18.2
33F/33A/37	0.0	0.0	14.3	0.0	7.1	3.7	0.0	71.4	50.0	57.1	91.7	85.7	74.1	81.2
Nonvaccine[b]	15.5	18.1	16.9	14.5	16.7	14.0	12.0	33.3	37.6	42.9	37.0	42.5	46.2	45.0
6C/6D	2.2	2.5	3.1	5.6	1.9	2.2	4.2	53.3	40.0	56.2	50.0	40.4	47.8	66.7
23A	6.5	15.6	16.7	13.0	26.7	26.6	18.4	9.7	25.0	18.5	26.1	40.7	36.5	28.6
15A/15F	80.0	92.5	95.5	88.2	78.2	76.3	59.5	86.7	95.0	97.7	94.1	89.1	92.1	75.7
23B	0.0	4.5	5.4	9.3	2.4	1.9	0.0	13.6	4.5	27.0	11.6	26.8	31.4	28.0
35B	5.0	4.4	4.1	1.6	1.4	4.6	6.9	40.0	60.0	62.2	54.1	69.9	72.4	71.3
16F	0.0	0.0	9.1	6.2	3.2	3.4	6.2	0.0	13.0	9.1	6.2	19.4	10.3	6.2
31	15.4	0.0	0.0	5.0	3.8	0.0	0.0	23.1	27.8	26.1	25.0	20.0	38.9	30.8
35F/47F	0.0	0.0	0.0	0.0	5.9	6.2	0.0	0.0	10.0	27.3	12.5	11.8	6.2	30.8
34	0.0	11.8	0.0	0.0	0.0	NA	25.0	0.0	11.8	8.3	18.2	0.0	NA	25.0
7C/7B/40	20.0	0.0	0.0	0.0	9.1	0.0	0.0	20.0	0.0	0.0	0.0	18.2	0.0	6.7
Nontypeable	15.4	30.8	13.6	0.0	22.6	20.0	0.0	23.1	53.8	40.9	33.3	58.1	35.6	37.5
All	18.9	19.8	23.5	18.0	18.2	15.7	13.0	35.7	38.1	46.6	40.1	44.7	43.1	40.9

[a] Percentage of nonsusceptible isolates according to the susceptible clindamycin (≤0.25 µg/mL) and erythromycin (≤0.25 µg/mL) breakpoints published in the CLSI M100-S27 document. NA, isolates not detected
[b] Nonvaccine was defined as those not present in the 3 vaccines available in the US

Conclusions

- PCV13 serotypes exhibited decreasing trends for nonsusceptibility during the study period, except for serotype 3, which showed stable rates for penicillin and ceftriaxone, but increasing rates for clindamycin and erythromycin over time
- The effect of the PCV13 vaccine on antimicrobial nonsusceptibility rates against PCV13 isolates causing infections in the US adult population can be noted 1–2 years after the vaccine was introduced in 2010
- Although nonsusceptibility rates decreased among PCV13 strains, rates for penicillin, clindamycin, and erythromycin (16.0%–40.0%) remained elevated in this serotype group in the last surveyed year (2015)
- Several nonvaccine serotypes showed elevated MIC results for penicillin and may represent populations with first-step mutations in the penicillin-binding proteins
- Further surveillance would enhance understanding of future antimicrobial patterns in *S. pneumoniae* in the context of adult pneumococcal vaccination programs

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