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Streptococcus pneumoniae Serotype Distribution and Antimicrobial Susceptibility Prior to and Post USA Introduction of 13-valent Pneumococcal Conjugate Vaccine

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Amended Abstract

Background: 13-valent conjugate vaccine (PCV13) was introduced in the USA in 2010. We assessed the distribution and susceptibility of *Streptococcus pneumoniae* serotypes in the USA (2011-2012) and compared results with those from a study performed in 2008.

Methods: 1,190 *S. pneumoniae* (07/11 - 06/12) were included. Identification was performed by biochemical algorithms. Serotyping was performed by *cpsB* sequencing and multiplex PCR. Susceptibility testing applied CLSI methods (M07-A9) and interpretations (M100-S23).

Results: The prevalence of serotype 19A decreased (4.1%; P=0.016) between study years, as did 3, 7F/7A and 16F (1.8, 4.4 and 1.5%, respectively). Other serogroups/types, such as 23A (+2.7%; P=0.011), 15B/C (+2.4%; P=0.015), 9N/9L (+1.5%; P=0.049) and 31 (+1.9%; P=0.002) had occurrence rates higher than in 2008. Ceftaroline MIC_{50}, MIC_{90} and MIC_{100} values for *S. pneumoniae* were ≤0.015, 0.12 and 0.5 µg/mL (100% susceptible), respectively. Vancomycin ($MIC_{50/90}$, 0.25/0.5 µg/mL; 100% susceptible), linezolid ($MIC_{50/90}$, 1/1 µg/mL; 100% susceptible) and levofloxacin ($MIC_{50/90}$, 1/1 µg/mL; 99.3% susceptible) were also active. Ceftaroline had MIC_{90} values of ≤0.12 µg/mL against all serotypes, except 19A (MIC_{90}, 0.25 µg/mL). 19A strains were least susceptible overall, with decreased susceptibility (8.8 - 30.2%) to all agents between periods, except ceftaroline, levofloxacin, vancomycin and linezolid (≥98.2% susceptible). Serotype 3 had decreased susceptibility to erythromycin (86.3% susceptible) and clindamycin (87.4% susceptible) compared with 2008 rates (92.9 and 94.3%, respectively), as did 35B and 15B/C to erythromycin. Serotype 23B had increased susceptibility to erythromycin. 19F had increased susceptibility rates (17.3 - 48.0%) to all drugs, except ceftaroline, levofloxacin, vancomycin and linezolid, which were ≥96.6% susceptible in both years.

Conclusions: 19A strains decreased in prevalence, but displayed increased resistance rates. 19F occurrence remained stable, but susceptible rates increased. Prevalence of non-PCV13 serotypes appear to be increasing. Ceftaroline had high potency against *S. pneumoniae*, regardless of serotype.

Introduction

Studies have demonstrated that PCV7, introduced in 2000, is efficacious for the prevention of non-invasive and invasive pneumococcal disease (IPD) and carriage. PCV7 has been highly successful not only in decreasing the rates of pneumococcal diseases and nasopharyngeal colonizers, but also in decreasing the rates of non-susceptible PCV7 serotypes among children under two years old by 2003. However, the vaccine use modified the epidemiology of pneumococcal disease and colonization, and further investigations documented an increase in the rates of carriage and infections caused by non-PCV7 serotypes. This trend has been mostly caused by serotypes 19A and 6A in the USA; moreover, the incidence of antibiotic-nonsuscceptible IPD in children has started to increase. A new 13-valent pneumococcal conjugate vaccine (PCV13), which includes serotypes 19A and 6A among others, was licensed in the USA in 2010. However, the impact of PCV13 on the pneumococcal disease, carriage and antimicrobial susceptibility profile remain to be documented.

Penicillin is the drug of choice for treatment of penicillin-susceptible pneumococcal disease. Despite the decrease of penicillin-nonsuscceptible isolates in 2003 brought about by PCV7, these rates have increased due to emergence of nonsuscceptibility among the replacement clones, achieving 15.9% of the USA isolates submitted as part of the SENTRY Antimicrobial Surveillance Program in 2009. As intermediate and resistant antimicrobial profiles complicate management of pneumococcal disease, additional therapeutic options would become a priority for patient care.

This study evaluated the serotype distribution and susceptibility profiles of *Streptococcus pneumoniae* collected from hospitalized patients in the USA (all age groups) during the respiratory disease season of 2011-2012 (i.e. post the introduction of PCV13) and compared results with those from a similar study that included isolates from 2008. In addition, the *in vitro* activity of ceftaroline, the active metabolite of the parenteral cephalosporin, ceftaroline fosamil, was assessed against both collections.

Methods

Bacterial strains. A total of 1,190 *S. pneumoniae* clinical isolates received as part of the "AWARE" (Assessing Worldwide Antimicrobial Resistance Evaluation) Program, component of SENTRY Program, from July 2011 through June 2012 were included in this investigation. These isolates were recovered from hospitalized patients in 63 medical centers located in the nine USA Census regions. Table 1 describes the distribution of Census region and specimen sources, which originated from blood or lower respiratory tract cultures. The number of isolates stratified by subject's age group is also listed in Table 1. Bacterial identification was performed by the participating microbiology laboratory and confirmed by the central laboratory (JMI Laboratories, North Liberty, Iowa). Confirmation of bacterial identification was performed by colony morphology, biochemical algorithms and Vitek®2, as needed. 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 singleplex PCR assay for further identification.

The results generated from the 2011-2012 collection were compared with those obtained from USA isolates submitted as part of the 2008 SENTRY Program, which were previously published by Jacobs et al. (2010). These isolates originated from several specimen sources and those recovered from specimen types other than blood or lower respiratory tract specimens were withdrawn from this analysis to achieve greater consistency between databases. Statistical analyses related to serotype distribution and susceptibility rates were reassessed on a total of 694 from the 2008 year sample (Table 1).

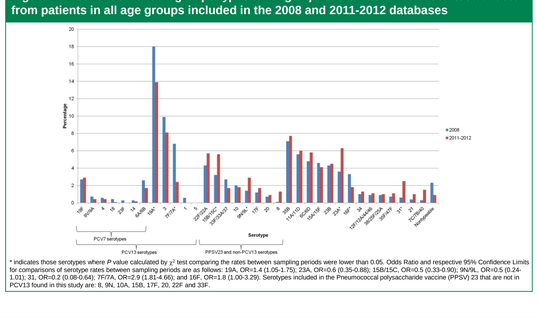
Antimicrobial susceptibility profile. Isolates included in both datasets were tested for susceptibility by broth microdilution methods, according to the recommendations of the Clinical and Laboratory Standards Institute (CLSI). Minimum inhibitory concentration (MIC) results for several anti-gram-positive agents were obtained using panels manufactured by Thermo Fisher Scientific (formerly TREK Diagnostics Systems/Sensititre; Cleveland, Ohio). Validation of the MIC values was performed by concurrent testing of CLSI-recommended (M100-S23, 2013) quality control (QC) strain *S. pneumoniae* American Type Culture Collection (ATCC) 49619. 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 the CLSI M100-S23 (2013) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2013) criteria.

Serotyping determination. Isolates from the AWARE Program (2011-2012) were subjected to PCR assays for amplification of the *cpsB* gene as previously described by Leung et al. (2012). Amplicons were sequenced on both strands and the nucleotide sequences were analyzed using the Lasergene software package (DNASTAR, Madison, Wisconsin). Sequences were compared with 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/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 purposes (between 6A/6B and 6C/6D). Isolates from the 2008 dataset were serotyped previously using the classical Quellung reactions.

Results

- Overall, the prevalence of PCV7-associated serotypes remained low between the 2011-2012 study and the 2008 study, and the most common PCV7 types, 19F and 6A/6B isolates, comprised only 1.7 - 2.9% and 2.6 - 2.7% of all isolates included, respectively (Figure 1)
- Serotypes 19A and 3 remained the first and second most prevalent types observed in 2008 and 2011-2012; but the occurrence rates for both decreased during the latter period. In addition, the occurrence of isolates associated with serogroup 7F/7A decreased significantly from 6.8% in 2008 to 2.4% in the second period (P<0.001; Figure 1)
- Most non-PCV13 serogroups/types demonstrated prevalence rates in 2011-2012 higher than 2008, except for 15A/15F, 16F, 33F/33A/37 and 10. However, among those serotypes exhibiting higher occurrence rates in the second period, only 23A, 15B/15C, 9N/9L and 31 were statistically significant (Figure 1)
- Ceftaroline had very similar $MIC_{50/90}$ values when tested against isolates collected during the 2008 ($MIC_{50/90}$, ≤0.008/0.12 µg/mL) and 2011-2012 ($MIC_{50/90}$, ≤0.015/0.12 µg/mL) periods (Tables 2 and 3). Moreover, ceftaroline showed a bi-modal pattern with modal MIC results at ≤0.008/≤0.015 and 0.12 µg/mL when tested against both populations of *S. pneumoniae* isolates
- Most serogroups/types (616/1180; 52.2%) exhibited ceftaroline MIC_{90} values of ≤0.03 µg/mL, while the serogroups 6, 15, 19 and serotypes 23A and 35B had higher MIC_{90} results (0.06 - 0.25 µg/mL; Table 2). Serotypes 19A and 35B were mostly responsible for the ceftaroline modal MIC at 0.12 µg/mL
- Ceftriaxone also exhibited a bi-modal MIC distribution, with a modal MIC result at ≤0.06 and a second mode at the CLSI susceptible breakpoint (i.e. 1 µg/mL; Table 2). A total of 103 (8.7%) isolates were non-susceptible to ceftriaxone and the majority of those (81/103; 78.6%) were associated to serotype 19A (Table 2)
- A greater proportion of 19A strains (49.4%) had ceftriaxone MIC results of ≥2 µg/mL than other serotypes, while the majority of 35B isolates (80.4%) had MIC values at the CLSI breakpoint for susceptibility (i.e. 1 µg/mL) or higher (Table 2)
- Overall, no major differences in susceptibility rates (>10.0%) were observed for the antimicrobial agents tested against *S. pneumoniae* between study time periods (Tables 3 and 4). Ceftaroline, levofloxacin, linezolid and vancomycin demonstrated antimicrobial coverage (i.e. susceptibility rates >90.0%) against both populations
- Isolates associated with serotype 19A demonstrated susceptibility rates greatly reduced for several agents, while serotype 19F isolates from 2011-2012 demonstrated susceptibility rates higher than those noted for 2008 (Table 4)
- Serogroups/types 6C/6D and 23B had increased erythromycin susceptibility rates between periods (increase of 11.6% and 12.0% respectively), while serogroups/types 33F/33A/37, 15B/15C and 35B showed decreased susceptibility rates of 27.1, 31.4 and 31.7%, respectively (Table 4)
- Decreased TMP/SMX susceptibility rates (ranging from 18.4% to 35.3%) between sampling years were observed against serogroups/types 15B/15C, 23B, 16F, 6A/6B and 33F/33A/37 (Table 4). Serogroup 6C/6D displayed increased rates for TMP/SMX from 21.2% in 2008 to 34.8% in 2011-2012.

Figure 1: Distribution of serogroups/types among *S. pneumoniae* clinical isolates collected from patients in all age groups included in the 2008 and 2011-2012 databases



* indicates those serotypes where *P* value calculated by χ^2 test comparing the rates between sampling periods were lower than 0.05. Odds Ratio and respective 95% Confidence Limits for comparisons of serotype rates between sampling periods are as follows: 19A, OR=1.4 (1.05-1.75); 23A, OR=0.6 (0.35-0.88); 15B/15C, OR=0.5 (0.33-0.90); 9N/9L, OR=0.5 (0.24-1.01); 31, OR=0.2 (0.08-0.64); 7F/7A, OR=2.9 (1.81-4.66); and 16F, OR=1.8 (1.00-3.29). Serotypes included in the Pneumococcal polysaccharide vaccine (PPSV) 23 that are not in PCV13 found in this study are: 8, 9N, 10A, 15B, 17F, 20, 22F and 33F.

Table 1. Source of *S. pneumoniae* clinical isolates included in the 2008 and 2011-2012 databases

Parameter Specimen type	Number of isolates (%) by dataset 2008	 2011-2012
Sputum	330 (47.6)	562 (47.2)
Bronchoalveolar lavage	76 (11.0)	208 (17.5)
Blood culture	184 (26.5)	165 (13.9)
Tracheal aspirate	8 (1.2)	136 (11.4)
Lower Respiratory Tract	17 (2.4)	56 (4.7)
Endotracheal tube	1 (0.1)	23 (1.9)
Invasive pulmonary	61 (8.8)	22 (1.8)
Pleural fluid	17 (2.4)	18 (1.5)
Age group		
≤18	144 (20.7)	182 (15.3)
19-49	152 (21.9)	310 (26.1)
≥50	367 (52.9)	698 (58.7)
Unknown	31 (4.5)	0 (0.0)
Census Region		
1	73 (10.5)	136 (11.4)
2	89 (12.8)	106 (8.9)
3	129 (18.6)	189 (15.9)
4	120 (17.3)	118 (9.9)
5	78 (11.2)	132 (11.1)
6	81 (11.7)	153 (12.9)
7	56 (8.1)	108 (9.1)
8	21 (3.0)	80 (6.7)
9	47 (6.8)	168 (14.1)
Total	694	1,190

Table 3. Activity of ceftaroline and comparator antimicrobial agents when tested against both populations of *S. pneumoniae* isolates included in the study

Population (number tested)/ Antimicrobial agent	Range	MIC (µg/mL) 50%	 90%	% Susceptible/Resistant[a] CLSI	 EUCAST
2008 (694)					
Ceftaroline	≤0.008 – 0.5	≤0.008	0.12	100.0 / -	99.0 / 1.0
Penicillin[b]	≤0.03 – >4	≤0.03	2	90.4 / 0.7	- / -
Penicillin[c]	≤0.03 – >4	≤0.03	2	61.1 / 19.0	61.1 / 9.6
Ceftriaxone	≤0.25 – 8	≤0.25	1	93.4 / 1.4	81.2 / 1.4
Amoxicillin/clavulanate	≤1 – 16	≤1	4	86.5 / 9.2	- / -
Erythromycin	≤0.25 – >2	≤0.25	>2	64.1 / 35.5	64.1 / 35.5
Clindamycin	≤0.25 – >2	≤0.25	>2	82.3 / 17.4	82.6 / 17.4
Levofloxacin	≤0.5 – >4	1	1	99.3 / 0.6	99.3 / 0.7
Trimethoprim/sulfamethoxazole	≤0.5 – >2	≤0.5	>2	69.3 / 21.7	76.1 / 21.7
Vancomycin	≤1 – 1	1	1	100.0 / -	100.0 / 0.0
Linezolid	≤0.12 – 2	1	1	100.0 / -	100.0 / 0.0
2011-2012 (1,190)					
Ceftaroline	≤0.015 – 0.5	≤0.015	0.12	100.0 / -	99.3 / 0.7
Penicillin[b]	≤0.06 – 8	≤0.06	4	90.0 / 1.3	- / -
Penicillin[c]	≤0.06 – 8	≤0.06	4	57.3 / 19.7	57.3 / 11.1
Ceftriaxone	≤0.06 – >8	≤0.06	1	91.3 / 1.3	79.0 / 1.3
Amoxicillin/clavulanate	≤1 – >8	≤1	8	85.2 / 11.0	- / -
Erythromycin	≤0.12 – >16	≤0.12	>16	58.9 / 40.4	58.9 / 40.4
Clindamycin	≤0.25 – >2	≤0.25	>2	81.9 / 17.5	82.5 / 17.5
Levofloxacin	≤0.12 – >4	1	1	99.3 / 0.6	99.3 / 0.7
Trimethoprim/sulfamethoxazole	≤0.5 – >4	≤0.5	>4	66.2 / 22.7	71.1 / 22.7
Vancomycin	≤0.12 – 0.5	0.25	0.5	100.0 / -	100.0 / 0.0
Linezolid	≤0.12 – 2	1	1	100.0 / -	100.0 / 0.0

a. Criteria as published by the CLSI (2013) and EUCAST (2013).
b. Criteria as published by the CLSI (2013) for 'penicillin parenteral (non-meningitis)'.
c. Criteria as published by the CLSI (2013) for 'penicillin (oral penicillin V)'.

Table 2. MIC distribution and antimicrobial activity of ceftaroline and ceftriaxone tested against the specific serogroups/types detected in the 2011-2012 collection

Serotype (no. tested)[a]	MIC (µg/mL) 50%	 90%	Number (cumulative %) of isolates inhibited at MIC (µg/mL)[b] ≤0.015	 0.03	 0.06	 0.12	 0.25	 0.5	 1	 2	 >2
Ceftaroline (1,180)	≤0.015	0.12	723 (61.3)	98 (69.6)	112 (79.1)	181 (94.4)	58 (99.3)	8 (100.0)			
15A/15F (50)	≤0.015	0.06	29 (58.0)	7 (72.0)	10 (92.0)	4 (100.0)					
15B/15C (63)	≤0.015	0.06	36 (57.1)	12 (76.2)	15 (100.0)						
23A (75)	0.03	0.06	29 (38.7)	32 (81.3)	13 (98.7)	1 (100.0)					
6A/6B (20)	0.06	0.12	6 (30.0)	1 (35.0)	10 (85.0)	3 (100.0)					
6C/6D (69)	0.06	0.12	24 (34.8)	3 (39.1)	34 (88.4)	8 (100.0)					
19F (35)	≤0.015	0.12	27 (77.1)	0 (77.1)	6 (94.3)	1 (97.1)	1 (100.0)				
35B (91)	0.12	0.12	7 (7.7)	1 (8.8)	5 (14.3)	77 (98.9)	1 (100.0)				
19A (164)	0.12	0.25	22 (13.4)	4 (15.9)	12 (23.2)	66 (63.4)	53 (95.7)	7 (100.0)			
Other (616)	≤0.015	0.03	547 (88.8)	38 (95.0)	13 (97.1)	15 (99.5)	3 (100.0)				
Ceftriaxone (1,187)	≤0.06	1	-	-	688 (58.0)	118 (67.9)	67 (73.5)	65 (79.0)	146 (91.3)	88 (98.7)	15 (100.0)
6A/6B (20)	0.25	2	-	-	5 (25.0)	2 (35.0)	3 (50.0)	6 (80.0)	1 (85.0)	3 (100.0)	
6C/6D (69)	0.25	1	-	-	22 (31.9)	3 (36.2)	10(50.7)	27 (89.9)	6 (98.6)	0 (98.6)	1 (100.0)
9V/9A (5)	1	-	-	-	0 (0.0)	0 (0.0)	0 (0.0)	2 (40.0)	1 (60.0)	2 (100.0)	
35B (92)	1	1	-	-	7 (7.6)	0 (7.6)	0 (7.6)	11 (19.6)	70 (95.7)	4 (100.0)	
19A (164)	1	2	-	-	22 (13.4)	6 (17.1)	6 (20.7)	2 (22.0)	47 (50.6)	70 (93.3)	11 (100.0)
19F (35)	≤0.06	2	-	-	26 (74.3)	1 (77.1)	0 (77.1)	0 (77.1)	3 (85.7)	3 (94.3)	2 (100.0)
Other (791)	≤0.06	0.12	-	-	606 (76.6)	106 (90.0)	37 (94.7)	17 (96.8)	18 (99.1)	6 (99.9)	1 (100.0)

a. MIC values not available for all 1,190 strains included in the study.
b. Lowest concentration tested for ceftriaxone, 0.06 µg/mL.

Table 4. Antimicrobial susceptibility profiles of most common serogroups/types observed among the 2008 and 2011-2012 sampling years

Serotype (No. tested/%, this study) (% previous study)	CPT[b] MIC_{90}	% susceptible per year[a] PEN 2008	 2012	CRO 2008	 2012	A/C 2008	 2012	ERY 2008	 2012	CLI 2008	 2012	LEV 2008	 2012	TMP/SMX 2008	 2012
19A (165/13.9) (18.0)	0.25	57.6	29.3	73.6	50.6	55.2	25.0	32.8	14.6	52.8	31.7	100.0	98.2	21.6	12.8
3 (96/8.1) (9.9)	0.03	98.6	100.0	98.6	100.0	98.6	100.0	92.9	86.3	94.3	87.4	100.0	100.0	98.6	97.9
35B (92/7.7) (7.1)	0.12	98.0	98.9	98.0	95.7	58.0	60.9	68.0	36.3	100.0	98.9	98.0	98.9	90.0	82.6
23A (75/6.3) (3.6)	0.06	100.0	100.0	100.0	98.7	100.0	98.7	80.0	74.7	80.0	84.0	100.0	98.7	88.0	77.3
11A/11D (71/6.0) (5.6)	≤0.015	100.0	98.6	97.4	98.6	97.4	98.6	71.8	73.2	94.9	98.6	100.0	100.0	89.7	80.3
6C/6D (69/5.8) (4.8)	0.12	100.0	98.6	100.0	98.6	100.0	100.0	33.3	44.9	93.9	95.7	100.0	100.0	21.2	34.8
22A/22F (68/5.7) (4.3)	≤0.015	100.0	100.0	98.5	100.0	98.5	100.0	86.7	86.8	100.0	98.5	100.0	98.5	96.7	92.6
15B/15C (67/5.6) (3.2)	0.06	100.0	100.0	100.0	100.0	100.0	100.0	72.7	41.3	95.5	96.8	100.0	100.0	77.3	57.6
23B (53/4.5) (4.3)	0.03	100.0	98.1	96.7	98.1	100.0	98.1	76.7	88.7	100.0	94.3	96.7	100.0	90.0	54.7
15A/15F (50/4.1) (4.6)	0.06	100.0	98.0	100.0	100.0	100.0	98.0	3.1	4.0	9.4	4.0	100.0	98.0	53.1	44.0
19F (35/2.9) (2.7)	0.12	47.4	85.7	68.4	85.7	47.4	82.9	26.3	71.4	36.8	82.9	94.7	100.0	26.3	74.3
9N/9L (34/2.9) (1.4)	≤0.015	100.0	100.0	100.0	100.0	100.0	100.0	100.0	97.1	100.0	100.0	100.0	100.0	90.0	94.1
31 (30/2.5) (0.6)	≤0.015	100.0	100.0	100.0	100.0	100.0	100.0	75.0	80.0	100.0	100.0	100.0	100.0	100.0	100.0
7F/7A (29/2.4) (6.8)	≤0.015	100.0	100.0	100.0	100.0	100.0	100.0	100.0	90.0	100.0	96.6	100.0	100.0	100.0	100.0
16F (22/1.8) (3.3)	≤0.015	100.0	100.0	100.0	95.5	100.0	95.5	95.7	86.4	95.7	86.4	100.0	100.0	95.7	77.3
10 (22/1.8) (2.0)	≤0.015	100.0	100.0	100.0	100.0	100.0	100.0	92.9	86.4	100.0	100.0	100.0	100.0	92.9	90.9
6A/6B (20/1.7) (2.6)	0.12	94.4	90.0	100.0	85.0	88.9	90.0	38.9	35.0	83.3	90.0	100.0	100.0	61.1	30.0
33F/33A/37 (20/1.7) (2.7)	≤0.015	100.0	100.0	100.0	100.0	100.0	100.0	42.1	15.0	100.0	95.0	100.0	100.0	31.6	5.0
17F (20/1.7) (1.2)	≤0.015	100.0	100.0	100.0	95.0	100.0	100.0	75.0	85.0	100.0	95.0	100.0	100.0	100.0	90.0
Overall (1,190)		90.4	90.0	93.4	91.3	86.5	85.2	64.1	58.9	82.3	81.9	99.3	99.3	69.3	66.2

a. Percentage of susceptible isolates according to the breakpoints published by the CLSI M100-S23 document. The breakpoints used for penicillin and ceftriaxone were ≤2 and ≤1 µg/mL, respectively. CPT = ceftaroline; PEN = penicillin G; CRO = ceftriaxone; A/C = amoxicillin/clavulanate; ERY = erythromycin; CLI = clindamycin; LEV = levofloxacin; TMP/SMX = trimethoprim/sulfamethoxazole.
b. All strains inhibited at the CLSI breakpoint for susceptibility (≤0.5ug/mL).

Conclusions

- Occurrences of PCV7 serogroups/serotypes remained low during both study periods. PCV13 serogroups/types demonstrated invariably lower prevalence rates in the 2011-2012 period (after PCV13 introduction) than in 2008
- The susceptibility rates for several antimicrobial agents tested against 19F increased in 2011-2012 when compared with those from 2008. In contrast, although the prevalence of 19A isolates decreased, the non-susceptibility rates continue to increase. These results suggest a decline in the number of 19A susceptible isolates, while resistant strains have persisted
- Other variations in susceptibility rates among serogroups/types between study periods were noticed mostly for erythromycin and/or trimethoprim/sulfamethoxazole. 15B/15C, 6C/6D and 35B showed high rates of erythromycin resistance (58.7, 53.6 and 63.7%, respectively), and this resistance phenotype concurrent with PCV13 may cause a synergistic selective pressure
- The results presented here indicate that changes in the *S. pneumoniae* epidemiology have occurred and will continue to happen as the PCV13 coverage expands, supporting continued surveillance for monitoring the *S. pneumoniae* serotype distribution and optimizing strategies for prevention and treatment of pneumococcal disease
- Several non-PCV13 serogroups/types may have the potential to escape the PCV13 effect, in particular those less susceptible to currently recommended agents for treating pneumococcal diseases. Therefore, ceftaroline may offer therapeutic advantages for treating pneumococcal infections.

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