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Changes in Pneumococcal Serotypes and Antimicrobial Resistance after Introduction of the 13-Valent Conjugate Vaccine in the United States

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Ongoing surveillance for *Streptococcus pneumoniae* is needed to assess the impact of the pneumococcal conjugate vaccine introduced in 2010 (PCV13). Forty-two U.S. centers submitted *S. pneumoniae* isolates between 1 October 2012 and 31 March 2013. Susceptibility testing was performed by use of a broth dilution method as recommended by the Clinical and Laboratory Standards Institute. Serotyping was performed by multiplex PCR and the Quellung reaction. Multidrug resistance (MDR) was defined as nonsusceptibility to penicillin (PNSP; MIC ≥ 0.12 μg/ml) combined with resistance to ≥2 non-β-lactam antimicrobials. Penicillin-resistant *S. pneumoniae* (PRSP) was defined as a penicillin MIC of ≥2 μg/ml. For the 1,498 isolates collected during 2012-13, the PRSP and MDR rates were 14.2 and 21.0%, respectively. These percentages were lower than rates obtained in a surveillance study conducted 4 years earlier in 2008-09 (17.0 and 26.6%, respectively). The most common serotypes identified in 2012-13 were 3, 35B, and 19A, each representing 9 to 10% of all isolates. The largest percentage of PNSP in 2012-13 were found in serotypes 35B (24.8%), 19A (23.5%), and 15A (10.3%). Predominant PRSP serotypes were 19A (54.5%), 35B (28.2%), and 19F (7.0%). Major MDR serotypes were 19A (38.5%), 15A (16.9%), 6C (8.3%), and 35B (6.4%). The change in prevalence of PCV13 serotypes (43.4 to 27.1%) was primarily due to a decrease in serotype 19A strains, i.e., 22% of all strains in 2008-09 to 10% of all strains in 2012-13. Among the PNSP subset, serotypes showing a proportional increase were 35B, 15B, and 23B. Among MDR strains, the largest proportional increases were observed in serotypes 35B, 15B, and 23A.

Streptococcus pneumoniae is the most common bacterial etiology of meningitis in the United States (1). Worldwide, morbidity and mortality due to pneumococcal infections is highest among young children below the age of 5 years, accounting for approximately one-third of the estimated 1.3 million deaths from pneumonia in 2011 (2). During the 1990s, treatment failures related to the emergence of antimicrobial resistance (3, 4) led to the development of a heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar; Wyeth) for children. PCV7 was introduced in the United States in 2000, and vaccine efficacy was demonstrated by a 30% reduction in cases of pneumococcal meningitis (5).

After PCV7 introduction, the epidemiology of pneumococcal disease changed and nonvaccine serotype strains began to emerge (6). From 1999-2000 to 2008-09, the percentage of PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) among clinical isolates in the United States decreased from 55 to 5%, and the percentage of serotype 19A increased from 2 to 22% (7). In March 2010, a new conjugate vaccine (PCV13) that includes additional coverage of serotype 19A, 1, 3, 5, 6A, and 7F strains received U.S. Food and Drug Administration (FDA) clearance. By 2010-11, serotype 19A was no longer increasing, but it was still the most common serotype, accounting for 20% of all isolates and 41% of penicillin-nonsusceptible *S. pneumoniae* (PNSP; MIC ≥ 0.12 μg/ml) in the United States (7).

The purpose of this national longitudinal study was to assess the impact of PCV13 on invasive and noninvasive pneumococcal disease by determining changes in serotype distribution in 2012-13 with comparison to 2008-09. The susceptibility of study isolates to multiple antimicrobial agents, including the new cephalosporin ceftaroline, was also determined. This represents one of the first large-scale reports to assess the impact of PCV13 on the epidemiology of pneumococcal disease in the United States. Information regarding serotype distribution and associated antimicrobial resistance phenotypes is critical in assessing vaccine efficacy and as a guide to future vaccine development.

MATERIALS AND METHODS

Isolates of *S. pneumoniae* causing invasive or noninvasive disease were collected during the 2012-13 respiratory infection season (1 October 2012 to 31 March 2013) from 42 U.S. medical centers. Participating institutions included pediatric hospitals, academic medical centers, acute care community hospitals, and Veterans Affairs hospitals. Each laboratory was instructed to submit up to 50 consecutive isolates of *S. pneumoniae* recovered from unique patients, along with demographic information, including patient age and gender, inpatient/outpatient status, and specimen type (source). Upon receipt in the laboratory, the organisms were stored at −70°C on Microbank beads (Pro-Lab Diagnostics).

The identification of the isolates was confirmed using conventional methods, including the bile solubility test. In addition, any isolate that could not be serotyped was tested using an AccuProbe *S. pneumoniae* culture identification test (GenProbe). Capsular serotypes were determined by using a multiplex PCR targeting the most common serotypes (8, 9) and the Quellung reaction with type-specific antisera (Statens Serum Institut) where necessary.

Antimicrobial susceptibility testing was performed using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method in Mueller-Hinton broth with 3% lysed horse blood at a final inoculum

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concentration of approximately 5×10^5 CFU per ml (10). Trays were incubated in ambient air for 20 to 24 h at 35°C before determining the MICs. *S. pneumoniae* ATCC 49619 was used as a quality control strain. Susceptibility breakpoints utilized were those outlined by CLSI (11). In 2008, the CLSI established new and separate breakpoints for parenteral penicillin therapy of meningitis and nonmeningeal infections, and for oral penicillin therapy. To allow for comparison to prior surveys, we applied both the "old" penicillin breakpoints (now the oral therapy breakpoints: susceptible [S], ≤0.06 μg/ml; intermediate [I], 0.12 to 1 μg/ml; and resistant [R], ≥2 μg/ml) and the "new" parenteral breakpoints in our analyses. For consistency with prior published reports, the multidrug resistance (MDR) phenotype was defined as nonsusceptibility to penicillin (PNSP; penicillin MIC ≥ 0.12 μg/ml) plus resistance to ≥2 other non-β-lactam antimicrobial classes. Penicillin-resistant *S. pneumoniae* (PRSP) was defined as an isolate with a penicillin MIC of ≥2 μg/ml. The 2012-13 surveillance data were compared to data derived from the same surveillance network collected during 2008-09 and 2010-11 (7, 12). Statistical significance was assessed using the two-tailed Fisher exact test. The University of Iowa institutional review board for human subjects research approved the protocol prior to initiation of the study. All laboratory work was performed at the University of Iowa Carver College of Medicine, Iowa City, IA.

RESULTS

A total of 1,498 clinical isolates were obtained from 42 U.S. medical centers during the 2012-2013 respiratory season. The age distribution of patients for isolates included in the study was 15% for 0 to 5 years, 8% for 6 to 20 years, 49% for 21 to 64 years, and 23% for ≥65 years. Patient age was not provided for 5% of the isolates. There were slightly more male (55%) than female (43%) patients (for 2% the gender was not known), and over half of the isolates (60%) were obtained from inpatients. Of the isolates from inpatients, the majority (86%) were isolated within the first 48 h of admission, suggesting community onset. Specimen sources for the isolates included lower respiratory tract (44%), blood (26%), middle ear fluid (5%), sinus (9%), and cerebrospinal fluid (1%). The submitting laboratory did not indicate the source for 15% of isolates.

The MIC distributions and resistance rates are outlined in Table 1. The overall PNSP rate was 35.0% (20.8% intermediate, 14.2% resistant). According to the breakpoints for nonmeningeal pneumococcal infections treated with parenteral penicillin, 7.7% of isolates were penicillin intermediate or resistant. Table 2 outlines the percentages of isolates in the penicillin- and multidrug-resistant categories for different specimen types. The lowest resistance rates were among isolates recovered from blood cultures.

Ceftaroline was the most active β-lactam agent, with an MIC_{50} of 0.008 μg/ml, MIC_{90} of 0.12 μg/ml, and all isolates susceptible (MIC ≤ 0.5 μg/ml) (Table 1). The ceftriaxone nonsusceptible rate for meningitis (MIC ≥ 1.0 μg/ml) was 16.1%. Only 4.5% of isolates were nonsusceptible to ceftriaxone with the nonmeningitis breakpoint (MIC ≥ 2 μg/ml) applied. As the penicillin MICs increased, the ceftaroline MIC shifted upward slightly. In contrast, few isolates remained susceptible to ceftriaxone if the penicillin MIC was ≥2 μg/ml (data not shown).

Comparison of susceptibility test results to surveillance conducted 4 years earlier (7) revealed significant changes (Table 3). In 2012-13, the prevalences of PRSP (14.2% versus 17.0%, $P = 0.03$) and MDR strains were lower (21.0% versus 26.6%, $P < 0.0001$) than in 2008-09.

The serotype distributions in 2012-13 compared to 2008-09 are summarized in Table 4. The most common serotypes identi-

TABLE 1 MIC distributions for 1,498 *S. pneumoniae* isolates obtained from 42 medical centers in the United States from 1 October 2012 to 31 March 2013[a]

Antimicrobial agent	No. of isolates (cumulative %) for which the antimicrobial agent MIC (μg/ml) was:											
	≤0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	>64	I (%)	R (%)
Penicillin	894 (60)	80 (65)	74 (70)	112 (77)	43 (80)	82 (86)	97 (92)	107 (99)	9 (100)					20.8	14.2
Ceftaroline	1,138 (76)	161 (87)	183 (99)	13 (99)	3 (100)										
Ceftriaxone	873 (58)	101 (65)	128 (74)	77 (79)	77 (84)	174 (95)	55 (99)	7 (99)	6 (100)					11.6	4.5
Vancomycin	1 (0.1)	3 (0.3)	32 (2)	842 (59)	618 (99)	2 (100)									
Erythromycin		883 (59)*	7 (59)	7 (60)	4 (60)	5 (60)	26 (62)	117 (70)	119 (78)	71 (83)	16 (84)		243 (100)	0.3	39.9
Clindamycin		1,248 (83)*	14 (84)	2 (84)	4 (85)		2 (85)	3 (85)		1 (85)	8 (86)	11 (86)	205 (100)	0.3	15.4
Tetracycline	3 (0.2)	12 (1)	336 (23)	793 (76)	50 (80)	5 (80)	1 (80)	4 (80)	9 (81)	17 (82)	163 (93)	103 (99)	2 (100)	0.3	19.6
TMP/SMX	3 (0.2)	4 (0.5)	185 (13)	766 (64)	108 (71)	79 (76)	91 (83)	47 (86)	157 (96)	44 (99)	12 (99)	2 (100)		11.3	17.5
Levofloxacin	1 (0.1)		1 (0.1)	7 (0.6)	223 (15)	1,207 (96)	47 (99)	1 (99)	1 (99)	5 (99)	5 (100)			0.07	0.7
Moxifloxacin	11 (0.7)	210 (15)	1,206 (95)	57 (99)	3 (99)		7 (99)	3 (99)	1 (100)					0.5	0.3

[a] I, intermediate; R, resistant; penicillin oral (I, 0.1 to 1 μg/ml; R, ≥2 μg/ml); ceftaroline (nonsusceptible, >0.5 μg/ml); ceftriaxone meningitis (I, 1 μg/ml; R, ≥2 μg/ml); vancomycin (nonsusceptible, >1 μg/ml); erythromycin (I, 0.5 μg/ml; R, ≥1 μg/ml); clindamycin (I, 0.5 μg/ml; R, ≥1 μg/ml); tetracycline (I, 4 μg/ml; R, ≥8 μg/ml); TMP/SMX (I, 1/19 to 2/38 μg/ml; R, ≥4/76 μg/ml); levofloxacin (I, 4 μg/ml; R, ≥8 μg/ml); moxifloxacin (I, 2 μg/ml; R, ≥4 μg/ml); *, ≤0.06 μg/ml.

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TABLE 2 Susceptibility profiles and serotypes of pneumococcal isolates stratified by specimen type for 2012-13[a]

Parameter	% of isolates						
	Blood (n = 385)	CSF (n = 20)	LRT (n = 664)	MEF (n = 70)	Sinus (n = 142)	Other (n = 217)	All specimen types (n = 1,498)
Penicillin MIC (μg/ml)							
≥0.12[b]	21.8	40.0	39.6	38.6	45.1	36.0	35.0
≥2[c]	8.1	15.0	16.6	25.7	14.1	14.5	14.2
≥8[d]	0.5	0.0	0.6	0.0	0.7	0.9	0.6
MDR (%)[e]	11.1	30.0	24.7	24.3	25.4	22.4	21.0
Serotypes							
19A	8.6	5.0	11.1	15.7	9.2	9.2	10.2
3	7.5	15.0	9.9	21.4	4.2	11.5	9.6
35B	5.4	5.0	10.4	11.4	14.1	7.8	9.1
11A	4.9	0.0	7.7	4.3	9.2	4.6	6.4
22F	10.9	5.0	4.2	0.0	4.9	3.2	5.7
6C	5.5	0.0	5.9	0.0	5.6	5.1	5.3
15A	2.1	10.0	5.7	0.0	4.9	2.8	4.1
23A	2.9	5.0	4.2	1.4	4.9	4.1	3.8

[a] CSF, cerebrospinal fluid, LRT, lower respiratory tract; MEF, middle ear fluid.
[b] Penicillin nonsusceptible for parenteral meningitis and oral therapy.
[c] Penicillin resistant for parenteral meningitis and oral therapy.
[d] Penicillin resistant according to all breakpoints, including parenteral nonmeningitis.
[e] Penicillin nonsusceptible (MIC ≥ 0.12 μg/ml) and resistant to ≥2 other classes of agents.

fied in 2012-13 were 19A (10.1%), 3 (9.6%), and 35B (9.1%). The largest percentages of PNSP in 2012-13 were found in serotypes 35B (24.8%), 19A (23.5%), and 15A (10.3%). Predominant PRSP serotypes in 2012-13 were 19A (54.5%), 35B (28.2%), and 19F (7.0%). Major MDR serotypes were 19A (38.5%), 15A (16.9%), 6C (8.3%), and 35B (6.4%).

The prevalence of PCV13 serotypes decreased from 43.4% of all isolates in 2008-09 to 27.1% in 2012-13. This change was primarily due to a drop in serotype 19A isolates from 22.3 to 10.1% of all isolates ($P < 0.0001$). Significantly fewer serotype 7F (5.8 to 2.3%, $P < 0.0001$) and PCV-related 6C strains (7.3 to 5.3%, $P = 0.02$) were also observed in 2012-13. There were significant increases in several non-PCV serotypes: 11A (4.0 to 6.4%, $P = 0.001$), 15B (2.0 to 3.5%, $P = 0.01$), 15C (1.5 to 2.7%, $P = 0.02$), and 35B (4.0 to 9.1%, $P < 0.0001$).

The percentages of 19A strains comprising PNSP and MDR phenotypes were 22.1 and 19.6% lower, respectively, in 2012-13 than in 2008-09 ($P < 0.0001$). Among the PNSP subset, serotypes showing a proportional increase from 2008-09 to 2012-13 were 35B (16.2% higher, $P < 0.0001$), 15B (2.9% higher, $P = 0.001$), and 23B (3.9% higher, $P = 0.0002$). Among MDR strains, the largest proportional increases were observed in serotype 35B (6.0%, $P < 0.0001$), 15B (4.9%, $P < 0.0001$), and 23A (3.8%, $P = 0.005$).

The recoveries of predominant serotypes from different specimen types were similar, with the following exceptions (Table 2). The percentage of serotype 3 isolates recovered from middle ear fluid specimens was higher than those for all other specimen types combined (21.4% versus 9.0%, $P = 0.003$). Blood cultures yielded more serotype 22F (10.9% versus 3.9%, $P = 0.0001$) and a smaller proportion of serotype 35B isolates (5.4% versus 10.3%, $P = 0.004$) than other specimen types.

With two exceptions, among the predominant serotypes the distribution of isolates among different patient age groups was similar (Fig. 1.). There were fewer serotype 3 (4.9% versus 10.4%, $P = 0.009$) and more serotype 35B (14.8% versus 8.1%, $P = 0.002$) recovered from patients 0 to 5 years old than from the other age groups.

TABLE 3 Comparison of 2012-13 susceptibility test results to surveillance conducted in 2008-09[a]

Parameter	No. of isolates (%)		
	2008-09 (n = 1,946)	2012-13 (n = 1,498)	P[f]
Penicillin			
Susceptible (MIC ≤ 0.06 μg/ml)[b]	1,213 (62.3)	974 (65.0)	NS
Intermediate (MIC 0.12–1 μg/ml)[c]	403 (20.7)	311 (20.8)	NS
Resistant (MIC ≥ 2 μg/ml)[d]	330 (17.0)	213 (14.2)	0.03
Penicillin (nonmeningitis parenteral)			
Susceptible (MIC ≤ 2 μg/ml)	1,714 (88.1)	1,382 (92.3)	<0.0001
Intermediate (MIC 4 μg/ml)	223 (11.5)	107 (7.1)	<0.0001
Resistant (MIC ≥ 8 μg/ml)	9 (0.5)	9 (0.6)	NS
MDR[e]	518 (26.6)	314 (21.0)	<0.0001

[a] Richter et al. (7).
[b] Penicillin-susceptible breakpoint for oral therapy or parenteral therapy for meningitis.
[c] Penicillin-intermediate breakpoint for oral therapy only.
[d] Penicillin-resistant breakpoint for oral therapy or parenteral therapy for meningitis.
[e] Penicillin nonsusceptible (MIC ≥ 0.12 μg/ml) and resistant to ≥2 other classes of agents.
[f] NS, not significant ($P > 0.05$).

DISCUSSION

This longitudinal study documents the predominant pneumococcal serotypes causing disease throughout the United States in the post-PCV13 era. The strengths of the study include widespread geography, large numbers of isolates, and performance of testing at a central reference laboratory using reference methods. Al-

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TABLE 4 Change in serotype distribution of *Streptococcus pneumoniae* isolates from 2008-09 to 2012-13[a]

	No. isolates (%)					
	All isolates		PNSP isolates		MDR isolates	
Serotype[b]	2008-09	2012-13	2008-09	2012-13	2008-09	2012-13
Heptavalent vaccine (PCV7)						
4*	7 (0.4)	16 (1.1)				
6B*	8 (0.4)	2 (0.13)	5 (0.7)	1 (0.2)	1 (0.2)	1 (0.3)
9V*	5 (0.3)		5 (0.7)		3 (0.6)	
14*	7 (0.4)	1 (0.07)	4 (0.6)	1 (0.2)	4 (0.8)	1 (0.3)
18C*	2 (0.1)	2 (0.13)				
19F*	61 (3.1)	47 (3.1)	40 (5.5)	17 (3.2)	37 (7.1)	17 (5.4)
23F*	5 (0.3)	4 (0.3)	4 (0.6)	3 (0.6)	3 (0.6)	3 (1.0)
Total	**95 (4.9)**	**72 (4.8)**	**58 (7.9)**	**22 (4.2)**	**48 (9.3)**	**22 (7.0)**
Additional serotypes in PCV13						
1*	10 (0.5)					
3*	165 (8.5)	144 (9.6)		2 (0.4)		
5*	1 (0.1)					
6A	26 (1.3)	4 (0.3)	19 (2.6)	4 (0.8)	5 (1.0)	2 (0.6)
7F*	113 (5.8)	34 (2.3)	1 (0.1)	2 (0.4)	1 (0.2)	
19A*	434 (22.3)	152 (10.1)	334 (45.6)	123 (23.5)	301 (58.1)	121 (38.5)
Total	**749 (38.5)**	**334 (22.3)**	**354 (48.3)**	**131 (25.0)**	**307 (59.3)**	**123 (39.2)**
PCV-related serotypes						
6C	141 (7.3)	79 (5.3)	74 (10.1)	42 (8.0)	51 (9.9)	26 (8.3)
9N	31 (1.6)	36 (2.4)	1 (0.1)	3 (0.6)		1 (0.3)
23A	86 (4.4)	57 (3.8)	52 (7.1)	50 (9.6)	10 (1.9)	18 (5.7)
23B	58 (3.0)	57 (3.8)	13 (1.8)	30 (5.7)	2 (0.4)	4 (1.3)
Other	22 (1.1)	18 (1.2)	4 (0.6)	2 (0.4)	4 (0.8)	
Total	**338 (17.4)**	**247 (16.5)**	**144 (19.6)**	**127 (24.2)**	**67 (12.9)**	**49 (15.6)**
Non-PCV serotypes						
11A*	77 (4.0)	96 (6.4)	2 (0.3)	8 (1.5)	1 (0.2)	3 (1.0)
15A	78 (4.0)	61 (4.1)	65 (8.9)	54 (10.3)	64 (12.4)	53 (16.9)
15B*	39 (2.0)	52 (3.5)	7 (0.9)	20 (3.8)	6 (1.2)	19 (6.1)
15C	29 (1.5)	40 (2.7)	10 (1.4)	11 (2.1)	8 (1.5)	11 (3.5)
16F	57 (2.9)	58 (3.9)				
22F*	95 (4.9)	85 (5.7)	1 (0.1)	1 (0.2)		1 (0.3)
35B	78 (4.0)	136 (9.1)	63 (8.6)	130 (24.8)	2 (0.4)	20 (6.4)
Other	274 (14.1)	280 (18.7)	20 (2.7)	9 (1.7)	7 (1.4)	5 (1.6)
Nontypeable	37 (1.9)	37 (2.5)	9 (1.2)	11 (2.1)	8 (1.5)	8 (2.5)
Total	**764 (39.3)**	**845 (56.4)**	**177 (24.1)**	**244 (46.6)**	**96 (18.5)**	**120 (38.2)**
All serotypes	**1,946**	**1,498**	**733**	**524**	**518**	**314**

[a] Serotyping results for all 2008-09 isolates and predominant PNSP serotypes were published previously (7). PCV, pneumococcal conjugate vaccine. PNSP, penicillin MIC ≥ 0.12 μg/ml. MDR, multidrug resistant (PNSP and resistant to at least two other classes of agents). Predominant serotypes that include >5% of the isolates are shaded. Total values are indicated in boldface.

[b] *, Serotypes in the 23-valent polysaccharide pneumococcal vaccine.

though isolates are included from patient age groups who do not routinely receive the conjugate vaccines, a relationship to PCV13 exists due to the herd effect. PCV13 is now FDA approved for adults but is not recommended for routine use.

The inclusion of isolates from all age groups and those causing noninvasive disease that tend to have higher rates of antimicrobial resistance (Table 2) distinguish this program from the Centers for Disease Control and Prevention (CDC) pneumococcal surveillance study (13). A limitation of our investigation is the lack of incidence data (i.e., our findings provide a proportional snapshot of serotypes causing disease). The success of PCV13 can be ascertained from the CDC surveillance program which documented a reduction in rates of invasive disease among young children in the United States from 21.1/100,000 in 2009 to 9/100,000 in 2012 (13). This invasive pneumococcal disease rate started at 87.4/100,000 in 1999 and fell dramatically with PCV7 use but remained in the 20 to 21/100,000 range during the 6 years prior to PCV13 implementation due to increases in serotype 19A (13).

In the present study, PCV13 serotypes decreased significantly as a proportion of all isolates over the 4-year period between sur-

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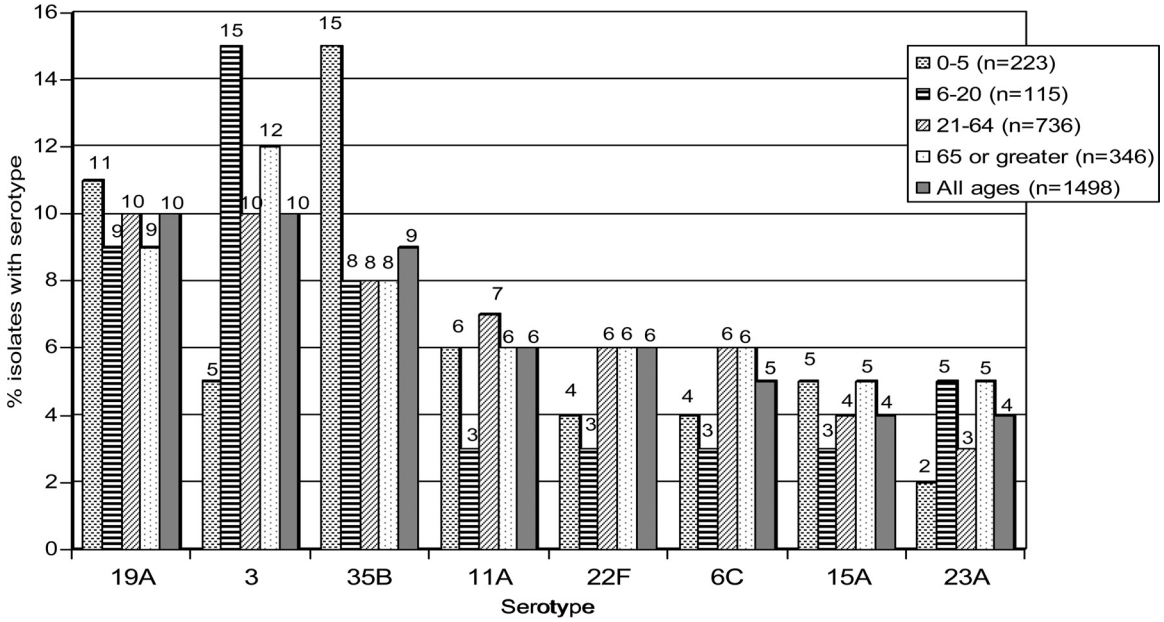

FIG 1 Distribution of predominant serotypes by patient age for 1,498 pneumococcal isolates recovered in 2012-13.

veys (from 43.4 to 27.1%), with the most pronounced decline for serotype 19A, which decreased from 22 to 10% of all isolates. Significant declines in PRSP and MDR (down 2.8 and 5.6%, respectively, since 2008-09) can be primarily attributed to the efficacy of PCV13 against serotype 19A strains that have dominated the pneumococcal population since 2004-05. A larger decrease in resistance rates was not realized because of proportional increases in replacement serotypes 35B, 23A, 23B, and 15B that have PNSP or MDR phenotypes.

It is early for the full impact of herd effect of PCV13 to be realized. Further declines in 19A strains and antimicrobial resistance are likely to follow since 19A comprises nearly a quarter of PNSP and more than a third of the MDR pneumococcal population. However, the persistence of serotype 19F strains (including a subset that comprises 5% of the MDR population) despite near elimination of other PCV7 serotypes suggests a remnant of 19A strains could also persist.

The lack of change in serotype 3 prevalence (9.6%) suggests marginal PCV13 activity against this serotype. It may also be explained by the higher prevalence of serotype 3 pneumococci among age groups that do not receive the vaccine. Recovery of serotype 3 isolates from children ≤5 years of age (4.9%) was similar to the 2008-09 period (4.1%). The high prevalence among middle ear fluid isolates (21%) isolates is of interest. The rare occurrence of antimicrobial resistance among serotype 3 isolates is reassuring, but invasive disease has been linked to high mortality (14, 15).

Invasive nonvaccine serotype 35B isolates with a penicillin-nonsusceptible phenotype have been recovered as early as 1995 in the United States (16) and 2002 in Japan (17). Our data demonstrate that serotype 35B strains have increased from 2% of all isolates in 1999-00 (7) to currently 9.1% of all isolates. Although this serotype tends to cause more noninvasive than invasive disease, its high prevalence among PNSP (24.8%) and among children 0 to 5 years of age (14.8%) may warrant its inclusion in future conjugate vaccines.

In Norway, an increase in invasive disease caused by serotypes 15A and 23B was noted in 2012 after PCV13 implementation a year earlier (18). Our data show similar trends with serotype 23B being the only PCV-related serotype to increase among PNSP. Although the overall prevalence of serotype 15A strains was low (4.1%), nearly all were MDR (53 of 61).

The overall decreases in PRSP and MDR rates are reassuring, but the availability of alternative agents for resistant strains is important. Our data confirms the potent activity of ceftaroline against ceftriaxone-resistant and MDR *S. pneumoniae* phenotypes. The ceftaroline MIC distribution reported here is similar to that described in earlier reports (12, 19).

Ongoing surveillance of antimicrobial susceptibility and serotype frequency will be critical in order to assess the impact of wider availability and broader use of PCV-13. It remains to be seen whether elimination of disease can be realized for a pathogen capable of extensive serotype diversity (>90 types). Performance of robust surveillance in countries where the incidence of pneumococcal disease is much higher will be important to ensure conjugate vaccines target relevant serotypes.

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