

Multicenter Surveillance of *Streptococcus pneumoniae* Isolates From Middle Ear and Mastoid Cultures in the 13-Valent Pneumococcal Conjugate Vaccine Era

Sheldon L. Kaplan,¹ Kimberly J. Center,^{2,3} William J. Barson,⁴ Philana Ling-Lin,⁵ José R. Romero,⁶ John S. Bradley,⁷ Tina Q. Tan,⁸ Jill A. Hoffman,⁹ Timothy R. Peters,¹⁰ Alejandra Gurtman,^{2,3} Daniel A. Scott,^{2,3} James Trammel,¹¹ William C. Gruber,^{2,3} Kristina G. Hulten,¹ and Edward O. Mason¹

¹Pediatric Infectious Diseases Sections, Baylor College of Medicine, Houston, Texas; ²Pfizer Vaccine Research, Collegeville, Pennsylvania; ³Pfizer Vaccine Research, Pearl River, New York; ⁴The Ohio State University College of Medicine and Public Health, Columbus; ⁵Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center, Pennsylvania; ⁶University of Arkansas for Medical Sciences, Little Rock; ⁷Rady Children's Hospital San Diego, California; ⁸Feinberg School of Medicine, Northwestern University, Chicago, Illinois; ⁹University of Southern California School of Medicine, Los Angeles; ¹⁰Wake Forest School of Medicine, Winston-Salem, North Carolina; and ¹¹InVentive Health Clinical, Princeton, New Jersey

Background. *Streptococcus pneumoniae* is a common cause of otitis media (OM) in children; mastoiditis remains an important complication of OM. Limited data are available on the impact of the 13-valent pneumococcal conjugate vaccine (PCV13) on pneumococcal otitis.

Methods. Investigators from 8 children's hospitals in the United States prospectively collected pneumococcal isolates from middle ear or mastoid cultures from children from 2011 to 2013. Serotype and antibiotic susceptibilities were determined and PCV13 doses for children documented.

Results. Over the 3-year period, the proportion of isolates included in PCV13 (plus a related serotype) decreased significantly ($P = .0006$) among the middle ear/mastoid isolates (2011, 50% [74/149]; 2012, 40.5% [47/116]; 2013, 29% [34/118]). The number of serotype 19A isolates in 2013 ($n = 12$, 10.2% of total) decreased 76% compared with the number of 19A isolates in 2011 ($n = 50$, 33.6% of total). Of the children from whom serotype 19A was isolated ($n = 93$), 55% had previously received <3 doses of PCV13. The most common non-PCV13 serotypes for the combined years were 35B ($n = 37$), 21 ($n = 20$), 23B ($n = 20$), 15B ($n = 18$), 11 ($n = 17$), 23A ($n = 14$), 15A ($n = 14$), and 15C ($n = 14$). The proportion of isolates with a penicillin minimal inhibitory concentration >2 $\mu\text{g/mL}$ decreased significantly over the 3 years (2011, 22% [35/154]; 2012, 20% [24/118]; 2013, 10% [12/120]; $P < .02$).

Conclusions. The number of pneumococcal isolates and the percentage of isolates with high-level penicillin resistance from cultures taken from children with OM or mastoiditis for clinical indications have decreased following PCV13 use, largely related to decreases in serotype 19A isolates.

Keywords. *Streptococcus pneumoniae*; conjugate vaccine; surveillance.

Streptococcus pneumoniae is one of the most common organisms isolated from children with otitis media. Randomized trials of the 7-valent pneumococcal conjugate

vaccine (PCV7-serotypes 4, 9V, 14, 18C, 19F, and 23F) found either very modest or no reduction of acute or recurrent otitis media in young children [1, 2]. Following introduction of the PCV7 in the United States in 2000, the frequency of office visits for acute otitis media (AOM) [3] and the proportion of pneumococcal isolates causing AOM that were PCV7 serotypes were substantially reduced [4]. Subsequently, however, non-PCV7 serotypes, especially serotype 19A, became important causes of AOM [5–7] and mastoiditis [8, 9]. Similar changes were noted in other areas of the

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Correspondence: Sheldon L. Kaplan, MD, Texas Children's Hospital, Feigin Center, Ste 1150, 1102 Bates Ave, Houston, TX 77030 (skaplan@bcm.edu).

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world where PCV7 was introduced [10–12]. Early data suggest that 13-valent pneumococcal conjugate vaccine (PCV13; which includes the PCV7 serotypes along with serotypes 1, 3, 5, 6A, 7F, and 19A and was introduced in the United States in 2010) is associated with reduced nasopharyngeal (NP) carriage of PCV13 serotypes in children with OM [13, 14], decreased isolation of PCV13 serotypes from children undergoing tympanocentesis or from spontaneous ear drainage [15], and decreased isolation of *S. pneumoniae* from middle ear cultures of children undergoing pressure equalization (PE) tube placement [16].

The purpose of this study was to describe the pneumococcal serotypes and antibiotic susceptibilities of pneumococcal isolates recovered from middle ear or mastoid cultures obtained during clinical management of children being seen at 8 children's hospitals in the United States from 1 January 2011 through 31 December 2013. Prior receipt of PCV7 and/or PCV13 was also captured.

METHODS

Investigators from 8 children's hospitals prospectively collected pneumococcal isolates from middle ear cultures (spontaneous drainage, PE tube placement, myringotomy) or mastoid surgical cultures. The study was approved with informed consent being waived by the institutional review boards of each participating hospital. Selected demographic and clinical information, antibiotic susceptibilities from the clinical laboratory of the respective children's hospital, and date and type of PCV administered prior to the infection for which the culture was obtained were entered onto a standard case report form. A PCV13 dose was counted if administered 2 or more weeks before the date that the *S. pneumoniae* was isolated from the middle ear or mastoid culture.

The patient database was maintained in a central office (Texas Children's Hospital and Baylor College of Medicine, Houston, Texas). Pneumococcal isolates were identified, and antimicrobial susceptibility testing was performed using standard methods in the microbiology laboratories of each hospital. The isolates were sent to the Infectious Disease Research Laboratory at Texas Children's Hospital for serotyping. Antibiotic susceptibility categories were as defined by the 2014 Clinical and Laboratory Standards Institute [17]. Pneumococcal isolates were serotyped using commercially available antisera (Statens Seruminstitut, Copenhagen, Denmark; Cedarlane Laboratories USA, Burlington, North Carolina) [18]. Serotype 6C was considered a PCV13-related serotype [19].

Dichotomous variables were analyzed using the χ^2 or χ^2 test for trend. True Epistat (Epistat Σ Services, Richardson, Texas) was the statistical program used.

RESULTS

The total numbers of isolates from middle ear or mastoid cultures each year were 154 in 2011, 118 in 2012, and 120 in 2013.

The total number of isolates from only mastoid cultures was 35 (19 in 2011, 7 in 2012, and 9 in 2013). The median age and age ranges for each study year were very similar (Table 1). Overall, 253 patients were aged <2 years, 103 were ≥ 2 years and <6 years, and 36 were ≥ 6 years. The distribution of ethnicities of the total group was white, 66%; Hispanic, 12%; black, 11.2%; other, 6.1%; and unknown, 4.8%.

The numbers of isolates per serotype each year and in total as well as the number of children who received 0–4 doses of PCV13 prior to culture are shown in Table 2. In 2011, 74 of 149 (50%) isolates were PCV13 plus a related serotype; in 2012 and 2013, these serotypes accounted for 47 of 116 (40.5%) and 34 of 118 (29%) of isolates, respectively ($P = .0006$ for the trend in proportion of PCV13 plus a related serotype isolate). If 6C is excluded as a related serotype, 64 of 149 (43%) isolates in 2011, 42 of 116 (36.2%) isolates in 2012, and 32 of 118 (27%) isolates in 2013 were PCV13 serotypes ($P = .008$). No serotype 1, 5, 6A, or 6B isolates were recovered in any surveillance year.

Serotype 19A was the most common serotype isolated in each year but in diminishing numbers. The number of serotype 19A isolates in 2013 ($n = 12$, 10.2% of total) decreased 76% compared with the number of 19A isolates in 2011 ($n = 50$, 33.6% of total). Fifty-five percent of the children with 19A isolated ($n = 93$) received <3 doses of PCV13 prior to recovery of the 19A isolate from the middle ear or mastoid culture. (Three or 4 doses of PCV13 had been received by 32 or 10 children, respectively, prior to these cultures). Thirteen serotype 19A isolates were recovered from mastoid cultures; 8 of these 13 patients had received <3 doses of PCV13.

Table 1. Age and Race/Ethnicity of Children From Whom *Streptococcus pneumoniae* was Isolated From Middle Ear or Mastoid Cultures, 2011–2013

Selected Features	Year		
	2011	2012	2013
Middle Ear Isolate			
Number	135	111	111
Median age, y	1.46	1.61	1.51
Age range, y	0.13–8.76	0.29–13.09	0.27–12.5
Mastoid Isolate			
Number	19	7	9
Median age, y	1.23	0.41	2.42
Age range, y	0.1–17.1	0.26–2.8	0.15–11.6
Race/Ethnicity for All Children			
White	100 (65%)	81 (69%)	77 (64%)
Black	18 (12%)	10 (8%)	16 (13%)
Hispanic	17 (11%)	17 (14%)	13 (11%)
Other	7 (4%)	7 (6%)	10 (8%)
Unknown	12 (8%)	3 (3%)	4 (4%)

Table 2. Serotype Distribution of Pneumococcal Isolates From Middle Ear or Mastoid Cultures and Number of 13-Valent Pneumococcal Vaccine Doses Received Prior to Infection: Combined 2011, 2012, and 2013 Results for All Children

Serotype	2011	2012	2013	Total	4 Doses ^a	3 Doses	2 Doses ^b	1 Dose	0 Doses	Unknown Doses
3	8	9	12	29	5	3	2	5	14	
6C	10	5	2	17	1	3	1	4	8	
7C	2	1	0	3	0	1	0	1	1	
7F	1	0	0	1	0	0	0	0	1	
9N	3	0	1	4	0	0	1	1	2	
10	5	1	3	9	2	2	1	1	3	
11	5	8	4	17	4	2	1	4	6	
12F	2	1	0	3	1	1	0	0	1	
13	1	0	0	1	0	0	0	0	1	
15A	6	1	7	14	1	6	2	3	2	
15B	7	5	6	18	7	6	1	2	2	
15C	5	3	6	14	6	3	2	1	2	
15F	0	0	1	1	1	0	0	0	0	
16	2	3	6	11	2	5	3	1	0	
17	0	2	1	3	3 ^c	0	0	0	0	
19A	50	31	12	93	10	32	13	23	13	2
19F	5	2	8	15	2	2	1	1	8	1
20	0	0	1	1	1	0	0	0	0	
21	4	10	6	20	5	3	2	6	4	
22F	4	1	4	9	2	2	1	1	2	1
23A	6	5	3	14	4	3	1	5	0	1
23B	3	8	9	20	4	7	1	5	3	
31	3	2	5	10	1	3	1	2	3	
33A	1	0	0	1	0	1	0	0	0	
33F	4	0	4	8	1	3	0	2	2	
34	0	1	1	2	1	0	0	0	1	
35B	10	15	12	37	10	13	1	12	1	
35F	0	1	2	3	1	1	0	0	1	
38	2	1	2	5	1	0	0	2	2	
Total	149	116	118	383						

^a Doses of PCV13.^b All patients who received either 1 or 2 doses of 13-valent pneumococcal conjugate vaccine (PCV13) and with serotype 3, 19A, or 19F isolates were aged ≤ 0.7 years at the time of immunization. Thus, none of these children were aged ≥ 12 months when they received either their first or second PCV13 dose. 7-valent pneumococcal conjugate vaccine doses were not included.^c 1 patient received 5 doses of PCV13.

The next most common PCV13 serotype isolated was serotype 3: 8 in 2011, 9 in 2012, and 12 in 2013. This increase in number of serotype 3 isolates recovered was not a significant trend with respect to the proportion of isolates being serotype 3 each year ($P = .14$). Three children had received 3 doses and 5 had received 4 doses of PCV13 prior to culture. Twenty-one children had received <3 PCV13 doses prior to culture. Thus, 72% of children received <3 doses of PCV13 prior to culture and almost half had not received any dose of PCV13. Among these children, 6 serotype 3 isolates were recovered from mastoid cultures; 4 of these 6 patients had received <3 doses of PCV13.

Serotypes 19F and 7F accounted for 15 isolates and 1 isolate for the combined years, respectively. Nine of the 16 children with these serotypes had not received any PCV13 doses. Of the 15 children with 19F isolates, 4 had received 3 or 4 doses of PCV13 and 7 had received 3 or 4 doses of PCV7. The child with the 7F isolate had not received any doses of PCV13.

In 2011, 75 isolates were non-PCV13 and related serotypes; in 2012, 69 isolates were non-PCV13 and related serotypes; and in 2013, 84 isolates were non-PCV13 and related serotypes. The most common non-PCV13 serotypes for the combined years were serotype 35B ($n = 37$), serotype 21 ($n = 20$), serotype 23B ($n = 20$), serotype 15B ($n = 18$), serotype 11 ($n = 17$), serotype

Table 3. Serotype Distribution of Pneumococcal Isolates From Mastoid Cultures and Number of 13-Valent Pneumococcal Vaccine Doses Received Prior to Infection: Combined 2011, 2012, and 2013 Results for All Children

Serotype	2011	2012	2013	Total	4 Doses ^a	3 Doses	2 Doses	1 Dose	0 Doses	Unknown
3	0	2	4	6	0	2	0	0	4	
6C	1	0	0	1	0	0	0	0	1	
12F	1	0	0	1	0	1	0	0	0	
15A	1	0	0	1	0	0	0	1	0	
15B	1	0	0	1	0	0	0	0	1	
19A	7	5	1	13	1	4	1	4	2	1
19F	2	0	1	3	0	2	0	0	0	1
22F	2	0	1	3	1	1	0	0	0	1
23A	1	0	0	1	0	0	0	0	0	1
33F	0	0	2	2	0	0	0	1	1	
35B	1	0	0	1	0	1	0	0	0	
38	1	0	0	1	0	0	0	0	1	
No Isolate ^b	1	0	0	1						1
Totals	19	7	9	35						

^a Doses of 13-valent pneumococcal conjugate vaccine.^b Isolate not available for serotyping.

23A (n = 14), serotype 15A (n = 14), serotype 15C (n = 14), serotype 16 (n = 11), and serotype 31 (n = 10).

Table 3 summarizes the number of isolates per serotype for mastoiditis cases each year. Serotype 19A was the most common serotype overall but declined over the years from 7 isolates in 2011 to 1 isolate in 2013. Serotype 3 was the second most common serotype without evidence that a decrease in numbers occurred over the 3-year study period. Although serotype 35B was the most common non-PCV13 serotype for all isolates, only 1 of 37 such isolates was recovered from mastoid cultures. In contrast, 3 of 9 serotype 22F isolates were from mastoid cultures.

Antibiotic Susceptibilities

The distribution of isolates based on minimal inhibitory concentrations (MICs) for penicillin is shown in Figure 1. Over the 3 years of study, the proportion of isolates with penicillin MIC > 2 µg/mL decreased significantly (2011, 22% [35/154]; 2012, 20% [24/118]; 2013, 10% [12/120]; $P = .008$). A significantly greater proportion of serotype 19A isolates had a penicillin MIC ≥ 4 µg/mL than non-serotype 19A isolates ($P < .001$; Figure 2). The non-serotype 19A isolates with penicillin MIC ≥ 4 µg/mL were serotypes 19F (n = 4), 35B (n = 2), 3 (n = 1), 15A (n = 1), and 23B (n = 1). The yearly distributions of isolates

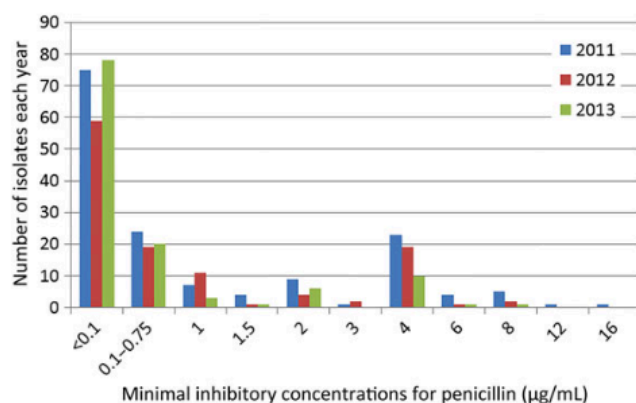
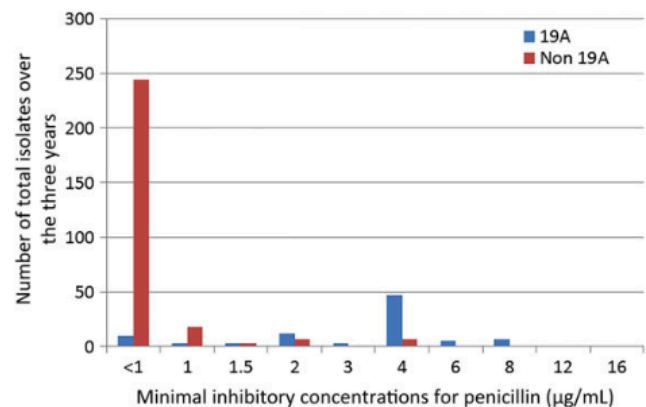
**Figure 1.** Distribution of the number of pneumococcal isolates for penicillin minimal inhibitory concentrations for each study year, 2011–2013.**Figure 2.** Penicillin minimal inhibitory concentration distribution for serotype 19A and non-19A serotype isolates for the study years 2011–2013.

Table 4. Antibiotic Susceptibilities for Erythromycin, Clindamycin, and Trimethoprim–Sulfamethoxazole for the *Streptococcus pneumoniae* Otitis Media Isolates, 2011–2013

Antibiotic and Susceptibilities	Year		
	2011	2012	2013
Percentage of Isolates			
Erythromycin			
S	50	55	54
I	18	19	19
R	32	25	26
Clindamycin			
S	60	79	81
I	11	5	6
R	29	15	13
Trimethoprim–sulfamethoxazole			
S	23	21	26
I	18	18	16
R	59	62	58

Abbreviations: I, intermediate; R, resistant; S, susceptible.

susceptible, intermediate, or resistant to erythromycin, trimethoprim–sulfamethoxazole, and clindamycin are shown in Table 4. Over the 3 years, the proportion of isolates susceptible to clindamycin increased ($P = .0004$). Serotype 19A isolates were more likely to be resistant to these 3 antibiotics than non-serotype 19A isolates (Table 5).

DISCUSSION

Since the introduction of PCV13 for routine use in infants and young children, the incidence of invasive pneumococcal disease (IPD) in children has decreased in the United States and other countries in which PCV13 has replaced routine administration of PCV7 [18,20–23]. Decreases in IPD caused by serotypes 19A, 7F, and 3 have been demonstrated [21]. Fewer studies have focused on the impact of PCV13 on the frequency of OM due to *S. pneumoniae*.

Several investigators have reported a decline in nasal colonization by PCV13-serotype pneumococci in children following

Table 5. Proportion of *Streptococcus pneumoniae* Serotype 19A Isolates vs Non-Serotype 19A Isolates Not Susceptible to Erythromycin, Clindamycin, or Trimethoprim–Sulfamethoxazole

Serotype	Erythromycin	Clindamycin	Trimethoprim–Sulfamethoxazole
Serotype 19A	89% (79/89)	79% (46/58)	95% (84/88)
Non-Serotype 19A	34% (94/278)	11% (21/188)	71% (196/277)

the introduction of PCV13 into national immunization programs [13,24–27]. Investigators in France reported that children presenting with AOM were significantly less likely to carry PCV13 serotypes (19A, 7F, 6C) in the nasopharynx if they had received at least 1 dose of PCV13 compared with children who had received PCV7 only [13]. Serotypes 15A and 11A were the most common non-PCV13 serotypes isolated in this study, consistent with the findings of other NP colonization studies in which the most common non-PCV13 serotypes isolated included 15A, 15B/C, 6C, 11A, 35B, 23B, 21, 23A, and 16F [13,24–27].

The impact of PCV13 on the frequency and etiologies of OM in children has been more difficult to assess since tympanocentesis for AOM is not routinely performed in clinical practice. In a preliminary report of an ongoing study that enrolled 60 children who had completed the 3-dose infant PCV13 series between October 2010 and September 2011, Pichichero et al [14] found that of 15 children who had tympanocentesis for AOM, only 1 child had *S. pneumoniae* (serotype 11) isolated from a middle ear fluid culture. In contrast, of 58 children enrolled in a separate but similarly designed study from October 2007 to September 2009, 7 of 15 pneumococcal isolates from children with AOM undergoing tympanocentesis were serotype 19A. Zhao et al [16] cultured middle ear fluids of 118 children undergoing PE tube placement between August 2012 and April 2013 for recurrent OM ($n = 112$), middle ear effusion ($n = 6$), and conductive hearing loss. Sixty-six patients had received PCV13 only and 25 had received some combination of PCV7 and PCV13. Only 1 *S. pneumoniae* isolate (serotype 16) was recovered from an 8-year-old patient. Utilizing the claims data from a large US managed healthcare plan, Marom et al [28] estimated that there was a significant drop in the observed OM visits in 2010 and 2011 and that they were lower than the projected number of visits for OM based on the trend for claims in 2005–2009. The decline in visits for children aged <2 years coincided with the introduction of PCV13. In the most comprehensive study to date on incidence of pneumococcal OM, Ben-Shimol et al [15] noted a marked reduction of OM caused by PCV13 serotypes in southern Israel following the sequential introduction of PCV7 and then PCV13 for routine use.

In our multicenter surveillance study, pneumococcal OM and mastoiditis isolates were obtained from a variety of sources including spontaneous otorrhea, middle ear fluid obtained at the time of PE tube placement, myringotomy cultures, and mastoid cultures, starting in January 2011, about 6 months after PCV13 was being widely used in the United States. Thus, our surveillance of pneumococcal isolates represents a combination of isolates from children with acute, recurrent, or chronic otitis media. There was a decrease in the total number of isolates in 2012 ($n = 118$) compared with 2011 ($n = 154$); however, in 2013 ($n = 120$), the number of isolates remained stable. Importantly,

the number and proportion of isolates that were PCV13 serotypes decreased substantially over the course of the study, especially for serotype 19A and the 6A-related serotype, 6C. Although almost 50% of the children from whom a serotype 19A isolate was recovered had received 3 or 4 doses of PCV13 prior to the episode, the number of serotype 19A isolates decreased by 75% when results for 2011 were compared with those for 2013. There was no decline in serotype 3 isolates, which has been noted in trials of other pneumococcal conjugate vaccines that contain serotype 3 for preventing AOM caused by *S. pneumoniae* [29]. However, in our study, almost half of the children from whom a serotype 3 strain was isolated had not received any doses of PCV13. Furthermore, in the study from southern Israel, OM caused by serotype 3 declined 51% following the introduction of PCV7 and then PCV13 compared with the prevaccine period [15]. In general, the non-PCV13 serotypes noted to be commonly carried in the nasopharynx in the post-PCV13 studies described previously are the most common serotypes among the OM isolates in our surveillance study, with serotype 35B and serogroup 15 (A/B/C combined) isolates predominating. Ben-Shimol et al [15] reported similar findings.

After PCV7 became widely used, mastoiditis caused by serotype 19A was increasingly recognized and became the most common pneumococcal serotype associated with mastoiditis in areas around the world [8, 30]. Others reported an increase in the frequency or severity of acute mastoiditis several years after PCV7 was introduced. This is consistent with serotype 19A being associated with a greater likelihood of causing complicated acute mastoiditis than perhaps other pneumococcal serotypes thought to be, in part, related to increased rates of antibiotic resistance in serotype 19A isolates [9, 31]. Marom et al [28] found that rates of mastoiditis insurance claims decreased significantly during 2009–2011 compared with 2001–2008 when the rates were stable. We noted that the number of pneumococcal isolates associated with mastoiditis declined in 2012 and 2013 compared with 2011, especially for serotype 19A, of which only 1 isolate was found in 2013. Serotype 3 was the second most common serotype recovered from children over the 3-year study; however, 4 of the 6 children with serotype 3 mastoiditis had not received any PCV13 doses. In 2013, the last year of the study, serotype 3 was the most common pneumococcal serotype isolated from children with mastoiditis, accounting for 4 of 9 isolates.

Over the 3-year surveillance period, the proportion of isolates with high-level penicillin resistance decreased significantly, mainly as a consequence of the reduction in the number of serotype 19A isolates, which were also much more likely to be multidrug resistant than the non-serotype 19A isolates. In 2013 overall, 90% of isolates had penicillin MIC ≤ 2 μ g/mL. Our isolates were a combination of isolates obtained from children with acute or chronic OM and likely overestimated the proportion of

pneumococcal isolates causing AOM that are resistant to penicillin. If serotype 19A isolates continue to decline, decreasing levels of penicillin resistance among OM isolates would be expected, perhaps to the point that the lower standard dose of amoxicillin (40–45 mg/kg/day) rather than the high dose of amoxicillin (80–90 mg/kg/day) could be considered the first-line treatment for AOM [32, 33].

Our study has a number of limitations. The isolates were collected from children for clinical indications from a variety of sources such as draining ears, surgical cultures from PE tube placement, and mastoid cultures. Thus, the isolates are representative of the spectrum of OM and not AOM specifically. Antibiotic susceptibilities were measured by the clinical microbiology laboratory of each children's hospital using techniques that were not uniform, as would be the case if susceptibilities were determined in a central laboratory. Our data are not population based, so rates of pneumococcal OM episodes cannot be determined. Finally, our isolates were obtained from children who were seen at the participating children's hospitals and may not be representative of children in the general population. However, a strength of our study is the multicenter design.

In summary, over a 3-year period starting approximately 6 months after the widespread use of PCV13 in the United States, we found a decrease in the number of pneumococcal isolates from cultures taken from children with OM or mastoiditis for clinical indications. This decline was largely related to decreases in serotype 19A, and the proportion of isolates that represented serotypes in PCV13 decreased significantly over the study period. In association with the decline in serotype 19A isolates, the percentage of isolates with high-level penicillin resistance also decreased significantly. Continued decreases in the frequency of pneumococcal OM along with declining rates of penicillin resistance may warrant consideration of modifying recommendations for amoxicillin dosing for treatment of AOM. Additional studies will help clarify the full impact of PCV13 on the frequency and management of AOM in children.

Notes

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Potential conflicts of interest. S. L. K. received a grant from Pfizer for a pneumococcal surveillance study. K. J. C., A. G., D. A. S., and W. C. G. are employed by Pfizer and hold stock in the company. J. T. is contracted by Pfizer to provide statistical support and is employed by inVentiv Health Clinical. All other authors report no potential conflicts.

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