Serotype 19A Is the Most Common Serotype Causing Invasive Pneumococcal Infections in Children

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KEY WORDS

Streptococcus pneumoniae, conjugate vaccine, surveillance

ABBREVIATIONS

PCV7—7-valent pneumococcal conjugate vaccine
CLSI—Clinical and Laboratory Standards Institute
MIC—minimal inhibitory concentration

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WHAT'S KNOWN ON THIS SUBJECT: Invasive pneumococcal disease declined impressively in US children after the introduction of the PCV7. Nonvaccine serotypes, especially 19A, are now responsible for almost all invasive isolates.

WHAT THIS STUDY ADDS: The results of this study further document and extend the most current information indicating that 19A is responsible for almost 50% of the invasive isolates in children. Multidrug resistance was noted in 30% of the 19A isolates in 2007 and 2008.

abstract

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OBJECTIVE: The purpose of this study was to monitor the clinical and microbiologic features of invasive infections caused by *Streptococcus pneumoniae* among children before and after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7).

DESIGN: We conducted a 15-year prospective surveillance study of all invasive pneumococcal infections in children. The sample included infants and children at 8 children's hospitals in the United States with culture-proven invasive *S pneumoniae* infections.

RESULTS: Since the implementation of routine PCV7 immunization in 2000, invasive infections have decreased yearly from 2001 through 2004, to a nadir of 151 infections; the rate then increased from 2005 through 2008. Compared with the pre-PCV7 era, a greater proportion of children with invasive pneumococcal infection had an underlying condition in the post-PCV7 period. Compared with the total number of annual admissions, the number of 19A isolates increased significantly from 2001 to 2008 ($P < .00001$). In 2007 and 2008, only 16 isolates (4%) were vaccine serotypes; 19A accounted for 46% (168 of 369) of the non-PCV7 serotypes. Thirty percent of the 19A isolates were multidrug resistant. Serotypes 1, 3, and 7F accounted for 22% of the non-PCV7 serotypes. Among children with invasive pneumococcal infections, the likelihood of a 19A serotype increased with the number of preceding PCV7 doses.

CONCLUSIONS: Since 2005, the number of invasive pneumococcal infections in children has increased at 8 children's hospitals, primarily as a result of serotype 19A isolates, one third of which were resistant to multiple antibiotics in 2007 and 2008. Continued surveillance is necessary to detect emerging serotypes after the planned introduction of 13-valent or other pneumococcal vaccines. *Pediatrics* 2010;125:429–436

Since the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7), invasive infections caused by *Streptococcus pneumoniae* have declined in children in the United States.[1–4] The Centers for Disease Control and Prevention (CDC) reported a 77% reduction in rates of invasive pneumococcal disease among children <5 years of age when comparing the pre-PCV7 years 1998–1999 to the post-PCV7 year 2005 in their 8-state Active Bacterial Core surveillance system.[5] However, the CDC and several groups have found that the number of pneumococcal infections caused by serotypes not found in the PCV7, primarily serotype 19A, is increasing.[6–12] In addition, multidrug antibiotic resistance among the 19A serotype isolates, related to several different clonal types, has become a major issue.[6,10,11,13]

Investigators from 8 children's hospitals have conducted prospective surveillance of invasive pneumococcal infections among children seen at their hospitals since September 1993. In this report, surveillance results for the full years 1994–2008 are described.

METHODS

The US Pediatric Multicenter Pneumococcal Surveillance Group consists of investigators from 8 children's hospitals who have been prospectively identifying children treated as inpatients or outpatients at their centers for invasive infections caused by *S pneumoniae* beginning in September 1993.[3] The dates of surveillance for this report include the period January 1, 1994, through December 31, 2008. The study was approved and informed consent was waived by the institutional review boards of each of the participating hospitals.

Systemic infections were documented by positive culture results from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, synovial fluid, peritoneal fluid, etc). The diagnosis of pneumococcal pneumonia required a chest radiograph showing pulmonary infiltrates, in addition to a positive culture result from blood, pleural fluid, or the lung. Mastoiditis was also considered an invasive infection, for which isolates were obtained from either middle-ear fluid or mastoid bone. The approach to obtaining blood cultures from febrile children without a focus was not uniform among the 8 children's hospitals. Demographic and clinical information was collected retrospectively and recorded on a standard case report form for each episode of infection. After licensure of PCV7 in February 2000, documentation of administration of PCV7 was sought through the medical charts or by contacting the patient's physician. The number of annual admissions for each of the 8 hospitals was obtained for the years 2001–2008.

The database was maintained in a central office (Baylor College of Medicine). All pneumococcal isolates were identified in the microbiology laboratories of each hospital by standard methods and sent to a central laboratory (Infectious Disease Research Laboratory, Texas Children's Hospital, Houston, TX). Antimicrobial susceptibility testing for penicillin and ceftriaxone was performed by standard microbroth dilution with Mueller-Hinton media supplemented with 3% lysed horse blood. Susceptibilities for erythromycin, clindamycin, and trimethoprim-sulfamethoxazole were determined by standard disk-diffusion testing. Susceptibility categories were "susceptible," "intermediate," or "resistant," as defined by the 2009 Clinical and Laboratory Standards Institute (CLSI).[14] Isolates were serotyped or serogrouped by the capsular swelling method by using commercially available antisera (Statens Seruminstitut [Copenhagen, Denmark]; Daco, Inc [Carpinteria, CA]).[15] Isolates were not available for serotyping in 197 of the 4790 cases over the period of the study.

Dichotomous variables were analyzed by using the χ^2 test, χ^2 test for trend, or log-likelihood ratio test. True Epistat (Epistat Σ Services [Richardson, TX]) was the statistical program used.

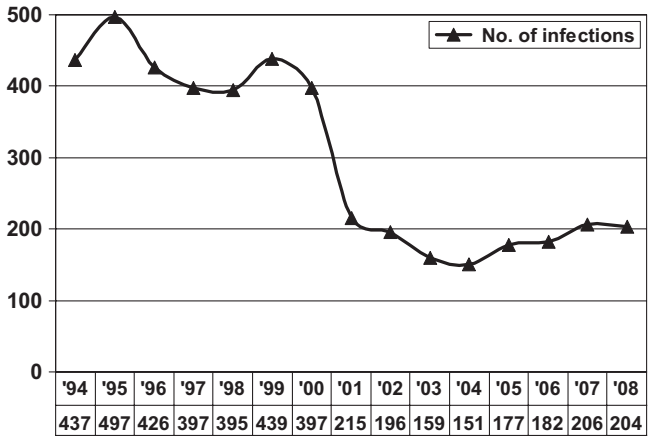

FIGURE 1
Number of invasive pneumococcal infections (y-axis) in children among 8 children's hospitals according to study years (x-axis) from 1994 to 2008. PCV7 was introduced in 2000.

RESULTS

After the introduction of PCV7 in spring of 2000, the number of invasive infections decreased yearly, from an average of 426 cases per year for the pre-PCV7 period (1994–2000) to a low of 151 cases in 2004 (Fig 1). This represented a 65% decline in cases in all age groups by 2004 compared with the av-

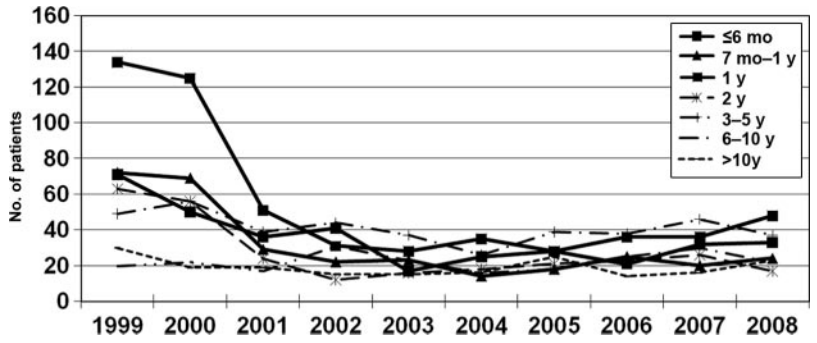

FIGURE 2
Age distribution of children with invasive pneumococcal infections among 8 children's hospitals according to study year from 1999 to 2008.

erage of the 7 years immediately preceding the introduction of PCV7. The decline among children in the 1-year-old age group was striking (Fig 2). However, the overall number of cases increased from 2005 through 2008, in which 204 cases occurred (Fig 1). Thus, the number of cases in 2007 and 2008 increased 35% compared with the number in 2004, whereas the number of admissions to all 8 hospitals increased 9% (96 472–105 367). After 2004, cases increased in all age groups except for children >10 years old (Fig 2). Increases after 2004 were seen at each of the 8 children's hospitals (see Fig 8, which is published as supporting information at www.pediatrics.org/content/full/125/3/429).

The increase in cases after 2004 resulted from a rise in nonvaccine cases, primarily serotype 19A (Fig 3). For 2007 and 2008 combined, only 16 (4.2%) of 385 available isolates were vaccine serotype (Table 1). Among the children represented by these 16 isolates, 8 received no PCV7 doses, 2 received 1 or 2 doses, 3 received 3 doses, 2 received 4 doses, and 1 had an unknown number of doses. Five patients had no underlying conditions, 5 had a malignancy, 2 had asthma, and 4 had a variety of underlying conditions.

For the 19A serotype, there were 18 isolates in 2001; by 2006–2008, there were >80 isolates per year. From 2001 through 2008, the annual number of 19A isolates increased significantly ($P < .001$) compared with the total number of annual hospital admissions among the 8 children's hospitals (Fig 3). Of the nonvaccine types, in 2007 and 2008, serotype 19A accounted for 168 (46%) of 369 isolates. Other relatively common or increasing non-PCV7 serotypes in 2007 and 2008 included 7F, 3, and 1, and serogroups 15, 22, 23 (not F), and 33. Serotype 19F was the most common of the PCV7 serotypes over these 2 years, accounting for 8 of 16 isolates.

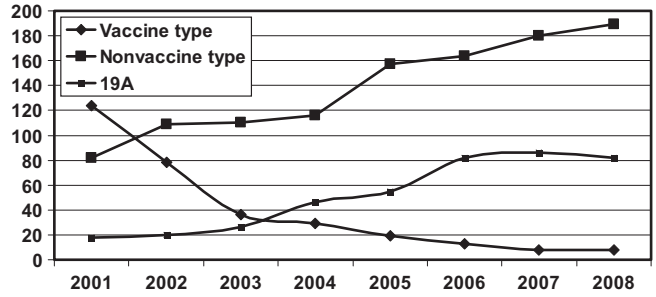

FIGURE 3
Number of invasive pneumococcal isolates (y-axis) that were vaccine serotype, nonvaccine serotype, or 19A in children from 8 children's hospitals according to study year from 2001 to 2008. The total annual admissions among the 8 children's hospitals were 91 950 in 2001, 94 055 in 2002, 95 809 in 2003, 96 472 in 2004, 99 008 in 2005, 101 116 in 2006, 103 524 in 2007, and 105 367 in 2008.

Sites of Infection

The proportion of cases that involved pneumococcal bacteremia without a source decreased from 56% (1658 of 2987) of cases before the PCV7 to 42% (621 of 1490) after the PCV7 ($P < .001$). In contrast, pneumonia accounted for an increasing proportion of cases after the PCV7 (28% [419 of 1490]) versus before the PCV7 (20% [606 of 2987]; $P < .001$). Bacterial meningitis accounted for a relatively stable proportion throughout the years (11%–17%; see Fig 9, which is published as supporting information at www.pediatrics.org/content/full/125/3/429).

When focusing on sites of infection for nonvaccine isolates after 2000, pneumonia accounted for more than 80% (47 of 58) of cases for serotype 1 and 53% (45 of 85) of cases for serotype 3 (Fig 4). For 19A isolates, 33% (135 of 415) of cases were pneumonia. Meningitis accounted for 20% (55 of 282) of the infections caused by the combined serotypes 6A, 7F, 22, and serogroups 15 and 33, which was twice the proportion for the other more common nonvaccine serotypes.

Underlying Conditions

In the pre-PCV7 years, an underlying condition was noted in an average of 30% of children each year (range: 28%–36%). This percentage has increased since 2000, reaching >41% of patients in 2006. The types and relative frequencies of underlying conditions for the pre- and post-PCV7 years are shown in Table 2. Of the children with underlying diseases, the proportion that had malignancies increased 44% for the post-PCV7 years (127 of 552

TABLE 1 Number of Isolates per Serotype and Year of Study

Serotype	2003	2004	2005	2006	2007	2008	Total	%
1	9	3	12	11	9	3	47	4.6
3	11	5	10	10	14	11	61	5.9
4[a]	2	1	0	1	1	1	6	0.6
5	3	5	1	0	1	0	10	1.0
6A	3	4	8	7	2	0	24	2.3
6B[a]	5	4	4	4	1	1	19	1.8
7F	2	6	7	10	15	29	69	6.7
7C	0	0	0	0	0	2	2	0.2
8	0	0	0	0	1	2	3	0.3
9V[a]	3	1	2	1	1	1	9	0.9
9 N	1	0	1	0	1	1	4	0.4
10	3	1	1	2	3	2	12	1.2
11	2	3	5	0	4	2	16	1.6
12	2	2	6	2	3	2	17	1.7
13	2	1	0	1	0	0	4	0.4
14[a]	6	2	2	2	0	1	13	1.3
Group 15	15	5	14	4	9	12	58	5.6
16	2	2	0	0	0	1	5	0.5
17	0	0	0	0	1	1	2	0.2
18C[a]	3	0	2	0	0	0	5	0.5
18 not C	1	0	1	0	0	0	2	0.2
19F[a]	14	17	6	4	5	3	49	4.8
19A	26	46	55	82	86	82	377	36.6
21	0	1	0	1	0	2	4	0.4
22	5	8	6	5	5	5	34	3.3
23F[a]	3	4	3	2	0	1	13	1.3
23 not F	2	6	5	7	7	10	37	3.6
24	0	0	1	0	1	0	2	0.2
31	4	0	0	0	0	1	5	0.5
33	7	6	9	8	5	4	39	3.8
34	0	1	1	1	2	0	5	0.5
35	1	3	1	0	0	0	5	0.5
38	0	0	0	0	3	2	5	0.5
Pool G	2	4	6	3	2	8	25	2.4
NT	7	4	7	10	6	7	41	4.0
Totals	146	145	176	177	188	197	1029	100

[a] Serotypes in the PCV7.

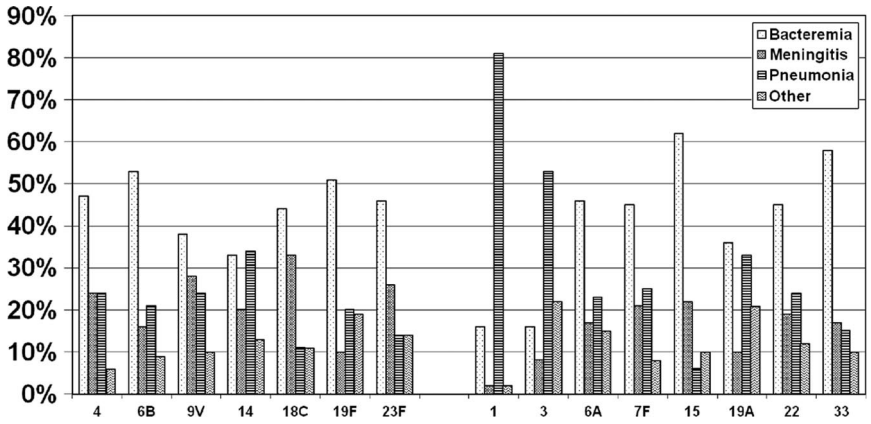

FIGURE 4
Site of infection related to serotype of invasive pneumococcal isolates from children at 8 children's hospitals: PCV7 serotypes and non-PCV7 serotypes from 2001 to 2008.

[23%]) versus the pre-PCV7 years (144 of 893 [16%]; $P < .001$).

For children with or without underlying conditions, the distribution of serotypes was generally similar over the years 2001–2008 (Table 6, which is published as supporting information at www.pediatrics.org/content/full/125/3/429). Serotypes 19A ($P = .002$) and 3 ($P < .001$) and serogroup 33 ($P = .005$) accounted for a greater proportion of isolates among the children without underlying conditions compared with children who had an underlying condition, whereas the opposite was true for serotype 6A ($P = .001$) and serogroup 15 ($P = .004$).

TABLE 2 Most Common Underlying Conditions in Children With Invasive Pneumococcal Infections: 1994–2000 Versus 2001–2008

Underlying Condition	1994–2000, *n* (%)	2001–2008, *n* (%)
Malignancies	144 (16)	127 (23)
Central nervous system	143 (16)	63 (11)
Cardiovascular	115 (13)	49 (9)
HIV	80 (9)	18 (3)
Hemoglobinopathy	72 (8)	26 (5)
Renal	71 (8)	36 (7)
Other	268	233
Total	893	552

Antibiotic Susceptibilities

Rates of resistance to erythromycin declined and clindamycin resistance rates were stable until 2004 when the rates for both began to increase, primarily because of the increase in serotype 19A isolates (Fig 5). Because the CLSI interpretive break points for penicillin susceptibility changed in 2008, the distribution of minimal inhibitory concentrations (MICs) for penicillin and ceftriaxone for the 2007 and 2008 isolates are shown in Figs 6 and 7 rather than the proportions that were susceptible, intermediate, or resistant. The MICs for both these antibiotics are higher for serotype 19A isolates compared with the non-19A isolates. Among the 19A isolates, the MIC_{90}, the median penicillin MIC, and the mode penicillin MICs were 4, 2, and 4 μg/mL, respectively. In contrast, among the non–serotype 19A isolates, the MIC_{90} was 0.25 μg/mL, and the median and mode MICs were both 0.01 μg/mL. Similarly for ceftriaxone, among the non–serotype 19 A isolates, the MIC_{90} was 0.5 μg/mL, and the median and mode MIC were both

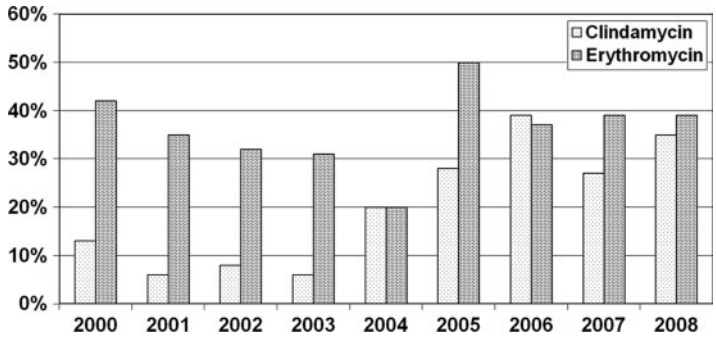

FIGURE 5
Proportion of isolates nonsusceptible (intermediate plus resistant) to clindamycin and erythromycin among invasive pneumococcal isolates from children at 8 children's hospitals from 2001 to 2008.

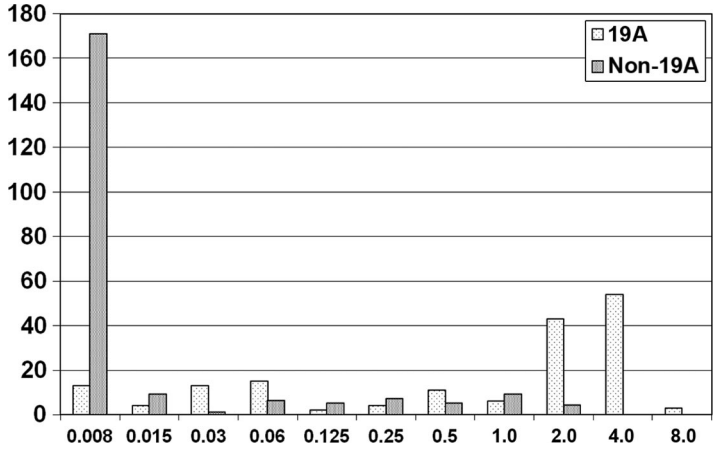

FIGURE 6
The number of invasive pneumococcal isolates per penicillin MIC for isolates recovered from children at 8 children's hospitals in 2007 and 2008: 19A versus non-19A isolates.

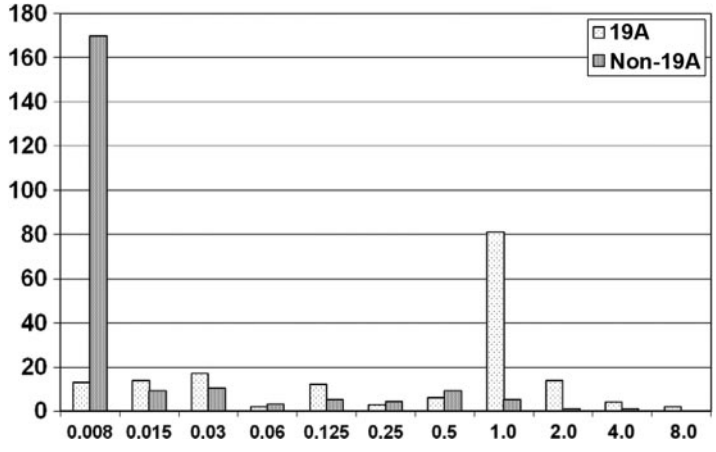

FIGURE 7
The number of invasive pneumococcal isolates per ceftriaxone MIC for isolates recovered from children at 8 children's hospitals in 2007 and 2008: 19A versus non-19A isolates.

0.015 μg/mL, whereas for the 19A isolates, the MIC_{90} and mode MICs were 1.0 μg/mL, and the median MIC was 0.06 μg/mL.

In 2007 and 2008, serotype 19A isolates were significantly more resistant than non-19A isolates to erythromycin, clindamycin, or trimethoprim-sulfamethoxazole ($P < .001$ for each; Table 3). In addition, 54% of the serotype 19A isolates (91 of 168) were nonsusceptible to erythromycin, clindamycin, and trimethoprim-sulfamethoxazole. Of these 91 isolates, 39 had a penicillin MIC of 2 μg/mL, 48 had a penicillin MIC of 4 μg/mL, 3 had a penicillin MIC of 8 μg/mL, and 1 had a penicillin MIC of 0.06 μg/mL. For these 91 isolates, the distribution of ceftriaxone MICs was 1 for 0.03 μg/mL, 72 for 1.0 μg/mL, 13 for 2.0 μg/mL, 3 for 4 μg/mL, and 2 for 8 μg/mL. Thus, 30% (51 of 168) of the serotype 19A isolates were multidrug resistant in 2007 and 2008.

PCV7 Doses and Invasive Pneumococcal Infection

For each of the years from 2004 to 2008, the number of PCV7 doses children had received before their episode of invasive pneumococcal infection was significantly associated with the likelihood that their isolate was a serotype 19A (Table 4). To determine if this association was related to age, we found that for children <5 years old, there was no significant association between age in years and proportion of isolates that were serotype 19A, except for 2005, in which the proportion of 19A isolates decreased with age (Table 5).

DISCUSSION

After the introduction of the 7-valent pneumococcal conjugate vaccine in the United States, a number of investigators reported marked declines in invasive pneumococcal infection in children as well as in people of other age groups who were not immunized.[1–5] However, within a very short time after the introduction of the PCV7, disease caused by nonvaccine serotypes, especially serotype 19A, emerged as a growing concern. The results of our study confirm and extend the degree to which serotype 19A has caused inva-

TABLE 3 Selected Antimicrobial Susceptibilities for Serotype 19A or Non-19A Isolates From Invasive Infections Among Children at 8 Children's Hospitals: 2007 and 2008

Serotype	Erythromycin, %[a]			Clindamycin, %[a]			TMP-SMX, %[a]		
	S	I	R	S	I	R	S	I	R
19A ($N = 168$)	32	2	66	44	0	56	18	5	77
Non-19A ($N = 215$)	84	4	12	94	1	5	81	2	17

TMP-SMX indicates trimethoprim-sulfamethoxazole; S, susceptible; I, intermediate; R, resistant.

[a] $P < .001$ for distribution of susceptibilities for serotype 19A versus non-19A isolates.

TABLE 4 Yearly Trends for Serotype of Invasive Pneumococcal Isolates and Number of PCV7 Doses Preceding the Infection for Children at 8 Children's Hospitals: 2003–2008

Doses	2003		2004		2005		2006		2007		2008	
	19A	Other	19A	Other	19A	Other	19A	Other	19A	Other	19A	Other
0	12	71	14	54	19	62	19	37	11	33	13	45
1	0	12	4	8	1	13	7	6	9	12	6	21
2	3	10	7	11	8	12	7	10	13	6	6	10
3	7	8	15	14	16	11	20	19	20	21	24	13
4	1	7	3	5	10	13	26	16	30	24	31	23
P	.06[a]		.004		.001		.008		.004		<.001	

[a] χ^2 for trend for each year. Data for PCV7 doses were available for 82%, 89%, 93%, 89%, 86%, and 92% of the cases for the years 2003, 2004, 2005, 2006, 2007, and 2008, respectively. If the number of PCV7 doses was unknown for a child, the case was not included in this analysis.

TABLE 5 Yearly Trends for Serotype of Invasive Pneumococcal Isolates and Age of Patient for Children at 8 Children's Hospitals: 2003–2008

Age	2003		2004		2005		2006		2007		2008	
	19A	Other	19A	Other	19A	Other	19A	Other	19A	Other	19A	Other
0–12 mo	7	30	15	23	22	24	27	19	22	27	25	30
1 y	8	16	11	24	11	17	19	17	20	15	29	17
2 y	3	12	11	6	7	14	11	10	15	8	9	8
3 y	2	13	2	5	2	11	9	6	13	6	6	11
4 y	2	7	3	8	6	6	2	7	3	6	1	7
5 y	0	13	1	6	2	11	5	9	6	6	6	3
P	.13[a]		.37		.05		.07		.59		.57	

[a] χ^2 for trend for each year.

sive infections in children over the 8 years since PCV7 has been administered routinely.[5–12] From 2001 to 2008, the annual number of serotype 19A isolates increased significantly among children with invasive pneumococcal infections at our 8 children's hospitals. In 2007 and 2008, >95% of the available isolates causing invasive pneumococcal infections among these children were nonvaccine serotypes; 46% of the nonvaccine serotype isolates were 19A. Currently, serotype 19A is the most common serotype for invasive disease in children. Serotype 19A also has become an important pneumococcal isolate causing otitis media and its complications such as mastoiditis.[16,17]

The proportion of invasive pneumococcal cases that were bacteremia alone declined but increased for pneumonia after the availability of PCV7 compared with cases before PCV7 use. Several studies have shown that in the post-PCV7 era, pneumococcal bacteremia has not been commonly detected in young children who have fever without a focus.[18–21] In contrast, the frequency of complicated pneumonias caused by non-PCV7 serotypes has increased in some areas of the United States.[22]

Serotypes 1, 3, and 7F also were important nonvaccine serotypes in our study and collectively accounted for 21% of the nonvaccine serotype isolates in 2007 and 2008. The numbers of isolates each year for serotypes 1 and 3 have been stable, whereas the 7F isolates seem to be on the rise. The majority of the infections caused by serotypes 1 and 3 isolates were pneumonia; ~30% of 19A and 7F isolates were associated with pneumonia. Serotype 19A also had a unique association with acute mastoiditis in 1 study.[17] Other notable serotypes or serogroups after 2001 were 6A, 15, 22, and 33.

As the number of children who have received PCV7 has increased and with a subsequent decline in invasive infections, the proportion of children with an underlying condition among children who have invasive pneumococcal infections has increased. Although the average yearly number of children with invasive pneumococcal infection and an underlying condition has decreased from 128 in the 7-year pre-PCV7 period compared with 69 over the 8 years after the PCV7, the underlying condition of malignancy was reduced the least relative to the other conditions. Perhaps the immunosuppression associated with malignancies is greater than that for the other underlying conditions. The serotype distribution was somewhat different for children with or without an underlying condition.

We chose to present the MICs for penicillin and ceftriaxone for 2007 and 2008 because these data really demonstrated the differences between serotype 19A and non-19A serotypes for these antibiotics. The use of the 2009 CLSI interpretive break points for susceptible, intermediate, and resistant to compare the penicillin and ceftriaxone susceptibilities blunts these differences substantially, considering the 2008 modifications for penicillin interpretive break points for nonmenin-

geal isolates, which increased the MIC considered intermediate or resistant for penicillin.[14] Nevertheless, 34% of the serotype 19A isolates in 2007 and 2008 combined would still be categorized as intermediate or resistant to penicillin. How this might relate to treatment failures associated with penicillin therapy is unclear and cannot be determined from our study. Penicillin alone is rarely administered empirically for pneumonia in our hospitals. In a multicenter study, pneumococcal pneumonia in children caused by isolates with penicillin MICs up to 4 μg/mL was treated successfully with intravenous penicillin or ampicillin.[23] In our study, serotype 19A isolates also were much more likely than the non–serotype 19A isolates to be resistant to erythromycin, trimethoprim-sulfamethoxazole, or clindamycin and to be resistant to $\geq$3 classes of antibiotics. Our results further extend the reports of several groups that have noted multidrug resistance for the serotype 19A isolates, related in part to expansion of the multidrug-resistant 320 clonal complex.[11,13,24] For some patients with invasive infection, such as pneumonia or pleural empyema caused by a multidrug-resistant serotype 19A isolate, linezolid or perhaps a newer quinolone might be the only oral agents available for completing therapy. Intravenous therapy with ceftriaxone and cefotaxime remains an appropriate treatment option for such patients as well.

Moore et al[13] and Hicks et al[12] have proposed that multiple factors are likely to explain why 19A has emerged as the most common serotype after the introduction of the PCV7 and stated that there are insufficient data to implicate PCV7 as the only or even the most important factor in the emergence of non-PCV7 serotypes. Capsular switching and antibiotic use are other important factors that contribute to the increased incidence of 19A isolates, which are often multidrug resistant.[25] The increase in the frequency of 19A isolates may also be related to the natural secular changes in serotype frequencies, as has been seen in South Korea, where in 1 hospital, before any PCV7 use, 19A isolates increased from 0 of 40 invasive pneumococcal isolates from 1991–1994 to 7 of 39 (18%) from 2001–2003.[26]

In our study, for the children who had an invasive pneumococcal infection, the number of PCV7 doses received before they developed that invasive pneumococcal infection correlated with having a serotype 19A isolated over each of the years from 2004 to 2008. These findings would support that in the United States, emergence of serotype 19A as the most common pneumococcal serotype causing invasive infections in children is related, at least in part, to the routine administration of PCV7 to infants and children. As more doses of PVC7 are administered, it is possible that there is a greater decline in carriage of vaccine serotypes, as seen in a study from the Netherlands in which 2 doses given at 2 and 4 months and 3 doses of PCV7 given at 2, 4, and 11 months were compared.[27] Nonvaccine serotype carriage was increased slightly at 24 months of age for children in the 3-dose group (43%) compared with those in the 2-dose group (40%), although this difference was nonsignificant. Compared with control children not receiving PCV7, 19A was the only serotype that was significantly increased in frequency of carriage for either the 2- or 3-dose regimens. So, it is possible that 19A nasopharyngeal carriage increases as more PCV7 doses are administered. This might result in a greater proportion of invasive isolates being 19A in children as the number of PVC7 doses increases among those children with invasive disease. Clearly, 19A has a greater ability to cause invasive disease than other non-PCV7 serotypes for reasons that are yet to be determined.

Our study was limited in that it was case based and not population based. However, the annual number of 19A isolates increased significantly over the years 2001–2008 compared with the total number of annual admissions for the 8 children's hospitals in this study over the same period. In addition, the combined annual admissions to our 8 children's hospitals increased 9% in 2008 compared with a 35% increase in invasive cases in these same years. Our study was also limited to only children's hospitals, so the population of children studied may be biased compared with all children with invasive infection. All information regarding receipt of the PCV7 may not have been ascertained; information regarding previous antibiotic administration was not collected. Furthermore, 4% of isolates were not available for typing.

CONCLUSIONS

In addition to the 7 serotypes in the current PCV7, serotypes 1, 3, 5, 6A, 7F, and 19A are included in a 13-valent pneumococcal conjugate vaccine under development.[28] For 2007 and 2008, these 6 additional serotypes accounted for 252 (68%) of 369 isolates that were non-PCV7 serotypes. Presumably, the 13-valent pneumococcal conjugate vaccine should be associated with an additional reduction in invasive pneumococcal infections in children, but continued surveillance will be required to document the impact of the expanded pneumococcal conjugate vaccine and to detect the emergence of new serotypes.

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