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# Decrease of Invasive Pneumococcal Infections in Children Among 8 Children's Hospitals in the United States After the Introduction of the 7-Valent Pneumococcal Conjugate Vaccine

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**ABSTRACT.** *Objective.* To monitor clinical and microbiologic features including antimicrobial susceptibility and serogroup distribution of invasive infections caused by *Streptococcus pneumoniae* among children before and after the introduction of routine administration of the 7-valent pneumococcal conjugate vaccine (PCV7).

*Design.* A 9-year (January 1, 1994 through December 31, 2002) prospective surveillance study of all invasive pneumococcal infections in children.

*Patients.* Infants and children cared for at 8 children's hospitals in the United States with culture-proven invasive infections caused by *S pneumoniae*.

*Results.* When compared with the mean of the years 1994 to 2000, the annual number of invasive pneumococcal infections for children  $\leq 24$  months of age declined 58% in 2001 and 66% in 2002. If only the serogroups in the PCV7 are considered, the number of cases in children  $\leq 24$  months old declined 63% and 77% in 2001 and 2002, respectively. The greatest decrease was observed for serogroup-14 isolates. The number of isolates in nonvaccine serogroups increased 28% in 2001 and 66% in 2002 for children  $\leq 24$  months old. Nonvaccine serogroup-15 and -33 isolates had the greatest increase in number. The proportion of all isolates nonsusceptible to penicillin increased yearly from 1994 to 2000, reached a plateau in 2001 at 45%, and declined to 33% in 2002. Decrease in nonsusceptibility to penicillin occurred entirely in the isolates with penicillin minimum inhibitory concentration  $\geq 2$   $\mu\text{g}/\text{mL}$ . Nonsusceptibility to penicillin increased slightly among nonvaccine-serotype isolates. Most infections after at least 2 doses of PCV7 were caused by nonvaccine-serotype isolates.

*Conclusions.* Since the introduction of the PCV7, the number of invasive pneumococcal infections caused by vaccine-serogroup isolates among 8 US children's hospi-

tals has decreased  $>75\%$  among children  $\leq 24$  months old. In addition, penicillin resistance decreased in 2002 for the first time since our surveillance began in 1993–1994. However, we have noted that replacement may be developing with serogroups 15 and 33. Furthermore, penicillin resistance seems to be increasing among nonvaccine serogroups. Surveillance must be continued to detect the emergence of changes in the distribution of serotypes as well as antibiotic susceptibility. *Pediatrics* 2004;113:443–449; *Streptococcus pneumoniae, conjugate vaccine, surveillance.*

ABBREVIATIONS. PCV7, 7-valent pneumococcal conjugate vaccine; CDC, Centers for Disease Control and Prevention; ABC, Active Bacterial Core; HIV, human immunodeficiency virus.

In the United States, *Streptococcus pneumoniae* has long been the most common organism associated with bacteremia and bacterial pneumonia in children. It became the most common cause of bacterial meningitis in children  $< 2$  years of age after the *Haemophilus influenzae* type b conjugate vaccine was introduced for universal administration to infants.<sup>1,2</sup> The 7-valent pneumococcal conjugate vaccine (PCV7) contains the 7 most common pneumococcal serotypes causing invasive infections in children in North America. These 7 serotypes also are the most likely to be resistant to antimicrobials. PCV7 was licensed in February 2000 in the United States for routine administration to young infants and children based on the large efficacy study conducted in northern California that demonstrated an estimated 97% efficacy of PCV7 for preventing invasive pneumococcal infection caused by the 7 serotypes included in the vaccine.<sup>3</sup>

Surveillance in the northern California Kaiser Permanente population postlicensure of PCV7 found the incidence of invasive disease caused by serotypes of pneumococci contained in the vaccine to have declined from a range of 51.5 to 98.2 cases per 100 000 person-years to 9.4 cases per 100 000 person-years for children  $< 1$  year old.<sup>4</sup> For children  $< 2$  years old, the incidence decreased from between 81.7 and 113.8 cases per 100 000 person-years to 38 cases per 100 000 person-years. This corresponds to an 87% and 58% reduction in disease caused by vaccine serotypes in the  $< 1$ - and  $< 2$ -year-old age groups, respectively.

The Centers for Disease Control and Prevention

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(CDC) track invasive pneumococcal infections in 12 states in the national Active Bacterial Core (ABC) surveillance. Whitney et al<sup>5</sup> reported that, when compared with the years before licensure of PCV7, the number of cases of invasive pneumococcal infections in children <24 months old were reduced significantly in 2001. In addition, the absolute number of infections caused by penicillin-nonsusceptible isolates declined significantly, although a reduction in the proportion of penicillin-nonsusceptible isolates had not yet occurred.

The US Pediatric Multicenter Pneumococcal Surveillance Group has been monitoring invasive pneumococcal infections since September 1993.<sup>6</sup> We report our findings for the years 1994–2000 (prevaccine) compared with the years 2001 and 2002, when the PCV7 was generally available to the population of children served by these hospitals.

## METHODS

The US Pediatric Multicenter Pneumococcal Surveillance Group consists of investigators from 8 children's hospitals who have been identifying children prospectively treated as inpatients or outpatients at their centers for invasive infections caused by *S pneumoniae*. The dates of surveillance for this report include the 9-year period from January 1, 1994 through December 31, 2002. Systemic infections were documented by positive cultures from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, synovial fluid, peritoneal fluid, etc). A chest radiograph showing pulmonary infiltrates in addition to a positive culture from blood, pleural fluid, or lung was required for the diagnosis of pneumococcal pneumonia. For children with mastoiditis, isolates were obtained from either middle-ear fluid or mastoid bone. Demographic and clinical information including antibiotics administered within 30 days before the invasive infection occurred was collected retrospectively and recorded on a standard case-report form for each episode of infection. Documentation of administration of PCV7 was sought after February 2000.

The database was maintained in a central office (Baylor College of Medicine, Houston, TX). All pneumococcal isolates were identified by standard methods in the microbiology laboratories of each hospital and then 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. Susceptibility categories were "susceptible," "intermediate," or "resistant" as defined for penicillin or ceftriaxone by the 2003 National Committee for Clinical Laboratory Standards.<sup>7</sup> For ceftriaxone, susceptibility categories were based on the site of infection, ie, meningitis versus a non-central nervous system infection. Isolates in the intermediate or resistant categories were considered together as nonsusceptible. Penicillin and ceftriaxone susceptibility results from the hospital microbiology laboratories of the individual investigators were used for 109 isolates unavailable for susceptibility testing in the central laboratory. The antibiotic-susceptibility testing for 6 isolates was not performed. Isolates were serotyped or serogrouped by the capsular swelling method using commercially available antisera (Statens Serum Institut, Copenhagen, Denmark; Daco, Inc, Carpinteria, CA).<sup>6</sup> For purposes of analysis, all isolates in a vaccine serogroup are included as a vaccine serotype.

Dichotomous variables were analyzed by using the  $\chi^2$  test or  $\chi^2$  test for trend. True Epistat (Epistat [Sigma] Services, Richardson, TX) was the statistical program used.

## RESULTS

### Decline in Invasive Infections

The mean number of invasive infections occurring from 1994 to 2000 has been compared with the years 2001 and 2002 for most of the analyses. For children

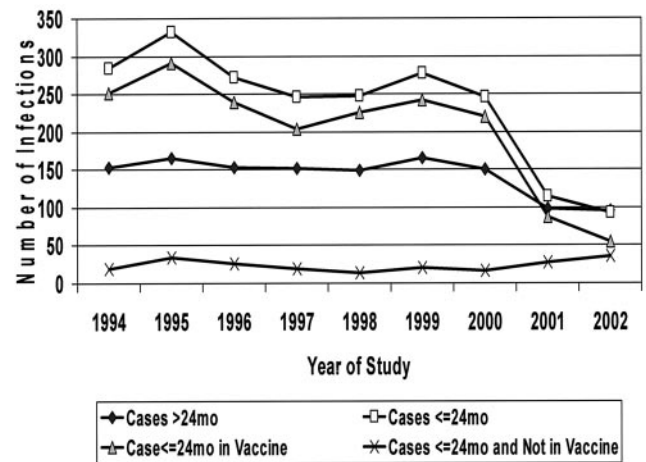


Fig 1. The number of pneumococcal isolates associated with invasive infections per year among 8 children's hospitals for cases based on age < or >24 months old and for serotypes contained or not contained in the PCV7 (1994–2002).

≤24 months old, the overall number of invasive pneumococcal infections declined 58% in 2001 and 66% in 2002, when compared with the mean of the years 1994–2000 (Fig 1). If only the serogroups in the PCV7 are considered, the number of cases in children ≤24 months old declined 63% and 77% in 2001 and 2002, respectively. As expected, the overall decline of cases in children >24 months old was substantially less: 36% in 2001 and 38% in 2002. Over the 9-year period, the number of cases in the ≤24-month-old group declined significantly when compared with the number of cases occurring in children >24 months old ( $P = .000005$ ). Using the number of cases among 4-year-olds each year as the baseline value, the number of cases for children <12 months old ( $P = .0068$ ), 12 to 24 months old ( $P = .0024$ ), and those >24 to 36 months old ( $P = .0084$ ) decreased significantly over the 9 years of the study. The number of cases of invasive disease caused by *S pneumoniae* by age group is shown in Fig 2. There was no substantial decline in the number of cases of invasive pneumococcal disease observed in children 3 and 4 years old, compared with baseline.

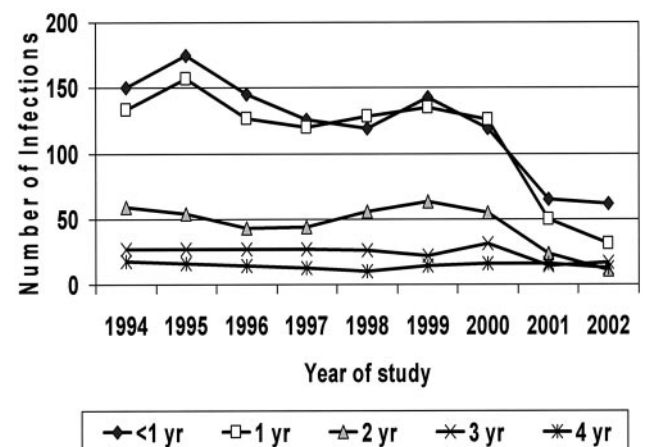
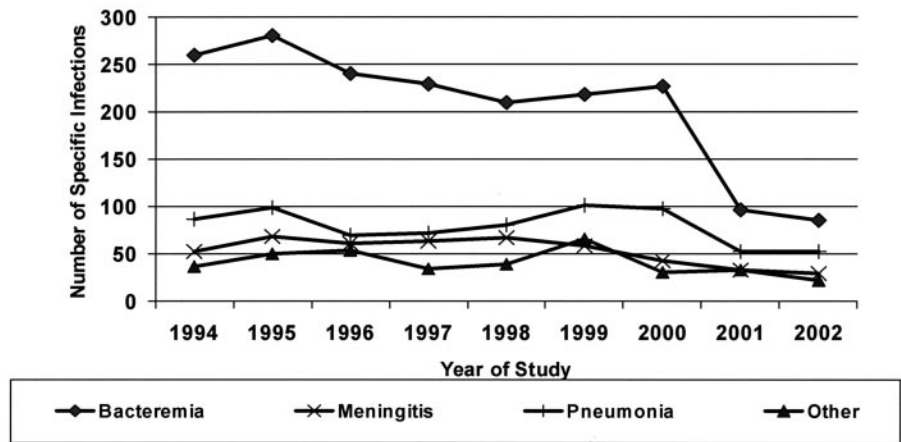


Fig 2. The number of pneumococcal isolates by age associated with invasive infections per year among 8 children's hospitals for 5 age groups (1994–2002).

Fig 3. The number of pneumococcal isolates per year associated with specific sites of infection among 8 children's hospitals (other category includes bone and joint infections, cellulitis, peritonitis, and other sites) (1994–2002).



### Increase in Infections Due to Serogroups of *S pneumoniae* Not in PCV7

Before the licensure of PCV7, nonvaccine serogroups accounted for 6.0%, on average, of the isolates recovered from children  $\leq 24$  months old. In 2002, nonvaccine-serogroup isolates were 37.6% of the total isolates (35 of 93) in this age group. The number of isolates in nonvaccine serogroups among children  $\leq 24$  months old increased 28% in 2001 and 66% in 2002, but this still accounted for only 35 isolates in 2002.

### Decline in Cases by Site of Infection

When considered by the site of infection, the greatest reduction in 2002 was observed for bacteremia alone (66%), followed by meningitis (56%) and pneumonia (39%). The differences in the rate of decline among these 3 sites were not significant by trend analysis when compared with each other (Fig 3). When other sites of infection (peritonitis, bone and joint, cellulitis, and other) are combined there was a 25% decline in 2001 and a 50% decline in 2002. In the years 1994–2000, the average number of cases of mastoiditis per year was 7.4, and in all but 1 year, at least 5 cases were identified (range: 1–12 per year). There were 9 cases of mastoiditis in 2001 and 1 case in 2002. Comparable declines in invasive cases occurred in all 8 centers and in children of white, African American, and Hispanic ethnicities. The proportion of children with underlying conditions did

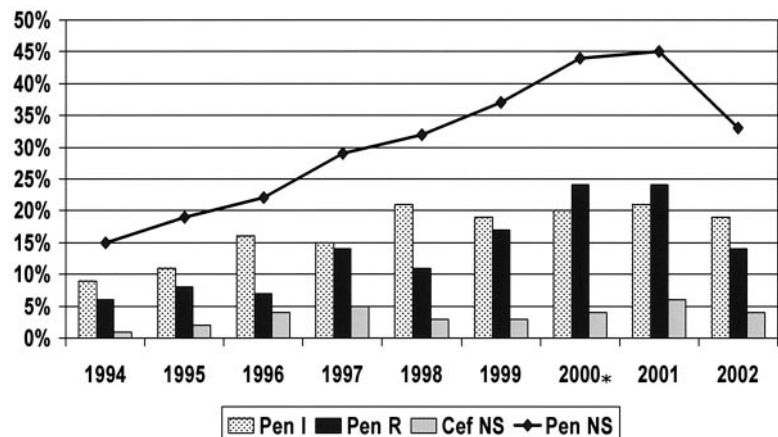
not change in the years 2001 (29%) and 2002 (36%), compared with the previous 7 years (28%–36%).

### Antibiotic Susceptibilities

Between 1994 and 2000, the proportion of invasive pneumococcal isolates that were nonsusceptible to penicillin increased each year and reached 44% in 2000. In 2001, 45% of isolates were nonsusceptible to penicillin; the rate declined to 33% in 2002 ( $P = .018$  for 2001 vs 2002) (Fig 4). Furthermore, the decline in the penicillin-nonsusceptible isolates occurred almost entirely among the isolates resistant to penicillin (minimum inhibitory concentration  $\geq 2 \mu\text{g}/\text{mL}$ ), with a 46% decrease in 2002 (13% penicillin resistant) compared with the rate in 2001 (24% penicillin-resistant). A similar pattern for decline in nonsusceptibility to ceftriaxone was observed; the proportion of isolates nonsusceptible to ceftriaxone was 4% in 2000, 6% in 2001, and 3% in 2002.

Among the isolates of *S pneumoniae* belonging to the serogroups contained in PCV7, the proportion that were nonsusceptible to penicillin increased yearly from 17% in 1994 to 54% in 2001. However, this proportion declined to 43% in 2002 (a 20% reduction). In contrast, among isolates of *S pneumoniae* with serogroups not contained in PCV7, the proportion nonsusceptible to penicillin varied from a low of zero in 1994 to a peak of 16% in 1996 and 1997 and then was between 6% and 12% through 2000. In 2001 and 2002, the proportions were 13% and 15%, respec-

Fig 4. Susceptibilities of penicillin and ceftriaxone for pneumococcal isolates associated with invasive infections among 8 children's hospitals (1994–2002).



tively. The proportion of children who had received an antibiotic in the 30 days before invasive pneumococcal disease did not change in 2001 (32%) or 2002 (35%), compared with the years 1994–2000 (28%–33%).

### Changes in the Prevalence of Specific Serogroups

Among the vaccine serogroups, the greatest decline occurred for serogroup-14 isolates: 65% in 2001 and 89% in 2002 (Table 1). The least decline was observed for serogroup-19 isolates: 19% in 2001 and 31% in 2002. The decline in the number of isolates among the other serogroups in the PVC7 ranged from 60% to 81% in 2002, compared with the years 1994 to 2000.

The numbers of non-PCV7 serogroup isolates for 1994–2002 are shown in Table 2. The average number of nonvaccine-serogroup isolates (including those that could not be serogrouped) for the years 1994–2000 was 49 (range: 33–68 per year). In 2001, the number of nonvaccine-serogroup isolates was 48; this increased by 37% to 67 in 2002. Although the numbers are small, the major contributors to the increase in nonvaccine-serogroup isolates were serogroups 15 and 33. The total number of serotype-15 isolates encountered from 1994 to 2000 was 34 (mean: 5 per year; range: 2–7 isolates per year). In 2002, 14 serogroup-15 isolates were identified. A total of 5 isolates were serogroup 33 for the years 1994–2000, but 11 such isolates occurred in 2002 ( $P = .003$ ). The average number of serotype-3 isolates was 6 per year (range: 2–10), but in 2002, 12 serotype-3 isolates were encountered. Similar increases were not evident for other non-PCV7 serogroups.

### Breakthrough Infections

Forty-seven children developed invasive pneumococcal infection after having received  $\geq 2$  doses of the PCV7; 21 occurred after 2 doses, 20 after 3 doses, and 6 after 4 doses. Underlying conditions were identified in 14 children including hemoglobinopathy (3), congenital heart disease (3), human immunodeficiency virus (HIV) (2), 1 each with malignancy, genetic defect, or central nervous system defect, and 3 with other conditions. The remaining 33 children were considered normal, but a formal immunologic evaluation was not part of the study; thus, subtle immunologic abnormalities may not have been recognized. One child with HIV infection developed 2 invasive infections after 2 doses and a third episode

**TABLE 1.** Decline in Invasive Pneumococcal Vaccine-Associated Isolates by Serogroup/Serotype Among 8 Children's Hospitals: 1994–2000 Versus 2001 and 2002

Serogroup/ Serotype	Mean 1994–2000, <i>n</i>	2001, <i>n</i>	Decline, %	2002, <i>n</i>	Decline, %
4	18	5	73	5	73
6	74	25	66	24	68
9	29	14	52	11	62
14	111	39	65	12	89
18	30	13	57	12	60
19	60	48	19	41	31
23	37	16	57	7	81

**TABLE 2.** The Number of Pneumococcal Isolates for Non-PCV7 Serogroups per Year Associated With Invasive Infections Among 8 Children's Hospitals: 1994–2002

Serogroup/ Serotype	Mean 1994–2000	Range	2001, <i>n</i>	2002, <i>n</i>
1	8	3–13	3	8
3	6	2–10	9	12
5	2	1–4	0	0
7	4	0–7	4	3
8	0	0–1	0	0
10	3	0–7	2	1
11	1	0–2	2	3
12	2	0–4	5	3
13	0	1–1	0	1
15	5	2–7	6	14
16	1	0–3	0	1
17	1	0–3	0	0
20	1	0–1	0	0
21	0	0–1	0	0
22	2	0–3	4	3
24	0	0–1	0	0
27	0	0–1	0	0
28	0	0–1	0	0
29	1	0–1	0	0
31	0	0–1	0	0
33	1	0–2	2	11
34	0	0–1	1	1
35	2	1–3	1	1
38	0	0–1	1	1
Pool G	0	0	1	2
Non-typeable	9	2–14	7	2
Total	49 (12.1)*	33–68 (7.9–14.1)	48 (23)	67 (37.4)

\* Percentage of the non-PCV7 serogroups of the total isolates per year.

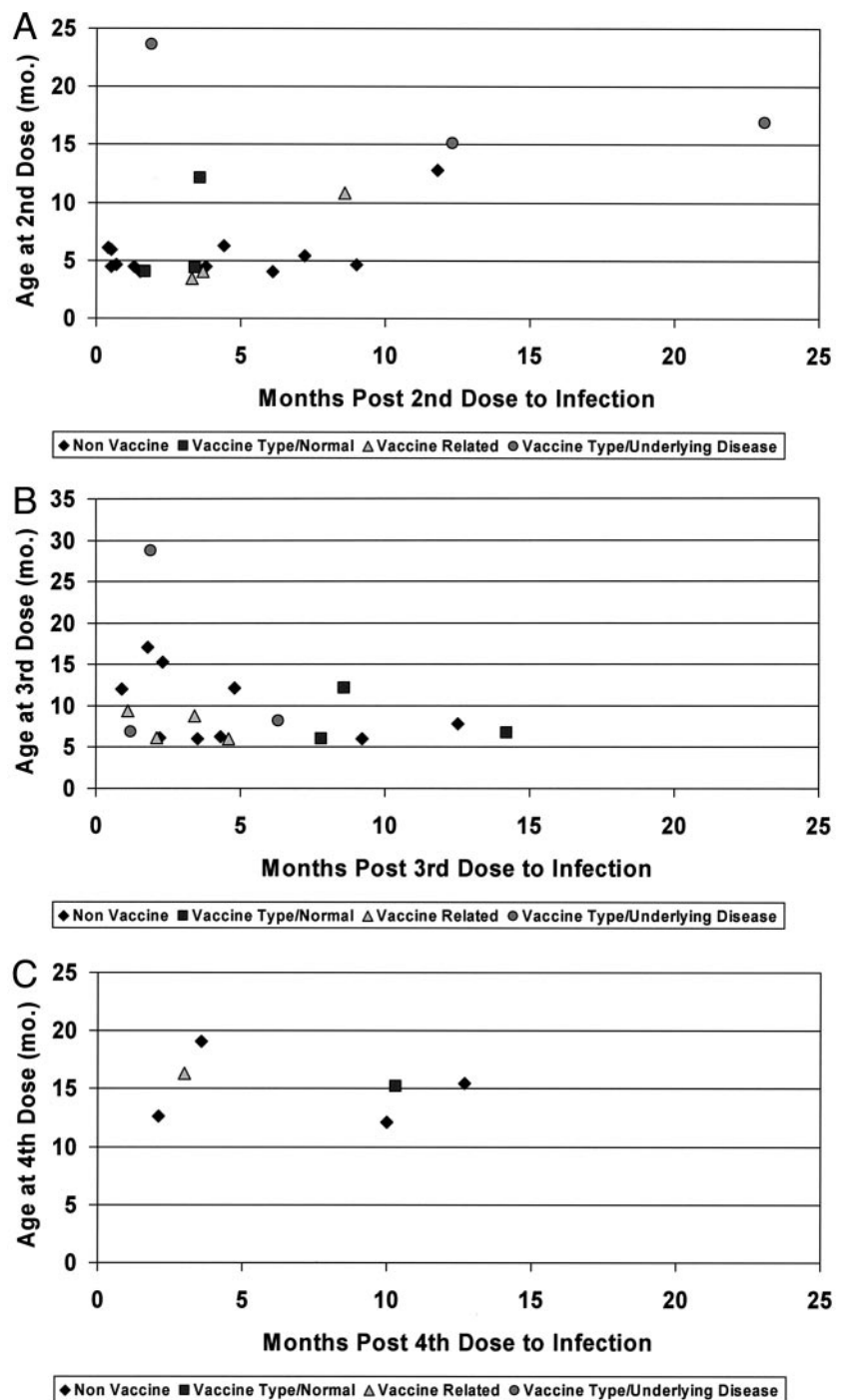
6 days after the third dose. The most common sites of infection were bacteremia ( $n = 27$ ), meningitis ( $n = 6$ ), and pneumonia ( $n = 6$ ). Among the 49 invasive isolates, 13 isolates (27%) were among the PCV7 serotypes (19F [6], 6B including 1 with mastoiditis [6], and 23F [1]). An additional 8 isolates were vaccine-related serotypes (19A [5], 6A [2], and 23B [1]). The majority of isolates were non-PCV7 serotypes (15 [7], 33 [5], 7 [2], 10 [2], 11 [2], 38 [2], 1 [1], 3 including 1 with mastoiditis [2], 12 [1], 22 [1], pool G [1], and 2 could not be typed).

The age of the patients at the time of the PCV7 dose after which the invasive infection occurred, the time after the PCV7 dose that the infection occurred, and host and serotype status are shown in Fig 5. Six invasive infections were recognized after 4 doses of the PCV7; only 1 presumably normal child had a vaccine-serotype isolate.

The number of deaths (percentage) of children who died in association with an invasive pneumococcal infection had a range from 5 to 8 (1.2%–1.6%) per year, respectively, for the years 1994–1998 but increased to 13 for both 1999 (2.9%) and 2000 (3.3%). Five deaths occurred in both 2001 (2.3%) and 2002 (2.6%).

### DISCUSSION

The number of invasive infections caused by *S pneumoniae* seen at 8 children's hospitals in the United States has declined by 66% for children <24 months of age within 2 years after recommendations for routine administration of the PCV7 to infants and



**Fig 5.** Invasive infections occurring in children after 2 (A), 3 (B), or 4 (C) doses of the PCV7: age in months of the patient at the time of the PCV7 dose versus the time interval between the PCV7 dose and development of invasive infection. Vaccine or nonvaccine serotype of the isolate and host status are depicted. (The second and third episodes in the child with HIV infection are not included.)

children. If only the serogroups contained in the PCV7 are considered, an almost 80% reduction was noted in this age group. Our findings extend those of Whitney et al,<sup>5</sup> who reported that, among the population included in the ABC network of the CDC, the rate of invasive pneumococcal infections for children <2 years old declined by 69% in 2001, compared with prevaccine rates; the decline for infection caused by serotypes included in the vaccine was 78%. In a separate analysis from the Children's Hospital of Pittsburgh, for children 3 to 36 months old, the number of invasive pneumococcal infections decreased from 45 to 57 per 100 000 for the years 1997–2000 to 9 per 100 000 in 2002.<sup>8</sup> Hsu et al<sup>9</sup> have been

performing surveillance of invasive pneumococcal infections throughout Massachusetts and found a 69% decline in invasive pneumococcal disease for children <5 years old for the period of October 1, 2001 through April 19, 2002, when compared with historical data. Thus, in many areas of the United States, substantial reductions in invasive pneumococcal infections have occurred despite the shortage of PCV7 beginning in the fall of 2001–2002, which may have modified the reduction in cases.

The greatest percentage decline occurred for bacteremia, followed by meningitis and pneumonia. In the CDC study, the rate of pneumococcal meningitis was reduced 59% in 2001 (similar to the 56% reduc-

tion we found in 2002). Complicated pneumococcal pneumonia in older children frequently is caused by isolates of *S pneumoniae* with serogroups not contained in the PCV7, especially serotypes 1 and 3.<sup>10</sup> Infection caused by serotypes not contained in the PCV7 occurs in pneumonia more so than for bacteremia alone and meningitis, which may, in part, explain the lower rates of reduction for bacteremic pneumococcal pneumonia compared with the other sites of invasive infection in our study.<sup>10</sup> In the Kaiser Permanente studies of PCV7, the risk of pneumonia with a positive chest radiograph was reduced by 32% in the first year of life and 23% in the first 2 years of life.<sup>11</sup>

Antibiotic resistance occurs most commonly in pneumococcal serotypes that are the most frequent cause of invasive infections in children, and these serotypes are components of the PCV7. It was hypothesized that the PCV7 would lead not only to a reduction in invasive disease but also that the pneumococcal isolates recovered would more likely be susceptible to antibiotics. The proportion of pneumococcal isolates from systemic infections that were nonsusceptible to penicillin increased steadily each year of our study since it was initiated in September 1993. After the introduction of the PCV7, the proportion of nonsusceptible isolates reached a plateau in 2001. In 2002, there was a significant reduction in the proportion of penicillin-nonsusceptible strains, comprised almost entirely of those resistant to penicillin. In addition, the proportion of isolates nonsusceptible to ceftriaxone using the 2003 National Committee for Clinical Laboratory Standards breakpoint criteria reached a high of 6% in 2001 but decreased to 3% in 2002. Although we do not know the overall use of antibiotics among the children in the communities from which our patients are derived has changed, the proportion of children receiving an antibiotic in the month before the systemic pneumococcal infection was no different in 2001 or 2002 compared with the previous 7 years. This suggests that the decline in antibiotic resistance is related less to any possible decrease in antibiotic use than to the decrease in invasive disease due to the antibiotic-resistant serotypes attributable to use of PCV7. In contrast, the proportion of nonvaccine-serotype isolates not susceptible to penicillin increased slightly in 2001 and 2002 compared with 2000. The number of isolates is relatively low, and continued surveillance will be important to determine whether penicillin resistance will increase among the nonvaccine-serotype isolates that have been generally susceptible to penicillin.

The estimated rate of invasive disease for each vaccine serotype decreased from 63% to 83% (78% overall) for children <2 years old in the CDC ABC study.<sup>5</sup> For all vaccine-related serotypes of *S pneumoniae*, the estimated decline was 50%. In our study, only the serogroup of the isolate was determined. For the serogroups in the vaccine, the decline for 2002 was between 31% for serogroup 19 (as the low) and 89% for serogroup 14 for all age groups and 77% overall for the vaccine serogroups among the chil-

dren up to 24 months of age. The CDC study found the rate of disease due to nonvaccine serotypes in 2001 had increased 27% over baseline for children <2 years old, although this was not a significant change. We found a 37% increase for nonvaccine serogroups in 2002 when compared with the years 1994–2000, but the number of isolates in this group remained relatively low: 67 isolates for 8 children's hospitals in 2002.

Several studies have found an increase in nasopharyngeal colonization by nonvaccine or replacement serotypes of *S pneumoniae* among children who received a conjugate pneumococcal vaccine.<sup>12–15</sup> In the randomized study of the efficacy of PCV7 for acute otitis media in Finland, episodes of acute otitis media caused by nonvaccine serotypes increased 33% for children receiving PCV7 versus placebo.<sup>16</sup> The nonvaccine serogroups with the greatest increase were 11, 33, 35, and 38. We found increases in the number of isolates for serogroups 15 and 33 in 2002, compared with the prevaccine years; these serogroups also were relatively common causes of invasive disease among children who received at least 2 doses of PCV7. Serogroups 15 and 33 may be emerging as replacement serotypes/serogroups, but the absolute numbers of isolates for these serotypes are quite low.

Among the 8 children's hospitals, 47 children were identified as having an invasive pneumococcal infection after receiving at least 2 doses of PCV7. Thirteen episodes were caused by vaccine serotypes (19F and 6B caused 6 each); 7 occurred in children without known underlying conditions predisposing them to systemic pneumococcal disease. Twenty-eight episodes were caused by nonvaccine-serotype isolates, and 8 episodes were caused by vaccine-related serotype isolates. Serotypes 15, 19A, and 33 were the most common nonvaccine serotypes and accounted for almost half of nonvaccine isolates recovered from vaccinated patients. Hsu et al<sup>17</sup> conducted surveillance of breakthrough invasive pneumococcal disease in Massachusetts from October 1, 2001 through September 30, 2002. They found 13 children with vaccine failure defined as an isolate with a vaccine serotype (serogroups 6 and 19 responsible for 11) in a child who completed the primary series or who was at least 1 year old and appropriately immunized. Disease caused by nonvaccine serotypes (serogroups 3 and 7 accounted for 11) was identified in another 28 children. Decreased immunoglobulin G<sub>4</sub> levels were found in 9 of 21 children undergoing an immune work-up. Physicians caring for otherwise healthy children who develop invasive pneumococcal infection after at least 3 doses of PCV7 or who have received a dose of PCV7 after 15 months of age should make every effort to determine the serotype of the invasive isolate. If the isolate is a vaccine serotype, an immune evaluation should be undertaken. Additional studies of children who develop invasive pneumococcal infection despite receiving the recommended doses are necessary to determine the appropriate evaluation of such children.

## CONCLUSIONS

The number of invasive cases of pneumococcal infection among 8 children's hospitals declined in 2002 by 66% for children <2 years old, when compared with the years 1994–2000. The proportion of isolates resistant to penicillin has decreased by almost 50%, the first time a decrease in resistance has been noted since surveillance began in September 1993. Serotype replacement with serogroup-15 and -33 isolates may be occurring. PCV7 has been successful in preventing invasive pneumococcal disease in children and has resulted in the added benefit of a decrease in penicillin resistance among invasive pneumococcal isolates despite the suboptimal availability of the vaccine. Continued surveillance of pneumococcal disease is critical to detect additional evidence of serotype replacement as well as to assess antibiotic susceptibility of the isolates, especially among nonvaccine serotypes.

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## UNTREATED CONTROLS

“A very important surgeon delivered a talk on the large number of successful procedures for vascular reconstruction. At the end of the lecture, a young student at the back of the room timidly asked, ‘Do you have any controls?’ The great man hit the podium and said, ‘Do you mean, “Did I not operate on half the patients?”’ . . . The hall grew very quiet and the voice at the back of the room very hesitantly replied, ‘Yes, that’s what I had in mind.’ The surgeon’s fist really came down as he thundered, ‘Of course not, that would have doomed half of them to their death!’ . . . The room was then quiet, and one could scarcely hear the small voice ask, ‘Which half?’”

Earl Peacock, quoted in: Gordis L. *Epidemiology*. Saunders; 1996

Submitted by Student

**Decrease of Invasive Pneumococcal Infections in Children Among 8 Children's Hospitals in the United States After the Introduction of the 7-Valent Pneumococcal Conjugate Vaccine**

Sheldon L. Kaplan, Edward O Mason, Jr, Ellen R. Wald, Gordon E. Schutze, John S. Bradley, Tina Q. Tan, Jill A. Hoffman, Laurence B. Givner, Ram Yogev and William J. Barson

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