

## ORIGINAL ARTICLE

# Effect of Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis

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## ABSTRACT

**BACKGROUND**

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Invasive pneumococcal disease declined among children and adults after the introduction of the pediatric heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, but its effect on pneumococcal meningitis is unclear.

**METHODS**

We examined trends in pneumococcal meningitis from 1998 through 2005 using active, population-based surveillance data from eight sites in the United States. Isolates were grouped into PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV7-related serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B), and non-PCV7 serotypes (all others). Changes in the incidence of pneumococcal meningitis were assessed against baseline values from 1998–1999.

**RESULTS**

We identified 1379 cases of pneumococcal meningitis. The incidence declined from 1.13 cases to 0.79 case per 100,000 persons between 1998–1999 and 2004–2005 (a 30.1% decline,  $P<0.001$ ). Among persons younger than 2 years of age and those 65 years of age or older, the incidence decreased during the study period by 64.0% and 54.0%, respectively ( $P<0.001$  for both groups). Rates of PCV7-serotype meningitis declined from 0.66 case to 0.18 case (a 73.3% decline,  $P<0.001$ ) among patients of all ages. Although rates of PCV7-related-serotype disease decreased by 32.1% ( $P=0.08$ ), rates of non-PCV7-serotype disease increased from 0.32 to 0.51 (an increase of 60.5%,  $P<0.001$ ). The percentages of cases from non-PCV7 serotypes 19A, 22F, and 35B each increased significantly during the study period. On average, 27.8% of isolates were nonsusceptible to penicillin, but fewer isolates were nonsusceptible to chloramphenicol (5.7%), meropenem (16.6%), and cefotaxime (11.8%). The proportion of penicillin-nonsusceptible isolates decreased between 1998 and 2003 (from 32.0% to 19.4%,  $P=0.01$ ) but increased between 2003 and 2005 (from 19.4% to 30.1%,  $P=0.03$ ).

**CONCLUSIONS**

Rates of pneumococcal meningitis have decreased among children and adults since PCV7 was introduced. Although the overall effect of the vaccine remains substantial, a recent increase in meningitis caused by non-PCV7 serotypes, including strains nonsusceptible to antibiotics, is a concern.

**S**TREPTOCOCCUS PNEUMONIAE IS THE MOST COMMON cause of bacterial meningitis in the United States and many countries worldwide.<sup>1-4</sup> Despite effective antimicrobial therapy, pneumococcal meningitis remains highly lethal and has substantial long-term sequelae.<sup>4,5</sup>

The pediatric heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth) has had a major effect on the incidence of pneumococcal disease in the United States.<sup>6</sup> PCV7 not only protects immunized children from pneumococcal disease<sup>7-11</sup> but also provides protection to non-immunized children and adults through herd immunity, resulting from reduced transmission of *S. pneumoniae* from immunized children.<sup>8,10,12,13</sup> Licensed in 2000, PCV7 is recommended by the Advisory Committee on Immunization Practices for all children in the United States 2 to 23 months of age and for children 24 to 59 months of age who are at increased risk for pneumococcal disease.<sup>14,15</sup> In 2006, coverage by PCV7 among children 19 to 35 months of age was estimated to exceed 68% for the full vaccine series of four or more doses and to exceed 87% with three or more doses.<sup>16</sup>

A potential effect of decreasing vaccine serotypes in circulation is the emergence of non-PCV7 pneumococcal serotypes. However, in persons not infected with the human immunodeficiency virus (HIV), increases in the incidence of invasive pneumococcal disease from non-PCV7 serotypes have been minor relative to reductions in PCV7-serotype disease.<sup>9,17</sup> The absence of substantial increases in rates of non-PCV7-serotype invasive disease, despite increased nasopharyngeal colonization with non-PCV7 serotypes, is presumably due to reduced invasive potential of some non-PCV7 serotypes.<sup>18</sup> In contrast, increases in non-PCV7-serotype invasive disease among adults with HIV infection is substantial, probably reflecting the increased vulnerability of this immunocompromised population to non-PCV7 serotypes.<sup>13</sup>

Active Bacterial Core surveillance, a component of the Centers for Disease Control and Prevention (CDC) Emerging Infections Programs Network, has conducted continuous, active, laboratory-based and population-based surveillance for invasive pneumococcal disease in eight states.<sup>19</sup> In a previous analysis of Active Bacterial Core surveillance data on invasive pneumococcal disease for older adults, the incidence of meningitis in persons 50 years of age or older did not change significantly between 1998-1999 and 2002-2003, whereas there

was a 57% reduction in the incidence of pneumococcal bacteremia without a known primary focus of infection.<sup>12</sup> In separate studies of pneumococcal disease in infants and children, both the Active Bacterial Core surveillance network and the U.S. Pediatric Multicenter Pneumococcal Surveillance Study Group found substantial declines in the incidence of pneumococcal meningitis.<sup>8,20</sup> Specifically, Whitney et al.<sup>8</sup> found a 56% reduction in the incidence of pneumococcal meningitis in children under 24 months of age in 2001 as compared with the prelicensure period. Kaplan et al.<sup>20</sup> found that the incidence of meningitis cases declined by 59% between 1994-2000 and 2002. To further investigate the effect of PCV7, we examined trends in pneumococcal meningitis among children and adults from 1998 through 2005.

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## METHODS

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### CASE ASCERTAINMENT AND CASE DEFINITIONS

Active Bacterial Core surveillance conducts continuous active surveillance for invasive pneumococcal disease through regular contact with clinical microbiology laboratories at each site.<sup>19,21</sup> Active Bacterial Core surveillance personnel routinely contact hospital and reference laboratories for notification about cases and isolates. Periodic audits of laboratory records ensure complete case ascertainment. Standardized case-report forms that include information on demographic characteristics, clinical syndromes, and outcomes of illness are completed for each identified patient. Pneumococcal isolates are collected and sent to reference laboratories for serotyping and susceptibility testing.

The case definition for pneumococcal meningitis was isolation of *S. pneumoniae* from cerebrospinal fluid or the clinical diagnosis of meningitis with pneumococcus isolated from another normally sterile site, usually blood. Only persons residing in Active Bacterial Core surveillance catchment areas were included.

### STUDY PERIOD AND POPULATION

We included patients with pneumococcal meningitis with culture dates from January 1, 1998, through December 31, 2005, occurring in eight Active Bacterial Core surveillance sites: California (San Francisco County), Connecticut (the entire state), Georgia (the 20-county Atlanta area), Maryland (the 6-county Baltimore metropolitan area), Minnesota (a 7-county area), New York (the 7-county Rochester area), Oregon (the 3-county Portland

area), and Tennessee (5 urban counties). In 2005, these surveillance areas represented an estimated 18,484,432 persons.<sup>22</sup> Until 2000, surveillance in Georgia did not include routine prospective collection of data on underlying medical conditions, including HIV and the acquired immunodeficiency syndrome (AIDS). Therefore, we excluded data from Georgia in 1998 and 1999 for analyses of underlying conditions. In addition, data from New York were excluded from analyses involving stratification on the basis of HIV–AIDS status, since HIV–AIDS status was not ascertained at that site in any year.

#### SEROTYPING AND ANTIMICROBIAL-SUSCEPTIBILITY TESTING

Isolates underwent serotyping with the use of the quellung reaction at the CDC or the Minnesota Public Health Laboratory.

#### Susceptibility Testing

Isolates underwent antimicrobial susceptibility testing according to the Clinical and Laboratory Standards Institute broth microdilution method.<sup>23</sup>

Testing was performed at the CDC, Minnesota Public Health Laboratory, or University of Texas Health Science Center at San Antonio. Isolates were classified as susceptible, of intermediate susceptibility, or resistant on the basis of 2007 breakpoints for minimal inhibitory concentrations, including those specifically relevant to meningitis (penicillin and cefotaxime), recommended by the Clinical and Laboratory Standards Institute (see the Supplementary Appendix, available with the full text of this article at NEJM.org).<sup>23</sup> Isolates determined to have intermediate susceptibility or to be resistant were considered nonsusceptible. Antibiotic-susceptibility testing was performed for penicillin, meropenem, rifampin, levofloxacin, cefotaxime, chloramphenicol, and vancomycin.<sup>24</sup>

#### Serotype Groupings

Approximately 90 serotypes of *S. pneumoniae* have been identified on the basis of serologic properties of their polysaccharide capsule. We classified these pneumococci into one of three serotype groups. PCV7 serotypes were those that matched serotypes included in the vaccine (serotypes 4, 6B, 9V, 14,

**Table 1.** Characteristics of the Study Patients with 1379 Cases of Pneumococcal Meningitis at Eight Surveillance Sites, 1998–2005.\*

Characteristic	Cases in Children (N=369)	Cases in Adults (N=1010)
Age		
Median	15 mo	53 yr
Range	2 days–17 yr	18 yr–93 yr
	<i>no. of cases (%)</i>	
Male sex	208 (56.4)	522 (51.7)
Race†		
White	198 (53.7)	558 (55.2)
Black	110 (29.8)	318 (31.5)
Other	17 (4.6)	31 (3.1)
Unknown	44 (11.9)	103 (10.2)
Surveillance site‡		
California	7 (1.9)	66 (6.5)
Connecticut	70 (19.0)	187 (18.5)
Georgia	119 (32.2)	219 (21.7)
Maryland	42 (11.4)	190 (18.8)
Minnesota	58 (15.7)	118 (11.7)
New York	14 (3.8)	57 (5.6)
Oregon	26 (7.0)	86 (8.5)
Tennessee	33 (8.9)	87 (8.6)
Death	31 (8.4)	225 (22.3)

**Table 1. (Continued.)**

Characteristic	Cases in Children (N = 369)	Cases in Adults (N = 1010)
Underlying conditions§		
COPD	0	49 (5.3)
Cerebrospinal fluid leakage	4 (1.2)	12 (1.3)
Congestive heart failure	0	52 (5.6)
Organ transplantation	1 (0.3)	8 (0.9)
Diabetes mellitus	0	145 (15.6)
Sickle cell anemia	9 (2.8)	3 (0.3)
Asplenia	2 (0.6)	41 (4.4)
Immunosuppressive therapy	4 (1.2)	52 (5.6)
HIV¶	3 (1.0)	100 (11.4)
Alcohol abuse	0	147 (15.8)
Cirrhosis	1 (0.3)	20 (2.1)
Atherosclerotic cardiovascular disease	0	101 (10.8)
Renal failure or dialysis	0	38 (4.1)
Immunoglobulin deficiency	1 (0.3)	4 (0.4)
Nephrotic syndrome	3 (0.9)	6 (0.6)
Systemic lupus erythematosus	1 (0.3)	14 (1.5)
Cancer	6 (1.9)	110 (11.8)
None	295 (91.0)	382 (41.0)

\* COPD denotes chronic obstructive pulmonary disease, and HIV human immunodeficiency virus.

† Race was self-reported for adults and reported by a parent or guardian for children.

‡ Surveillance was conducted through the Active Bacterial Core surveillance group of the Centers for Disease Control and Prevention. Sites included California (San Francisco County), Connecticut (the entire state), Georgia (the 20-county Atlanta area), Maryland (the 6-county Baltimore metropolitan area), Minnesota (7 counties), New York (the 7-county Rochester area), Oregon (the 3-county Portland area), and Tennessee (5 urban counties).

§ Patients could have more than one underlying condition. Reports were available regarding 1259 cases; data were excluded from Georgia in 1998 and 1999 and for the 15 children and 22 adults for whom underlying conditions were unknown.

¶ Reports of HIV were available for 308 children and 877 adults, for a total of 1188 of the 1259 patients; data were excluded for the 16 children and 55 adults in New York, since HIV–AIDS status was not ascertained at that site in any year.

18C, 19F, and 23F). PCV7-related serotypes were those within the same serogroup as the PCV7 serotypes that were either assumed or known to be cross-reactive with PCV7 serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B). These designations were the same as those used in previous studies,<sup>25,26</sup> with one exception. Serotype 19A was excluded from the group of PCV7-related serotypes because of evidence of lack of effectiveness of PCV7 against this serotype,<sup>26</sup> as well as data indicating that PCV7 elicits nonfunctional antibodies in response to the 19A polysaccharide.<sup>27</sup> All other serotypes, including 19A, were designated as non-PCV7 serotypes. All group classifications were made before data analysis began, and no post hoc changes in classification were made.

For 110 of the 1379 cases (8.0%) for which serotyping results were missing, serotypes were as-

signed, for purposes of incidence-rate calculations, on the basis of the known serotype distributions for a given year, age group, and race. If there were no known serotype distributions available for a particular age and race, then the missing serotypes were assigned on the basis of age group alone.

#### STATISTICAL ANALYSIS

We used SAS (version 9.1, SAS Institute) for data analysis. Rates of pneumococcal meningitis, expressed as the number of cases per 100,000 persons, were calculated with the use of age-specific data from the U.S. Census Bureau (for 1998–2000) or age-specific, postcensus population estimates (for 2001–2005).<sup>28</sup>

Because PCV7 was licensed in 2000, changes in the incidence of pneumococcal meningitis between 2-year periods were assessed by comparing

**Table 2. Mean Annual Incidence of Pneumococcal Meningitis at Eight Surveillance Sites, According to Age Group, Serotype Group, and Years (1998–2005).\***

Serotype and Age	1998–1999			2000–2001			2002–2003			2004–2005			2004–2005 vs. 1998–1999	
	No. of Cases	Cases per 100,000 Persons	P Value	No. of Cases	Cases per 100,000 Persons	P Value	No. of Cases	Cases per 100,000 Persons	P Value	No. of Cases	Cases per 100,000 Persons	P Value	Relative Difference in Incidence %	Absolute Difference in Incidence percentage points
<b>All serotypes</b>														
All ages	374	1.13	0.42	372	1.06	0.03	344	0.96	0.03	289	0.79	<0.001	-30.1	-0.34
Age group														
<2 yr	93	10.16	0.02	66	6.86	<0.001	33	3.30	<0.001	37	3.66	<0.001	-64.0	-6.50
2–4 yr	13	0.95	0.13	23	1.63	0.01	3	0.21	0.01	13	0.87	0.85	-8.4	-0.08
5–17 yr	16	0.27	0.28	25	0.39	0.13	28	0.43	0.13	19	0.29	0.87	9.5	0.03
18–39 yr	62	0.56	0.41	55	0.47	0.52	57	0.49	0.52	46	0.40	0.10	-28.1	-0.16
40–64 yr	118	1.18	0.49	140	1.29	0.33	154	1.33	0.33	139	1.14	0.80	-3.3	0.04
≥65 yr	72	1.90	0.44	63	1.64	0.67	69	1.77	0.67	35	0.87	<0.001	-54.0	-1.03
<b>PCV7 serotypes</b>														
All ages	220	0.66	0.27	208	0.59	<0.001	109	0.30	<0.001	65	0.18	<0.001	-73.3	-0.49
Age group														
<2 yr	75	8.20	0.002	44	4.57	0.002	10	1.00	<0.001	6	0.59	<0.001	-92.8	-7.60
2–4 yr	12	0.88	0.85	14	0.99	0.001	1	0.07	0.001	2	0.13	0.01	-84.7	-0.74
5–17 yr	6	0.10	0.12	14	0.22	0.34	11	0.17	0.34	6	0.09	1.00	-7.8	0.01
18–39 yr	34	0.30	0.06	21	0.18	0.04	19	0.16	0.04	11	0.10	0.001	-68.7	-0.21
40–64 yr	62	0.62	0.19	85	0.78	0.03	47	0.41	0.03	29	0.24	<0.001	-61.6	-0.38
≥65 yr	31	0.82	0.90	30	0.78	0.17	21	0.54	0.17	11	0.27	0.001	-66.5	-0.54
<b>PCV7-related serotypes</b>														
All ages	48	0.14	1.00	50	0.14	0.30	64	0.18	0.30	36	0.10	0.08	-32.1	-0.05
Age group														
<2 yr	11	1.20	0.35	7	0.73	0.13	5	0.50	0.13	2	0.20	0.01	-83.5	-1.00
2–4 yr	1	0.07	0.22	5	0.35	1.00	1	0.07	1.00	0	0.00	0.48	-100.0	-0.07
5–17 yr	0	0.00	0.03	6	0.09	0.50	2	0.03	0.50	2	0.03	0.50	—	0.03
18–39 yr	12	0.11	0.84	11	0.09	0.52	9	0.08	0.52	6	0.05	0.16	-51.6	-0.06
40–64 yr	13	0.13	0.55	11	0.10	0.03	31	0.27	0.03	22	0.18	0.40	39.0	0.05
≥65 yr	11	0.29	0.83	10	0.26	0.44	16	0.41	0.44	4	0.10	0.07	-65.6	-0.19

Non-PCV7 serotypes		106	0.32	114	0.32	0.95	171	0.48	0.001	188	0.51	<0.001	60.5	0.19
All ages														
Age group														
<2 yr	7	0.77	15	1.56	0.14	18	1.80	0.07	0.07	29	2.87	0.001	275.3	2.11
2–4 yr	0	0.00	4	0.28	0.13	1	0.07	1.00	1.00	11	0.74	0.001	—	0.74
5–17 yr	10	0.17	5	0.08	0.20	15	0.23	0.55	0.55	11	0.17	1.00	1.4	0.00
18–39 yr	16	0.14	23	0.20	0.34	29	0.25	0.07	0.07	29	0.25	0.07	75.6	0.11
40–64 yr	43	0.43	44	0.40	0.83	76	0.66	0.03	0.03	88	0.72	0.005	68.1	0.29
≥65 yr	30	0.79	23	0.60	0.34	32	0.82	0.90	0.90	20	0.50	0.12	–37.0	–0.29

\* The eight Active Bacterial Core surveillance sites were in California, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee. Serotypes of the heptavalent pneumococcal conjugate vaccine (PCV7) were 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV7-related serotypes were 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B. Non-PCV7 serotypes included 3, 7F, 10A, 11A, 12F, 15A, 15B/C, 16F, 19A, 22F, 33F, 35B, 35F, and 38. All P values are two-sided and were calculated for exact comparisons of the 2-year interval with the baseline interval (1998–1999).

the rates from periods after 1998–1999 with the rate in 1998–1999 as relative risks. These risks are reported as the percent changes  $([\text{relative risk} - 1] \times 100)$  in the rates between the two periods, together with the associated exact P values. Percentages were compared with the use of Fisher's exact test, and trends were examined with the use of the Cochran–Armitage trend test. All subgroup analyses were prespecified. Two-sided P values of less than 0.05 were considered to indicate statistical significance and were not adjusted for multiple testing. Underlying conditions included in the analysis are listed in the Supplementary Appendix.

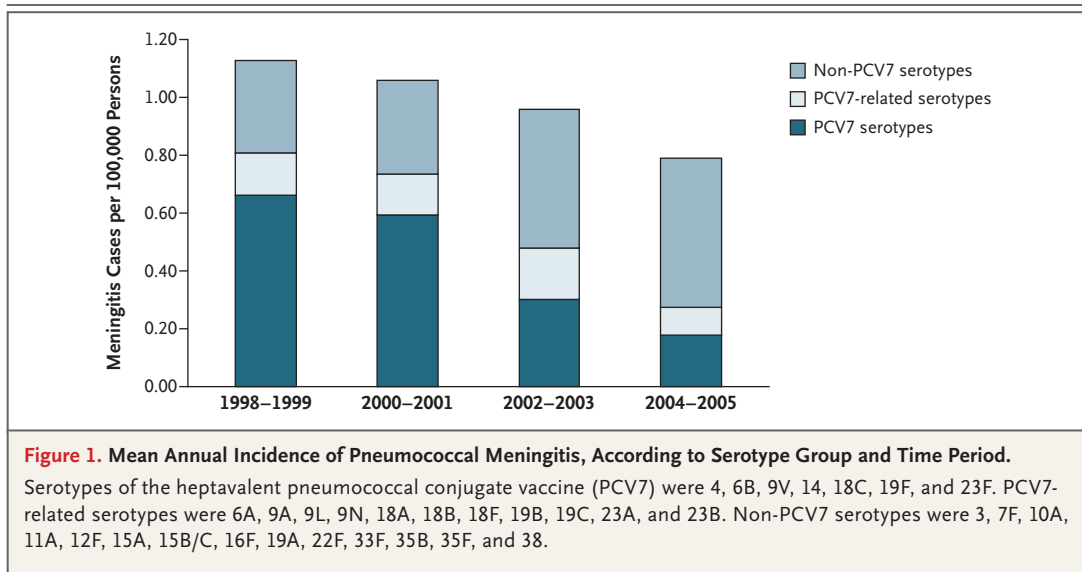
## RESULTS

We identified 1379 cases of pneumococcal meningitis during the study period (Table 1). The ages of the patients ranged from 2 days to 93 years. The median age of the children was 15 months and of the adults 53 years. The case fatality rate was 8.4% among children and 22.3% among adults.

The adults with pneumococcal meningitis who were HIV-positive and those who were HIV-negative differed significantly with respect to age (median, 43 vs. 54 years;  $P < 0.001$ ), sex (male, 69.0% vs. 49.4%;  $P < 0.001$ ), and race (black, 71.0% vs. 26.7%;  $P < 0.001$ ). Case fatality rates were similar for the HIV-positive and HIV-negative adults (23.0% and 20.7%,  $P = 0.83$ ). Serotype groupings of isolates did not differ significantly according to HIV status of the patient.

### INCIDENCE OF PNEUMOCOCCAL MENINGITIS

Overall, rates of pneumococcal meningitis declined by 30.1% between the 1998–1999 baseline period and 2004–2005, from 1.13 cases to 0.79 case per 100,000 persons ( $P < 0.001$ ) (Table 2). Among patients younger than 2 years of age, rates of meningitis decreased by 64.0% between 1998–1999 and 2004–2005, while among those 65 years of age or older, rates decreased by 54.0% ( $P < 0.001$  for both comparisons). For those 2 to 4 years of age and 5 to 17 years of age, there were too few cases to make firm conclusions about trends. Among patients 18 to 39 years of age, there was a decline in the rate of meningitis by 28.1% between 2004–2005 and 1998–1999 ( $P = 0.10$ ). In the analysis of trends in the percentage of case patients with underlying illness according to age and infective serotype (PCV7, PCV7-related, or non-PCV7), no significant trends were found.



#### PCV7-Serotype Disease

Among all age groups, the incidence of pneumococcal meningitis caused by PCV7 serotypes declined from 0.66 case per 100,000 persons in 1998–1999 to 0.18 case per 100,000 in 2004–2005 (a decline of 73.3%,  $P < 0.001$ ) (Fig. 1 and Table 2). In five of the six age groups examined, the incidence of PCV7-serotype meningitis declined significantly between 1998–1999 and 2004–2005 (Table 2), with the percent decreases ranging from 92.8% for the target population of the vaccine (children <2 years of age) to 61.6% among persons who were 40 to 64 years of age. For patients 5 to 17 years of age, there were too few cases of PCV7-serotype disease to make meaningful conclusions.

#### PCV7-Related-Serotype Disease

Rates of PCV7-related-serotype disease declined by 32.1% between 1998–1999 and 2004–2005, from 0.14 case to 0.10 case per 100,000 persons for all age groups ( $P = 0.08$ ). In addition to the significant 83.5% decline in the rate of PCV7-related cases within the vaccine's target population (children <2 years of age), among persons who were 65 years of age or older, there was a nonsignificant reduction in the rate of PCV7-related cases (a decline of 65.6%,  $P = 0.07$ ).

#### Non-PCV7-Serotype Disease

For all age groups, rates of non-PCV7-serotype disease increased significantly from 0.32 case to 0.51 case per 100,000 persons from 1998–1999 to 2004–2005 (an increase of 60.5%,  $P < 0.001$ ). Al-

though this increase was driven mostly by a relative increase of 275% among children younger than 2 years of age ( $P = 0.001$ ), significant increases in the rate of non-PCV7-serotype meningitis were also found among children 2 to 4 years of age ( $P = 0.001$ ) and adults 40 to 64 years (an increase of 68.1%,  $P = 0.005$ ). A nonsignificant increase of 75.6% in the rate of non-PCV7 meningitis was observed among adults 18 to 39 years of age ( $P = 0.07$ ).

To explore the potential role of HIV in the increase in the incidence of meningitis from non-PCV7 serotypes among adults, we conducted a separate analysis of the incidence of non-PCV7-serotype disease, excluding all 100 patients who were known to be HIV-positive. In the HIV-negative subgroup, from 1998–1999 to 2004–2005, the incidence of non-PCV7-serotype disease increased from 0.14 case to 0.24 case per 100,000 persons for adults 18 to 39 years of age (an increase of 67.1%,  $P = 0.15$ ) and from 0.41 case to 0.54 case per 100,000 persons for those 40 to 64 years of age (an increase of 31.9%,  $P = 0.22$ ). No patients who were 65 years or older were known to be HIV-positive.

We also examined trends in the incidence of pneumococcal meningitis caused by specific non-PCV7 strains. From 1998–1999 to 2004–2005, the rate of disease from serotype 19A increased from 0.02 case to 0.08 case per 100,000 persons ( $P < 0.001$ ), and the rate of disease from the 22F serotype increased from 0.03 to 0.08 per 100,000 persons ( $P = 0.003$ ). Rates of disease from serotypes 11A

**Table 3. Distribution of 1239 Cases of Pneumococcal Meningitis, 1998–2005, According to Serotype Grouping.\***

Serotype	1998–1999 (N=338)	2000–2001 (N=333)	2002–2003 (N=316)	2004–2005 (N=252)	P Value 2004–2005 vs. 1998–1999
<i>no. of cases (%)</i>					
PCV7 serotypes					
All	199 (58.9)	185 (55.6)	105 (33.2)	58 (23.0)	<0.001
4	23 (6.8)	28 (8.4)	15 (4.7)	13 (5.2)	0.49
6B	25 (7.4)	32 (9.6)	14 (4.4)	10 (4.0)	0.11
9V	20 (5.9)	9 (2.7)	9 (2.8)	4 (1.6)	0.01
14	43 (12.7)	35 (10.5)	11 (3.5)	2 (0.8)	<0.001
18C	18 (5.3)	18 (5.4)	19 (6.0)	9 (3.6)	0.43
19F	32 (9.5)	30 (9.0)	14 (4.4)	17 (6.7)	0.29
23F	38 (11.2)	33 (9.9)	23 (7.3)	3 (1.2)	<0.001
PCV7-related serotypes					
All	43 (12.7)	45 (13.5)	57 (18.0)	30 (11.9)	0.80
6A	23 (6.8)	32 (9.6)	32 (10.1)	14 (5.6)	0.61
9N	6 (1.8)	3 (0.9)	7 (2.2)	5 (2.0)	1.00
23A	6 (1.8)	2 (0.6)	9 (2.8)	7 (2.8)	0.41
Other	8 (2.4)	8 (2.4)	9 (2.8)	4 (1.6)	0.57
Non-PCV7 serotypes					
All	96 (28.4)	103 (30.9)	154 (48.7)	164 (65.1)	<0.001
3	15 (4.4)	21 (6.3)	19 (6.0)	15 (6.0)	0.45
7F	7 (2.1)	3 (0.9)	6 (1.9)	11 (4.4)	0.15
10A	6 (1.8)	7 (2.1)	3 (0.9)	6 (2.4)	0.77
11A	4 (1.2)	4 (1.2)	15 (4.7)	11 (4.4)	0.02
12F	14 (4.1)	10 (3.0)	9 (2.8)	4 (1.6)	0.09
15A	3 (0.9)	1 (0.3)	5 (1.6)	7 (2.8)	0.11
15B/C	14 (4.1)	13 (3.9)	12 (3.8)	17 (6.7)	0.19
16F	1 (0.3)	6 (1.8)	5 (1.6)	6 (2.4)	0.046
19A	5 (1.5)	7 (2.1)	16 (5.1)	28 (11.1)	<0.001
22F	8 (2.4)	5 (1.5)	20 (6.3)	26 (10.3)	<0.001
33F	1 (0.3)	5 (1.5)	6 (1.9)	5 (2.0)	0.09
35B	3 (0.9)	5 (1.5)	6 (1.9)	9 (3.6)	0.04
35F	4 (1.2)	4 (1.2)	6 (1.9)	2 (0.8)	1.00
38	2 (0.6)	4 (1.2)	6 (1.9)	4 (1.6)	0.41
Other	9 (2.7)	8 (2.4)	20 (6.3)	13 (5.2)	0.13

\* For 1998–2005, 140 isolates lacking serotype or susceptibility data were excluded. P values are two-sided and were calculated with the use of Fisher's exact test.

and 35B at least doubled, but these changes were not significant.

#### CHANGES IN PERCENTAGES OF CASES CAUSED BY SPECIFIC SEROTYPES

The proportion of total cases caused by non-PCV7 serotypes 11A, 16F, 19A, 22F, and 35B increased

significantly between 1998–1999 and 2004–2005 (Table 3). The increases associated with serotypes 19A and 22F were particularly notable: serotype 19A represented 1.5% (5 cases) of the total number in 1998–1999, but 11.1% (28 cases) in 2004–2005 ( $P<0.001$ ). Likewise, the percentage of the total number of cases that were due to serotype

22F increased from 2.4% (8 cases) in 1998–1999 to 10.3% (26 cases) in 2004–2005 ( $P<0.001$ ).

#### ESTIMATED COVERAGE BY VACCINES IN DEVELOPMENT

Currently, both 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13, respectively) are in phase 3 clinical trials.<sup>29,30</sup> PCV10 includes, in addition to the PCV7 serotypes, serotypes 1, 5, and 7F and would have covered 27.4% of cases in 2004–2005. PCV13, which includes the PCV10 types plus serotypes 3, 6A, and 19A, would have covered 50.0% of cases in that year.

#### ANTIBIOTIC SUSCEPTIBILITY

The incidence of meningitis caused by isolates that were nonsusceptible to penicillin, meropenem, or cefotaxime decreased significantly between 1998–1999 and 2004–2005 (Table 4). Trends in disease caused by isolates nonsusceptible to chloramphenicol were not examined because of the small number of these isolates. Overall, 27.8% of isolates were nonsusceptible to penicillin, 5.7% to chloramphenicol, 16.6% to meropenem, and 11.8% to cefotaxime (Table 1 in the Supplementary Appendix). In 2004–2005, the percentages of isolates that were of intermediate susceptibility and resistant to penicillin were 17.5% and 9.9%, respectively; to chloramphenicol, 0.0% and 4.4%; to meropenem, 4.0% and 7.5%; and to cefotaxime, 6.3% and 2.8%.

All isolates were susceptible to vancomycin, and more than 99.0% of isolates were susceptible to levofloxacin and rifampin. A total of 40.8% of PCV7 isolates and 33.1% of PCV7-related isolates were nonsusceptible to penicillin. Lower percentages of PCV7-serotype isolates were nonsusceptible to chloramphenicol, meropenem, and cefotaxime (8.4%, 28.0%, and 20.3%, respectively). Similarly, the percentage of PCV7-related and non-PCV7 isolates that were nonsusceptible to chloramphenicol, meropenem, or cefotaxime did not exceed 14.9%. Although we found relatively low levels of nonsusceptibility to penicillin among non-PCV7 isolates overall (12.4%), decreased susceptibility was common among isolates of serotypes 15A (62.5%), 19A (60.7%), and 35B (69.6%).

No significant overall trends were found in the percentage of isolates nonsusceptible to penicillin or chloramphenicol (Fig. 2). For penicillin, however, there was a significant decreasing trend from 1998 through 2003 ( $P=0.01$ ). The proportion of penicillin-nonsusceptible isolates in 2005

was significantly higher than that in 2003 ( $P=0.04$ ). Significant declines were found in the percentage of isolates that were nonsusceptible to meropenem and cefotaxime during the study period ( $P<0.001$  and  $P=0.003$ , respectively). For both antibiotics, the proportion of nonsusceptible isolates was higher in 2005 than in 2004 but not significantly so ( $P=0.33$  and  $P=0.51$ , respectively). The percentages of non-PCV7 isolates that were nonsusceptible to penicillin, meropenem, and cefotaxime increased between 1998–1999 and 2004–2005 ( $P<0.001$ ,  $P=0.05$ , and  $P=0.01$ , respectively) (Fig. 1C in the Supplementary Appendix).

#### DISCUSSION

These data show that the overall rates of pneumococcal meningitis decreased substantially from 1998–1999 to 2004–2005. Similar to earlier studies,<sup>8,20</sup> our study revealed a decline of 64% in the incidence of meningitis during the study period among children younger than 2 years of age. We also found that the incidence of both PCV7-serotype disease and PCV7-related-serotype disease decreased significantly, by 73% and 32%, respectively, among all patients. The incidence of PCV7-serotype disease decreased significantly in all but one of the age groups examined, whereas the incidence of disease from PCV7-related serotypes decreased among patients younger than 2 years of age and those 65 years of age or older. Rates of non-PCV7-serotype disease increased significantly, by 61%, during the study period. Although the rise in non-PCV7 disease was primarily driven by an increase in non-PCV7-serotype disease in the vaccine's target population, children younger than 2 years of age, the magnitude of this increase (2.10 cases per 100,000 persons) was small relative to the corresponding decrease in PCV7-serotype disease (7.61 cases per 100,000 persons).

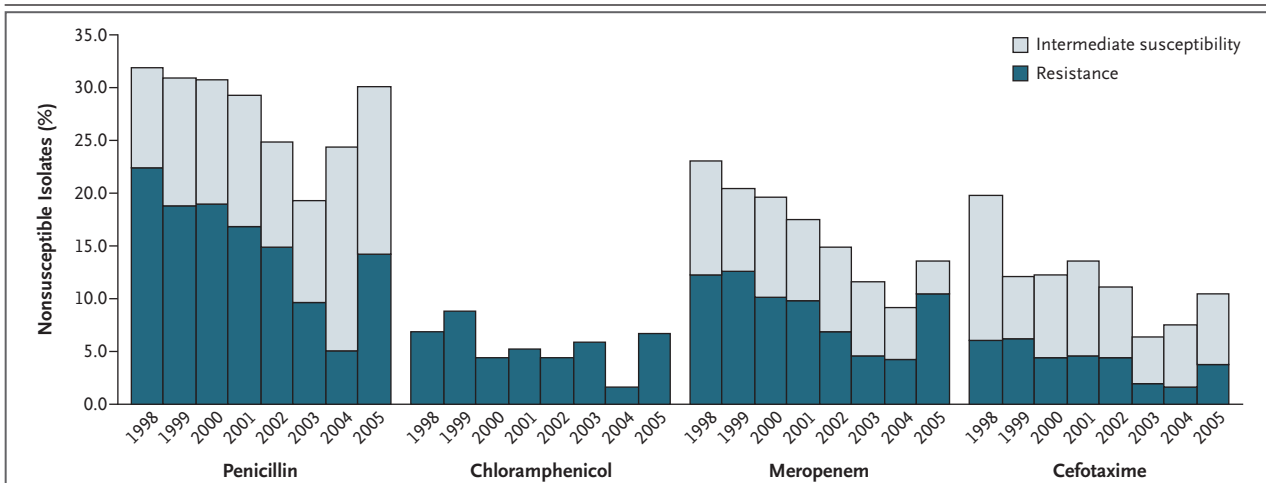
The results of previous analyses of Active Bacterial Core surveillance data indicated that routine vaccination of young children with PCV7 has caused significant declines in the incidence of all invasive pneumococcal disease, not only in the age group targeted but also among older children and adults.<sup>7–10,12</sup> The current study confirms that this effect holds for pneumococcal meningitis, especially for children younger than 2 years of age and adults 65 years of age or older.

Recently, Whitney et al.<sup>26</sup> examined the effectiveness of PCV7 for various pneumococcal sero-

**Table 4. Mean Annual Incidence of Pneumococcal Meningitis at Eight Surveillance Sites, According to Age Group, Antibiotic Susceptibility, and Years (1998–2005).\***

Susceptibility and Age	1998–1999		2000–2001		2002–2003		2004–2005		2004–2005 vs. 1998–1999		
	No. of Cases	Cases per 100,000 Persons	No. of Cases	Cases per 100,000 Persons	No. of Cases	Cases per 100,000 Persons	No. of Cases	Cases per 100,000 Persons	Relative Difference in Incidence %	Absolute Difference in Incidence percentage points	
<b>Penicillin nonsusceptible</b>											
All ages	106	0.32	100	0.28	70	0.19	69	0.19	0.001	-41.1	-0.13
Age group											
<2 yr	36	3.93	22	2.29	8	0.80	14	1.39	0.001	-64.8	-2.55
2–4 yr	6	0.44	12	0.85	1	0.07	2	0.13	0.16	-69.5	-0.31
5–17 yr	2	0.03	6	0.09	4	0.06	5	0.08	0.46	130.5	0.04
18–39 yr	22	0.20	10	0.09	8	0.07	11	0.10	0.05	-51.6	-0.10
40–64 yr	21	0.21	33	0.30	33	0.28	28	0.23	0.78	9.5	0.02
≥65 yr	19	0.50	17	0.44	16	0.41	9	0.22	0.06	-55.2	-0.28
<b>Meropenem nonsusceptible</b>											
All ages	73	0.22	62	0.18	42	0.12	29	0.08	<0.001	-64.0	-0.14
Age group											
<2 yr	29	3.17	15	1.56	5	0.50	5	0.50	<0.001	-84.4	-2.67
2–4 yr	5	0.37	7	0.50	1	0.07	1	0.07	0.11	-81.7	-0.30
5–17 yr	2	0.03	5	0.08	4	0.06	2	0.03	1.00	-7.8	0.00
18–39 yr	12	0.11	5	0.04	4	0.03	4	0.03	0.05	-67.7	-0.07
40–64 yr	14	0.14	19	0.17	21	0.18	15	0.12	0.85	-12.0	0.02
≥65 yr	11	0.29	11	0.29	7	0.18	2	0.05	0.01	-82.8	-0.24
<b>Cefotaxime nonsusceptible</b>											
All ages	52	0.16	43	0.12	28	0.08	23	0.06	<0.001	-60.0	-0.09
Age group											
<2 yr	21	2.30	11	1.14	2	0.20	5	0.50	0.001	-78.4	-1.80
2–4 yr	5	0.37	4	0.28	0	0.00	1	0.07	0.11	-81.7	-0.30
5–17 yr	2	0.03	4	0.06	3	0.05	2	0.03	1.00	-7.8	0.00
18–39 yr	11	0.10	4	0.03	1	0.01	4	0.03	0.07	-64.8	-0.06
40–64 yr	7	0.07	12	0.11	17	0.15	10	0.08	0.81	17.3	0.01
≥65 yr	6	0.16	8	0.21	5	0.13	1	0.02	0.06	-84.2	-0.13

\* The eight Active Bacterial Core surveillance areas were in California, Connecticut, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee. All P values are two-sided and were calculated for exact comparisons of the 2-year interval with the baseline interval (1998–1999). Minimal inhibitory concentration breakpoints for susceptible strains, strains of intermediate susceptibility, and resistant strains were (in micrograms per milliliter): 0.06 or less, 0.12 to 1.00, and 2.00 or more, respectively, for penicillin; 0.25 or less, 0.50, and 1.00 or more for meropenem; and 0.50 or less, 1.00, and 2.00 or more for cefotaxime.



**Figure 2.** Percentage of Pneumococcal Isolates, from 1239 Cases, That Were Nonsusceptible to Various Antibiotics, According to Year and Degree of Nonsusceptibility.

For 1998–2005, 140 isolates lacking serotype or susceptibility data were excluded. The total number of isolates tested was 147 in 1998, 191 in 1999, 179 in 2000, 154 in 2001, 161 in 2002, 155 in 2003, 119 in 2004, and 133 in 2005. In 2002, only 160 of the 161 isolates were tested for susceptibility to chloramphenicol.

types in a case–control study. They found that the effectiveness of one or more doses of vaccine against disease caused by a vaccine serotype was 96% in healthy children; the effectiveness against meningitis in particular was also 96%. For serotypes within the same serogroup as the vaccine types, the effectiveness against serotype 6A was approximately 75%, and there was no evidence of protection against serotype 19A. Although we did not find any significant change in the rate of meningitis from serotype 6A overall, we did find that the rate of meningitis from serotype 19A increased significantly during the study period, supporting the lack of vaccine effectiveness against this serotype. One explanation for the apparent lack of reduction in the rate of pneumococcal meningitis caused by serotype 6A is that some of the isolates classified as 6A may actually be 6C, a newly identified serotype that cannot be distinguished from 6A by means of standard serotyping.<sup>31</sup>

Several studies of pneumococcal disease found that rates of antibiotic-resistant invasive pneumococcal disease declined in both young children and older persons after the introduction of PCV7.<sup>20,25,32</sup> This observation is most likely due to the fact that the introduction of conjugate vaccines has led to a reduction in the rates of nasopharyngeal carriage of, and disease caused by, penicillin-nonsusceptible isolates.<sup>33</sup> Likewise, in the current study, we found a substantial decline

in incidence of pneumococcal meningitis due to serotypes that are nonsusceptible to antibiotics, indicating a strong public health effect of PCV7 on nonsusceptible infections. However, if vaccination results in a new group of serotypes colonizing the nasopharynx, sustained exposure to antibiotics may promote further development of nonsusceptibility to penicillin among non-PCV7 serotypes. Indeed, mathematical models have predicted that high levels of exposure to antibiotics may limit the success of the pneumococcal conjugate vaccine.<sup>34</sup>

In addition, antibiotic resistance remains a serious concern for physicians treating pneumococcal meningitis, since relatively few available drugs can attain therapeutic concentrations in cerebrospinal fluid. Despite the decrease in incidence of nonsusceptible pneumococcal meningitis, we observed a recent resurgence in the proportion of nonsusceptible isolates among the remaining cases, which has implications for empirical therapy for pneumococcal meningitis. We also found that although nonsusceptibility to penicillin occurs mostly among PCV7-serotype isolates, the percentages of isolates of several non-PCV7 serotypes that are nonsusceptible to penicillin have increased over time.

Our study has several limitations. Data used in this analysis were collected through abstraction from medical records by multiple staff members.

Therefore, there may be inconsistencies due to differences in medical records among sites and in completeness of the data about chronic illnesses. Since this study represents an ecologic analysis, no definitive causal link may be made between the use of PCV7 and our findings.

Our data provide strong evidence of the benefit of PCV7 in reducing rates of pneumococcal meningitis, including those caused by strains non-susceptible to antimicrobial agents. Decreases in disease rates represent a direct effect of the vaccine within the immunized population as well as an indirect benefit resulting from decreased transmission of PCV7-type pneumococci from immunized children to nonimmunized children and adults. Despite these decreases, the recent increase in the proportion of pneumococcal meningitis isolates that are non-susceptible to antimicrobial agents indicates that antimicrobial resistance is a clinical concern. In addition, increases in the rates of disease from non-PCV7 serotypes indicate the need for continued development of more broadly protective vaccines. Given that pneumococcal meningitis remains highly lethal, with approximately 1 in 12 cases in children and 1 in 5 cases in adults resulting in death in our study, additional prevention measures are needed.

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