MAJOR ARTICLE

Incidence of Pneumococcal Disease Due to Non–Pneumococcal Conjugate Vaccine (PCV7) Serotypes in the United States during the Era of Widespread PCV7 Vaccination, 1998–2004

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(See the editorial commentary by Hanage, on pages 1282–4.)

Background. Widespread use of pneumococcal conjugate vaccine (PCV7) resulted in decreases in invasive disease among children and elderly persons. The benefits may be offset by increases in disease due to serotypes not included in the vaccine (hereafter, "nonvaccine serotypes"). We evaluated the effect of PCV7 on incidence of disease due to nonvaccine serotypes.

Methods. Cases of invasive disease were identified in 8 geographic areas through the Centers for Disease Control and Prevention's Active Bacterial Core surveillance. Serotyping and susceptibility testing of isolates were performed. We calculated the incidence of disease for children aged <5 years and adults aged ⩾65 years. We compared rates of serotype-specific disease before and after PCV7 was licensed for use.

Results. The annual incidence of disease due to nonvaccine serotypes increased from an average of 16.3 cases/100,000 population during prevaccine years (1998–1999) to 19.9 cases/100,000 population in 2004 for children aged <5 years ($P = .01$) and from 27.0 cases/100,000 population during prevaccine years to 29.8 cases/100,000 population in 2004 for adults aged ⩾65 years ($P = .05$). Significant increases in the incidences of disease due to serotypes 3, 15, 19A, 22F, and 33F were observed among children during this period ($P < .05$ for each serotype); serotype 19A has become the predominant cause of invasive disease in children. The incidence of disease due to these serotypes also increased among elderly persons.

Conclusions. The incidence of pneumococcal disease caused by nonvaccine serotypes is increasing. Ongoing surveillance is needed to monitor the magnitude of disease caused by nonvaccine serotypes, to ensure that future vaccines target the appropriate serotypes.

Streptococcus pneumoniae causes a wide spectrum of illnesses, ranging from upper respiratory tract infections to severe invasive diseases, such as meningitis and bacteremia. Young children and older adults are particularly susceptible to invasive pneumococcal disease. In 2000, the 7-valent protein-polysaccharide conjugate vaccine (PCV7 [Prevnar]; Wyeth Lederle Vaccines) was licensed for use in infants and young children in the United States and led to a dramatic decrease in the rate of invasive pneumococcal disease [1, 2]. The rate of invasive pneumococcal disease decreased from an aver-

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age of 25.1 cases/100,000 population in 1999 to 12.6 cases/100,000 population in 2004. The decrease, although most marked in the vaccine's target age group, was also significant among older children, adults, and elderly persons [3, 4].

Conjugate vaccines protect against nasopharyngeal carriage and disease due to the capsular serotypes included in the vaccine, as well as to some vaccine-related serotypes, particularly serotype 6A [1, 5]. Of the ~90 different *S. pneumoniae* serotypes, the 7 most commonly found to cause invasive pneumococcal disease in children are targeted by PCV7. Despite the success of PCV7, reduction in the rate of carriage of certain serotypes appears to create an ecological niche that can be filled by serotypes not included in the vaccine (hereafter, "nonvaccine serotypes"), a phenomenon known as serotype replacement [6–8]. Increases in rates of nasopharyngeal carriage and otitis media caused by nonvaccine serotypes have been demonstrated in persons who received pneumococcal conjugate vaccine [5, 9–13]. This raised concern about the potential for an increased rate of invasive disease due to nonvaccine serotypes. Early studies of the impact of vaccination in the United States found that, among children, increases in the rate of disease due to nonvaccine serotypes were either small in magnitude or limited to a single geographic location [14–16]. More-recent data showed larger increases in the incidence of serotype 19A among children and of multiple nonvaccine serotypes among adults 18–64 years of age with HIV/AIDS [17, 18]. However, 2 studies, one in Alaska and the other in northern California, did not show evidence of invasive disease due to nonvaccine serotypes (so-called replacement invasive disease) [19, 20]. To date, no report has evaluated age-specific trends of replacement over time; it is unclear whether disease caused by nonvaccine serotypes differs in severity from disease caused by vaccine serotypes.

We used population-based surveillance data from the Active Bacterial Core surveillance (ABCs) system of the Centers for Disease Control and Prevention (CDC) to evaluate the effects of widespread PCV7 vaccination on the incidence of invasive pneumococcal disease due to nonvaccine serotypes among young children and older adults during 1998–2004 and to characterize disease according to serotype, host factors, and disease outcomes.

METHODS

Between 1 January 1998 and 31 December 2004, the ABCs, an active, laboratory-based surveillance system, monitored invasive pneumococcal infections in 8 states as part of the Emerging Infections Program at the CDC. The following sites were included in the analysis: San Francisco County, California; the state of Connecticut; Atlanta, Georgia (20 counties); the Baltimore, Maryland, metropolitan area (6 counties); Minneapolis–St. Paul, Minnesota (7 counties); Rochester, New York (7 counties); Portland, Oregon (3 counties); and areas in Tennessee (5 metropolitan counties). In 2004, there were 19,122,248 residents in the regions under surveillance, with 1,312,144 persons aged <5 years and 2,074,079 aged ⩾65 years.

Invasive pneumococcal disease was defined as the recovery of *S. pneumoniae* from culture of a normally sterile body fluid, such as blood or cerebrospinal fluid (CSF), obtained from residents of the surveillance areas. To maximize reporting, surveillance personnel routinely contacted all participating microbiological laboratories and conducted periodic audits of laboratory records. A standardized questionnaire was used to collect data on demographic characteristics, past medical history, clinical syndromes, and disease outcomes. Data regarding comorbid conditions were collected at all surveillance sites; Georgia began collecting these data in 2000.

Pneumococcal isolates were sent to 1 of 2 reference laboratories for serotyping. The Minnesota Department of Health served as the reference laboratory for isolates obtained from patients in the Minneapolis–St. Paul surveillance area; all other isolates were serotyped at the CDC. Serotyping was performed by observing the Quellung reaction in the presence of serotype-specific antisera. Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F were grouped as vaccine serotypes; all other serotypes were considered nonvaccine serotypes. Serotypes 15B and 15C were designated as serogroup 15 because of previously noted reversible serotype switching between them [21].

Susceptibility testing was performed on isolates by means of the broth microdilution method at the CDC, the Minnesota Department of Health, or the University of Texas Health Science Center in San Antonio. Isolates were described as susceptible, intermediately susceptible, or resistant on the basis of definitions established by the Clinical and Laboratory Standards Institute [22]. Intermediately susceptible strains and resistant strains were classified as nonsusceptible.

Because of the large burden of disease among young children and elderly persons and because of the recent publication of data on adults aged 18–64 years, we focused the analyses on children aged <5 years and adults aged ⩾65 years. We calculated the annual incidence of invasive pneumococcal disease, using US Census Bureau data. We compared the average annual rate of disease due to vaccine serotypes during the final 2 prevaccine years (1998–1999) with the rates during 2001–2004, with special emphasis on the comparison between 1998–1999 and 2004. We compared the rates of disease caused by nonvaccine serotypes for the same periods. Statistical analyses for individual serogroups or serotypes were performed only if ⩾50 isolates from the serogroup or serotype were recovered during 1998–2004. For serotype-specific rate calculations, cases with missing serotype data were accounted for by multiplying the overall disease rate by the yearly proportions of serotype-specific disease in each age group. The same methods were used to compare

penicillin susceptibility patterns for individual serogroups and serotypes before and after PCV7 introduction.

Serotypes in the 23-valent polysaccharide vaccine (PPV23) but not in PCV7 include 1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F. The rates of invasive disease due to these serotypes before introduction of PCV7 (1998–1999) was compared with the rates after the vaccine was introduced.

We compared the rates of hospitalization for treatment of invasive disease caused by vaccine serotypes before the introduction of PCV7 with those after PCV7 introduction; comparisons between the same periods were performed for nonvaccine serotypes. We investigated changes in mortality and case-fatality rates between the prevaccine and postvaccine years for disease due to vaccine serotypes and disease due to nonvaccine serotypes. We also examined comorbid conditions among patients with disease caused by either vaccine or nonvaccine serotypes. The comorbid conditions included but were not limited to chronic obstructive pulmonary disease, asthma, diabetes, smoking, HIV infection, alcoholism, immunosuppressive therapy, renal failure, liver disease, and heart failure.

Statistical analyses were performed using SAS, version 9 (SAS Institute). We calculated the relative risk of disease and associated 95% CIs, using the Mantel-Haenszel χ^2 test and the Fisher exact test. Relative risks were calculated by comparing age-specific and serotype-specific incidences for prevaccine years (1998–1999) with those for 2004. Two-sided P values of <.05 were considered statistically significant.

RESULTS

From 1998 through 2004, a total of 23,718 cases of invasive pneumococcal disease were identified at the study sites. Invasive pneumococcal disease in children <5 years of age accounted for 4767 (20%) cases; 4073 (85%) had isolates available for serotyping. Invasive disease in adults aged ⩾65 years accounted for 7131 cases (30%); 6324 (89%) had isolates available for serotyping. Blood and CSF were the most common sites of infection. In children aged <5 years, infection was identified from a blood or CSF isolate in 95% and 4% of cases, respectively. For adults aged ⩾65 years, isolates from blood and CSF accounted for 97% and 1%, respectively, of all invasive disease cases.

Age group–specific disease. The overall annual rate of invasive pneumococcal disease among children aged <5 years decreased from an average of 95.2 cases/100,000 population during 1998–1999 to 22.6 cases/100,000 population in 2004. This finding was affected by a marked decrease in the rate of disease due to vaccine serotypes, from an annual average of 78.9 cases/100,000 population during 1998–1999 to 2.7 cases/100,000 population in 2004. The annual rate of invasive disease due to nonvaccine serotypes increased from an average of 16.3 cases/100,000 population during 1998–1999 to 19.9 cases/100,000 population in 2004 (figure 1*A*). Disease caused by nonvaccine serotypes accounted for 17% of all cases during prevaccine years, compared with 88% of cases in 2004. Serotypes 3, 19A, 22F, and 33F and serogroup 15 were the predominant replacement serotypes in children aged <5 years (table 1). The annual rates of disease caused by these 5 serotypes increased from 5.8 to 14.3 cases/100,000 population between the baseline period (1998–1999) and 2004. Of note, rates of disease due to the 7 PCV7 serotypes and 2 nonvaccine serotypes (6A and 12F) decreased significantly during the study period. Although incremental decreases in the rates of invasive pneumococcal disease caused by vaccine serotypes occurred, the rates of disease due to nonvaccine serotypes have increased incrementally, most notably for serotype 19A (figure 2*A*).

The overall annual rate of invasive disease among adults aged

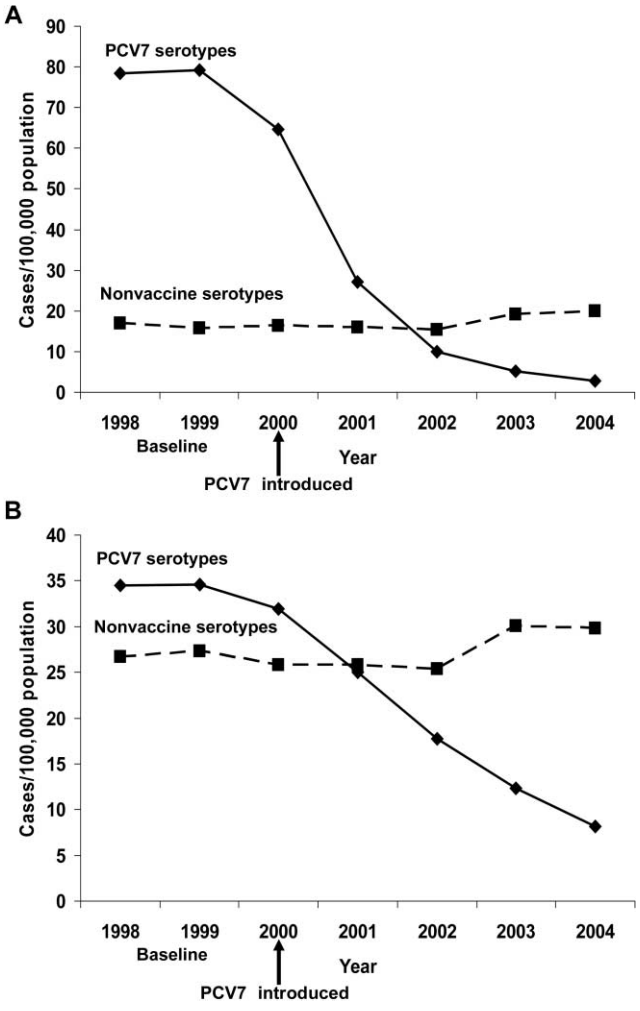

Figure 1. Rates of invasive pneumococcal disease among children aged <5 years *(A)* and adults aged ⩾65 years *(B),* by serotype and year. The 7-valent pneumococcal conjugate vaccine (PCV7) includes serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F.

Table 1. Invasive pneumococcal disease among children and older adults before (1998–1999) and after (2004) introduction of the 7-valent pneumococcal conjugate vaccine (PCV7).

Age, serotype[a]	Total no. of cases		No. of cases/ 100,000 population		Relative risk (95% CI)[b]	*P*
	1998–1999	2004	1998–1999	2004		
<5 years						
Overall	1150	297	95.2	22.6	0.2 (0.2–0.3)	<.01
PCV7[c]	953	36	78.9	2.7	0.03 (0.02–0.05)	<.01
Nonvaccine						
Overall	197	261	16.3	19.9	1.2 (1.1–1.4)	.01
3	5	13	0.4	1.0	2.5 (1.1–5.7)	.03
6A	59	12	4.8	0.9	0.2 (0.1–0.3)	<.01
7F	8	12	0.6	0.9	1.4 (0.6–2.9)	.42
12F	16	7	1.3	0.5	0.4 (0.2–0.9)	.03
15	11	31	0.9	2.4	2.7 (1.5–4.6)	<.01
19A	30	103	2.5	7.8	3.2 (2.3–4.4)	<.01
22F	7	20	0.5	1.5	2.8 (1.4–5.5)	<.01
33F	9	21	0.7	1.6	2.3 (1.2–4.4)	.01
38	6	8	0.5	0.6	1.3 (0.5–3.1)	.62
⩾65 years						
Overall	1213	788	61.5	38.0	0.6 (0.6–0.7)	<.01
PCV7	681	171	34.5	8.2	0.2 (0.2–0.3)	<.01
Nonvaccine						
Overall	532	617	27.0	29.8	1.1 (1.0–1.2)	.05
3	72	84	3.6	4.1	1.1 (0.9–1.5)	.4
6A	77	67	3.9	3.3	0.8 (0.6–1.1)	.21
7F	24	21	1.2	1.0	0.8 (0.5–1.4)	.51
9N	14	8	0.7	0.4	0.5 (0.3–1.2)	.13
11A	30	33	1.5	1.6	1.1 (0.7–1.6)	.8
12F	42	15	2.1	0.7	0.3 (0.2–0.6)	<.01
15	16	29	0.8	1.4	1.8 (1.1–3.0)	.02
16F	9	19	0.4	0.9	2.1 (1.1–4.1)	.02
19A	44	83	2.2	4.0	1.8 (1.3–2.4)	<.01
22F	54	72	2.7	3.5	1.3 (0.9–1.7)	.12
23A	8	34	0.4	1.6	4.0 (2.2–7.2)	<.01
31	11	11	0.5	0.5	1.0 (0.5–2.1)	.94
33F	12	30	0.6	1.5	2.5 (1.5–4.3)	<.01
35	20	43	1.0	2.1	2.0 (1.3–3.1)	<.01
38	11	14	0.6	0.7	1.1 (0.6–2.3)	.64

Note. Data for 1998–1999 are annual averages.

[a] Individual serotypes are specified if ⩾50 isolates were collected through the Active Bacterial Core surveillance (ABCs) system of the Centers for Disease Control and Prevention.

[b] Relative risks and CIs were calculated with the Mantel-Haenszel χ^2 test and the Fisher exact test.

[c] Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are included in the 7-valent pneumococcal conjugate vaccine (PCV7).

⩾65 years decreased from 61.5 cases/100,000 population during 1998–1999 to 38.0 cases/100,000 population in 2004. This finding was affected by a large decrease in the rate of disease due to vaccine serotypes, from an average of 34.5 cases/100,000 population during 1998–1999 to 8.2 cases/100,000 population in 2004. The annual rate of invasive disease caused by nonvaccine types increased from an average of 27.0 cases/100,000 population during 1998–1999 to 29.8 cases/100,000 population in 2004 (figure 1*B*). The difference in the rate of disease due to nonvaccine serotypes between 1998–1999 and 2004 for adults aged ⩾65 years was similar to the difference for children aged <5 years (3.6 vs. 2.8 cases/100,000 population). Disease caused by nonvaccine serotypes accounted for an average of 44% of all cases during 1998 and 1999, compared with 78% of cases

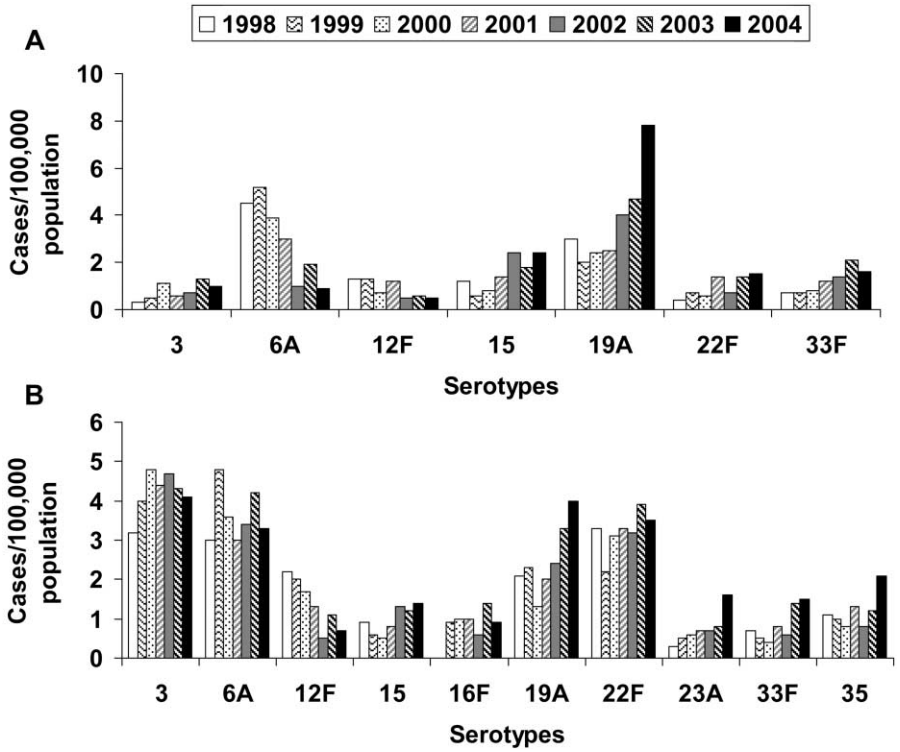

Figure 2. Change in serotype-specific incidence of invasive pneumococcal infections among children aged <5 years *(A)* and adults aged ⩾65 years *(B)*. Serotypes included are those associated with a significant increase or decrease in disease incidence among children aged <5 years or adults aged ⩾65 years ($P < .05$) between the average of 2 baseline years (1998 and 1999) before 7-valent pneumococcal conjugate vaccine introduction and 2004.

in 2004. The predominant replacement serotypes in children aged <5 years were also replacement serotypes in adults ⩾65 years (table 1); increases in serotypes 19A and 33F and serogroup 15 were significant ($P < .05$), and increases in the rates of disease due to serotypes 3 and 22F were not significant. As seen in children, the rate of serotype 12F disease decreased among older adults. The rates of invasive disease due to nonvaccine serotypes 16F, 23A, and 35 increased among adults aged ⩾65 years but not among children aged <5 years. Incremental increases in rates of disease due to serotypes 15, 19A, 23A, 33F, and 35 were observed annually among older adults ($P < .01$ for all, by means of the χ^2 test for trend) (figure 2*B*).

PPV23 and invasive disease. Is there evidence that PPV23 adds further protection from replacement invasive disease for persons ⩾65 years of age? The rate of disease caused by the 16 serotypes unique to PPV23 for adults aged ⩾65 years increased from 17.2 cases/100,000 population in prevaccine years to 18.7 cases/100,000 population in 2004. However, during prevaccine years, PPV23-specific serotypes accounted for 64% of cases due to nonvaccine (i.e., non-PCV7) serotypes, compared with 63% of such cases in 2004. In contrast, the rate of disease caused by PPV23-only serotypes among children aged <5 years increased from 7.9 to 14.8 cases/100,000 population between the prevaccine years and 2004. In prevaccine years, PPV23-specific serotypes accounted for 48% of cases of disease due to nonvaccine serotypes, compared with 74% of such cases in 2004.

Hospitalization and comorbid conditions. The annual rate of hospitalization for invasive pneumococcal disease among children aged <5 years decreased from an average of 27.2 admissions/100,000 population during 1998–1999 to 10.1 admissions/100,000 population in 2004 (table 2). This finding was affected by a decrease in the rate of hospitalization for disease due to vaccine serotypes; the rate of hospitalization for disease due to nonvaccine serotypes increased. During prevaccine years, disease caused by nonvaccine serotypes accounted for only 20% of hospitalizations for invasive pneumococcal disease, compared with 87% in 2004 ($P < .001$). In 2004, the prevalence of comorbid conditions was higher among children with disease due to vaccine serotypes but did not differ significantly from the prevalence for children with disease due to nonvaccine serotypes (29% vs. 20%; $P = .28$).

The annual rate of hospitalization for invasive pneumococcal disease in adults ⩾65 years decreased from 50.6 admissions/100,000 population during prevaccine years to 31.9 admissions/100,000 population in 2004 (table 2). As in children aged <5

Table 2. Hospitalization for invasive pneumococcal disease among children and older adults before (1998–1999) and after (2004) introduction of the 7-valent pneumococcal conjugate vaccine (PCV7).

Age, serotype	Total no. of hospitalizations		No. of hospitalizations/100,000 population		Relative risk (95% CI)[a]	*P*
	1998–1999	2004	1998–1999	2004		
<5 years						
Overall	329	133	27.2	10.1	0.4 (0.3–0.5)	<.001
PCV7[b]	264	17	21.8	1.3	0.06 (0.04–0.10)	<.001
Nonvaccine	65	116	5.4	8.8	1.6 (1.3–2.1)	<.001
⩾65 years						
Overall	998	661	50.6	31.8	0.6 (0.6–0.7)	<.001
PCV7[b]	560	144	28.4	6.9	0.2 (0.2–0.3)	<.001
Nonvaccine	438	517	22.2	24.9	1.1 (1.0–1.3)	.04

Note. Data for 1998–1999 are annual averages.

[a] Relative risks and CIs were calculated with the Mantel-Haenszel χ^2 test and the Fisher exact test.

[b] Serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F are included in the 7-valent pneumococcal conjugate vaccine (PCV7).

years, this finding was affected by a decrease in the rate of hospitalization for disease due to vaccine serotypes. During prevaccine years, disease caused by nonvaccine serotypes accounted for only 44% of hospitalizations due to invasive pneumococcal disease, compared with 78% in 2004 ($P < .001$). The prevalence of underlying comorbid conditions in 2004 was not significantly different among older adults with disease due to vaccine serotypes, compared with older adults with disease due to nonvaccine serotypes (92% vs. 89%; $P = .28$).

Mortality. The annual mortality rate among children aged <5 years with disease due to vaccine serotypes decreased from 0.5 deaths/100,000 population during 1998–1999 to 0.2 deaths/100,000 population in 2004. However, because the mortality rate associated with disease due to nonvaccine serotypes increased from 0.1 deaths/100,000 population during the prevaccine years to 0.4 deaths/100,000 population in 2004, the overall mortality rate among children did not change during the study period. The case-fatality rate in this age group increased for disease due to vaccine serotypes and disease due to nonvaccine serotypes, but the overall number of deaths remained small. The annual case-fatality rate for disease caused by vaccine serotypes increased from an average of 0.1% (1 of 795 cases) during prevaccine years to 10% (3 of 31 cases) in 2004 ($P = .004$). The annual case-fatality rate for disease due to nonvaccine serotypes increased slightly from 1% (1 of 165 cases) during prevaccine years to 2% (5 of 224 cases) in 2004 ($P = .2$).

The annual mortality rate among adults aged ⩾65 years with disease due to vaccine serotypes decreased from 4.6 deaths/100,000 population during prevaccine years to 1.7 deaths/100,000 population in 2004 (relative risk [RR], 0.4; 95% CI, 0.3–0.5). The annual mortality rate for older adults with disease due to nonvaccine serotypes decreased slightly from 5.4 deaths/100,000 population during 1998–1999 to 4.5 deaths/100,000 population in 2004 (RR, 0.84; 95% CI, 0.7–1.1). The annual case-fatality for disease due to vaccine serotypes increased from 19% (92 of 497 cases) during prevaccine years to 31% (36 of 115 cases) in 2004 ($P = .002$). The annual case-fatality rate for older adults with disease due to nonvaccine serotypes decreased from 30% (106 of 349 cases) during prevaccine years to 21% (93 of 452 cases) in 2004 ($P = .002$); in 2004, the case-fatality rate was higher for older adults with disease due to vaccine serotypes than for those with disease due to nonvaccine serotypes ($P = .01$).

Replacement serotypes and antimicrobial resistance. Among the primary serotypes causing replacement disease, nonsusceptibility to penicillin or other antimicrobials was most common for serotype 19A in both age groups. The percentage of serotype 19A isolates that were nonsusceptible to penicillin (including isolates with intermediate susceptibility or resistance to penicillin) among children aged <5 years increased slightly between the prevaccine years (63% [19 of 30 isolates]) and 2004 (74% [76 of 103 isolates]; $P = .27$). However, among children, a marked increase in the percentage of serotype 19A isolates that were resistant to penicillin was observed during the study period (from 10% during prevaccine years to 31% in 2004; $P = .002$). Among children, the percentage of serotype 19A isolates that were nonsusceptible to erythromycin increased significantly between the prevaccine years (23% [7 of 30 isolates]) and 2004 (46% [47 of 103 isolates]; $P = .03$). For adults aged ⩾65 years, the percentage of 19A isolates that were nonsusceptible to penicillin decreased slightly between the prevaccine

years (59% [26 of 44 isolates]) and 2004 (58% [48 of 83 isolates]; $P = .89$), whereas the percentage of isolates that were nonsusceptible to erythromycin increased between the prevaccine years (38% [12 of 32 isolates]) and 2004 (73% [35 of 48]; $P = .10$).

Nonsusceptibility to penicillin and erythromycin also increased among serogroup 15 isolates recovered from children aged <5 years between the prevaccine years (0% [0 of 11 isolates]) and 2004 (6% [2 of 31 isolates]; $P = .39$). Nonsusceptibility to penicillin and erythromycin among serogroup 15 isolates was much higher for adults aged ⩾65 years and increased in this group between the prevaccine years (14% [2 of 14 isolates]) and 2004 (53% [10 of 19 isolates]; $P = .11$). Of interest, resistance to both agents was confined to serotype 15A isolates. In contrast, nearly all serotype 3 and serotype 22F isolates were susceptible to both penicillin and erythromycin, and only nonsusceptibility to erythromycin was common for serotype 33F isolates.

DISCUSSION

The introduction of PCV7 in 2000 resulted in a dramatic reduction in the incidence of invasive pneumococcal disease. However, there has been a progressive increase in replacement disease due to nonvaccine serotypes among children aged <5 years and adults aged ⩾65 years. The size of these increases remains small compared with the overall decrease in the incidence of invasive disease, and it is notable that the increase in the incidence of disease due to nonvaccine serotypes among young children and elderly persons was much smaller than that previously reported for adults 18–64 years of age with HIV/AIDS [18].

Although there are ~90 pneumococcal serotypes and although only 7 serotypes are included in PCV7, the increase in disease caused by nonvaccine serotypes was primarily associated with a small number of serotypes. An increase in disease caused by nonvaccine serotypes was noted in a network of 8 pediatric hospitals; among children aged ⩽24 months, 28% more nonvaccine serotypes were recovered in 2001 and 68% more were recovered in 2002, compared with the average annual percentage recovered during prevaccine years [15]. The serotypes that exhibited the greatest increase included serogroups 15 and 33; these serogroups were also identified to be important replacement serogroups in our study. An increase in invasive disease due to nonvaccine serotypes was also observed in the Intermountain West during 1996–2003: data from the prevaccine period for the population described in the report revealed a higher proportion of cases of invasive disease caused by nonvaccine serotypes than the proportion reported for the general US population during the same period [16]. In addition, Byington et al. [16] observed a statistically significant increase in the proportion of cases due to serogroup 3 during the study period; this serotype was also a key replacement serotype in our study.

The nonvaccine serotype 19A is now the predominant agent of invasive pneumococcal disease among children and the second most common agent among older adults. There are many possible explanations for why serotype 19A has become the predominant replacement serotype causing invasive disease in children. This serotype was the most commonly carried nonvaccine serotype before PCV7 introduction, and it is also frequently resistant to antibiotics; both factors might have permitted it to fill the niche left by PCV7 serotypes. Another possible explanation is that the serotype 19A capsule may make the serotype more invasive than other nonvaccine serotypes. A ranking of serotype-specific odds ratios for invasiveness that also included PCV7 serotypes showed that serotype 19A had the seventh highest odds ratio for its ability to cause invasive disease [23]. Serotypes 3 and 19A have been commonly associated with invasive disease and were more prevalent among invasive pneumococcal isolates than among pneumococcal carriage isolates [24]. Finally, PCV7-serotype pneumococci may, through capsular switching, acquire a 19A capsule in order to escape the effects of the vaccine [25]. Multilocus sequence typing has been used to identify the genetic relatedness of invasive serotype 19A isolates obtained at ABCs sites from children <5 years of age [17]. Since the introduction of PCV7, clones typically found with PCV7 serotypes are now exhibiting serotype 19A capsules.

Antibiotic resistance to penicillin and/or erythromycin was common among some of the serotypes that have increased in prevalence since PCV7 introduction. Overall, the incidence of invasive disease due to nonsusceptible strains has decreased precipitously as the overall incidence of invasive disease has decreased [2]. Simultaneously, the rate of disease due to penicillin-nonsusceptible strains of serotype 19A increased from 0.3 to 1.2 cases/100,000 population between 1999 (the prevaccine period) and 2004 (the postvaccine period) [2]. The increase in disease caused by nonsusceptible serotype 19A isolates is a result of both an overall increase in the incidence of 19A disease and an increase in the proportion of serotype 19A isolates that are nonsusceptible. An increased prevalence of penicillin resistance among serotype 19A isolates may represent increased carriage and exposure to antibiotic pressure [26]. Capsular switching may also play an important role in conferring a high level of resistance among replacement serotypes [27]. An analysis of PFGE patterns for isolates from Israel, Costa Rica, and the United States revealed that penicillin-nonsusceptible clones of nonvaccine serotypes were closely related to serotypes included in an 11-valent vaccine.

Because this is an ecological study of group characteristics, the observed increases in the rates of disease due to certain

nonvaccine serotypes cannot be definitively causally linked to the introduction of PCV7, even though the increases began after introduction of the vaccine. Natural shifts in the distribution of pneumococcal serotypes occur over time [28], and we found evidence for this in our analysis. For example, we found decreases in the incidence of disease due to some nonvaccine serotypes, such as 12F, that were not likely associated with PCV7 use. However, the major changes reported here are likely associated with PCV7 use; the decrease in invasive disease in children <5 years of age is due to marked reductions in disease caused by PCV7 serotypes, and the incremental decreases have continued as vaccine coverage has increased. The decrease in the incidence of invasive disease among adults aged ⩾65 years, which accompanied the decreased incidence of disease in the vaccine's target population, was affected by a decrease in the rate of disease caused by serotypes included in PCV7 (without accompanying decreases in the rates of disease due to the remaining 16 serotypes covered by PPV23) and likely represents a herd-immunity effect of this vaccine [4]. It is important to recognize that patient vaccination records for PPV23 were limited, and it is difficult to determine the effect of PPV23 on replacement disease. However, use of PPV23 may have protected older adults against disease caused by serotypes unique to PPV23: children aged <5 years had an increase in the proportion of cases of replacement disease due to these serotypes, but older adults did not.

Although there was a marked decrease in the rate of hospitalizations for children aged <5 years, the overall mortality rate among children did not change. This was due to an increase in the case-fatality rate among children with disease caused by vaccine or nonvaccine serotypes. This likely reflects an increase in comorbid conditions in this population in 2004, compared with prevaccine years. However, there may be other contributing factors that we were unable to assess.

Changes in the epidemiology of invasive pneumococcal disease have been marked since the licensing of PCV7 for widespread use in infants and children in the United States. Expanded-valent vaccines are in development and should address disease caused by some of the predominant replacement serotypes, as well as by serotypes that are common in developing countries. A pneumococcal vaccine that is not serotype specific would, if effective, be an ideal solution to the problem of invasive disease; several such common-antigen vaccines are being investigated. Concern over replacement disease should not cloud the fact that use of PCV7 has prevented serious illness and saved lives in the places where it is in use. Although tracking trends in disease caused by nonvaccine serotypes and developing new vaccines are important steps, the more important action is to begin to use the currently available conjugate vaccines in as many places as possible.

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