MAJOR ARTICLE

Sustained Reductions in Invasive Pneumococcal Disease in the Era of Conjugate Vaccine

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Background. Changes in invasive pneumococcal disease (IPD) incidence were evaluated after 7 years of 7-valent pneumococcal conjugate vaccine (PCV7) use in US children.

Methods. Laboratory-confirmed IPD cases were identified during 1998–2007 by 8 active population-based surveillance sites. We compared overall, age group–specific, syndrome-specific, and serotype group–specific IPD incidence in 2007 with that in 1998–1999 (before PCV7) and assessed potential serotype coverage of new conjugate vaccine formulations.

Results. Overall and PCV7-type IPD incidence declined by 45% (from 24.4 to 13.5 cases per 100,000 population) and 94% (from 15.5 to 1.0 cases per 100,000 population), respectively ($P < .01$ for all age groups). The incidence of IPD caused by serotype 19A and other non-PCV7 types increased from 0.8 to 2.7 cases per 100,000 population and from 6.1 to 7.9 cases per 100,000 population, respectively ($P < .01$ for all age groups). The rates of meningitis and invasive pneumonia caused by non-PCV7 types increased for all age groups ($P < .05$), whereas the rates of primary bacteremia caused by these serotypes did not change. In 2006–2007, PCV7 types caused 2% of IPD cases, and the 6 additional serotypes included in an investigational 13-valent conjugate vaccine caused 63% of IPD cases among children <5 years-old.

Conclusions. Dramatic reductions in IPD after PCV7 introduction in the United States remain evident 7 years later. IPD rates caused by serotype 19A and other non-PCV7 types have increased but remain low relative to decreases in PCV7-type IPD.

Streptococcus pneumoniae (pneumococcus) is a major bacterial cause of pneumonia, meningitis, and sepsis worldwide, resulting in almost 1 million childhood deaths annually [1]. Before 7-valent pneumococcal conjugate vaccine (PCV7) was introduced in late 2000 for US children <5 years old, ~65,000 cases of invasive pneumococcal disease (IPD) occurred annually. Children aged <5 years accounted for about 25% of IPD episodes, and 80% of disease in this age group was caused by the 7 serotypes included in the vaccine [2].

PCV7 uptake was rapid: estimated coverage of ⩾3 doses by 24 months of age for successive US birth cohorts increased from 9% for children born in 1999 to

Received 4 June 2009; accepted 7 August 2009; electronically published 30 November 2009.

Potential conflicts of interest: L.H.H. received lecture honoraria from Wyeth and consulting fees from Merck. W.S. received a consulting fee from Wyeth and is a member of Safety Evaluation Committee for experimental vaccine trials for Merck. N.M.B. has served on adult vaccine advisory boards for Wyeth and Merck. All other authors report no potential conflicts.

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The Journal of Infectious Diseases 2010;201:32–41
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0022-1899/2010/20101-0006$15.00
DOI: 10.1086/648593

Presented in part: 48th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy/46th Annual Meeting of the Infectious Diseases Society of America, Washington, DC, 25–28 October 2008.

Financial support: Emerging Infections Programs, Centers for Disease Control and Prevention.

The Centers for Disease Control and Prevention's Emerging Infections Programs provided funding but made no other contributions to the design and conduct of this study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of this manuscript.

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93% for those born in 2006 [3, 4]. Shortly after PCV7 introduction, IPD incidence declined rapidly, not only among children targeted for vaccination but also among unvaccinated children and adults [5, 6], demonstrating strong direct and indirect vaccine effects. The potential for vaccination to contribute to the emergence of serotypes not included in the vaccine, so-called "replacement disease," has been a concern. However, increases in the incidence of non-PCV7 serotypes in the general US population have been modest to date [7–11]. With the reduction in rates of PCV7-type IPD, non-PCV7 serotypes now account for a higher proportion of IPD. Whether these serotypes are associated with more severe infections than PCV7 types is unknown. We analyzed surveillance data collected through an active laboratory- and population-based system to evaluate changes in IPD 7 years after PCV7 introduction in the United States and to measure potential serotype coverage of new conjugate vaccine formulations.

METHODS

We identified IPD cases through Active Bacterial Core surveillance (ABCs), an active population- and laboratory-based system [5, 12]. For this analysis, we included cases identified between 1 January 1998 and 31 December 2007 in 8 continuously participating ABCs sites: selected counties in California, Georgia, Maryland, Minnesota, New York, Oregon, and Tennessee and the state of Connecticut. The total population under surveillance was 19,060,270, according to 2007 postcensus population estimates.

We defined IPD cases as isolation of *S. pneumoniae* from normally sterile sites such as blood, cerebrospinal fluid, or pleural fluid. Regular audits of participating laboratories ensured completeness of reporting. Medical charts were reviewed to attain demographic and clinical information. Isolates were serotyped at the Streptococcus Laboratory of the Centers for Disease Control and Prevention (CDC) or the Minnesota Department of Health Laboratory using latex agglutination and confirmation by the Quellung reaction. We assigned serotypes to the following mutually exclusive categories: (1) PCV7 types (4, 6B, 9V, 14, 18C, 19F, and 23F), (2) PCV7-related types (serotypes in the same serogroups as the PCV7 types, excluding 19A), (3) serotype 19A (analyzed separately because of its distinct epidemiology [7, 13, 14]), and (4) non-PCV7 types. Serotypes 6A and 6C, included in the PCV7-related group, could not be distinguished using the Quellung reaction and were reported as type 6A/C [15]. We calculated the proportion of IPD cases caused by serotypes included in PCV7 and the 23-valent pneumococcal polysaccharide vaccine (PPV23) (PCV7 plus serotypes 1, 2, 3, 5, 7F, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, and 33F), as well as in 2 new conjugate vaccines, PCV10 (PCV7 plus serotypes 1, 5, and 7F) [16] and PCV13 (PCV10 plus types 3, 6A, and 19A) [17].

We calculated annual IPD incidence rates (cases per 100,000 population) using US Census Bureau population estimates for prevaccine baseline years (1998–1999) and race-bridged postcensus population estimates [18] for postvaccine years (2000–2007) as denominators. Serotype-specific rates were calculated by imputing serotype for cases with missing isolates based on age group–specific distribution of cases with known serotypes. We assessed changes in incidence by calculating relative risks and 95% confidence intervals (CIs), expressed as percentage changes in rates of disease ([relative risk − 1] × 100%). We calculated case-fatality ratios (CFRs) as the proportion of case patients with known outcome who died during their hospitalization or illness episode. Outcome was unknown or missing for <1% of patients.

Patients with any of the following chronic illnesses were classified as having a comorbid condition: human immunodeficiency virus (HIV) infection (with or without AIDS), Hodgkin disease, leukemia, myeloma, nephrotic syndrome, dialysis, immunoglobulin deficiency, asplenia, organ or bone marrow transplant, sickle cell disease, immunosuppressive therapy, cerebrospinal fluid leak, cirrhosis, diabetes, congestive heart failure, cardiomyopathy, atherosclerotic cardiovascular disease, chronic obstructive pulmonary disease, or alcohol abuse. Patients from Georgia were excluded from the analysis of comorbid conditions, because this information was not collected there before year 2000.

To examine the independent contributions of comorbid conditions and serotype to severe IPD outcomes, we constructed 2 separate multivariable logistic regression models, one for children <5 years and one for adults ⩾18 years old, evaluating serotype group (PCV7 types vs all other types) and presence of comorbid conditions as predictors of death or hospitalization due to IPD. Death was not evaluated as an outcome in the first model, because very few deaths were identified among children. Similarly, because the majority of adult patients (94%–97% annually) were hospitalized, hospitalization was not evaluated as an outcome in the second model. We assessed 2-way interactions and colinearity of covariables in the models.

Using methods described elsewhere [19], we estimated the annual number of IPD cases and deaths prevented, including PCV7-type IPD cases prevented among vaccinated children and unvaccinated children and adults through reduced transmission from vaccinated children [20]. We estimated coverage for ⩾1 or ⩾3 doses of PCV7 for each birth cohort during 1997–2006, as described elsewhere [3], and applied this range of coverage estimates to obtain the number of cases prevented annually among vaccinated children. We reported only the estimates applying PCV7 coverage for ⩾3 doses, because results obtained using the range of coverage estimates were similar (data not shown). We used SAS, version 9.1 (SAS Institute), and EpiInfo, version 3.3.2 (CDC), software for statistical analysis; χ^2 or

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Fisher's exact tests were used to compare the proportions of patients with IPD who were hospitalized or had comorbid conditions and to compare CFRs in 2006–2007 with those in 1998–1999. Differences were considered statistically significant at $P < .05$ (2-sided P values).

ABCs case reporting and isolate collection were considered to be surveillance activities and were exempt from CDC institutional review. The surveillance protocol was also evaluated by each participating surveillance site, and either the protocol was deemed exempt from review or appropriate institutional review board approval was obtained. Informed consent was not required by the CDC or individual site institutional reviews.

RESULTS

From 1998 to 2007, 30,032 cases of IPD were identified, including 5410 among children aged <5 years. Eighty-nine percent of cases (range, 87%–90% by year) had isolates available for serotyping. The IPD incidence for all ages declined from 24.4/100,000 population ($n = 4048$) in 1998–1999 to 13.5 cases per 100,000 population ($n = 2576$) in 2007 (−45%; 95% CI, −47% to −42%) (Table 1). The incidence of PCV7-type IPD for all ages decreased significantly, and the incidence of IPD caused by non-PCV7 types and serotype 19A increased significantly in 2007 compared with baseline (Table 1).

Changes in overall and PCV7-type IPD by age group. Overall IPD rates declined from baseline through 2002 and leveled off from 2004 through 2007 (Figure 1), whereas PCV7-type IPD rates continued to decline (Figure 2*A* and 2*B*). In 2007, children <5 years old, the PCV7 target age group, accounted for 12% of all IPD cases, compared with 28% at baseline. Among children <2 months old, too young to be immunized, the overall IPD incidence decreased from 49.5 at baseline to 25.0 cases per 100,000 population in 2007 (−50%; 95% CI, −1% to −74%), and the incidence of PCV7-type IPD in this age group decreased from 35.2 to 2.3 cases per 100,000 population (−94%; 95% CI, −52% to −99%). Among adults, the greatest absolute decreases in overall IPD rates were seen among those ⩾65 years old (rate difference, −22.2 cases per 100,000 population). The relative reductions in PCV7-type IPD were similar across adult age groups, ranging from 87% among 50–64-year-old persons to 92% among ⩾65-year-old persons (Table 1).

In 2006–2007, PCV7 serotypes accounted for only 2% of all IPD among children aged <5 years, compared with 83% at baseline. The proportions of IPD cases caused by PCV7-type strains decreased from 56% to 10% and from 56% to 9% among 18–64-year-old and ⩾65-year-old adults, respectively (Table 2).

Changes in IPD caused by serotypes other than PCV7 types. We evaluated trends in IPD caused by PCV7-related serotypes (excluding 19A) to determine whether PCV7 may have had population-level effects on potentially cross-reactive serotypes. IPD caused by PCV7-related serotypes declined significantly among children aged <5 years, remained stable among older children and young adults, and increased significantly among ⩾50-year-old adults (Table 1). Reductions in PCV7-related serotypes among children <5 years were due mostly to declines in rates of serotype 6A/C IPD, for which we observed an 82% decline (from 5.1 to 0.9 cases per 100,000 population; 95% CI, −67% to −90%). No changes in rates of serotype 6A/C IPD were observed among 18–64-year-old adults, but among adults aged ⩾65 years, IPD rates caused by this serotypes increased 70% (from 2.2 to 3.8 cases per 100,000 population; 95% CI, +25% to +131%). The rate of IPD caused by serotype 23A increased from 0.2 to 0.5 cases per 100,000 population (+147%; 95% CI, +13% to +450%) and from 0.4 to 2.2 cases per 100,000 population (+514%; 95% CI, +227% to +980%) among 50–64-year-old and >65-year-old adults, respectively. No changes in other PCV7-related serotypes were observed among children or adults of any age group.

The incidence of IPD caused by serotype 19A increased significantly among all age groups (Table 1). Although percentage changes were large (range, +144% to +344%), absolute rate increases in each age group were relatively small (range, 0.4–8.5 cases per 100,000 population) compared with observed reductions in PCV7-type IPD (Figure 2*A* and 2*B*). Similarly, non–PCV7-type IPD rates increased significantly among children <5 years and all adults, and absolute rate differences ranged from 0.6 to 4.2 cases per 100,000 population (Table 1). The incidence of IPD caused by the 16 serotypes included in PPV23 but not in PCV7 increased 26% (from 16.7 to 21.1 cases per 100,000 population; 95% CI, +12% to +42%) among ⩾65-year-old adults and 48% (from 4.9 to 7.4 cases per 100,000 population; 95% CI, 27% to 72%) among 18–64-year-old adults. In 2006–2007, 47% of IPD episodes among children <5 years old were due to serotype 19A, with an additional 46% caused by other non-PCV7 types; the most common non-PCV7 serotypes were 7F (9%), 22F (5%), 33F (5%), and 3 (5%). In 2006–2007, the proportions of IPD cases among children <5 years old covered by serotypes contained in PCV7, PCV10, and PCV13 were 2%, 12%, and 68%, respectively. In 2006–2007, the proportions of IPD cases among ⩾65-year-old adults covered by serotypes contained in PCV7, PCV10, PCV13, and PPV23 were 9%, 16%, 50%, and 65%, respectively (Table 2).

Changes by syndrome and disease severity. Overall rates of bacteremia without focus, invasive pneumonia, and meningitis decreased significantly among all age groups, with the exception of meningitis among adults, for which reductions in PCV7-type disease were offset by increases in non–PCV7-type disease (Table 3). Rates of hospitalization (per 100,000 population) decreased significantly among all age groups. However, the proportion of pediatric and older adult patients resulting in hospitalization in 2006–2007 was higher than in 1998–1999

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Table 1. Changes in Incidence of Invasive Pneumococcal Disease, by Age Group and Serotype, 1998–1999 Average (Baseline) versus 2007

	Incidence, cases per 100,000 population		Change in rate (2007 vs baseline)	
Age group, serotype[a]	1998–1999 (n = 4048)	2007 (n = 2576)	Rate difference, cases per 100,000 population	Change, % (95% CI)
All ages				
All types	24.4	13.5	−10.9	−45 (−47 to −42)
Vaccine types	15.5	1.0	−14.5	−94 (−95 to −93)
Vaccine-related types	2.0	1.9	−0.1	−4 (−16 to +9)
19A	0.8	2.7	1.9	+253 (+203 to +310)
Nonvaccine types	6.1	7.9	1.8	+29 (+21 to +38)
<5 years				
All types	98.7	23.6	−75.1	−76 (−79 to −73)
Vaccine types	81.9	0.4	−81.5	−100 (−100 to −99)
Vaccine-related types	7.3	1.7	−5.6	−77 (−85 to −64)
19A	2.6	11.1	8.5	+324 (+214 to +472)
Nonvaccine types	6.8	10.3	3.5	+51 (+20 to +90)
5–17 years				
All types	4.2	2.4	−1.8	−43 (−55 to −26)
Vaccine types	2.4	0.2	−2.2	−94 (−97 to −85)
Vaccine-related types	0.2	0.2	0.0	+4 (−59 to +164)
19A	0.2	0.6	0.4	+212 (+54 to +535)
Nonvaccine types	1.5	1.4	−0.1	−2 (−31 to +40)
18–49 years				
All types	13.3	8.0	−5.3	−40 (−45 to −35)
Vaccine types	7.6	0.7	−6.9	−91 (−93 to −88)
Vaccine-related types	1.1	1.1	0.0	+1 (−22 to +29)
19A	0.4	1.4	1.0	+259 (+166 to +384)
Nonvaccine types	4.2	4.8	0.6	+14 (+1 to +29)
50–64 years				
All types	24.0	19.8	−4.2	−18 (−25 to −9)
Vaccine types	12.8	1.7	−11.1	−87 (−90 to −83)
Vaccine-related types	1.9	2.6	0.7	+35 (+1 to +80)
19A	0.7	3.2	2.5	+344 (+202 to +551)
Nonvaccine types	8.6	12.3	3.7	+43 (+25 to +64)
⩾65 years				
All types	60.1	37.9	−22.2	−37 (−42 to −32)
Vaccine types	33.7	2.7	−31.0	−92 (−94 to −89)
Vaccine-related types	5.8	7.2	1.4	+25 (+1 to +54)
19A	2.2	5.4	3.2	+144 (+84 to +223)
Nonvaccine types	18.3	22.5	4.2	+23 (+9 to +38)

[a] Vaccine types include seven 7-valent pneumococcal conjugate vaccine (PCV7) serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F). Vaccine-related types include serotypes in the same serogroup as PCV7 serotypes (6A, 9A, 9B, 9L, 9N, 18A, 18B, 18F, 19C, 23A, and 23B), excluding serotype 19A; serotype 6A includes recently identified serotype 6C [15], which is not distinguished from type 6A by the Quellung reaction. Nonvaccine types include serotypes other than vaccine serotypes, vaccine-related serotypes, and serotype 19A

(56% vs 32% among children aged <5 years [$P < .001$]; 97% vs 94% among adults aged ⩾65 years [$P = .003$]). These observations raised the hypotheses that non-PCV7 serotypes might be more virulent than PCV7 serotypes or that the populations may have become more susceptible to circulating pneumococcal strains and more likely to experience adverse outcomes.

To test these hypotheses, we evaluated trends in the prevalence of comorbid conditions among persons with IPD. From baseline to 2006–2007, the proportion of patients with IPD who had ⩾1 comorbid condition increased from 3% to 7% among children aged <5 years ($P = .003$), from 52% to 59% among adults 18–64 years old ($P < .001$), and from 69% to 81% among those ⩾65 years old ($P < .001$). In multivariable analysis

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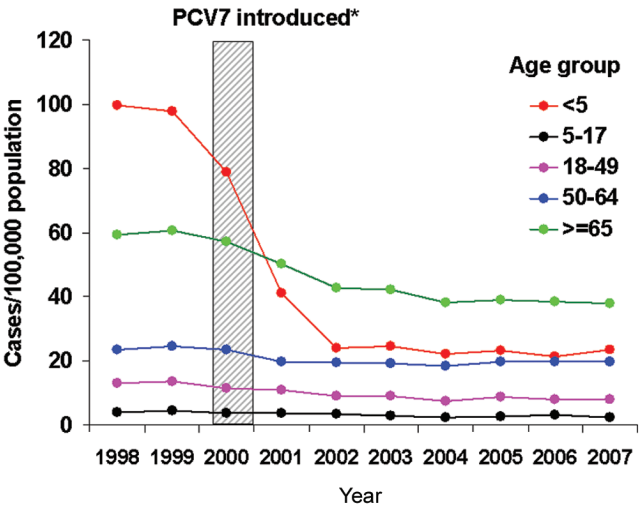

Figure 1. Changes in overall invasive pneumococcal disease (IPD) incidence rates by age group, 1998–2007. *Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000.

controlling for serotype group (PCV7 types vs all other types) and presence of comorbid conditions, case patients <5 years old with comorbid conditions were more likely than those without them to be hospitalized (adjusted odds ratio [aOR], 9.9; 95% CI, 3.0–33.0); hospitalization was equally common among PCV7 types and all other types (aOR, 1.3; 95% CI, 0.3–5.3).

Among children aged <5 years old, the CFR increased from 0.7% at baseline to 1.4% in 2006–2007 ($P = .08$), whereas the overall IPD mortality rate remained stable (Table 3). There were no changes in the CFR among adults 18–64 years old (11% vs 10%; $P = .197$) or ⩾65 years old (19% vs 18%; $P = .657$), but mortality rates due to overall and PCV7-type IPD declined significantly among all adult age groups. In a multivariable model controlling for age, presence of comorbid conditions, and serotype group (PCV7 types vs all others), infections in ⩾18-year-old adult patients with comorbid conditions were more likely to be fatal than those occurring in adults without comorbid conditions (aOR, 1.5; 95% CI, 1.2–1.9), whereas serotype group did not affect the likelihood of fatal outcome (aOR, 1.1; 95% CI, 0.8–1.5).

Estimating changes in IPD burden in the United States. Compared with the expected number of PCV7-type IPD cases in the absence of vaccination, an estimated 5200–43,100 fewer cases occurred annually during 2000–2007. Among vaccinated children aged <5 years, based on PCV7 coverage data for ⩾3 doses, an estimated 2700–14,000 fewer PCV7-type cases occurred annually. Among unvaccinated children and adults, 2500–29,000 fewer PCV7-type cases occurred annually. After accounting for an annual increase of 2900–10,500 cases caused by serotypes other than PCV7 types, an estimated 211,000 fewer IPD cases occurred during 2000–2007. An estimated 13,000 fewer IPD-related deaths occurred in the United States since the introduction of PCV7.

DISCUSSION

Introduction of PCV7 in the United States has been associated with dramatic reductions in the burden of IPD, and marked public health benefits remain evident 7 years later. In our surveillance areas, the overall IPD incidence in 2007 was 45% lower for all age groups and 76% lower for children aged <5 years compared with prevaccine baseline incidence. Overall disease rates in 2007 among children aged <5 years (23.6 cases per

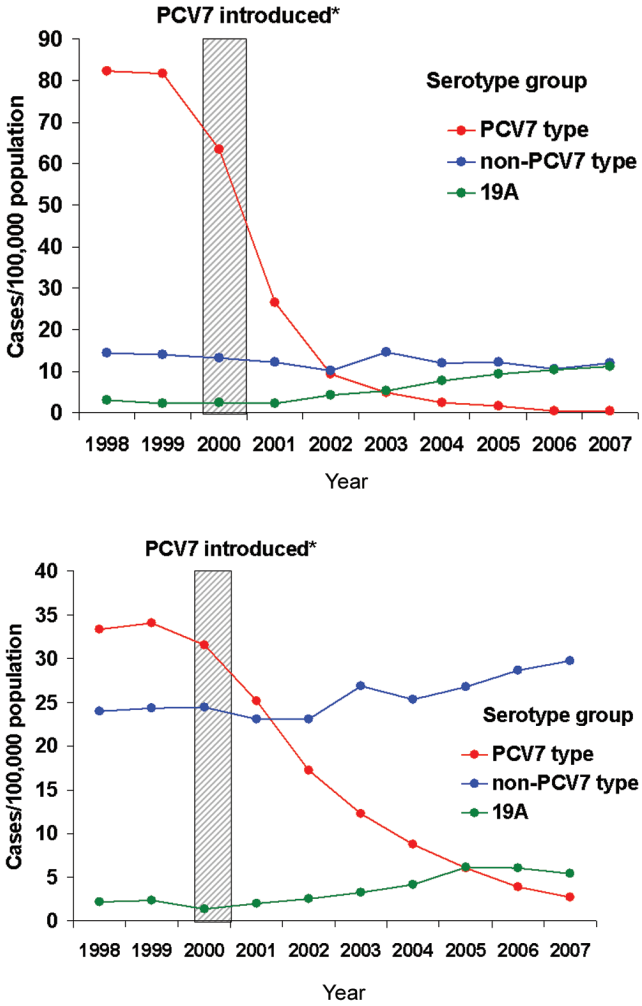

Figure 2. Changes in invasive pneumococcal disease (IPD) incidence by serotype group among children aged <5 years *(A)* and adults aged ⩾65 years *(B)*, 1998–2007. *Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000.

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Table 2. Distribution of Pneumococcal Serotypes by Age Group before and after Introduction of 7-Valent Pneumococcal Conjugate Vaccine (PCV7)

	Proportion of strains, by age group, %					
	<5 years		18–64 years		⩾65 years	
Vaccine serotype and formulation	1998–1999 (n = 1903)	2006–2007 (n = 519)	1998–1999 (n = 2983)	2006–2007 (n = 2461)	1998–1999 (n = 1982)	2006–2007 (n = 1432)
14	32.9	0.2	12.3	0.5	16.2	1.4
19F	11.1	1.2	4.1	1.4	3.8	1.4
6B	10.7	0.2	5.2	0.7	7.1	1.4
18C	8.8	0.4	3.4	0.9	2.8	0.1
23F	6.9	0	6.8	0.6	9.2	1.1
4	6.8	0.2	14.5	4.3	8.2	2.0
9V	5.5	0	9.6	1.3	8.7	1.2
PCV7	82.7	2.2	55.9	9.7	56.0	8.6
1	0.7	0.4	2.4	0.7	1.2	0.4
7F	0.7	9.3	3.8	12.0	2.0	7.3
5	0.1	0	0.2	0.2	0.1	0
PCV10	84.2	11.9	62.3	22.6	59.3	16.3
3	0.4	5.0	4.5	7.8	6.0	9.2
6A/6C[a]	5.1	3.7	4.0	5.6	6.5	9.5
19A	2.6	47.2	2.9	16.6	3.7	14.9
PCV13	92.3	67.8	73.7	52.6	75.5	49.9
9N	0.4	0.6	2.3	3.3	1.1	1.5
12F	1.3	1.5	5.6	3.9	3.0	2.1
15B/C	0.9	3.9	1.0	2.1	1.0	1.9
33F	0.7	4.8	0.8	3.3	0.9	2.7
22F	0.6	4.8	3.6	8.0	4.5	7.1
10A	0.2	2.7	0.8	1.5	0.7	1.2
11A	0.2	0.8	1.9	2.4	2.4	4.4
2	0	0	0	0	0	0
8	0	0	1.3	1.8	0.7	1.0
17F	0	0.4	0.3	1.5	0.2	1.3
20	0	0.2	0.7	0.9	0.6	1.1
PPV23[a]	91.5	83.8	88.0	75.7	84.1	64.7
9A	1.4	0	1.0	0.1	1.0	0.1
18B	0.2	0.2	0.1	0.1	0	0.1
23A	0.2	1.7	0.5	2.2	0.6	5.5
23B	0.2	1.4	0.1	1.2	0.2	1.7
38	0.5	2.7	0.7	1.2	1.0	1.5
Nontypeable	0.3	0.8	0.2	0.8	0.3	1.0
35B	0.2	0.6	0.5	2.1	0.9	2.3
16F	0.1	1.5	0.5	3.1	0.8	4.4
15A	0.1	1.5	0.3	2.4	0.3	4.3
35F	0.1	0.4	0.7	1.1	0.7	1.2
Others	0.1	1.7	3.4	4.4	3.6	3.7

[a] Serotype 6A is included in 13-valent pneumococcal conjugate vaccine (PCV13) and not in PPV23. Serotype 6A includes recently identified serotype 6C [15], which is not distinguished from type 6A by the Quellung reaction.

100,000 population) and adults ⩾65 years old (37.9 cases per 100,000 population) remain below the US Department of Health and Human Services Healthy People 2010 objectives (children aged <5 years, 46 cases per 100,000 population; adults aged ⩾65 years, 42 cases per 100,000 population). Our data complement the findings of recent studies documenting reductions in meningitis [21], noninvasive pneumonia [22], otitis media [23, 24], and pneumococcal infections resistant to antibiotics [25] after PCV7 introduction. Although noninvasive pneumococcal disease is more common than invasive disease,

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Table 3. Changes in Disease Rates, by Serotype Group, Clinical Syndrome, and Disease Severity, among Patients with Invasive Pneumococcal Disease, 1998–1999 and 2006–2007

	All serotypes			Vaccine serotypes			Other than vaccine serotypes		
Age, clinical syndrome, and disease severity	1998–1999	2006–2007	P^a	1998–1999	2006–2007	P	1998–1999	2006–2007	P
Age <5 years, no. of cases	1126	289		934	6		192	284	
Overall	98.7	22.6	<.001	81.9	0.4	<.001	16.8	22.1	<.001
Clinical syndrome[b]									
Bacteremia without focus	67.9	10.1	<.001	56.6	0.3	<.001	11.4	9.8	0.10
Invasive pneumonia	16.3	8.3	<.001	13.3	0.1	<.001	3.0	8.2	<.001
Meningitis	4.7	1.7	<.001	3.8	0.1	<.001	0.9	1.6	.02
Hospitalization									
Hospitalized	31.4	12.6	<.001	25.3	0.3	<.001	6.1	12.3	<.001
Outpatient	67.3	9.8	<.001	56.6	0.2	<.001	10.7	9.7	0.27
Mortality, deaths/ 100,000 population	0.7	0.3	.08	0.6	0.0	.001	0.1	0.3	.09
Age 18–64 years, no. of cases	1660	1387		930	133		730	1254	
Overall	15.7	11.3	<.001	8.8	1.1	<.001	6.9	10.2	<.001
Clinical syndrome									
Bacteremia without focus	4.1	1.7	<.001	2.3	0.1	<.001	1.8	1.6	0.11
Invasive pneumonia	10.5	8.3	<.001	5.9	0.8	<.001	4.6	7.5	<.001
Meningitis	0.9	0.8	0.53	0.5	0.1	<.001	0.4	0.7	<.001
Hospitalization									
Hospitalized	14.4	10.3	<.001	8.1	1.0	<.001	6.3	9.3	<.001
Outpatient	1.3	1.0	.003	0.7	0.1	<.001	0.6	0.9	<.001
Mortality, deaths/ 100,000 population	1.6	1.1	<.001	0.9	0.1	<.001	0.7	1.0	.03
Age ⩾65 years, no. of cases	1136	791		638	68		498	723	
Overall	60.1	38.2	<.001	33.7	3.3	<.001	26.4	34.9	<.001
Clinical syndrome									
Bacteremia without focus	14.4	6.4	<.001	7.8	0.5	<.001	6.5	5.9	.26
Invasive pneumonia	42.8	29.0	<.001	24.4	2.4	<.001	18.5	26.6	<.001
Meningitis	1.9	1.5	.14	0.8	0.1	<.001	1.1	1.4	.28
Hospitalization									
Hospitalized	56.7	36.7	<.001	31.9	3.1	<.001	24.8	33.7	<.001
Outpatient	3.4	1.3	<.001	1.9	0.2	<.001	1.5	1.1	.15
Mortality, deaths/ 100,000 population	11.2	7.0	<.001	5.1	0.5	<.001	6.2	6.5	.58

NOTE. Unless otherwise specified, values represent average rates (cases per 100,000 population) at baseline (1998 and 1999) and after introduction of the 7-valent pneumococcal conjugate vaccine (2006 and 2007).

[a] P values determined with χ^2 or Fisher's exact test comparing the estimated numbers of case and noncase patients (total surveillance population minus estimated number of case patients) in 2006 and 2007 (combined years) with the estimated number of case and noncase patients in 1998 and 1999 (combined years).

[b] Clinical syndromes are not mutually exclusive, except for bacteremia without focus.

surveillance for invasive disease avoids the difficulty of distinguishing between upper respiratory tract colonization and true infection and allows detection of serotype-specific changes in disease incidence.

Following a dramatic decline after PCV7 introduction, overall IPD incidence rates during 2002–2007 have been steady. However, sustained year-to-year reductions in the incidence of PCV7-type IPD in the vaccine target population as well as unvaccinated populations strongly suggest continued benefits of the vaccine. The incidence of IPD caused by vaccine serotypes has declined to <1 cases per 100,000 population among children aged <5 years. Beneficial indirect effects of PCV7 among unvaccinated populations documented in earlier studies [5, 6, 26] were still evident in 2007 for ages. Among infants <2 months old, we found that reductions in overall and vaccine-type IPD reported previously [20] have continued and remain substantial, a finding relevant to developing countries, where pneumococcal infections are acquired earlier in life [27]. Our data also show evidence of herd immunity among children aged 5–17 years, many of whom are too old to have received PCV7. Despite large reductions in overall and PCV7-type IPD rates among adults of all ages, rates in 2007 remain high compared with disease rates in children, especially among older adults.

Although PCV7-type IPD incidence continued to decline through 2007, further reductions in overall IPD during 2002–2007 were offset by increases in IPD serotypes not included in PCV7, predominantly serotype 19A. Rates of IPD caused by serotype 19A have increased for all ages, making this serotype now the most common among all age groups. Importantly, absolute increases in rates of non–PCV7-type IPD remain mod-

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est in comparison with the reductions in PCV7-type IPD observed since 2000. However, recent studies reported more prominent increases in non-PCV7 serotypes in some populations, and these increases have partially eroded disease reductions observed after PCV7 introduction [28–31]. The reasons for the varying magnitude of increases in non-PCV7 serotypes among different populations are unknown, but differences in the frequency of comorbid conditions or immunosuppression [28, 32], antibiotic use [33], serotype distributions, or environmental conditions [31] could be important. Although the effect of increases in nonvaccine serotypes on overall IPD rates was less apparent in other studies [5, 26], increases in non-PCV7 types have been observed in recent studies of carriage and acute otitis media [27, 34, 35].

We observed significant increases in the incidence of meningitis and invasive pneumonia caused by nonvaccine serotypes but not in the incidence of primary bacteremia caused by these serotypes. This observation may relate to changes in the circulating serotypes and their ability to cause different clinical syndromes [8–10, 36–38]. Although the incidence of hospitalization or death associated with IPD decreased, we observed increases in the proportions of patients with IPD who were hospitalized among all age groups and increases in CFRs among children compared with pre-PCV7 years. Increases in nonvaccine serotypes were more prominent among hospitalized patients than among outpatients. These findings raised the question of whether, in the setting of widespread immunization with PCV7, nonvaccine serotype cases are more likely than PCV7-type cases to be associated with death or hospitalization. As in another recent study [39], we found that the presence of comorbid conditions, and not infection with nonvaccine serotypes, had greater influence on IPD severity. Reductions in IPD after PCV7 introduction may have been greater among healthy individuals than among those with underlying comorbid conditions. The latter group is at increased risk of severe outcomes of IPD because of their comorbid conditions, irrespective of the serotype to which they are exposed.

We considered whether increased use of PPV23 could explain the observed reductions in IPD among adults. This seems unlikely, given that increases in PPV23 coverage have been modest [40], declines in IPD were limited to PCV7-type cases, and rates of IPD caused by serotypes that were only in PPV23 increased. The finding that the rate of IPD caused by the serotypes unique to PPV23 has increased in the elderly (subjects ⩾65 years old) also merits comment. A likely explanation is increased carriage of these strains by children vaccinated with PCV7 and subsequent increased exposure of elderly adults who were still susceptible to these strains. The possibility that PPV23 is at least somewhat protective against these serotypes should be considered. However, these ecologic data cannot prove the relative contribution of PPV23 to the observed trends.

Factors other than PCV7 introduction may have played a role in some of the observed increases in the incidence of non–PCV7-type IPD. The distribution of pneumococcal serotypes, including serotype 19A, can change over time in the absence of vaccine [41, 42]. In addition, characteristics of circulating pneumococcal strains that place them at selective advantage, such as the ability to cause invasive disease [36, 43], prevalence in nasopharyngeal carriage [36], resistance to commonly prescribed antibiotics [7, 43], and age-based susceptibility to different serotypes [41], could contribute to changes in serotype distribution.

This study has certain limitations. Our surveillance areas may not be representative of the United States as a whole. We adjusted for differences in age and racial distributions between our study population and the United States, but there may be residual confounding. We could not directly explore the relationship between PCV7 coverage and IPD incidence, because vaccination status was not available for individual IPD cases. Influenza activity [44] and reductions in smoking prevalence among adults [45] may also have independently contributed to changes in disease incidence. However, these factors were unlikely to have influenced rates of IPD caused by PCV7 serotypes more than other types, and the relative magnitude of the declines, sustained over several years, support the hypothesis that the observed IPD trends are associated with PCV7 introduction. Changes in clinical practices after PCV7 introduction, such as decreases in blood culturing among children presenting with an acute febrile illness, may have influenced the findings of increases in nonvaccine serotypes among hospitalized patients and not among outpatients, as well as increases in these serotypes among patients with meningitis or invasive pneumonia and not among those with primary bacteremia. We did not distinguish between serotypes 6A and 6C for all years of our study, and we were therefore unable to evaluate the contribution of these serotypes to the observed differences in IPD trends among adults versus children [46].

After consistently robust reductions in IPD rates during the first 3 years of PCV7 use in the United States, the overall trends during 2002–2007 reached an equilibrium between reductions in PCV7-type IPD and increases in non-PCV7 serotypes. This equilibrium and the emergence of non-PCV7 serotypes, especially among persons with underlying illnesses, highlight the need for several important prevention measures [28, 32]. First, improving coverage with existing vaccines [47, 48] is important, because disparities in coverage with the pediatric vaccine [4] and low coverage with PPV23 continue, despite the long-standing availability of PPV23 [49]. Second, new higher-valency conjugate vaccines are in development. Assuming their effectiveness is similar to that of PCV7, they may be able to prevent pneumococcal disease caused by a greater variety of serotypes. Use of conjugate vaccines among adults, especially those with

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underlying illnesses, may also play an important role, as was recently suggested by a study of PCV7 among HIV-infected adults [50]. Third, common protein vaccines now under development may provide broad protection against pneumococcal diseases, regardless of the serotype involved, therefore eliminating the issue of changes in the prevailing serotypes. Finally, introduction of pneumococcal conjugate vaccines into more countries should be a high priority [51], given the large burden of disease globally and sustained reductions in disease observed in the United States.

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CDC. Chris Van Beneden, Tami H. Skoff, Carolyn Wright, Elizabeth Zell, Saundra Mathis, Richard Facklam, Alma R. Franklin, Patricia L. Shewmaker, and Delois Jackson.

Acknowledgments

We are grateful for the contributions of members of the ABCs/Emerging Infections Program Network.

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