

Invasive Pneumococcal Disease a Decade after Pneumococcal Conjugate Vaccine Use in an American Indian Population at High Risk for Disease

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(See the editorial commentary by Vanderkooi and Kellner, on pages 1247–1248.)

Background. Before 7-valent pneumococcal conjugate vaccine (PCV7) introduction, invasive pneumococcal disease (IPD) rates among Navajo were several-fold those of the general US population. Only 50% of IPD cases in children involved PCV7 serotypes.

Methods. We conducted active, population-based surveillance for IPD for the period 1995–2006. We documented case characteristics and serotyped the isolates.

Results. Over 12-year period, we identified 1508 IPD cases, 447 of which occurred in children aged <5 years. Rates of IPD due to vaccine serotypes among children aged <1 year, 1 to <2 years, and 2 to <5 years decreased from 210, 263, and 51 cases per 100,000 population, respectively in 1995–1997 to 0 cases in 2004–2006 ($P < .001$). Among adults aged ≥ 65 years, rates of IPD due to vaccine serotypes decreased 81% (95% confidence interval, -98% to -9% ; $P = .02$). Rates of nonvaccine serotype IPD were unchanged in all age strata except for persons aged 18 to <40 years, among whom the rate decreased by 35% from 27 to 18 cases per 100,000 population (95% confidence interval, -57% to -1% ; $P = .03$).

Conclusions. Vaccine-serotype IPD has virtually been eliminated in the PCV7 era among Navajo of all ages. Overall rates of nonvaccine-serotype IPD have not increased, although increases have occurred for some individual types. Rates of all-serotype IPD among Navajo children remain 3–5-fold greater than in the general US population.

Routine infant immunization with 7-valent pneumococcal conjugate vaccine (PCV7) in the United States and elsewhere has remarkably reduced the burden of *Streptococcus pneumoniae* (pneumococcus) disease. The least-developed countries in Africa and Asia—regions accounting for >90% of annual pneumococcus-related deaths—are positioned to introduce pneumococcal conjugate vaccine (PCV) through Global Alliance for Vaccines and Immunisation (GAVI) Alliance financing

[1] and World Health Organization policy statements [2]. Various countries are reporting the impact of PCV7. However, some reports lack robust pre-vaccine period data on disease burden or serotypes. Careful interpretation of PCV impact data is essential to assure that appropriate inferences are drawn.

Before the availability of PCV7, Navajo, White Mountain Apache, and Alaska Natives had rates of invasive pneumococcal disease (IPD) 5–20-fold greater than those of the general US population [3–6]. A community-randomized PCV7 efficacy trial was conducted among Navajo and White Mountain Apache during 1997–2000 [7]; immediately before the trial, only 50% of IPD cases among Navajo children were due to PCV7 serotypes [4]. PCV7 was introduced into the infant immunization schedule after the trial, allowing the analysis of PCV7 impact during a decade of use.

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Table 1. Incidence of Invasive Pneumococcal Disease (IPD) by Age, Serotype, and 3-Year Period

Serotype, period	No. of cases per 100,000 population (95% CI), by age										All ages
	<1	1 to <2	2 to <5	5 to <18	18 to <40	40 to <65	≥65	<2	<5	>18	
All-serotype IPD											
1995–1997	385 (298–490)	426 (334–535)	99 (74–130)	15 (10–21)	30 (24–38)	80 (66–96)	162 (126–205)	405 (341–479)	222 (191–256)	60 (53–68)	66 (61–73)
1998–2000	341 (254–449)	388 (295–501)	36 (22–61)	14 (9–20)	30 (23–38)	72 (59–87)	178 (141,221)	365 (300–440)	167 (139–199)	60 (53–68)	58 (52–64)
2001–2006	230 (177–294)	172 (126–228)	27 (17–41)	14 (11–19)	20 (16–25)	70 (61–80)	157 (133–184)	201 (165–242)	96 (81–114)	54 (49–59)	47 (43–51)
2001–2003	251 (1758–350)	194 (128–282)	26 (13–47)	11 (7–17)	20 (15–27)	57 (46–71)	150 (117–189)	223 (171–285)	105 (82–132)	48 (41–55)	43 (38–48)
2004–2006	208 (138–300)	148 (91–229)	27 (14–49)	17 (12–24)	20 (14–26)	82 (68–97)	163 (130–203)	178 (131–236)	88 (67–113)	59 (52–67)	51 (45–56)
Reduction for 1995–1997 vs 2004–2006, % (95% confidence interval)	46 (15–67)	65 (42–80)	73 (47–87)	16.0 (–43 to 51)	35 (4–57)	–3 (–34 to 21)	1 (–38 to 29)	56 (39–69)	61 (47–71)	2 (–17 to 18)	24 (12–40)
VT IPD^a											
1995–1997	210 (147–291)	263 (192–351)	51 (33–74)	2 (<1 to 5)	3 (1–6)	11 (6–18)	21 (10–40)	236 (188–294)	124 (101–150)	8 (5–11)	20 (17–24)
1998–2000	161 (103–239)	214 (147–302)	25 (12–44)	2 (<1 to 4)	8 (4–12)	22 (15–31)	25 (12–44)	187 (142–243)	90 (70–114)	14 (11–19)	19 (16–22)
2001–2006	26 (10–53)	29 (13–58)	6 (2–14)	1 (<1 to 3)	2 (<1 to 4)	7 (4–10)	14 (7–23)	27 (15–45)	15 (9–23)	5 (4–7)	5 (4–6)
2001–2003	50 (20–104)	50 (20–104)	12 (4–28)	2 (<1 to 5)	3 (1–6)	8 (4–14)	22 (10–40)	50 (28–84)	27 (16–43)	10 (7–14)	8 (6–10)
2004–2006	0.0 (0–27)	0.0 (0–27)	<1 (0–9)	<1 (0–3)	2 (<1 to 5)	5 (2–10)	4 (<1 to 14)	0 (0–14)	<1 (0–5)	3 (2–5)	2 (1–4)
Reduction for 1995–1997 vs 2004–2006, % (95% confidence interval)	100 (86–100)	100 (90–100)	100 (90–100)	72 (–182 to 99)	40 (–135 to 870)	54 (–16 to 83)	81 (9–98)	100 (94–100)	100 (95–100)	57 (16–79)	89 (81–94)
NVT IPD^a											
1995–1997	175 (118–250)	169 (113–243)	51 (33–74)	13 (8–18)	27 (21–35)	69 (56–84)	141 (107–181)	172 (131–222)	97 (77–120)	53 (46–73)	46 (42–52)
1998–2000	181 (119–263)	174 (114–255)	13 (5–29)	12 (8–18)	22 (16–29)	50 (39–63)	155 (121–196)	177 (133–232)	79 (60–102)	46 (40–53)	40 (35–44)
2001–2006	208 (158–269)	142 (101–195)	22 (13–35)	13 (10–17)	18 (14–22)	63 (55–73)	143 (120–169)	175 (142–214)	83 (69–100)	49 (44–54)	42 (39–46)
2001–2003	201 (134–291)	144 (88–222)	17 (7–35)	9 (5–15)	18 (13–24)	49 (38–62)	128 (98–165)	172 (127–229)	79 (60–103)	41 (35–48)	36 (31–40)
2004–2006	215 (144–309)	148 (91–229)	27 (14–49)	17 (11–24)	18 (13–24)	77 (64–92)	159 (125–198)	182 (134–240)	89 (68–115)	56 (49–63)	48 (43–54)
Reduction for 1995–1997 vs 2004–2006, % (95% confidence interval)	20 (–111 to 28)	12 (–60 to 53)	46 (–13 to 76)	–33 (–133 to 24)	35 (1–57)	–12 (–48 to 16)	–13 (–61 to 20)	–6 (–57 to 29)	8 (–30 to 35)	–6 (–28 to 12)	4 (–12 to 18)

NOTE: Data are no. of cases per 100,000 population (95% confidence interval), unless otherwise indicated Annual rates, by age strata, are available from authors. NVT, nonvaccine type; VT, vaccine type.
^a VT and NVT rates may not sum to all-serotype rates because some cases had multiple serotypes detected.

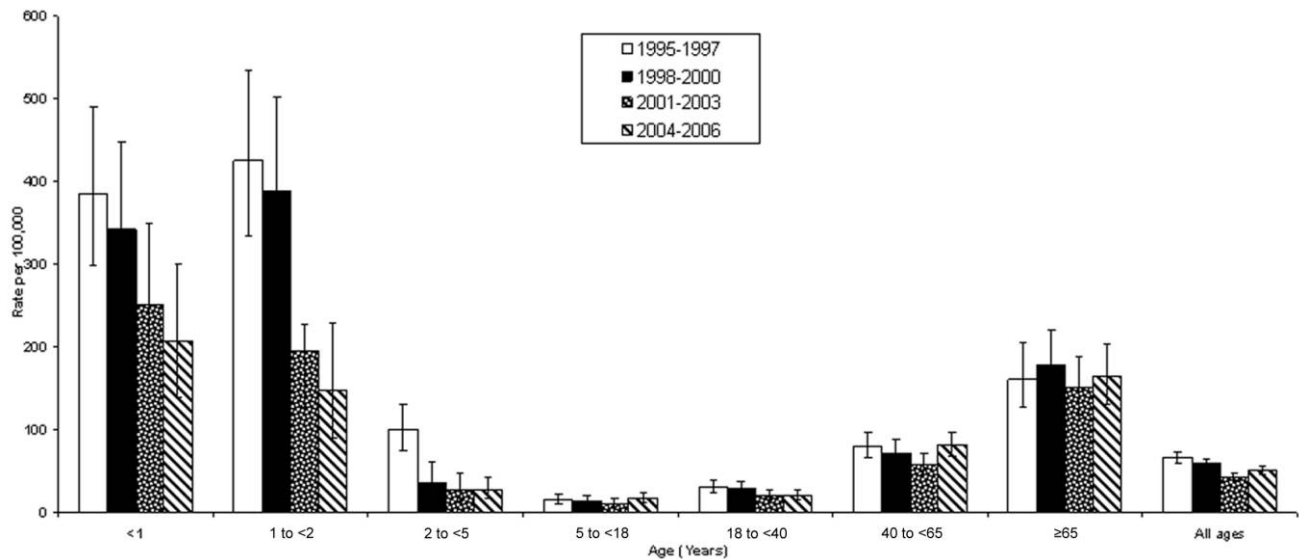


Figure 1. Rate of all-serotype invasive pneumococcal disease among Navajo, by age and time period. *White bars*, 1995–1997; *black bars*, 1998–2000; *dotted bars*, 2001–2003; *striped bars*, 2004–2006.

IPD epidemiology among Navajo is characterized by (1) high rates of IPD [4] and colonization [8], (2) a significant proportion of disease caused by non-PCV7 serotypes [4, 5], and (3) a high burden of all-cause respiratory disease [9] all within a context of low infant mortality and high access to medical care.

MATERIALS AND METHODS

The Navajo Nation, in the southwestern United States, is the largest American Indian reservation, with >200,000 tribal members living on or around the 25,000 mile² (>65,000 km²) reservation; ~4000 children are born annually. Health care is administered free of charge to registered tribal members through the tribe or the Indian Health Service (IHS), an agency of the US federal government. Six hospitals on the reservation provide inpatient and outpatient care; 21 additional facilities offer outpatient services.

We have conducted active, laboratory and population-based surveillance for IPD on and around the Navajo Nation since 1988. Clinical microbiology laboratories at IHS and non-IHS facilities serving Navajo residents were contacted daily to weekly to identify IPD cases. We collected available isolates and information on underlying medical conditions, clinical syndrome, and illness outcome by record review.

An IPD case was defined as isolation of pneumococcus from a normally sterile site in a Native American residing on or adjacent to the Navajo reservation. Serotypes were determined for the isolates (Quellung reaction, Arctic Investigations Pro-

gram, Centers for Disease Control and Prevention) with commercial antisera (Statens Serum Institute). Isolates were categorized as PCV7 vaccine type (VT; types 4, 6B, 9V, 14, 18C, 19F, or 23F) or PPV23 (23-valent pneumococcal polysaccharide vaccine) VT (serotype 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17E, 18C, 19A, 19F, 20, 22F, 23F, or 33F). Non-vaccine-type (NVT) strains were those not found in the relevant formulation or identified as nontypeable. For serotype-specific counts and rate calculations, missing serotype data were imputed for each age/time-period strata, assuming that isolates not serotyped had the same serotype distribution as those typed. Within an age/time strata, the proportion of disease caused by each serotype was calculated from the serotyped isolates. These proportions were applied to the cases in that age/time strata for which serotype information was not available (eg, if a serotype made up 50% of the total known serotypes for a given age/time strata then 50% of the unknown serotype cases in that age/time strata were assigned to that serotype). VT and NVT case counts, rates, and proportions were calculated using the imputed serotype case counts. Although a greater proportion of isolates were not typed during the pretrial period, there was no difference in the proportion of isolates not typed by age strata or sex in each time period ($P>.25$ for all χ^2 tests).

We defined 4 periods, combining calendar years to increase denominators, mitigate year-to-year random variability and reduce statistical uncertainty: 1995–1997 (pre-trial), 1998–2000 (trial), 2001–2003 (early routine use), and 2004–2006 (late routine use). PCV7 was administered on the Navajo Nation during the trial from 3 July 1997 through 31 August 2000. In 1997, a

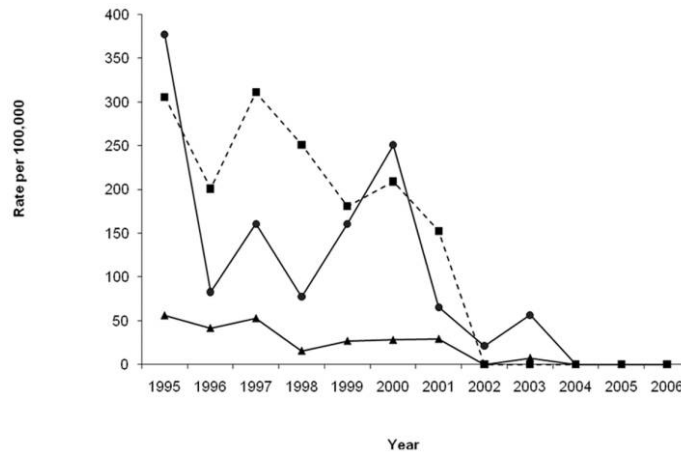


Figure 2. Rates of vaccine serotype invasive pneumococcal disease among Navajo children. Rates include imputed data for cases without serotype data. *Solid line with circles*, age of <1 year; *dotted line with squares*, age of 1 to <2 years; *solid line with triangles*, age of 2 to <5 years.

total of 716 Navajo infants were randomized to receive PCV7; 52 received 3 doses of PCV7 by the end of that year; therefore, we included 1997 in the pretrial period.

All PCV7 doses administered during the trial were documented in study records. Subsequently, we manually or electronically enumerated PCV7 doses administered at IHS facilities through December 2004, when coverage levels plateaued. To understand whether clinical practices changed from 1998 to 2006, we used electronic medical records to estimate the monthly proportion of febrile (ie, temperature >39.4°C [>102.9°F]) children aged <2 years who had a blood sample collected for culture.

Incidence rates and immunization coverage were calculated using IHS user population statistics for denominators. “Users”

are defined as American Indians of any tribe whose residence is on or immediately surrounding the reservation and who have had contact with the IHS facility in the preceding 3 years. Rates were rounded to the nearest whole number. Proportional rate reduction was calculated as follows: $[1 - \frac{\text{Period 2 rate}}{\text{Period 1 rate}}] \times 100\%$.

Statistical inference was made using the Poisson distribution, with incidence rates compared between time periods using exact methods. Time trends were analyzed by the χ^2 test with a single degree of freedom. Statistical calculations were performed using Stata software, version 9 (Stata Corp), or Visual Foxpro, version 8.0 (Microsoft). *P* values $\leq .05$ were considered to be statistically significant; all *P* values were determined using 2-sided tests.

This study was approved by the institutional review boards

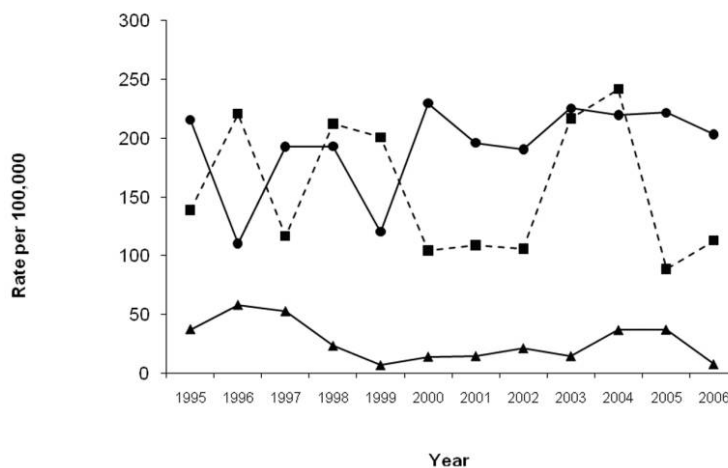


Figure 3. Rates of nonvaccine serotype invasive pneumococcal disease among Navajo children aged <5 years, by year. Rates include imputed data for cases without serotype data. *Solid line with circles*, age of <1 year; *dotted line with squares*, age of 1 to <2 years; *solid line with triangles*, age of 2 to <5 years.

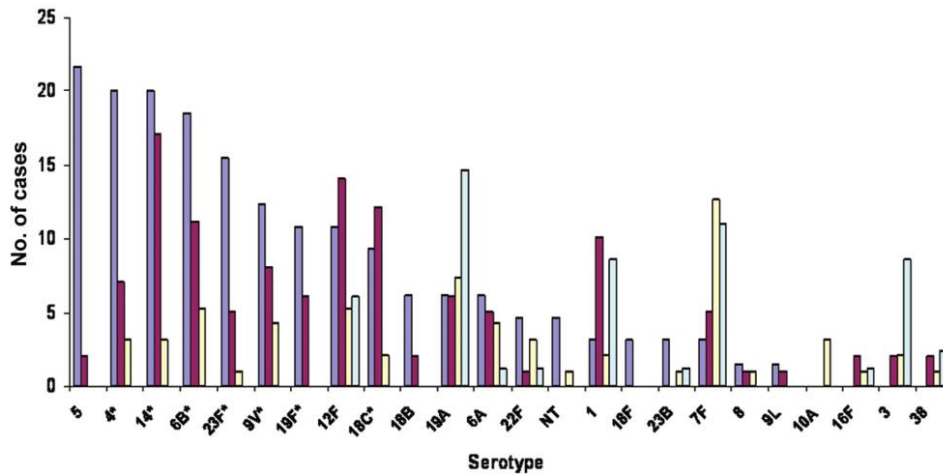


Figure 4. Distribution of serotypes among leading causes of invasive pneumococcal disease among children aged <5 years. Case counts are imputed to account for missing serotype data. *Dark blue bars*, 1995–1997; *red bars*, 1998–2000; *yellow bars*, 2001–2003; *light blue bars*, 2004–2006. *Serotypes contained in 7-valent pneumococcal conjugate vaccine.

of Johns Hopkins Bloomberg School of Public Health, the Navajo Nation, and the National IHS.

RESULTS

During the period 1995–2006, we identified 1508 IPD cases; 839 (56%) occurred in male patients. Cases were more common in winter (November–March) than summer months (data not shown). Most cases were single episodes of disease ($n = 1396$); 44 individuals had recurrent episodes. Isolates were available for typing for 1245 cases (83%). Typing completeness varied by surveillance period: 300 (64%) of 469 isolates from 1995–1997, 390 (97%) of 401 from 1998–2000, and 555 (87%) of 638 from 2001–2006.

The all-age, all-serotype IPD serotype rate decreased 24%, from 67 cases per 100,000 population in 1995–1997 to 51 cases per 100,000 population in 2004–2006 ($P < 0.001$) (Table 1 and Figure 1). The all-age VT IPD rate decreased 89%, from 20 cases per 100,000 population in 1995–1997 to 2 cases per 100,000 population in 2004–2006 ($P < 0.001$). All-age NVT IPD rates did not differ between these 2 time periods (46 vs 49 cases per 100,000 population, respectively; $P = .6$) (Table 1).

Of the 1508 cases, 447 (30%) occurred in children aged <5 years; serotypes were determined for 364 (81%) of these cases. The annual rate of all-serotype IPD decreased 61% ($P < 0.001$) among children aged <5 years between 1995–1997 and 2004–2006. The decrease in rate by more narrow age strata ranged from 46% to 73% (Table 1). Reductions in overall IPD rates in these children were attributable to the near elimination of VT IPD (Table 1 and Figure 2). The proportion reduction in each age stratum was 100% ($P < 0.001$); during 2004–2006, there

were no reported cases of VT IPD among children aged <5 years.

Age-stratified rates of NVT IPD are shown in Figure 3. There was no significant change in NVT IPD rates among children aged <5 years overall or in narrower age strata after PCV7 use. During 2004–2006, 33% and 42% of cases among children aged <5 years were caused by serotypes in the 10- and 13-valent PCV, respectively.

The serotype distributions of invasive isolates among children aged <5 years, by era, are shown in Figure 4. Rates of IPD due to serotypes 5 and 18B decreased by 100% ($P < 0.001$ and $P = .03$, respectively) from 1995–1997 to 2004–2006. Significant absolute rate increases were observed for IPD due to serotype 1 (10 cases per 100,000 population; 95% confidence interval [CI], 3–19 cases per 100,000 population), serotype 3 (13 cases per 100,000 population; 95% CI, 5–22 cases per 100,000 population), serotype 7F (13 cases per 100,000 population; 95% CI, 2–23 cases per 100,000 population), and serotype 19A (15 cases per 100,000 population; 95% CI, 3–28 cases per 100,000 population).

Rates of all-serotype, VT, and NVT IPD among children aged <2 months were evaluated (Table 2). There has been an elimination of VT disease without replacement NVT disease in these youngest infants.

Rates of overall, VT, and NVT IPD among children aged 5 to <18 years during the period 2004–2006 were unchanged from the period 1995–1997. Serotypes were determined for 99 (87%) of 112 cases during 1995–2006. When considered as individual serotypes, only the rate for serotype 5 changed, decreasing from 3 to 0 cases per 100,000 population ($P = .01$). The rate of serotype 1 IPD remained unchanged at 8 cases per 100,000

Table 2. Rates of Invasive Pneumococcal Disease (IPD) among Children Aged <2 Months, 1995–2006

Period	All-serotype IPD		VT IPD		NVT IPD	
	No. of cases per 100,000 population	No. of cases (95% CI)	No. of cases per 100,000 population	No. of cases (95% CI)	No. of cases per 100,000 population	No. of cases (95% CI)
1995–1997 ^a	315	9 (144–598)	70	2 (9–253)	175	5 (57–408)
1998–2000	402	10 (193–739)	40	1 (1–224)	361	9 (165–686)
2001–2003	43	2 (1–240)	0	0 (0–159)	43	2 (1–240)
2004–2006 ^a	267	6 (98–581)	0	0 (0–164)	178	4 (49–456)
Post-vaccine introduction period (2001–2006) ^a	153	8 (62–316)	0	0	109	6 (36–255)

NOTE. NVT, nonvaccine type; VT, vaccine type.

^a Two cases in these periods were not serotyped. They are included in the all-serotype rate but were not imputed for the VT or NVT rates; thus, the sum of these rates do not equal the all-serotype rate.

population in 2004–2006, compared with 6 cases per 100,000 population in 1995–1997 ($P = .4$).

We observed 949 cases of IPD among persons aged ≥ 18 years; serotypes were determined for 782 cases (82%). During 1995–1997, the proportion of IPD cases among adults due to PCV7 serotypes was 12%. Rates of all-serotype IPD were unchanged in 2004–2006, compared with 1995–1997; this was also true for rates of NVT IPD. However, the rate of PCV7 VT IPD in 2004–2006 was 57% ($P < .01$) lower than in 1995–1997.

Among adults aged 18 to <40 years, the proportion of IPD cases due to PCV7 serotypes was only 10% in 1995–1997. After PCV7 routine use, there was a 35% decrease ($P = .02$) in the rate of all-serotype IPD. Rates of VT IPD did not change ($P = .25$), and rates of NVT IPD decreased by 37% ($P = .02$). Comparisons of serotype-specific rates between the prevaccine and routine-use eras revealed significant decreases in the rates of IPD due to serotypes 1 and 5 and a significant increase in the rate of IPD due to 7F (data not shown).

Among adults aged 40 to <65 years, 14% of IPD cases were caused by PCV7 serotypes in 1995–1997. No change has been seen in the all-serotype rate, VT rate or NVT rate in 2004–2006 compared with 1995–1997 (Table 1). However, there have been significant declines in serotype 1, 5, and 16 IPD rates, and increases due to serotype 12F, 17F and non-typeable pneumococci (data not shown). The leading causes of IPD during 2004–2006 in this age group were serotypes 7F, 12F, and 19A with rates of 8, 14, and 8 per 100,000 respectively.

Among adults > 65 years, the proportion of IPD caused by PCV7 serotypes prior to the trial was 13%. There has been no change in overall or NVT IPD rates, but a decline in the VT IPD (81% decrease; $P = .02$) (Table 1). Significant decreases were seen for serotypes 4 and 5, and increases were seen for rates of serotypes 6A, 12F, 19A, and 16F IPD (data not shown).

The rates of disease caused by serotypes in PPV23 but not in PCV7 provide an internal contemporaneous control for interpreting the PCV7 VT changes among adults. There was no

change in the rate of IPD due to the 16 serotypes in PPV23 but not in PCV7 over the surveillance period for any adult age strata. Risk factors for disease, clinical course, and outcomes among adult Navajo persons with IPD prior to PCV are reported elsewhere [5].

We evaluated the syndrome and age distribution of IPD among children aged <5 years in the routine vaccine era. Of the 64 cases, most involved pneumonia (42%) or bacteremia without focus (36%), whereas 22% involved meningitis. The majority of meningitis cases occurred among children aged <2 years; type 7F (4 cases [29%]) was the predominant cause. Similarly, most cases of bacteremia without focus occurred among children aged <2 years, whereas cases of pneumonia were evenly distributed across the 2 age groups.

Blood samples were the most common source of pneumococci (99% in 1995–1997 and 98% in 2001–2006) among children aged <5 years. Pneumococcus was isolated from cerebrospinal fluid samples in 14 cases (7%) in the pretrial period and in 12 cases (9%) during 2001–2006. The specimen sources for the remaining cases included pleural fluid, bone, and joint fluid.

Most children with IPD (59%) were treated as outpatients. Of the 183 cases involving hospitalization, the mean duration of stay was 7 days; 75 patients (41%) were transferred to another facility because of disease acuity or bed availability. The proportion of patients treated as inpatients did not change between 1995–1997 and 2004–2006 (37% and 50% respectively; $P = .07$).

Of the 297 cases among children aged <5 years with a known outcome (outcome was not determined for pretrial cases), 6 (2%) were fatal. Five patients had meningitis, and 1 had pneumonia. No pediatric IPD-related fatalities occurred during 1999–2006. In the years since PCV7 use, the proportion of febrile children aged <2 years for whom blood cultures were performed decreased from 55.7% in 1998 to 46.1% in 2006 ($P < .001$).

PCV7 coverage is shown in Figure 5. During 1998–2000,

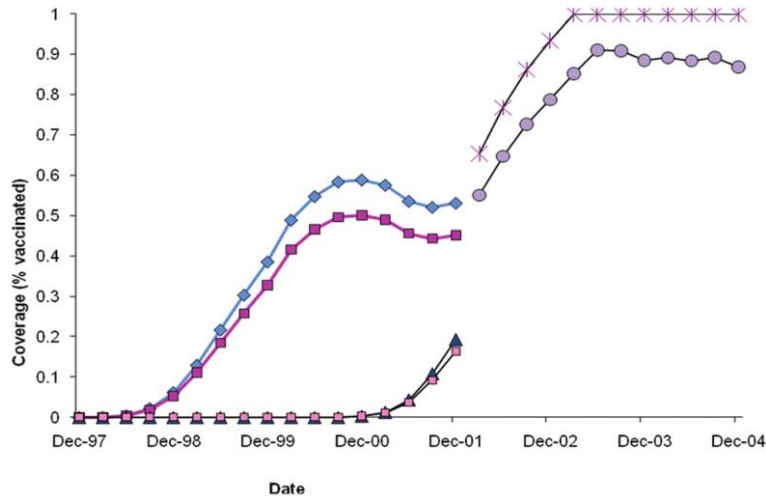


Figure 5. Proportion of 19–35-month-old children who have received 3 doses of 7-valent pneumococcal conjugate vaccine (PCV7), by time and by community. Lower bounds were calculated using User Population as the denominator. Upper bounds used only those children receiving their primary care at Indian Health Services in the denominator. *Blue diamonds with blue line*, upper bound on PCV7-randomized communities; *pink squares with pink line*, lower bound on PCV7-randomized communities; *blue triangles with black line*, upper bound on meningococcal C vaccine (MnCC)-randomized communities; *light pink squares with black line*, lower bound on MnCC-randomized communities; *purple crosses*, upper bound on Navajo-wide communities; *purple circles*, lower bound on Navajo-wide communities.

22% of Navajo infants aged 3–4 months (regardless of their trial participation or community of residence) received >1 dose of PCV7. For those residing in PCV7-randomized communities, coverage in this age strata peaked at 54% in September 1999; trial enrollment stopped in January 2000. In late October 2000, PCV7 vaccination became routine, including catch-up for children aged <5 years. By March 2001, a total of 88% of 3–4-month old infants living in PCV7-randomized communities and 77% of those in control communities had received >1 dose of PCV7. The proportion of 19–35-month-old children who received >3 PCV7 doses was 53% in PCV7-randomized communities and 19% in control communities by December 2001 and increased to >85% by December 2004. By 2005 and 2006, these proportions were 94% and 92%, respectively (Diana Hu, Navajo Area IHS Pediatric Consultant, personal communication).

DISCUSSION

In the PCV7 era, VT IPD has been virtually eliminated from the Navajo Nation, a community at high risk for pneumococcal disease. Approximately 28 annual cases of IPD among Navajo children <5 years are averted by PCV7. In spite of this success, the 2004–2006 rate of overall IPD, entirely NVT strains, among Navajo children aged <5 years (88 cases per 100,000 population) remains >4-fold that of the general US population (20.4 cases per 100,000 population) [10].

As in the general US population [11], unvaccinated Navajo children and adults have benefited from routine PCV7 use. We

observed no cases of VT IPD among infants aged <2 months since May 2003. Rates of VT IPD among adults have decreased by >50% (range by age strata, 42%–81%) with 14 cases in the routine-use era compared with 29 in the prevaccine era. There has been no reduction in the IPD rate from the 16 serotypes in PPV23 but not in PCV7, providing evidence that the reduction in PCV7 serotypes among adults is not attributable to improved PPV23 use [12].

There is concern in the United States and Europe [13–16] about NVT replacement disease following PCV introduction. Contrasting with observations from the Alaska Native population [14], a group sharing important epidemiologic characteristics with Navajo (ie, household crowding, low indoor air quality, high burden of respiratory illnesses, and availability of running water), increases in overall NVT IPD are not seen among Navajo. This lack of significant replacement disease, where PCV7 has been in use now for >12 years, is an important finding. Replacement disease is anticipated to be prominent in settings with high disease burden from NVT strains, as found among the Navajo. Although no increase in the overall NVT disease rate was seen in any age strata <5 years, certain serotypes have increased in rate (types 1, 3, 7F, and 19A), whereas others have decreased (types 5 and 18B). The decline in the serotype 5 IPD rate since PCV7 introduction is notable as a serotype with epidemic potential. To explore whether type 5 incidence in the prevaccine period influenced inferences about NVT rates, we repeated the analyses removing serotype 5 from all time-periods. NVT rates were statistically higher in 2004–2006 than in 1995–1997 for some age groups (<1 year, 5 to <18 years, 40

to <65 years, and ≥ 65 years; data not shown). However, secular trends in serotype prevalence are a recognized part of pneumococcal epidemiology, and such micro-epidemics from other serotypes (eg, type 12F) may be occurring in the vaccine period also. We therefore chose 1995–1997 as the comparison era closest vaccine introduction; secular changes in disease rates have been ongoing since at least 1989 in the <5 age group [5].

Although changes in serotype-specific NVT IPD rates are associated temporally with PCV7 introduction, ascribing the effect entirely to PCV7 would mistakenly ignore secular trends in the serotype distribution of IPD causing strains [17]; the role of cofactors, such as antimicrobial use [18, 19]; and other drivers of serotype distribution, such as clonal introduction and capsular serotype switching. These latter analyses are being reported separately. We evaluated whether clinical blood culture practices had changed over the surveillance period since this would impact observed IPD rates. Fewer medically attended febrile children had a blood culture collected as the introduction of PCV7 progressed likely resulting in somewhat fewer detected IPD cases.

The proportion of isolates in the baseline era that were serotyped is also a study limitation. The pretrial IPD surveillance activity was resource limited; thus, isolates were sometimes discarded by the clinical lab before collected by the surveillance team. We do not believe that this introduced a bias in serotype distribution, because all isolates were equally likely to have been missed.

Why more replacement IPD has not been observed is a matter of speculation; it may yet occur. PCV7 introduction on Navajo was more gradual than in the general US population and Alaska Native communities. PCV7 was used in the randomized, clinical trial for 3.5 years followed by rapid immunization of the remaining half of the community. Furthermore, antibiotic use, although prevalent, is limited in formulary by the IHS. Recommendations for amoxicillin as first-line therapy of otitis media are respected. Azithromycin is not available for general use among young children through the Navajo IHS facilities. This restricted formulary likely contributes to the low rates of antimicrobial resistance among pneumococcal isolates circulating in the community.

The notable impact of PCV7 on pneumococcal disease in this population is tempered by the finding that the remaining all-age IPD rate is 4-fold that of the general US population. This disease burden, attributable to NVT strains, is unchanged from the pre-PCV7 era. Strategies to reduce it should include reduction of indoor air pollution; control of viral coinfections, such as influenza and respiratory syncytial virus infection among infants and children; increased availability of running water in homes; and reduction in risk factors, such as diabetes, alcohol abuse, and cardiac disease among adults. Expanded valency PCV products could further reduce, but not erase this

health disparity. Even if PCV13 is 100% effective for vaccine serotypes, rates of IPD among children aged <5 years will remain ~ 20 cases per 100,000 population.

The study implications for other geographic settings are that PCV7 has significantly reduced pneumococcal morbidity in this population at high risk for IPD. There has been minimal replacement disease from NVT strains following a decade of PCV7 use; the factors protecting the community from significant degrees of replacement disease are not clearly understood but likely include the vaccine introduction pattern, restricted antibiotic use, and intrinsic characteristics of the strains circulating in the community.

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