

Invasive Pneumococcal Disease Caused by Nonvaccine Serotypes Among Alaska Native Children With High Levels of 7-Valent Pneumococcal Conjugate Vaccine Coverage

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BEFORE INTRODUCTION OF 7-VALENT pneumococcal conjugate vaccine (PCV7), Alaska Native children and adults experienced an excess burden of invasive pneumococcal disease (IPD) compared with non-Native Alaskans.¹ The greatest disparity in IPD was among children younger than 2 years for whom the annualized rate (450/100 000 per year) was 3 times higher than for non-Native Alaskan children younger than 2 years who have rates similar to the overall US population.^{1,2} Introduction of PCV7 into the routine childhood vaccination schedule resulted in decreases in vaccine-type IPD and consequent decreases in all IPD among US children.³⁻⁸ 7-Valent pneumococcal conjugate vaccine was licensed in February 2000 and introduced into the routine childhood vaccine schedule for all Alaskan children on January 1, 2001.⁹

For editorial comment see p 1825.

Context With routine childhood vaccination using heptavalent pneumococcal conjugate vaccine, one concern has been the potential for emergence and expansion of replacement disease caused by serotypes not contained in the heptavalent conjugate vaccine.

Objective To determine whether replacement disease is associated with the overall decline in invasive pneumococcal disease among Alaska Native children.

Design, Setting, and Patients Alaska statewide longitudinal population-based laboratory surveillance of invasive *Streptococcus pneumoniae* infections from January 1, 1995, through December 31, 2006.

Main Outcome Measures Incidence and types of pneumococcal disease in children younger than 2 years.

Results In the first 3 years after introduction of routine vaccination with heptavalent pneumococcal conjugate vaccine, overall invasive pneumococcal disease decreased 67% in Alaska Native children younger than 2 years (from 403.2 per 100 000 in 1995-2000 to 134.3 per 100 000 per year in 2001-2003, $P < .001$). However, between 2001-2003 and 2004-2006, there was an 82% increase in invasive disease in Alaska Native children younger than 2 years to 244.6/100 000 ($P = .02$). Since 2004, the invasive pneumococcal disease rate caused by nonvaccine serotypes has increased 140% compared with the prevaccine period (from 95.1 per 100 000 in 1995-2000 to 228.6 in 2004-2006, $P = .001$). During the same period, there was a 96% decrease in heptavalent vaccine serotype disease. Serotype 19A accounted for 28.3% of invasive pneumococcal disease among Alaska children younger than 2 years during 2004-2006. There was no significant increase in nonvaccine disease in non-Native Alaska children younger than 2 years.

Conclusions Alaska Native children are experiencing replacement invasive pneumococcal disease with serotypes not covered by heptavalent pneumococcal conjugate vaccine. The demonstration of replacement invasive pneumococcal disease emphasizes the importance of ongoing surveillance and development of expanded valency vaccines.

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In the first 3 years after PCV7 introduction, vaccine-type IPD rates (from 1995-2000 to 2001-2003) decreased by 91% and total IPD rates decreased by 65% among Alaska Native children younger than 2 years.¹⁰ Additionally, PCV7-type *Streptococcus pneumoniae* nasopharyngeal colonization declined

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in rural Alaska Native children and adults, whereas the overall rate of *S pneumoniae* colonization remained unchanged.^{10,11}

Before introduction of PCV7 vaccine (1995-2000), vaccine serotypes accounted for 74% of known serotype IPD in Alaska Native and 81% in non-Native Alaska children younger than 2 years.¹⁰ With the introduction of PCV7, one concern has been the potential for nonvaccine serotypes to emerge and erode the disease prevention gains made through the use of PCV7. Using ongoing laboratory surveillance, we evaluated IPD in Alaska children for evidence of emergence of nonvaccine serotype disease.

METHODS

Population

Alaska's population of 626 932 (2000 US Census) includes 119 499 (19%) Alaska Native and American Indians, 5304 of whom are younger than 2 years. The Alaska Native people are a diverse group that includes Eskimo, Aleut, Athabascan, Tsimshian, Haida, Tlingit, and American Indian groups. Sixty percent of Alaska Natives live in rural communities; many live in isolated villages with populations ranging from 50 to 1000 persons. The majority receive care through the Alaska Native health system, a statewide tribally operated health delivery system consisting of primary care village clinics, regional hospitals, and a referral hospital. Race, which was routinely determined by the admitting hospital as part of registration, was evaluated based on whether study participants were either Alaska Natives or not.

Vaccine Coverage

We evaluated PCV7 vaccination status in 19- through 35-month-old Alaska Native children between September 30, 2003, and September 30, 2006, using the electronic health records from tribal facilities for Native Alaska persons who access the tribally operated health system. Quarterly reports of immunization rates obtained from these electronic records

are submitted to the Indian Health Service Immunization Program (http://www.ihs.gov/medicalprograms/epi/index.cfm?module=health_issues&option=immunizations&cat=sub_3). We report the proportion of 19- through 35-month-old Alaska Native children who had received 3 or more doses of PCV7 and the proportion who received at least 1 dose of PCV7 by 3 months of age. In addition to these immunization rates obtained through tribal programs, we obtained the rate for 3 or more doses of PCV7 reported by race/ethnicity for 19- through 35-month-old Alaskans who were identified as "American Indian or Alaska Native only, non-Hispanic" and for the overall US population of this age group in the National Immunization Survey public-use files for July 1, 2003, through June 30, 2004.¹² The National Immunization Survey is an ongoing, random-digit-dialed telephone survey that provides national and state-level estimates by race and ethnicity of vaccination coverage among children aged 19 through 35 months.¹³

Invasive Disease Surveillance

Since 1986, the Centers for Disease Control and Prevention (CDC) Arctic Investigations Program has conducted population-based laboratory surveillance for IPD among persons of all races throughout Alaska. Cases reported from January 1, 1995, through December 31, 2006, are included in this study. This public health surveillance is exempt from institutional review board approval; however, a manuscript of this article was reviewed and approved by the Alaska Native Tribal Health Consortium board of directors and by the CDC.

A case of IPD is defined by an isolate of *S pneumoniae* from a normally sterile body site in an Alaska resident with illness occurring in Alaska. Clinical laboratories in the state send invasive isolates and data from the patient record to the CDC laboratory in Anchorage, where identification and serotyping are performed using stan-

dard methods.^{1,2} Case data were obtained from the clinical laboratories, medical record, or patient's clinician and included demographic information, such as age and race, clinical presentation, underlying conditions, and outcome. Age and race were assessed because of their relationship to IPD rates. The CDC annually has each participating laboratory review its list of submitted samples with its laboratory log sheets and submit information on missed *S pneumoniae* isolates. The CDC also reviews state death certificate codes for *S pneumoniae* infection to identify possible missed cases. These results have shown an isolate submission rate of 90%. Disease severity was measured by the proportion of patients who were hospitalized and the proportion who had meningitis and bacteremia with no other focus.

Antimicrobial Susceptibility

Minimum inhibitory concentration (MIC) was determined for each IPD isolate by agar dilution (1995-1999) or microbroth dilution (2000-2006), and for colonizing pneumococci by E test (AB BIODISK, Piscataway, NJ) or by agar dilution. Interpretation was based on Clinical and Laboratory Standards Institute standards.¹⁴

Molecular Typing

Pulsed-field gel electrophoresis was performed with *Sma*I enzyme on all invasive 19A isolates received from 1995-2006. Six invasive 19A isolates representing the major pulsed-field gel electrophoresis clusters were subjected to multilocus sequence typing using procedures described elsewhere.¹⁵⁻¹⁷ Clonal complexes were assigned using the eBURST algorithm¹⁸ with the software available at <http://www.mlst.net>.

Colonization Studies

From 1998 to 2004, the CDC conducted annual community-wide pneumococcal colonization surveys in March and April among persons of all ages in 8 rural Alaska villages (total population 3858, 95% Alaska Native,

2000 Census). These cross-sectional observational surveys were conducted in April and May of each year in 2 regions of rural Alaska. Nasopharyngeal swab samples were processed to identify and serotype pneumococci as described for invasive isolates. Approval for the study was obtained from the CDC and the Alaska Area institutional review board and board of directors from participating tribal corporations. Written informed consent was obtained from each adult and parent of participating children and written assent was obtained from children aged 7 through 18 years. Results through 2003 were previously published.^{10,19}

Statistical Analysis

Statistical differences in disease rates were assessed using an exact test with a mid *P* calculation.²⁰ We examined changes in clinical presentation and colonization using a χ^2 test for trend. Risk ratios (RRs) were used to compare IPD rates between Alaska Natives and non-Native Alaskans. All analyses were conducted using STATA version 5.0 (STATA Corp, College Station, Tex). All *P* values are 2-sided.

Denominators for calculating incidence of IPD were based on population estimates from the Alaska Department of Labor and Work Force Development,²¹ which provides annual population estimates by age and race that are based on census figures. Cases included in this analysis were those with onset beginning January 1, 1995, through December 31, 2006. Baseline (prevaccine period) rates of IPD were based on cases reported during 1995 through 2000. Because of increasing rates of antimicrobial nonsusceptibility during the mid 1990s, baseline antimicrobial susceptibility data are based on cases reported from 1998 through 2000. Antimicrobial susceptibility testing was performed on all isolates received for cases through December 31, 2006. For pulsed-field gel electrophoresis and multilocus sequence typing, prevaccine period data were for 19A iso-

lates submitted from 1995 through 2000 and were compared with data for 19A isolates submitted from 2001 through 2006.

RESULTS

Vaccine Coverage

Between September 30, 2003, and September 30, 2006, the proportion of 19-through 35-month-old Alaska Native children documented in electronic health records as having received at least 3 PCV7 doses increased from 88% to 96%. Data tables from the National Immunization Survey for July 2003 through June 2004 for children aged 19 through 35 months estimated that 92.6% (95% confidence interval [CI], 84.7%-100%) of Alaskan children who were identified as American Indian or Alaska Native only, non-Hispanic had received at least 3 doses of PCV7 compared with 64.6% (95% CI, 55.7%-73.5%) for non-Hispanic white Alaskans and 70.5% (95% CI, 69.5%-71.5%) for the overall US population in this age group.¹² Data tables from the National Immunization Survey for this period also estimated that 61.1% (95% CI, 60.0%-62.2%) of US children aged 19 through 35 months had received at least 1 dose of PCV7 by age 3 months. In comparison, local audits of electronic records for September 30, 2003, showed that 75% of Alaska Native children aged 19 through 35 months had documentation of at least 1 dose of PCV7 by 3 months of age.

Invasive Pneumococcal Disease Rates

From January 1, 1995, through December 31, 2006, a total of 1478 cases of IPD were reported in Alaska for persons of any race; isolates were available for 90% of IPD cases. The annual IPD rate in Alaskans for the prevaccine years 1995-2000 was 23.0/100 000 (range, 19.8-26.7). During this prevaccine period, the rate of IPD for children younger than 2 years was 403.2 among Alaska Native children compared with 135.5 for non-Native Alaska children (TABLE 1 and TABLE 2).

We updated previously published data of IPD rates in Alaska Native persons during the first 3 years after introduction of PCV7.¹⁰ In the 3 years after introduction of PCV7 (2001-2003), IPD decreased 67% among Alaska Native children younger than 2 years ($P < .001$; Table 1) and 61% in non-Native Alaska children in the same age group ($P < .001$; Table 2). There was also an 82% decrease in IPD among Alaska Native children aged 2 through 4 years ($P < .001$; Table 1) but no significant change among non-Native Alaska children in the same age group ($P = .66$; Table 2).

Compared with the baseline period, overall IPD rates decreased 68% during 2004-2006 for non-Native Alaska children younger than 2 years ($P < .001$) but only by 39% for Alaska Native children ($P = .003$). Between 2001-2003 and 2004-2006, IPD rates did not change for non-Native Alaska children younger than 2 years (Table 2) but increased 82% among Alaska Native children ($P = .02$; Table 1).

Change in Rates for PCV7 and Non-PCV7 Serotype IPD

The decreases in IPD rates for Alaska Native and non-Native Alaska children younger than 2 years were due to decreases in serotypes included in PCV7. Between baseline and 2001-2003, PCV7 serotype IPD decreased 92% in Alaska Native children and 80% in non-Native Alaska children younger than 2 years old. Overall, between baseline and 2004-2006, IPD due to PCV7 serotypes declined 97% in all Alaska children younger than 2 years (96% in Alaska Native and 98% in non-Native Alaska children). Between baseline and 2001-2003, there was no change in the rate of non-PCV7 serotype IPD among Alaska Native and non-Native Alaska children younger than 2 years (Table 1 and Table 2). However, between 2001-2003 and 2004-2006 the rate of non-PCV7 type IPD increased 130% among Alaska Native children younger than 2 years (Table 1 and FIGURE 1).

Compared with non-Native Alaska children, the RR of PCV7-type IPD for Alaska Native children younger than 5 years decreased from 2.84 (95% CI, 2.15-3.77) in the prevaccine period to 1.08 (95% CI, 0.34-2.94) in 2001-2006. In contrast, the RR for non-PCV7 type IPD in Alaska Native vs non-Native Alaska children younger than 5 years did not change: 3.91 (95% CI, 2.27-6.81) to 4.31 (95% CI, 2.93-6.41). Likewise, there was no change in the RR of all IPD for Alaska Native vs non-Native Alaska children from the prevaccine period (RR, 3.13; 95% CI, 2.47-3.96) to 2001-2006 (RR, 3.13; 95% CI, 2.46-4.87).

For Alaska children of all races younger than 2 years, there were 65 cases of IPD during 2004-2006 (46 in Alaska Native and 19 in non-Native Alaska children). Of the serotypes causing these 65 cases, only 3 (5%) were

PCV7 serotypes. Non-PCV7 serotypes 3, 6A, 7F, and 19A accounted for 38 (58%) of these cases and 19 (29%) were 19A (FIGURE 2). Of 21 IPD cases in 2- through 4-year-old children (10 in Alaska Native children, 11 in non-Native Alaska children) during 2004-2006, none were caused by PCV7 serotypes.

IPD in Adults

Between the baseline and 2004-2006, PCV7 serotype IPD decreased among both Alaska Native and non-Native Alaska adults 18 years or older (Table 1 and Table 2). Among adults 45 years or older, non-PCV7 serotype IPD increased in Alaska Native ($P < .001$) and in non-Native Alaska adults ($P = .03$). Accordingly, among adults older than 45 years overall IPD rates increased 43% for Alaska Natives ($P = .03$) but declined 24% for non-Native Alaskans ($P = .02$).

Clinical Presentation and Disease Severity

Overall, 57% of Alaska children younger than 5 years old during 2004-2006 presented with pneumonia. The proportion of IPD cases with meningitis in children younger than 5 years did not change over the 3 time periods; however, there was an increase in the proportion of cases with empyema (from 2% to 13%, P for trend $< .001$), an increase in the proportion of cases with pneumonia and bacteremia (from 40% to 57%, $P = .007$), and a decrease in bacteremia with no other focus (from 54% to 40%, $P = .02$). During 2004-2006, cases of empyema in Alaska children younger than 5 years were from several serotypes: 1 case each of 3, 7F, 9V, 12F, 15A, 22F, and 33F, and 4 cases of 19A. The proportion of IPD cases in Alaskans younger than 5 years who were hospitalized increased from 39% (109/279) in 1995-2000 to 62%

Table 1. Rates of Invasive *Streptococcus Pneumoniae* by Time Period, Age Group, and Vaccine Serotype in Alaska Natives, 1995-2006*

Age, y	Rate per 100 000 (No.)			1995-2000 vs 2001-2003		1995-2000 vs 2004-2006		2001-2003 vs 2004-2006	
	1995-2000	2001-2003	2004-2006	% Change (95% CI)	P Value	% Change (95% CI)	P Value	% Change (95% CI)	P Value
Conjugate vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F									
<2	275.3 (84)	23.4 (4)	10.6 (2)	-92 (-98 to -77)	<.001	-96 (-100 to -86)	<.001	-54 (-96 to 218)	.39
2-4	47.0 (21)	0	0	-100 (-100 to -63)	<.001	-100 (-100 to -66)	<.001	NA	NA
5-17	5.9 (12)	1.0 (1)	0	-84 (-100 to 0)	.04	-100 (-100 to -30)	.007	-100 (-100 to 3825)	.50
18-44	6.0 (16)	5.7 (8)	2.0 (3)	-5 (-65 to 135)	.93	-66 (-94 to 18)	.07	-64 (-94 to 48)	.12
≥45	14.5 (22)	13.4 (11)	4.3 (4)	-8 (-60 to 99)	.85	-70 (-93 to -12)	.02	-68 (-93 to 0)	.05
Total	22.3 (155)	6.5 (24)	2.3 (9)	-71 (-82 to -54)	<.001	-90 (-95 to -80)	<.001	-65 (-86 to -21)	.006
Nonconjugate vaccine serotypes									
<2	95.1 (29)	99.3 (17)	228.6 (43)	4 (-86 to 49)	.88	140 (47 to 200)	<.001	130 (29 to 331)	.003
2-4	13.4 (6)	8.7 (2)	39.6 (10)	-35 (-94 to 261)	.64	195 (0 to 890)	.04	357 (0 to 4186)	.03
5-17	8.3 (17)	5.7 (6)	7.6 (8)	-32 (-78 to 82)	.44	-8 (-66 to 124)	.86	31 (-59 to 369)	.60
18-44	16.2 (43)	17.9 (25)	23.1 (34)	11 (-35 to 85)	.68	42 (-12 to 129)	.13	29 (-25 to 125)	.34
≥45	32.3 (49)	53.5 (44)	71.2 (66)	66 (8 to 154)	.02	121 (50 to 226)	<.001	33 (-11 to 200)	.14
Total	20.7 (144)	25.6 (94)	41.4 (161)	24 (-6 to 62)	.11	100 (59 to 152)	<.001	61 (25 to 111)	<.001
All cases									
<2	403.2 (123)	134.3 (23)	244.6 (46)	-67 (-80 to -48)	<.001	-39 (-58 to -14)	.003	82 (8 to 215)	.02
2-4	73.9 (33)	13.0 (3)	39.6 (10)	-82 (-97 to -44)	<.001	-46 (-76 to 11)	.08	204 (-22 to 1624)	.08
5-17	15.7 (32)	8.6 (9)	7.6 (8)	-46 (-77 to 17)	.10	-51 (-81 to 8)	.06	-11 (-70 to 161)	.82
18-44	25.6 (68)	25.1 (35)	27.2 (40)	-2 (-37 to 49)	.93	6 (-30 to 59)	.77	8 (-33 to 75)	.74
≥45	56.6 (86)	74.2 (61)	80.9 (75)	31 (-77 to 84)	.11	43 (3 to 97)	.03	9 (-23 to 56)	.62
Total	49.1 (342)	35.7 (131)	46.0 (179)	-27 (-41 to -11)	.002	-6 (-22 to 13)	.48	29 (2 to 63)	.03

Abbreviation, CI, confidence interval; NA, not applicable because the rate for both periods is 0.

*Disease caused by unknown serotypes accounted for 12.6% of invasive pneumococcal disease cases from 1995 through 2000, 9.9% of cases from 2001 through 2003, and 5.0% of cases from 2004 through 2006. Data for 1995 through 2003 were previously published¹¹; however, some numbers and rates may be slightly different in this article because of updated information for this period.

NONVACCINE SEROTYPES OF PNEUMOCOCCAL DISEASE

(51/82) in 2004-2006 (P for trend $<.001$).

Antimicrobial Susceptibility

The proportion of all IPD isolates with reduced antimicrobial susceptibility de-

creased from 1998-2000 to 2004-2006 for penicillin (MIC >2.0 $\mu\text{g/mL}$, from 9% to 3%, $P<.001$), erythromycin (MIC >1.0 $\mu\text{g/mL}$, from 19% to 7%, $P<.001$), and trimethoprim-sulfamethoxazole (MIC $>4/76$ $\mu\text{g/mL}$, from 22% to 10%,

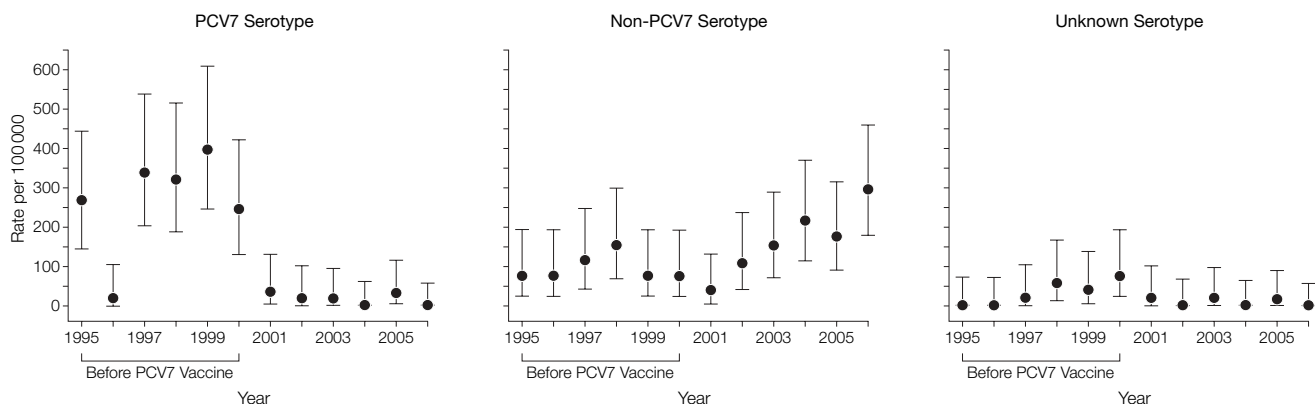
$P<.001$). Similar decreases in antimicrobial resistance were observed among children younger than 5 years old (penicillin MIC >2 $\mu\text{g/mL}$, from 15% to 5%, $P=.04$; erythromycin, from 33% to 8%; $P=.001$; trimethoprim-sulfamethoxa-

Table 2. Rates of Invasive *Streptococcus Pneumoniae* by Time Period, Age Group, and Vaccine Serotype in Non-Native Alaskans, 1995-2006*

Age, y	Rate per 100 000 (No.)			1995-2000 vs 2001-2003		1995-2000 vs 2004-2006		2001-2003 vs 2004-2006	
	1995-2000	2001-2003	2004-2006	% Change (95% CI)	P Value	% Change (95% CI)	P Value	% Change (95% CI)	P Value
Conjugate vaccine serotypes: 4, 6B, 9V, 14, 18C, 19F, and 23F									
<2	101.3 (86)	20.6 (9)	2.3 (1)	-80 (-91 to -60)	<.001	-98 (-100 to -87)	<.001	-89 (-100 to -20)	.01
2-4	13.6 (17)	7.4 (5)	0	-46 (-84 to 53)	.23	-100 (-100 to -58)	<.001	-100 (-100 to 0)	.03
5-17	1.0 (6)	2.5 (8)	0.6 (2)	155 (-22 to 791)	.09	-36 (-94 to 25)	.62	-75 (-97 to 26)	.07
18-44	4.1 (50)	1.1 (7)	0.8 (5)	-73 (-90 to -41)	<.001	-80 (-94 to -51)	<.001	-27 (-82 to 167)	.61
≥ 45	11.4 (102)	7.1 (35)	2.2 (12)	-38 (-59 to -8)	.01	-81 (-90 to -65)	<.001	-69 (-85 to -39)	<.001
Total	8.9 (261)	4.1 (64)	1.3 (20)	-54 (-65 to -39)	<.001	-86 (-92 to -78)	<.001	-70 (-83 to -49)	<.001
Nonconjugate vaccine serotypes									
<2	23.6 (20)	29.7 (13)	39.0 (17)	26 (-42 to 167)	.51	65 (-19 to 232)	.13	31 (-40 to 193)	.47
2-4	4.0 (5)	7.4 (5)	13.9 (10)	85 (-58 to 703)	.35	146 (8 to 1191)	.02	87 (-42 to 599)	.26
5-17	2.5 (15)	1.6 (5)	2.2 (7)	-36 (-82 to 84)	.40	-11 (-69 to 132)	.83	40 (-62 to 462)	.58
18-44	3.6 (43)	2.9 (18)	4.2 (26)	-20 (-56 to 42)	.44	18 (-30 to 97)	.50	47 (-22 to 180)	.21
≥ 45	10.5 (94)	6.7 (33)	14.6 (80)	-36 (-58 to -4)	.02	39 (2 to 89)	.03	117 (43 to 237)	<.001
Total	6.1 (177)	4.8 (74)	8.7 (140)	-21 (-41 to 4)	.08	44 (15 to 81)	.001	84 (38 to 147)	<.001
All cases									
<2	135.5 (115)	52.6 (23)	43.6 (19)	-61 (-76 to -39)	<.001	-68 (-81 to -47)	<.001	-17 (-5 to 59)	.55
2-4	19.2 (24)	16.3 (11)	15.3 (11)	-15 (-63 to 80)	.66	-21 (-65 to 68)	.54	-6 (-63 to 138)	.88
5-17	3.8 (23)	4.7 (15)	2.8 (9)	25 (-40 to 149)	.51	-25 (-69 to 68)	.48	-40 (-77 to 47)	.23
18-44	9.1 (110)	4.8 (30)	6.2 (38)	-48 (-66 to -21)	<.001	-32 (-55 to -1)	.03	29 (-22 to 116)	.30
≥ 45	24.3 (217)	16.3 (80)	18.4 (101)	-33 (-49 to -15)	.002	-24 (-41 to -4)	.02	13 (-16 to 54)	.41
Total	16.7 (489)	10.2 (159)	11.1 (178)	-39 (-49 to -27)	<.001	-34 (-44 to -21)	<.001	8 (-13 to 35)	.45

*Disease caused by unknown serotypes accounted for 10.4% of invasive pneumococcal disease cases from 1995 through 2006, 13.2% of cases from 2001 through 2003, and 10.1% of cases from 2004 through 2006. Data for 1995 through 2003 were previously published¹⁰; however, some numbers and rates may be slightly different in this paper because of updated information for this period.

Figure 1. Rates of Invasive Pneumococcal Disease in Alaska Native Children Younger Than 2 Years, by Year and Serotype, 1995-2006



PCV7 indicates 7-valent pneumococcal conjugate vaccine. Error bars indicate 95% confidence interval.

zole, from 38% to 18%, $P = .003$). The proportion of IPD isolates that were resistant to ceftriaxone was less than 1% during all periods.

Molecular Typing

Pulsed-field gel electrophoresis analysis of 92 IPD serotype 19A isolates received at the Arctic Investigations Program from 1995 through 2006 showed 63 isolates (68.5%) that shared identical or highly similar banding patterns. The only other cluster was a distinct group of 26 isolates (28.3%). Multilocus sequence typing of representative isolates from these 2 clusters grouped the larger cluster with clonal complex 199 (CC199) and the smaller cluster with clonal complex 172 (CC172). Although CC199 accounted for 81% of the 19A isolates before PCV7 and 65% after PCV7 vaccination, 19A isolates of CC172 increased more than 3-fold from 9.5% of 19A isolates during 1995-2000 to 34% of isolates after PCV7 introduction (2001-2006).²²

Colonization

Adding 2004 results to previously reported results of annual colonization surveys in 8 villages during 1998-2003,^{10,11,19} we obtained 2869 additional nasopharyngeal swabs during 2004 (15 598 total for 1998-2004). In 2004, 41% of persons were colonized with *S pneumoniae*. Among all ages, the proportion of persons with pneumococcal colonization who carried a PCV7 serotype progressively declined from 41% during 1998-2000 to 5% in 2004. Colonization with non-PCV7 types increased after introduction of PCV7 (from 47% of colonized persons in 1998-2000 to 88% in 2004). In particular, colonization with serotype 19A increased in all age groups from less than 0.5% of colonized persons in 1998-2000 to 3% in 2003 and 15% in 2004 ($P < .001$ for trend; TABLE 3).

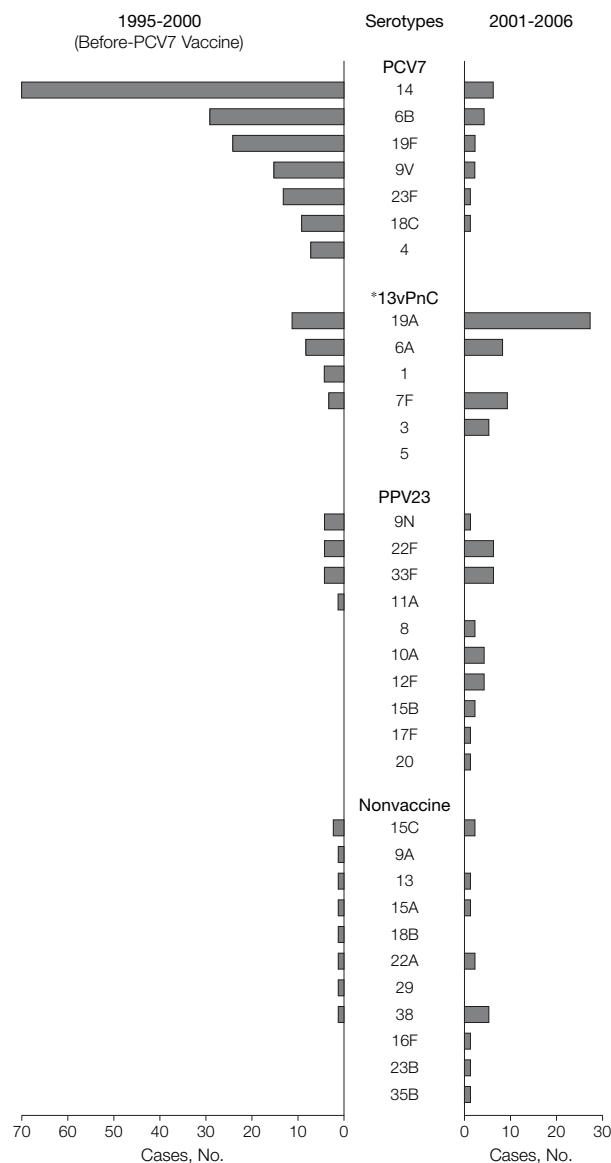
COMMENT

The PCV7 vaccine has nearly eliminated IPD caused by vaccine serotypes in Alaskan children younger than 5 years. However, this dramatic suc-

cess has been blunted by a substantial increase in non-PCV7 serotype IPD in Alaska Native children. Through 2003 the adjusted overall decline in IPD in Alaska Native children younger than 2 years (67%) was similar to that reported elsewhere in the United States (69%).⁷ However, a more than doubling of non-PCV7 serotype disease between 2001-2003 and 2004-2006

eroded the overall decline to 41%. The illnesses due to IPD replacement disease among Alaska Native children were similar to IPD cases before PCV7 introduction except for increases in the proportion of hospitalized IPD, pneumonia, and empyema cases. An increasing proportion of IPD cases associated with empyema have been reported in other populations.^{23,24} However, in

Figure 2. Cases of Invasive Pneumococcal Disease by Serotype Among Alaskan Children Younger Than 2 Years, 1995-2000 and 2001-2006.



PCV7 indicates 7-valent pneumococcal conjugate vaccine.

*13-Valent pneumococcal polysaccharide conjugate vaccine under development.

Table 3. Nasopharyngeal Colonization With Serotype 19A Among Persons Colonized With *Streptococcus pneumoniae* in 8 Rural Villages, 1998-2004*

Age, y	No./Total (%) of Cases						
	1998	1999	2000	2001	2002	2003	2004
0-1	1/43 (2.3)	0/40 (0)	0/43 (0)	0/48 (0)	1/63 (1.6)	2/58 (3.5)	12/73 (16.4)
2-4	0/93 (0)	0/73 (0)	0/85 (0)	0/106 (0)	0/113 (0)	8/107 (7.5)	32/117 (27.3)
5-17	1/283 (0.3)	0/265 (0)	0/311 (0)	0/500 (0)	1/488 (0.2)	27/630 (4.3)	97/602 (16.2)
≥18	0/101 (0)	0/68 (0)	0/106 (0)	0/266 (0)	0/266 (0)	4/413 (1.0)	28/377 (7.4)

*Results through 2003 were previously published.^{10,19}

other populations many of these cases were associated with serotype 1, which has not been found in any IPD cases in Alaskan children younger than 2 years since PCV7 was introduced.

The capsular polysaccharide appears to be the most important determinant of *invasiveness*—the likelihood that the pneumococci that establish colonization in the nasopharynx will cause an IPD and the 90 known capsular serotypes may be heterogeneous in their invasiveness.^{25,26} Data on serotype-specific invasiveness from a prospective study of pneumococcal colonization during the first 2 years of life in Oxfordshire, England, led Sleeman et al²⁷ to speculate that serotypes 8, 12F, and 19A may be more likely than other non-PCV7 serotypes to contribute to changes in disease patterns in immunized populations. Increases in the number of IPD cases caused by each of these 3 serotypes in Alaskan children lend credence to this hypothesis (Figure 2).

An increase in non-PCV7 type IPD after widespread use of PCV7 has also been observed in adults infected with human immunodeficiency virus²⁸ and in some Alaska Native adult age groups.²⁹ In Alaska Native adults, the increase in non-PCV7 disease has offset the indirect effect of PCV7 vaccine in decreasing adult PCV7 disease.²⁹ This increase is consistent with our findings of increased colonization with non-PCV7 type pneumococci among Alaska Native adults in rural communities after introduction of childhood PCV7.¹⁹ Adults infected with human immunodeficiency virus and Alaska Native persons are at increased risk for IPD; the occurrence of replacement disease in

these high-risk populations may signify a limit to the usefulness of the currently available vaccine.

Non-PCV7 replacement IPD was preceded by an absolute increase in non-PCV7 serotype colonization concomitant with a decrease in PCV7 serotype colonization.^{10,11,19} Replacement of PCV7 serotypes by nonvaccine serotypes in the nasopharynx and middle ear fluid has been reported in other populations.³⁰⁻³⁴ In Gambia, carriage of nonvaccine serotypes was found in 79% of children receiving 3 doses of a pneumococcal conjugate vaccine compared with 42.5% of control children.³² In a pneumococcal conjugate vaccine trial in Finland, serotype replacement following vaccination resulted in an increase in acute otitis media caused by nonvaccine serotypes.³⁵ In 2004, Ghaffar et al³⁶ hypothesized that the reduction of PCV7 type colonization and replacement by non-PCV7 colonization after a booster dose of vaccine suggested the possibility that widespread vaccination would result in replacement of pneumococci mainly by non-PCV7 serotypes.

Although replacement colonization has been well documented, replacement IPD with nonvaccine serotypes has not led to an overall increase in disease in other child populations.^{3,7,37} Of note, replacement IPD has not been demonstrated among Navajo children³⁸ or Australian aboriginal children.³⁹ Although these populations have similar characteristics of IPD and colonization, introduction of PCV7 occurred at a slower rate among Navajo children than among Alaska Native children (because of a vaccine trial)⁴⁰ and PCV7 was introduced later with a dif-

ferent schedule (3 primary doses with a booster of 23-valent pneumococcal polysaccharide vaccine at 18 months) in aboriginal children.³⁹ It is possible that the prompt introduction of PCV7 to high-coverage levels and subsequent dramatic decline in PCV7 carriage¹⁰ in Alaska opened a niche for opportunistic replacement serotypes. The PCV7 coverage rate in 19- through 35-month-old Alaska Native children during July 2003 through June 2004 (92.6%) was higher than the rate in any individual state (http://www.cdc.gov/nip/coverage/NIS/03-04/tab29a_3pcv_race_iap_0304.xls) or in the overall US population (70.5%).

An additional factor contributing to replacement disease is the presence of pneumococcal types that are able to occupy the colonization role previously filled by PCV7 types and that are able to cause invasive disease. An example of this in Alaska is serotype 19A, which now accounts for over one quarter of all IPD cases in Alaskan children younger than 2 years. At present, 19A is the most important cause of IPD by replacement serotypes in the United States.^{23,41-43} Data from the CDC's Active Bacterial Core Surveillance sites (<http://www.cdc.gov/abcs>) suggest that some of the increase in rates of infection with serotype 19A and other nonvaccine serotypes may be due to serotype switching within certain vaccine-type strains.^{41,44} Serotype switching has not been demonstrated in our population.²² Instead, the increase in 19A colonization and disease in Alaska appears to be secondary to clonal expansion, predominantly due to an increase in CC172, which has not been found with great frequency in other parts of the

United States.⁴¹ In all areas, the increase in 19A IPD was detected 3 to 4 years after introduction of PCV7, indicating that replacement is a gradual but steady process. Although serotype 19A has played a key role in Alaska, other serotypes have also contributed to the replacement disease increases.

Before PCV7 use in Alaska, PCV7 serotypes accounted for 86% of invasive isolates nonsusceptible to penicillin, erythromycin, or trimethoprim-sulfamethoxazole.² From baseline to 2001-2003 the proportion of isolates with reduced susceptibility to these antimicrobials declined.^{10,11} Similarly, in the ABC surveillance, rates of IPD caused by penicillin-nonsusceptible strains and strains nonsusceptible to multiple antibiotics decreased between 1999 and 2004 among children and adults.⁴² Although there was an increase in drug-resistant infection caused by non-PCV serotypes (primarily 6A and 19A), this effect remained small. This early decline in antibiotic resistance appears to have plateaued; however, the proportion of isolates fully resistant to penicillin remains lower than the baseline period.

We cannot determine to what extent the observed changes in disease rates and serotype distribution are due to the introduction of vaccine or to other factors; however, the dramatic decrease in PCV7 type disease accompanied by an unparalleled increase in nonvaccine serotypes suggest that these are vaccine effects. It is possible that changes in blood culture collection practices could influence the rates of IPD; however, it is unlikely to account for such a dramatic shift in serotype distribution. Case reporting for 2006 may not be 100% complete because the reconciliation process has not been completed. However, any additional cases detected will be of unknown serotypes and not affect trends in PCV7 or non-PCV7 serotypes. Some of the subgroup comparisons presented herein are based on small numbers of cases and therefore have limited power to detect differences.

The rapid success of PCV7 in Alaska has led to the near elimination of PCV7-

serotype disease and elimination of a health disparity for types covered by the vaccine. However, for Alaska Native children there now exists a substantially elevated risk for IPD from serotypes not contained in PCV7. The demonstration of replacement IPD in Alaska Native children may signify a limit to the usefulness of the currently available vaccine and emphasizes the importance of development of extended valency vaccines or vaccines not dependent on serotype-specific prevention. These data also highlight the value of continued surveillance and other epidemiological investigations to monitor the effects of pneumococcal vaccines.

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Study concept and design: Singleton, Hennessy, Hammitt, Hurlburt, Butler, Rudolph.

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REFERENCES

- Davidson M, Parkinson AJ, Bulkow LR, Fitzgerald MA, Peters HV, Parks DJ. The epidemiology of invasive pneumococcal disease in Alaska, 1986-90: ethnic differences and opportunities for prevention. *J Infect Dis*. 1994;170:368-370.
- Rudolph KM, Parkinson AJ, Reasonover AL, Bulkow LR, Parks DJ, Butler JC. Serotype distribution and antimicrobial resistance patterns of invasive isolates of *Streptococcus pneumoniae*: Alaska, 1991-1998. *J Infect Dis*. 2000;182:490-496.
- Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. *JAMA*. 2006;295:1668-1674.
- Kaplan SL, Mason EO, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics*. 2004;113:443-449.
- Ramani RR, Hall WN, Boulton M, Johnson DR, Zhu B. Impact of PCV7 on invasive pneumococcal disease among children younger than 5 years: a population-based study. *Am J Public Health*. 2004;94:958-959.
- Black SB, Shinefield HR, Hansen J, Elvin L, Luafer D, Malinoski F. Postlicensure evaluation of the effectiveness of seven valent pneumococcal conjugate vaccine. *Pediatr Infect Dis J*. 2001;20:1105-1107.
- Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003;348:1737-1746.
- Centers for Disease Control and Prevention. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease—United States, 1998-2003. *MMWR Morb Mortal Wkly Rep*. 2005;54:893-897.
- Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2000;49(RR-9):1-35.
- Hennessy TW, Singleton RJ, Bulkow LR, et al. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in Alaska Natives: progress towards elimination of a health disparity. *Vaccine*. 2005;23:5464-5473.
- Moore MR, Hyde TB, Hennessy TW, et al. Impact of a conjugate vaccine on community-wide carriage of nonsusceptible *Streptococcus pneumoniae* in Alaska. *J Infect Dis*. 2004;190:2031-2038.
- Centers for Disease Control and Prevention. Estimated Vaccination Coverage With 3+ Pneumococcal Among Children 19-35 Months of Age by Race/Ethnicity and by State and Immunization Action Plan Area—US; National Immunization Survey, Q3/2003-Q2/2004. http://www.cdc.gov/nip/coverage/NIS/03-04/tab29a_3pcv_race_iap_0304.xls. August 30, 2006.
- Salmon DA, Smith PJ, Navar AM, et al. Measuring immunization coverage among preschool children: past, present and future opportunities. *Epidemiol Rev*. 2006;28:27-40.
- National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically*. Wayne, Pa: Clinical and Laboratory Standards Institute/NCCLS; 2003.
- Rudolph KM, Parkinson AJ, Roberts MC. Molecular analysis by pulsed-field gel electrophoresis analysis and antibiogram of *Streptococcus pneumoniae* serotype 6B isolates from selected areas within the United States. *J Clin Microbiol*. 1998;36:2703-2707.
- McEllistrem MC, Stout JE, Harrison LH. Simplified protocol for pulsed-field gel electrophoresis analy-

- sis of *Streptococcus pneumoniae*. *J Clin Microbiol*. 2000;38:351-353.
17. Enright MC, Spratt BG. A multilocus sequence typing scheme for *Streptococcus pneumoniae*: identification of clones associated with serious invasive disease. *Microbiology*. 1998;144:3049-3060.
 18. Feil EJ, Li BC, Aanens DM, et al. eBURST: inferring patterns of evolutionary descent among clusters of related bacterial genotypes from multilocus sequence typing data. *J Bacteriol*. 2004;186:1518-1530.
 19. Hammitt LL, Bruden DL, Butler JC, et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J Infect Dis*. 2006;193:1487-1494.
 20. Rothman KJ. *Modern Epidemiology*. Boston, Mass: Little Brown & Co; 1986.
 21. State of Alaska Department of Labor and Workforce Development. <http://almis.labor.state.ak.us/?PAGEID=67&SUBID=115>. Accessed September 1, 2006.
 22. Rudolph KM, Beall B, Reasonover A, et al. Characterization of invasive serotype 19A isolates in Alaska before and after introduction of the 7-valent pneumococcal conjugate vaccine. In: Program and abstracts of the 5th International Symposium on Pneumococci and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract SY3.182006:125.
 23. Byington CL, Korgenski MT, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr Infect Dis J*. 2006;25:250-254.
 24. Tan TQ, Mason EO Jr, Wald ER, et al. Clinical characteristics of children with complicated pneumonia caused by *Streptococcus pneumoniae*. *Pediatrics*. 2002;110:1-6.
 25. Brueggeman AB, Peto TE, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive disease potential of *Streptococcus pneumoniae* in children. *J Infect Dis*. 2004;190:1203-1211.
 26. Sjostrom K, Spindler C, Ortvist A, et al. Clonal and capsular type decide whether pneumococci will act as a primary or opportunistic pathogen. *Clin Infect Dis*. 2006;42:451-459.
 27. Sleeman KL, Griffiths D, Shackley F, et al. Capsular serotype-specific attack rates and duration of carriage of *Streptococcus pneumoniae* in a population of children. *J Infect Dis*. 2006;194:682-688.
 28. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. *Ann Intern Med*. 2006;144:1-9.
 29. Hammitt LL, Hennessy TW, Bruden D, et al. Indirect effect of heptavalent conjugate vaccine on pneumococcal colonization and invasive disease in adults. In: Program and abstracts of the 5th International Symposium on Pneumococci and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract PO7.26:231.
 30. Dagan R, Muallem M, Melamed R, Leroy O, Yagupsky P. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. *Pediatr Infect Dis J*. 1997;16:1060-1064.
 31. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonvalent conjugate vaccine on carriage of antibiotic resistant *Streptococcus pneumoniae* in day-care centers. *Pediatr Infect Dis J*. 2003;22:532-540.
 32. Obaro SK, Adegbola RA, Banya WA, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. *Lancet*. 1996;348:271-272.
 33. McEllistrem MC, Adams JM, Patel K, et al. Acute otitis media due to penicillin non-susceptible *Streptococcus pneumoniae* before and after the introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis*. 2005;40:1738-1744.
 34. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonvalent pneumococcal conjugate vaccine. *J Infect Dis*. 1999;180:1171-1176.
 35. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med*. 2001;344:403-409.
 36. Ghaffar F, Barton T, Lozano J, et al. Effect of the 7-valent pneumococcal conjugate vaccine on nasopharyngeal colonization by *Streptococcus pneumoniae* in the first 2 years of life. *Clin Infect Dis*. 2004;39:930-938.
 37. O'Brien KL, Shaw J, Weatherholtz R, et al. Epidemiology of invasive *Streptococcus pneumoniae* among Navajo children in the era before use of conjugate pneumococcal vaccines, 1989-1996. *Am J Epidemiol*. 2004;160:270-278.
 38. O'Brien KL, Weatherholtz R, Millar EV, et al. Replacement invasive pneumococcal disease 9 years after introduction of PCV among a population at high risk for IPD: the Navajo Experience. In: Program and abstracts of the 5th Annual International Symposium on Pneumococcus and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract P04.17:189.
 39. Krause VL, Cook H, Selvey CE. Impact of 7vPCV and 23vPPV booster in eligible children in the Northern Territory of Australia: impressive, but not the total answer. In: Program and abstracts of the 5th International Symposium on Pneumococci and Pneumococcal Disease; April 2-6, 2006; Alice Springs, Australia. Abstract SY1.032006:55.
 40. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomized trial. *Lancet*. 2003;362:355-361.
 41. Pai R, Moore MR, Pilishvili T, Gertz RE, Whitney CG, Beall B. Postvaccine genetic structure of *Streptococcus pneumoniae* serotype 19A from children in the United States. *J Infect Dis*. 2005;192:1988-1995.
 42. Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant *Streptococcus pneumoniae*. *N Engl J Med*. 2006;354:1455-1463.
 43. Flannery B, Schrag S, Bennett NM, et al. Impact of childhood vaccination on racial disparities in invasive *Streptococcus pneumoniae* infections. *JAMA*. 2004;291:2197-2203.
 44. Porat N, Arguedas A, Spratt BG, et al. Emergence of penicillin-nonsusceptible *Streptococcus pneumoniae* clones expressing serotypes not present in the antipneumococcal conjugate vaccine. *J Infect Dis*. 2004;190:2154-2161.