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# Epidemiology of Invasive *Streptococcus pneumoniae* among Navajo Children in the Era before Use of Conjugate Pneumococcal Vaccines, 1989–1996

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*Streptococcus pneumoniae* is the most common cause of invasive bacterial disease among children worldwide. The authors aimed to determine the incidence, clinical characteristics, and serotype distribution of invasive pneumococcal disease (IPD) among Navajo children in the southwestern United States. Active population-based laboratory surveillance for IPD among resident members of the Navajo Nation under 18 years of age was conducted between 1989 and 1996. During this 8-year period, 706 cases of IPD were identified. The rate of disease varied by age, with the highest rate being observed among children aged 6–11 months (727 cases/100,000 person-years), followed by children aged 0–11 months, 0–23 months, and 0–59 months (568, 537, and 272 cases/100,000 person-years, respectively). Among children aged 0–23 months, 60.3% of cases were caused by serotypes in the seven-valent conjugate pneumococcal vaccine (71.5% from 1989–1993 and 58.3% from 1994–1996). Navajo children are at increased risk of IPD in comparison with the general US population. The distribution of disease-causing serotypes is similar to that of many countries in the developing world. Prevention strategies should include the use of licensed pneumococcal protein conjugate vaccine; however, a substantial proportion of disease is caused by nonvaccine serotypes. These data are critical for assessing the impact of these vaccines in this high-risk population.

child; incidence; Indians, North American; pneumococcal vaccines; *Streptococcus pneumoniae*

Abbreviation: IHS, Indian Health Service.

*Streptococcus pneumoniae* (pneumococcus) is a major cause of illness in populations throughout the developed and developing world (1, 2). The burden of disease is greatest among young children; however, the absolute rates of disease and the serotype distribution of isolates vary considerably between and within countries (3, 4) (table 1). It is estimated that approximately 1.9 million deaths per year among children under 5 years of age are attributable to acute respiratory infections, of which a significant proportion are due to pneumococcus (5). Understanding the epidemiologic characteristics of pneumococcal disease within a population is important for the design and evaluation of prevention strategies. Of particular importance in the era of polysaccharide protein conjugate pneumococcal vaccines is the serotype distribution of pneumococci causing disease and the age distribution of people afflicted with pneumococcal illness.

It is commonly held that Native American populations suffer high rates of acute respiratory illness in general and pneumococcal disease in particular. Indeed, recommendations for use of pneumococcal polysaccharide vaccines among children aged 2–4 years in these populations are based in large part on this perception (6, 7). However, published data on the epidemiology of pneumococcal disease in Native Americans are largely limited to Alaska Natives and the White Mountain Apache tribe (8–10). The aim of this study was to describe the epidemiology and clinical characteristics of pneumococcal disease in the largest American Indian tribe in the United States, the Navajo

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**TABLE 1. Incidence (number of cases per 100,000 person-years) of invasive pneumococcal disease in various pediatric populations worldwide between 1970 and 1998**

| Study location and/or population (ref. no.) | Study period | Age group (years) | | |
|---|---|---|---|---|
| | | <1 | <2 | <5 |
| Australia—Aborigines (28) | 1985–1990 | | 2,053 | 542.7 |
| United States—White Mountain Apaches (8) | 1983–1990 | | 1,820 | |
| United States—Alaska Natives (9) | 1980–1986 | | 1,195 | |
| United States—Alaska Natives (10) | 1986–1990 | | 624 | |
| South Africa—Soweto residents (29) | 1996–1997 | 349 | | |
| New Zealand—Pacific Islanders (30) | 1984–1992 | 276 | | 117 |
| The Gambia (31) | 1993–1995 | 224 | | |
| South Africa—Soweto residents (29) | 1986–1987 | 179 | | |
| New Zealand—Maoris (30) | 1984–1992 | 158 | | 67 |
| United States—all races (20) | 1995–1998 | | 166.9 | |
| New Zealand—all races (30) | 1984–1992 | 121 | | 56 |
| Israel—Bedouins (25) | 1989–1998 | | | 139 |
| Israel—Jews (25) | 1989–1998 | | | 45 |
| Finland (23) | 1985–1989 | | 45.3 | 24.2 |
| England/Wales (27) | 1995–1997 | 37.1–48.1 | | |
| Sweden (24) | 1970–1980 | | 25.8 | |
| Germany (32) | 1997–1998 | 18.9 | 16.0 | 8.9 |

Nation, in the era before routine use of polysaccharide protein conjugate pneumococcal vaccines. The surveillance was conducted in part to prepare for a phase III efficacy trial of a seven-valent polysaccharide protein conjugate pneumococcal vaccine now licensed in the United States (under the trade name Prevnar), the United Kingdom, and approximately 50 other countries (under the trade name Prevenar) (Wyeth Vaccines, Pearl River, New York). The phase III efficacy trial took place between April 1997 and October 2000 and is the subject of a separate report (11).

## MATERIALS AND METHODS

### Study site

The study was conducted in the Navajo Nation, one of the largest American Indian tribes in the United States, consisting of approximately 200,000 members and a reservation covering more than 25,000 square miles (>40,000 $km^2$) in northern Arizona, western New Mexico, and southern Utah. Health care on the reservation is administered through the Indian Health Service (IHS), an agency of the federal Department of Health and Human Services. Located throughout the reservation are six hospitals providing inpatient and outpatient care, two health-care facilities which operate extensive outpatient clinics, seven full-time health centers, and 12 part-time health stations providing more limited outpatient services.

### Surveillance

Active population-based laboratory surveillance for invasive pneumococcal disease was carried out from January 1, 1989, through December 31, 1996. We contacted microbiology laboratories serving residents of the Navajo reservation at least weekly to inquire about isolation of *S. pneumoniae* from a normally sterile body fluid. Laboratories participating in the surveillance included laboratories at the IHS health facilities on the reservation; private, non-IHS-run health facilities on or surrounding the reservation; and referral care facilities located elsewhere in the states surrounding the reservation. For each case identified, a case report form was completed on the basis of information available in the medical record. The case report form recorded information on demographic factors, the clinical course of the infection, potential risk factors for disease, and the outcome of the infection. The clinical syndrome documented by the physician in the clinical chart was recorded. Cases with a positive blood culture but no clinical syndrome identified were categorized as having bacteremia without focus. These cases, by definition, could only be included in this clinical syndrome category, whereas all other cases could have multiple clinical syndromes.

### Case definition

We defined a case of invasive pneumococcal disease as isolation of pneumococcus from a normally sterile site in a Navajo tribal member who was under 18 years of age at the time of pneumococcal isolation. Isolation of pneumococcus that occurred 30 or fewer days after the last date of isolation was considered part of the previous episode if the serotype was identical or if no information on serotype was available. Recurrent disease was defined as a second episode of pneumococcal disease occurring more than 30 days after the

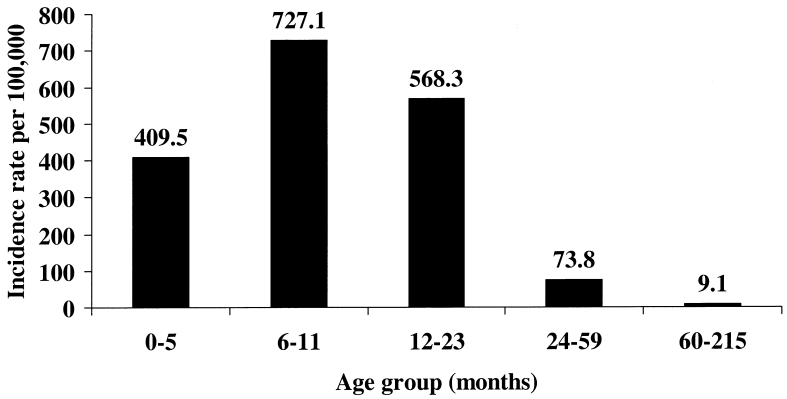


**FIGURE 1.** Rate of invasive pneumococcal disease among Navajo children, by age group, 1989–1996.

previous isolation, regardless of serotype, or fewer than 30 days after the previous isolation if the serotype was different. Recurrent cases were included in case counts and rate calculations.

### Pneumococcal isolation and serotyping

Whenever possible, the pneumococcal isolate was recovered from the clinical laboratory where it was initially isolated and sent to collaborating laboratories in Alaska or Israel for identity confirmation and serotyping. Serotyping was carried out by means of the Quellung reaction using antisera obtained from the Statens Serum Institute (Copenhagen, Denmark). Invasive isolates that were found to be nontypeable were confirmed as such by the Streptococcal Reference Laboratory at the Centers for Disease Control and Prevention (Atlanta, Georgia).

### Statistical analysis

Data were entered and cleaned using Excel and Visual FoxPro (Microsoft Corporation, Redmond, Washington). All analyses were conducted in Stata, release 7 (Stata Corporation, College Station, Texas), or EpiInfo 2000 (Centers for Disease Control and Prevention). Relative risks and 95 percent confidence intervals were used to compare the risks of hospitalization between various age groups and the risks of clinical syndromes by age. To calculate rates of disease, we used year- and age-specific User Population denominator data available from the IHS. The User Population data are statistics generated annually for each of the administrative areas of the IHS. For any given year, the User Population includes all persons who have had contact with the IHS at any time in the preceding 3 years.

### Ethical considerations

This study was approved by the institutional review boards of the Johns Hopkins University, the Navajo Nation, and the IHS.

## RESULTS

### Disease rates

For the 8-year period between January 1, 1989, and December 31, 1996, 706 cases of invasive pneumococcal disease were identified among Navajo children under 18 years of age. The average annual incidence of invasive pneumococcal disease varied by age (figure 1), with the highest rates being observed among children aged 6–11 months (727 cases/100,000 person-years). Overall rates of disease among children aged 0–11 months, 0–23 months, and 0–59 months were 568, 537, and 272 cases/100,000 person-years, respectively. The rate of disease varied by year, with a gradual trend of decreasing incidence over the time period of surveillance for children aged 0–23 months (figure 2). There was slight variation in the percentage of cases by season, with a greater proportion of cases being observed in the late fall and winter months than in the summer months (figure 3).

### Clinical disease

Information on clinical syndrome was completed for 616 (87.3 percent) of the cases. The distribution of syndromes by age (table 2) shows that children aged 0–5 months were at greater risk of meningitis than children aged 6 months–18 years (relative risk = 5.0, 95 percent confidence interval: 3.0, 8.1) and that pneumonia was more commonly diagnosed among those aged 2–18 years than among those under age 2 years (relative risk = 1.7, 95 percent confidence interval: 1.4, 2.1). Among the children with information on clinical syndrome, 64 (10.4 percent) were diagnosed with more than one syndrome that was likely to be associated with pneumococcus. Otitis media was a secondary diagnosis in 60 of these 64 episodes.

*S. pneumoniae* was isolated from blood alone in 647 cases (91.6 percent), from cerebrospinal fluid alone in five cases (0.7 percent), from other normally sterile body fluids alone in two cases (0.3 percent), from both blood and cere-

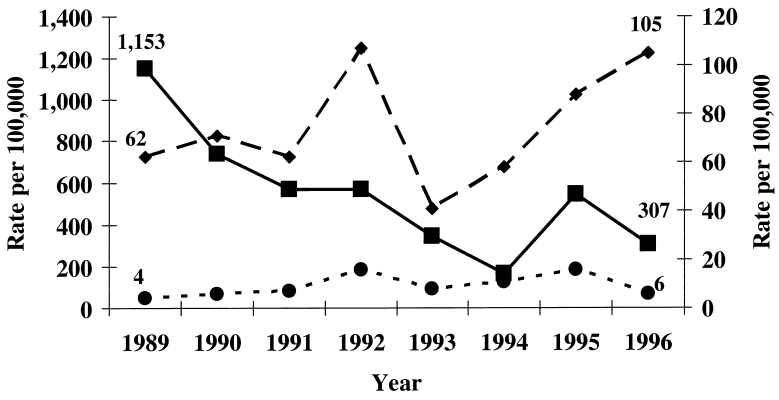


**FIGURE 2.** Trends in the rate of invasive pneumococcal disease among Navajo children, by age group, 1989–1996. Solid line with squares: ages 0–23 months (left-hand *y*-axis scale); dashed line with diamonds: ages 24–59 months (right-hand *y*-axis scale); dashed line with circles: ages 60–215 months (right-hand *y*-axis scale).

brospinal fluid in 47 cases (6.7 percent), and from both blood and another body fluid in five cases (0.7 percent).

Of the 706 episodes of invasive pneumococcal disease, 56.5 percent occurred among males. In total, 231 children (32.7 percent) were hospitalized for their illness, and of these, 77 (33 percent) were transferred to a hospital off the reservation. Transfers are usually made because of the acuity of the patient's illness (i.e., a requirement for intensive care) or because of bed shortages. The median duration of hospitalization among children not transferred was 4 days (range, 1–25 days), and among those transferred it was 10 days (range, 1–31 days). Of the children aged 0–5 months, 69.4 percent were hospitalized for their illness, as compared with 26.8 percent of children aged 6 months or more (relative risk = 4.7, 95 percent confidence interval: 3.1, 6.9). Ten children had two episodes of invasive pneumococcal disease with dates of culture separated by more than 30 days (defined as recurrences), and one child had three episodes. The range of intervals between episodes was 1 month–6 years, with a median interval of 13 months. Only one child had information on serotype available for both episodes; this child had type 6B meningitis at 20 months of age, followed 17 months later by type 6B bacteremic pneumonia.

The overall case fatality ratio was 1.0 percent (seven deaths). Of these seven children, two had meningitis, and the remainder had pneumococcal bacteremia presenting as pneumonia ($n$ = 1) or presumed sepsis ($n$ = 4); only one of these children had a known underlying condition (Navajo neuropathy—a condition of unknown etiology (but suspected to result from a mitochondrial defect) characterized by progressive, multiorgan disease manifesting predominantly as degenerative sensorimotor neuropathy, liver disease, serious systemic infections, and corneal ulcerations (12)). Two of the children had concomitant infection with another bacterium (*Yersinia pestis* and *Haemophilus influenzae*). The child with *Y. pestis* and pneumococcal bacteremia was an otherwise healthy 8-year-old who appeared in the emergency room with fever, exquisitely tender inguinal adenopathy, hypoxemia, and hypotension. The child died of bubonic plague despite treatment in the intensive care unit. The autopsy report identified the cause of death as *Y. pestis* septicemia, although the blood culture grew both *Y. pestis* and *S. pneumoniae*. The cases resulting in death were distributed over the entire time period and occurred among children in various age groups (three cases among children aged 0–23 months and four among children aged 24–215 months).

### Serotype distribution

Of the 706 cases identified, 281 isolates (39.8 percent) were available for serotyping. This proportion varied by year of culture (29 percent serotyped in 1989–1993 and 63 percent in 1994–1996). The distribution of serotypes among children aged 0–23 months is shown in figure 4. Overall, the most common serotypes for this age group were those included in the seven-valent conjugate pneumococcal vaccines; however, the proportion of disease accounted for by these serotypes varied by time period (table 3). A total of

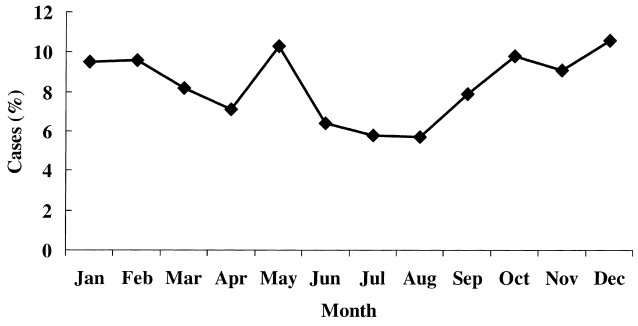


**FIGURE 3.** Monthly distribution of cases of invasive pneumococcal disease among Navajo children aged 0–215 months, 1989–1996.

**TABLE 2. Percentage of *Streptococcus pneumoniae* cases associated with a specific clinical syndrome, by age group, Navajo Nation, 1989–1996**

| Clinical syndrome | No. of cases | Age group (months) | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | 0–5 | 6–11 | 12–23 | 24–59 | 60–215 | |
| Bacteremia without a source | 151 | 26.5 | 15.5 | 23.2 | 23.5 | 17.9 | 21.4 |
| Pneumonia | 214 | 19.4 | 24.7 | 29.4 | 42.5 | 48.2 | 30.3 |
| Otitis media | 231 | 23.5 | 46.5 | 37.9 | 18.9 | 7.1 | 32.7 |
| Meningitis | 54 | 24.5 | 7.5 | 2.9 | 3.8 | 8.9 | 7.7 |
| Cellulitis | 9 | 0 | 4.0 | 0.7 | 0 | 0 | 1.4 |
| Arthritis | 8 | 2.0 | 0 | 1.5 | 1.9 | 0 | 1.1 |

11 serotypes were required to account for 80 percent of invasive disease over the entire 8-year time period among children aged 0–23 months. The serotype distributions for cases occurring among children aged 24–59 months and children aged 60–215 months are shown in table 3 by time period. Table 4 shows the proportions of isolates of types included in the seven-, nine-, and 11-valent polysaccharide protein conjugate vaccines and the 23-valent polysaccharide vaccine in each age group for the entire 8-year time period. The relative contribution of types 1 and 5 beyond that of the seven-valent serotypes increased by age group (5 percent among children aged 0–23 months, 12 percent among children aged 24–59 months, and 57 percent among children aged 60–215 months).

There were no statistically significant associations between individual serotypes and clinical syndrome (data not shown).

## DISCUSSION

The rates of invasive pneumococcal disease described in this paper are among the highest documented globally. Table 1 lists age-specific rates found in diverse populations in the most recent time periods and provides a basis for comparison with the rates reported here. Over the past decade, Navajo children have had rates of pneumococcal disease that are fourfold higher than those of the general US population. The reasons for this elevated risk are not known and have not been studied in this population. However, the question has been assessed in some Alaska Native populations (13). Participation in group day care and the presence of a household member who chewed tobacco were identified as significant risk factors, while breastfeeding was found to be protective (13). Breastfeeding is very common among Navajo women, with more than 70 percent initiating breastfeeding, but tobacco smoking is relatively uncommon, with approximately 20 percent of Navajo adults reporting that they smoke (our unpublished data). It is likely that in the Navajo population, environmental exposures (i.e., exposure to wood- or coal-burning stoves), the living conditions of some families, exposure to large numbers of children in extended family settings, and other socioeconomic factors play a role in the increased risk of disease. The standard of care among physicians working for the IHS is the same as

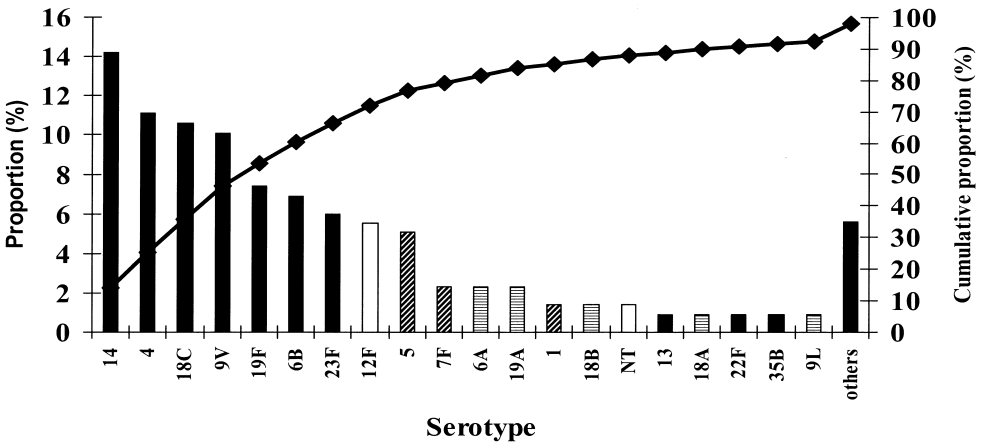


**FIGURE 4.** Distribution of serotypes in cases of invasive pneumococcal disease among Navajo children aged 0–23 months, 1989–1996. Solid black bars: serotypes in seven-valent conjugate pneumococcal vaccine; bars with horizontal lines: potentially cross-reactive serotypes of those in seven-valent conjugate pneumococcal vaccine; bars with diagonal lines: serotypes included in the nine- or 11-valent conjugate vaccine but not in the seven-valent conjugate vaccine; open bars: serotypes not included in any conjugate vaccine formulation. The line graph with diamonds represents the cumulative proportion of serotypes.

**TABLE 3. Distribution of *Streptococcus pneumoniae* isolates by serotype, age group, and study time period, Navajo Nation, 1989–1996**

| Serotype | Age group (months) and time period | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0–23 | | | | 24–59 | | | | 60–215 | | | |
| | 1989–1993 | | 1994–1996 | | 1989–1993 | | 1994–1996 | | 1989–1993 | | 1994–1996 | |
| | No. | % | No. | % | No. | % | No. | % | No. | % | No. | % |
| 1 | 3 | 2.4 | 0 | 0 | 0 | 0 | 2 | 7.1 | 4 | 50 | 3 | 20 |
| 2 | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3 | 1 | 0.8 | 0 | 0 | 1 | 7.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4 | 13 | 10.6 | 11 | 11.5 | 4 | 28.6 | 2 | 7.1 | 0 | 0 | 1 | 6.7 |
| 5 | 0 | 0 | 11 | 11.5 | 0 | 0 | 3 | 10.7 | 0 | 0 | 6 | 40 |
| 6A | 2 | 1.6 | 3 | 3.1 | 0 | 0 | 1 | 3.6 | 0 | 0 | 1 | 6.7 |
| 6B | 6 | 4.9 | 9 | 9.4 | 0 | 0 | 4 | 14.3 | 0 | 0 | 0 | 0 |
| 7C | 1 | 0.8 | 3 | 3.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7F | 2 | 1.6 | 3 | 3.1 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| 8 | 0 | 0 | 0 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 | 0 |
| 9F | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9L | 1 | 0.8 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9N | 2 | 1.6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 9V | 17 | 13.8 | 5 | 5.2 | 2 | 14.3 | 3 | 10.7 | 0 | 0 | 0 | 0 |
| 11A | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 12.5 | 0 | 0 |
| 12F | 4 | 3.3 | 8 | 8.3 | 1 | 7.1 | 1 | 3.6 | 1 | 12.5 | 2 | 13.3 |
| 13 | 2 | 1.6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14 | 20 | 16.3 | 11 | 11.5 | 1 | 7.1 | 2 | 7.1 | 1 | 12.5 | 0 | 0 |
| 15B | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15C | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16 | 0 | 0 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 16F | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18 | 0 | 0 | 0 | 0 | 1 | 7.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18A | 1 | 0.8 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 18B | 1 | 0.8 | 2 | 2.1 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| 18C | 17 | 13.8 | 6 | 6.3 | 3 | 21.4 | 1 | 3.6 | 1 | 12.5 | 0 | 0 |
| 18F | 1 | 0.8 | 0 | 0 | 0 | 0 | 2 | 7.1 | 0 | 0 | 1 | 6.7 |
| 19 | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19A | 3 | 2.4 | 2 | 2.1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 19F | 8 | 6.6 | 8 | 8.3 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| 22A | 0 | 0 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 22F | 1 | 0.8 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 23B | 0 | 0 | 1 | 1.0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 23F | 7 | 5.7 | 6 | 6.3 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| 24B | 1 | 0.8 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 6.7 |
| 33F | 1 | 0.8 | 0 | 0 | 1 | 7.1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 35B | 2 | 1.6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 38 | 0 | 0 | 1 | 1.0 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| NT | 1 | 0.8 | 3 | 3.1 | 0 | 0 | 1 | 3.6 | 0 | 0 | 0 | 0 |
| Total | 123 | 100 | 96 | 100 | 14 | 100 | 28 | 100 | 8 | 100 | 15 | 100 |
| 7-valent | 88 | 71.5 | 56 | 58.3 | 10 | 71.4 | 14 | 50.0 | 2 | 25.0 | 1 | 6.7 |

**TABLE 4. Numbers and proportions of *Streptococcus pneumoniae* cases serotyped for each formulation of polysaccharide protein conjugate pneumococcal vaccine, by age group, Navajo Nation, 1989–1996**

| Age group (months) | No. of cases serotyped | Vaccine formulation | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 7-valent | | 9-valent | | 11-valent | | 23-valent | |
| | | No. | % | No. | % | No. | % | No. | % |
| 0–11 | 101 | 67 | 66 | 77 | 76 | 78 | 77 | 89 | 88 |
| 12–23 | 113 | 76 | 67 | 80 | 71 | 85 | 75 | 97 | 86 |
| 24–59 | 42 | 24 | 57 | 29 | 69 | 31 | 74 | 36 | 86 |
| 60–215 | 23 | 3 | 13 | 16 | 70 | 16 | 70 | 20 | 87 |
| Total | 279 | 170 | 61 | 202 | 72 | 210 | 75 | 242 | 87 |

that among physicians practicing in the general US population—namely, obtaining blood cultures among febrile infants receiving medical care. This practice is less common among practitioners in other countries, which probably contributes to some of the differences in disease rates observed between countries; however, it does not explain the differences in rates among populations within the United States.

To our knowledge, there are no studies evaluating the possible role of individual or population genetic characteristics in rates of invasive pneumococcal disease, so it is not possible to assess whether genetic factors play a role. It is notable that in the United States, the three Native American populations in whom high rates of invasive pneumococcal disease have been shown (i.e., White Mountain Apache, Alaska Native, and now Navajo) are believed to have a common genetic heritage. However, these are also the only Native American populations in the United States in which invasive pneumococcal disease has been systematically studied; there are no equivalent data on rates of pneumococcal disease in other tribes that do not share this common heritage. By contrast, there are other countries with subpopulations that have elevated rates of disease (i.e., Israeli Bedouins, Australian Aborigines) but no known genetic association with other subpopulations or with Native Americans. This suggests that elevated rates are more likely to be related to nongenetic risk factors, such as those noted above. Furthermore, the declining rate of disease among Navajo children under 2 years of age during the surveillance time period also suggests that elevated rates of disease are probably nongenetic in origin.

We have shown that among Navajo children under 2 years of age, the rate of invasive pneumococcal disease has been declining continuously since 1989, such that by 1996, the year just prior to the initiation of an efficacy trial of conjugate pneumococcal vaccine among the Navajo, the rate had fallen to 307 cases/100,000 person-years, from 1,153 cases/100,000 in 1989. There were no new specific pneumococcus prevention strategies implemented during this time period in the pediatric population; however, *H. influenzae* type b protein conjugate vaccine was introduced among 2-month-old children as part of the routine vaccination program during this time period.

The decline in the incidence of invasive pneumococcal disease may be related to one or more of several factors, including improvements in overall health, improvements in living conditions, increased use of oral antibiotics for childhood illnesses, or a decline in blood culturing as a result of routine use of *H. influenzae* type b vaccine. The routine practice of obtaining blood cultures among IHS physicians follows that of other physicians in the United States—namely, blood culture is recommended for young, highly febrile children (i.e., fever ≥39.0°C) through 36 months of age, especially those with a high white blood cell count and those in the youngest age groups (14, 15). Although we did not specifically collect information on use of pneumococcal polysaccharide vaccine, it has never been recommended for children under 2 years of age and has not been routinely used in this population among children older than 2 years of age. It is possible that the 23-valent polysaccharide pneumococcal vaccine was used sporadically in the pediatric population of the Navajo Nation, but even if this were the case it would not explain a declining incidence in children under 2 years of age.

Trends in rates of invasive pneumococcal disease among young children in the general US population are more difficult to assess, because reports come from disparate geographic locations, blood-culturing practices have changed over time, and the prevalence of known risk factors for disease varies by geographic location and time period, making comparisons between surveillance areas difficult to interpret. Nevertheless, among children under 2 years of age in the general US population, there does not appear to have been any substantial or notable decline in the incidence of invasive pneumococcal disease over the past 15 years (16–20).

The serotype distribution in cases of invasive pneumococcal disease in this high-risk pediatric population has also changed over the past decade. As is typical in the general US pediatric population, most cases of disease during the 8-year surveillance period were caused by serotypes contained in the seven-valent conjugate pneumococcal vaccine. However, concomitant with a decline in the incidence of disease has been an increase in the proportion of cases caused by serotypes not included in the seven-valent vaccine. In the years just prior to commencement of the

phase III efficacy trial of the seven-valent conjugate pneumococcal vaccine, only about half of the isolates causing disease were of those seven serotypes. Prevnar was introduced in this population as a routine childhood vaccine in the fall of 2000 and has resulted in a significant reduction in the number of pediatric cases of invasive pneumococcal disease (21). The baseline data described here are critical for assessing the impact of vaccination in this high-risk community. However, because of the contemporary distribution of disease-causing serotypes, other prevention strategies may be necessary to achieve disease reductions in the range of those seen throughout the rest of the United States. Such strategies might include combined conjugate vaccine and polysaccharide vaccine schedules or common protein vaccines, which currently are investigational. Although the rates of disease in this population are high, the severity of disease as judged by the clinical syndrome distribution, the length of hospital stays, and the case fatality ratio is not different from that documented in lower-risk populations in the United States or other parts of the world. The case fatality ratio in this series (1.1 percent) is in the range of ratios reported for the general US population (20), Israeli Jews (22), Finns (23), and Swedes (24).

The observation that invasive pneumococcal disease is somewhat more common in the winter than in other seasons is not new. This peak in pneumococcal disease during the winter months has been more pronounced in other populations. It may relate to the seasonality of respiratory viral infection, which is a known risk factor for invasive pneumococcal disease; to increases in exposure to respiratory particulate matter (i.e., indoor wood- or coal-burning stoves); or to other atmospheric changes occurring during winter. Other investigators have noted a spring peak in incidence, but the reasons for this peak are not clear (22, 25, 26). The seasonal trends in this Navajo population were not particularly pronounced in comparison with those observed in other populations, which emphasizes this population's risk of disease throughout the year.

The age distribution of cases occurring in this population differed from that of the general US population insofar as the peak of disease occurred at age 6–11 months (727 cases/100,000 person-years) among Navajo children, whereas the peak in the general US population occurs at age 12–23 months (184.2 cases per 100,000) (20). The reason for the earlier peak in the disease rate is not known, but it may relate to timing or intensity of nasopharyngeal colonization, exposure to other pathogens that increase the risk of invasive pneumococcal disease (e.g., respiratory viruses), or other environmental risk factors. Of the 544 cases occurring among children under 2 years of age, eight (1.5 percent) occurred among children who had not yet reached 30 days of age and 40 (7.4 percent) occurred among children under 3 months of age. This contrasts with much higher proportions found among children in England and Wales (27) but is similar to proportions in the rest of the United States.

This study had several limitations. First, the rates of disease should be viewed as a minimum estimate. It is possible and even likely that there are residents of the Navajo Nation who received care for invasive pneumococcal disease at health care facilities other than those at which we were conducting surveillance. Furthermore, over the course of the surveillance period there were times when the laboratories were contacted at frequencies that were less than daily. Although audits were done on a semiannual or annual basis to identify cases that had been missed prospectively, it is possible that cases occurred at the surveillance sites that were not reported. Second, not all isolates causing disease were collected; consequently, only about one third of the isolates were serotyped. Isolates were collected by study staff from the clinical laboratory when the isolates were still available at the time the laboratory was contacted. The laboratories did not systematically save specific types of isolates because of resistance patterns or disease severity; thus, there is no reason to believe there was a systematic bias in the collection of isolates. For this reason, we believe that the serotype proportions accurately represent the distribution of disease-causing isolates in the population. Third, clinical syndromes were recorded on the basis of the treating physician's diagnosis. There was no attempt to characterize the clinical syndrome of each episode on the basis of a priori objective criteria.

Health disparities, including a high incidence of some infectious diseases such as pneumococcal infection, continue to impose a harsh burden on Native American communities. Defining the epidemiology of such diseases is often the first step in a series that leads to effective prevention and/or treatment and consequent reduction of morbidity and mortality. The epidemiology also directs how we should evaluate the impact of new prevention strategies. In this case, continued surveillance for rates and serotype distributions of invasive pneumococcal disease in an era of conjugate pneumococcal vaccine use is critical to assess the benefits as well as the possible shortcomings of the prevention tool. Only in this way can we strategically design, assess, and implement appropriate prevention strategies for communities that suffer a disproportionate burden of disease.

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## REFERENCES

1. World Health Organization. Bacterial etiology of serious infections in young infants in developing countries: results of a multicenter study. The WHO Young Infants Study Group. Pediatr Infect Dis J 1999;18(suppl 10):S17–22.
2. Preventing pneumococcal disease among infants and young chil-

dren: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2000; 49:1–29.
3. Sniadack DH, Schwartz B, Lipman H, et al. Potential interventions for the prevention of childhood pneumonia: geographic and temporal differences in serotype and serogroup distribution of sterile site pneumococcal isolates from children—implications for vaccine strategies. Pediatr Infect Dis J 1995;14:503–10.
4. Hausdorff WP, Bryant J, Paradiso PR, et al. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000;30:100–21.
5. Williams BG, Gouws E, Boschi-Pinto C, et al. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet 2002;2:25–32.
6. American Academy of Pediatrics. Immunizations for Native American children. Pediatrics 1999;104:564–7.
7. Prevention of pneumococcal disease. MMWR Morb Mortal Wkly Rep 1997;46:1–24.
8. Cortese MM, Wolff M, Almeido-Hill J, et al. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med 1992;152:2277–82.
9. Davidson M, Schraer CD, Parkinson AJ, et al. Invasive pneumococcal disease in an Alaska Native population, 1980 through 1986. JAMA 1989;261:715–18.
10. Davidson M, Parkinson AJ, Bulkow LR, et al. The epidemiology of invasive pneumococcal disease in Alaska, 1986–1990: ethnic differences and opportunities for prevention. J Infect Dis 1994;170:368–76.
11. O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003;362:355–61.
12. Singleton R, Helgerson SD, Snyder RD, et al. Neuropathy in Navajo children: clinical and epidemiologic features. Neurology 1990;40:363–7.
13. Gessner BD, Ussery XT, Parkinson AJ, et al. Risk factors for invasive disease caused by *Streptococcus pneumoniae* among Alaska native children younger than two years of age. Pediatr Infect Dis J 1995;14:123–8.
14. American College of Emergency Physicians. Clinical policy for the initial approach to children under the age of 2 years presenting with fever. Ann Emerg Med 1993;22:628–37.
15. Baraff LJ, Bass WJ, Fleisher GR, et al. Practice guideline for the management of infants and children 0 to 36 months of age with fever without a source. Pediatrics 1993;82:1–12.
16. Filice GA, Darby CP, Fraser DW. Pneumococcal bacteremia in Charleston County, South Carolina. Am J Epidemiol 1980;112: 828–35.
17. Breiman RF, Spika JS, Vavarro VJ, et al. Pneumococcal bacteremia in Charleston County, South Carolina: a decade later. Arch Intern Med 1990;150:1401–5.
18. Bennett NM, Buffington J, LaForce FM. Pneumococcal bacteremia in Monroe County, New York. Am J Public Health 1992;82: 1513–16.
19. Zangwill KM, Vadheim CM, Vannier AM, et al. Epidemiology of invasive pneumococcal disease in southern California: implications for the design and conduct of a pneumococcal conjugate vaccine efficacy trial. J Infect Dis 1996;174:752–9.
20. Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive *Streptococcus pneumoniae* infections in the United States, 1995–1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001;285:1729–35.
21. O'Brien KL, Weatherholtz R, Millar E, et al. Effect of conjugate pneumococcal vaccine on invasive pneumococcal disease (IPD) among Navajo. (Abstract). Presented at the Fourth International Symposium on Pneumococci and Pneumococcal Disease, Helsinki, Finland, May 9–13, 2004.
22. Dagan R, Englehard D, Piccard E. Epidemiology of invasive childhood pneumococcal infections in Israel. The Israeli Pediatric Bacteremia and Meningitis Group. JAMA 1992;268: 3328–32.
23. Eskola J, Takala A, Kela E, et al. Epidemiology of invasive pneumococcal infections in children in Finland. JAMA 1992; 268:3323–7.
24. Berman LA, Norrby R, Trollfors B. Invasive pneumococcal infections: incidence, predisposing factors, prognosis. Rev Infect Dis 1985;7:133–42.
25. Fraser D, Givon-Lavi N, Bilenko N, et al. A decade (1989–1998) of pediatric invasive pneumococcal disease in 2 populations residing in 1 geographic location: implications for vaccine choice. Clin Infect Dis 2001;33:421–7.
26. Dowell SF, Whitney CG, Wright C, et al. Seasonal patterns of invasive pneumococcal disease. Emerg Infect Dis 2003;9:573–9.
27. Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001;183:239–46.
28. Torzillo PJ, Hanna JN, Morey F, et al. Invasive pneumococcal disease in central Australia. Med J Aust 1995;162:182–6.
29. Karstaedt A, Khoosal M, Crewe-Brown H. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J 2000;19:454–7.
30. Voss L, Lennon D, Okesene-Gafa K, et al. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. Pediatr Infect Dis J 1994;13:873–8.
31. Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive pneumococcal disease in the Western Region, The Gambia. Pediatr Infect Dis J 1998;17:23–8.
32. von Kries R, Siedler A, Schmitt H, et al. Proportion of invasive pneumococcal infections in German children preventable by pneumococcal conjugate vaccines. Clin Infect Dis 2000;31: 482–7.