MAJOR ARTICLE

# Invasive Pneumococcal Disease among Navajo Adults, 1989–1998

**James P. Watt,[1,2] Katherine L. O'Brien,[2] Andrea L. Benin,[1,3] Cynthia G. Whitney,[1] Katherine Robinson,[1] Alan J. Parkinson,[4] Raymond Reid,[2] and Mathuram Santosham[2]**

[1]Respiratory Diseases Branch, Division of Bacterial and Mycotic Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Center for American Indian Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [3]Robert Wood Johnson Clinical Scholars Program, Yale University School of Medicine, New Haven, Connecticut; and [4]Arctic Investigations Program, Centers for Disease Control and Prevention, Anchorage, Alaska



**Compared with white and black persons in the United States, some Native American groups are at increased risk for invasive pneumococcal disease (IPD). To characterize the epidemiology of IPD among Navajo adults, we conducted active surveillance for IPD on the Navajo Nation and reviewed medical records of patients with IPD. For 1997–1998, the annual incidence (cases per 100,000 persons) was 56 for Navajos aged 18–64 years and 190 for Navajos aged ⩾65 years. The corresponding rates were 10 and 57 for white and 44 and 82 for black persons in the United States. The case-fatality rate was 14%. Eighty percent of cases were caused by serotypes included in the 23-valent pneumococcal polysaccharide vaccine. Navajo adults have rates of IPD that are 3–5-fold higher than those of the general US population. Additional research is needed to understand the reasons for this elevated risk and to develop prevention strategies.**

*Streptococcus pneumoniae*, or pneumococcus, is a leading cause of community-acquired pneumonia, bacteremia, and meningitis among children and adults. Some indigenous groups in the United States, including Alaska Natives, White Mountain Apache, and Navajo children, have higher rates of pneumococcal disease than does the general population [1–5]. The burden of pneumococcal disease among Navajo adults has not been previously analyzed. Information about the epidemiology and the serotype distribution of invasive pneumococcal disease (IPD) will be useful for the evaluation of current prevention strategies and the development of new prevention tools. The long-standing partnership between the Center for American Indian Health (CAIH), the Navajo Nation, and the Indian Health Service (IHS) allowed us to study the epidemiology of IPD in this potentially high-risk population. This report describes the basic epidemiology of IPD and serotype distribution of invasive pneumococcal isolates among Navajo adults.

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Correspondence: Dr. James P. Watt, Center for American Indian Health, 621 N. Washington St., Baltimore, MD 20015 (jwatt@jhsph.edu).

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## PATIENTS, MATERIALS, AND METHODS

***Study site.*** The study was conducted on the Navajo Nation, the largest American Indian nation in the United States, consisting of ~235,000 tribal members and an area covering >25,000 square miles in northern Arizona, western New Mexico, and southern Utah. Health care in the Navajo Nation is administered through the IHS, an agency of the federal Department of Health and Human Services. IHS operates 6 hospitals with microbiology facilities in and around the Navajo Nation.

***Surveillance.*** CAIH, in collaboration with the Navajo Nation and IHS, has conducted active, population, and laboratory-based surveillance for IPD in the Navajo Nation since 1989. CAIH staff members regularly visit each of the 6 IHS hospital microbiology

laboratories that serve patients in the Navajo Nation to identify cases of IPD. Non-IHS hospital laboratories located near the Navajo Nation are contacted weekly to identify any additional cases among Navajo tribal members. Basic demographic information is recorded for all cases, and, whenever possible, a subculture of the pneumococcal isolate is obtained from the hospital laboratory. The resources available for surveillance have varied from year to year. Surveillance was most intensive beginning in 1995, when preparations for a large phase 3 trial of pneumococcal conjugate vaccine began.

***Case definition and inclusion criteria.*** IPD was defined as isolation of pneumococcus from a normally sterile body site. Persons with IPD were included in the study if the case patient was aged ⩾18 years, had at least one-eighth Navajo ancestry, and was a registered user of the IHS services in the Navajo area and if the date of culture was from 1 January 1989 through 31 December 1998 and ⩾30 days after any previous isolation of pneumococcus from a sterile site.

***Clinical definitions.*** Sepsis was defined as a clinical diagnosis of sepsis plus evidence of hypotension or end organ failure (e.g., azotemia or altered mental status). Alcohol abuse was defined as recent evidence of alcohol abuse in the medical record along with a clinical diagnosis of alcoholism, complications of alcohol abuse (i.e., alcoholic hepatitis), or multiple medical visits related to alcohol (i.e., acute intoxication and alcohol-related trauma). Pneumonia was defined as a clinical diagnosis of pneumonia with ⩾1 of the following findings: evidence of pneumonia on a chest radiograph, signs or symptoms consistent with pneumonia (i.e., cough, dyspnea, or rales), or hypoxia.

***Laboratory methods.*** Whenever possible, pneumococcal isolates were obtained from the clinical laboratory where they were initially isolated and sent to the Arctic Investigations Program, Centers for Disease Control and Prevention (CDC; Anchorage, AK), for identity confirmation and serotyping. Serotyping was performed by means of the Quellung reaction using antisera obtained from the Statens Serum Institute.

***Medical record review.*** Medical records of all persons with IPD identified by CAIH were requested from the appropriate IHS hospital. Archived records were retrieved from federal record centers. Medical records were abstracted by means of a standardized chart review form. If the records at a patient's primary service unit were incomplete, or if a patient had no record of pneumococcal polysaccharide vaccination, then records were reviewed at each service unit where the patient had received care. For the analysis of underlying illnesses and vaccination status, we only considered the first episode of IPD for persons who had multiple episodes.

***Surveillance audit.*** For the purpose of evaluating the completeness of the surveillance system, laboratory records were reviewed at each IHS hospital for the period of 1997–1998. All sterile site pneumococcal isolates from adult Navajo patients were recorded and compared with the surveillance database. Any cases not previously identified were added to the surveillance database.

***Data management and analysis.*** Data were entered into an EpiInfo database (CDC), and a check program was used to reduce errors in data entry. Data were analyzed using SAS software, version 8 (SAS Institute). Two-sided Fisher's exact tests were used to compare categorical variables, and Student's *t* test was used to compare mean values for continuous variables. Comparison data were obtained from published and unpublished data collected by the CDC's Emerging Infections Program Network/Active Bacterial Core Surveillance (ABCs), an active surveillance system that collects information on IPD in a population of 16 million persons. Methods for ABCs have been previously reported [4, 6].

***Calculation of incidence rates.*** To determine incidence rates, we used the average number of cases occurring in 1997 and 1998 as the numerator. Two years of data were averaged to reduce the impact of year-to-year variability of disease incidence in a small population. These 2 years were selected because they were likely to be the years of most complete surveillance for 2 reasons. First, they were years of intensive surveillance related to a pediatric pneumococcal conjugate vaccine trial; and second, intensive surveillance audits were conducted for both years. For the denominator, we used data from IHS on the number of registered users of IHS services on the Navajo Nation in 1997. These data include not only persons who used clinical services, but also anyone who registered with the IHS system, and thus approximate the total population of the Navajo Nation. In 1997, the populations of registered by IHS were 14,720 persons aged ⩾65 years and 124,634 persons aged 18–64 years.

***Ethics considerations.*** This study was approved by the institutional review boards of the Johns Hopkins Bloomberg School of Public Health, the CDC, the Navajo Nation, and the IHS. This study was also approved by the Navajo Area IHS Health Board.

## RESULTS

***Surveillance.*** During the period of 1989–1998, we identified 630 episodes of IPD among 596 Navajo adults. Twenty-three persons had 2 episodes; 7 persons had 3 episodes; 3 persons had 4 episodes; and 1 person had 5 episodes. Substantially more cases per year were identified during the period of 1995–1998, the years of more intensive surveillance (figure 1). Our audit of laboratory records identified 14 cases in 1997–1998 that were not identified by routine surveillance, representing 14 (7%) of all 196 cases identified during those 2 years. Thus, the sensitivity

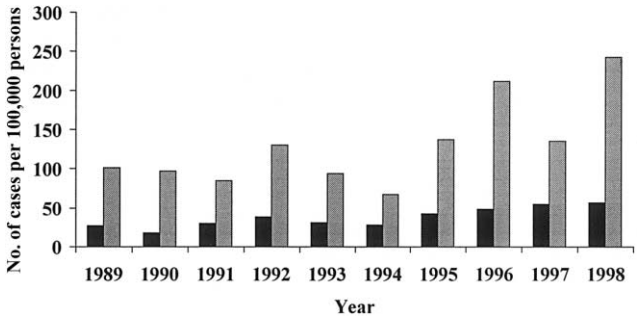


**Figure 1.** Incidence of invasive pneumococcal disease, by year and age group, among Navajo adults. *Solid bars,* persons aged 18–64 years; *hatched bars,* persons aged ⩾65 years.

of the routine surveillance system was estimated to be 93%. During 1997–1998, the average annual incidences of IPD among Navajo adults aged 18–64 years and ⩾65 years were 56 and 190 cases per 100,000 persons, respectively. For Navajo adults aged ⩾65 years, the annual rate of IPD was similar in men and women (181 and 197 cases per 100,000 persons, respectively). However, among Navajo adults aged 18–64 years, IPD was significantly more common among men than among women (70 vs. 43 cases per 100,000 persons per year, respectively; $P < .01$). The mean age of persons with IPD was significantly lower for men than for women (50 years vs. 57 years; $P < .001$).

***Medical record review.*** We were able to locate and review the medical records for 561 (94%) of the 596 patients. Information on location of treatment and outcome was available for 581 (92%) of the 630 IPD episodes identified. Among these episodes, 515 (89%) resulted in hospitalization and 161 (28%) required admission to an intensive care unit. Eighty episodes (14%) resulted in death. Patients with IPD aged ⩾65 years were significantly more likely to die (34 [22%] of 154 patients) than were those aged 18–64 years (46 [11%] of 427; $P < .001$).

Clinical information was available for 569 IPD episodes, and >1 clinical syndrome could be present for each episode. Pneumonia was the most common syndrome: it occurred in 459 episodes (81%). In addition, 107 episodes (19%) met our definition of sepsis. Bacteremia without focus (38 episodes [7%]), peritonitis/intraabdominal focus (27 episodes [5%]), septic arthritis (17 episodes [3%]), and meningitis (17 episodes [3%]) were less common syndromes present in IPD episodes.

Medical histories were available for 556 persons with IPD. The most common underlying medical conditions among these case patients are listed in table 1. Some risk factors that have been common in other populations of patients with IPD were uncommon among Navajo adults with IPD. HIV infection was only documented in the medical records of 2 persons. Current cigarette smoking was documented for 7% of cases, but we could not determine whether a history of smoking was consistently recorded in the medical records. Women with IPD were significantly more likely than men with IPD to have cancer (9% vs. 4%; $P < .05$), obesity (16% vs. 9%; $P < .01$), and collagen vascular disease (10% vs. 4%; $P < .01$). Alcohol abuse was more common among men with IPD than among women with IPD (50% vs. 14%; $P < .0001$). Most of the underlying conditions were more common in patients aged ⩾65 years (table 1). One notable exception was alcohol abuse, which was present among 42% of patients aged 18–64, compared with 13% of patients aged ⩾65 years ($P < .0001$). Alcohol abuse was present in 59% of male case patients aged 18–64 years. Patients with a medical indication for receipt of pneumococcal polysaccharide vaccine (PPV23) had a significantly higher case-fatality rate (16%; 61 deaths among 379 first episodes) than did those without a medical indication (6%; 10 deaths among 167 first episodes; $P < .0001$). For patients aged 18–64 years with a medical indication for receipt of PPV23, the case-fatality rate was also significantly higher (14%; 37 deaths among 263 first episodes), compared with those without a medical indication (2%; 2 deaths among 128 first episodes; $P < .0001$).

Overall, we found documentation that 274 (49%) of 556 Navajo adults with IPD had received PPV23 before the date of their pneumococcal culture. Vaccination was significantly more common for patients with IPD aged ⩾65 years than for those aged 18–64 years (117 [75%] of 157 vs. 157 [39%] of 399 patients; $P < .0001$). Among those aged 18–64 years, vaccination was significantly more common in patients with IPD and underlying medical conditions that are indications for vaccination than in those without such conditions (143 [53%] of 270 vs. 14 [11%] of 129 patients; $P < .0001$). The median time since the last dose of PPV23 was 4.1 years (interquartile range, 1.9–6.6 years).

***Serotype analysis.*** Pneumococcal serotype data were avail-

**Table 1. Underlying medical conditions and risk factors among adult Navajos with invasive pneumococcal disease by age, 1989–1998.**

| Underlying condition or risk factor | No. (%) of subjects, by age | | | |
|---|---|---|---|---|
| | 18–64 years ($n$ = 399) | ⩾65 years ($n$ = 157) | All ($n$ = 556) | $P$[a] |
| Alcohol abuse | 169 (42.4) | 20 (12.7) | 189 (34.0) | <.001 |
| Diabetes mellitus | 81 (20.3) | 50 (32.0) | 131 (23.6) | <.01 |
| Chronic heart disease[b] | 32 (8.0) | 41 (26.1) | 73 (13.1) | <.001 |
| Chronic renal failure | 34 (8.5) | 30 (19.1) | 64 (11.5) | <.001 |
| Collagen vascular disease | 28 (7.0) | 27 (17.2) | 55 (9.9) | <.001 |
| Chronic lung disease[c] | 22 (5.5) | 24 (15.3) | 46 (8.3) | <.001 |
| Cancer | 17 (4.3) | 16 (10.2) | 33 (5.9) | .02 |
| Any underlying condition | 270 (67.7) | 116 (73.9) | 386 (69.4) | NS |

[a] Comparison of proportion with condition between age groups.
[b] Includes congestive heart failure, history of myocardial infarction, angina, and cardiomyopathy.
[c] Includes chronic obstructive pulmonary disease, history of pneumonectomy, bronchiectasis, pulmonary fibrosis, pneumoconioses, and chronic restrictive lung disease.

**Table 2. Distribution of invasive pneumococcal serotypes among Navajo adults with invasive pneumococcal disease, 1989–1998.**

| Serotype | No. (%) of isolates |
|---|---|
| 1 | 51 (15.8) |
| 12F | 43 (13.3) |
| 5 | 36 (11.1) |
| 4 | 24 (7.4) |
| 7F | 17 (5.3) |
| 6A | 13 (4.0) |
| 8 | 13 (4.0) |
| 9V | 11 (3.4) |
| 19A | 10 (3.1) |
| 14 | 9 (2.8) |
| 16 | 9 (2.8) |
| 3 | 9 (2.8) |
| 18C | 6 (1.9) |
| 22F | 6 (1.9) |
| 17F | 5 (1.5) |
| 23F | 5 (1.5) |

**NOTE.** There were 4 isolates each of serotypes 18B, 19F, 31, 6B, and 7C and not typeable isolates, 3 isolates each of serotypes 13 and 38; 2 isolates each of serotypes 10A, 23B, 35A, 35B, 35F, and 9N; and 1 isolate each of serotypes 11A, 12A, 15A, 15B, 15C, 16F, 18F, 23A, 24B, 24F, 33F, 34, 35, and 9L.

able for 323 (51%) of 630 episodes (table 2). Overall, 80% of episodes with known serotype were caused by a serotype included in the 23-valent PPV (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). An additional 9% of cases were caused by a potentially cross-reactive serotype (i.e., a serotype in the same serogroup as one in the 23-valent PPV). Only 20% of cases were caused by serotypes included in the 7-valent pneumococcal conjugate vaccine currently licensed in the United States (4, 6B, 9V, 14, 18C, 19F, and 23F), with an additional 11% of cases caused by potentially cross-reactive serotypes. The investigational 11-valent pneumococcal conjugate vaccine includes serotypes (1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F) responsible for 54% of IPD in Navajo adults. An additional 12% of cases are caused by cross-reactive serotypes.

## DISCUSSION

Approximately 100 cases of IPD and 14 deaths due to IPD occur among Navajo adults living on the Navajo Nation each year. Compared with the US white population as measured by ABCs in 1998, the annual incidence of IPD is >5 times higher among Navajo adults aged 18–64 years (56 vs. 10 cases per 100,000 persons) and >3 times higher among Navajo adults aged ⩾65 years (190 vs. 57 cases per 100,000 persons; figure 2). IPD is a severe illness in Navajo adults, with 28% of cases requiring intensive care and 14% of patients dying. The case-fatality rate increased with age and was similar to that reported for the general US population through the ABCs program [4].

Because this was a descriptive study, it offers only suggestions of the reasons for elevated IPD rates among Navajo adults. A large proportion of case patients had an underlying medical risk factor for IPD. Sixty-eight percent of case patients aged 18–64 years had an underlying medical risk factor, whereas 74% of case patients aged ⩾65 years had an underlying medical risk factor. However, medical risk factors alone may not explain the elevated rates of disease, because underlying medical conditions are common among persons with IPD in other settings. Among cases of IPD in the general US population, 59% of those aged 18–64 years had an underlying medical risk factor [4], and a review of IPD cases in Sweden found that 81% of patients had underlying medical conditions [7]. It is possible that the particular medical conditions prevalent among Navajo adults, or the prevalence or severity of those conditions in the population, place Navajo adults at greater risk for IPD. Additional research is needed to understand the contribution of underlying medical conditions to IPD risk in Navajo adults. Other factors that could put Navajo adults at increased risk should be evaluated, including decreased PPV effectiveness, indoor air pollution, crowding, and exposure to children in day care.

The distribution of serotypes was somewhat different among Navajo adults than in the general US population [4]. Serotypes 1, 12F, and 5, each of which caused >10% of cases among Navajo adults, were less common in the general US population. However, the proportion of cases among Navajo adults caused by serotypes included in PPV23 (80%) was similar to that seen in the CDC ABCs surveillance system (86%–88%) [4]. Although there are some differences in the effectiveness of PPV23 against different serotypes [8] and in the relative invasiveness of different sero-

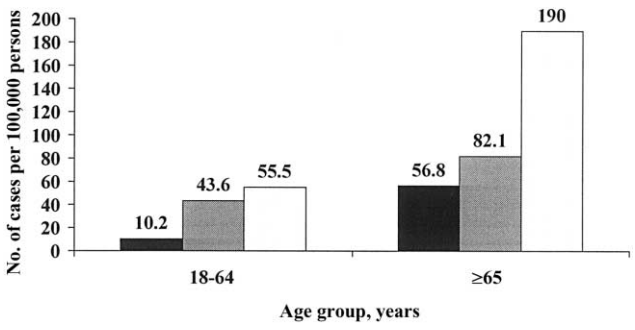


**Figure 2.** Invasive pneumococcal disease rates among Navajo adults (1997 and 1998) and white and black adults in the United States (1998). *Solid bars,* white persons; *hatched bars,* black persons; *dotted bars,* Navajo persons.

types, it is unlikely that the differences in prevalent serotypes alone explains the manifold elevation in IPD rates among Navajo adults relative to the general US population.

Use of the recently approved 7-valent pneumococcal conjugate vaccine represents a highly effective strategy for reducing the burden of pneumococcal disease in children, including American Indians [9–11]. PPV23, however, remains the main tool for prevention of pneumococcal disease in adults. The reported effectiveness of PPV23 against IPD (i.e., isolation of pneumococcus from a normally sterile body fluid) has been variable (range, 0%–81%) [8, 12–17]. A recent study of PPV23 effectiveness in Navajo adults found overall effectiveness of only 26% and 35% using 2 different methods [18]. The 95% CIs for both of those estimates included 0% effectiveness. It is possible that reduced effectiveness of PPV23 in this population contributes to the elevated IPD risk. Decreased responsiveness to polysaccharide antigens could represent one possible explanation for low effectiveness of PPV23 in this population. A decreased response to *Haemophilus influenzae* type b polysaccharide vaccine has been described in some Native American children [19]. There are no data on pneumococcal polysaccharide vaccine immunogenicity available for Navajo adults or children.

Strategies to improve prevention of IPD in this high-risk population are needed. Ongoing efforts to reduce the burden of medical risk factors, particularly alcohol abuse and diabetes, may help reduce the IPD incidence as well. Increasing the proportion of persons vaccinated with PPV23 may offer some benefit to Navajo adults. However, because coverage is already higher than that of the general US population and the vaccine effectiveness is low, the benefit of PPV23 is likely to be limited for Navajo adults [18]. Furthermore, PPV23 has limited effectiveness against noninvasive pneumococcal pneumonia, which is the most common serious pneumococcal illness in adults [17, 18, 20].

A more effective vaccine would be of great benefit in this population. Pneumococcal conjugate vaccines containing serotypes responsible for the majority of cases, such as the investigational 11-valent vaccine, could be considered. Vaccines based on conserved pneumococcal proteins are currently in clinical trials. These vaccines, if safe and effective, should be evaluated in an effort to reduce the disproportionate disease burden among Navajo adults. In addition, further investigation of factors that might place Navajo adults at high risk for IPD is needed. A case-control study of medical and environmental risk factors in this population has recently been completed, and analysis is ongoing (authors' unpublished data). This study may increase our understanding of the elevated disease burden in this population and guide the development of other prevention strategies.

This study has several limitations because of its retrospective design. It is likely that the surveillance system missed some cases of IPD, particularly in the early part of the study period. It is unlikely that missed cases differed in any systematic way from those identified. The incidence rates were calculated by using the cases from 1997 and 1998, the 2 years for which intensive laboratory audits were conducted. If cases were missed, the disease burden among Navajo adults and the magnitude of the increased risk in this population would be underestimated. The analysis of serotype distribution could be affected by the significant proportion of cases for which a pneumococcal isolate was not available for serotyping. However, it is unlikely that there are any systematic differences in serotypes between those cases for which an isolate was recovered and those for which one was not. Some patients may have received PPV23 at clinical sites other than those where we conducted chart reviews. Our estimate of the percentage of case patients who had received PPV23 should be viewed as a minimum estimate.

Navajo adults have higher rates of IPD than does the general US population. It is likely that Navajo adults are at increased risk for other forms of pneumococcal disease, particularly nonbacteremic pneumococcal pneumonia. Additional research is needed to better understand the causes of this increased risk. Because the effectiveness of PPV23 appears to be limited in this population, new strategies to prevent pneumococcal disease are needed.

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