# High Incidence Rates of Invasive Pneumococcal Disease in the White Mountain Apache Population

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• ***Objective.***—**In this article we determine the incidence and clinical spectrum of invasive pneumococcal disease in the White Mountain Apache population, a group known to have a high incidence of invasive disease due to *Haemophilus influenzae* type b.**

***Design.***—**Patients from whom cultures of normally sterile body sites yielded *Streptococcus pneumoniae* were identified retrospectively through review of hospital laboratory records from a 6.8-year period. Clinical data were reviewed and incidence rates were computed.**

***Setting.***—**The Whiteriver Indian Health Service Hospital is located on the 1.7-million–acre White Mountain Apache Reservation in eastern Arizona.**

***Patients.***—**Approximately 10 000 members of the White Mountain Apache Tribe reside on or near the reservation and receive health care through the Whiteriver Indian Health Service Hospital.**

***Outcome Measures.***—**The average annual incidence rates of invasive pneumococcal disease were calculated and clinical characteristics were reviewed.**

***Results.***—**One hundred thirty-eight cases of invasive pneumococcal disease were identified. The average annual incidence rate was 207 per 100 000 population, and 156 per 100 000 population when adjusted for age by direct standardization to the 1988 US population. The incidence rate was highest in children between 1 and 2 years—2396 per 100 000. The overall case-fatality rate was 5%. Pneumococcal pneumonia was the diagnosis in 79% of the patients 5 years of age or older. Alcohol abuse, identified in 66% of the cases in adults, was the most common underlying medical condition.**

***Conclusion.***—**The incidence rates in White Mountain Apaches are the highest reported for any population. A vaccine effective in children would greatly benefit this population.**

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*Streptococcus pneumoniae* continues to cause significant morbidity and mortality worldwide. There are an estimated 40 000 pneumococcal-related deaths yearly in the United States alone and the pneumococcus is believed to be responsible for a considerable proportion of the 4 to 5 million deaths annually in all children with acute respiratory disease.[1-3] Children in certain Native American populations have a high incidence of bacterial meningitis and appear to be at increased risk for lower respiratory tract infections and otitis media.[4-11] The purpose of this study was to determine the incidence of invasive pneumococcal disease in the White Mountain Apache population and examine its clinical spectrum.

## PATIENTS AND METHODS

### Population

The great majority of the 10 147 enrolled members of the White Mountain Apache Tribe reside on or near the 1.7-million–acre White Mountain Apache Reservation in eastern Arizona.[12] Inpatient and outpatient health care is provided on the reservation at the Whiteriver (Ariz) Indian Health Service Hospital. This hospital operates one outlying clinic, and together these facilities provide all the on-reservation health care. The Phoenix Indian Medical Center is the referral facility and is located 200 miles southwest of Whiteriver.

Approval for reviewing laboratory and medical records was granted by the White Mountain Apache Tribal Council, the Phoenix Area Research Committee, the Indian Health Service, and The Johns Hopkins University Committee on Human Volunteers.

### Case Identification

As part of an ongoing immunization project, hospital bacteriology records were reviewed for reports of cultures from which *S pneumoniae* was isolated. Laboratory records were reviewed regularly from August 1, 1983, through May 31, 1990, in Whiteriver. In addition, the laboratory records of the referral center were available for review beginning January 1, 1988, and were

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Table 1.—Average Annual Incidence and Case-Fatality Rates of Invasive Pneumococcal Disease in White Mountain Apache Patients, March 1983 Through May 1990

| Age Group, y | Mean Population | No. of Cases | Case Fatality, % | Incidence Rate per 100 000 |
|---|---|---|---|---|
| <2 | 654 | 81 | 0 | 1820 |
| 2-4 | 971 | 15 | 7 | 227 |
| 5-9 | 1096 | 4 | 0 | 54 |
| 10-19 | 2532 | 6 | 0 | 35 |
| 20-29 | 1612 | 9 | 22 | 82 |
| 30-39 | 1144 | 6 | 33 | 77 |
| 40-49 | 770 | 7 | 0 | 134 |
| 50-59 | 521 | 4 | 50 | 113 |
| ≥60 | 514 | 6 | 0 | 172 |
| **All Ages** | **9814** | **138** | 5 | 207 |

reviewed through May 31, 1990. Death logs were available in Whiteriver and were reviewed from August 1, 1983, through May 31, 1990.

Invasive pneumococcal disease was defined as the isolation of *S pneumoniae* from blood, cerebrospinal fluid, or other normally sterile body site (eg, pleural fluid, synovial fluid). The medical records of inpatients and outpatients with invasive pneumococcal disease were reviewed for clinical information.

Pneumococcal meningitis was defined by isolation of the organism from the cerebrospinal fluid, or cerebrospinal fluid pleocytosis (>100 white blood cells per cubic millimeter) and isolation of the organism from the blood. The diagnosis of pneumococcal pneumonia was given to a patient with *S pneumoniae* isolated from blood and the presence of a new infiltrate on a roentgenogram of the chest as documented in the radiologist's report or, when a roentgenogram was not obtained, by isolation of the organism from the blood and the diagnosis of pneumonia by the clinician. Pneumococcal otitis media was defined by isolation of the organism from the blood and the clinical diagnosis of acute otitis media. Patients without localized disease who were given an initial diagnosis of gastroenteritis, upper respiratory tract infection, or pharyngitis were recorded as having fever without source. Patients who had several clinical diagnoses with a single episode of pneumococcal disease were counted once using the following hierarchy:

endocarditis>>meningitis>>empyema>>pericarditis>>peritonitis>>pneumonia>>cellulitis>>otitis media>>fever without source.

Episodes of recurrent invasive disease, defined as isolation of *S pneumoniae* from cultures separated by at least 2 months, were counted as separate events. A relapse was defined as the occurrence of two cultures from which the organism was isolated within a 2-month period. Individuals with relapses were counted only once.

Typing of bacteremic isolates was performed using the quellung reaction with pneumococcal antisera from the Statens Seruminstitut (Copenhagen, Denmark), including the antiserum pools A to I. Strains showing a positive quellung reaction with the pools were then typed with individual type-specific serum samples. Factor serum samples were not available.

Only those patients identified as members of the White Mountain Apache Tribe and residing on or near the reservation were included in the analysis.

### Statistical Analyses

The annual numbers of births and dates of birth in Whiteriver were obtained from hospital records and were used to compute birth rates. For calculation of overall incidence rates and rates in adults, population statistics were based on the 1980 and 1990 US Census.[13,14] The population statistics for intermediate years were computed assuming a constant annual rate of growth.

Incidence rates were computed as cases per person year using previously cited population statistics. Age-adjusted rates were computed using direct standardization to the 1988 US population.[15] Comparisons of mean ages by diagnosis were done using analysis of variance. Tests of distribution of cases by sex were based on a binomial test. Contingency tables and their $\chi^2$ statistics were used to compare proportions in different populations. Trends in incidence rates were analyzed by Poisson regression. The software used was SAS and STATISTIX for statistical computations, and FOXPLUS and SAS for data management.

## RESULTS

One hundred thirty-eight episodes of invasive pneumococcal disease were identified in 131 patients. All patients had *S pneumoniae* recovered from blood cultures. The organism was additionally recovered from cerebrospinal fluid in two patients and, in one patient each, from pleural fluid, pericardial fluid, and peritoneal fluid. Forty-one isolates from blood cultures were available to be serotyped—all were in children younger than 3 years and represented 43% of the episodes in this age group. Eleven serotypes or serogroups were identified; the most common were 18 (20%), six (20%), four (15%), 19(12%), nine (10%), and 14(7%). Two of these isolates were not typeable. Of the 41 isolates available for serotyping, 37 (90%) were found to be serotypes/serogroups represented in the current 23-valent vaccine.

Twenty-two percent of cases were detected during the warmest months, May through August, when only cases from complete years were analyzed. The overall incidence rate in 1984 was lower than in the subsequent years ($P=.01$). There was no temporal trend in incidence rates over this period.

The overall annual incidence rates of invasive pneumococcal disease were 207 per 100 000 population in White Mountain Apaches and 156 per 100 000 when adjusted for age by direct standardization to the 1988 US population (Table 1). The highest incidence occurred in children between 1 and 2 years of age: 2396 per 100 000. The incidence of pneumococcal meningitis was nine per 100 000 in children younger than 5 years.

Overall, there was a male predominance (male:female ratio, 82:56). In children younger than 2 years, the distribution was nearly equal (male:female ratio, 40:41). Females

**Table 2.—Primary Diagnoses in 138 Cases of Invasive Pneumococcal Disease in White Mountain Apache Patients***

| | Age Group, y (%) | | | | | |
|---|---|---|---|---|---|---|
| | 0-1 | 2-4 | 5-19 | 20-64 | >65 | Total |
| No. of cases with diagnosis | | | | | | |
| Pneumonia | 29 (36) | 9 (60) | 8 (80) | 21 (78) | 4 (80) | **71** |
| Fever without source | 26 (32)† | 2 (13) | 2 (20) | 2 (7) | . . . | **32** |
| Otitis media | 25 (31) | 2 (13) | . . . | . . . | . . . | **27** |
| Meningitis | . . . | 1 (7) | . . . | 1 (4) | 1 (20) | **3** |
| Endocarditis | 1 (1) | . . . | . . . | 1 (4) | . . . | **2** |
| Periorbital cellulitis | . . . | 1 (7) | . . . | . . . | . . . | **1** |
| Empyema | . . . | . . . | . . . | 1 (4) | . . . | **1** |
| Peritonitis | . . . | . . . | . . . | 1 (4) | . . . | **1** |
| **Total** | **81** | **15** | **10** | **27** | **5** | **138** |

*Patients with multiple clinical diagnoses with single episode of pneumococcal disease are listed once using the hierarchy presented in the text.
†Clinical diagnosis: fever without source (16), upper respiratory tract infection (six), and gastroenteritis (four).

predominated in infants younger than 1 year (male:female ratio, 11:17), though not significantly. The male-to-female ratio was highest in patients 20 years of age and older (27:5) and was reduced to 7:4 after excluding all cases in which alcohol abuse was included in the patient's medical problem list at the time the culture was obtained.

Seventy-nine children younger than 2 years had a single episode of pneumococcal disease and five had recurrences. Underlying medical conditions were present in two of these five children: one with reactive airway disease requiring frequent hospitalization and the other with reactive airway disease and recurrent pneumonia. Serotype information was available for two children with recurrent disease. One patient had disease from serotypes 1 and 4; the other was a healthy child with isolates from serogroup 18 at 6 and 11 months of age.

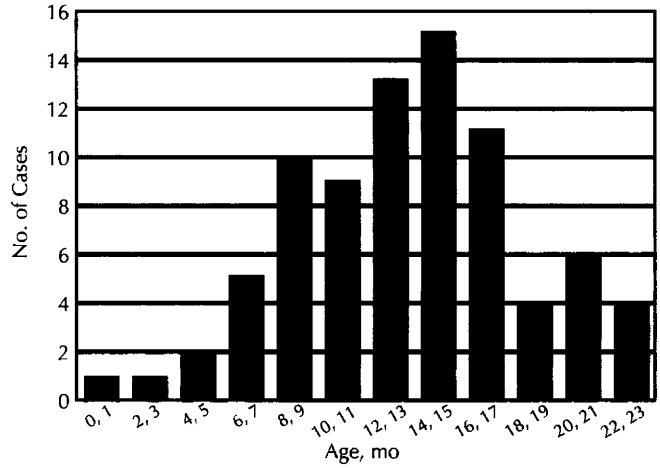
Two adults had recurrent pneumococcal disease. A 24- and a 25-year-old man, each with a history of alcohol abuse, had two episodes of pneumococcal pneumonia separated by 36 and 30 months, respectively. Isolates were not available for serotyping.

The clinical spectrum of disease is presented in Table 2. Pneumonia was the most common primary diagnosis overall, accounting for 51% of total cases and 79% of cases in patients 5 years of age or older. In children younger than 2 years of age, the most frequent primary diagnoses were pneumonia (36%), fever without source (32%), and otitis media (31%). More than one focus of infection was identified in 14% of children younger than 2 years. Thirty-seven percent of children diagnosed with pneumonia had concurrent otitis media. Nonspecific symptoms were often present. Gastroenteritis was listed as a primary or secondary diagnosis in 11% of patients younger than 2 years. Febrile seizures occurred in 6% of the episodes in children younger than 2 years.

The distribution of cases by age in infants is presented in the Figure. The median age of children younger than 5 years with invasive pneumococcal disease was 15.2 months (mean, 16.6±8.1 months). There were no significant differences in mean ages when patients younger than 5 years were separated by diagnosis.

With the exception of one adult with pneumococcal peritonitis, all positive cultures of initially hospitalized patients were obtained on the day of admission. Ninety-one percent of the adults were hospitalized during their course of illness, compared with 36% of the children younger than 2 years.

Sixteen percent of the episodes in children younger than 2 years of age occurred in patients with underlying medical conditions, while 81% of the episodes in adults occurred in patients with underlying conditions (Table 3). Alcohol abuse, identified as an underlying condition if included in the patient's medical problem list at the time the culture was obtained, was the most common underlying condition and was reported in 66% of the cases in patients 20 years of age and older. As in patients without alcohol abuse, pneumonia was the most common primary diagnosis (71%) in these patients.




*Distribution of cases of invasive pneumococcal disease by age in White Mountain Apache infants.*

Six adults and one child died during their hospitalization for pneumococcal disease. Case-fatality rates were zero in children less than 2 years, 7% in children between 2 and 5 years of age, and 22% in adults 20 years and older. Fatal pneumococcal meningitis occurred in a previously healthy 31-month-old girl. The median age of adults with fatal disease was 34 years (range, 26 to 59 years). Alcohol abuse was reported in five of the six adults with fatal pneumococcal disease; the sixth patient was 60 years old and had no identified underlying condition. Sixty-seven percent of deaths in adults occurred within 48 hours of hospital admission.

## COMMENT

The annual incidence rate of invasive pneumococcal disease in White Mountain Apaches is the highest reported for any population (Table 4).[3,16-21] Overall, the annual inci-

**Table 3.—Underlying Medical Conditions in White Mountain Apache Patients With Invasive Pneumococcal Disease***

| | Age Group, y | | | | |
|---|---|---|---|---|---|
| | 0-1 | 2-4 | 5-19 | 20-64 | >65 |
| No. of cases | 81 | 15 | 10 | 27 | 5 |
| Congenital heart disease† | 3 | ... | ... | ... | ... |
| Chronic lung disease‡ | 9 | ... | 1 | ... | ... |
| Concurrent varicella infection | 1 | 1 | ... | ... | ... |
| Ventriculoperitoneal shunt§ | ... | ... | 1 | ... | ... |
| Other‖ | ... | 1 | ... | ... | ... |
| Alcohol abuse alone¶ | ... | ... | 1 | 18 | ... |
| Alcohol abuse and COPD | ... | ... | ... | ... | 1 |
| Alcohol abuse and diabetes | ... | ... | ... | 2 | ... |
| COPD alone | ... | ... | ... | 1 | 1 |
| Rheumatoid arthritis | ... | ... | ... | 1 | 1 |
| Congestive heart failure | ... | ... | ... | ... | 1 |
| No. of cases where patient had underlying condition | 13 | 2 | 3 | 22 | 4 |
| Cases where patient had underlying condition, % | 16 | 13 | 30 | 81 | 80 |

*One condition entry per case. COPD indicates chronic obstructive pulmonary disease.
†Down syndrome and congenital heart disease (one).
‡Bronchopulmonary dysplasia (two); reactive airway disease (RAD) requiring frequent hospitalization (four); recurrent pneumonia (RP), more than three episodes (one); and RAD and RP (three).
§Case not meningitis.
‖Hypsarrhythmia, not receiving corticotropin.
¶Identified as underlying condition if included in patient's medical problem list when culture was obtained. Four patients in this group additionally had diagnosis of alcohol withdrawal at presentation.

**Table 4.—Annual Incidence Rates of Invasive Pneumococcal Disease (per 100 000 Population) in Various Populations**

| Population | Overall Incidence | Overall, Age-Adjusted* | Age, y | | | | |
|---|---|---|---|---|---|---|---|
| | | | 0-1 | 0-2 | 2-19 | 20-59 | >60 |
| White Mountain Apache, 1983-1990 | 207 | 156 | 1252 | 1820 | 81 | 94 | 172 |
| Alaska, 1980-1986[3] | 105 | 96 | ... | 1195 | 52 | 37 | 145 |
| Oklahoma, 1984[16] | 16.4 | ... | 97 | ... | ... | ... | ... |
| Centers for Disease Control, 26 states, 1978-1979[18]‡ | 9.4 | ... | ... | ... | ... | ... | ... |
| Hawaii, 1986-1987[17] | 9 | ... | ... | 103 | ... | ... | 22† |
| West Virginia, 1978-1980[19]§ | 8.6 | ... | ... | ... | ... | 3 | 19 |
| South Carolina, 1974-1976[20] | 8.5 | ... | ... | 35 | ... | ... | 21 |
| Sweden, 1970-1980[21]‖ | 7 | ... | ... | 26 | 3 | 5 | 13.5 |

*Direct standardization to 1988 US population.
†Sixty-five years or more.
‡Included results of middle ear aspirates.
§Rates for age groups only calculated from tables referenced and exclude meningitis.
‖Rates for some age groups calculated from tables referenced.

dence rates in the White Mountain Apache population are 30 times higher than those reported in Sweden, 13 to 25 times higher than those reported for other non-Native US populations, and twice those reported for Alaskan Natives. The overall age-adjusted incidence rate for the White Mountain population is 1.6 times that of the Alaskan Natives. White Mountain Apache children less than 2 years of age have an annual incidence rate 70 times higher than Swedish children, 18 to 52 times higher than other non-Native US children, and 1.5 times that of Alaskan Native children. The incidence of pneumococcal meningitis in children is considerably lower than that reported for Alaskan Native children.

The number of isolates that were serotyped is not large enough to make conclusions regarding serotype distribution. It is interesting to note, however, that serotype 14 was recovered infrequently in our study (three of 41), but was the first or second most common serotype in seven of eight studies of invasive pneumococcal disease in children in the United States and Canada.[22-29] Surveillance of serotypes in this population will be continued and preventive strategies need to address these findings.

The clinical spectrum of invasive pneumococcal disease has been reported only among inpatients in most studies.[22-24,30] Two previous studies have reported disease in inpatients and outpatients younger than 2 years of age.[3,21]

White Mountain Apache children with pneumococcal disease show a lower proportion of meningitis than children in Sweden and Alaska, a higher proportion of otitis media and fever without source, and an intermediate proportion of pneumonia. These findings may, in part, be a reflection of the frequency with which blood cultures are obtained. Periodic chart reviews during the study period revealed that approximately 50% to 60% of children younger than 2 years who presented to the hospital with a temperature of greater than 39°C had a blood culture obtained as part of the evaluation. Early diagnosis of, and treatment for, pneumococcal bacteremia may contribute to the low incidence of pneumococcal meningitis during the time period studied. The high proportion of bacteremic Apache children with otitis media as the primary or secondary focus is consistent with the apparently high incidence of otitis media in Native American children.[10,11,31] In all populations studied, *S pneumoniae* is the most common pathogen recovered from the middle ear in acute otitis media.[32-35] In previous studies, underlying medical conditions have been reported in 10% to 67% of children with invasive pneumococcal disease.[3,21,22,27,28,30] Sixteen percent of the episodes described here occurred in children with underlying medical conditions. The highest proportion of underlying conditions was reported in Alaskan Native children and included the following conditions; iron deficiency anemia, low birth weight, and previous pneumonia.[3] These specific factors were not included in our analysis. In both the Alaskan Native and White Mountain Apache children, 6% of children with one episode of invasive pneumococcal disease in the first 2 years of life had a second episode.

Our report that 81% of the adult cases from Whiteriver occurred in patients with underlying conditions is comparable with that reported for other adult populations (52% to 90%).[3,15,19-21,36] Alcohol abuse was the most common underlying condition in adults with invasive disease in South Carolina (42%), Alaska (39%), Sweden (32%), and West Virginia (19%), as well as in the White Mountain Apaches (66%).

The numbers of cases of invasive pneumococcal disease in males have outnumbered those in females in many studies.[17,18,20,22,37] The male-to-female ratio in White Mountain Apache adults (5.4:1) appears to be among the highest reported, with high ratios being described for Alaskan Native adults (5:1) and inpatients in Israel (3:1).[3,30] This ratio was greatly diminished when patients with alcohol abuse were excluded.

Case-fatality rates in White Mountain Apaches (children younger than 2 years, 0%; adults, 22%) were in the lower range of those previously reported (children younger than 2 years, 1% to 15%; adults, 14% to 38%).[27,30,36,38,39] Early diagnosis and treatment due to availability of medical care may have contributed to these relatively low rates. The low case-fatality rate in children reflects the lower proportion of pneumococcal meningitis in this population and may reflect the relatively lower percentage of children with identified underlying medical conditions. There were no deaths among the six patients older than 60 years. The low prevalence of alcohol abuse (one of six) in this subset of patients with pneumococcal disease may be a factor in the low case-fatality rate.

The incidence of pneumococcal disease in Apache adults presented herein is likely an underestimate of the true disease burden, since bacteremia may only be detected in approximately 25% to 35% of episodes of pneumococcal pneumonia.[40,41] Although isolates from adults were not regularly serotyped in this study, 88% of bacteremic cases in other populations are caused by strains in the currently licensed pneumococcal vaccine.[27,42] The majority of adult cases in this study occurred in patients with a history of alcohol abuse—a group at high risk and for whom the current pneumococcal vaccine is recommended. The routine use of the current vaccine in the White Mountain Apache adult population should be strongly considered.

Pneumococcal polysaccharide vaccines, however, do not appear to be effective in the age group at highest risk: children younger than 2 years of age.[43-46] White Mountain Apache children represent a well-defined population with an extraordinarily high rate of invasive disease. The reasons for the high rate in this population are not clear. Children in certain Native American groups appear to be at increased risk for lower respiratory tract infections, otitis media, and gastroenteritis and have high rates of bacterial meningitis and invasive disease due to another encapsulated organism, *Haemophilus influenzae* type b.[5-11,35,47,48] The peak age-specific incidence of invasive *H influenzae* type b disease in White Mountain Apache children occurs earlier (4 to 7 months of age) than for pneumococcal disease.[6,47] Compared with that in white children, the antibody response to *H influenzae* type b polysaccharide vaccine is significantly impaired in White Mountain Apache children.[49] The genetic, environmental, and nutritional factors responsible for this immunologic impairment and the increased rates of infection require further investigation. Recent advances in the development of conjugate pneumococcal vaccines and other vaccine strategies bring hope of reducing the morbidity and mortality from pneumococcal disease in this high-risk population.[50-53]

An immunization project in White Mountain Apache infants was ongoing during the period covered in this article and has been completed. In a randomized, double-blind, placebo-controlled trial, a hyperimmune globulin given approximately every 3 months to Apache children younger than 2 years was found to be efficacious in protecting these infants against invasive pneumococcal disease. Therefore, the incidence rates presented in our article for infants are most likely underestimates of the actual rates.

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