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# Invasive pneumococcal disease epidemiology and effectiveness of 23-valent pneumococcal polysaccharide vaccine in Alaska Native adults ☆

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**Abstract**

Alaska Native persons have age-adjusted invasive pneumococcal disease (IPD) rates two- to three-fold greater than non-Native Alaskans. To characterize IPD epidemiology and 23-valent polysaccharide pneumococcal vaccine (PPV-23) effectiveness in Alaska Native adults we reviewed IPD cases from Alaska-wide, laboratory-based surveillance. Sterile site isolates were serotyped. Vaccine effectiveness (VE) was estimated using the indirect cohort method. 394 cases (44.5 cases/100,000/year) occurred in 374 Alaska Native adults (36.0% aged ≥55 years). Underlying conditions included heavy alcohol use (65.7%), smoking (60.8%) and COPD (25.0%). Overall VE was 75% (95% confidence interval [CI]: 27%, 91%) but declined with increasing age; for persons ≥55 years (VE = <0; 95% CI: <0, 78%; $p = 0.713$). Alaska Native adults experience high rates of IPD. The majority of IPD cases occurred in persons with underlying conditions and behaviors associated with increased risk of IPD in other populations. PPV-23 vaccine effectiveness was confirmed in younger Alaska Native adults but not among adults ≥55 years.


*Keywords:* Alaska Native; Pneumococcal disease; Pneumococcal polysaccharide vaccine

## 1. Introduction

*Streptococcus pneumoniae* (pneumococcus) is a leading cause of community-acquired pneumonia, bacterial meningitis, and acute otitis media in the United States [1]. Invasive pneumococcal disease (IPD), primarily bacteremia and meningitis, causes a disproportionate amount of illness and death among the very young, the elderly, those with underlying conditions, and certain ethnic groups [2]. Compared with the general US population, higher rates of IPD have been reported for several indigenous populations in North America, including Alaska Native, Navajo, White Mountain Apache, and Inuit of northern Canada ([2–7], CDC unpublished). The age-adjusted annual rate of IPD among Alaska Native persons during 1991–1998 was 58 cases/100,000 persons; 2.6-fold higher than the rate for people of other ethnicities living in Alaska [3]. Reasons for the increased rates of IPD among Native Americans are multifactorial [7].

Immunization and risk reduction are the foundations of pneumococcal disease prevention, and the Advisory Committee on Immunization Practices (ACIP) recommends that

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23-valent pneumococcal polysaccharide vaccine (PPV-23) be considered for Native Americans aged ≥2 years [1]. While observational studies have indicated effectiveness of PPV-23 for prevention of IPD among the elderly and persons with certain underlying medical conditions [9–14], a recent epidemiological study among Navajo adults found limited to no vaccine effectiveness depending on age strata or underlying conditions, suggesting that PPV-23 may be inadequate for preventing IPD in that population [15]. To better characterize the epidemiology of IPD and to evaluate the success of PPV-23 immunization programs among Alaska Native adults, we reviewed medical records of IPD cases identified during 15 years of prospective surveillance and estimated vaccine effectiveness by comparing serotype distribution among vaccinated and unvaccinated persons with IPD using the indirect cohort method [16].

## 2. Materials and methods

### 2.1. Setting

Cases of IPD occurring in Alaska Native adults aged 20 years and older during 1986–2000 were identified through ongoing, state-wide surveillance for IPD conducted by the Arctic Investigations Program of the Centers for Disease Control and Prevention (CDC) in Anchorage, Alaska [3].

### 2.2. Data collection

Personnel at 26 clinical laboratories in Alaska submitted isolates of *S. pneumoniae* from normally sterile body sites, along with basic clinical and demographic information for the case, including age, gender, ethnicity, and body site of the isolate. Additional clinical information, including clinical manifestations, mortality, underlying medical conditions, and vaccination history were collected from the health care provider, from a review of the complete outpatient and inpatient medical charts at the facility, and from electronic medical records that are shared between tribal facilities. Submitted isolates were identified as *S. pneumoniae* by colony morphology, susceptibility to ethylhydocuprineine hydrochloride (Optochin Difco, Detroit), and bile solubility. Serotyping was performed by Quellung reaction. All cases occurring among Alaska Native adults reported with illness onset from the beginning of surveillance in January 1986 through December 2000 were included. Case-patients living in the metropolitan areas of Anchorage, Fairbanks, or Juneau, Alaska at the time of illness were classified as urban, whereas all others were classified rural.

A case-patient was determined to have an underlying condition when the paper or electronic medical record contained a purpose of visit, hospital discharge diagnosis or physician narrative indicating a condition of interest (e.g. cancer with chemotherapy, other immune deficiency, congestive heart failure, chronic pulmonary diseases, chronic liver diseases, nephrotic syndrome, chronic renal failure, diabetes, smoking, alcohol abuse, pregnancy, homelessness, sickle cell anemia) considered an indication for vaccination by the Advisory Committee on Immunization Practices (ACIP). A case-patient was considered to have heavy alcohol use if the record contained a purpose of visit, a provider narrative, or hospital discharge diagnosis with any of the following diagnoses or ICD-9 codes during the 2 years before pneumococcal illness onset: 303.9 (alcohol dependency), 303.01 (acute alcohol intoxication), 303.90–303.93 (alcohol dependence), 305.0–305.02 (alcohol abuse), 291.0 (delirium tremens), 291.2 (alcoholic dementia), 291.8 (alcoholic psychosis), 291.81 (alcohol withdrawal), 535.3 (alcoholic gastritis), 571.1 (acute alcoholic hepatitis), 571.2 (alcohol cirrhosis liver), 571.3 (alcohol liver damage). A case-patient was considered to have chronic lung disease if the medical record indicated chronic obstructive pulmonary disease, bronchiectasis, or pulmonary fibrosis.

### 2.3. Statistical methods

Proportions were compared with chi-square tests or Fisher's exact test, as appropriate. Mantel–Haenszel tests were used for adjusted chi-square tests. Odds ratios and risk ratios were calculated with 95% confidence intervals (95% CI) using Epi-info version 6 (CDC, Atlanta). Multiple logistic regression was used to simultaneously assess the impact of multiple risk factors in urban versus rural cases. Model selection was done with a backward process initially including all of the factors listed in Table 2. In addition, the significance of two-way interactions was assessed. Vaccine effectiveness was estimated by comparing the proportion of infections caused by serotypes included in PPV-23 (vaccine-type serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, or 33F) among vaccinated and unvaccinated persons (indirect cohort method) [16]. Serotypes not included in the vaccine but in the same serogroup as a vaccine-type (e.g., 6A) are potentially cross-reactive and were classified as vaccine-related. Vaccine effectiveness was expressed as 1 minus the odds ratio times 100%. Population statistics used to calculate rates were derived from US 1990 and 2000 Census figures. The Anchorage, Fairbanks, and Juneau metropolitan areas are considered urban; all others were considered rural.

## 3. Results

### 3.1. Incidence of invasive pneumococcal disease

From 1986 through 2000, 394 cases of IPD occurred among Alaska Native adults aged 20 years and older living in Alaska. The number of cases reported each year ranged from 18 to 40. Cases occurred year-round; seasonal variation was subtle, although 23% of cases occurred in September and October (Fig. 1). The annual incidence of disease was

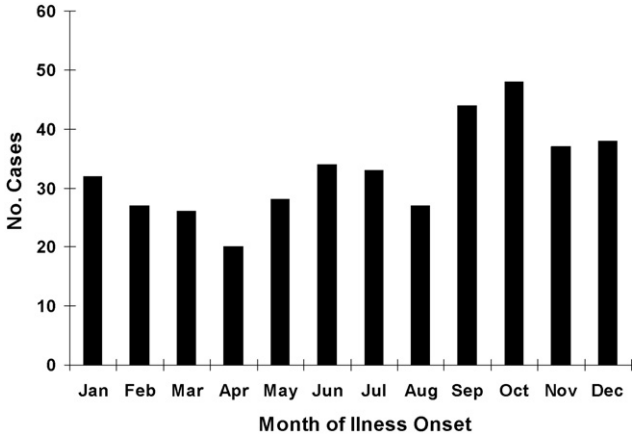


Fig. 1. Number of invasive pneumococcal disease cases occurring in Alaska Native adults by month of year, 1986–2000.

45.5 cases/100,000 persons, and 69 cases (17.5%) were fatal. Rates of disease and case fatality were greater among persons 50 years of age and older (Fig. 2); however, rates among urban 50–64 year olds were higher than among urban 65–79 year olds. Rates of disease were higher among Alaska Native adults living in urban areas (65.1) compared with those living in rural areas (37.3) ($p < 0.001$). Age at time of illness ranged from 20 to 96 years (median 48 years; 36.0% ≥55 years). Twenty (5.1%) cases of recurrent invasive pneumococcal disease occurred 1–97 months after the previous episode (median 30 months). Two persons had two recurrences. Clinical syndromes included pneumonia with bacteremia in 334 (84.8%) cases, meningitis in 28 (7.1%), empyema in 13 (3.3%), endocarditis in 7 (1.8%), septic arthritis in 5 (1.3%), peritonitis in 5 (1.3%), and pericarditis in 3 (0.8%).

### 3.2. Descriptive epidemiology

Medical records were available for collection of complete information on underlying conditions and vaccine history for 370 (93.9%) cases. Ten (41.7%) of the 24 cases for whom medical records were not available for review were fatal; of the remaining 14, eight persons had died of unrelated causes prior to the medical record review. The most common underlying conditions were heavy alcohol use (65.7%), cigarette smoking (60.8%), past tuberculosis infection or disease (35.4%), and chronic obstructive pulmonary disease (COPD) (25.1%) (Table 1). Fewer than 10 patients had undergone splenectomy, had renal failure requiring dialysis, or were diagnosed with HIV infection; none had sickle cell disease. Of cases for which complete record review was possible, 59 (15.9%) were fatal. Factors associated with death included age ≥55 years and rural residence (Table 1). Of 370 adult cases, 224 (60.5%) were aged <55 years, the age of recommended universal pneumococcal vaccination in Alaska [18]; and 193 (86.2%) of cases aged <55 years had underlying conditions that are included in current ACIP recommendations for pneumococcal vaccination [1]. Of 49 women aged <40 years, 10 (20.4%) were pregnant when pneumococcal infection was diagnosed. Eight pregnant case-patients had pneumonia with bacteremia, one had amnionitis with bacteremia, and one had primary bacteremia; all survived. Underlying conditions in cases among pregnant patients included cigarette smoking in six and asthma in three cases.

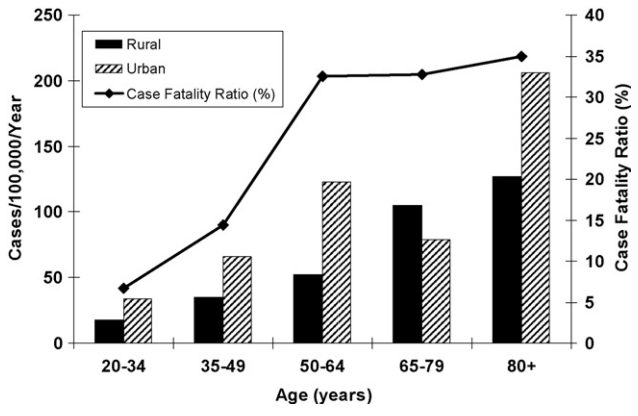


Fig. 2. Rates and case fatality ratio of invasive pneumococcal disease by age group and rural vs. urban residence status, in Alaska Native adults, 1986–2000.

Compared to Alaska Native adults with IPD living in rural Alaska, those from urban areas were more likely to be female, smoke cigarettes, use alcohol heavily, be homeless, or have an underlying medical condition considered to be an indication for PPV-23 in univariate analysis (Table 2). In multivariable analysis, urban residence was independently associated with female sex, homelessness, underlying illness, and cigarette smoking. Specific data are not available on the relative prevalence of all underlying conditions and other factors associated with pneumococcal infection in the general AN adult rural and urban populations as defined above. While smoking is more common in rural Alaskan adults; [35] it is possible that underlying medical conditions and homelessness are more common in urban settings.

Vaccination with ≥1 dose of pneumococcal polysaccharide vaccine was documented for 141 (38.1%) case-patients; 28 had been vaccinated twice; 12, three times; and 3, four times prior to the disease episode. Of the 43 case-patients who had been vaccinated more than once, 21 had received at least one dose of 14-valent vaccine prior to 1984. Pneumococcal vaccination was documented for 58.2% of persons aged ≥55 years. Among 194 persons <55 years of age with an underlying medical condition for which ACIP recommends vaccination, 52 (26.8%) had been vaccinated. Of 135 persons of all ages who had been hospitalized during the 2 years before illness onset, 52.6% were vaccinated. Overall, 67 (18.1%) case-patients had documentation of influenza vaccination within 2 years of pneumococcal illness onset, and 15 (22.4%) of these persons had no documentation of ever having been vaccinated against pneumococcal disease.

Table 1
Characteristics of 370 Alaska Native adults with invasive pneumococcal disease, Alaska, 1986–2000

| Characteristics | Age <55 years | Age ≥55 years | Total | | |
|---|---|---|---|---|---|
| | (*n* = 224) No. (%) | (*n* = 146) No. (%) | (*n* = 370) No. (%) | Case fatality ratio (%)[a] | Risk ratio for death[a] (95% confidence interval)[b] |
| Male sex | 133 (59.4) | 71 (48.6) | 204 (55.1) | 18.6 | 1.6 (0.9, 3.0) |
| Age ≥55 years | | | 146 (39.5) | 21.9 | **2.1** (**1.1**, **3.7**) |
| Rural residence | 116 (51.8) | 88 (60.3) | 204 (55.1) | 21.1 | **2.5** (**1.3**, **4.9**) |
| Underlying conditions | | | | | |
| Heavy alcohol use[c] | 171 (76.3) | 72 (49.3) | 243 (65.7) | 16.5 | 1.1 (0.6, 2.1) |
| Cigarette smoking | 158 (70.5) | 67 (45.9) | 225 (60.8) | 12.9 | 0.6 (0.3, 1.0) |
| Tuberculosis[d] | 56 (25.0) | 75 (51.4) | 131 (35.4) | 15.3 | 0.9 (0.5, 1.7) |
| COPD[c] | 27 (12.1) | 66 (45.2) | 93 (25.1) | 17.2 | 1.1 (0.6, 2.2) |
| Injection drug use | 52 (23.2) | 4 (2.7) | 56 (15.1) | 15.8 | 1.0 (0.4, 2.3) |
| Non-cutaneous cancer[c] | 14 (6.3) | 31 (21.2) | 45 (12.2) | 24.4 | 1.9 (0.8, 4.2) |
| Congestive heart failure[c] | 6 (2.7) | 36 (24.7) | 42 (11.4) | 14.3 | 0.9 (0.3, 2.2) |
| Asthma | 14 (6.3) | 13 (8.9) | 27 (7.3) | 18.5 | 1.2 (0.3, 3.5) |
| Corticosteroid use[c,e] | 11 (4.9) | 13 (8.9) | 24 (6.5) | 16.7 | 1.1 (0.3, 3.3) |
| Diabetes mellitus[c] | 4 (1.8) | 14 (9.6) | 18 (4.9) | 16.7 | 1.1 (0.2, 3.9) |
| Bronchiectasis[c] | 10 (4.5) | 8 (5.5) | 18 (4.9) | 11.1 | 0.9 (0.1, 3.8) |
| Chronic renal insufficiency[c] | 6 (2.7) | 7 (4.8) | 13 (3.5) | 23.1 | 1.6 (0.3, 6.5) |

[a] Case fatality ratio is number of deaths/number of cases. The case fatality ratio and risk ratio for death reflect the total cases, and do not relate to the columns labeled age <55 year and age ≥55 years.
[b] The risk ratio for death is the ratio of the case fatality ratio for cases with the given risk factor, compared with the case fatality ratio for all cases without that given risk factor.
[c] ACIP recommends immunization for adults of all ages with these conditions.
[d] Active, treated, or latent.
[e] During the year prior to illness onset.

### 3.3. Vaccine effectiveness

For estimating PPV-23 effectiveness, we excluded 52 persons for whom a viable isolate for serotyping was not available and 18 persons who received only 14-valent pneumococcal vaccine. Of the remaining 300 patients (median age 45 years), 97 (32.3%) had received at least one dose of PPV-23. The median interval from most recent dose of PPV-23 until onset of invasive pneumococcal disease was 2.6 years (range: 46 days to 10.1 years); 80% were vaccinated <5 years before illness onset. Vaccine serotypes or related serotypes infected 87.6% of vaccinated and 96.6% of unvaccinated persons. Thus, overall effectiveness of PPV-23 for preventing invasive disease caused by serotypes included in the vaccine and related serotypes was 75% (95% CI: 27%, 91%). Estimates of vaccine effectiveness were essentially unchanged if eight cases with vaccine-related serotypes (four cases with 6A and one each with 9A, 15A, 18F, and 23A) were excluded from the calculation (75% [95% CI: 28%, 92%]); vaccine-related serotypes are included with vaccine-type serotypes in subsequent calculations. Vaccine effectiveness for the 287 episodes of first-time invasive pneumococcal disease was 78% (95% CI: 32%, 93%). Of serotypes recovered in >10 cases, vaccine effectiveness was documented for serotypes 1, 4, 7F, 8, and 12F (Table 3).

Vaccine effectiveness during the first 5 years after immunization was 77% (95% CI: 38%, 92%; $p = 0.002$), but did not

Table 2
Characteristics of Alaska Native adults living in urban (*n* = 166) and rural (*n* = 204) Alaska at time of illness onset, 1986–2000.

| Characteristic | Urban, No. (%) | Rural, No. (%) | OR (95% CI)[a] |
|---|---|---|---|
| Female sex | 93 (56.0) | 73 (35.8) | 2.3 (1.5, 3.6) |
| Cigarette smoking | 113 (68.1) | 112 (54.9) | 1.8 (1.2, 2.8) |
| Heavy alcohol use | 120 (72.3) | 123 (60.3) | 1.7 (1.1, 2.7) |
| Injection drug use | 31 (18.7) | 25 (12.3) | 1.6 (0.9, 3.0) |
| Homelessness | 19 (11.4) | 5 (2.5) | 5.2 (1.8, 18.0) |
| ACIP indication | 155 (93.4) | 166 (81.4) | 3.2 (1.5, 7.0) |
| Influenza vaccination | 32 (19.3) | 35 (17.2) | 1.2 (0.7, 2.0) |
| Age <55 years | 108 (65.1) | 116 (56.9) | 1.4 (0.9, 2.2) |

[a] Odd ratio (95% confidence interval), for urban residents compared with rural residents.

Table 3
Serotype-specific 23-valent pneumococcal polysaccharide effectiveness estimates based on distribution of serotypes recovered from Alaska Natives with invasive pneumococcal disease, 1986–2000

| Serotype | No. of persons | | Vaccine effectiveness, % (95% confidence interval) | *p*-Value |
|---|---|---|---|---|
| | Vaccinated | Not vaccinated | | |
| 1 | 6 | 22 | 84 (31, 97) | $p = 0.010$ |
| 3 | 10 | 12 | 51 (<0, 89) | $p = 0.413$ |
| 4 | 12 | 27 | 74 (6, 93) | $p = 0.039$ |
| 7F | 5 | 25 | 88 (47, 98) | $p = 0.003$ |
| 8 | 2 | 14 | 92 (43, 99) | $p = 0.007$ |
| 9V | 9 | 10 | 48 (<0, 88) | $p = 0.514$ |
| 12F | 8 | 32 | 85 (43, 96) | $p = 0.003$ |
| 14 | 4 | 10 | 77 (<0, 96) | $p = 0.107$ |
| 20 | 4 | 8 | 71 (<0, 95) | $p = 0.211$ |

Table 4
Vaccine effectiveness estimates by age and underlying conditions, Alaska Native adults, 1986–2000

| Characteristics | Vaccine-type isolates,[a] No. (%) | Nonvaccine-type isolates, No. | Vaccine effectiveness, % (95% confidence interval) | *p*-Value |
|---|---|---|---|---|
| Age 20–39 years | | | | |
| Vaccinated | 12 (75.0) | 4 | 100 (78, 100) | $p < 0.001$ |
| Unvaccinated | 95 (100) | 0 | | |
| Age 40–54 years | | | | |
| Vaccinated | 24 (82.8) | 5 | 73 (<0, 96) | $p = 0.113$ |
| Unvaccinated | 54 (94.7) | 3 | | |
| Age ≥55 years | | | | |
| Vaccinated | 49 (94.2) | 3 | <0 (<0, 78) | $p = 0.716$ |
| Unvaccinated | 47 (92.1) | 4 | | |
| Heavy alcohol use | | | | |
| Vaccinated | 49 (84.5) | 9 | 80 (30, 95) | $p = 0.005$ |
| Unvaccinated | 138 (96.5) | 5 | | |
| Cigarette smoking | | | | |
| Vaccinated | 46 (86.8) | 7 | 80 (17, 96) | $p = 0.012$ |
| Unvaccinated | 132 (95.1) | 4 | | |
| Tuberculosis[b] | | | | |
| Vaccinated | 34 (87.2) | 5 | 64 (<0, 95) | $p = 0.258$ |
| Unvaccinated | 57 (95.0) | 3 | | |
| Chronic lung disease[c] | | | | |
| Vaccinated | 36 (92.3) | 3 | 74 (<0, 100) | $p = 0.321$ |
| Unvaccinated | 47 (97.9) | 1 | | |
| Age <55 years and ACIP indication | | | | |
| Vaccinated | 35 (83.3) | 7 | 88 (45, 98) | $p = 0.002$ |
| Unvaccinated | 125 (97.7) | 3 | | |

[a] Includes vaccine-related serotypes (6A [four isolates] and 9A, 15A, 18F, and 23A [one isolate each]).
[b] Active, treated, or latent.
[c] Chronic obstructive pulmonary disease, bronchiectasis, or pulmonary fibrosis (not asthma).

appear to persist after 5 years (effectiveness point estimate 36% [95% CI < 0, 92%] $p = 0.517$). Estimated effectiveness was similar for first doses of PPV-23 (75% [95% CI: 19%, 92%] $p = 0.011$) and for revaccination (74% [95% CI < 0, 94%] $p = 0.051$).

The median age of persons included in the vaccine effectiveness analysis was 45 years. Vaccine effectiveness declined with increasing age (Table 4). Vaccine effectiveness was documented for persons with heavy alcohol use and cigarette smoking. Vaccine effectiveness remains statistically significant for both heavy alcohol users and smokers among the younger age group alone, or if age is adjusted across both groups. Point estimates of vaccine effectiveness were >60% for persons with chronic lung diseases or with latent, active, or treated tuberculosis, but confidence intervals included zero for both groups.

## 4. Discussion

### 4.1. Factors contributing to high rates of IPD

The age-adjusted rate of IPD among Alaska Native adults was more than two-fold higher than the rate among non-Native Alaskan adults and a sample US adult population [2,3]. The age-specific rate among urban Alaska Native adults 50–64 years (122.6/100,000/year) was five-fold higher than the rate in similarly aged US adults (23.5) identified through active surveillance. Rates of IPD among Alaska Native adults living in urban areas were nearly twice that of those living in rural Alaska. The increased risk of disease among urban residents may be accounted for, at least in part, by factors that have been previously associated with higher risk of IPD. While it is possible that some of these factors, such as underlying illness, homelessness, and intravenous drug use may be more common in residents of urban areas of Alaska, the relative prevalence of these conditions in urban and rural adults is not known. The higher rate of disease among urban compared with rural Alaska Native adults contrasts sharply with the rate for children. Annual IPD rates among Alaska Native children aged <2 years during 1991–1997, prior to availability of conjugate vaccine, were twice as high in rural areas (659/100,000) compared with urban areas (325/100,000) [8]. In adults, IPD risk may be more influenced by health factors and personal habits than by environmental conditions such as household crowding or lack of running water. The seasonal increase in disease rates occurring in September and October coincides with the start of the school year and may be result from newly acquired colonization of *S. pneumoniae* transmitted from household school children [17].

### 4.2. Vaccine effectiveness

The overall effectiveness of PPV-23 for prevention of IPD among Alaska Native adults in our study of 75% (95% CI: 27, 91%) was considerable higher than the estimates among Navajo adults determined by case–control (26%, 95% CI: −29%, 58%) and indirect cohort analyses (35%, 95% CI: −33%, 69%) [15]. Possible explanations for the difference include younger median age among Alaska Native patients (45 years) compared with those in the Navajo study (59 years), differences in underlying conditions (cigarette smoking was more common and diabetes was less common among Alaska Native adults) and other undetermined environmental or biological differences. Effectiveness estimates among the Navajo varied by underlying conditions. The lack of documented effectiveness for older Alaska Native adults is consistent with the effectiveness findings among the Navajo and contrasts with findings from case control and indirect cohort studies among non-Native adults demonstrating effectiveness of PPV-23 for prevention of IPD among the immunocompetent elderly [9,10,12–14]. Diminishing immune responsiveness to polysaccharide antigens and lower PPV-23 effectiveness has been associated with advancing age and may contribute to the increased risk of IPD among the elderly [9]. The age-related increase in IPD among Alaska Native adults occurs at a younger age compared with people of other ethnicities living in Alaska, suggesting that exposure increases with age in a way disproportionate compared with non-Native elderly, or that decreased immune responses may occur at younger age in Alaska Native adults. Alternatively, our inability to demonstrate vaccine effectiveness in older adults may be an artifact of the small number of nonvaccine-type infections in the subgroup analysis. However, the high risk of disease in Alaska Native elders justifies use of PPV-23 even though benefit may be modest and not possible to document in this study.

Recommendations for PPV-23 use in Alaska are expanded from national recommendations of the ACIP in that the age of universal immunization is 55 years and revaccination is recommended every 6 years [18,19] Anti-pneumococcal antibodies decline 3–5 years after vaccination [20,22]. In this analysis, point estimates of vaccine effectiveness were almost identical for first doses of PPV-23 and revaccination, although the confidence interval included 0%. Repeated immunization with polysaccharide antigens has been associated with decreased antibody responses [22–25]; however, a single revaccination six or more years after a first dose of PPV-23 stimulated comparable mean antibody levels in high-risk and elderly Alaskans [19].

Our analysis suggests that PPV-23 is effective for preventing IPD among Alaska Native adults aged <55 years with underlying conditions, and previous analyses in non-Native populations demonstrate that vaccination of older adults [31] and younger adults with underlying conditions [32] are cost effective. Because 86.2% of IPD in Alaska Native adults <55 years occurred in persons with identifiable underlying conditions, identifying and vaccinating these patients should have priority. Use of electronic reminder systems and standing orders programs [33] which identify patients based on high risk conditions or ICD-9 coded visits can improve immunization rates in these groups. However, vaccination alone will not reduce the disease disparity in persons with behavioral risk factors. Cigarette smoking is associated with higher rates of IPD in adults [34]. Alaska Native adults have high rates of cigarette smoking and Alaska Native youth are three to four times more likely to smoke cigarettes than non-Native Alaska youth [35]. Alcoholism is also associated with increased risk of IPD in adults [4,11,36]. The proportion of hospitalizations that are related to alcohol among American Indians and Alaska Natives is 2.5-fold higher than that for the general US population [37] and the rate of mortality from alcoholism was nearly six times that in the general US population [38]. In our case series and previous studies [4], conditions related to alcohol dependence were the most frequent underlying conditions in Alaska Native adults with IPD. For patients with alcoholism, much medical care is obtained in hospital emergency departments, and pneumococcal vaccination of adults in emergency care settings may provide an important opportunity to improve vaccine coverage among at-risk adults [39,40]. In addition to vaccination, risk reduction and treatment of the underlying conditions are critical to reducing the burden of IPD in this population.

Introduction of the heptavalent pneumococcal conjugate vaccine into the routine US childhood vaccination schedule in 2000 has resulted in decreases of vaccine-type IPD among children as well as among adults (the so-called indirect effect) [41], presumably by preventing transmission to susceptible adults through reduction in colonization among vaccinated children [17]. In Alaska, after PCV7 vaccine was introduced in 2001 the overall IPD rate declined among non-Native persons aged 45 years and older, but not Alaska Native adults in this age group; however, there was a 40% decline in invasive disease due to PCV7 serotypes in all Alaskans aged ≥18 years [42].

Our analysis has several limitations. Data on underlying conditions was collected by retrospective medical record review only. We were unable to systematically collect history of vaccinations administered at non-tribal health facilities; however, non-systematic errors (not related to serotype distribution) would lead to underestimates of vaccine effectiveness. Lastly, the numbers of cases were small for estimating vaccine effectiveness in subgroups.

## 5. Conclusions

Alaska Native adults experience high rates of IPD. The majority of these infections occurred in persons with underlying conditions and behaviors associated with increased risk of IPD in other populations. Vaccination with PPV-23 is effective for preventing IPD in younger Alaska Native adults and those with certain underlying conditions. The PPV-23

vaccine is not perfect and future vaccines based on antigens common to all pneumococci may prove more effective in preventing IPD in adults [43]. Vaccine delivery should target adults with known underlying conditions; however, risk reduction and treatment of underlying conditions should also receive priority.

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