MAJOR ARTICLE

Effectiveness of the 23-Valent Polysaccharide Vaccine against Invasive Pneumococcal Disease in Navajo Adults

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Invasive pneumococcal disease occurs 2–3-fold more often among Navajo adults than among adults in the general United States population. The objective of this observational study was to determine the effectiveness of the 23-valent pneumococcal polysaccharide vaccine (PPV23) among Navajo adults. Active surveillance identified cases of invasive pneumococcal disease during 1996–1997. Three control patients per case patient were matched according to underlying medical conditions, sex, age, and location of medical care. Effectiveness was calculated by regression analysis of case-control sets and by indirect cohort methodology. Diabetes and alcoholism occurred in 41% and 43% of 108 case patients, respectively; 62% of case patients and 64% of control patients were immunized. Overall vaccine effectiveness was 26% (95% confidence interval [CI], −29% to 58%); 15% (95% CI, −116% to 67%) for patients with diabetes and −5% (95% CI, −141% to 54%) for patients with alcoholism. Overall vaccine effectiveness, as determined by use of the indirect cohort methodology, was 35% (95% CI, −33% to 69%). PPV23 was not significantly effective among Navajo adults and may be inadequate to prevent serious pneumococcal disease in this population.

Pneumococcal disease is a major cause of morbidity and mortality worldwide, yet the only specific prevention option for adults is the 23-valent polysaccharide pneumococcal vaccine (PPV23). The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) recommends routine use of PPV23 for persons at high risk for disease or complications of disease, including individuals aged ⩾65 years and those aged <65 years with certain underlying medical conditions [1]. In addition, the ACIP recommends that the vaccine should be considered for use among certain Native American populations (those aged <65 years), because they live in settings where high rates of pneumococcal disease have been documented [1]. Among the Navajo, laboratory-based active surveillance for invasive pneumococcal disease has demonstrated annual rates of disease among those aged ⩾65 years of 78–235 cases/100,000 population [2]; in contrast, the annual rate for the same age group in the general US population is 59.7 cases/100,000 population [3]. Elevated incidence rates also have been documented among Alaska Natives and the White Mountain Apache tribe [4, 5].

Although PPV23 is used to prevent invasive pneumococcal disease, observational studies of its effectiveness have had varied results. In studies of both the 14-valent [6] and the 23-valent [7–9] vaccines, effectiveness has ranged from 0% to 81%. Effectiveness has been shown

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to be highest among healthy persons (61%–77%) [6–8, 10], whereas, among persons with human immunodeficiency virus (HIV) infection or multiple underlying medical conditions, the effectiveness is lower (0%–49%) [7, 11].

The effectiveness of PPV23 in Navajo adults is unknown. Possible reasons for the high rates of disease in the Navajo population may include either failure to vaccinate or failure of the vaccine. Preliminary data indicate that the proportion of Navajo adults who are vaccinated with PPV23 is high: 73% of persons aged ⩾65 years and 54% of persons with indications for vaccination aged 18–64 years (authors' unpublished data). Therefore, we undertook the present study to assess the effectiveness of PPV23 among Navajo adults.

PATIENTS AND METHODS

We evaluated effectiveness of PPV23 by using 2 approaches: (1) a retrospective, clinic-based, case-control study and (2) an indirect cohort analysis. The study involved all 8 Indian Health Service (IHS) hospitals and health centers and 1 private hospital (Sage Memorial Hospital, Ganado, AZ) in the Navajo Reservation of Arizona and New Mexico.

Case-control study. A case patient was defined as a Navajo adult (⩾18 years) who was registered at 1 of the 9 medical facilities participating in the study and who had invasive pneumococcal disease in 1996 or 1997. Invasive pneumococcal disease was defined as isolation of *Streptococcus pneumoniae* from a normally sterile body fluid, such as blood or cerebrospinal fluid. Case patients were identified through an existing system of active, laboratory-based surveillance conducted by the Johns Hopkins Center for American Indian Health (Baltimore, MD). Because healthy adults aged <65 years are not routinely vaccinated, according to local policy, case patients who were aged <65 years and had no underlying medical illnesses that corresponded to an indication for vaccination were excluded from the case-control study. Because we needed to be able to ascertain whether patients had been vaccinated, we also excluded those patients whose medical records could not be found.

Control patients were chosen from randomly-selected medical records of adult Navajo registered at the medical facilities. These clinic-based control patients were matched to their respective case patients by IHS service unit, age (birthday within 5 years of the case patient's birthday), sex, chronic medical condition (using risk levels which are defined below), and known duration of the chronic condition by use of methods similar to those used in previous studies [6–9, 12]. If a case patient's medical condition had been present ⩾10 years, then the control patient must have had the matching condition for ⩾10 years before the year of the case patient's illness. If the case patient had the condition for <10 years, then the control patient must have had the matching condition diagnosed within 2 years of the year that the case patient was diagnosed with the condition. Control patients must have been alive as of January 1 of the year of the case patient's illness (1996 or 1997).

Underlying medical conditions of the case patients were grouped into 3 risk levels on the basis of the degree of immunocompromise and risk for pneumococcal disease [1]. The high-risk level ("risk level 1") included persons with conditions associated with severe immunocompromise: renal transplantation, nephrotic syndrome, hematologic cancers, metastatic cancers, drug-induced immunosuppression (defined as ⩾20 mg/day of prednisone or use of another immunosuppressive medication), systemic lupus erythematosis on immunosuppressive medications, anatomical or functional asplenia, or AIDS. Patients with solid-organ tumors without metastases were included only in risk level 1 if the patient was receiving immunocompromising medications, such as chemotherapy. The moderate risk level ("risk level 2") included patients without a level 1 condition but who had a history of alcoholism, diabetes mellitus (type 1 or 2), chronic cardiac disease (congestive heart failure or chronic angina), chronic pulmonary disease (chronic obstructive pulmonary disease, emphysema, or asthma with daily medications), chronic renal failure requiring dialysis, and liver disease (cirrhosis or alcoholic hepatitis). The low risk level ("risk level 3") was defined as patients aged ⩾65 years with no level 1 or level 2 conditions.

If a case patient had 1 underlying medical condition and was categorized as risk level 1, then the case patient was matched with control patients who had any diseases in risk level 1. If the case patient had 1 underlying condition and was categorized as risk level 2, control patients were selected with the same medical condition. If a case patient had multiple underlying conditions, control patients were matched by the disease in the highest risk level present for the case patient. If the case patient's highest risk level was risk level 2 and the case patient had >1 underlying condition in that risk level, then the condition with longest duration was chosen for matching. If the conditions had all existed for the same duration, then the control patient was matched according to the disease that was listed as the first *International Classification of Diseases 9* (ICD-9) code on the hospital discharge from the admission for pneumococcal disease. If age was the only indication for vaccination of the case patient (risk level 3), then control patients were chosen without underlying disease and were matched according to service unit, age, and sex.

To identify control patients, we performed a search of the computerized medical record system at each IHS service unit hospital or health center. We developed lists of potential control patients by searching for the pertinent ICD-9 codes for the underlying disease conditions and then randomly selected control patients from the list of potential control patients with the appropriate conditions. If the list of potential control patients had <10 names, then we systematically expanded the criteria

for age range and duration of the underlying disease until we found at least 1 control patient. If the medical record of a selected control patient was not initially available, we selected other control patients but also reviewed the charts of the originally selected patient at a later time. Therefore, some case patients were matched with >3 control patients.

Patients with any history of invasive pneumococcal disease were excluded from the control group. To ensure that we did not misclassify as control patients those who might have had invasive pneumococcal disease that had not been detected, patients also were excluded from the control patient group if they had a radiologically confirmed pneumonia with a Gram stain of sputum that was consistent with pneumococcus or if they had been hospitalized for pneumonia in the 10 years before the date that the case patient became ill. All charts of control patients were reviewed only to the date when their matched case patient had the culture that was positive for pneumococcus.

A structured data collection form was used to abstract demographic information, disease history, vaccine history, visits to hospitals and clinics, and information on medical conditions, from charts of every case and every control patient. When the medical record indicated that a study patient had received care at other local medical facilities, we examined medical records at each of those facilities for vaccination history and evidence of pneumococcal disease or pneumonia.

We assumed that the medical records were complete. Because healthcare at IHS facilities is provided without charge to all Navajo, and because the distance to receive care at non-IHS facilities is often far, it is unlikely that a significant amount of care was provided for these patients at non-IHS facilities. For the few patients whose medical records indicated that they had received care at non-IHS facilities, we examined the records at those facilities for evidence of vaccination and history of pneumococcal disease. For patients seen at multiple IHS facilities, we reviewed their medical record at each facility where they had a record of having had an encounter. In this way, we minimized both misclassification bias and ascertainment bias regarding vaccination.

Definitions. Patients were defined as having been immunized if they had documentation in their medical record of having received at least 1 pneumococcal vaccination after 1 January 1984 (the date when use of PPV23 began) and before the date the case patient became ill. We reviewed the medical records for only certain underlying medical conditions; we focused on severe illnesses and illnesses that are considered to be vaccine indications [1]. We excluded minor conditions and those conditions that alone are unlikely to increase the risk for invasive pneumococcal disease, such as hypertension. Alcoholism was defined as a diagnosis of alcoholism in the medical record or >1 medical encounter for alcohol-related injuries.

Pneumonia was defined as a diagnosis of pneumonia in the medical chart and documentation of at least 1 of the following: (1) chest radiograph reading indicative of pneumonia; (2) respiratory difficulty, such as cough or shortness of breath; (3) hypoxia with an oxygen saturation <93% or an abnormal arterial blood gas; or (4) crackles on physical examination. Sepsis was defined as a diagnosis documented in the medical chart of sepsis plus either hypotension (systolic blood pressure <90 mm Hg or use of pressor medications) or evidence of end-organ failure (e.g., acute renal failure and disseminated intravascular coagulation).

Case-control analysis. Multivariable, conditional, logistic regression was used to calculate matched, adjusted odds ratios (ORs) for vaccination; vaccine effectiveness was calculated by subtracting the OR for vaccination from 1 and multiplying by 100%. In all regression models, we adjusted for the presence of an underlying disease other than diabetes, alcoholism, and cancers; we also evaluated the contributions of the specific medical conditions of alcoholism and diabetes. We assessed the contributions of other potential confounding variables, including the amount of time that had elapsed since vaccination, receipt of influenza vaccine in the year before the case patient became ill, the number of PPV23 doses, and age. We assessed the contributions of all 2-way interactions. We did not include smoking as a variable, because the prevalence of smoking documented in the medical charts was extremely low. A low prevalence of smoking among Navajo was confirmed by anecdotal report and by prospectively collected data from a study looking at risk factors for pneumococcal disease (authors' unpublished data).

Because of constraints due to the sample size, we could not adjust for the time that had elapsed since vaccination and multiple vaccinations by use of the same multivariable model. Instead, to assess the impact of those variables, we created a model based on variables that combined the time that had elapsed since vaccination (<5 years or ⩾5 years) and the number of doses of vaccine (1 or ⩾2 doses) and calculated the effectiveness of the vaccine by these categories. We also tested models that were limited to case patients with disease due to serotypes included in the vaccine. Statistical analyses were conducted by use of SAS software (SAS institute). $P \leqslant .05$ was considered to be statistically significant; all P values were 2-tailed.

We based the sample size for the case-control study on the ability to detect a vaccine effectiveness of 59% (OR, 0.41) with a lower 95% confidence limit (CI) of 33% [10]. With power of 96%, an $\alpha = 0.05$, and 3 control patients/1 case patient, assuming that 60% of the control patients had been vaccinated, we would need a minimum of 100 case patients [13, 14]. We assumed that ~75 cases occurred per year; therefore, to achieve at least the necessary sample size, we included all possible case patients from 1996 and 1997.

Indirect cohort study. For this analysis, we included all patients identified with invasive pneumococcal disease between 1989 and 1998 for whom serotype information was available.

Table 1. Characteristics of case and control patients.

Characteristic	Case patients (n = 108)	Control patients (n = 330)	P[a]
Age, median years (IQR)	58.6 (44–71)	58.8 (41–71)	.6[b]
Male sex	60 (56)	182 (55)	1.0[c]
Risk level			.7[b]
Level 1	16 (15)	39 (12)	
Level 2	81 (75)	256 (78)	
Level 3	11 (10)	35 (11)	
Underlying diseases, no. (IQR)	2 (1–3)	1 (1–2)	<.0001[d]
Presence of any disease other than diabetes, alcoholism, or cancer	68 (63)	120 (36)	<.0001[c]
Underlying disease			
Alcoholism	46 (43)	147 (45)	.5[c]
Diabetes	44 (41)	143 (43)	.9[c]
Renal disease	28 (26)	26 (8)	<.0001[c]
Cardiac disease	27 (25)	50 (15)	.02[c]
Lung disease	19 (8)	3 (9)	.02[c]
Cirrhosis or liver disease	17 (16)	24 (7)	.006[c]
Rheumatologic disease	13 (12)	11 (3)	.002[c]
Cancers	9 (8)	29 (9)	.4[c]
Vaccinated with PPV23			
⩾1 doses	67 (62)	211 (64)	.72[c]
⩾2 doses	20 (19)	80 (24)	.2[c]
⩾3 doses	2 (2)	10 (3)	.6[c]
PPV23 doses, median no. (range)	1 (0–3)	1 (0–4)	.3[d]
Time since last vaccination, median years (IQR)			
⩾1 PPV23	4.1 (2.4–5.7)	3.6 (2.3–5.4)	.3[b]
⩾2 PPV23	2.2 (1.1–3.8)	2.8 (1.5–4.2)	.4[b]
1 PPV23 only	4.5 (3.2–6.5)	4.3 (3.0–6.8)	.6[b]

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; PPV23, 23-valent pneumococcal polysaccharide.

[a] P is for the difference in presence of characteristic for case vs. control patient groups.
[b] P is unmatched.
[c] P is matched.
[d] P is matched using Cochran-Mantel-Haenszel general association statistics for stratified R × 2 tables.

This method has been described in detail elsewhere [10, 15]. In brief, the proportion of vaccinated patients was compared between patients with disease due to serotypes contained in the vaccine and those with disease due to serotypes not in the vaccine. Vaccine effectiveness was calculated as 1 minus the OR for vaccination multiplied by 100%. We excluded from this analysis all episodes of disease that were due to serotypes not included in PPV23 but that were of the same serogroup as serotypes that are included in PPV23 (i.e. vaccine-related serotypes).

We classified persons with multiple episodes of invasive pneumococcal disease as having had vaccine-type disease if any one of their episodes was due to an organism with a serotype present in the vaccine. There was no difference in the results when we repeated the analysis and classified persons as having vaccine-type disease only if their first episode of disease was caused by an organism with a serotype present in the vaccine. We needed a sample size of at least 200 subjects for adequate power to detect vaccine efficacy of 59%, assuming that the distribution of disease and serotype between unvaccinated and vaccinated subjects was the same as had been found in a previous study [10].

Serotype testing and classification. All available pneumococcal isolates were serotyped at the Arctic Investigations Program, CDC. Isolates were chosen for serotyping without regard to inclusion in the study or vaccination status of the patient; all personnel performing serotype analyses were unaware of both patients' inclusion in the study and their vaccination status. Serotyping was performed by use of the Quelling reaction.

Serotypes were categorized as vaccine type (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20,

Table 2. Vaccine effectiveness for ⩾1 doses of pneumococcal polysaccharide vaccine, adjusted for underlying medical conditions, for all case patients ($n = 108$) and for case patients with disease due to serotypes in the vaccine ($n = 54$).

Subgroup	Case patients	Control patients	Vaccine effectiveness, % (95% CI)[a]
Disease due to all serotypes			
All patients	67/108 (62)	211/330 (64)	26 (−29 to 58)
With alcoholism	24/46 (52)	73/147 (50)	5 (−141 to 54)
With diabetes[b]	36/44 (82)	119/143 (83)	15 (−116 to 67)
Without diabetes or alcoholism	16/28 (57)	43/71 (61)	52 (−28 to 82)
Nondiabetic[b]	31/64 (48)	92/187 (49)	27 (−47 to 63)
Nonalcoholic	43/62 (69)	138/183 (76)	42 (−23 to 72)
Disease due to serotypes in the vaccine			
All patients	33/54 (61)	108/165 (65)	38 (−44 to 73)
With alcoholism	9/24 (38)	30/73 (41)	19 (−157 to 75)
With diabetes[b]	17/20 (85)	65/75 (87)	31 (−182 to 83)
Without diabetes or alcoholism	10/14 (71)	24/33 (73)	52 (−140 to 90)
Nondiabetic[b]	16/34 (47)	43/90 (48)	31 (−90 to 75)
Nonalcoholic	24/30 (80)	78/92 (85)	49 (−78 to 85)

NOTE. Data are no. of patients vaccinated/total no. of patients (%), unless otherwise indicated. CI, confidence interval; OR, odds ratio.

[a] Vaccine effectiveness = (1 − adjusted matched OR for vaccination) × 100%.

[b] Adjusted for alcoholism.

22F, 23F, and 33F), vaccine related (6A, 7, 7A, 7B, 7C, 9A, 9L, 10, 10F, 10B, 10C, 11F, 11B, 11D, 12, 12A, 12B, 15F, 15A, 15C, 17A, 18A, 18F, 18B, 19B, 19C, 22A, 22B, 23A, 23B, 33A, 33B, and 33C), or nonvaccine type (a type not in the vaccine or related to a vaccine type).

RESULTS

Case-control study. We identified 163 case patients during 1996 and 1997. Of those, 112 were either aged ⩾65 years or had underlying medical conditions and thus were considered to be potential study patients. Of the 112 case patients, we successfully found matching control patients for 108 and included these 108 in the case-control analysis.

Of the 108 case patients, 3 had >1 episode of illness during 1996 and 1997, thus accounting for 115 episodes of illness in 1996 and 1997. Of these 115 episodes, 80% (92) involved pneumonia, 24% (28) involved sepsis, 5% (6) involved bacteremia without sepsis, 4% (5) involved peritonitis, 3% (4) involved meningitis, 3% (4) involved joint infections, and 10% (11) involved another clinical syndrome. Most episodes resulted in hospitalization (94%); 37% (42) of the episodes required admission to an intensive care unit, and 17% (20) required mechanical ventilation. The case-fatality rate was 16% (18 episodes resulted in death). Age of the case patients ranged from 20 to 95 years.

Case patients were matched to 1–7 control patients for a total of 330 control patients. Age distributions were similar for both case and control patients; median age was 58.6 years for case patients (range, 20–95 years) and 58.8 years for control patients (range, 18–92 years) (table 1).

Underlying illness. Of 108 case patients, 16 were assigned to risk level 1, 81 to risk level 2, and 11 to risk level 3. Alcoholism and diabetes were common among case patients (43% and 41%, respectively). Case patients generally had more underlying illnesses than did control patients (table 1); more case patients than control patients had ⩾2 underlying diseases ($P = .0002$).

Vaccination rates and vaccine effectiveness. Sixty-two percent of case patients and 64% of control patients had documentation in their medical records of having been vaccinated with PPV23. Similar proportions of case and control patients had received multiple doses of PPV23 (20 [19%] case patients and 80 [24%] control patients; $P = .2$). There was no difference between case patients and control patients in the time that had elapsed from their last vaccination to the date the case patient became ill (table 1).

PPV23 was not significantly effective in this population; overall vaccine effectiveness was 26% (95% CI, −29% to 58%) (table 2). For patients with diabetes, the point estimate for effectiveness was 15% (95% CI, −116% to 67%). The point estimate for vaccine effectiveness was lower for alcoholic patients: −5% (95% CI, −141% to 54%). There were no significant contributions from potential confounding variables, in-

Table 3. Vaccine effectiveness for ⩾2 doses of pneumococcal polysaccharide vaccine vs. no vaccinations, adjusted for underlying medical conditions, for all case patients and for case patients with disease due to vaccine serotype.

Cases included	Case patients		Control patients		Vaccine effectiveness,[a] % (95% CI)
	N	Vaccinated, no. (%)	*N*	Vaccinated, no. (%)	
All serotypes	61	20 (33)	199	80 (40)	40 (−27 to 72)
Vaccine serotypes only	31	10 (32)	94	37 (39)	43 (−79 to 82)

NOTE. Persons who received 1 vaccine dose were excluded. *N,* no. of persons who received 0 or ⩾2 vaccinations; no., no. of persons vaccinated; OR, odds ratio.

[a] Vaccine effectiveness = (1 − adjusted matched OR for vaccination) × 100%.

cluding the amount of time that had elapsed since vaccination, receipt of influenza vaccine in the year before the case patient became ill, the number of doses of PPV23, or age. Likewise, there were no significant contributions from any of the 2-way interactions between variables.

For the 54 case patients with disease due to a serotype found in the vaccine, the point estimate for vaccine effectiveness was 38% overall (95% CI, −44% to 73%), 31% for patients with diabetes (95% CI, −182% to 83%), and 19% for alcoholic patients (95% CI, −157% to 75%) (table 2).

Having received ⩾2 doses of PPV23 did not increase the effectiveness of the vaccine (table 3). When we stratified by the number of doses and the time since vaccination, there were no differences in vaccine effectiveness, regardless of whether patients had received their last doses of PPV23 <5 years or ⩾5 years before illness or whether they had received 1 versus ⩾2 doses of vaccine (table 4).

Indirect cohort study. During 1989–1998, 606 episodes of invasive disease were identified in 577 case patients. Of these episodes, serotype information was available for 312 (51%); 1 episode was caused by 2 serotypes (i.e., 313 isolates were found from 312 episodes). Of the 313 isolates recovered, 251 (80%) were serotypes present in the PPV23 vaccine, 29 (9%) were a vaccine-related serotype, 57 (18%) were serotypes in the 7-valent conjugate pneumococcal vaccine (4, 6B, 9V, 14, 19F, 23F, and 18C), and 177 (60%) were serotypes 1, 12F, 5, 4, 7F, and 8 (these were the 6 most common serotypes found). For the 278 patients represented by these 312 episodes with serotype information available, vaccine effectiveness was determined to be 35% (95% CI, −33% to 69%), by the indirect cohort analysis (table 5).

The distribution of serotypes in the indirect cohort study is slightly different from that of the case-control study. This difference occurred because we excluded from the case-control study patients aged <65 years without underlying medical illness, whereas, for the indirect cohort study, we included all patients with a serotype available.

DISCUSSION

Our results indicate that PPV23 is not significantly effective among Navajo adults; the 95% CIs around all point estimates of effectiveness included zero. By use of case-control methodology, the point estimate for overall effectiveness of the vaccine was 26%; results that were obtained by use of indirect cohort methodology were similar (35%). The point estimate

Table 4. Vaccine effectiveness, by no. of vaccinations and time elapsed since the last vaccination.

Category	Case patients (*n* = 108)	Control patients (*n* = 330)	Vaccine effectiveness, % (95% CI)[a]
Not vaccinated	41 (38)	119 (36)	Reference
1 PPV23			
<5 years before illness	26 (24)	79 (24)	20 (−54 to 59)
⩾5 years before illness	21 (19)	52 (16)	20 (−64 to 62)
⩾2 PPV23			
Most recent vaccination <5 years before illness	18 (17)	71 (22)	41 (−29 to 73)
Most recent vaccination ⩾5 years before illness	2 (2)	9 (3)	33 (−250 to 87)

NOTE. Data are no. (%) of case patients or control patients, unless otherwise indicated. CI, confidence interval; PPV23, 23-valent pneumococcal polysaccharide.

[a] Adjusted for the presence of any disease other than diabetes, alcoholism, and cancers.

Table 5. Effectiveness of vaccination by the indirect cohort analysis; case patients from 1989 to 1998 ($n = 278$).

Vaccination status	Total no.	Vaccine-type disease	Nonvaccine-type disease	Vaccine effectiveness, % (95% CI)[a]
Vaccinated, ⩾1 PPV23	129	110 (85)	19 (15)	35 (−33 to 69)
Not vaccinated	149	134 (90)	15 (10)	

NOTE. Data are no. (%) of case patients, unless otherwise indicated. CI, confidence interval; OR, odds ratio; PPV23, 23-valent pneumococcal polysaccharide.

[a] Vaccine effectiveness = (1 − adjusted matched OR for vaccination) × 100%.

of PPV23 effectiveness for the subgroup of diabetic patients (15%) was similar to the overall effectiveness; for the subgroup of alcoholic patients, point estimates for vaccine effectiveness were near zero. On the basis of this study, we cannot comment on the effectiveness of PPV23 in healthy Navajo adults aged <65 years. Effectiveness of PPV23 among Navajo adults may be lower than the effectiveness for other adult populations in the United States.

Although we could not directly evaluate the effectiveness of revaccination, we were able to show that patients who received ⩾2 doses of PPV23 demonstrated a point estimate for vaccine effectiveness that was not statistically different from the estimate for those who had received ⩾1 doses (26% vs. 40%). Repeat vaccination with the polysaccharide vaccine does not generally increase antibody levels to concentrations as high as after the initial vaccination [16, 17].

The results of this study differ from results of 4 previous case-control studies, which have documented a range of vaccine effectiveness from 47% to 81% for the 14-valent [6] or 23-valent [7–9] vaccines (table 6). However, the results are similar to a case-control study of the 14-valent vaccine in men at a Veteran's Administration hospital, which found that the vaccine

Table 6. Observational studies of the effectiveness of polysaccharide pneumococcal vaccine against invasive pneumococcal disease.

Study,[a] subgroup	Vaccinated		Patients with alcoholism	Patients with diabetes	Vaccine effectiveness, % (95% CI)
	Case patients	Control patients			
Shapiro et al. 1991 [7]					
All patients	13	20	13	5	47 (30 to 59)
Patients with disease due to serotype in the vaccine					56 (42 to 67)
Immunocompetent patients					61 (47 to 72)
Immunocompromised patients					21 (−55 to 60)
Sims et al. 1988 [8]					
Immunocompetent patients	8	21	16	15	70 (36 to 86)
Immunocompromised patients					Excluded from study
Farr et al. 1995 [9]					
All patients	7	17	46	8	81 (34 to 94)
Shapiro et al. 1984 [6]					
All patients	7	18	NA	NA	67 (13 to 87)
Immunocompetent patients					77 (27 to 93)
Immunocompromised patients					0 (−1228 to 93)
Forrester et al. 1987 [12]					
All patients	29	24	NA	NA	−21 (−221 to 55)
Patients with disease due to serotype in the vaccine					0 (−774 to 96)
Breiman et al. 2000 [11]					
Immunocompromised patients	25	37	NA	NA	49 (12 to 70)

NOTE. Data are percentages of patients, unless otherwise indicated. CI, confidence interval; NA, not available from paper.

[a] Shapiro et al. [7] ($n = 1054$; 11 hospitals in Connecticut; and 23-valent vaccine); Sims et al. [8] ($n = 122$; 1 hospital in Philadelphia; and 23-valent vaccine); Farr et al. [9] ($n = 85$; 1 hospital, University of Virginia; and 23-valent vaccine); Shapiro et al. [6] ($n = 90$; 1 hospital, Yale–New Haven; and 14-valent vaccine); Forrester et al. [12] ($n = 89$ [all men]; 1 Veterans Administration hospital; and 14-valent vaccine); Breiman et al. [11] ($n = 176$; 4 hospitals in Atlanta and 6 in San Francisco; and 23-valent vaccine).

was ineffective [12]. The largest, most comprehensive of the case-control studies was performed by Shapiro et al. [7] and documented a overall vaccine effectiveness of 47% and an effectiveness of 56% for serotypes in the 23-valent vaccine. For immunocompromised patients, Shapiro et al. [7] found a vaccine effectiveness of 21% (95% CI, −55% to 60%), which is similar to that in our study and the study at the Veteran's Administration hospital [12]. Patient populations in these previous studies differed from ours in the prevalence of diabetes and alcoholism. Whereas, in our study, 43% patients had alcoholism and 41% had diabetes, in the large case-control study, only 13% of patients had diabetes and 5% had alcoholism [7]. In the other case-control studies, the prevalences of diabetes and alcoholism were 15% and 16% [8] and 8% and 46% [9], respectively (table 6).

Several reasons could explain why the PPV23 may be less effective in this population than in other populations. The high prevalence of chronic diseases, such as diabetes and alcoholism, may be one reason. Because patients with poorly controlled diabetes [18–21] and alcoholic patients may have increased susceptibility to pneumococcal disease [22–24], they may need a higher level of antibodies to prevent disease. In addition, alcoholic patients may respond poorly to pneumococcal polysaccharide vaccine [25, 26]; we documented an exceptionally low effectiveness for alcoholic patients. The large proportion of alcoholic patients and patients with diabetes may make this population immunologically similar to the immunocompromised group studied by Shapiro et al. [7] and the population of veterans studied by Forrester et al. [12]. Human genetic factors are another postulated reason for difference in effectiveness. No studies have evaluated the immunogenicity of this polysaccharide vaccine in Navajo persons.

Lower effectiveness also may be related to the distribution of serotypes among the Navajo. Among Navajo adults, the 6 most common serotypes, accounting for 60% of the episodes, were serotypes 1, 12F, 5, 4, 7F, and 8. In contrast, in the general population of persons aged ⩾65 years, the 8 most common serotypes responsible for 60% of illness are serotypes 14, 4, 9V, 6B, 23F, 19F, 3, and 22F [3]. Vaccine efficacy may vary from serotype to serotype; data on efficacy for the specific serotypes in the 23-valent vaccine are limited [10]. The vaccine may be less effective for the predominant serotypes among the Navajo in contrast to the serotypes that predominate for the general population.

We designed this study to have 96% power to detect a true vaccine effectiveness of 59% if we enrolled 100 case patients, assuming that 60% of control patients had received the vaccine and if 3 control patients were obtained for each case patient. In the end, we enrolled 108 case patients, and 64% of the control patients had received vaccine. As a result, we had adequate power to find, if it existed, a vaccine-effect similar to what has been documented previously. Thus, we are confident that the low magnitude of our point estimates reflects a true low effectiveness of the vaccine in the population.

Our study had the potential to be subject to biases related to its retrospective nature. One important potential source of bias is misclassification of vaccination status. To avoid misclassification, we reviewed charts at every clinic or hospital where the patient had been seen. Another concern was that case patients could be at more risk for invasive disease because of the presence of more chronic illnesses. To control for this potential confounding effect, we matched control patients to case patients as closely as possible according to underlying disease and further controlled for underlying disease in the multivariable regression models. It is possible that we were unable to completely control for confounding factors due to underlying disease, perhaps because of undiagnosed diabetes or alcoholism; many Navajo have undetected diabetes [27].

In summary, Navajo persons are at high risk for pneumococcal disease and at high risk for pneumococcal disease that is severe [28]. The polysaccharide pneumococcal vaccine, the only tool currently available for prevention of disease in adults, is not adequately effective. However, because this vaccine may benefit some persons, until new tools are available for prevention of pneumococcal disease, we do not recommend changing the current guidelines for the use of PPV23 in Navajo adults. New vaccines are needed for adults; the 7-valent pneumococcal protein–conjugate vaccine, shown to be effective in children [29], should be evaluated for safety and effectiveness in adults. However, on the basis of serotype distribution in Navajo adults, the 7-valent vaccine has the potential to prevent only 18% of disease. A vaccine covering >7 serotypes is needed to provide protection for Navajo adults. Because vaccines directed against common pneumococcal protein antigens have the potential to provide protection across all serotypes, these vaccines will be important to evaluate in both Navajo adults and adult populations in general [30–32].

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