Reactions after 3 or More Doses of Pneumococcal Polysaccharide Vaccine in Adults in Alaska

Frances J. Walker, Rosalyn J. Singleton, Lisa R. Bulkow, Raymond A. Strikas, and Jay C. Butler

1National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia; and 2Alaska Native Tribal Health Consortium and 3Arctic Investigations Program, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Anchorage, Alaska

(See the editorial commentary by Whitney on pages 1736–7)

Background. Following vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV), pneumococcal antibody levels decline to prevaccination levels within 6–10 years. The Advisory Committee on Immunization Practices does not recommend routine revaccination because data on the safety and effectiveness of additional doses are insufficient.

Methods. To determine whether medically attended adverse events occur more frequently after the third dose of PPV than after the first or second dose, we performed a retrospective review of medical records from a computer database for health care facilities that serve more than one-half of the Alaska Native population. All persons who had received ≥3 PPV doses (n = 179) were included in the review, as were a randomly selected comparison group of 181 persons who had received 1 or 2 doses.

Results. Only 1 (0.55%) of 179 persons who had received ≥3 PPV doses and 4 (2.76%) of 181 persons in the comparison group had a medically attended adverse event, and no severe adverse events were recorded.

Conclusion. We found no difference in the risk of medically attended adverse events following ≥3 doses of PPV, compared with 1 or 2 doses.

Following vaccination with 23-valent pneumococcal polysaccharide vaccine (PPV), pneumococcal antibody levels decline to prevaccination levels within 6–10 years, with a more rapid decline in certain groups [1–6]. In addition, an epidemiologic study suggests that the clinical effectiveness of PPV declines with time after vaccination [7]. The Advisory Committee on Immunization Practices (ACIP) does not recommend routine revaccination, because data on the safety and effectiveness of additional doses are insufficient [8]. However, the ACIP does recommend 1 revaccination after ≥5 years for adults with certain medical conditions, such as functional or anatomic asplenia, HIV infection, leukemia, lymphoma, Hodgkin disease, multiple myeloma, chronic renal failure, nephrotic syndrome, and other conditions associated with immunosuppression or immunosuppressive chemotherapy. High rates of pneumococcal infection in Alaska Native adults and evidence from a local study of increased immunogenicity after revaccination [1] led the State of Alaska to lower the age of universal vaccination to 55 years and to recommend routine revaccination every 6 years for all adults who receive PPV [9, 10].

Early pneumococcal revaccination studies found no increase in the number of severe adverse events after a second dose, compared with the number occurring after the first dose, especially when the interval between doses was ≥4 years [1, 4, 11]. Some studies reported an increase in local reactions when the interval between vaccinations was <2 years [12, 13]. All of these studies were small, ranging from 7 to 127 patients, and, in some studies, the first dose was the 14-valent pneumococcal vaccine. In a larger study by Jackson et al. [14], patients aged ≥50 years who were revaccinated after 5 years were more likely to report sizeable local reactions at the injection site and limitation of movement than were patients who had received only 1 dose, but neither group had any severe reactions. The study
by Jackson et al. [14] and other studies found that sizeable local reactions to PPV vaccination and revaccination appear to be associated with higher vaccine type–specific antibody levels before vaccination, suggesting an Arthus-type reaction caused by the formation of antibody-antigen complexes at the injection site [6, 12, 14, 15].

No studies have evaluated the risk of adverse events following ≥3 pneumococcal vaccinations. Because of the Alaska recommendation of routine revaccination, we performed a retrospective review of inpatient and outpatient records in Alaska to determine whether medically attended local or systemic adverse events were more common after the third dose of PPV than they were after first or second doses.

METHODS

We performed a search of computer-based immunization records in the Resource and Patient Management System (RPMS) for patients receiving care at Alaska Native health care facilities to identify all persons who received ≥3 pneumococcal vaccinations from December 1978 through October 1999. The RPMS database includes data from outpatient and inpatient visits from the tribally operated Yukon Kuskokwim Delta Regional Hospital (YKDRH) and outlying clinics, the Alaska Native Medical Center (ANMC), and most village clinics throughout the state. Together, YKDRH and ANMC serve more than one-half of the Alaska Native population. Electronic records include types of vaccinations, including dates and lot numbers; diagnoses at the time of hospital discharge, with _International Classification of Disease, Ninth Revision_ (ICD-9) codes and narratives for 7 regional hospitals serving Alaska Natives; and dates, facility, and purpose of visit for outpatient visits at ≥100 village and regional clinics. The present study was approved by the Indian Health Service Alaska Area Institutional Review Board.

We randomly selected a sample comparison group from all adults who received at least 1 pneumococcal vaccine dose at the ANMC in 1990 or later, frequency matched by 10-year age groups with the group that received ≥3 doses. Alaska Natives from all regions of the state may receive care at ANMC, because Anchorage serves as a hub and because ANMC serves as a referral facility for Alaska Natives. Third doses of PPV were given mostly in the 1990s. If a chart was unavailable, we selected the next patient in the sample for that age group until a sufficient number of records were reviewed or until no more charts were available.

We defined medically attended adverse events as local symptoms at the injection site (e.g., redness, tenderness, swelling, pain, and limitation of movement) or systemic symptoms (e.g., unexplained fever, rash, urticaria, myalgia, and pruritus) for which care was sought within 30 days after pneumococcal vaccination. We reviewed computer and paper medical records to verify vaccinations and collect information on demographic characteristics, simultaneous vaccinations, underlying medical conditions, and possible adverse events. Paper charts included copies of many visits to village clinics, regional clinics, hospitals, and visiting nurse visits.

We examined RPMS electronic records for visits on the date of immunization, and we recorded, for every patient, the purpose of the visit, the next outpatient visit, the next hospitalization, and the diagnoses at discharge after receipt of a dose of PPV. We then requested paper charts for every patient to examine data from every visit or hospitalization following vaccination to identify possible adverse events. Paper charts included those from all inpatient and outpatient visits to ANMC and YKDRH and, often, copies of paper charts from visits to city and village clinics, to regional clinics, and by visiting nurses. Some charts were not available, and some volumes were incomplete. A vaccination was considered to be verified if it was specifically cited in the electronic record for the visit or on the paper chart. A special effort was made to find paper charts for any person whose record indicated a possible adverse event or a duplicate entry, including an adverse reaction to any vaccine, a descriptive diagnosis or ICD-9 code that could be related to vaccine side effects, an outpatient or hospital visit within 7 days after receipt of a PPV dose without a stated purpose of visit, or a dose received within 12 months after receipt of the previous dose. This resulted in visits to village clinics by research nurses to review records for 60 patients in the study. Vaccinations were excluded if they were duplicate entries or there was no evidence on the chart that a vaccination occurred on the vaccination date. If paper records were not available, the electronic record was accepted. One village elected not to participate in the study, so all patients from that village (_n_ = 4) were excluded from the present study.

Underlying medical conditions for which PPV is recommended were defined as follows: chronic heart disease (i.e., congestive heart failure and cardiomyopathies), chronic lung disease (i.e., emphysema, chronic obstructive pulmonary disease, bronchiectasis, pulmonary fibrosis, or interstitial lung disease), diabetes, splenectomy, liver disease (i.e., cirrhosis, chronic alcoholic hepatitis, or alcoholic liver disease), HIV/AIDS, other immune deficiencies, chronic kidney disease (i.e., chronic renal insufficiency or renal failure), history of cancer, and chronic alcoholism.

We performed all analyses using SAS statistical software, version 8.2 (SAS Institute). We tested differences in proportions using the χ² or Fisher’s exact tests and differences in continuous variables using the Kruskal-Wallis test.

RESULTS

Of 246 persons initially identified in the RPMS immunization database as having received ≥3 vaccinations, 179 (73%) received ≥3 PPV doses. The rest were duplicate or incorrect
entries or lacked evidence of vaccination during the visit listed in the database. Because of the lack of availability of charts or vaccination records, 35% of the vaccinations (43.9% in the group that had received ≥3 doses and 10.6% in the comparison group) could not be verified with paper charts, particularly those vaccinations that were administered during the 1970s and early 1980s. Of 181 patients in the comparison group, 35 (19.3%) received 2 doses of PPV. All adverse events were verified with paper charts. With respect to the patients who had had an outpatient or inpatient visit within 7 days after vaccination—the likely period for reporting an adverse event—we found that, in the group that had received ≥3 doses, a total of 78 doses (75.7%) were verified with paper charts, and, in the comparison group, 53 doses (81.5%) were verified. For 37 visits for which doses were not verified, 31 had a purpose of visit that did not suggest an adverse reaction (e.g., eye exam, mastectomy follow-up, or arthritis), and 6 had no reason specified in the electronic record for the visit.

Many patients (46.8%) had a provider visit within 30 days after receipt of a pneumococcal dose (after 41.7% of vaccinations in the ≥3 dose group and after 60.2% of vaccinations in the comparison group), and 21.4% of all patients had a visit within 7 days after a vaccination (after 18.1% of vaccinations in the ≥3 dose group and after 30.1% of vaccinations in the comparison group).

Of 179 adults who had received ≥3 vaccinations (range, 3–5 vaccinations; total of 569 doses), only 1 (0.6%) had a medically attended adverse event (tachycardia and arm redness) after receipt of the third dose. None had experienced medically attended adverse events following first or second doses. Among the comparison group of 181 persons, 4 (2.2%) had medically attended adverse events: 2 after the first dose (rash with periorbital swelling in one and arm pain in another) and 2 after the second dose (myalgia with arm tenderness in one and arm redness and swelling in another) (table 1). Only 35 persons received 2 doses, for a total of 216 doses in the comparison group. One patient who reported a reaction to pneumococcal vaccination was given a diagnosis of a probable viral infection by her physician, and her case was not considered to be an adverse event case in the present study. There were no serious adverse events or hospitalizations. None of the 5 patients with a medically attended adverse event received any subsequent doses of PPV. The difference in medically attended adverse events between the group that received ≥3 doses and the comparison group was not statistically significant (relative risk, 0.40; 95% CI, 0.07–2.31; $P = 0.372$, Fisher’s exact test). However, because of the underlying low rate of adverse events, the study had only 43% power ($\alpha = 0.05$) to detect a 3-fold increase in events for the group that had received ≥3 vaccinations.

Patients in the group that had received ≥3 doses were slightly older at the time of their third dose, compared with patients in the comparison group at the time of their first dose, with a median age of 69.5 and 63.5 years, respectively (table 2). Patients who received ≥3 doses of PPV were more likely to have ≥1 underlying medical condition for which pneumococcal vaccination is recommended—a total of 76.5%, compared with 64.1% of the patients in the comparison group ($P = .01$, $\chi^2$).

Persons in the group that had received ≥3 vaccinations were more likely to have diabetes ($P < .01$) or chronic lung disease ($P < .0001$) than were patients in the comparison group.

All 3 medically attended adverse events following revaccination occurred when PPV was administered at an interval

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### Table 1. Case reports of adverse events following pneumococcal polysaccharide vaccination (PPV) in Alaskan adults.

<table>
<thead>
<tr>
<th>Group, patient</th>
<th>Sex, age in years</th>
<th>Medical history</th>
<th>PPV dose</th>
<th>Setting, time of visit</th>
<th>Adverse event</th>
<th>Other vaccine given</th>
<th>Treatment</th>
<th>Duration of symptoms, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>F, 67</td>
<td>Splenectomy, colon cancer, diabetes</td>
<td>1st</td>
<td>VC, 2 days after PPV</td>
<td>Redness at PPV site</td>
<td>Influenza vaccine</td>
<td>None noted</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>F, 53</td>
<td>Reactive airway disease, drug allergies, smoking</td>
<td>1st</td>
<td>ED, 1 day after PPV</td>
<td>Diffuse maculopapular rash, pruritus, periorbital swelling, and tenderness at PPV site</td>
<td>Antihistamine, steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>F, 72</td>
<td>COPD, drug allergies, past reaction to influenza vaccine</td>
<td>1st</td>
<td>ED visit for COPD, 1 day after PPV</td>
<td>Complained of arm pain; no swelling or other symptoms</td>
<td>None noted</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>M, 70</td>
<td>COPD, degenerative joint disease</td>
<td>2nd</td>
<td>ED, 1 day after PPV</td>
<td>Fever (temperature, 37°C), myalgia, tachycardia, and weakness; redness and tenderness (25 × 15 cm) at PPV site</td>
<td>Influenza vaccine</td>
<td>Analgesic, antibiotic</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>F, 73</td>
<td>Chronic sinusitis</td>
<td>2nd</td>
<td>Saw physician same day as PPV</td>
<td>Redness (5 cm) and swelling (1 cm) at PPV site</td>
<td>Influenza vaccine</td>
<td>Analgesic, ice pack</td>
<td>NA</td>
</tr>
</tbody>
</table>

**NOTE.** COPD, chronic obstructive pulmonary disease; ED, emergency department; NA, not available; VC, village clinic.
Table 2. Characteristics of patients, by number of pneumococcal vaccinations.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>≥3 doses (n = 179)</th>
<th>1–2 doses (n = 181)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>110 (61.5)</td>
<td>104 (57.5)</td>
<td>.44</td>
</tr>
<tr>
<td>Age, median years</td>
<td>69.5</td>
<td>63.6</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Age group, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>4 (2.2)</td>
<td>10 (6.5)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>14 (7.8)</td>
<td>18 (9.9)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>23 (12.9)</td>
<td>30 (16.6)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>54 (30.2)</td>
<td>58 (32.0)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>59 (33.0)</td>
<td>51 (28.2)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>25 (14.0)</td>
<td>14 (7.7)</td>
<td></td>
</tr>
<tr>
<td>≥1 high-risk condition</td>
<td>137 (76.5)</td>
<td>116 (64.1)</td>
<td>.01</td>
</tr>
<tr>
<td>≥2 high-risk conditions</td>
<td>60 (33.5)</td>
<td>41 (22.7)</td>
<td>.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>45 (25.1)</td>
<td>25 (13.8)</td>
<td>.007</td>
</tr>
<tr>
<td>Chronic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>57 (31.8)</td>
<td>24 (13.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Heart</td>
<td>22 (12.3)</td>
<td>21 (11.6)</td>
<td>.84</td>
</tr>
<tr>
<td>Liver</td>
<td>4 (2.2)</td>
<td>4 (2.2)</td>
<td>.99</td>
</tr>
<tr>
<td>Kidney</td>
<td>3 (1.7)</td>
<td>7 (3.9)</td>
<td>.21</td>
</tr>
<tr>
<td>History of cancer</td>
<td>32 (17.9)</td>
<td>37 (20.4)</td>
<td>.54</td>
</tr>
<tr>
<td>Immunocompromised status</td>
<td>6 (3.4)</td>
<td>2 (1.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Chronic alcoholism</td>
<td>51 (28.5)</td>
<td>50 (27.6)</td>
<td>.85</td>
</tr>
</tbody>
</table>

* Age at the time of receipt of third dose for the group that received ≥3 vaccinations, or age at the time of receipt of the first dose for the comparison group. Age was matched by decade in the study design, so a statistical test may not be appropriate.

b Included cancer, asplenia, HIV/AIDS, chronic obstructive pulmonary disease (COPD)/emphysema, chronic alcoholism, and chronic heart, kidney, or liver disease.

c Included emphysema and COPD.

d Included congestive heart failure and cardiomyopathies.

e Included cirrhosis, chronic alcoholic hepatitis, and alcoholic liver disease.

f Included chronic and acute renal failure and chronic renal insufficiency.

F To our knowledge, only 1 previous report, which involved 2 subjects, has examined adverse events after receipt of ≥3 doses of PPV in the clinical setting [16]. In the present study, we identified 179 Alaskans who received ≥3 pneumococcal vaccinations. Of these, only 1 had a vaccine-related adverse event that led to a medical care visit.

Table 2. Characteristics of patients, by number of pneumococcal vaccinations.

We found no serious adverse events following 425 revaccinations in our study groups. Similarly, Jackson et al. [14] found no serious adverse events among 901 primary vaccinees and 513 patients revaccinated after 5 years. That prospective study used study diaries, including recorded temperature, and found that a higher proportion of revaccinees experienced a local reaction at the injection site, redness or swelling, arm soreness, and limitation of arm movement, compared with patients who were vaccinated for the first time. However, only 1 primary vaccinee and 2 revaccinated persons had medically attended adverse events. Another study of 61 revaccinees found no serious adverse events following revaccination [17].

In a retrospective cohort study that used the claims data of 23,663 New York State Medicare beneficiaries, Shih et al. [18] reported that patients who had been revaccinated had a higher crude relative risk of emergency room visits, hospitalizations, and physician office visits within 14 days after PPV revaccination, compared with patients who had received only 1 vaccination with PPV. Furthermore, they found a higher relative risk of limb pain, unspecified allergic/adverse reaction, and adverse reaction to vaccine and/or other substances, but not of fever, malaise, upper arm pain, swelling, rash, urticaria, infection, or angioneurotic edema. They did not evaluate simultaneous influenza vaccination. Other studies with active patient follow-up have reported a higher risk of adverse local reactions with PPV revaccination, compared with the risk after the primary dose, but these studies involved 14-valent PPV and small sample sizes and lacked appropriate comparison groups [12, 13].

The findings of early studies suggest that local adverse events occur more frequently when the interval between PPV doses is <4 years, based on small samples (12–17 adults) with only short intervals [8, 12, 16]. However, other studies that included patients with longer or variable intervals have found that the interval since the time of the last dose is not associated with an increased risk of adverse events [14, 18, 19]. In a multivariable analysis, Shih et al. [18] found higher odds of emergency room visits and office visits within 14 days after vaccination for Medicare beneficiaries who had been revaccinated <5 years after the first dose, compared with beneficiaries who
had received only 1 vaccination with PPV, but not when compared with beneficiaries who had been revaccinated after \(\geq 5\) years. In the present study, each of the 3 adverse events that occurred after revaccination involved patients for whom the interval between vaccinations was 4–5.6 years. In fact, 44.5% of all revaccinations were given after an interval shorter than the minimum 5 years recommended by ACIP. We found that shorter intervals were more common before 1990, and were especially common before 1983, when the recommendation about intervals was made by ACIP.

In evaluating adverse events associated with PPV revaccination, some studies have found that higher prevaccination antibody levels are more closely associated with adverse reactions than is time since the previous dose [6, 12, 14, 20]. Several studies have found smaller increases in antibody levels after revaccination than after receipt of the primary dose [4, 12, 13]. In a study among Alaska Natives, antibody levels for 12 serotypes increased similarly after first and second doses, but, after an average of 7 years after the primary vaccination, they were equivalent to levels before primary vaccination [1]. It is possible that the low number of adverse events following \(\geq 3\) vaccinations in the present study, regardless of the interval after the previous dose, was because of low levels of circulating antibody before receipt of the third dose, but this information was not available.

Most revaccinees in the present study (70.3%; 76.5% of patients in the group that received \(\geq 3\) doses and 64.1% of patients in the comparison group) had chronic conditions for which PPV is recommended [8], which may help to explain the low number of medically attended adverse events. Although most persons with high-risk conditions respond to PPV, some studies have noted suboptimal antibody levels in persons with chronic disease, particularly immunocompromised persons [8, 21]. Jackson et al. [14] found the relative risk of sizable local reactions following revaccination was highest among healthy subjects, lower among chronically ill subjects, and not significant for immunocompromised subjects.

The 3 revaccinees who had medically attended adverse events had received influenza vaccine simultaneously with PPV, but a total of 31.6% of all PPV doses in the present study were given with influenza vaccine. All of the local adverse events occurred at the PPV injection site. The ACIP has recommended that PPV be offered to adults at the same time as influenza vaccine, and there is no evidence of increased serious adverse effects when the vaccines are administered simultaneously [8, 22, 23].

The actual number of persons who received \(\geq 3\) vaccinations may be fewer than that reported, because we were unable to verify all vaccinations. Although we were unable to verify all 569 doses in the paper records for this group (which may have overestimated the denominator), we were able to examine the reason for inpatient and outpatient visits within 7 days after all vaccinations. We determined that all visits were for reasons unrelated to immunization, except for 6 visits in which the purpose of the visit was unknown. All adverse events that were identified in the present study were well documented in the electronic and paper medical records.

There are several possible explanations regarding the low numbers of reported local or systemic adverse events detected in the present study. First, as a retrospective study with no active patient follow-up, mild local reactions were not likely to be detected through chart review. However, because there is reasonably good access to medical care in village and city clinics and 21.4% of patients had a physician contact within 7 days after vaccination, serious adverse events were more likely to be reported to providers. In a study with patient follow-up of 52 vaccinated or revaccinated Alaska Natives, 5 participants reported mild local reactions, and 1 reported malaise and fever, but none had reported these events to their providers [1]. Second, the present study did not have a sufficient sample size to detect rare events, such as severe febrile or anaphylactic adverse events. With the limited number of Alaskans who received \(\geq 3\) doses, we also did not have sufficient power to say there was no increase in the risk of medically attended adverse events. Third, there is no information on the expected antibody response to a third, fourth, or fifth dose of PPV. It is possible that patients who receive multiple revaccinations do not have a sufficient concentration of type-specific antibody to cause an Arthus-type reaction. There is some evidence that antibody levels for older, chronically ill revaccinees diminish considerably after 1 year [24], but there is no other information about the persistence of antibody concentrations following revaccination [25]. Finally, patients who are repeatedly revaccinated are likely to be a self-selected group of persons who did not experience any adverse reaction to previous doses.

In conclusion, we found no evidence of an increased risk of medically attended adverse events associated with \(\geq 3\) doses of PPV. A prospective study evaluating immunogenicity and adverse events associated with PPV revaccination in Alaska is ongoing. The State of Alaska continues to recommend pneumococcal revaccination every 6 years for Alaskans who are at high risk for pneumococcal disease.

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