Safety of Revaccination With Pneumococcal Polysaccharide Vaccine

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To prevent invasive pneumococcal disease, the Centers for Disease Control and Prevention's (CDC's) Advisory Committee on Immunization Practices (ACIP) recommends vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV) for all persons aged 65 years or older and for younger persons with medical conditions that are associated with an increased risk of serious pneumococcal disease. Evidence that postvaccination antibody levels5-5 and protective efficacy6 may decline over time suggests that vaccine-induced protection may not be lifelong. Therefore, onetime revaccination after 5 or more years is recommended for 2 groups: (1) persons aged 65 years or older vaccinated before the age of 65 years and (2) previously vaccinated persons aged 64 years or younger who are immunocompromised because of underlying medical conditions or medications.

Compliance with these recommendations may be limited in part by concerns about the safety of revaccination with PPV. These concerns originated with 2 studies that reported a higher than expected frequency and severity of local injection site reactions. The risk of adverse events associated with revaccination of elderly and chronically ill persons 5 or more years after first vaccination, as is currently recommended, has not been well defined.

Objective To determine whether revaccination with PPV at least 5 years after first vaccination is associated with more frequent or more serious adverse events than those following first vaccination.

Design Comparative intervention study conducted between April 1996 and August 1997.

Participants Persons aged 50 to 74 years either who had never been vaccinated with PPV (n = 901) or who had been vaccinated once at least 5 years prior to enrollment (n = 513).

Intervention PPV vaccination.

Main Outcome Measures Postvaccination local injection site reactions and pre-vaccination concentrations of type-specific antibodies.

Results Those who were revaccinated were more likely than those who received their first vaccinations to report a local injection site reaction of at least 10.2 cm (4 in) in diameter within 2 days of vaccination: 11% (55/513) vs 3% (29/901) (relative risk [RR], 3.3; 95% confidence interval [CI], 2.1-5.1). These reactions resolved by a median of 3 days following vaccination. The highest rate was among revaccinated patients who were immunocompetent and did not have chronic illness: 15% (33/228) compared with 3% (10/337) among comparable patients receiving their first vaccinations (RR, 4.9; 95% CI, 2.4-9.7). The risk of these local reactions was significantly correlated with prevaccination geometric mean antibody concentrations.

Conclusions Physicians and patients should be aware that self-limited local injection site reactions occur more frequently following revaccination compared with first vaccination; however, this risk does not represent a contraindication to revaccination with PPV for recommended groups.

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Among persons revaccinated,\textsuperscript{1} we pro-
be limited.

To better define currently recom-
med risk of adverse events
among persons revaccinated,\textsuperscript{1} we pro-
spectively enrolled more than 1400 per-
sons between the ages of 50 and 74 years and
compared postvaccination events
among persons being revaccinated after
5 or more years with those being vacci-
nated for the first time.

\textbf{METHODS}

\textbf{Study Population}

Participants, members of Group Health Cooperative (GHC) of Puget Sound, Se-
attle, Wash, were enrolled between April
1996 and August 1997. Eligibility re-
quired patients be either between the ages
of 65 and 74 years or between the ages
of 50 and 64 years with at least 1 chronic
medical condition for which ACIP cri-
tera recommends pneumococcal vac-
nination.\textsuperscript{1} Among those groups, persons
were eligible for first vaccination if they
had never received pneumococcal vac-
cine and had been continuously en-
rolled at GHC since 1983 (to allow com-
plete ascertainment of immunization
status since licensure of the 23-valent vac-
cine). Persons were eligible for revacci-
nation if they had exactly 1 prior docu-
mented vaccination with the 23-valent vac-
cine (≥5 years prior to study enrollment)
and did not report a significant ad-
verse event.

Vaccination status was initially deter-
mined through GHC computerized im-
munization registries, an online record
system maintained since its 1991 devel-
opment in conjunction with the CDC’s
Vaccine Safety Datalink Project.\textsuperscript{13} Vac-
cination data are entered online and on
medical charts on the day of adminis-
tration. Between 1983 and 1990, vacci-
nations were recorded in the chart and
1 copy forwarded for entry into a phar-
acy-based registry. Both registries were
used for initial determining vaccination
status, which was verified by interview
of all subjects. Discrepancies were re-
solved by reviewing the medical chart.

Medical conditions indicated for vac-
cination were indicated by an \textit{International
Classification of Diseases, Ninth Revi-
sion (ICD-9)} computer databases of
hospitalization discharge diagnoses and di-
agnoses of outpatient and emergency de-
partment visits and GHC pharmacy pre-
scriptions. We used a tumor and an online
diabetes registry to identify patients with
either systemic malignancies or diabetes
mellitus. Since asplenia is a condition that
may not be ascertained reliably through
computerized records, participants were
asked at the time of their enrollment visit
whether they had ever had all or part of
their spleen removed.

Participants were classified as immu-
nocompromised if they had any of the fol-
lowing: asplenia, leukemia, lymph-
oma, Hodgkin disease, multiple myelo-
ma, generalized malignancy, chronic
renal failure, nephrotic syndrome, im-
munosuppressive chemotherapy, and
organ or bone marrow transplant. Per-
sons without these conditions (immu-
nocompetent) were further classified
based on other chronic underlying con-
ditions. Immunocompetent particip-
ants with diabetes, cardiac disease,
Pulmonary disease, or cirrhosis were clas-
sified as chronically ill, and immuno-
competent participants without those
conditions were classified as healthy.

\textbf{Study Procedures}

Persons potentially eligible for enroll-
ment from these databases were sent a let-
ter informing them of the study and were
then contacted by telephone. Persons con-
firmed as eligible were scheduled for an
enrollment visit, during which they were
vaccinated intramuscularly in the left del-
toid, using a 1.6-cm (6/8-in) needle, with
0.5 mL of a single lot (lot 432683) of 23-
valent pneumococcal vaccine (Pnu-
Immun; Lederle Laboratories, Pearl River,
NY) containing 25 µg/dose of each cap-
sular polysaccharide component.

Participants were given a study diary
and a supply of single-use thermometers
(Tempa-DOT, PyMaH Corporation,
Flemington, NJ). They were instructed
to record their oral temperature on the
evening of their vaccination and in the
morning and evening of the following 6
days and to record systemic symptoms
and local adverse reactions for 13 days af-
ter vaccination. They were instructed to
assess the maximal diameter of any red-
ness or swelling at the site of injection us-
ing a measurement tool consisting of
circles of varying diameters (2.5, 5.1, and
10.2 cm [1, 2, and 4 in]) printed on a
transparency sheet. The maximal area of
redness or swelling was that which could
not be encompassed by the largest circle
and was recorded as greater than 10.2 cm
(4 in). Participants were also asked
whether they had sought medical atten-
tion for an adverse reaction during the fol-
low-up period. They were contacted by
telephone at 1, 5, and 12 days after their
vaccination to remind them to complete
and return their study diaries.

Participants’ primary care physicians
were notified by letter of their patient’s
enrollment and asked to contact the study
investigator if the participant was evalu-
ated for an adverse event after vaccina-
tion. To identify medical evaluations that
may not have been reported by either the
participant or the physician, GHC data-
bases recording outpatient visits and hos-
pitalsizations were used to identify en-
counters that occurred within 13 days
after vaccination. In the outpatient da-
tabase, visits are associated with up to 2
ICD-9–coded diagnoses. Visits without
an associated diagnosis and visits asso-
ciated with a diagnosis possibly indica-
tive of an injection site reaction (eg, der-
matitis, shoulder region disease) were
identified. The hard copy medical rec-
ords for these patients, as well as for pa-
tients hospitalized during the fol-
low-up period, were obtained for review.

Study procedures were approved by
GHC and CDC institutional review boards.
A 10-mL blood specimen was col-
lected prior to vaccination from all the
participants; a random 25% of partici-
pants were selected at the time of enroll-
ment for a 28-day postvaccination blood
draw. Serotype-specific antcapsular IgG
antibody to serotypes 4, 14, and 23F was
measured in a blinded fashion using a
modified enzyme-linked immunosor-
bent assay protocol as previously de-
scribed\textsuperscript{14} on a subset of serum speci-
mens selected to include participants both with and without local adverse reactions after vaccination.

The significance of any difference in means was tested using the t test and differences in proportions were assessed using the χ² statistic. Fisher exact 2-tailed P values were reported and were unadjusted for multiple comparisons. Geometric mean concentrations were calculated after log transformation. Tests for trend to assess any increase in prevacination titers with significant local adverse reactions were performed after dividing the sample into quartiles based on the distribution of the first vaccination values. Multivariate analysis was conducted using conditional logistic regression.

RESULTS

A total of 5012 persons identified as potentially eligible were sent an introductory letter. Of those, 890 (18%) were not subsequently contacted, 641 (13%) were contacted and determined to be ineligible, and 3481 (69%) were confirmed eligible. Of those eligible, 1543 (44%) of the 3481 consented to participate and 1435 were enrolled. Of those enrolled, 1420 (99%) returned completed study diaries. Six subjects were identified as ineligible after enrollment: 2 were revaccinated less than 5 years after first vaccination, 1 had received 2 prior vaccinations, and 3 had received the 14-valent vaccine. None of these 6 had severe or unusual adverse events following vaccination but were excluded from this analysis. Postvaccination follow-up was therefore available for 1414 eligible subjects (513 were revaccinated and 901 received their first vaccination) (TABLE 1).

Adverse Events

No serious or unexpected adverse events associated with vaccination were identified. One participant died of cardiac arrest resulting from preexisting coronary artery disease, and 3 persons were hospitalized for causes unrelated to vaccination during the follow-up period.

Three participants indicated in their study diary that they had sought medical care for an adverse event following vaccination; these charts were reviewed. One participant (a healthy immunocompetent revaccinated patient) presented for outpatient evaluation of swelling and redness at the injection site 2 days after vaccination. The subject was afebrile, was noted to have a swelling from the deltoid region to the mid forearm, and was instructed to take diphenhydramine hydrochloride and erythromycin. Two participants were evaluated for a rash after vaccination. One had a diffuse papulovesicular rash on the trunk with onset 7 days after his first vaccination; pathologic finding of a punch biopsy was interpreted as superficial perivascular and interstitial dermatitis. The other subject developed a maculopapular rash on the buttocks 1 week after revaccination; a biopsy specimen was not obtained.

An additional 456 participants had at least 1 outpatient visit during the follow-up period recorded in the automated GHC databases. The majority of these visits were assigned diagnoses that were not consistent with a vaccine reaction. Review of medical records available for 44 of the 48 visits that either had no associated diagnosis or had a diagnosis possibly indicative of a local reaction identified no adverse events potentially related to vaccination.

Events Reported by Study Diary

Systemic symptoms after vaccination were reported by a similar proportion of patients who had been revaccinated and those who had received their first vaccination (TABLE 2). Elevated temperature was infrequently reported in the 6 days following vaccination. At the time of enrollment, a substantial proportion of participants reported the presence of systemic symptoms during the preceding week: 17% reported fatigue, 25% muscle aches, 36% joint pain, 15% headache, and 5% rash.

Local injection site reactions were significantly more common among those who had been revaccinated and were most often reported within the first 2 days after vaccination (TABLE 3). Within the first 2 days following vaccination, arm soreness was the most commonly reported symptom (74% of revaccinated patients vs 57% of patients vaccinated for the first time) (relative risk [RR], 1.3; 95% confidence interval [CI], 1.2-1.4) and persisted until days 3 to 6 after vaccination in a minority of subjects (17% of revaccinated patients vs 11% of patients vaccinated for the first time) (RR, 1.5; 95% CI, 1.2-2.0).

To further examine the association of revaccination and local adverse reactions, a sizable local adverse reaction was defined as at least 10.2 cm (4 in) of redness or swelling within 2 days of vaccination. Patients who were revaccinated were significantly more likely to have a sizable local reaction (TABLE 4). Of the 84 participants who reported a sizable local reaction, 10 (12%) also reported severe limitation of arm movement and 15 (18%) reported severe arm soreness within 2 days of vaccination.
In a conditional logistic regression model controlling for age, revaccination status, presence of immunocompromising or chronic underlying conditions, and sex, revaccination was independently associated with a sizable local reaction (odds ratio [OR], 3.6; 95% CI, 2.3-5.7). Among revaccinated immunocompetent patients, risk of a sizable local reaction did not significantly vary by number of years since first vaccination (Figure). Subjects with sizable local reactions reported complete resolution of redness and swelling at the injection site by a median of 3 days (range, 1-8 days) after vaccination. The duration to complete resolution did not vary by vaccination status.

### Serologic Results

Among immunocompetent healthy subjects, prevaccination geometric mean concentrations to serotypes 4, 14, and 23F tended to be higher among the previously vaccinated group (Table 5). In general, an increase in geometric mean concentration following the study vaccination was demonstrated among both those receiving their first vaccination and those being revaccinated. Quartile distributions of antibody concentrations were defined for each serotype based on the distribution of prevaccination concentrations among those who were vaccinated for the first time. For all 3 serotypes, the trend toward a higher risk of a sizable local reaction in the higher quartiles was either statistically significant or bordered on significance among both groups (Table 6). Postvaccination antibody concentrations were not related to risk of local injection site reactions (data not shown).

### Comment

Among our study population of elderly and high-risk adults, local injection site reactions were commonly reported following both first vaccination and revaccination (≥5 years after first vaccination) with PPV. The rate of these reactions was, however, significantly higher among patients who had been revaccinated. Specifically, revaccination was associated with an approximately 3-fold higher risk of a sizable local reaction, defined as an area of redness or swelling at the injection site, cm

### Table 2. Proportion of Subjects Reporting Systemic Symptoms or Elevated Temperature, by Day Since Vaccination and by Vaccination Status*

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Days 0-2</th>
<th>Days 3-6</th>
<th>Days 7-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Vaccination</td>
<td>Revaccination</td>
<td>First Vaccination</td>
<td>Revaccination</td>
</tr>
<tr>
<td>Nausea</td>
<td>32 (4)</td>
<td>28 (5)</td>
<td>33 (4)</td>
</tr>
<tr>
<td>Headache</td>
<td>102 (11)</td>
<td>70 (13)</td>
<td>97 (11)</td>
</tr>
<tr>
<td>Rash</td>
<td>33 (4)</td>
<td>20 (4)</td>
<td>16 (2)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>78 (9)</td>
<td>50 (10)</td>
<td>66 (7)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>101 (11)</td>
<td>75 (15)</td>
<td>90 (10)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>121 (13)</td>
<td>89 (18)</td>
<td>108 (12)</td>
</tr>
<tr>
<td>Temperature ≥37.5°C (99.5°F)</td>
<td>68 (8)</td>
<td>53 (10)</td>
<td>67 (7)</td>
</tr>
<tr>
<td>Temperature ≥38.6°C (101.5°F)</td>
<td>4 (0.4)</td>
<td>4 (1)</td>
<td>2 (0.2)</td>
</tr>
</tbody>
</table>

*P < .05 for all comparisons of revaccination (n = 513) vs first vaccination (n = 901). NR indicates not recorded. All data are presented as number (percentage).

### Table 3. Proportion of Subjects With Local Adverse Reactions, by Interval Following Vaccination and by Vaccination Status*

<table>
<thead>
<tr>
<th>Maximal diameter of redness or swelling at the injection site, cm</th>
<th>Days 0-2</th>
<th>Days 3-6</th>
<th>Days 7-13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>190 (21)</td>
<td>196 (38)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥5.08 [2 in]</td>
<td>87 (10)</td>
<td>126 (25)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥7.62 [3 in]</td>
<td>53 (6)</td>
<td>93 (18)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥10.2 [4 in]</td>
<td>29 (3)</td>
<td>55 (11)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any tenderness at site</td>
<td>460 (51)</td>
<td>352 (69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any soreness in arm</td>
<td>515 (57)</td>
<td>380 (74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe soreness in arm</td>
<td>20 (2)</td>
<td>25 (5)</td>
<td>.01</td>
</tr>
<tr>
<td>Any limitation of arm movement</td>
<td>163 (18)</td>
<td>167 (32)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Moderate or greater limitation of arm movement (cannot raise above head)</td>
<td>25 (3)</td>
<td>50 (10)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Severe limitation of arm movement (cannot raise above shoulder)</td>
<td>7 (1)</td>
<td>25 (5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Data are presented as number (percentage) of subjects first vaccinated (n = 901) and revaccinated (n = 513).
redness or swelling at least 10.2 cm (4 in) in diameter. These reactions were self-limited and resolved by a median of 3 days after vaccination. The risk of a sizable local reaction was highest among revaccinated immunocompetent healthy patients (15%) and was approximately 5-fold higher than among the comparable group of patients who were vaccinated for the first time. We found that the risk of a sizable local reaction correlated with higher concentrations of prevaccination type-specific antibody, among both patients who had been vaccinated for the first time and those revaccinated. This association has been previously reported and is consistent with the occurrence of a localized Arthus-type reaction (type 3 hypersensitivity reaction), caused by formation of antibody-antigen complexes at the injection site. We did not identify any serious adverse events associated with vaccination among either group, a finding that is consistent with the previously established safety profile of this vaccine.8,14,15,18,20

The results of 3 previous studies of adults revaccinated with the 23-valent pneumococcal vaccine at least 5 years after their first vaccination11,12 have not been interpreted as indicative of an elevated risk of local injection site reactions following revaccination.3 However, several features of the design of these 3 studies conferred a limited ability to identify a significant increase in the risk of local reactions among patients who had been revaccinated compared with those who had been vaccinated for the first time. All of the studies had small sample sizes (15,11,12 and 127 revaccinated patients, respectively) and 2 did not include a concurrently enrolled comparison group.3,11 In addition, none of the 3 studies attempted to characterize local injection site reactions quantitatively.

In our study, the risk of a sizable local injection site reaction was not associated with duration since first vaccination. This suggests that extending the minimum interval between first vaccination and revaccination may not be necessary to further reduce the risk of reactions. The results of our study support those of a previous study3 that found a high incidence of reactions among patients who had been revaccinated after 5 years.12,13

Table 4. Risk of a Sizable Local Reaction (≥10.2 cm [4 in] of Redness or Swelling), by Vaccination Status and Underlying Disease Classification*

<table>
<thead>
<tr>
<th>Population</th>
<th>First Vaccination</th>
<th>Revaccination</th>
<th>RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>29/901 (3)</td>
<td>55/513 (11)</td>
<td>3.3 (2.1-5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Immunocompromised†</td>
<td>3/85 (4)</td>
<td>3/50 (6)</td>
<td>1.7 (0.4-8.1)</td>
<td>.67</td>
</tr>
<tr>
<td>Chronically ill‡</td>
<td>16/479 (5)</td>
<td>19/235 (8)</td>
<td>2.4 (1.3-4.6)</td>
<td>.009</td>
</tr>
<tr>
<td>Healthy§</td>
<td>10/337 (3)</td>
<td>39/228 (15)</td>
<td>4.9 (2.4-9.7)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*RR indicates relative risk, CI, confidence interval.
†Patients with asplenia, renal failure, lymphoma, myeloma, renal transplant, nephrotic syndrome, or taking immuno-suppressive medications.
‡Patients with chronic cardiovascular or pulmonary disease, diabetes mellitus, or cirrhosis.
§Patients who were not chronically ill or immunocompromised.

Table 5. Geometric Mean (95% Confidence Intervals) Concentrations (µg/mL) of Antibodies to Serotypes 4, 14, and 23F

<table>
<thead>
<tr>
<th>Population</th>
<th>First Vaccination</th>
<th>Revaccination</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>(n = 60)</td>
<td>(n = 82)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.7 (2.1-3.5)</td>
<td>3.0 (2.5-3.6)</td>
<td>.46</td>
</tr>
<tr>
<td>14</td>
<td>4.7 (3.5-6.3)</td>
<td>9.7 (7.3-12.9)</td>
<td>.001</td>
</tr>
<tr>
<td>23F</td>
<td>3.4 (2.7-4.3)</td>
<td>5.5 (4.4-6.9)</td>
<td>.006</td>
</tr>
<tr>
<td>Immunocompromised</td>
<td>(n = 8)</td>
<td>(n = 6)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.0 (0.7-6.2)</td>
<td>3.1 (1.2-7.8)</td>
<td>.49</td>
</tr>
<tr>
<td>14</td>
<td>2.2 (1.0-5.7)</td>
<td>7.1 (0.9-55.3)</td>
<td>.18</td>
</tr>
<tr>
<td>23F</td>
<td>3.4 (1.5-7.4)</td>
<td>7.3 (2.3-21.3)</td>
<td>.18</td>
</tr>
<tr>
<td>Immunocompetent chronically ill</td>
<td>(n = 23)</td>
<td>(n = 26)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3.4 (2.3-5.2)</td>
<td>3.4 (2.2-8.1)</td>
<td>.96</td>
</tr>
<tr>
<td>14</td>
<td>6.3 (4.0-9.9)</td>
<td>12.1 (6.1-23.8)</td>
<td>.09</td>
</tr>
<tr>
<td>23F</td>
<td>4.6 (3.1-6.8)</td>
<td>6.4 (3.8-10.9)</td>
<td>.29</td>
</tr>
<tr>
<td>Immunocompetent healthy</td>
<td>(n = 29)</td>
<td>(n = 56)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.4 (1.7-3.4)</td>
<td>2.9 (2.3-3.6)</td>
<td>.35</td>
</tr>
<tr>
<td>14</td>
<td>4.5 (2.9-7.1)</td>
<td>9.3 (6.8-12.8)</td>
<td>.009</td>
</tr>
<tr>
<td>23F</td>
<td>2.7 (1.9-3.8)</td>
<td>5.0 (3.8-6.6)</td>
<td>.007</td>
</tr>
</tbody>
</table>

*All subjects with postvaccination results are included in the prevaccination group, but some subjects with prevaccination sera results did not have postvaccination sera tested.
cination beyond 5 years would not significantly reduce the frequency of local adverse reactions following revaccination.

Limitations of our study include the lack of an unvaccinated or placebo comparison group, which would have allowed for correction for background rates of events, a factor that is most relevant for reported systemic symptoms. Another limitation was the lack of blinding to vaccination status, with the attendant potential for bias in the ascertainment or reporting of adverse events. Quantification of adverse events and the high rate (99%) of return of study diaries should have, however, decreased the potential for these types of biases. Finally, our sample size of 1414 participants did not provide adequate power to detect rare adverse events that may be associated with vaccination.

What is the significance of these findings for patient care? Revaccination administered in accordance with the current recommendations is associated with a higher rate of self-limited injection site reactions compared with first vaccination. Physicians should be aware of the expected frequency and severity of these reactions and should inform patients of this risk during the informed consent process. When comparing the risks and benefits of revaccination, however, we do not believe that the risk of these reactions outweighs the potential benefits of protection from invasive pneumococcal infection. The risk of local reactions should not, therefore, be interpreted as a contraindication to revaccination in accordance with current recommendations.

Furthermore, these results do not suggest that inadvertent revaccination of adults aged 50 years or older, as may occur if vaccination is provided to persons with incomplete documentation of prior vaccination status, is likely to be associated with a substantive risk of serious or significant adverse events. These results may therefore serve to lower barriers to appropriate vaccination of persons at increased risk of invasive pneumococcal infection.

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