ORIGINAL CONTRIBUTION

Safety of Revaccination With Pneumococcal Polysaccharide Vaccine

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Context Revaccination of healthy adults with pneumococcal polysaccharide vaccine (PPV) within several years of first vaccination has been associated with 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 prevaccination 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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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.[1] Evidence that postvaccination antibody levels[2-5] and protective efficacy[6] 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]: (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 following revaccination of healthy adults within 2 years of their first vaccination.[7,8] Subsequent studies of children with sickle cell disease[9] and healthy children[10] revaccinated approximately 3 to 4 years after their first vaccination also reported higher rates of local adverse reactions and fever. Conversly, 3 studies of adults revaccinated after an interval of at least 5 years did not report a significantly higher

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risk of adverse events following revaccination.[3,11,12] However, because 2 of the studies had a small sample size and 1 lacked an appropriate comparison group their ability to identify increased risk may be limited.

To better define currently recommended expected risk of adverse events among persons revaccinated,[1] we prospectively enrolled more than 1400 persons between the ages of 50 and 74 years and compared postvaccination events among persons being revaccinated after 5 or more years with those being vaccinated for the first time.

METHODS

Study Population

Participants, members of Group Health Cooperative (GHC) of Puget Sound, Seattle, Wash, were enrolled between April 1996 and August 1997. Eligibility required 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 criteria recommends pneumococcal vaccination.[1] Among those groups, persons were eligible for first vaccination if they had never received pneumococcal vaccine and had been continuously enrolled at GHC since 1983 (to allow complete ascertainment of immunization status since licensure of the 23-valent vaccine). Persons were eligible for revaccination if they had exactly 1 prior documented vaccination with the 23-valent vaccine (≥5 years prior to study enrollment) and did not report a significant adverse event.

Vaccination status was initially determined through GHC computerized immunization registries, an online record system maintained since its 1991 development in conjunction with the CDC's Vaccine Safety Datalink Project.[13] Vaccination data are entered online and on medical charts on the day of administration. Between 1983 and 1990, vaccinations were recorded in the chart and 1 copy forwarded for entry into a pharmacy-based registry. Both registries were used for initial determining vaccination status, which was verified by interview of all subjects. Discrepancies were resolved by reviewing the medical chart.

Medical conditions indicated for vaccination were indicated by an *International Classification of Diseases, Ninth Revision (ICD-9)* computer databases of hospitalization discharge diagnoses and diagnoses of outpatient and emergency department visits and GHC pharmacy prescriptions. 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 immunocompromised if they had any of the following: asplenia, leukemia, lymphoma, Hodgkin disease, multiple myeloma, generalized malignancy, chronic renal failure, nephrotic syndrome, immunosuppressive chemotherapy, and organ or bone marrow transplant. Persons without these conditions (immunocompetent) were further classified based on other chronic underlying conditions. Immunocompetent participants with diabetes, cardiac disease, pulmonary disease, or cirrhosis were classified as chronically ill, and immunocompetent participants without those conditions were classified as healthy.

Study Procedures

Persons potentially eligible for enrollment from these databases were sent a letter informing them of the study and were then contacted by telephone. Persons confirmed as eligible were scheduled for an enrollment visit, during which they were vaccinated intramuscularly in the left deltoid, using a 1.6-cm (⅝-in) needle, with 0.5 mL of a single lot (lot 432683) of 23-valent pneumococcal vaccine (Pnu-Immune; Lederle Laboratories, Pearl River, NY) containing 25 µg/dose of each capsular 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 after vaccination. They were instructed to assess the maximal diameter of any redness or swelling at the site of injection using 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 attention for an adverse reaction during the follow-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 evaluated for an adverse event after vaccination. To identify medical evaluations that may not have been reported by either the participant or the physician, GHC databases recording outpatient visits and hospitalizations were used to identify encounters that occurred within 13 days after vaccination. In the outpatient database, visits are associated with up to 2 *ICD-9*–coded diagnoses. Visits without an associated diagnosis and visits associated with a diagnosis possibly indicative of an injection site reaction (eg, dermatitis, shoulder region disease) were identified. The hard copy medical records for these patients, as well as for patients hospitalized during the follow-up period, were obtained for review.

Study procedures were approved by GHC and CDC institutional review boards.

A 10-mL blood specimen was collected prior to vaccination from all the participants; a random 25% of participants were selected at the time of enrollment for a 28-day postvaccination blood draw. Serotype-specific anticapsular IgG antibody to serotypes 4, 14, and 23F was measured in a blinded fashion using a modified enzyme-linked immunosorbent assay protocol as previously described[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 χ^2 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 relation of increasing prevaccination 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 as 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.

Table 1. Characteristics of 1414 Study Participants by Vaccination Status

Characteristic	First Vaccination, No. (%) (n = 901)	Revaccination, No. (%) (n = 513)	*P* Value
Male	501 (56)	229 (45)	<.001
White	819 (91)	480 (94)	.09
Age, y			
50-64	129 (14)	86 (17)	.22
65-74	772 (86)	427 (83)	
Immunocompromised*	85 (9)	50 (10)	.02§
Immunocompetent			
Chronically ill†	479 (53)	235 (46)	
Healthy‡	337 (37)	228 (44)	
Years since first vaccination, median (range)	NA	6 (5-13)	

*Patients with asplenia, renal failure, lymphoma, myeloma, renal transplant, or nephrotic syndrome, or who were taking immunosuppressive medications.
†Patients with chronic cardiovascular or pulmonary disease, diabetes mellitus, or cirrhosis.
‡Patients who were not chronically ill or immunocompromised.
§χ^2 Test for multiple proportions.

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

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

	Days 0-2		Days 3-6		Days 7-13	
Adverse Reactions	First Vaccination	Revaccination	First Vaccination	Revaccination	First Vaccination	Revaccination
Nausea	32 (4)	28 (5)	33 (4)	17 (3)	18 (2)	16 (3)
Headache	102 (11)	70 (13)	97 (11)	57 (11)	85 (10)	39 (8)
Rash	33 (4)	20 (4)	16 (2)	15 (3)	13 (1)	5 (1)
Myalgia	78 (9)	50 (10)	66 (7)	33 (7)	62 (7)	27 (5)
Arthralgia	101 (11)	75 (15)	90 (10)	57 (11)	76 (8)	40 (8)
Fatigue	121 (13)	89 (18)	108 (12)	59 (12)	73 (8)	47 (9)
Temperature ≥37.5°C (99.5°F)	68 (8)	53 (10)	67 (7)	37 (7)	NR	NR
Temperature ≥38.6°C (101.5°F)	4 (0.4)	4 (1)	2 (0.2)	5 (1)	NR	NR

*$P > .05$ 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*

	Days 0-2			Days 3-6			Days 7-13		
	First Vaccination	Revaccination	*P*	First Vaccination	Revaccination	*P*	First Vaccination	Revaccination	*P*
Maximal diameter of redness or swelling at the injection site, cm									
Any	190 (21)	196 (38)	<.001	49 (5)	44 (9)	.03	12 (1)	6 (1)	>.99
≥5.08 [2 in]	87 (10)	126 (25)	<.001	20 (2)	31 (6)	<.001	0 (0)	2 (0.4)	.13
≥7.62 [3 in]	53 (6)	93 (18)	<.001	13 (1)	19 (4)	.008	0 (0)	1 (0.2)	.36
≥10.2 [4 in]	29 (3)	55 (11)	<.001	5 (1)	10 (2)	.03	0 (0)	1 (0.2)	.36
Any tenderness at site	460 (51)	352 (69)	<.001	92 (10)	75 (15)	.02	15 (2)	6 (1)	.50
Any soreness in arm	515 (57)	380 (74)	<.001	100 (11)	87 (17)	.002	23 (3)	11 (2)	.72
Severe soreness in arm	20 (2)	25 (5)	.01	1 (0.1)	0 (0)	>.99	1 (0.1)	0 (0)	>.99
Any limitation of arm movement	163 (18)	167 (32)	<.001	28 (3)	23 (5)	.19	9 (1)	5 (1)	>.99
Moderate or greater limitation of arm movement (cannot raise above head)	25 (3)	50 (10)	<.001	1 (0.1)	1 (0.2)	>.99	1 (0.1)	1 (0.2)	>.99
Severe limitation of arm movement (cannot raise above shoulder)	7 (1)	25 (5)	<.001	0 (0)	0 (0)	Undefined	0 (0)	0 (0)	Undefined

*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[10,12,15-17] 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 vaccination[3,11,12] have not been interpreted as indicative of an elevated risk of local injection site reactions following revaccination.[1] 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,[3] 26,[11] and 127[12] revaccinated patients, respectively) and 2 did not include a concurrently enrolled comparison group.[3,13] In addition, none of the 3 studies attempted to characterize local injection site reactions quantitatively.

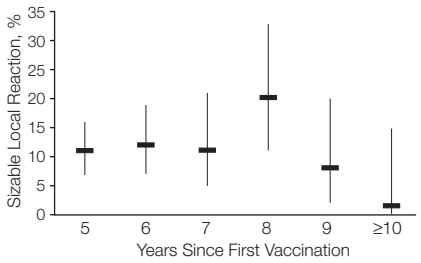
In our study, the risk of a sizable local injection site reaction was not associated with duration since first vaccination. This suggests that extending the minimum interval between first vaccination and revac-

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

Population	No. (%) of Subjects		RR (95% CI)	*P* Value
	First Vaccination	Revaccination		
All subjects	29/901 (3)	55/513 (11)	3.3 (2.1-5.1)	<.001
Immunocompromised†	3/85 (4)	3/50 (6)	1.7 (0.4-8.1)	.67
Immunocompetent	26/816 (3)	52/463 (11)	3.5 (2.2-5.6)	<.001
Chronically ill‡	16/479 (3)	19/235 (8)	2.4 (1.3-4.6)	.009
Healthy§	10/337 (3)	33/228 (15)	4.9 (2.4-9.7)	<.001

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

Figure. Risk of Sizable Local Reaction Following Revaccination as a Function of Years Since First Vaccination



Proportion of immunocompetent revaccinated patients (point estimate and mid *P* 95% confidence interval) with sizable local reactions (≥10.2 cm [4 in] redness or swelling within 2 days of vaccination), by years since first vaccination.

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

Population	Serotype	Prevaccination		*P*	Postvaccination*		*P*
		First Vaccination	Revaccination		First Vaccination	Revaccination	
All subjects		(n = 60)	(n = 82)		(n = 54)	(n = 65)	
	4	2.7 (2.1-3.5)	3.0 (2.5-3.6)	.46	4.7 (3.7-5.9)	3.8 (3.1-4.7)	.17
	14	4.7 (3.5-6.3)	9.7 (7.3-12.9)	.001	20.9 (15.1-29.1)	13.4 (9.8-18.4)	.05
	23F	3.4 (2.7-4.3)	5.5 (4.4-6.9)	.006	8.3 (6.4-10.8)	7.4 (5.8-9.4)	.50
Immunocompromised		(n = 8)	(n = 6)		(n = 7)	(n = 6)	
	4	2.0 (0.7-6.2)	3.1 (1.2-7.8)	.49	4.3 (1.7-10.4)	5.3 (2.3-12.1)	.67
	14	2.2 (1.0-5.7)	7.1 (0.9-55.3)	.18	9.2 (2.0-42.6)	15.4 (1.9-120.3)	.62
	23F	3.4 (1.5-7.4)	7.3 (2.3-23.1)	.18	6.7 (2.3-18.9)	14.0 (6.7-29.2)	.19
Immunocompetent chronically ill		(n = 23)	(n = 20)		(n = 20)	(n = 16)	
	4	3.4 (2.3-5.2)	3.4 (2.2-5.1)	.96	6.4 (4.4-9.4)	4.6 (3.1-6.8)	.22
	14	6.3 (4.0-9.9)	12.1 (6.1-23.8)	.09	28.4 (17.4-46.3)	18.9 (10.2-35.4)	.28
	23F	4.6 (3.1-6.8)	6.4 (3.8-10.9)	.29	12.4 (8.6-17.9)	8.6 (5.8-12.6)	.15
Immunocompetent healthy		(n = 29)	(n = 56)		(n = 27)	(n = 43)	
	4	2.4 (1.7-3.4)	2.9 (2.3-3.6)	.35	3.8 (2.8-5.3)	3.4 (2.6-4.4)	.54
	14	4.5 (2.9-7.1)	9.3 (6.8-12.8)	.009	20.7 (13.3-32.3)	11.6 (8.1-16.7)	.05
	23F	2.7 (1.9-3.8)	5.0 (3.8-6.6)	.007	6.6 (4.4-9.7)	6.4 (4.6-8.8)	.91

*All subjects with postvaccination results are included in the prevaccination group, but some subjects with prevaccination sera results did not have postvaccination sera tested.

Table 6. Proportion of Subjects With Sizable Local Reactions, by Quartile Distribution of Type-Specific Prevaccination Antibody Concentrations and by Vaccination Status

	No. (%) of Subjects					
	Type 4		Type 14		Type 23F	
Quartile*	First Vaccination	Revaccination	First Vaccination	Revaccination	First Vaccination	Revaccination
1	0/16 (0)	1/15 (7)†	2/15 (13)	0/9 (0)	2/15 (13)	2/14 (14)
2	4/14 (29)	6/20 (30)	1/15 (7)	3/14 (21)	2/15 (13)	2/10 (20)
3	2/15 (13)	9/28 (32)	2/15 (13)	8/21 (38)	3/15 (20)	4/18 (22)
4	7/15 (47)	12/19 (63)	8/15 (53)	17/38 (45)	6/15 (40)	20/40 (50)
χ^2 Test for trend *P* value	.006	.001	.008	.007	.07	.007

*Quartiles defined by distribution of prevaccination antibody concentrations in micrograms per milliliter among first vaccinations. Type 4: 1, 0.4-1.4; 2, 1.5-2.6; 3, 2.7-5.1; 4, 5.2-19.0. Type 14: 1, 0.4-1.8; 2, 1.9-4.9; 3, 5.0-11.6; 4, 11.7-18.6. Type 23F: 1, 0.5-1.6; 2, 1.7-3.2; 3, 3.3-6.3; 4, 6.4-26.2.
†*P*>.05 for all comparisons of first vaccination vs revaccination within each type-specific quartile distribution.

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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