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Reactivity and Antibody Responses of Volunteers Given Two or Three Doses of Pneumococcal Vaccine (41934)

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Abstract. Pneumococcal antibody responses and adverse reactions were assessed in 12 healthy volunteers who received either two (10 volunteers) or three (2 volunteers) doses of pneumococcal polysaccharide vaccines at 1 or 2 year intervals. The volunteers were given hexavalent (types 1, 3, 4, 7F, 8, 12F) octavalent (types 14, 19F added) nonavalent (type 5 added), and tridecavalent (types 6A, 6B, 9N, 18C, 23F added; type 5 removed) pneumococcal vaccines. Local and systemic reactions following any of the vaccines, either first, second, or third doses, were low, and these were mild; fever did not occur. Twelve volunteers received types 1, 3, 4, 7F, 8, and 12F in two doses of vaccine, and four volunteers received types 14 and 19F in two doses of vaccine. Primary immunization induced significant antibody rises to these antigens in most volunteers, but a second dose of vaccine did not further increase antibody levels to the same antigens; when it also contained new antigens, antibody rises usually developed to these antigens. Although the data are limited to detailed studies of only 12 persons, the results suggest that additional studies of this issue would seem appropriate.

The pneumococcal polysaccharide vaccine licensed in 1977 contained purified polysaccharide antigens of 14 capsular types that commonly caused bacteremic disease among children and adults (1). Recently, the composition of pneumococcal vaccine was revised, and the 14-valent pneumococcal vaccine has been replaced by a 23-valent vaccine. This change was made to broaden protection by including additional capsular antigens and to improve the stability of certain antigens. Our previous studies showed that pneumococcal antibody measured by radioimmunoassay persists at increased levels for at least 5 years after administration of pneumococcal vaccine (2).

The previous guidelines for the use of pneumococcal vaccine in high risk persons indicate that repeat immunization need not be carried out sooner than 5 years after the initial administration of vaccine (3). The guidelines for pneumococcal vaccine usage, however, also caution against repeated immunization at any time (1). This recommendation has support from the results of one study which reported that readministration of pneumococcal vaccine was associated with increased adverse reactions (4). The introduction of a 23-valent pneumococcal vaccine, however, poses a dilemma for the physician; namely, should persons who have been immunized with the 14-valent vaccine be given the 23-valent vaccine? In an attempt to provide data to answer this question, we have examined the occurrence of adverse reactions and the levels of antibodies in volunteers who received two or three pneumococcal vaccines as participants in several trials of the antigenicity of pneumococcal vaccine.

Materials and Methods. *Study population.* Healthy volunteers were recruited from the cadre of office workers and students at the West Side Veterans Administration Medical Center in Chicago, Illinois, as previously described (2). Their ages when they first volunteered ranged from 22 to 38 years (median 26 years). Volunteers were informed on each occasion of the nature of the vaccine evaluation, and they consented to participate. These studies had the approval of the Human Studies Committee of the West Side Veterans Administration Medical Center and, subsequently, also the Human Studies Committee of the Veterans Administration Medical Center, Huntington, West Virginia.

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TABLE I. COMPOSITION AND SCHEME OF ADMINISTRATION OF PNEUMOCOCCAL VACCINES

Vaccine composition	Capsular type (Danish nomenclature)													Number who received vaccine	
														First	Second
Hexavalent	1	3	4	7F	8	12F								10 (2)[a]	1
Octavalent	1	3	4	7F	8	12F	14	19F						1	3 (2)
Nonavalent	1	3	4	7F	8	12F	14	19F	5					1	4
Tridecavalent	1	3	4	7F	8	12F	14	19F		6A	6B	9N	18C	23F	0	4 (2)[b]

[a] Number who received pneumococcal vaccine combined with inactivated influenza virus types A2/Aichi/2/68 and B/Mass/1/61.

[b] Two volunteers received tridecavalent-influenza vaccine as third vaccine.

We immunized 12 volunteers with two or three pneumococcal vaccines during three vaccine trials conducted at approximately 13-month intervals starting in October 1973. At that time, volunteers could participate in reimmunization if a 1-year interval had elapsed since the previous receipt of pneumococcal vaccine. Ten persons received two pneumococcal vaccines and two persons received three pneumococcal vaccines. Eight volunteers received their second pneumococcal vaccine 1 year after the first vaccine, and four volunteers received their second vaccine 2 years later. The third vaccine was given 1 year after the second vaccine to only two persons.

Vaccines and immunization. The four different polyvalent pneumococcal vaccines (kindly provided by Lederle Laboratories) employed in these vaccine trials were a hexavalent vaccine of types 1, 3, 4, 7F, 8, and 12F; an octavalent vaccine of types 1, 3, 4, 7F, 8, 12F, 14, and 19F; a nonavalent vaccine of types 1, 3, 4, 7F, 8, 12F, 14, 19F, and 5; and, a tridecavalent preparation of types 1, 3, 4, 7F, 8, 12F, 14, 19F, 6A, 6B, 9N, 18C, and 23F (Table I). As a consequence, 12 volunteers received types 1, 3, 4, 7F, 8, and 12F twice, and 2 of these 12 volunteers received these types three times; 4 of the volunteers received types 14 and 19F twice; none of the volunteers received types 6A, 6B, 9N, 18C, and 23F twice (Table II). We monitored local and systemic reactions 24, 48, and 72 hr after administration of vaccine (5).

Antibody determinations. Type-specific antibody levels were determined before and 1 month after administration of vaccine by using radioimmunoassay (RIA) techniques as previously described (3, 5, 6). Antibody levels were expressed as nanograms of antibody nitrogen per milliliter. Twofold or greater rises were considered as significant (2, 4). All serum specimens were tested simultaneously in two successive assays. For technical reasons, antibody was not determined to type 5. Antibody to type 6B was not determined since the 6A and 6B polysaccharides exhibit extensive cross-reactivity (7).

Statistical analyses. Statistical tests were done by employing statistical analysis software (Stats Plus, from Human Systems Dynamics, Northridge, Calif.) and an Apple II+ microcomputer. Mean pre- and postvaccine antibody responses by capsular type after the

TABLE II. NUMBER OF VACCINEES RECEIVING MULTIPLE DOSES OF PNEUMOCOCCAL VACCINE BY CAPSULAR TYPE

Number of doses of antigen	Number of volunteers who received indicated capsular type													
	1	3	4	7F	8	12F	14	19F	5	6A	6B	9N	18C	23F
1	12	12	12	12	12	12	11	11	5	6	6	6	6	6
2	12	12	12	12	12	12	4	4	0	0	0	0	0	0
3	2	2	2	2	2	2	0	0	0	0	0	0	0	0

first and second pneumococcal vaccines were compared using paired t tests.

Results. Most of the 12 volunteers who received two doses of capsular antigens of types 1, 3, 4, 7F, 8, and 12F developed twofold or greater rises after the first dose, but very few developed rises in levels of antibody following the second dose of polysaccharide antigen (Table III). None of the four volunteers who received two doses of types 14 and 19F developed rises in antibody to those types after the second dose. The fewest rises in antibody were detected to capsular type 12; 5 of 12 volunteers failed to develop even twofold rises after two doses of antigen. Eleven of the twelve volunteers had twofold or greater rises to four or more capsular types (types 1, 3, 4, 7F, 8, and 12F), but following receipt of the second vaccine, only one volunteer had twofold rises to four of these same capsular types.

When antibody responses to individual capsular types 1, 3, 4, 7F, 8, and 12F were analyzed after the first and second doses of pneumococcal vaccines, the level of antibody detected before administration of the second vaccine was in the range of antibody values exhibited by volunteers who developed at least a twofold rise after the first vaccine, and a further rise in antibody did not occur (Fig. 1). Too few volunteers received two doses of types 14 and 19 to analyze the antibody responses to these types in this manner.

TABLE III. FREQUENCY OF PNEUMOCOCCAL ANTIBODY RISES BY CAPSULAR TYPE AMONG VOLUNTEERS WHO RECEIVED TWO DOSES OF PNEUMOCOCCAL VACCINE

Capsular type	Number tested	Twofold or greater rise in pneumococcal antibody		No rise after either dose
		First vaccine	Second vaccine (Number who also had twofold rise after first dose)	
1	12	5	2 (2)	7
3	12	10	1 (1)	2
4	12	5	2 (1)	6
7F	12	11	0	1
8	12	11	1 (1)	1
12F	12	4	1 (0)	7
14	4	2	0	2
19F	4	1	0	3

When types 6A, 9N, 18C, and 23F were included for the first time in the second or third vaccine, three of seven volunteers developed antibody rises to three or four of these types, and three volunteers developed antibody rises to one or two of these types. One of the seven volunteers failed to develop antibody rises to any of these four capsular types.

Following the first dose of pneumococcal vaccine, the mean antibody to types 1, 3, 4, 7F, 8, and 14 increased significantly (paired t test, $P < 0.01$ for types 3, 4, 7F, 8, and 14, and $P = 0.03$ for type 1) (Table IV). After the second dose of pneumococcal vaccine, the mean levels of antibody to any type were not significantly changed.

Adverse reactions were few (Table V). No volunteer developed fever or rash. After the first vaccine, three volunteers had both local pain and tenderness, and one volunteer had the single systemic symptom of malaise. One volunteer had minimal induration for 1 day only. After the second vaccine, three volunteers had systemic findings of malaise or chills, which were mild and lasted only 1 day, associated with symptoms of local pain and tenderness, and three volunteers had both local pain and tenderness. None had induration. One volunteer had local symptoms only after both vaccines. The occurrence of adverse local and systemic reactions was unrelated to levels of antibody to capsular types 1, 3, 4, 7F, 8, and 12F before vaccination with either the first or second pneumococcal vaccine. One of the two volunteers who received three vaccines had local pain and tenderness after the second and third vaccines; the other volunteer had local pain and tenderness, and erythema only after the third vaccine.

Discussion. Repeated immunization with pneumococcal vaccine of 12 healthy volunteers evoked only minimal adverse reactions. The local and systemic reactivity after a second dose of pneumococcal vaccine appeared similar than after the first dose of vaccine. Volunteers who received second doses of pneumococcal vaccine which contained 13 polysaccharide antigens developed more reactions than did volunteers who received octavalent or nonavalent pneumococcal vaccines as a second vaccine. Other vol-

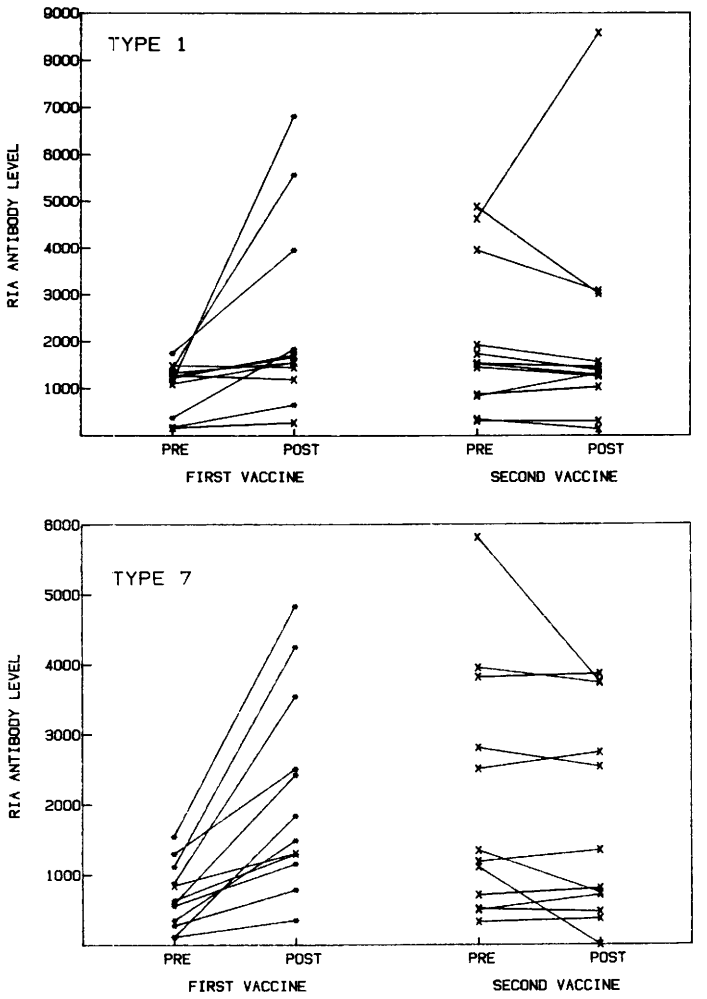

FIG. 1. Type specific pneumococcal antibody responses of volunteers who received two doses of pneumococcal vaccine. Top panel, type 1; bottom panel, type 7F. (* —— *, Twofold rise in antibody; × —— ×, no rise in antibody.)

unteers in these studies (data not shown) who were given only a tridecavalent pneumococcal vaccine manifested local and systemic reactions that were similar in occurrence and intensity to those of volunteers who received the tridecavalent vaccine as a second pneumococcal vaccine.

Our findings differ from those of Borgono and co-workers who reported the occurrence of Arthus-like reactions among volunteers given a second dose of pneumococcal vaccine (4). Seven volunteers who received two doses of a dodecavalent pneumococcal vaccine 13 months apart developed marked local reactions after the second dose of vaccine, but not after the first dose. The reactions consisted mainly of induration, soreness, and erythema; a few volunteers had temperatures between 99 and 99.9°F, but none had fever (temperature greater than 100°F). Infants 3–5 months of age who received two doses of a 12-valent pneumococcal vaccine 6 months apart exhibited only mild reactions after either dose of vaccine. Borgono and co-workers suggested that adverse reactivity after the second dose of vaccine might have been due to a large amount of circulating pneumococcal antibody. However, some of our volunteers with

TABLE IV. PNEUMOCOCCAL ANTIBODY LEVEL BY CAPSULAR TYPE AMONG VACCINEES WHO RECEIVED TWO PNEUMOCOCCAL VACCINES

	Mean ng antibody nitrogen/ml to indicated capsular type before and after first and second dose of polysaccharide antigen					
	First dose			Second dose		
Capsular type	Number tested	Prevaccine	Postvaccine	Number tested	Prevaccine	Postvaccine
1	12	1054	2353[a]	12	2002	2038
3	12	290	2011[b]	12	1488	1644
4	12	1985	3646[b]	12	3729	4161
7F	12	690	2146[b]	12	2058	1741
8	12	355	3484[b]	12	2594	2538
12F	12	1842	3408	12	3596	2648
14	4	752	1908[b]	4	1306	1151
19F	4	727	1087	4	1766	2018

[a,b] Postvaccine level significantly greater than prevaccine level by paired t test: [a] $P < 0.05$, [b] $P < 0.01$.

large amounts of antibody did not develop adverse local reactions or developed only a mild one.

Most of the volunteers in this study developed twofold or greater rises in antibody to capsular types 1, 3, 4, 7F, 8, and 12F after the first dose of vaccine. However, few volunteers exhibited further rises in antibody following a second dose of vaccine even though the levels of prevaccine antibody often were of the same magnitude as the levels before receipt of the first pneumococcal vaccine. This finding raises the question of how a second dose of polysaccharide antigen is processed so that it fails to elicit a further rise in antibody. Similar findings were reported by Heidelberger in seven persons given a second dose of a pneumococcal vaccine 5 to 6 years after the first vaccine (7). Repeated immunization failed to induce antibody to the previously administered polysaccharide antigens, but the new antigens in the second dose of vaccine produced satisfactory antibody responses (7).

Although our data are limited to detailed studies of only 12 persons, the results suggest that the conduct of additional studies of this issue would seem appropriate. A logical direction would be the revaccination of adults who received the 14-valent pneumococcal

TABLE V. RELATION OF VACCINE VALENCY TO ADVERSE REACTIONS AMONG VOLUNTEERS GIVEN TWO OR THREE DOSES OF PNEUMOCOCCAL VACCINE

	Adverse reaction									
	First dose					Second dose				
		Systemic		Local			Systemic		Local	
Vaccine composition	Number tested	Fever	Malaise, chills	Pain, tend.[a]	Eryth.	Number tested	Fever	Malaise, chills	Pain, tend.	Eryth.
Hexavalent	10	0	1	1	2	1	0	0	0	0
Octavalent	1	0	0	1	0	3	0	0	1	1
Nonavalent	1	0	0	1	0	4	0	2	2	1
Tridecavalent	0	—	—	—	—	4[b]	0	1	2	0

[a] Eryth., erythema; Tend., tenderness; Fever, temperature > 100°F.

[b] Two volunteers also received a tridecavalent vaccine as a third vaccine. Both had local pain and tenderness, and one had erythema; neither had induration nor systemic reactions.

vaccine with the new 23-valent vaccine. Such studies could provide data on the occurrence of adverse reactions and the optimum time interval between repeated immunization with pneumococcal vaccine.

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