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Long-Term Persistence of Antibody following Immunization with Pneumococcal Polysaccharide Vaccine[1] (41643)

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Abstract. Thirty-seven healthy volunteers who received a pneumococcal polysaccharide vaccine were tested 4, 5, or 6 years after immunization for circulating type-specific pneumococcal antibody by radioimmunoassay of their sera. Each volunteer was immunized with one of four different pneumococcal vaccines containing 50 μg of each of 6, 8, 9, or 13 capsular polysaccharides; a few volunteers received octavalent or tridecavalent pneumococcal vaccines combined with bivalent influenza virus vaccine in a single syringe. Four years after immunization, the mean antibody level was 90% of the level achieved 4 weeks after vaccination. Among volunteers tested 5 years after immunization (including three 6 years after vaccination), the mean antibody level was 76% of that 4 weeks after inoculation. These findings confirm the long-term persistence of vaccine-induced type-specific pneumococcal antibodies and suggest that the interval between repeated doses of pneumococcal vaccine should be at least 5 years.

Pneumococcal (*Streptococcus pneumoniae*) vaccine composed of purified polysaccharides of 14 capsular types was licensed in 1977 for general use. A single dose of this vaccine, containing 50 μg of each capsular antigen, induces high levels of type-specific antibody to each of the 14 types in most recipients (1, 2). The magnitude of the antibody response varies with the individual capsular type and depends upon the immune responsiveness of the subject (1, 2). Normal adults develop high antibody levels, but children less than 2 years of age and individuals receiving immunosuppressive therapy respond poorly to some or all of the antigens (1). Vella and co-workers reported that vaccine-induced pneumococcal antibody in normal adults persisted at least 3.5 years at approximately 50% of the peak level which had been observed at 4 to 6 weeks after administration of a single dose of vaccine (2, 3).

We investigated the duration of vaccine-induced pneumococcal antibody in normal adults 4 and at 5 years after administration of vaccine. In this report, we describe the persistence of vaccine-induced antibody at levels only slightly lower than the levels achieved 1 month after administration of a single dose of polyvalent pneumococcal polysaccharide vaccine.

Materials and Methods. *Population.* Volunteers were recruited from among the groups of medical students, clerks, and office personnel at the West Side Veterans Administration Medical Center in Chicago, Illinois, and among men participating in the Salvation Army programs located on West Madison and West Monroe Streets (skid row). Each volunteer was informed of the nature of the vaccine evaluation and consented to participate; this investigation was approved by the Human Studies Committee of the West Side Veterans Administration Medical Center and later by the Human Studies Committee of the Huntington Veterans Administration Medical Center and the Institutional Review Board of the Marshall University School of Medicine. At the time of vaccine administration, none of the volunteers was acutely ill and none had debilitating disease or was receiving immunosuppressive therapy. All volunteers received pneumococcal vaccine only during the course of this investigation and not at any time subsequently.

Vaccinees from the West Side Veterans Administration Medical Center were located for follow-up serum specimens by telephone con-

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tact in the medical center if they were still employed there or by telephone and by letters to their homes if they were no longer employed at the center. Men enrolled in the Salvation Army program were located through its medical center on West Monroe Street or by door-to-door inquiry at each of the skid row "hotels." Thirty-seven vaccinees from the original vaccinated groups were located for this study. The ages of vaccinees ranged from 23 to 66 years; seven vaccinees were aged 20 to 29 years, 15 were 39 to 49 years, and 15 were 50 to 66 years. Eleven of the vaccinees were medical students, clerks, or office personnel at the medical center and 26 were homeless men. Ten of the 11 medical center personnel were less than 49 years of age and 14 of 26 homeless men were more than 50 years of age. All the homeless men were ambulatory, performed day work, and were enrolled in the Salvation Army abstinence from alcohol program.

Vaccines. Four different polyvalent pneumococcal polysaccharide vaccines containing 50 μg each of 6, 8, 9, or 13 capsular types were kindly provided by Lederle Laboratories, Pearl River, New York. Their type composition is listed in Table I. Most vaccinees received either the octavalent or tridecavalent pneumococcal vaccine. Two preparations, the octavalent vaccine and the tridecavalent vaccine, also were combined with an inactivated bivalent influenza A and B virus vaccine (in a single syringe) and these "combination vaccines" were given in a single injection. The influenza virus components were 700 CCA (chick cell agglutinating) units of A_2/Aichi/2/68 and 300 CCA units of B/Mass/1/71 per dose.

Pneumococcal vaccine was administered subcutaneously in the arm in a 0.5-ml volume. Local and systemic reactivities, if any, were evaluated at 15 min, 24 hr, and 72 hr following vaccine administration. Each of the four polyvalent pneumococcal vaccines caused minimal local tenderness and erythema which lasted 24 hr or less; usually the vaccinee reported no adverse reaction to injection of vaccine. Vaccinees who received a combination octavalent or tridecavalent pneumococcal and influenza vaccine also reported only local reactions. These combination vaccines caused fewer and less severe reactions than a hexavalent-influenza combination previously reported (4).

Antibody determinations. Of the 37 vaccinees, 16 vaccinees had been immunized 4 years earlier, 18 had been immunized 5 years earlier, 3 had been immunized 6 years earlier. Serum for measurement of pneumococcal antibody was obtained usually 1 month after vaccination and at either 4, 5, or 6 years later. Approximately 20 ml of venous blood was collected, allowed to clot at room temperature, and the serum was separated aseptically and stored at −20°C until tested. Antibody was measured by radioimmunoassay (RIA) according to the method of Schiffman *et al.* (5). Antibody levels were expressed as nanograms of antibody nitrogen per milliliter. The

TABLE I. COMPOSITION OF PNEUMOCOCCAL VACCINES AND OF VACCINATED GROUPS

Vaccine	Capsular types in vaccine (50 μg of each polysaccharide; Danish nomenclature)	Number of vaccinees in indicated follow-up group	
		4 Years postvaccine	5 Years[b] postvaccine
Hexavalent	1, 3, 4, 7F, 8, 12F	1	1
Octavalent	1, 3, 4, 7F, 8, 12F, 14, 19F	5	14
Octavalent-influenza[a]		2	1
Nonavalent	1, 3, 4, 7F, 8, 12F, 14, 19F, 5	0	1
Tridecavalent	1, 3, 4, 7F, 8, 12F, 14, 19F, 6A, 6B, 9N, 18C, 23F	7	3
Tridecavalent-influenza[a]		1	1
Total who received any vaccine		16	21

[a] Contains inactivated A_2/Aichi/2/68 and B/Mass/1/61.
[b] Includes three vaccinees tested at 6-year follow-up.

1-month, and the 4-, 5-, or 6-year serum specimens from each vaccinee were tested at the same time; all sera were tested in two runs with the same lot of antigen for each capsular type.

Statistical analyses. The mean level of type-specific antibody at 1 month and 4 years and at 5 or 6 years after immunization were compared by paired *t* tests. Since the 6-year postvaccine group included only three vaccinees, their data were combined with those of the 5-year postvaccine group (designated the 5-year follow-up group). By using one way analysis of variance (ANOVA), the mean level of antibody was compared by age group at 1 month and 4 and 5 years later, and the mean level of antibody was compared for the groups of medical center individuals and homeless men irrespective of length of follow-up.

Results. Pneumococcal vaccinees possessed moderate or high levels of antibody 1 month after vaccination to capsular types 1, 3, 4, 8, 12F, 14, and 23F (Table II). The geometric mean antibody level to each of these types exceeded 1000 ng of antibody nitrogen/ml. By contrast, low levels of antibody were induced to types 6A, 7F, 9N, 18C, and 19F; the geometric mean antibody levels at 1 month ranged from slightly more than 100 to 634 ng of antibody nitrogen/ml. Since the vaccinees tested at 4 years and the vaccinees tested at 5 years comprised two separate groups, their mean antibody levels 1 month after immunization were calculated separately and, in most instances, their values were similar. Four years after vaccine, levels of pneumococcal antibody had waned only slightly (Fig. 1). Five years after immunization, the levels of type-specific antibody were similar or somewhat lower than those of the group of vaccinees tested 4 years after vaccination (Table II). Since sera of fewer vaccinees in the 5-year follow-up group were assayed for antibodies to types 6A, 9A, 18C, and 23F, levels to these types were combined with those of the 4-year group.

The ratios of the late to the 1-month postvaccine antibody levels by pneumococcal type for the 4-year postvaccine group and the 5- or 6-year postvaccine group reflected the slight waning of antibody over time (Table II). For the 4-year postvaccine group, the average antibody level for all capsular types as a group was 90% of the antibody level achieved 1 month after vaccine. At the 5-year follow-up, the average antibody level for all types as a

TABLE II. PNEUMOCOCCAL ANTIBODY LEVEL BY TYPE AMONG VACCINEES 4 AND 5 YEARS FOLLOWING IMMUNIZATION WITH A PNEUMOCOCCAL VACCINE

Capsular type	4-Year follow-up group geometric mean antibody level at indicated time		Ratio of 4 years/ 1 month levels	5-Year follow-up group[a] geometric mean antibody level at indicated time			Ratio of 5 years/ 1 month levels
	No. of subj.	1 Month postvaccine	4 Years postvaccine		No. of subj.	1 Month postvaccine	5 Years postvaccine	
1	16	2423	2086	0.86	21	1883	1262*	0.67
3	16	2723	1378†	0.50	21	2329	1531	0.66
4	12	4178	4622	1.11	17	5078	6220*	1.22
6A	12	222	190	0.86	—[b]	—	—	—
7F	16	170	240	1.41	20	224	219	0.98
8	16	2780	1850†	0.67	20	2515	1573*	0.63
9N	12	499	348	0.70	—[b]	—	—	—
12F	5	3816	2970	0.78	18	2034	1199*	0.59
14	11	3194	1609*	0.50	17	1605	1233*	0.77
18C	6	634	868	1.40	—[b]	—	—	—
19F	11	112	89	0.79	15	149	79*	0.53
23F	5	1446	1716	1.19	—[b]	—	—	—
Mean ratio			0.90				0.76	

[a] Includes three vaccinees tested at 6-year follow-up.

[b] Data for these capsular types combined with 4-year follow-up group because of few values in the 5- or 6-year follow-up group.

*,† The 4- and 5-year postvaccine geometric mean antibody levels differ significantly from 1-month postvaccine level by paired *t* test at $P < 0.05$ (*) or $P < 0.01$ (†).

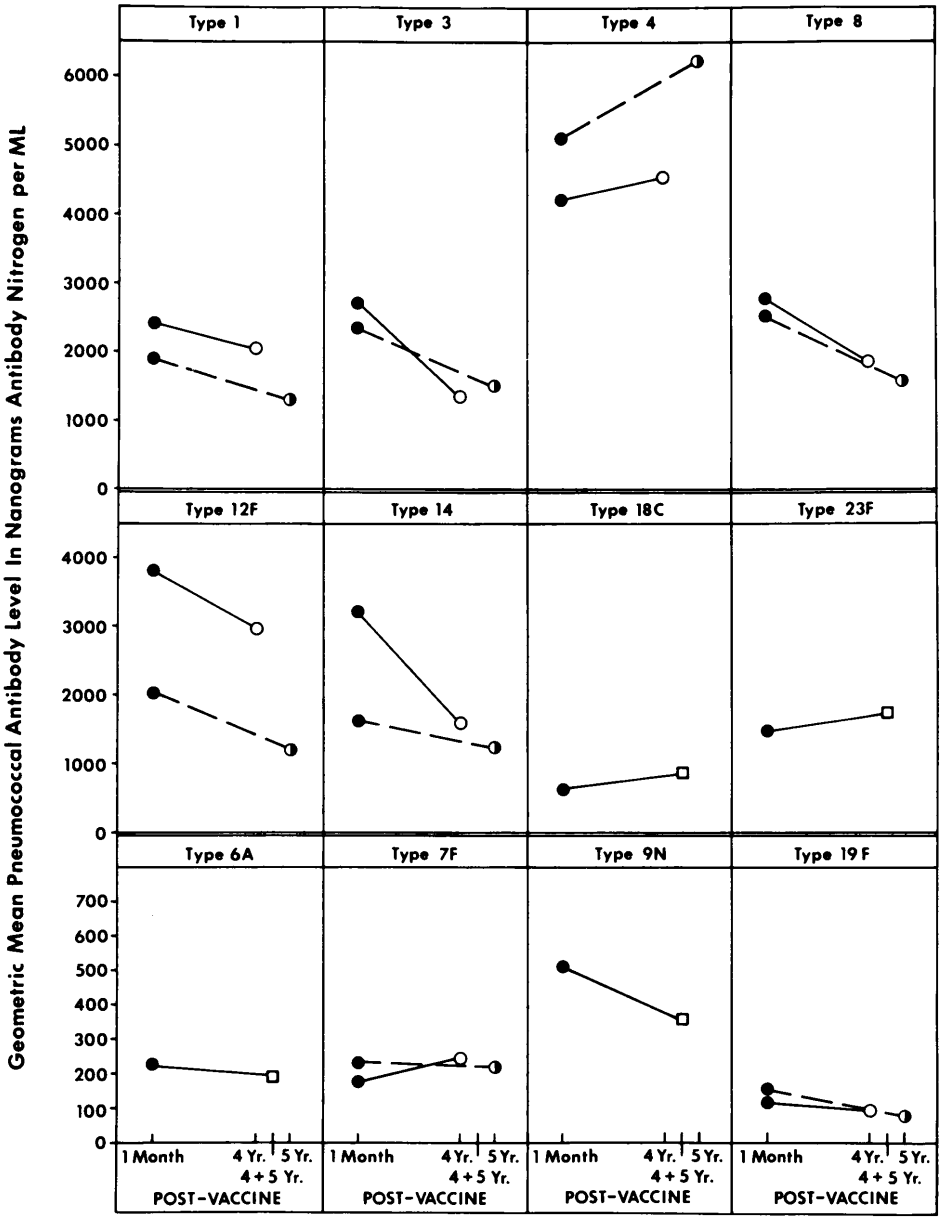

FIG. 1. Persistence of type-specific antibody at 4 years and at 5 years following immunization with pneumococcal polysaccharide vaccine.

group was 76% of the 1-month postvaccine level.

When geometric mean antibody levels by type were compared among vaccinees according to age groups of 20–29, 30–39, and 50–66 years and combined data from the 4-year and 5- to 6-year follow-up groups, no significant differences were detected for any of the types (type 23 was not tested because there were too few individuals who received it). Similarly, when geometric mean antibody levels by type were compared among groups of vaccinees from the medical center and skid row, no significant differences were detected for the types tested (types 1, 3, 4, 7, 8, 12, 14, and 19F). The mean level of antibody by type among vaccinees who received a pneumococcal polysaccharide vaccine alone com-

pared to those who received pneumococcal polysaccharide vaccine combined with influenza virus vaccine was not tested statistically because only five vaccinees received a "combination" vaccine.

Discussion. The results of our pneumococcal-vaccine evaluation indicate that type-specific pneumococcal antibody induced following immunization persists for at least 5 years, usually at levels only slightly lower than the levels achieved 1 month after vaccination. Antibody responses to types 1, 3, 4, 8, 12F, 14, and 23F were greater than 1000 ng of antibody nitrogen/ml, but antibody responses to types 6A, 7F, 9N, 18C, and 19F were less than 900 ng of antibody nitrogen/ml. Antibody responses only to types 6A and 19F were approximately 200 ng antibody nitrogen/ml or less.

For types 18C, 23F, 4, and 7F, the long term follow-up antibody levels were slightly higher than the 1-month postvaccine levels. These findings suggests that antibody to these types wanes slowly and that some vaccinees might have experienced colonization with these types in the interval between the 1 month and the long-term follow-up specimens (6). None of the vaccinees reported having had pneumonia or any infection of a serious nature requiring in hospital care after immunization with pneumococcal vaccine. It is unlikely that they would have developed serious infections with types 4 or 23F because the mean antibody levels for these types were high.

Data are lacking on the level of antibody that affords protection against each capsular type. It is likely that patients with high levels of antibody (for example more than 1000 ng of antibody nitrogen/ml) are protected (7, 8). Schiffman has suggested that no less than 200 to 300 ng of antibody nitrogen/ml may be a "protective level" (5, 9). This level has been estimated by analysis of data from four differing sources: the type specific antibody induced by pneumococcal vaccine in infants at 6, 12, or 24 months of age; type specific pneumococcal antibody levels among individuals prior to the onset of a bacteremic illness; correlation of RIA antibody levels with opsonic activity among children colonized by pneumococci; and, RIA antibody levels in pooled sera from healthy adults (10). In each instance, the mean level of pneumococcal antibody was 200 to 300 ng of antibody nitrogen/ml. However, more data are needed on the levels of type-specific pneumococcal antibodies in preinfection sera of individuals who develop bacteremic illness due to types in the vaccine. It is not surprising that, of the several vaccine failures reported recently, types 6 and 19 accounted for many of these infections (1). In our vaccinees, the lowest antibody responses were to these two types.

Data on the persistence of pneumococcal antibody are essential in order to develop recommendations concerning readministration of pneumococcal vaccine to individuals at high risk of infection. When the vaccine was licensed initially, reimmunization was not recommended earlier than 3 years because of the greater likelihood of adverse reactions in those persons with high levels of antibodies. In 1950, Heidelberger and co-workers showed that pneumococcal antibodies induced by injection of polysaccharides persisted for 2 years at levels as high as one-half of the peak level measured 2 months after vaccination (11). Vella found that vaccine-induced pneumococcal antibodies persisted for 3.5 years (3). Similarly, antibody to the polysaccharides of Group C *Neisseria meningitidis* lasted 4 years after vaccination at levels of 30% or more of the level achieved 1 month after vaccine administration (12).

At present, the current recommendation for repeated doses of the commercially available tetradecavalent vaccine leaves open the issue of when to reimmunize, except to not do so earlier than 5 years after initial immunization. Since vaccinees in our study exhibited high levels of antibody to most types that lasted at least 5 years, it is reasonable to consider that reimmunization may not be necessary for 6 years or longer. We are continuing our studies of the persistence of antibodies in pneumococcal vaccinees to provide additional data on this topic.

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