PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 157, 148-154 (1978)

Vaccination and Revaccination with Polyvalent Pneumococcal Polysaccharide Vaccines in Adults and Infants (40010)

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Polyvalent pneumococcal capsular polysaccharide vaccines have proven safe and effective in eliciting antibody formation and in preventing in adults illnesses caused by *Streptococcus pneumoniae* (pneumococcus) (1-7). Important unanswered problems relate (a) to antibody responses and to clinical reactions on primary immunization and revaccination in infants, (b) to antibody responses and clinical reactions on revaccination in adults, (c) to the relationship between the height of circulating antibody and clinical reactions to vaccination in adults, and (d) to the persistence of anti-pneumococcal antibody in human subjects following vaccination. This report summarizes the findings in human vaccination studies carried out in Chile and in the United States that provide information relating to these questions.

Materials and methods. Vaccines. All the polyvalent pneumococcal capsular polysaccharide vaccines were prepared by methods described earlier (6, 7). All pneumococcal capsular-type designations were those of the American system of nomenclature. The polysaccharides from which the vaccines were made were prepared in the laboratories of Dr. Thomas H. Stoudt, Dr. Dennis J. Carlo, Bernard L. Wilker, Karl Nollstadt, James Lago, and William A. Sklarz of the Merck Sharp & Dohme Research Laboratories, Rahway, N.J. The adult human dose of vaccine was administered in a 0.5-ml volume and contained 50 μg of each capsular polysaccharide. Infants were given half the adult dose of vaccine in a 0.25-ml volume containing 25 μg of each polysaccharide. The vaccines were in physiological saline solution containing 0.25% USP phenol as preservative. Tests for release of final product were in accordance with the general regulations of the Bureau of Biologics and were in compliance with the tentative specific regulations being developed by that agency (8).

Clinical testing. The adult subjects in Study 454 were employees of Merck & Co., Inc., West Point, Pa. The initial dose of vaccine was given during January 1976. The second dose was administered 13 months later. The infants in Studies 378 and 378D were participants in a large field trial initiated during July 1974 in Santiago, Chile, to measure the protective efficacy of pneumococcal vaccine. A sample of the children was selected at random for measuring antibody responses on primary vaccination and on revaccination.

Unless otherwise stated, blood samples for serologic assay for pneumococcal antibody were taken immediately prior to and 1 month after vaccine was given. All subjects were overtly in good health at the time of vaccination and all tests were carried out under Investigational New Drug regulations employing written informed consent for subject participation. Appropriate observations for local and systemic reactions were carried out by physicians and qualified nurses aided by record forms provided to adult participants and to parents and guardians.

Antibody assays. The sera were stored frozen until tested by a standard radioimmune assay (9) using radiolabeled type-specific pneumococcal polysaccharides ob-

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0037-9727/78/1571-0148$01.00/0

tained from Dr. Gerald Schiffman. For each type, all serum samples from a particular individual were tested together in the same assay, except that the zero-time and 1-month sera in Study 378 were assayed first and the 13- and 14-month samples were tested later. Serum titers were measured as nanograms of antibody N per milliliter of serum, and a twofold or greater increase in the amount of antibody between the first and second serum sample was taken as indicative of a significant antibody response.

Results. Adults. Seven adult persons who had received a 0.5-ml dose of 12-valent pneumococcal vaccine, Lot 561/C-D194, subcutaneous or intramuscularly 13 months earlier were given a second dose of the same vaccine by the subcutaneous route. Observations were made of antibody responses and clinical reactions. Table I shows that nearly all the subjects had responded initially to the capsular polysaccharides in the vaccine and that there was no important further increase in antibody after the second dose of vaccine was given. There was, however (see Table II), substantially greater local clinical reaction at the injection site after the second dose than after the first. Mild fever was somewhat more frequent on revaccination, but the greatest difference was in the kind and severity of local response. The reaction after initial injection was usually limited to mild soreness at the injection site that lasted up to 3 days. In contrast, nearly all persons displayed induration with erythema in addition to soreness after revaccination, and this finding persisted for a slightly longer time period in some of the individuals.

The findings with these seven persons were entirely consistent with studies in 10 additional persons who were vaccinated

TABLE I. INITIAL AND REVACCINATION ANTIBODY RESPONSES IN SEVEN ADULTS GIVEN POLYVALENT (12 TYPE) PNEUMOCOCCAL VACCINE (STUDY 454)

		RIA antibody titer (ng of antibody N/ml)					RIA antibody titer (ng of antibody N/ml)		
Pneumococcal capsular type	Blood sample time (months)	Twofold or greater increase (number/total)	Geometric mean	Mean increase (−fold)	Pneumococcal capsular type	Blood sample time (months)	Twofold or greater increase (number/total)	Geometric mean	Mean increase (−fold)
1	0[a]		412		12	0		372	
	1	7/7	≥1,419	3.4		1	7/7	2,377	6.4
	13[a]	7/7	2,167	5.3		13	6/7	2,046	5.5
	14	7/7	2,506	6.1		14	6/7	2,201	5.9
3	0		1,230		14	0		958	
	1	6/7	5,537	4.5		1	6/7	6,881	7.2
	13	5/7	2,820	2.3		13	6/7	6,045	6.3
	14	5/7	3,510	2.9		14	7/7	5,989	6.3
4	0		2,452		19	0		963	
	1	7/7	11,235	4.6		1	7/7	3,917	4.1
	13	5/7	7,795	3.2		13	7/7	4,045	4.2
	14	6/7	8,563	3.5		14	7/7	4,253	4.4
6	0		370		23	0		5,016	
	1	7/7	1,766	4.8		1	6/7	18,828	3.8
	13	7/7	1,824	4.9		13	3/7	11,838	2.4
	14	7/7	2,206	6.0		14	3/7	14,237	2.8
8	0		485		51	0		282	
	1	7/7	5,868	12.1		1	7/7	1,597	5.7
	13	7/7	6,741	13.9		13	7/7	1,770	6.3
	14	7/7	7,197	14.8		14	7/7	2,189	7.8
9	0		642		56	0		3,271	
	1	7/7	7,365	11.5		1	7/7	27,566	8.4
	13	7/7	5,713	8.9		13	7/7	23,398	7.2
	14	7/7	5,572	8.7		14	7/7	24,412	7.5

[a] Time vaccine was given.

TABLE II. LOCAL AND SYSTEMIC REACTIONS IN SEVEN ADULTS WHO WERE VACCINATED WITH POLYVALENT PNEUMOCOCCAL VACCINE INITIALLY AND AGAIN 13 MONTHS LATER

	Initial vaccination						Revaccination					
	No. with reaction on day						No. with reaction on day					
Reaction	0	1	2	3	4	5	0	1	2	3	4	5
Local												
Soreness	6	6	3	2			6	6	5	3	2	1
Erythema		1	1				2	7	4	3	1	
Induration							6	6	5	3	1	1
Systemic												
Chills							1	2				
Temperature												
Fever (max., 0)												
<99°F	6	6	7	6	7	7	4	5	6	5	6	5
99-99.9°F		1					3	2	1	1		
Not taken	1			1						1	1	2

and revaccinated at the same time periods used above with either of two additional lots of vaccine.

Infants. Table III shows that infants 6–24 months of age, who were given a single 0.25-ml dose of Lot 561/C-D194 12-valent pneumococcal vaccine, produced less antibody than did adults and showed varied serologic responses to the different types as well. Importantly, however, at least 50% of the infants did show a significant antibody increase to 10 of the 12 capsular types. The highest postvaccination antibody titers were against types 3, 4, 8, 9, and 56, and the lowest responses were against types 6, 12, 14, and 23. There were no substantial differences in responses in the 6- to 12-month age group compared with the 13- to 24-month age group. Limitations in the volumes of available sera precluded tests of sera from all the individuals against all the pneumococcal capsular types in the vaccine.

Infants 3–5 months of age (Study 378) who received Lot 561/C-D194 vaccine were revaccinated 6 months later. The results are shown in Table IV. The antibody increases on primary immunization were considerably less for most of the capsular types than seen in the older infants (Table III) and they declined rapidly for those types in which the best antibody responses had occurred. In addition, the geometric mean antibody titers following vaccination were generally low. In contrast to adults (see above), there was a substantially greater-fold increase in mean titer on revaccination, and this response was greatest for those serotypes in which there had been the highest initial response.

Infants in a second group (Study 378D), who had been vaccinated at 3 months of age, were revaccinated 21 months later. Blood samples had not been taken to measure antibody responses to the initial vaccination, but the titers of 21 months were roughly in the same range as for the children in Study 378 following the first vaccine dose. In contrast with the children in Study 378, who were given their booster dose at 9–11 months of age, these children showed responses with very high titer against all capsular types.

The infants showed very mild local reactions limited mostly to erythema and possible soreness in a portion of the group. In contrast to adults, there were no marked local reactions on revaccination in infants, and this finding was probably due to the smaller amount of pneumococcal capsular antibody in these persons (see below) at the time of revaccination.

Relationship between pneumococcal antibody titer and reactions. The cause for local brachial and systemic reactions in persons given pneumococcal capsular vaccine is not known with certainty but appears to be due to local reaction between the injected antigen and circulating antibody at the site in which the vaccine was

TABLE III. ANTIBODY RESPONSE, ACCORDING TO AGE, ON PRIMARY IMMUNIZATION OF INFANTS AND CHILDREN WITH POLYVALENT PNEUMOCOCCAL POLYSACCHARIDE VACCINE (STUDY 378)

Capsular type	Blood sample time (months)	Age of recipient: 6–12 months[a] Twofold or greater increase (number/total)	6–12 months[a] Geometric mean	6–12 months[a] Mean increase (-fold)	13–24 months[a] Twofold or greater increase (number/total)	13–24 months[a] Geometric mean	13–24 months[a] Mean increase (-fold)
1	0		120			136	
	1	25/31 (81)[b]	372	3.1	13/16 (81)	479	3.5
3	0		95			132	
	1	29/31 (94)	2200	23.2	14/14 (100)	3448	26.1
4	0		535			773	
	1	18/26 (69)	2084	3.9	10/15 (67)	1998	2.6
6	0		25			43	
	1	12/24 (50)	48	1.9	5/16 (31)	57	1.3
8	0		64			157	
	1	30/32 (94)	1112	17.4	14/16 (88)	1335	8.5
9	0		172			275	
	1	26/30 (87)	892	5.2	12/17 (71)	1060	3.9
12	0		33			37	
	1	11/24 (46)	57	1.7	12/16 (75)	80	2.2
14	0		95			124	
	1	4/10 (40)	112	1.2	4/10 (40)	173	1.4
19	0		40			60	
	1	17/20 (85)	169	4.2	9/10 (90)	255	4.3
23	0		44			67	
	1	13/16 (81)	102	2.3	5/10 (50)	100	1.5
51	0		52			88	
	1	25/29 (86)	279	5.4	9/11 (82)	416	4.7
56	0		88			195	
	1	24/29 (83)	838	9.5	11/15 (73)	1326	6.8

[a] 12-valent, Lot 561/C-D194, vaccine was used.
[b] Number within parentheses indicates percentage of total.

given. Support of this concept was shown in the findings presented in Table V which records the clinical reactions in 20 persons who were given vacccine, but who had different amounts of circulating antibody against the homologous capsular types at the time of vaccination. While there was no precise correlation between amount of pneumococcal antibody and the appearance of induration, persons with a large amount of antibody showed a greater chance of having more severe of a reaction than did those with a smaller amount of antibody.

Discussion. The present study of 12-valent pneumococcal vaccine in adults has confirmed previously published data (1–7) showing the ability of the vaccine to induce specific antibodies against the homologous types. The duration of protective effect of the vaccine is presently unknown, but it has been shown in previous studies (2, 10) with different pneumococcal vaccines that antibody induced by the vaccine was present at one-fifth to one-half or more of its peak values 2 or 3 years after a single injection. In some individuals, abundant residual antibody persisted 8 years after vaccination. The present study in adult volunteers showed only minor decline in antibody 13 months after the initial vaccine dose, and there was no substantial booster response when a second dose of vaccine was given at that time. There was, however, substantial increase in the degree of local reaction at the injection site after the second dose of vaccine which resulted in development of erythema and palpable induration. The optimal time for revaccination to achieve meaningful elevations in titer with least clinical response remains to be determined.

The correlation between the total amount of circulating homologous antipneumococcal capsular antibodies against

TABLE IV. INITIAL AND REVACCINATION ANTIBODY RESPONSES IN INFANTS GIVEN POLYVALENT (12-TYPE) PNEUMOCOCCAL VACCINE (STUDIES 378 AND 378D)[a]

	Study 378 (infants, 3–5 months)				Study 378D (infants, 3 months)			
Capsular type	Blood sample time (months)	Twofold or greater increase (number/total)	Geometric mean titer	Mean increase (-fold)	Blood sample time (months)	Twofold or greater increase (number/total)	Geometric mean titer	Mean increase (-fold)
1	0[b]		32		–[b]			
	1	4/8 (50)[c]	63	2.0	–			
	6[b]	1/8 (13)	42	1.3	21[b]		110	9.2
	7	6/8 (75)	118	3.7	22	30/31	1014	
3	0[b]		45		–[b]			
	1	5/5 (100)	525	11.7	–			
	6[b]	4/5 (80)	132	2.9	21[b]		136	
	7	5/5 (100)	386	8.6	22	30/31	3330	24.4
6	0[b]		20		–[b]			
	1	0.9 (0)	16	−1.3	–		40	
	6[b]	1/9 (10)	21	1.0	21[b]		198	
	7	0/9 (0)	19	−1.1	22	24/24		5.0
8	0[b]		76		–[b]			
	1	4/4 (100)	881	11.6	–			
	6[b]	4/5 (80)	357	4.7	21[b]		236	
	7	5/5 (100)	867	11.4	22	30/31	2980	12.6
9	0[b]		24		–[b]			
	1	7/7 (100)	107	4.5	–			
	6[b]	5/5 (100)	92	3.9	21[b]		136	
	7	6/6 (100)	176	7.4	22	29/29	1575	11.5
12	0[b]		14		–[b]			
	1	1/7 (14)	14	1.0	–			
	6[b]	3/7 (43)	22	1.6	21[b]		48	
	7	3/7 (43)	24	1.7	22	28/30	317	6.6
14	0[b]		74		–[b]			
	1	1/8 (12)	78	1.1	–			
	6[b]	1/8 (12)	64	−1.2	21[b]		48	
	7	3/8 (38)	96	1.3	22	17/22	293	6.2
19	0		55		–[b]			
	1	0/5 (0)	71	1.3	–			
	6[b]	0/5 (0)	68	1.2	21[b]		155	
	7	4/6 (67)	277	5.1	22	24/26	837	5.4
51	0[b]		27		–[b]			
	1	4/6 (67)	66	2.4	–			
	6[b]	4/6 (67)	75	2.7	21		80	
	7	5/6 (83)	95	3.5	22	19/20	637	8.0
56	0[b]		81		–[b]			
	1	3/4 (75)	269	3.3	–			
	6[b]	1/2 (50)	132	1.6	21[b]		310	
	7	4/4 (100)	578	7.1	22	28/28	4083	13.2

[a] Types 4 and 23 responses omitted because of too small number of serologic tests run due to small volume of serum.

[b] Time when vaccine was given.

[c] Number within parentheses indicates percentage of total.

all the types in the vaccine and the reaction to the vaccine is strongly suggestive of antigen–antibody formation at the local site with attendant Arthus-like (11) pathologic responses. Such reactions, while self-limited and generally mild, do impose restrictions on revaccination at a time when no substantial increase in antibody can be achieved. The possibility for reducing the amount of antigen per dose of vaccine to minimize local reactions on revaccination needs to be studied.

As with meningococcal polysaccharide vaccines (12), infants responded less well to pneumococcal vaccine than did adults. This was especially true of 3-month-old

TABLE V. RELATIONSHIP BETWEEN AMOUNT OF CIRCULATING PNEUMOCOCCAL ANTIBODIES AND DEGREE OF LOCAL REACTION TO POLYVALENT PNEUMOCOCCAL CAPSULAR POLYSACCHARIDE VACCINES

Local reaction		Total antibody N for 12 types, at time of vaccination (μg/ml)
Subject	Degree of reaction[a]	
18-47	Slight to none	1,786
25-34	Slight to none	2,034
16-34	Slight to none	2,184
29-34	Slight to none	2,639
17-34	Slight to none	6,776
2-34	Slight to none	8,194
11-44	Slight to none	15,504
12-44	Slight to none	19,725
2-44	Slight to none	21,514
19-47	Slight to none	34,143
Total group		114,499
15-34	Mod. w/induration	14,389
7-34	Mod. w/induration	16,358
25-44	Mod. w/induration	23,446
15-47	Mod. w/induration	28,149
1-34	Mod. w/induration	30,774
18-44	Mod. w/induration	40,026
13-34	Mod. w/induration	40,054
9-34	Mod. w/induration	44,100
17-44	Mod. w/induration	62,751
14-47	Mod. w/induration	131,081
Total group		431,128

infants. There were considerable differences among the capsular types. Antibody induced by the vaccine in early infancy tended to decline quite rapidly. There was a marked advantage to booster immunization of infants at 9-11 months of age, especially for those capsular types in which a primary response had been achieved. Maximal antibody production was obtained, however, when the children were revaccinated at 2 years of age and showed antibody responses against all types that approached the titers achieved in adults. These findings provide a basis for hope that the vaccine will prove useful in infants and young children in preventing severe pneumococcal disease and bacteremia in cases of asplenia or impaired splenic function, as well as in preventing pneumonia, otitis media, and meningitis in normal children.

Summary. Adult persons developed substantial antibody increases against essentially all pneumococcal capsular types following injection of polyvalent pneumococcal vaccine containing 50 μg of each capsular polysaccharide per dose. Revaccination 13 months after the previous immunization did not evoke important further increases in antibodies and there was substantially greater local reaction at the injection site than when the previous dose was given. This finding appeared due to local reaction of antigens with circulating antibodies in the area of injection, since there was a correlation between the measured amount of circulating pneumococcal antibodies and the degree of reaction. Infants less than 2 years of age who were given a half-dose of vaccine generally responded poorly when compared with adults. In studies of 3- to 5-month-old infants, there was some increase in antibodies when a booster dose of vaccine was given 6 months after the first. Very high level antibody responses against all capsular types were obtained when revaccination was delayed until 2 years of age.

Joan R. Goshow, B.A., Violet Holmes, B.S., Gail C. Lowden, A.B., M.S., and Joan M. Staub, B.S., provided important technical assistance.

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Received September 26, 1977. P.S.E.B.M. 1978, Vol. 157.