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Pneumococcal Vaccine: Dose, Revaccination, and Coadministration with Influenza Vaccine (40596)

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Polyvalent pneumococcal capsular polysaccharide vaccine (1–7) was first licensed for general use in the USA in 1977 and has been used extensively in persons who are at high risk to illnesses caused by infections with pneumococci (8). The introduction of new vaccines leaves unanswered questions that are the subject of continuing research. The present report gives the findings in clinical trials to measure antibody responses and clinical reactions when vaccine was given in graded amounts in vaccination and revaccination and when pneumococcal and influenza vaccines were given individually or at the same time in opposite arms.

Materials and methods. Vaccines. Pneumococcal capsular type designations are given in both the American and Danish systems since the American system was used previously by us and since there is a new consensus in the USA (9) to employ the Danish system. The polysaccharides from which the pneumococcal vaccine (lot 686/C-E515) was made were prepared in the Merck Sharp and Dohme Research Laboratories, Rahway, N.J. by Dr. Thomas Stoudt and his associates and characterization and formulation were as described earlier (2). The vaccine was prepared to contain 50, 25, or 12.5 μg per 0.5-ml dose of each pneumococcal polysaccharide type in physiological saline solution containing 0.25% USP grade phenol. Tests for release of final product were according to the general regulations of the Bureau of Biologics and were in compliance with the guidelines for pneumococcal vaccine developed by the same agency. Polyvalent influenza vaccine lot C-F550 was prepared in the laboratories of Merck Sharp and Dohme and was made of whole virus. Each 0.5-ml dose was standardized to contain 20 μg each of A/USSR/90/77 (H_1N_1), A/Texas/1/77 (H_3N_2) and B/Hong Kong/5/72 hemagglutinating antigen.

Clinical testing. Pneumococcal vaccine study 526. A graded dose–response investigation was carried out in 92 adult employees of Merck and Company who were 21 to 62 years of age. Twenty-three of the subjects had received the same vaccine 1 to 1.5 years earlier in the standard dose containing 50 μg of each type of capsular polysaccharide. Study 530, in which both pneumococcal and influenza vaccines were given, was carried out by one of us (A. J. Carlson) at the offices of Pediatric Medical Associates, Havertown, Pennsylvania, among persons 21 to 70 years of age. All vaccines were given intramuscularly. All subjects were bled immediately prior to vaccination and 1 month later. 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. Appropriate observations for local and systemic reactions were carried out 4 hr after vaccination (Day 0) and for 10 days thereafter by physicians and qualified nurses aided by record forms provided to adult participants.

Antibody assays. The sera were stored frozen until assayed for antibody content. Antibody against pneumococci was measured by radioimmune assay (10) using radiolabeled type-specific pneumococcal polysaccharides obtained from Dr. Gerald Schiffman. All serum samples from a particular individual were tested together in the same assay for each type. Serum titers were measured as nanograms of antibody N per milliliter of serum, and a twofold or greater increase in

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the amount of antibody between the first and second serum sample was taken as indicative of a significant antibody response. The assays for influenza antibody were kindly performed for us by Dr. Gary Noble at the National Center for Disease Control, Atlanta, Georgia.

Results. Study 526, graded dose–response to pneumococcal vaccine on primary administration and revaccination. The findings in groups of 22 to 24 adult persons who received pneumococcal vaccine intramuscularly in 0.5-ml amount containing 50, 25, or 12.5 μg of each capsular antigen are shown in Fig. 1. There was an overall small but distinct difference in antibody responses according to dose level with progressively smaller doses giving progressively lesser responses in most instances. Most of these differences were not statistically significant at the $P = 0.05$ level. Only types 4 and 19 showed a significant reduction in antibody response level when the dose was lowered from 50 to 12.5 μg. In the present example, 80% or more of the persons who received the 50 μg per antigen dose gave a fourfold or greater increase in antibody to each of the 14 serotypes. Such increase was found for only 9 of the 14 serotypes (64%) in those who received 25 or 12.5 μg per dose.

Previous clinical studies (3, 5) showed that persons who were revaccinated with 50 μg per antigen vaccine 13 months after an initial dose of 50 μg per antigen vaccine showed increased local and systemic reactions. In the present study, groups of seven or eight persons were revaccinated with one-half (25 μg, each antigen), one-fourth (12.5 μg), or one-eighth (6.25 μg) the full dose of antigen (50 μg) that was given 1 to 1.5 years earlier. Table I shows that there was little, if any, greater local or systemic reaction among revaccinated persons compared with individuals receiving vaccine for the first time in the comparable 25- and 12.5-μg dose range tested. It was of importance that (see Table II), as previously shown, antibody persisted following the initial vaccine dose and that only a few individuals showed a ≧ twofold increase in antibody against only 3 of the 14 serotypes represented.

Study 530. Simultaneous administration of pneumococcal and influenza vaccines. Groups of 23 to 25 adult persons were given 0.5 ml of pneumococcal vaccine (50 μg per antigen), 0.5 ml of polyvalent influenza vaccine, or 0.5 ml of each vaccine in opposite arms. Figure 2 shows that there was slightly less increase in mean pneumococcal antibody titer (for nine of the serotypes) when the pneumococcal vaccine was given at the same time as influenza vaccine compared with giv-

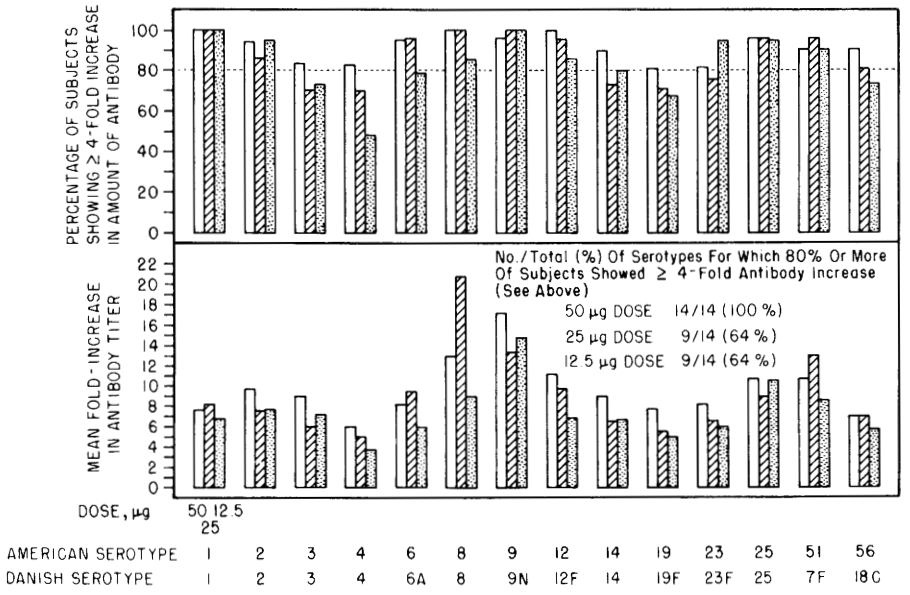

FIG. 1. Homologous antibody responses, according to serotype, among adult persons who received primary immunization with graded doses of 14-valent pneumococcal polysaccharide vaccine.

TABLE I. COMPARISON OF LOCAL AND FEBRILE REACTIONS AMONG PERSONS WHO RECEIVED PNEUMOCOCCAL VACCINES IN GRADED DOSES ON PRIMARY VACCINATION AND ON REVACCINATION (STUDY 526)

Vaccination			Percentage with reaction on day:					
Pneumococcal antigen per type (μg)	Sequence	Reaction	0	1	2	3	4	5
50	Primary (24 persons)	Local (arm)	38	42	25	4		
		Fever						
		99–99.9°F (0)	4			4	4	8
		100–100.9						
		101.2	4					
25	Primary (23 persons)	Local (arm)	30	39	17			
		Fever						
		99–99.9	13		9	4		9
		100		4				
25	Revaccination[a] (7 persons)	Local (arm)	100	100	57			
		Fever						
		99–99.9	14		14			
12.5	Primary (22 persons)	Local (arm)	32	27	5			
		Fever						
		99–99.9	9	9	5	9	9	5
12.5	Revaccination[a] (8 persons)	Local (arm)	100	88	12			
		Fever						
		99–99.9	25	12				12
6.25	Revaccination[a] (8 persons)	Local (arm)	75	75	38	12	12	12
		Fever						
		99–99.9	38		12			

[a] These persons had been vaccinated 1 to 1.5 years earlier with the same vaccine in 50 μg per antigen dose.

TABLE II. ANTIBODY RESPONSES TO PNEUMOCOCCAL POLYSACCHARIDE ANTIGENS AMONG ADULT PERSONS GIVEN A SECOND VACCINE DOSE, IN GRADED AMOUNT, 12 TO 18 MONTHS AFTER PRIMARY IMMUNIZATION WITH PNEUMOCOCCAL VACCINE OF FULL STRENGTH (50 μg PER SEROTYPE) (STUDY 526)

Serotype		Mean fold increase in antibody after dose (μg)[a]			No. of persons/total showing ≧two-fold increase after dose (μg)		
American	Danish	25	12.5	6.25	25	12.5	6.25
1	1	1.6	1.5	1.6	2/7	4/8	0/8
2	2	1.3	1.5	1.1	1/6	1/6	1/8
3	3	1.1	1.0	1.1	0/7	0/8	0/8
4	4	0.9	1.1	1.0	0/7	0/8	0/7
6	6A	1.0	1.0	1.0	0/7	0/8	0/8
8	8	1.0	1.0	1.0	0/7	0/8	0/8
9	9N	1.0	1.0	0.9	0/6	0/7	0/7
12	12F	1.0	1.0	1.0	0/7	0/8	0/8
14	14	1.1	1.0	1.1	0/5	0/7	0/5
19	19F	0.9	1.0	1.0	0/6	0/7	0/7
23	23F	1.0	1.0	0.9	0/6	0/6	0/7
25	25	1.3	1.2	1.5	1/6	1/6	2/8
51	7F	1.0	1.0	1.1	0/6	0/7	0/8
56	18C	0.9	1.0	1.1	0/7	0/6	0/8

[a] Micrograms of each serotype per dose.

ing it alone. This reduction is statistically significant ($P < 0.05$) only for type 8. Table III presents the mean prevaccination and postvaccination titers for six of the serotypes. It is seen that the mean postvaccination titers were very high for all of the serotypes indicating no great importance for the small depressions in titer resulting from simultaneous vaccine administration. Table IV shows that there was no significant reduction ($P > 0.05$) in antibody response against the influenza virus strains among the subjects tested, whether given influenza vaccine alone or at the same time with pneumococcus vaccine.

Table V compares the local and febrile reactions among the recipients of vaccines given singly or in combination. There was no increase in local reaction to either vaccine when given with the other, and the systemic reactions were no greater following simultaneous administration than when the influenza vaccine was given alone.

Discussion. Polyvalent pneumococcal capsular polysaccharide vaccine has been well accepted in the USA where about 3 million doses were distributed from the time of introduction in early 1978 through the end of the year. The vaccine is presently released under tentative guidelines issued by the Bureau of Biologics of the U.S. Food and Drug Administration. Each dose of the vaccine contains

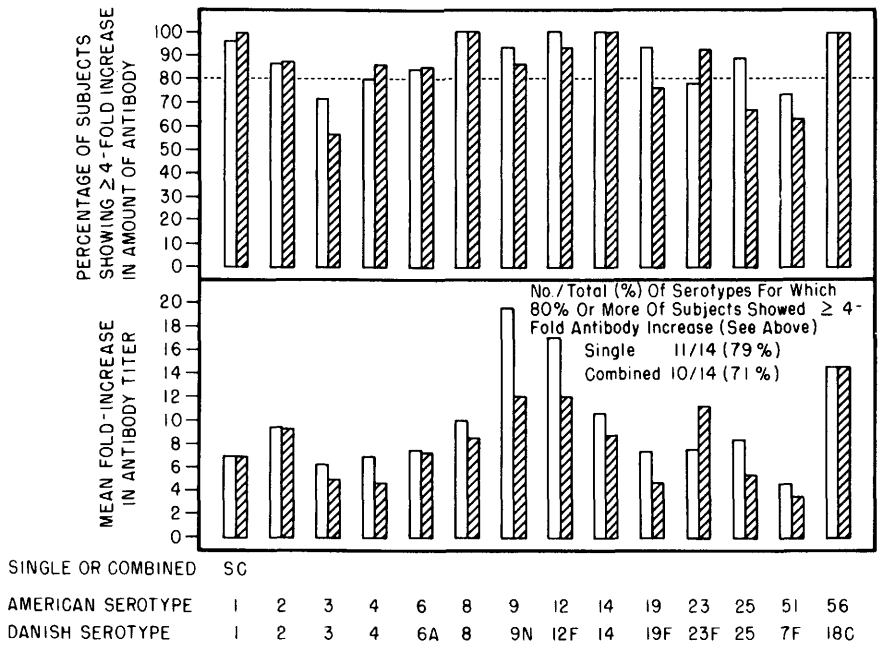

FIG. 2. Antibody responses to pneumococcal antigens among adult persons given 14-valent pneumococcal vaccine alone or given influenza vaccine at the same time in the opposite arm (Study 530).

TABLE III. GEOMETRIC MEAN TITERS, SIX SEROTYPE EXAMPLES, AMONG PERSONS IN STUDY 530 (FIG. 2) WHO RECEIVED PNEUMOCOCCAL VACCINE ALONE OR PNEUMOCOCCAL AND INFLUENZA VACCINES AT THE SAME TIME

Serotype (Danish)	Vaccination	Geometric mean titer		
		Prevaccination	Postvaccination	Fold increase
1	Pneumo.	421	2887	6.9
	Pneumo. plus influenza	419	2856	6.8
3	Pneumo.	944	5760	6.1
	Pneumo. plus influenza	783	3699	4.7
7F	Pneumo.	272	2718	10.0
	Pneumo. plus influenza	261	2227	8.5
8	Pneumo.	438	8548	19.5
	Pneumo. plus influenza	400	4808	12.0
19F	Pneumo.	246	2014	8.2
	Pneumo. plus influenza	432	2255	5.2
23F	Pneumo.	4911	22,663	4.6
	Pneumo. plus influenza	5157	17,860	3.5

50 μg each of 14 designated pneumococcal capsular polysaccharides. According to present guidelines, the vaccine must induce a fourfold or greater increase in homologous antibody against each serotype as measured in the radioimmunoassay, but any person whose prevaccination serum titer is greater than the geometric mean postvaccination titer of all the persons in the group may be eliminated for computation purpose. It was shown in the present studies that smaller doses of antigen, i.e., 25 and 12.5 μg per dose, gave remarkably good antibody responses to most of the serotype antigens. The 50-μg dose alone, however, allowed the vaccine to meet the current guidelines and there is no evident reason to alter them. Vaccine given in the 50 μg per antigen dose is well tolerated and cognizance needs to be taken that protective efficacy of the vaccine was established based on 50 μg per antigen vaccine.

The duration of protective effect of the

TABLE IV. COMPARISON OF INFLUENZA HI ANTIBODY RESPONSES AMONG PERSONS WHO RECEIVED INFLUENZA VACCINE ALONE OR SIMULTANEOUSLY WITH PNEUMOCOCCAL VACCINE (STUDY 530)[a]

Vaccine	Influenza test antigen	Bleeding time (months)	Initially seronegative		Initially seropositive		Total group			Fold rise
			≥40 No./total	GMT	≥40 No./total	GMT	≥40 No./total	%	GMT	
Influenza	A/USSR/90/77	0		<10[b]	7/11	52	7/16	44	15	
		1	3/5	25	10/11	124	13/16	81	76	5
Influenza + pneumo.	A/USSR/90/77	0		<10	6/8	62	6/13	46	13	
		1	2/5	53	8/8	147	10/13	77	99	8
Influenza	A/Texas/1/77	0		<10	5/8	31	5/16	31	6	
		1	7/8	320	7/8	226	15/16	94	269	45
Influenza + pneumo.	A/Texas/1/77	0		<10	0/3	10	0/13	0	2	
		1	8/10	130	2/3	50	10/13	77	104	52
Influenza	B/Hong Kong/5/72	0		<10	3/9	27	3/16	19	6	
		1	4/7	40	9/9	148	13/16	81	84	14
Influenza + pneumo.	B/Hong Kong/5/72	0		<10	3/9	27	3/13	23	10	
		1	3/4	40	9/9	118	12/13	92	84	8

[a] The influenza antibody assays were performed at the Center for Disease Control.
[b] <10 = 1 for calculation of GMT.

TABLE V. COMPARISON OF LOCAL AND FEBRILE REACTIONS AMONG PERSONS WHO RECEIVED PNEUMOCOCCAL OR INFLUENZA VACCINES ALONE OR BOTH VACCINES SIMULTANEOUSLY IN OPPOSITE ARMS (STUDY 530)

Vaccine group	Reaction	Percentage with reaction on day: 0	1	2	3	4	5
Pneumococcal vaccine (23 persons)	Local (arm)	39	48	26	9	4	4
	Fever						
	99–99.9	13	26	9		4	13
	100.4		4				
Influenza vaccine (24 persons)	Local (arm)	17	25	17	12	8	8
	Fever						
	99–99.9	25	21	33	17	12	12
	100.2		4				
Pneumococcal plus influenza vaccine (25 persons)	Local (arm)						
	Pneumococcal site	16	40	32	8	4	
	Influenza site	12	40	8	4		
	Fever						
	99–99.9	8	12	8	4		
	100–100.9		4	4	4	4	4
	101		4				

vaccine is presently unknown, but it was shown in previous studies (11, 12) 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. Eventual need for revaccination must, however, be considered. Previous clinical studies (3) showed that all of seven persons who were revaccinated with 50 μg per antigen vaccine 13 months after an initial dose of 50 μg per antigen vaccine showed increased systemic and local reactions characterized by greater local soreness, erythema, and induration that lasted for a longer time period. There was fever in three persons on revaccination and two experienced chills. This was believed to be due to a local "Arthus-like" reaction caused by antigen–antibody reaction at the injection site. In the present study employing one-half or one-fourth the antigen dose (25 μg or 12.5 μg per antigen), there was no marked local or systemic reaction in persons vaccinated 12 to 18 months earlier with 50 μg per antigen dose vaccine. The individuals in the study had not as yet shown substantial decline in their antibody levels, and there was no real increase in antibody on revaccination. The findings in the study demonstrated a means whereby safety of the vaccine on revaccination could be achieved but the time interval between vaccination and revaccination was not long enough to test for ability of the reduced dose to restimulate antibody production.

Pneumococcal vaccine is currently recommended by the Advisory Committee on Immunization Practices (8) of the U.S. Public

Health Service for routine use in persons at high risk to illnesses and death caused by pneumococci. This high-risk group is generally considered to include persons having chronic conditions such as chronic heart disease of any etiology, chronic bronchopulmonary diseases, chronic renal failure, and diabetes mellitus or other chronic metabolic disorders. In addition, persons with splenic dysfunction or asplenia and all persons 50 years of age or older are considered to be at increased risk. This is essentially the same group as that for which viral influenza vaccine is recommended (13). Practical considerations that include the number of required contacts between patients and medical personnel make it highly desirable to give as many different vaccines at the same time as is medically and scientifically acceptable. It was of importance in the present study that persons given pneumococcal and influenza vaccines in opposite arms at the same time showed no decrease in antibody to influenza virus and the slight decrease in antibody against a few of the pneumococcal serotypes were so small as to be judged of no importance in relation to protective efficacy of the vaccine. Importantly, there was no increase in local or systemic reactions in persons who received the two vaccines at the same time as compared with the same vaccines given singly. These findings, that reveal the compatibility of the two vaccines, are of importance since simultaneous administration greatly facilitates achievement of immunization against both agents, especially in populations that are difficult to reach.

Summary. Current pneumococcal vaccine contains 14 specific capsular polysaccharide antigens, each in 50-μg amount. Reduction of dosage to 25 or 12.5 μg per type gave reduced antibody responses in human subjects for most of the serotypes and these were less than current requirements of the U.S. Food and Drug Administration. Specific antibody following vaccination declines slowly and there was no worthwhile increase in antibody on revaccination 1 to 1.5 years following prior vaccination. Reduction in the dosage of antigen to one-half or one-fourth the 50 μg per antigen amount eliminated the enhanced local and systemic reactions noted previously when the full vaccine amount was given but the time interval between vaccination and revaccination was not long enough to test for the ability of the reduced dose to restimulate antibody production. Pneumococcal and influenza virus vaccines given at the same time into opposite arms showed no important reduction in antibody response to either vaccine and there was no increase in local or systemic reactions compared with that found when the vaccines were given alone.

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