Antibody Response to Booster Dose of Diphtheria and Tetanus Toxoids and Pertussis Vaccine

Thirteen years after inoculation of institutionalized subjects

V. K. VOLK, M.D., Dr.P.H., R. Y. GOTTSHALL, Ph.D., H. D. ANDERSON, Ph.D.
FRANKLIN H. TOP, M.D., W. E. BUNNEY, Ph.D., and ROBERT E. SERFLING, Ph.D.

IN 1943 several groups of mentally ill adult patients in the Pontiac State Hospital, Pontiac, Mich., were inoculated with different combinations of diphtheria and tetanus toxoids, pertussis and typhoid vaccines, and scarlet fever toxin, according to defined dosage schedules. The subjects' reactions were studied, and their specific immune responses were measured in terms of circulating antibodies. The results formed the basis for a series of reports which demonstrated that responses to each antigen were excellent in all combinations studied (*1–4*). In 1956 many of the subjects from this investigation were still in residence at the hospital and available for a study of their responses to a booster dose of antigen.

These institutionalized subjects represented a different population from the noninstitutionalized subjects reported earlier (*5*). Not only did they differ with respect to their age and environment, but owing to an institutional policy, they had received subsequent boosters of diphtheria and tetanus toxoids. Even before we gave them the injections in 1943, the institutionalized subjects had received numerous Schick tests and booster injections of diphtheria toxoid at intervals throughout their hospitalization, extending back as far as 1932.

The study reported here was designed primarily to measure the responses of 290 institutionalized subjects to a small dose of diphtheria and tetanus toxoids to determine whether their responses differed from those of the noninstitutionalized subjects, reported previously, who had not been given intervening booster injections (*5*). Secondarily, the investigation was concerned with the effect of a small dose of pertussis vaccine on production of agglutinins. Because pertussis may occur in older children and adults, even though injected with pertussis vaccine in infancy (personal communication from Dr. Harold J. Lambert, July 1963), there is a growing interest in the extension of pertussis boosters beyond preschool age. It seemed

Dr. Volk is commissioner, Saginaw County Health Department, Saginaw, Mich. Dr. Gottshall is chief, antigens and antisera unit, biologic products section, and Dr. Anderson is chief, biologic products section, division of laboratories, Michigan Department of Health, Lansing. Dr. Top is head, department of hygiene and preventive medicine, State University of Iowa, Iowa City. Dr. Bunney is vice president and director of manufacturing operations, E. R. Squibb & Sons, New York City. Dr. Serfling is chief, Statistics Section, Epidemiological Branch, Communicable Disease Center, Public Health Service, Atlanta, Ga.

Maud G. Gilbert, Saginaw County Health Department, and Frances Angela, Michigan Department of Health laboratories, gave technical assistance in this study.

This study was made in cooperation with the technical committee on immunization, epidemiology section, American Public Health Association, and was supported in part by research grant E–1115 from the National Institute of Allergy and Infectious Diseases, Public Health Service.

important, therefore, to inoculate adults with a small dose of pertussis vaccine to obtain reaction rates and to measure antigenic responses to this antigen. A combination of diphtheria and tetanus toxoids and pertussis vaccine, aluminum phosphate adsorbed, was chosen for this injection.

Methods

The 290 subjects were grouped according to their injection histories (table 1). Group 1 had received primary injections of diphtheria, scarlet fever, and pertussis antigens. Tetanus toxoid was not included. Group 2 had received primary injections of diphtheria, pertussis, scarlet fever, typhoid, and tetanus antigens. Group 3 had received primary injections of diphtheria and tetanus toxoids either singly or combined. Injections were given by the hospital staff. Each subject had had a well-authenticated history of primary injections and interim booster injections. The subjects in group 3 were not part of the original studies (*1*, *2*) but were included here to compare responses with groups 1 and 2. All three groups had received numerous booster doses of diphtheria and tetanus antigens between 1943 and 1956.

Blood specimens were taken from all subjects in the three groups, and each subject was given an intramuscular booster injection of 0.2 ml. of DTP. Antibody titrations were made at subsequent intervals of 1 and 2 weeks and 2, 6, 12, and 24 months.

A registered nurse from the Saginaw County Health Department assembled a complete history of each subject's inoculations from the records of the previous study and the interim institutional records. She also gave all of the injections, drew all of the blood samples, and assisted in the tabulation of data.

The booster dose of antigen, a routine product of the division of laboratories, Michigan Department of Health, contained 4 Lf (Limes flocculation) units of diphtheria toxoid and 2 Lf units of tetanus toxoid in a 0.2 ml. dose. The diphtheria toxoid had a purity of 1,490 Lf units per milligram of protein nitrogen. The tetanus toxoid had a purity of 1,508 Lf units per milligram of protein nitrogen. The pertussis component contained 4.8 opacity units in 0.2 ml. Each dose also contained 0.11 mg. of aluminum in the form of aluminum phosphate. Antigenicity tests on the combined products, performed according to the Minimum Requirements of the National Institutes of Health, indicated that each human dose of 0.5 ml. injected into the guinea pig produced 5 units of diphtheria antitoxin per milliliter of serum and 6 units of tetanus antitoxin per milliliter of serum. Antigenicity tests on the pertussis component indicated 8.4 mouse protective units per milliliter.

Details of the procedures for diphtheria and tetanus antitoxin titrations have been described earlier (*5*). The tests for pertussis agglutinins were performed according to the method of Kendrick, Lawson, and Miller (*6*). The tubes were incubated at 40° C. for 1 hour, and titers were read after overnight incubation at room temperature. Agglutination tests on serum samples from the preinjection and 1- and 2-week specimens, and frequently the 2-month specimens, were made concurrently. All results are expressed as the reciprocal of the dilution.

Table 1. Grouping of 290 institutionalized subjects, according to history of inoculations

Group	Number of subjects	Primary injections		Booster injections	
		Number	Antigens	Intervening boosters	Study booster
1	106	2	Diphtheria, scarlet fever, pertussis.	Diphtheria, tetanus	Diphtheria, tetanus, pertussis.
2	35	2	Diphtheria, pertussis, scarlet fever, typhoid, tetanus.	Diphtheria, tetanus	Diphtheria, tetanus, pertussis.
3	149	1, 2, or 3	Diphtheria, tetanus	Diphtheria, tetanus	Diphtheria, tetanus, pertussis.

When fold increases and geometric means were calculated, the titers of <1:10 were assigned a value of 5. The serum titrations were performed in the Michigan Department of Health laboratories.

Results

The results are presented in two sections: first, the data for each group, and second, analysis of the data to determine effects of age, sex, and history of Schick tests and booster injections of diphtheria and tetanus toxoids on antibody response. The response (tables 2–4) is presented in terms of fold increase (the ratio of the highest observed titer following the booster to the prebooster titer). The highest postbooster titer was usually observed at 2 weeks; when no 2-week titer was obtained, the 1-week or 2-month titer was used. In general, the lower the prebooster titer the greater the fold increase in the antitoxin titer.

Diphtheria titers. The fold increases in diphtheria antitoxin for the subjects in each of the three groups are shown in table 2. Of the 106 subjects in group 1, prebooster and 2-week or 2-month samples were available from 103. None of the subjects had a diphtheria antitoxin titer below 0.01 unit prior to the booster injection. All 35 subjects in group 2 had adequate numbers of serum specimens, and 1 had a prebooster diphtheria antitoxin titer of < 0.01

Table 2. Fold increase in diphtheria antitoxin titers between prebooster and highest observed postbooster titers in three groups who had received a booster dose of 0.2 ml. of DTP

Prebooster range in antitoxin units	Number of subjects with corresponding fold increases in titers														
	1–<2	2–<4	4–<8	8–<16	16–32	32–64	64–128	128–256	256–512	512–1,024	1,024–2,048	2,048–4,096	4,096–8,192	8,192–16,384	Total
Group 1															
<0.001															
0.001–<0.01															
0.01–<0.05			1		2										3
0.05–<0.2			1	1	2	6	1	2			1				14
0.2–<1.0			1	11	9	11	7	4							43
1.0–<5.0	1	9	10	9	4	3	2								38
5.0–<10.0		2		2											4
10.0–<20.0		1													1
Total	1	12	13	23	17	20	10	6			1				103
Group 2															
<0.001															
0.001–<0.01								1							1
0.01–<0.05							1								1
0.05–<0.2						1	1	1	1	1					5
0.2–<1.0			1		4	2	2	1	1						11
1.0–<5.0			2	2	4	2	1								11
5.0–<10.0			3	1											4
10.0–<20.0				1	1										2
Total			6	4	9	5	5	3	2	1					35
Group 3															
<0.001					3				1					2	6
0.001–<0.01					2	2	2	2		2					10
0.01–<0.05			1		2		5	4	1						13
0.05–<0.2			1	3	4	5	4	4	1	1					23
0.2–<1.0	2		4	4	3	10	13	4	4	1					45
1.0–<5.0	1	2	5	9	3	2		2							24
5.0–<10.0		2	2	4											8
10.0–<20.0		1	1												2
Total	3	5	14	20	17	19	24	16	7	4				2	131

unit. In group 3, prebooster and 2-week and 2-month postbooster samples were available from 131 of the 149 subjects. Sixteen subjects had prebooster diphtheria titers below 0.01 unit of antitoxin, and all attained antitoxin levels generally accepted as protective (0.01–0.05 unit per ml.). In general, the prebooster titers for diphtheria antitoxin were high, a reflection of frequent exposure to diphtheria antigens.

Tetanus titers. The fold increases in tetanus antitoxin for the subjects in each of the three groups are shown in table 3. Of the 103 subjects in group 1, 4 had prebooster tetanus antitoxin titers below 0.01 unit. Of the 35 subjects in group 2, the lowest prebooster titers observed were between 0.2 and 1 unit, well above the titer generally accepted as protective (0.01–0.05 unit per ml.). In group 3, 15 of 131 subjects had prebooster tetanus antitoxin titers below 0.01 unit. Without exception, all subjects with tetanus antitoxin titers <0.05 unit per ml. responded vigorously to the booster injection, and the remainder had satisfactory titers.

Pertussis titers. The fold increases in pertussis agglutinin titers for the subjects in each of the three groups are shown in table 4. Of the 103 subjects in group 1, 14 failed to show more than a twofold increase in pertussis agglutinin titers. In group 2, of the 35 subjects

Table 3. Fold increase in tetanus antitoxin titers between prebooster and highest observed postbooster titers in three groups who had received a booster dose of 0.2 ml. of DTP

Prebooster range in antitoxin units	Number of subjects with corresponding fold increases in titers													
	1–<2	2–<4	4–<8	8–<16	16–32	32–64	64–128	128–256	256–512	512–1,024	1,024–2,048	2,048–4,096	4,096–8,192	8,192–16,384	Total
Group 1															
<0.001															
0.001–<0.01									1		1	1	1		4
0.01–<0.05				1			1	1	2		1				6
0.05–<0.2					1	1		2		1	1				6
0.2–<1.0			2	7	12	16	12	5							54
1.0–<5.0		2	10	10	3		1								26
5.0–<10.0		2		2		1									5
10.0–<20.0		1	1												2
Total		5	13	20	16	18	14	8	3	1	3	1	1		103
Group 2															
<0.001															
0.001–<0.01															
0.01–<0.05															
0.05–<0.2															
0.2–<1.0		1		1	1	2									5
1.0–<5.0		3	6	4	1										14
5.0–<10.0		1	6	2											9
10.0–<20.0	1	4	1												6
20.0–<40.0		1													1
Total	1	10	13	7	2	2									35
Group 3															
<0.001								1	1				3	2	7
0.001–<0.01						1			2	2	2			1	8
0.01–<0.05				1			1	1	1	2	2				8
0.05–<0.2					2			1		1			1		5
0.2–<1.0	3	1	5	8	13	9	4	3							46
1.0–<5.0	1	5	14	9	9	2									40
5.0–<10.0			4	3	1										8
10.0–<20.0		3	6												9
Total	4	9	29	21	25	12	5	6	4	5	4		4	3	131

evaluated, 11 failed to show more than a twofold increase in agglutinin titers. Of the 131 subjects in group 3, 32 failed to show more than a twofold increase in titers. In general, the fold increases to this small booster injection of pertussis antigen were lower than those observed for the diphtheria and tetanus toxoid components of the DTP antigen. Subjects in group 3 received no pertussis antigen in the primary inoculation series, in contrast to groups 1 and 2, yet the apparently inconsequential differences in postbooster titers between the groups indicate little effect of previous experience with the pertussis antigen in institutionalized adults.

Titer Changes After Booster

The frequency distribution and geometric mean titers for the three groups that were studied for 24 months are shown in tables 5–7. We had intended to draw prebooster and postbooster blood specimens from each subject at 1 and 2 weeks and 2, 6, 12, and 24 months. However, it was impossible to obtain all these samples on schedule, and we therefore selected for this analysis only those subjects from whom samples were obtained on schedule. This changed the total number of subjects for each group as follows: group 1, 87; group 2, 20; and group 3, 80.

Diphtheria titers. In the selected groups, the prebooster serums of all subjects in groups 1 and 2 had diphtheria antitoxin titers generally accepted as protective (0.01–0.05 unit per ml.), while in group 3 there were eight subjects with lower titers (table 5). The geometric mean prebooster titers of the three groups, 0.7, 0.6, and 0.3 unit, probably reflected frequent exposure to diphtheria antigens. The maximum postbooster titers were generally observed at 2 weeks. The geometric means were 11.8, 19.1, and 9.9 units, respectively. At the 24-month interval, again all subjects in groups 1 and 2

Table 4. Fold increase in pertussis agglutinin titer between the prebooster and highest observed postbooster titer [1]

Titer range	Number of subjects with corresponding fold increase in titer								Total
	1	2	4	8	16	32	64	128	
Group 1									
<10	1	3	3	6	15	11	4	1	44
10	--	2	5	9	9	2	1	--	28
20	--	3	1	5	2	2	--	--	13
40	--	4	7	5	--	--	--	--	16
80	--	--	--	1	--	--	--	--	1
160	--	1	--	--	--	--	--	--	1
Total	1	13	16	26	26	15	5	1	103
Group 2									
<10	2	3	4	1	3	1	--	--	14
10	--	1	4	1	3	--	2	--	11
20	--	1	--	1	2	--	--	--	4
40	1	3	1	1	--	--	--	--	6
80	--	--	--	--	--	--	--	--	--
160	--	--	--	--	--	--	--	--	--
Total	3	8	9	4	8	1	2	--	35
Group 3									
<10	5	7	10	13	11	7	1	--	54
10	2	4	8	15	8	1	1	--	39
20	2	5	4	4	1	1	--	--	17
40	1	5	11	3	--	--	--	--	20
80	--	1	--	--	--	--	--	--	1
160	--	--	--	--	--	--	--	--	--
Total	10	22	33	35	20	9	2	--	131

[1] Antigen injected for primary inoculations for the three groups are shown in table 1.

had titers generally accepted as protective, but three subjects in group 3 had titers between 0.001 and 0.01 unit. The geometric mean titers at 24 months were 1.3, 1.7, and 0.7 units, respectively. For comparison, we have also recorded the geometric mean titers which were reported previously (*5*) for 45 noninstitutionalized subjects who received DT 7 to 13 years after primary injections. This group of subjects had a geometric mean titer as follows: prebooster, 0.06 unit; 2-week postbooster, 6.3 units; and 24-month postbooster, 0.7 unit of diphtheria antitoxin per milliliter of serum.

Tetanus titers. Tests on the prebooster serum specimens showed three subjects in group 1, and four in group 3, with tetanus antitoxin titers below 0.01–0.05 unit of antitoxin per milliliter (table 6). In group 3, all but one subject had

Table 5. Frequency distribution and geometric mean titers at prebooster and successive postbooster intervals: diphtheria response

Titer range	Prebooster titers	Interval from booster					
		Weeks		Months			
		1	2	2	6	12	24
Group 1 (87 subjects)							
<0.001							
0.001–<0.01							
0.01–<0.05	3					1	5
0.05–<0.2	12	1	1	2	3	6	4
0.2–<1	31	11	2	8	10	16	22
1–<5	36	16	14	23	42	45	43
5–<10	4	27	18	22	21	16	10
10–<20	1	17	20	13	8	2	2
20–<40		11	18	12	2	1	1
40–<80		4	8	6	1		
>80			6	1			
Geometric mean	0.7	5.6	11.8	5.7	3.1	2.0	1.3
Group 2 (20 subjects)							
<0.001							
0.001–<0.01							
0.01–<0.05	2				1		1
0.05–<0.2	3	1		2	1	2	2
0.02–<1	4	1	2	1	1	4	3
1–<5	7	2	1	3	8	6	9
5–<10	3	2	1	3	4	6	2
10–<20	1	5	3	4	3	2	2
20–<40		3	6	5	1		1
40–<80		4	5	1	1		
>80		1	2	1			
Geometric mean	0.6	9.3	19.1	8.0	3.6	2.5	1.7
Group 3 (80 subjects)							
<0.001	3						
0.001–<0.01	5	1	1	1	3	1	3
0.01–<0.05	8	2	1	1	2	5	10
0.05–<0.2	12	3	1	2	4	8	9
0.2–<1	25	11	4	13	13	15	18
1–<5	18	21	15	14	24	25	25
5–<10	7	13	12	12	11	15	11
10–<20	2	14	11	16	17	8	2
20–<40		11	15	13	5	2	2
40–<80		4	16	5	2	1	
>80			4	3			
Geometric mean	0.3	3.8	9.9	5.2	3.7	1.6	0.7
Geometric mean titers: Noninstitutionalized subjects who received DT boosters 7–13 years after primary immunization	0.06	1.8	6.3	1.7	1.7	1.0	0.7

titers of 0.2 or more units of antitoxin at the 2-week postbooster interval. The respective prebooster geometric mean titers were 0.6, 4.6, and 0.8 units of antitoxin per milliliter. At the 2-week maximum, the titers were 19.1, 25.1, and 17.3 units. At 24-month postbooster, the titers were 0.6, 2.5, and 0.7 units. The geometric mean tetanus antitoxin titers for the noninstitutionalized subjects reported earlier were: prebooster, 0.13; 2-week postbooster, 24.5, and 24-month postbooster, 3.0 units per milliliter (*5*).

Pertussis agglutinin titers. Tests on the prebooster serums showed the number of subjects with pertussis agglutinin titers < 1:10 were:

Table 6. Frequency distribution and geometric mean titers at prebooster and successive postbooster intervals: tetanus response

Titer range	Prebooster titers	Interval from booster					
		Weeks		Months			
		1	2	2	6	12	24
Group 1 (87 subjects)							
<0.001							
0.001–<0.01	3						
0.01–<0.05	4						2
0.05–<0.2	4	1			1	4	16
0.2–<1	44	1		4	31	54	47
1–<5	25	16	4	30	47	24	18
5–<10	5	20	18	28	6	4	4
10–<20	2	14	26	20	2	1	
20–<40		11	21	4			
40–<80		1	16	1			
80–<120							
>120			2				
Geometric mean	0.6	11.5	19.1	5.9	1.5	0.9	0.6
Group 2 (20 subjects)							
<0.001							
0.001–<0.01							
0.01–<0.05							1
0.05–<0.2							
0.2–<1	2				1	1	2
1–<5	8	2		2	8	14	13
5–<10	5	4	1	7	4	4	3
10–<20	4	4	5	6	6	1	1
20–<40	1	8	11	4	1		
40–<80		3	2	1			
80–<120			1				
>120							
Geometric mean	4.6	17.7	25.1	11.7	5.5	3.2	2.5
Group 3 (80 subjects)							
<0.001	3	1	1				
0.001–<0.01	1					1	2
0.01–<0.05	5			1	2	3	5
0.05–<0.2	3	2			5	5	12
0.2–<1	23	17	1	6	17	33	30
1–<5	32	15	6	21	29	28	27
5–<10	6	18	9	24	19	6	3
10–<20	7	15	22	14	5	2	
20–<40		10	17	10	2	1	1
40–<80			20	3	1	1	
80–<120		1	2				
>120			2	1			
Geometric mean	0.8	9.2	17.3	6.1	2.0	1.0	0.7
Geometric mean titers: Noninstitutionalized subjects who received DT boosters 7–13 years after primary immunization	0.13	8.4	24.5	3.9	6.2	3.7	3.0

group 1, 40 of 87; group 2, 11 of 20; and group 3, 38 of 80 (table 7). The geometric mean titers for the three groups were 9.8, 7.9, and 9.6; at the 2-week maximum, 93.1, 49.3, and 51.0; and at 12 months, 29.4, 18.6, and 16.7. Titers were not determined at 24 months.

Factors in Antitoxin Response

Examination of the data led to selection of the following factors for analysis: age, sex, history of Schick tests, number and frequency of diphtheria boosters, and number and frequency of tetanus boosters. Classification of the data according to sex, history of Schick tests, and Schick reactions is shown in table 8. The subsequent analysis followed this classification of the patients, except that the data were not subdivided by 1932–36 Schick history.

Schick testing was carried out extensively by the Pontiac State Hospital staff in two periods, 1932–36 and 1945–56. Both sexes were tested equally in the latter period, but in 1932–36 more men than women were given the Schick test. Thus, the sexes had to be considered separately for any effects related to the earlier Schick testing program. Administration of diphtheria toxoid is correlated with response to the Schick test, because a positive reaction was usually, but not invariably, followed by injection of a booster dose of diphtheria toxoid. Conversely, persons who were Schick negative were given a diphtheria toxoid booster in only a few instances.

Table 9 presents an analysis of the data given in table 8 with averages on age, number of Schick tests, number of doses of diphtheria and

Table 7. Frequency distribution and geometric mean titers at prebooster and successive postbooster intervals: pertussis response

Titer range	Prebooster titers	Interval from booster				
		Weeks		Months		
		1	2	2	6	12
Group 1 (87 subjects)						
<10	40	4	1	3	11	5
10	24	10	2	1	21	20
20	11	28	6	8	28	21
40	11	13	17	21	22	38
80		22	22	23	4	2
160	1	7	24	24		1
320		2	11	5	1	
640		1	4	2		
Geometric mean	9.8	13.2	93.1	72.7	18.6	29.4
Group 2 (20 subjects)						
<10	11	2	1	1	5	2
10	7	6	1	1	5	5
20		7	4	6	5	6
40	2	2	5	5	3	7
80			5	5	1	
160		2	3	1	1	
320		1		1		
640			1			
Geometric mean	7.9	21.4	49.3	38.7	15.7	18.6
Group 3 (80 subjects)						
<10	38	5	4	5	7	15
10	22	20	10	9	18	19
20	8	21	11	10	19	25
40	11	14	14	17	27	17
80	1	15	18	17	5	1
160		4	17	19	2	3
320		1	5	2	2	
640			1	1		
Geometric mean	9.6	25.9	51.0	48.4	23.6	16.7

tetanus toxoids, and geometric mean titers of the prebooster, 2-week, and 24-month postbooster titers. The fold increase in antibody titers from prebooster to 2-week postbooster is also given. The average age of the patients in the various groups was generally in the upper fifties or low sixties. In two groups, however, the mean age was lower, 48.8 years for women in group 2, who were always Schick negative, and 53.7 years for men in group 2, who had one or more positive Schick tests. Standard deviations of the ages in each group indicate considerable variability in age composition. Within study groups men, on the average, received more Schick tests than women. This is related to the 1932–36 Schick testing of men mentioned above. In group 3, the sex difference by number of Schick tests was significant: for men the average number of tests was "always Schick negative," 8.4, and "sometimes positive," 9.9, and for women, 1.1 and 2.3.

The mean number of doses of diphtheria toxoid administered was associated with response to the Schick test, ranging from an average of 0 to 0.2 for those who were always Schick negative, and from 1.3 to 3.3 for those who had one or more positive Schick tests. Administration of the tetanus antigen was somewhat more frequent in groups 1 and 2, ranging from 2.9 to 3.1, than in group 3, in which the range was 2.3 to 2.5.

Diphtheria titers. In each group men tended to have higher diphtheria titers 2 weeks after booster injections than women but, in general, men had higher prebooster titers. In either sex those who had been Schick negative persistently attained higher titers and greater fold increase at 2 weeks than those who had had one or more Schick positive reactions. Women in group 3, who had had one or more positive Schick tests, exhibited low prebooster and 2-week titers, but the fold increase compared favorably with other groups.

Tetanus titers. At the 2-week postbooster

Table 8. Classification of subjects by sex, Schick test history, and Schick reactions

Number of Schick tests	Reactions	Schick tests						Total both sexes
		Men			Women			
		1945–56 and 1932–36	1945–56	Total	1945–56 and 1932–36	1945–56	Total	
Group 1								
0–4	Always negative		1	1		2	2	3
	1 or more positive							
5 or more	Always negative	13	7	20	1	39	40	60
	1 or more positive	14	4	18		16	16	34
Total		27	12	39	1	57	58	97
Group 2								
0–4	Always negative		1	1		2	2	3
	1 or more positive							
5 or more	Always negative	2	6	8		12	12	20
	1 or more positive	7	3	10		6	6	16
Total		9	10	19		20	20	39
Group 3								
0–4	Always negative	1	11	12		36	36	48
	1 or more positive		4	4		26	26	30
5 or more	Always negative	5	12	17		2	2	19
	1 or more positive	11	20	31	2	1	3	34
Total		17	47	64	2	65	67	131

interval, group 2 showed relatively higher average titers but lower fold increases than the other two groups. Tetanus toxoid was included in the primary injection series of groups 2 and 3.

Discussion

In a previous study, the satisfactory response of noninstitutionalized children to a booster dose given 7 to 13 years after the primary course of multiple antigen injections (with no intervening boosters), suggested that "the present practice of giving a booster injection every 3 or 4 years may not be necessary" (*5*).

In this study of institutionalized adults, the length of time taken to reach the maximum diphtheria and tetanus antitoxin levels following a booster injection, the maximum titers achieved, and the rate of fall during the 24-month postbooster interval were the same as observed in noninstitutionalized children (*5*) even though many interim Schick tests and diphtheria or tetanus toxoid injections were administered in the institution. This study appears to add additional evidence supporting the suggested doubtful value of booster injections given every 3 to 4 years.

In another institutionalized group (Lapeer State Home and Training School) for mentally retarded, the subjects were not given intervening booster doses of antigens. In this group, the diphtheria titers at the time of the booster injection reflected general protection, which suggests natural stimulation by toxigenic diphtheria strains known to exist in this institution. On the other hand, the tetanus antitoxin titers were even lower in the Lapeer group than were observed in the noninstitutionalized subjects (*5*), supporting the assumption that no intervening stimulation with tetanus antigen had occurred in either group. The question then remains whether the routine practice of giving booster injections at short defined intervals is actually necessary in institutions. In other words, it seems possible that the level of protection to diphtheria or tetanus is adequate following a booster given 7 to 13 years after the usual course of antigen injections, regardless of

Table 9. Analysis of factors by group and Schick test history

Number of patients, age, Schick tests, boosters, and geometric mean titers	Schick tests											
	Group 1				Group 2				Group 3			
	Always negative		Some positive		Always negative		Some positive		Always negative		Some positive	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Number of patients	20	40	18	16	8	12	10	6	17	36	31	26
Mean age in years	57. 4	57. 4	59. 4	62. 8	61. 9	48. 8	53. 7	62. 3	59. 4	59. 1	55. 0	58. 5
Standard deviation	10. 3	12. 5	8. 9	12. 2	12. 0	15. 1	12. 4	16. 7	8. 5	15. 0	10. 2	12. 5
Mean number of Schick tests	12. 0	8. 9	13. 9	9. 3	10. 9	9. 2	12. 2	9. 0	8. 4	1. 1	9. 9	2. 3
Mean number of doses of diphtheria toxoid	. 2	. 05	3. 0	2. 1	0	0	2. 8	1. 3	0	. 1	3. 3	2. 3
Geometric mean diphtheria antitoxin titers:												
Prebooster	1. 24	. 46	. 54	. 74	1. 09	. 31	. 84	. 83	1. 06	. 29	. 45	. 02
2 week	17. 94	12. 75	7. 47	8. 20	35. 16	16. 93	10. 51	10. 02	39. 06	13. 11	9. 95	. 62
Fold increase	14	28	14	11	32	54	13	12	37	46	22	27
24 month	2. 01	1. 14	1. 16	. 69	3. 14	1. 17	1. 21	1. 15	4. 23	. 58	. 65	. 03
Mean number of doses of tetanus toxoid	3. 0	3. 0	3. 0	3. 1	3. 0	3. 0	2. 9	3. 0	2. 5	2. 4	2. 5	2. 3
Geometric mean tetanus antitoxin titers:												
Prebooster	. 72	. 59	. 83	. 25	4. 14	2. 21	5. 84	2. 59	2. 98	. 14	1. 19	. 21
2 week	16. 94	21. 81	20. 41	10. 97	23. 13	14. 84	32. 49	22. 74	34. 55	4. 60	22. 79	3. 54
Fold increase	24	37	25	45	6	7	6	9	12	33	19	17
24 month	. 47	. 70	. 59	. 27	1. 51	2. 17	5. 10	2. 61	1. 49	. 41	. 92	. 12

age or sex, whether or not such interim injections have been given and whether or not the persons are institutionalized.

Responses to the pertussis boosters were not striking, as measured by the agglutination test. Correlation between pertussis agglutinin titer and degree of protection has not been established. A definite need exists for a test which will measure the degree of protection against pertussis in human subjects. Under these circumstances pertussis agglutinin titers may not be as meaningful a measure of protection as are diphtheria and tetanus antitoxin titers.

There is evidence that older children and adults, even those injected with pertussis antigen in infancy, contract pertussis, and that perhaps pertussis protection becomes ineffective in some persons after 3–5 years from the last injection of the antigen so there may be a need for extending booster doses of pertussis antigen beyond the preschool booster (personal communication from Dr. Harold J. Lambert, July 1963). Unfortunately, the number and severity of reactions limit the acceptability of pertussis booster injections in older persons until an effective and relatively nontoxic pertussis antigen becomes available.

The local reactions observed in 305 subjects following a 0.2 ml. dose of DTP, reported earlier (*7*), were recorded as 46 percent severe, 30 percent moderate, 22 percent mild, and only 2 percent showed no reactions. Severe local reactions were usually accompanied by mild systemic reactions; moderate and mild local reactions were not.

Summary

In 290 institutionalized subjects who had received primary inoculations 13 years previously and had numerous booster doses of diphtheria and tetanus toxoids, a rapid and vigorous increase in circulating antibody followed a booster injection containing 4 Lf (Limes flocculation) units of diphtheria antigens and 2 Lf units of tetanus antigens, aluminum phosphate adsorbed, combined with 1.7 protective units of pertussis vaccine.

All the subjects responded satisfactorily to the diphtheria and tetanus booster. The responses to the small amount of pertussis antigen in the booster dose were weak, as measured by the agglutination test. The maximum response to each antigen was observed 2 weeks after inoculation, followed by a slow decline through a 2-year period.

The subjects were divided into three groups according to their inoculation histories. Each of these groups carried higher prebooster diphtheria and tetanus titers than observed in an earlier study of noninstitutionalized children who had not received interim boosters. After the booster injection, however, the maximum mean titers attained and the rate of decline over a 2-year period were essentially the same in the institutionalized and noninstitutionalized subjects.

The results of the study provided further evidence of the possible doubtful value of giving booster injections of diphtheria and tetanus toxoids every 3 to 4 years.

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