

Influence of age on the response to *Streptococcus pneumoniae* vaccine in patients with recurrent infections and normal immunoglobulin concentrations

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Background: A deficient antibody response to polysaccharide antigens is determined by measuring the response to the 23-valent pneumococcal polysaccharide vaccine. However, the diagnosis of this specific antibody deficiency is hampered by the lack of sufficient data and standardized testing of the response to pneumococcal polysaccharides.

Methods: All patients evaluated in our allergy/immunology clinic for recurrent respiratory infections between 1995 and 1997 without immunoglobulin, IgG subclass, or other known primary or secondary immunodeficiency were included in this analysis. IgG antipneumococcal serotypes 1, 3, 4, 6B, 9V, 14, 18C, 19F, and 23F were determined by a modified ELISA protocol. An adequate IgG antibody response to an individual serotype was arbitrarily defined as a postimmunization antibody titer of 1.3 µg/ml or greater or at least four times the baseline value.

Results: A total of 113 patients fulfilling the criteria for inclusion in this analysis were divided into five age groups. The geometric means for preimmunization and postimmunization pneumococcal antibody titers for all serotypes increased with age. For post-immunization antibody concentrations, there was a sharp increase in the specific antibody concentrations in adults in comparison with all pediatric age groups ranging in age from 7 months to 16 years. Similarly, the number of serotypes to which there was an adequate response also increased with age.

Conclusion: We conclude that the definition of what constitutes an adequate response to pneumococcal immunization needs further definition. It is clear, however, that age has an important influence on the intensity of the response to most pneumococcal polysaccharides. Correlation studies between antibody concentrations in different IgG subclasses, functional studies, and protection studies against mucosal and invasive pneumococcal infections are in progress, and these should contribute to a refined definition of a normal response. The availability of a standardized method for the measurement of IgG antibodies against relevant pneumococcal serotypes is an important step toward this goal. (*J Allergy Clin Immunol* 1998;102:215-21.)

Key words: *S pneumoniae*, pneumococcal polysaccharide vaccine, antibody, age

A deficient antibody response to bacterial polysaccharide antigens in patients with normal immunoglobulin and IgG subclass concentrations has been described as a specific antibody deficiency syndrome.¹ This lack of antibody response is becoming one of the most frequently recognized immune abnormalities in patients over 2 years of age with recurrent respiratory infections.^{2,3} A deficient response to polysaccharide antigens is determined by measuring the response to the 23-valent pneumococcal polysaccharide vaccine, presently the only means of analyzing the immune response to polysaccharide antigens in humans. However, the diagnosis of this specific antibody deficiency is hampered by the lack of sufficient data and standardized testing of the response to pneumococcal polysaccharides.⁴

The Centers for Disease Control and Prevention are coordinating the standardization of an ELISA for the measurement of IgG antibody concentrations against the *Streptococcus pneumoniae* serotypes included in the new, experimental conjugate pneumococcal vaccines to allow better comparison of results obtained in different clinical trials of these vaccines. The serotypes selected are those most frequently causing infections in both developed and developing countries: 1, 4, 5, 6B, 9V, 14, 18C, 19F, and 23F.⁵ Several of these serotypes, namely 6B, 23F, 14, 9V, 19A, and 19F, are also those that have developed the highest percentages of antibiotic resistance in the United States.^{6,7} The frequency with which these serotypes cause infections and their increasing resistance to antibiotics indicate that an analysis of the immune response to these serotypes is relevant to the evaluation of patients with recurrent infections.

We introduced the new ELISA protocol into our clinical laboratory in 1995. A key feature of this assay, adapted from a method described by Koskela,⁸ is the absorption of all patient sera with *S. pneumoniae* polysaccharide C and the possibility of fully titrating all antibody concentrations. Our results show that the intensity of the response to pneumococcal polysaccharides increases significantly with age for all serotypes

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TABLE I. Indications for the use of the pneumococcal vaccine in our clinic

Disease	Number of episodes	
	2 to 5 years	Older than 5 years
URI with antibiotics*	>4	>2
Otitis with antibiotics†	>3	>2
Sinusitis‡	>2	>1
Chronic, resistant sinusitis§	>1	>1
Pneumonia (after age 2 years)	>2	>2
Need preventative antibiotics	≥1	≥1
Allergy to antibiotics for treatment of respiratory infections	≥1	≥1

*In the preceding 12 months.

†After tube placement.

‡Per year.

§Per month.

tested. This increase must be considered in defining abnormal responses to pneumococcal polysaccharides in patients with recurrent infections.

METHODS

Patient population

Patients referred to our allergy/immunology clinic for recurrent infections are evaluated according to a standard protocol, which includes a detailed history of infections, antibiotic use, and a laboratory evaluation, including immunoglobulin and IgG subclass determinations and the measurement of specific antibodies to pneumococcal polysaccharides. All patients evaluated between 1995 and 1997 who did not have immunoglobulin, IgG subclass, or other known primary or secondary immunodeficiency were included in this analysis. As part of their evaluation, patients in this study received one dose of a 23-valent pneumococcal vaccine (Pnu-Immune; Lederle-Praxis Biologicals, Pearl River, N.Y.). Antipneumococcal polysaccharide antibodies were measured before and 4 to 6 weeks after immunization. The presence of other factors predisposing patients to recurrent respiratory infections (e.g., chronic allergic inflammation or passive smoke exposure) was not an exclusion criterion for this analysis. Healthy adults who volunteered to receive the vaccine were also included in the study and compared with adults evaluated for recurrent respiratory infections.

Adequate IgG antibody response

For the purposes of evaluation, an adequate IgG antibody response to an individual serotype was arbitrarily defined as a post-immunization antibody concentration 1.3 µg/ml or greater or a minimum fourfold increase over the baseline (preimmunization) value.

Indications for immunization with pneumococcal vaccine

In our clinical practice, indications for evaluating the presence of an antibody deficiency are similar to our indications for the use of the pneumococcal polysaccharide vaccine (Table I). These indications are based on historical information about infections and antibiotic treatment only because in most instances proof of all past infections is impossible to obtain. Although pneumococcal immunization is not recommended for patients under 2 years of age, it may be clinically effective in some younger patients. After observing adequate clinical and immunologic responses in some 1 year old patients, we included all patients younger than 2 years in the analysis presented here, regardless of their individual response to immunization.

ELISA for antipneumococcal IgG

IgG antipneumococcal serotypes 1, 3, 4, 6B, 9V, 14, 18C, 19F, and 23F were determined by a modified ELISA protocol.^{8,9} This procedure involves the binding of optimal concentrations of individual pneumococcal serotype polysaccharides (ATCC, Rockville, Md.) on the surface of microtiter plates (Nunc Maxisorp, catalog no.439454). Standard, control, and serum samples, diluted in 0.01 mol/L phosphate-buffered saline containing 0.05% polyoxy-ethylene-sorbitan monolaurate (Tween 20) and 1.0% bovine serum albumin, were preabsorbed for 30 minutes at 37° C with *S. pneumoniae* C-polysaccharide (500 µg/ml in undiluted serum; Statens Serum Institut, Denmark). Four twofold dilutions of both patient and control samples were then added to their respective wells, and the plates were incubated for 2 hours at room temperature. The wells were then washed three times with phosphate-buffered saline/0.05% Tween 20. A titrated amount of horseradish peroxidase-labeled mouse anti-human IgGfC monoclonal antibody (Hybridoma Reagent Laboratories, Baltimore, Md.) was added, and the plates were incubated in the dark for 2 hours at room temperature. After another washing step, the bound enzyme was detected by the addition of tetramethyl-benzidine-dihydrochloride (Sigma Chemical Co., St. Louis, Mo.) in citrate phosphate buffer. The serotype-specific IgG antibody concentration (in micrograms per milliliter) was calculated by measuring the absorbance (optical density at 450 nm) against a standard curve obtained with twofold serial dilutions of a serum pool (standard) prepared from six healthy adults who had been immunized with the 23-valent polysaccharide vaccine (Lederle-Praxis Biologicals). Serotype-specific IgG levels in this standard had previously been determined by using the FDA 89-SF reference sample (CBER; U.S. Food and Drug Administration, Rockville, Md.). The antibody concentration against serotype 3, which is not included in the conjugate vaccines, was determined by cross-standardization of our standard against the assigned IgG values for the other serotypes in the FDA 89-SF sample.

Before clinical use, evaluation of linearity in this assay showed an excellent correlation ($r = 0.99$) between observed and expected results, with minimum detectable concentrations ranging from 0.04 to 0.1 µg/ml for all nine serotypes tested. The interassay precision (percent coefficient of variation), determined by assaying a sample in 20 separate tests, ranged from 10.2% to 14.4% for the same serotypes.

Data collection and analysis

Data for the study was collected from patient charts, recorded on specially designed data-entry forms, and then entered into a program written with Epi Info 6.03, a database and statistics program distributed by the Centers for Disease Control and Prevention.

Log-transformed values for preimmunization and postimmunization pneumococcal antibody titers were used to minimize the effect of a few very high values and to calculate the geometric means. Comparisons of patient groups were done with the chi-square test or Kruskal-Wallis one-way analysis of variance.

RESULTS

A total of 113 patients fulfilling the criteria for inclusion in this analysis were divided into the following age groups: (1) under 2 years old ($n = 14$), (2) 2 to 5 years old ($n = 44$), (3) 6 to 10 years old ($n = 25$), (4) 11 to 16 years old ($n = 10$), and (5) adults ($n = 20$; 10 with recurrent infections and 10 healthy adults).

In patients with recurrent respiratory infections, the geometric means for preimmunization and postimmunization pneumococcal antibody titers for all serotypes

TABLE II. Response to immunization with the 23-valent pneumococcal polysaccharide vaccine: Preimmunization and postimmunization pneumococcal antibody titers in children and adults with recurrent infections

Serotypes		Age groups				
		<2 yrs (n = 14)	2-5 yrs (n = 44)	6-10 yrs (n = 25)	11-16 yrs (n = 10)	Adults (n = 10)
1	Pre	0.09*	0.15	0.21	0.67	0.99
		0.04-0.72	0.04-0.80	0.04-1.26	0.12-4.70	0.22-6.44
	Post	1.20	1.01	1.89	1.64	3.30
3	Pre	0.33-3.63	0.12-9.20	0.42-11.2	0.61-4.72	1.14-7.72
		0.20	0.27	0.30	0.25	0.90
	Post	0.07-1.73	0.05-2.96	0.07-7.37	0.07-2.11	0.21-4.80
4	Pre	1.04	0.77	0.85	0.90	2.00
		0.17-4.33	0.07-8.87	0.07-10.61	0.33-2.84	0.07-27.68
	Post	0.05	0.09	0.14	0.60	0.67
6B	Pre	0.03-0.36	0.04-0.77	0.04-0.95	0.13-4.89	0.12-2.61
		0.68	0.73	0.88	1.48	1.48
	Post	0.20-2.51	0.18-17.50	0.19-5.20	0.31-28.4	0.26-6.26
9V	Pre	0.09	0.15	0.40	0.74	0.81
		0.08-0.63	0.07-1.50	0.08-7.06	0.10-5.36	0.22-3.27
	Post	0.22	0.50	1.32	1.64	2.99
14	Pre	0.08-2.36	0.08-11.27	0.08-33.84	0.34-6.53	0.77-11.51
		0.11	0.13	0.18	0.49	0.49
	Post	0.06-2.40	0.02-0.67	0.06-0.85	0.06-2.07	0.27-2.37
18C	Pre	0.59	1.10	1.32	1.64	2.00
		0.06-1.71	0.06-15.70	0.07-14.44	0.40-10.41	0.53-8.71
	Post	0.15	0.18	0.31	0.60	2.21
19F	Pre	0.10-0.76	0.06-1.69	0.10-1.79	0.10-6.97	0.10-8.66
		0.25	0.64	2.70	5.45	22.08
	Post	0.10-1.00	0.09-19.28	0.10-23.92	0.12-115.35	0.10-294
23F	Pre	0.09	0.12	0.26	0.40	0.74
		0.05-0.31	0.05-0.75	0.05-2.54	0.06-2.85	0.10-7.78
	Post	0.90	0.96	1.81	1.10	6.65
23F	Pre	0.05-6.08	0.05-17.59	0.08-20.24	0.20-3.87	1.00-101.4
		0.15	0.17	0.31	0.81	1.34
	Post	0.05-1.84	0.08-1.43	0.08-1.72	0.08-6.00	0.26-3.74
23F	Pre	0.44	0.77	1.37	2.70	3.30
		0.08-12.7	0.08-13.81	0.08-7.08	0.37-8.77	0.08-63.0
	Post	0.09	0.17	0.26	0.81	1.10
23F	Pre	0.04-0.62	0.05-5.31	0.04-2.45	0.08-5.66	0.18-5.58
		0.25	0.58	1.04	1.34	2.45
	Post	0.08-1.62	0.08-7.93	0.08-7.52	0.08-23.96	0.08-8.78

Preimmunization antibody concentrations were significantly different ($p < 0.05$) among the age groups (Kruskall-Wallis) for all serotypes. Differences in post-immunization concentrations were significant for serotypes 1, 6B, 9V, 14, 18C, 19F, and 23F.

*Values are geometric means ($\mu\text{g/ml}$) and range.

increased significantly with age (Table II). Postimmunization-specific antibody concentrations in adults were generally higher than those in any pediatric group. However, the pattern of increases across the age groups was different for the various serotypes. For example, adult postimmunization antibody concentrations were strikingly higher than those of any pediatric age group for serotypes 14 and 18C, but no different from the 11 to 16 year old group for serotype 4. It is also notable that, for serotypes 1 and 3, postimmunization antibody concentrations were higher in children under 2 than in the 2 to 5 year old group.

Preimmunization antibody concentrations in general ran parallel to postimmunization concentrations for the different age groups (Table II). The increase in antibody concentrations after immunization expressed as

fold increases over baseline, however, followed three different patterns. Mean fold increases were notably higher in children than in adolescents and adults for serotypes 1, 4, 9V, and 18C (Table III), whereas they were similar in all age groups for serotypes 3, 6B, 19F, and 23F. For serotype 14, a striking pattern of increase according to age was noted, with very low mean fold increases in young children but sharply higher mean fold increases in adolescents and adults.

The percentage of patients in each group showing adequate antibody responses also varied for the different serotypes studied (Table IV). For example, 32% to 75% of 2 to 5 year old children had adequate responses for the serotypes studied, whereas 70% to 90% of adults had adequate responses (Table IV). On an individual basis, the concentration of preimmunization antibodies was not

TABLE III. Response to immunization with the 23-valent pneumococcal polysaccharide vaccine: Mean fold-increase over baseline in each age group

Serotypes	Age groups				
	<2 yrs (n = 14)	2-5 yrs (n = 44)	6-10 yrs (n = 25)	11-16 yrs (n = 10)	Adults (n = 10)
1	16.8 (4.0-44.4)	12.8 (0.3-70.8)	21.4 (1.2-140.0)	3.6 (0.9-8.1)	4.5 (1.2-13.2)
3	6.8 (1.0-19.1)	4.3 (0.6-15.6)	4.4 (0.3-13.6)	4.0 (1.3-12.9)	3.2 (0.2-9.7)
4	17.9 (2.7-62.7)	18.3 (0.8-174.3)	11.2 (0.8-40.0)	6.4 (0.9-40)	4.0 (0.6-13.9)
6B	4.9 (0.9-29.5)	5.0 (0.3-31.9)	6.1 (0.7-53.7)	3.2 (0.8-11.8)	3.9 (1.6-7.4)
9V	9.0 (0.6-23.0)	21.6 (1.0-261.0)	14.3 (0.9-68.0)	4.4 (1.1-15.3)	4.5 (2.0-8.1)
14	2.4 (0.2-7.4)	7.6 (0.1-58.9)	14.7 (0.5-91.0)	33.9 (0.1-94.9)	20.3 (1.0-64.9)
18C	26.1 (1.0-121.6)	21.6 (0.2-302.0)	14.8 (1.0-86.8)	4.5 (0.8-12.9)	11.5 (2.9-17.3)
19F	4.6 (0.5-11.0)	6.7 (0.4-41.0)	5.5 (1.0-25.5)	4.3 (0.8-11.7)	7.7 (0.2-51.2)
23F	3.4 (0.9-10.0)	6.1 (0.2-49.1)	6.9 (1.0-39.4)	2.4 (0.3-7.2)	3.3 (0.4-9.2)

Values are mean fold increase (range).

TABLE IV. Percentage of population with adequate responses*

Serotypes	Age groups				
	<2 yrs (n = 14)	2-5 yrs (n = 44)	6-10 yrs (n = 25)	11-16 yrs (n = 10)	Adults (n = 10)
1	100%	73%	80%	70%	90%
3	71%	48%	56%	40%	70%
4	93%	70%	72%	50%	70%
6B	29%	32%	60%	40%	80%
9V	64%	73%	72%	60%	60%
14	29%	48%	84%	90%	90%
18C	93%	75%	80%	50%	90%
19F	50%	48%	64%	80%	70%
23F	43%	52%	56%	40%	80%

*Adequate response equals fourfold increase over baseline or postimmunization titer of 1.3 µg/ml or greater.

predictive of the response to polysaccharide immunization. Some patients with very low preimmunization antibody concentrations had either a total lack of response or an excellent response with postimmunization antibody concentrations above 1.3 µg/ml (data not shown). Conversely, although the majority of patients with preimmunization titers above 1.3 µg/ml had further increases after immunization, others had no increase.

An analysis of the antipolysaccharide responses in the same individual revealed that there was no correlation between responses to the different serotypes tested. Furthermore, no response to an individual serotype was predictive of the response to other serotypes. For instance, complete absence of a response to serotype 14 in children was not predictive of inability to respond to any other individual serotype or to any group of serotypes despite the fact that this serotype induced the highest responses measured in adults (data not shown).

The number of serotypes to which patients had adequate responses increased with age (Fig. 1). No child under 2 years had adequate responses to all nine serotypes tested, whereas 50% of adults with recurrent infections did have adequate responses. Conversely, adequate responses to two or fewer serotypes were detected in children and adolescents, but not in adults.

We found no differences in preimmunization anti-

body concentrations or in antibody responses to individual serotypes when we compared 10 healthy adult subjects to the 10 adult patients with recurrent respiratory tract infections (Fig. 2).

DISCUSSION

Current recommendations for the use of the pneumococcal polysaccharide vaccine are designed to protect against pneumonia and invasive disease in individuals at risk.¹⁰ The indications for the use of the vaccine in our clinic are based on the importance of *S. pneumoniae* as the cause for otitis media and sinusitis, as well as on the emerging antibiotic resistance of several pneumococcal serotypes. Pneumococci cause 20% to 40% of otitis media¹¹ and variable percentages of sinusitis. It has been estimated that in 1 year, pneumococci cause 7,000,000 episodes of otitis media and 3000 episodes of meningitis.¹⁰ Pneumococci frequently causing otitis media include serotypes 6B, 14, 19A, and 23F,^{12,13} which are the same serotypes found to have developed resistance to antibiotics in the United States and elsewhere.^{6,7,14,15} All are included in the 23-valent pneumococcal polysaccharide vaccines and in the panel of serotypes for which we test the development of IgG antibodies.

Pneumococcal immunization and evaluation of the resulting IgG antibody response against pneumococcal polysaccharide serotypes included in the vaccine is an

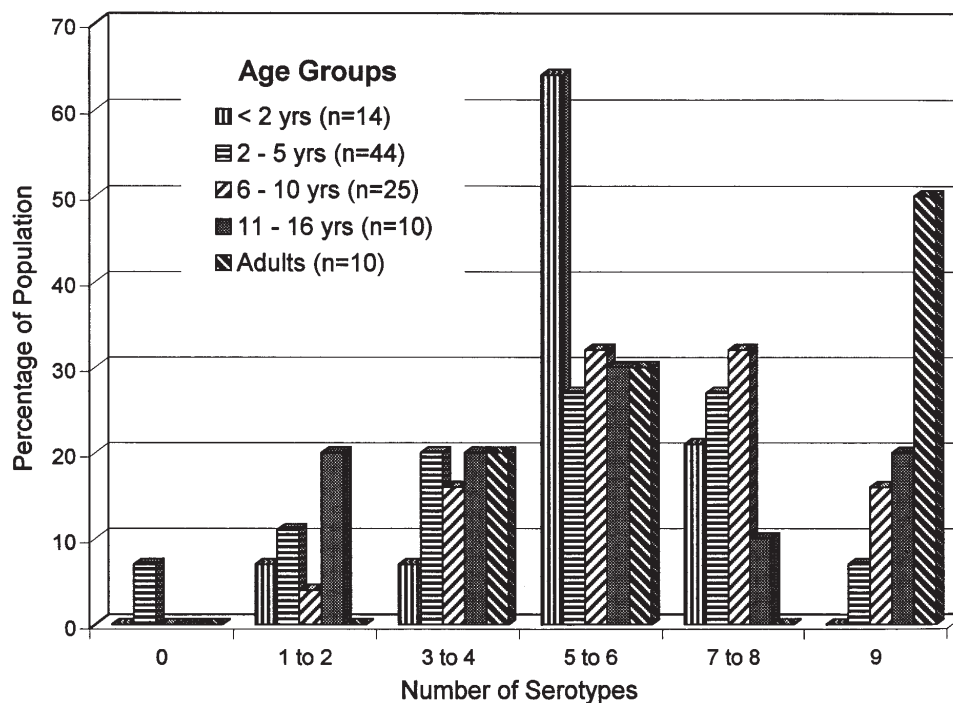


FIG. 1. Percentage of patients in each age group who had adequate responses to none, one to two, three to four, five to six, seven to eight, or all nine serotypes tested. See text for definition of adequate response to individual serotypes.

accepted method of identifying deficiencies in the development of antibodies against polysaccharide antigens.¹⁶⁻¹⁹ The interpretation of the IgG response to pneumococcal serotypes must take into account both the response to individual serotypes and the collective response to all serotypes against which IgG antibodies are measured.

An age-dependent development of the ability to develop both IgM and IgG antibodies against the various pneumococcal serotype polysaccharides has been shown in several immunization trials with polyvalent pneumococcal vaccines.²⁰⁻²³ When IgM and IgG responses were evaluated separately, three types of responses to different serotypes were observed in 2 to 18 month old children: high IgM and IgG antibodies against serotype 3; intermediate responses with IgM titers higher than IgG titers to serotype 23; and little or no IgM or IgG response to serotypes 6, 18, and 19.²⁴ The results obtained in our laboratory confirm these earlier observations and show that the intensity of the response to different serotypes varies with age even in patients older than 2 years.

Two criteria for the interpretation of the immune response to pneumococcal polysaccharides have been proposed in the literature: (1) the difference between preimmunization and postimmunization antibody concentrations and (2) the postimmunization antibody concentration regardless of the increase after immunization.

Increases in antibody concentration alone are unlikely to be an appropriate way of interpreting the immune response. By extending each antibody determination to the lowest limits of detection (e.g., 0.04 μ g/ml in the

assay used in our laboratory) a twofold increase to 0.08 still means a level far below the putative protective level (see below). On the other hand, our results confirm previous observations that patients with high preimmunization antibody concentrations tend to have smaller fold increases than those with low preimmunization concentrations.^{20,22,25,26} Therefore in addition to the increase in antibodies induced by immunization, it is important to consider the antibody concentration reached, regardless of whether it was induced by infection before the immunization or by the immunization itself.

Antibody concentrations protective against infection have not yet been defined for any pneumococcal serotype. Systemic pneumococcal infection rarely occurs in adults with serotype-specific antibodies greater than 250 to 300 ng antibody N/ml.²⁷ In children, antibody concentrations of 200 ng antibody N/ml or greater were correlated with decreased nasopharyngeal colonization with specific pneumococcal serotypes.²² For the antibody concentrations used here, expressed in micrograms per milliliters, the equivalent of these putative protective titers has been estimated to be 1.3 μ g/ml on the basis of a conversion factor of 160 ng antibody N/ml to 1 μ g/ml (Halsey JF, Laboratory Director, IBT Reference Laboratory, personal communication). Ongoing prospective studies of the protection conferred by experimental conjugate vaccines, in which antibody response is measured with the same assay and correlated with protection against infections, should better define protective antibody concentrations in the future.

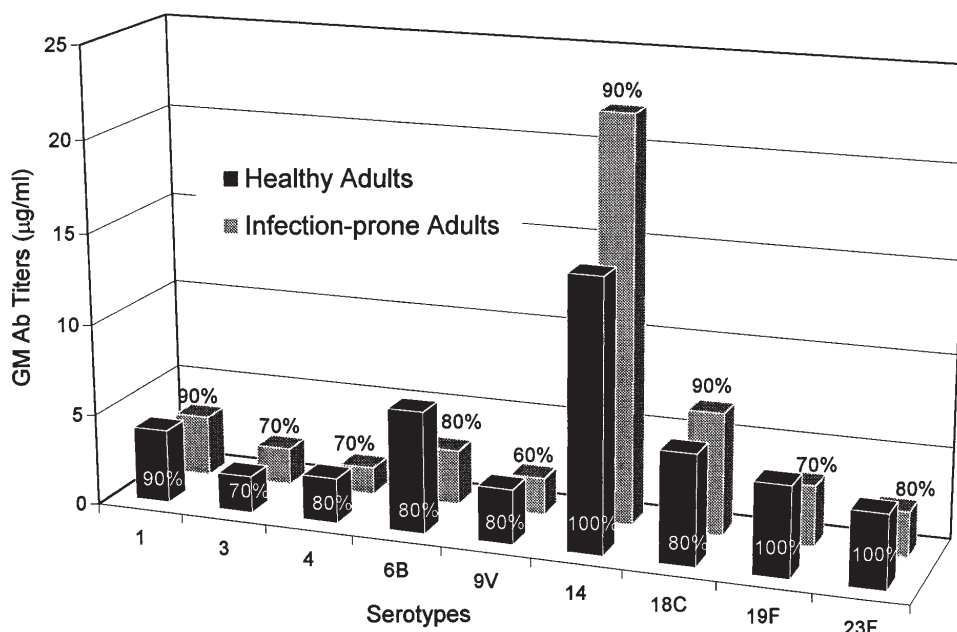


FIG. 2. Comparison of geometric mean antibody concentrations (*bars*) and percentage of each population with adequate responses to various serotypes in healthy and infection-prone adults. See text for definition of adequate response.

These studies will also have to address the important question of age raised by our data: Do adults, who have significantly higher antibody concentrations than children, also require higher antibody concentrations to be protected? Although no answers are available at this time, it is possible to postulate that the shift from predominant IgG1 to predominant IgG2 responses, which occurs with age,^{28,29} may also effect a change in the antibody concentrations required for effective opsonization and phagocytosis. Ongoing studies of opsonophagocytosis may provide some answers to these questions.

In our clinics we use a working definition of an adequate response (i.e., either an increase in antibody titer at least fourfold over baseline or a final concentration of 1.3 μg/ml or greater regardless of the increase over baseline). Although anecdotal observations support this working definition, prospective studies of protection against infections must be completed to confirm its clinical validity.

The clinical assessment of overall response to pneumococcal immunization depends on the number of serotypes to which each patient is able to mount an adequate response. As our results clearly show, age also influences the spectrum of responses to the various serotypes included in the vaccine. The number of adequate serotype responses that should be considered normal for each age group needs a better definition. The simple summation of antibody concentrations against several serotypes to assess normality is not an adequate measure of the immune response to pneumococcal immunization because individuals with very high

responses to a few serotypes may have a much higher total antibody concentration than patients with an even, adequate response to all serotypes tested.

For laboratories that continue to use other well-established methods of antipneumococcal antibody detection, it will be important to examine the influence of age on their results. It should be noted, however, that without a full titration of low and high antibody concentrations, the effect of age may be missed because very low antibody concentrations in young children and much higher concentrations in many adults would not be taken into account.

No dominant antigenic serotype was identified in this study, which is contrary to previous findings in our own clinic and in other centers in which results obtained without absorbing patient sera with polysaccharide C suggested a predominant role for responses to serotypes 3 and 7.^{2,30} Thus the results presented here indicate that it will not be possible to evaluate immune response to polysaccharides in general by determining the response to only one or a few serotypes.

Whether the response to immunization in normal individuals in each age group would be different from the responses in patients with recurrent infections reported here is a question impossible to answer in our research setting. Only patients with normal levels of IgM, IgG, IgG subclasses, and IgA were included in this study to exclude known abnormalities in the response to pneumococcal polysaccharides of patients with IgG2 subclass and other immunodeficiencies.^{31,32} A few normal children studied, mostly siblings of patients with recurrent infections, had responses within the ranges observed in

patients with recurrent infections. Furthermore, most patients immunized in our clinic had a noticeable clinical improvement in accord with their adequate antibody response to pneumococcal immunization, ruling out an antibody deficiency. Moreover, comparison of the responses of adults with recurrent upper respiratory infections to those of healthy adults in our study suggests that there may not be significant differences between the responses observed in normal populations and patients as a group. It is possible, however, to separate individual patients who clearly differ from the majority by using the objective criteria discussed above.

We conclude that age has an important influence on the intensity of the response to most pneumococcal polysaccharides. To develop a clinically useful definition of a normal response to pneumococcal immunization, it will be necessary that ongoing studies of the correlation between antibody concentrations in different IgG subclasses, of antibody function, and of protection against mucosal and invasive pneumococcal infections take this influence of age into account. The availability of a standardized method for the measurement of IgG antibodies against relevant pneumococcal serotypes is an important step towards this goal.

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