

Anti-pneumococcal antibody response in normal subjects: A meta-analysis

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Background: The diagnosis of anti-polysaccharide antibody deficiency is based on the presence of normal serum immunoglobulin levels and the lack of specific antibody response to polysaccharide antigens, such as the pneumococcal vaccine. However, a normal response to pneumococcal vaccine is not well defined. "Modified meta-analysis" was undertaken in an attempt to define the normal antibody response to pneumococcal vaccine.

Methods: Studies identified by a MEDLINE search were selected. Data of the normal control groups, rather than the patient groups, were collated for analysis.

Results: Twenty-three studies fulfilled the selection criteria. Prevacination antibody titers, postvaccination titers, and post- to prevaccination titer ratios varied widely. On the basis of weighted mean ratios, serotype 8 appeared to be the most antigenic. It appeared that normal subjects do not mount a response of even a twofold increase in antibody titer to all the serotypes present in the vaccine. Moreover, no minimal absolute antibody level that could be of diagnostic value, either before or after vaccination, was evident.

Conclusion: Response to pneumococcal vaccine among normal subjects varies widely. Better designed and prospective studies are needed to define the parameters of a normal antibody response to pneumococcal vaccine so that uniform guidelines of interpretation can be formulated. (*J Allergy Clin Immunol* 1996;98:205-15.)

Key words: Immunodeficiency, antibody, pneumococcal vaccine, anti-polysaccharide antibody, *Streptococcus pneumoniae*, meta-analysis, antibody deficiency

Antibody deficiency syndromes have long been recognized as a cause of recurrent bacterial infections. Traditionally, the diagnosis of antibody deficiency relied on the documentation of decreased serum immunoglobulin levels.^{1,2} It has recently become apparent that in certain diseases, Wiskott-Aldrich syndrome being the prime example, the immunoglobulin levels may be normal (or even increased), but the patient is unable to mount a significant specific antibody response on challenge.^{3,4} The inability to mount a response to anti-polysaccharide antibodies has received particular scrutiny.

It is well established that the ability to mount antibody responses to polysaccharides of encapsulated bacteria matures much later than the ability

Abbreviations used

CWP:	Cell wall polysaccharide
PAD:	Anti-polysaccharide antibody deficiency
PCP:	Pneumococcal capsular polysaccharide
RIA:	Radioimmunoassay
WMR:	Weighted mean ratio

to mount antibody responses to protein antigens.⁵⁻⁸ Adequate anti-polysaccharide antibody titers are usually not attained until the age of 24 months or later.⁵⁻⁸ Bacterial polysaccharides are believed to behave as the so-called thymus-independent type 2 antigens. The major characteristics of an antibody response against thymus-independent type 2 are the delayed maturation of response, the restricted immunoglobulin isotype, and the lack of establishment of memory.^{9,10} It is therefore conceivable that a patient may have a normal antibody response to thymus-dependent antigens and normal immunoglobulin levels and yet be unable to mount an anti-polysaccharide antibody response.

Anti-polysaccharide antibody deficiency (PAD), therefore, is a form of immunodeficiency in which

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Received for publication May 30, 1995; revised Sept. 12, 1995; accepted for publication Sept. 14, 1995.

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0091-6749/96 \$5.00 + 0 1/1/69407

TABLE I. Inclusion and exclusion criteria

Inclusion criteria

1. Control group is identified as healthy or immunocompetent.
2. Method of assay used for antibody titers (RIA or ELISA) is clearly identified.
3. Pre- and postvaccination antibody titers to distinct serotypes are available.
4. Time interval between pre- and postvaccination titer determinations is ≥ 2 weeks and ≤ 3 months.
5. The studies that used ELISA should have titers for IgG antibody.

Exclusion criteria

1. Control group includes subjects < 2 years old.
2. Control group with nonspecified or unclear health status.
3. The study is a surveillance or vaccine trial done in a general population with no control group.

the diagnosis is based mainly on a clinical history of recurrent infections, normal serum immunoglobulin levels, and the inability to mount an adequate antibody titer response, *in vivo*, to unconjugated polysaccharide vaccines. This syndrome was first described in a patient with recurrent infections and no detectable antibody response after vaccination with unconjugated polysaccharide vaccines, which included meningococcal, unconjugated *Haemophilus influenzae* type B, and pneumococcal vaccines.¹¹ Since that report, attempts to diagnose patients with presumed PAD have resulted in widespread use of vaccination as a diagnostic tool. Currently, the pneumococcal vaccine is the only *unconjugated* polysaccharide vaccine that is readily available for which antibody titer determinations are commercially obtainable. However, there are no standardized assays to measure anti-pneumococcal polysaccharide antibody nor are there uniform criteria for interpretation of the response to such vaccines.^{12, 13} Our present knowledge about postvaccination responses to pneumococcal capsular polysaccharides (PCPs) is mostly derived from studies of seroepidemiology, assessment of vaccine efficacy, and determination of immune status against pneumococcal infections. The differentiation between a normal and an abnormal specific antibody response remains uncertain. Diagnostic laboratories differ in their assay methods (radioimmunoassay [RIA] or ELISA), in the number of selected pneumococcal serotypes (analyzed individually or in combination), and in the interpretation (absolute titer vs fold-increase) of a normal response. Indeed, there are no well established criteria for a

normal antibody response to pneumococcal vaccine. Because of the lack of such criteria, over- or underdiagnosis of PAD may occur. The importance of making the right diagnosis is amplified by the prolonged and costly treatment (replacement with intravenous immunoglobulins) used for PAD.^{1, 2} A large, multicenter, prospective study involving various age groups, various population groups, and a standardized method for measuring serotype-specific antibodies would be ideal but is unavailable. Numerous publications have focused on examining the efficacy of pneumococcal vaccines as determined by the incidence of clinical infections. Numerous publications have also examined the antibody titer response to such vaccines in an effort to determine the immunocompetence of various patient populations. We reasoned that most such studies should have examined the antibody response of a control (i.e., healthy, immunocompetent) group. We therefore decided to examine such studies and to pool the data from various *control* groups to determine the normal antibody response to pneumococcal vaccine. Although this is not meta-analysis in the usual sense of the term wherein data from subjects in the *experimental*, rather than the *control*, groups are examined and pooled, we believe that this approach is consistent with the definition of meta-analysis.

METHODS

A MEDLINE search of the English literature was done with the following search terms (alone and in combination): *Streptococcus pneumoniae*, pneumococcus, vaccine, polysaccharide, and antibody. A literature search was done independently by each of the authors, and results were pooled. The search was limited to studies published between 1977 and 1993, during which time the multivalent pneumococcal vaccines became available. A total of 86 studies were identified. With the inclusion and exclusion criteria listed in Table I, a total of 23 studies were selected for analysis.¹⁴⁻³⁶ Because our goal was to determine the antibody response in *normal* subjects, no attention was paid to the experimental group. By the same token, we did not think it was necessary to use only double-blind studies as a selection criterion because our focus was on the normal rather than the patient population.

Data from the control subjects in these selected studies were extracted. The data from these subjects were grouped into either RIA (studies that used RIA for antibody determination) or ELISA (studies that used ELISA) groups. The numbers of subjects were then pooled according to each of the available pneumococcal serotypes. This was done separately for the RIA and ELISA groups. To assess as many serotypes as possible, and because not all studies determined the response of

an identical set of serotypes, analyses were conducted only on selected serotypes. We selected 12 serotypes (1, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, and 23F) for the RIA group. Selection of these serotypes was based on the number of pooled subjects. All of these selected serotypes had more than 100 (an arbitrary cutoff) pooled subjects. Because the number of selected ELISA studies and their data were limited, all the serotypes that were assessed in three or more of the selected studies were used for analysis. Thirteen serotypes (1, 2, 3, 4, 6A, 7F, 8, 9N, 12F, 14, 18C, 19F, and 23F) were selected from the ELISA group.

Data were analyzed according to each assay group (RIA or ELISA). The prevaccination titer, the postvaccination titer, and their ratios were compiled for each serotype from the original studies. To measure the variability of response to the different serotypes, the range of the post- to prevaccination titer ratio of each particular serotype was determined. The fraction of studies that demonstrated a twofold, threefold, or fourfold increase in antibody titer response was also determined. The frequency of such fold increase, as reported in the original studies (when available), was also collated and compared with the data derived from our analysis. The range of absolute postvaccination titers was derived from the data of individual RIA studies only. This was not applicable to the ELISA studies because there was no uniformity in the unit of antibody concentration reported. We also determined the weighted mean ratio (WMR) as a measure of the relative antigenicity of each serotype. The WMR of an individual serotype was calculated by using the formula:

$$WMR_t = \frac{\sum_{i=1}^n N_i R_i}{N_{total}}$$

where t is the serotype in question, N_i is the number of subjects in each individual study, R_i is the corresponding mean ratio of post- to prevaccination titer of the serotype, and N_{total} is the total number of pooled subjects of the particular serotype.

RESULTS

Data selection

Twenty-three studies fulfilled the selection criteria and are listed in Table II. These included 15 studies that used RIA, seven that used ELISA, and one that used both methods for antibody determinations. Overall, there were 17 groups (two control groups in study no. 11) for RIA and eight groups for ELISA. The intervals between determination of vaccination and postvaccination titer ranged from 2 weeks to 3 months. However, the mode was an interval of 1 month. The age distribution of the subjects varied and overlapped among the different studies. The number of pooled subjects (Tables III

and IV) of each serotype also varied and ranged (depending on the serotype) from 160 to 271 for RIA groups and from 38 to 83 for ELISA groups.

Fold increase in antibody titer

The postvaccination to prevaccination titer ratios of each serotype showed intraserotype (ratio ranges), as well as interserotype (difference between serotypes as determined in each study) variability (Tables III and IV) and ranged from a minimum of 1.1 to a maximum of 43.6. The ratio range of each corresponding serotype also differed between the two assay groups but did not follow a certain pattern. No single study consistently showed all, or nearly all, of the highest or lowest ratios across the different serotypes determined.

Proportions of studies with two-, three-, or fourfold increase in antibody titer to selected serotypes

It is often stated, though not documented, that a normal antibody response to vaccination should include at least a two-, three-, or fourfold increase in antibody titer to all of the serotypes included in the pneumococcal vaccine. Consequently, if a patient responded with a twofold increase to only one or some, but not all, of the selected serotypes determined, then there is a tendency to label this patient a nonresponder. We have determined the percentages of studies with two-, three-, and fourfold increase in antibody titer to each serotype. In the RIA group all of the individual studies showed a twofold increase in response to serotypes 3, 6, 7, 8, 9, 14, and 23. The rest of the serotypes demonstrated a twofold or greater increase in 58% to 92% of the studies. When a threefold increase was examined, we found that only serotypes 3 and 8 showed such a response in all the studies; the remaining serotypes showed a threefold increase in 33% to 90% of the studies. None of the serotypes showed a fourfold increase in all of the studies, although serotype 8 showed such an increase in 14 of 15 studies; the other serotypes showed a fourfold increase in 17% to 80% of the studies. Similar variability was observed within the ELISA group (Table IV). The percentage of studies with a twofold or greater increase ranged from 25% to 100%. Serotypes 2, 8, 9, and 14 showed a consistent twofold increase in titers across all studies. Only serotype 2 showed a consistent three- or fourfold increase in all ELISA studies. These observations imply that normal subjects may not always respond to *all* the serotypes even with a twofold increase in antibody titer. When the data

TABLE II. List of selected studies and descriptions

Study no.	Reference	Control group		Vaccine*	Interval†
		No. of subjects	Age group or range (yr)		
RIA					
1	Sullivan et al. ¹⁴	27	2-15	13 valent	3 wk
2	Siber et al. ¹⁵	10	7-57	12 valent	3 wk
3	Minor et al. ¹⁶	17	23-62	12 valent	3-6 wk
4	Giebink et al. ¹⁷	12	5-15	14 valent	2-6 wk
5	Simberkoff et al. ¹⁸	25	54‡	14 valent	3-4 wk
6	Lazarius et al. ¹⁹	23	47-85	14 valent	4-6 wk
7	Beam et al. ²⁰	10	<60	14 valent	4 wk
8	Ammann et al. ²¹	20	28-42	2 valent	2 wk
9	Addiego et al. ²²	15	Adults	14 valent	3 wk
10	Ammann et al. ²³	20	<60	14 valent	3-4 wk
11	McMahon et al. ²⁴	21(a)	21-73	23 valent	20-55 days
		23(b)	20-63	23 valent	20-55 days
12	Mufson et al. ²⁵	12	22-38	3 valent	4 wk
13	Mufson et al. ²⁶	25	22-49	23 valent	4 wk
14	Pirovino et al. ²⁷	10	34-63	14 valent	1-3 mo
15	Winston et al. ²⁸	11	26-38	14 valent	6 wk
RIA & ELISA					
16	Chudwin et al. ²⁹	18	Adults	2 valent	2-3 wk
ELISA					
17	Barrett et al. ³⁰	9	22-42	8 valent	3-4 wk
18	Ruben et al. ³¹	17	23-41	14 valent	4 wk
19	Musher et al. ³²	15	20-34	23 valent	4 wk
20	Giebink et al. ³³	10	20-35	14 valent	4-8 wk
21	Birgens et al. ³⁴	12	Adults	14 valent	4 wk
22	Frederiksen et al. ³⁵	12	22-64	14 valent	3-4 wk
23	Hosea et al. ³⁶	9	26-46	14 valent	4 wk

*Number of serotypes included in the pneumococcal vaccine used.

†Time interval after vaccination when sera were obtained for determination of postvaccination titers.

‡Average age.

from the two assay groups were combined, only serotypes 8, 9, and 14 showed a consistent twofold increase in titers across all studies (serotype 2 was not available in the RIA studies).

Data of individual subjects from original studies

The data presented in Tables III and IV relied on geometric mean of antibody titer reported in each study. It would have been ideal if the pre- and postvaccination titers were available for each individual; this would have allowed pooling of the individual data from a large number of subjects. However, although the raw data of individual subject responses (post- to prevaccination titers) were not available, the percentages of response among these subjects (equal to or greater than twofold increase in antibody titers) were reported in some of the studies (Table V). We used these

individual response data to compare our pooled, and hence indirect data, with the original observations. There were six studies (one of which had two normal groups) with such data. The data of the original studies also suggested a wide variability in normal antibody response. Intraserotype differences were also evident from one study to another. Percentage of studies with a twofold or greater increase in titer ranged from 10% to 100%. No single serotype showed a 100% response across all studies. Furthermore, no one study showed 100% response to all serotypes. Another interesting observation was that none of these studies showed a consistent (100%) response to the serotypes considered to be very antigenic, namely serotypes 3, 7, 8, and 9.⁸ Again, these data indicate that even with determinations of antibodies against some of the most antigenic serotypes, not all normal subjects will respond with a twofold increase in antibody titers.

TABLE III. Antibody response in studies in which RIA was used for antibody determination

Serotype	Groups*	No. of subjects†	Ratio range‡	Percent of studies with§		
				>2× Increase	>3× Increase	>4× Increase
1	13	201	1.3-5.5	58	33	17
3	15	271	3.0-23.4	100	100	73
4	12	194	1.6-7.4	83	58	42
6 (6A)	9	160	2.4-7.6	100	78	44
7	13	219	2.2-6.4	100	62	31
8	15	256	3.2-17.3	100	100	93
9	10	179	2.4-13.1	100	90	80
12	12	206	1.4-11.8	67	50	25
14	14	243	2.0-43.6	100	57	50
18	12	204	1.7-8.5	92	67	33
19	13	228	1.1-17.7	69	38	23
23	12	224	2.1-5.9	100	67	50

*Total number of control groups from selected RIA studies.

†Sum total of subjects from the control groups of studies that analyzed the particular serotype.

‡Range of post- to prevaccination antibody titers.

§Percentage of control groups with corresponding fold increase in antibody titer.

TABLE IV. Antibody response in studies in which ELISA was used for antibody determination

Serotype	Groups*	No. of Subjects†	Ratio range‡	Percent of studies with§		
				>2× Increase	>3× Increase	>4× Increase
1	4	50	1.9-7.6	76	50	50
2	3	38	4.6-19.2	100	100	100
3	5	63	1.7-11.2	80	60	40
4	6	83	1.5-4.6	83	33	17
6(6A)	4	47	1.5-3.1	25	25	0
7	5	69	1.3-3.7	60	20	0
8	4	53	2.0-38.9	100	75	50
9	3	38	2.2-6.8	100	67	33
12	3	38	1.4-2.7	33	0	0
14	5	66	2.1-6.3	100	40	40
18	4	50	1.2-4.5	75	50	50
19	5	62	1.3-6.9	80	60	40
23	5	59	1.6-12.4	80	20	20

*Total number of control groups from selected ELISA studies.

†Sum total of subjects from the control groups of studies that analyzed the particular serotype.

‡Range of pre- to postvaccination antibody titers.

§Percentage of control groups with the corresponding fold increase in antibody titer.

WMR

From the above analysis of ratio ranges, it appeared that serotypes 8, 9, and 14 should be included in the examination of the adequacy of anti-pneumococcal antibody response. To confirm this conclusion and to obtain a more uniform assessment of response, we chose to calculate the post- to prevaccination antibody ratio as a WMR for each serotype (see Methods) in order to give weight to the ratio of each study according to the number of subjects involved. This served as a better method for comparison of the summations

of the response to the different serotypes. Moreover, this allowed us to rank the various serotypes according to their "antigenicity." As shown in Fig. 1, serotype 8 had the highest WMRs and thus was the most antigenic in both assay groups. Among the RIA studies, serotype 8 was followed by serotypes 3, 9, and 14.

Among the ELISA studies, serotype 8 also had the highest WMR, followed by serotypes 2, 3, 1, and 9. It is known that the polycapsular polysaccharide of each serotype differs in its degree of antigenicity and therefore would be expected to

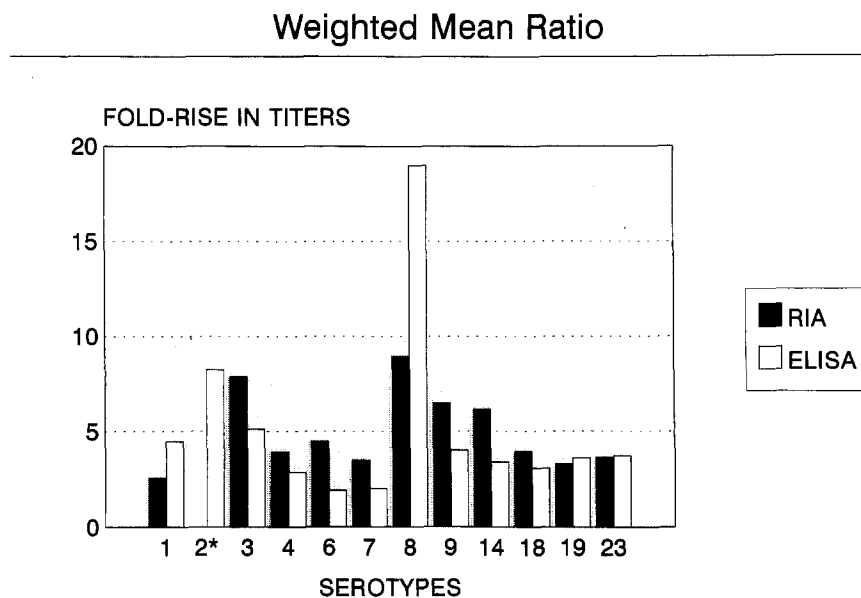


FIG. 1. Immunogenicity of various serotypes. A WMR for each serotype of post- to prevaccination antibody titers was calculated as described in Methods. Data are presented separately for studies in which RIA or ELISA was used for antibody measurement.

follow a certain rank order in the degree of its antibody response.^{5,8} When the serotypes were ranked according to their antigenicity (Fig. 1), there was no observable similarity in the ranking pattern between RIA and ELISA groups, except for serotypes 8 and 3. The reasons for this observation are not clear, although these findings suggest either interassay (technical) variability or data selection bias. Additionally, in contrast to ELISAs, it is well known that RIAs do not distinguish antibody response by immunoglobulin isotypes. The differences in concentration of isotypes other than IgG may be another reason for this apparent discrepancy between the two assays.³⁷

Absolute postvaccination antibody titers

It has been suggested that most normal subjects respond to pneumococcal vaccine with a certain minimum titer, which is considered protective.³⁸ We therefore sought to determine whether a minimum titer could be established from the pooled data of normal subjects. The distribution of the postvaccination titers (geometric means) of various serotypes varied widely. Interstudy variabilities were obvious, as shown in Fig. 2. No single study consistently showed the highest or lowest level of postvaccination titer across all serotypes. The control group of study no. 4,¹⁷ which consisted of subjects aged 5 to 15 years, was the least responsive, showing the lowest levels of postvaccination

titers for seven of 11 serotypes. Subjects of study no. 6,¹⁹ who ranged in age from 47 to 85 years, were also less responsive. These findings are consistent with previous observations that response to certain serotypes does not reach adult levels until much later in life and also that response to PCP is less than optimal at the extremes of age.³⁹ On the other hand, study no. 1,¹⁴ with subjects whose age range is comparable to those in study no. 4, showed higher postvaccination titers. Age distribution among subjects overlapped from one study to another. Although the majority of the postvaccination titers were more than 500 ng of antibody nitrogen per milliliter, there was a considerable overlap with the prevaccination titers. The wide distribution of the postvaccination antibody titers and their overlap with the prevaccination titers make it almost impossible to determine a biologically meaningful absolute postvaccination antibody titer as a cutoff level.

Also apparent in Fig. 2 is that the degree of response was independent of the level of prevaccination antibody titers. In other words, the existence of a high antibody titer did not neutralize the serotype in the vaccine, at least not to a degree that precluded a biologic response.

DISCUSSION

Since Ambrosino et al.¹¹ reported a case of PAD, the use of vaccination as a tool for diagnos-

TABLE V. Incidence of twofold or greater antibody response to individual serotypes in seven different studies

Serotype	Response*							Range (%)†
	Study number							
	4	7	11a	11b	12	13	14	
1	33 (4/12)	40	10	17	42	ND	100	10-100
3	58 (7/12)	70	57	83	83	92	ND	57-92
4	83 (10/12)	90	29	61	42	ND	80	29-90
6	67 (8/12)	100	ND	ND	ND	ND	ND	67-100
7	100 (12/12)	90	71	91	92	ND	90	71-100
8	83 (10/12)	100	71	91	92	ND	100	71-100
9	83 (10/12)	100	57	74	ND	ND	ND	57-100
12	100 (12/12)	50	29	48	33	ND	ND	29-100
14	75 (9/12)	80	71	35	50	80	ND	35-80
18	83 (10/12)	70	71	83	ND	ND	70	70-83
19	58 (7/12)	70	33	39	25	88	ND	25-88
23	58 (7/12)	80	43	65	ND	88	ND	43-88

Original data derived from some of the selected RIA studies. Study numbers are as listed in Table II.

ND, Not done.

*Response according to percentage of subjects in the original control groups with response of antibody titer equal to or greater than twofold increase. Proportions are given in parentheses.

†Percent range of subjects with equal to or greater than twofold increase in antibody titer.

ing immunodeficiency has increased dramatically. The pneumococcal vaccine remains the only readily available unconjugated polysaccharide vaccine and is thus the most widely used. No clear guidelines or data exist for the interpretation of the antibody response to this vaccine. In particular, there are no clear answers or guidelines for the following questions. (1) What is the normal range of increase of antibody titer to a particular serotype? (2) Is there a minimal absolute level below which a person is considered a nonresponder? (3) Should one respond to all serotypes? (4) Is a twofold (instead of a three- or fourfold) increase in antibody titer to a given serotype abnormal? (5) If a subject responded to the "most antigenic" serotype only, does this rule out PAD? In this meta-analysis of published studies on the normal antibody response to the pneumococcal vaccine, we attempted to answer some of these questions.

The most conspicuous result of our analysis is the wide variability in anti-polysaccharide antibody response. This variability is evident regardless of the method of antibody determination and regardless of how one chooses to express the data: fold increase, absolute level, or number of serotypes with a two-, three-, or fourfold increase in titer.

There was a wide variability in the post- to prevaccination antibody ratios, which could not be explained by the presence of outliers. It is readily apparent that not *all* serotypes induced even a

twofold increase in antibody titer. This conclusion is strengthened by comparing our meta-analysis to the analysis of studies in which the individual responses were available. A recent trend has been to examine the antibody response to 12, rather than four, serotypes. Our data suggest that increasing the number of serotypes examined may not necessarily make interpretation easier.

Several possibilities may explain this variability in antibody response. First, not all studies undertook the effort to distinguish antibody response to cell wall polysaccharide (CWP) from PCP. Commercial pneumococcal vaccines and reagents used in assays are known to contain varying amounts of CWP.^{12, 40, 41} The concentrations of CWP in these preparations (vaccines or assay reagents) may vary from 18% to 50%.³² Because of the presence of varying amounts of CWP in the assay reagents, falsely high antibody titers, which are nonserotype-specific, may be obtained. This type of error is known to occur in both RIAs and ELISAs.³² To complicate matters further, normal subjects may have varying amounts of anti-CWP antibodies.^{13, 32} Problems caused by CWP and anti-CWP antibodies have only recently begun to be addressed. One solution is to preadsorb serum with CWP before the actual assay of serotype-specific antibodies. Only one of our selected studies addressed this issue.³² It is highly probable that both the presence of varying amounts of CWP in the reagents and the

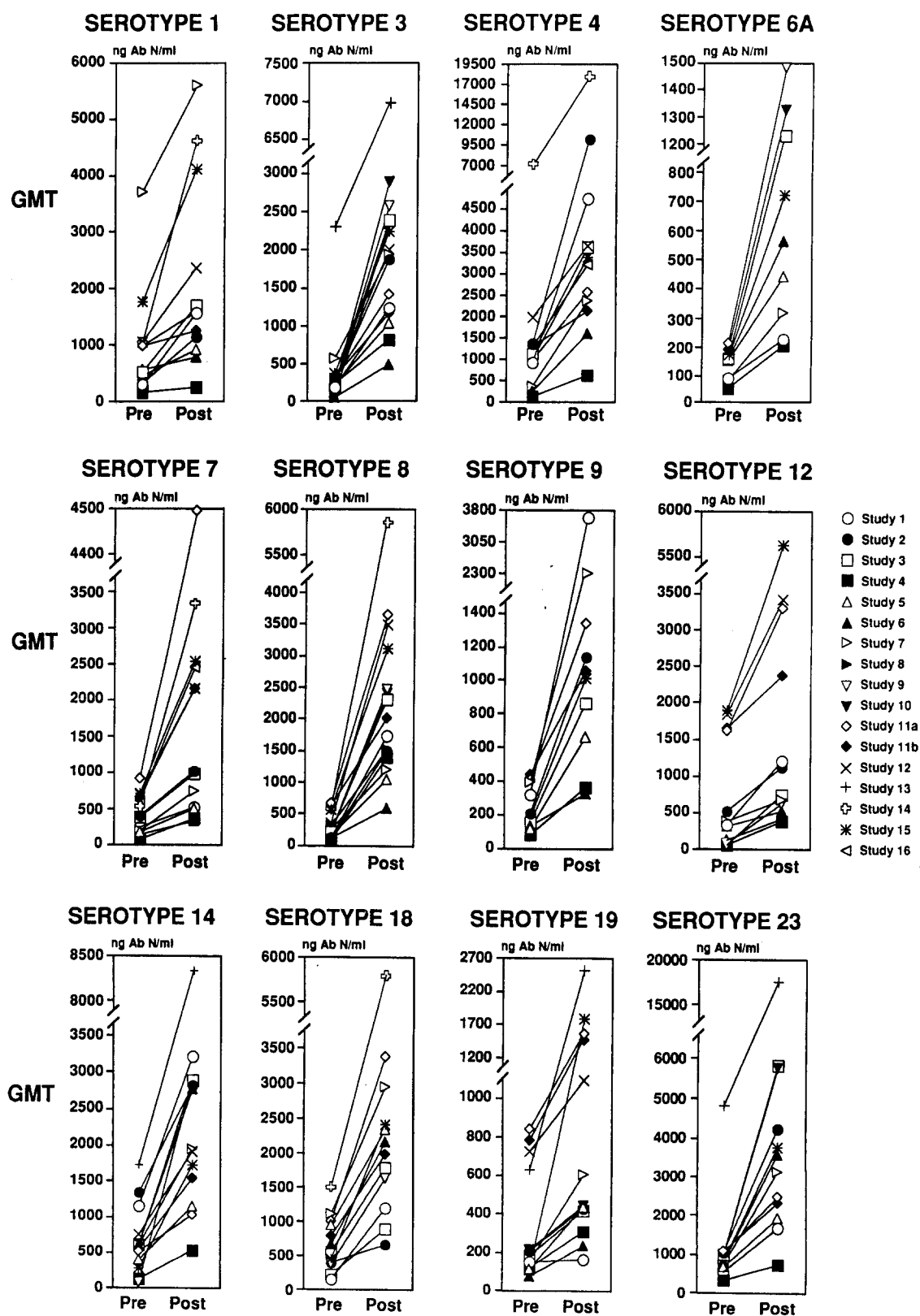


FIG. 2. "Absolute" pre- and postvaccination antibody titers. Geometric mean of pre- and postvaccination antibody titer, and reference from which data were extracted, are presented for each serotype. All of these studies are in the RIA group.

presence of varying concentrations of anti-CWP in the sera contributed significantly to the variabilities of the different parameters that we have observed in this analysis. Moreover, the significance of the presence of CWP in the vaccine itself is not known. Whether CWP plays a role in the stimulation and synthesis of serotype-specific or serotype-nonspecific antibody is also unclear. The presence of other contaminants in the pneumococcal polysaccharide vaccines and reagents may also influence the anti-pneumococcal polysaccharide antibody assays. An example of such contaminants is the blood group antigens.¹² Serotype 14 capsular polysaccharide has a structure similar to blood group A antigen, and thus it may be recognized by anti-A isohemagglutinin.⁴² How these contaminants influence the outcome of antibody assays is still unknown.

A second possible explanation for this variability may be that the degree of response is age-dependent. Although it is known that anti-polysaccharide antibody response may not be detectable before 2 years of age, it has been suggested that such a response may not reach optimal levels until much later in life.^{5, 8} Consequently, any study attempting to determine normal response should include adequate numbers in various age groups (e.g., 2 to 5, 5 to 10, and 10 to 15 years). Similarly, antibody response in older patients may decline, and various geriatric age groups need to be examined.^{40, 43} Nevertheless, even taking these problems into consideration, a wide variability in antibody response remains.

A third possibility for this wide variability is that in the RIA studies, the antibody titers are for total antibody and not IgG in particular. Although IgG was measured in the ELISA studies, not all of the studies differentiated between responses to CWP and PCP. Moreover, it has been suggested that ELISA antibody titers are more likely to be influenced by the exact time after vaccination at which serum is obtained.³⁷

Perhaps the most important possible explanation for this variability is the pneumococcal vaccine itself. This may not be the ideal vaccine for examination of anti-polysaccharide antibody response. It is a multivalent vaccine and thus may not have a sufficient concentration of any given serotype. Indeed, this drawback is evident even when one examines the efficacy studies as determined by protection against disease rather than by antibody titers. It is estimated that, regardless of the age group, the efficacy of pneumococcal vaccine is about 47% to 70%.⁴⁴⁻⁴⁹ Therefore if one assumes

that clinical efficacy is due to antibody protection, then one expects only 47% to 70% of the subjects to mount a "significant" antibody response. In other words, the multivalent pneumococcal vaccine may not be the ideal vaccine with which to test the adequacy of anti-polysaccharide antibody response.

It is thus apparent that there is a need for a prospective, multicenter study to establish the normal parameters of anti-polysaccharide antibody responses. Such a study should include adequate numbers of subjects in each of several age groups, should avoid measuring anti-CWP antibody, and should measure IgG by ELISA at a set time point (e.g., 4 weeks) after vaccination. In the absence of such a study, we believe that we can draw certain conclusions from our meta-analysis, which could serve as guidelines for further evaluation of anti-polysaccharide antibody response. The following conclusions can be drawn.

1. It is clear that there is a wide variability in the anti-pneumococcal antibody response of normal subjects.
2. There does not appear to be a minimal absolute antibody level that could be of diagnostic value, either before or after immunization.
3. It is apparent that normal subjects need not respond to *all* serotypes.
4. Not all normal subjects will respond to all serotypes with a twofold or greater increase in antibody titer.
5. Contrary to prevailing anecdotes, serotype 8, rather than serotype 3, appears to be the most immunogenic.
6. Serotypes 2, 8, 3, 9, and 14 appear to be more antigenic, compared with other serotypes, and should be included in any panel examining the anti-pneumococcal antibody response. This conclusion from our meta-analysis is in agreement with previous studies on the antigenicity of various pneumococcal serotypes.^{5, 8}
7. Unconjugated polysaccharide vaccines, other than the pneumococcal vaccine, need to be investigated for their immunogenicity.

We thank Dr. Leon Burmeister for his invaluable assistance with statistical analysis.

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