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Comparison of Two Different Criteria for Specific Antibody Deficiency in Patients With Chronic and Recurrent Rhinosinusitis

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Abstract

Background: Specific antibody deficiency (SAD) is highly associated with chronic rhinosinusitis (CRS) and is defined by inadequate post-vaccination percentage of protective ($\geq$1.3 ug/mL) pneumococcal antibody serotypes divided by total tested serotypes (post-pPA).

Objective: Although $<$70% post-pPA has been used commonly as the criterion for SAD, we sought to evaluate the clinical outcome of a different definition of SAD.

Methods: 203 patients aged 6 to 70 years with CRS were classified, retrospectively by pre-vaccination pPA (pre-pPA) and post-pPA by two different criteria. Using 70% as the threshold for adequate pneumococcal antibody (PA) response, patients were classified as: Group A (adequate pre-pPA), Group B (inadequate pre-pPA, adequate post-pPA), Group C (inadequate pre-pPA, inadequate post-pPA, SAD). Using 50% as the threshold, patients were similarly classified as: Group A', B' and C'.

Results: The recurrence rate of sinusitis during the next one year in Group A (pre-pPA $\geq$70%) was significantly less than that of Group A' (pre-pPA $\geq$50%) (10% vs. 34%, P $=$.03). Group A had lower incidence of sinusitis than Group B (pre-pPA $<$ 70%, post-pPA $\geq$70%) (10% vs. 34%, P $=$.025). Among Group B' patients, the recurrence rate of sinusitis was significantly less among those with post-pPA of $\geq$70% than those with 50%–69% (28% vs. 69%, P $<$.01).

Conclusion: Employment of a 70% pPA threshold for SAD in comparison to a 50% threshold would decrease the incidence of sinusitis in the next one year by vaccinating patients in 51–69% pPA range. Pre-existing PAs (Group A) yielded a higher protection against sinusitis than vaccine-acquired antibodies (Group B).

Keywords

allergic rhinitis, asthma, chronic rhinosinusitis, pneumococcal serotypes, specific antibody deficiency

Introduction

Specific antibody deficiency (SAD) is defined as an inadequate antibody response to polysaccharide antigens such as *S. pneumoniae* in an individual with normal responses to protein antigens as well as normal levels of immunoglobulins and IgG subclasses, in the absence of other primary or secondary immunodeficiencies.[1–3] The assessment of an immune response to polysaccharide antigen requires evaluation of the concentration and function of each antibody to diverse serotypes of different immunogenicity. Even the discordant results of PA testing from the same samples by different laboratories have been reported.[4–6] It has been difficult to interpret the contribution of individual parameters. Of the parameters suggesting adequate vaccine responses, such as a $\geq$2–4 fold rise of individual serotype titers or a pPA (percentage of protective [$\geq$1.3 ug/mL] pneumococcal antibody serotypes divided total tested serotypes) ranging between 50-80%,[1,7,8] we chose to analyze our data using 2 different definitions for comparison. One definition was established in 2012 by an expert panel affiliated

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with the American Academy of Allergy, Asthma & Immunology,[1] and characterized adequate response as ≥70% of serotypes with titers ≥1.3 ug/mL. The other definition employed by some investigators used threshold of ≥50% for an adequate response[9,10] The guidelines recommend using only the serotypes present in the PPV for the calculation if patients received PCV. We chose to include all serotypes to evaluate the immune status resulting both from vaccinations and natural exposures or infections from all strains. We have already published our data on pPA 70% criteria in the this journal.[11]

Methods

Study Design

This retroactive study was conducted using electronic medical chart review of patients treated between 2008 and 2018 at a tertiary care allergy-immunology clinic in Los Angeles, California. This study was approved by the Institutional Review Board and Human Subjects Committee at Lundquist Institute and Harbor-UCLA Medical Center.

Since patients with recurrent respiratory symptoms were screened for SAD with PA titers, the CPT code for PA testing was used for initial recruitment of the study subjects. These patients were further evaluated to determine if they met inclusion and exclusion criteria. Patients aged 6–70 years who had a history of chronic rhinosinusitis (>12 weeks) or recurrent rhinosinusitis (>1x/year) were selected for the study. Subjects were excluded if they had any history of autoimmune disorder, malignancy, or primary/secondary immunodeficiency. A total of 203 patients met initial criteria, but only 186 were noted to have follow-up visits.

Classification of Clinical Conditions

A diagnosis of sinusitis was given when a patient fulfilled the widely used criteria[12] of a positive history for sinusitis, and evidence of sinusitis on a sinus CT scan or nasal endoscopy. Sinusitis was classified into acute or chronic sinusitis using 12 weeks of symptoms as the distinguishing criteria. Recurrent sinusitis was arbitrarily defined as more than one episode of acute sinusitis per year (Immune Deficiency Foundation lists two or more serious sinusitis as a warning sign for primary immune deficiency). Since it was difficult to distinguish chronic sinusitis from recurrent sinusitis in many instances, both categories were considered to be chronic rhinosinusitis or recurrent sinusitis (CRS).

Classification of Immune Status by Laboratory Testing

Immune status was assessed with levels of immunoglobulins G, A, M, and E, and of IgG antibodies to *S. pneumoniae*, *Hemophilus influenzae*, and *Tetanus* (Luminex Assay, by LabCorp and Quest Diagnostics). In patients who were evaluated prior to 2010, 14 serotypes were reported: 1, 3, 4, 5, 8, 9(9 N), 12(12 F), 14, 19 (19 F), 23(23 F), 26(6B), 51(7 F), 56(18 C), and 68(9 V). After 2010, 23 serotypes were reported: 1, 3, 4, 8, 9(9 N), 12(12 F), 14, 17(17 F), 19(19 F), 2, 20, 22(22 F), 23(23 F), 26(6B), 34(10 A), 43(12), 5, 51(7 F), 54(15B), 56(18 C), 57 (19 A), 68(9 V), and 70(33 F). An individual PA titer of ≥1.3 ug was considered protective as recommended by the working group. Based on the percentage of protective (≥1.3 ug/mL) pneumococcal antibody serotypes divided by total tested serotypes (pPA), we classified the patients' total PA status into different groups, utilizing pre- and post-pPA by two different criteria. First, 70% was used as the threshold for adequate PA (pneumococcal antibody) response regardless of history of prior immunization with either unconjugated (PPV-23) or conjugated vaccine (PCV-7 or -13). Patients were divided into groups based on pre and post-pPA vaccine responses: Group A (adequate pre-pPA), Group B (inadequate pre-pPA, adequate post-pPA), and Group C (inadequate pre-pPA, inadequate post-pPA, SAD). In comparison, 50% was used as the threshold and patients were similarly classified based on vaccination responses into the following groups: Group A', B' and C'. These groups were also combined and analyzed: Group A + B (responders) vs. Group C (SAD), and Group A (adequate pre-pPA) vs. Group B + C (inadequate) as well as Group A'+B' vs. Group C' and Group A' vs. Group B'+C'. Group A' was subdivided into Group A'A (pre-pPA: ≥70%), Group A'B (pre-pPA: 50–69%, post-PA: ≥70%), and Group A'C (pre-pPA: 50–69%, post-PA: < 70%). Group B' was subdivided into Group B'B (pre-PA: < 50%, post-pPA: ≥70%) and Group B'C (pre-PA: < 50%, post-pPA: 50–69%) (Figure 1).

Evaluation of Allergic Conditions

Allergy skin tests were used to detect sensitization to respiratory and food allergens including dust mites, cat/dog dander, molds, and pollens of grasses, trees, and weeds specific to Southern California.

Total serum IgE and specific IgEs to inhalant allergens for Southern California (LabCorp, Burlington, North Carolina) were employed to detect the kind and extent of sensitization. The diagnosis of asthma or rhinitis was assigned by the relevant ICD 9 or 10 codes. These conditions were designated as allergic based on the presence of positive reaction to any allergen(s) on the skin test or in the laboratory report of specific serum IgE.

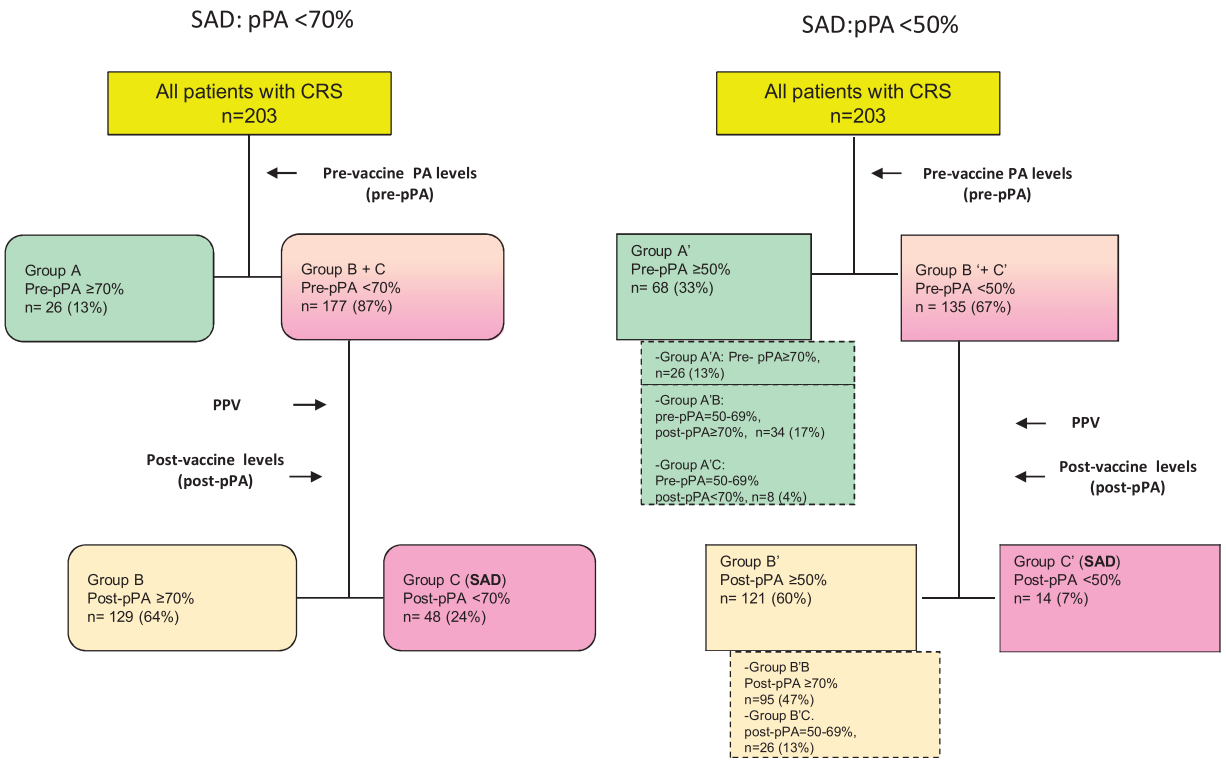

Figure 1. Flow chart of pPA state/response analysis among 203 sinusitis patients utilizing 2 different thresholds for adequate pPA. Group A, B, and C were classified by 70% pPA. Group A', B', and C' were classified by 50% pPA. Group A' consists of Group A'A, A'B, and A'C. Group B' consists of Group B'C and B'B. Abbreviations: pPA, percentage of protective (≥1.3 ug/mL) pneumococcal antibody serotypes divided by total tested serotypes; Pre-pPA, pre-vaccination pPA; Post-pPA, post-vaccination pPA; PPV, pneumococcal polysaccharide vaccine.

Statistical Analysis

Data were tabulated and stratified by individual groups, A, B, and C (SAD) and as combined groups, A + B and B + C. An identical approach was taken for individual groups, A', B,' and C' (SAD') and as combined groups, A'+B' and B'+C'. Other combinations of groups were also analyzed: adequate pre-pPA (Group A) vs. inadequate pre-pPA (Group B + C). Median, interquartile markers, and Mann-Whitney test results were reported for continuous variables while frequencies, column percentages and chi-square test results were reported for categorical variables. The statistical program R (r-project.org) was used for all analyses.

Results

Data from 203 patients with diagnosis of chronic rhinosinusitis or recurrent sinusitis (CRS) and with one-year follow-up were analyzed separately and in combination. The data from the combined (CRS) group were used for this report since the separate and combined analyses were not significantly different from each other. For the analysis of recurrent sinusitis during1 year follow-up, 186 patients were available for analysis.

Prevalence of SAD and Clinical Conditions With 70% and 50% pPA Threshold

The prevalence of SAD was higher in the 70% pPA group compared to the 50% group (24% vs. 7%, $P < .001$) (Table 1). With employment of the 70% threshold for SAD, there was no statistically significant difference in prevalence of asthma, allergies, or rhinitis between groups. When the 50% threshold was used for SAD definitions, the prevalence of asthma was significantly higher in group C' (71%, SAD group) than in Group A' (49%) ($P < .01$) and Group B' (36%) ($P < .01$). There was no difference in the prevalence of allergic sensitization or rhinitis (Tables 1 and 2).

Patterns of Recurrent Sinusitis Among 186 Follow-Patients (With 17 Patients Failing to Return) During the 1 Year Following the Initial Visit Among 3 Immunological Groups Defined by 70% and 50% Threshold

With the 70% pPA threshold for SAD, the recurrence rate of sinusitis increased progressively from Group A to B to C (10%, 34% and 73%) with significance (A vs. B, $p = .03$, A vs. C, $P < .001$, B vs. C, $P < .001$).

Table 1. Demographics and Clinical Characterization of 203 Study Subjects by Post-Vaccination Responses Using 70% vs. 50% pPA Threshold.

	Patients Number (% of Total Patient Number)	Median Age	Race (White/ Non-White)	Male/Female	Allergy Sensitization (%)	Asthma (%)	AR/NAR (%)
Total number (% of total number.)	203	38	173/30	78/125	125(62)	87 (43)	153(75)
Group A	26 (13)	30	21/5	7/19	14 (54)	11 (42)	20(77)
Group A'	68 (33)	30	55/13	24/44	41 (60)	33 (49)	48 (71)
Group B:	129 (64)	37	112/17	52/77	83(64)	54 (42)	100(78)
Group B'	121 (60)	39	107/14	50/71	76 (63)	44 (36)	95 (79)
Group C:	48 (24)	42	40/8	19/29	28(58)	22 (46)	33 (69)
Group C'	14 (7)	43	11/3	4/10	8 (57)	10 (71)	10 (71)
Group AB	155 (76)		133/22	59/96	97 (63)	65(42)	120 (77)
Group A'B'	189 (93)		162/27	74/115	111(63)	76(43)	132(76)
Group BC	177 (87)		152/25	71/106	111(63)	76(43)	133(75)
Group B'C'	135 (67)		117/17	54/81	84(62)	54(40)	105(78)

Group A (pre-pPA $\geq$70%), Group B (pre-pPA $<$ 70%, post-pPA $\geq$70%), Group C (pre-pPA $<$ 70%), post-pPA $<$ 70%, SAD); Group A' (pre-pPA $\geq$50%), Group B' (pre-pPA $<$ 50%, post-pPA $\geq$50%), Group C' (pre-pPA $<$ 50%, post-pPA $<$ 50%, SAD).
Group AB (Group A+ B), Group A'B'(Group A' + B'), Group BC (Group B + C), Group B'C' (Group B' + C').
Abbreviations: pPA, percentage of protective ($\geq$1.3 ug/mL) pneumococcal antibody serotypes divided by total tested serotypes.
Pre-pPA, pre-vaccination percentage of protective ($\geq$1.3 ug/mL) pneumococcal antibody serotypes divided by total tested serotypes; Post-pPA, post-vaccination percentage of protective ($\geq$1.3 ug/mL) pneumococcal antibody serotypes divided total tested serotypes.

Table 2. Prevalence Rate and P Values of Allergic Conditions Among Different Groups.

	Asthma		Allergy		Rhinitis	
Group Prevalence	Group A 42% Group B 42% Group C 46%	Group A' 49% Group B' 36% Group C' 71%	Group A 54% Group B 64% Group C 58%	Group A' 60% Group B' 63% Group C' 57%	Group A 77% Group B 78% Group C 69%	Group A' 71% Group B' 79% Group C' 71%
Chi-square P-value	.89	.02 ↓	.53	.89	.48	.45
Post-hoc analyses of P values among Groups A', B', C'	Group A' vs Group B'	.08				
	Group B' vs. Group C'	$<$.01				
	Group A' vs. Group C'	$<$.01				

Group A (pre-pPA $\geq$ 70%), Group B (pre-pPA $<$ 70%, post-pPA $\geq$ 70%), Group C (pre-pPA $<$ 70%), post-pPA $<$ 70%, SAD); Group A' (pre-pPA $\geq$ 50%), Group B' (pre-pPA $<$ 50%, post-pPA $\geq$ 50%), Group C' (pre-pPA $<$ 50%, post-pPA $<$ 50%, SAD).

The percentage of patients with recurrence of sinusitis was higher in Group B even after pPAs were normalized after vaccination compared to Group A (34% vs. 10%, P = .025). When the 50% pPA threshold was employed, the recurrence rate of sinusitis similarly increased progressively as in the 70% group from Group A' to B' to C' (34%, 39%, and 82%) with significance only among Groups A' vs. C' and Groups B' vs. C' (P $<$ .01 for both). Compared to the 70% Groups, the sinusitis recurrence rates of the 50% groups were statistically higher only in Group A' (Group A vs. A': 10% vs. 34%, P = 0.03 (Tables 3 and 4, and Figure 2).

Potential Consequences on Recurrent Sinusitis Among 186 Patients in the Following Year Using 2 Different Definitions of Adequate PA Status

Out of 203 patients, 186 patient returned in the next one year for follow-up visits. Using the 50% definition, patients with pre-pPA between 50-69% would have

Table 3. Recurrence of Sinusitis (Antibiotics Treatment) in One Year Follow-up Among 186 Follow-up Patients.

Group	No. of patients	Abx rx-0	Abx rx-1	Abx rx-2	Abx rx-3	Patients treated with abx	Surgery	Prophylactic abx	Ig rx
A	21	19	1	0	1	2 (10%)	1 (4%)	0	0
B	121	80	35	6	0	41 (34%)	5 (4%)	0	0
C	44	12	16	15	1	32 (73%)	5 (10%)	4 (8%)	3 (6%)
A'	61	40	14	6	1	21 (34%)	3 (5%)	2 (3%)	0
B'	114	69	33	12	0	45 (39)	6 (5%)	2 (2%)	1 (4%)
C'	11	2	5	3	1	9 (82%)	1 (9%)	0	0
A'A	21	19	1	0	1	2 (10%)	1 (4%)	0	0
A'B	33	19	11	3	0	14 (42%)	1 (3%)	0	0
A'C	7	2	2	3	0	5 (71%)	1 (14%)	2 (29%)	0
B'B	88	61	24	3	0	27 (33%)	3 (3%)	0	0
B'C	26	8	9	9	0	18 (69%)	3 (12%)	2 (8%)	1 (4%)

Group A (pre-pPA $\geq$70%), Group B (pre-pPA $<$ 70%, post-pPA $\geq$70%), Group C (pre-pPA $<$ 70%), post-pPA $<$ 70%, SAD); Group A' (pre-pPA $\geq$50%), Group B' (pre-pPA $<$ 50%, post-pPA $\geq$50%), Group C' (pre-pPA $<$ 50%, post-pPA $<$ 50%, SAD).
Group A'A (pre-pPA $\geq$70%), Group A'B (pre-pPA = 50–69%, post-pPA $\geq$70%), Group A'C (pre-PA = 50–69%, post-pPA $<$ 70%).
Group B'B (post-pPA $\geq$50%), Group B'C (post-pPA = 50–69%).
Abbreviations: Abx rx -0, 1, 2, and 3; antibiotics treatment numbers in one-year follow-up.
Ig rx, immunoglobulin replacement therapy.

Table 4. P- Values of Recurrence Rate among Different Groups.

Groups	P values
A vs. B	.03
A vs. C	<.001
B vs. C	<.001
A' vs. B'	.51
A' vs. C'	<.001
B' vs. C'	<.001
A vs. A'	.03
B vs. B'	.37
C vs. C'	.53

Group A (pre-pPA $\geq$70%), Group B (pre-pPA $<$ 70%, post-pPA $\geq$70%), Group C (pre-pPA $<$ 70%), post-pPA $<$ 70%, SAD); Group A' (pre-pPA $\geq$50%), Group B' (pre-pPA $<$ 50%, post-pPA $\geq$50%), Group C' (pre-pPA $<$ 50%, post-pPA $<$ 50%, SAD).
Group A'A (pre-pPA $\geq$70%), Group A'B (pre-pPA = 50–69%, post-pPA $\geq$70%), Group A'C (pre-PA = 50-69%, post-pPA $<$ 70%).
Group B'B (post-pPA $\geq$50%), Group B'C (post-pPA = 50–69%).

been considered PA-adequate and would not have been vaccinated. However, with the 70% threshold utilized in our study, such patients were considered PA-deficient and were vaccinated. Among 42 such patients in our study group, 33 (Group A'B) responded adequately and 7 (Group A'C) did not. Among these responders, 42% had recurrence of sinusitis in the next one year. The recurrence rate of the 7 non-responders (Group A'C) was 71% ($P < .01$). Among 125 patients with pre-PA fraction $< 50\%$ (Group B' + Group C'), 114 (Group B') had post-pPA $\geq$50%. These patients would have been considered adequate responders by the 50% method. But among these, with employment of the 70% approach, 88 patients with post-pPA $\geq$70% would have been classified as Group B (Group B'B) and 26 with post-pPA between 50-69% as Group C (Group B'C). A higher proportion of Group B'C patients experienced recurrent sinusitis compared to Group B'B: 69% vs.33% ($P < .001$) (Table 3 and Figures 1 and 2).

Discussion

The prevalence of SAD has been reported to be 5–10% in children[13] and 20–40% in adults with recurrent infections.[9,10] Our analyses found the prevalence of SAD in patients with CRS is 7% with 50% pPA and 24% with 70% pPA. The rate is expected to vary depending on the parameters used for screening including age groups,[14] diagnostic categories (sinusitis, recurrent infections, etc.), and the thresholds of pPA (50% vs. 70%).[9,10] Considering the number of different parameters for assessing PA state/response, it is not surprising to observe differences in the literature with regards to SAD statistics including its prevalence and its relationship with allergic diseases as seen in our analysis.

The efficacy of pneumococcal vaccines has been demonstrated against invasive and non-invasive pneumococcal diseases including CRS in both children and adults.[10,15–18] Our study similarly demonstrated that vaccine responders had less frequent sinusitis compared to non-responders during the follow-up period. This indicates an adequate number of protective titers against *S. pneumoniae* is necessary for the prevention of recurrent sinusitis since *S. pneumoniae* is the most common

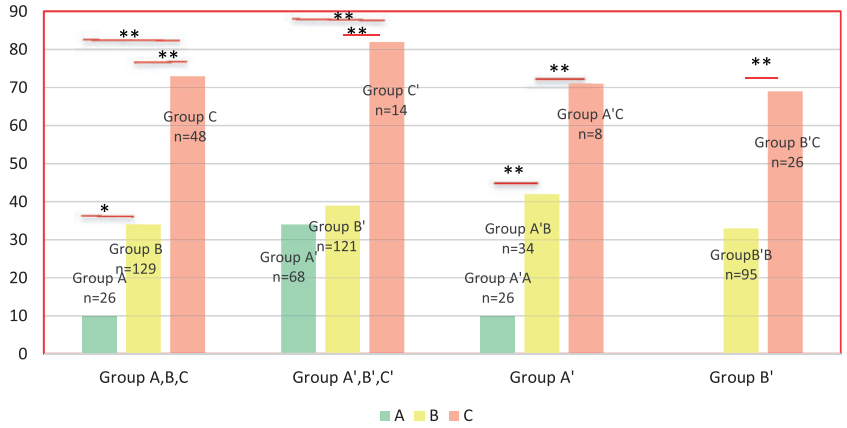

Figure 2. Recurrence rates of sinusitis during the 1 year after the initial visit by 2 different methods of interpreting PA status. See Figure 1 for definitions of groups: A, B, C, A', B', C' A'A, A'B, A'C, B'B, B'C. * $P < .05$; ** $P < .01$.

pathogen for sinusitis and pre and post-pPAs reflect B cell function against polysaccharide antigens present on the surface of other major bacteria associated with sinusitis such as *H. influenzae* and *Moraxella catarrhalis*.[19,20]

Interestingly, Group A had a lower incidence of sinusitis than Group B during the follow-up period although the average pre -pPA of Group A and post-pPA of Group B were not statistically different (the data not shown), suggesting that the pre-existing PA from Group A (pre-pPA ≥70%) yielded a higher protection against sinusitis than the vaccine-acquired antibodies in Group B (post-pPA ≥70%). However this was not the case for Group A' (pre-pPA ≥50%) and Group B' (post-pPA ≥50%), indicating the pre-existing PAs did not provide any superiority over vaccine-induced ones when the pre- and post- pPA thresholds were set low. All of these may suggest that initial robust PA levels are associated with strong B cell function that protects against subsequent sinusitis.

An important question remains as to the minimum pPA to prevent respiratory infection—in particular: 70% pPA vs. 50% pPA. When a 50% pPA was used as a screening criterion either for pre-vaccination or post-vaccination PA status, patients with PA in the 50-69% range would have missed the opportunity to benefit from vaccination. Our patients in this range of pPA had vaccinations since they were treated by the 70% pPA protocol. Our data showed the vaccine responders in the 50-69% range had experienced sinusitis, significantly, less frequently in the next one year compared to the non-responders (Group A'B[42%] vs. Group A'C[71%], Group B'B[33%] vs. Group B'C[69%]). This is consistent with previous reports showing that patients with CRS whose post pPA in 50-69% had more frequent use of antibiotics during the follow-up period compared to the patients who had pPA ≥70%.[9,10]

Our study showed that the prevalence of allergic sensitization among our population (62%) was higher, compared to the general population as reported by NHANES (45% in patients ≥6 years of age).[21] The prevalence of rhinitis (75%) and asthma (43%) were more common in our total study group as compared to the general population (20-30% and 7-8% in the United States).[22–24] There are reports in the literature showing association of asthma and rhinitis with SAD.[7–10] When individual groups, Group A, B, and C, were compared using the 70% pPA criterion, there was no significant differences in prevalence of asthma and rhinitis. However, Among the 50% pPA groups the asthma prevalence was higher in Group C' compared to Group B' and higher among SAD (Group C') compared to non-SAD (Group A'+B'), consistent with the previous report by Keswani.[9] This illustrates that clinical correlation with SAD may vary depending on the criteria used for the definition of SAD.

This study has limitations. First, the study population was derived from an allergy and immunology clinic where patients with recurrent respiratory problems were likely overrepresented, skewing the prevalence rate of sinusitis. However, our goal was to find the prevalence of SAD among such populations with recurrent respiratory infections. Second, as our study population encompassed a large age range, the vaccinations received varied depending on patient lifespan and included PPV-14, PPV-23, PCV-7, and PCV-13, it is possible that the pre-PAs may have been affected by these vaccines. However, this was intended as a real-time study dealing with patients as they presented regardless of their vaccination status. Third, in the absence of functional antibody assay, evaluation of PA status could only be approximated by expert guidelines based on the values of varying numbers of PA provided by different commercial laboratories. Forth, two different laboratories were used for the PA levels; 189 patients (93%) by Labcorp and 14 patients by Quest Diagnostics. Discrepancy in the PA values between different

laboratories has been reported[5] and is a confounder for our analysis. Since each group, A, B, C, A', B', and C' had very similar composition in their laboratory source, we expect a minimal effect in our group to group comparison analysis. Fifth, the percentage of sinusitis recurrence during the following one year was tabulated using the number of patients who kept their appointments, which may also have increased the sinusitis rate as patients who experienced relief might have chosen not to return.

In summary, SAD is a common immune defect associated with patients with recurrent respiratory symptoms that deserves to be treated with vaccination. We recommend using a 70%, rather than a 50%, pPA threshold for definition of SAD, which would increase pneumococcal vaccination rates and reduce the recurrent sinusitis and likely other infections. Pre-existing PAs (Group A) yielded a higher protection against sinusitis than vaccine-acquired antibodies (Group B). Further studies are needed to confirm our findings and to find the different genetic defects associated with this condition.

Ethical Approval

This study was approved by our institutional review board.

Declaration of Conflicting Interests

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Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

There are no human subjects in this article and informed consent is not applicable.

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