Comparative Immune Responses of Patients with Chronic Pulmonary Diseases during the 2-Year Period after Pneumococcal Vaccination

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Antibody responses to a 23-valent pneumococcal vaccine for Streptococcus pneumoniae serotypes 6B, 14, 19F, and 23F in 84 patients with chronic pulmonary diseases over a 2-year period after vaccination were examined by using a third-generation enzyme-linked immunosorbent assay. Of these patients, 28 (31%) were low responders who had developed increases of at least twofold in the levels of serotype-specific immunoglobulin G (IgG) in sera for none of the four serotypes at 1 month after vaccination. Although no specific clinical features of low responders were evident, their prevaccination levels of IgG for all serotypes were higher than those of responders. In responders, the levels of IgG specific for serotypes 14 and 23F in sera were greatly increased 1 month after vaccination and those specific for serotypes 6B and 19F were moderately increased. In contrast, no significant increases in the levels of IgG specific for serotypes 6B, 19F, and 23F in the low responders during the same period were found, but the levels of IgG specific for serotype 14 did increase. Although a rapid decline in the levels of IgG for all serotypes in responders between 1 month and 6 months after vaccination was found, the levels of IgG specific for serotypes 14 and 23F in sera remained higher than the prevaccination levels for at least 2 years after vaccination. These data suggest the need for the revaccination of responders but not low responders among patients with chronic pulmonary diseases. Revaccination as early as 3 years postvaccination is recommended for responders to increase the reduced levels of IgG in sera, especially those specific for the weak vaccine antigens.

Streptococcus pneumoniae is an important cause of pneumonia and serious invasive diseases in children and adults (4, 13, 14). The increased rate of drug-resistant pneumococci in recent years emphasizes the need for preventing pneumococcal infections by vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV) (3, 16, 19, 28).

Patients with chronic pulmonary diseases, such as chronic obstructive pulmonary diseases (COPD), are highly susceptible to pneumonia or acute exacerbation caused by S. pneumoniae (25). Since previous investigators reported the efficacy of PPV for preventing invasive pneumococcal diseases in patients, including those with chronic pulmonary diseases and other chronic illnesses, PPV is recommended for these patients (8, 9, 26). The nature of the effects of PPV in preventing pneumonia or acute exacerbation among patients with chronic pulmonary diseases, however, remains controversial (1, 11, 27, 30).

Antibodies to pneumococcal capsular polysaccharide (PPS) and complement provide protection against S. pneumoniae strains with homologous or cross-reactive capsular serotypes (18). Using a variety of methodologies, previous investigators have reported the concentrations of PPS-specific immunoglobulin G (IgG) in sera from patients with chronic pulmonary diseases, including COPD (7, 11, 22, 29). No studies, however, have examined the levels of serotype-specific IgG in sera from patients with chronic pulmonary diseases by using the third-generation enzyme-linked immunosorbent assay (ELISA) that has recently been recommended by the World Health Organization (31).

Two previous studies reported a substantial proportion of poor responders to PPV among elderly adults or patients with COPD who were receiving steroid therapy (12, 21). However, these studies failed to demonstrate the kinetics of the immune responses of this group. In addition, antibody avidity is an indicator of the strength with which an antibody binds to a complex antigen, and high-avidity antibodies are superior to low-avidity antibodies in terms of opsonophagocytic killing of S. pneumoniae (2, 20). No previous studies have examined the avidities of antibodies in sera from patients with chronic pulmonary diseases before and after pneumococcal vaccination.

The objective of this study, therefore, was to examine the concentrations of serotype-specific IgG and the avidity of IgG in sera from patients with chronic pulmonary diseases by using the third-generation ELISA before and after pneumococcal vaccination. We also attempt to characterize a subset of low responders among these patients and demonstrate the differ-
ence in the kinetics of serotype-specific IgG between responders and low responders over a 2-year period after vaccination.

MATERIALS AND METHODS

Study subjects and vaccination. Eighty-four patients with chronic pulmonary diseases were enrolled in this study after providing written informed consent at 1 of 13 hospitals in the districts of Kyushu and Okinawa, Japan, between November 2001 and December 2003. The ages of the study subjects ranged from 40 to 88 years (median, 70.0 years), and 58 (69%) were male (Table 1). Of these, 28 patients (33.3%) had previously received oral steroids, inhaled steroids, or both. Each patient received a single intramuscular dose of 0.5 ml of a PPV (Pneumovax, Banyu, Japan). The dose contained 25 μg of each of 23 pneumococcal serotypes; 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. None of these subjects had previously been vaccinated with a PPV. Blood samples were collected from the patients immediately before vaccination and 1 month, 6 months, 1 year, and 2 years after vaccination. Sera were separated by centrifugation, divided into small aliquots, and stored at −80°C until used. All of the subjects were evaluated for serotype-specific IgG in sera before vaccination and at 1 month, 6 months, 1 year, and 2 years after vaccination. The ages of these 40 subjects ranged from 40 to 80 years (mean, 67 years), and 25 (62.5%) were male. The chronic pulmonary diseases among these 40 subjects were COPD (n = 14), sequelae of pulmonary tuberculosis (n = 15), bronchial asthma (n = 4), bronchiectasis (n = 3), and pneumoconiosis (n = 3). All studies described herein were approved by the institutional review board of each institution which is a member of the Pneumococcal Vaccine Trialist Group in Kyushu and Okinawa, and a signed consent form was obtained from each subject.

Measurement of anti-PPS IgG. Since the preabsorption of serum to both cell wall polysaccharides (CWPs) and type 22F PPS could increase the correlation in the kinetics of serotype-specific IgG between responders and low responders over a 2-year period after vaccination.

TABLE 1. Comparative clinical characteristics of all subjects, responders, and low responders with chronic pulmonary diseases

| Characteristic | Value for group |
|---------------|----------------|
|               | All subjects (n = 84) | Responders (n = 58) | Low responders (n = 26) |
| Mean age ± SD (yr) | 68.1 ± 9.1 | 67.76 ± 8.77 | 69 ± 9.90 |
| No. of males (%) | 58 (69) | 40 (69) | 18 (69) |
| No. with chronic pulmonary disease (%) | | | |
| Chronic obstructive pulmonary disease | 27 (32.1) | 17 (29) | 10 (38) |
| Sequelae of pulmonary tuberculosis | 26 (31.0) | 19 (33) | 7 (27) |
| Bronchiectasis | 12 (14.3) | 6 (10) | 6 (23) |
| Bronchial asthma | 8 (9.5) | 7 (12) | 1 (4) |
| Pneumoconiosis | 6 (7.1) | 4 (7) | 2 (8) |
| Intestinal pneumonia | 3 (3.6) | 3 (5) | 0 (0) |
| Diffuse panbronchiolitis | 2 (2.4) | 2 (3) | 0 (0) |
| No. receiving steroid therapy (%) | 10 (11.9) | 9 (16) | 1 (4) |
| Inhaled and oral steroid | 12 (14.3) | 7 (12) | 5 (18) |
| Oral steroid alone | 6 (7.1) | 5 (9) | 1 (4) |

was then incubated at 37°C for 5 h in a humidified chamber. The U.S. reference pneumococcal antiserum (89-SF), courtesy of Carl Frasch, was adsorbed to CWPs, but all other samples were adsorbed to CWPs (5 μg/ml) and 22F PPS (10 μg/ml) in phosphate-buffered saline–0.05% Tween 20 at room temperature for 30 min. Fifty microliters of the adsorbed sera was diluted twofold and added to the wells of a microtiter plate. The microtiter plates were incubated for 2 h at room temperature. After washing of the plates, 100 μl of diluted goat anti-human IgG–alkaline phosphatase conjugate was added to each well, and the plates were incubated for 2 h at room temperature. After washing of the plates, 100 μl of substrate solution (1-mg/ml p-nitrophenyl phosphate) was added to each well and the plates were again incubated for 2 h at room temperature. The reaction was stopped by the addition of 1 ml of 0.5 M NaOH to all of the wells, and the optical density at 405 nm was measured with a reference filter of 600 nm. The concentrations of serotype-specific IgG were calculated based on a comparison with the internal standard reference serum 89-SF. We defined individual subjects as responders if they developed a twofold increase in serotype-specific IgG for at least one of the four serotypes and as low responders if they developed a twofold increase in serotype-specific IgG for none of the four serotypes at 1 month postvaccination.

Measurement of the avidity of anti-PPS IgG. The avidity of serotype-specific IgG in sera was measured by using ELISA according to a previously described method (2). Twenty-eight of the 40 patients subjected to the full course of measurements of serotype-specific IgG in sera before vaccination and at 1 month, 6 months, 1 year, and 2 years were included in the avidity assay because of the limited volume of stored serum. The serum samples preadsorbed to CWPs and 22F PPS were added to the coated microtiter plates, and the plates were incubated for 2 h at room temperature. After washing of the plates, 0.5 M sodium thiocyanate was added to each well and the plates were incubated for 15 min at room temperature. After washing of the plates, diluted goat anti-human IgG–alkaline phosphatase conjugate was added to each well. After incubation for 2 h at room temperature, the substrate solution was added to the plates, followed by incubation for 2 h at room temperature. The optical density at 405 nm was measured. The avidity index was expressed as the percentage of antibodies that remained bound to the antigens after incubation with sodium thiocyanate.

Statistical analysis. The average antibody concentrations, increases (n-fold), and absolute increases are expressed as the geometric means. Differences in geometric mean concentrations (GMCs) of serotype-specific IgG over time were assessed by using the Friedman test and the Wilcoxon signed-rank test, and the differences in IgG levels between responders and low responders were assessed by using the Mann-Whitney U test for independent samples.

RESULTS

Anti-PPS IgG levels before and 1 month after vaccination. The GMCs of IgG antibodies specific for four serotypes in sera before vaccination ranged from 3.05 μg/ml for serotype 23F to 6.35 μg/ml for serotype 14 (Table 2). When the threshold of the protective levels of serotype-specific IgG against invasive pneumococcal diseases in sera is assumed to be 1 μg/ml (24), the percentages of patients who showed higher levels were 92% for serotype 6B, 99% for serotype 14, 96% for serotype 19F, and 92% for serotype 23F, much higher than those reported previously for elderly subjects (24). One month after vaccination, significant increases in the GMCs of serotype-specific IgG for all serotypes compared to those before vaccination were found for all subjects (P < 0.01) (Table 2). Increases in GMCs of serotype-specific IgG exceeding twofold were, however, found only for serotypes 23F and 14.

Responders and low responders to PPV. With the definition of responders and low responders in this study, the numbers of responders and low responders were 58 (69.0%) and 26 (31.0%), respectively (Table 1). No significant differences in age, sex, frequency of specific chronic pulmonary disease, and steroid use were found between the two groups. Interestingly, the prevaccination levels of serotype-specific IgG in low responders were higher than those in responders for all serotypes, although no significant differences were found between...
Influence of steroid therapy. The geometric mean increases (n-fold) in levels of serotype-specific IgG antibody in sera from all 84 subjects, and those for type 23F at 2 years postvaccination (Table 2). The GMCs of IgG specific for types 6B and 19F were significantly higher in responders than in low responders (P < 0.01) (Table 2). The GMCs of serotype-specific IgG for all serotypes decreased up to 68 to 81% between 1 month and 6 months after vaccination (Table 3). The GMCs of IgG specific for types 6B and 19F declined below prevaccination levels at 6 months postvaccination and those for type 23F at 2 years postvaccination.

**TABLE 2. Comparison of GMCs and geometric increases (n-fold) in levels of serotype-specific IgG antibody in sera from all 84 subjects, responders, and low responders before and 1 month after vaccination**

| Serotype | Time point | GMC of IgG (µg/ml) (95% CI) in sera from: | Geometric mean increase (n-fold) (range) in IgG from sera: |
|----------|------------|------------------------------------------|-----------------------------------------------------------|
|          |            | All subjects (n = 84) | Responders (n = 58) | Low responders (n = 26) | All subjects (n = 84) | Responders (n = 58) | Low responders (n = 26) |
| 6B       | Pre        | 4.33 (3.51–5.36) | 3.9 (3.01–5.04) | 5.48 (3.80–7.89) | 1.49 (0.5–8.69) | 1.75 (0.53–8.69) | 1.04 (0.5–1.61) |
|          | 1 mo       | 6.44 (5.11–8.11)** | 6.81 (5.04–9.21)** | 5.68 (4.02–8.03) | 2.34 (0.6–46.33) | 3.17 (0.83–46.33) | 1.19 (0.6–1.84) |
| 14       | Pre        | 6.35 (5.25–7.68) | 5.82 (4.71–7.17) | 7.73 (5.14–11.63) | 1.38 (0.35–11.41) | 1.61 (0.82–11.41) | 0.95 (0.35–1.82) |
|          | 1 mo       | 14.84 (11.51–19.14)** | 18.42 (13.45–22.52)** | 9.16 (6.17–13.60)** | 2.13 (0.53–38.49) | 2.88 (0.67–38.49) | 1.1 (0.53–1.95) |
| 19F      | Pre        | 5.25 (4.29–6.43) | 4.74 (3.70–6.07) | 6.62 (4.62–9.48) | 1 mo       | 6.44 (5.11–8.11)** | 6.81 (5.04–9.21)** | 5.68 (4.02–8.03) | 2.34 (0.6–46.33) | 3.17 (0.83–46.33) | 1.19 (0.6–1.84) |
|          | 1 mo       | 7.27 (6.04–8.75)** | 7.63 (6.09–9.55)** | 6.53 (4.63–9.21) | 1.38 (0.35–11.41) | 1.61 (0.82–11.41) | 0.99 (0.35–1.82) |
| 23F      | Pre        | 3.05 (2.53–3.67) | 2.91 (2.37–3.57) | 3.37 (2.24–5.07) | 1 mo       | 6.51 (5.01–8.46)** | 8.39 (6.10–11.52)** | 3.7 (2.45–5.58)# | 3.17 (0.83–46.33) | 1.19 (0.6–1.84) |
|          | 1 mo       | 6.44 (5.11–8.11)** | 6.81 (5.04–9.21)** | 5.68 (4.02–8.03) | 1.38 (0.35–11.41) | 1.61 (0.82–11.41) | 0.99 (0.35–1.82) |

**TABLE 3. GMCs and geometric increases (n-fold) in levels of serotype-specific IgG antibody in sera from all 40 patients before vaccination and 1 month, 6 months, 1 year, and 2 years after vaccination**

| Serotype | Time point | GMC of IgG (µg/ml) (95% CI) | Geometric mean increase (n-fold) (range) | Absolute increase (µg/ml) (range) |
|----------|------------|----------------------------|----------------------------------------|----------------------------------|
| 6B       | Pre        | 3.54 (2.6–4.81) | 1.42 (0.5–6.13) | 1.06 (–1.98–18.21) |
|          | 1 mo       | 5.03 (3.61–7.02)** | 0.98 (0.09–3.33) | 0.69 (0.11–3.29) |
|          | 6 mos      | 3.48 (2.46–4.92) | 0.93 (0.25–2.67) | 0.93 (0.25–2.67) |
|          | 1 yr       | 3.28 (2.4–4.5) | 0.69 (0.11–3.29) | 0.69 (0.11–3.29) |
|          | 2 yrs      | 2.43 (1.7–3.48) | 0.37 (0.05–0.58) | 0.37 (0.05–0.58) |
| 14       | Pre        | 5.47 (4.41–6.79) | 2.02 (0.78–13.06) | 1.12 (–2.75–85.13) |
|          | 1 mo       | 11.04 (8.24–14.78)** | 1.64 (0.41–11.33) | 1.64 (0.41–11.33) |
|          | 6 mos      | 8.96 (6.64–12.08)** | 1.47 (0.73–8.44) | 1.47 (0.73–8.44) |
|          | 1 yr       | 8.03 (6.12–10.54)** | 1.26 (0.27–8.14) | 1.26 (0.27–8.14) |
|          | 2 yrs      | 6.92 (5.22–9.17)* | 0.85 (0.22–5.46) | 0.85 (0.22–5.46) |
| 19F      | Pre        | 4.87 (3.75–6.31) | 1.35 (0.67–11.41) | 1.05 (–1.89–19.3) |
|          | 1 mo       | 6.56 (5.07–8.49)** | 0.94 (0.14–12.25) | 0.94 (0.14–12.25) |
|          | 6 mos      | 4.6 (3.51–6.03)** | 0.89 (0.35–1.82) | 0.89 (0.35–1.82) |
|          | 1 yr       | 4.35 (3.46–5.48) | 0.69 (0.11–2.93) | 0.69 (0.11–2.93) |
|          | 2 yrs      | 4.15 (3.19–5.41) | 0.52 (0.16–1.82) | 0.52 (0.16–1.82) |
| 23F      | Pre        | 2.6 (2.03–3.32) | 2.13 (0.67–38.49) | 1.16 (–2.83–79.1) |
|          | 1 mo       | 5.54 (3.73–8.23)** | 1.44 (0.47–27.29) | 1.44 (0.47–27.29) |
|          | 6 mos      | 3.74 (2.61–5.37)* | 1.26 (0.39–18.54) | 1.26 (0.39–18.54) |
|          | 1 yr       | 3.28 (2.29–4.5)* | 0.90 (0.14–12.96) | 0.90 (0.14–12.96) |
|          | 2 yrs      | 2.33 (1.61–3.36) | 0.69 (0.11–3.29) | 0.69 (0.11–3.29) |

* Pre, prevaccination; CI, confidence interval; †, P < 0.05 (for comparison with prevaccination value); **, P < 0.01 (for comparison with prevaccination value); #, P < 0.05 (for comparison with value for responders, at 1 month after vaccination).
3). The GMCs of serotype 14-specific IgG 2 years postvaccination were still significantly higher than prevaccination GMCs ($P < 0.05$) (Table 3). The estimated time points after vaccination when the levels of serotype-specific IgG returned to the prevaccination levels, calculated using the logarithmic trend line, were 0.5 years for serotype 6B, 6.9 years for serotype 14, 0.6 years for serotype 19F, and 1.7 years for serotype 23F.

We next compared the kinetics of serotype-specific IgG in sera from responders ($n = 27$) and low responders ($n = 13$) during the 2-year period after vaccination (Fig. 1). The increases in type-specific IgG for all serotypes in responders 1 month after vaccination were statistically significant. While a moderate increase in IgG for serotype 6B or 19F was found, a substantial increase in IgG for serotypes 14 and 23F at the same time point was found. A rapid decline in serotype-specific IgG in sera for all four serotypes in responders within 1 year after vaccination was also found. In the case of the responders, the time intervals required for the GMCs to return to prevaccination levels were calculated to be 0.87 years for serotype 6B, 8.3 years for serotype 14, 1.1 years for serotype 19F, and 2.5 years for serotype 23F. The persistence of serotype-specific IgG above the prevaccination level was, therefore, highly varied for each serotype. In contrast, no significant increases in IgG specific for any of the serotypes in low responders at 1 month after vaccination were found. These levels remained unchanged or decreased slightly compared to the prevaccination levels for serotypes 14 and 23F between 1 month and 2 years postvaccination, while these levels decreased significantly compared to the prevaccination levels at 1 year and 2 years after vaccination for serotype 19F and at 2 years after vaccination for serotype 6B ($P < 0.05$ for serotype 19F; $P < 0.01$ for serotype 6B).

**Avidity index of anti-PPS IgG.** The avidity indices of serotype-specific IgG for all four serotypes in sera from all subjects, responders, and low responders before vaccination and 1 month and 2 years after vaccination are shown in Table 4.
Overall, no significant difference in the avidity indices for all four serotypes in all subjects between the time points before vaccination and at 1 month after vaccination was found. In addition, the avidity indices for all subjects, responders, and low responders for all four serotypes remained unchanged, except those for serotype 6B in low responders and serotype 19F in all subjects and responders, for up to 2 years after vaccination. The avidity indices were lower among low responders than among responders for all four serotypes, although the differences were statistically insignificant before vaccination and 1 month and 2 years after vaccination.

### DISCUSSION

This study examined the differences in the clinical characteristics and immune responses to PPV of responders and low responders in a group of patients with chronic pulmonary diseases over a 2-year period after vaccination. Although significant increases in the levels of IgG specific for four major serotypes were found after pneumococcal vaccination, the immune responses to PPV were highly varied. Although 31% of patients with chronic pulmonary diseases were defined as low responders to PPV, no significant demographic feature was found among these subjects. Rubins et al. reported that 20% of elderly patients were found to be poor responders to PPV while none of the healthy young adults examined were poor responders, but these investigators employed the second-generation ELISA and defined a poor responder as a patient who developed a twofold increase in serotype-specific IgG for fewer than two of seven serotypes tested at both 1 and 3 months after vaccination (21). de Roux et al. also evaluated the nonresponders to PPV of each serotype who developed neither a twofold increase nor an increase of at least 1 μg/ml by using the second-generation ELISA among patients with COPD who were receiving inhaled steroids or systemic steroids (12). The frequencies of nonresponders who developed a twofold increase for fewer than two of seven serotypes were 17% and 21% among COPD patients receiving inhaled steroids and those receiving systemic steroids, respectively, in this study.

The frequency of low responders to PPV in our study, therefore, is somewhat higher than those reported in these studies (12, 21). Although additional absorption to PPS 22F reduced the levels of serotype-specific IgG, the prevaccination levels of serotype-specific IgG in sera were higher than 1 μg/ml in nearly all of our patients. A tendency for increased prevaccination levels of serotype-specific IgG in the sera of low responders was also found. A recent study similarly demonstrated that elderly subjects with higher levels of serotype-specific IgG (≥5 μg/ml) in sera before vaccination tended to respond to PPV at a lower magnitude (6). The high proportion of low responses in our study may be due to the increased prevaccination levels of serotype-specific IgG in the sera of patients with chronic pulmonary diseases.

Another finding in this study is the rapid decline in the levels of serotype-specific IgG in sera 6 months after vaccination in patients with chronic pulmonary diseases. A previous study by Davis et al. reported the kinetics of levels of pneumococcal antibodies to 12 serotypes in sera from patients with COPD after vaccination with 14-valent PPV (11). Using a radioimmunoassay, the authors similarly demonstrated a gradual decline in PPS-specific antibody levels in sera over 2 years. The levels of PPS-specific IgG at 2 years postvaccination were still higher than the prevaccination levels. Sankilampi et al. also demonstrated that the concentrations of serotype-specific IgG in the elderly, as determined by the second-generation ELISA, declined to levels similar to the prevaccination levels at 3.0 years after vaccination with PPV for serotype 6B, 3.8 years for serotype 19F, 4.7 years for serotype 23F, and 7.7 years for serotype 14 in the elderly (23). A recent study reported a rapid decline of serotype 6B-specific IgG levels in sera, as determined by second-generation ELISA, at 1 year postvaccination among long-term-care residents who were 60 years of age or older (6). These data and ours indicate a gradual decline in the levels of serotype-specific IgG in sera, and these levels return to the prevaccination levels within 1 to 4 years after pneumococcal vaccination in patients with chronic pulmonary diseases or elderly patients (6, 23). In addition, the levels in sera of IgG specific for serotypes 6B, 19F, and 23F, which are weak vaccine antigens, declined faster than those of IgG specific for serotype 14 among these subjects (14). More importantly, the present study clearly demonstrates differences in the kinetics of serotype-specific IgG in sera from responders and low responders. Since low responders exhibited no significant increases in the levels of IgG specific for serotypes 6B, 19F, and 23F in sera at 1 month postvaccination, the frequency of low responders of 31% affected the kinetics of serotype-specific IgG in sera for all study subjects. Nevertheless, we found that the time point for the serotype-specific IgG to return to the prevaccination level was less than 3 years for such weak vaccine antigens, even in responders, while the time point for serotype 14 was longer than 8 years in these subjects. These data suggest that pneumococcal revaccination may be required especially for these weak vaccine antigens as early as 3 years after the initial pneumococcal vaccination for responders with chronic pulmonary diseases. Although the use of pneumococcal conjugate vac-
cines may be a possible strategy currently available for low responders, revaccination with PPV may also be effective, especially for low responders whose levels of serotype-specific IgG in sera are relatively reduced before revaccination.

The avidity indices of serotype-specific IgG in prevaccination sera determined for four serotypes in our study were similar to data reported in a recent publication by Bogaert et al., who used serum samples collected from patients with COPD (5). A common finding in that study and ours is that the avidity index is the highest for serotype 14 and the lowest for serotype 6B. No significant increase in the avidity index of IgG specific for any of the four serotypes was found before and 1 month after vaccination with 23-valent PPV in this study. Although several previous studies demonstrated significant increases in the avidity indices among infants after immunization with a pneumococcal conjugate vaccine (2, 32), the discrepancy between the findings of these studies and ours may be due to differences in the type of pneumococcal vaccine used or differences in target subjects.

In summary, this study demonstrates differences in immune responses to PPV between responders and low responders among patients with chronic pulmonary diseases over a 2-year period after pneumococcal vaccination. Our data suggest that responders should be revaccinated at as early as 3 years post-vaccination in order to increase the attenuated levels of serotype-specific IgG, especially for the weak vaccine antigens. Further studies will be required to clarify the proportion of low responders in other subsets of elderly or young adults for which PPV is recommended (9).

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