Antibody Responses to Pneumococcal Polysaccharide Vaccine in Taiwanese Patients with Chronic Obstructive Pulmonary Disease

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Background/Purpose: A study was undertaken to assess the antibody responses to a 23-valent pneumococcal polysaccharide vaccine and clinical outcome in Taiwanese patients with chronic obstructive pulmonary disease (COPD).

Methods: From January to December 1999, 80 Taiwanese patients with COPD were enrolled. Each patient received a 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23). Specific IgG antibodies to pneumococcal capsular antigens of serotypes 4, 6B, 7F, 9V, 14, 18C, 19F, and 23F were measured before vaccination, and 6 weeks and 52 weeks after vaccination.

Results: Detectable prevaccination IgG antibody (>1 μg/mL) was found in the range of 27.5% of patients for serotype 7F to 96.2% for serotype 14. Antibody concentrations in prevaccination sera were not different between middle-aged (<65 years old) and elderly patients (≥65 years old). The percentage of elderly patients with postvaccination antibody concentration >2-fold higher than that prior to vaccination ranged from 84% for serotype 18C to 90% for serotypes 7F, 9V, and 19F. The change in antibody level (fold and absolute increases) postvaccination was not significantly different among the different age groups.

Conclusion: Taiwanese elderly adults with COPD, even in advanced age, can mount a significant antibody response to pneumococcal polysaccharide vaccine. This study may support the existing recommendation that pneumococcal vaccine be offered to persons ≥65 years old with COPD. [J Formos Med Assoc 2007;106(3):196–203]

Key Words: antibody response, chronic obstructive pulmonary disease, pneumococcal polysaccharide vaccine
Pneumococcal antibody in COPD patients

Invasive pneumococcal infection is still unknown, but one study revealed that the overall mortality rate of 42.5% for elderly patients (≥ 65 years old) with invasive infection was higher than that of 22.4% for patients aged 19–64 years.3 Although effective antimicrobial drugs have reduced case fatality, pneumococcus remains a common global cause of morbidity and mortality among elderly people.4,5

In recent years, the widespread emergence of antimicrobial resistance in S. pneumoniae has become a major global concern.6,7 The Asian region is one of the epicenters for pneumococcal resistance and Taiwan has one of the highest levels of antibiotic-resistant pneumococci in the world.7 Therefore, prevention of infection by vaccination with pneumococcal polysaccharide is encouraged for persons at high risk for serious pneumococcal disease, such as the elderly and individuals with certain underlying medical conditions such as COPD, congestive heart failure, diabetes mellitus, and immunocompromised patients.8

In 1911, Wright et al9 developed a crude whole-cell pneumococcal vaccine to immunize South African gold miners, a group with an extremely high incidence of serious infection.9 Subsequently, a number of other investigators conducted clinical trials on the safety and efficacy of the polysaccharide vaccines against pneumococci of various serotypes. Although there are at least 90 known serotypes of S. pneumoniae, the currently available 23-valent vaccine can cover more than 90% of the serotypes that are causing invasive pneumococcal infection in Taiwan.7

Good immunogenicity is essential for the efficacy of any vaccine. Serum antibodies to the capsular polysaccharides are known to mediate protection against pneumococcal infection in a serotype-specific manner and the presence of IgG antibody levels > 1 μg/mL have demonstrated good correlation with significant opsonophagocytic activity.8 Although some studies have shown satisfactory antibody responses to pneumococcal vaccination in the elderly, no study from Asian countries has assessed the antibody response in populations with the specific disease. In the present study, we determined the immunogenicity of 80 patients with COPD before and after pneumococcal polysaccharide vaccination in Taiwan and evaluated the outcome of these patients.

Materials and Methods

Setting and study population

Ninety-six Taiwanese patients with COPD were sequentially enrolled at the outpatient clinics of National Taiwan University Hospital, an 1800-bed tertiary medical center, from 1999 to 2000. The diagnosis of COPD was made with compatible clinical history and symptom, risk factor, and an irreversible component of airflow obstruction in pulmonary function test. Of the 96 patients, 16 patients (16%) were lost to follow-up, leaving 80 patients who completed the study and were valid subjects for analysis. To evaluate the possible differences in antibody response with regard to age, the 80 patients were divided into three age groups as follows: 11 patients in the middle aged group (50–64 years); 38 in the elderly group (65–74 years), and 31 in the advanced age group (75–93 years). None of these patients were hospitalized or had acute illness at the time of vaccination. None of them had received pneumococcal vaccination prior to this study. Each patient received a single 0.5-mL subcutaneous injection of a 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23; Merck & Co., Inc., West Point, PA, USA) containing 25 μg of capsular polysaccharide (CPS) from each of the following pneumococcal types: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. Blood samples were drawn before vaccination (80 patients), and 6 weeks (80 patients) and 52 weeks (16 patients) after vaccination. The sera were stored frozen at −20°C until analyzed.

Methods

Specific anti-CPS IgG concentrations (μg/mL) for the eight pneumococcal serotypes, 4, 6B, 7F, 9V, 14, 18C, 19F and 23F, in pre- and postvaccination serum samples were determined using an
enzyme-linked immunosorbent assay. All serum samples were absorbed with cell-wall polysaccharide to remove cross-reactive antipneumococcal antibodies. Each plate included paired pre- and postvaccination samples, positive laboratory reference standard serum with a known concentration of IgG to a specific CPS (based on the common reference serum 89-SF), and negative laboratory reference serum that contained no IgG to the individual polysaccharide.

Statistical analysis
Statistical analyses were performed using SPSS version 10.0 (SPSS Inc., Chicago, IL, USA) for Windows. An antibody fold increase was calculated by dividing the postvaccination antibody concentration by the prevaccination antibody concentration. An absolute antibody rise between the pre- and postvaccination concentrations (μg/mL) was obtained by subtracting the pre- from the postvaccination levels. Differences in geometric mean concentrations (GMC) of specific IgG between prevaccination and postvaccination sera were calculated by the paired t test. The changes in antibody levels (number of folds and absolute increase) among age groups were calculated by one-way ANOVA.

Results
Of the 80 patients who completed the study, 70 (87.5%) were male and 65 (81.25%) were smokers. Table 1 shows the demographic and clinical characteristics of the 80 patients.

Serum IgG antibody concentrations prior to vaccination
The proportions of the three age groups of patients with prevaccination (baseline) and postvaccination antibodies against the eight serotypes are shown in Table 2. Among the different serotypes, these COPD patients had relatively higher prevaccination antibody levels for serotypes 9, 14, 18C and 19F than for serotypes 4, 6B, 7F and 23F (Figure 1). The percentages of low baseline antibody levels (<1 μg/mL) were the highest (81.1%) against serotype 4 in patients <65 years old and lowest against serotype 14 in all three age groups (0–5.26%). Overall, the percentage of patients’ detectable prevaccination IgG antibody (>1 μg/mL) ranged from 27.5% for serotype 7F to 96.2% for serotype 14 (Figure 2). There were no significant differences in baseline antibody concentrations against the eight serotypes among the three age groups.

Postvaccination antibody concentrations, fold increase, and absolute antibody rises
Among the vaccinated patients, 100% of patients in the elderly group had antibody concentration >1 μg/mL for serotypes 14 and 19, and 87–94% for other serotypes 6 weeks after vaccination. Elderly patients had a significant elevation in GMCs in the serum of CPS-specific IgG to all eight vaccine serotypes 6 weeks after immunization, and the GMCs were not significantly different between middle-aged and elderly adults (Table 2).
Table 2. Pre- and postvaccination antibody levels in 80 patients with chronic obstructive pulmonary disease*

<table>
<thead>
<tr>
<th>Serotype</th>
<th>Age group</th>
<th>GMC of IgG, μg/mL (95% CI)</th>
<th>% subjects with IgG &lt; 1 μg/mL</th>
<th>Mean fold rise</th>
<th>% subjects with 2-fold antibody rise</th>
<th>Absolute rise</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
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<tr>
<td>4</td>
<td>&lt;65</td>
<td>1.11 (0.40–1.82)</td>
<td>8.69 (3.02–14.36)</td>
<td>81.81</td>
<td>0.00</td>
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<td></td>
<td>65–74</td>
<td>1.51 (0.34–2.68)</td>
<td>10.18 (5.60–14.77)</td>
<td>57.89</td>
<td>10.53</td>
<td>17.99</td>
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<td></td>
<td>≥75</td>
<td>1.27 (0.81–1.73)</td>
<td>12.22 (6.62–17.82)</td>
<td>51.31</td>
<td>3.23</td>
<td>15.04</td>
</tr>
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<td>6B</td>
<td>&lt;65</td>
<td>1.42 (0.63–2.20)</td>
<td>12.65 (2.91–22.40)</td>
<td>45.45</td>
<td>9.09</td>
<td>10.06</td>
</tr>
<tr>
<td></td>
<td>65–74</td>
<td>1.87 (1.14–2.60)</td>
<td>33.65 (7.79–59.51)</td>
<td>47.37</td>
<td>7.89</td>
<td>20.45</td>
</tr>
<tr>
<td></td>
<td>≥75</td>
<td>1.74 (0.38–3.10)</td>
<td>22.31 (13.82–30.81)</td>
<td>48.39</td>
<td>3.23</td>
<td>24.71</td>
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<td>7F</td>
<td>&lt;65</td>
<td>1.01 (0.47–1.55)</td>
<td>24.38 (0.16–48.61)</td>
<td>72.73</td>
<td>0.00</td>
<td>31.29</td>
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<td>65–74</td>
<td>1.26 (0.62–1.90)</td>
<td>12.06 (7.40–16.72)</td>
<td>58.42</td>
<td>18.42</td>
<td>21.74</td>
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<td>≥75</td>
<td>1.44 (0.15–2.73)</td>
<td>14.42 (6.56–22.30)</td>
<td>64.52</td>
<td>6.45</td>
<td>21.21</td>
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<tr>
<td>9V</td>
<td>&lt;65</td>
<td>3.49 (0.01–6.96)</td>
<td>33.60 (8.53–58.66)</td>
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<td>0.00</td>
<td>13.50</td>
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<td>65–74</td>
<td>2.73 (1.26–4.19)</td>
<td>21.93 (12.08–31.77)</td>
<td>36.64</td>
<td>10.53</td>
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<td>≥75</td>
<td>2.14 (0.94–3.33)</td>
<td>40.95 (12.39–71.52)</td>
<td>32.26</td>
<td>6.45</td>
<td>24.49</td>
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<td>14</td>
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<td>5.51 (2.14–8.89)</td>
<td>50.00 (16.44–83.56)</td>
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<td>59.29 (28.69–89.90)</td>
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<td>2.94 (0.63–5.24)</td>
<td>22.10 (9.25–43.95)</td>
<td>27.27</td>
<td>0.00</td>
<td>17.55</td>
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<td>2.71 (1.70–3.77)</td>
<td>20.23 (12.36–28.11)</td>
<td>31.58</td>
<td>7.89</td>
<td>12.16</td>
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<td>30.89 (12.19–49.60)</td>
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<td>3.23</td>
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<td>4.09 (2.16–6.02)</td>
<td>52.60 (8.66–96.54)</td>
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<td>0.00</td>
<td>11.15</td>
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<td>38.38 (19.87–56.90)</td>
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<td>0.00</td>
<td>16.95</td>
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<td>59.13 (20.55–97.71)</td>
<td>13.33</td>
<td>0.00</td>
<td>35.73</td>
</tr>
<tr>
<td>23F</td>
<td>&lt;65</td>
<td>1.66 (0.70–2.61)</td>
<td>24.96 (8.85–41.07)</td>
<td>27.27</td>
<td>0.00</td>
<td>16.88</td>
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<td></td>
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<td>1.84 (1.15–2.52)</td>
<td>15.01 (9.29–20.74)</td>
<td>57.89</td>
<td>13.16</td>
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<tr>
<td></td>
<td>≥75</td>
<td>2.73 (1.14–4.33)</td>
<td>15.90 (10.01–21.78)</td>
<td>36.67</td>
<td>3.23</td>
<td>11.33</td>
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</table>

*Fold increases (post/pre antibody concentration) and absolute rise (post – pre antibody concentration in μg/mL) are expressed as geometric means. GMC = geometric mean concentration; CI = confidence interval. Differences between pre- and postvaccination GMCs in all age groups for all serotypes are statistically significant (p < 0.05, and 95% CI analysis).

Figure 1. Capsular antibody titers (μg/mL) in 80 patients with chronic obstructive pulmonary disease before immunization with pneumococcal polysaccharide vaccine. Error bars show 95% confidence interval for the geometric mean concentrations for IgG antibodies.
Similarly, mean fold rise and absolute increase in CPS-specific IgG were generally comparable among the three groups at 6 weeks after vaccination. Because the mean fold rise may not accurately represent differences in immune responses among populations, we further compared the proportions of elderly patients and younger subjects who achieved at least a 2-fold increase in antibody levels for the serotypes (Table 2 and Figure 2). Compared with elderly patients, the proportion of younger subjects with a 2-fold antibody rise was greater for all eight serotypes. But the majority (63.3–96.67%) of elderly patients had a 2-fold antibody rise. Thus, by these criteria, at least eight of the 23 vaccine polysaccharides appeared to be highly immunogenic in the aged COPD patients.

Among the 16 patients with sera samples tested for capsular IgG antibody at 52 weeks after vaccination, a remarkable decrease in the mean capsular IgG antibody titer was found for all eight serotypes (Figure 3).

**Discussion**

Exacerbations of COPD cause morbidity, hospital admission and mortality, and strongly influence health-related quality of life. COPD exacerbations have been associated with a number of etiologic factors, including infection and pollution episodes. The most common bacteria resulting in exacerbation of COPD is *S. pneumoniae*. In light of the increased risk of pneumococcal disease with advancing age, and the cost associated with infection and the rising rates of drug resistance, vaccination has emerged as a public health priority.
Despite convincing reports in certain cohorts, controversy still exists over the effectiveness of the pneumococcal polysaccharide vaccine (PPV) in older subjects. Observational studies consistently indicated 50–70% aggregate effectiveness in preventing invasive pneumococcal disease in elderly among serotypes found in PPV.12–14 But it is more difficult to demonstrate that PPV provided protection against nonbacteremic pneumonia in older persons.15,16 Because of its role in reduction of invasive pneumococcal diseases, PPV is cost-effective or even cost-saving.17–19 However, there are few data available on the serotype distribution of isolates of invasive pneumococcal disease in adults in Asia. Whether vaccination with PPV is worthwhile depends on the burden of pneumococcal disease and the cost and effectiveness of vaccination and treatment. In Asia, these factors must be evaluated and more studies should be done before a clear recommendation is given for widespread use of pneumococcal vaccine in national immunization programs.

In the present study, we measured concentrations of CPS-specific IgG in baseline sera and after immunization of adults with the 23-valent vaccine in order to establish the effectiveness of pneumococcal vaccine in Asian COPD patients. The majority of adults had appreciable levels (>1 μg/mL) of natural antibody to CPS prior to immunization, presumably reflecting antibodies acquired during life as a result of colonization or previous infection with *S. pneumoniae* or cross-reacting organisms especially in patients with COPD. Besides, several studies have suggested that elderly women may have lower prevaccination antibody levels to CPS and smoking seems to be associated with higher antibody levels. In our study group, the majority were males and almost all had a history of smoking. Thus, the prevaccination antibody levels in our study group may be attributable to both sex and smoking status. Our findings regarding prevaccination antibody levels to CPS in elderly subjects are generally in agreement with previous reports.20 We also noted that elderly adults had similar prevaccination levels to those of a younger cohort as has been recently reported.21–23

In the present study, the COPD patients had relatively higher prevaccination antibody levels to serotypes 9, 14, 18C and 19F than to serotypes 4, 6B, 7F and 23F. This may suggest that the higher-level serotypes, especially serotype 14, were the more prevalent isolates of pneumococcal infection in patients with COPD. In recent studies, serotype 6B, 14, 19F and 23F were the major serotypes of clinical isolates of *S. pneumoniae* in Taiwan.7 These differences may be attributable to the limited size of the patient group in this study, which focused on COPD. However, further studies on the exact serotype distribution of pneumococcal infection isolates in COPD patients are needed.

Evaluation of the change in antibody level between pre- and postvaccination in patients with COPD in this study revealed that after vaccination, all eight type-specific geometric mean antibody titers were significantly higher than those before vaccination in all subjects. Even with advanced age (≥75 years), individuals seemed to retain the ability to quantitatively respond to pneumococcal vaccine. The overall percentage of elderly patients (≥65 years) with antibody concentrations >1 μg/mL to the eight antigens increased with vaccination from 59.34% to 93.84%. The majority of the subjects had 2-fold increases in specific antibody after vaccination. This suggests that aged Asians with COPD are capable of mounting a significant antibody response as shown in a previous report,24 and that COPD patients may benefit from pneumococcal vaccination.

We analyzed the differences in antibody responses between middle-aged (50–64 years) and elderly (≥65 years) patients. The anti-CPS antibody responses (including fold and absolute increase) to the eight serotypes assayed in the elderly or advanced-aged (>75 years) groups were similar to those of the middle-aged group (p < 0.05). This finding supports previous reports21,22,25 of comparable antibody responses to CPS between older and younger individuals.

Finally, we noted that there were significantly different antibody responses to CPS among different serotypes. Serotypes 7F and 19F appeared
to be the most immunogenic in terms of fold rise. In contrast, types 4, 14 and 23F, which elicited relatively low fold increases in specific antibody, were poorly immunogenic in our study group. This finding is somewhat different from a previous study, which found that serotype 14 seemed to have good immunogenicity. Serotype 4 accounts for many of the vaccine failures seen in clinical trials and was also a leading cause of invasive pneumococcal infection in several reports. Besides, serotypes 23F and 19F are the most common non-susceptible pneumococci in Taiwan. Although such population-based data on pneumococcal disease in Asian adults are lacking, our findings suggest that the redesigning efforts of further pneumococcal vaccines to improve immunogenicity in Asian adults should pay more attention to serotypes 4, 14 and 23F.

In this study, a significant decrease in capsular IgG antibody to all the eight serotypes was found 1 year after vaccination, and only for serotypes 6B, 14, 19F and 23F were the levels 1 year after vaccination higher than those before vaccination ($p < 0.05$). Several previous studies showed that antibodies to some serotypes might decline to prevaccination levels 3–7 years after vaccination. Further studies to understand the chronologic changes in capsular IgG antibody levels for these COPD patients are needed.

There are some limitations to this study. First, it was not a randomized control trial so we did not have a COPD control group (nonvaccinated) to better evaluate the efficacy. Second, although all the patients had prevaccination and 6-week serologic determination, only 16 patients had follow-up serologic data at 52 weeks after vaccination. Third, avidity of the induced antibodies is important and this was not investigated in this study.

In summary, Taiwanese elderly adults with COPD, even in advanced age, can mount a significant antibody response to pneumococcal polysaccharide vaccine, according to our results. Therefore, our results may support the existing recommendation that pneumococcal vaccine be offered to everyone with chronic lung disease who are ≥65 years old.

References