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# Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease

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ABSTRACT

To determine the clinical efficacy of combined vaccination with 23-valent pneumococcal vaccine (PV) and influenza vaccine (IV) against pneumonia and acute exacerbation of chronic lung diseases (CLD), we conducted an open-label, randomized, controlled study among 167 adults with CLD over a 2-year period. Subjects were randomly assigned to a PV + IV group ($n = 87$) or an IV group ($n = 80$). The number of patients with CLD experiencing infectious acute exacerbation ($P = 0.022$), but not pneumonia ($P = 0.284$), was significantly lower in the PV + IV group compared with the IV group. When these subjects were divided into subgroups, an additive effect of PV with IV in preventing infectious acute exacerbation was significant only in patients with chronic obstructive pulmonary diseases ($P = 0.037$). In patients with CLD, the Kaplan–Meier survival curves demonstrated a significant difference for infectious acute exacerbation ($P = 0.016$) between the two groups. An additive effect of PV with IV on infectious acute exacerbation was found during the first year after vaccination ($P = 0.019$), but not during the second year ($P = 0.342$), and was associated with serotype-specific immune response in sera of these patients who used PV during the same period.



## 1. Introduction

Acute exacerbation frequently occurs among patients with chronic lung diseases (CLD), such as chronic obstructive pulmonary disease (COPD) and sequelae of pulmonary tuberculosis (SPTB) [1,2]. Morbidity, mortality and health-care costs of these patients largely result from on acute exacerbations [3]. Acute exacerbations are primarily triggered by bacterial or viral pathogens in COPD and SPTB. While *Streptococcus pneumoniae* (*S. pneumoniae*) is the most commonly identified cause of community-acquired pneumonia (CAP) by accounting for 16.5–38.9% of CAP among adults [4,5], this pathogen is also responsible for 8–25% of acute exacerbation in patients with CLD or COPD, which makes it a major bacterial pathogen [2,6,7]. Viral pathogens are also capable of inducing acute exacerbation of COPD, and the influenza virus was frequently detected in 5–29% of exacerbation of COPD [8,9].

Since antibodies to pneumococcal capsular polysaccharide (PPS) and complement provide protection against *S. pneumoniae* with homologous or cross-reactive capsular serotypes [10], pnemococcal polysaccharide vaccine (PV) is effective for preventing invasive pneumococcal diseases in patients with chronic illness, such as CLD. PV is, therefore, recommended for these patients [11–13]. Although the previous studies reported that PV is not effective in preventing pneumonia or acute exacerbation in patients with COPD [14–16], a recent, prospective study demonstrated an effect of PV in preventing pneumonia in such patients with less than 65 years of age with severe airflow obstruction [17]. In addition, a retrospective study previously reported the additive effects of PV with influenza vaccine (IV) in the reduction of hospitalization

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stays and death among elderly persons with CLD [18,19]. Although a large-scale prospective study demonstrated the additive effects of PV and IV in reducing hospital mortality due to pneumonia among elderly persons [20], no prospective study has been conducted to find the additive effects of PV combined IV for preventing pneumonia or acute exacerbation in patients with CLD. This open-label, randomized, controlled study was designed to determine whether PV and IV combined are superior to IV alone in preventing pneumonia or acute exacerbation among patients with CLD.

## 2. Materials and methods

### 2.1. Study design

For this study, 191 patients with CLD in a stable condition were enrolled after providing written informed consent at the respiratory clinic of 13 hospitals in the district of Kyushu and Okinawa, Japan between November 2001 and April 2002. All potentially eligible subjects (at least twice as many as the enrolled cases) were contacted by the members of the Pneumococcal Vaccine Trialist Group, belonging to one of these hospitals. As the study investigators, these doctors had a role in selecting the subjects for the study enrollment. Inclusion criteria were patients with CLD who previously experienced acute exacerbations, were able to comply with a schedule of monthly clinical visits and were between 40 and 80 years of age. Patients who were pregnant or had immunocompromised conditions such as active malignant diseases, renal insufficiency in dialysis or HIV infection, hypogammaglobulinemia or anatomical or functional asplenia and who had previously received 23-valent PV (Pneumovax, Banyu, Japan) were excluded. The enrollees were randomly assigned in equal proportion to either the group receiving PV and IV (The Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) or IV alone. By sealed envelope, each study site was randomly allocated either 10 or 20 cases. Equal numbers of sealed envelopes each containing a card indicating either the PV + IV group or the IV group were prepared, and each study participant chose an envelope. This vaccine allocation was done by the study investigators. In addition, the doctors who screened the subjects also conducted the exclusions and enrollments.

While the participants in the PV + IV group were separately immunized with 0.5 ml of PV and 0.5 ml of IV on separate occasions in 1 month intervals, the participants in the IV group were immunized with 0.5 ml of IV alone. All participants received IV once in both the 2001/2002 and 2002/2003 seasons. For this study, our group used a trivalent, split-virion, influenza vaccine, containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2, and B/Johannesburg/5/99 for the 2001/2002 season; and for the 2002/2003 season, the study was conducted using vaccine containing A/NewCaledonia/20/99H1N1, A/Panama/2007/99H3N2 and B/Guangdong/7/97.

Demographic data were obtained from each participant at the time of enrollment. All participants were examined, typically once a month, at each hospital by physicians who were the members of the Pneumococcal Vaccine Trialist Group at each study hospital in the Kyushu and Okinawa districts. Patients were also asked to visit each study hospital for examination by a study physician, if they developed a fever, cough and sputum, or experienced breathlessness during the 2-year follow-up period.

To monitor the concentrations of anti-PPS IgG, serum samples were collected from the patients of the PV + IV group immediately before and at 1 month, 6 months, 1 year, and 2 years after the initial pneumococcal vaccination. Separated sera were stored frozen at −80 °C until used. All studies described herein were approved by the institutional review board of each institution.

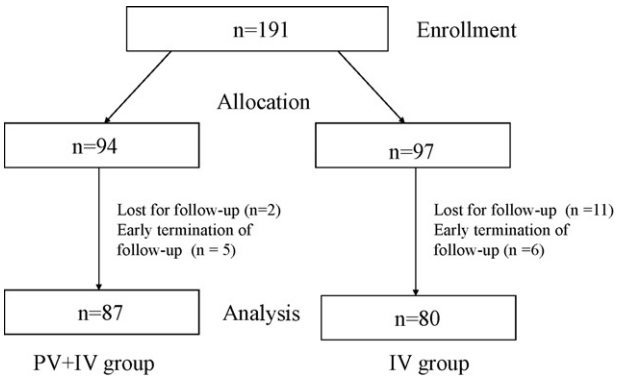


**Fig. 1.** Flow diagram of study patients with chronic lung disease.

### 2.2. Study population

One hundred and ninety-one patients with CLD were assigned to either the PV + IV group ($n = 94$) or to the IV group ($n = 97$) (Fig. 1). During 2-year follow-up period, 2 and 11 subjects were lost from the PV + IV group and IV groups, respectively. In addition, an early termination of follow-up occurred for 5 subjects for the PV + IV group and for 6 subjects in the IV group because they wanted to withdraw from the study. Subsequently, 87 subjects in the PV + IV group and 80 subjects in the IV group completed the analysis.

### 2.3. Outcome measures

The outcome measured was recorded as either the time to the first episode of pneumonia or to acute exacerbation after the enrollment in this study. A pneumonia diagnosis was based on either clinical symptoms (cough, sputum or fever) plus increased white blood cell counts or serum C-reactive protein, and the appearance of a new infiltration on a chest radiograph [21]. Acute exacerbation in CLD was defined by criteria as previously described [22]: (1) increased dyspnea, (2) increased sputum volume and (3) increased sputum purulence, and (4) absence of newly appeared infiltration on a chest radiograph. Acute exacerbation was diagnosed when two of the three respiratory symptoms existed or when one of these and one of additional symptoms, such as a fever without any other causes or increased cough was present [23]. When the laboratory examinations revealed an increase in their white blood cell counts or serum C-reactive protein, in addition to the clinical symptoms of acute exacerbation, patients were diagnosed as infectious acute exacerbation, and were therefore classified into one of two categories: either infectious or non-infectious acute exacerbation. Furthermore, when *S. pneumoniae* was isolated from purulent sputum in cases of acute exacerbation, patients were diagnosed as pneumococcal acute exacerbation as a subcategory of infectious acute exacerbation.

### 2.4. Measurement of anti-PPS IgG

Serum samples for serotype-specific IgG were available from only 35 of 87 patients with CLD in the PV + IV group for all intervals—1 month, 6 months, 1 year, and 2 years. 7 subjects died during the 2-year period, and 45 of the remaining subjects lacked at least one serum sample from the time interval at either 6 months, 1 year or 2 years. The concentrations of serotype-specific IgG were measured as previously described elsewhere [24]. The US reference

pneumococcal antiserum (89-SF), courtesy of Dr. Carl Frasch, was adsorbed to CWPS, but all other samples were adsorbed to CWPS (5 μg/ml) and 22F PPS (10 μg/ml) [25]. Serotype-specific IgG was determined for the four serotypes (6B, 14, 19F and 23F) that are the most prevalent among adult patients with pneumococcal infections in the US and Japan [5,26].

### 2.5. Statistical analysis

The case numbers of patients with COPD, SPTB, and other CLDs, and the case number of patients experiencing pneumonia, infectious acute exacerbation, pneumococcal acute exacerbation, and non-infectious acute exacerbation and the case numbers of death were compared using a $\chi^2$-test. A Kaplan–Meier estimator was used to calculate the survival curve for subjects who developed neither pneumonia nor infectious or non-infectious acute exacerbation during the 2-year study period. The Cox's proportional hazard model was used to evaluate the effect of PV on the incidence of pneumonia and infectious or non-infectious exacerbation both in the first and second 1-year. The effects of age (age older than 55 years, 65 years, and older than 75 years) and female sex were considered in multivariate analysis. Differences in geometric mean concentrations (GMCs) of serotype-specific IgG over time were assessed using the Wilcoxon signed-ranks test. An interim target sample size of 82 was chosen to ensure that there would be at least an 80% chance to detect a difference of 0.2 (0.2 vs. 0.4) episodes per person per year, with a one-sided alpha level of 0.05, in the frequency of admission due to pneumonia between groups of PV + IV and IV. Data was considered to be statistically significant, if the $P$ values were less than 0.05.

## 3. Results

Ages (mean ± S.D. years) and male sex (%) were 69.0 ± 9.0 and 63.5 for total subjects, 67.8 ± 9.5 and 69.0 for the PV + IV group, and 70.1 ± 7.4 and 57.5 for the IV group. The numbers of patients with three subcategories of CLD (COPD, SPTB and other CLDs) in the PV + IV and the IV groups are shown in Table 1. Other CLDs were bronchiectasis ($n$ = 20; 10 for the PV + IV group and 10 for the IV group), bronchial asthma ($n$ = 13, 6 for the PV + IV group and 7 for the IV group), pneumoconiosis ($n$ = 14, 7 for the PV + IV group and 7 for the IV group), interstitial pneumonia ($n$ = 9, 3 for the PV + IV group and 6 for the IV group), diffuse panbronchiolitis ($n$ = 5, 4 for the PV + IV group and 1 for the IV group), and sarcoidosis ($n$ = 1 for the IV group). Fifty-nine subjects received home oxygen therapy (HOT) (27 for the PV + IV and 32 for the IV), and 11 subjects (6 for the PV + IV and 5 for the IV) were treated with noninvasive positive pressure ventilation (NPPV). While a significant difference was found in the number of patients with SPTB between the two groups, no significant difference was found in the number of patients with COPD or other CLDs, nor in the number of patients receiving either HOT or NPPV.

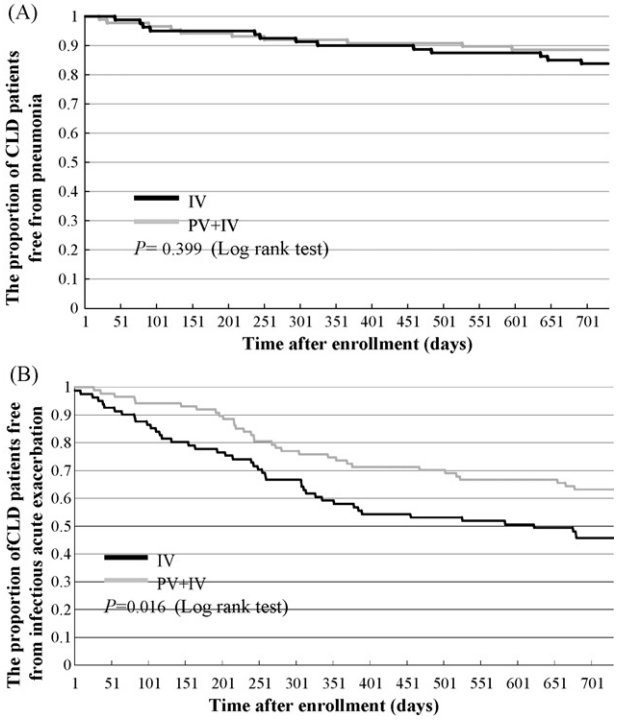


**Fig. 2.** Kaplan–Meier survival curves for patients with chronic lung diseases (CLD) showing the proportion of subjects free from pneumonia (A) and infectious acute exacerbation (B) between PV + IV group and IV group during the follow-up period.

The incidence of pneumonia (0.096 episodes/(patient year)) with CLD in this study was twice as higher as those of previous cohort studies of COPD patients (0.047–0.055 episodes/(patient year)) [14,17]. No significant difference was found in the number of patients developing pneumonia between the PV + IV group and the IV group (Table 1). Similarly, no significant difference was found in the Kaplan–Meier survival curves for pneumonia between the two groups ($P$ = 0.399, Fig. 2A).

**Table 1**
Demographic features and outcome of patients with chronic lung diseases (CLD)

| Characteristics | No. of patients (%) | | | P-value |
|---|---|---|---|---|
| | All subjects ($n$ = 167) | PV + IV group ($n$ = 87) | IV group ($n$ = 80) | |
| Subcategories of CLD | | | | |
| COPD | 55 (32.9) | 24 (27.6) | 31 (38.8) | 0.125 |
| Sequelae of pulmonary tuberculosis | 50 (30.0) | 33 (37.9) | 17 (21.3) | 0.018 |
| Other CLDs | 62 (37.1) | 30 (34.5) | 32 (40.0) | 0.461 |
| Outcome | | | | |
| Pneumonia | 25 (32.9) | 13 (27.6) | 12 (38.8) | 0.284 |
| Acute exacerbation | | | | |
| Infectious | 76 (45.5) | 32 (36.8) | 44 (55.0) | 0.022 |
| Pneumococcal | 6 (3.6) | 1 (1.1) | 5 (6.3) | 0.106 |
| Non-infectious | 15 (9.0) | 9 (10.3) | 6 (7.5) | 0.557 |
| Death | 14 (8.4) | 7 (8.0) | 7 (8.8) | 0.870 |

PV: pneumococcal polysaccharide vaccine, IV: influenza vaccine, COPD: chronic obstructive pulmonary disease. Acute exacerbations are classified into two categories: infectious and non-infectious acute exacerbation. Infectious acute exacerbation involves pneumococcal acute exacerbation.

**Table 2**
Outcome of patients with COPD, sequelae of pulmonary tuberculosis (SPTB) and other chronic lung diseases (CLDs) **by vaccine group** during 2 years after vaccination

| Subcategories of CLD/outcome | No. of patients (%) | | *P*-value |
|---|---|---|---|
| | PV + IV group ($n$ = 87) | IV group ($n$ = 80) | |
| COPD | | | |
| Pneumonia | 6 (**6.9**) | 5 (**6.3**) | 0.615 |
| Acute exacerbation | | | |
| Infectious | 9 (**10.3**) | 21 (**26.3**) | 0.037 |
| Non-infectious | 5 (**5.7**) | 2 (**2.5**) | 0.315 |
| SPTB | | | |
| Pneumonia | 3 (**3.4**) | 2 (**2.5**) | 0.218 |
| Acute exacerbation | | | |
| Infectious | 10 (**11.5**) | 7 (**8.7**) | 0.442 |
| Non-infectious | 2 (**2.3**) | 3 (**3.8**) | 0.594 |
| Other CLDs | | | |
| Pneumonia | 4 (4.6) | 5 (6.3) | 0.379 |
| Acute exacerbation | | | |
| Infectious | 13 (**14.9**) | 16 (**20.0**) | 0.599 |
| Non-infectious | 2 (2.3) | 1 (1.3) | 0.616 |

PV: pneumococcal polysaccharide vaccine, IV: influenza vaccine, COPD: chronic obstructive pulmonary diseases. Acute exacerbations are classified into two categories: infectious and non-infectious acute exacerbation.

The incidence of acute exacerbation (0.53 episodes/(patient year)) in this study was slightly lower than those of previous studies of COPD patients (0.85–1.08 episodes/(patient year)) [27,28]. No significant difference was found in the number of CLD patients with pneumococcal acute exacerbation ($P$ = 0.106) or non-infectious acute exacerbation ($P$ = 0.557) between the two groups (Table 1). In contrast, a significant difference was found in the number of CLD patients with infectious acute exacerbation ($P$ = 0.022) between the two groups (Table 1). The Kaplan–Meier survival curves for CLD patients with infectious acute exacerbation ($P$ = 0.016, Fig. 2B) also demonstrated a significant difference between the two groups. However, no significant difference was found in the mortality during the 2-year period after vaccination in both groups (Table 1).

Furthermore, we examined the number of patients experiencing pneumonia and infectious or non-infectious acute exacerbation in each subcategory (Table 2). No significant difference was found in the number of patients with COPD, SPTB and other CLDs experiencing either pneumonia or non-infectious acute exacerbation. In contrast, a significant difference was found in the number of patients with COPD experiencing infectious acute exacerbation ($P$ = 0.037), but not in the number of patients with SPTB ($P$ = 0.442) or other CLDs ($P$ = 0.599). In COPD patients, the

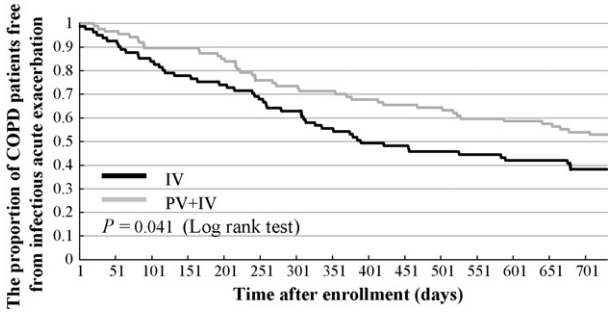


**Fig. 3.** Kaplan–Meier survival curve for patients with chronic obstructive pulmonary diseases (COPD) showing the proportion of subjects free from infectious acute exacerbation between PV + IV group and IV group during the follow-up period.

Kaplan–Meier survival curves for infectious acute exacerbation demonstrated a significant difference between the two groups ($P$ = 0.041, Fig. 3), while no significant difference was found in the Kaplan–Meier survival curves for pneumonia ($P$ = 0.543) or non-infectious acute exacerbation ($P$ = 0.426) in COPD patients (data not shown).

While neither a univariate nor multivariate analysis demonstrated a significant association between any variables and the probability of either pneumonia or non-infectious acute exacerbation in either the first or second year, a significant association between the receipt of PV and a low probability of infectious acute exacerbation was found in patients with CLD in the first year, but not in the second year by a single variable analysis ($P$ = 0.019) or multivariate analyses ($P$ = 0.016, Table 3). No significant association was demonstrated between any variable, such as age older than 55 years, age older than 65 years, age older than 75 years or the female sex and the probability for infectious acute exacerbation, in either the first or second year.

The GMCs of serotype-specific IgG for four serotypes in sera from the 35 patients with CLD during the 2 years after their vaccinations are shown in Table 4. Before vaccination, the GMCs ranged from 2.6 μg/ml for serotype 23F to 5.69 μg/ml for serotype 14. One month after vaccination, significant increases in the GMCs of serotype-specific IgG were found for all serotypes in all subjects, compared to those before vaccination ($P$ < 0.01, Table 4). The GMCs of serotype-specific IgG declined below pre-vaccination levels at 6 months post-vaccination for types 6B and 19F. In contrast, the GMCs of serotype-specific IgG remained above the pre-vaccination levels for type 23F and type 14 at 2 years post-vaccination, although they had declined from the immediate post-vaccine levels. Serotype-

**Table 3**
Estimated result of Cox's proportional hazard model for pneumonia, infectious acute exacerbation, and non-infectious acute exacerbation in patients with chronic lung diseases during the first and the second year

| Period | Variables | Pneumonia | | Acute exacerbation, infectious | | Acute exacerbation, non-infectious | |
|---|---|---|---|---|---|---|---|
| | | Hazard ratio (95% CI) | *P*-value | Hazard ratio (95% CI) | *P*-value | Hazard ratio (95% CI) | *P*-value |
| First year | PV | 0.70 (0.31–1.60) | 0.402 | 0.58 (0.37–0.91) | 0.019 | 1.40 (0.50–3.94) | 0.522 |
| | PV | 0.72 (0.32–1.68) | 0.452 | 0.56 (0.35–0.90) | 0.016 | 1.56 (0.54–4.52) | 0.411 |
| | Age older than 55 years old | N.A. | N.A. | 1.02 (0.33–3.12) | 0.973 | 1.97 (0.22–17.4) | 0.543 |
| | Age older than 65 years old | 1.05 (0.13–8.52) | 0.963 | 1.15 (0.40–3.27) | 0.798 | 0.33 (0.03–3.76) | 0.375 |
| | Age older than 75 years old | 2.63(0.33–20.8) | 0.359 | 0.92 (0.31–2.75) | 0.878 | 1.97 (0.23–17.1) | 0.534 |
| | Female | 0.41(0.14–1.23) | 0.113 | 1.01 (0.63–1.61) | 0.972 | 1.01 (0.33–3.08) | 0.982 |
| Second year | PV | 0.54 (0.13–2.25) | 0.397 | 0.65 (0.26–1.59) | 0.342 | 0.99 (0.28–3.51) | 0.987 |
| | PV | 0.47 (0.11–2.05) | 0.314 | 0.64 (0.25–1.64) | 0.351 | 1.03 (0.26–3.98) | 0.969 |
| | Age older than 55 years old | N.A. | N.A. | 1.11 (0.11–10.76) | 0.93 | 1.36 (0.12–14.97) | 0.800 |
| | Age older than 65 years old | 0.31 (0.31–3.05) | 0.315 | 1.46 (0.18–12.1) | 0.725 | 0.36 (0.03–4.29) | 0.418 |
| | Age older than 75 years old | 0.60 (0.61–5.77) | 0.655 | 0.81 (0.09–7.73) | 0.857 | 1.09 (0.11–10.78) | 0.939 |
| | Female | 0.22 (0.27–1.84) | 0.163 | 1.18 (0.47–2.99) | 0.72 | 1.18 (0.32–4.37) | 0.797 |

N.A.: not applicable, PV: pneumococcal polysaccharide vaccine, CI: confidence interval.

**Table 4**
Serotype-specific IgG in sera from 35 patients with chronic lung diseases before 1 month, 6 months, 1 year and 2 years after vaccination

| Serotype | Time point | GMC of IgG (μg/ml) (95% CI) |
|---|---|---|
| 6B | Pre | 3.46(2.51–4.76) |
| | 1 month | 5.26(3.78–7.54)* |
| | 6 months | 3.51(2.48–5.1) |
| | 1 year | 3.41 (2.48–4.85) |
| | 2 year | 2.68(1.86–3.97) |
| 14 | Pre | 5.69(4.44–7.03) |
| | 1 month | 12.63(8.76–16.61)* |
| | 6 months | 10.35(7.17–13.6)* |
| | 1 year | 8.97(6.36–11.47)* |
| | 2 year | 7.76(5.53–10.07)* |
| 19F | Pre | 4.91 (3.67–6.55) |
| | 1 month | 7.05 (5.37–9.3)* |
| | 6 months | 4.81 (3.56–6.49) |
| | 1 year | 4.60(3.56–5.93) |
| | 2 year | 4.58 (3.46–6.05) |
| 23F | Pre | 2.60(1.97–3.42) |
| | 1 month | 5.82(3.71–9.12)* |
| | 6 months | 4.06 (2.72–6.05)* |
| | 1 year | 3.56(2.48–5.1)* |
| | 2 year | 2.8(1.9–4.1) |

GMC: geometric mean concentration, CI: confidence interval.
* $P < 0.01$ (for comparison with pre-vaccination value).

specific IgG responses to PV, therefore, were found primarily in sera during the first year, but not during the second year, following vaccination.

## 4. Discussion

This study demonstrated an additive effect of PV with IV in preventing infectious acute exacerbation, but not pneumonia or non-infectious acute exacerbation, when compared to IV alone in patients with CLD. When theses subjects were divided into three subgroups according to their type of CLD, an additive effect of PV with IV in preventing infectious acute exacerbation was found only in COPD patients, but not in patients with SPTB or other pulmonary diseases. Since no attempt was made to blind the clinical assessors to the vaccine allocation in this study, the possibility of the bias on the clinical assessment obtained by the investigators can not be dismissed.

Although this was an open-label, randomized controlled study on a small scale, the enrolled patients with CLD in this study were at a high risk for pneumonia or acute exacerbation. Since pneumococci has a major role in the development of pneumonia associated with respiratory viruses such as influenza virus, these viruses contribute to the pathogenesis of bacterial pneumonia among children [29]. Other investigators have also demonstrated that influenza neuraminidase facilitated bacterial adherence of *S. pneumoniae*, and resulted in secondary bacterial pneumonia in mice [30,31]. Based on the interaction between influenza virus and pneumococci on the pathogenesis of bacterial pneumonia, an additive or synergistic effect of the combined vaccination with PV and IV in preventing pneumococcal pneumonia can be expected.

A large prospective study in Sweden reported the additive effects of PV with IV in reducing pneumococcal pneumonia as well as invasive pneumococcal diseases, compared to no vaccination, among adults aged 65 years or older during the first 6 months after vaccination [32]. The authors demonstrated the additive effect of PV with IV only in reducing the hospital mortality due to pneumonia, compared to a vaccination with IV alone or PV alone, at 1-year after vaccination [20]. Another investigator, however, did not find an additive effect of PV with IV in preventing pneumococcal pneumonia as well as pneumonia, compared to IV alone, among the same population during a 2-year period after vaccination [33].

A double-blind, randomized placebo-controlled trial in Thailand recently reported that IV was found highly effective in preventing the influenza-related acute respiratory illness, but not acute exacerbation or pneumonia, in COPD patients [23]. Since no effect of IV was found for preventing acute exacerbation among patients with COPD, our data suggests not only the importance of PV in addition to IV among patients with CLD, but also the role of pneumococcal infection in the pathogenesis of acute exacerbation in such patients.

Although no significant difference was found in the number of patients with pneumococcal acute exacerbation between the two groups in this study, a reduced number of pneumococcal infections in the PV + IV group may suggest the contribution of protective immunity raised by PV in such patients. More importantly, the additive effect of PV with IV on infectious acute exacerbation was significant during the first year, but not the second year after vaccination. This effect was associated with an immune response of serotype-specific IgG to PV, which was prominent in all serotypes during the first year.

Although the protective concentrations of serotype-specific IgG are not known, most of CLD patients showed a level of IgG much higher than the threshold (0.35 μg/ml) that predicts protection in infants against invasive disease at a population level after immunization with pneumococcal conjugate vaccine in this study [34]. A recent study also reported that higher levels of antipneumococcal antibodies did not correlate with protection from pneumococcal colonization in patients with COPD [35]. Therefore, the question arises as to why an additional increase of IgG in sera is required for preventing infectious acute exacerbation in COPD patients. A recent report demonstrated that the levels of anti-serotype-1 IgG in bronchoalveolar lavage (BAL) fluid were less than 10 ng/ml in 25 of 49 HIV-uninfected adults, while the mean level of serotype-1 specific IgG in sera of such subjects was 1608 ng/ml [36]. Thus, the level of specific IgG in the neat BAL fluid is at least 161 times lower than that in sera. According to this information and the data of levels of specific IgG in sera of patients with CLD before (2.60–5.69 μg/ml) and after vaccination (5.26–12.63 μg/ml) in this study, the levels of specific IgG in BAL fluid are estimated to be less than 35.3 ng/ml before vaccination and less than 78.5 ng/ml after vaccination, respectively. Since we found a significant effect of PV + IV on infectious acute exacerbation, compared with IV alone, the levels of serotype-specific IgG that rise higher than approximately 35 ng/ml in the lower airway fluid may be critical for preventing infectious acute exacerbation in patients with COPD.

Furthermore, the cost of acute exacerbation on patients with COPD creates a significant economic impact [3]. The literatures reports that the estimated costs for hospitalization due to acute exacerbation will range from $5655 to $7413 in developed countries [37–39]. The reduced frequency (27.2%) of acute exacerbation in the PV + IV group in this study, compared to the IV group, has significant economic implications for patients with COPD.

In conclusion, this pilot study demonstrated an additive effect of PV in combination with IV on infectious acute exacerbation of patients with COPD. This effect was closely associated with serotype-specific immune response to PV that was primarily found during the first year after vaccination. Further studies on a larger scale are required to investigate the additive effects of PV and IV on the incidence of acute exacerbation in COPD patients with various levels of airflow limitations.

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